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Perimidines: a unique π-amphoteric heteroaromatic system

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Data on the physicochemical characteristics, theoretical calculations, reactivity and synthetic methods for perimidines are summarized. Although perimidine and some of its simple 2-substituted derivatives were obtained by Sachs back in 1909, their chemistry and key physical properties remained unknown until the early 1970s. Subsequent studies revealed many fundamental features of the perimidine system, previously not encountered in the heterocyclic series. The first comprehensive review on perimidines was published forty years ago. The period that has passed since 1980 led to the emergence of new directions and trends. Several hundred new publications have appeared, the generalization of which has become the main purpose of this article. This primarily concerns the obtaining of highly nucleophilic and stable perimidine carbenes, new methods of electrophilic substitution and oxidation, establishment of a close relationship between perimidines and proton sponges, and modern theoretical calculations. Based on perimidines, many different polycondensed systems have been obtained. Applied research has developed especially rapidly in recent years. Many new compounds based on perimidines related to chemosensors, analytical reagents, dyes, metal catalysts, electronic devices, nanotechnology, and medical chemistry have been proposed. Some information under review is presented as Supplementary Materials. It contains six tables, which include data on the basicity constants of perimidines, details of some synthetic methods for perimidines and fused analogs and also a list of biological activities of perimidines.
The bibliography includes 387 references.

1. Introduction

According to the classification proposed by Albert [1] in his pioneering textbook, all heteroaromatic compounds can be rationally divided into π-excessive and π-deficient (for further development of this concept see Refs 2, 3). The typical representatives of the former are pyrrole, furan, thiophene and their benzologues. In them, the heteroatom (it is called pyrrole-like) contributes two electrons into the π-ensemble, due to which the ring systems acquire nucleophilic properties and display a high activity in electrophilic substitution and oxidation reactions. These compounds are also characterized by low ionization potentials. The group of π-deficient systems primarily includes azines, the main representatives of which are pyridine, pyrimidine, pyrazine and many of their analogues. The nitrogen heteroatom in these compounds (commonly called pyridine-like) donates only one electron into the aromatic ensemble and, due to its electronegativity, exhibits an electron-withdrawing character to a greater extent. Correspondingly, nucleophilic substitution and reduction reactions are especially characteristic of π-deficient heterocycles. An intermediate group of heteroaromatic systems includes azoles, for example, imidazole, pyrazole, benzimidazole, *etc*. They are distinguished by the presence of heteroatoms of both types in their heterorings. In principle, the systems of such a kind could be considered as π-amphoteric. However, in practice, each azole is more inclined to either π-excessive (*e.g.*,

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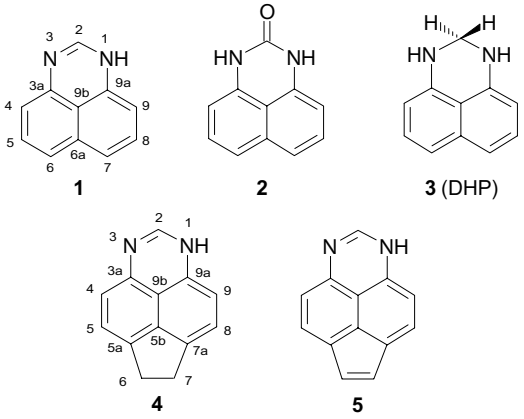
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pyrazole) or π-deficient systems (*e.g.*, benzimidazole).[4] Against this background, as was shown in a large series of works by one of the authors of this review, the naphtho[1,8-*de*]pyrimidine system, better known as 1*H*-perimidine (**1**, the name approved by IUPAC), stands out for its unique properties. The fact is that perimidines exhibit equally high activity both towards electrophilic and nucleophilic reagents, and are also easily oxidized and reduced. To date, perimidine is the only truly π-amphoteric system. Although perimidine and some of its simple 2-substituted derivatives were obtained by Sachs[5] back in 1909, their chemistry and key physical properties remained unknown until the early 1970s. Subsequent studies revealed many fundamental features of the perimidine system, previously not encountered in the heterocyclic series. The first comprehensive review on perimidines, which included literature until June 1980, was published forty years ago.[6] Since then, several hundred new publications have appeared, the generalization of which has become the main purpose of this article. Although the period that has passed since 1980 has brought not so much fundamentally new knowledge regarding the chemistry and electronic features of perimidines, it nevertheless led to the emergence of new directions and trends. This primarily concerns the obtaining of highly nucleophilic and stable perimidine carbenes, new methods of electrophilic substitution and oxidation, establishment of a close relationship between perimidines and proton sponges, and modern theoretical calculations. Based on perimidines, many different polycondensed systems have been obtained. Applied research has developed especially rapidly in recent years. Many new compounds based on perimidines related to chemosensors, analytical reagents, dyes, metal catalysts, electronic devices, nanotechnology, and medicinal chemistry have been proposed. In order to the review to be panoramic and to have a solid character, along with the achievements of the last four decades, fundamental discoveries and observations made in the 1970s were also introduced.

Structures 1 – 5



Apart from the parent compound **1**, four other important representatives of this series, namely 1*H*-perimidin-2(3*H*)-one (**2**), 2,3-dihydro-1*H*-perimidine (**3**, DHP), 6,7-dihydro-1*H*-cyclopenta[*gh*]perimidine (**4**, aceperimidine) and 1*H*-cyclopenta[*gh*]perimidine (**5**, aceperimidylene), will be often mentioned in this review.

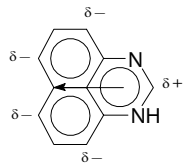
A notable feature of this review is the attached Supplementary Materials (https://doi.org/10.1070/RCR4963). It includes six items containing an exhaustive list of the experimental pK_a values of the known perimidines, four synthetic tables and a summary of the biological screening directions that researchers were interested in.

The following abbreviations and designations are used in the review:

Bn — benzyl,
BODIPY — boron-dipyrromethene,
CBT — 1-chlorobenzotriazole,
CNDO — complete neglect of differential overlap,
COD — 1,5-cyclooctadiene,
CSD — Cambridge Structural Database,
CTC — charge transfer complex,
Cy — cyclohexyl,
Dabcyl — 4-(dimethylamino)azobenzene-4′-carboxylic acid,
DAN — 1,8-diaminonaphthalene,
DCE — 1,2-dichloroethane,
DCM — dichloromethane,
DHP — 2,3-dihydroperimidine,
DMAD — dimethyl acetylenedicarboxylate,
DMAN — 1,8-bis(dimethylamino)naphthalene,
ESR — electron spin resonance,
Fu — furyl,
HBOB — bis(oxalato)boronic acid,
HOMO — highest occupied molecular orbital,
IHB — intramolecular hydrogen bond,
IP — ionization potential,
LAH — lithium aluminium hydride,
LED — light emitting diode,
LUMO — lowest occupied molecular orbital,
mCPBA — 3-chloroperbenzoic acid,
MHMDS — alkali metal hexamethyldisilazide,
Naph — naphthyl,
NBS — N-bromosuccinimide,
NHC — *N*-heterocyclic carbenes,
NMP — *N*-methylpyrrolidone,
PPA — polyphosphoric acid,
SPEEK — sulfonated poly(ether ether ketone),
TIPB — 2,4,6-triisopropylbenzene,
TPS — (triisopropylphenyl)sulfonyl,
Th — thienyl,
Ts — tosyl (p-toluenesulfonyl),
XRD — X-ray diffraction.

2. Structure and aromaticity

The π-resonance stabilization of the perimidine molecule is lower than that of isomeric naphthoimidazoles **6**, **7**.[6] Of the 14 π-electrons that constitutes the perimidine system, one is not peripheral. This leads to reducing its aromaticity. On the other hand, in the heterocyclic ring there is a formal excess of π-electrons (seven instead of the Hückel six). This results in the polarization of the π-cloud towards the naphthalene ring, as seen in structure **1a** (Fig. 1).[2,3] This shift was repeatedly confirmed in the 1970s by the quantum mechanics calculations carried out both by the Hückel[7–9] and complete neglect of differential overlap (CNDO/2) methods.[10,11]

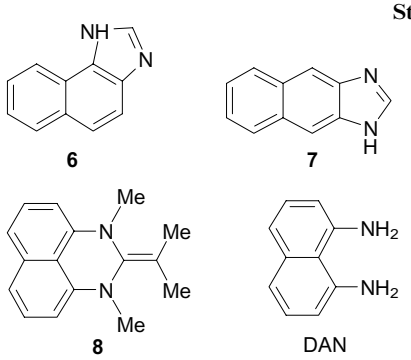


1a

Figure 1. Polarization scheme of 1*H*-perimidine.

It is noteworthy that the electron density distribution in the 1,8-diaminonaphthalene (DAN) moiety of **1** is extremely uneven, with a small positive charge on the C(5) and C(8) carbons and considerable negative charges in positions 4(9) and 6(7). The smaller transfer of the π-electrons from the heteroring to the naphthalene system also takes place in naphthoimidazoles **6**, **7**.[8,11,12] The CNDO/2 method revealed an interesting feature in the latter. In perimidine **1** the polarization of the C=N bond is mainly caused by the displacement of π-electrons[10] while in naphthoimidazoles **6**, **7** (Ref. 11) and in benzimidazoles[10] it is due to the displacement of σ-electrons.

Structures 6–8



6 **7** **8** DAN

Later,[13] studies have been conducted to optimize the geometry of compound **8** at the Hartree–Fock level followed by the Individual Gauge for Localized Orbitals (IGLO) calculations of the NMR chemical shifts. Analysis of the electronic structure of **8** by photoelectron spectroscopy and semi-empirical calculations has also been carried out.[13]

Recently, a theoretical study of perimidine and its derivatives has been performed at the B3LYP/6-311++G(d,p) level including Gauge-including atomic orbital (GIAO) calculations of NMR absolute shieldings.[14] One of the aspects that has been studied in detail is tautomerism both annular and functional of 2-hydroxy (and their radical cations), 2-thiol, 2-amino and 2-alkyl perimidines. Another was the acid-base equilibrium involving perimidine anion and cation. The protonation of 2-aminoperimidines (cyclic guanidines) and the properties of perimidine carbene (dimerization and addition to carbon dioxide), biperimidine, dihydroperimidine, and spiro bidihydroperimidine were also studied. Theoretical calculations indicate that the proposed 2-ammonio-1*H*-perimidine structure (refcode, ZIFNIR) is not correct; the true structure should be a 2-aminoperimidinium salt like all guanidinium cations (see Sections 3.4 and 5.2).

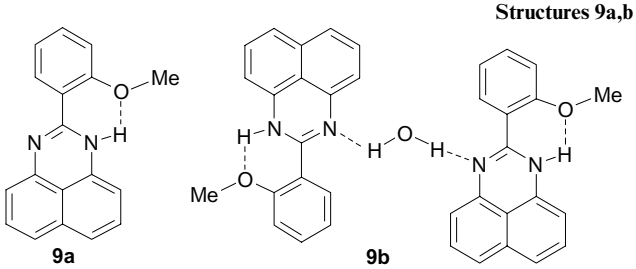
3. Physical properties

3.1. X-Ray crystallography

A search in the Cambridge Structural Database (CSD) [15, 16] on perimidines defined as represented below affords 304 hits, including organometallic compounds. Some representative examples are shown in Fig. 2.

X-Ray diffraction determination of the crystal structures of 2-(2-methoxyphenyl)perimidine (**9a**, PEKREC) and its hemihydrate (**9b**, PEKRIG) has been carried out.[17] The study shows that the two types of crystals obtained simultaneously are not a case of conformational polymorphism but an example of host – guest structures. The orange anhydrous **9a** is approximately flat due to an intramolecular hydrogen bond (IHB), while yellow crystal of another type **9b** contains a water molecule joining two molecules of 2-(2-methoxyphenyl)perimidine. The structure of this hemihydrate is not flat.

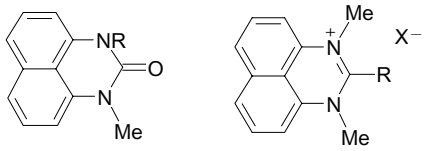
Structures 9a,b



9a **9b**

Two X-ray crystal structures of 1-methyl-1*H*-perimidin-2(3*H*)-one (**10**, PIPNUX) and 1,3-dimethyl-1*H*-perimidin-2(3*H*)-one (**11a**, PIPPAF) have been published.[18] The first molecule exists as oxo tautomer and forms dimers by hydrogen bridges of type N – H···O linking molecules through a centre of crystallographic symmetry. Each molecule is packed with itself, head-to-head, while in compound **11a** the stacking of molecules corresponds to the head-to-tail situation.

Structures 10 – 12



10 (R = H),
11a (R = Me)

12 (R = H, Me, Ph)

The structures of 2-(2-hydroxyphenyl) (ZEHHUP), 1-methyl-2-(2-methoxyphenyl)- (ZEHHEZ), 1-methyl-2-phenyl- (ZEHHID) and 2-(9-anthryl)perimidines (ZEHHOJ) [19] have also been determined. In general, as compared with 2-perimidinones, a higher degree of planarity of the heterocyclic ring is observed. When this planarity is lost as in 1-methyl-2-(2-methoxyphenyl)perimidine, it is due to the effects of packing in the crystal. Oxo/hydroxy tautomerism of ZEHHUP has been studied.[14]

3.2. Colour and electronic spectra

Perimidine is a yellow compound and its electronic spectrum shows three absorption bands at 400, 330 and 235 nm (bands α, β and γ).[20] The latter two are very intense ($\log \varepsilon = 4.1 - 4.6$) and attributed respectively to the transfer of the pyrrole nitrogen electrons to the LUMO π*-orbital of the naphthalene ring [21] and to electronic transitions in the naphthalene ring itself. Both are observed in the spectra of 2,3-dihydroperimidine and 1,8-diaminonaphthalene and derivatives.[20] The α-band has a reduced intensity ($\log \varepsilon \approx 3.0$) and usually appears as a shoulder. It is assumed that α-band is responsible for the colour of the perimidines. Since the yellow colour and this band persists in the spectrum of perimidinium salts, it cannot be attributed to an n – π* transition. From the calculated data,[7] it is inferred that this band is due to the transfer of electrons from the naphthalene to the heterocyclic ring. This explains why strongly electron-donating substituents in position 2 such as amino, alkoxy *etc*., which decrease the electron

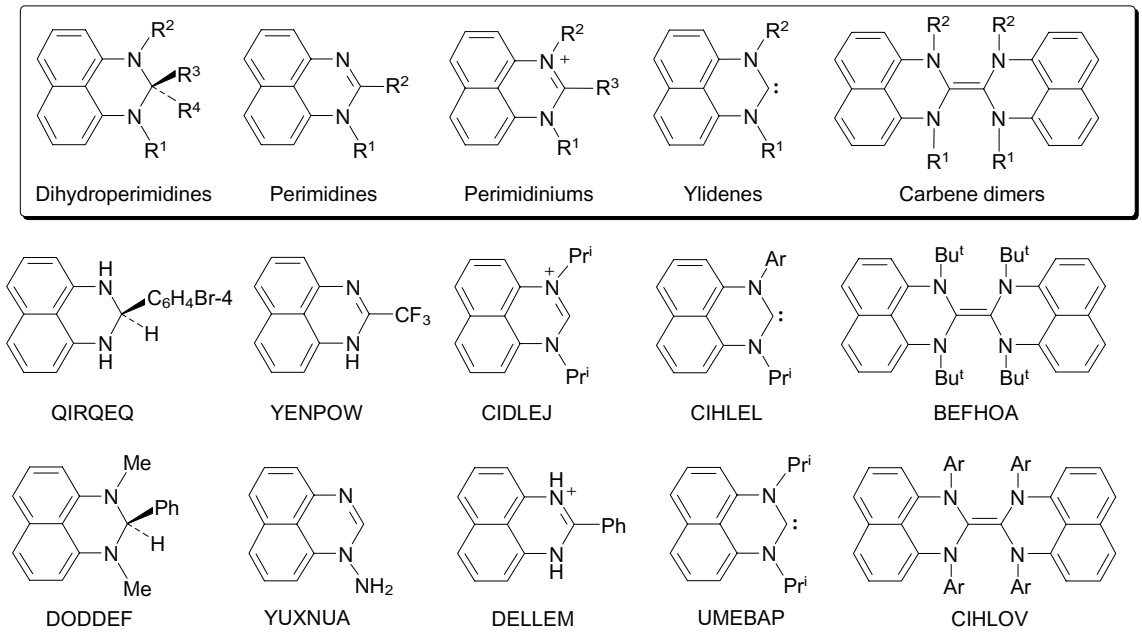


Figure 2. Some examples of perimidines found in the CSD together with their refcodes.

deficiency of the heteroring, lead to the complete disappearance of the colour.[12] Similar discolouration is observed at hydrogenation of the C–N bond (2,3-dihydroperimidines). On the other hand, strong electron-withdrawing substituents in position 2 deepen the colour of compounds, *e.g.*, 2-cyanoperimidines are red (λ_{max} = 460 nm, $\log\varepsilon$ = 3.09, MeOH)[22] and 2-benzoylperimidine is dark red (λ_{max} = 508 nm, $\log\varepsilon$ = 3.04, MeOH).[23]

Regarding substitution in the other part of the molecule, groups with vacant π orbitals introduced in *ortho*- and *para*-positions of the naphthalene ring significantly change the electronic spectrum of the perimidines and the colour intensifies. An intense band due to the π–π* transition appears in the region with the longest wavelength, whose position depends on the properties of the substituents as electron acceptors. For example, for 4-acetyl-1-methyl- and 9-acetylperimidines the λ_{max} is 405 and 416 nm respectively ($\log\varepsilon$ = 4.11 and 4.00), while the values for 1-methyl-4-nitro- and 9-nitroperimidines are 445 and 460 nm ($\log\varepsilon$ = 3.96 and 3.99).[21]

One of us has provided more detailed data on UV spectra of nitroperimidines,[24] 2-aminoperimidines[21,25] and DHP, perimidinones and thioperimidinones.[21] Minkin *et al.*[7] have studied the reactivity of various positions in perimidine, 1-methyl-, 2-methyl-, 2-phenyl-, 2-(*p*-nitrophenyl)- and 2-(*o*-hydroxyphenyl)perimidine (ZEHHUP) through MO calculations, dipolar moments, UV and IR spectra and luminescence. Thiel *et al.*[26] have studied the UV/VIS spectroscopic properties of 1*H*-perimidine-2-dithiocarboxylic acid derivatives. The obtained data reveals that the absorption bands of higher wavelength are due to π–π* transitions that are in line with those obtained previously for high electronic affinity substituents in position 2.

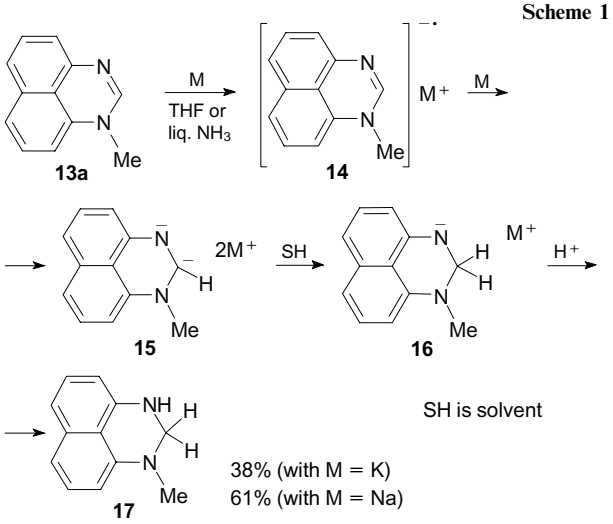
3.3. Properties as donor and acceptor of electrons

Research on photoelectronic spectroscopy of perimidine and its 2-methyl-, 2-trifluoromethyl- and 2-ethoxycarbonyl derivatives has revealed the following values of the first ionization potential, IP-1: 7.08, 6.90, 7.23 and 7.00 eV, respectively.[27] Similar IP-1 values in the range of 6.85–6.90 eV were obtained for 2,3-dihydroperimidines as using photoelectron spectroscopy[28] and mass spectrometry.[21] In general, the π-donor capacity of perimidines is greater than that of naphthoimidazoles **6**, **7**, DAN and even phenothiazines. This is also reflected in the enhanced intensities of double-charged ion peaks in perimidines mass spectra.[29]

It is interesting that perimidine in the crystalline state gives a narrow single and symmetrical electron spin resonance (ESR) signal with a width of ≈7 Oe.[20] The signal intensity obeys the Curie law ($1/T$). The number of spins causing this signal is approximately 10^{17} per gram, which corresponds to one spin per 5–10 thousand molecules. The nature of this signal is presumably associated with the formation of charge transfer complexes (CTCs) between neighbouring molecules in some nodes of the crystal lattice, in which one of them acts as a π-donor and the other as a π-acceptor. In favour of this is the fact that perimidines and DHPs indeed form intensely coloured CTCs with various π-acids, including weak ones such as 1,3,5-trinitrobenzene or 4-nitrobenzaldehyde.[20,30] In terms of their ability to act as an electron acceptor, perimidines occupy a position between azines and imidazoles. In this way, the perimidinium salts **12** are polarographically reduced with greater difficulty than the azinium cations but more easily than benzo- and naphtho[1,2-*d*]imidazolium cations.[31,32] The ease of reduction of the naphtho[2,3-*d*]imidazolium cations is almost identical to that of the perimidinium cations.

Some information on radical-cation and radical-anion species is also available. Thus, it was demonstrated that 1-methylperimidine (**13a**) on treatment with sodium in THF at −60 °C produces a dark-green coloured radical anion **14** (Scheme 1).[33] Its ESR spectrum consists of 42 components of the hyperfine structure. From this it was calculated that the largest spin densities (ρ_e = 0.22) are localized on the C(2) and C(6) atoms. Interestingly, on prolonged standing or heating the solution becomes diamagnetic and changes colour from dark-green to brown-red, which was assigned to the sequential formation of *N*,*C*-dianion **15** and mono-*N*-anion **16**. The absence of dianion **15** in the brown-red reaction mixture was confirmed by chemical experiments. When compound **13a** was reduced with Na or K in liquid ammonia, the reaction developed much faster than in THF and, after adding NH_4Cl to the reaction mixture, 1-methyl-2,3-dihydroperimidine **17** was formed in moderate yield.

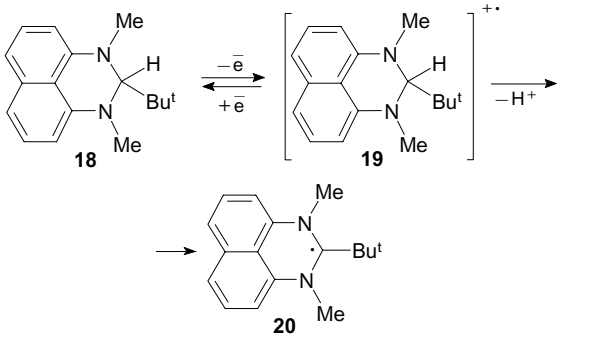
Scheme 1



13a **14** **15** **16** **17**

To observe radical cations, the electrochemical oxidation of perimidines and DHPs was studied using a stationary platinum electrode in anhydrous DMF.[34] Compounds with a 2-*tert*-butyl group were chosen as objects of study in order to minimize the processes of radical coupling. In the case of DHP derivative **18**, the first wave (E_{ox} = 0.73 V relatively to the AgCl electrode) was single-electron and partially reversible (Scheme 2). However, the radical cation **19**, generated under these

Scheme 2

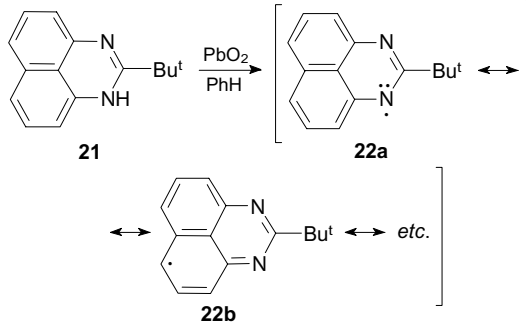


18 **19** **20**

conditions, turned out to be unstable and lost a proton with the formation of radical **20** following its rapid degradation. Nevertheless, the ESR spectrum of **20**, which has a hyperfine structure, was recorded during its chemical generation by oxidation of **18** with Ag_2O or reduction of 1,3-dimethyl-2-*tert*-butylperimidinium iodide with zinc metal. During the oxidation of **18** with aluminium chloride in nitrobenzene, the ESR spectrum of radical cation **19** was recorded, consisting of an unresolved singlet with a width of $\Delta H \approx 30$ Oe.

Oxidation of 2-*tert*-butylperimidine **21** with lead dioxide in benzene led to the formation of an unstable σ-radical **22** (Scheme 3). Judging by its ESR spectrum, most of the spin density in it is localized on the heteroatoms (two resonance structures of type **22a**) rather than on the carbon atoms (five structures of type **22b**).[34] In 2002, Morita *et al.*[35] reported the synthesis by the same method of a green coloured and very stable crystalline radical from 2,5,8-tris-(*tert*-butyl)perimidine.

Scheme 3



21 **22a** **22b**

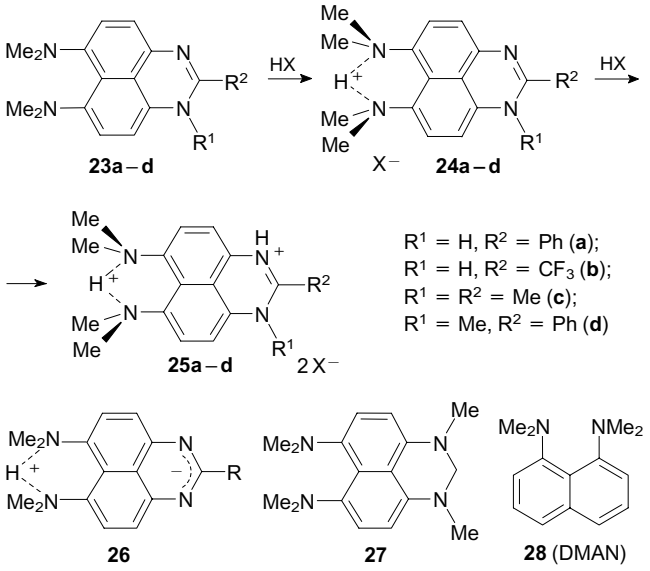
3.4. Ionization constants

Perimidine is a stronger base than benzimidazole, naphthoimidazoles and azines.[36,37] The perimidinium ion and its alkyl-substituted derivatives have $pK_a \approx 6$ in aqueous solution (for the full survey of pK_a values see Table S1, Supplementary Materials, https://doi.org/10.1070/RCR4963).

The basicity of 2,3-dihydroperimidines is two orders of magnitude lower in water[38] and five orders of magnitude lower in acetonitrile[39] than that of perimidines.[40] This is because DHPs have an almost flat structure, which facilitates the conjugation of the lone electron pairs of both nitrogen atoms with the aromatic ring. Data on the basicity of 1-alkyl,[35,41] 2-alkyl,[39,40,42] 2-aryl[25] and nitro perimidines[24] and 2,3-dihydroperimidines[38] are available. The X-ray crystallography data indicating that the protonation of 2-amino-1*H*-perimidine takes place on the amino group (ZIFNIR)[15,43] is probably wrong, the cation must correspond to the protonation on the N(3)[14] (see Section 5.2).

6,7-Bis(dimethylamino)perimidines **23** is a special case (Scheme 4).[44] Those are close analogues of 1,8-bis(dimethylamino)naphthalene (**28**, DMAN), commonly known as a 'proton sponge'. Compounds **23a**,**b** with a free NH group have been shown to exist as such and not as zwitterionic species **26**. However, unlike ordinary perimidines, they are first protonated at the *peri*-NMe_2 groups (proton sponge-like behaviour) producing salts of type **24**. The second protonation occurs at the heterocyclic ring to give dications **25**. Notably, similar to DMAN diamines, compounds **23** seem to be kinetically inactive bases [reduced rate of the proton addition(elimination) in combination with low nucleophilicity of the *peri*-NMe_2 groups]. Such an assumption stems from the fact that unlike protonation, the

Scheme 4



23a – d **24a – d** **25a – d** **26** **27** **28** (DMAN)

alkylation of **23** proceeds exclusively at the nitrogen ring heteroatom to yield the corresponding 1,3-dialkylperimidinium salts (azole-like behaviour). The basicity of **23** (pK_a 8.4 – 9.3 in DMSO, which corresponds to 13.5 – 14.5 for the water scale) is nearly two orders of magnitude higher than that of DMAN (pK_a 7.5 in DMSO and 12.1 in H_2O) and much higher than that of perimidines, which allows classifying 6,7-bis(dimethylamino)perimidines as neutral superbases. Staab and co-workers[45] have synthesized 6,7-(dimethylamino)-1,3-dimethyl-2,3-dihydroperimidine **27** and demonstrated that its basicity (pK_a 15.0 in H_2O, 10.4 in DMSO) somewhat exceeds that of perimidines **23a – d**.

3.5. Dipole moments

Experimental dipole moments of seven perimidine derivatives (in dioxane, 30 °C) were reported.[7] The enlarged dipole moment of perimidine (3.18 D) is consistent with its highly asymmetrical electronic structure. Of all the older quantum mechanics methods[7,9,10,25] used to calculate the dipole moment, the CNDO method[11,38] shows the best agreement with the experimental data. Recent theoretical calculations also reproduce adequately this value.[14]

3.6. Fluorescence spectroscopy

The fluorescence of perimidine and some of its derivatives[7,46] is less intense than that of naphthoimidazoles **7**.[47] While DAN and 2,3-dihydroperimidines fluoresce when irradiated with UV light, simple perimidines do not. 4(9)- and 6(7)-Acylperimidines[47] show intense fluorescence. The fluorescence of 2-(2′-hydroxyphenyl)-1*H*-perimidine, its photophysics and photostability have been studied by Catalán and co-workers[48,49] 2-Aryl (naphthyl, phenalenyl) and 2-heteroaryl (pyrrolyl, pyridinyl) perimidines exhibit enhanced quantum yields.[50]

3.7. Infrared spectroscopy

The most interesting regions of the spectrum are at 3100 – 3500 and 1500 – 1700 cm^{-1} where the stretching bands of the N – H, C=C and C=N bonds are located. In crystalline species of perimidines and their 2-substituted derivatives, there are no stretching bands due to free N – H groups, but a broad band from 3200 to 2500 cm^{-1} indicating the molecule association *via* intermolecular hydrogen

bonds. In dilute solutions in CH_2Cl_2 an intense and sharp band is observed at 3420 cm^{-1} due to free ν(NH).[51] In some crystalline species, when the NH group is involved in an intramolecular hydrogen bond, the N—H band is also narrow and intense. Scaled theoretical calculations reproduce conveniently the IR spectrum of **1**.[14]

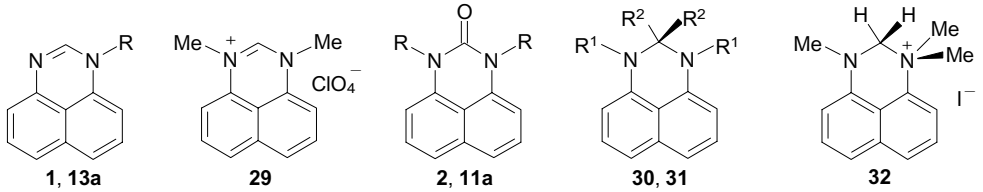
Infrared spectral data for 4(9)-nitro-[52] and 4(9)-acylperimidines,[53] perimidine, 2-methyl- and 2-arylperimidines were reported.[7,51] In the 1590 – 1650 cm^{-1} region, perimidines with a free N—H group display three bands of modest intensity. In the case of perimidinium salts, the ν(CN) band is shifted to 20—35 cm^{-1} higher, which is typical of cyclic amidines.[52] 1-Methyl-2,3-dihydroperimidine shows a strong broadened band of ν(NH) at 3410 and 3370 cm^{-1} measured in $CHCl_3$ and Nujol, respectively.[38]

3.8. Magnetic properties and ^{1}H NMR spectra

As a result of the abnormally high asymmetry of the π-electron cloud, perimidine is characterized, *e.g.*, in comparison with naphthoimidazoles **6** and **7**, by an appreciable paramagnetic component of its ring current and a reduced diamagnetic susceptibility.[20] Correspondingly, in the ^{1}H NMR spectrum, signals of aromatic H-4 and H-9 protons are shifted upfield (about 0.8 – 1.2 ppm) compared to naphthalene and naphthoimidazoles (Table 1). In perimidines with a free N—H group, there is a rapid exchange of the N—H proton between positions 1 and 3, and the pairs of the ring protons H-4(9), H-5(8) and H-6(7) become equivalent appearing as a doublet of doublets. In 1-alkylperimidines[6] these protons become not equivalent, resulting in two groups of well-resolved signals, with the proton H-9 located at a higher field.

However, several examples of NH-perimidines have been described in which rapid prototropy between nitrogen atoms is strongly inhibited, either as a result of intramolecular hydrogen bonds, as in 9-acyl- or 9-nitroperimidines,[52 – 54] or under influence of strong electron-withdrawing groups in positions 2 and 6(7).[55 – 57] The chelated N—H proton in 9-acyl-, 9-formyl- and 9-nitroperimidines commonly resonates as a broadened peak at δ 11.5 – 12.5 ppm. The H-2 signal in perimidine proton spectra often overlaps with those of H-5, H-6, H-7 and H-8 protons, which appear as a complex multiplet. In perimidinium cations the H-2 signal is displaced downfield in a

Table 1. ^{1}H NMR data of some perimidine derivatives (data of the authors).



1, **13a** **29** **2**, **11a** **30**, **31** **32**

R = H (**1**, **2**), Me (**11a**, **13a**); R^1 = Me, R^2 = H (**30**); R^1 = R^2 = Me (**31**)

Compound	NH or NMe	Chemical shift (δ) /ppm						
		H-2 or Me-2	H-4	H-5	H-6	H-7	H-8	H-9
1 [a]	10.53	7.32	6.38	7.09	6.99	6.99	7.09	6.38
	br s	s	br t	t	dd	dd	t	br t
13a [b]	3.12	7.20	6.95	7.20	7.20	7.20	7.20	6.20
	s	m	dd	m	m	m	m	dd
29 [c]	3.55	9.00	7.08	7.59	7.70	7.70	7.59	7.08
	s	s	d	t	d	d	t	d
2 [a]	10.00	—	6.49	7.17	7.06	7.06	7.17	6.49
	br s		br d	t	br d	br d	t	br d
11a [b]	3.42	—	6.54	7.35	7.27	7.27	7.35	6.54
	s		dd	t	dd	dd	t	dd
30 [b]	3.03	4.18	6.55	7.35	7.23	7.23	7.35	6.55
	s	s	dd	m	dd	dd	m	dd
31 [b]	2.94	1.39	6.59	7.31	7.19	7.19	7.31	6.59
	s	s	dd	t	dd	dd	t	dd
32 [b]	3.47	4.75	6.94	7.55 – 7.65	7.50	7.95	7.55 – 7.65	8.04
	s (NMe)	6.25	dd	m	dd	dd	m	dd
	3.98	two br s						
	br s (N^+Me_2)	(CH_2)						
32 [d]	3.15	4.97	7.07	7.66	7.59	8.07	7.66	7.86
	s (NMe)	br s (CH_2)	dd	m	dd	br d	m	br d
	3.58							
	br s (N^+Me_2)							

[a] DMSO-d_6, 250 MHz; [b] $CDCl_3$, 300 MHz; [c] DMSO-d_6, 250 MHz; [d] CD_3CN, 250 MHz.

greater extent than other protons.[58, 59] When an electron-withdrawing group (nitro,[52] acyl [53] or sulfo [60]) is introduced into the naphthalene ring of perimidine, the ^{1}H NMR spectrum is greatly simplified.

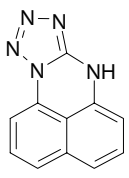
Elguero *et al.*[61] and Claramunt *et al.*[62] have described in detail the spectra of 2-perimidinone [61] and 2-azidoperimidines [62] among others. GIAO/B3LYP/6-311 + + G(d,p) calculated absolute shieldings transformed into chemical shifts by empirical equations [14] reproduce the experimental data of perimidine and some of its derivatives.[18, 20]

The NMR spectra of 2,3-dihydroperimidines in the aromatic region have a pattern similar to that of perimidines except for a slight downfield shifts of all ring protons. For DHPs without any substituents in position 2 the most interesting is an appearance of proton signals of μ-CH_2 group. In bases of symmetric DHPs, both geminal protons are magnetically equivalent giving a two-proton singlet at $\delta \approx 4$ ppm. However, in 1,1,3-trimethyl-2,3-dihydroperimidinium salts like **32** these protons behave in a different way. In $CDCl_3$ solution the spectrum of **32** shows two very broad signals for the CH_2 group centred at δ 4.75 and 6.25 ppm. In contrast, in polar media (CD_3CN) both signals coalescence into a broad two-proton peak at δ 4.97 ppm. We are dealing here with the flipping of the CH_2 group relative to the ring system plane, which strongly slows down in the nonpolar medium.

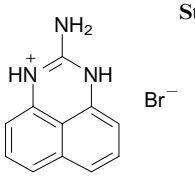
3.9. ^{13}C NMR spectra

The first reports on ^{13}C NMR spectra concerned tetrazolo[1,5-*a*]perimidine (**33**) [62] and the hydrobromide of 2-aminoperimidine (**34**).[63] In 1988, Woodgate *et al.*[54] discussed and assigned carbon signals for other 38 perimidines (15.04 MHz, DMSO-d_6) which were mainly derivatives of perimidine-2-thione but also perimidine itself, 1-methylperimidine, perimidin-2-one and several quaternary salts. The following main conclusions were made: 1) in spectra of perimidine and its symmetrical derivatives with rapid annular prototropy, the pairs of carbon atoms C-4/C-9, C-5/C-8, C-6/C-7 and C-3a/C-9a give common signals, which greatly simplifies the spectrum; 2) in general, the chemical shifts in ^{13}C and ^{1}H NMR spectra vary in parallel. Thus, for perimidine **1**, the C-2 signal (146.3 ppm) is the most deshielded while C[4(9)] (106.9 ppm) resonates at the highest field. For asymmetric 1-methylperimidines, the C-2, C-4 and C-9 peaks appear at δ 146.3, 100.6 and 114.9 ppm; 3) in perimidine derivatives, where prototropy is rapid, three signals are observed for the quaternary carbons. Of these, the C-9b has a relatively large relaxation time, so it gives a characteristic wide signal whose position is not greatly affected by the nature of the substituents in the naphthalene ring; 4) the position of the C-9b signal is slightly shifted upfield upon the protonation of the heterocyclic ring. Thus, while in perimidines with an electron donating substituent at C-2, the resonance of the C-9b atom appears at 120 – 124 ppm, in the perimidinium salts it appears around 119 ppm. The C-3a and C-9a atoms show a similar displacement.

Structrures 33, 34



33



34

Perimidine is an exception, and its protonation causes a shift by + 3.5 ppm in the C-9b signal due to the absence of the compensating effect of an electron donating group; 5) in perimidin-2-one **2** (Refs 18, 61) or perimidine-2-thione [54] the C-9b resonates at 113.6 and 116.1 ppm, respectively. In such cases, the predominant tautomer is not π-deficient and looks more like 1,8-diaminonaphthalene (C-8a, δ = 117.7 ppm). The peaks of C-6a and C-3a/C-9a atoms in perimidine appear at 135.3 and 141.0 ppm, respectively,[18, 54] the last signals being more intense than those of other quaternary carbons.

An exhaustive ^{1}H and ^{13}C NMR spectroscopic study of a series of 2-arylperimidines [20] has been conducted, with a complete assignment of all protons and carbons through the corresponding homonuclear (^{1}H – ^{1}H) and heteronuclear (^{1}H – ^{13}C) correlation experiments.

The *N*,*N*-acetal α-carbon atoms of the cyclic ketene **8** resonate at very high fields [13] in accordance with IGLO calculations of chemical displacements. For recent and more accurate theoretical calculations of ^{13}C chemical shifts of several perimidine derivatives, see Ref. 14.

Perimidine protonation causes an electron density shift from the naphthalene rings to the protonated nitrogen atoms. This results in deshielding of the C-4/C-9 and C-6/C-7 and shielding (– 10 ppm) of the C-3a and C-9a atoms. This effect distinguishes the signals of these carbons from that of the carbon 6a. Although the relative order of chemical shifts of carbons in the ^{13}C spectrum of perimidine is the same as for DAN, in the spectra of the former all signals (except C-9b and of course C-2) exhibit a pronounced displacement to higher field,[54] according to the π-excessive character of perimidine system.[6] The C-2 signal usually appears around 146.3 ppm showing again higher π-deficiency of this atom in comparison with the C-2 in benzimidazole (141.5 ppm).[64]

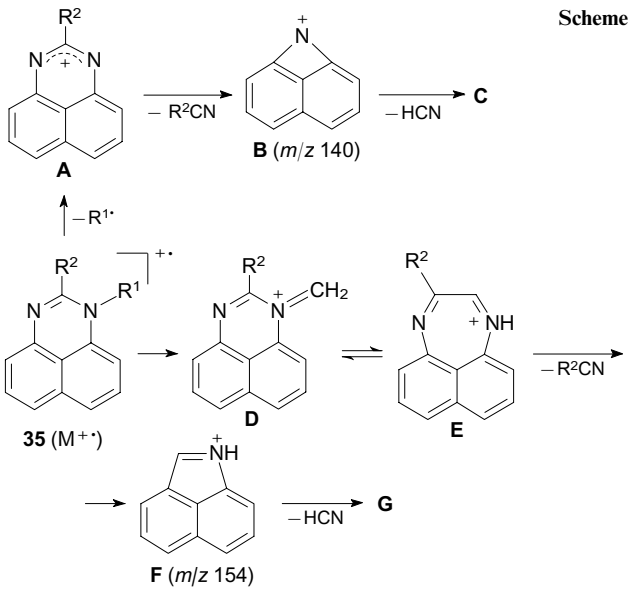
The protonation of the nitrogen heteroatom or the presence of an electron-withdrawing substituent in position 2 causes an additional downfield shift of the C-2 signal. In addition to the ^{13}C NMR spectra discussed by Woodgate *et al.*[54] data on other perimidines can be found [28, 65] (see also Section 5.7, concerning perimidin-2-one [18, 54, 61]).

3.10. Mass spectrometry

Until 1980, only scattered data could be found on mass spectra of some 2-substituted perimidines [66] and DHPs.[66, 67] Klyuev *et al.*[29] were the first to publish the mass spectra of various perimidines and dihydroperimidines and discuss them in detail. Perimidines, as electron-excessive heterocycles (like indoles or carbazoles), are distinguished by their high resistance to electronic impact. Another important feature of perimidines is the formation of a very intense peak of a double charged molecular ion M^{2+}. According to the authors,[29] the presence of these peaks is associated with the high π-donor character of the perimidines [20] and the DHPs.[21] The M^{2+} peaks are only absent in cases where the π-donor capacity is reduced by the presence of an electron-withdrawing group or when the molecular ion is unstable. Scheme 5 represents a typical fragmentation processes for perimidines **35** (in most of them R^1 and R^2 = H, Alk or Ar).

Two common routes of initial fragmentation of the molecular ion, which is usually the most intense, are the loss of either a substituent bound to nitrogen to give ion **A** or a hydrogen atom from the *N*-Me group to give ion **D**. In the first fragmentation path the signal of **A** is often the basic one. Ion **A** then ejects R^2CN and turns into an ion with *m*/*z*

Scheme 5

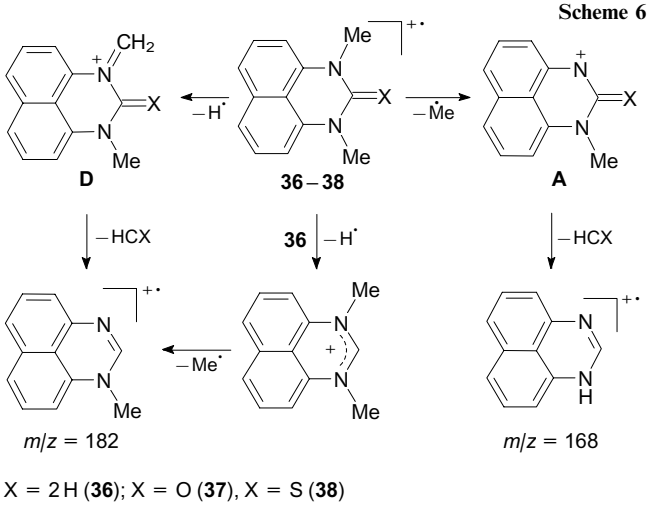


140. This peak, presumably belonging to species **B**, is present in the mass spectrum of the parent perimidine and in almost all of its 1- and 2-substituted derivatives.[66] When the nitrogen-bound group is benzyl, the base peak appears at *m*/*z* 91 (benzyl cation rearranges into tropylium ion).

The second fragmentation path predominates in the case of 1-methyl-2-phenylperimidine. The decay of ion **D** presumably proceeds through its rearrangement into 1,4-diazapleiadiene cation **E**, and leads to an ion with *m*/*z* 154, which is attributed to benz[*c*,*d*]indole cation **F**. The subsequent fragmentation of ions **B** and **F** is not clearly defined and is conditionally assigned as leading to a set of species **C** and **G**. The formation of $(M-1)^+$ and $(M-2)^+$ ions with intense peaks is characteristic of perimidines with phenyl substituents in positions 1 or 2.

For M^+ ions derived from 1,3-dimethyl derivatives of DHP, perimidinone and perimidine-2-thione (Scheme 6, structures **36**–**38**), the first two fragmentations are analogous to 1-substituted perimidines. The resulting ions **A** and **D** eject HCX and give perimidinium (*m*/*z* 168) and 1-methylperimidinium ions (*m*/*z* 182). The formation of the latter is proved by the presence of peaks with *m*/*z* 154, 140 and 127, characteristic of typical perimidine structures, in the mass-spectra of compounds **37** and **38**. Mass spectrometry has been used to determine the gas phase structure of 2-perimidinone **2**.[61] The spectrum is characterized by an intense signal at *m*/*z* 166 corresponding to the loss of water from the molecular ion M^+ (*m*/*z* 184). This result contrasts with that obtained for 2-benzimidazolone and diphenylurea, used as a model, where the only observed process is decarbonylation.

Scheme 6



X = 2H (**36**); X = O (**37**), X = S (**38**)

3.11. Tautomerism

The analogy between perimidines and imidazoles is clearly evident when considering the process of 'annular prototropy', *i.e.* tautomerism involving the proton attached to the nitrogen atoms at positions 1 and 3. The results obtained for the more studied field of benzimidazoles[68–71] can be extended to perimidines:

1) a proton transfer requires other molecules as shuttles and the mechanism involves hydrogen bonds;

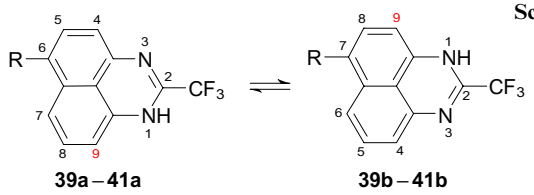
2) the barriers are in the range of dynamic NMR studies (DNMR) in solution being very dependent on the nature of the solvent;

3) in the solid state there is no prototropy since these molecules crystalize as long chains (catemers);

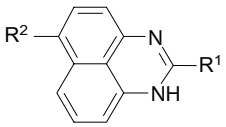
4) substituents forming intramolecular hydrogen bonds can slow down the proton transfer with a concomitant increase of the barrier.

Regarding perimidines monosubstituted in the naphthalene ring, usually the difference in properties of 6-R- and 7-R-perimidines is small and as a result, their NMR pattern looks as averaged spectra of the two forms 1*H*-6-R and 1*H*-7-R. However, with the additional presence of a bulky (Bu^t) and especially strongly electron-withdrawing group such as CF_3 in position 2, the tautomerism can slow down so much that both forms are clearly observed. Thus, it was shown that in solutions of 6(7)-formyl-, 6(7)-acetyl- and 6(7)-*p*-toluenesulfonyl-2-trifluoromethyl-perimidines (**39**–**41**) in non-polar solvents, both NH-tautomers are easily detected using ^{1}H NMR spectroscopy, sometimes even on heating up to 130 °C (Scheme 7).[55,56] Notably, the 1*H*-7-R form usu-

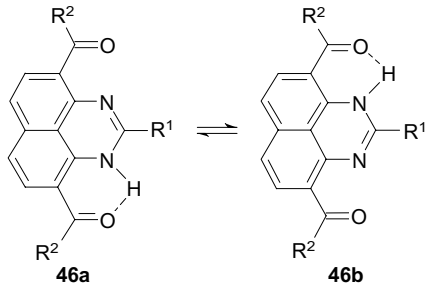
Scheme 7



R = CHO (**39**), Ac (**40**), $O_2SC_6H_4Me$-4 (**41**)



R^1 = H: R^2 = CHO (**42**), Ac (**43**),
R^1 = Bu^t: R^2 = CHO (**44**), Ac (**45**)

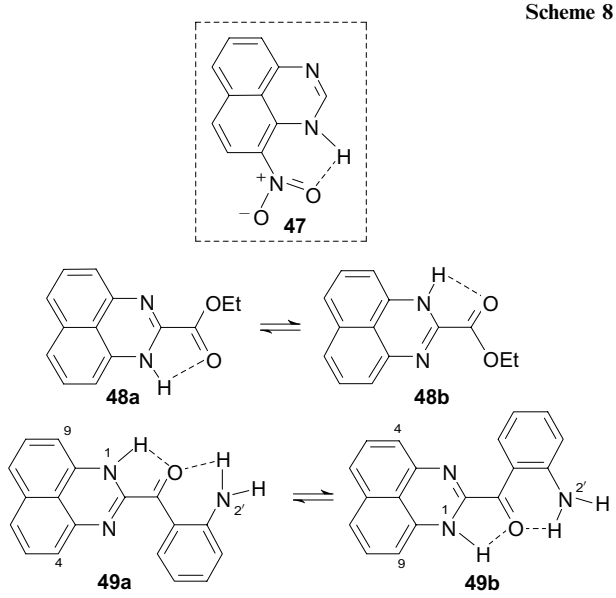


R^1 = H, CF_3;
R^2 = H, Me

ally predominates over 1*H*-6-R, apparently due to its higher stability caused by the more efficient π-conjugation of the C(7)-substituent with the pyrrole NH group. In polar solvents (DMSO-d_6, CD_3CN), the proton transfer rate in compounds **39**–**41** increases sharply and the spectra of the two forms merge, becoming indistinguishable. The peculiarities of annular tautomerism in the related compounds **42**–**46** have been.[72] It is most likely that the strong inhibition of annular tautomerism in compounds **39**–**41** and **44**–**45** is caused by a decrease in the basicity of the pyridine nitrogen atom in combination with steric hindering from the bulky substituent in position 2.

Another way of freezing the annular prototropy consists of substituting positions 4 and 9 with groups that are capable to form IHB with the NH proton. Amongst these substituents are NO_2,[24] RCO,[53, 57] RSO_2 (Ref. 72) and some other groups. Formation of the corresponding hydrogen chelates, *e.g.*, **47**, shifts the balance to the 1*H*-tautomer (Scheme 8). More complex example of such kind, when NH proton can chelate two carbonyl-containing *ortho* substituents, is represented by compounds **46**.[57]

Scheme 8

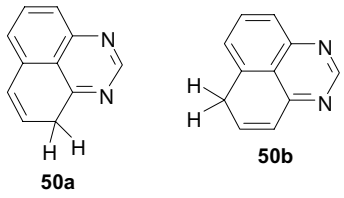


Several examples of slowing down annular prototropy due to the formation of IHB with a suitable substituent at position 2 are also known. For instance, the ^{13}C and ^{1}H NMR spectra of 2-ethoxycarbonylperimidine **48** in $CDCl_3$ at room temperature show a simple pattern corresponding to rapid proton migration between nitrogen atoms.[73] However, upon cooling to −60 °C, the spectra become asymmetric due to the splitting of the signals of aromatic protons, especially H-4 and H-9. The reason for this is the formation of isoenergetic chelated forms **48a** and **48b**. Based on the coalescence temperature, it was calculated that the activation energy required for this, $\Delta G^{\#}$, which actually relates to freezing the free rotation of the CO_2Et group around the C–C bond, is ~50.6 kJ mol^{-1}. The greater difficulty of freezing tautomerism in **48** compared with 4(9)-substituted perimidines is noteworthy. Obviously, this is due to the lower stability of the five-membered chelate ring in **48** compared to the six-membered one in compounds **46** or **47**. In the same manner 2-(2-aminobenzoyl)perimidine equilibrates between degenerated forms **49a** and **49b** with the bifurcated hydrogen bonds O···H–N.[74] Interestingly, in the ^{1}H NMR spectrum (DMSO-d_6) the N(1)H proton and the unchelated proton of the NH_2 group are invisible, while the chelated proton of the latter appears as a rather sharp peak at δ 7.43 ppm. Both O···N(1) and O···N(2′) distances are nearly equal (2.784 and 2.783 Å, respectively).

Annular prototropy connected with the NH proton migration to positions 4(9) and 6(7) is theoretically possible and although 4*H*-perimidine (**50a**) and 6*H*-perimidine (**50b**) have never been detected, the carbonyl and some other derivatives of these tautomeric forms are well known.

Tautomerism involving functional groups, like OH, NH_2, SH, *etc*. will be discussed in Section 5.

Structures 50



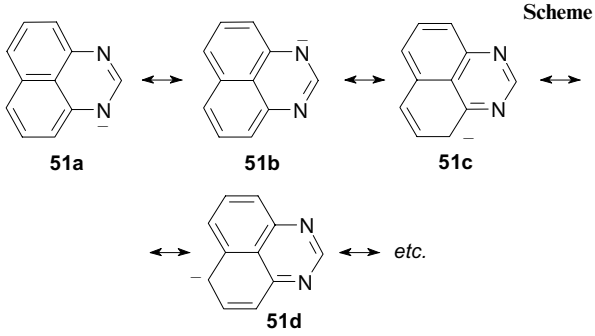
4. Chemical properties

4.1. Oxidation and reduction reactions

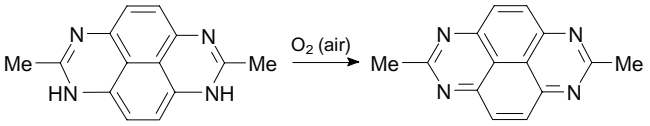
Freshly prepared perimidine has a clear yellow colour. However, during storage, it gradually turns greenish and then green, which is caused by its low ionization potential and slow autooxidation. In an alkaline medium, due to the formation of the *N*-anion, oxidation of perimidine proceeds almost instantly with the formation of a black and insoluble crystalline product of unknown nature, which, according to the elemental analysis, has the composition $(C_{11}H_7N_2O)_x$.[36] Other perimidines with a free NH group are also oxidized under these conditions. An exception are compounds containing strong electron-withdrawing groups in the naphthalene ring [NO_2,[52] RCO,[53] SO_3H (Ref. 60)]. The ease of autooxidation of the *N*-anion, along with the colour and dual reactivity, is another remarkable feature of the perimidine system that is not characteristic of other *N*-unsubstituted NH-heterocycles. Only phenothiazines approach perimidine in terms of the *N*-anion oxidation behaviour.[75] Scheme 9 shows the *N*-anion resonance hybrids **51**.

It is likely that the oxidation of the *N*-anion begins with the formation of the radical species due to the loss of an electron from the π-HOMO and subsequent radical recombination and further autooxidation steps. Perimidines with an expanded π-electronic system or with electron-donating substituents can undergo fast autooxidation even in a neutral form. For example, red compound **52**, prepared by cyclization of 1,4,5,8-tetraaminonaphthalene with acetic

Scheme 9



Scheme 10

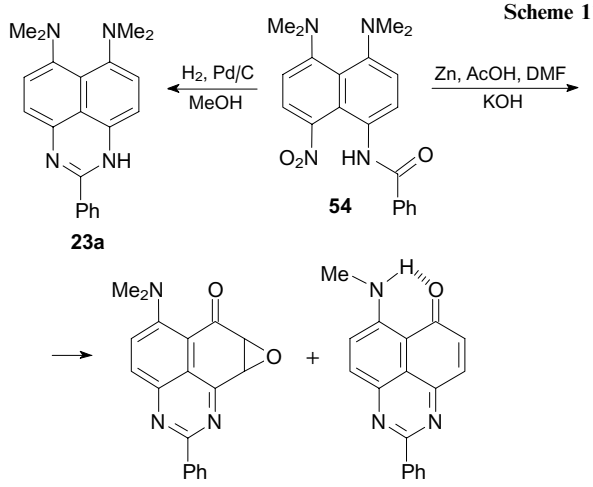


52 **53** (84%)

anhydride, is rapidly oxidized in air to form almost colourless and stable tetrazapyrene **53** (Scheme 10).[76]

Ozeryanskii and co-workers[44] observed a deep oxidative transformation during cyclization of 4-nitro-5-benzoylamino derivative of DMAN **54** (Scheme 11). Catalytic reduction of **54** with hydrogen gas in a neutral medium led to perimidine **23a** as the only isolated product. However, the reduction of **54** with zinc in acetic acid followed by alkalization of the reaction mixture gave only diazapyrenone derivatives **55** and **56**, whose structures were proved by XRD.

Scheme 11

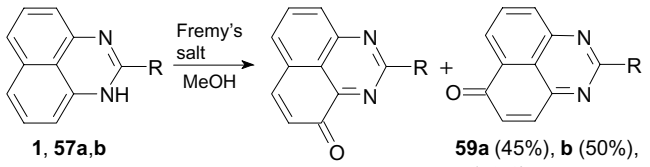


Perimidines are also very sensitive towards other oxidants. Thus, Fremy's salt (dipotassium nitrosodisulfonate) converts parent compound **1** and its 2-methyl and 2-phenyl derivatives **57** into a mixture of commensurate quantities of 4*H*-perimidin-4-ones **58** and 6*H*-perimidin-6-ones **59** (Scheme 12).[77,78] This reaction has also been carried out for perimidines bearing alkyl substituents in the naphthalene ring and for certain 2,3-dihydroperimidines.[77,78]

Oxidation of perimidines **1**, **57** [R = H, CO_2Et, $C(O)NHCH_2CH_2NMe_2$] with 3-chloroperbenzoic, trifluoroperacetic acids or Fremy's salt has been published.[79] Similar perimidinones are also formed upon oxidation of 4(9)- and 6(7)-hydroxyperimidines[80–82] by air oxygen or $FeCl_3$. Recently, the first example of oxidation of perimidines into naphthoquinones has been described.[83] Treating mixture of 1-R-6-amino- and 1-R-7-aminoperimidines **60a**,**b** with the Fremy's salt led to *ortho*-quinones **61a**,**b** in 10%–44% total yield (Scheme 13).

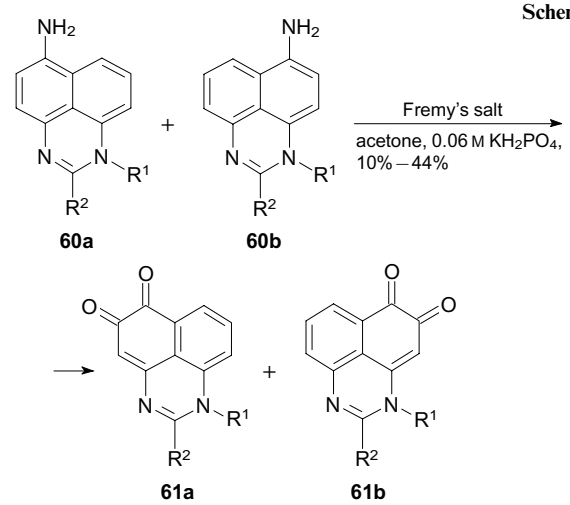
The yellow compound **63**, obtained by oxidation of 2,3,2′,3′-tetrahydrodiperimidinyl **62**, is easily reduced by alkali metals (potassium) or thallium in THF to the corresponding radical anions or dianions (Scheme 14). The radical anions form paramagnetic complexes **64a**,**b** with the above metal ions; structures of the complexes were confirmed by the ESR spectra. In the case of K^+, the

Scheme 12



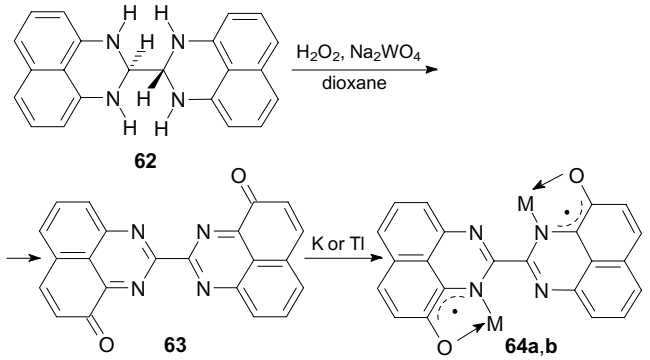
57: R = Me (**a**), Ph (**b**); **58**, **59**: R = H (**a**), Me (**b**), Ph (**c**); Fremy's salt = $K_2[NO(SO_3)_2]$

Scheme 13



R^1 = Me, Et; R^2 = Me, Et, cyclo-Pr, Bn, Ph, C_6H_4Me-4, 2-Th, *etc.*; Bn is benzyl, Th is thienyl

Scheme 14

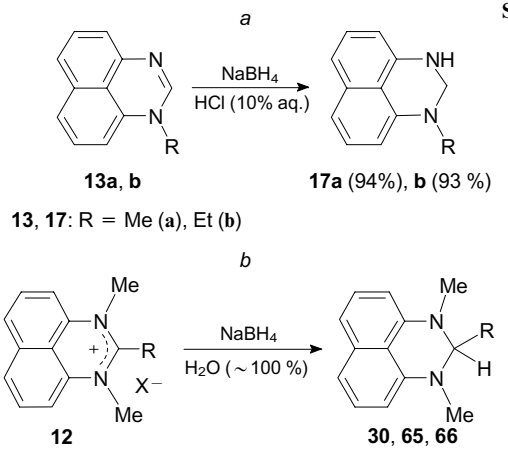


64: M^+ = K (**a**), Tl (**b**)

spectrum has a hyperfine structure indicating delocalization of an unpaired electron.[84]

1-Substituted perimidines are easily reduced to DHPs such as **17** using Birch procedure (Na/liq. NH_3)[33] or on treatment with $LiAlH_4$ (Ref. 38) or $NaBH_4$ in acidic medium[85] (Scheme 15*a*). Perimidinium salts **12** are reduced by alkaline metal tetrahydroborates to DHPs **30**, **65**, **66** (Scheme 15*b*).[38] Numerous examples of oxidative aromatization of DHPs to perimidines or 1,3-di-R-perimidinium salts are discussed in Section 7; see also oxidative conversions of perimidines and DHPs into perimidin-2-ones,

Scheme 15



perimidine-2-thiones and perimidine-2-selenones in Section 6.2.

4.2. Introduction of a substituent on the nitrogen atom

Scheme 16 shows the main types of substituents which were directly introduced into position 1 of the perimidine and its C-substituted derivatives.

N-Alkylation of perimidines is usually carried out in a basic medium (KOH – EtOH or, better, KOH – DMSO system) under inert atmosphere to prevent autooxidation of the *N*-anion.[36,86] For primary alkyl halides, yields of compounds **13** in the KOH – EtOH system vary between 40% – 70%,[36,86] but in DMSO they reach 80% and can be even higher[87] (for the use of NaOH – DMF system, see Ref. 83). Alkylation of 2-methylperimidine, aceperimidine **4** and aceperimidilene **5** has been also performed in KOH – DMSO.[87]

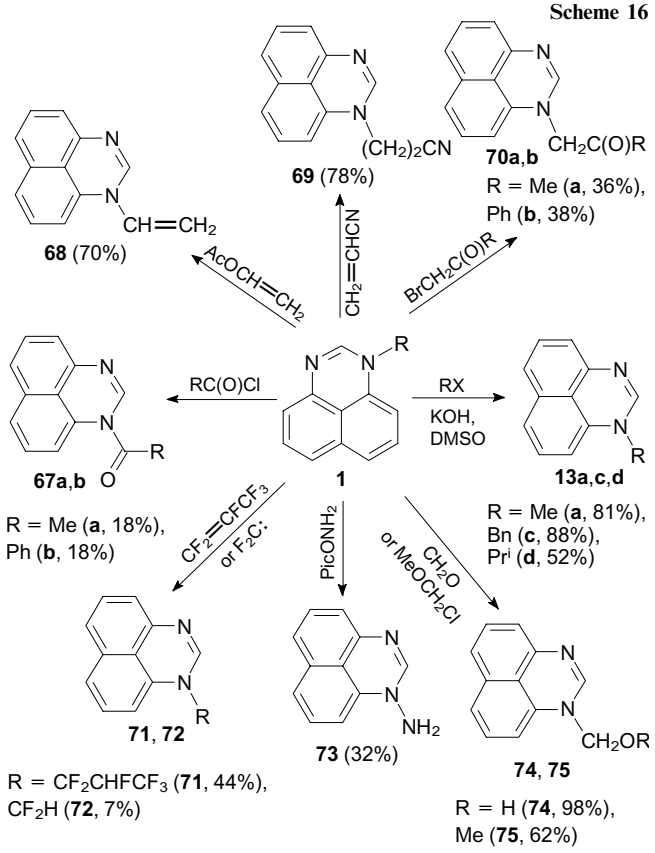
Unlike this, the reactions with $PhCH_2Cl$ and allyl bromide in the KOH – EtOH medium proceed with tarring to give, apart from 1-benzyl- and 1-allylperimidines (10% – 13%), considerable amounts (30%) of 4-benzyl- and 4-allylperimidines, confirming the ambident nature of the perimidine *N*-anion (see Scheme 9).[88] Nevertheless, the use of the KOH – DMSO system justifies itself in this case also, providing 88% yield of 1-benzylperimidine **13c** as the only reaction product.[88] Yet, minor benzylation in position 4 can still occur, but only for 2-methylperimidine. For isoalkyl halides the yields are lower.[36,89] In cases of less reactive alkyl halides, high boiling solvents (toluene, xylene, *etc.*) are recommended.[90,91]

If an alkylating reagent is highly active or the reaction product is sensitive to an alkaline environment, it is advisable to carry out the procedure under neutral conditions. In such cases, a molar ratio alkylating agent : perimidine = 1 : 2 is often used. The second equivalent of the substrate is needed to intercept hydrogen halide from the quaternary salt formed initially. Another variation of this approach involves the use of a ~1 : 1 substrate : alkylating agent ratio, isolation of the quaternary salt followed by its deprotonation with a suitable soft base. Both procedures were successfully applied to obtain 1-acyl (**67a**,**b**),[58] 1-acetonyl and 1-phenacyl (**70a**,**b**),[92] 1-amino (**73**)[93] and 1-methoxymethyl (**75**)[36] derivatives. The use of alkali is also not required in the reactions of *N*-vinylation,[94] cyanoethylation[95] and hydroxymethylation[36] to get compounds **68**, **69** and **74**, respectively. In contrast, the reaction of perfluoroalkenes with perimidine giving rise to compounds **71** proceeds better in the presence of alkali or fluoride anion.[96] Interaction of **1** with difluorocarbene, generated from difluorochloromethane, results in the formation of 1-difluoromethylperimidines **72**.[97]

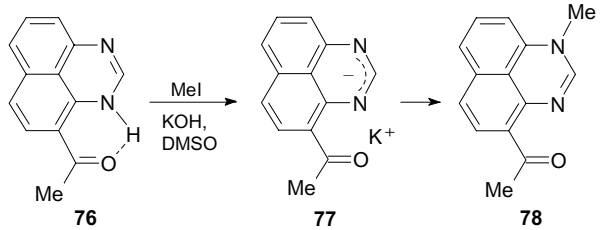
In general, the *N*-substitution reactions are sensitive to steric hindrance. Thus, 2-methyl, 2-ethyl and 2-phenylperimidines[98,99] cannot be *N*-alkylated with benzyl chloride, isopropyl, allyl or phenacyl bromides.[88,92] Perimidines substituted on the C-4(9), *e.g.*, **76**, are exclusively alkylated on the nitrogen atom most removed from the substituent (Scheme 17). The 1,4-disubstituted perimidines, *e.g.*, **78**, are not further quaternized by MeI.[31,52,53,88] In those cases where an intramolecular hydrogen bond is formed between the C-4(9) substituent and the NH group (see structure **76**), the alkylation is highly dependent on the solvent used. For example, methylation of **76** does not occur in an alcoholic medium, but it proceeds successfully in the more basic KOH – DMSO system, which facilitated the breaking of the IHB and the formation of anion **77**.

Alkylation of 6(7)-substituted perimidines gives a mixture of hardly separable 1,6- and 1,7-disubstituted isomers, the first one usually predominating.[100] Both isomers give the same quaternary salt.[52,53,101] When the nucleophilicity

Scheme 16



Scheme 17



of the *N*-anion is reduced, as in case of 4(9)- and 6(7)-nitroperimidines, the yield of the alkylation product becomes lower.[52] Unlike benzimidazoles, perimidines do not enter the Ullman arylation[36] (see, however, Section 4.6). 2,2′-Biperimidine adds to a styrene molecule across the N–H bonds.[102] There are many other variations of the *N*-substitution reactions. For example, they often occur as the secondary process at the preparation of some 2- and 4(9)-substituted perimidines from DAN (see Section 6.1 and Table S3, Supplementary Materials, https://doi.org/10.1070/RCR4963). *N*-Substitution reactions of perimidin-2-ones, perimidine-2-thiones and 2,3-dihydroperimidines will be discussed in Sections 5.5 and 5.7.

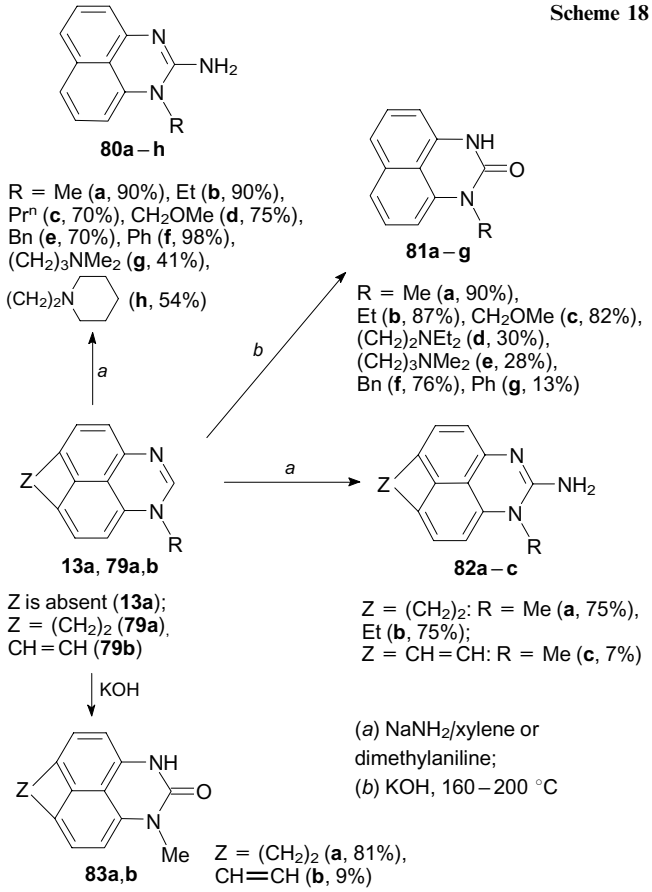
4.3. Reactions of perimidines with nucleophiles

Due to the high electron deficiency of position 2, the reduced aromaticity of the heteroring, and well-known specificity of the *peri*-condensed systems, reactions of perimidines and their quaternary salts with nucleophiles are characterized by enhanced ease and diversity. In general terms, they include the direct substitution of the C(2)–H hydrogen atom, the addition of a nucleophile across the C=N bond, heterocyclic ring-opening with subsequent ring closure, disproportionation processes, *etc*. It is likely that the mechanism of some of these reactions includes a radical or ylide-carbene intermediate (Section 5.8).

1-R-Perimidines **13a** and 1-R-aceperimidines **79a** are aminated with sodium amide[90,91,103] and hydroxylated with melted powdered alkali[91,104,105] furnishing 1-R-2-aminoperimidines **80a–h**, **82a**,**b** and 1-R-perimidinones **81a–g** and **83a** generally in good yields (Scheme 18). These reactions, pioneered in the azine series at the beginning of the 20th century by Russian chemist Chichibabin, are accompanied by vigorous evolution of hydrogen gas and require rather high temperature (in average 120–180 °C). The reactivity of perimidines is usually lower than that of azines, benzimidazoles and naphthoimidazoles. The reactivity of perimidines in the Chichibabin reaction was evaluated by measuring the hydrogen evolution rate.[106] The amination and hydroxylation of 1-R-aceperimidylenes **79b** are more difficult and proceed with a low yield and considerable tarring (*cf*. data for **82c** and **83b**).[107]

The following two reactions, developed after the publication of the previous review,[6] are remarkable examples of the extrusion of the C(2) atom in 1-R-perimidines and 1,3-dialkylperimidinones, which allow obtaining hardly available *N*-monoalkyl- and *N*,*N*′-dialkyl derivatives of 1,8-diaminonaphthalene in good yields. In the first case,

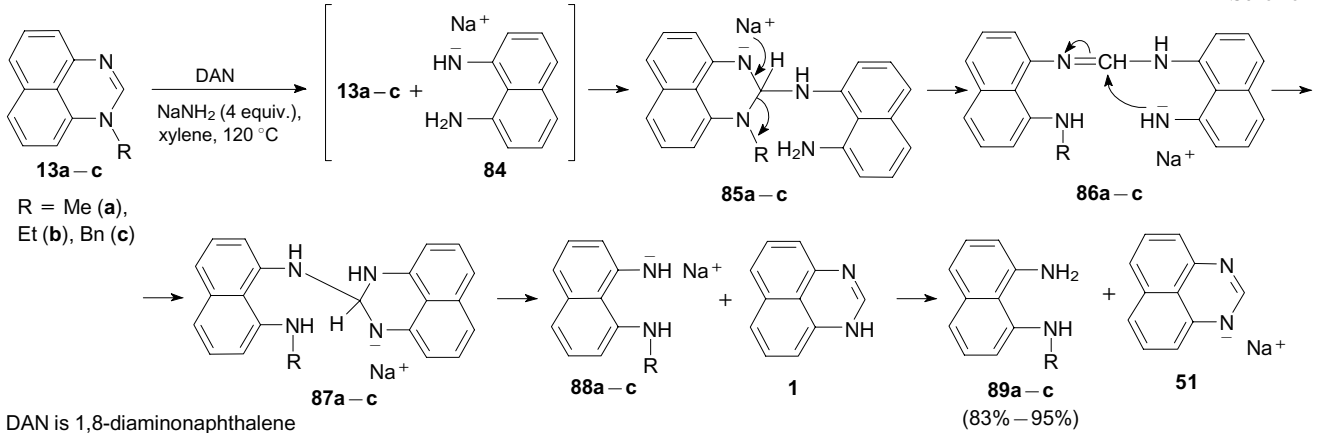
Scheme 18



1-R-perimidines **13a–c** are treated with DAN in the presence of an excess of sodium amide (Scheme 19).[108] Presumably, the reaction starts with the formation of the DAN monoanion **84**, which is the active nucleophile. It adds to the C(2) atom of the starting perimidine molecule to form σ-complex **85**. The latter undergoes a chain of transformations associated with the heteroring opening and the closure of a new one (**86** → **87** → **88** → **89**). The transformation is irreversible because its other product, *i.e*. perimidine anion **51**, is unable to react with nucleophiles **88**, unlike the 1-R-perimidines **13a–c**.

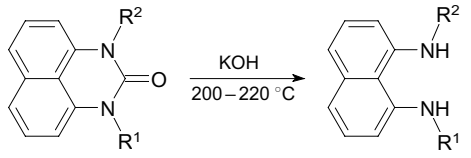
In the second reaction (Scheme 20), the nucleophile is powdered melted (anhydrous) potassium hydroxide.[109] The extrusion of the C=O group from perimidinones **11** gives *N*,*N*′-disubstituted derivatives of DAN **90a–d**. The process

Scheme 19



DAN is 1,8-diaminonaphthalene

Scheme 20



11a – d **90a** (97%), **b** (74%), **c** (92%), **d** (80%)

$R^1 = R^2$ = Me (**a**), Bn (**b**); R^1 = Me: R^2 = Et (**c**), Bn (**d**)

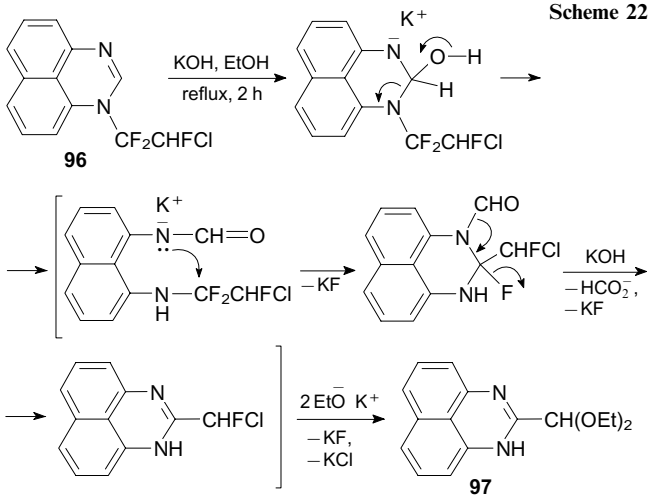
is substantially facilitated by the presence of a nitro group in the naphthalene ring.[110]

When trying to carry out the Emmert's reaction by treatment of 1-R-perimidines **13a**,**b**,**e**,**f** with dilithium benzophenone in dry THF, dimeric compounds **93** with one open heteroring were isolated in good yields instead of the expected 2-(α-hydroxybenzhydryl)perimidines (Scheme 21). The proposed reaction mechanism involves dimerization of the initially formed radical anion **91**, aromatization of dianion **92**, accompanied by intramolecular transfer of the hydride ion and reductive cleavage of another heterocyclic ring. The last stage of the process seems to be the formation of the *N*,*N*′-dianion of compounds **93** and its conversion into the neutral base **93**, when water is added to the final reaction mixture.[111] Interestingly, compounds **93**, when oxidized with MnO_2, are converted (possibly *via* the azomethine intermediate **94**) into a mixture of *N*,*N*′-dialkyl-2,2′-diperimidines **95** and 1-alkylperimidines **13**. Despite the low to moderate yields of **95**, this reaction is of certain importance due to the lack of satisfactory methods for the preparation of such dimers.

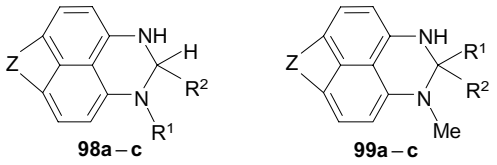
In the context of the high tendency of perimidines to nucleophilic recyclizations, we should recall the long-known conversion of 1-(1,1,2-trifluoro-2-chloroethyl)perimidine **96** into perimidine-2-carbaldehyde diethylacetal **97**. The reaction proceeds by heating **96** in a KOH – EtOH mixture (Scheme 22).[112] Despite the low yield of **97** (4%) and complex reaction path, it provides a way to still little-studied derivatives of perimidine-2-carbaldehyde (see Section 5.6).

Unlike *N*-substituted derivatives of imidazoles, benzimidazoles and naphthoimidazoles, 1-R-perimidines, 1-R-aceperimidines and 1-R-aceperimidylenes are not virtually metallated at the position 2. Instead, they add various organometallic reagents to the C=N bond, producing 2,3-dihydroperimidines **98a – c** or **99a – c** in high yields.[33, 107, 113, 114] Only in one case, upon treatment of

Scheme 22



Structures 98, 99



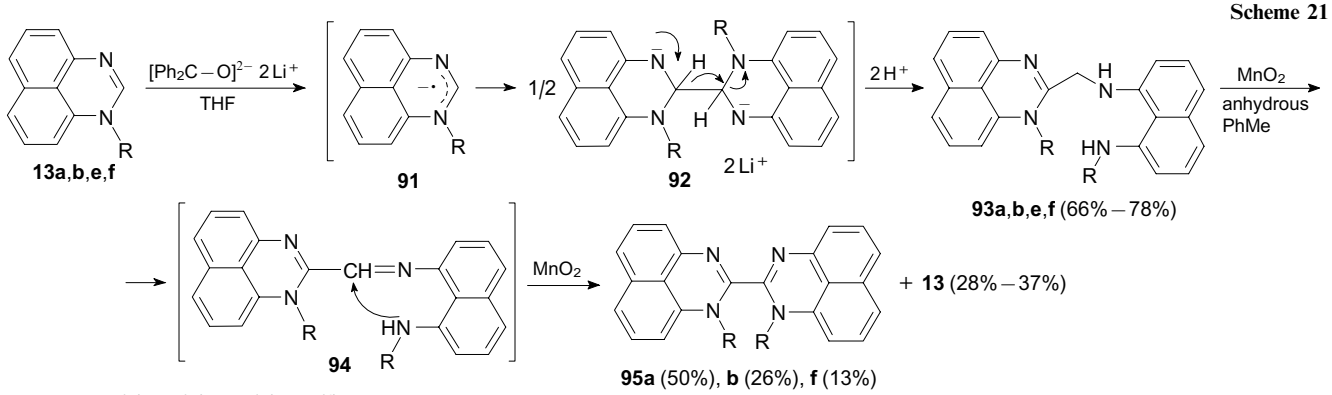
98a – c **99a – c**

Z is absent (**a**), $(CH_2)_2$ (**b**), CH=CH (**c**);
98: R^1 = H, R^2 = Bu^n, Ph, C_6H_4Me-4, 2-Th, 2-Naph, Me, Bu^n;
99: $R^1 = R^2$ = Bu, Ph, Me, R^1 = Me, R^2 = Bu^n

1-methylperimidine with n-butyllithium and subsequent carbonization of the reaction mixture with CO_2, 1-methylperimidinyl-2-carboxylic acid was isolated in 8% yield, indicating a slight metallation. Extensive studies of the kinetics of the basic H/D exchange in 1-methyl derivatives of perimidine, aceperimidine, aceperimidylene, isomeric naphthoimidazoles and benzimidazole have shown that the balance between competing for metallation and addition reactions is determined by combination of such factors as aromaticity of the substrate, polarization of the C=N bond and value of positive charge on the C(2) atom.[114]

Very unexpected results were obtained when treating 1-methylperimidine **13a** with phenylsodium and phenyllithium, followed by the addition of benzophenone in order to trap the metallation product (Scheme 23 *a*).[113] When phenylsodium was used without subsequent addition of benzophenone, the only reaction product was DHP derivative **101**. However, if benzophenone was added to

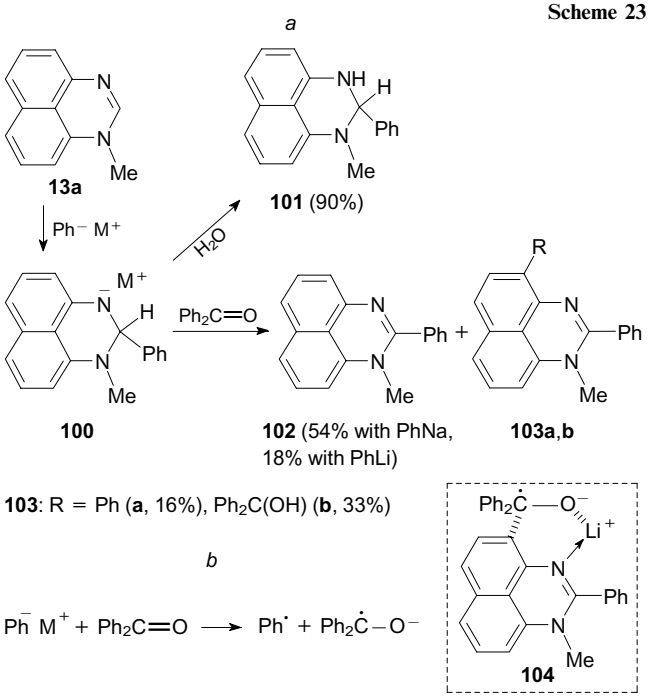
Scheme 21



13a,**b**,**e**,**f** **91** **92** **93a**,**b**,**e**,**f** (66% – 78%) **94** **95a** (50%), **b** (26%), **f** (13%)

13: R = Me (**a**), Et (**b**), Pr^n (**e**), Ph (**f**)

Scheme 23



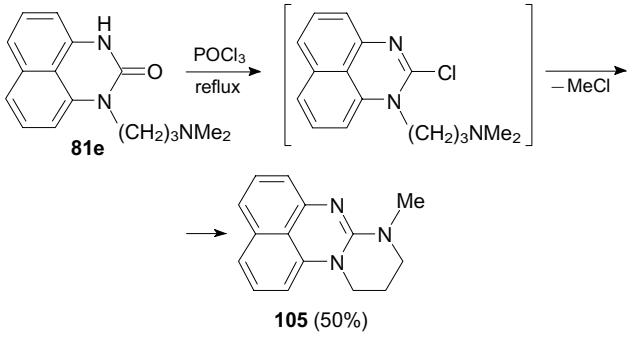
the final reaction mixture, two other compounds were isolated, namely, 1-methyl-2-phenylperimidine **102** and 1-methyl-2,4-diphenylperimidine **103a**. When phenylsodium was replaced by phenyllithium, the main reaction product turned to be alcohol **103b**, while the yield of **102** dropped to 18%. Since an authentic sample of **101** was not dehydrogenated by benzophenone, its absence among the reaction products means that it is the *N*-anion **100** that undergoes aromatization. Apparently, C(4)-substituents then enter compound **102** *via* the radical pathway. Indeed, in the above experiments an excess of PhM and benzophenone was used. Therefore, the one-electron transfer between these reagents could lead to the generation of the phenyl radical and the benzophenone radical anion (Scheme 23 *b*). Since the former is more active than the benzophenone radical anion, when using phenylsodium it should attack position 4 first. In contrast, when phenyllithium is used, the high coordination activity of Li^+ ion can cause a significant stabilization of the transition complex **104** and thus place the α-hydroxybenzhydryl group into position 4.

The reaction of 1-methylperimidine with naphthyllithium in THF and subsequent treatment of the mixture with benzophenone or CO_2 provide 1-methyl-2,3-dihydroperimidine (30%) and 1-methyl-2-(α-naphthyl)perimidine (14%) along with considerable amount of the unchanged starting material.[33] The formation of the 2-naphthyl derivative supposedly proceeds *via* the radical mechanism.

1*H*-Perimidin-2(3*H*)-one and its 1-R-substituted derivatives were converted into 2-chloroperimidines by heating with $POCl_3$ through the nucleophilic displacement of the carbonyl group[90, 103, 105] (see also Section 5.7).

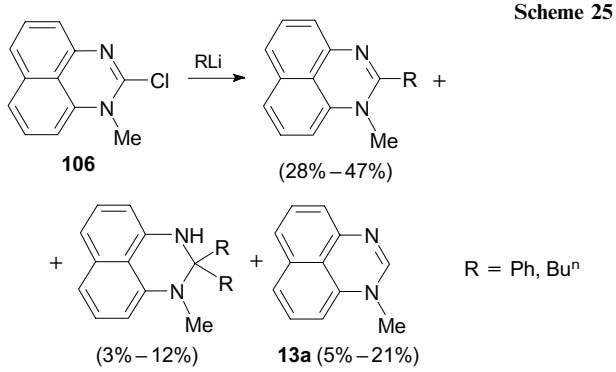
Halogen atom in 2-chloroperimidines can be very smoothly replaced by NH_2,[115] NHR,[90, 115] NR_2,[90] $NHNH_2$,[116] N_3,[62, 105] SR[54] and other nucleophilic groups. 1-Methyl and 1-ethylperimidines react with potassium cyanide to afford the corresponding 2-cyano derivatives, which in turn are transformed into 2-carbamoyl-1*H*-perimidines by heating in polyphosphoric acid.[22] A noteworthy example of the tandem nucleophilic substitution of the C=O group in **81e** by a chlorine atom followed by an intramolecular replacement of the latter by a tertiary nitrogen atom to produce the tetrahydro derivative of pyrimido[1,2-*a*]perimidine **105** is shown in Scheme 24.[90]

Scheme 24



Reaction of 1-methyl-2-chloroperimidine **106** with phenyl- and butyllithium mainly proceeds as the Wurtz reaction (Scheme 25).[117]

Scheme 25

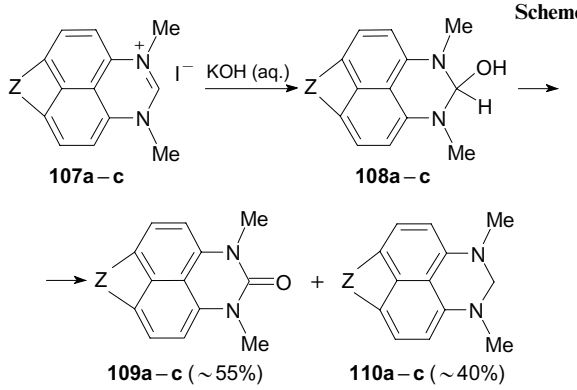


1-Methylperimidine-2-sulfonic acid, when heated with water, gives 1-methylperimidinone, indicating the ease of nucleophilic substitution of the 2-SO_3H group.[79]

4.4. Reactions of perimidinium salts with nucleophiles

Perimidinium salts exhibit much higher and sometimes specific reactivity towards nucleophiles in comparison with neutral perimidines. Most vivid is their behaviour in an alkaline media. Thus, when treated with aqueous alkali, 1,3-dialkylaceperimidinium and 1,3-dialkylaceperimidilenium salts **107a–c** are quantitatively converted into a mixture of the corresponding perimidin-2-one **109** and the DHP derivative **110** (Scheme 26).[59, 107] This reaction was also carried out for perimidinium salts containing in the naphthalene ring such substituents as NO_2, C(O)Me,[100] Cl (Ref. 101) and SO_3H.[60] Actually, the process looks like a redox disproportionation of the carbinol pseudobase **108**, resembling the Cannizzaro reaction. As in the latter, the reducing agent is likely the *O*-anion of carbinol **108** transferring the hydride ion to the initial salt **107**. It is noteworthy that the yield of perimidinone **109** always noticeably exceeds that of dihydroperimidine **110**, which indicates the presence of a second oxidation channel for **108**. Probably, air oxygen takes part in this process, oxidizing the *O*-anion of **108**. The oxidation of highly active carbene-ylide species,

Scheme 26



Z is absent (**a**), $(CH_2)_2$ (**b**), CH=CH (**c**)

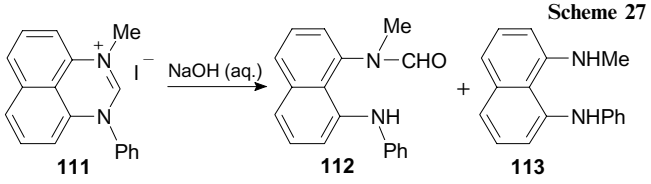
concurrently formed from **107**, cannot be excluded as well (see Section 5.8).

1-Phenyl-3-methylperimidinium iodide **111** differs in its behaviour from salts **107** and resembles benzimidazolium and naphthoimidazolium salts. The main products that are formed after short reflux of **111** in sodium hydroxide solution are the acyclic pseudobase **112** and the *N*-phenyl-*N′*-methyl derivative of DAN **113** (Scheme 27). This can be attributed to the electron-withdrawing nature of the *N*-phenyl group enhancing the positive charge in position 2 and thus weakening the stability of the heterocyclic ring.[58] Such explanation is also valid for 1-acylperimidines and 1-R-3-acylperimidinium salts (Scheme 28). Neutral 1-acylperimidines **67** are very sensitive to water, and even after a short heating in undried ethanol they are quantitatively converted into the *N*-formyl-*N′*-acyl derivative of DAN **114**. The hydrolysis of 1-R-3-acylperimidinium salts **115** is also fast but its direction depends on the nature of R, basicity of the media and counter-ion type. *N*-Acetylperimidinium salts **115a**,**c** undergo deacylation to form 1-methylperimidinium salts **13**·HX regardless on a counter-ion. *N*-Benzoylperimidinium salts **115b**,**d** in water give a mixture of **13**·HX (73%) and acyclic pseudo-base **116** (26%), while in the benzene–Et_3N system **116** becomes the single product formed in high yield.[58]

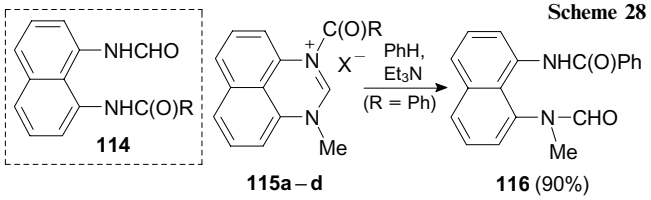
On heating with alkali, C(2)-substituted 1,3-dialkylperimidinium salts are commonly converted into acyclic compounds of type **112** with C(O)R group instead of formyl.[99]

Another reaction of great synthetic importance in the perimidine chemistry is recyclization of 1-R-3-aroylperimidinium salts. In the first step, 1-R-perimidines **13** react with

Scheme 27



Scheme 28

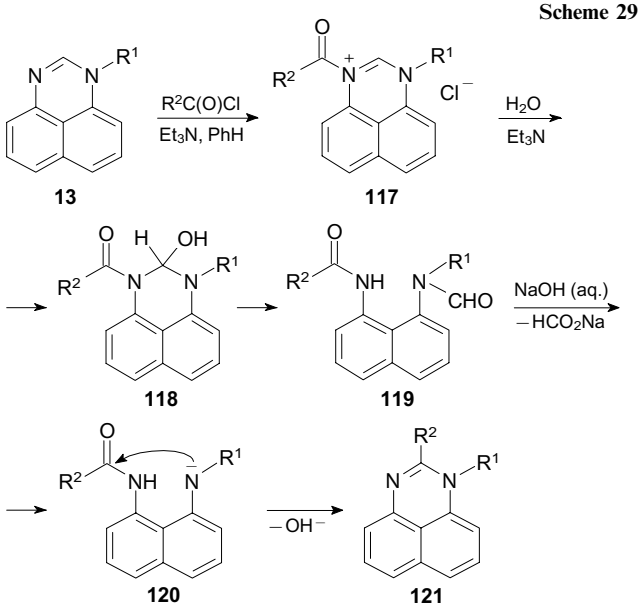


X = Cl: R = Me (**a**), Ph (**b**); X = ClO_4: R = Me (**c**), Ph (**d**)

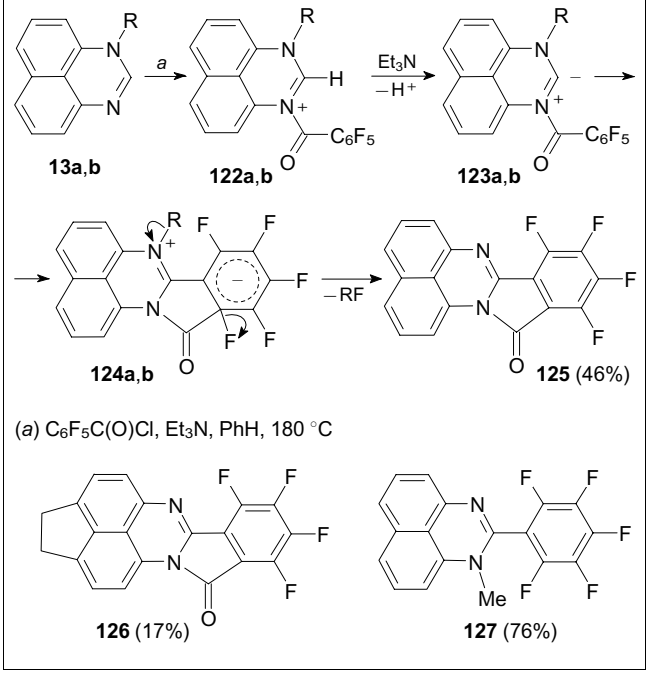
aromatic, heteroaromatic or vinyl aromatic acid chlorides in undried benzene–Et_3N system, producing *N*-aroylperimidinium salts **117** and then carbinol pseudobase **118** (Scheme 29).[118] The latter undergoes a heteroring opening, giving rise to *N*-aroyl-*N′*-formyl-1,8-diaminonaphthalenes **119**, which can be isolated. Subsequent heating of **119** with an aqueous alkali leads to removing the formyl group, heterocyclic ring closure and the formation of 1,2-disubstituted perimidine **121** in a high total yield. The list of perimidines, aceperimidines and aceperimidylenes obtained by this method is given in the Supplementary Materials (see Table S2, https://doi.org/10.1070/RCR4963). To clarify the influence of the various *N*-substituents on the ring transformation reaction, kinetic studies were carried out.[41]

A marvelous deviation from the above ring transformation reaction was observed at treatment of 1-methyl- and 1-ethylperimidines **13a**,**b** and also 1-methylaceperimidine

Scheme 29



Scheme 30



with perfluorobenzoyl chloride (Scheme 30).[42] In all these cases, red-violet phthaloperinones **125** and **126** were isolated as the sole reaction products. The most reasonable mechanism of this transformation seems to consist of the transient formation of very reactive carbene-ylide (**122** → **123**), which undergoes the intramolecular nucleophilic substitution of the *ortho*-fluorine atom in $C_6F_5C(O)$ group accompanied by a loss of RF molecule. The primarily desired 1-R-2-pentafluorophenylperimidines **127** were easily prepared *via* standard cyclization of the corresponding DANs with perfluorobenzoyl chloride.

4.5. Electrophilic substitution reactions

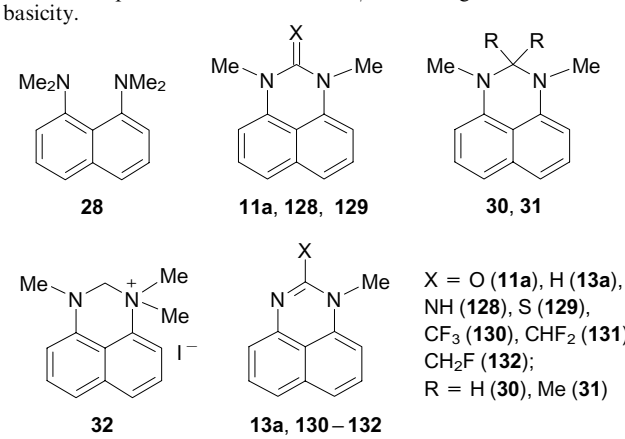
Perimidine is one of the most reactive heterocycles towards electrophiles due to its high π-donor capacity and large negative π-charges at positions 4(9) and 6(7). Commonly, electrophilic reagent is directed exclusively on these positions, though the substitution into 4(9) positions (*ortho* to the heterocyclic N atoms) can be considerably hindered by the presence of bulky groups (including methyl) at the nitrogen atoms. Only such small species as D^+ and, to some extent, Cl^+ can enter into the positions 4 and 9 in such cases.

4.5.1. Acid-catalyzed H/D exchange

This simple reaction was studied using 1-methylperimidine **13a**, its fluoromethyl derivatives **130** – **132**, 2,3-dihydroperimidines **30** – **32**, 1,3-dimethylperimidin-2-one **11** as well as its imino **128** and thione **129** analogues. For this, the substrate was kept in CD_3CO_2D solution at 80 °C for 30 min and for 5 h at room temperature, after which a set of protons exchanged was determined using ^1H NMR measurements. The research results are shown in Table 2. As can be seen, highly basic DMAN **28** taken for comparison does not exchange protons under these conditions, which obviously results from its complete conversion to a low-active cation. For the same reason, no exchange occurs for sufficiently basic **13** and **128**. In contrast to these compounds, low basic perimidin-2-one **11**, perimidine-2-thione **129** and DHPs **30** and **31**, which are not protonated to a significant extent by acetic acid, exchange protons in all four active positions of the naphthalene moiety. As for salt **32**, a positive charge in it is localized on one nitrogen atom allowing the second nitrogen to activate the benzene ring bound to it. Therefore, only two ring protons exchange in this cation. In the case of perimidines **130** – **132**, despite their reduced basicity, exchange under the mentioned conditions occurs only to a small extent. Apparently, in these substrates, the passivation of the naphthalene ring is mainly due to the negative inductive effect of fluorine atoms.

The H/D exchange in perimidine **1** and its alkyl derivatives also takes place in D_2SO_4, but with simultaneous sulfonation.[60] In C_2H_5OD the H/D exchange of the *ortho* protons in **1** can proceed *via* the *N*-anion.[42]

Table 2. Dependence of the acidic H/D exchange on the substrate basicity.



Substrate	pK_a (MeCN, 25 °C)	Number of exchangeable protons	Supposed substrate form	Ref.
28	18.18	0	Cation	119
128	17.89	0	Cation	119
11a	4	2 [a]	Neutral	119
129	4	4	Neutral	119
30	8.67	4	Neutral	119
31	10.51	4	Neutral	119
32	–	2	Monocation	119
13a	13.70	0	Cation	119
130	6.64	0.6	Neutral	42
131	9.30	0.4	Neutral	42
132	12.30	2.0	Neutral	42

[a] Incomplete H/D exchange in **11** was assigned to the low solubility of this compound in CD_3CO_2D.

4.5.2. Acylation, formylation and related transformations

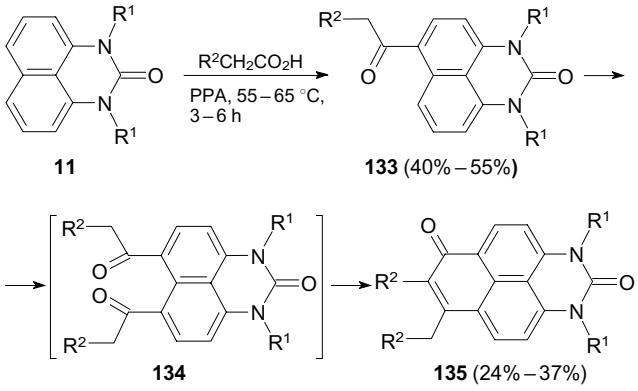
Usually, electrophilic acylation of perimidine is carried out with carboxylic acids in polyphosphoric acid (PPA). If a perimidine substrate has a free N(1) – H group, under kinetically controlled conditions (70 – 85 °C) the corresponding 6(7)-acyl derivative is the major product, which is formed together with some amount of 4(9)-isomer. In contrast, at 120 – 150 °C (thermodynamic control) the 4(9)-acylperimidine becomes the sole product because of its stabilization by the strong IHB of the C=O···H – N type.[53, 120] NH-Unsubstituted 6(7)-acylperimidines can be prepared with higher regioselectivity using acid chlorides in the $CH_2Cl_2 - AlCl_3$ system.[121] Acetylation of 1-methylperimidine produces a mixture of 6-, 7- and 4-acetyl derivatives, in which the first two isomers prevail.

Under analogous conditions, 1,3-dimethyl-2,3-dihydroperimidine **30** forms only 6(7)-acyl derivatives.[47, 122] The reaction of parent DHP **3** with acetic acid in PPA at 50 °C proceeds at position 4(9) and is accompanied with dehydrogenation giving rise to 4-acetylperimidine.[121] 4- and 6-Acyl derivatives of DHP can also be synthesized by reduction of 4- and 6-acylperimidines with $NaBH_4$ in AcOH.[121]

1*H*-Perimidin-2(3*H*)-one **2** is acylated with carboxylic acids in PPA forming a mixture of 4(9)- and 6(7)-acyl derivatives.[122] The acylation of 1,3-dialkylperimidinones **11** takes place only at position 6(7). When acetic and propionic acids are used, 6(7)-acylperimidinones **133** together with phenalenones **135** are formed.[47, 122] The latter seems to result from the intramolecular aldol condensation of diketone **134** (Scheme 31). It was evidenced by conducting aldol condensation with authentic diketones **134**, which were obtained under specially selected conditions. Perimidine-2-thiones are less reactive and form only 6(7)-acyl derivatives under similar conditions.[47, 122]

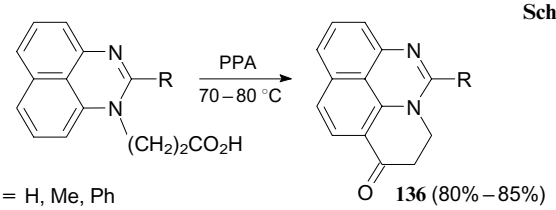
Intramolecular acylation, exemplified by Scheme 32, has been also reported for perimidines and perimidinones.[95] Perimidinone **2** undergoes double acylation by diethyl malonate at positions 1 and 9.[123]

Scheme 31



R^1 = Me, Et; R^2 = H, Me; PPA is polyphosphoric acid

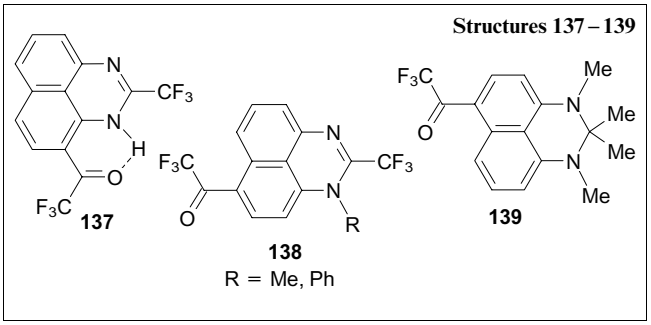
Scheme 32



R = H, Me, Ph

Perimidines containing the CF_3 group at position 2 are resistant to carboxylic acids in PPA. However, due to their low basicity (see Table 2) an equilibrium amount of the neutral form can likely exist under less acidic conditions providing the acylation with stronger electrophilic agents, for example, trifluoroacetic anhydride.[39] Indeed, being treated with $(CF_3CO)_2O$ at 100 °C, 2-(trifluoromethyl)perimidine gives 9-(trifluoroacetyl) derivative **137** in 86% yield. Under the same conditions, 1-methyl and 1-phenyl-2-(trifluoromethyl)perimidines produce only C(7)-substituted derivatives **138** (58% and 90%, respectively).[39] 2-(Difluoromethyl)- and 2-(fluoromethyl)-perimidines also undergo trifluoroacetylation giving rise to the corresponding 9-acyl derivatives in relatively low yields.[42] In contrast, their 1-methyl derivatives produce a mixture of 6- and 7-(trifluoroacetyl)perimidines. Trifluoroacetylation of 1,3-dimethylperimidin-2-one takes place at position 6(7) in quantitative yield.[39] Notably, 1,3-dimethylperimidine-2-thione is also converted into 6-trifluoroacetyl-1,3-dimethylperimidone under the same conditions. Apparently, this results from preliminary trifluoroacetylation of sulfur atom followed by hydrolysis of the $=S^+C(O)CF_3$ group. 2,3-Dihydroperimidines, *e.g.*, **30**, react with $(CF_3CO)_2O$ to give a complex mixture of deeply coloured resinous products. The only DHP derivative that was able to undergo trifluoroacetylation was compound **31**, which forms ketone **139** in 21% yield.[39]

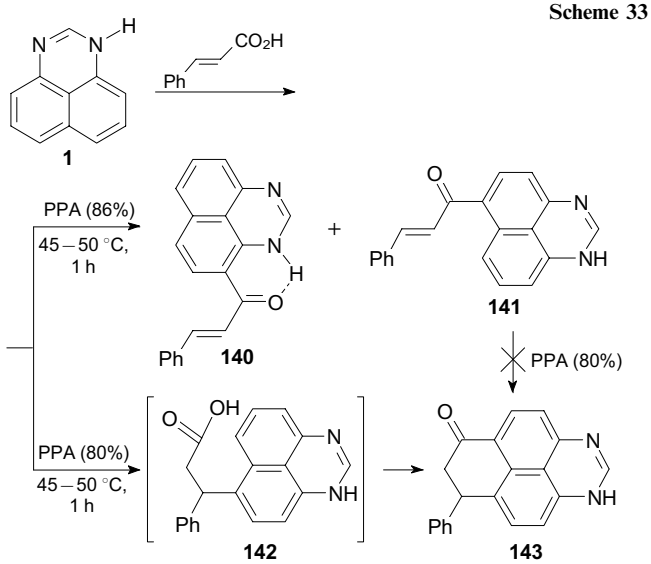
Structures 137 – 139



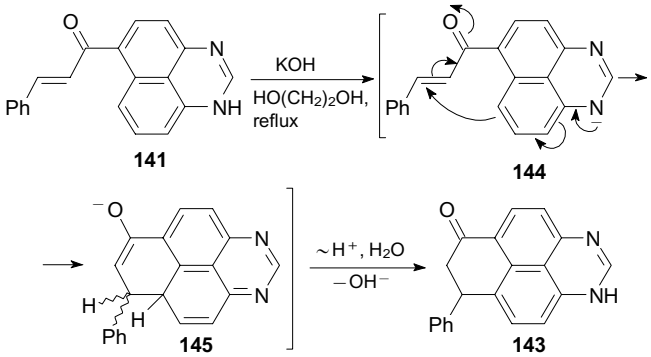
Alkaline hydrolysis of the trifluoroacetyl groups in the aforementioned compounds, including 6-(trifluoroacetyl)-1,3-dimethylperimidin-2-one, gives rise to the corresponding carboxylic acids.[42]

Interesting results were obtained upon acylation of the parent perimidine with cinnamic acid in PPA (Scheme 33).[124] The reaction strongly depends on the concentration of PPA. Thus, in 86% PPA a mixture of 4(9)- **140** and 6(7)-cinnamoylperimidines **141** is produced with the latter being predominant. However, when using standard 80% PPA, the process changes its course leading to the formation of a phenalenone derivative **143**. Probably, in this case, the initial process is the acid-catalyzed Michael addition of the perimidine molecule across α,β-conjugated C=C bond to form an intermediate acid **142**, which rapidly cyclizes into **143**. Indirectly this assumption is supported by the fact that 6(7)-cinnamoylperimidine **141** is not transformed into **143** when heated with PPA. Surprisingly, conversion **141** → **143** can be carried out in KOH – ethylene glycol system (Scheme 34).[120] This time, due to the formation of the highly nucleophilic anion **144**, we deal with the base-catalyzed cyclization *via* the intramolecular Michael addition (**144** → **145** → **143**). Similarly, cyclization of 4(9)-cinnamoylperimidine **140** with KOH in aqueous 2-propanol leads to 7-phenyl-7*H*-pyrido[1,2,3-*cd*]perimidin-9(8*H*)-one.[120]

Scheme 33



Scheme 34



The Lewis acid-catalyzed interaction of perimidine **1** with cinnamoyl and 4-bromocinnamoyl chlorides proceeds rather unexpectedly.[125] In both cases, the same product is formed, which corresponds to 6-hydroxy derivative of 1,3-diazapyrene **147** (Scheme 35). As seen, aluminium bromide promotes aromatization of dihydrophenalenone **143** *via* elimination of an ArH molecule. The preference of phenolic form **147** over the keto form **146** reflects the general tendency of heteroaromatic systems, which consists of greater stability of the azine-like tautomeric structures in comparison with the azole-like ones. Under the same conditions, 1-methylperimidine **13a** yields an inseparable mixture of isomeric diazapyrenones **148** and **149** in a 3 : 1 ratio (see Scheme 35).[126] Perimidinones **2**, **10** and **11** react with cinnamoyl chloride similarly.[126, 127] For a review on 1,3-diazapyrenes, see Ref. 128.

Perimidin-2-one **2** reacts with aroyl chlorides without catalyst at 180 °C affording 4(9)-aroyl derivatives **150**. Their subsequent *N*-alkylation provides dyes **151** (Scheme 36).[129]

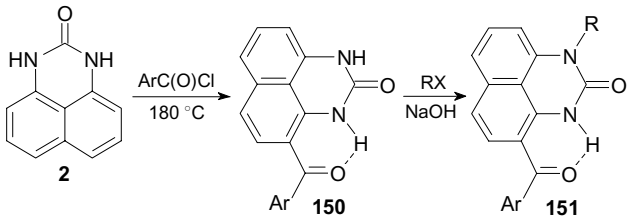
Condensation of 2,3-dihydroperimidines with the squaric acid accompanied by azeotropic water removal leads to a new type of dyes **152**, **153** and related compounds.[130 – 132] These products have intense absorption bands up to 800 nm.

An exhaustive study on the formylation of perimidinones, DHPs and perimidines has been carried out.[133, 134] 1,3-Dialkylperimidinones **11a**,**b** undergo the Vilsmeier reaction at 80 – 90 °C to form 6-carbaldehydes **154** in good yields (Scheme 37). Prolonged heating of the latter with an excess of the Vilsmeier reagent leads to their gradual isomerization into 4-carbaldehydes **155**.

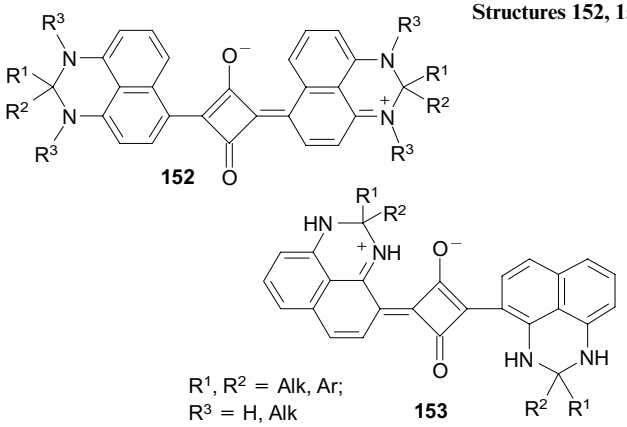
Formylation of 1,3-dimethyl- **30** and 1,2,2,3-tetramethyl-DHP **31** is more complicated and less regioselective. Isolated mono- and dialdehydes are shown in Scheme 38.[134] The 6,7-diformyl derivative of **31** deserves special attention as a rare example of the hydration-resistant naphthalene *peri*-dialdehydes.

Under conditions of the Vilsmeier reaction, perimidine **1** and its 1- and 2-methyl derivatives seem to exist in a low reactive cationic form due to their relatively high basicity. This can explain why these substrates undergo formylation with difficulty even at 90 – 100 °C to produce the corresponding 4(9)- and 6(7)-carbaldehydes in a total yield of less than 10%.[133, 134] In contrast, less basic 2-(trifluoromethyl)-perimidine **156** is easily formylated at 30 – 35 °C furnishing a mixture of 4(9)- and 6(7)-monoaldehydes **157** and **39** together with dialdehydes **158a – c** (Scheme 39). Its *N*-methyl derivative **130** is formylated (80 °C, 3.5 h) producing 4-, 6- and 7-formyl derivatives in a ratio of 22 : 20 : 58.

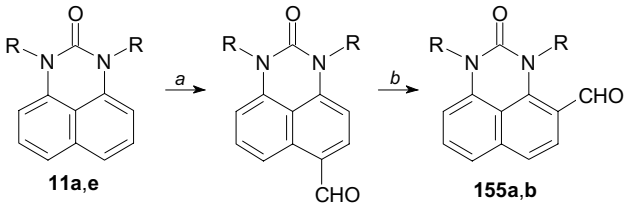
Scheme 36



Structures 152, 153

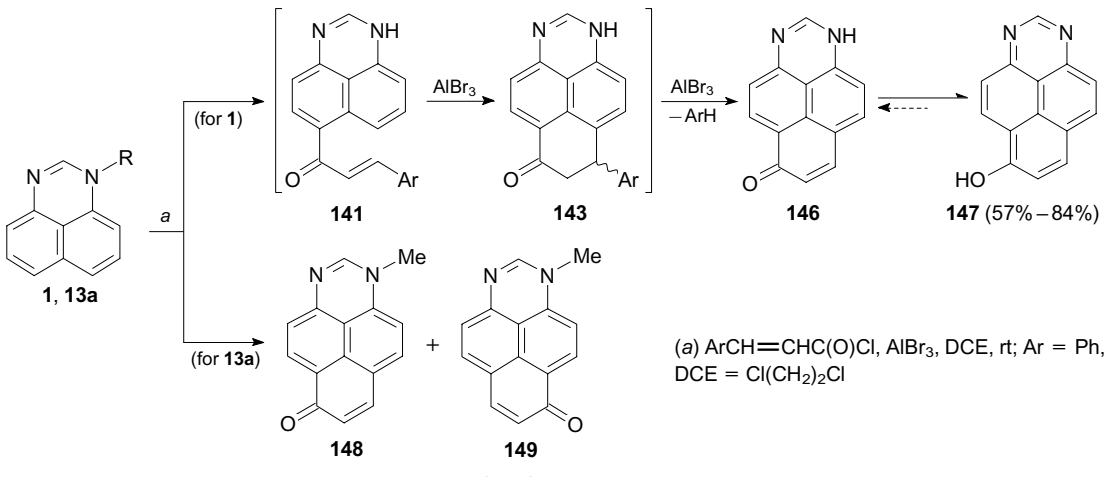


Scheme 37



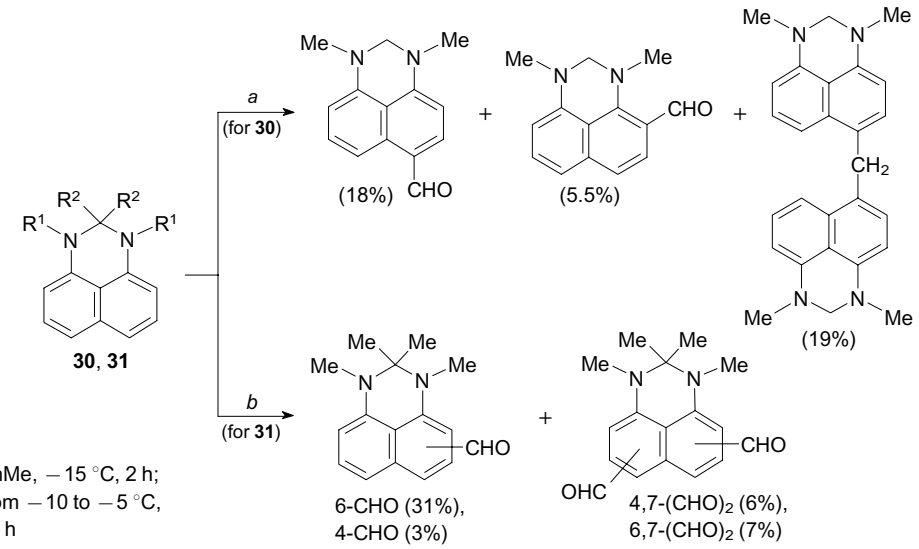
(*a*) $POCl_3$, DMF, 80 – 90 °C, 2.5 h; (*b*) $POCl_3$, DMF, 60 – 80 °C, 5.5 h (20%); **11**: R = Me (**a**), Et (**e**); **154**, **155**: R = Me (**a**), Et (**b**)

Scheme 35

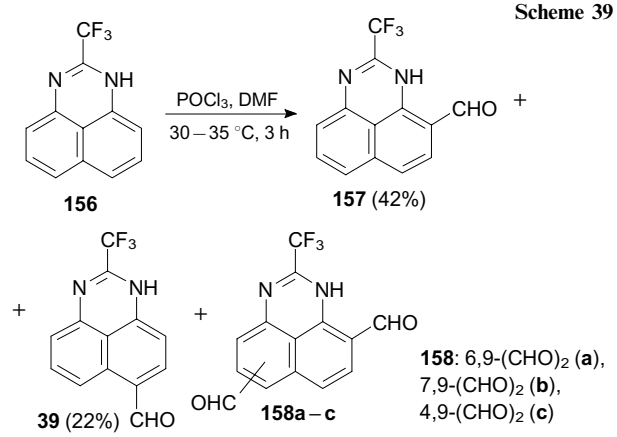


(*a*) ArCH=CHC(O)Cl, $AlBr_3$, DCE, rt; Ar = Ph, C_6H_4Br-4; DCE = $Cl(CH_2)_2Cl$

Scheme 38

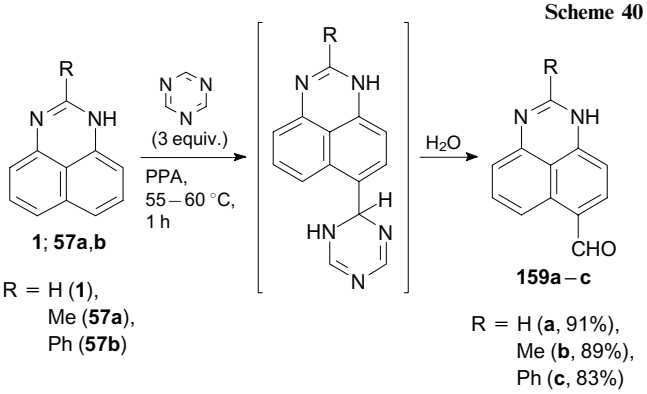


Scheme 39



It is known that under the action of nucleophiles 1,3,5-triazines easily undergo ring opening, due to which they can be used as organic reagents with a masked formyl or acyl group. Aksenov *et al.*[135] used this fact to formylate and acylate perimidines and to synthesize triazapyrenes. Thus, short heating of **1** and its 2-methyl- and 2-phenyl derivatives **57a**,**b** with a 3-fold excess of 1,3,5-triazine in PPA afforded perimidine-6(7)-carbaldehydes **159a – c** in excellent yields (Scheme 40). Replacing 1,3,5-triazine by its 2,4,6-trisubstituted derivatives turned to be fruitful for preparation 6(7)-acylperimidines.[136]

Scheme 40



Treating 6(7)-acylperimidines **160** with 1,3,5-triazine in PPA at 100 °C leads to heterocyclization into 1,3,7-triazapyrenes **161** as shown in Scheme 41.[137] The latter compounds can also be obtained in 52% – 78% yields directly from 2-R-perimidines by heating them with 1,3,5-triazines in PPA at 100 – 180 °C.[138]

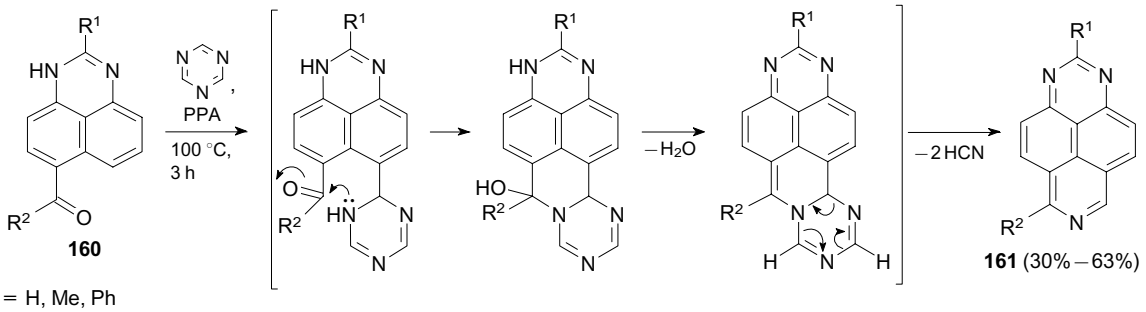
As a part of their work on using PPA in the electrophilic substitution reactions in the perimidine series, Aksenov and his group[139 – 141] also studied the Houben – Hoesch reaction. It was found that the interaction of perimidine **1** and 2-phenylperimidine **57b** with an excess (2.3 equiv.) of aryl cyanides in PPA at 150 °C produces the corresponding 6,8-diaryl-1,3,7-triazapyrenes **164a – d** in good to moderate yields (Scheme 42).[140,141] Although the mechanism of the transformation has not been studied, due to the high acidity of the medium, the reaction most likely occurs as a tandem process including the attachment of the aryl nitrilium ion to the initially formed imine **162** with the subsequent cyclization of intermediate **163**. Interestingly, the interaction of **1**, **57a**,**b** with benzonitrile in the presence of 1,3,5-triazine (PPA, 70 – 80 °C) leads to the formation of 6-phenyl-1,3,7-triazapyrenes **165** (see Scheme 42).[140] Its unsymmetrical structure indicates that the second α-carbon atom of the pyridine ring may originate from the triazine reagent.

4.5.3. Alkylation and related transformations

As it has been mentioned above (Section 4.2), the perimidine *N*-anion has the ambident character and its reactions with benzyl and allyl halides give some amount of the C-4(9) alkylation product along with the corresponding *N*-alkylperimidine.[88] In the previous section, we presented several examples of the Michael addition of the perimidine naphthalene ring to α,β-unsaturated carbonyl compounds, which can also be assigned to alkylation reactions. Additional examples are given below.

Perimidine **1** reacts with 3-phenylpropiolic acid in PPA furnishing the Michael addition product **166**, the latter cyclizes into phenolic compound **147** (Scheme 43 *a*).[126] 1,3-Diazapyrenes **168** are formed by heating perimidine **1** and 2-R-perimidines **57a**,**b** with α,β-unsaturated carbonyl compounds in PPA or H_2SO_4.[142 – 145] The reaction seems to start with the formation of the addition product **167**, which cyclizes as shown in Scheme 43 *b*. Perimidinones and 1-methylperimidine behave similarly.[126,146] Salt **169**, gener-

Scheme 41

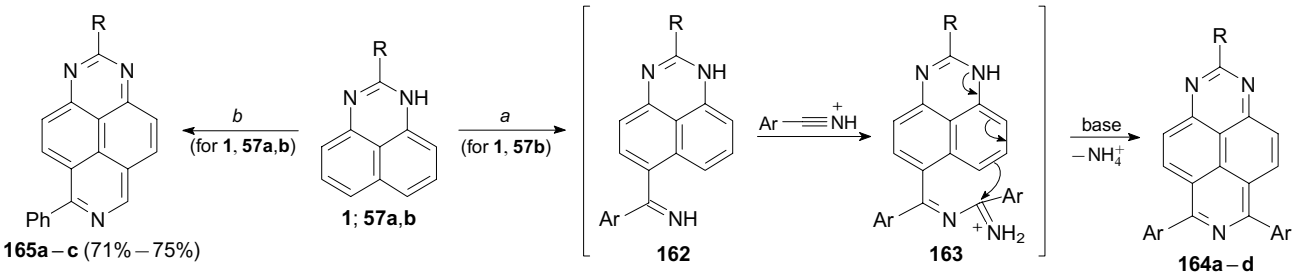


160

R1, R2 = H, Me, Ph

161 (30%–63%)

Scheme 42



165a–c (71%–75%)

1; **57a**,**b**

162

163

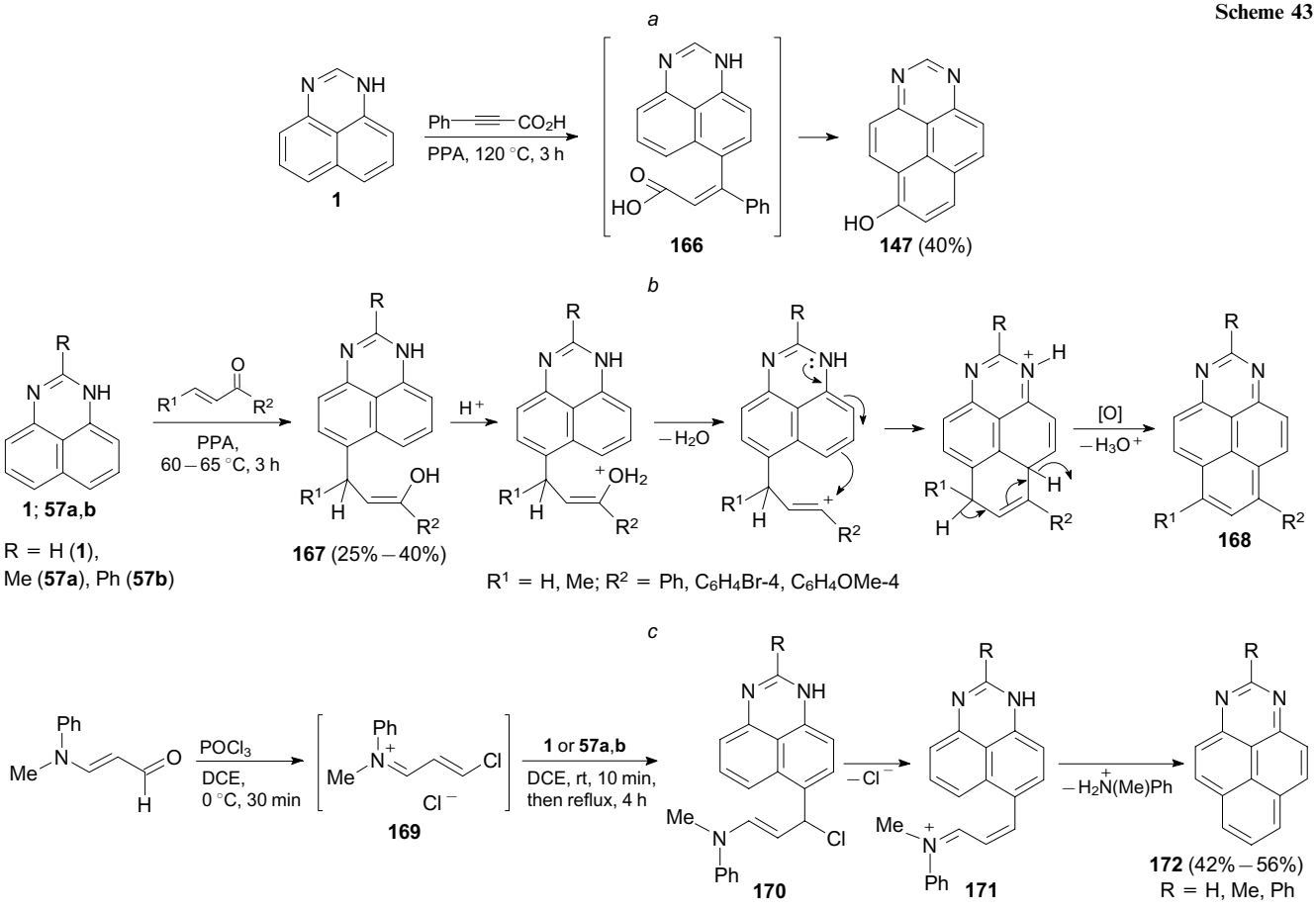
164a–d

(*a*) ArCN, PPA, 150 °C, 6 h; **164**: R = H: Ar = Ph (**a**, 68%), C_6H_4Br-4 (**b**, 77%), $C_6H_4NO_2$-4 (**c**, 49%); R = Ar = Ph (**d**, 30%);
(*b*) 1,3,5-triazine (3 equiv.), PhCN, PPA, 70–80 °C; **165**: R = H (**a**), Me (**b**), Ph (**c**)

ated *in situ* from 3-(*N*-methyl-*N*-phenylamino)acrolein and being a vinylogue of the Vilsmeier reagent, reacts with perimidines to form 1,3-diazapyrenes **172**.[147] Apparently, the reaction pathway includes two successive S_E2Ar steps proceeding *via* intermediates **170** and **171** (Scheme 43 *c*).

Being treated with 5-bromopyrimidine in methanesulfonic acid, 2-R-perimidines are converted into 6(7)-

Scheme 43



1

166

147 (40%)

1; **57a**,**b**

R = H (**1**),
Me (**57a**), Ph (**57b**)

167 (25%–40%)

168

R1 = H, Me; R2 = Ph, C_6H_4Br-4, C_6H_4OMe-4

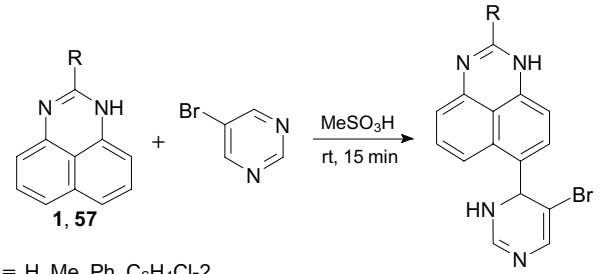
169

170

171

172 (42%–56%)
R = H, Me, Ph

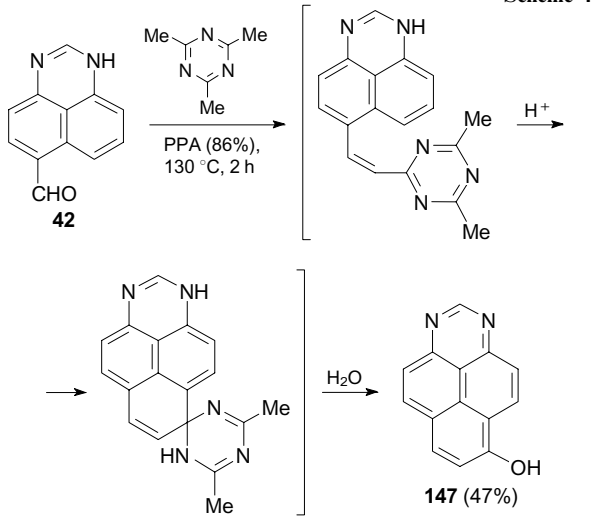
Scheme 44



(5-bromo-3,4-dihydropyrimidin-4-yl) derivatives **173** in nearly quantitative yield (Scheme 44).[148]

The reaction of perimidine-6(7)-carbaldehyde **42** with trimethyltriazine in PPA starts from the aldol-type condensation (Scheme 45).[137] Subsequent intramolecular electrophilic attack of the triazine moiety on the perimidine *peri*-position gives rise to 6-hydroxy-1,3-diazapyrene **147**.

Scheme 45

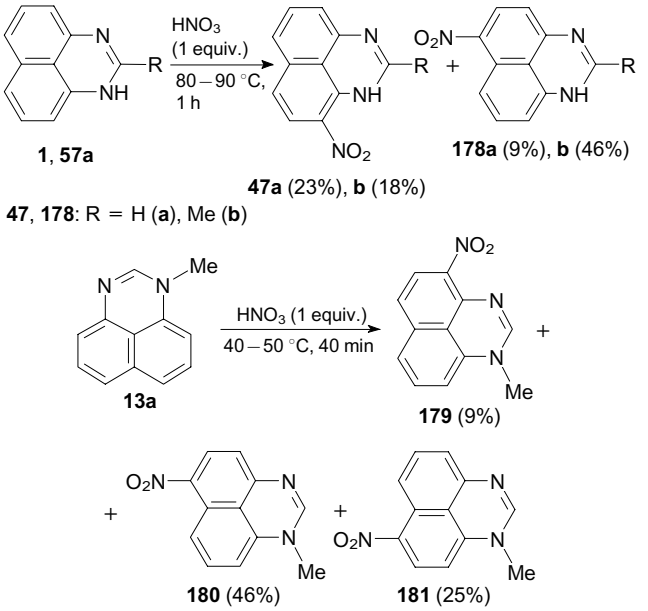


Heating 6-(hydroxymethyl)-1,3-dimethyl-2,3-dihydroperimidine **174** with Al_2O_3 in benzene affords 6,6′-diperimidinylmethane **175** as a main product (Scheme 46).[149] Obviously, the latter is formed *via* electrophilic replacement of the CH_2OH group in the starting alcohol by the intermediate $ArCH_2^+$ cation. Similarly, 6-(hydroxymethyl)perimidinone **176** rapidly reacts with conc. HCl giving rise to aldehydes **177** and **154a**. Compound **177** probably results from the electrophilic attack by the corresponding $ArCH_2^+$ cation on the position 7 of the starting molecule **176** followed by dehydrogenation of the CH_2OH group.

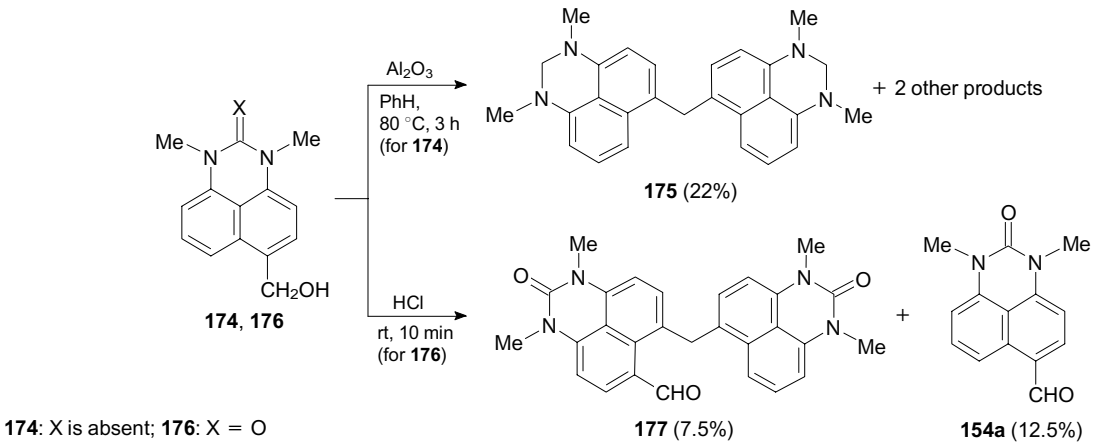
4.5.4. Nitration

Perimidines are highly reactive in the nitration reaction, resembling phenols. Mono-, di-, tri- and tetranitrations were reported, with nitro groups being exclusively inserted in positions 4(9) and 6(7).[52] Nitric acid, nitrous acid and nitrogen dioxide having similar potency were tested as nitrating agents. Acetic acid was used preferably to carry out the reaction. The most problematic is the mononitration of compounds with a free NH group, in particular perimidine itself. Due to abundant tarring, the total yield of 4(9)-(**47a**) and 6(7)- (**178a**) nitro derivatives, which are formed in a 2.5 : 1 ratio, is ~30% (Scheme 47).[52] Nitration of 2-methylperimidine **57a** provides significantly better results (64% total yield). Notably, in this case the ratio of 4(9)-(**47b**) and 6(7)-nitro derivatives (**178b**) reverses (~1 : 2.5). Probably, the HNO_3 as oxidizing agent homolytically tears

Scheme 47



Scheme 46

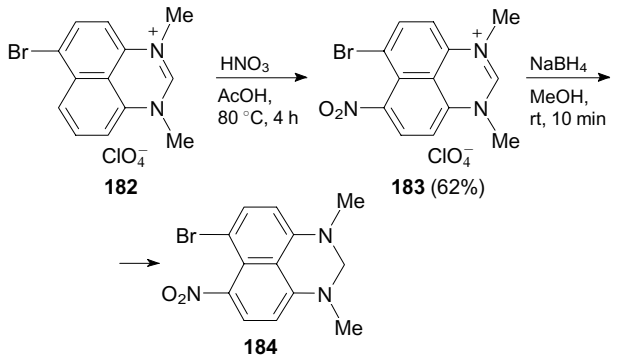


off the hydrogen atom of the NH group and the resulting radical undergoes recombination and oxidation reactions. This explanation is supported by the fact that 1-methylperimidine **13a** is nitrated without tarring, forming in a high total yield a mixture of 4-, 6- and 7-nitro derivatives **179**–**181** with a strong predominance of the *para*-isomers (see Scheme 47).[52]

Further nitration of mono-, di- and trinitroperimidines, which are difficult to oxidize, proceeds without tarring.[52] When 1- and 2-methylperimidines are nitrated with 2 equivalents of nitric acid, a mixture of 6,9-, 6,7- and 7,9-dinitro derivatives is formed. The use of nitric acid in a 8-fold excess leads to a mixture of 4,6,9- and 6,7,9-trinitroperimidines. Heating this mixture with an excess of fuming HNO_3 gives rise to 4,6,7,9-tetranitro derivatives in up to 90% yields.[52]

It appears that only the first nitration of perimidine proceeds *via* the perimidinium cation. Indeed, 1,3-dimethylperimidinium salt is selectively nitrated into position 6(7) under the same conditions as perimidine.[100] However, next nitration of 6-nitro-1,3-dimethylperimidinium salt gives rise to only traces of the dinitro derivative even on prolonged reflux with fuming HNO_3.[24] 6-Bromo-1,3-dimethylperimidinium perchlorate **182** is nitrated yielding compound **183** (Scheme 48).[150] Notably, the treatment of this salt with $NaBH_4$ does not affect the NO_2 group and results in the formation of DHP derivative **184**.

Scheme 48



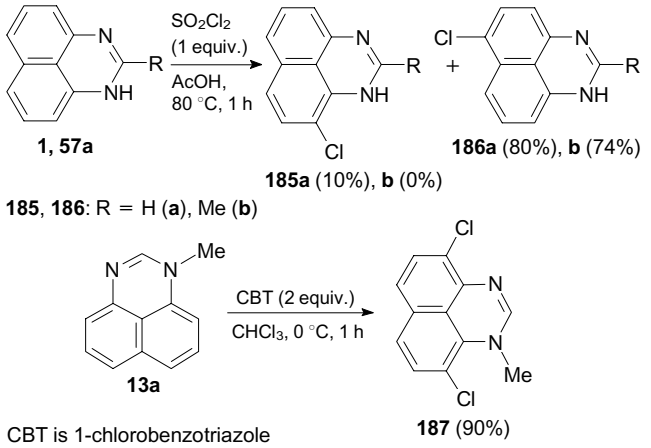
Nitration of aceperimidines was also described.[151,152] 1,3-Dimethylperimidin-2-one can be converted into the 6,7-dinitro derivative (30% yield) on treating with HNO_3/AcOH (30 °C, 1 h).[153]

Perimidines and aceperimidines are readily nitrated with nitrogen dioxide in acetic acid.[152] Interestingly, nitration of perimidines and aceperimidines can also be carried out with alkali metal nitrites in acetic acid.[83,152] The reaction takes place at room temperature and makes it possible to introduce up to three nitro groups into the naphthalene ring. For example, 2-methyl-6,7-dinitroperimidine is converted into 2-methyl-6,7,9-trinitroperimidine in 79% yield by treating with 1 equivalent of $NaNO_2$. A radical cation mechanism has been suggested for the nitration of π-excessive polynuclear aromatics with nitrites.[154]

4.5.5. Halogenation

Perimidines were chlorinated using sulfuryl chloride in acetic acid and 1-chlorobenzotriazole (CBT) in acetonitrile or chloroform.[89] Reactions of perimidine and 2-methylperimidine with 1 equivalent of SO_2Cl_2 resulted in the formation of 4(9)- and 6(7)-chloro derivatives **185a** and **186a**,**b** with a strong predominance of the latter (compound **185b** was not observed) (Scheme 49). Obviously, this indicates that the reaction proceeds predominantly through the perimidinium cation. Treatment of **1** with SO_2Cl_2 (2 equiv.) gives a mixture of mono-, di- and trichloroperimidines, while the use of a 3-fold excess of the electrophile affords the 4,6,7-trichloro derivative in a high yield. 4,6,7,9-Tetrachloroperimidine could not be obtained using SO_2Cl_2, while in the case of 2-methylperimidine **57a** such compound was isolated. Chlorination of **1** and **57a** with CBT, which is not only an electrophile, but also an oxidizing agent, did not succeed due to tarring (*cf.* data on the nitration in Section 4.5.4). At the same time, 1-methylperimidine **13a** reacted with CBT (1 equiv.) without tarring, forming a hard-to-separate mixture of 4-chloro, 9-chloro and 4,9-dichloro derivatives in a percentage ratio of 10 : 53 : 37. Upon chlorination of **13a** with two equivalents of CBT, 4,9-dichloride **187** was isolated in 90% yield (see Scheme 49). This experiment is important for better understanding of electrophilic substitution reactions in the perimidines series, since it confirms a higher electron density in the *ortho* positions of a neutral perimidine molecule as compared to *para* positions, in full accordance with quantum chemical calculations and ^{1}H NMR spectra. Subsequent chlorination of **187** yields 4,7,9-trichloro- and 4,6,7,9-tetrachloroperimidines. Due to steric hindrance the chlorination of 1-isopropylperimidine with a large excess of CBT affords only the 4,6,7-trichloro derivative.

Scheme 49



As expected, the 1,3-dimethylperimidinium cation is chlorinated mainly at the *para* positions by both above reagents.[101] Chlorination of perimidine with liquid Cl_2 in an autoclave at 250 °C results in perchloro-5,6-dihydro-4*H*-perimidine.[155]

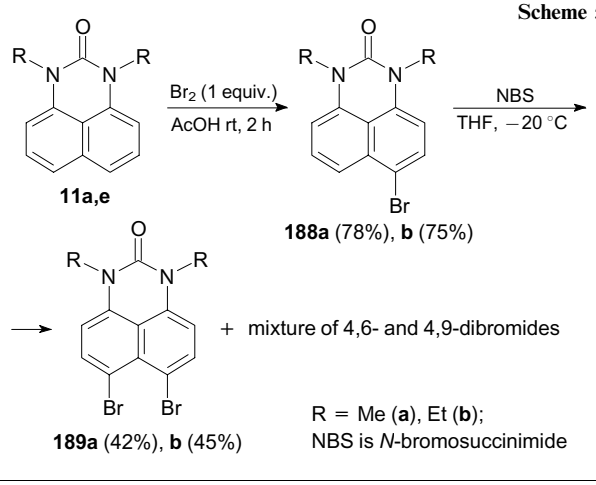
In connection with the *ortho*-dichlorination of 1-methylperimidine **13a**, the question of how the low basic 1,3-dimethylperimidinone **11a** would behave towards CBT became rather intriguing. It turned out that on treatment of **11a** even with 1 equivalent of CBT in chloroform, its 4,9-dichloro derivative is formed as a single product in 30% yield, while more than half of the compound **11a** remains unchanged.[101] Such a result indicates that the second chlorination of **11a** proceeds faster than the first one. Apparently, due to the remoteness of positions 4 and 9 from each other, the inductive effect of chlorine, which usually inactivates the electrophilic substitution in a ben-

zene ring, has little importance, thereby not masking its electron-donating resonance effect. Chlorination of **11a** with two and three equivalents of CBT leads to the formation of 4,9-dichloride and 4,6,9-trichloride, respectively, in almost quantitative yield. Under the action of a large excess of CBT, a mixture of tri- and tetrachlorides is formed in ~1 : 1 ratio.

Chlorination of 1,3-dimethyl-2,3-dihydroperimidine **30** under the action of CBT leads to complete resinification. However, using the SO_2Cl_2 – AcOH system as an electrophile, 4,9-dichloro, 4,6,9-trichloro, and 4,6,7,9-tetrachloro derivatives of **30** were obtained.[101]

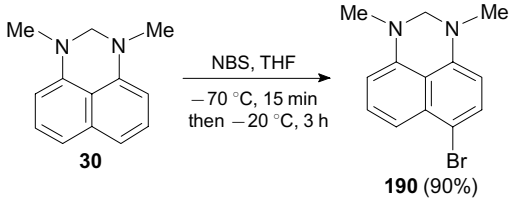
Bromination of perimidines has also been reported. Treatment of 2-methylperimidine **57a** with Br_2 in acetic acid provides mono- and dibromo derivatives whose structures have not been established.[156] Nitration of 2-aminoperimidine hydrobromide leads to the introduction of a bromine atom into the naphthalene ring together with the nitro groups.[157] 1,3-Dialkylperimidinones **11a**,**b** react with bromine in acetic acid at room temperature to produce the corresponding 6-bromo derivatives **188a**,**b** in good yields (Scheme 50).[158] The latter compounds can be transformed into 4,6,7,9-tetrabromoperimidinones by refluxing with a large excess of Br_2 in acetic acid for 3 h. In order to obtain synthetically important *peri*-dibromides **189a**,**b** from 6-bromides **188**, different brominating systems were tested.[158] In all cases a mixture of 6,7-, 4,6- and 4,9-dibromo isomers was formed. The best result was obtained using N-bromosuccinimide in THF at −25 °C (see Scheme 50). In this case, 6,7-dibromo-1,3-dialkylperimidinones **189a**,**b** were isolated in 42% – 45% yield together with 4,6- (~27%) and 4,9-dibromo (~30%) derivatives. As far as we know, this is currently the only case of *peri*-dibromination of a naphthalene ring with such a good selectivity. Subsequent bromination of the mixture of 4,6- and 4,9-dibromo compounds led to 4,6,9-tribromo-1,3-dimethylperimidinone in 90% yield. Isomeric 4,6,7-tribromo-1,3-dimethylperimidinone was synthesized by treating the 6,7-dibromide **189a** with NBS – THF at room temperature.

Scheme 50



Despite the high sensitivity of 2,3-dihydroperimidines towards electrophiles and oxidants (Sections 4.1 and 7), the treatment of 1,3-dimethyl-DHP **30** with NBS in THF at −70 °C results in the formation of 6-bromo derivative **190** in 90% yield (Scheme 51).[150] An attempt of further bromination of **190** resulted in a complex mixture of oxidation and polybromination products. 6-Bromo- and 6,7-dibromo-

Scheme 51



1,3-dialkyl-2,3-dihydroperimidines can be obtained in good yields by reduction of the corresponding brominated perimidinones with $LiAlH_4$ in anhydrous diethyl ether.[150]

The 1,3-dimethylperimidinium perchlorate is efficiently brominated at position 6 when treated with bromine in refluxing AcOH.[150]

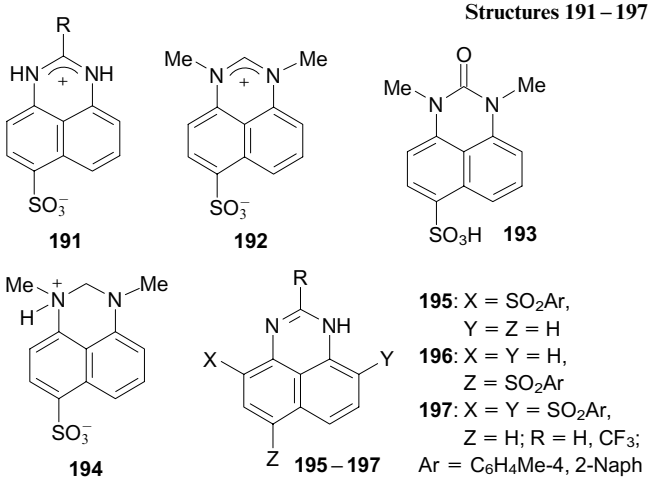
Iodination of 1,3-dialkylperimidionones into position 6 was accomplished by treating with iodine in dichloroethane in the presence of HgO.[158] Subsequent bromination of 6-iodo derivatives with NBS in tetrahydrofuran at −65 °C to −25 °C gives rise to 7-bromo-6-iodo-1,3-dialkylperimidin-2(3*H*)-ones in 25 – 26% yield.

4.5.6. Sulfonation and synthesis of sulfones

The NH-unsubstituted 2-R-perimidines are sulfonated with conc. H_2SO_4 at 10 – 20 °C for 10 – 30 min to afford 2-R-perimidine-6(7)-sulfonic acids nearly in a quantitative yield. The latter normally exist as zwitterions **191**.[60, 86, 159] 1,3-Dimethylperimidinium perchlorate and 1,3-dimethylperimidinone **11a** are sulfonated with the same ease to give compounds **192** and **193**.[60] On the contrary, the sulfonation of 1,3-dimethyl-2,3-dihydroperimidine **30** requires moderate heating (70 °C) and produces zwitterion **194**. The lower reactivity of **30** is attributed to its existance under strongly acidic conditions in a dicationic form, in which one of the nitrogen atoms along with the C-6(7) atom of the naphthalene ring are protonated.

Reactions of perimidine **1** and 2-trifluoromethylperimidine **156** with arenesulfonic acids (1.5 equiv.) or their sodium salts in 82% – 86% PPA (140 – 150 °C, 1.5 h) produce a mixture of the corresponding 4(9)-arenesulfonyl **195** (14% – 46%), 6(7)-arenesulfonyl **196** (31% – 44%) and 4,9-di(arenesulfonyl)perimidines **197** (5%).[55, 57, 72] Treating sulfones **195** and **196** with $NaBH_4$ in AcOH causes reduction of the heterocyclic C=N bond to give 4(9)- and 6(7)-arenesulfonyl-2,3-dihydroperimidines.[72]

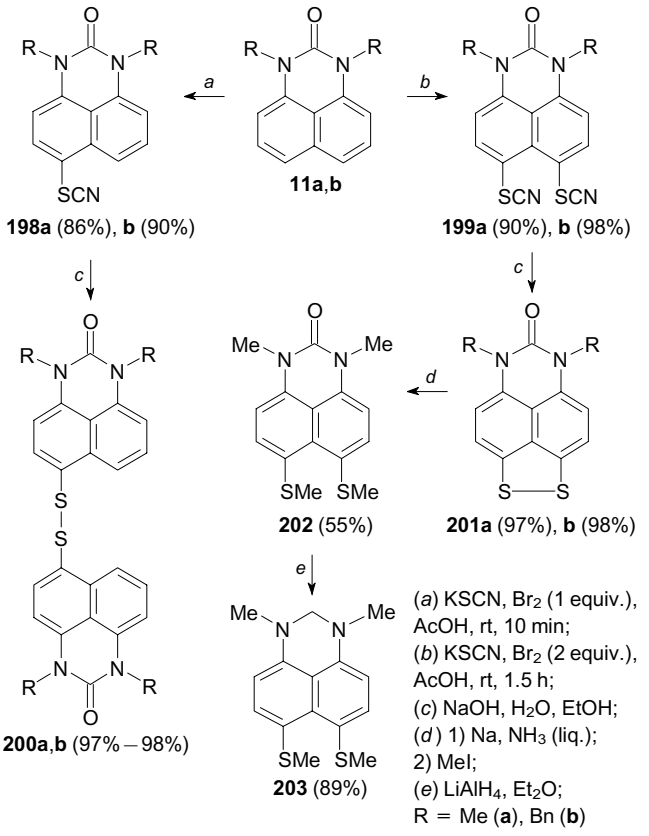
Structures 191 – 197



4.5.7. Thiocyanation

Electrophilic thiocyanation of 1,3-dialkylperimidinones **11a**,**b** was carried out by reaction with potassium thiocyanate and bromine in acetic acid (Scheme 52).[160] The reaction proceeds *via* the *in situ* generation of dithiocyanogen $(SCN)_2$. Using equimolar amounts of the $(SCN)_2$, 6-thiocyano derivatives **198** were obtained, while the reaction with two equivalents of $(SCN)_2$ gave 6,7-di(thiocyano)perimidinones **199** as the only products. Alkaline hydrolysis of **198** and **199** in water–ethanol solution rapidly and quantitatively affords disulfides **200** and **201**, respectively, as a result of inter- and intramolecular oxidative coupling of the intermediate thiolate anions. Reduction of the S–S bond in **201a** with Na in liq. NH_3 and subsequent *S*-methylation of the intermediate *S*,*S*-dianion yields 6,7-di(methylthio)perimidinone **202**, which can be transformed into 2,3-dihydroperimidine **203** by treating with $LiAlH_4$ in ether. The last conversion is especially important, since DHPs, *e.g.*, **30**, as well as perimidines could not be used in the thiocyanation reaction.

Scheme 52

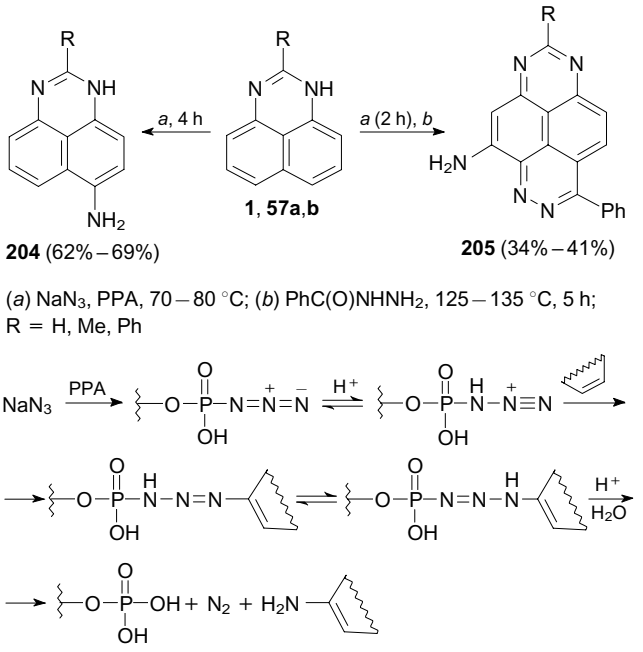


Treating 1,3-dialkyl-2,3-dihydroperimidines and perimidine itself with KSCN–Br_2–AcOH gives rise to inseparable mixtures of products.

4.5.8. Electrophilic amination

Aksenov and co-workers[161,162] proposed the sodium azide–PPA system as a new reagent for electrophilic *C*-amination of perimidines. Thus, treatment of the parent compound **1** and its 2-methyl- and 2-phenyl derivatives **57a**,**b** with this reagent resulted in the formation of 6(7)-aminoperimidines **204** in good yields (Scheme 53). A mechanism for this transformation was proposed suggesting the

Scheme 53



participation of the protonated azido derivative of PPA as an actual electrophile.

It was also shown that the reaction of NH-unsubstituted perimidines **1** and **57a**,**b** with NaN_3–PPA followed by addition of benzoyl hydrazine gives rise to 10-amino-1,2,6,8-tetraazapyrenes **205** (see Scheme 53).[163]

4.5.9. Azo coupling

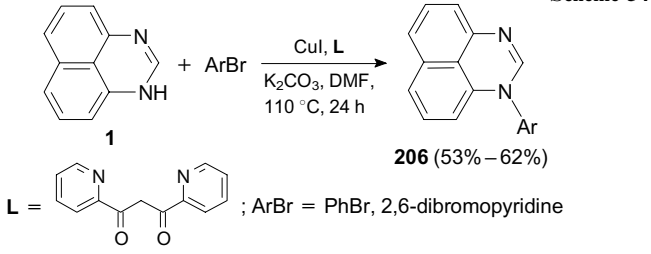
As Sachs[5] has shown in his early study, perimidines are excellent azo components and when treated with diazonium salts give rise to blue azo compounds. There are a huge number of patents describing the synthesis of such perimidine- and dihydroperimidine-based azo compounds (see, for example,[164–169] and Section 10.1). The reaction occurs mainly at positions 6(7), though for the NH free dihydroperimidines C(4)-substitution has been also documented.

4.6. Transition metal-catalyzed coupling

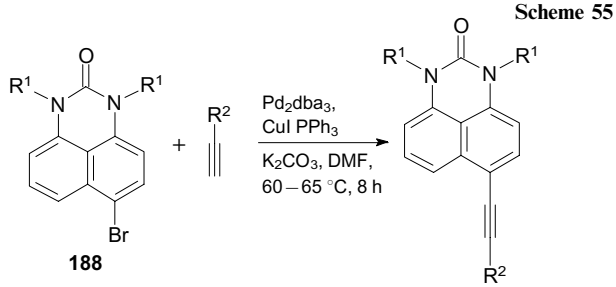
An efficient copper-catalyzed *N*-(het)arylation of perimidine using pyridine-functionalized 1,3-diketone as a ligand have been described.[170] *N*-Arylperimidines **206** were obtained in moderate yields (Scheme 54).

A series of mono-, di-, tri- and tetra-alkynyl derivatives of 1,3-dialkylperimidinones **207**–**209** have been synthesized from the corresponding bromides *via* the Sonogashira reaction (Scheme 55).[171] *peri*-Dialkynylperimidinones were tested for thermal or electrophile-initiated cyclizations resulting in the formation of some new polynuclear hetero-

Scheme 54

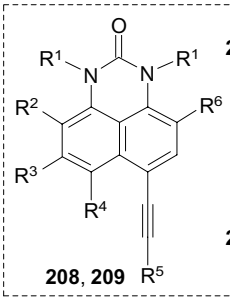


Scheme 55



188

R^1 = Me, Et; R^2 = Ph, C_6H_4Me-4, $SiMe_3$ **207** (66% – 77%)
dba is dibenzylidene acetone



208, **209**

208: R^3 = H: R^2 = R^6 = H,
R^4 = C≡CR^5;
R^2 = R^6 = C≡CR^5, R^4 = H;
R^2 = H; R^4 = R^6 = C≡CR^5;
R^2 = R^4 = R^6 = C≡CR^5;
R^2 = H, R^4 = Br, R^6 = C≡CR^5;
R^5 = $SiMe_3$;
209: R^4 = H: R^2 = R^3 = R^6 = C≡CR^5;
R^5 = $SiMe_3$

cyclic compounds, mostly derivatives of 3,5-diazadibenzo-[*cdk*]fluoranthrene.

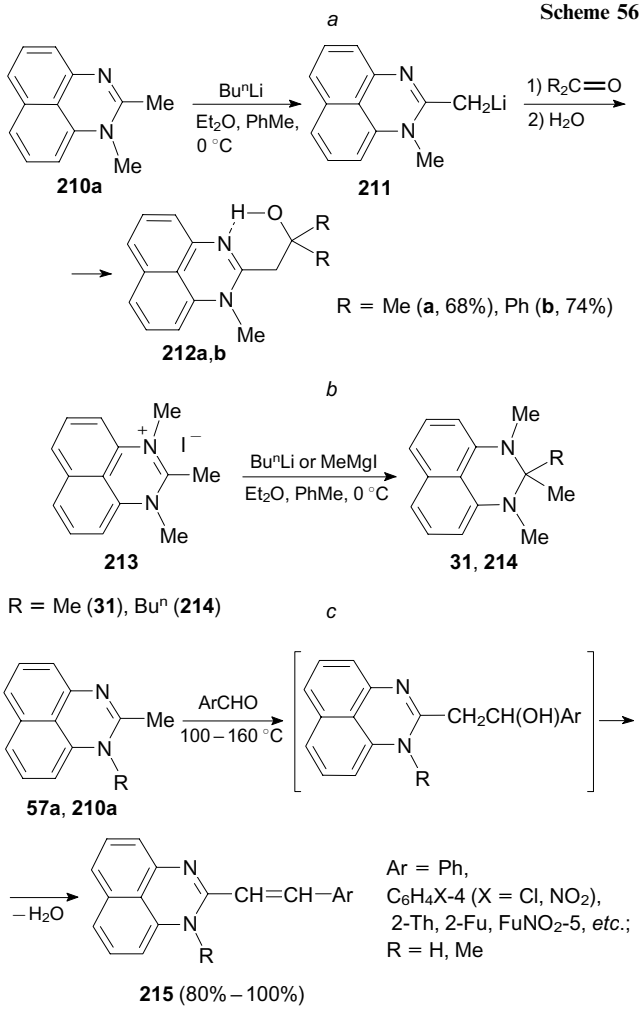
5. Properties of selected perimidine derivatives

This Section is devoted almost exclusively to the properties of functional groups at position 2 of the perimidine system, since they differ in much greater specificity compared to substituents in the naphthalene part of the molecules. In particular, many C(2)-substituents are prone to tautomeric transformations and reactions with bifunctional (usually carbonyl-containing) reagents. Most of these reactions are accompanied with the annelation of a new heterocyclic ring across the N(1) – C(2) bond. A summary of the resulting condensed heterosystems is provided in the Supplementary Materials (see Table S4, https://doi.org/10.1070/RCR4963).

5.1. 2-Methyl- and 2-methylene-active perimidines

The methyl group of 2-methylperimidines is attached to the strongly electron-deficient C(2) atom and therefore exhibits increased CH-acidity and ability to enter into condensation reactions. Indeed, kinetic measurements of the basic H/D exchange in a series of 1,2-dimethylperimidines and related imidazole systems revealed the following order of decreasing CH-acidity of the 2-Me group: perimidine > naphtho[2,3-*d*]imidazole > benzimidazole > naphtho[1,2-*d*]imidazole > imidazole; the difference in the rate constants between the first and the last member of this series is about 4 orders of magnitude.[172] Accordingly, when treated with butyllithium, compound **210a** forms 2-lithium methyl derivative **211**, which, when intercepted by acetone or benzophenone, gives tertiary alcohols **212a**,**b** with a chelated OH group in good yields (Scheme 56 *a*). Unlike base **210a**, 1,2,3-trimethylperimidinium iodide **213** reacts with butyllithium or methylmagnesium iodide, forming exclusively dihydroperimidines **214** and **31** (Scheme 56 *b*). Thus, appearance of the onium centre in salt **213** sharply shifts the subtle balance between the deprotonation of the 2-Me group and addition of the nucleophile to the ring C=N bond towards the latter reaction (see Section 4.4). When interacting with aromatic or heteroaromatic aldehydes,

Scheme 56



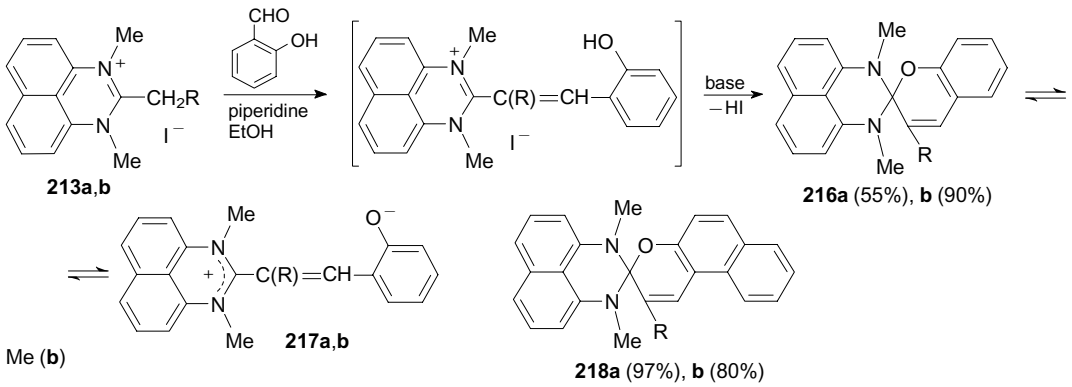
2-methyl- and 1,2-dimethylperimidines form the corresponding 2-styryl derivatives **215** in almost quantitative yields (Scheme 56 *c*), the reaction giving good results both without solvent[173] and with acetic anhydride as a catalyst and medium.[174]

The interaction of perimidinium salts **213** with salicylic aldehyde or 2-hydroxynaphthalene-1-carbaldehyde, gave colourless spiropyrans **216** and **218** very resistant to ring opening (Scheme 57).[174] Nevertheless, compounds **216a** and **218a** showed thermochromic properties and **218b** demonstrated photochromic ones, reversibly transforming upon heating and irradiation, respectively, into raspberry-red merocyanines of type **217**.[98]

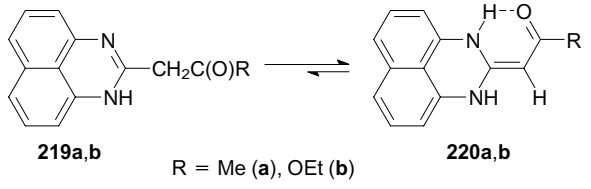
When an α-carbonyl-containing substituent is introduced into the 2-Me group, the $CH_2C(O)R$ substituent becomes methylene-active and one of its proton jumps onto the nitrogen atom, forming the so-called ketene-aminal tautomeric form (**219** → **220**) (Scheme 58). Ketene aminals are actually enamines, containing a strongly activated C=C bond, which is involved in a 6π-electron resonance-stabilized chelate ring. This is especially noticeable in the ^{1}H NMR spectra, in which peaks of the chelated OH and non-chelated NH protons are observed at δ 13.8 and 10.7 ppm, respectively; one-proton singlet of the =CH proton appears at δ 4.8 – 5.6 ppm.[18, 175]

Perimidine ketene aminals easily react at the methine carbon atom with relatively weak electrophiles such as diazonium salts.[176] They found a special application as a

Scheme 57

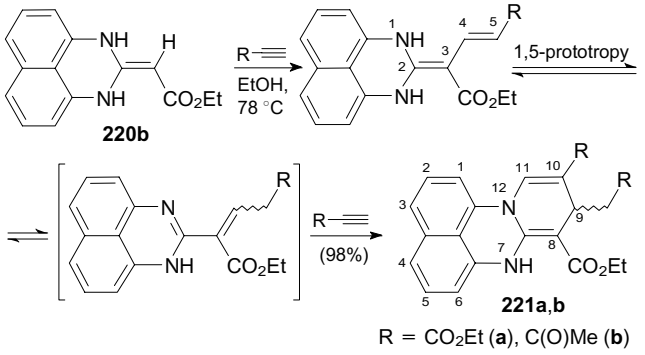


Scheme 58



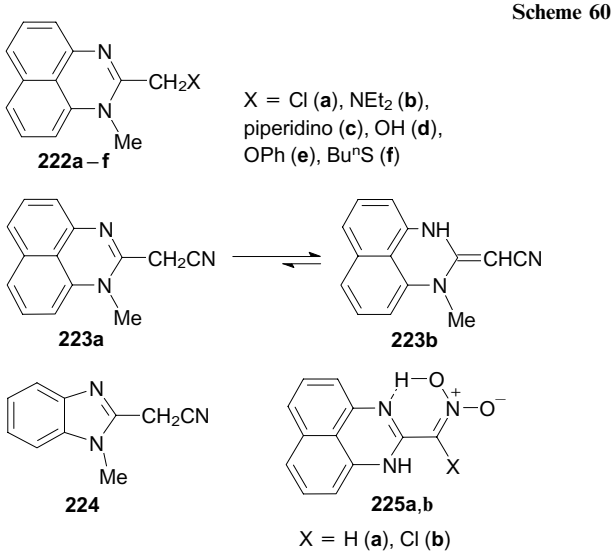
convenient material for the synthesis of polynuclear condensed ring systems. For example, ethyl 2-(1*H*-perimidin-2(3*H*)-ylidene)acetate **220b** enters into tandem [2 + 2 + 2]cycloaddition with terminal alkynes, forming pyrido[1,2-*a*]perimidine derivatives **221** in almost quantitative yield (Scheme 59).[177] Other examples of using ketene-aminals to obtain [*a*]-fused multinuclear perimidine systems are collected in the Supplementary Materials (see Table S3, https://doi.org/10.1070/RCR4963).

Scheme 59



1-R-2-Chloromethylperimidines behave as typical S_N1 substrates, quantitatively exchanging chlorine atom for N-, O- and S-nucleophiles for several minutes at room temperature.[178] ^{1}H NMR and IR spectroscopy data clearly showed that 2-chloro- **222a** as well as 2-amino-, 2-hydroxy(aryloxy)- and 2-thiomethylperimidines **222b–f** exist in solution exclusively in methylene form (Scheme 60). At the same time, 2-cyanomethylperimidines adopt the methylidene form **223b**, as evidenced by the presence in their ^{1}H NMR spectra of one-proton signals of the =CH and NH protons, which easily exchange when D_2O is added. It is noteworthy that 2-cyanomethylbenzimidazole **224** exists as such, apparently, because of the greater aromaticity and somewhat lower basicity of the benzimidazole system. According to the IR spectroscopy data, orange-coloured 2-nitromethylperimi-

Scheme 60

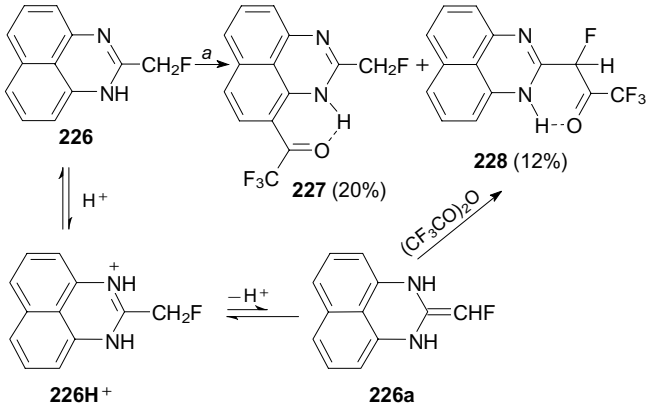


dines **225a,b** exist in a chelate form with a proton localized mainly on the oxygen atom of the NO_2 group.[179]

The tautomeric behaviour of 2-fluoromethyl- and 2-difluoromethylperimidines is also of interest.[42] Although the former compound exists, according to the ^{1}H NMR data, in the methylene form **226** (δ_{CH_2} = 4.9 ppm, $CDCl_3$), its trifluoroacetylation gives two products **227** and **228**, both with the N–H···O chelated bonds and $CF_3C(O)$ groups attached to position 4(9) and to the methylene unit, respectively (Scheme 61). Presumably, the formation of **228** results from cation **226H$^+$**, which, due to the acidifying action of the onium centre and the fluorine atom, equilibrates with a certain amount of aminal **226a**, comparable in its C-nucleophilicity with position 9 in methylene form **226**. In the case of 2-difluoromethylperimidine, a product of type **228** is not obtained, which can be explained by the lower nucleophilicity of the corresponding ketene-aminal form due to −I effect of two fluorine atoms.

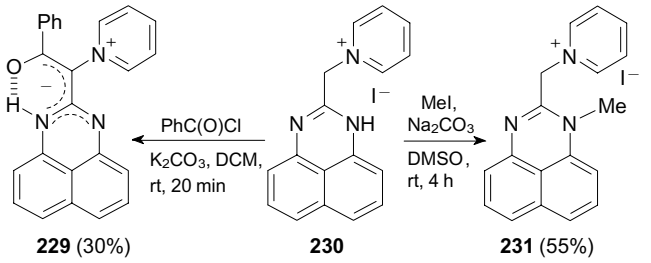
To some extent, *N*-(2-perimidinylmethyl)pyridinium salt **230** exhibits similar behaviour as compound **226** (Scheme 62).[180] Despite the strongly acidifying nature of the pyridinium nucleus, **230** exists in the methylene form (δ_{CH_2} = 5.6 ppm, DMSO-d_6). However, under the action of acyl chlorides, aryl isothiocyanates or CS_2 in the presence of a base, the CH_2 group of **230** undergoes acidic ionization followed by the addition of the above electrophiles and formation of the chelated ylides **229**. It is interesting that the methylation of **230** in the basic medium proceeds at the perimidine NH group giving rise to salt **231**.

Scheme 61



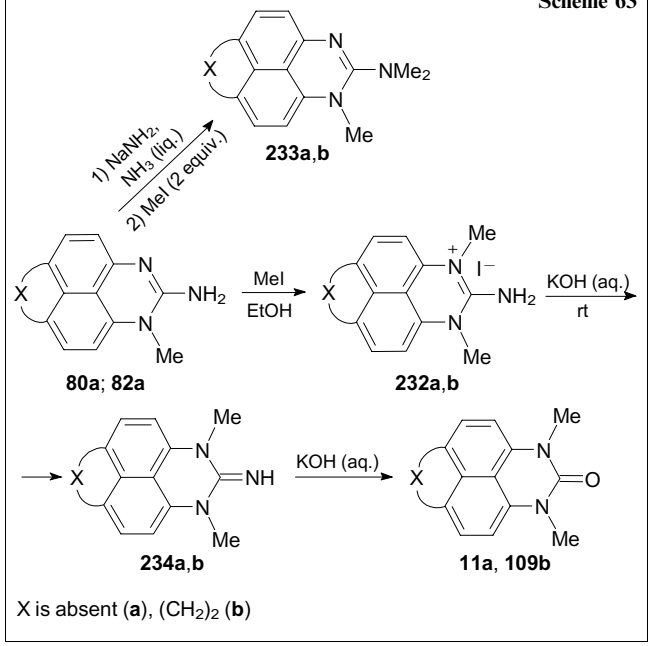
(*a*) $(CF_3CO)_2O$, 100 °C, sealed tube

Scheme 62



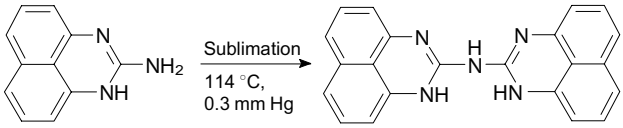
DCM = CH_2Cl_2

Scheme 63



X is absent (**a**), $(CH_2)_2$ (**b**)

Scheme 64



235 (colourless) **236** (yellow)

5.2. 2-Aminoperimidines

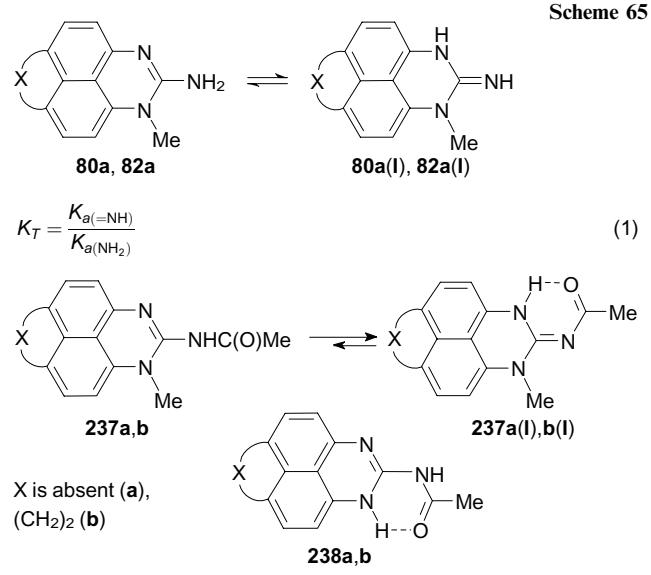
In various Sections of the review, at least seven methods for the preparation of 2-aminoperimidines are mentioned. Most of them start from 1,8-diaminonaphthalene or its mono-*N*-substituted derivatives, which are cyclized by the action of different nitrogen-containing reagents (Section 6.2). Two other methods are based on the amination of 1-R-perimidines with sodium amide or nucleophilic substitution of chlorine in 2-chloroperimidines treated with the corresponding amines (Section 4.3). Perhaps the most common is the last of these methods, which allows placing into position 2 all types of the amino groups: primary or secondary ones.

Like 2-aminoimidazoles and -azines, 2-aminoperimidines **80**, 2-aminoaceperimidines **82a**,**b** and 2-aminoaceperimidilenes **82c** are monoacidic bases, which are protonated at the ring aza group. Their basicities, *e.g.* $pK_a = 7.94$ (**80a**) and 8.22 (**82a**), are about 0.8 – 1 order higher than those of 2-aminoimidazoles (see Table S1, Supplementary Materials, https://doi.org/10.1070/RCR4963). Methylation of amines **80a** and **82a** in a neutral medium gives 1,3-dimethyl-2-aminoperimidinium salts **232** in nearly quantitative yields. When treated with alkali, the latter turn into more basic imines **234a** ($pK_a = 9.15$) and **234b** ($pK_a = 9.34$). When heated in an alkaline medium, compounds **234** are smoothly hydrolyzed to the corresponding perimidinones **11a** and **109b** (Scheme 63).[25,181] Exhaustive methylation of the 2-amino group, giving 2-dimethylamino derivatives **233a**,**b** in high yields, was carried out in liquid ammonia in the presence of sodium amide.[182]

2-Aminoperimidines are easily acylated at the NH_2 group, but they poorly react with aldehydes, forming the corresponding azomethines in a low to moderate yields.[181] It was found that vacuum sublimation of 2-aminoperimidine **235** leads to the formation of 2,2′-diperimidinylamine **236** (Scheme 64).[54]

Like 2-aminoimidazoles,[68,69] 2-aminoperimidines exist in the amino form **80a**, **82a** predominantly (Scheme 65). However, due to the increased basicity and lower aromaticity of perimidines, about 2% of the imino forms **80a(I)**, **82a(I)** are present in the tautomeric equilibrium. So, for amines **80a** and **82a**, the corresponding constants K_T (calculated by Eqn 1, where $K_{a(=NH)}$ and $K_{a(NH_2)}$ are acidic

Scheme 65



$$K_T = \frac{K_{a(=NH)}}{K_{a(NH_2)}} \quad (1)$$

X is absent (**a**), $(CH_2)_2$ (**b**)

ionization constants of the protonated imino and dimethylamino forms) are 0.0186 and 0.0178, respectively, that is 1 – 3 logarithmic units higher than that of 1-methyl-2-amino derivatives of naphthoimidazoles **6** and **7**, benzimidazole and 4,5-diphenylimidazole. This tendency is even more manifested in 2-acetamino derivatives.[183] Thus, compounds **237a**,**b** in the solid state and in solution exist as chelated imines **237a**,**b**(**I**), whereas in the benzimidazole series such a shift occurs only when at least one chlorine atom is introduced into the acetylamino group. Interestingly, 2-acetylaminoperimidines with a free N(1) – H group exist in the chelated amino form **238a**,**b**. Evidently, in this case the free energy gain is provided by both keeping the aromaticity of the heterocyclic system and formation of a stronger IHB.

Bekhli and co-workers[184] investigated tautomerism in 2-alkylaminoperimidines[115] and perimidine-2-carbamates. The former of these compounds exists predominantly in the amino form, while the chelated imino structure is more characteristic of the latter.

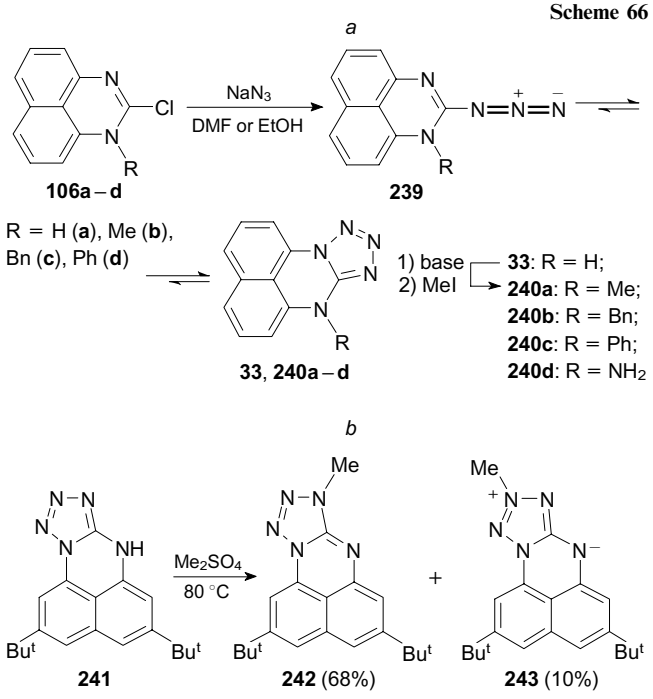
5.3. 2-Hydrazinoperimidines

Two methods for the preparation of 2-hydrazinoperimidines are described, which consist of nucleophilic substitution of a chlorine atom[116] or a MeS group[185,186] by heating 2-chloro- or 2-methylthioperimidines with hydrazine. In almost all cases, 2-hydrazinoperimidines were further reacted with bifunctional carbonyl containing electrophiles to produce 2-(1-pyrazolyl)perimidine or 1,2,4-triazolo[4,3-*a*]perimidine derivatives. A summary of the relevant data is given in the Supplementary Materials (see Table S4, https://doi.org/10.1070/RCR4963).

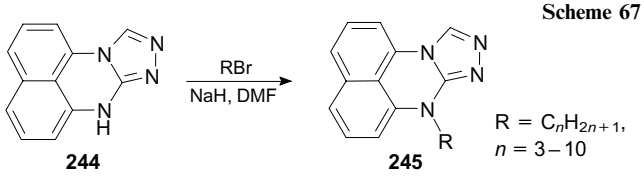
5.4. 2-Azidoperimidines

2-Azidoperimidines are formed in good yields by heating chlorides **106a** – **d** with sodium azide in ethanol or dimethyl sulfoxide.[62,105] Unlike their imidazole analogues, these compounds both in the crystalline state and in solution exist in the form of tetrazolo[1,5-*a*]perimidines **33**, **240a** – **d** due to the lower aromaticity of the perimidine system. The anion of **33** is methylated with methyl iodide and aminated with hydroxylamine-*O*-sulfonic acid[187] into a six-membered rather than five-membered ring, forming compounds **240a**,**d** in good to moderate yields (Scheme 66 *a*). Using compound **241** as an example, it was shown that under neutral conditions, methylation of tetrazolo[1,5-*a*]perimidines proceeds exclusively at the more nucleophilic nitrogen atoms of the tetrazole ring to form compound **242** and isomeric zwitterion **243** (Scheme 66 *b*).[188]

Scheme 66



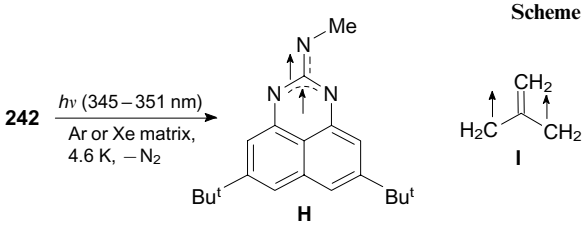
Scheme 67



It is noteworthy that the direction of the alkylation of tetrazole **33** and triazolo[4,3-*a*]perimidine **244** in an alkaline medium is the same (Scheme 67).[116]

Interestingly, irradiation of compound **242** in butyronitrile or Ar (Xe) matrix has led to the elimination of the N_2 molecule and generation of biradical **H** existing in the triplet form according to the EPR spectrum and theoretical calculations. This species has been considered an analogue of the seminal trimethylenemethane biradical **I** (Scheme 68).[188]

Scheme 68

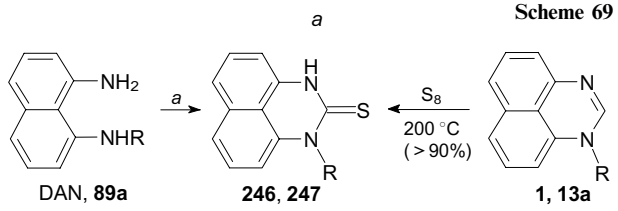


5.5. Perimidine-2(3*H*)-thiones and -selenones

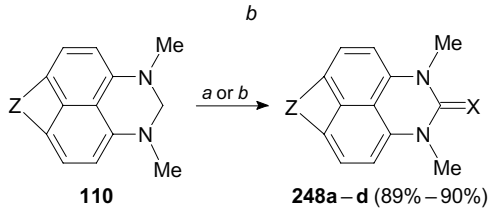
2-Mercaptoperimidines **246**, **247**, like α- and γ-mercapto derivatives of azoles and azines, exist in the thione form. Commonly, they are obtained by reacting DAN and its mono-*N*-substituted derivatives **89** with carbon disulfide in NaOH – EtOH solution.[189,190] Another effective way to perimidine-2-thiones consists in the fusion of perimidines with elemental sulfur (Scheme 69 *a*).[103] This method was also extended to 2,3-dihydro derivatives of perimidines and aceperimidines **110**, which upon fusion with sulfur and selenium afford the corresponding thiones and selenones **248a** – **d** in about 90% yields (Scheme 69 *b*).[38] Woodgate *et al.*[54] have developed the preparation of perimidine-2-selenone **249** *via* the interaction of 2-chloroperimidine **106a** with NaSeH (Scheme 69 *c*). Similarly, it is also possible to introduce an alkyl(aryl)thio group into position 2. Alkylation[54,190] and acylation[189] of perimidine-2-thiones, as a rule, proceed on the sulfur atom.

A rare example of an intramolecular arylation of sulfur atom in perimidine-2-thione is shown in Scheme 70.[191] Dianion **250**, generated by treatment of thione **246** with BuLi, reacts with pentafluorobenzoyl chloride furnishing, *via* *N*-benzoyl intermediate **251**, the multinuclear condensed heterocyclic compound **252**. Interestingly, the use of pyridine or Et_3N instead of butyllithium failed to afford **252** since both these bases led to the formation of the monoanion only.

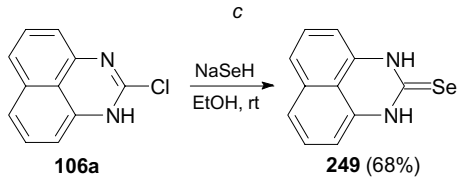
Scheme 69



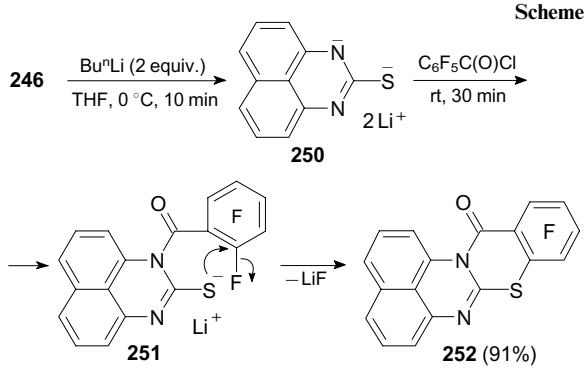
(*a*) CS_2, KOH, EtOH, reflux, 68% yield; R = H (DAN, **246**, **1**), Me (**89a**, **247**, **13a**)



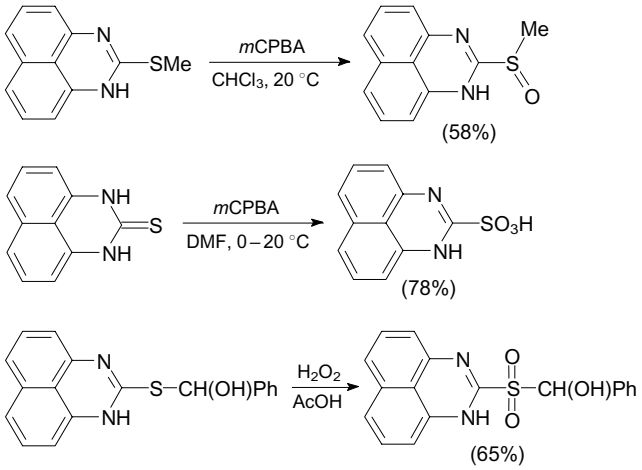
(*a*) S_8, 130 °C, 1 h; (**b**) Se, 160 °C, 1.5 h; **248**: X = S: Z is absent (**a**), $(CH_2)_2$ (**b**); X = Se: Z is absent (**c**), $(CH_2)_2$ (**d**)



Scheme 70



Scheme 71

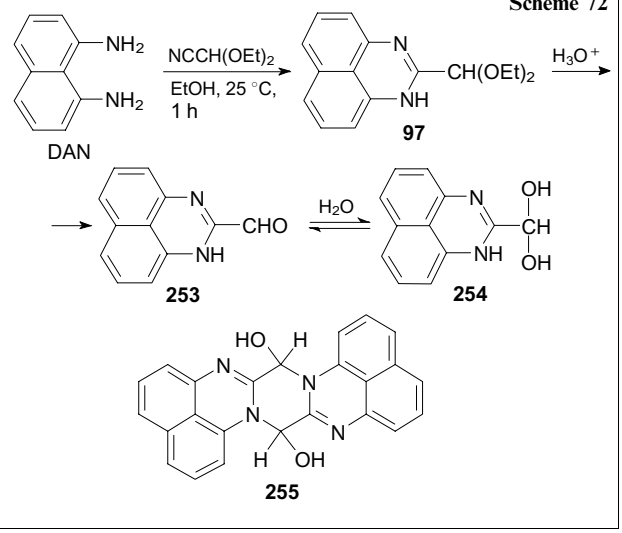


Perimidine-2-thiones or 2-alkylthioperimidines can be oxidized under mild conditions with various peroxides to form sulfoxides,[190] sulfonic acids[54] or sulfones[189] (Scheme 71).

5.6. Perimidine-2-carbaldehydes, -carboxylic and -thiocarboxylic acids

As far as is known, only one representative of perimidine-2-carbaldehydes has been described to date, namely, compound **253** (Scheme 72).[66] Its synthesis was carried out in two steps. In the first step, DAN was reacted with diethoxyacetonitrile leading to the formation of diethyl acetal **97** (see Scheme 22 and Ref. 112). Acid hydrolysis of **97** and subsequent neutralization of the reaction mixture yielded aldehyde **253**, which showed an increased tendency to hydration and dimerization. Thus, in the ^{1}H NMR spectrum of the crude product in DMSO-d_6 at 20 °C, two singlets of hydrated and non-hydrated CHO groups at δ = 5.65 and 9.55 ppm (integral intensities 7 : 3) were observed. When the temperature was raised to 80 °C, the hydrated form **254** disappeared and a peak at 9.60 ppm remained in the spectrum. After recrystallization from chloroform, the aldehyde was also obtained in a non-hydrated form. However, in the solid state, according to the IR data, it was a mixture of monomer **253** ($\nu_{C=O}$ 1700 cm^{-1}) and dimer **255** (ν_{OH} 3320 cm^{-1}, width 70 cm^{-1}). It is noteworthy that the formation of such cyclic dimers is also characteristic of aldehydes of other *N*-unsubstituted azoles, *e.g.*, benzimidazole, 1,2,4-triazole and pyrazole. Along with diethyl acetal **97**, the oxime and thiosemicarbazone of aldehyde **253** were also obtained.[192]

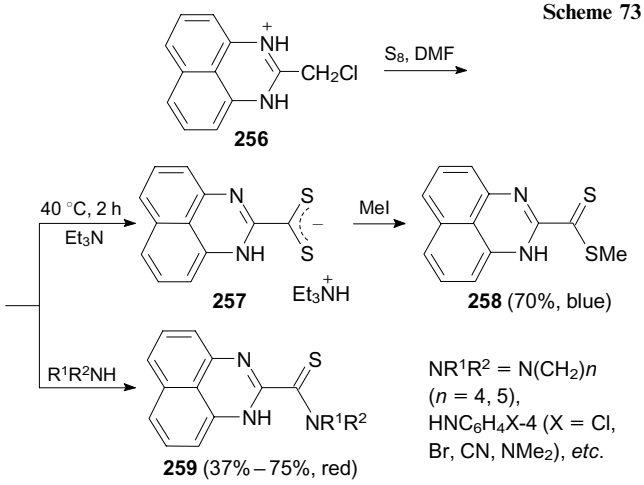
Scheme 72



There is very little information on (perimidin-2-yl) ketones except the already mentioned 2-benzoylperimidines (see structure **49**).[23,74] Perimidine-2-carboxylic acid seems to be unstable due to easy decarboxylation but its ethyl ester **48** has been prepared and studied.[71] Nitrile and amide of this acid were also described.[22]

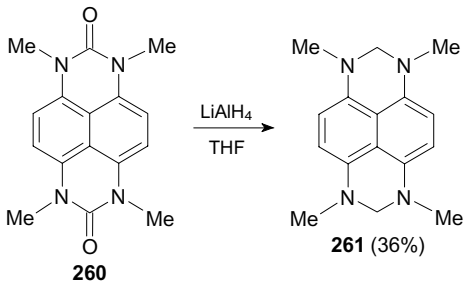
It was disclosed by Thiel *et al.*[26] that 2-(chloromethyl)-perimidinium hydrochloride **256** is thiolated with sulfur under fairly mild conditions in the presence of triethylamine, forming the triethylammonium salt of perimidine-2-dithiocarboxylic acid **257** (Scheme 73). The latter compound, without preliminary isolation, can be further methylated with methyl iodide to afford product **258**. This ester attracted the attention of researchers because of its deep blue colour (λ_{max} 608 nm, log ε 2.99), which is not typical of other dithiocarboxylic acid esters. Thiolation of **256** in the presence of primary and secondary amines (instead of Et_3N) gave red-coloured amides of perimidine-2-thiocarboxylic acid **259**.

Scheme 73



heating NH-unsubstituted perimidinones with $POCl_3$ (Refs 90, 103, 105, 116, 188) (see also Scheme 24). Finally, the reduction of the C=O group in 1,3-disubstituted perimidinones with $LiAlH_4$ is synthetically important, leading to the formation of the corresponding 2,3-dihydroperimidines (Scheme 74).[155] Other examples of this kind are given in Section 8.

Scheme 74



5.7. Perimidin-2(3*H*)-ones

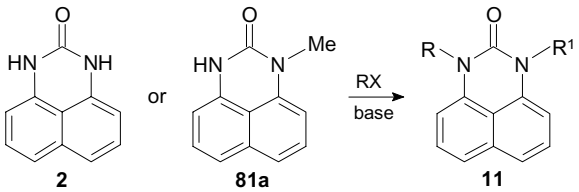
Perimidin-2-ones are one of the most important and versatile perimidine derivatives due to their stability, availability and rich reactivity. At least six methods are known for preparing parent perimidinone **2** and its 1-R- and 1,3-di-R-substituted derivatives. Three of them start from DANs, which are used in cyclizations with urea, methyl(ethyl) chloroformate, phosgene or potassium cyanate in an acidic medium (Section 6.2). In the other three methods, the starting compounds are 1-R-perimidines, 1,3-dialkylperimidinium salts or 2-chloroperimidines, which are respectively subjected to direct hydroxylation (Section 4.3), alkaline disproportionation (Section 4.4) or nucleophilic substitution.

As for the reactivity of perimidinones, we have already mentioned the synthetically significant extrusion of the C=O group by heating 1,3-dialkylperimidinones with melted KOH (see Scheme 20). In fact, the C=O group appears here as a protective one in the synthesis of hardly accessible derivatives of DAN. Another common reaction is the exchange of the C=O group for a chlorine atom when

Due to the sufficiently high NH-acidity, perimidinone **2** in an alkaline medium is readily transformed into its anion, which reacts with an excess of an alkylating agent to afford the corresponding 1,3-dialkylperimidinone **11** in good yield. It is recommended to carry out this reaction in dipolar aprotic solvents, such as acetone, dimethyl sulfoxide or *N*-methylpyrrolidone (NMP). Probably, these media not only increase nucleophilicity of the anionic centre, but also favour the formation of perimidinone dianion. Despite generally good yields of 1,3-dialkylperimidinones, up to 5% – 7% of a monoalkyl derivative, for example **81a**, is usually formed as a by-product. As shown by Claramunt *et al.*[18] in relation to of compounds **81b**,**h**, under appropriate conditions monoalkylperimidinones can also become target products. Their preparative value lies in the possibility to produce asymmetric 1,3-dialkylperimidinones during second alkylation. A summary of the relevant data is given in Table 3.

Taking into account the ambident nature of the perimidine-*N*-anion, one could expect the formation of a certain

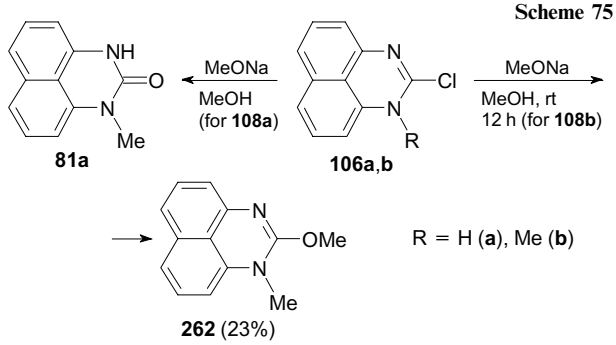
Table 3. 1,3-Dialkylperimidinones prepared by alkylation of perimidinones **2** and **81a**.



Compound	R	R[1]	Starting compound	Solvent	Reagent and conditions	Yield (%)	Ref.
11a	Me	Me	**2**	Acetone	MeI, KOH, rt, 1 h	73	109
11b	Bn	Bn	**2**	Acetone	BnCl, KOH, 1 h	79	109
11c	Me	Et	**81a**	Acetone	EtBr, KOH, rt, 1 h	75	109
11d	Me	Bn	**81a**	Acetone	BnCl, KOH, 1 h	87	109
11a	Me	Me	**2**	NMP	Me_2SO_4, NaOH,	84	189
11e	Et	Et	**2**	NMP	Et_2SO_4, NaOH,	78	189
11f	Pr^n	Pr^n	**2**	NMP	Pr^nBr, NaOH	77	189
11g	Bu^n	Bu^n	**2**	NMP	Bu^nBr, NaOH	74	189
11h	n-C_8H_{17}	n-C_8H_{17}	**2**	NMP	n-$C_8H_{17}Br$, NaOH	46	189
81b	Et	H	**2**	Acetone	EtI, K_2CO_3, KOH, reflux, 4 h	50	18
81h	Pr^n	H	**2**	Acetone	EtI, K_2CO_3, KOH, reflux, 4 h	44	18
11a	Me	Me	**2**	DMSO	MeI, KOH, 100 °C, 1 h	98	87

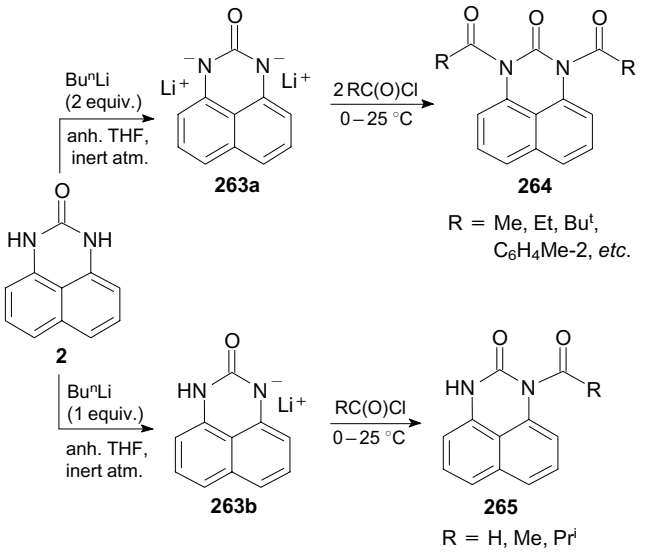
amount of 2-methoxyperimidine during the alkylation of **2**. However, no signs of this have yet been reported. In this regard, an attempt was made to obtain such compounds by exchanging the chlorine atom in 2-chloroperimidines **106a**,**b** for a methoxy group (Scheme 75).[18] It was found that the interaction of **106a** with sodium methoxide gives exclusively 1-methylperimidinone **81a**, apparently due to the isomerization of the initially formed 2-methoxy derivative. The experiment on methoxylation of chloride **106b** was more successful. 1-Methyl-2-methoxyperimidine **262** was isolated in a reasonable yield as colourless crystals with melting point of 113 – 114 °C. It should be noted that an attempt to perform the direct ethoxylation of 1-methylperimidine with the dry sodium ethoxide at 200 – 250 °C, undertaken by analogy with the successful hydroxylation of 1-R-perimidine with KOH (Section 4.3), failed and resulted in the formation of compound **81a** in 7% yield.[104] It is noteworthy that Sachs[5] described the synthesis of 2-ethoxyperimidine by means of cyclization of DAN with diethyl carbonate.

Scheme 75



Preparation of *N*-acylperimidinones is a special case due to the lability of these compounds and the ease of acylation of the naphthalene core. For this reason, it was proposed to obtain *N*-mono- or *N*,*N*′-dilithium perimidinones **263a**,**b** at the first step by treating **2** with one or two equivalents of n-butyllithium in dry THF (Scheme 76). Their subsequent reactions with acyl chlorides or anhydrides (0 – 15 °C, 15 min) lead to the desired *N*-acyl **265** or *N*,*N*′-diacylperimidinones **264** in 49% – 93% yields.[193] Monoacetylation of

Scheme 76



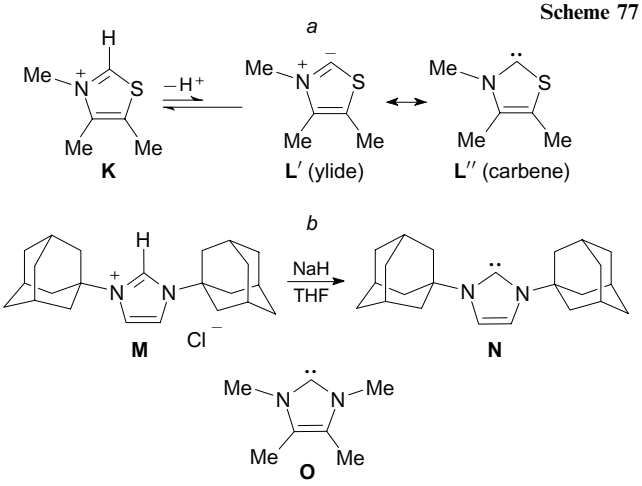
2 in 13% yield under alkaline conditions (acetone, KOH/K_2CO_3, AcCl) was also described.[18] Noteworthy is the strong difference in the melting points of 1-acetylperimidinone reported in Refs 18, 193 (177 – 179 °C and 273 – 274 °C, respectively), which requires additional research.

Comprehensive studies of the physicochemical characteristics of perimidinone, 1-methyl-perimidinone, 1,3-dimethylperimidinone and a number of related compounds, including XRD analysis, mass spectrometry, and ^1H and ^{13}C NMR spectroscopy have also been carried out.[18]

5.8. Perimidine-based carbenes: synthesis, properties, transition metal complexes and applications

N-Heterocyclic carbenes (NHCs) represent a large family of extremely important compounds with two-coordinated carbon atom. Breslow was the first to suggest the existence of NHCs. Back in 1957, he hypothesized that the mechanism of the action of thiamine enzymes responsible for acyloin condensation is due to the deprotonation of the C(2) – H bond in 1,3-thiazolium core **K**, leading to the formation of an intermediate, which can be drawn as a zwitterion ylide **L**′ or neutral carbene **L**″ (Scheme 77 *a*).[194] The subsequent numerous efforts to confirm this hypothesis led in the early 1990s to isolation of the first stable crystalline carbenes, such as **N** and **O**, from 1,3-disubstituted imidazolium salts, *e.g.*, **M** (Scheme 77 *b*).[195]

Scheme 77

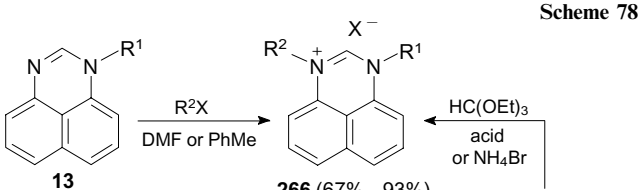


N-Heterocyclic carbenes are known to be strong σ-donor and weak π-acceptor ligands.[196 – 201] NHCs successfully compete with phosphine ligands due to compatibility with aerobic conditions, greater thermal stability and environmental friendliness. The (benz)imidazole-based carbenes are the most popular architectures of stable nucleophilic singlet carbenes, successfully used as ligands in transition metal-catalyzed reactions. However, it was demonstrated that changing heterocyclic ring size affects the donor strength and steric impact of the ligand. In particular, being a part of an electron-rich, π-extended heteroaromatic 6-membered ring, divalent carbon of the perimidine-based NHCs shows a stronger σ-donor ability. The perimidine structure favours the *N*-bound groups to be closer to the carbene atom, increasing the steric screening on both the carbene centre and a coordinated metal. These features should enable perimidine-based NHCs to provide steric protection and electronic activation to coordinately

unsaturated metal complexes that are key intermediates in catalytic transformations.

A general method for accessing perimidine-based NHCs is the deprotonation of appropriate 1,3-disubstituted perimidinium salts **266** (*cf.* Scheme 30**)**. The latter can be obtained *via* quaternization of 1-alkylperimidines **13** (Refs 202, 203) or heterocyclization of *N*,*N*′-disubstituted 1,8-diaminonaphthalenes **90** (Scheme 78).[204, 205] The following are two examples of the preparation of frequently used asymmetric perimidinium salts. *N*-Benzyl-*N*′-methyl perimidinium chloride was synthesized in a one-pot fashion by successive methylation (MeI, KOH) and benzylation (BnCl) of perimidine in EtOH under reflux.[206] In another case, perimidine was subjected by Cu-catalyzed *N*-phenylation and subsequent *N*-alkylation with methyl or isopropyl iodide.[206]

Scheme 78



13 **266** (67%–93%) **90** (65%–93%)

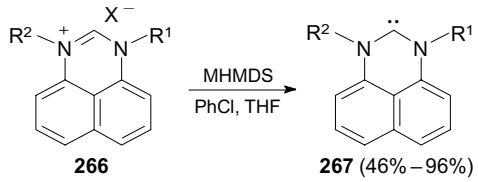
R^1, R^2 = Me, Bu^n, Bn, CH_2Mes, $(CH_2)_2OMe$, n-$C_{10}H_{21}$, CH_2TIPB;
TIPB = $C_6H_2Pr^i_3$-2,4,6;
Mes = $C_6H_2Me_3$-2,4,6;
X = Cl, Br, I

R^1, R^2 = Pr^i, *neo*-C_5H_{11}, cyclo-C_7H_{13}, Bn, $CH_2C_6H_4Me$-4, $C_6H_3Me_2$-3,5;
X = Cl, Br, OTs; Ts = $SO_2C_6H_4Me$-4

Free neutral carbenes **267** were accessed from salts **266** *via* smooth and rapid deprotonation with alkali metal hexamethyldisilazide (MHMDS) and were easily crystallized from diethyl ether or hexane (Scheme 79).[204, 205, 207] The use of $NaOBu^t$ base resulted in the addition of alkoxide to the C(2) atom of the starting compound.[204] Attempts to deprotonate of less sterically hindered 1-benzyl-3-isopropyl-, 1,3-bis(neopentyl)- and 1,3-diarylperimidinium salts led to enetetramines **268**.[205, 207]

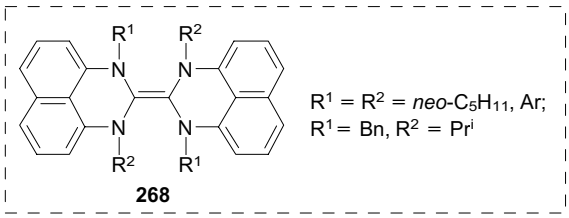
The *in situ* formation of the neutral perimidin-2-ylidene **267a** by deprotonation of salt **269** was proven by trapping

Scheme 79



266 **267** (46%–96%)

R^1 = R^2 = Pr^i, X = Cl; R^1 = Pr^i, cyclo-C_7H_{13}, R^2 = *neo*-C_5H_{11}, Bn, $CH_2C_6H_4Me$-4, X = OTs, Br; MHMDS = $MN(SiMe_3)_2$ (M = Li, Na, K)

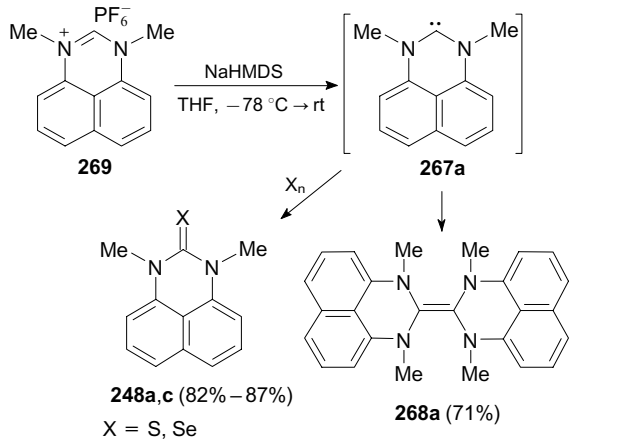


268

R^1 = R^2 = *neo*-C_5H_{11}, Ar;
R^1 = Bn, R^2 = Pr^i

experiments with elemental sulfur and selenium, which provided the corresponding thione **248a** and selenone **248c** in high yields (Scheme 80).[208] When the carbene **267a** was generated in the absence of any scavenger, the dimer **268a** was obtained.

Scheme 80

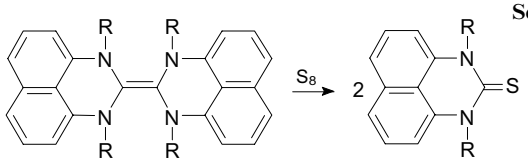


269 **267a** **248a**,**c** (82%–87%) **268a** (71%)

X = S, Se

No evidence of free carbene in the NMR spectra of **268a** up to 100 °C has been observed.[207] However, dimer **268b** reacted with sulfur to quantitatively furnish the corresponding perimidine-2-thione **248e** (Scheme 81).[207]

Scheme 81



268b **248e**

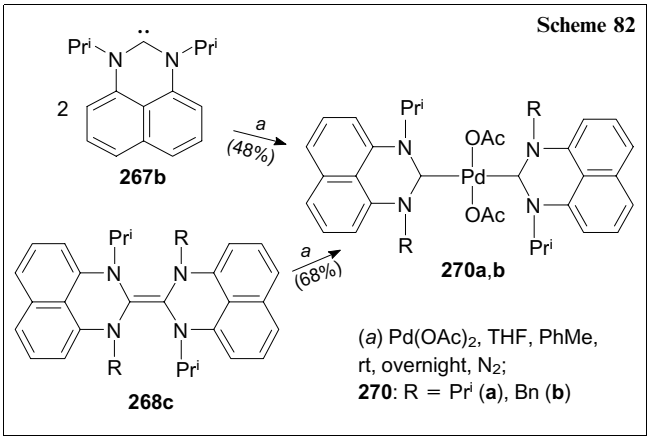
R = $C_6H_3Me_2$-3,5

The donor abilities of perimidine-based NHCs have been analyzed using the Tolman electronic parameter.[207–209] It was shown that the perimidine-based NHCs are stronger electron donors than PMe_3 and imidazole-based carbenes but weaker than the acyclic carbene $C(NPr^i_2)_2$. Fundamental characteristics of perimidin-2-ylidenes such as the crucial role of steric protection provided by the N-R substituents in prohibiting the thermodynamically favoured carbene dimerization and the weak π-acceptor nature of these ligands have been supported through structural and spectroscopic analyses.[205]

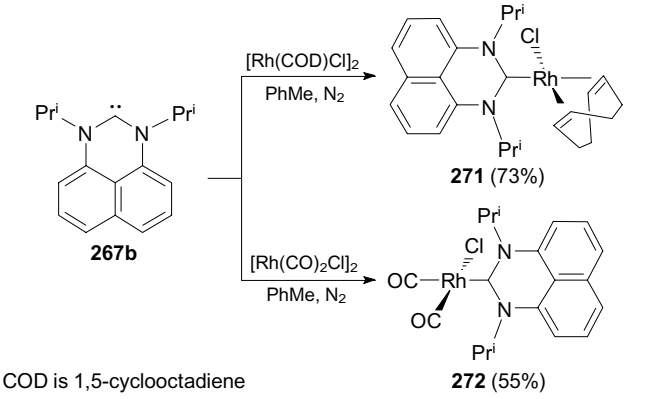
Direct reaction of two equivalents of carbene **267b** with $Pd(OAc)_2$ was used to obtain the bis(carbene) Pd^{II} species **270a** (Scheme 82).[205] Interaction of dimer **268c** with $Pd(OAc)_2$ gave similar complex **270b**. According to the X-ray data, the average $N-C_{carbene}$ bond length in **270a**,**b** is slightly shorter than that in free carbene species. This feature is consistent with the concept that the carbene does not participate in significant $Pd-C_{carbene}$ π-bonding. The two coordinated carbene ligands are coplanar, with their planes approximately perpendicular to the Pd pseudo-square planar coordination.

The ability of carbene **267b** to stabilize catalytically relevant metal complexes was also demonstrated by their reactions with Rh^I species yielding metal–carbene complexes **271** and **272** (Scheme 83).[207] Enetetramines **268** can

Scheme 82



Scheme 83



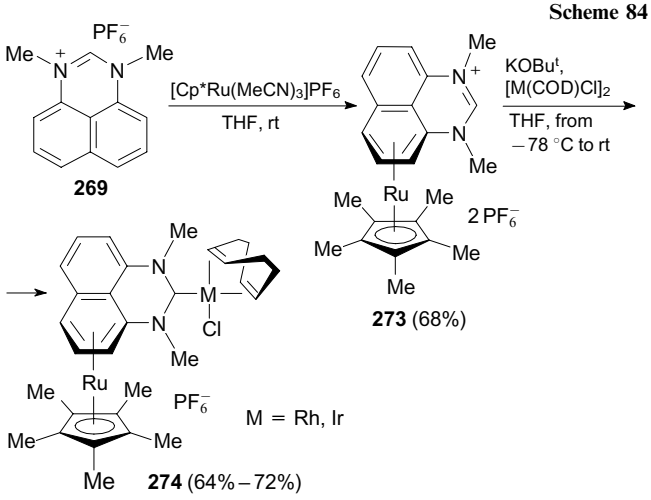
also be used as carbene synthons for the preparation of similar complexes. Compound **268b** (R = 3,5-Me$_2$C$_6$H$_3$) reacted with [Rh(CO)$_2$Cl]$_2$ in minutes at room temperature to yield the corresponding *N*,*N*′-diaryl analogue of complex **272**.[207] The structures of **271** and **272** have been determined by single-crystal X-ray diffraction analysis. Spectroscopic and crystallographic studies of these rhodium – carbene complexes revealed the sterically demanding nature of the carbene ligands, which is manifested in the observation of hindered Rh – C$_{carbene}$ bond rotation and through % V_{bur} measurements. *N*,*N*′-Dimethyl and *N*,*N*′-diethyl analogues of **271** and **272** have also been synthesized.[210]

Cationic bimetallic complexes **274** have been prepared starting from proligand **273** bearing Cp*Ru moiety (Scheme 84).[208]

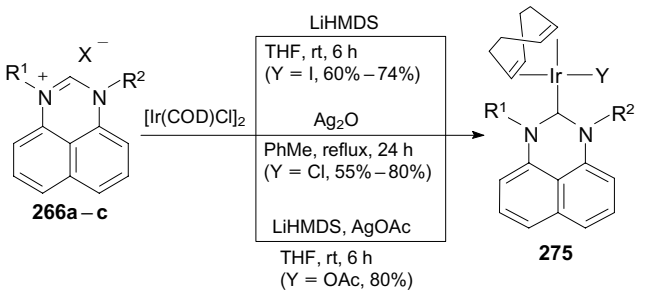
The reactions of perimidinium salts **266** with [Ir(COD)Cl]$_2$ in the presence of a base produced complexes **275** (Scheme 85).[206]

Ortho-C – H bond activation of the phenyl group attached to the perimidine nitrogen atom was observed when treating complex **275a** (R = Me) with **266a** (X = I), LiHMDS and a slight excess of AgOAc (Scheme 86).[206] Carboxylate complexes **275a** (R = Me, Ph) react with 2-phenylpyridine in refluxing toluene to give phenylpyridine-ligated Ir^{III}-complexes **278a**,**b** (see Scheme 86). On the basis of deuterium labelling experiments and the formation of 1,3-cyclooctadiene from the reaction mixture, a C – H bond of the phenyl group attached to the perimidine or pyridine ligand was activated by the carboxylate group bound to the iridium atom. Subsequent oxidative addition of the perimidine *N*-phenyl group was the key to producing complex **276**. It was also shown that the cyclometallated

Scheme 84

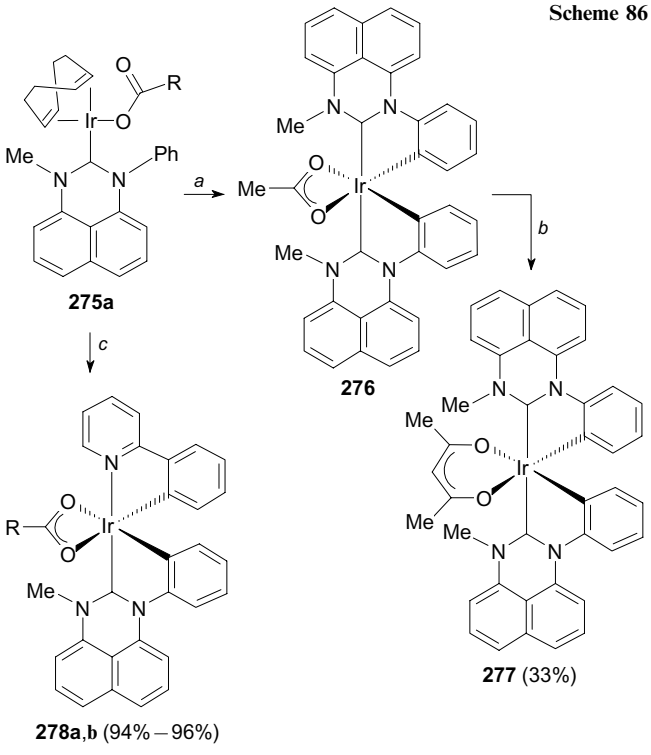


Scheme 85



R^1 = Me: R^2 = Ph (**a**) or Bn (**b**); R^1 = Pr^i, R^2 = Ph (**c**); X = I, Cl

Scheme 86

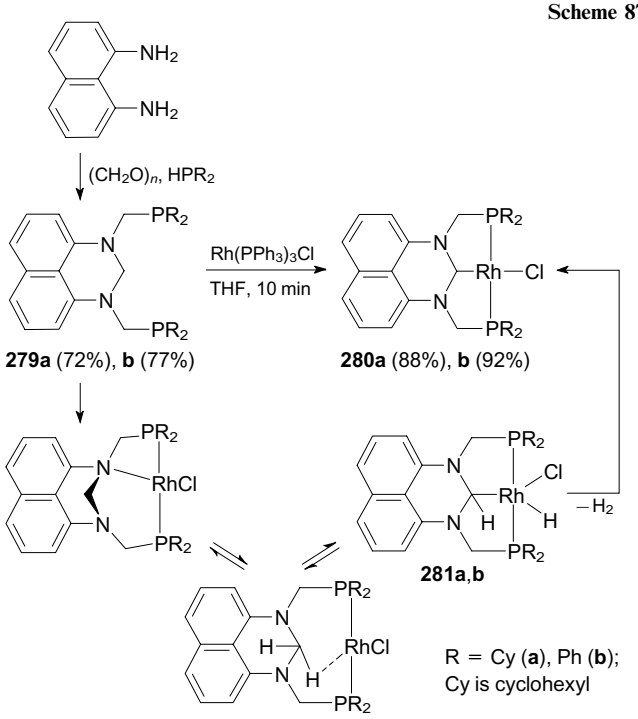


(*a*) **266a**, LiHMDS, AgOAc, PhMe, reflux, 24 h;
(*b*) MeC(O)CH$_2$C(O)Me, Na$_2$CO$_3$, PhMe, reflux, 6 h;
(*c*) 2-Ph-pyridine, PhMe, 120 °C, 24 h, argon; R = Me (**a**), Ph (**b**)

complex **276** reacts with sodium acetylacetonate to form the **277** species, which exhibits phosphorescent emission at $\lambda_{max} = 555$ nm ($\tau = 0.65$ μs, $\Phi_{PL} = 0.0018$) in CH_2Cl_2 solution at room temperature.

N-Heterocyclic pincer carbene Rh-complexes **280** have been generated *via* chelate-assisted double C – H activation of readily accessible substituted 2,3-dihydroperimidine proligands **279** with $[Rh(PPh_3)_2Cl]$ (Scheme 87).[211] Unlike complexes **271** and **272**, where NHC-ligand is an *axial* donor, the pincer systems **280** incorporate an NHC-ligand as an *equatorial* group. The facility of the reactions leading to **280**, without recourse to a sacrificial hydrogen acceptor, may be attributed to chelation assistance. A possible mechanism includes initial binding of the proligand *via* the phosphine group, encouraging adjacent amine centre to interact with the metal. The proximity of the CH_2 group to the metal centre might promote interaction with one of the C – H bonds, resulting in the oxidative addition to give Rh – H intermediate **281** (see Scheme 87). Subsequent loss of dihydrogen could then occur either *via* an addition/reductive elimination sequence or σ-metathesis pathway.

Scheme 87

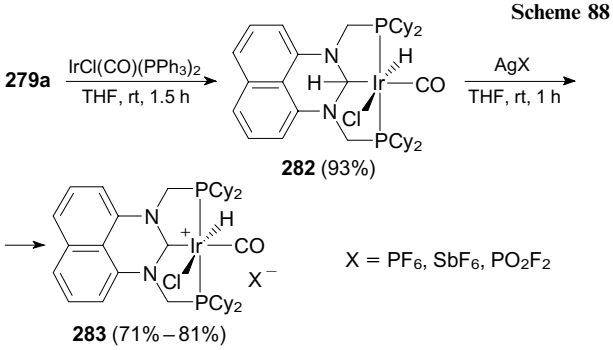


The reaction of **279a** with $[IrCl(CO)(PPh_3)_2]$ resulted in only single C – H activation to form an iridium hydride complex **282** (Scheme 88).[211] By treatment with various silver salts the latter can be transformed into the corresponding carbene-ligated salts **283** *via* hydride abstraction.

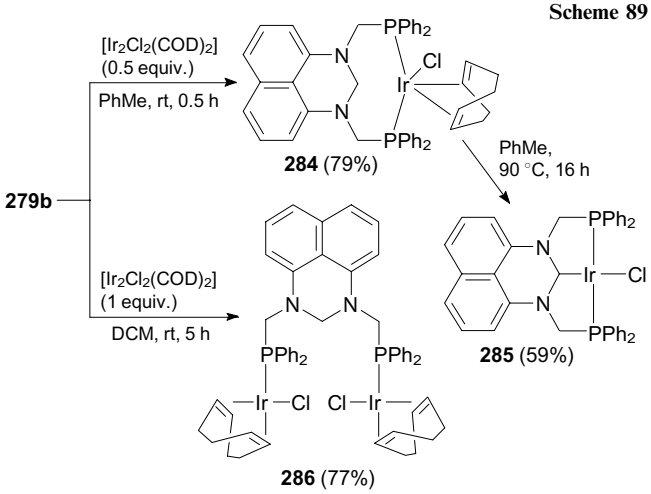
The reaction of proligand **279b** with $[Ir_2Cl_2(COD)_2]$, depending on the conditions and amount of the metal complex used, gave mono- **284** or bimetallic species **286** (Scheme 89).[212] Prolonged heating of the complex **284** in toluene led to its conversion into 4-coordinate Ir-complex **285** *via* double geminal C – H activation.

The possibility of obtaining such pincer carbenes *via* double C – H activation is attractive, not only in terms of atom economy, but from the perspective of microreversibility, *i.e.* that the reverse reaction, hydrogenation of the M=C double bond provides an intriguing possibility for

Scheme 88



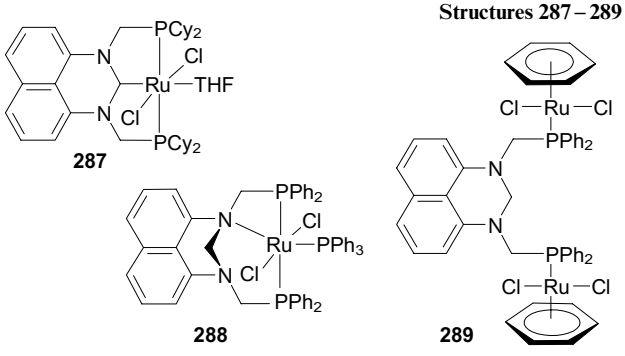
Scheme 89



small molecule activation. Given the propensity of perimidine-based carbene Ir-complexes to support an octahedral geometry and + 3(d^6) oxidation number, the reactivity of Ir^I-complex **285** towards oxidative addition of H_2 was investigated.[212] Bubbling H_2 into a solution of **285** in toluene returned this complex unchanged. However, the corresponding trihydrido Ir^{III}-complex was synthesized through reaction of **285** with an excess of $NaBH_4$ (MeOH, toluene, 3 days) in 77% yield.

Reaction of proligands **279a**,**b** with $[RuCl_2(PPh_3)_3]$ in THF for 48 h gave markedly different results. Compound **279a** formed carbene complex **287**, whereas P – Ph analogue **279b** yielded the asymmetric PNP ruthenium complex **288**.[213] Treating **279b** with $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ in MeOH at room temperature overnight afforded the homobimetallic complex **289**.[214] In the authors' opinion, the reduced reactivity of the proligand CH_2 group towards d^8 Ru^{II} centre, relative to those in the d^8 Rh^I and Ir^I systems, is due to the

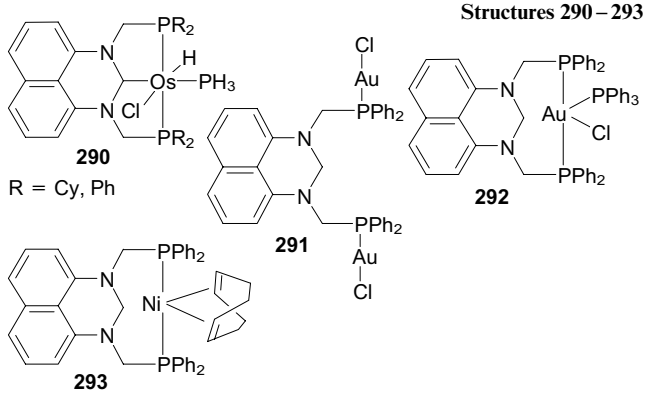
Structures 287 – 289



less electron rich metal centre. The notable difference in the reactivity of **279a** and **279b** may also be attributed to electronic factors, *e.g.*, the increased σ-basicity of the PCy_2 group facilitating C – H oxidative addition to form **287**. The solvent binding sites in these complexes were readily available for other substrates, particularly due to its location *trans* to the carbene, and were observed to react with carbon monoxide or mesityl isocyanide.

Reactions of **279a** and **279b** with $[OsCl_2(PPh_3)_3]$, producing the NHC-complex **290**, proceeded considerably faster (rt, 30 min) than the analogous reactions with ruthenium.[215] Furthermore, the double C – H activation was observed in both cases, reinforcing the observation that 5d-metals more readily enter the C – H activation process than do their 4d-counterparts (Os > Ru). In contrast, the reaction of proligand **279b** with [AuCl(THT)], where THT is tetrahydrothiophene, proceeded over 20 h at room temperature affording homobimetallic complex **291**. Treating **279b** with $[AuCl(PPh_3)]$ (MeOH, rt, 1 week) afforded complex **292**.[216] The Ni^0-complex **293** has been prepared by the interaction of **279b** with $[Ni(\eta^4\text{-COD})_2]$ in THF for 3 days.[216]

Structures 290 – 293

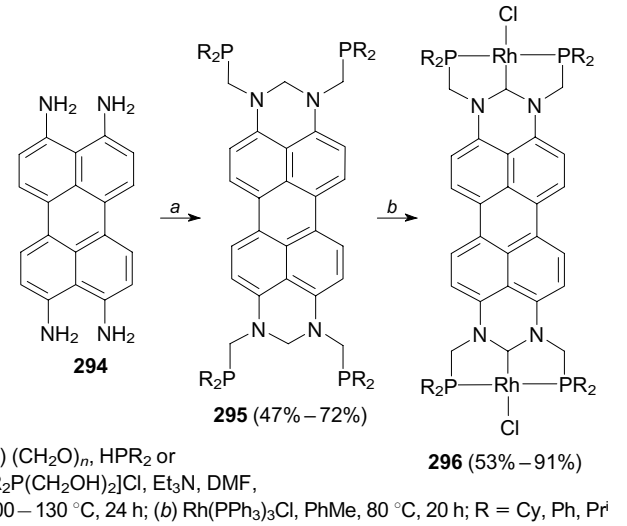


Gade and co-workers[217] have shown that the double C – H activation protocol may be extended to the highly auxochromic 3,4,9,10-tetraaminoperylene scaffold **294** allowing the synthesis of dinuclear rhodium bis(carbene) complex **296** either directly with the corresponding phosphine and paraformaldehyde or with the phosphonium salt and triethylamine base (Scheme 90). Reaction of **295** with $Rh(PPh_3)_3Cl$ led to a double geminal C – H activation and coordination of the ditopic PCP pincer to the rhodium centres, yielding the Rh(I) chloro complexes **296**. These were found to be suitable starting materials for further ligand exchange of the chloride (Scheme 91). The most characteristic feature in the absorption spectra of all compounds is the intense π→π* transition band of the perylene core. The fluorescence quantum yields of ligands **295** were found to be between 72% and 86%. Upon coordination to rhodium, the intraligand transition in the absorption spectra is only slightly shifted, whereas the fluorescence is almost completely quenched.

Not only perimidinium salts may serve as precursors for the synthesis of the perimidine-based carbene complexes. For example, Au-complex **297** was synthesized by reaction of 1,8-diaminonaphthalene with μ-(1,2-diisocyanobenzene)-bis(chlorogold) in THF (50 °C, 20 h).[218]

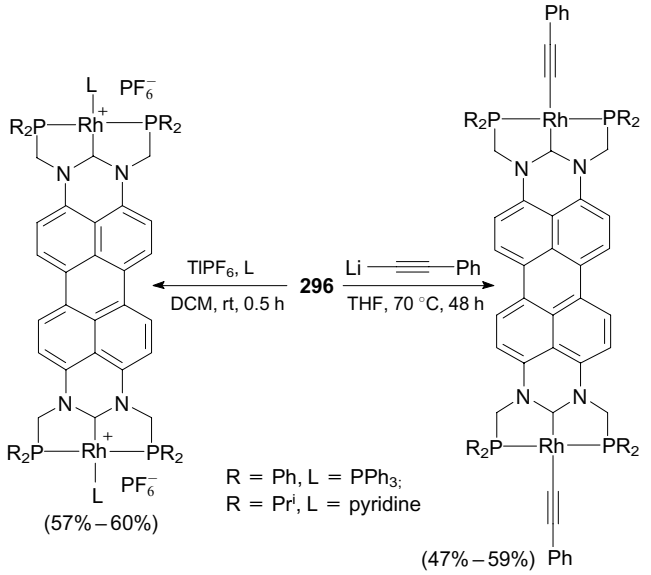
Although the nature of the NHC ligand in complexes has a tremendous influence on the rate of catalyzed reac-

Scheme 90

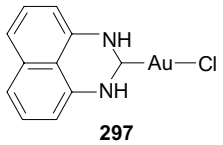


(*a*) $(CH_2O)_n$, HPR_2 or $[R_2P(CH_2OH)_2]Cl$, Et_3N, DMF, 100 – 130 °C, 24 h; (*b*) $Rh(PPh_3)_3Cl$, PhMe, 80 °C, 20 h; R = Cy, Ph, Pr^i

Scheme 91



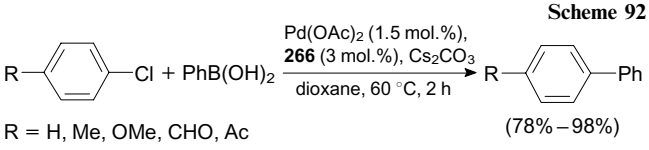
Structure 297



tions, the use of 1,3-dialkylperimidin-2-ylidene ligands in coupling reactions is a neglected area. It has been shown that *in situ* prepared three-component system $Pd(OAc)_2$ – 1,3-dialkylperimidinium salt **266** – Cs_2CO_3 catalyzes the Suzuki cross-coupling of even deactivated aryl chlorides with phenylboronic acids under mild conditions produces biaryls in excellent yields (Scheme 92).[219]

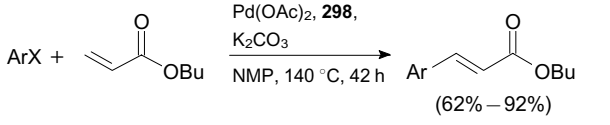
Easily accessible lutidine-bridged bis-perimidinium bromide **298** was found to be an efficient precatalyst in combination with $Pd(OAc)_2$ for Heck (Scheme 93) and Suzuki coupling reactions under aerobic conditions.[220] The protocols are characterized by good yields even with very low catalyst loading and are compatible with a wide choice

Scheme 92



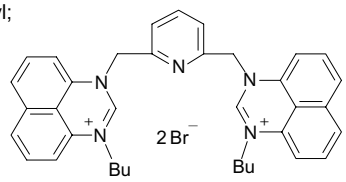
R = H, Me, OMe, CHO, Ac

Scheme 93



Ar = Ph, C_6H_4Me-2, C_6H_4Me-3, C_6H_4Me-4, C_6H_4OMe-4, C_6H_4Ac-4, $C_6H_4CF_3$-2, $C_6H_4CF_3$-4, $C_6H_3Me_2$-3,5, 1-Naph; X = Br, I;
Naph is naphthyl;

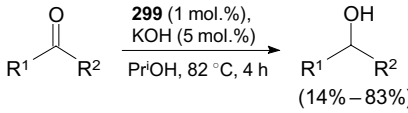
298 =



of functional groups. The use of perimidine-based catalysts gave better results compared to imidazole and benzimidazole analogues.

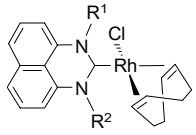
Complexes of the types [(NHC)Rh(COD)Cl] **299** and [(NHC)Rh$(CO)_2$Cl], where NHC is perimidine-based carbenes, have been prepared by the reactions of [Rh(μ-OMe)(COD)]$_2$ with perimidinium bromides **266** in boiling 1,2-dichloroethane.[203] They were tested as catalysts for transfer hydrogenation reaction of aliphatic and aromatic ketones (Scheme 94). The complex with Pr^i and 2,4,6-triisopropylbenzyl (CH_2TIPB) groups attached to the nitrogen atoms of perimidine scaffold showed the highest catalytic activity. When compared with the other [(NHC)Rh(COD)X] catalysts having imidazol-2-ylidene or benzimidazol-2-ylidene ligand, perimidine-based analogues were found to be less active. The ruthenium complexes **288** and **289** have been shown to be suitable catalysts for this reaction.[214]

Scheme 94



R^1 = Me: R^2 = n-C_5H_{11}, Ph, C_6H_4Cl-2, C_6H_4Br-4;
R^1 = Et, R^2 = Ph, $R^1–R^2$ = $(CH_2)_5$;

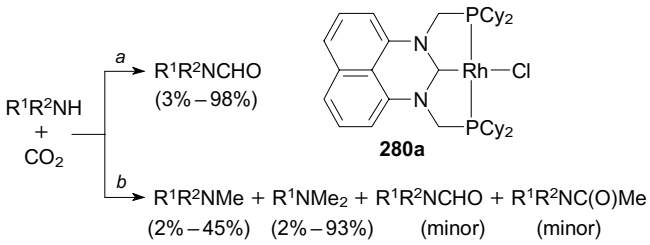
299 =



(R^1, R^2 = Pr^i, CH_2Mes, CH_2CH_2OMe, CH_2TIPB)

The Rh^I-complex **280a** was found to be an active catalyst for the *N*-formylation and *N*-methylation of a wide range of primary and secondary aromatic and aliphatic amines using CO_2 as the carbon source and phenylsilane as the reducing agent (Scheme 95).[221] Selectivity between the formylation and methylation reactions was achieved by varying the solvent, temperature and the quantity of hydrosilane added.

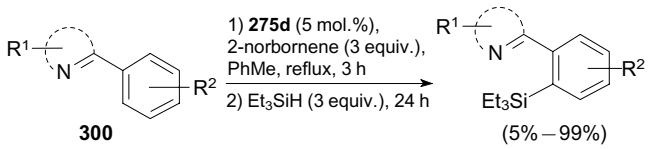
Scheme 95

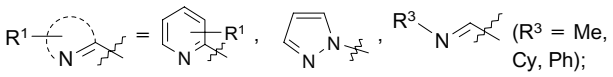


(a) $PhSiH_3$ (1 equiv.), **280a** (5 mol.%), THF, 50 °C, 16 h;
(b) $PhSiH_3$ (4 equiv.), **280a** (5 mol.%), PhMe, 90 °C, 16 h;
R^1R^2NH = 4-X-$C_6H_4NH_2$, $AlkNH_2$, $BnNH_2$, Ph_2NH, PhMeNH, $PhC(O)NH_2$, *etc*.

The C–H activation–dehydrogenative silylation of pyridyl and iminyl substrates **300** with triethylsilane was achieved using perimidine-based Ir^I-complex **275d** as a catalyst in the presence of 2-norbornene as a hydrogen scavenger (Scheme 96).[222]

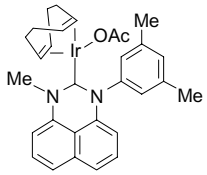
Scheme 96





R^1 = H, 6-Me, 4-Me; R^2 = H, Me, OMe, CF_3;

275d =



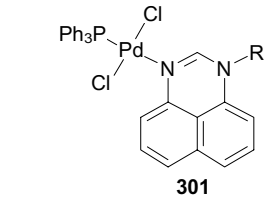
The NHC–Rh^I-complexes, including perimidine-based ones, were tested as prospective antitumour drug candidates. Pronounced antiproliferative effects were noted for all complexes, along with moderate inhibitory activity of thioredoxin reductase and efficient binding to biomolecules (DNA, albumin). Unfortunately, insufficient solubility of perimidine-based Rh^I-complexes in aqueous environment limits their biological application.[210]

5.9. Other metal complexes of perimidines

Complexes of the type [$PdCl_2(PPh_3)$L], where L is 1-alkylperimidine, have been prepared by heating of [$PdCl_2(PPh_3)_2$] with 1-alkylperimidines in toluene. These *N*-coordinated perimidine complexes **301** demostrated high catalytic activity in the Suzuki reaction.[202] Mononuclear Pd^{II} complexes with bidentate *trans*-chelating pyrazole ligands **302** have been shown to be an active precatalyst for the Heck coupling of aryl halides and *tert*-butyl acrylate in the presence of Et_3N in MeOH under mild conditions (70 °C).[223]

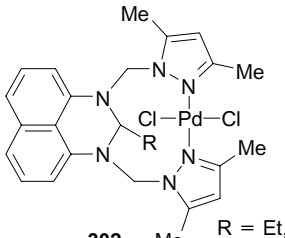
2-(2-Methyl-2,3-dihydro-1*H*-perimidin-2-yl)benzene-1,3-diol **303** has been used as a ligand in the Ru-catalyzed transfer hydrogenation of ketones (Scheme 97).[224]

Structures 301, 302



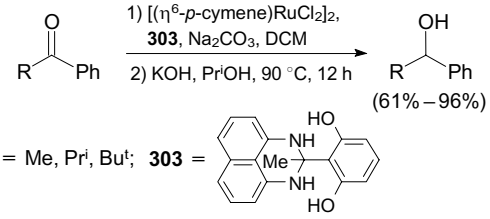
301

R = $(CH_2)_2OMe$, Bn, $(CH_2)_2Ph$



302 R = Et, Ph, Bn

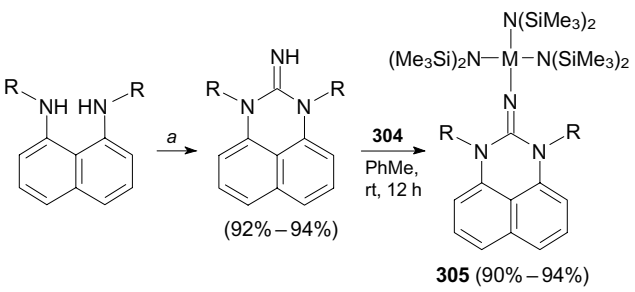
Scheme 97



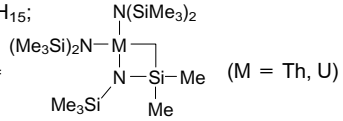
A novel class of complexes **305** possessing a perimidin-2-iminato moiety was introduced in 2017 by Eisen group (Scheme 98).[225] The complexation of the 2-iminoperimidine ligands with early actinides (Th, U) resulted in potent catalysts **305** for insertion of alcohols (primary, secondary, tertiary, aromatic) into carbodiimides to produce the corresponding isoureas in short reaction times in excellent yields (Scheme 99). It should be noted that similar actinide complexes possessing imidazolin-2-iminato ligand did not catalyze this transformation.

Synthesis of the thorium perimidin-2-iminato complex **306** was accomplished by a one-pot reaction between the $Cp^*_2Th(CH_3)_2$ and 1,3-diisopropyl-1*H*-perimidin-2(3*H*)-imine in toluene at room temperature.[226] Complex **306** was utilized as a precatalyst for the dimerization of aldehydes

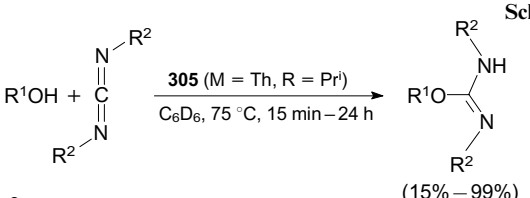
Scheme 98



(*a*) 1) BrCN, PhMe, 110 °C, 12 h; 2) KOH (aq.), Et_2O, rt, 30 min;
R = Pri, cyclo-C_7H_{15};

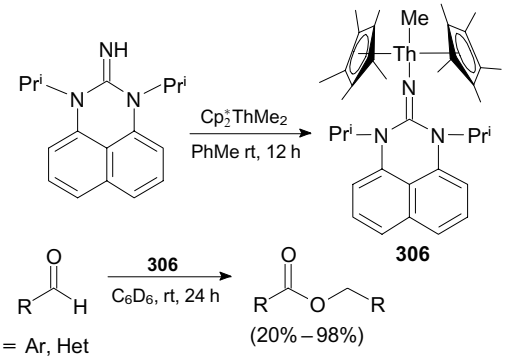
304 =  (M = Th, U)

Scheme 99



R^1, R^2 = Alk, Ar

Scheme 100

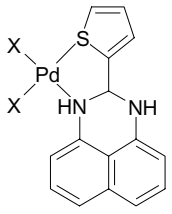


R = Ar, Het

(the Tishchenko reaction) to give the corresponding esters in high yields and at room temperature (Scheme 100).

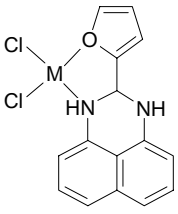
A series of mononuclear complexes **307** – **310** were synthesized by the reaction of hetarene-2-carbaldehydes with 1,8-diaminonaphthalene followed by treatment with metal salts.[227,228] The perimidine ligands and their complexes showed potential antioxidant and antimicrobial activities. Pd^{II}-Complexes **307** possess more significant antimicrobial activity than 2-(2-thienyl)-2,3-dihydro-1*H*-perimidine itself. The Re^{I}-complexes **309** have been tested as DNA intercalators.[229]

Structures 307 – 310



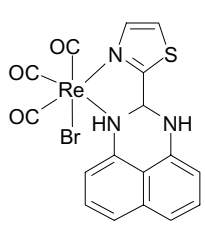
307

X = Cl, OAc

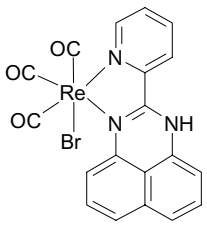


308

M = Co, Ni, Cu, Zn



309



310

6. Synthesis of perimidines and 2,3-dihydroperimidines *via* cyclization reactions

Most synthetic methods to obtain perimidines are based on the reaction of DANs with carbonyl compounds. The use of carboxylic acids and their derivatives directly affords the corresponding perimidines, while cyclization with aldehydes and ketones normally gives rise to DHPs. The latter can be converted into perimidines by dehydrogenation. A complete survey of data on syntheses of perimidines developed before 1980 is summarized in a review [6]. Here we discuss only key points of these methods. In fact, over the past 40 years, very few breakthrough methods for the synthesis of perimidines have appeared. Most investigations of this period were aimed on improving the already existing methods or obtaining perimidine derivatives with specific properties.

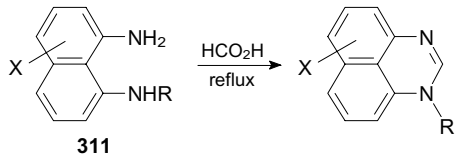
6.1. Synthesis of perimidines from 1,8-diaminonaphthalenes

6.1.1. Carboxylic acids as cyclizing agents

Of all carboxylic acids, formic acid, which acts both as a cyclizing agent and a solvent, reacts smoothly with DAN and its derivatives **311**. The protocol usually consists of short reflux and results in the formation of the corresponding perimidines in high yields (Scheme 101). In the case of aromatic acids, yields are greatly reduced and the process is accompanied by tarring.[230] The synthesis of 2-substituted perimidine using higher homologues of formic acid proceeds in low yields, however the reaction becomes more efficient at fusion of the reactants[231] or at using 4 N hydrochloric acid as a catalyst.[230,232] For example, the yields of 2-hydroxymethyl- and 2-(α-hydroxybenzyl)perimidines, prepared by condensation of DAN with glycolic and mandelic acid in an acidic medium, are 72% and 42%, respectively. α- and β-Amino acids do not react with DAN, but γ-aminobutyric and piperidine-4-carboxylic acids give the corresponding perimidines in less than 5% yields.[230] A more complete summary of the previous data on these reactions can be found in the Supplementary Materials (see Table S3, https://doi.org/10.1070/RCR4963).

With the exception of malonic and oxalic acids, dicarboxylic α,ω-aliphatic acids react with DAN to form ω-(perimidin-2-yl)alkane-carboxylic acids. Oxalic acid affords a mixture of perimidine **1** and 2,2′-bisperimidine **95** (R = H).[5,232] Reaction with malonic acid leads to a mixture of 2-methylperimidine **57a** and perimidinone **2**.[233]

Scheme 101



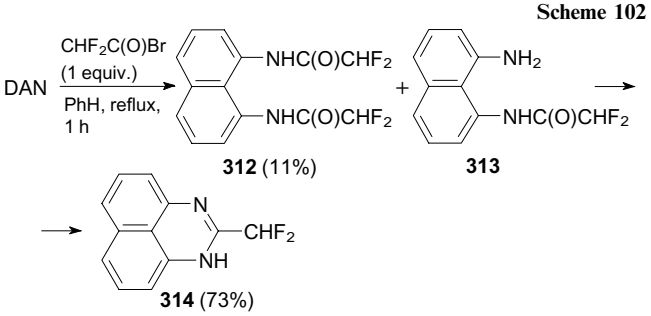
311

R = H, Alk, Ar; X = Hal, OH, SO_3H, NO_2, PhN=N, *etc.*

6.1.2. Acyl halides

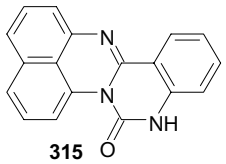
Unlike carboxylic acids, acyl halides are almost universal cyclizing agents, which allow placing an aliphatic, aromatic or heterocyclic substituent into position 2 of the perimidine system in good yields. The reaction is carried out by heating DAN and acyl chloride in a neutral medium (usually in benzene). The only drawback of this method is the formation of 5% – 10% of *N*,*N*′-diacyl derivative (*e.g.*, **312**) of DAN as a by-product. This compound, however, is easy to separate due to its poor solubility. The direct precursor of 2-R-perimidine is monoamide **313**, which undergoes rapid heterocyclization. A typical example of the reaction is shown in Scheme 102.[42]

Scheme 102



312 (11%) **313** **314** (73%)

Structure 315



315

The method is also suitable for the synthesis of 1,2-disubstituted perimidines[42,234] and also 1,4-bis(perimidin-2-yl)benzene and 1,5-bis(perimidin-2-yl)naphthalene,[46] although *N*-(2,4-dinitrophenyl)-DAN is not converted into the corresponding perimidines on treatment with acyl halides.[228] The reaction of DAN with oxalyl chloride yields 2,2′-bisperimidine **95** (R = H).[33] Cyclization of DAN with 2-isocyanobenzoyl chloride gives quinazolino[3,4-*a*]perimidin-6(5*H*)-one **315** as a result of secondary addition of the perimidine NH group to the isocyanate functionality.[235]

Along with acyl chlorides, examples of successful use for the DAN cyclization of acyl bromides and acyl fluorides are known.[159]

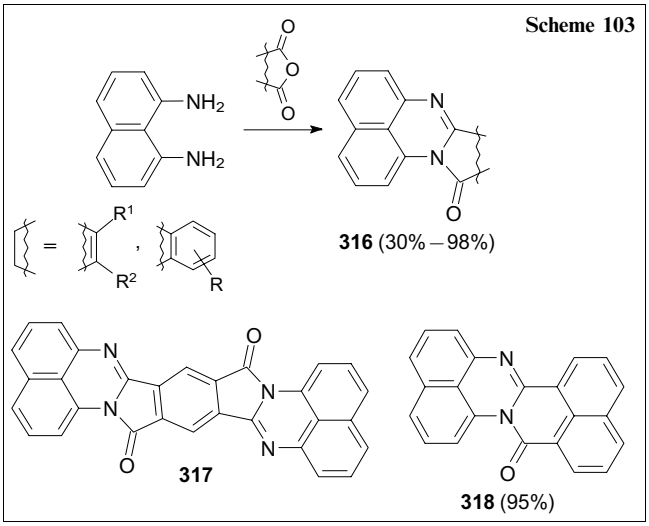
Mechanism of the cyclization of 8-amino-1-[(trifluoroacetyl)amino]naphthalene into **156** has been thoroughly studied by Hibbert and co-workers.[236 – 238]

6.1.3. Acid anhydrides

Commonly, acid anhydrides, if available, are superior to other reagents for introduction of alkyl or aryl substituents into position 2 of the perimidine system. Thus, heating DAN with acetic[230,239] and trifluoroacetic anhydrides[234] leads to the formation of 2-methyl and 2-trifluoromethyl perimidines, respectively, in excellent yields. Other 2-alkyl, 2-aryl as well as 1,2-disubstituted perimidines and aceperimidines can be obtained similarly from DAN or its mono-NR-substituted derivatives.[5,98,99,156,229,240] Interestingly, 8-amino-1-(dimethylamino)naphthalene is also converted into 1,2-dimethyl-1*H*-perimidine under reflux with Ac_2O. The reaction is accompanied with a loss of the *N*-methyl group; at room temperature the process stops at the mono-*N*-acylation stage.[227]

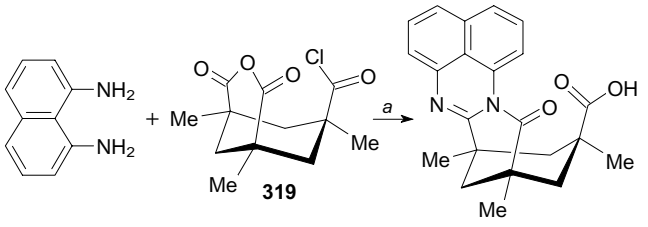
In the case of cyclic anhydrides (succinic, maleic, phthalic, naphthalic and their derivatives), the so-called perinones **316** are formed as a result of the tandem cyclization (Scheme 103).[5,80,241 – 244] Heating DAN with pyromellitic dianhydride or naphthalic anhydride gives rise to perinones **317** and **318**, respectively.[243,245] Noteworthy,

Scheme 103



316 (30% – 98%) **317** **318** (95%)

Scheme 104



(*a*) Et_3N, PhMe, reflux

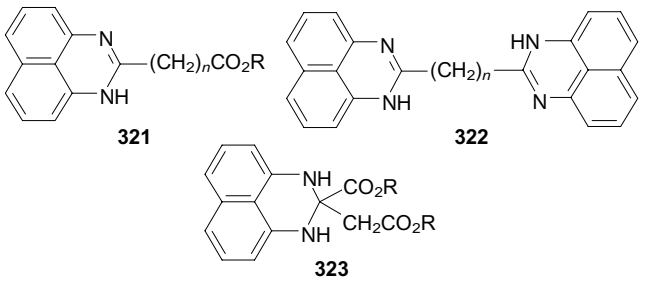
320 (60%)

when the cyclizing reagent involves both cyclic anhydride and acyl chloride functionalities, the former can be more active (see conversion **319** → **320** in Scheme 104).[246] Nanographene-based perinones have been recently obtained by the reaction of *edge*-oxidized nanographene with 1,8-naphthalenediamine derivatives[247] (see Section 10.1).

6.1.4. Esters and iminoesters

Perimidines can be readily obtained by treating DAN with carboxylic acid esters. As far back as 1909, Sachs[5] found that diethyl carbonate reacts with DAN to form 2-ethoxyperimidine in nearly quantitative yield. Reaction of DAN with diethyl oxalate and ethyl oxamate gave 2-(ethoxycarbonyl)- and 2-(amidocarbonyl)-perimidines, respectively.[5] 2-(Cyanomethyl)perimidine was synthesized from DAN using isobutyl cyanoacetate as a cyclizing agent. The use of equimolar amount of dicarboxylic acid diesters provides compounds **321**, while the same reaction with a 2-fold excess of DAN yields α,ω-bis(perimidinyl-2)alkanes **322**.[231] The interaction of DAN with dialkyl acetylenedicarboxylates proceeds as the Michael addition furnishing 2,3-dihydroperimidines **323**.[248, 249]

Structures 321 – 323



The reaction of DAN with acetoacetic ester is of special interest. Refluxing the reactants without solvent leads to the formation of 2-acetonylperimidine, while at room temperature the keto group of diethyl acetoacetate is involved in cyclization yielding 2-methyl-2-(ethoxycarbonylmethyl)-2,3-dihydroperimidine.[5, 230] On heating, the latter loses an ethyl acetate molecule to give 2-methylperimidine.

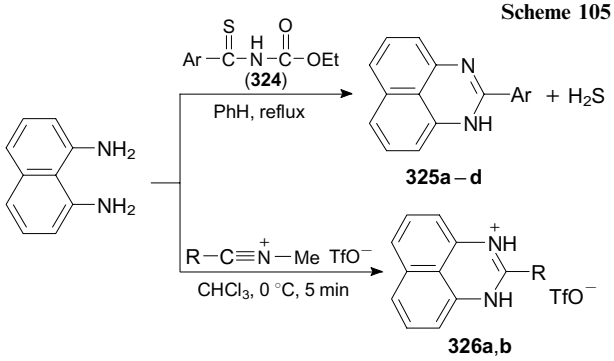
Perimidines bearing CH_2CO_2Et, $CH(OEt)_2$, $CH{=}N{-}OH$, CH_2CH_2NHR', 2-pyridyl or 4-pyridyl substituent in position 2, were synthesized using the iminoesters of the corresponding carboxylic acids as cyclizing agents.[66, 250]

The reactions of DAN with trialkyl orthoformates producing perimidine were also reported.[251, 252]

6.1.5. Carboxamides, thioamides and nitriles

As a rule, carboxamides, due to their low acylation ability, are inactive in cyclization of DAN into perimidines. A rare exception is the cyclization of DAN with caprolactam under acidic conditions yielding 2-(ω-aminopentyl)perimidine.[253] A claim that the above-mentioned reaction of DAN with ethyl oxamate produces the 2-(ethoxycarbonyl)perimidine as a second product was not supported by an accurate examination of the experimental data.[230] The *N*-ethoxycarbonyl thioamides **324** represent an interesting example of a dual reactivity.[254] Although on treatment with this reagent most of bifunctional nucleophiles cyclize normally on the ethoxycarbonyl group, DAN reacts with its thioamide group forming 2-arylperimidines **325a – d** in high yields (Scheme 105).

Scheme 105

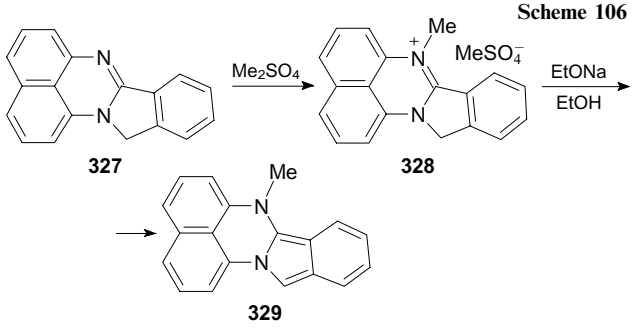


325: Ar = Ph (**a**, 95%), $C_6H_4Pr^i$-4 (**b**, 72%), C_6H_4OMe-4 (**c**, 86%), 2-Th (**d**, 88%); **326**: R = Me (**a**, 58%), Ph (**b**, 72%)

At high temperature the dihydrochloride of DAN reacts with acetonitrile and butyronitrile affording 2-methyl- and 2-n-propylperimidines, respectively.[255] In contrast, reaction of DAN with *N*-methylnitrilium salts rapidly proceeds even at 0 °C yielding salts **326a**,**b**.[256]

The reaction of DAN with *ortho*-chloromethyl benzonitrile seems to start from *N*-alkylation followed by double intramolecular nucleophilic addition of both amine nitrogen atoms to the C≡N bond with the final formation of 12*H*-isoindolo[2,1-*a*]perimidine **327**.[257] Interestingly, the quaternization of **327** with the following deprotonation of salt **328** produce yellow-coloured and formally aromatic 22π-electronic system **329**, which, however, manifests low stability (Scheme 106). The reaction of DAN with acrylonitrile derivatives was also reported.[258]

Scheme 106



6.1.6. Amidines

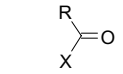
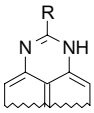
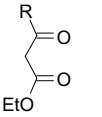
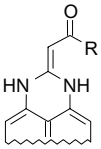
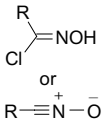
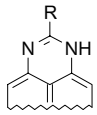
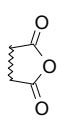
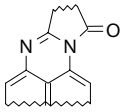
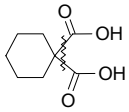
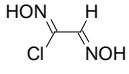
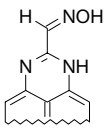
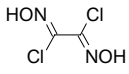
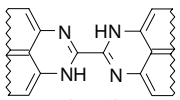
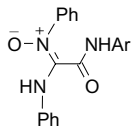
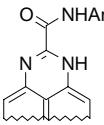
Perimidine **1** can be prepared by reaction of DAN with formamidine [37] or *N*,*N*-diphenylformamidine.[226] Perimidine is also formed by heating DAN with *s*-triazines as masked amidines.[259–261]

An additional survey of recent data on the use of carboxylic acids and their synthetic equivalents for the synthesis of perimidines is given in Table 4.

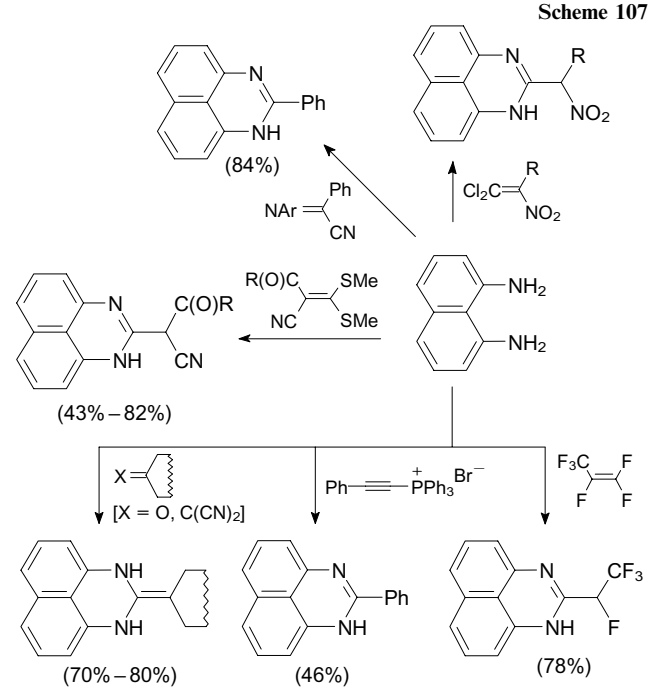
6.1.7. Unsaturated activated compounds

It is also possible to perform the cyclization of DAN into perimidines using unsaturated activated compounds, such as cyanobenzylideneanilines,[270] nitroolefins,[179] quinone derivatives,[271,272] 7,7′,8,8′-tetracyanoquinodimethane,[273] 2-dicyanomethyleneindane-1,3-dione,[273] 2-(2,4,7-trinitro-9*H*-fluoren-9-ylidene)propane-dicarbonitrile,[273] 1-acyl-1-cyano-2,2-dimethyl-mercaptoethylenes,[274] hexafluoropropene,[275] ethynylphosphonium salts.[276] Some of these transformations are presented in Scheme 107.

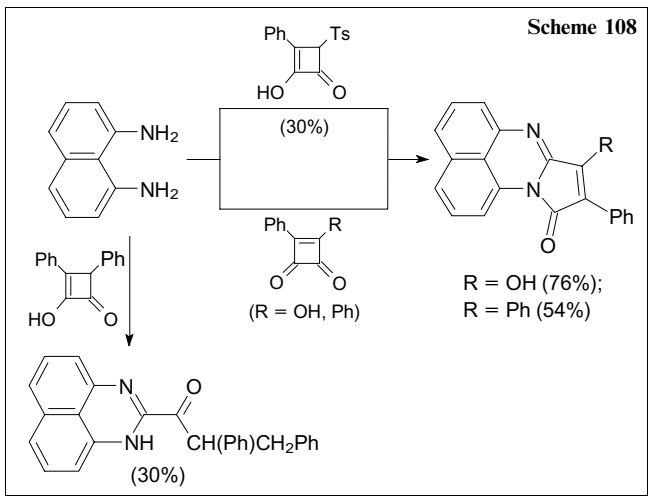
Table 4. Carboxylic acids and their synthetic equivalents as cyclizing agents for the conversion of DANs into perimidines.

Carbonyl compounds	Conditions	Product (yield)	Ref.
 R = CH_2OH, X = OH; R = CO_2Et, X = Cl; R = CH_2CN, X = NH_2	120–200 °C or Et_3N, DCM, −5 °C → rt	 (48%–59%)	262
 R = Ph, OEt	K_2CO_3, MW or reflux	 R = Ph (90%)	263, 264, 265
 R = Ph, 9-anthryl, β-D-glucopyranosyl, *etc.*	EtOH, reflux	 (30%–68%)	266
 phthalic tetrahydrophthalic hexahydrophthalic succinic maleic citraconic	DMF, Ac_2O, pyridine, rt or MW, 180 °C	 (62%–90%)	267, 268
			
	Abs. EtOH, rt	 (47%)	192
	Abs. EtOH, $NaHCO_3$, rt	 (43%)	192
	MeCN, TsOH, reflux	 (45%–74%)	269

Scheme 107



Scheme 108



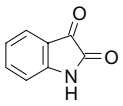
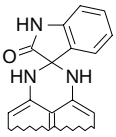
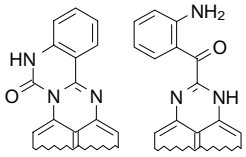
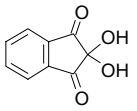
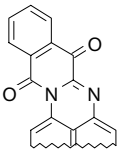
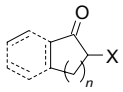
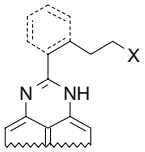
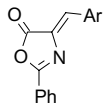
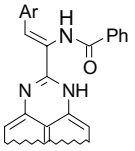
6.1.8. Cyclic carbonyl compounds

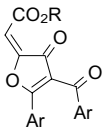
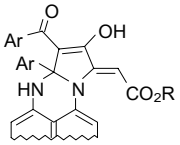
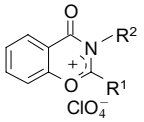
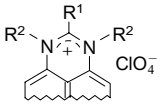
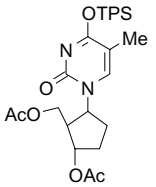
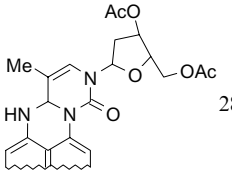
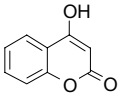
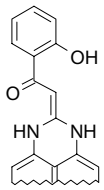
In some cases, reactions of DAN with cyclic carbonyl compounds, *e.g.*, cyclobutenones or cyclobutene-1,2-diones, are accompanied with recyclizations leading to the formation of 2-R-perimidines or fused compounds across the N(1)–C(2) bond of perimidines (Scheme 108).[241,242,277] Some additional examples are depicted in Table 5.

6.2. 2-Aminoperimidines, perimidin-2(3*H*)-ones and perimidine-2(3*H*)-thiones

2-Aminoperimidine can be prepared by reaction of DAN with cyanic bromide [284,285] or cyanamide.[286] When DAN is fused with ammonium thiocyanate [5] or thiourea,[90] 2-aminoperimidine is formed together with perimidine-2-thione. 2-Arylamino [5,287] and 2-dimethylaminoperimidines [288] were synthesized *via* cyclization of DAN with aryl isothiocya-

Table 5. Some examples of cyclizations of DAN with cyclic carbonyl compounds.

Carbonyl compounds	Conditions	Product	Ref.
	AcOH, TsOH, reflux	 (45%)	74
		 (9%) (6%)	
	MeOH, TsOH, rt	 (23%)	74
 n = 1, 2; X = CO_2Et, CN, SO_2Ar	$YbCl_3$, EtOH, reflux	 (34% – 98%)	278
	AcOH, MW, 120 °C	 (77% – 90%)	279

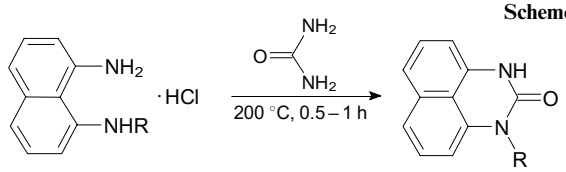
Carbonyl compounds	Conditions	Product	Ref.
	MeOH, reflux	 (72% – 79%)	280
 R^1 = Me, Et, Ph, C_6H_4OH-2, CH=CHPh; R^2 = H, Me	80 °C	 (56% – 77%)	281
 TPS is (triisopropylphenyl)sulfonyl	THF, reflux	 (63% – 78%)	282
	EtOH, reflux	 (89%)	283

nates and dimethyl(trichloromethyl)amine, respectively. Reaction of DAN with *S*-methyl isothiourea and chlorocarbonic esters affords perimidine-2-carbamates.[289]

Reaction of DAN with carbon disulfide [5, 290, 291] or with potassium xanthate [5] produces perimidine-2-thione.

Potassium cyanate, carbonic or chlorocarbonic esters,[5] phosgene [5, 228] and urea [103, 105, 116] were used as cyclizing agents for the perimidinone synthesis (Scheme 109). Perimidinone was also prepared by carbonylation of DAN with carbon monoxide in the presence of selenium and oxygen.[292]

Scheme 109



R = H (**2**, 100%), Ph (**81g**,84%)

2, **81g**

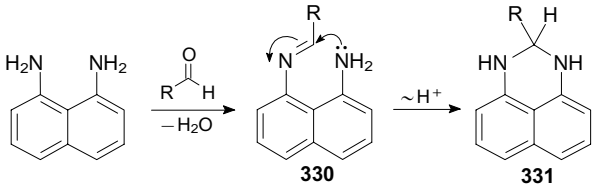
6.3. Synthesis of 2,3-dihydroperimidines from 1,8-diaminonaphthalenes

2,3-Dihydroperimidines are valuable compounds not only on their own, but also as a starting material for obtaining perimidines (Section 7) and proton sponges (Section 9). We have already discussed the synthesis of DHPs by reduction of 1-R-perimidines, perimidinones, 1,3-disubstituted perimidinium salts, or *via* addition of organometallic reagents to the latter (see Sections 4.1 and 5.7). The preparation of DHPs by the interaction of DAN with aldehydes and ketones is a more general and widely used method.

6.3.1. Aldehydes as cyclizing agents

DAN reacts with virtually any aliphatic, aromatic and heteroaromatic aldehyde, including monosaccharides.[220, 227, 293 – 306] The reaction usually proceeds in a short time and under mild conditions, giving the corresponding DHPs **331** in yields close to quantitative (Scheme 110). The ease of the process can be explained by the proximity effect

Scheme 110



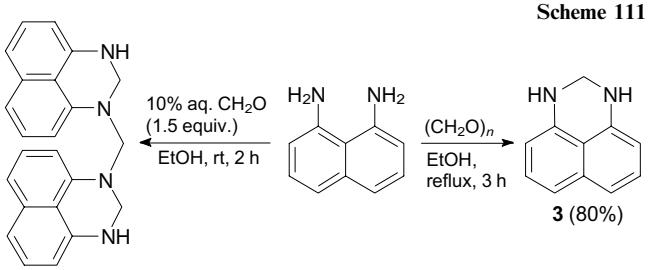
330 **331**

of the nucleophilic and electrophilic centres in the intermediate azomethine **330**, which almost instantly undergo cyclization. This is supported by the fact that there is still no information on the isolation of azomethines **330** (there are very few reports on the isolation of some azomethines upon the ractions of DAN with quinones and ketones, see Section 6.3.2).

An extensive summary of DHPs obtained according to Scheme 110 is given in the Supplementary Materials (see Table S5, https://doi.org/10.1070/RCR4963). Its analysis leads to the following conclusions: 1) aromatic aldehydes generally react somewhat more easily than aliphatic ones; 2) cyclizations with aldehydes containing electron-donating groups slow down; 3) sterically hindered aldehydes, for example, 2-fluoro-6-chlorobenzaldehyde, give a slightly lower yield. A traditional solvent for the cyclization is an alcoholic medium, but good results were also obtained using benzene as solvent. Recently, Harry *et al.*[307] have proposed solvent-free cyclization by simply grinding the reagents in a mortar. In this case, the reaction time is reduced to 5 minutes at room temperature without yield decreasing.

Some complications were observed when preparing the parent DHP **3**.[308] It was shown that the interaction of DAN with one equivalent of aqueous 10% formaldehyde gives a mixture of commensurate amounts of **3** and bis(2,3-dihydro-1*H*-perimidin-1-yl)methane **332**. Compound **3** was obtained in the individual state by boiling DAN with paraformaldehyde in ethanol, whereas **332** was synthesized using a 1.5-fold excess of aqueous formaldehyde (Scheme 111).

Scheme 111



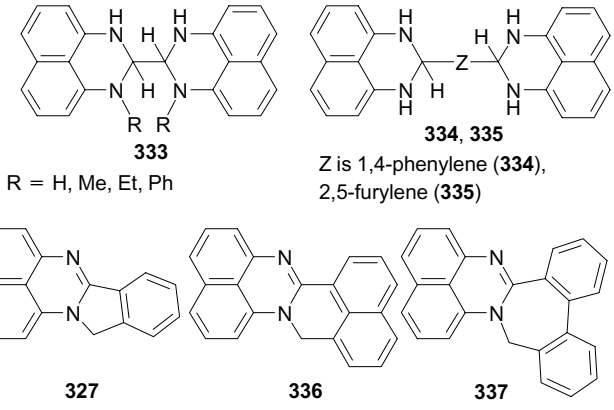
332 (60%) **3** (80%)

N-Substituted and *N*,*N*′-disubstituted DANs are also able to undergo similar cyclizations, though the former with some difficulty.[227, 300, 308] Dialdehydes behave differently in cyclizations with DAN. Glyoxal,[111, 308] benzene-1,4-dialdehyde and furan-2,5-dialdehyde[300] give the expected DHPs **333** – **335**.[300, 307] At the same time, the use of phthalaldehyde, naphthalene-1,8-dialdehyde and biphenyl-2,2′-dialdehyde results in the formation of condensed perimidines **327**, **336**, **337**, respectively.[309]

In recent years, many efforts have been made to find effective catalysts for the cyclization of DAN with aldehydes. The following catalysts have been proposed: $Zn(OAc)_2 \cdot 2H_2O$,[310] $NiCl_2 \cdot 6H_2O$,[311] [BTBA]Cl – $FeCl_3$,[312] 2% W nano-CuY Zeolite,[313] SiO_2 nanoparticles,[314] nickel-decorated SBA-15 nanocomposite,[315] Fe_3O_4 nanoparticles immobilized on zeolite – SO_3H,[316] chitosan hydrochloride and some others.[317]

In fact, the above reaction needs no catalyst. Nevertheless, very recently, effective, catalyst-free, eco-friendly, on water protocol for the cyclization of DAN with aliphatic and (hetero)aromatic aldehydes (H_2O, rt, 30 min) has been

Structures 333 – 337



333
R = H, Me, Et, Ph

334, **335**
Z is 1,4-phenylene (**334**), 2,5-furylene (**335**)

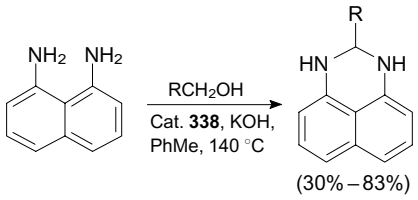
327 **336** **337**

reported.[311] Moreover, simple grinding of DAN with aliphatic and (hetero)aromatic aldehydes using mortar and pestle for 5 min yields 2,3-dihydroperimidines.[307] Ketones were not reactive under the same conditions.

It has also been shown that Mn(I) complex **338** catalyzes dehydrogenative coupling of DAN with primary alcohols producing the corresponding 2-substituted 2,3-dihydroperimidines (Scheme 112).[318]

Cu-Catalyzed condensation of 2-[(2-bromophenyl)ethynyl)]benzaldehydes **339** with DAN produced dihydroisoquinolino[2,1-*a*]perimidines **340** bearing a 2-bromophenyl

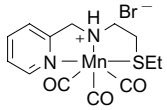
Scheme 112



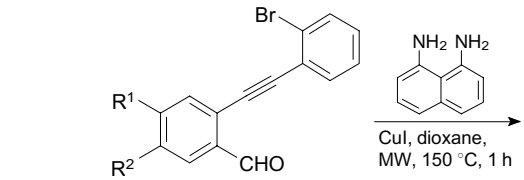
(30% – 83%)

R = Ph, C_6H_4X (X = 4-Me, 4-OMe, 4-F, 4-Cl, 2-OMe, 2-SEt), 2-Naph, 2-Fu, 2-Th, n-C_7H_{15};

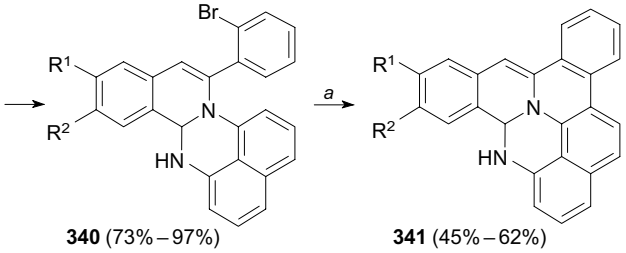
338 =



Scheme 113



339



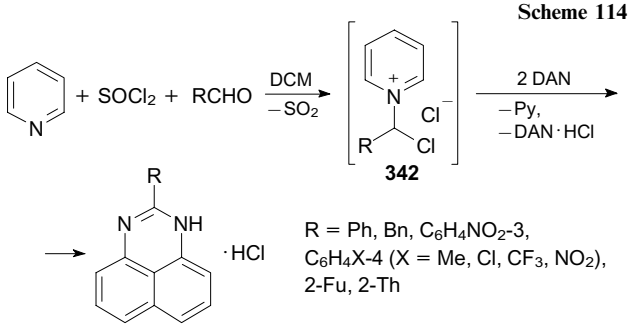
340 (73% – 97%) **341** (45% – 62%)

(*a*) $Pd(OAc)_2$, PPh_3, K_3PO_4, DMF, 130 °C, 4 h;
R^1 = H, Me, F; R^2 = H, OMe, F

group. Subsequent Pd-catalyzed C – H-arylation provided dibenzo[1,2 : 7,8]quinolizino[3,4,5,6-*kla*]perimidine derivatives **341** (Scheme 113).[319] Alternatively, compounds **341** were also obtained in one-pot procedure *via* a $Cu(OAc)_2$-catalyzed domino cyclization of DAN and debromo analogs of aldehydes **339** under aerobic conditions (Cs_2CO_3, dioxane, 100 °C, O_2 balloon).[320] Derivatives of quinolizino[3,4,5,6-*kla*]perimidine are widely applied as dye lasers and electroluminescent materials.[320]

Prepared *in situ* from pyridine, thionyl chloride and (het)arylaldehyde, *N*-(1-haloalkyl)pyridinium chlorides **342** react with DAN yielding 2-(het)aryl-perimidines (Scheme 114).[321] Interestingly, interactions of DAN with preliminarily isolated salts **342** give rise to 2-R-2,3-dihydroperimidines.

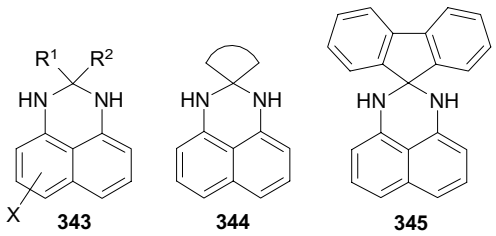
Scheme 114



6.3.2. Ketones as cyclizing agents

Ketones (acetone, acetophenones, diacetyl) react with DAN and its derivatives to afford 2,2-disubstituted 2,3-dihydroperimidines **343**.[239, 297, 322 – 327] Reactions of DAN with cyclic ketones (cycloalkanones, 2-indanone, ninhydrin, piperidin-4-one) lead to spirodihydroperimidines **344**.[297, 328, 329] For example, condensation with 9-fluorenone affords 1′,3′-dihydrospiro[fluorene-9,2′-perimidine] **345**.[330]

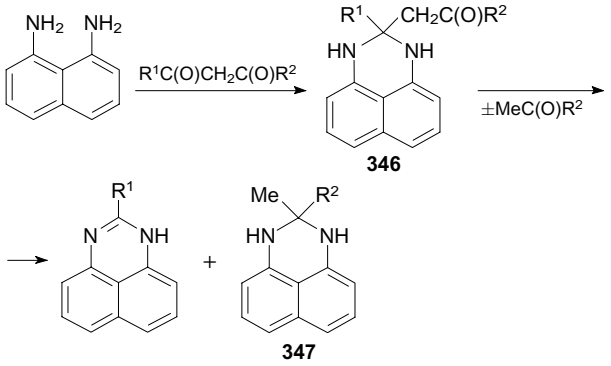
Structures 343 – 345



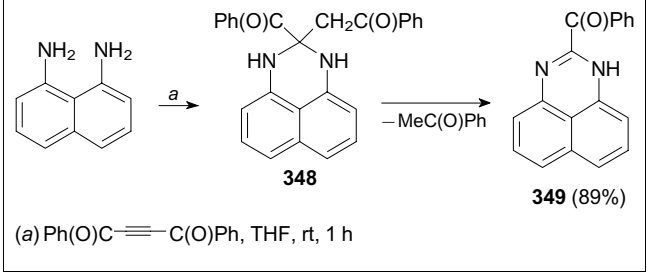
The use of 1,3-diketones as cyclizing agents results in the formation of compounds **346** (Scheme 115). Being heated, the latter eliminate a $R^2C(O)Me$ molecule giving rise to 2-R-perimidines and dihydroperimidines **347**, which are the products of subsequent interaction of DAN with the eliminated ketone $R^2C(O)Me$.[5, 331] In cases of asymmetric ketones, *e.g.*, benzoylacetone, the aliphatic keto-group reacts with DAN more readily than the aromatic one. In the reaction of DAN with ethyl aroylpyruvates, the C(2)=O group takes part in cyclization.[332] *N*,*N*′-Disubstituted DANs, *e.g.*, **90a**, react with acetone to yield 1,2,2,3-tetramethyl-2,3-dihydroperimidines.[333] Ytterbium(III) triflate[334] and bis(oxalato)boronic acid (HBOB)[335] have been used as catalysts for the DHPs synthesis.

The interaction of DAN with dibenzoylacetylene proceeds as a two-step Michael addition resulting in the

Scheme 115



Scheme 116

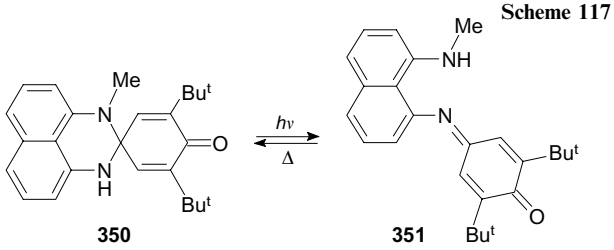


formation of compound **348** (Scheme 116).[23] When heated, the latter compound easily loses an acetophenone molecule giving 2-benzoylperimidine **349**.

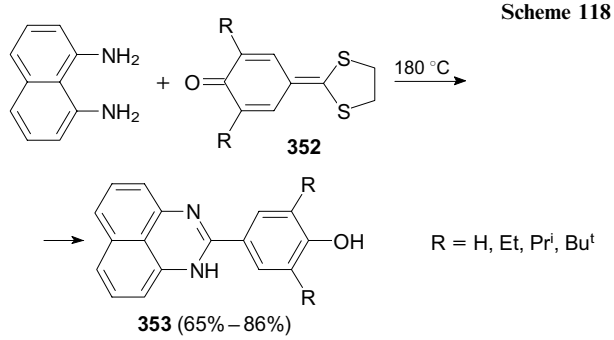
The reaction of DAN with 1,3-diphenylpropane-1,2,3-trione proceeds on the central carbonyl group.[331] Similarly, 2,2-dihydroxy-1*H*-indene-1,3(2*H*)-dione participates in the cyclization *via* the C(2) atom.[74] When isatin and alloxan were used as cyclizing agents, only their keto groups, rather than the amide carbonyl, are involved into the cyclization.[5, 336]

Quinones as cyclic ketones enter the spirocyclization with *peri*-diamines. Thus, DAN reacts with 2,6-bis(*tert*-butyl)benzoquinone, forming 2,3-dihydroperimidine **350** (Scheme 117).[337 – 339] This compound is interesting because

Scheme 117



Scheme 118



it exists in two stable states **350** and **351**, which can be switched photochemically or electrochemically. The less coloured DHP form **350** is more stable under ordinary conditions. Similar switching of the 2,3-dihydroperimidine and azomethine forms was also reported[340] (see also Section 10.1).

It is noteworthy that, in contrast to quinones, quinomethides of type **352** enter the cyclization with DAN *via* the methide functionality, forming a DHP derivative, which exists in the aromatic form **353** (Scheme 118).[271]

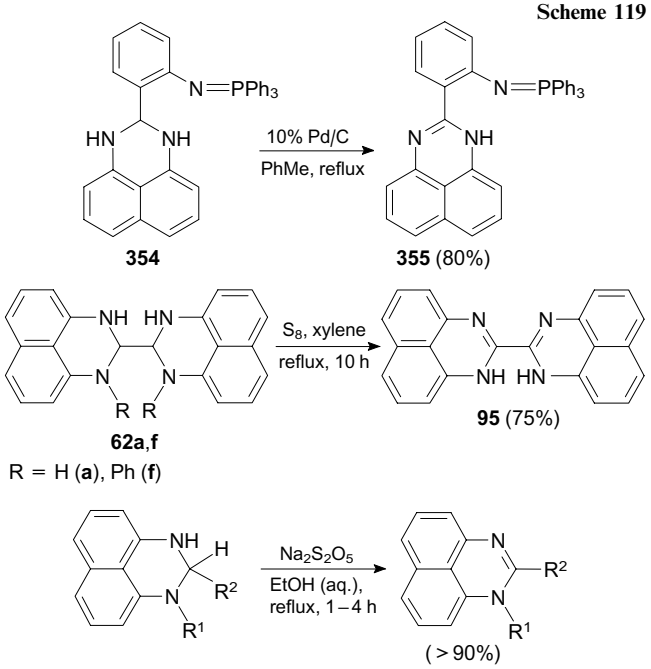
7. Synthesis of perimidines from 2,3-dihydroperimidines

One of the best synthetic approaches to perimidines consists in the preparation of 2,3-dihydroperimidines from DAN and aldehydes followed by dehydrogenation of the DHPs. At least eight reagents have been proposed for this purpose. In terms of scope, efficiency and ease of use they can be divided into two groups. The three main representatives of the first group are palladium on carbon,[230, 301, 302] sulfur[232, 308, 340, 341] and sodium pyrosulfite $Na_2S_2O_5$ (see [290, 342]) (Scheme 119). They are used to oxidize DHPs containing one or two unsubstituted NH groups. The first two reagents require prolonged boiling of the reaction mixture in toluene or xylene, providing generally a good yield of the desired perimidine. In the case of sulfur, there are some limitations associated with the partial replacement of halogen by sulfur in halogen-containing substrates or their possible destruction. For example, compound **62a** is converted into 2,2′-diperimidine **95** in 75% yield, while in its analogue **62f** cleavage of the internuclear C – C bond occurs along with dehydrogenation. Against this background, the great advantage of $Na_2S_2O_5$ is the exceptional smoothness of the process, which is conducted in a water – ethanol medium. Commonly, the dehydrogenation with $Na_2S_2O_5$ is not complicated by side reactions and the resulting perimidine does not require additional purification. Besides, sodium pyrosulfite is indispensable for the synthesis of perimidines containing easily oxidizable groups, in particular, polyhydroxyalkyl introduced in position 2 through the reaction of DAN with monosaccharides (glucose, galactose, and arabinose were tested).[290] The only limitation of using $Na_2S_2O_5$ is its inapplicability to aromatic aldehydes containing strong electron-withdrawing groups such as NO_2 or CN in the ring. It should be noted that both processes, the preparation of DHP and its aromatization with $Na_2S_2O_5$ or Pd/C, can be carried out in a one-pot manner.[230, 342] The aromatization of the DHPs is also significantly hindered in the presence of the *N*-phenyl and *N*-acyl groups.[58, 59, 300]

Chloranil[117] and manganese dioxide[111, 117] can also be included in the first group of dehydrogenating agents. They give good yields of perimidines, but the experience of their use is yet insufficient.

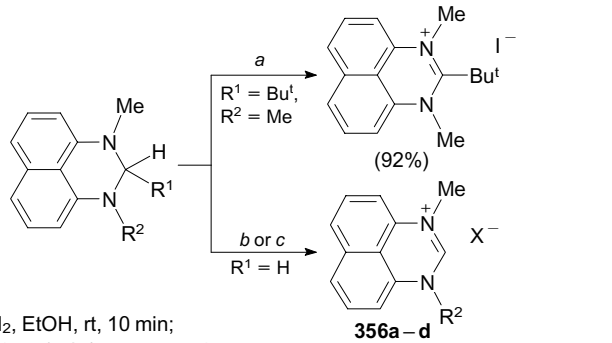
The second group of dehydrogenating agents is intended for the conversion of 1,3-disubstituted DHPs into perimidinium salts. It includes iodine,[34, 38] trityl perchlorate[58] and 1,3,5-trinitrobenzene.[59] Typical examples of the corresponding reactions, which are characterized by high rate, mild conditions and good yields, are shown in Scheme 120. A comparative kinetic study on the dehydrogenation of 1,3-dimethyl-2-R-DHPs and related benzimidazolines using 1,3,5-trinitrobenzene was carried out.[30]

Scheme 119



R^1 = H, Me, Ph; R^2 = H, Me, Ph, C_6H_4Me-4, 2-Fu, 2-Th, D-glucopentahydroxypentyl, *etc.*

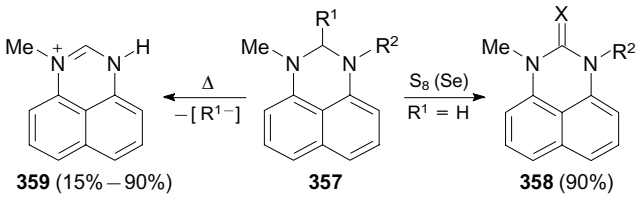
Scheme 120



(*a*) I_2, EtOH, rt, 10 min;
(b) $C_6H_3(NO_2)_3$-2,4,6, MeCN, rt;
(*c*) $Ph_3C^+ClO_4^-$, DCM, rt, < 5 min;
R^2 = C(O)R^3;
356: R^2 = Me (**a**, 90%), Ph (**b**, 85%), X^- =
356: R^3 = Me (**d**, 78%), Ph (**e**, 73%); X^- = ClO_4^-

There are some other methods of dehydration of DHPs. Thus, heating **357** (R^1 = H) with sulfur or selenium leads to the thiones or selenones **358** (Scheme 121).[38] Under conditions of thermolysis or when heated in acetic acid, some 2-R^1-substituted DHPs are aromatized *via* elimination of the R^1 group to produce salts **359**.[296]

Scheme 121



357: R^1 = Ar, Het, R^2 = H, Me; **358**: R^2 = Me: X = S, Se

Synthesis and aromatization of DHPs can be carried out in a one-pot manner.[342, 343] For example, heating DAN with 2-formyl-5,10,15,20-tetraphenylporhyrin in *o*-dichlorobenzene and nitrobenzene (210 °C, 1 h) affords the corresponding perimidine, whose cationic derivatives are highly efficient singlet oxygen generators.[344] Paragamian *et al.*[230] reported the synthesis of 2-alkyl, 2-aryl- and 2-hetaryl-substituted perimidines by refluxing DAN with aldehydes in xylene in the presence of 10% Pd/C.

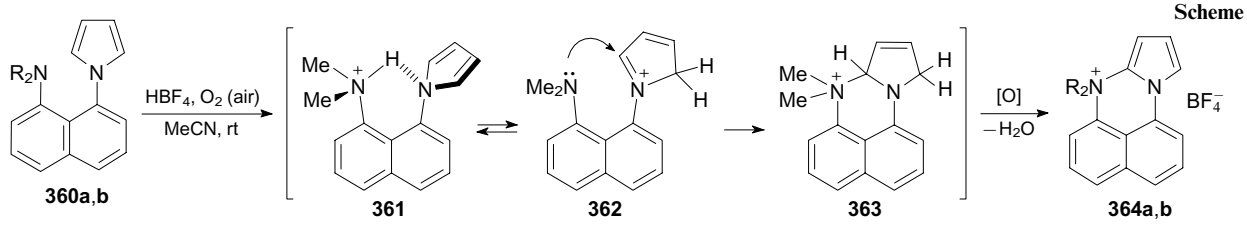
8. Miscellaneous perimidines syntheses

Recently, it has been found that 1-dialkylamino-8-(pyrrolyl-1)naphthalenes **360a**,**b**, upon treatment with an equimolar amount of HBF_4 under ambient conditions, quantitatively produce 7,7-dialkyl-7*H*-pyrrolo[1,2-*a*]perimidine-7-ium tetrafluoroborates **364a**,**b**.[345] The reaction proceeds in a highly selective manner and represents the first case of nucleophilic substitution of hydrogen in the initially inactivated pyrrole ring. The proposed mechanism of this unusual transformation is shown in Scheme 122. It includes the transient formation of ammonium salt **361**, pyrrolium salt **362** (as result of a slow proton transfer) and fast ring closure (**362** → **363**) followed by also fast oxidation step **363** → **364**.

In terms of the structure of compounds **364**, this work partly echoes two other studies of the mid-1980s. In one of them, Tamura *et al.*[346] performed a 1,3-dipolar cycloaddition between dimethyl acetylenedicarboxylate (DMAD) and ylides **366** and **371**, generated *in situ* by treating perimidinium salts **365** and **370** with K_2CO_3 (Schemes 123, 124). The products of these reactions represented two types of substances: 1-(pyrrol-1-yl)- **368** and 1-(pyrazol-1-yl)-8-aminonaphthalenes **373**, as well as derivatives of pyrrolo[1,2-*a*]-perimidine **369** and pyrazolo[1,2-*a*]perimidine **374**. As can be seen in the above Schemes 123 and 124, the naphthalene derivatives are obtained through intermediates **367** and **372** *via* breaking the C – N bond with accompanying proton transfer, whereas the formation of **369** and **374** should proceed through dehydrogenation (probably by DMAD) and elimination of a methane molecule, respectively.

In another study conducted by Pozharskii and co-workers[347] 1-phenacyl-3-methylperimidinium salts **365** were treated with ammonium acetate in acetic acid to synthesize imidazo[1,2-*a*]perimidine derivatives **378** (Scheme 125).[347] Due to the low concentration of ammonia under acidic conditions, the reaction proceeded slowly and required prolonged heating. Like the above-mentioned work,[346] its products were the same types of compounds — *peri*-disubstituted naphthalenes **377** and imidazo[1,2-*a*]perimidines **378**, among which naphthalenes **377** prevailed. When

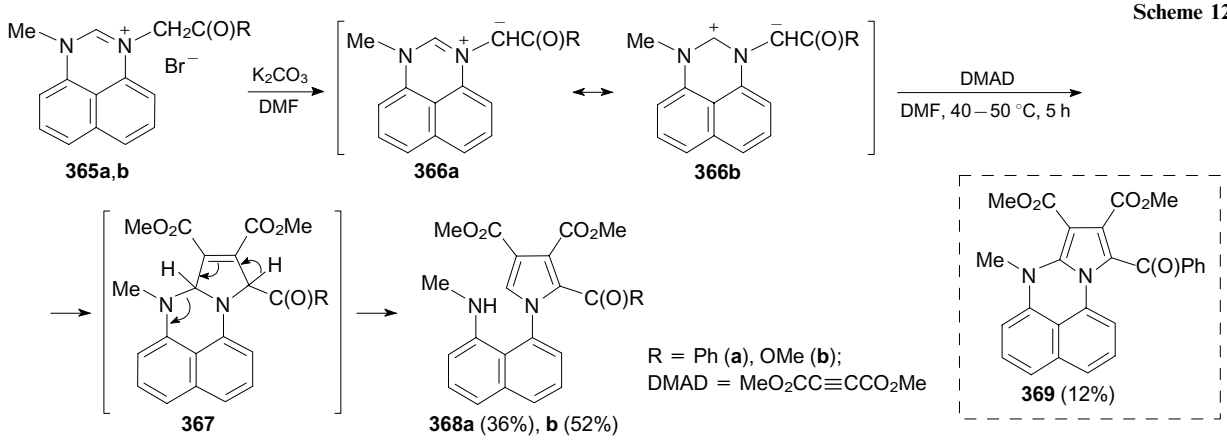
Scheme 122



360a,**b** **361** **362** **363** **364a**,**b**

NR_2 = NMe_2 (**a**), pyrrolidino (**b**)

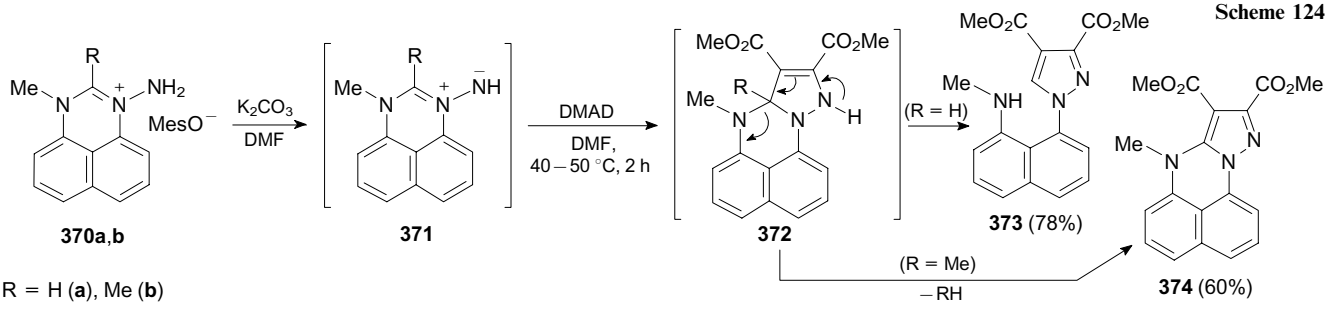
Scheme 123



365a,**b** **366a** **366b** **367** **368a** (36%), **b** (52%) **369** (12%)

R = Ph (**a**), OMe (**b**);
DMAD = $MeO_2CC{\equiv}CCO_2Me$

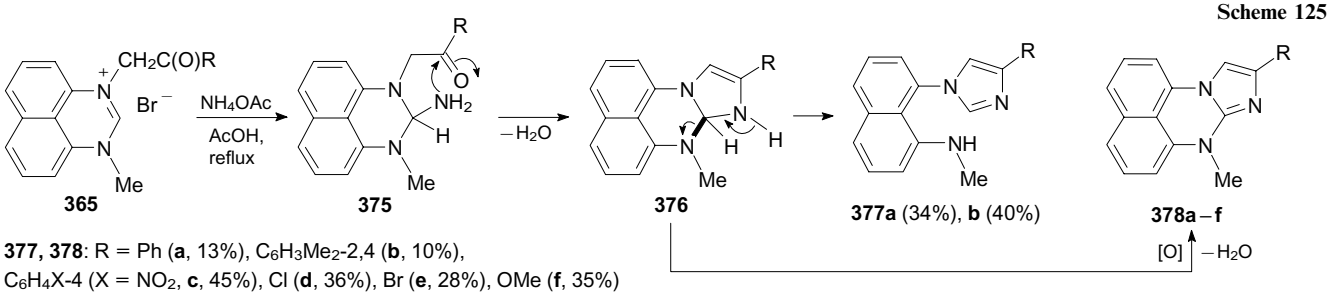
Scheme 124



370a,**b** **371** **372** **373** (78%) **374** (60%)

R = H (**a**), Me (**b**)

Scheme 125

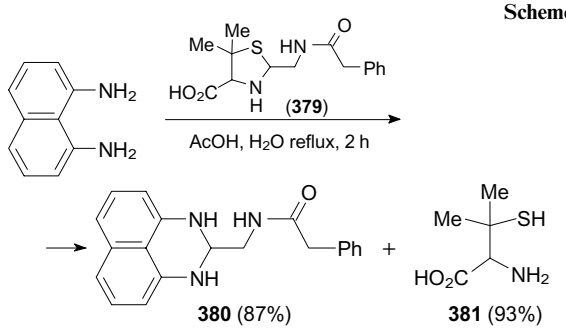


R = phenyl or *m*-xylyl, both products were obtained. In the case of electron-withdrawing aryl substituents ($C_6H_4NO_2$-4, C_6H_4Cl-4, *etc.*), the only reaction product was the corresponding imidazoperimidine **378**.

Apparently, the direction of stabilization of the 2,3-dihydroperimidine intermediate **376** is ultimately determined by the electron deficiency of the C(2) atom of the future imidazole ring. If it is large enough, the C–N bond (highlighted in bold in structure **376**) is maintained, which ensures the formation of compounds **378**. The necessary dehydrogenating agent, by analogy with the reaction shown in Scheme 125, can be atmospheric oxygen and partially electron-withdrawing group such as NO_2, *e.g.*, in **378c**.

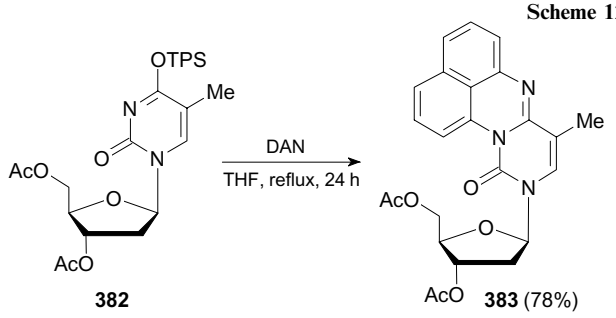
Refluxing DAN with benzylpenicilloic acid **379** in aqueous acetic acid produces *N*-[(2,3-dihydro-1*H*-perimidin-2-yl)methyl]-2-phenylacetamide **380** together with penicillamine **381** (Scheme 126).[348] The latter is a degradation product of penicillin, which is clinically used for the treatment of cystinuria, Wilson's and rheumatoid diseases. The possibility of this reaction, proposed for practical use, is determined by the high nucleophilicity of DAN (*cf.* Scheme 20).

Scheme 126



In the framework of the program for the thermal stabilization of polynucleoside duplexes using the intercalation effect involving polycondensed heteroaromatics, the first perimidine-containing nucleosides like **383** were synthesized (Scheme 127).[282]

Scheme 127



9. Interrelation between perimidines and proton sponges

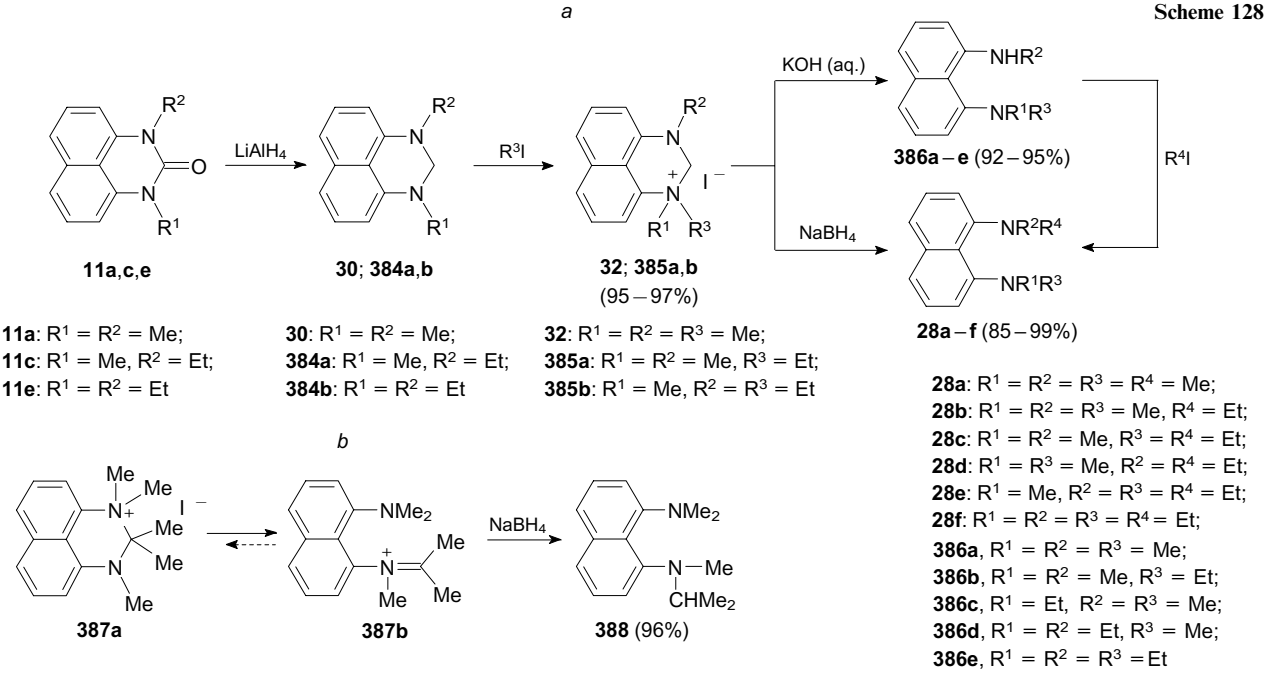
As one can see, there is a close structural similarity between 2,3-dihydroperimidines and perimidines, on the one hand, and proton sponge (DMAN, **28**), on the other. This also applies to the preparation of the both types of compounds, which ultimately stems from 1,8-diaminonaphthalenes. From this, one can predict the existence of some synthetic interrelation between DHPs and DMANs. Indeed, as far back as 1981, it was shown that 1,1,3-trialkyl-2,3-dihydroperimidinium salts **32** and **385a**,**b**, easily prepared from 1,3-dialkylperimidones **11** or 1,3-dialkyl-DHPs **384a**,**b**, can be used as convenient proton sponge precursors (Scheme 128 *a*).[85] Two kinds of such transformations have been proposed. The first one is based on the treatment of salts **32** and **385a**,**b** with aqueous alkali, resulting in the formation of *N*,*N*,*N*′-trialkyl-1,8-diaminonaphthalenes **386a**–**e**, which are then alkylated to afford proton sponges **28a**–**f**. In the second preparative variation, salts **32** and **385a**,**b** were directly reduced by LAH into DMAN derivatives. Both methods can be applied for the preparation of acenaphthene proton sponges.

Despite the nearly quantitative yields of **28** and **386**, this approach has little value for the parent sponge **28a** since its more practical synthesis consists of exhaustive methylation of DAN.[87, 349] In contrast, the similar synthesis of DMANs with different substituents at the nitrogen atoms is indispensable in many cases. For example, proton sponges with all possible combinations of *N*-methyl and *N*-ethyl groups were obtained *via* such protocol.[85] Notably, sterically overcrowded DHP salts, for example **387a**, preferably exist in acyclic form **387b**, which can be reduced to monoisopropyl sponge **388** with sodium borohydride (Scheme 128 *b*).[333] Besides, this is also a method of choice for the preparation of such DMAN derivatives as 4,5-dibromo-1,8-bis(dimethylamino)naphthalene (**189** → **389**)[158, 350] or partially hydrogenated benzo[*h*]quinoline **390** and quino[7,8-*h*]quinoline **391** (Scheme 129).[351]

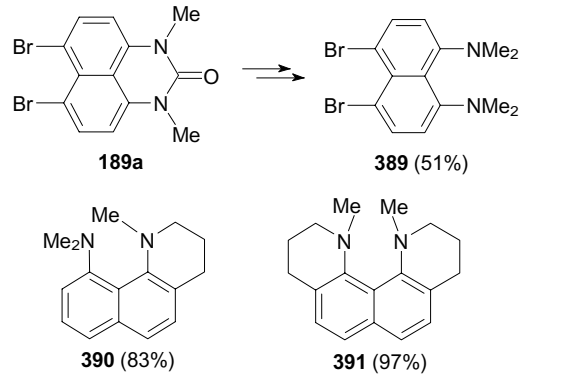
Later, it became clear that the transformation of DHPs into DMAN derivatives could be reversed. It turned out that DMAN is oxidized by transition metal complexes (Ir^{3+}, Rh^{3+}, Ru^{3+}), *e.g.*, **392**, losing a hydride ion and converting into methylene iminium cation **393**, which rapidly cyclizes into 1,1,3-dihydroperimidinium salt **32** (Scheme 130).[352, 353] Thus, 2,3-dihydroperimidinium salts and DMANs actually form a redox-system interconverting through the related iminium intermediate.

In the synthetic sense, intramolecular version of this reaction, in which the hydride ion migrates to a suitable

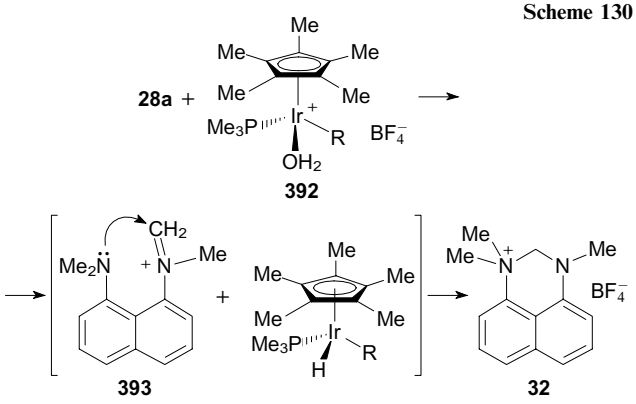
Scheme 128



Scheme 129



Scheme 130

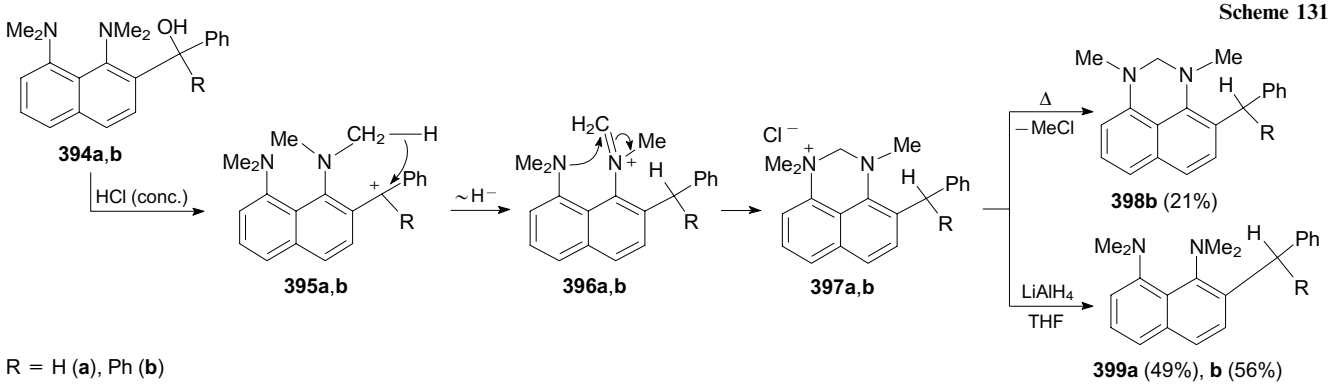


electron-withdrawing *ortho*-substituent triggering subsequent cyclization, is more fruitful.[354] For example, being treated with hydrochloric acid, alcohols **394a**,**b** instantly generate the red-coloured resonance-stabilized carbocations **395a**,**b** (Scheme 131). The latter quickly accept a hydride ion from the methyl group initiating the formation of the methylene iminium intermediate **396a**,**b** and its subsequent cyclization into colourless salts **397a**,**b**. These salts can be converted into 4-substituted DHPs **398a**,**b** or 2-substituted DMANs **399a**,**b** through thermal elimination of methyl chloride or LAH reduction, respectively. Many other transformations of such kind belonging to the family of the so-called T-amino reactions have been reported.[355, 356]

10. Applications

From the above it follows that perimidines are readily available compounds possessing a unique set of reactivity and physico-chemical properties. For this reason, perimidine derivatives represent an ideal starting material for a

Scheme 131



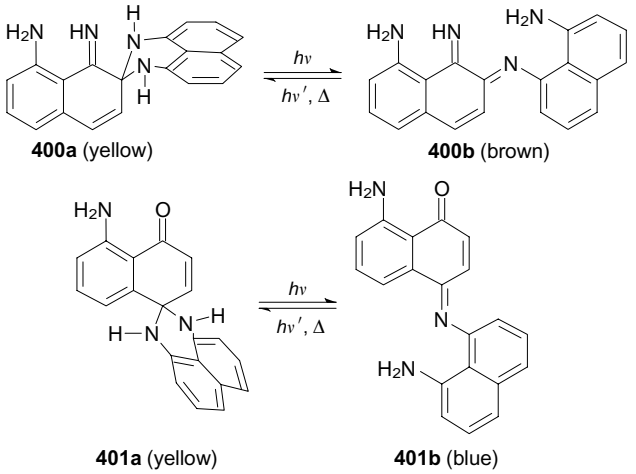
R = H (**a**), Ph (**b**)

wide range of practical applications, including industrial chemistry, modern electronic technology, biotechnology and medicinal chemistry.

10.1. Non-biological applications

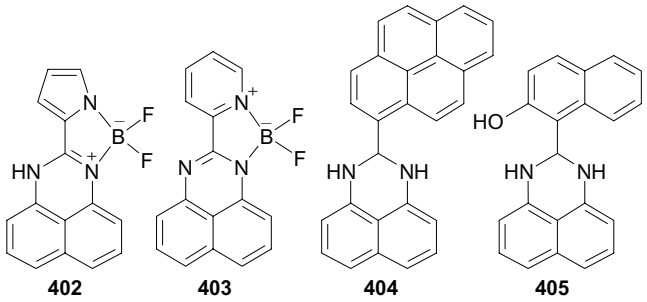
For many decades after the discovery of perimidines, applied research in this area focused almost entirely on dyes and pigments. Old works on this topic were cited before.[1] To a significant extent, interest in the perimidine dyes and pigments remains today.[357–363] Particular attention is drawn to perinones (pyrroloperimidine derivatives) as bright, light- and thermo-resistant pigments for industrial plastic, synthetic and natural fibres. In addition, some of them are recommended as fluorescent sensors, LEDs and various optoelectronic devices.[364–372] Most of these and other developments stem from the remarkable photophysical properties of the perimidine system. Thus, we have already mentioned photo-, thermo-, and electrochromic compounds in this series (see Schemes 57 and 117). In addition, spirodihydroperimidines **400** and **401** formed by oxidation of DAN with MnO_2, exhibit photochromism both in solution and in polymer matrices (Scheme 132). As can be seen, in this case, too, the tendency of dihydroperimidines to ring–chain tautomerism lies in the basis of the phenomenon.[340, 373]

Scheme 132



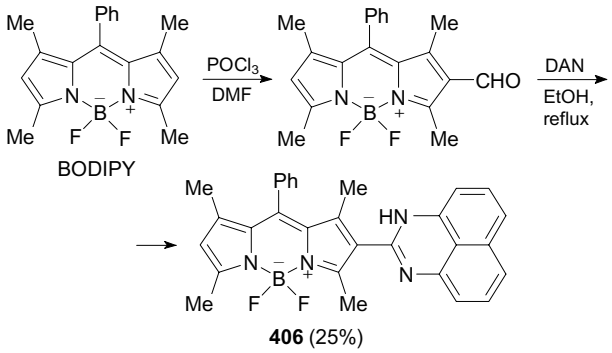
Recently, more information on materials of a somewhat different profile, especially related to such areas as chemosensors and visualization techniques, have appeared. The perimidine structure incorporates an effective fluorophore component, which is 1,8-diaminonaphthalene. The high fluorescence quantum yield of this compound shared by many naphthalene derivatives, has inspired their use as fluorophores. However, in the perimidines themselves the fluorescence is strongly depressed, which was attributed to the loss of excitation energy caused by electron transfer from the heterocyclic ring to the naphthalene moiety.[7, 50] Few attempts were made to increase the performances of perimidines as fluorescent dyes. Lamperti *et al.*[50] used two strategies: (i) locking the perimidine and its C(2)-substituent with BF_2 moiety (compounds **402** and **403**); and (ii) saturating the perimidine ring with π-expanded fragments. The second strategy demonstrated superior efficacy in enhancing the fluorescence properties. Thus, compounds **404** and **405** demonstrated fluorescence quantum yields comparable to those of DAN.

Structures 402–405



It is known that the so-called BODIPY dyes, which attract a lot of attention, are characterized by a high quantum yield and brightness depending very little on the medium. In 2017, Li *et al.*[374] obtained the first perimidine-containing BODIPY **406** *via* condensation of β-formyl-BODIPY and DAN (Scheme 133). Note that addition of a base to a solution of **406** completely suppresses emission. However, in an acidic environment the emission dramatically increases due to the formation of the perimidinium cation. Thus, compound **406** is actually a fluorescence switch.

Scheme 133

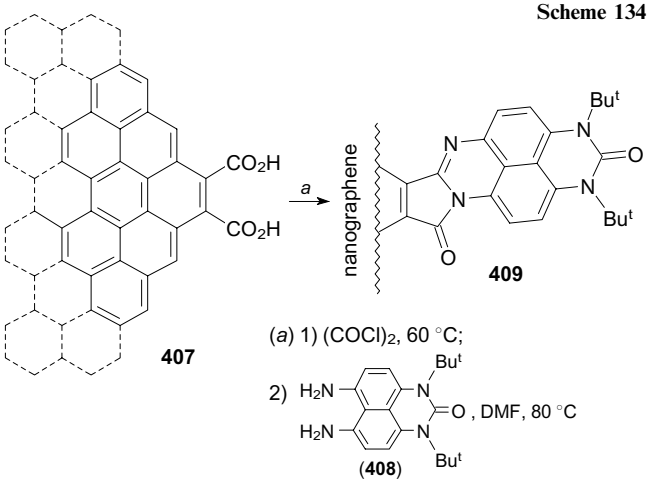


Due to the quantum-size effect, nanographenes are able to photoluminesce in a wide UV and visible range. Recently, Yamato *et al.*[247] treated *edge*-oxidized nanographene **407** with some DANs including 6,7-diaminoperimidinone **408** (Scheme 134). Thus the modified nanographene **409** displayed significantly red shifted absorption and emission (> 1000 nm) in the near-infrared region and was recommended for bioimaging, because it did not damage living tissues.

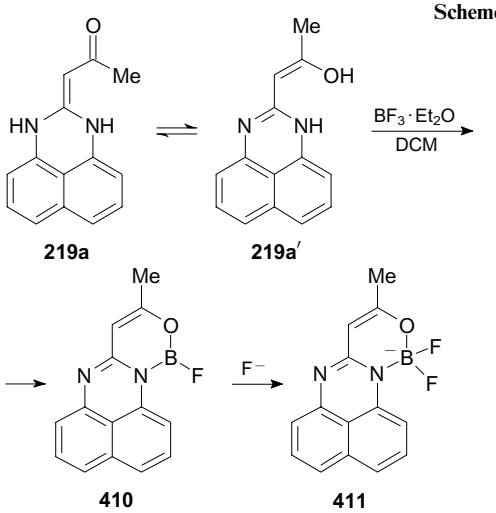
Perimidine-boron complex **410** has been synthesized by treatment of ketene aminal **219a** with $BF_3 \cdot Et_2O$ (Scheme 135).[375] Compound **410** reacts with a fluoride ion in a 1 : 1 stoichiometry to afford brightly fluorescent perimidine-boron difluoride **411**, which behaves as a highly selective and sensitive probe to detect F^- in living cells.

The hypochlorite anion (ClO^-) is a widely used (industrially and domestically) reactive oxygen species. Even human immune system generates scanty quantities of hypochlorite in response to infection. Goswami *et al.*[376] have developed perimidine-based fluorescent molecular sensor **405** for accurate and selective detection of ClO^- in environmental and biological samples. It can be prepared by condensation of 1,8-diaminonaphthalene with 1-formyl-2-naphthol as a fluorophore. The sensor demonstrates a sensitive 'turn-on' fluorescence response *via* the ClO^--

Scheme 134

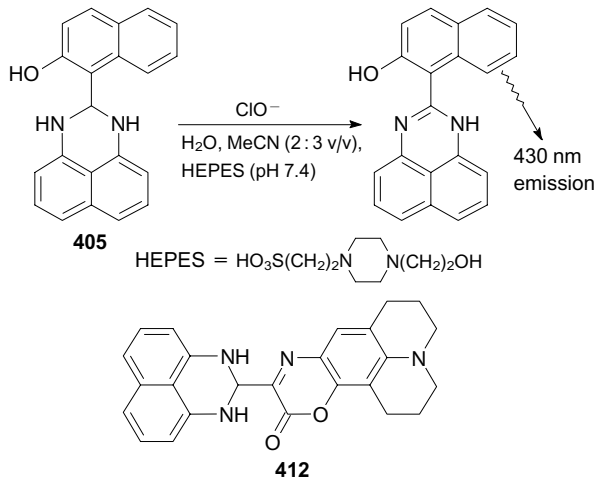


Scheme 135



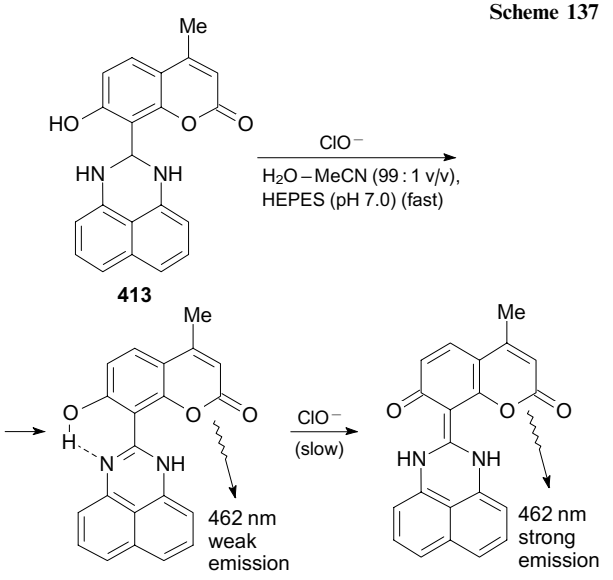
selective dehydrogenation of the dihydroperimidine unit (Scheme 136). Another sensor of this kind (**412**) has been synthesized by Fan *et al.*[377] Unfortunately, despite a selective and sensitive response towards ClO^-, both sensors have a low solubility in water, which requires addition of a large amount of organic solvent (MeCN or DMF).

Scheme 136



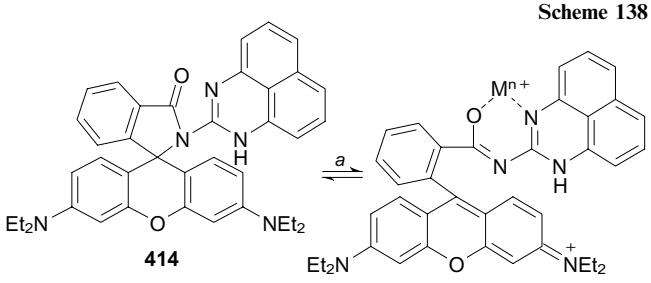
Sensor **413**, synthesized by condensation of DAN with 8-formyl-7-hydroxy-4-methylcoumarin, is soluble in water containing only 1% organic solvents.[378] The sensor shows a weak fluorescence, but ClO^--selective dehydrogenation of its dihydroperimidine unit initiates a strong fluorescence at 462 nm. This 'turn-on' response facilitates sensitive detection of ClO^-. Several spectroscopic analyses and *ab initio* calculations revealed that this 'turn-on' response by ClO^- is triggered by intramolecular proton transfer from the coumarin OH group to the imine nitrogen of the formed perimidine unit (Scheme 137).

Scheme 137



Perimidine-based rhodamine dye **414** senses ions such as Al^{3+}, Fe^{3+} and Fe^{2+} *via* the 'turn-on' fluorescence and colour change (colourless to pink) under various experimental conditions (Scheme 138).[379] Varying concentration of **414** makes it possible differentiate Al^{3+} from Fe^{3+} ion. At low concentration ($c = 10^{-4}$ mol L^{-1}), only Al^{3+} ion shows 'turn-on' fluorescence with sharp colour change. Sensing of Fe^{2+} ion through 'turn-on' fluorescence and colour change has been possible *via* the *in situ* Fenton's oxidation reaction.

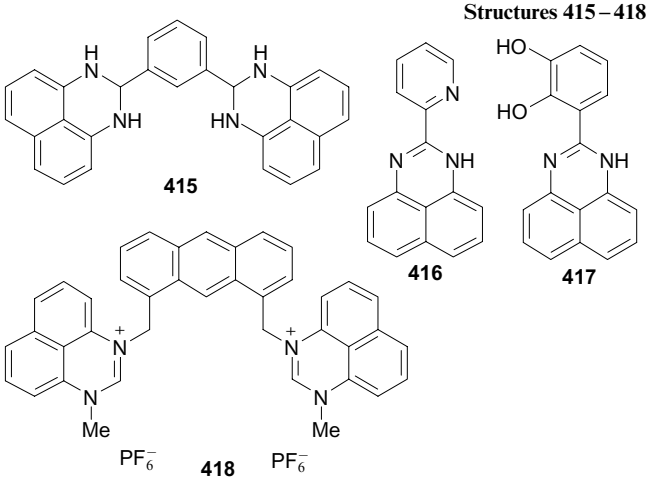
Scheme 138



(*a*) M^{n+}, F^- or PO_4^{3-}; $M^{n+} = Al^{3+}$, Fe^{3+}, Fe^{2+}

Compounds **415**–**417** were tested as specific synthetic receptors for the recognition of transition metal ions. They demonstrated high affinity and selectivity towards Cu^{2+} ions. The minimum detectable concentrations of Cu^{2+} ions for the synthetic receptors **415**, **416** and **417** were 39 nmol L^{-1} (MeCN),[380] 75 nmol L^{-1} [H_2O : DMSO, 99 : 1 (v/v)][381] and 270 nmol L^{-1} [H_2O : DMSO, 99 : 1 (v/v)],[381] respectively.

Structures 415 – 418

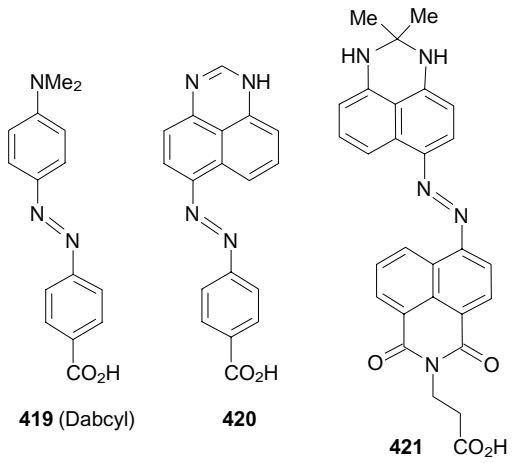


A supramolecular anion receptor **418** have been synthesized.[382] To detect anions, this receptor utilizes perimidine C(2)–H, anthracene C(9)–H and aliphatic CH_2 and *N*-Me hydrogen bonding capacities. Compound **418** has considerable binding affinity for weakly basic anions even in polar solvent such as DMSO, being selective for the nitrite ion.

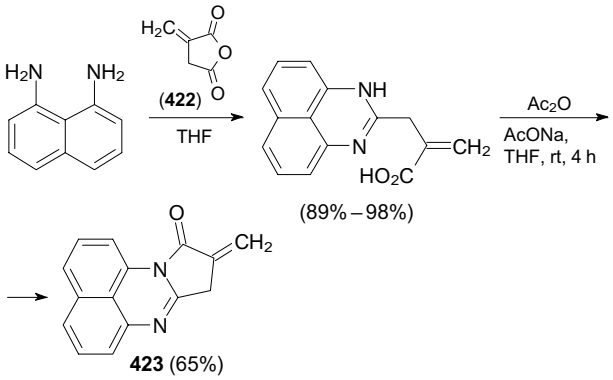
Along with fluorophores, the so-called fluorescence quenchers are widely employed in analytical and biotechnological studies, for example, for detection of nucleic acids. To date, rather small number of effective quenchers is known, since each of them is suitable only for a certain part of the visible spectrum. The most famous of them is 4-(dimethylamino)azobenzene-4′-carboxylic acid (Dabcyl), which quenches the luminescence of fluorophores emitting from violet to green light (390 – 520 nm). The common structural feature of the quenchers is the presence of a long conjugation chain with strong donor and acceptor substituents on its termini. Based on this fact, quenchers **420** and **421** were prepared. The latter are structurally similar to Dabcyl, but include the perimidine and 2,3-dihydroperimidine residues instead of the NMe_2 group.[383] These compounds make it possible to interrupt emission in a wider spectral region, including the red one.

Fernández-Gijón *et al.*[384] obtained methylideneperinones **423** by double cyclization of DAN with itaconic anhydride **422** (Scheme 139). This compound is of interest because of its white luminescence, which can find a number of applications, including LEDs and optical bleaches. The

Structures 419 – 421



Scheme 139

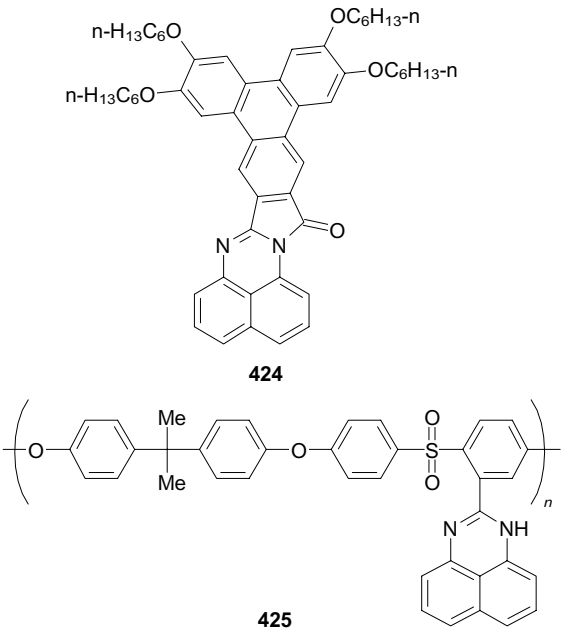


presence of the *exo* C=C bond in **423** allows its copolymerization with styrene, acrylates and other unsaturated monomers.

Mesomorphic perinone derivative **424** was synthesized by condensation of DAN and triphenylene dicarboxylic anhydride.[385] This discotic mesogen self-assembles into supramolecular columnar hexagonal mesophases with high clearing transition temperatures, demonstrating a strong tendency for π-stacking in the liquid crystal state owing to its perfect planarity. Compound **424** demonstrates strong absorption bands at 266 – 450 nm and emission from 468 to 603 nm. Furthermore, the solution of **424** in THF at a concentration as low as 0.45 wt.% exhibited organogel phases due to strong intermolecular π – π interactions between the large aromatic cores. Actually, compound **424** can be qualified as a new type of discotic liquid crystals, applicable for the creation of organic semiconductor materials and sensors.

Blend membranes consisting of sulfonated poly(ether ether ketone) (SPEEK, an acidic polymer) and various amounts of 1*H*-perimidine tethered polysulfone (a basic polymer) **425** have been synthesized.[386] They show an increased proton conductivity and decreased ion-exchange capacity and liquid uptake in water and methanol – water solutions compared to plain SPEEK. The blend membranes

Structures 424, 425



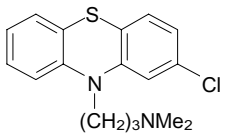
also exhibit better electrochemical performance and lower methanol crossover in direct methanol fuel cells compared to plain SPEEK and Nafion 115 membranes due to an enhancement in proton conductivity through acid-base interactions and an insertion of the 1*H*-perimidine groups into the ionic clusters of SPEEK.

Examples of the use of perimidine derivatives as catalysts and ligands are given in Sections 5.8 and 5.9.

10.2. Biological applications

In connection with the rapid development of medicinal chemistry that began at the turn of the 1950s and 1960s, the attention of scientists began to switch more and more to the search for drugs among perimidine derivatives. Hope for success was associated with three circumstances. Firstly, the perimidine structure includes such a promising pharmacophore as the pyrimidine scaffold. Secondly, by analogy, *e.g.*, with acridines, the flat trinuclear perimidine system makes promising the development of drugs, whose mechanism of the action is associated with the intercalation effect. Lastly, in the 1950s, under the influence of the resounding success of chlorpromazine **426**, a drug for the treatment of schizophrenia, Albert Szent-Györgyi (the discoverer of vitamin C) proposed that the charge transfer effects, in particular, electron-donating properties of a drug, can be crucial in the treatment of nervous disorders.[387] The biological properties of chlorpromazine as a simple derivative of such well-known electron donor as phenothiazine (IP-1 = 7.6 eV) seemed to support this hypothesis.

Structure 426



426 (Chlorpromazine)

In the context of the foregoing, it is not surprising that most of the studies on biological screening of perimidines, which are even stronger electron-donors than phenothiazines (Section 3.3), were focused on the search for anticancer, antimicrobial, and neurotropic drugs. A list of these and other areas of perimidine bioscreening (excluding numerous patents) is given in the Supplementary Materials (see Table S6, https://doi.org/10.1070/RCR4963). Unfortunately, we do not yet have information about the creation of any approved medicines related to these works.

It should be borne in mind that along with the search for drugs, perimidines are tested for the possibility of their use in biotechnology (see Schemes 126 and 127).

11. Conclusion

This review revealed at least three of the most innovative trends of the perimidine chemistry. Undoubtedly, the first of these is the synthesis and study of the stable perimidine-based carbenes and their complexes with transition metals. The latter have a great potential for creating novel effective catalysts for modern organic reactions, especially such as cross-coupling, C – H activation and metathesis. The second direction seems to be a demonstration of a close interconnection between perimidines and such significant class of organic compounds as proton sponges and neutral superbases in general. Synthesis of 6,7-bis(dimethylamino)-perimidines, the strongest bases among perimidines, lies at the centre of these studies. Finally, applied research aimed at creating new materials on the basis of perimidines for electronic techniques, biotechnology, dye industry, pharmacology, *etc.*, is becoming more and more important. Along with this, further progress in the development of classical directions of the perimidine chemistry, in particular, new methods of electrophilic substitution and cyclizations based on it, cannot be missed. It is hoped that many years of efforts to find effective drugs based on perimidines in the coming future will finally succeed.

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