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Recent advances in the chemistry of pyridazine — an important representative of six-membered nitrogen heterocycles

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The review is devoted to recent advances in the chemistry of pyridazine — a six-membered heterocycle containing two nitrogen atoms in adjacent positions. The practical significance of title compounds is demonstrated and published data of the last decade devoted to them are considered systematically. The modern synthetic approaches to pyridazine derivatives are described in detail, analyzed and classified according to the precursor molecules involved in ring closure. The chemical properties of pyridazines are considered, including both reactions of the diazine ring and reactions of various substituents attached to the ring. Particular attention is given to the application of some pyridazine derivatives as pharmaceuticals, optical materials and ligands for catalysis.
The bibliography includes 180 references.

Contents

1. Introduction 394
2. Formation of the pyridazine ring 395
   2.1. Formation of one bond 395
   2.2. Formation of two bonds 397
      2.2.1. Formation of two bonds from [4 + 2] fragments 397
      2.2.2. Formation of two bonds from [3 + 3] fragments 400
   2.3. Formation of three bonds 401
   2.4. Ring expansion 404
   2.5. Cycloaddition 405
3. Pyridazine ring reactivity 406
   3.1. Electrophilic attack on pyridazine nitrogen atoms 407
   3.2. Reactivity of pyridazine carbon atoms 408
   3.3. Reduction reactions 409
   3.4. Radical reactions 409
   3.5. Cycloaddition reactions 409
   3.6. Reactions of hydropyridazines 409
4. Reactivity of substituents in the pyridazine ring 410
   4.1. Alkyl groups 410
   4.2. Carboxy and ester groups 411
   4.3. Cyano groups 411
   4.4. Amino groups 412
   4.5. Hydrazino groups 413
   4.6. Hydroxy and oxo groups 414
   4.7. Thiol and thione groups 415
   4.8. Halogen atoms 416
      4.8.1. Replacement of a halogen by a metal 416
      4.8.2. Replacement of a halogen atom in cross-coupling reactions 417
      4.8.3. Nucleophilic aromatic substitution in pyridazines 417
   4.9. Organometallic derivatives of pyridazines 419
   4.10. Pyridazine *N*-oxides 420
   4.11. Supramolecular complexes with pyridazines 421
5. Applications of pyridazines 421
6. Conclusion 426

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1. Introduction

Pyridazines (1,2-diazines) are among the most important six-membered nitrogen heterocyclic compounds, which are of enormous interest, first of all, because of their biological activity. Indeed, about 9% of unique structures of pharmaceutical products approved by the US Food and Drug Administration (FDA) contain heterocycles that are depicted in Fig. 1; most often, the drug products contain pyridine and pyrimidine moieties.[1]

Pyridazines rarely occur in nature; therefore, they have not attracted much attention of researchers for a long time. Since the 1970s, the popularity of pyridazines started to increase, which finally resulted in the synthesis of a variety of derivatives, which are successfully used in pharmaceutics and agrochemistry (Fig. 2). Some pharmaceutical products based on pyridazines are actively applied in medicine: indeed, the drugs Hydralazine and Azelastine were included in the list of Top 200 Brand Name Drugs by Prescription (2016), while Lynparza occupied the 162th line in the list of Top 200 Brand Name Drugs by Retail Sales (2018).[2]

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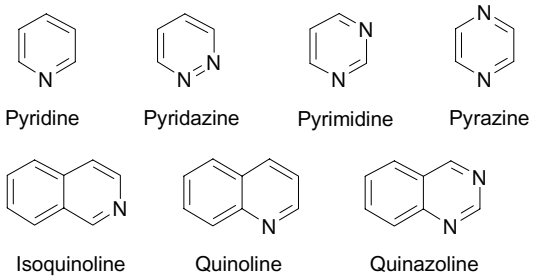


Figure 1. Six-membered nitrogen heterocycles and their benzannulated analogues often present in the molecules of pharmaceutical agents.[1]

Hydralazine was also noted as one of the most frequently used components for combination drugs based on hydrochlorothiazide.[3]

The number of studies on pyridazines published in the last decade is rather large. Mention should be made of a group of reviews,[4–14] which analyze numerous studies and identify future trends in the 1,2-diazine chemistry. Considering the analyzed and systematically arranged data, we defined parts of the present review. They are devoted to the synthesis of pyridazines, reactivity of fully conjugated and non-conjugated rings and substituents at the diazine system. Practical applications of these compounds are considered separately.

The following abbreviations are used in the review:

p-ABSA — 4-acetamidobenzenesulfonyl azide,

Aliquat 336 — methyltrioctylammonium chloride (Starks catalyst),

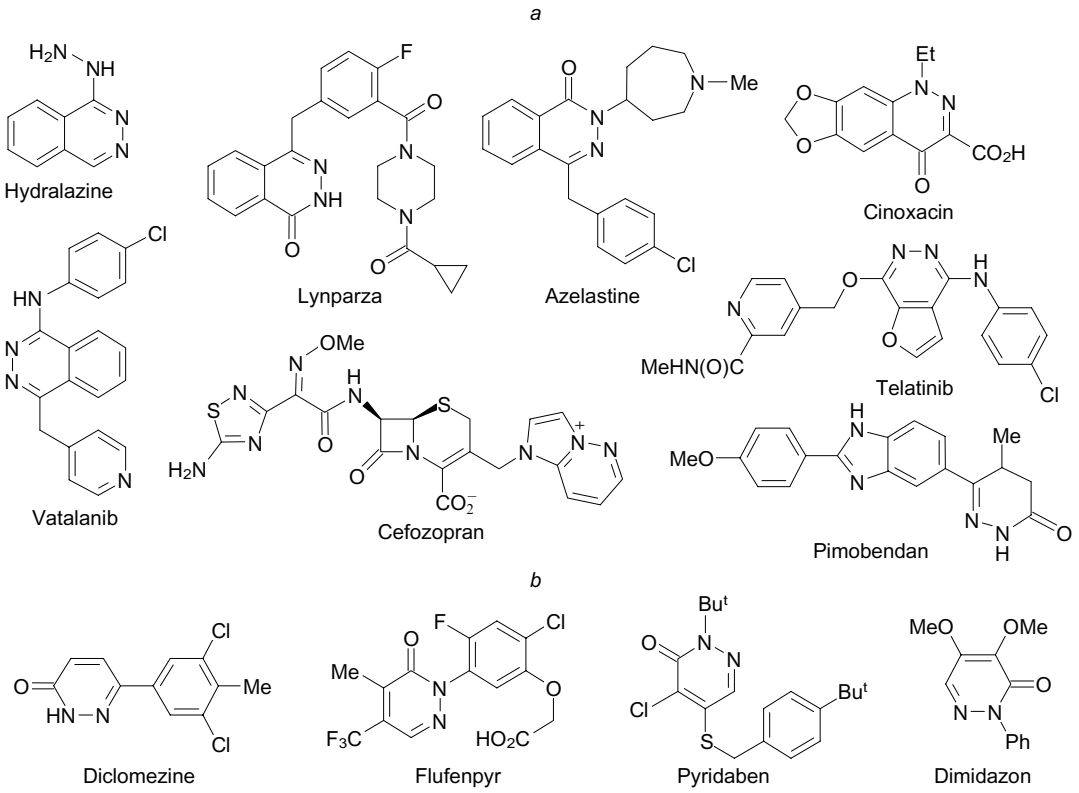


Figure 2. Pyridazine derivatives used in pharmaceutics (*a*) and agrochemistry (*b*).

Boc — *tert*-butoxycarbonyl,
BQ — benzoquinone,
Cbz — benzyloxycarbonyl,
COD — (1*Z*,5*Z*)-cycloocta-1,5-diene,
DABCO — 1,4-diazabicyclo[2.2.2]octane,
dba — dibenzylideneacetone,
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
DCB — 1,2-dichlorobenzene,
DCE — 1,2-dichloroethane,
DIAD — diisopropyl azodicarboxylate,
DIB — di(acetoxy)iodobenzene,
DIBAL-H — diisobutylaluminium hydride,
DIPEA — *N*,*N*-diisopropylethylamine,
DMA — dimethylacetamide,
DMAP — 4-dimethylaminopyridine,
DME — 1,2-dimethoxyethane,
DPP — diphenyl phosphate,
DPPA — diphenylphosphoryl azide,
dppf — 1,1′-bis(diphenylphosphino)ferrocene,
dppp — 1,3-bis(diphenylphosphino)propane,
ERG — electron-releasing group,
esp — 3,3′-(1,3-phenylene)bis(2,2-dimethylpropanoic acid),
EWG — electron-withdrawing group,
Fu — furyl,
HATU — bis(dimethylamino)methylene-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide,
HMPT — hexamethylphosphoramide,
IBX — 2-iodoxybenzoic acid,
Mes — mesityl (2,4,6-trimethylphenyl),
MS — molecular sieves,
MW — microwave radiation,
Naph — naphthyl,
NMIL — nanomagnetic ionic liquid,
NMP — *N*-methyl-2-pyrrolidone,
1,10-Phen — 1,10-phenanthroline,
PIFA — bis(trifluoroacetoxy)iodobenzene,
PPA — polyphosphoric acid,
Py — pyridyl,
RL — Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide],
rt — room temperature,
TBS — *tert*-butyldimethylsilyl,
TCCA — trichloroisocyanuric acid,
TEMPO — (2,2,6,6-tetramethylpiperidin-1-yl)oxyl,
TFA — trifluoroacetic acid,
TFDA — trimethylsilyl fluorosulfonyldifluoroacetate,
THF — tetrahydrofuran,
Th — thienyl,
TMP — 2,2,6,6-tetramethylpiperidine,
TMS — trimethylsilyl,
Ts — *p*-toluenesulfonyl (tosyl),
UST — ultrasonic treatment.

2. Formation of the pyridazine ring

A variety of synthetic approaches to the assembly of pyridazine systems were comprehensively covered in the literature.[1,5] Methods for the synthesis of pyrimidines, pyrazines, pyridazines and triazines based on transition metal catalysis are described in detail.[15] A special review [16] is devoted to the preparation of α-trifluoromethylpyridazines. All methods for the synthesis of these compounds available from the literature can be divided into the following large groups: methods based on the formation of one, two or three bonds; on ring expansion; and on cycloaddition.

2.1. Formation of one bond

The synthetic routes to pyridazine derivatives based on the formation of only one bond can be subdivided into four groups according to the position of this bond in the resulting ring: C(4)–C(5), C(3)–C(4), N(2)–C(3) or N(1)–N(2) bond (Fig. 3).

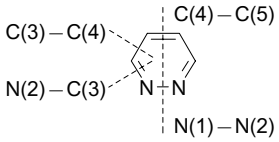
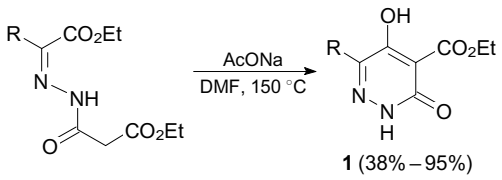


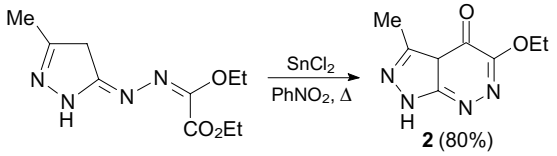
Figure 3. Approaches to the assembly of the pyridazine ring *via* the formation of one bond (here and below, the forming bond is designated by the dashed line).

Examples of C(4)–C(5) cyclization implementing this synthetic strategy for the synthesis of pyridazinones **1** and **2** *via* the Claisen condensation of the appropriate substrates were reported.[17,18] (Scheme 1).

Scheme 1



R = Ph, Het, Bu^{i}, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-$C_4H_7CH_2$, Bu$^{t}CH_2$

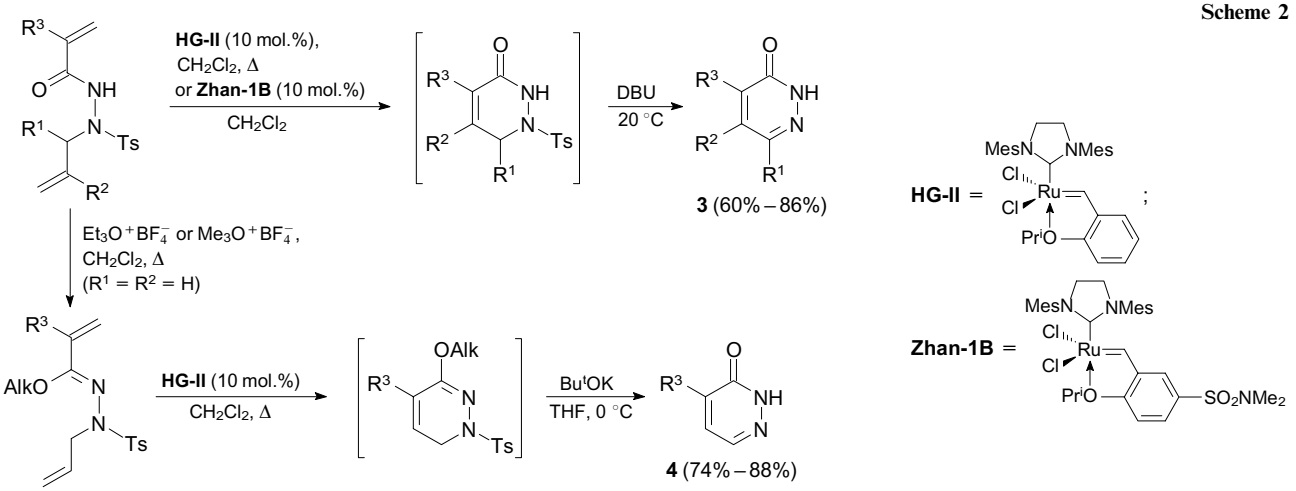


The metathesis reaction was proposed as an original C(4)–C(5) method for the synthesis of pyridazin-3(2*H*)-ones **3** and **4** (Scheme 2).[19] An important circumstance is the application of second-generation Grubbs catalysts, HG-II and Zhan-1B, characterized by easy handling, commercial availability and high substrate tolerance. In some cases, the yield of the reaction products slightly increased upon *O*-alkylation of the initial compounds.

The formation of the C(3)–C(4) bond in 2-methylphthalazin-1(2*H*)-ones **5** containing substituents in the benzene ring can be accomplished in the presence of palladium(II) acetate *via* intramolecular oxidative C–H/C–H cross-coupling involving benzoquinone or by the Heck reaction with the corresponding iodide (Scheme 3; the positions of the substituents in the substrate are indicated).[20]

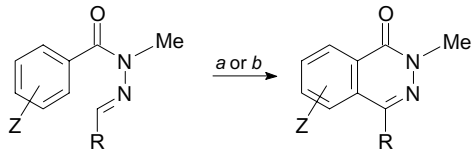
A simple, but efficient method for cyclization of the N(2)–C(3) bond is refluxing of 1,2,5-thiadiazole-3,4-dicarboxylic acid dihydrazide in concentrated formic acid, resulting in closing of the pyridazinedione and thiadiazole fused system **6** (Scheme 4).[21]

Scheme 2



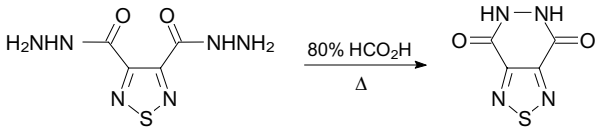
Alk = Me, Et; R^1, R^2 = H, Me; R^3 = H, Me, CF_3, Ph, OEt; Mes is 2,4,6-trimethylphenyl (mesityl), Ts is *p*-toluenesulfonyl (tosyl), DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene

Scheme 3



(*a*) $Pd(OAc)_2$, BQ, AcOH, 120 °C (for R = H; Z = H, 4-MeO, 4-Br, 3-Me, 2-Me, 3,4-Me_2, 3,4-$(MeO)_2$, 3,5-Me_2, 3,4-benzo);
(*b*) $Pd(OAc)_2$, AcOK, DMF, 130 °C (for R = H, Me, Ph; Z = 2-I);
BQ is benzoquinone

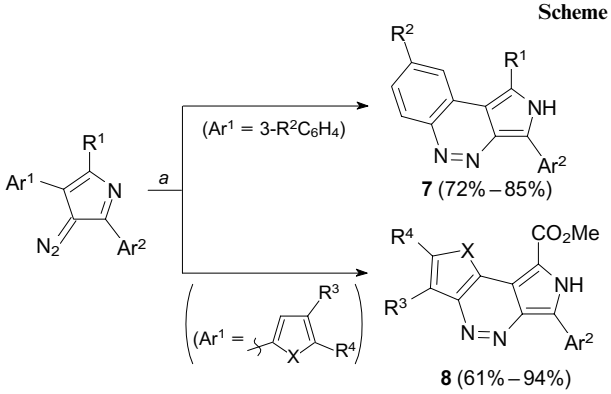
Scheme 4



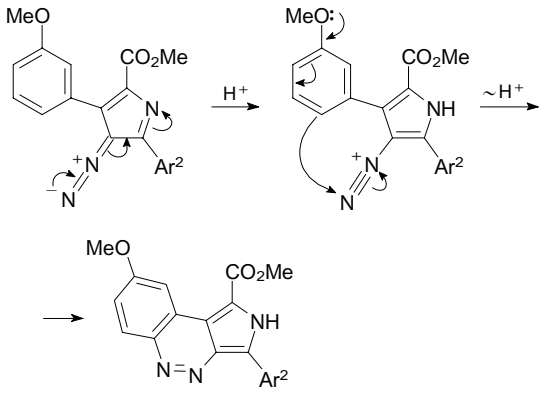
An unusual method for the N(2) – C(3) assembly of the pyridazine ring giving rise to pyrrolo[3,4-*c*]pyridazines **7** and **8** is refluxing of 4-diazopyrrole-2-carboxylates in an acid medium (Scheme 5).[22] After protonation of the pyrrole nitrogen atom, the pyridazine ring is closed *via* an electrophilic attack by the positively charged diazo group on the electron-releasing aromatic moiety (shown for Ar^1 = 3-$MeOC_6H_4$).

4-Hydroxypyridazines **9** and **10** were prepared by the diaza-Wittig reaction according to the N(2) – C(3) synthetic strategy (Scheme 6).[23–25] The essence of the reaction is oxidation of substituted α-diazo-β-keto-δ-hydroxybutanes with 2-iodoxybenzoic acid (IBX) and subsequent diazine ring closure on treatment with phosphine. In the development of this method, the $Bu^n_3P - Pr^i_2O$ system was demonstrated to be more beneficial for phosphorylation than the hexamethylphosphorous triamide (HMPT) – CH_2Cl_2 system, since it provides higher product yields and tolerates a larger number of electron-withdrawing groups (EWG), such as carbonyl and sulfonic groups, in the initial molecule.

Scheme 5

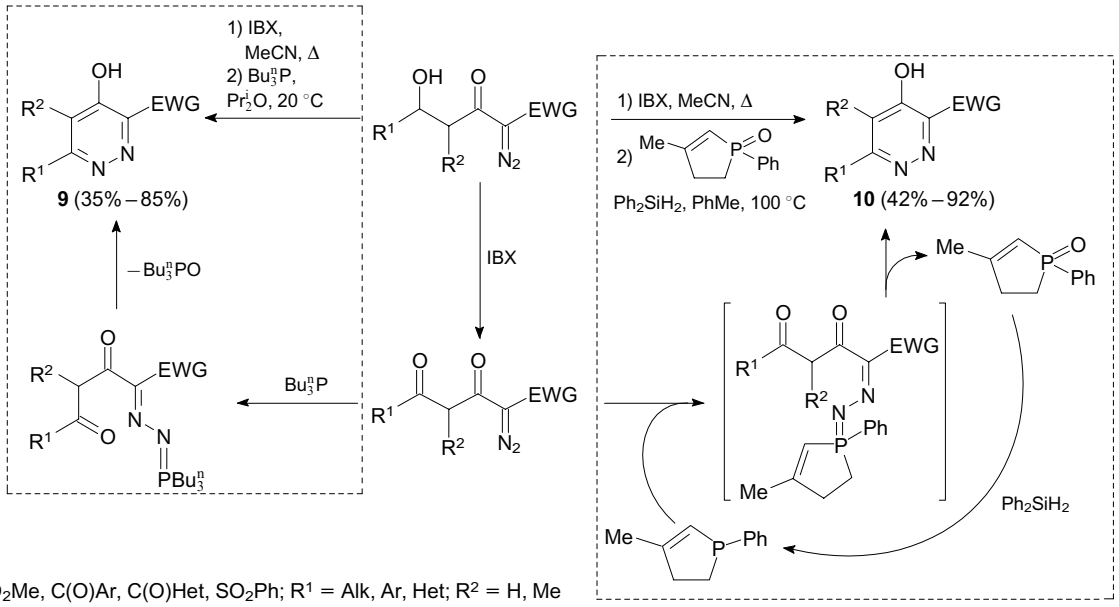


(*a*) 25% H_2SO_4, Δ; Ar^1 = Ph, 3-$MeOC_6H_4$, 2-Th, benzofuran-2-yl, benzo[*b*]thiophen-2-yl; R^1 = Ph, CO_2Me; R^2 = H, OMe; R^3 = R^4 = H, $R^3 - R^4$ is benzo; X = S, O; Th is thienyl



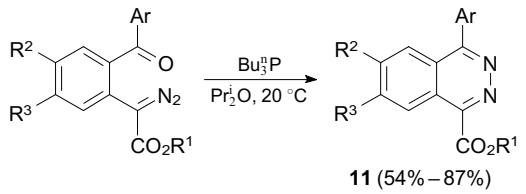
The next efficient step towards improvement of this procedure was the use of organocatalysis. Phospholene oxide served as the catalyst; in the first step it was reduced with diphenylsilane to give the corresponding phospholene, which was introduced into the diaza-Wittig reaction. The back phospholene oxidation into phospholene oxide closed the catalytic cycle. The modified procedure provided higher product yields for all types of substrates used in the reaction

Scheme 6

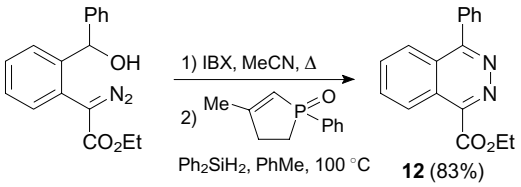


EWG = CO_2Me, C(O)Ar, C(O)Het, SO_2Ph; R^1 = Alk, Ar, Het; R^2 = H, Me

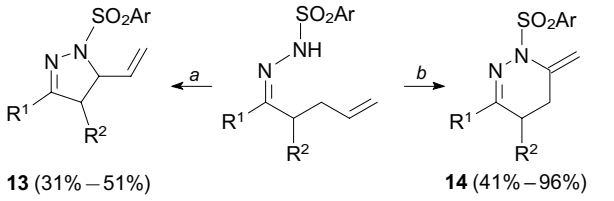
Scheme 7



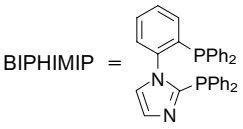
R^1 = Me, Et; R^2 = R^3 = H, OMe; $R^2 – R^3$ is benzo



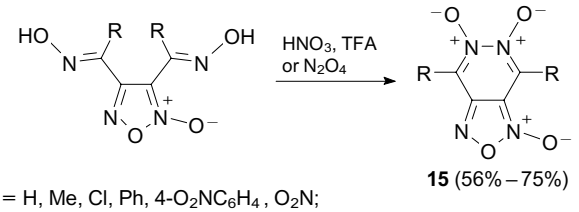
Scheme 8



(*a*) $Pd(OAc)_2$, BIPHIMIP, TsOH, BQ, THF, 45 °C (5-*exo-trig*);
(*b*) $Pd(OAc)_2$, BIPHIMIP, BQ, THF, 45 °C (6-*endo-trig*);
R^1 = Ar, Het, n-C_5H_{11}; R^2 = H, Ph; $R^1 – R^2$ = *o*-$C_6H_4CH_2CH_2$, $(CH_2)_5$



Scheme 9



R = H, Me, Cl, Ph, 4-$O_2NC_6H_4$, O_2N;
TFA is trifluoroacetic acid

and expanded the range of substrates from carbonyl-containing to phenylsulfonyl-containing derivatives.

Substituted phthalazines **11** and **12** were obtained by the diaza-Wittig reaction under the same conditions (Scheme 7).[25, 26]

Depending on the conditions, Pd-catalyzed C – H oxidative cyclization of allyl-*N*-sulfonylhydrazones may follow two pathways (Scheme 8).[27] When the reaction is carried out in the presence of *p*-toluenesulfonic acid, 5-*exo-trig*-cyclization is the preferred pathway, giving 5-vinylpyrazolines **13** in moderate yields. When $Pd(OAc)_2$ in combination with a phosphine ligand and an oxidant is used, 6-*endo-trig*-cyclization takes place, implementing the N(2) – C(3) approach, resulting in the formation of 6-methylidenetetrahydropyridazines **14** in moderate to quantitative yields.

The preparation of unusual 1,2,5-oxadiazolo[3,4-*d*]pyridazine 1,5,6-trioxides **15** according to the N(1) – N(2) strategy was described (Scheme 9).[28] Interesting examples of pyridazine ring closure *via* oxidative N – N bond formation are also considered in the review.[29]

2.2. Formation of two bonds

The synthesis of pyridazines by formation of two bonds can be accomplished in three ways: starting from penta- and monoatomic fragments ([5 + 1]); tetra- and diatomic fragments ([4 + 2]); and two triatomic fragments ([3 + 3]). Examples of [5 + 1] assembly are considered in several reviews.[1, 5, 9] This approach is mainly used to prepare cinnolines by diazotization of anilines that have a reactive electron-releasing group containing at least two carbon atoms in the *ortho*-position to the amino group. The other methods are considered below.

2.2.1. Formation of two bonds from [4 + 2] fragments

The possible retrosynthetic approaches for the assembly of pyridazines from tetra- and diatomic groups are depicted in

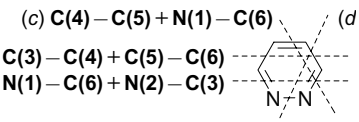
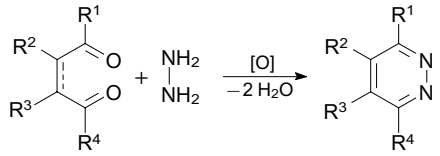


Figure 4. Approaches to the assembly of the pyridazine ring *via* cyclization of tetra- and diatomic fragments ([4 + 2]).

Fig. 4. As will be shown below, strategies involving the formation of N(1) – C(6) and N(2) – C(3) (pathway *a*) or C(4) – C(5) and N(1) – C(6) bonds (pathway *c*) are used most often for assembly of the pyridazine system. In most cases, a synthetic chart starting from hydrazine and the corresponding 1,4-dicarbonyl compounds (in the former case) or appropriate diatomic (C_2) components is most convenient. Methods based on the formation of the C(3) – C(4) and C(5) – C(6) bonds (pathway *b*) can be implemented by means of cycloaddition reactions, for example, the Diels – Alder reaction (see Section 2.5). The least beneficial approach is the formation of N(1) – N(2) and C(5) – C(6) bonds (pathway *d*), because the one-step process is faced with certain synthetic difficulties (it is easier to use starting compounds with a ready N – N group: hydrazines, hydrazones, diazo compounds and so on).

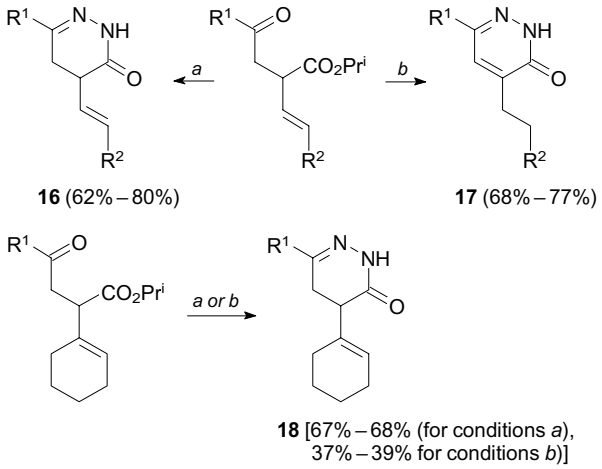
The pyridazine synthesis from 1,4-dicarbonyl compounds and hydrazines is one of the most facile and efficient methods implementing the N(1) – C(6) + N(2) – C(3) strategy (Scheme 10). The applicable sources of carbonyl group in the precursors include both typical aldehyde, ketone, ester, carboxyl and nitrile functions and their synthetic equivalents, such as the 1,1-dibromomethyl or 1,1,1-trichloromethyl group of (*Z*)-2,4,4,4-tetrachlorobut-2-enal, which was converted to 3,5-dichloropyridazine.[30,31] The reaction is carried out with hydrazine or its salts.[32–34] Ethanol or acetic acid is usually used as the solvent. When the 1,4-dicarbonyl compound contains a saturated moiety between the carbonyl groups, oxidative aromatization is required; the oxidants used for this purpose include DMSO,[35] bromine in an acid,[36,37] hydrogen peroxide in an acid, phenyldiazonium chloride [38] and copper(II) chloride.[39] It was shown that the use of microwave radiation (MW) increases the reaction rate and the yields of products.[40,41] In some cases, a base such as potassium carbonate or piperidine may be added for additional activation.[42]

Scheme 10



The features of cyclization of several oxostyryl butanoates with hydrazine (Scheme 11) have been studied.[34] It was shown that the reactant ratio has a considerable influence on the reaction: taking starting compounds in equimolar amounts results in conventional closure of the non-aromatic 4,5-dihydropyridazin-3(2*H*)-one ring (**16**), while a tenfold excess of hydrazine brings about isomerization to give 4,6-disubstituted pyridazin-3(2*H*)-one **17**. When a cyclohexenyl substituent is present in the initial 1,4-dicarbonyl compound, isomerization does not take place regardless of the hydrazine amount, because the

Scheme 11



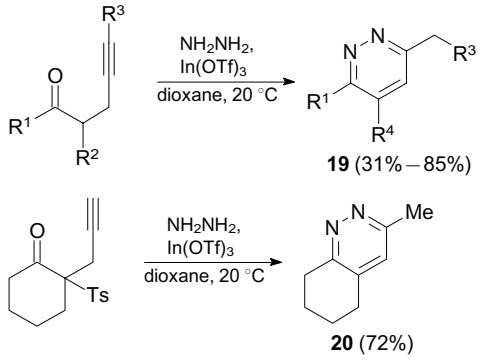
(*a*) $NH_2NH_2 \cdot H_2O$ (1 equiv.), AcOH (0.5 equiv.), CH_2Cl_2, 60 °C;
(*b*) $NH_2NH_2 \cdot H_2O$ (10 equiv.), AcOH (10 equiv.), CH_2Cl_2, 60 °C;
R^1 = CO_2Pr^i, 4-ClC_6H_4; R^2 = Ar, Bn

trisubstituted double bond is more stable than a disubstituted one. This accounts for the formation of 4,5-dihydropyridazin-3(2*H*)-ones **18** as the only products.

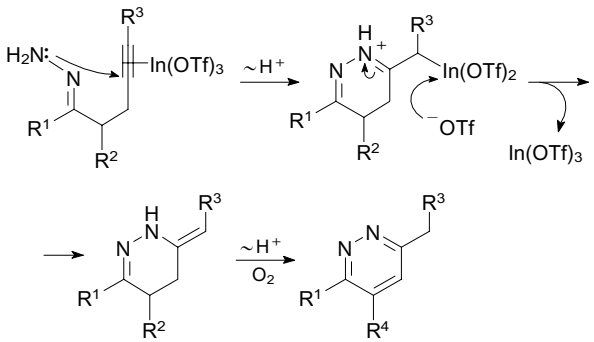
The 6-*exo*-*dig*-cyclization of γ-alkynones with hydrazine activated by indium(III) triflate was proposed for the synthesis of 3,4,6-trisubstituted pyridazines **19** and **20** (Scheme 12).[43] In the case of substrates containing a benzoyl or tosyl group as R^2, this group was eliminated, thus giving 4-unsubstituted products.

The condensation of 6-hydrazinyluracil and substituted glyoxals with the formation of C(4) – C(5) and N(1) – C(6)

Scheme 12

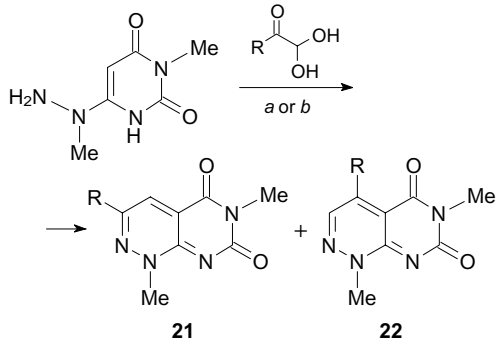


R^1 = Ar, Het; R^2 = R^4 = Ar, Het, CO_2Et; R^4 = H: R^2 = Bz, Ts;
R^3 = H, Me, Et



bonds was proposed for the synthesis of pyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione derivatives **21** and **22** (Scheme 13).[44] It was shown that regioselectivity of the reaction varies depending on the conditions: the reaction conducted in 1,2-dichloroethane (DCE) yields only the 3-substituted isomer, whereas the use of water and sodium acetate results in the formation of a mixture of 3- and 4-substituted isomers.

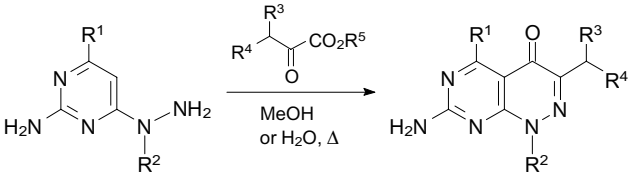
Scheme 13



(*a*) DCE, Δ (19% – 85% total yield, **21** : **22** = 1 : 0);
(*b*) AcONa, H_2O, Δ (43% – 65% total yield, **21** : **22** from 1 : 0 to 2 : 5);
R = Me, Bu^t, Ar

A similar strategy with esters of dibasic oxoacids being used as the C(2)-component was applied to prepare compounds **23** (Scheme 14).[45] After hydrolysis of the ester group, these products were evaluated as dihydropteroate synthase inhibitors.

Scheme 14

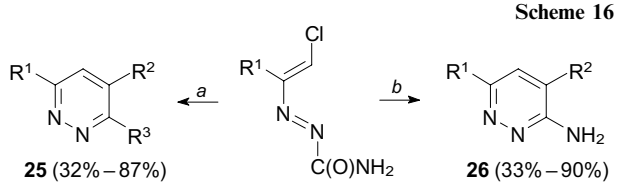


R^1 = NH_2, OH; R^2 = Me, Bn; R^3 = H, Me;
R^4 = CO_2H, CO_2Et, CH_2CO_2H, CH_2CO_2Me, CH_2CO_2Et;
R^5 = Me, Et

A series of pyrazolo[3,4-*c*]pyridazine derivatives **24** were prepared from ethyl 2-arylhydrazono-3-oxobutyrates and potassium cyanoacetohydroxamate in moderate yields (Scheme 15).[46]

1,2-Diazabuta-1,3-dienes can act as the C(2) – N(2) component by reacting with compounds containing an active methylene group (Scheme 16).[47] The reaction includes displacement of the chlorine atom followed by

Scheme 16

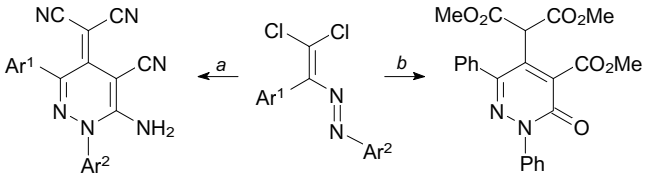


(*a*) 1) $R^2CH_2C(O)R^3$, DIPEA, $CHCl_3$, 20 °C; 2) MeONa, MeOH, Δ;
(*b*) 1) R^2CH_2CN, DIPEA, $CHCl_3$, 20 °C; 2) MeONa, MeOH, Δ;
R^1 = Me, Ph; R^3 = Me: R^2 = CO_2Alk, C(O)NHAr, SO_2Ar, $C_6H_4NO_2$-4, 2-Th; $R^2 – R^3$ = $C(O)(CH_2)_3$; DIPEA is *N*,*N*-diisopropylethylamine

ring closure under the action of sodium methoxide and by aromatization, resulting in the formation of 3,4,6-substituted pyridazines **25** and **26**.

By using 4,4-dichloro-1,2-diazabuta-1,3-diene as the C(2) – N(2) component in the reactions with malononitrile and dimethyl malonate, one can prepare heterocyclization products **27** and **28**. The reaction includes condensation of two carbon acid molecules and subsequent heterocyclization (Scheme 17).[48]

Scheme 17



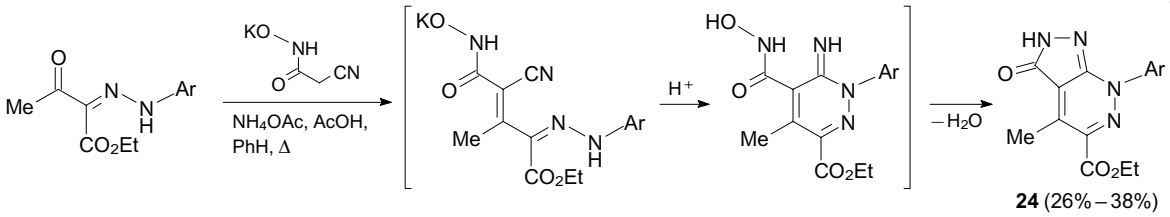
(*a*) $NCCH_2CN$, NaH, THF, 20 °C;
(*b*) $MeO_2CCH_2CO_2Me$, NaH, THF, 20 °C (for Ar^1 = Ar^2 = Ph)

2-Hydrazones of 1,2,3-tricarbonyl derivatives can serve as C(2) – N(2) components, while carbon acids with an activated methylene group or alkyl acetylenedicarboxylate can be utilized as the C(2) fragments. These reagents were used to prepare pyridazines **29** and **30** (Scheme 18).[49 – 51]

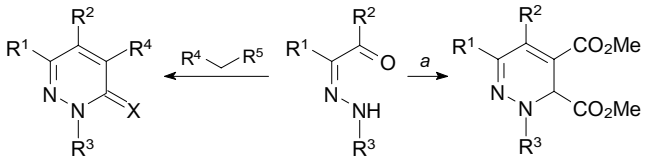
Similar methods accompanied by ultrasonic treatment (UST) were employed to obtain pyridazines **31** and **32** (Scheme 19).[52]

Arylhydrazones of 2-oxo-1,3-dinitriles and -1,3-dicarbonyl compounds can react with cyanoacetylurea to afford pyridazine heterocycles **33** – **35** (Scheme 20).[53] After attack on the hydrazone by the acyl or nitrile group of the cyanoacetylurea anion, the pyridazine ring can be closed either at the amide group of the initial compound with elimination of urea, yielding products **34a**,**b**, or at the nitrile group (**33**, **35**). In the latter case, cyclization with the urea residue additionally takes place. The reaction route depends

Scheme 15



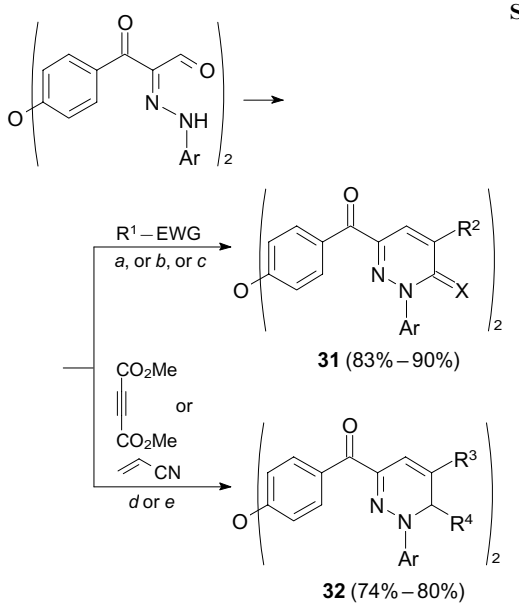
Scheme 18



29 (59% – 89%) **30** (79% – 91%)

(*a*) $MeO_2CC{\equiv}CCO_2Me$, PPh_3, DCE, 20 °C;
R^1 = C(O)Ar, C(O)Het; R^2 = H, Me, Ph; R^3 = Ar, Het;
R^4 = CN, Bz; R^5 = CN, CO_2Et; X = NH, O

Scheme 19

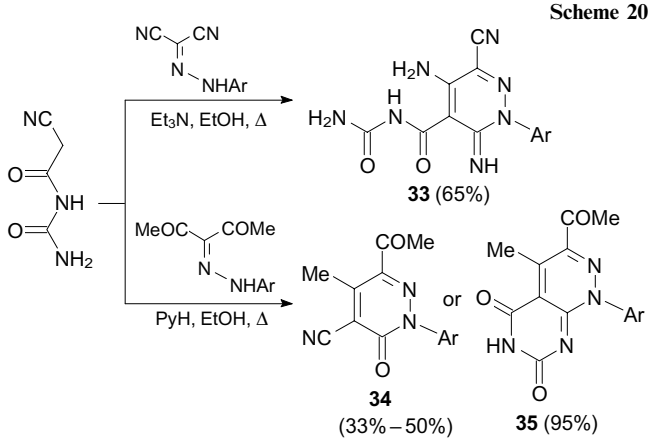


31 (83% – 90%)

32 (74% – 80%)

(*a*) US, PhMe; (*b*) US, PyH; (*c*) US, Ac_2O;
(*d*) US, PPh_3, CH_2Cl_2; (*e*) US, DABCO, EtOH;
Ar = 4-MeC_6H_4, 4-$F_3CC_6H_4$; EWG = CO_2H, CO_2Et, CN;
R^1 = CH_2CN, CH_2CO_2Et, CH_2Bz, CH_2NHBz, $CH{=}PPh_3$;
R^2 = CN, CO_2Et, Bz, NHBz, H; R^3 = CO_2Me, CN; R^4 = CO_2Me, H;
X = O, NH; Py is pyridyl, DABCO is 1,4-diazabicyclo[2.2.2]octane

Scheme 20



33 (65%)

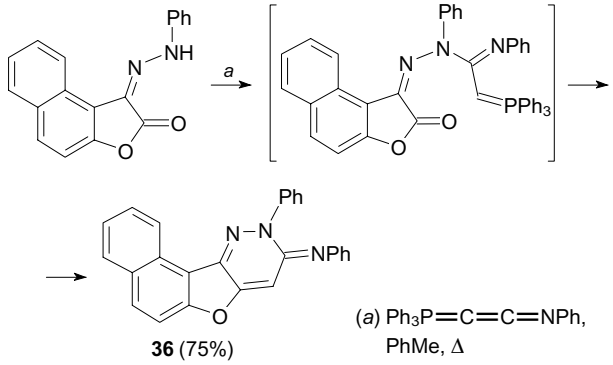
34 (33% – 50%) **35** (95%)

Ar = 4-$MeOC_6H_4$ (**33**, **34a**), 4-$O_2NC_6H_4$ (**34b**), 4-ClC_6H_4 (**35**)

on the substituent in the benzene ring of the aromatic moiety.

An unusual compound to be used as the C(2)-component is (*N*-phenyliminovinylidene)triphenylphosphorane, which was employed to prepare heterocycle **36** (Scheme 21).[54]

Scheme 21



36 (75%)

(*a*) $Ph_3P{=}C{=}C{=}NPh$, PhMe, Δ

2.2.2. Formation of two bonds from [3 + 3] fragments

The concept of pyridazine ring assembly from two triatomic fragments ([3 + 3]) may imply two possible types of coupling — formation of C(3) – C(4) + N(1) – C(6) bonds and N(1) – N(2) + C(4) – C(5) bonds (Fig. 5). However, the latter approach is less preferred since the N – N bond formation is energetically unfavourable (see Section 2.2.1).

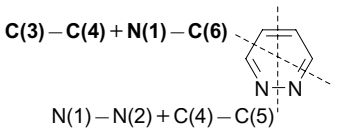


Figure 5. Approaches to the assembly of the pyridazine ring from [3 + 3] fragments.

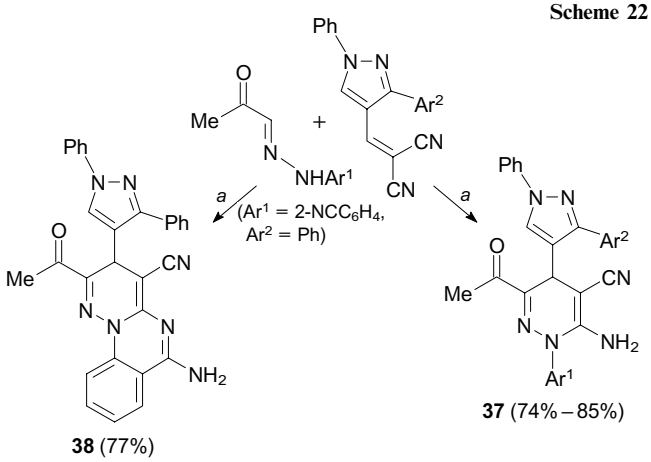
In the synthesis of dihydropyridazines **37**, 2-oxoaldehyde hydrazones can act as the C – N(2) components, with alkylidenemalononitriles being used as the C(3)-components (Scheme 22).[55] When a 2-cyanophenyl substituent is present in the starting arylhydrazone, additional cyclization takes place, giving rise to fused polyheterocyclic system **38**.

A regioselective method for the synthesis of pyridazines from chalcone epoxides and diazodicarbonyl compounds has been reported (Scheme 23).[56] The diazodicarbonyl compound is deacylated under the action of the ethoxide anion, and then the diazo ester anion nucleophilically attacks the chalcone epoxide. The resulting intermediate eliminates a water molecule, then the ethoxide anion cleaves the epoxide ring, and the enolate attacks the diazo group to yield 5-hydroxy-4,6-diarylpyridazine-3-carboxylates **39**.

A synthetic route to pyrrolo[1,2-*b*]pyridazines **40** based on 1*H*-pyrrole-1-amine derivatives and also involving chalcones has been developed (Scheme 24).[57] The reaction mechanism includes a nucleophilic attack on the pyrrole ring, isopropyl group migration and aromatization of the system.

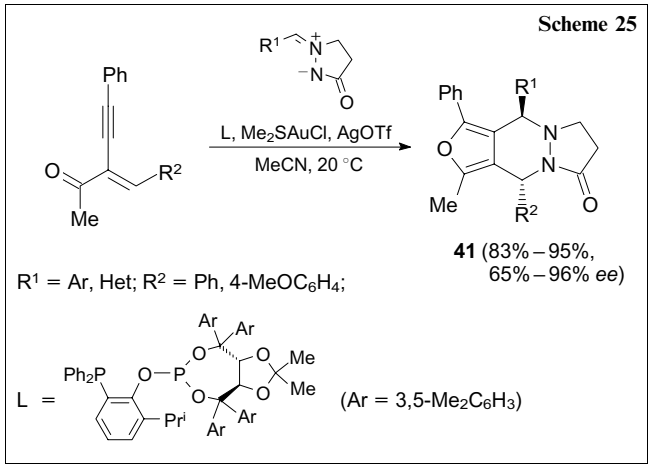
Furo[3,4-*d*]pyrazolo[1,2-*a*]tetrahydropyridazinones **41** were prepared *via* a cyclization – intramolecular [3 + 3]

Scheme 22



(*a*) PyH, dioxane, Δ; Ar^1 = Ph, 4-ClC_6H_4; Ar^2 = Ph, 4-MeC_6H_4 , 4-ClC_6H_4

Scheme 25

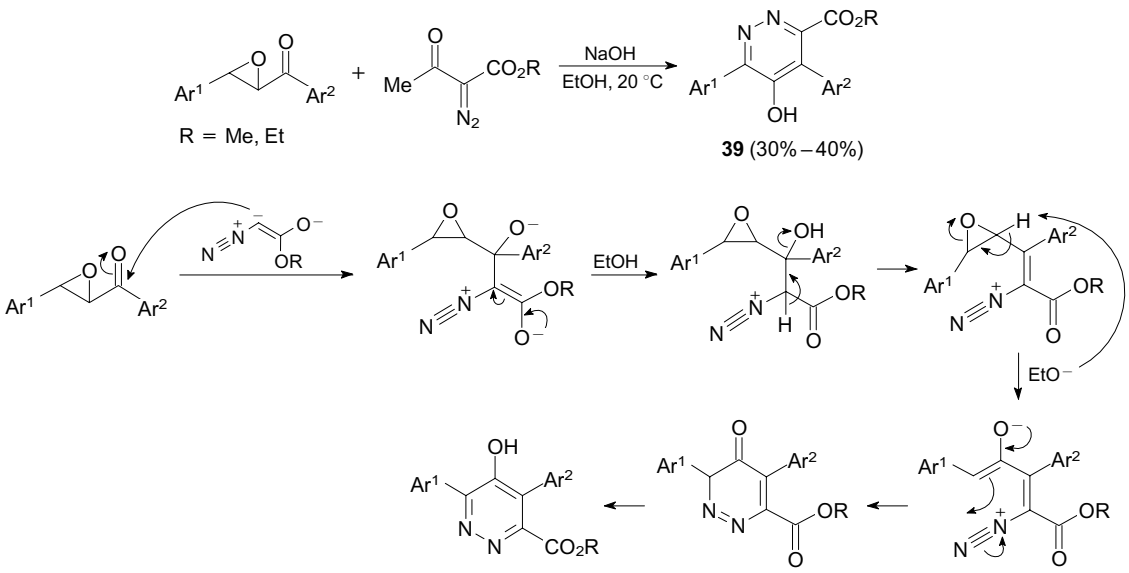


cycloaddition tandem process involving 2-(alkyn-1-yl)alk-2-en-1-ones and azomethine imines in the presence of a chiral Au catalyst generated *in situ* (Scheme 25).[58] The target products can be obtained in high yields and with high enantioselectivity: the enantiomeric excess (*ee*) reaches 95%.

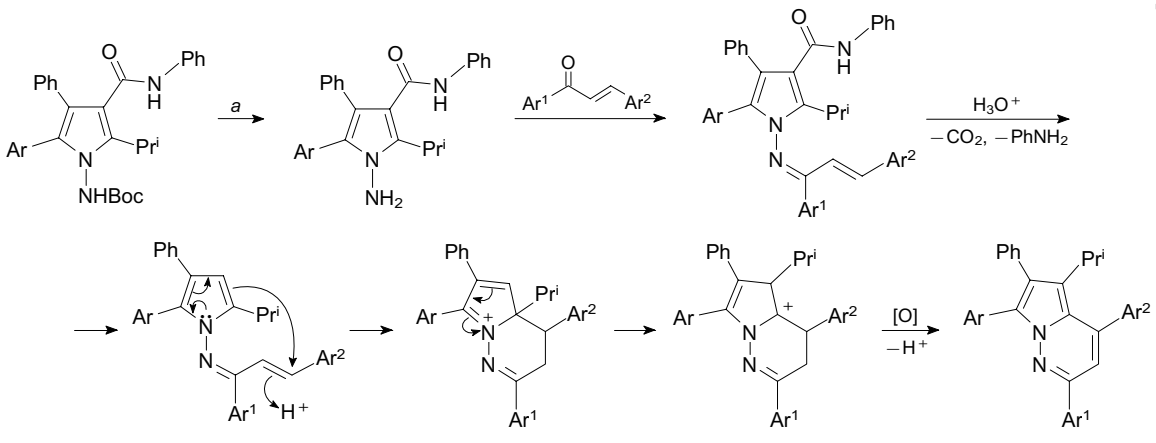
2.3. Formation of three bonds

The approaches to the formation of the pyridazine system *via* the formation of three bonds can be divided into three groups according to the number of atoms in the fragments that close the ring: [2 + 2 + 2], [1 + 2 + 3] and [1 + 1 + 4]

Scheme 23



Scheme 24



(*a*) TsOH, PhMe – cyclo-C_6H_{12} (3 : 2), Δ; Boc is *tert*-butoxycarbonyl

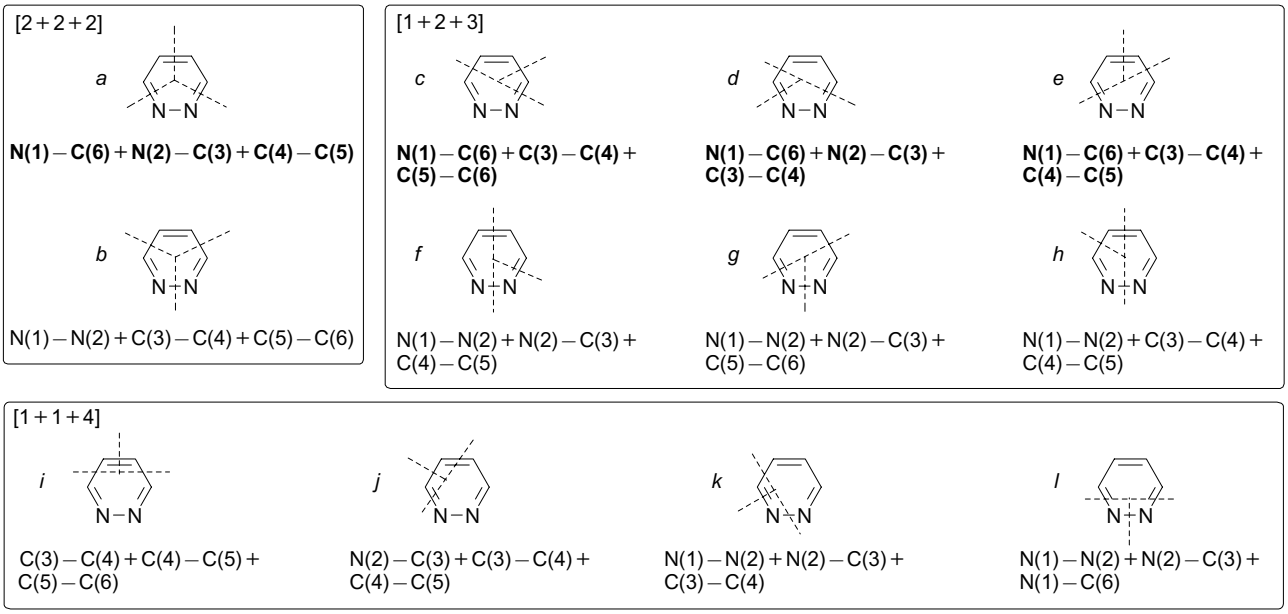


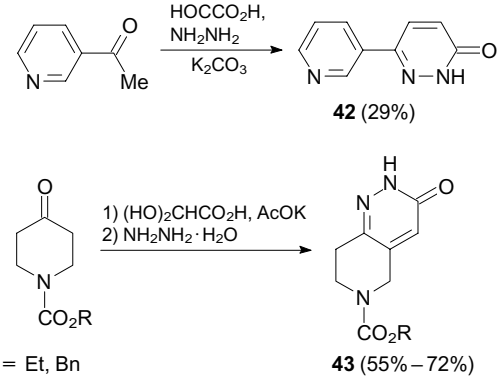
Figure 6. Approaches to the assembly of the pyridazine ring by the formation of three bonds.

protocols (Fig. 6). Considering all possible combinations gives 12 pathways (*a*–*l*), six of which (*b*, *f*–*h*, *k*, *l*) imply energetically unfavourable formation of N–N bonds. Methods based on the [1 + 1 + 4] protocol (*i*, *j*) associated with C–C bond formation may be difficult to implement in a multicomponent reaction. Thus, four strategies can be listed for the three-component synthesis of pyridazines associated with the formation of N(1)–C(6) + N(2)–C(3) + C(4)–C(5) bonds (*a*); N(1)–C(6) + C(3)–C(4) + C(5)–C(6) bonds (*c*); N(1)–C(6) + N(2)–C(3) + C(3)–C(4) bonds (*d*); or N(1)–C(6) + C(3)–C(4) + C(4)–C(5) bonds (*e*).

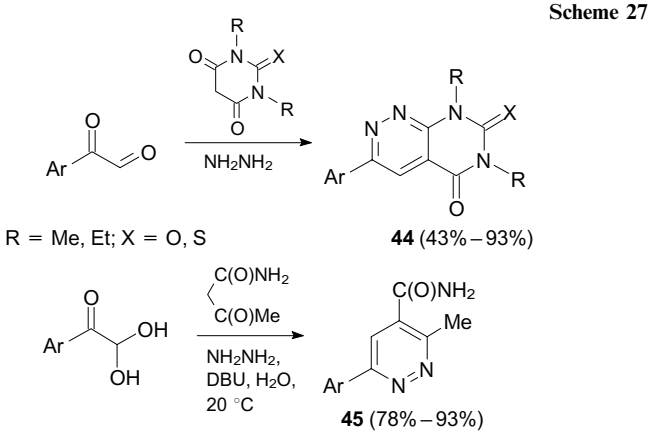
A simple example corresponding to formation of N(1)–C(6), N(2)–C(3) and C(4)–C(5) bonds is the preparation of pyridazin-3(2*H*)-ones **42** and **43** from appropriate ketones, glyoxylic acid and hydrazine (Scheme 26).[59, 60]

Similarly, the reactions of arylglyoxals and hydrazine with barbituric or thiobarbituric acid or acetoacetamide are accompanied by the formation of 3-arylpyrimido[4,5-*c*]-pyridazine-5,7(6*H*,8*H*)-diones (or their thio analogues) **44** or 6-aryl-3-methylpyridazine-4-carboxamides **45** (Scheme 27).[61–63] An interesting case corresponding to the

Scheme 26



Scheme 27

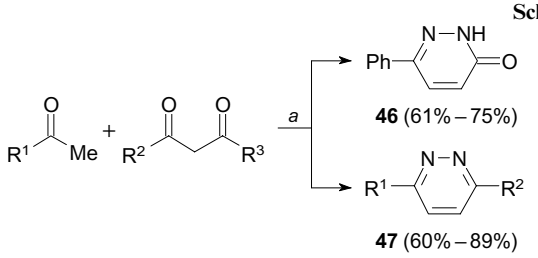


N(1)–C(6) + N(2)–C(3) + C(4)–C(5) strategy is the synthesis of 3,6-substituted pyridazines **46** and **47** from readily available methyl ketones and 1,3-dicarbonyl compounds with the participation of hydrazine (Scheme 28).[64] A distinctive feature of this method is efficient intermediate elimination of one acyl group of the dicarbonyl precursor induced by excess hydrazine. The use of ethyl benzoylacetates results, in all cases, in the selective formation of pyridazinone **46**, irrespective of the nature of substituents R^3 in the benzoyl moiety.

The formation of the pyridazine ring of compounds **48** according to the N(1)–C(6) + C(3)–C(4) + C(5)–C(6) strategy occurs *via* condensation of 2-[4-(2-thienyl)pyrimidin-2-ylthio]acetohydrazide, benzaldehyde and malononitrile (Scheme 29).[65]

One more example of using this strategy is the synthesis of pyridazine-3-carboxamide derivatives **49** by reacting oxamic acid thiohydrazides with chlorovinylaldehydes obtained from the corresponding ketones through the Vilsmeier–Haack reaction. The subsequent 6π-electrocyclic closure of the pyridazine ring is accompanied by elimination of molecular sulfur (Scheme 30).[66, 67]

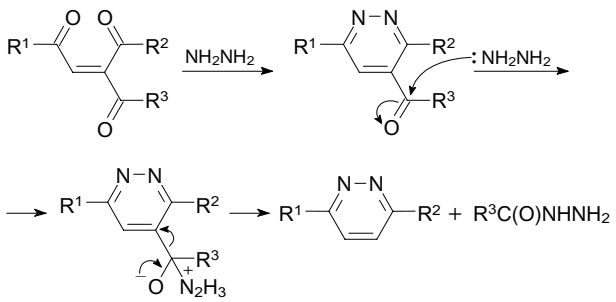
Scheme 28



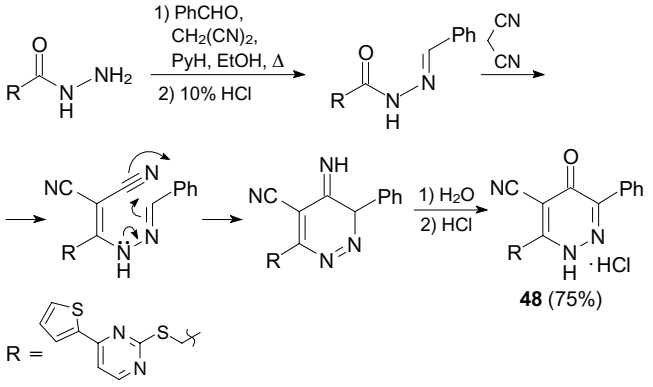
46 (61% – 75%)

47 (60% – 89%)

(*a*) 1) CuO, I_2, DMSO, 70 °C; 2) $NH_2NH_2 \cdot H_2O$, Bu^{t}OH, Δ;
46: R^1 = Ph, R^2 = OEt: R^3 = Ar, 2-Fu;
47: R^1 = Ar, Het; R^2, R^3 = Me, Ph, 4-$MeOC_6H_4$; Fu is furyl

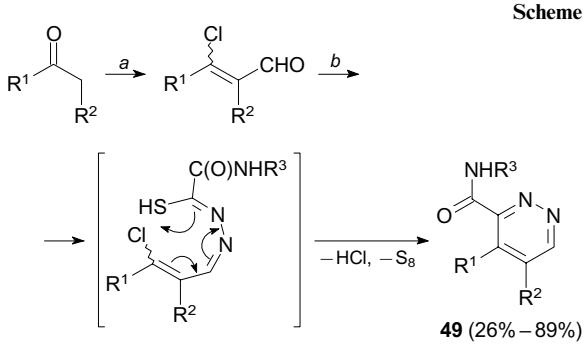


Scheme 29



48 (75%)

Scheme 30

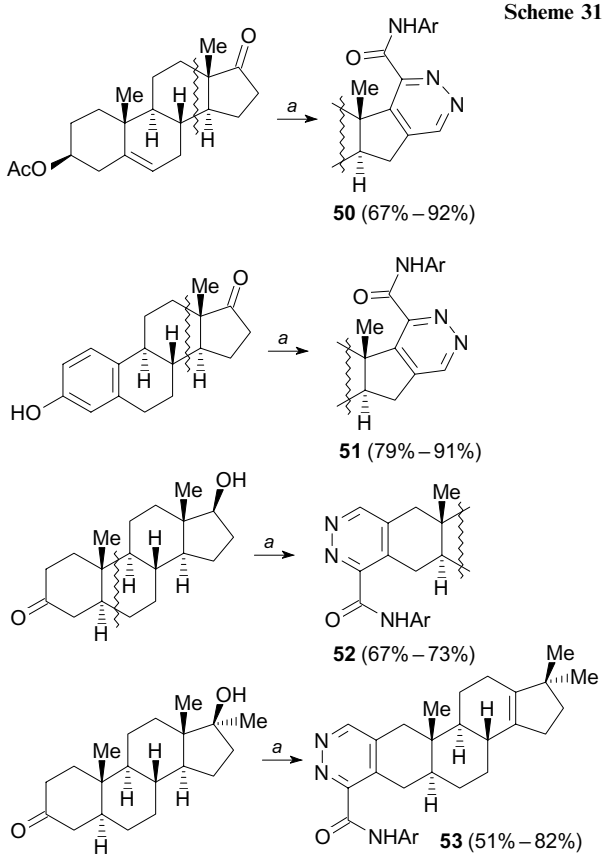


49 (26% – 89%)

(*a*) $POCl_3$, DMF, CH_2Cl_2, Δ; (*b*) $H_2NNHC(S)C(O)NHR^3$, TsOH;
R^1, R^2 = Alk; $R^1 - R^2$ = $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_2CH(Ph)CH_2$, $(CH_2)_2CH(Bu^t)CH_2$, $(CH_2)_2N(CO_2Et)CH_2$, $(CH_2)_2OCH_2$; R^3 = Ar, Bn

This method was successfully used to modify a number of steroids to give annulated pyridazines **50** – **53** (Scheme 31). It is worth noting that in the case of 3-keto-17α-methyl-17β-hydroxyandrostane, the substrate also

Scheme 31



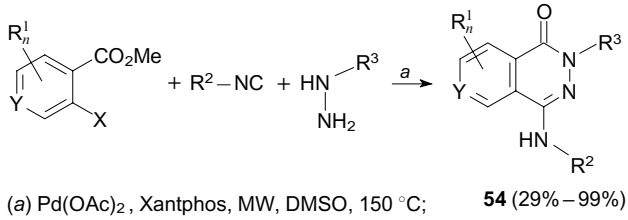
(*a*) 1) $POCl_3$, DMF, CH_2Cl_2, Δ; 2) $H_2NNHC(S)C(O)NHAr$, TsOH

underwent the Wagner – Meerwein rearrangement, which resulted in compound **53**.

A palladium-catalyzed reaction was used to implement the approach involving formation of the N(1) – C(6) + N(2) – C(3) + C(3) – C(4) bonds for the synthesis of 4-aminophthalazinones **54** (Scheme 32, substituent positions in the substrate are indicated).[68]

An example of the N(1) – C(6) + C(3) – C(4) + C(4) – C(5) strategy is a reaction catalyzed by activated magnesium oxide or phosphotungstic acid. Under these conditions, methylglyoxal arylhydrazones, benzaldehydes and 1,3-dicarbonyl compounds react to afford dihydropyrida-

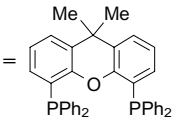
Scheme 32



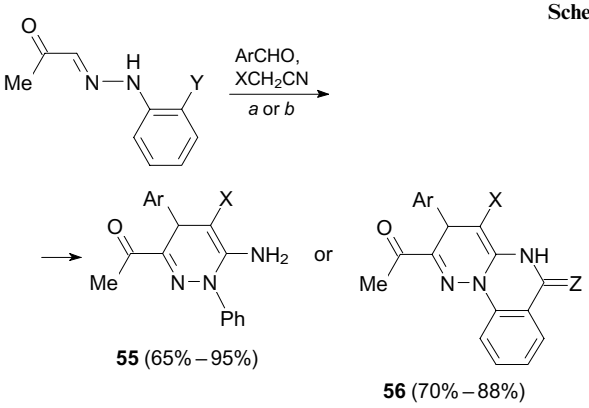
54 (29% – 99%)

(*a*) $Pd(OAc)_2$, Xantphos, MW, DMSO, 150 °C;
X = Cl, Br, I, OTf; Y = CH, N; R^1_n = H, 5-Cl, 4-F, 5-CF_3, 4,5-benzo, 4-Me, 3-OMe, 5-OMe, 5-NH_2, 4-morpholino, 4-$(NHCH_2C_6H_4F$-4);
R^2 = Bu^t, $CMe_2CH_2Bu^t$; R^3 = H, Me, Ph, 4-$F_3CC_6H_4$;

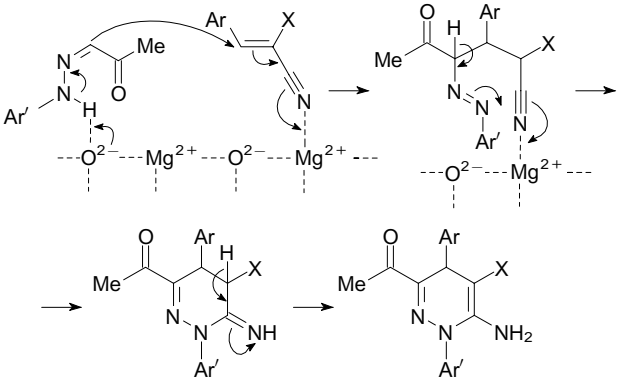
Xantphos =



Scheme 33



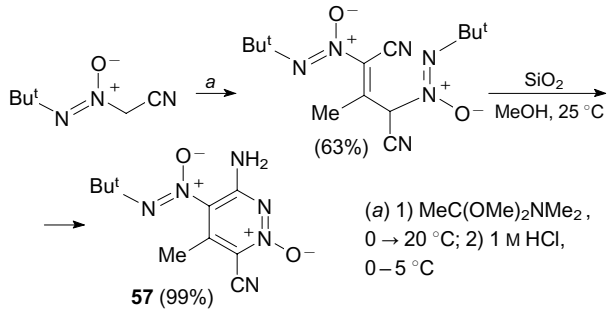
(*a*) Et_3N, MgO, MeCN, Δ; (*b*) Et_3N, $H_3PW_{12}O_{40}$, MeCN, rt;
X = CN, CO_2Et; Y = H, CN, CO_2Et; Z = O, NH



zine derivatives **55** and **56** (Scheme 33).[69] The authors proposed a possible reaction mechanism.

An interesting reaction with formation of the N(1) – C(6), C(3) – C(4) and C(4) – C(5) bonds of the pyridazine system is depicted in Scheme 34.[70] The reaction of (*tert*-butyl-*NNO*-azoxy)acetonitrile with *N*,*N*-dimethylacetamide dimethylacetal followed by treatment with silica gel affords derivative **57**.

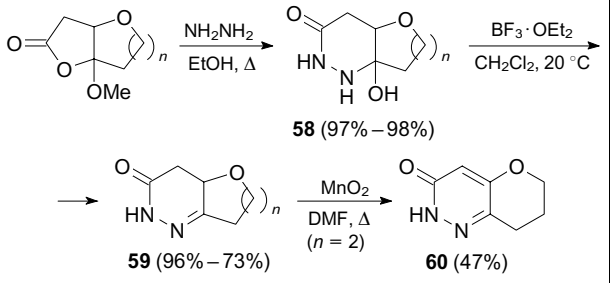
Scheme 34



2.4. Ring expansion

The expansion of the hydroxyfuranone ring continues the synthetic strategy towards pyridazines based on the [4 + 2] fragment; in this case, the furan ring acts as the C(4) component, while the N(2) component is again represented by hydrazine (Scheme 35).[71] After the formation of the tetrahydropyridazinone system, dehydration and oxidation can be conducted one after the other with successive formation of compounds **58** – **60**.

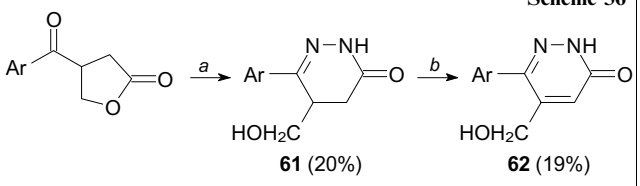
Scheme 35



n = 1, 2

Benzoyl-γ-butyrolactones and hydrazine also served as the starting compounds for the synthesis of pyridazinones; first, they were converted to 6-aryl-5-hydroxymethyl-4,5-dihydropyridazin-3(2*H*)-ones **61** (Scheme 36).[72] The subsequent ring aromatization giving 6-aryl-5-hydroxymethylpyridazin-3(2*H*)-ones **62** was induced by oxidation with manganese dioxide under acetyl protection of the hydroxyl group.

Scheme 36



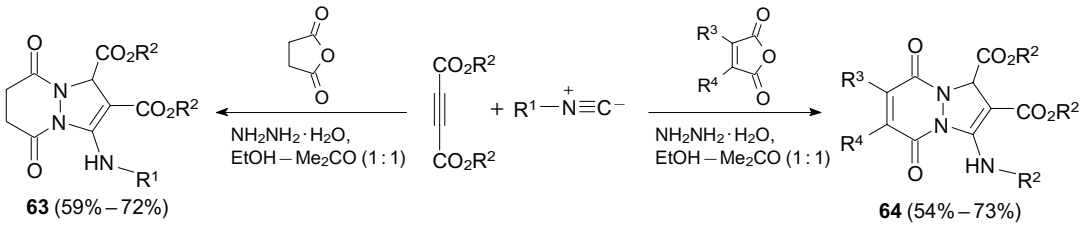
(*a*) NH_2NH_2, EtOH, Δ;
(*b*) 1) Ac_2O, PyH, 20 °C; 2) MnO_2, $CHCl_3$, Δ; 3) 2 M HCl, Δ

The simple strategy of assembly of the pyridazine core using the hydrazine N(2) component and a five-membered oxygen-containing heterocycle may be a part of the synthesis of functionalized pyrazolopyridazine-5,8-diones **63** and **64** (Scheme 37).[73]

A similar idea was utilized to prepare 1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-diones **65**, containing amino and cyano groups (Scheme 38).[74] Maleic or phthalic anhydride was allowed to react with hydrazine, and the pyrazole moiety was assembled from malononitrile and aldehydes. Catalysis by the nanomagnetic ionic liquid (NMIL), composed of $Fe_3O_4@SiO_2$ bearing surface-grafted piperidinium cations and surrounded by benzene-1,3-disulfonate anions, $\{Fe_3O_4@SiO_2@(CH_2)_3-{}^+NH(CH_2)_5\}_2[C_6H_4(SO_3^-)_2$-1,3], was the key issue of the synthesis. Apparently, the NMIL particles activate the electrophilic groups of the reactants owing to the presence of positively charged pyridinium groups.

The synthesis of nickel(II) complexes with 10,20-dimesityl-5,15-diazaporphyrin **66** was accompanied by the formation of derivatives **67** as by-products, resulting from the rearrangement of one pyrrole ring of the ligand to give a pyridazine moiety (Scheme 39).[75] The key goal of that study was to prepare unrearranged complexes, the yield of which was subsequently increased by complete elimination of the formation of by-products; therefore, the preparative value of this process is moderate. Nevertheless, this transformation can be of interest for further research, since the products represent a new class of complex compounds potentially possessing interesting physical properties.

Scheme 37

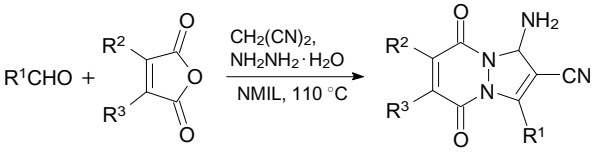


63 (59% – 72%)

64 (54% – 73%)

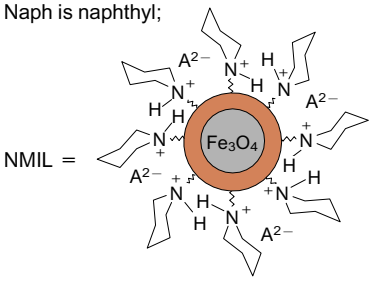
R^1 = Alk, Bn; R^2 = Me, Et, Bu^t; R^3 = R^4 = H; $R^3 - R^4$ is benzo, tetrachlorobenzo

Scheme 38

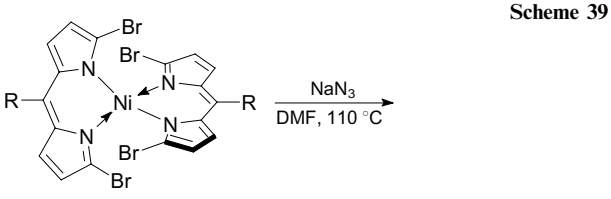


65 (60% – 94%)

R^1 = Ar, CH_2Bn, 2-Naph; R^2 = R^3 = H; $R^2 - R^3$ is benzo;
Naph is naphthyl;



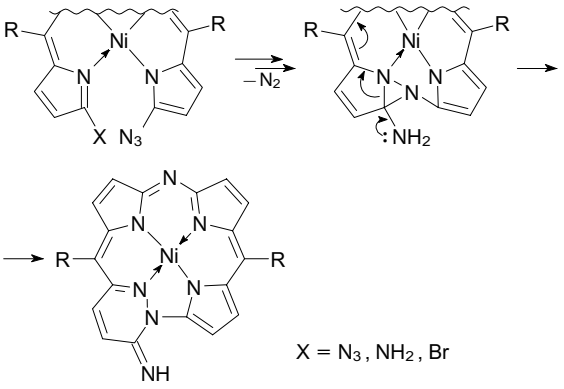
Scheme 39



66 (12%)

67 (13% – 20%)

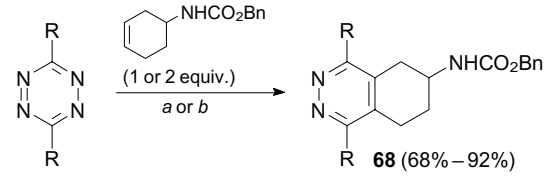
R = Mes; X = O, NH



2.5. Cycloaddition

As noted above, a facile approach to the formation of the pyridazine ring implementing the C(3) – C(4) + C(5) – C(6) strategy is the use of cycloaddition reactions. The inverse electron demand Diels – Alder reaction of 1,2,4,5-tetrazines is used most often. For example, 3,6-substituted pyridazines **68** were obtained in this way (Scheme 40).[76] When the reaction is carried out in refluxing acetonitrile, the second tetrazine equivalent serves as the oxidant.

Scheme 40

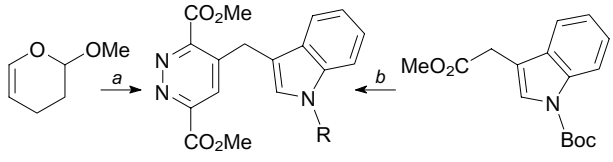


68 (68% – 92%)

(*a*) 1) CH_2Cl_2, 20 °C; 2) PIFA (for R = CO_2Me);
(*b*) MeCN, Δ (for R = 2-Py);
PIFA is bis(trifluoroacetoxy)iodobenzene

Two procedures used for the synthesis of 4-[(1*H*-indol-3-yl)methyl]pyridazine-3,6-dicarboxylates **69** were compared: first, a combination of the Diels – Alder and Fischer reactions and second, a combination of Tebbe methylenation and the Diels – Alder reaction (Scheme 41).[77] The total yield of the product was found to be higher in the latter case.

Scheme 41



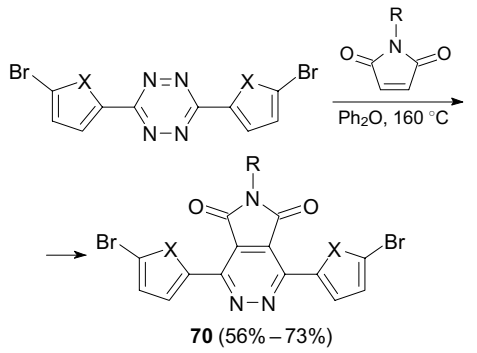
69

(*a*) 1) 3,6-di(methoxycarbonyl)tetrazine, dioxane, 20 °C;
2) $PhNHNH_2$, AcOH, MeOH (for R = H, 9% yield);
(*b*) 1) μ-chlorobis(cyclopentadienyl)(dimethylaluminium)-μ-methylenetitanium (Tebbe reagent), THF, –40 → 20 °C;
2) 3,6-di(methoxycarbonyl)tetrazine, dioxane, 20 °C (for R = Boc, 43% yield)

The Diels – Alder reaction was also applied to synthesize conjugated compounds **70**, which were utilized in the design of electrochromic copolymers (Scheme 42).[78]

A deoxyuridine triphosphate derivative containing a vinyl group in position 5 was used as an unusual substrate for the assembly of the pyridazine ring (Scheme 43).[79] Compound **71** produced in the reaction with 3,6-di(2-pyri-

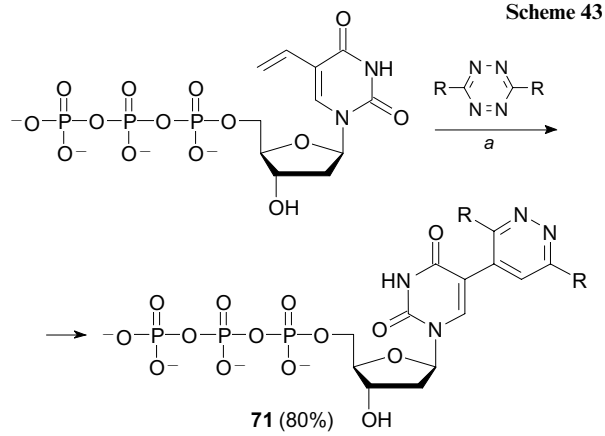
Scheme 42



70 (56% – 73%)

X = O, S; R = n-C_6H_{13}, $CH_2CH(C_8H_{17}$-n)$C_{10}H_{21}$-n

Scheme 43



71 (80%)

(*a*) O_2 (air), dioxane, H_2O, 20 °C; R = 2-Py

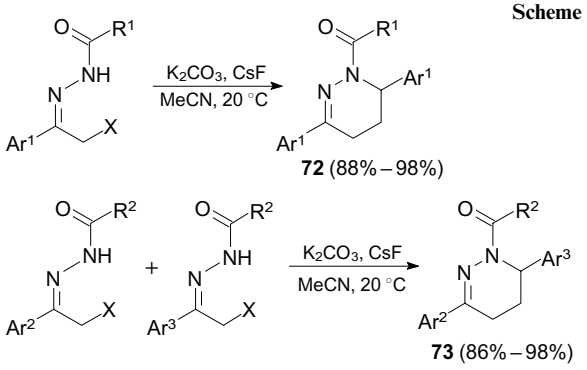
dyl)tetrazine could find use in polymerase chain reaction for fluorescence determination and visualization of cellular DNA. A similar synthetic strategy was described for a library of DNA-encoded compounds.[80]

An interesting method was proposed for the synthesis of tetrahydropyridazines, namely, cyclodimerization of α-halo-*N*-acylhydrazones (Scheme 44).[81,82] The reaction mechanism includes conversion of the substrate, under the action of a base, to substituted 1,2-diazabuta-1,3-diene, which further undergoes [4 + 2] cycloaddition, eliminates an acyl group and a nitrogen molecule after an attack by the fluoride anion and adds a proton to give 1-acyl-3,6-diaryl-1,4,5,6-tetrahydropyridazines **72**. It was found that this protocol can be rather easily modified to enable cross-cyclodimerization involving two different α-halo-*N*-acylhydrazones taken in 2 : 1 ratio. In this case, the reaction gives product **73** as a single regioisomer.

A similar method for the synthesis of substituted tetrahydropyridazines **74** is also based on the Diels – Alder reaction; however, in this case, the formation of diazabutadiene is facilitated by the use of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) (Scheme 45).[83]

The cascade process based on [4 + 2] cycloaddition with the subsequent nucleophilic attack by the pyrazole moiety on the formed 4,5-dihydropyridazine ring results in the diastereoselective formation of product **75** (Scheme 46).[84] The minor diastereomer **75′** is one of the other three possible isomers.

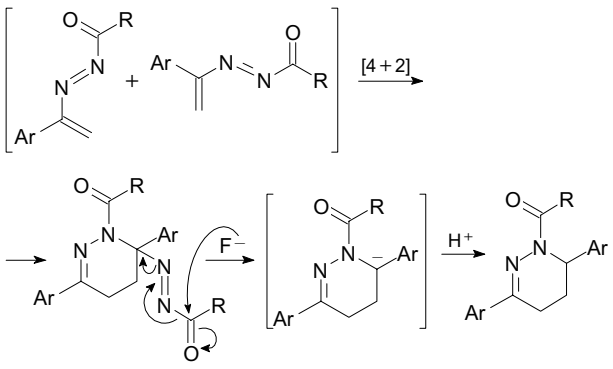
Scheme 44



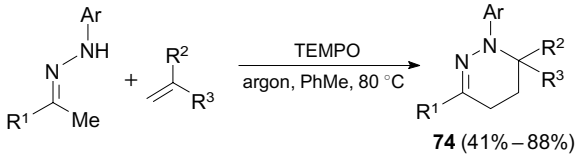
72 (88% – 98%)

73 (86% – 98%)

X = Br, Cl; R^1 = Me, Ar, 2-Fu; R^2 = Me, Ph; Ar^1 = Ph, 4-NCC_6H_4, 4-MeC_6H_4, 3,4-$Cl_2C_6H_3$, 2-Naph; Ar^2 = 4-PhC_6H_4, 2-Naph, 4-NCC_6H_4, 4-$O_2NC_6H_4$, 4-ClC_6H_4, 3,4-$Cl_2C_6H_3$; Ar^3 = 4-PhC_6H_4, 4-MeC_6H_4



Scheme 45



74 (41% – 88%)

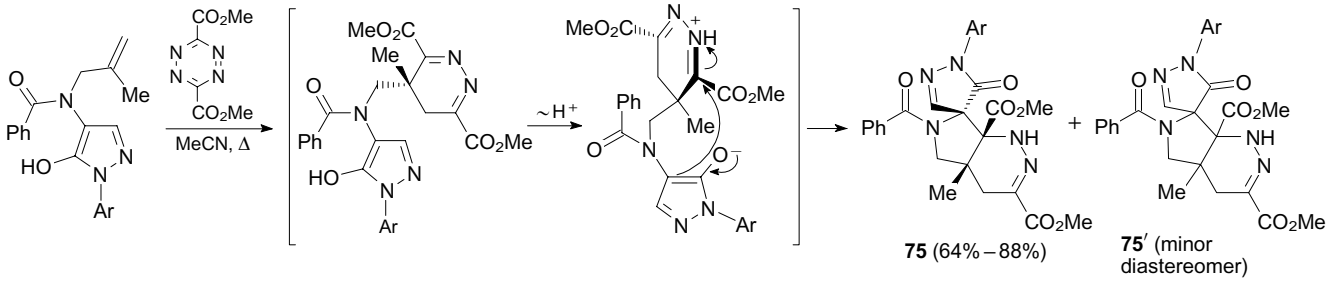
R^1 = Me, Bu^t, Ar, 2-Th; R^2 = CO_2Alk, CO_2Bn, CO_2Ph, C(O)NHPh, Ar, Het; R^3 = H, Me

An unusual synthetic route to 5-fluorine-substituted pyridazines **76** includes a series of successive [2 + 1] and [3 + 2] cycloadditions involving terminal alkynes, difluorocarbene and diazocarbonyl compounds (Scheme 47).[85] The conditions of generation of difluorocarbene varied depending on the degree of electron deficiency of alkynes.[86]

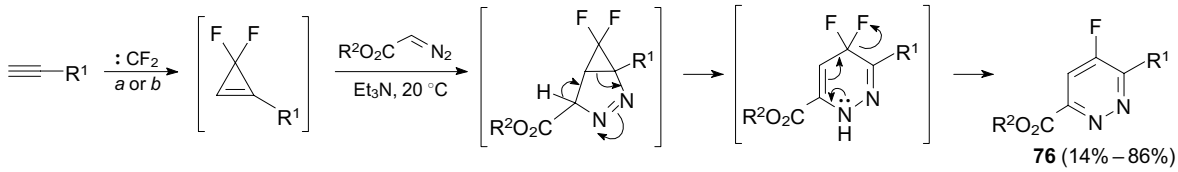
3. Pyridazine ring reactivity

The key structural feature of pyridazines determining their reactivity is the presence of two neighbouring nitrogen atoms in the aromatic six-membered ring (Scheme 48). This causes relative intertness of pyridazines towards electrophilic substitution reactions and higher reactivity towards nucleophilic substitution reactions compared with pyridine derivatives, which contain only one nitrogen atom in the aromatic ring. The electrophilic attack is directed to only one nitrogen atom, as the positive charge on this atom deactivates the second nitrogen atom. Pyridazines are weaker bases (pK_{aH} = 2.3) than pyridines (pK_{aH} = 5.2), because the second nitrogen atom has a destabilizing action

Scheme 46

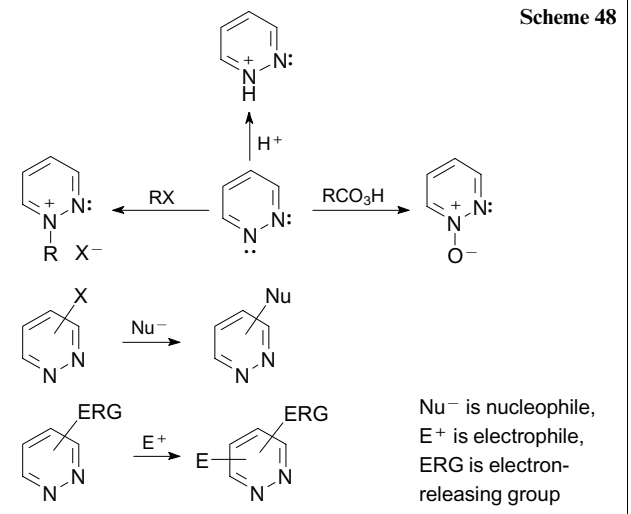


Scheme 47

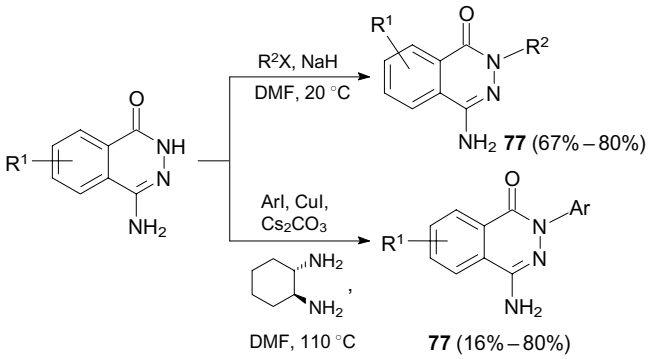


(*a*) $TMSCF_3$, NaI, THF, 110 °C; (*b*) TFDA, NaF, diglyme, 120 °C; R^1 = Ar, Het, Bn, cyclo-C_3H_5, cyclo-C_6H_{11}, CH_2OAc, $CH_2CH_2NBoc_2$, $CH(CH_2CH_2)_2NTs$; R^2 = Et, Bn, Bu^t; TMS is trimethylsilyl, TFDA is trimethylsilyl fluorodisulfonyldifluoroacetate

Scheme 48



Scheme 49



R^1 = H, OMe, Me, Cl,morpholino; R^2 = Me, Bn, All; X = Br, I

on the formed pyridazinium cation. However, this does not prevent the formation of salts with alkyl halides or *N*-oxides with peroxy acids.

3.1. Electrophilic attack on pyridazine nitrogen atoms

Examples of introducing alkyl substituents to pyridazine nitrogen atoms are found in the literature quite often. Typical cases are nucleophilic substitution followed by deprotonation of the diazinium salt.[17, 32, 40] A modification of this technique with the use of ultrasonic treatment is known.[87] There are examples of selective *N*-alkylation and *N*-arylation of 4-aminophthalazin-1(2*H*)-ones to give 4-amino-2-aryl(alkyl)phthalazin-1(2*H*)-ones **77** both by the classical procedure and in the presence of a Cu catalyst (Scheme 49).[68]

Diazinium salts **78** and **79** were isolated and the former were found to exhibit antibacterial properties[88, 89] (Scheme 50).

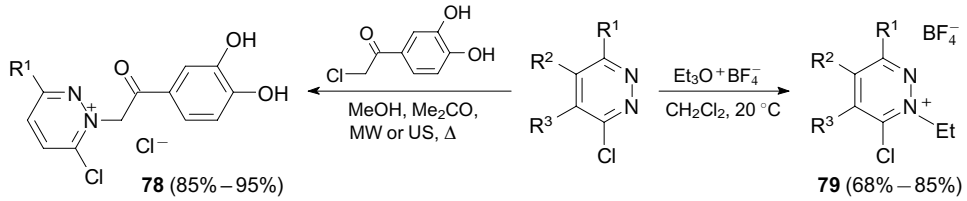
The possibility of electrophilic attack on the nitrogen atoms in the pyridazine system opens the route to imidazo[1,2-*b*]pyridazines **80** and **81** (Scheme 51).[90, 91]

A method was proposed for the synthesis of 6-chloro-1,2,4-triazolo[1,5-*b*]pyridazines **82** by addition of nitrile to 3-aminopyridazine catalyzed by Cu^I and Zn^{II} salts, followed by intramolecular oxidative formation of the N – N bond (Scheme 52).[92]

The key step of the synthesis of ferroceno[*d*]pyridazine derivatives **83**, potential antitumour agents, is the closure of the imidazoline or tetrahydropyrimidine rings at the pyridazine C – N bond *via* the Appel or Mitsunobu reaction of substituted hydroxyalkylaminoferroceno[*d*]pyridazines (Scheme 53).[93] The influence of diastereomer configuration on the yields of reaction products was studied. For example, if the R^1 or R^2 group in the aliphatic moiety of the starting compound is phenyl, partial dehydrogenation products **84** were isolated.

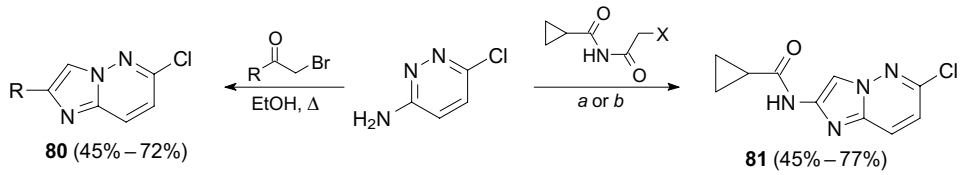
The condensation of 3,6-dihydroxypyridazine, acetylenedicarboxylate and isonitrile was proposed for the synthesis of 1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-dione derivatives **85** (Scheme 54).[94]

Scheme 50



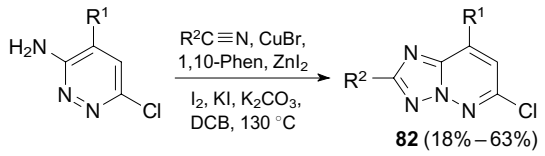
78: R^1 = H, Me, 4-BrC_6H_4, 4-MeC_6H_4; R^2 = R^3 = H; **79**: R^1 = Cl, 2,4-Me_2-pyrazol-1-yl; R^2 = R^3 = H; R^2 – R^3 is benzo

Scheme 51



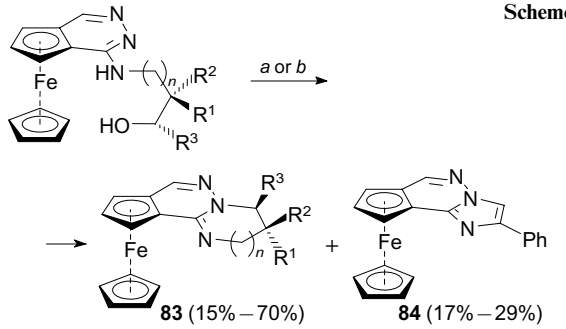
(*a*) Na_2HPO_4, DMA; (*b*) K_3PO_4, DMA, 80 °C; R = Me, F_3C, 4-MeC_6H_4, 4-$F_3CC_6H_4$; X = Cl, Br; DMA is dimethylacetamide

Scheme 52



R^1 = H, MeO; R^2 = Me, Ar, Het;
1,10-Phen is 1,10-phenanthroline, DCB is 1,2-dichlorobenzene

Scheme 53



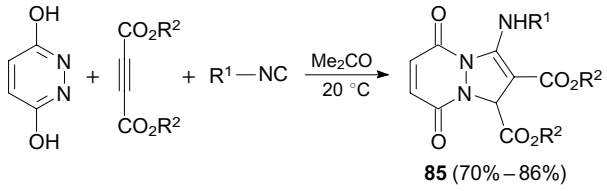
(*a*) CBr_4, PPh_3, CH_2Cl_2, 20 °C; (*b*) DIAD, PPh_3, THF, 20 °C;
R^1 = H, Me, Pr^i, Bn, Ph; R^2 = H, Ph, CH(OH)Ph; R^3 = H, Ph;
n = 0, 1; for **84**: R^1 = Ph, R^2 = R^3 = H; R^2 = Ph,
R^1 = R^3 = H; DIAD is diisopropyl azodicarboxylate

It was shown that 4-aminophthalazin-1(2*H*)-ones undergo the Groebke – Bienaymé – Blackburn reaction to give 3-amino-2-arylimidazo[2,1-*a*]phthalazin-6(5*H*)-ones **86** (Scheme 55).[68]

3.2. Reactivity of pyridazine carbon atoms

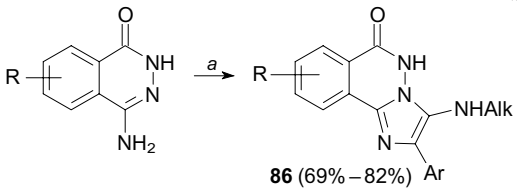
Many interesting cases of electrophilic attack on the pyridazine carbon atoms were considered in previous reviews.[1,5] A classical example of such reactions is bromination of 3-amino-6-chloropyridazine **87** (Scheme 56).[95] The reaction pathway is dictated by more pronounced electron-donor properties of the amino group compared to chlorine.

Scheme 54



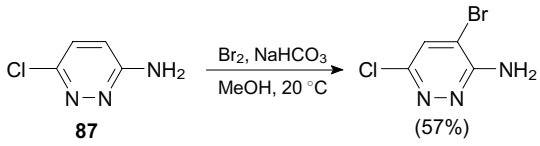
R^1 = Bu^t, cyclo-C_6H_{11}, Bn, CH_2CO_2Et, $CMe_2CH_2Bu^t$, 2,6-$Me_2C_6H_3$;
R^2 = Me, Et, Bu^t

Scheme 55



(*a*) ArCHO, AlkNC, $TsOH \cdot H_2O$, DMSO, 70 °C; R = H, 6-Me, 7-Me

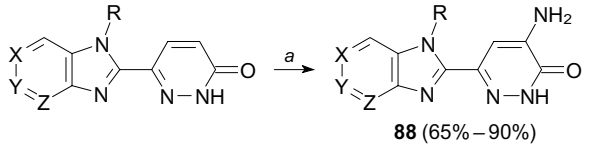
Scheme 56



Examples of nucleophilic attack on the pyridazine ring were also reported. The synthesis of 4-aminopyridazin-3(2*H*)-ones **88** by the reaction of pyridazinones with hydrazine is a well-known and reliable method for introducing an amino group into the pyridazine ring (Scheme 57).[96]

The enantioselective functionalization of pyridazines with alkenes into position 4 was accomplished to give substituted (*S*)-4-(1-arylethyl)pyridazines **89**. The reaction proceeds in the presence of a Cu catalyst, a chiral bis-phosphine ligand and methyldimethoxysilane (Scheme 58).[97] The organocopper derivative formed intermediately upon alkene hydrocupration acts as the nucleophile.

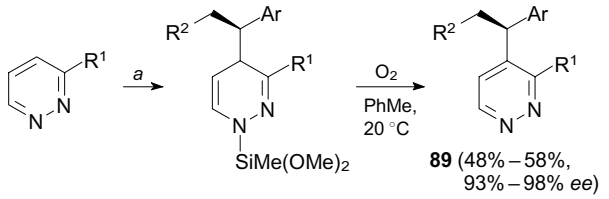
Scheme 57



88 (65% – 90%)

(*a*) $NH_2NH_2 \cdot H_2O$, Δ; X, Y = CH, N; Z = CH, N, C(O); R = H, Me

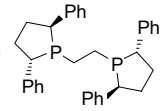
Scheme 58



89 (48% – 58%, 93% – 98% *ee*)

(*a*) (*E*)-$R^2CH{=}CHAr$, $HSiMe(OMe)_2$, $Cu(OAc)_2$, (*S*,*S*)-Ph-BPE, THF, 20 °C; R^1 = H, OMe; R^2 = H, CH_2OMe;

(*S*,*S*)-Ph-BPE =



An efficient method for introduction of the cyano group into the pyridazine ring is the Reissert – Henze reaction (Scheme 59).[98] It is noteworthy that in the case of 4-fluorobenzyl substituent, only derivative **90** tosylated into the benzylic position was isolated. The reaction regioselectivity depending on substituents present in the ring was studied and the conditions of the preparation of 3-cyanopyridazines **91** and **92** were optimized; the total yield of these products varied from 58% to 80% and their ratio varied from 1 : 0.8 to 1 : 28.

3.3. Reduction reactions

The reduction of pyridazine derivatives **68** with zinc in acetic acid follows an unusual pathway. In this case, reductive contraction of the pyridazine ring to a pyrrole ring takes place, giving benzyl(4,5,6,7-tetrahydro-2*H*-isoindol-5-yl)carbamates **93** (Scheme 60).[76]

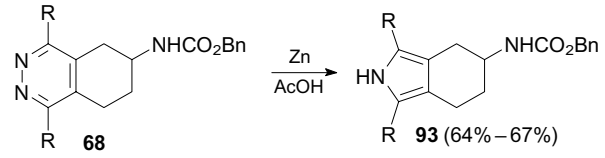
3.4. Radical reactions

In some cases, carbon substituents are introduced into position 5 of the pyridazine ring using the Minisci nucleophilic radical substitution. For example, derivatives **94** and **95** were synthesized in this way (Scheme 61).[36, 95]

3.5. Cycloaddition reactions

Pyridazines undergo cycloaddition reactions. The preparation of compounds **96** – **98** based on the [4 + 2] cycloaddition

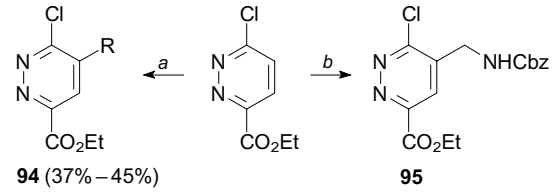
Scheme 60



68 **93** (64% – 67%)

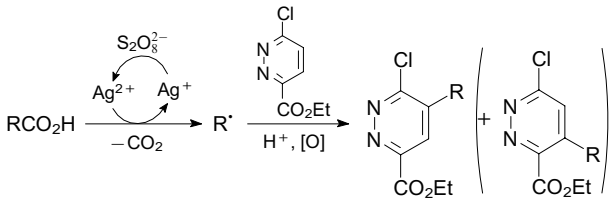
R = CO_2Me, 2-Py

Scheme 61



94 (37% – 45%) **95**

(*a*) RCO_2H, $(NH_4)_2S_2O_8$, $AgNO_3$, H_2SO_4 (conc.), H_2O, 70 °C; (*b*) $CbzNHCH_2CO_2H$, $(NH_4)_2S_2O_8$, $AgNO_3$, TFA, H_2O, 70 °C; R = Bn, Pr^i; Cbz is benzyloxycarbonyl



of 4,5-dicyanopyridazine to various substrates with subsequent transformations is described in detail in a review[99] (Scheme 62).

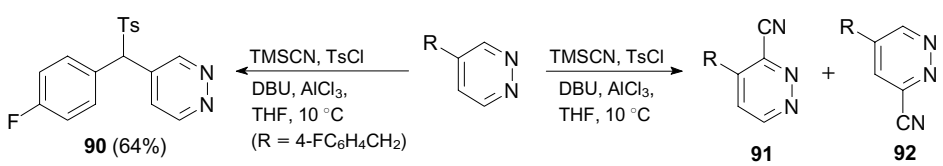
Pyridazine derivatives alkylated at the nitrogen atom with α-halocarbonyl compounds can be involved in 1,3-dipolar cycloaddition. For example, this method was used to synthesize pyrrolo[1,2-*b*]pyridazines **99** – **103** (Scheme 63).[100 – 102] The 1,3-dipole was generated from the corresponding pyridazinium bromide under the action of a base.

3.6. Reactions of hydropyridazines

The exocyclic double bond in methylidenetetrahydropyridazines can undergo *exo* – *endo* migration and, after that, the corresponding dihydropyridazines are easily aromatized to give substituted pyridazines **104** (Scheme 64).[103]

A large number of derivatives **105** – **115** containing a hexahydropyridazine moiety were prepared for studying their ability to inhibit the inducible NO-synthase (Schemes 65, 66).[104] The synthesis of the starting compounds shown in Scheme 66 was reported by the same research group in an earlier publication.[105]

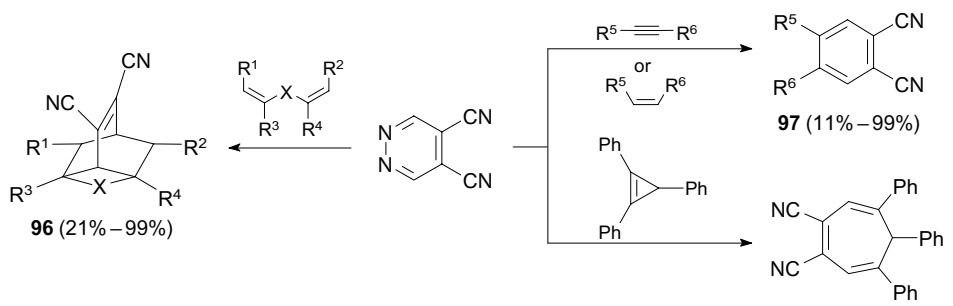
Scheme 59



90 (64%) **91** **92**

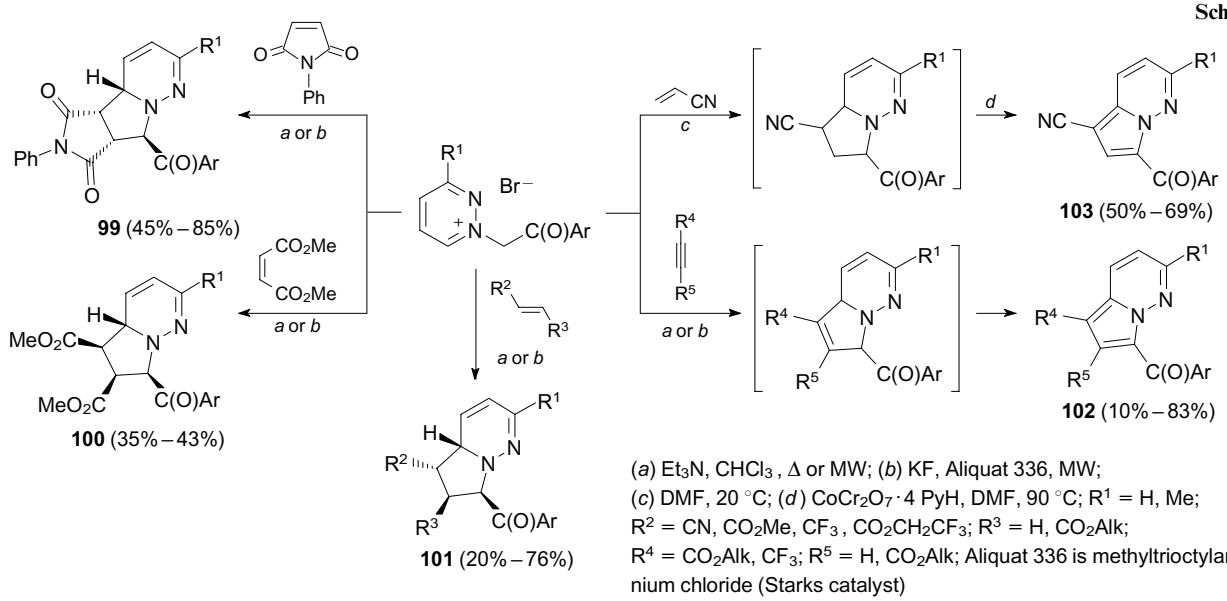
R = Me, Et, Pr^i, Bu^t, $PhCH{=}CH$, Ph, MeO, EtO, Pr^iO, CF_3CH_2O, PhO, BocNH, piperidino, morpholino

Scheme 62



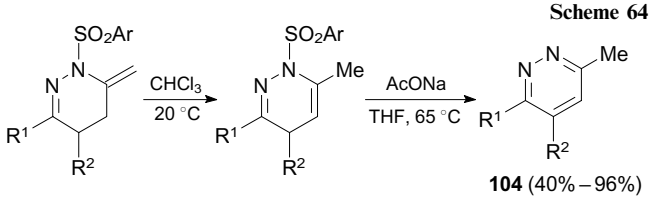
X = $(CH_2)_n$ (n = 1, 2, 3), CH_2OCH_2, $CH_2N(Ac)CH_2$, CH_2SCH_2, CH_2O, C(O)O

Scheme 63



(*a*) Et_3N, $CHCl_3$, Δ or MW; (*b*) KF, Aliquat 336, MW;
(*c*) DMF, 20 °C; (*d*) $CoCr_2O_7 \cdot 4$ PyH, DMF, 90 °C; R^1 = H, Me;
R^2 = CN, CO_2Me, CF_3, $CO_2CH_2CF_3$; R^3 = H, CO_2Alk;
R^4 = CO_2Alk, CF_3; R^5 = H, CO_2Alk; Aliquat 336 is methyltrioctylammonium chloride (Starks catalyst)

Scheme 64



R^1 = Ar, 2-Naph, n-C_5H_{11}; R^2 = H, Ph;
$R^1 - R^2$ = *o*-$C_6H_4CH_2CH_2$, $(CH_2)_5$

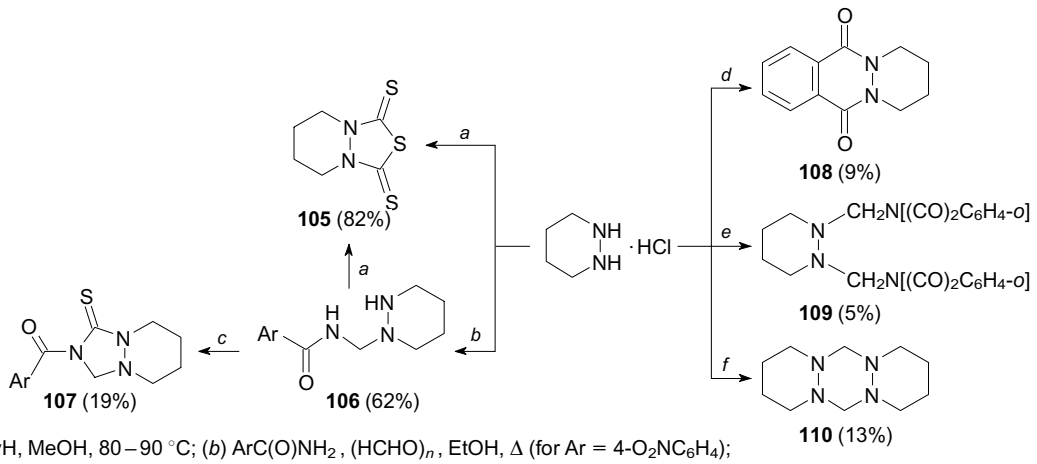
4. Reactivity of substituents in the pyridazine ring

4.1. Alkyl groups

The α-position of alkyl substituents in pyridazines is activated. A standard approach to functionalization of alkyl groups is halogenation, for example, as in the synthesis of 3,6-bis(chloromethyl)pyridazine **116** (Scheme 67).[106]

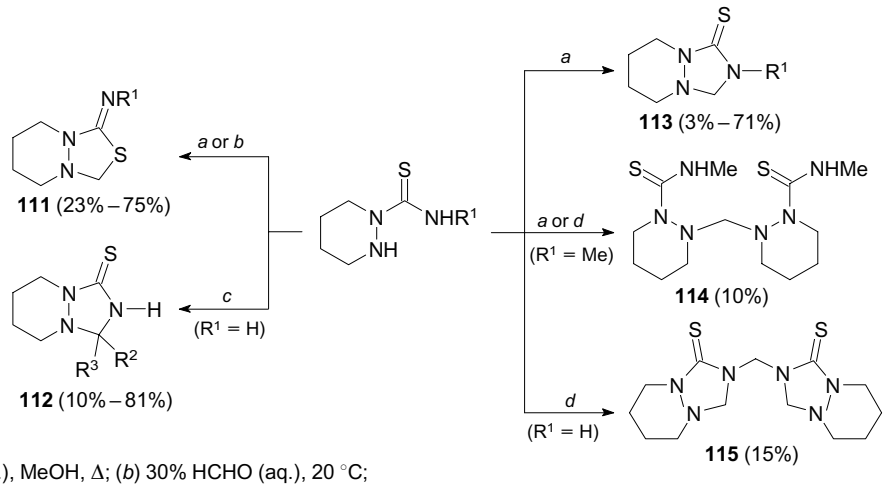
The cyclization involving 3-methylpyridazine-4-carboxamides and Vilsmeier reagents was successfully carried out

Scheme 65



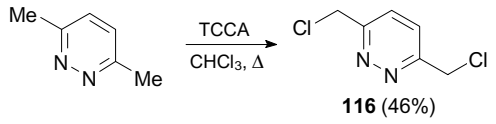
(*a*) CS_2, PyH, MeOH, 80 – 90 °C; (*b*) $ArC(O)NH_2$, $(HCHO)_n$, EtOH, Δ (for Ar = 4-$O_2NC_6H_4$);
(*c*) CS_2, PyH, MeOH, 20 °C; (*d*) *o*-$C_6H_4(CO)_2NK$, 30% HCHO (aq.), MW;
(*e*) *o*-$C_6H_4(CO)_2NH$, 30% HCHO (aq.), PyH, EtOH, Δ; (*f*) *o*-$C_6H_4(CO)_2NK$, 30% HCHO (aq.), H_2O, Δ

Scheme 66



(*a*) 30% HCHO (aq.), MeOH, Δ; (*b*) 30% HCHO (aq.), 20 °C;
(*c*) $R^2C(O)R^3$, TsOH, Δ; (*d*) $(HCHO)_n$, MS, 140 – 150 °C; **111**: R^1 = H, Ph; **112**: R^2, R^3 = Alk, Ar; **113**: R^1 = Me, Ph;
MS are molecular sieves

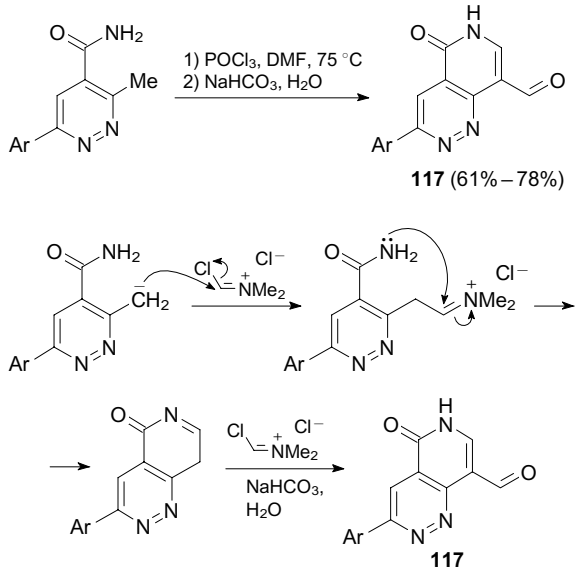
Scheme 67



TCCA is trichloroisocyanuric acid

to prepare compound **117** (Scheme 68).[63] The reaction was facilitated by enhanced acidity of the methyl group at the electron-withdrawing pyridazine ring; considering this fact, a possible reaction mechanism was proposed.

Scheme 68

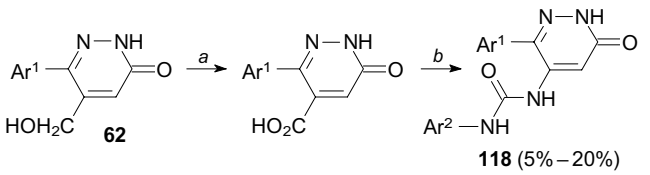


4.2. Carboxy and ester groups

Ureidopyridazinone derivatives **118** were synthesized using the strategy consisting of stepwise oxidation of 5-hydroxymethylpyridazinones **62** to the corresponding acids, conversion of the acids to acyl azides and application of Curtius rearrangement (Scheme 69).[72]

The presence of the ester group in pyridazines can serve for the preparation of a broad range of derivatives. For

Scheme 69



(*a*) 1) MnO_2, THF, 20 °C; 2) $AgNO_3$, EtOH, H_2O, 20 °C;
3) 10% NaOH (aq.), 20 °C;
(*b*) 1) DPPA, Et_3N, PhMe, 80 °C; 2) Ar^2NH_2, THF, Δ;
DPPA is diphenylphosphoryl azide

example, ethyl 5-fluoro-6-phenylpyridazine-3-carboxylic acid was converted to derivatives **119** – **122** (Scheme 70).[85]

Amides **123** and **124** were prepared using bis(dimethylamino)methylene-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide (HATU), which generates an activated ester during the reaction, and the ester readily reacts with the required amine (Scheme 71).[95]

An interesting method for functionalization of pyridazine-3-carboxylic acids is the palladium-catalyzed cross-coupling accompanied by decarboxylation, which resulted in the synthesis of a number of substituted 3-(het)arylpyridazines **125** (Scheme 72).[107]

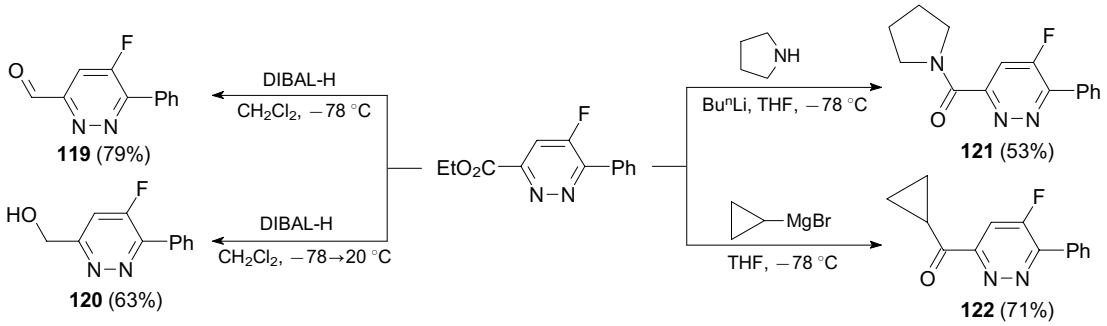
4.3. Cyano groups

For cyanopyridazines, examples of nitrile group displacement by the nucleophilic aromatic substitution mechanism were reported. This aspect was considered in sufficient detail for 4,5-dicyanopyridazine in a review [99] (Scheme 73); this approach resulted in the preparation of compounds **126** – **129**.

The last steps of the synthesis of 4-oxo-1,4-dihydropyridazine-3-carboxamide and its methylated analogue include hydrolysis of the nitrile group giving the corresponding amides **130** (Scheme 74).[108]

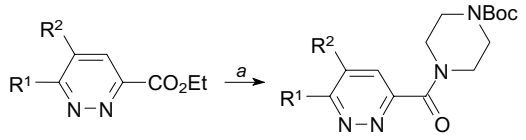
Reactions of urea and hydroxylamine with 4-cyanodihydropyridazinones were investigated (Scheme 75).[109] By using hydroxylamine, it is possible to prepare hydroxamic acid amide **131**. In the case of urea, the attack on the cyano group is followed by ring closure involving the oxo group of pyridazinone to give compound **132**.

Scheme 70



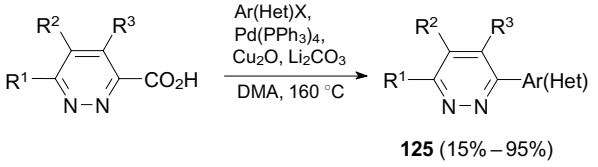
DIBAL-H is diisobutylaluminium hydride

Scheme 71



(*a*) 1) NaOH, MeOH, 30 °C; 2) $BocN(CH_2CH_2)_2NH$, HATU, DIPEA, DMF, 30°C; **123**: R^1 = Cl, R^2 = Bn (58%);
124: R^1 = $N(CH_2CH_2CH_2CHBn)$-cyclo, R^2 = CH_2NHCbz (72%)

Scheme 72

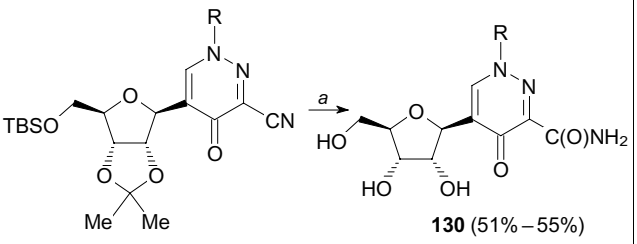


X = Cl, Br, I; R^1 = H, Ph; R^2 = H, Me, Ph; R^3 = H, Me

Complex heterocyclic system **133** containing a pyridazine ring was synthesized (Scheme 76).[110] The thiophene ring was assembled with the participation of the cyano and thio groups at the pyridazine system.

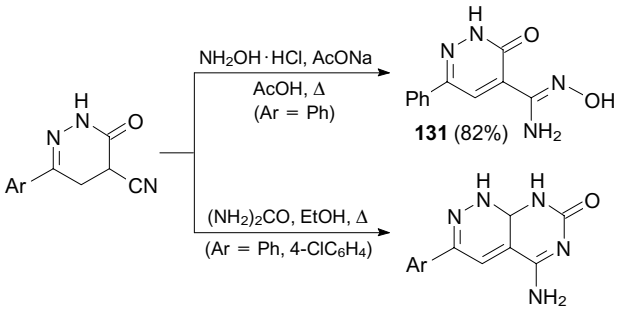
The thiophene ring of molecule **134** was assembled on the basis of substituted pyridazin-3(2*H*)-one with methyl and cyano groups in neighbouring positions (Scheme 77).[50] Probably, the reaction proceeds efficiently owing to the high acidity of the methyl group.

Scheme 74



(*a*) 1) H_2O_2, Et_3N, MeOH; 2) TFA (aq.); R = H, Me;
TBS = Bu^tMe_2Si

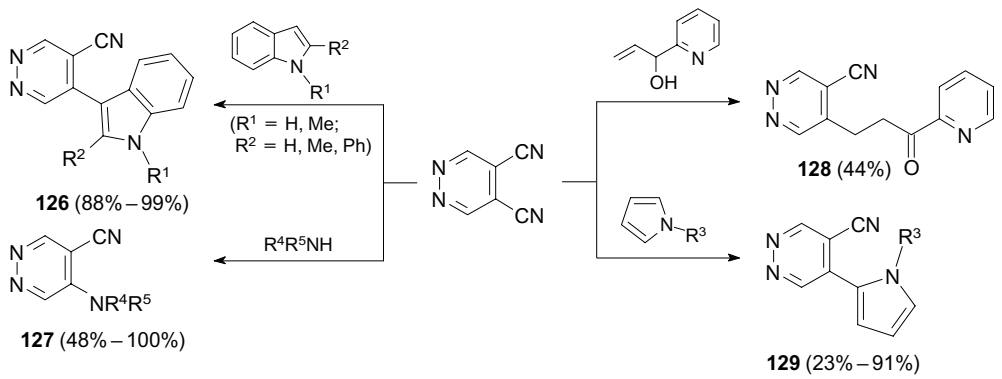
Scheme 75



4.4. Amino groups

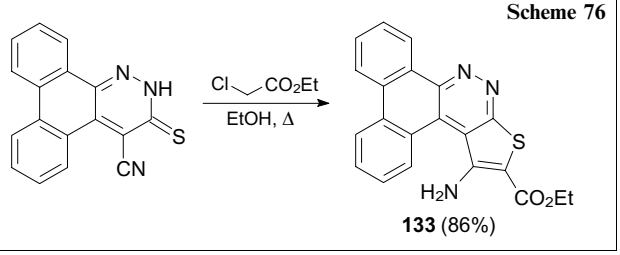
Amino groups in pyridazines are readily alkylated, which was utilized to prepare *N*-benzyl-*N*-methyl-4-bromo-6-chloropyridazine-3-amine **135**. The same reaction can serve for the preparation of fused nitrogen heterocycles. For example, 4,5-diaminopyridazinone and pyridazinone-

Scheme 73



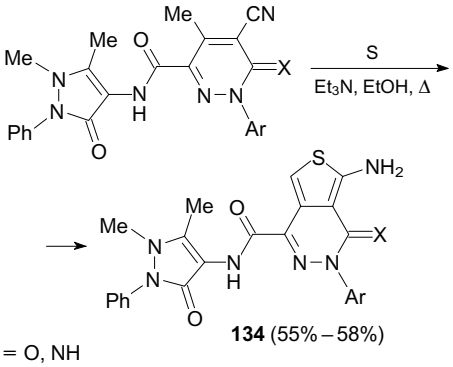
R^1 = H, Me; R^2 = H, Me, Ph; R^3 = H, Me, Ph, NMe_2; R^4, R^5 = Alk

Scheme 76



133 (86%)

Scheme 77

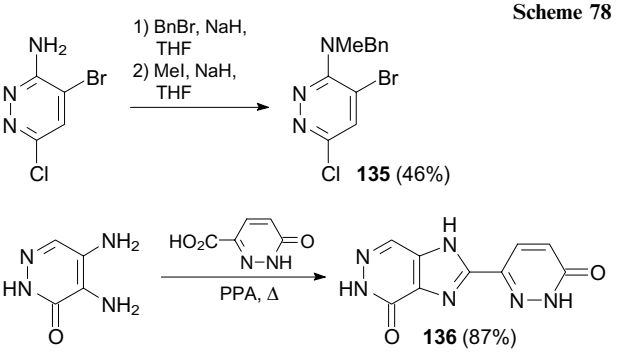


134 (55% – 58%)

X = O, NH

3-carboxylic acid in polyphosphoric acid (PPA) are converted to 1,5-dihydro-4*H*-imidazo[4,5-*d*]pyridazin-4-one **136** (Scheme 78).[95,96]

Scheme 78

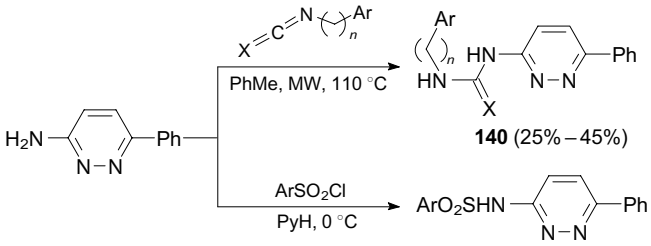


135 (46%)

136 (87%)

The preparation of polymers exhibiting photoelectric properties was based on thiophene derivatives of pyrazino[2,3-*d*]pyridazine **137** and [1,2,5]thiadiazolo[3,4-*d*]pyridazine **138** (Scheme 79).[111] The synthesis was started from [1,2,5]oxadiazolo[3,4-*d*]pyridazine, which was converted to 4,5-diaminopyridazine **139**.

Scheme 80



140 (25% – 45%)

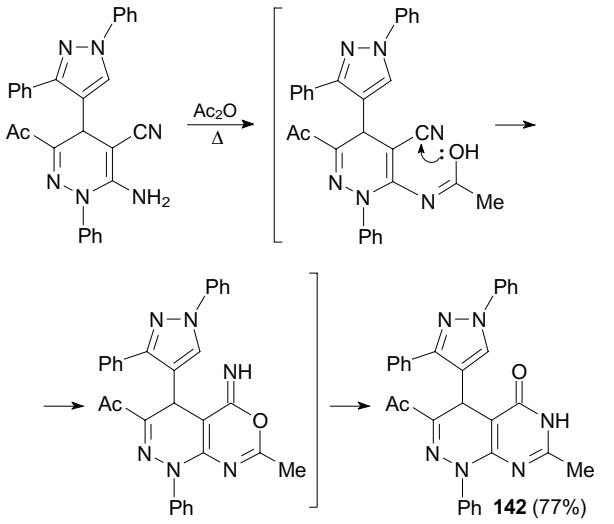
141 (80% – 85%)

X = O, S; *n* = 0, 1, 2

The reactions of 3-amino-6-phenylpyridazine with substituted isocyanates, isothiocyanates and sulfonyl chlorides open the way towards the corresponding ureas and their thio analogues **140** and sulfonamides **141** (Scheme 80).[112]

The acylation of the 3-amino-4-cyanopyridazine derivative with acetic anhydride (Scheme 81) [55] does not stop after acylation of the amino group. The neighbouring cyano group is also subjected to the nucleophilic attack, resulting in closure of the ring, which undergoes the Dimroth rearrangement. This gives rise to the pyrimidine moiety fused to pyridazine, that is, compound **142**.

Scheme 81

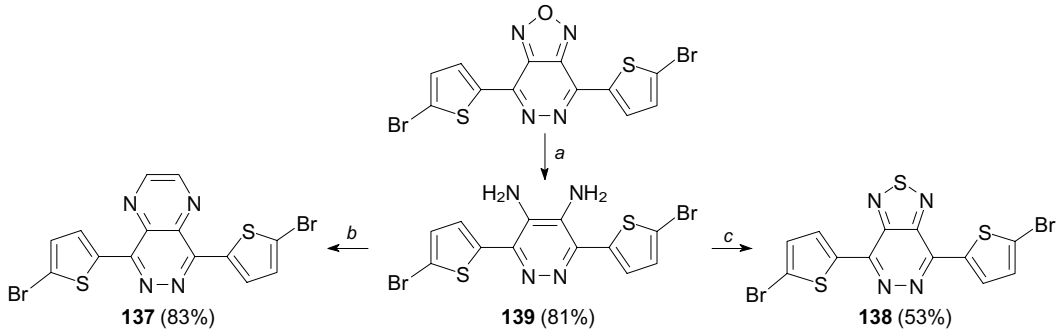


142 (77%)

4.5. Hydrazino groups

An example of reactions of hydrazino groups at the pyridazine ring routinely used in organic synthesis is the formation of hydrazides, such as compound **143**.[113] The

Scheme 79

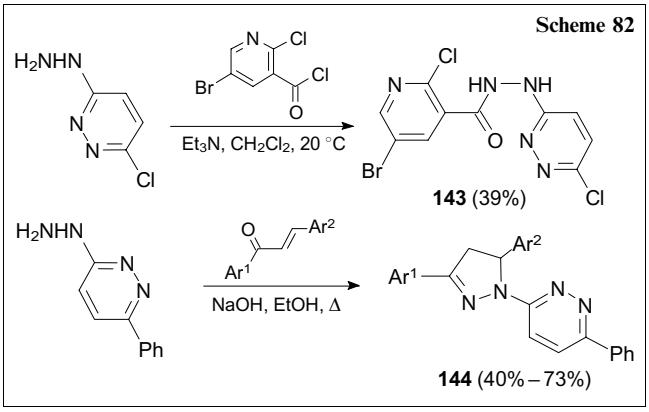


137 (83%) **139** (81%) **138** (53%)

(*a*) $(NH_4)_2SO_4$, $NaBH_4$, EtOH, 20 °C; (*b*) $(CHO)_2$, AcOH, Δ; (*c*) $SOCl_2$, Et_3N, CH_2Cl_2, Δ

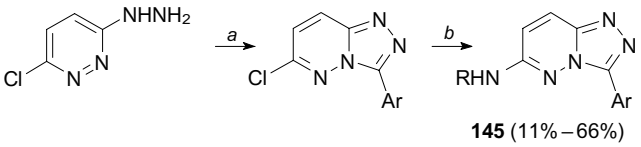
reaction of a similar hydrazine with chalcones is accompanied by closure of a five-membered ring, thus giving dihydropyrazole derivatives **144** (Scheme 82).[114]

Scheme 82



The reaction of 6-chloro-3-hydrazinylpyridazine with acyl halides followed by refluxing with $POCl_3$ leads to triazole ring closure, resulting in the formation of *N*-cycloalkyltriazolo[4,3-*b*]pyridazine derivatives **145** (Scheme 83).[115] Among these compounds, Pim-1 kinase inhibitors were found.

Scheme 83

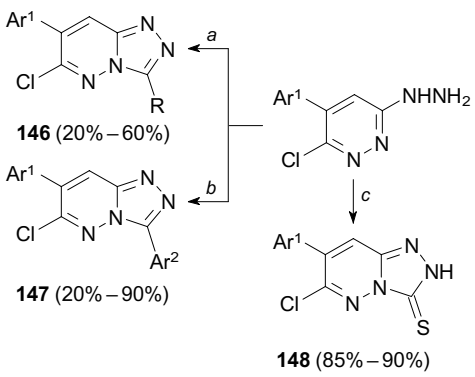


(*a*) 1) ArC(O)Cl, MeCN, 20 °C; 2) $POCl_3$, MeCN, 80 °C;
(*b*) RNH_2, 70°C; R = cyclo-C_3H_5, $CH_2C_3H_5$-cyclo, cyclo-C_4H_7, cyclo-C_6H_{11}

5-Aryl-6-chloro-3-hydrazinopyridazine derivatives were used to close a conjugated 1,2,4-triazole ring in reactions with electrophiles such as orthoesters, substituted benzaldehydes and carbon disulfide (Scheme 84).[116] Triazolo[4,3-*b*]-pyridazines **146** – **148** were thus formed in moderate to high yields.

The hydrazine moiety served as the basis for the synthesis of a number of fused systems **149** – **153** containing a pyridazine core (Scheme 85).[117] It was found that some of the obtained compounds possess antibacterial activity.

Scheme 84



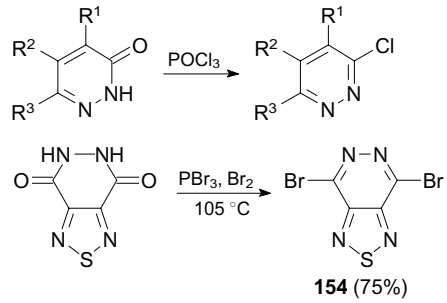
(*a*) $RC(OEt)_3$, AcOH, Δ; (*b*) 1) Ar^2CHO, AcOH, EtOH, Δ; 2) $PhNO_2$; (*c*) CS_2, PyH, Δ; R = H, Me, Et

4.6. Hydroxy and oxo groups

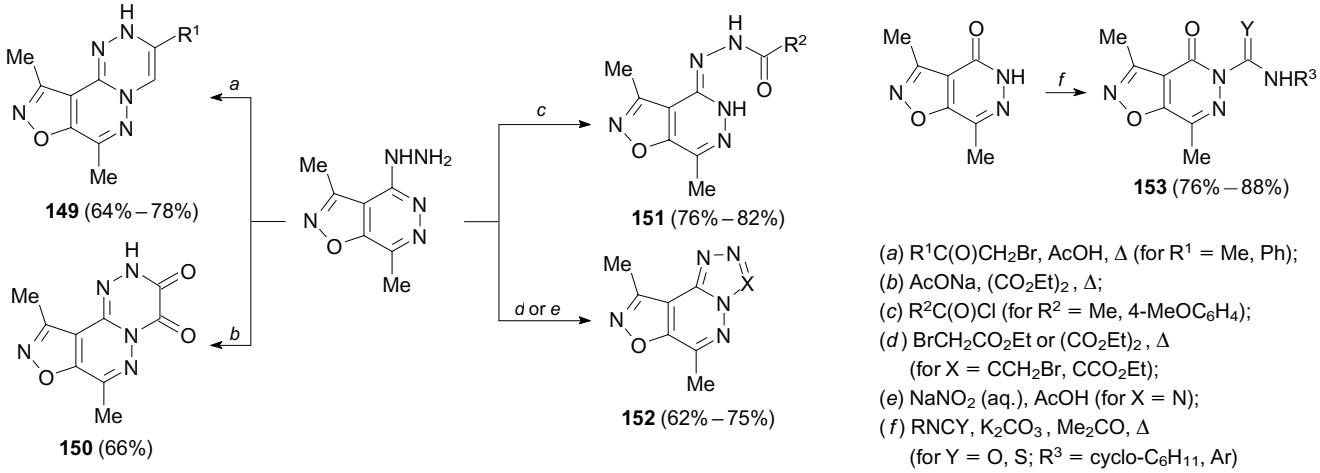
The most frequently encountered transformation of the oxo group in pyridazinones is deoxohalogenation, most often, deoxochlorination with the participation of phosphorus(V) oxochloride (Scheme 86). Bromination of the oxo group in pyridazinones was also reported; an example is the synthesis of 4,7-dibromo[1,2,5]thiadiazolo[3,4-*d*]pyridazine **154**.[21] A mixture of phosphorus tribromide and bromine, which generates *in situ* more reactive phosphorus pentabromide, acts as the brominating agent.

Closure of four types of heterocycles **155** – **158** coupled to the pyridazine system was described (Scheme 87).[24] The synthesis is accompanied by intramolecular nucleophilic

Scheme 86

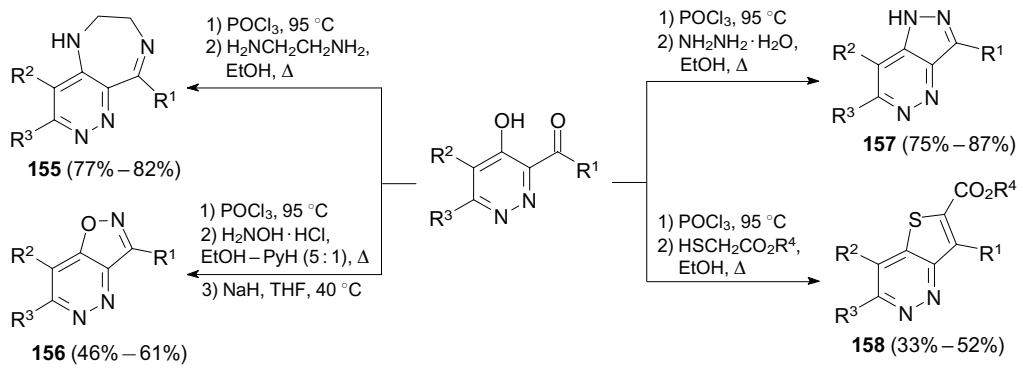


Scheme 85



(*a*) $R^1C(O)CH_2Br$, AcOH, Δ (for R^1 = Me, Ph);
(*b*) AcONa, $(CO_2Et)_2$, Δ;
(*c*) $R^2C(O)Cl$ (for R^2 = Me, 4-$MeOC_6H_4$);
(*d*) $BrCH_2CO_2Et$ or $(CO_2Et)_2$, Δ
(for X = CCH_2Br, CCO_2Et);
(*e*) $NaNO_2$ (aq.), AcOH (for X = N);
(*f*) RNCY, K_2CO_3, Me_2CO, Δ
(for Y = O, S; R^3 = cyclo-C_6H_{11}, Ar)

Scheme 87



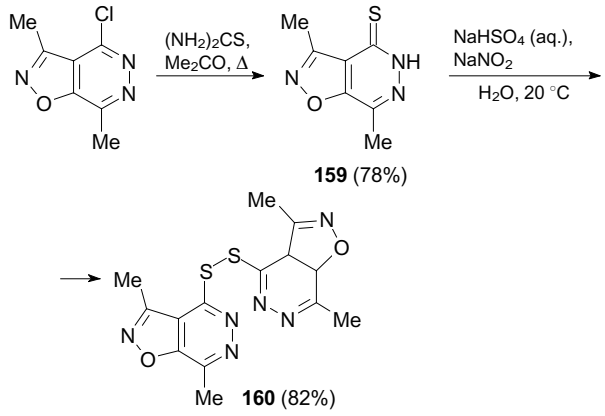
R^1 = OMe, Ar, 2-Th; R^2 = H, Me; R^3 = Et, Pr^i, cyclo-C_6H_{11}, Ph, 2-FC_6H_4, 2-Th; R^4 = Me, Et

attack on the acyl groups at the C(3) atom of the starting pyridazine containing a hydroxy group in position 4.

4.7. Thiol and thione groups

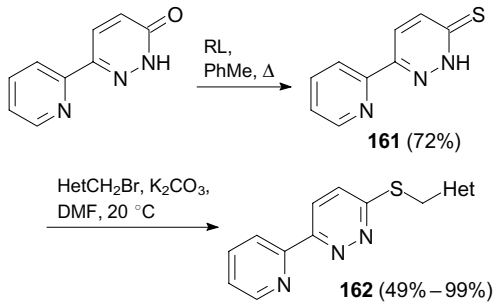
3,7-Dimethylisoxazole[4,5-*d*]pyridazine-4(5*H*)-thione (**159**) was prepared by the reaction of a similar 4-chloro-substituted pyridazine with thiourea (Scheme 88).[117] Then this product was subjected to dimerization to give disulfide **160**.

Scheme 88

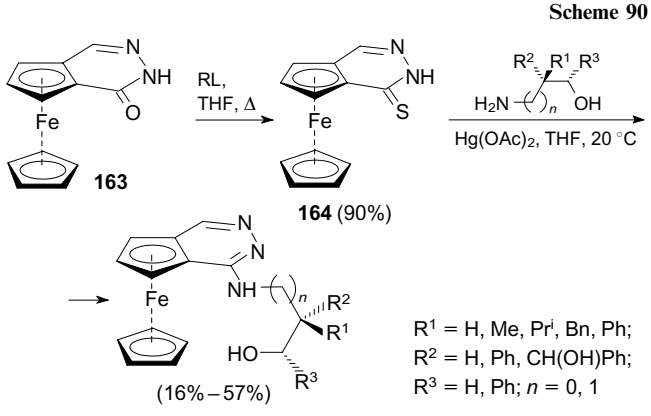


The reaction of pyridazinones with the Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide, RL] was used for the synthesis of thiopyridazines, for example, 6-(2-pyridyl)pyridazine-3(2*H*)-

Scheme 89

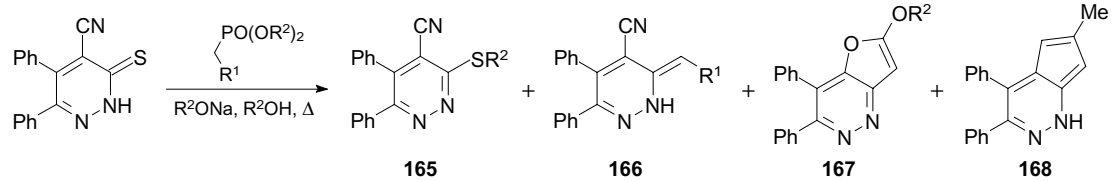


Scheme 90



R^1 = H, Me, Pr^i, Bn, Ph;
R^2 = H, Ph, CH(OH)Ph;
R^3 = H, Ph; n = 0, 1

Scheme 91



R^1	R^2	Yield (%)			
		165	**166**	**167**	**168**
CO_2Me, CO_2Et	Me, Et	15	35	35	–
C(Me)=CH_2	Et	15	25	–	15
CN, 4-$MeOC_6H_4$, pyrrolidino, phthalimido	Et	15	30 – 35	–	–

thione **161** (Scheme 89).[118] The subsequent alkylation afforded a series of 3-alkylthio-6-(2-pyridyl)pyridazines **162** possessing neuroprotective properties as EAAT2 protein activators.

The synthesis of a series of substituted ferroceno[*d*]pyridazines is based on conversion of pyridazinone **163** to thione **164** followed by displacement of the sulfur atom *via* the reaction with amino alcohols in the presence of mercury(II) acetate (Scheme 90).[93]

The reaction of 3-thioxo-5,6-diphenyl-2,3-dihydropyridazine-4-carbonitrile with the Horner–Wadsworth–Emmons reagents gives product mixture **165**–**168** (Scheme 91),[119] which is attributable to the thione–thiol equilibrium.

4.8. Halogen atoms

The reactions involving halogen atoms present as substituents in the ring are among the most developed trends of pyridazine chemistry. The high popularity of these methods is due to the convenience of preparation of starting compounds and to high diversity and efficiency of the transformations, first of all, reactions with organometallic compounds,[120] cross-coupling and nucleophilic aromatic substitution.

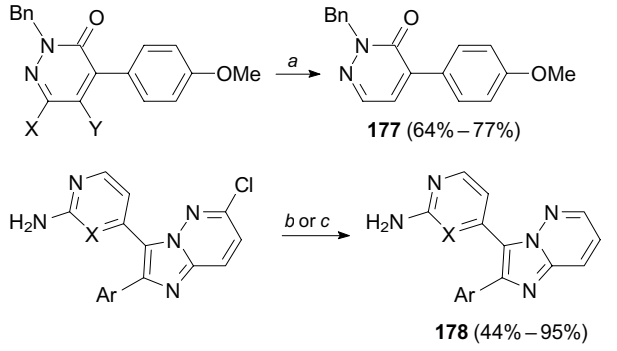
4.8.1. Replacement of a halogen by a metal

The reactivity of organomagnesium derivatives of halopyridazin-3(2*H*)-ones towards a broad range of electrophiles was studied in detail (Scheme 92).[121, 122] In the case of pyridazinones containing a bromine atom in position 4, bromine was replaced by magnesium, and this was followed by regioselective electrophilic attack giving substitution products at position 4 — compounds **169a**,**b** and **170**. For 5-substituted pyridazinones, bromine was also exchanged for magnesium, which was followed by attack on position 5 by the electrophile; however, the methoxy group was replaced by the hydrocarbon group of the Grignard reagent, thus being converted to compounds **171** (see Scheme 92).

2-Benzyl-4-bromo-5-methoxypyridazin-3(2*H*)-one was also reacted with benzoyl chloride; however, the preparation of the desired 4-benzoyl-2-benzyl-5-methoxypyridazin-3(2*H*)-one (**169b**) required the use of transmetallation in the presence of CuCN, because the standard procedure resulted in the double substitution product at the carbonyl group — compound **172**. Transmetallation in the presence of $MnBr_2$ gave homocoupling product **173** in a good yield (see Scheme 92).

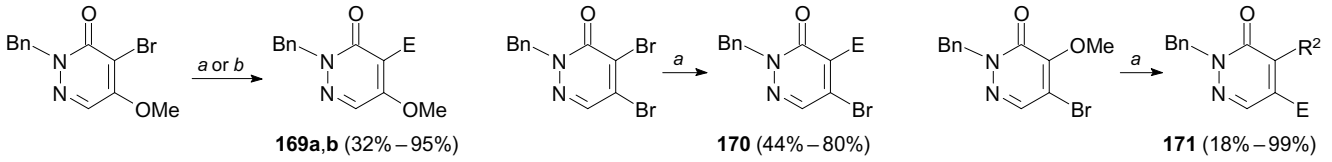
An unusual influence of conditions on the reactions with formylating agents, giving products of bromine and methoxy group displacement **174** and **175**, was found; the

Scheme 93

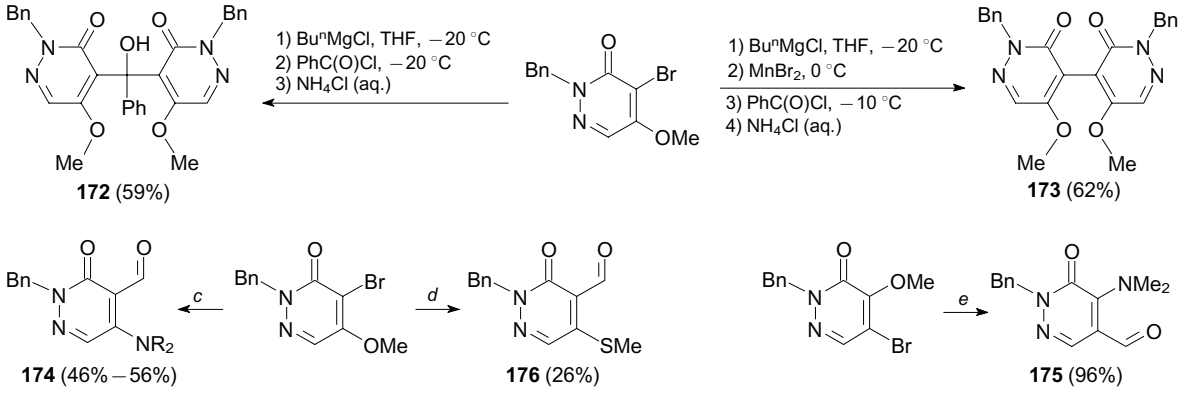


(*a*) H_2, K_2CO_3, Pd/C, EtOAc, rt (for X = H, Y = Cl; X = Cl, Y = H); (*b*) H_2, Pd/C, AcOH, 50 °C; (*c*) H_2, Pd/C, Et_3N, DMF, rt (for X = CH, N)

Scheme 92



(*a*) 1) R^1MgCl, THF, −20 °C; 2) electrophile, −20 °C; 3) NH_4Cl (aq.); (*b*) 1) Bu^nMgCl, THF, −20 °C; 2) CuCN, −20 °C; 3) PhC(O)Cl, −20 °C; 4) NH_4Cl (aq.) [for E = Bz (**169b**)]; electrophile = D_2O, H_2O, PhCHO, Ph_2CO, $PhC(O)CO_2Me$, DMF, cyclo-$(CH_2)_5NCHO$, TsCN, MeSSMe, Me_2SO_4, I_2; **169a**, **170**, **171**: E = D, H, PhCH(OH), $Ph_2C(OH)$, $PhC(OH)CO_2Me$, CHO, CN, SMe, Me, I; R^1 = Bu^n, Pr^i, Ph, Mes; R^2 = R^1, OMe



(*c*) 1) Bu^nMgCl, THF, −20 °C; 2) R^2NCHO; 3) MeOH, 20 °C; 4) NH_4Cl (aq.); R_2N = Me_2N, $(CH_2)_5N$;
(*d*) 1) Bu^nMgCl, THF, −20 °C; 2) DMF, −20 °C; 2) NaSMe, −20 °C; 3) NH_4Cl (aq.);
(*e*) 1) MesMgBr, THF, −20 °C; 2) DMF, −20 °C; 3) MeOH, rt; 4) NH_4Cl (aq.)

addition of NaSMe to the reaction medium gave rise to methylthio derivative **176** (see Scheme 92).

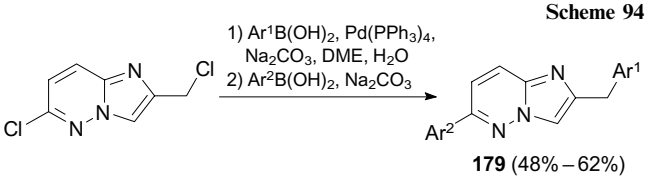
Examples of efficient catalytic hydrogenolysis of the C – Cl bond involving palladium were reported, such as syntheses of compounds **177** and **178** (Scheme 93).[123, 124]

4.8.2. Replacement of a halogen atom in cross-coupling reactions

Cross-coupling is an efficient method frequently used for functionalization of pyridazines.[125] Examples of using Suzuki – Miyaura,[90, 95, 126, 127] Buchwald – Hartwig,[21, 128] Stille,[126] Negishi[129, 124, 127] and Ullmann reactions[21] were reported. The Suzuki – Miyaura reaction makes it possible to accomplish selective one-pot exchange of different chlorine atoms in 6-chloro-2-chloromethylimidazo[1,2-*b*]pyridazine for aryl groups to give products **179** (Scheme 94).[129] It is possible to introduce two different aryl groups by displacing chlorine atoms in both the benzylic position and pyridazine ring.

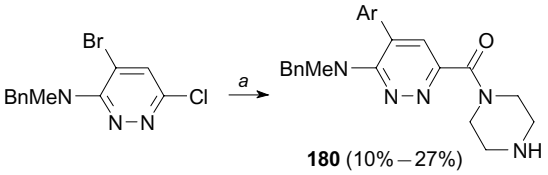
A combination of the Suzuki – Miyaura reaction and aminocarbonylation for pyridazines containing both bromine and chlorine atoms gives rise to compounds **180**; however, the overall yields of the target products do not exceed 27% (Scheme 95).[95]

Scheme 94



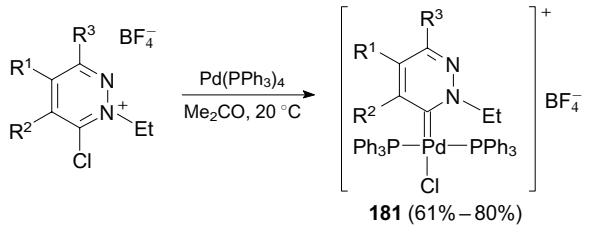
Ar^1 = Ph, 4-FC_6H_4, 3-Fu; Ar^2 = Ph, 4-$MeOC_6H_4$, 3-Th

Scheme 95

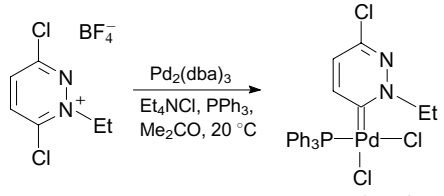


(*a*) 1) $ArB(OH)_2$, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, Cs_2CO_3, dioxane, H_2O, 30 °C; 2) CO, $BocN(CH_2CH_2)_2NH$, $Pd(OAc)_2$, dppp, K_3PO_4, Et_3N, DMF, 110 °C; 3) TFA, CH_2Cl_2; Ar = Ph, Het; dppp is 1,3-bis(diphenylphosphino)propane

Scheme 96



$R^1 = R^2$ = H; $R^1 – R^2$ is benzo; R^3 = Cl, 3,5-dimethylpyrazol-1-yl



dba is dibenzylideneacetone

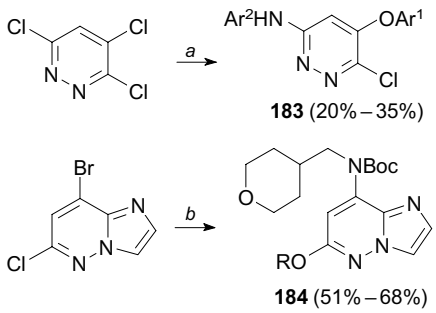
Palladium carbene complexes **181** and **182** were prepared from pyridazinium salts. Their molecules contain an exocyclic Pd – C bond with respect to the pyridazine ring (Scheme 96).[89]

4.8.3. Nucleophilic aromatic substitution in pyridazines

The nucleophilic aromatic substitution is often used for the synthesis of pyridazine derivatives. Quite a few such reactions with the participation of various *N*-nucleophiles,[35, 60, 113, 130 – 132] *O*-nucleophiles[91, 95, 133 – 136] and *S*-nucleophiles[137] are known. There are examples of selective successive nucleophilic substitution in which halogen atoms located in different positions of the pyridazine ring are displaced to give several *N*-phenyl-6-chloro-5-phenoxypyridazine-3-amines **183** and imidazo[1,2-*b*]pyridazine derivatives **184** (Scheme 97).[128, 138] The course of substitution is determined by higher reactivity of the halogen atom in position 5 compared to position 3.

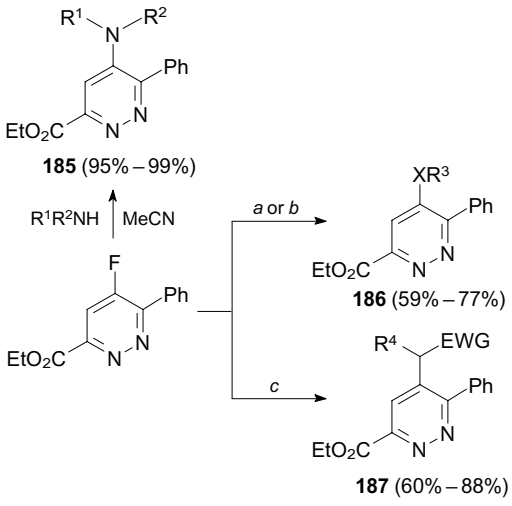
Nucleophilic substitution involving the fluorine atom at the pyridazine ring can be utilized in reactions with *N*-, *O*-, *S*- and *C*-nucleophiles (Scheme 98).[85] This approach pro-

Scheme 97



(*a*) 1) Ar^1OH, NaH, DMF; 2) Ar^2NH_2, HCl, EtOH;
(*b*) 1) $O(CH_2CH_2)_2CHCH_2NH_2$, DIPEA, EtOH, Δ;
2) Boc_2O, DMAP, THF, 50 °C; 3) ROH, NaH, NMP, rt;
R = cyclo-C_6H_{11}, Ar; DMAP is 4-dimethylaminopyridine

Scheme 98

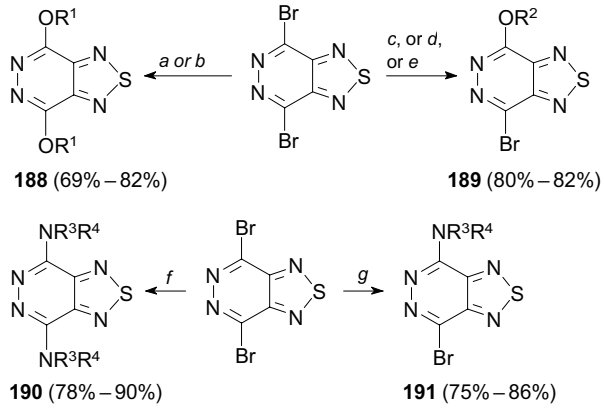


(*a*) R^3XH, TFA, rt (for $R^3 = CH_2C_3H_5$-cyclo, X = O);
(*b*) R^3XNa, MeCN, 100 °C (for R^3 = Et, X = S);
(*c*) R^4CH_2(EWG), DBU, DMSO, 80 °C (for $R^4 = CO_2Me$, H;
EWG = CO_2Me, NO_2); R^1R^2NH = PhMeNH, morpholino

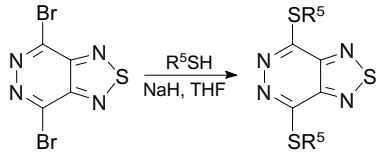
vides an efficient synthesis of a variety of pyridazine derivatives **185** – **187**.

The nucleophilic substitution in 4,7-dibromo[1,2,5]thiadiazolo[3,4-*d*]pyridazine was studied in detail (Scheme 99).[21] Reactions for several *O*-, *N*- and *S*-nucleophiles were carried out to give products **188** – **194**. For *O*- and *N*-nucleophiles and for the synthesis of symmetrical and unsymmetrical pyridazine derivatives, conditions for the displacement of only one bromine atom were selected.

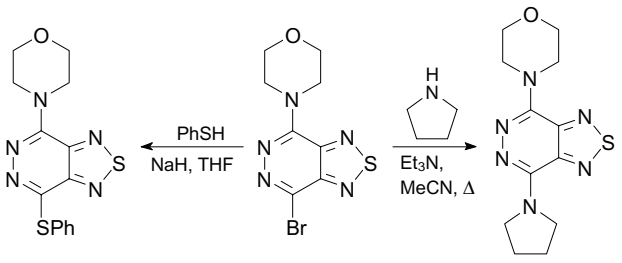
Scheme 99



(*a*) R^1ONa, MeOH, 20 °C (for R^1 = Me); (*b*) R^1ONa, DMF, 90 °C (for R^1 = Ph); (*c*) R^2ONa, H_2O, $CHCl_3$, 20 °C (for R^2 = H); (*d*) R^2ONa, MeOH, 20 °C (for R^2 = Me); (*e*) R^2ONa, THF, 20 °C (for R^2 = Ph); (*f*) R^3R^4NH, Et_3N, MeCN, 80 °C; (*g*) R^3R^4NH, Et_3N, CH_2Cl_2, 20 °C (for R^3, R^4 = H, Alk, Ar)

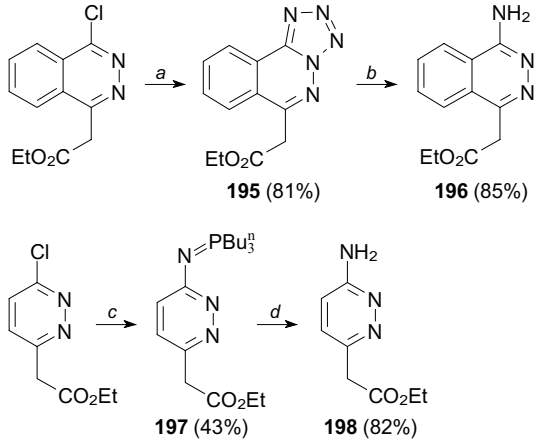


R^5 = Ph, n-C_6H_{13}, n-$C_{12}H_{25}$



For the introduction of an amino group into the pyridazine ring, a different procedure was successfully used, instead of displacement of the chlorine atom; in particular, on treatment with sodium azide, the 4-chlorophthalazine derivative underwent nucleophilic substitution and tetrazole ring closure to afford compound **195**. This product was efficiently reduced in the presence of tri-n-butylphosphine (owing to the tetrazole – azide tautomerism) giving ethyl 2-(4-aminophthalazin-1-yl)acetate **196** (Scheme 100).[139] It is worth noting that this method proved to be inapplicable for analogous 3-chloropyridazine, because tetrazole ring closure furnished a more stable

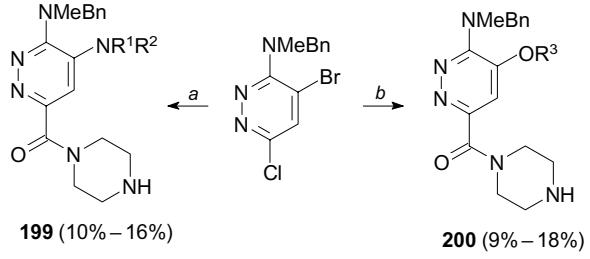
Scheme 100



(*a*) NaN_3, DMF, 60 °C; (*b*) 1) Bu^n_3P, PhMe, 110 °C; 2) H_2O – MeCN (1 : 1), 80 °C; (*c*) NaN_3, Bu^n_3P, DMSO, 120 °C; (*d*) H_2O – MeCN (1 : 1), 70 °C

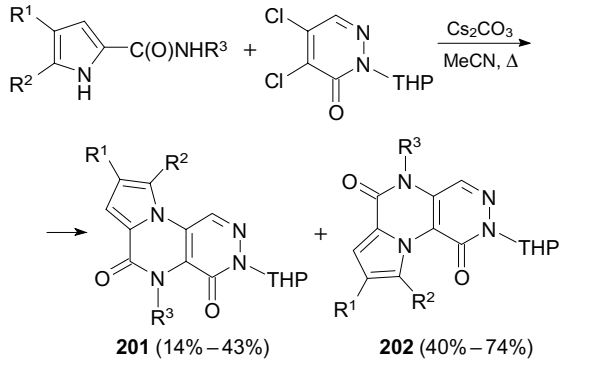
product, which could not be reduced with tri-n-butylphosphine. Nevertheless, by simultaneous use of sodium azide and tri-n-butylphosphine, resulting in the formation of

Scheme 101



(*a*) 1) R^1R^2NH, CsF, DIPEA, DMSO, 110 °C; 2) CO, $BocN(CH_2CH_2)_2NH$, $Pd(OAc)_2$, dppp, K_3PO_4, Et_3N, DMF, 110 °C; 3) TFA, CH_2Cl_2; (*b*) 1) R^3OH, NaH, DMF, 30 °C; 2) CO, $BocN(CH_2CH_2)_2NH$, $Pd(OAc)_2$, dppp, K_3PO_4, Et_3N, DMF, 110 °C; 3) TFA, CH_2Cl_2; $R^1 – R^2$ = $(CH_2)_4$, $(CH_2CH_2)_2O$, $(CH_2CH_2)_2NMe$; R^1 = Me: R^2 = CH_2CH_2OMe, Bn; R^3 = Pr^i, CHMeEt, CH_2Bu^i, CH_2Bn, $CH_2CH_2N(CH_2CH_2)_2O$

Scheme 102



R^1 = R^2 = H; $R^1 – R^2$ =  ; R^3 = Alk, Ar; R^4 = H, F, MeO;

THP is tetrahydropyran-20-yl

iminophosphorane **197**, it was possible to synthesize amino derivative **198**, although in a lower yield.

In the preparation of two libraries of compounds (**199** and **200**), the nucleophilic S_{AE} substitution at the most activated position 5 was followed by aminocarbonylation of the C(3) atom (Scheme 101).[95]

The reactions of protected 4,5-dichloropyridazin-3(2*H*)-one with pyrrole-2- and indole-2-carboxamides have been reported [140] (Scheme 102). In all cases, mixtures of regioisomeric nucleophilic substitution products **201**, **202** were obtained.

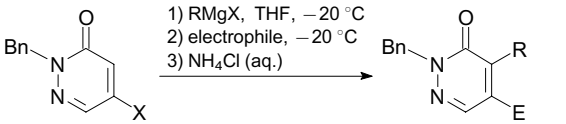
4.9. Organometallic derivatives of pyridazines

Organometallic derivatives of pyridazines open the route to a relatively convenient and often selective insertion of electrophiles into the C – H bond.[122, 124, 141] The reactions of 5-halo-substituted pyridazinones and alkylmagnesium halides with a number of electrophiles giving products **203** were studied (Scheme 103). It was noted that bromo derivatives react with a smaller number of electrophiles than chloro derivatives. Indeed, the latter are able to react with Br_2, ICl and $MeSO_2SMe$ with replacement of hydrogen at the pyridazine C(4) atom by the alkyl group of a Grignard reagent. The reaction mixture was found to contain no 5-bromo or 5-iodo derivatives, which is due to higher nucleofugality of bromine and iodine atoms compared to chlorine.

The accumulation of experimental data and determination of the reaction mechanism culminated in the successful use of this reaction in the selective alkylation of substituted pyridazinones into position 4 (Scheme 104). The choice of an electrophile (Br_2) convenient for the formation of a good leaving group in the intermediate compound was the key issue. A version of this reaction representing oxidative nucleophilic substitution resulted in a series of 4-substituted pyridazin-3(2*H*)-ones **204**.

The same authors [124] described the strategy of so-called lactam directed *ortho*-C – H metallation. According to this

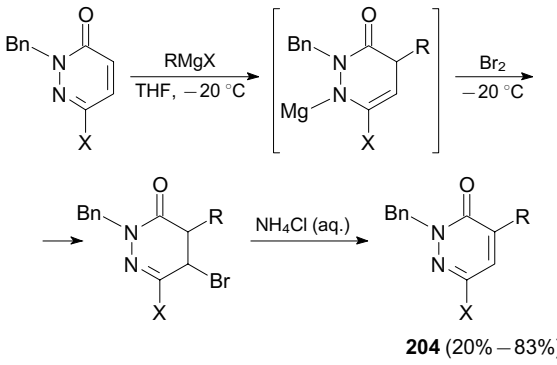
Scheme 103



203 (14% – 93%)

R = Pr^i, Bu^n, Ph; X = Cl, Br: electrophile = D_2O, PhCHO, $PhC(O)CO_2Me$, furfural; E = D, PhCH(OH), $PhC(OH)CO_2Me$, 2-FuCH(OH); X = Cl: electrophile = Br_2, ICl; E = Cl; electrophile = $MeSO_2SMe$, E = SMe

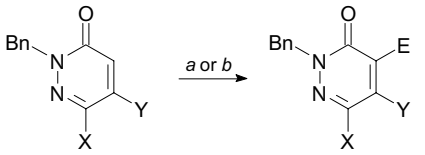
Scheme 104



204 (20% – 83%)

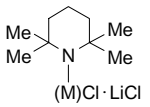
X = H, Cl; R = Pr^i, Bu^n, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 3,5-$Cl_2C_6H_3$

Scheme 105

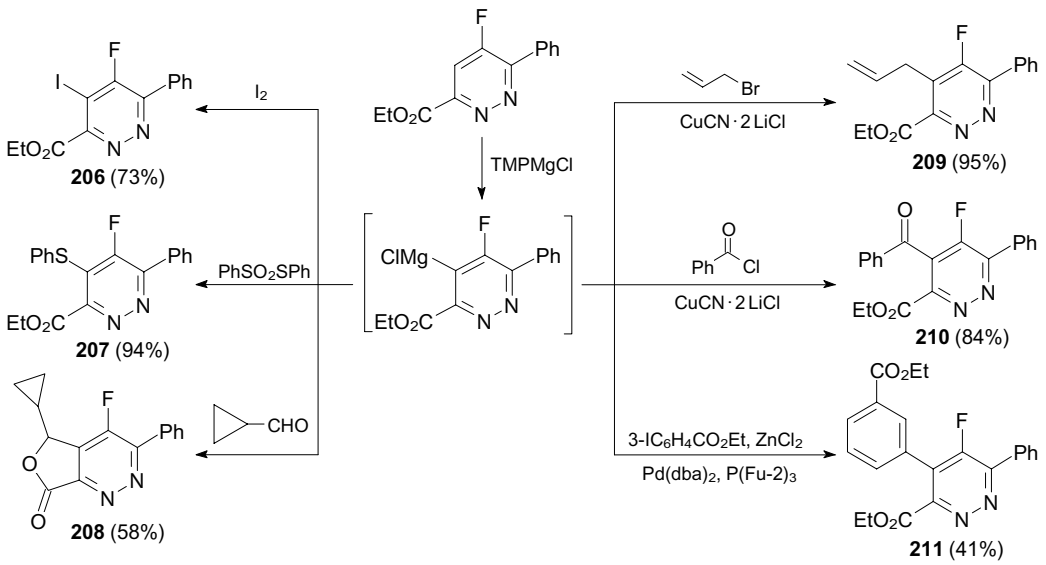


205 (37% – 91%)

(*a*) 1) TMPMgCl·LiCl, THF, −20 °C; 2) electrophile, −20 °C; 3) NH_4Cl (aq.) [for electrophile = $MeSSO_2Me$, PhCHO, furfural, $PhC(O)CO_2Me$, PhC(O)Cl; E = SMe, PhCH(OH), 2-FuCH(OH), $PhC(OH)CO_2Me$, Bz];
(*b*) 1) TMPZnCl·LiCl, THF, 20 °C; 2) Br_2 or I_2, 20 °C (for E = Br, I);
X, Y = H, Cl; Cl, H;

TMP(M)Cl·LiCl =  [(M) = Mg, Zn]

Scheme 106



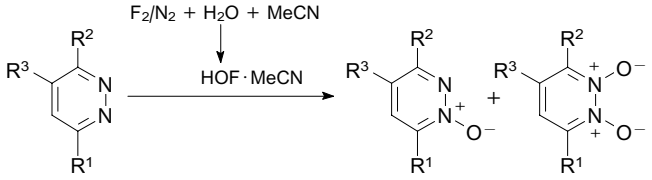
strategy, the hydrogen atom in position 4 of pyridazinone is replaced by a metal atom on treatment with Knochel – Hauser bases (which are less nucleophilic than Grignard reagents) and, after that, the intermediate is reacted *in situ* with an electrophile to give the corresponding substitution products **205** (Scheme 105).

Ethyl 5-fluoro-6-phenylpyridazine-3-carboxylate was employed as a versatile building block in the synthesis of various pyridazine derivatives. The above strategy resulted in the synthesis of a number of modified pyridazines **206** – **210** in high yields (Scheme 106).[85] Negishi coupling was also carried out (see Section 4.8.2), and product **211** was isolated in a moderate yield.

4.10. Pyridazine *N*-oxides

The efficient synthesis of pyridazine *N*-oxides was reported (Scheme 107).[142] The oxidation of nitrogen atoms is due to the formation of hypofluorous acid, one of the most potent oxidants, in the fluorine – water – acetonitrile system. This method is suitable for the synthesis of both *N*-oxides **212** and *N*,*N*′-dioxides **213**.

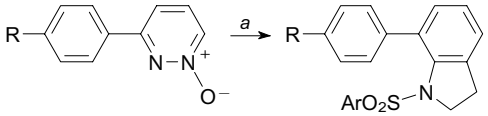
Scheme 107



212 (15% – 100%) **213** (0% – 85%)

R^1 = H, Me, Cl, Br; R^2 = H, Me, Cl, Br, CN; R^3 = H, Me

Scheme 109



215 (56% – 60%)

(*a*) 1) Me_2SO_4, KOH, CH_2Cl_2, 70°C; 2) pyrrole, $Rh_2(esp)_2$, 0 °C; 3) $NaBH_3CN$, AcOH, 0 °C; 4) $ArSO_2Cl$, PyH, 0 °C; R = H, CN; Ar = 4-$MeOC_6H_4$

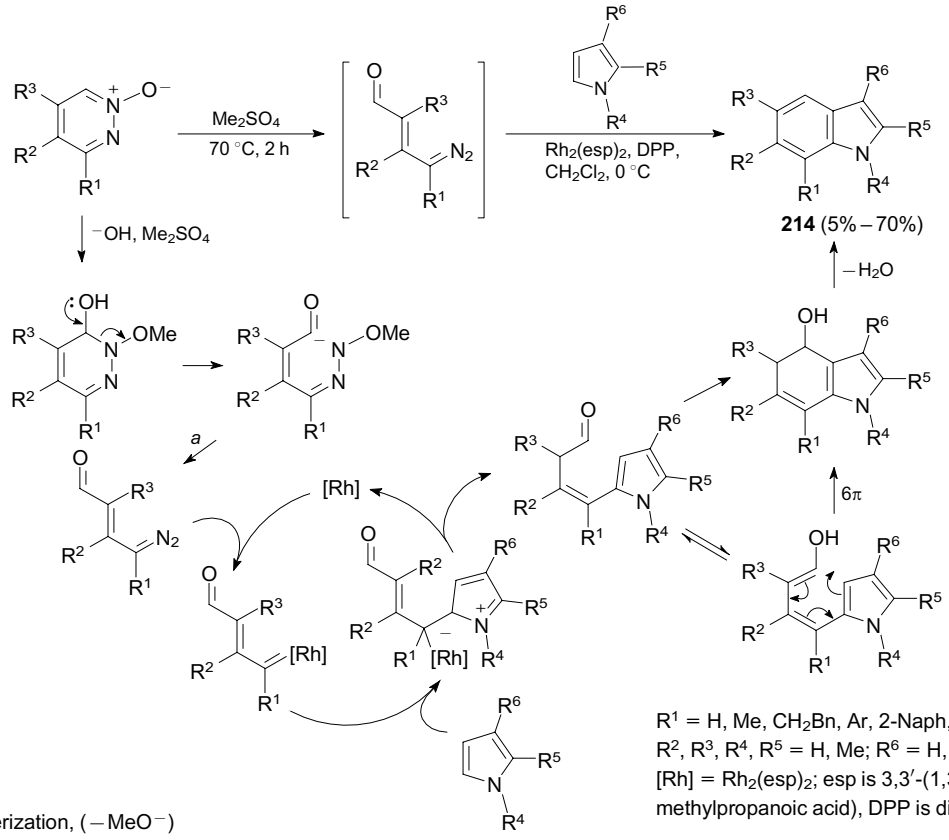
Pyridazine *N*-oxides can be used for the synthesis of alkyl-, 7-aryl- and 7-styrylindoles. Efficient transannulation was described.[143] The key reaction steps included opening of the pyridazine ring, Rh-catalyzed elimination of nitrogen with intermediate formation of metallocarbene and the reaction of the metallocarbene with pyrroles, resulting in substituted indoles **214** (Scheme 108).

This reaction was applied for the synthesis of 7-arylindolines **215**, which possess anticancer activity (Scheme 109). The saturated moiety was formed during the subsequent reduction and *N*-sulfonylation of the pyrrole ring.

3,5-Diamino-4,6-dinitropyridazine 1-oxide (**216**) was investigated as a compound with high detonation properties (Scheme 110).[31] The last steps of the synthesis included nitration of 3,5-dimethoxypyridazine 1-oxide and replacement of methoxy groups by amino groups on treatment with ammonia.

The photochemical method for direct synthesis of 1*H*-pyrazoles **217** from pyridazine *N*-oxides demonstrated a good efficiency for a range of different substrates, which

Scheme 108

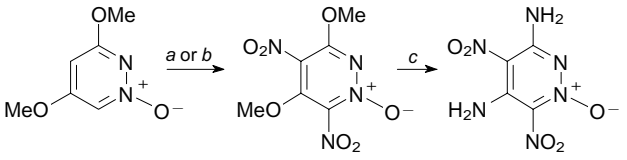


214 (5% – 70%)

(*a*) *Z* – *E*- isomerization, (– MeO^-)

R^1 = H, Me, CH_2Bn, Ar, 2-Naph, (*E*)-CH═CHAr; R^2, R^3, R^4, R^5 = H, Me; R^6 = H, Me, Et; [Rh] = $Rh_2(esp)_2$; esp is 3,3′-(1,3-phenylene)-bis(2,2-dimethylpropanoic acid), DPP is diphenyl phosphate

Scheme 110



216 (95%)

(*a*) 20% oleum, 100% HNO_3, 50 °C (25% – 30% yield);
(*b*) 20% oleum, $NaNO_3$, 60 °C (13% yield);
(*c*) NH_3 (aq.), MeCN, Δ

finally furnished compound **218**, a promising NK-3 receptor antagonist, in a high yield (Scheme 111).[144]

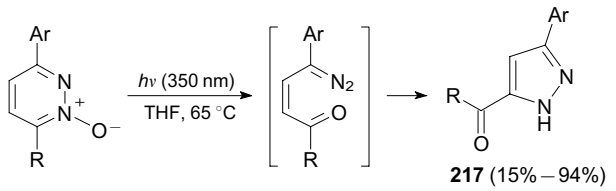
4.11. Supramolecular complexes with pyridazines

Macrocyclic [2]rotaxane moieties **219** and **220** were prepared on the basis of pyridazines (Scheme 112).[145] The formation of complex **219** with unsubstituted pyrene proceeded *via* pyrene coordination, the formation of a dication and ring closure. [2]Rotaxane **220** was obtained in a similar way, with the linear part being also constructed from pyrene with long-chain substituents containing an alkyne and polyether moieties and triphenyl anchors at the chain ends.

5. Applications of pyridazines

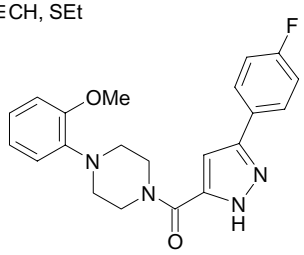
A study[146] is devoted to evaluation of the practical significance and description of the most favourable properties of

Scheme 111



217 (15% – 94%)

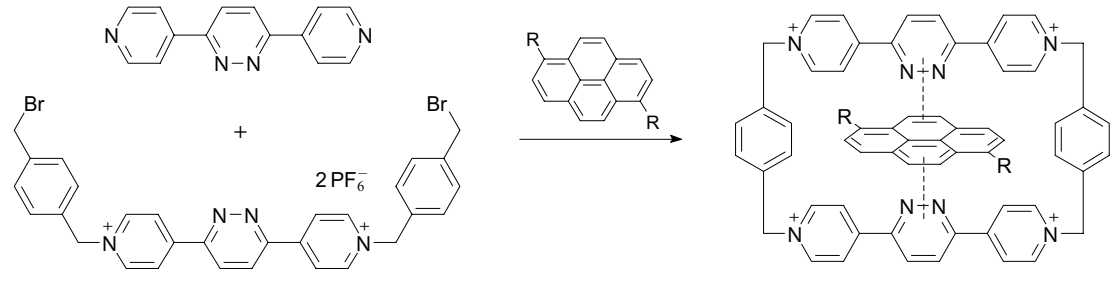
R = $N(CH_2CH_2)_2X$ (X = CH_2, O, S, NH), $N(CH_2)_4$, $N(CH_2)_3$, NHPh, NHBn, NHAll, NHCH(Me)CH(OH)Ph, OAlk, $OCH(Me)CH{=}CH_2$, OPh, $OCH_2C{\equiv}CH$, SEt



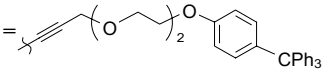
218 (90%)

pyridazine structures. A large number of examples of applications of pyridazines as pharmacologically active agents are given in reviews.[1, 5, 9, 147] Pyridazine derivatives often demonstrate antitumour activities; therefore, they are expected to be used against a broad range of cancer diseases. The key mechanism of action of these compounds is inhibition of various kinases. Among them, mention should be made of Bruton tyrosine kinase inhibitors

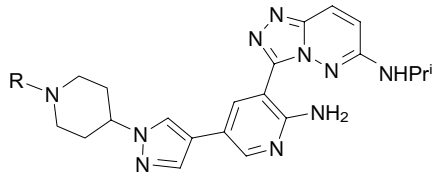
Scheme 112



219, **220**

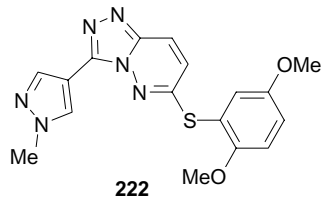
R = H (**219**, 92%), X (**220**, 84%); X = 

Structures 221 – 226

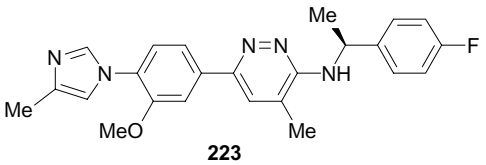


221

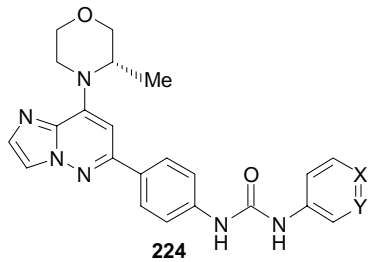
R = Me, CH_2CH_2OH



222

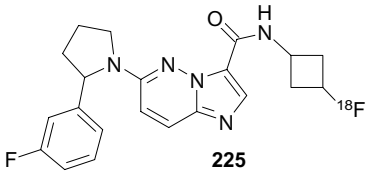


223

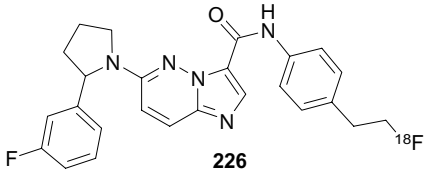


224

X = N, Y = CH; X = CH, Y = N

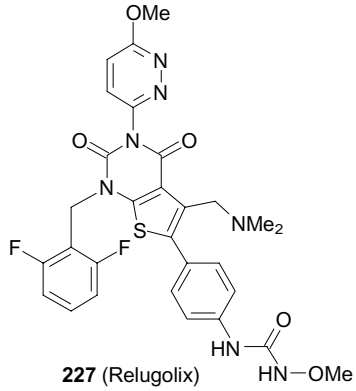


225

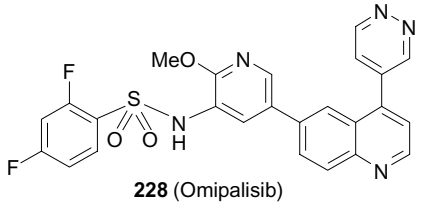


226

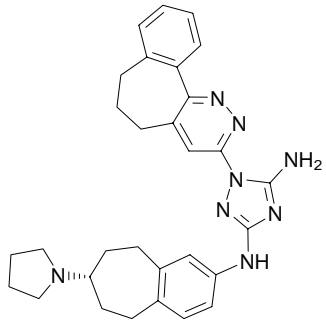
Structures 227 – 229



227 (Relugolix)



228 (Omipalisib)



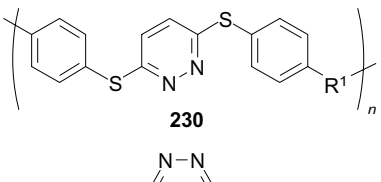
229 (Bemcentinib)

(**221**),[113] LRRK2 kinase inhibitors (**222**)[148] and γ-secretase modulators (**223**).[149] Compounds **224** show considerable antiproliferative activity, especially against A549 and H460 non-small cell lung cancer.[150] Derivatives **225** and **226** demonstrated good efficiency towards inhibition of Trk receptors and, when labelled with ^{18}F isotopes, they proved to be potential PET imaging agents (PET is positron emission tomography).[151] This fact was successfully confirmed by experiments in rats, in particular, their specific binding in brain areas rich in TrkB/C receptors was identified.

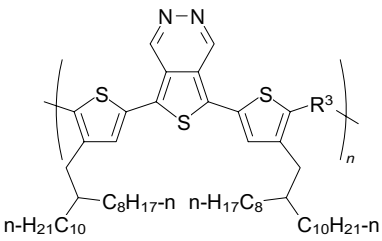
Special mention should be made of some pharmacologically active agents, which were obtained in the last decade and are in various phases of clinical trials. The agent Relugolix (RVT-601, TAK-385, **227**) is a gonadotropin-releasing hormone antagonist (GnRH) applied for the treatment of uterine fibroid.[152] Currently, this compound is in phase III clinical trials for the treatment of endometriosis and prostate cancer. The agent Omipalisib (GSK2126458, GSK458, **228**), a potent and selective PI3K/mTOR signaling pathway inhibitor, was evaluated in phase I clinical trials in subjects with solid tumours, lymphoma and idiopathic pulmonary fibrosis and can be regarded as a new drug candidate for direct use or in a combination therapy of patients with neurocutaneous melanocytosis (NCM).[153] Compound **229** (Bemcentinib, R428, BGB324) is the first low-molecular-weight AXL kinase inhibitor of this class, which was proposed for the treatment of some types of cancer such as non-small cells lung cancer (NSCLC), triple negative breast cancer (TNBC), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), melanoma and metastatic pancreatic cancer.[154, 155] Currently, this agent is in phase II clinical trials.

Quite a few pyridazine derivatives demonstrate interesting physical properties. A review[156] describes the application of pyridazine-based π-conjugated structures as functional materials possessing luminescent and nonlinear-optical properties in organic electronics and for the development of liquid crystals. Particular attention was given to supramolecular complexes for the molecular recognition, membrane transport of drugs and design of macrostructures and devices at the molecular level. Films fabricated from polymers **230** possess interesting optical properties, in particular, high refractive indices and birefringence.[137] Polymers **231** were synthesized and found[78] to have high optical contrast, high switching speed and high colouration efficiency. For donor-acceptor polymer semiconductors **232**, physical and electrochemical properties were thor-

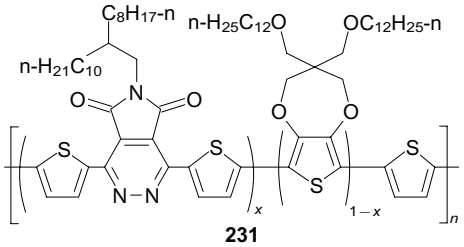
Structures 230 – 233



230

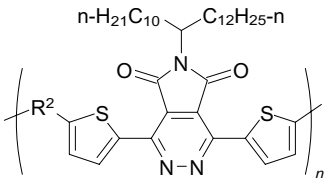


233

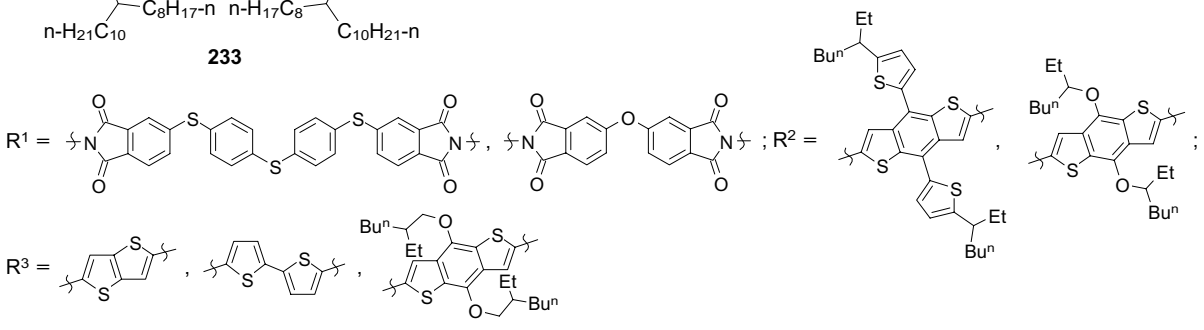


231

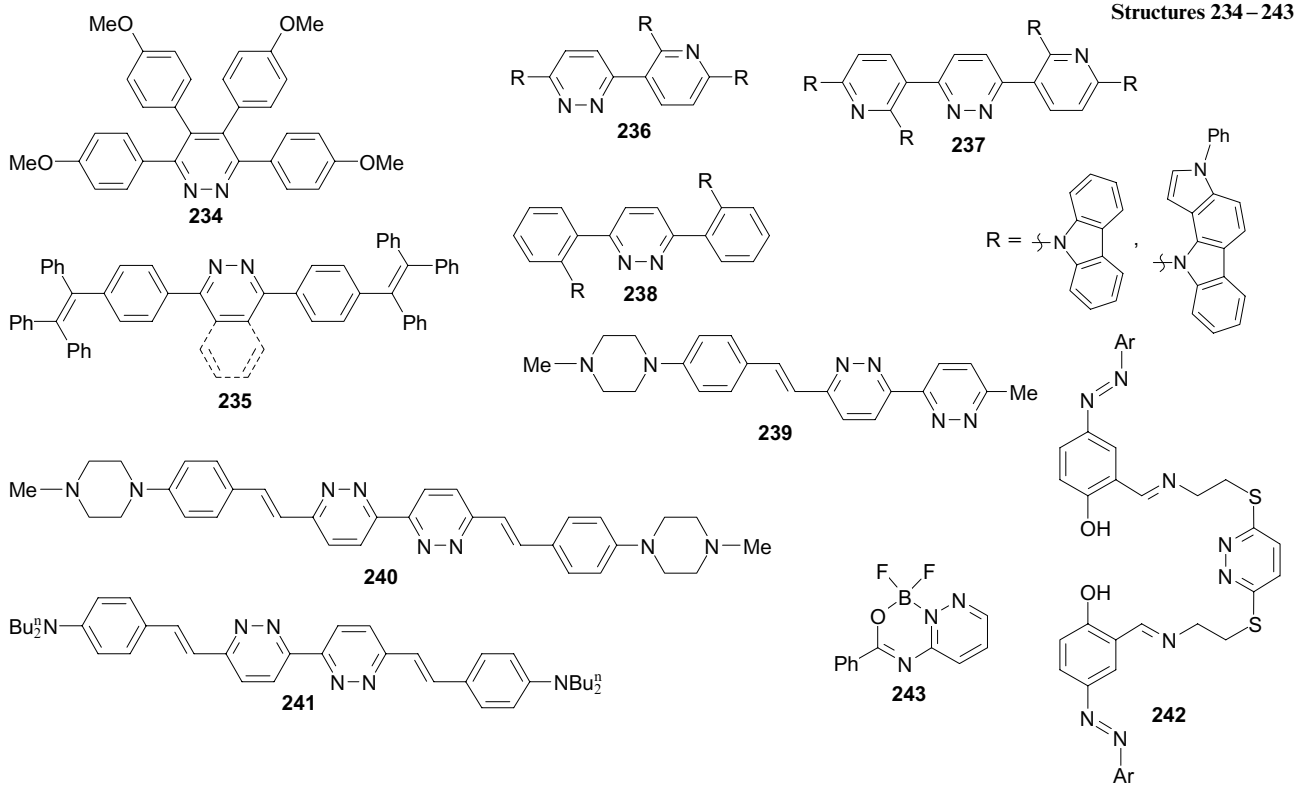
x = 0.1, 0.3, 0.5



232



Structures 234 – 243

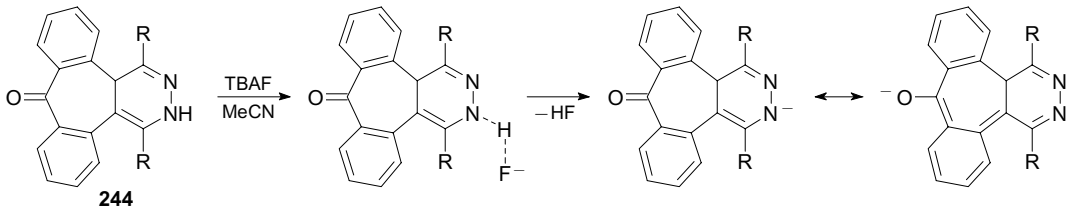


oughly studied, which demonstrated good prospects for the use of these compounds in the design of organic thin-film transistors and solar cells.[157] Three types of polymers **233** were studied as p-type semiconductors and proposed as appropriate materials for the manufacture of organic field effect transistors.[158]

Luminescent characteristics of compound **234** were studied in solution and in the solid state.[159] Protonation of the pyridazine ring induces a change in the luminescence intensity and a colour change from blue (λ = 406 nm) to orange-red (λ = 630 nm). The results made it possible to design a sensing film possessing high sensitivity to trifluoroacetic acid, which is efficiently controlled by UV radiation. A similar sensitivity to acids was shown for compound **235**, which was also proposed for determination of organic acids.[160] The synthesis and study of luminescence characteristics of compounds **236** and **237** were reported; in addition, the single crystal structure of unsymmetrical pyridazine **236** was thoroughly investigated, and relatively high thermal stability was established.[161] Similar compounds **238** were employed for the fabrication of green phosphorescent organic light-emitting diodes.[162] Bis-pyridazines **239** and **240** were studied for photophysical properties; a higher solvatochromic sensitivity was found for symmetrical compound **240** in comparison with asymmetric derivative **239**.[163] This interesting feature was used for the design of a film based on polymethyl methacrylate, which is applied to detect organic solvents on the basis of their polarity. Bipyridazine **241** also showed good fluorescent properties, clear-cut solvatochromism and was considered promising for the design of organic light emitting diodes; the compound was found to function as a ligand giving stable complexes with Cu^{2+}, Pt^{2+}, Ni^{2+} and Ir^{3+} (Ref. 164). Compounds **242** forms coloured complexes with the Cu^{2+} ions.[165] Boron-containing blue fluorophore **243** demonstrated fluorescent properties in solution and in the solid state and was proposed for the introduction of biological labels and design of sensors.[166]

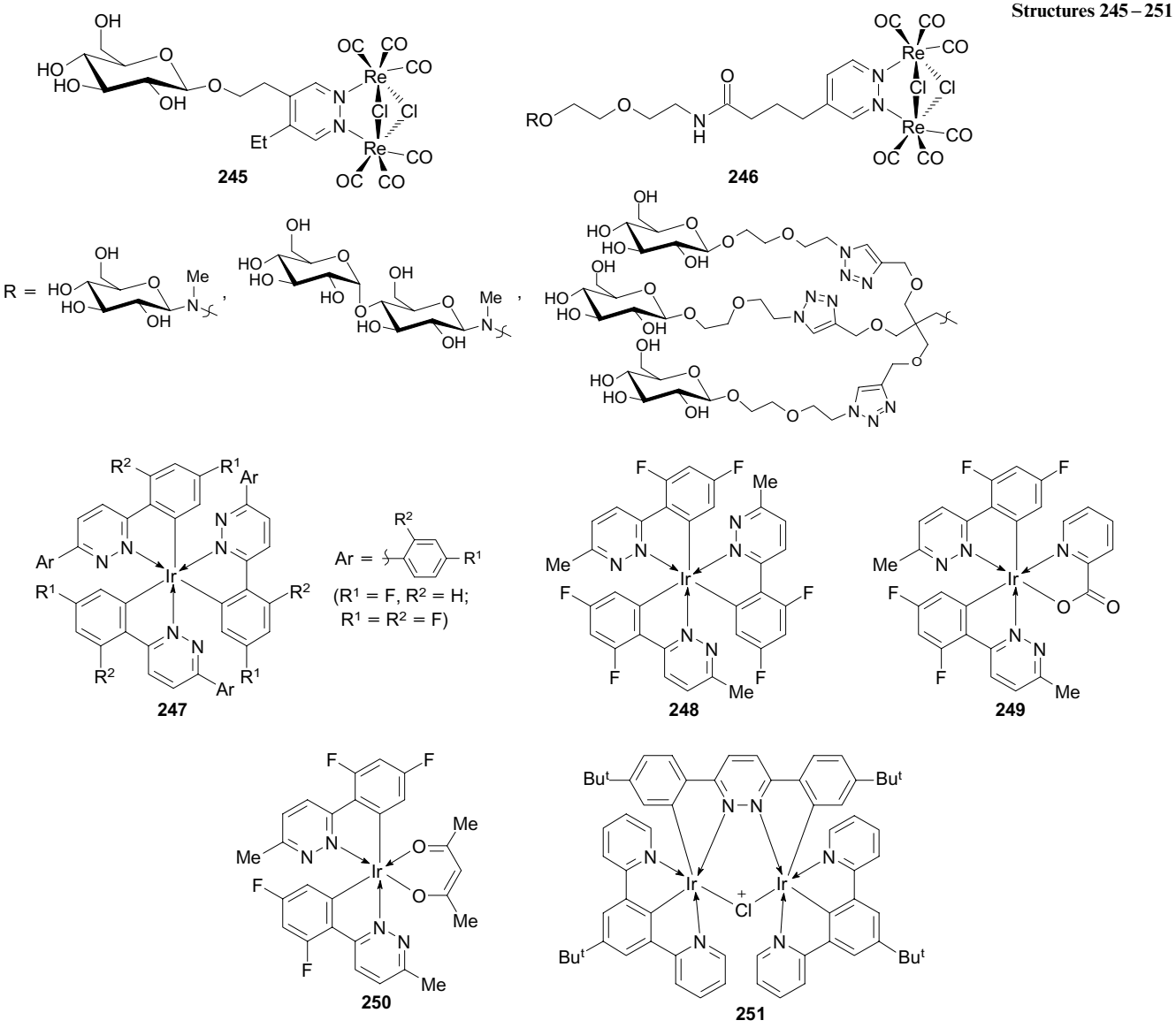
Dihydropyridazines **244** can be used for selective and sensitive detection of fluorine ions (Scheme 113).[167] The NH protons in these structures are sufficiently acidic for deprotonation under the action of fluoride anion, which leads to a considerable colour change due to charge delocalization and to accompanying fluorescence quenching. Large Stokes shifts, high quantum yields and long fluorescence lifetimes make these compounds suitable for the design of potential efficient chemosensors.

Scheme 113



R = CO_2Me, 2-Py (**244**)

Structures 245 – 251



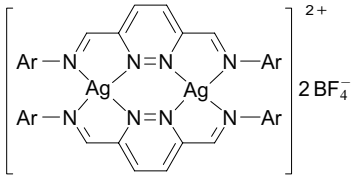
Good photophysical properties may be inherent in not only organic molecules based on pyridazine, but also in their complexes with transition metals. A review[168] is devoted to the studies of photophysical characteristics of luminescent binuclear rhenium(I) complexes containing 1,2-diazine ligands. Luminescent glycosylated luminophores **245** and **246** based on binuclear rhenium complexes were reported.[169] The photophysical properties were studied in detail and assays on internalization of human cervical adenocarcinoma cells were carried out. The complexes have high cell permeability, selectivity to various organelles, low cytotoxicity and fast internalization. All this makes compounds **245** and **246** appropriate agents for the use in cell imaging.

Iridium(III) complexes **247** – **250** were studied as potential materials for organic light-emitting diodes (OLEDs).[170 – 173] Compounds **247** were demonstrated to have enhanced luminescent and electrochemical characteristics with increase in the number of fluorine atoms in the ligands in comparison with unsubstituted precursor. The binuclear iridium complexes are also of interest for their physical properties. For example, cationic complex **251** shows broadband emission in the red region (λ = 520 – 720 nm). This complex exhibited the ability to penetrate into cells and concentrate in mitochondria. However, its application as a fluorescence biolabel is hampered by high dark toxicity.

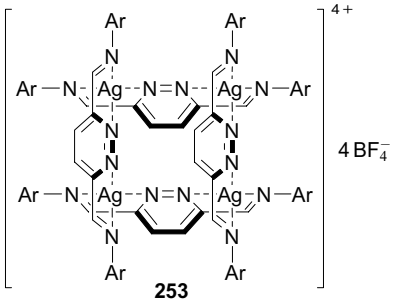
Bidentate ligands based on pyridazine-3,6-dicarbaldehyde imines have been reported.[174, 175] It was found that two types of complexes (**252** and **253**) can be distinguished; in one type of complexes, silver atoms are in a tetrahedral environment of nitrogen atoms. Similar derivatives were applied to prepare palladium complexes **254** and **255**. Pyridazine-3,6-dicarbaldehyde imines were found to behave as both tetradentate and bidentate ligands.

Pyridazine-based bis-carbene ligands are often used to prepare complexes of various transition metals, for example, compounds **256** and **257**.[106] The Ru^{II}, Pd^{II}, Ni^{II} and Cu^{I} complexes (**258** – **261**) with a bis-carbene ligand containing pyridazine and pyridine moieties were studied in detail.[176] The most interesting structure is inherent in copper(I) complex **261** containing a triangular Cu_3 core at the centre.

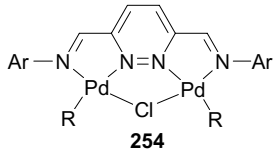
Structures 252 – 261



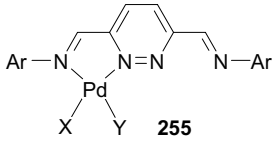
252



253

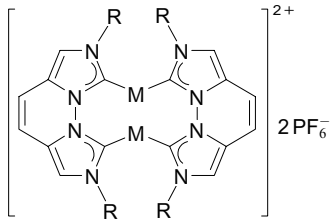


254



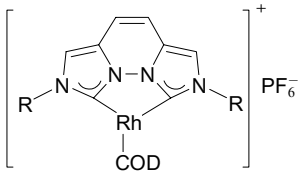
255

252, **253**: Ar = 4-MeC_6H_4, 4-MeOC_6H_4, 2-PhC_6H_4, 2,4-$Me_2C_6H_3$, 3,5-$Cl_2C_6H_3$;
254, **255**: R = Cl, Me; Ar = 2,6-$Pr^i_2C_6H_3$; X = Y = Cl; X = Me, Y = Cl; X = Cl, Y = Me

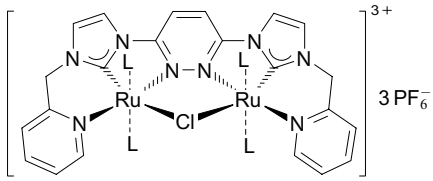


256

M = Cu, Ag, Au

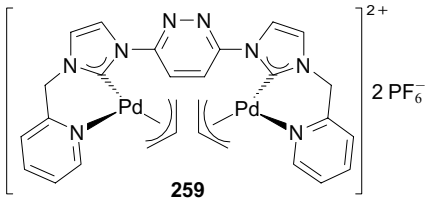


257

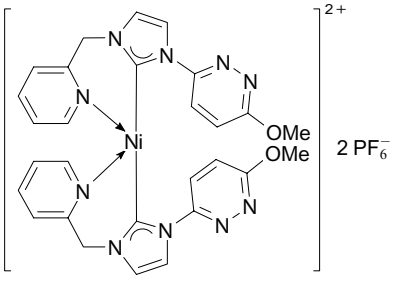


258

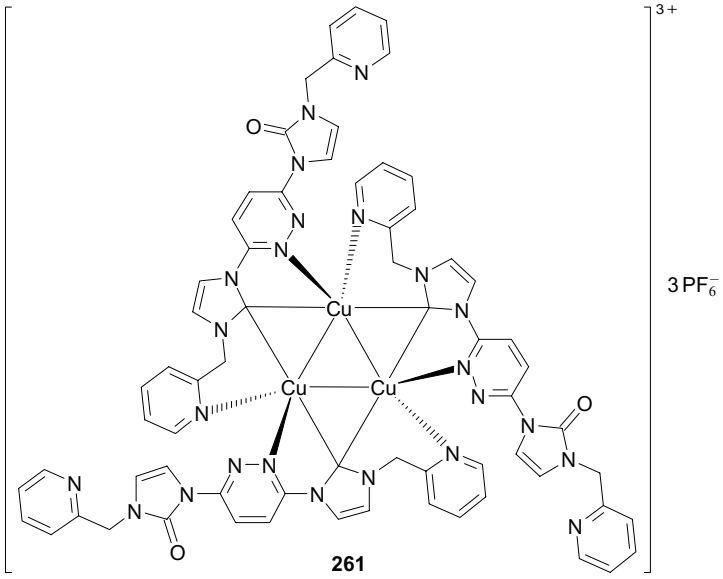
L = MeCN



259

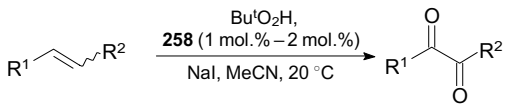


260



261

Scheme 114



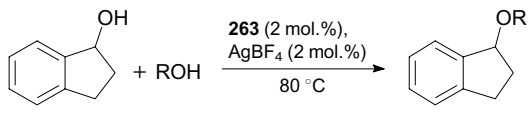
262 (58% – 92%)

R^1 = Ar; R^2 = Ph, Pr^n, 2-Th;
$R^1 – R^2$ = C_6H_4 – N(Me), C_6H_4 – N(Bn)

Ruthenium(II) complex **258** was efficiently utilized for catalytic oxidation of several alkenes and substrates containing double bonds to diketones **262** (Scheme 114).

Other examples of application of pyridazine-containing catalysts in organic synthesis are also known. For example, gold-containing catalyst **263** was favourable for efficient ether formation reaction (Scheme 115).[177]

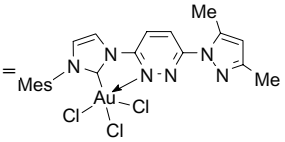
Scheme 115



(68% – 91%)

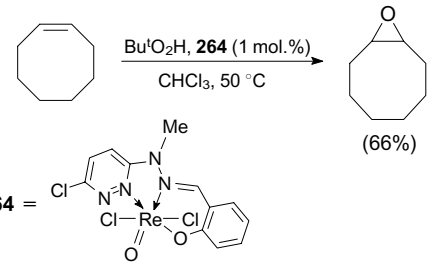
R = Et, Pr^n, Pr^i, Bu^i, iso-C_5H_{11}, $CH(CH_2)_6$

263 =

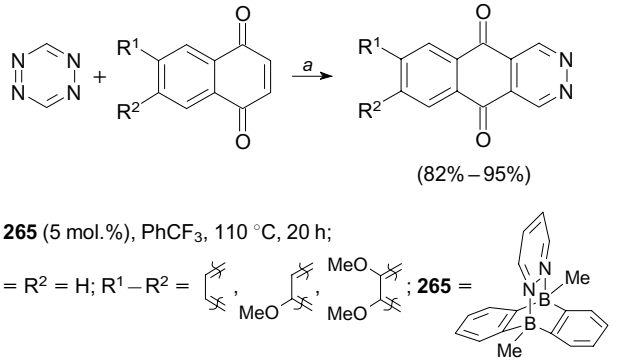


Rhenium catalyst **264** with a pyridazine moiety in the ligand was developed for epoxidation of cyclooctene in the presence of *tert*-butyl hydroperoxide (Scheme 116).[178]

Scheme 116



Scheme 117



An interesting example of a transition metal-free heterocyclic catalyst is the pyridazine complex with bis-borane **265** (Scheme 117).[179] The catalyst, which was used in the inverse electron demand Diels – Alder reaction, is air- and moisture-stable and has a high catalytic efficiency.

6. Conclusion

Over the last decade, numerous synthetic approaches to the preparation of pyridazines have been developed and the reactivities of both the diazine ring and the substituents have been studied. Studies on optimization and expansion of the range of possible substrates for the already known popular methods are in progress, including synthesis from [4 + 2] components, electrophilic attack on the pyridazine nitrogen atoms and nucleophilic aromatic substitution reactions. Some transformations have not been extensively studied, for example, reduction of the pyridazine ring, [4 + 2] cycloaddition and reactions involving radicals. Also, new results have been obtained for transition metal-catalyzed reactions and reactions involving organometallic reagents; conceptually new synthetic approaches were described, including those using organocatalalysis and photochemical activation. Interesting achievements were demonstrated in the chemistry of pyridazine *N*-oxides and *N*,*N*′-dioxides. Convenient reactions for the assembly of pyridazine rings made a contribution to successful modification of nucleotides and DNA and to supramolecular chemistry, providing the synthesis of [2]rotaxanes. It is important to note the development of applications of pyridazines as physiologically active compounds, materials with promising properties, ligands and catalysts.[180]

The above material provides the conclusion that the chemistry of pyridazines is a promising area of heterocyclic chemistry and that in the near future, one should expect numerous works related to both new chemical transformations and new practical applications of these compounds.

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