DOI: 10.1070/RCR4891

Ring opening reactions of nitrogen heterocycles

Andrey V. Smolobochkin,* Almir S. Gazizov, Alexander R. Burilov, Mikhail A. Pudovik, Oleg G. Sinyashin

Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center, Russian Academy of Sciences, ul. Arbuzova 8, 420088 Kazan, Russian Federation

Published data on ring opening reactions of nitrogen-containing cyclic compounds resulting in various acyclic products are integrated and systematized. The reactions of common five-, six- and seven-membered nitrogen heterocycles containing one to four nitrogen atoms in the ring and having various structures (mononuclear, polynuclear, fused, saturated, unsaturated and aromatic) are considered. Special emphasis is made on the potential of nitrogen heterocycles for the synthesis of polyfunctional open-chain compounds. The advantages and disadvantages of the proposed approaches are noted. Data on the biological activities of some ring opening products of the title heterocycles are presented. The text is arranged according to the type of reagents and catalysts used.
The bibliography includes 196 references.

Contents

1. Introduction 1104
2. C – N bond cleavage by reducing agents 1105
3. C – N bond cleavage by oxidants 1107
4. C – N bond cleavage by acids and electrophilic reagents 1111
5. Cleavage of the C – N bond by basic reagents 1115
6. Metal-catalyzed C – N bond cleavage 1118
7. Miscellaneous C – N bond cleavage reactions 1120
8. Ring opening in heterocycles containing several nitrogen atoms 1123
9. Conclusion 1124

1. Introduction

Synthesis of new and already known polyfunctional compounds by ring opening reactions is used less often than synthesis *via* transformations of open-chain compounds. Nevertheless, ring opening-based approaches to the synthesis of acyclic products are of obvious interest because they often give bifunctional derivatives. Furthermore, most ring opening reactions have high stereoselectivity, which is important for the preparation of single stereoisomers. It is also noteworthy that opening of one endocyclic bond in bi- or polycyclic molecules gives, in some cases, heterocycles of larger size that cannot or can hardly be synthesized by other methods.

Nitrogen heterocycles are among the most important and often encountered classes of organic compounds. Numerous reviews consider various aspects of the chemistry of this compound class. A significant role in their chemical reactivity belongs to reactions involving cleavage of the carbon – nitrogen bond. Nevertheless, no systematic analy-

A.V.Smolobochkin. Candidate of Chemical Sciences, Researcher at the IOPC FRC KazSC RAS.
E-mail: smolobochkin@iopc.ru
Current research interests: chemistry of heterocyclic and organophosphorus compounds and nitrogen-containing acetals.
A.S.Gazizov. Doctor of Chemical Sciences, Senior Researcher at the same Institute. Telephone: +7(843)272 – 7344, e-mail: agazizov@iopc.ru
Current research interests: chemistry of calixarenes, nitrogen-containing acetals and heterocylic compounds.
A.R.Burilov. Doctor of Chemical Sciences, Professor, Head of Laboratory of the same Institute.
Telephone: +7(843)272 – 7344, e-mail: burilov@iopc.ru
Current research interests: chemistry of nitrogen- and phosphorus-containing calix[4]resorcinarenes, acetals, aldehydes and acyclic polyphenols, supramolecular chemistry.
M.A.Pudovik. Doctor of Chemical Sciences, Professor, Chief Researcher at the same Institute.
Telephone: (843)272 – 7324, e-mail: pudovik@iopc.ru
Current research interests: chemistry of organophosphorus and -silicon compounds and calixarenes.
O.G.Sinyashin. Academician, Doctor of Chemical Sciences, Professor, Director of the IOPC FRC KazSC RAS.
Telephone: +7(843)273 – 9365, e-mail: oleg@iopc.ru
Current research interests: chemistry of organoelement compounds; synthesis, structure and properties of organophosphorus and -metallic compounds; chemistry of fullerenes and their organic derivatives; electrochemical synthesis and catalysis.

Received 29 March 2019
Translation: Z.P.Svitanko

© 2019 Uspekhi Khimii, Russian Academy of Sciences and Turpion Ltd.

sis of these reactions in terms of their applicability to the synthesis of bi- and polyfunctional molecules has yet been carried out.

There are still some exceptions, namely, a series of review publications[1–3] devoted to pyridine ring opening, which cover the period up to 2002, and one more review.[4] Intensive studies along this line are apparently associated with both the availability of pyridine and its derivatives and the synthetic value of the obtained products. Therefore, in this review, we consider publications on this subject that appeared after 2002. Some attention is given to reactions of N-oxides of heterocyclic compounds; their chemistry is described in a number of reviews.[5–7] We do not address ring opening reactions for small rings (aziridine[8–10] and azetidine[11–13] derivatives) or hydrolysis of lactams,[14,15] which do not differ fundamentally from the well-studied hydrolysis of acyclic carboxylic acid amides. The ring–chain tautomerism of nitrogen heterocycles constitutes a fairly large area of organic chemistry. Tautomerization accompanied by C–N bond cleavage often takes place as an intermediate step of chemical reactions; in this case, the final products retain their ring structure and, therefore, these transformations are beyond the scope of our review.

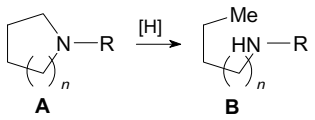
Thus, the review summarizes data on the reactions of five-, six- and seven-membered nitrogen heterocycles from the standpoint of their significance for the synthesis of various classes of acyclic compounds. In our opinion, it is most convenient to classify the reactions in terms of the type of reagent used to cleave the carbon–nitrogen bond. According to this classification, opening of a heterocyclic moiety can be induced by oxidants, reducing agents, bases and acids, electrophilic reagents and transition metal catalysts. A separate part deals with the relatively few examples of opening of heterocycles containing several nitrogen atoms.

The following abbreviations are used:
B — base,
Boc — *tert*-butoxycarbonyl,
Bu^t_2Bpy – 4,4′-di-*tert*-butyl-2,2′-bipyridine,
Cbz — benzyloxycarbonyl,
Cy — cyclohexyl,
de — diastereomeric excess,
dppe – 1,2-bis(diphenylphosphino)ethane,
DPZ — dicyanopyrazine,
ee – enantiomeric excess,
EDTA — ethylenediaminetetraacetate,
er — enantiomeric ratio,
Fmoc – 9-fluorenylmethoxycarbonyl,
Fu — furyl,
MB – Methylene Blue,
mCPBA – *m*-chloroperbenzoic acid,
Naph — naphthyl,
NMO — *N*-methylmorpholine *N*-oxide,
Ns — 4-nitrobenzenesulfonyl (nosyl),
PIDA – phenyliodine(III) diacetate,
Py — pyridyl,
rt — room temperature,
TBS — *tert*-butyldimethylsilyl,
Tf — trifluoromethanesulfonyl (triflyl),
Th — thienyl,
TMP – *meso*-tetramesitylporphyrin,
TMS — trimethylsilyl,
Trs — 2,4,6-triisopropylbenzenesulfonyl,
Ts — 4-methylbenzenesulfonyl (tosyl).

2. C–N bond cleavage by reducing agents

The reductive cleavage can proceed for most classes of nitrogen heterocyclic compounds (**A**) and the reactions give mainly various amines (**B**) (Scheme 1). Many of the reactions are conducted in the presence of catalysts. Platinum group metals (ruthenium, palladium, platinum) supported on carbon and Raney nickel are widely used for heterogeneous catalytic reduction. High popularity is gained by samarium(II) iodide as a single-electron reducing agent, which allows many reactions to be conducted under mild conditions. Other reducing agents used for this purpose include sodium dithionite, boranes, hydroxylamine and its salts and sodium in liquid ammonia.

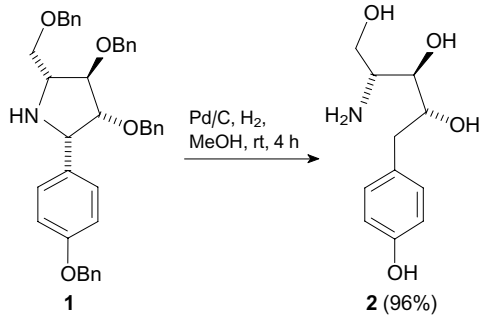
Scheme 1



Many ring opening products show biological activities; therefore, high stereoselectivity of the reactions is important. However, a considerable drawback of the above-described methods is the necessity to use expensive metal catalysts, elevated pressure and temperature, and explosive hydrogen.

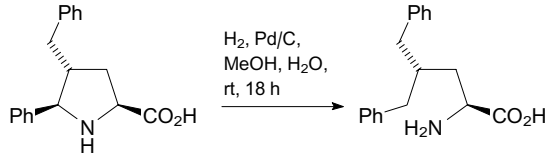
Zhou *et al.*[16] described the Pd-catalyzed stereoselective opening of the pyrrolidine ring of compound **1** (Scheme 2). The target product **2** was isolated in a virtually quantitative yield.

Scheme 2



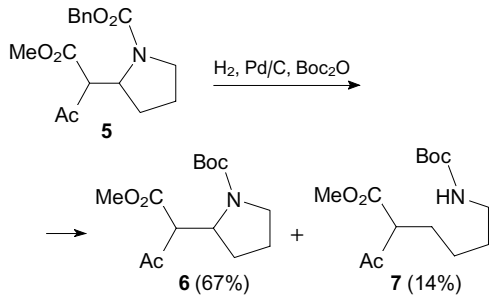
The ring in 4,5-disubstituted proline **3** is opened in a similar way to give (*S*)-2-amino-4-benzyl-5-phenylpentanoic acid (**4**) (Scheme 3).[17]

Scheme 3



Palladium-catalyzed hydrogenation of pyrrolidine **5** in the presence of di-*tert*-butyl dicarbonate (Boc_2O) affords carbamate **6** in a moderate yield (Scheme 4). Acyclic amine **7** was formed as a by-product. The formation of compound

Scheme 4

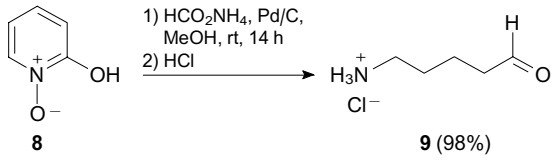


Boc is *tert*-butoxycarbonyl

7 is attributable to opening of the five-membered ring *via* the retro-Michael reaction.[18]

A convenient method for the synthesis of 5-aminopentanal is the reductive cleavage of the pyridine ring upon the addition of anhydrous ammonium formate to a methanol solution of 2-hydroxypyridine *N*-oxide (**8**) containing carbon-supported palladium. The reaction affords amino aldehyde hydrochloride **9** in an almost quantitative yield (Scheme 5). The applicability of this method is restricted by the fact that the presence of some other substituents in the pyridine ring results in the formation of only piperidine derivatives.[19]

Scheme 5



Treatment of pyrrolidine **10** with lithium bis(trimethylsilyl)amide followed by hydrogenation produced N-protected amine **11** in one step in a high yield (Scheme 6).[20]

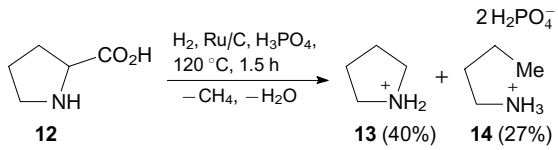
Scheme 6



Tf is trifluoromethanesulfonyl (triflyl), TMS is trimethylsilyl

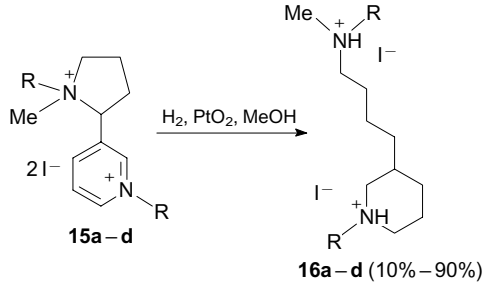
Verduyckt *et al.*[21] reported Ru-catalyzed hydrogenation–decarbonylation of proline (**12**) (Scheme 7). Note that methane is released instead of carbon dioxide. A considerable disadvantage of this method is that mixtures of products **13** and **14** are formed, with the latter being isolated in a relatively low yield.

Scheme 7



The catalytic hydrogenation of nicotine salts **15a–d** results in tertiary amines **16a–d** (Scheme 8), which show a pronounced hypotensive action.[22] It is noteworthy that the pyridine ring is not cleaved, but is only reduced to a piperidine ring. The authors give no explanation to this selectivity.

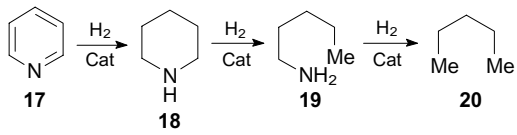
Scheme 8



R = H (**a**), Me (**b**), Et (**c**), Pr^n (**d**)

Hydrogenation of pyridine **17** over stacked cobalt and molybdenum catalyst beds physically separated by alumina was accomplished with a continuous flow of hydrogen (at a pressure of 3 MPa). As a result, compounds **18–20** were isolated.[23] The same products were obtained by using tungsten phosphite as a catalyst (Scheme 9).[24] However, it is rather difficult to implement these methods in laboratory, because high hydrogen pressure is required.

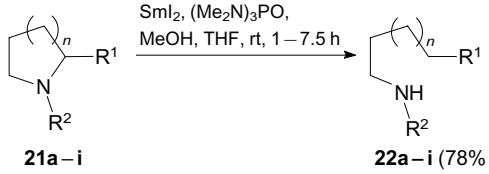
Scheme 9



Cat = Co–Mo/Al_2O_3 or WP

The reduction of azacyclanes **21a–i** with samarium(II) iodide in the presence of hexamethylphosphoramide in a mixture of methanol and tetrahydrofuran affords open-chain compounds **22a–i**.[25] This method can be used to

Scheme 10



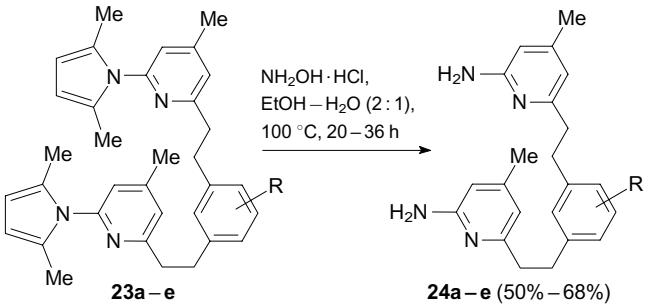
Compound	*n*	R^1	R^2	Compound	*n*	R^1	R^2
a	1	CO_2Me	Bn	**f**	2	Ac	Boc
b	1	CO_2Pr^i	Bn	**g**	2	CO_2Et	Me
c	2	Ac	Me	**h**	2	CO_2Et	Bn
d	2	Ac	Bn	**i**	2	CO_2Et	Ac
e	2	Ac	Ac				

prepare a broad range of substituted amines in good yields (Scheme 10).

We do not consider in detail the studies [26–31] describing hydrogenation of pyrrole in the presence of platinum group metals, because these reactions give pyrrolidine as the major product (with minor amount of butylamine). Considerable drawbacks of this process are poisoning of expensive catalysts and drastic reaction conditions (high pressure and temperature). However, when pyrrole and its derivatives are treated with hydroxylamine, ring opening takes place to give oximes. The latter react with sodium metal in ethanol to be converted to butane-1,4-diamines.[32]

For the synthesis of biologically active molecules containing a free amino group, a pyrrole moiety is often used as a protecting group. In a series of works [33–37] describing the synthesis of nitric oxide synthase inhibitors, 2,5-dimethylpyrrole protecting groups of compounds **23a–e** were removed by treatment with hydroxylamine hydrochloride at 100 °C. Amines **24a–e** were isolated in moderate yields (Scheme 11).

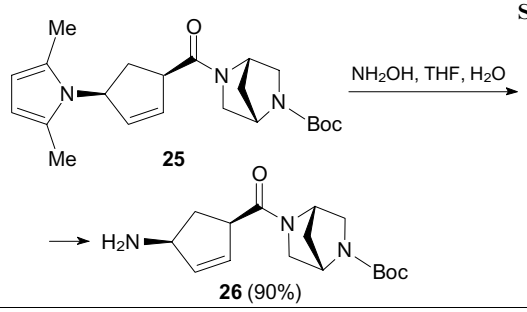
Scheme 11



R = H (**a**), 4-CN (**b**), 4-Br (**c**), 5-Br (**d**), 4-CH_2NH_2 (**e**)

A similar transformation in aqueous THF takes place for compound **25** and gives amine **26** in a high yield (Scheme 12).[38]

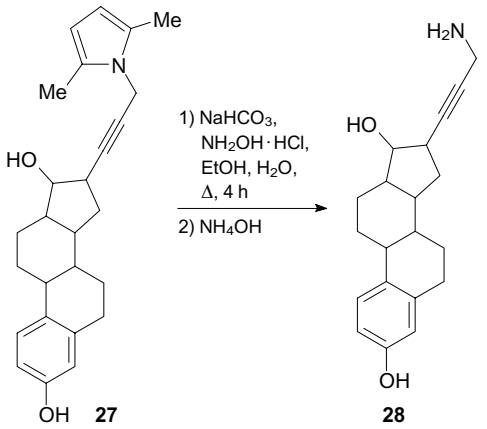
Scheme 12



Refluxing of compound **27** in aqueous ethanol in the presence of sodium hydrogen carbonate and hydroxylamine hydrochloride gives rise to the steroid estrynamine **28** (Scheme 13). The product was isolated in a low yield, which precludes the use of this method for estrynamine synthesis.[39]

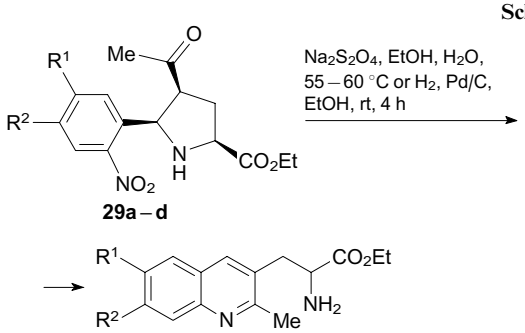
Nyerges *et al.*[40,41] demonstrated that, apart from palladium, sodium dithionite can also be employed as a reducing agent. For example, substituted prolines **29a–d** were converted to quinoline derivatives **30a–d** (Scheme 14). The authors do not present the mechanism of formation of

Scheme 13



quinolines, but suggest that the reaction starts with reduction of the nitro group, which is followed by intramolecular condensation of amino and keto groups. The second step of the reaction is the reductive opening of the pyrrolidine ring to give quinoline derivative **30**. The driving force of the last step is the possibility of aromatization of the quinoline system.

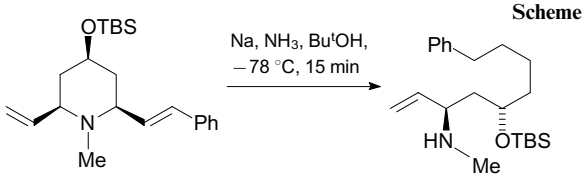
Scheme 14



$R^1 = R^2$ = H (**a**); R^1 = Br, R^2 = H (**b**); $R^1 = R^2$ = MeO (**c**); $R^1–R^2$ = OCH_2O (**d**)

The piperidine ring of compound **31** is opened on treatment with Na/NH_3 in *tert*-butyl alcohol with cooling. The reaction affords diastereomerically pure acyclic amine **32** (Scheme 15).[42]

Scheme 15



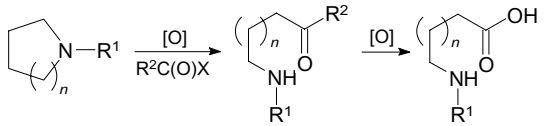
de is diastereomeric excess, TBS is *tert*-butyldimethylsilyl

3. C–N bond cleavage by oxidants

One more popular method that can be used to convert cyclic precursors **A** to valuable acyclic products is oxidative ring

cleavage. Depending on the choice of the reagent, compound **A** is oxidized to either carbonyl compounds **C** or carboxylic acids **D** (Scheme 16). Organic and inorganic compounds of various classes can serve as oxidants, *e.g.*, peroxides (hydrogen peroxide, *m*-chloroperbenzoic acid), salts (potassium permanganate, sodium periodate), oxides (ruthenium and osmium tetroxides), elemental substances (oxygen, ozone, iodine) and enzymes (rabbit liver homogenate). From the green chemistry standpoint, photooxidation is a promising method, since in this case, there is no need to use toxic and metal-containing compounds. In some cases, catalysts are used in addition to oxidants, which increases the reaction selectivity and the product yield.

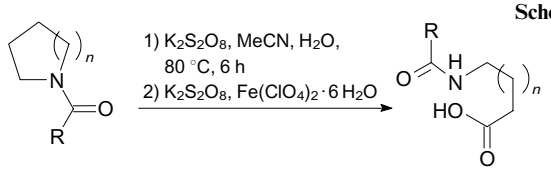
Scheme 16



The oxidative cleavage of nitrogen heterocycles is a convenient method for the preparation of a broad range of biologically active compounds. Some reactions of this type occur in living organisms, giving rise to amides, amino acids, *etc*. Low cost and ready availability are also important benefits of the oxidants used.

Che and co-workers[43] proposed an efficient method for converting cyclic amines **33a**–**e** to organic acids **34a**–**e** in the presence of an iron complex and potassium peroxydisulfate as the oxidant (Scheme 17).

Scheme 17

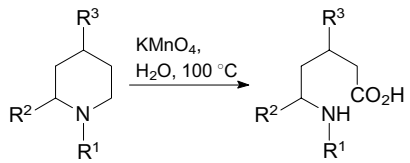


33a–**e** **34a**–**e** (60%–78%)

n = 1: R = Ph (**a**), Boc (**b**); *n* = 2: R = Ph (**c**), Boc (**d**);
n = 3, R = Ph (**e**)

Oxidation of piperidines **35a**,**b** with potassium permanganate in boiling water was carried out[44,45] to give acids **36a**,**b** (Scheme 18). The procedure is rather easily implementable, but the final products are formed in moderate yields.

Scheme 18

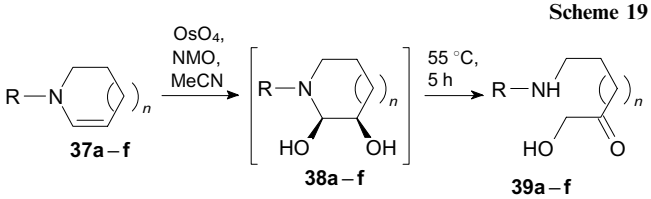


35a,**b** **36a**,**b** (32%–53%)

R^1 = Boc, R^2 = Me, R^3 = H (**a**); R^1 = 3-$NO_2C_6H_4C(O)$,
R^2 = H, R^3 = Me (**b**)

α,β-Unsaturated cyclic amines **37a**–**f** are oxidized in the presence of OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) to afford α,β-*cis*-dihydroxylated compounds **38a**–**f**, which are converted to keto alcohols **39a**–**f**.[46] The reactions are conducted under mild conditions and give the target products in good isolated yields (Scheme 19).

Scheme 19

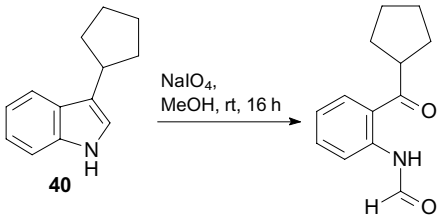


37a–**f** **38a**–**f** **39a**–**f** (62%–96%)

n = 0: R = Bz (**a**); *n* = 1: R = Bz (**b**), CO_2Ph (**c**);
n = 2: R = Bz (**d**), CO_2Ph (**e**), CO_2Me (**f**)

A ring opening reaction of compound **40** was reported to proceed in the presence of sodium periodate in methanol and to produce formamide **41** (Scheme 20).[47]

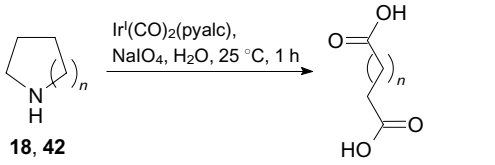
Scheme 20



40 **41** (75%)

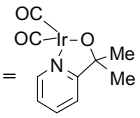
Crabtree and co-workers[48] synthesized dicarboxylic acids **43a**,**b** by oxidation of cyclic amines **18** (*n* = 2) and **42** (*n* = 1). Thus, dicarboxylic acids were readily obtained from available reactants under mild conditions (Scheme 21).

Scheme 21



18, **42** **43a**,**b** (50%–71%)

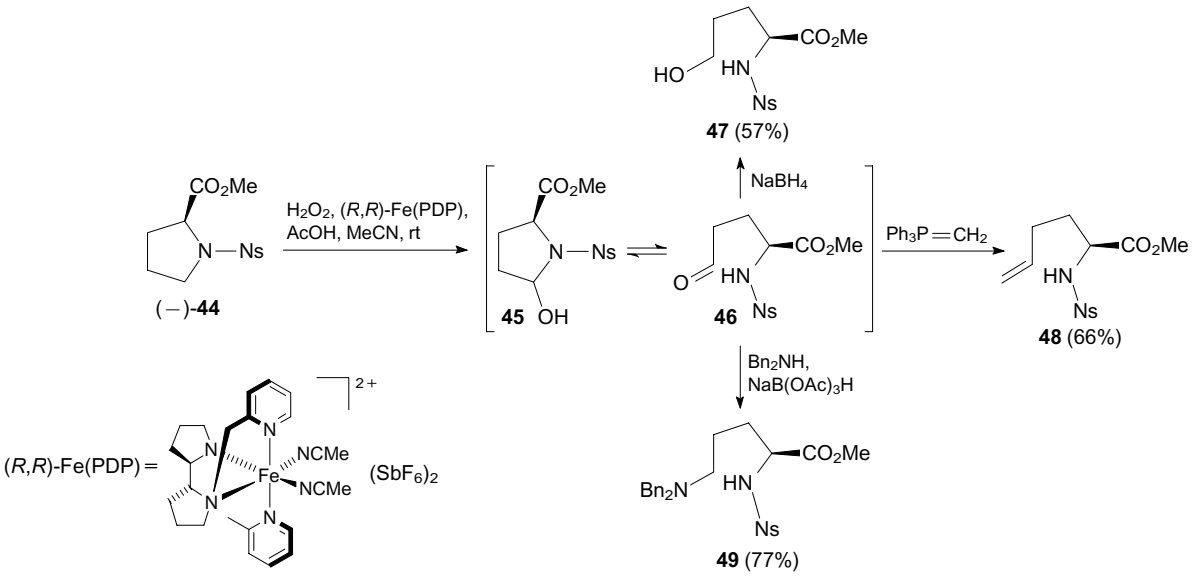
43: *n* = 2 (**a**), 1 (**b**); $Ir^I(CO)_2$(pyalc) =



Osberger *et al.*[49] reported an original method for the oxidation of protected proline **44** to 5-hydroxyproline **45**, which exists in equilibrium with aldehyde **46**. The subsequent reduction, olefination and reductive amination *in situ* give compounds **47**–**49** (Scheme 22). The proposed approach can be used to synthesize quite a number of compounds with retention of configuration of the chiral centre.

Cocquet *et al.*[50] carried out oxidative cleavage of piperidine ring in compounds **50a**–**d** on exposure to visible light (λ = 630 nm) in the presence of Methylene Blue (MB) as a

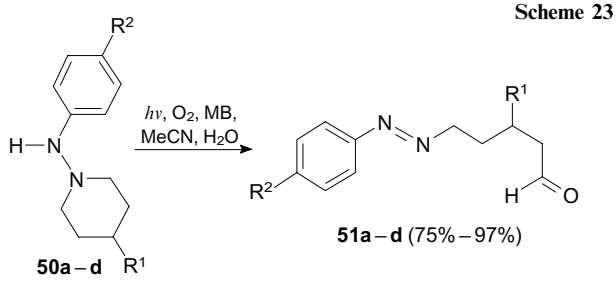
Scheme 22



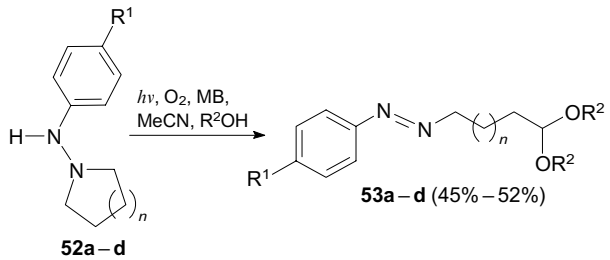
Ns is 4-nitrobenzenesulfonyl (nosyl)

photosensitizer and water as a nucleophile. All of these reactions give rise to corresponding aldehydes **51a** – **d**. The reaction of compounds **52a** – **d** performed under similar conditions in the presence of alcohols results in the synthesis of acetals **53a** – **d**, but the purity and yields of these products are much lower (Scheme 23).

Scheme 23



R^1 = H: R^2 = H (**a**), NO_2 (**b**), CO_2Et (**c**); R^1 = Me, R^2 = H (**d**)

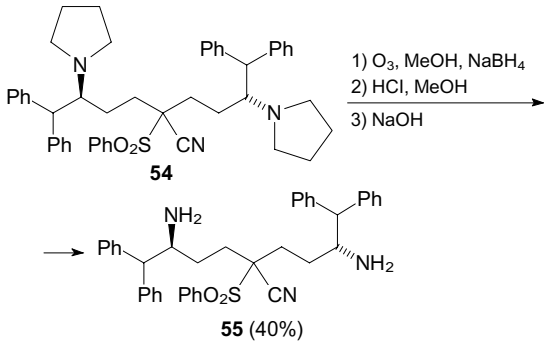


n = 1, R^1 = NO_2, R^2 = Me (**a**); n = 2, R^2 = Me: R^1 = NO_2 (**b**), CO_2Et (**c**); n = 2, R^1 = CO_2Et, R^2 = Et (**d**)

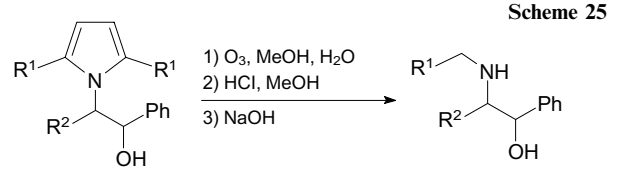
Pyrrole ring opening of compound **54** affords diamine **55** with retention of configurations of the chiral centres (Scheme 24).[51,52]

A similar transformation of compounds **56a** – **c** gives rise to amino alcohols **57a** – **c** (Scheme 25).[53]

Scheme 24



Scheme 25

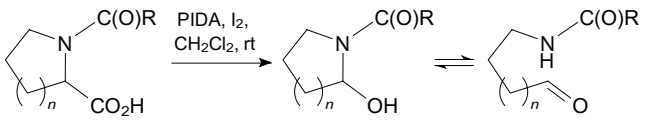


R^1 = R^2 = H (**a**); R^1 = Me: R^2 = H (**b**), Bn (**c**)

The reaction of proline derivative **58a** with phenyliodine(III) diacetate (PIDA) and iodine in dichloromethane was studied in detail. Unlike decarboxylation of 1-benzoylpyrrolidine-2-carboxylic acid (**58b**), which gives a mixture of tautomers **59b** and **60b** in 1.3 : 1 ratio, the reaction of proline **58a** yields amino aldehyde **60a** as the only product. In the case of a six-membered ring (compound **61**), the reaction gives only acyclic aldehyde **62** (Scheme 26).[54]

Using oxidative decarboxylation of 1-benzoylpiperidine-2-carboxylic acid (**61**), Boto *et al.*[55] developed a synthesis of *N*-(5-oxopentyl)benzamide (**62**). 2,3-Disubstituted piperidine **63** was isolated as a by-product. The proposed method is preferable for the synthesis of 2,3-disubstituted piperidines, since the authors were able to select conditions for these compounds to be formed as the major products with good stereoselectivity (Scheme 27).

Scheme 26



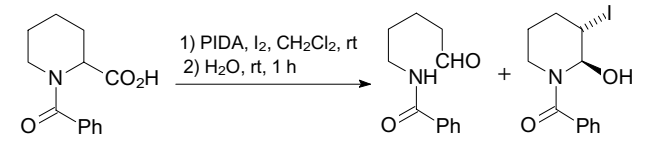
58,**a**,**b**, **61** **59b** **60**,**a**,**b**, **62** (61% – 66%)

58: *n* = 1: R = Bu^t (**a**), Ph (**b**); **61**: *n* = 2, R = Ph

59b: *n* = 1, R = Ph

60: *n* = 1: R = Bu^t (**a**), Ph (**b**); **62**: *n* = 2, R = Ph

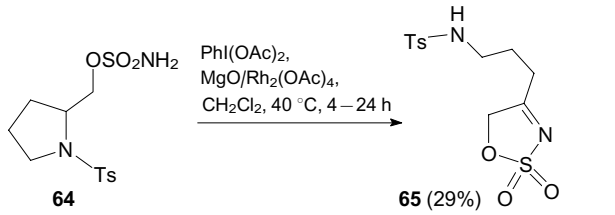
Scheme 27



61 **62** (59%) **63** (8%)

Attention should be drawn to a study[56] devoted to ruthenium-catalyzed pyrrolidine ring opening of compound **64**, providing the synthesis of oxathiazole **65** (Scheme 28).

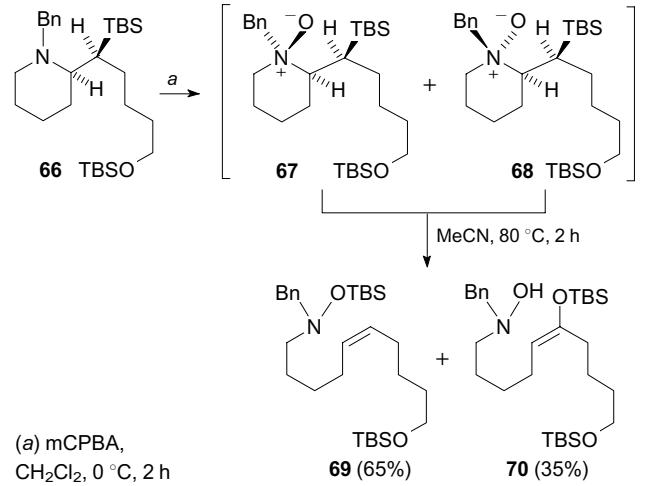
Scheme 28



64 **65** (29%)

The oxidation of compound **66** with *m*-chloroperbenzoic acid (mCPBA) results in the formation of a mixture of N-oxides **67** and **68**, the thermolysis of which furnishes alkenes **69** and **70** (Scheme 29).[57]

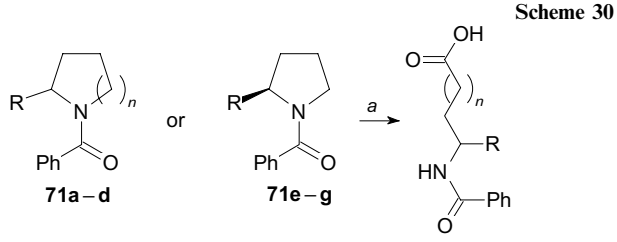
Scheme 29



66 **67** **68** **69** (65%) **70** (35%)

A publication of 2005[58] describes the oxidation of amides **71a** – **g** with 2,4-dichloropyridine *N*-oxide catalyzed by the ruthenium complex of *meso*-tetramesitylporphyrin (TMP). It is noteworthy that upon oxidation of N-acylprolines **71e** – **g**, the configuration of the chiral centre in glutamates **72e** – **g** is retained, which may be useful for the application in peptide chemistry (Scheme 30).

Scheme 30



71a – **d** **71e** – **g** **72a** – **g** (41% – 91%)

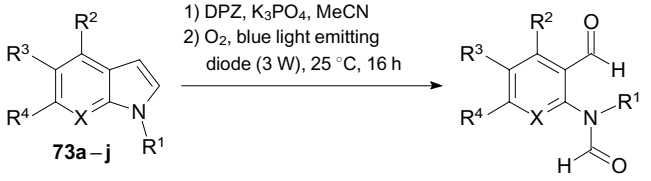
(*a*) Ru(TMP)Cl$_2$, 2,4-dichloropyridine *N*-oxide, PhH, 40 °C, 12 h;

72: R = H: *n* = 1 (**1**), 2 (**b**), 3 (**c**); *n* = 2, R = Me (**d**);

n = 1: R = CO$_2$H (**e**), C(O)HN CO$_2$Et (**f**), C(O)HN Pr^i CO$_2$Et (**g**)

Photooxidation of compounds **73a** – **j** in the presence of dicyanopyrazine (DPZ) as the sensitizer gave rise to formylformanilides **74a** – **j** in high yields.[59, 60] A similar result is obtained when manganese(III) *meso*-tetraphenylporphin complexes are used as catalysts (Scheme 31).[61]

Scheme 31

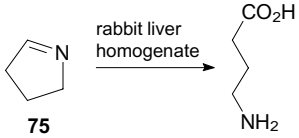


73a – **j** **74a** – **j** (53% – 86%)

Compound	X	R^1	R^2	R^3	R^4
a	CH	Me	H	H	H
b	CH	Bn	H	H	H
c	CH	Me	OMe	H	H
d	CH	Me	H	F	H
e	CH	Me	H	Cl	H
f	CH	Me	H	Br	H
g	CH	Me	H	Me	H
h	CH	Me	H	H	Br
i	CH	Me	H	H	OBn
j	N	Me	H	H	H

Here, mention should be made of a study of Nayar and Callery,[62] who described the oxidative cleavage of the dehydropyrrolidine ring of compound **75** using the rabbit liver homogenate. The reaction yielded γ-aminobutyric acid

Scheme 32



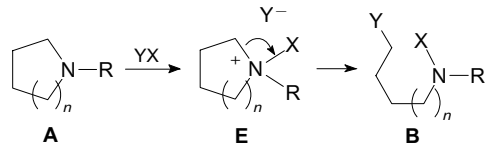
75 **76**

(**76**) (Scheme 32). It is difficult to evaluate the synthetic potential of this method, since the product yield is not indicated in the publication.

4. C – N bond cleavage by acids and electrophilic reagents

Ring opening reactions induced by acids or electrophilic reagents are widely used in the chemistry of pyrrolidine and piperidine derivatives. The key step of these reactions is the formation of cyclic cations **E** under the action of acids or electrophiles; the C – N bond cleavage in cations **E** gives open-chain structures **B** (Scheme 33). The acid catalysts can be represented by both Brønsted (TfOH, CF_3CO_2H, AcOH, HCl, TsOH) and Lewis acids [*e.g.*, $Sn(OTf)_2$], while the electrophiles are usually formates (isopropyl chloroformate, isobutyl chloroformate, ethyl chloroformate, *tert*-butyl formate, β-naphthyl chlorothionoformate), acid anhydrides, acid chlorides, cyanogen bromide and iodomethane.

Scheme 33

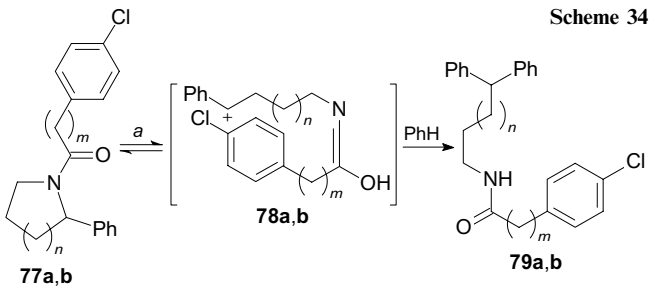


Acid-catalyzed reactions proceed, most often, at atmospheric pressure under rather mild conditions. Note that many acids are inexpensive and readily accessible. In this aspect, the use of acids as catalysts of C – N bond cleavage appears more attractive than the use of metal complexes. Nevertheless, a considerable drawback of this method is low stereoselectivity of ring opening reactions.

The electrophilic reactions accompanied by ring opening are mainly intermolecular. Therefore, functionalization of the cyclic precursor can also be carried out within a single reaction step, and polyfunctional acyclic products can be prepared in this way.

King *et al.*[63, 64] described an acid-catalyzed transformation of compounds **77a**,**b**. The authors assumed that ring opening gives carbocations **78a**,**b**, which react with benzene being converted to diphenylbutanes **79a**,**b** (Scheme 34). The reaction is conducted at elevated temperature in the presence of excess trifuoromethanesulfonic acid.

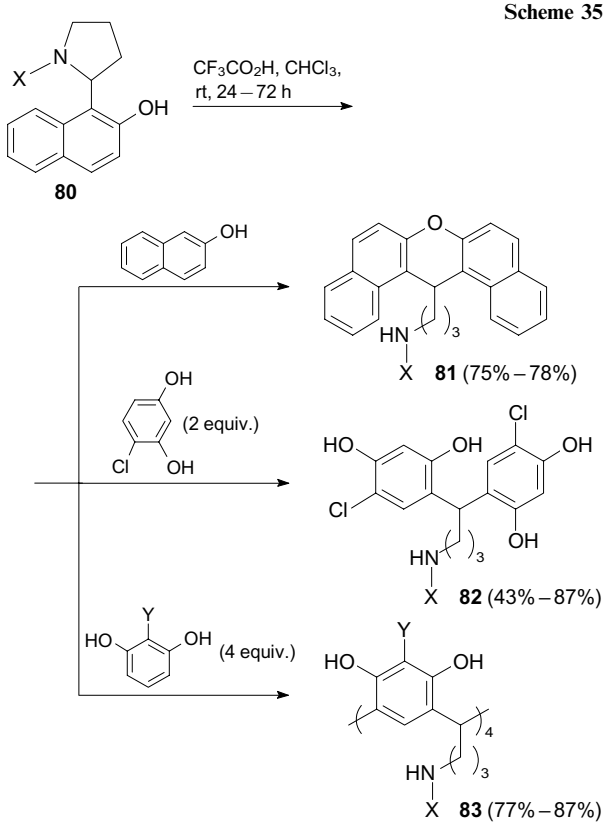
Scheme 34



(*a*) TfOH, PhH, Δ, 1 h; $m = 0$, $n = 1$ (**a**, 87%); $m = 1$, $n = 2$ (**b**, 95%)

The tetrahydropyrrole ring in 2-arylpyrrolidines **80**, described by Gazizov and co-workers,[65 – 67] can also be cleaved under the action of strong acids. Unlike the researchers cited above,[63, 64] the authors used trifuoroacetic acid rather than superacids. A study of the reaction of 2-naphthylpyrrolidines **80** with 2-naphthol in chloroform in the presence of trifuoroacetic acid demonstrated that under these conditions, pyrrolidine ring opening also takes place to yield new dibenzoxanthenes **81** containing urea and sulfonamide moieties. The reaction conducted in the presence of excess 4-chlororesorcinol unexpectedly generated diarylbutanes **82** with two resorcinol moieties. The mechanism of this reaction includes protonation of the amide or sulfone group of pyrrolidine and subsequent N – C bond cleavage. The carbocation thus formed reacts with a phenol molecule to give the corresponding polyphenol.[68] The reactions between 2-arylpyrrolidine and a resorcinol taken in equimolar amounts can serve for the synthesis of calix[4]resorcinarenes **83** as the major products formed in 80% yield (Scheme 35).

Scheme 35



Y = H, Me, OH; X = C(O)NHR (R = H, Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$O_2NC_6H_4$, 1-Naph), SO_2R (R = Me, Ph, 4-MeC_6H_4, 2-Naph, 3-Py); Naph is naphthyl, Py is pyridyl

Pyrrolidine ring opening of compound **84** taking place in DMSO in the presence of excess hydrochloric acid deserves attention. Tosylamine **85** containing a vinyl group in the molecule is formed as the reaction product (Scheme 36).[69]

Treatment of compound **86** with hydrochloric acid gives two products, methyl 2-(isoquinolin-1-yl)acetate (**87**) and methyl 2-(phenylimino)acetate (**88**).[70] Only compound **87** was isolated from the reaction mixture in a pure state in a moderate yield (Scheme 37).

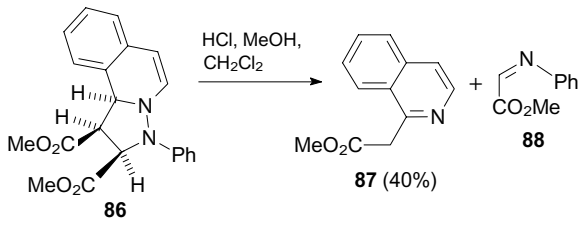
Refluxing of compound **89** with *p*-toluenesulfonic acid in benzene gives spiro compound **90** as an intermediate,

Scheme 36

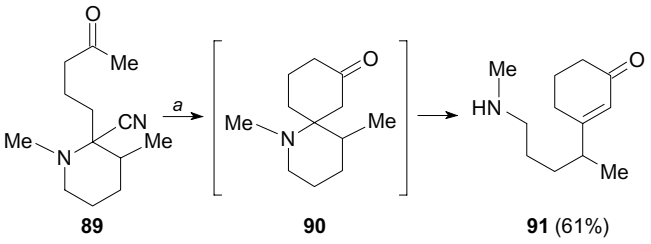


Bu$^t_2$Bpy is 4,4′-di-*tert*-butyl-2,2′-bipyridine, Ts is 4-methylbenzenesulfonyl

Scheme 37



Scheme 38

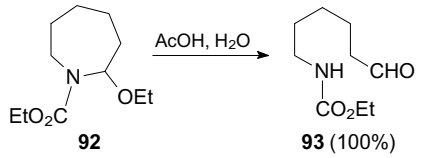


(*a*) TsOH, PhH, Δ, 21 h

which then undergoes a retro-Michael reaction to be converted to amine **91** (Scheme 38).[71]

By treatment of ethyl 2-ethoxyazepine-1-carboxylate **92** with acetic acid, Nagasaka *et al.*[72] prepared aldehyde **93** in a quantitative yield (Scheme 39). It is noteworthy that the proposed method favourably compares with other synthetic routes towards 6-aminohexanal derivatives, such as oxidation of 6-aminohexan-1-ol on treatment with pyridinium chlorochromate,[73,74] which is a toxic and carcinogenic chemical. The Swern oxidation of 6-aminohexan-1-ol can also be used to obtain aldehydes in moderate yields.[75–78] The major drawback of this method is the formation of toxic by-products — dimethyl sulfide and carbon(II) oxide.

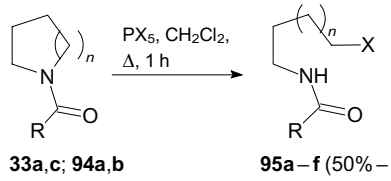
Scheme 39



The von Braun degradation of amides **33a**,**c** and **94a**,**b** serves as a convenient method for the synthesis of amides **95a**–**f** containing a halogen atom.[79–82] The reaction mixture was refluxed in the presence of phosphorus pentahalide for 1 h (Scheme 40).

Imidazolines **96a**–**c** were converted to di(amino) acids. Amino acids **97a**–**c** were prepared in three steps. In the first

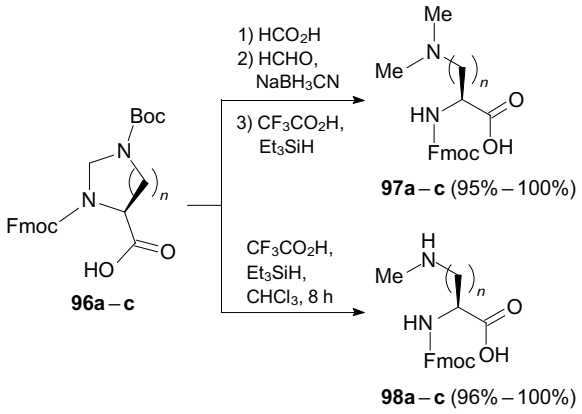
Scheme 40



Product **95**	Substrate	*n*	R	X
a	**33a**	1	Ph	Cl
b	**33c**	2	Ph	Cl
c	**94a**	1	2,4-$Cl_2C_6H_3$	Cl
d	**94b**	2	2,4-$Cl_2C_6H_3$	Cl
e	**33a**	1	Ph	Br
f	**94a**	1	2,4-$Cl_2C_6H_3$	Br

step, the Boc protection of compounds **96a**–**c** is removed in pure formic acid and then reductive amination is carried out using sodium cyanoborohydride. At the final step, the reaction mixture is treated with a mixture of trifuoroacetic acid and triethylsilane in chloroform. The target amino acids **97a**–**c** are isolated in high yields. Treatment of the starting acids **96a**–**c** with a $CF_3CO_2H-Et_3SiH$ mixture affords amino acids **98a**–**c** (Scheme 41).[83]

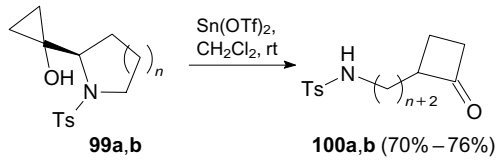
Scheme 41



n = 1 (**a**), 2 (**b**), 3 (**c**); Fmoc is 9-fluorenylmethoxycarbonyl

The addition of tin(II) triflate to compounds **99a**,**b** in dichloromethane at room temperature leads to the formation of cyclobutanone derivatives **100a**,**b** (Scheme 42). The authors assume that Lewis acid chelation to oxygen of the sulfonyl group weakens the C—N bond, which leads to cleavage of the heterocycle. Then the three-membered ring is expanded to the corresponding cyclobutanone. A substantial drawback of the proposed method is racemization of the product and the use of expensive Lewis acid.[84]

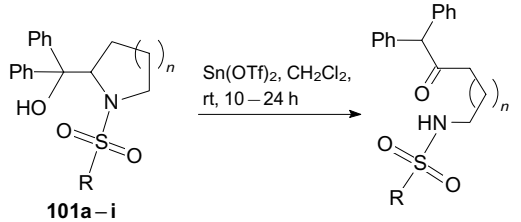
Scheme 42



n = 1 (**a**), 2 (**b**)

Selvakumar *et al.*[85] studied the ring opening reaction of sulfonylated heterocycles **101a**–**i** in the presence of Lewis acids. The reaction gives good yields of amino ketones **102a**–**i** (Scheme 43). The authors believe that ring opening proceeds *via* 1,2-hydride shift.

Scheme 43



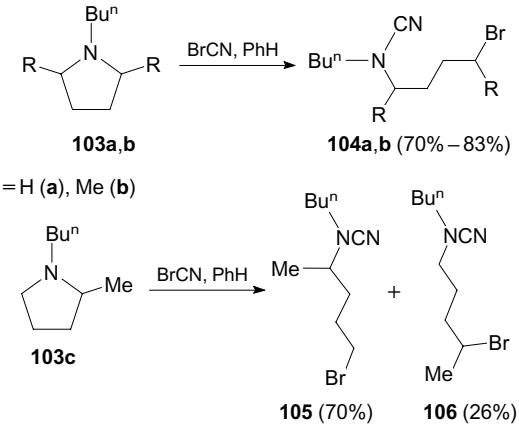
101a–**i** **102a**–**i** (44% – 88%)

n = 1: R = 4-MeC_6H_4 (**a**), 4-BrC_6H_4 (**b**), 4-FC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 4-$O_2NC_6H_4$ (**e**), 2-$O_2NC_6H_4$ (**f**), Ph (**g**), Me (**h**), 4-MeC_6H_4 (**i**)

Most of the above-listed acid-catalyzed heterocycle cleavage reactions are intramolecular. However, analogous intermolecular reactions involving electrophilic reagents are also known. The first step of these reactions is generation of a cyclic cation upon electrophilic attack on the nitrogen atom, which is followed by C–N bond cleavage and formation of an acyclic product.

The von Braun reaction between tertiary amines and cyanogen bromide, resulting in the formation of cyanamides, was investigated in detail.[86,87] First, the authors carried out the reaction of symmetrical pyrrolidines **103a**,**b** with cyanogen bromide, which gave bromo cyanamides **104a**,**b**. When unsymmetrical pyrrolidine **103c** was used, two isomeric bromoalkyl cyanamides **105** and **106** were formed (Scheme 44).

Scheme 44



103a,**b** **104a**,**b** (70% – 83%)

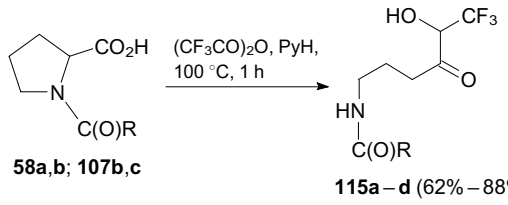
R = H (**a**), Me (**b**)

103c **105** (70%) **106** (26%)

The reaction of *N*-acylprolines **58a** and **107a**–**e** with trifuoroacetic anhydride is conducted in the presence of pyridine with cooling (Scheme 45). In this reaction, intermediate **108** is attacked, in the form of tautomer **109**, by trifuoroacetic anhydride thus yielding cation **110**. The subsequent successive steps involving intermediates **111**–**113** finally furnish oxazoles **114a**–**f**.[88] It is noteworthy that the reaction mechanism is similar to the mechanism of the Dakin–West reaction.

Kawase *et al.*[89,90] described the fragmentation of proline derivatives **58a**,**b** and **107b**,**c** induced by trifuoroacetic anhydride under conditions of the Dakin–West reaction. The reaction proceeds *via* the formation of oxazolium salt intermediates, which then undergo ring opening (Scheme 46). As opposed to the above-mentioned study,[88] in this case, the reaction was carried out at reflux, which promoted cleavage of the oxazolium ring at the final step and formation of open-chain ketones **115a**–**d**. It is noteworthy that compounds **114a**–**f** and **115a**–**d** possess antitumour activity.[91]

Scheme 46



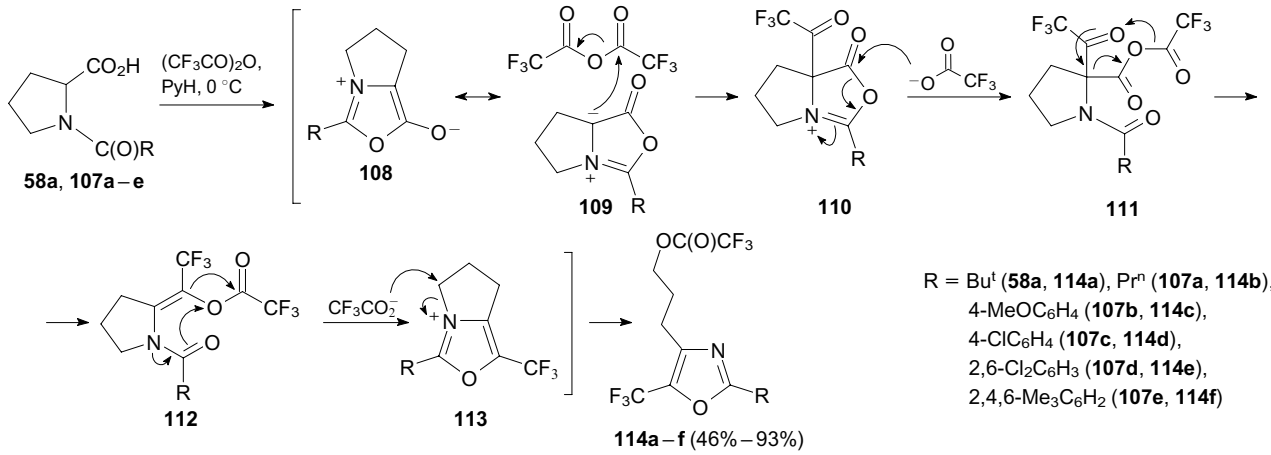
58a,**b**; **107b**,**c** **115a**–**d** (62% – 88%)

115: R = Bu^t (**a**), Ph (**b**), 4-$MeOC_6H_4$ (**c**), 4-ClC_6H_4 (**d**)

b-Naphthyl chlorothionoformate (**116**) reacts with pyrrolidine derivatives **117a**,**b** at room temperature to give intermediates **118a**,**b** (Scheme 47).[92] It is of interest that under these conditions, only pyrrolidine derivatives undergo ring opening to give thiocarbamates **119a**,**b**.

A paper of Yu *et al.*[93] addresses ring opening reactions of 1-substituted pyrrolidines **117a** and **120a**,**b**. These com-

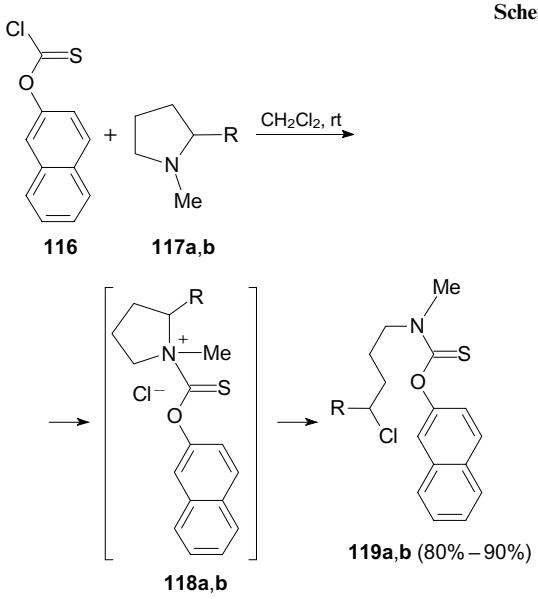
Scheme 45



58a, **107a**–**e** **108** **109** **110** **111** **112** **113** **114a**–**f** (46% – 93%)

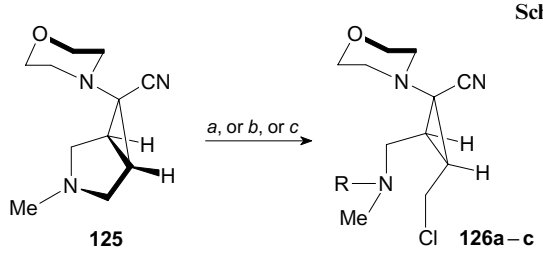
R = Bu^t (**58a**, **114a**), Pr^n (**107a**, **114b**), 4-$MeOC_6H_4$ (**107b**, **114c**), 4-ClC_6H_4 (**107c**, **114d**), 2,6-$Cl_2C_6H_3$ (**107d**, **114e**), 2,4,6-$Me_3C_6H_2$ (**107e**, **114f**)

Scheme 47



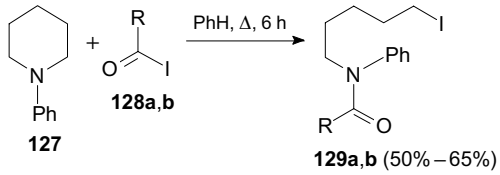
R = H (**a**), 3-Py (**b**)

Scheme 49



(*a*) BrCN, $CHCl_3$ (95% yield); (*b*) $H_2C{=}CHO(O)CCl$, CH_2Cl_2 (73%); (*c*) $Cl_3CCH_2O(O)CCl$, PhH (71%);
R = CN (**a**), $CO_2CH{=}CH_2$ (**b**), $CO_2CH_2CCl_3$ (**c**)

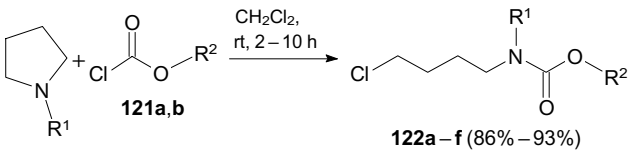
Scheme 50



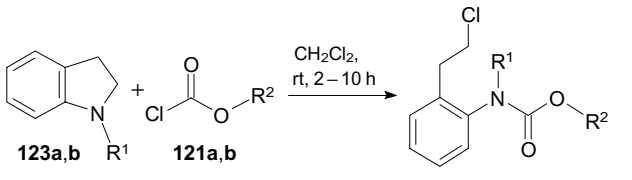
R = Me (**a**), Ph (**b**)

pounds are allowed to react with isopropyl chloroformate (**121a**) and isobutyl chloroformate (**121b**) yielding (4-chlorobutyl)alkylcarbamate **122a – f**. Advantages of this method include high rate, mild reaction conditions and diversity of the obtained products. Similarly, reactions of chloroformates with N-substituted indolines **123a**,**b** afford compounds **124a – d** (Scheme 48).

Scheme 48



120: R^1 = Et (**a**), C(O)Et (**b**); **121**: R^2 = Pr^i (**a**), Bu^i (**b**);
122: R^1 = Me: R^2 = Pr^i (**a**), Bu^i (**b**); R^1 = Et: R^2 = Pr^i (**c**), Bu^i (**d**);
R^1 = C(O)Et: R^2 = Pr^i (**e**), Bu^i (**f**)



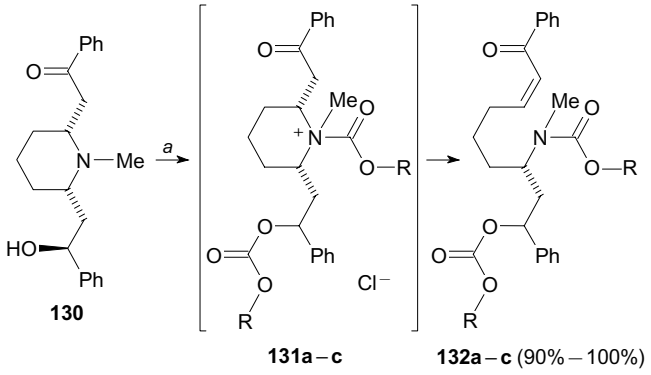
123: R^1 = Me (**a**), Et (**b**); **124**: R^1 = Me: R^2 = Pr^i (**a**), Bu^i (**b**);
R^1 = Et: R^2 = Pr^i (**c**), Bu^i (**d**)

On treatment with alkylating reagents (cyanogen bromide, vinyl chloroformate and trichloroethyl chloroformate), compound **125** undergoes cleavage of the C – N bond in the pyrrolidine ring and is thus converted to compounds **126a – c**, respectively (Scheme 49).[94]

The reaction between *N*-phenylpiperidine (**127**) and acyl iodides **128a**,**b** taken in equimolar amounts in refluxing benzene resulted in the synthesis of amides **129a**,**b** (Scheme 50).[95]

The reaction of (–)-lobeline (**130**), an alkaloid with a broad range of biological activities, with acyl chlorides was investigated[96 – 98] (Scheme 51). Presumably, piperidine ring opening proceeds *via* the formation of quaternary acylammonium salts **131a – c**. As a result, alkenes **132a – c** were obtained in good yields. Dehydrohalogenation of alkanes is known to be among the methods for the synthesis of alkenes. Therefore, the use of potassium carbonate as a base was probably favourable for the formation of alkenes **132a – c**. A similar reaction reported by Voronkov *et al.*[95] resulted in the isolation of the corresponding halides, because the reaction was carried out without a base.

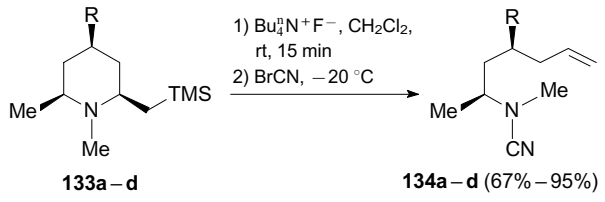
Scheme 51



(*a*) ROC(O)Cl, K_2CO_3, MeCN; R = Me (**a**), CH_2CCl_3 (**b**), CH_2Ph (**c**)

Substituted piperidines **133a – d** with a trimethylsilylmethyl group in position 2 undergo regioselective ring opening on treatment with tetra-n-butylammonium fluoride and cyanogen bromide (Scheme 52). Products **134a – d** contain cyanamide and terminal alkene functional groups. This

Scheme 52

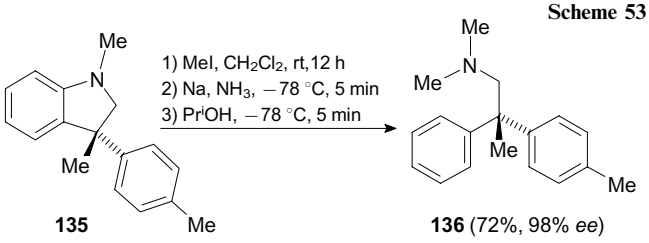


R = H (**a**), OTBS (**b**), OH (**c**), Ac (**d**)

method is of interest for stereoselective synthesis of alkylamine derivatives containing several chiral centres.[99 – 101]

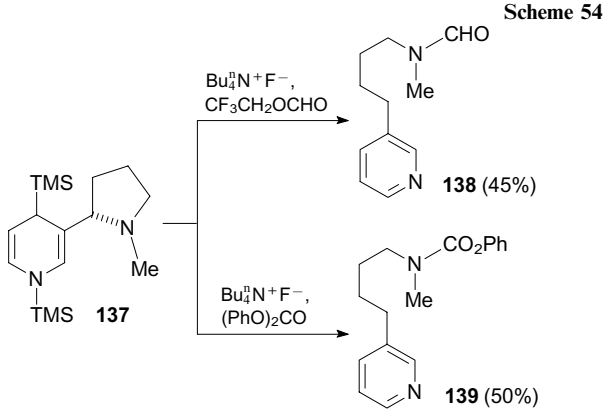
Torigoe *et al.*[102] described stereoselective synthesis of the corresponding tertiary amine from the substituted indoline **135**. The substrate was methylated with methyl iodide in dichloromethane, and the resulting ammonium salt was treated with sodium in liquid ammonia. The C – N bond was cleaved at −78 °C, which gave amine **136** in a good yield and with high enantiomeric excess (*ee*) (Scheme 53).

Scheme 53



Treatment of nicotine derivative **137** with tetra-n-butylammonium fluoride in 2,2,2-trifuoroethyl formate gives formamide **138**. Conduction of the same reaction with phenyl carbonate directs the reaction towards carbamate **139** (Scheme 54).[103]

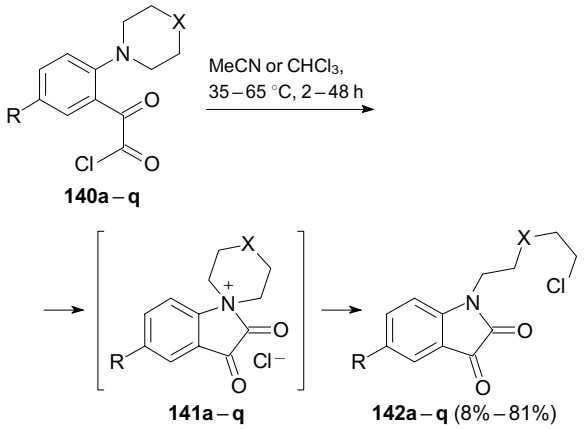
Scheme 54



It was found[104] that compounds **140a – q** undergo transformations accompanied by ring opening under relatively mild conditions; the reactions involve the intermediate formation of carbocations **141** and furnish substituted *N*-chloroalkylisatins **142a – q** (Scheme 55).

Treatment of nitroenamine **143** with acid chlorides, ethyl chloroformate or *tert*-butyl formate in aqueous sodium hydroxide followed by acidification with concentrated HCl cleaves the C – N bond in the seven-membered ring.[105] The authors assumed that intermediate **144** formed

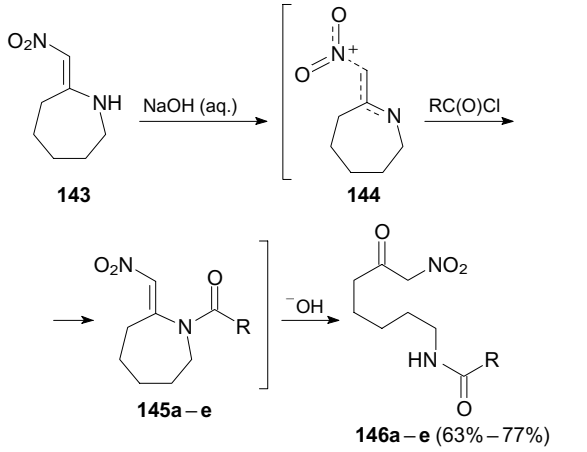
Scheme 55



X is absent: R = Cl (**a**), Br (**b**), F (**c**), Me (**d**), OMe (**e**);
X = CH_2: R = Cl (**f**), Br (**g**), F (**h**), Me (**i**); X = CH_2CH_2: R = Cl (**j**), Br (**k**), F (**l**), Me (**m**); X = O: R = Cl (**n**), Br (**o**), F (**p**), Me (**q**)

in basic media reacts with acid chlorides to give *N*-acyl derivatives **145a – e**. This is followed by alkaline hydrolysis, resulting in crystalline nitro *N*-acylamino ketones **146a – e** (Scheme 56).

Scheme 56

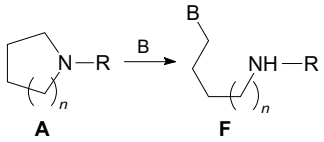


R = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-$O_2NC_6H_4$ (**c**), EtO (**d**), Bu^tO (**e**)

5. Cleavage of the C – N bond by basic reagents

This Section describes the reactions in which ring opening in substrates **A** is induced by alkalis, alkali metal compounds, Grignard reagents or Wittig reagents. C – N bond cleavage under the action of basic reagents affords acyclic molecules **F** of various classes — alcohols and carbonyl or unsaturated compounds (Scheme 57). It is noteworthy that these reactions are often intermolecular, being accompanied by incor-

Scheme 57

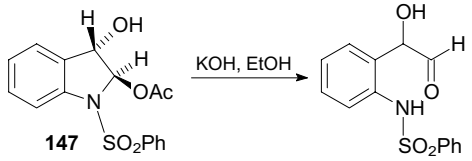


B is base

poration of a fragment of the basic reagent into the molecule of the resulting amine.

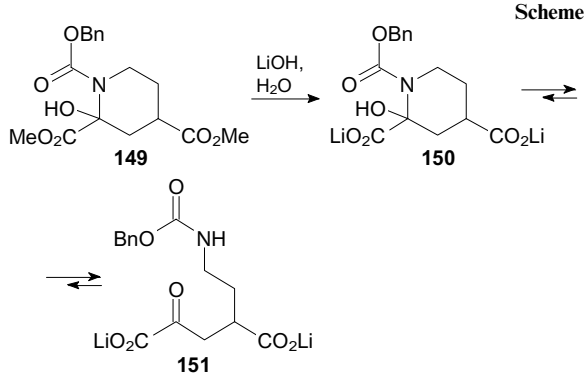
On treatment with an ethanol solution of potassium hydroxide, substituted indoline **147** is converted to aldehyde **148** in a moderate yield (Scheme 58).[106]

Scheme 58



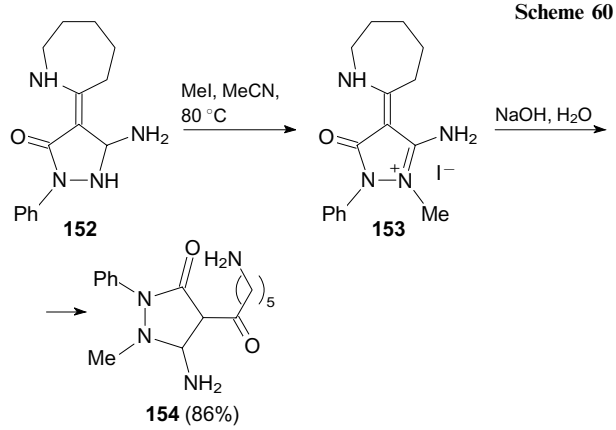
Compound **149** was found to react with an aqueous solution of lithium hydroxide to give dilithium salt **150**, which exists in solution (according to ^{1}H NMR data) in tautomeric equilibrium with compound **151**. Whereas in deuterochloroform, cyclic product **150** is predominantly formed, in the case of deuterated water, open-chain form **151** is the major product (Scheme 59).[107]

Scheme 59



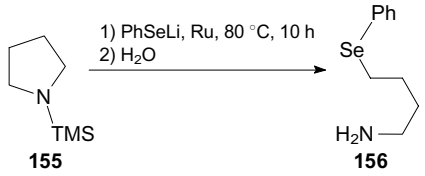
The methylation of compound **152** leads to heterocycle **153**, which undergoes azepine ring opening on treatment with aqueous alkali, thus yielding amine **154** (Scheme 60).[108]

Scheme 60



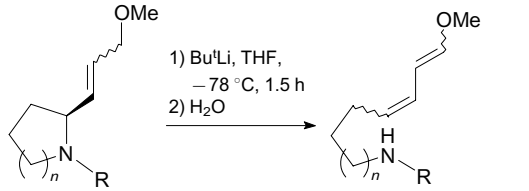
Heating *N*-trimethylsilylpyrrolidine (**155**) with a solution of lithium benzeneselenolate and subsequent treatment of the reaction mixture with water affords primary amine **156** in a high yield (Scheme 61).[109]

Scheme 61



The pyrrolidine and piperidine rings of compounds **157a**–**d** are cleaved in the presence of *tert*-butyllithium to give 1,3-dienes **158a**–**d**. The products were isolated as mixtures of geometric isomers. Changes in the reaction conditions (the solvent, the base or temperature) resulted in changes in the ratio of the isomeric reaction products (Scheme 62).[110]

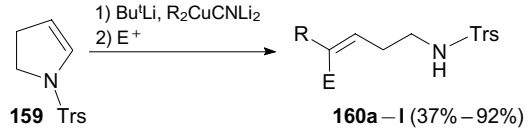
Scheme 62



n = 1: R = Boc (**a**), Me (**b**); *n* = 2: R = Boc (**c**), Me (**d**)

Cuprate-induced opening of the pyrroline ring in compound **159** followed by introduction of an electrophile was used to prepare alkenes **160a**–**l** containing a sulfonamide moiety in the molecule (Scheme 63).[111] Compound **160g** was isolated in a low yield. The authors suggested that the reaction involves the formation of (trimethylstannyl)-lithium, which initiates side reactions.

Scheme 63

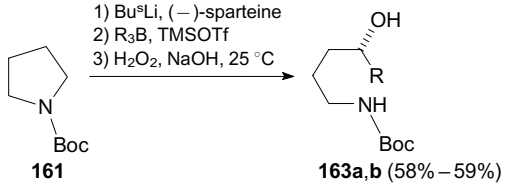


E = H: R = Me (**a**), CH_2=CH (**b**), Bu^n (**c**), Bu^s (**d**) Bu^t (**e**), Ph (**f**);
E = Me: R = Me_3Sn (**g**), Bu^t (**h**); R = Bu^t: E = All (**i**), I (**j**), Me_3Sn (**k**);
E = Me_3Sn, R = Me (**l**); Trs is 2,4,6-triisopropylbenzenesulfonyl

Coldham *et al.*[112] reported reactions that included the lithiation of *N*-Boc-pyrrolidine **161** and *N*-Boc-indoline **162**, the subsequent electrophilic substitution and rearrangement. Finally, amino alcohols **163a**,**b** and **164a**,**b** were isolated as mixtures in which one enantiomer predominated (Scheme 64).

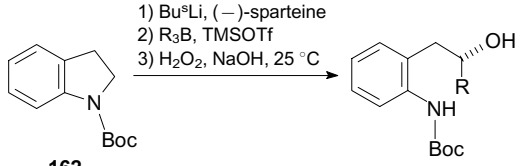
The tosylhydrazones of cyclic amino aldehydes **165** are converted to acyclic unsaturated amides **166a**–**g** on treatment with aromatic and aliphatic Grignard reagents.[113] It was assumed that treatment of compound **165** with organylmagnesium bromides induces elimination of tosyl bromide giving rise to intermediates **167**, which lose a nitrogen molecule being thus converted to final alkenes **166a**–**g** *via* anions **168** (Scheme 65).

Scheme 64



161 **163a**,**b** (58% – 59%)

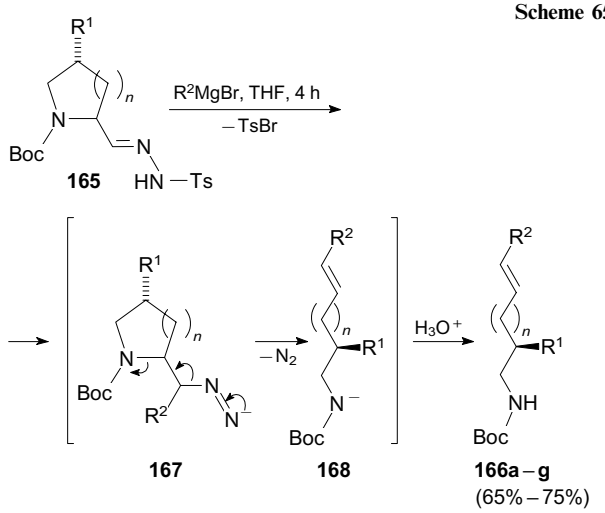
R = Et (**a**, *er* = 95 : 5), Bu^n (**b**, *er* = 92 : 8)



162 **164a**,**b** (64% – 67%)

R = Et (**a**, *er* = 97 : 3), Bu^n (**b**, *er* = 96 : 4);
er is enantiomeric ratio

Scheme 65

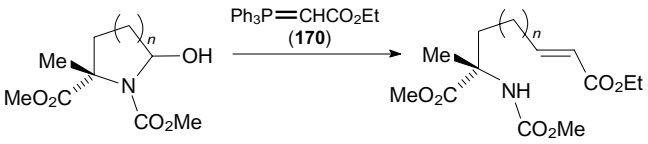


165 **167** **168** **166a – g** (65% – 75%)

n = 1, R^1 = H: R^2 = Ph (**a**), 4-MeOC$_6$H$_4$ (**b**), Pr^n (**c**);
n = 1, R^1 = BnO: R^2 = Ph (**d**), 4-MeOC$_6$H$_4$ (**e**);
n = 2, R^1 = H: R^2 = Ph (**f**), 4-MeOC$_6$H$_4$ (**g**)

One more example of synthesis of such alkenes is provided by the reaction of azacyclanes **169a**,**b** with phosphorane **170**, which furnishes compounds **171a**,**b** (Scheme 66).[114]

Scheme 66

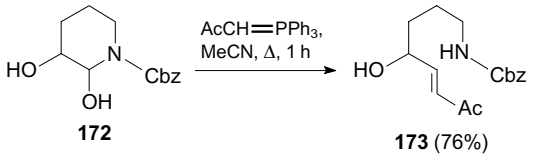


169a,**b** **171a**,**b** (63% – 67%)

n = 1 (**a**), 2 (**b**)

The Wittig reaction of compound **172** was used to prepare alkene **173** in which the double bond had *E*-configuration, according to ^{1}H NMR data (Scheme 67).[115]

Scheme 67

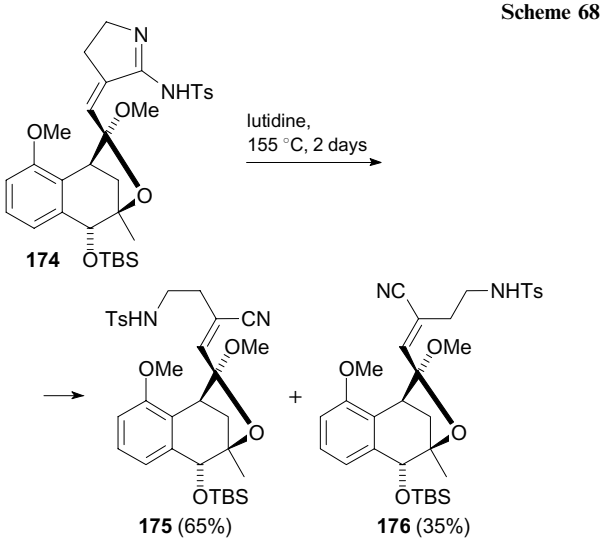


172 **173** (76%)

Cbz is benzyloxycarbonyl

By heating tosylated amidine **174** in lutidine (2,6-dimethylpyridine), two stereoisomeric nitriles **175** and **176** were obtained. The reaction was accompanied by migration of the tosyl group from the exocyclic to endocyclic nitrogen atom (Scheme 68).[116]

Scheme 68

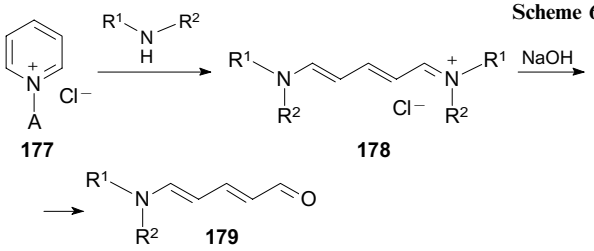


174 **175** (65%) **176** (35%)

Aminopentadienals (aldehydes, or Zincke salts), which are prepared by pyridinium ring opening, are promising substrates often used as synthetic building blocks. The antimalarial activity of Zincke aldehydes should be noted.[117] A method for the synthesis of these compounds was described more than a hundred years ago;[118 – 121] however, this method still attracts attention of chemists, since it is facile and reproducible. Reactions of this type are considered in several comprehensive reviews (see, for example, Refs 3 and 4), which, in particular, discuss the putative mechanism of pyridine ring opening. Below we consider only publications not included in the mentioned reviews.[3, 4]

The procedure of conversion of Zincke salts has barely changed since 1903. Treatment of activated pyridinium salts **177** (A is the activating group) with amines induces ring

Scheme 69

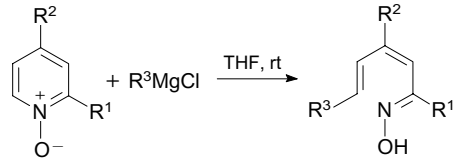


177 **178** **179**

opening and gives intermediates **178**, which are converted in alkaline media to functionally substituted dienes **179** in high yields (Scheme 69).[122–132] Nitrobenzene fragments are used most often for activation. Yet another method for the synthesis of aminopentadienals is the reaction of esters of 3-aminoacrylic acid with propionic acid derivatives.[133–135] A considerable drawback of this approach is the complexity of preparation of the starting acids and, hence, the large numbers of synthetic steps.

The reactions of the Grignard reagents with pyridine *N*-oxides **180** proceed similarly to the Zincke reaction; in this case, oximes **181a–h** rather than aldehydes are formed (Scheme 70). The proposed method serves as an efficient synthetic approach towards substituted alkenes, which are of interest as synthetic building blocks.[136]

Scheme 70



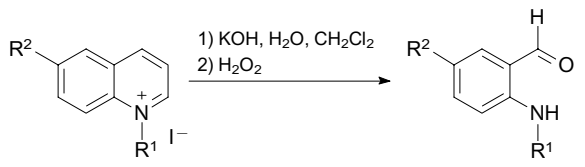
180 **181a–h** (76%–95%)

Compound **181**	R^1	R^2	R^3	Compound **181**	R^1	R^2	R^3
a	Me	H	Ph	**e**	H	OBn	Ph
b	H	Me	Ph	**f**	H	OBn	Naph
c	H	Ph	Ph	**g**	H	OBn	C≡CPh
d	H	Cl	Ph	**h**	H	OBn	Th

Th is thienyl

A series of studies[137–142] describes the ring opening in quinolinium salts **182a–e** in an alkaline solution of hydrogen peroxide, resulting in the formation of *N*-alkyl-2-aminobenzaldehydes **183a–e**. Attention is drawn by ready accessibility of reactants and mild reaction conditions (Scheme 71). Compound **183c** was isolated in 33% yield; this is due to side reactions, which can involve the allyl group.

Scheme 71



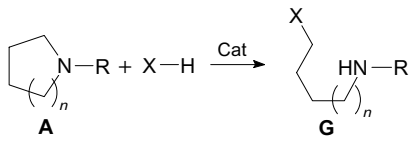
182a–e **183a–e** (33%–84%)

R^2 = H: R^1 = Me (**a**), Et (**b**), All (**c**); R^1 = Me: R^2 = Me (**d**), OMe (**e**)

6. Metal-catalyzed C–N bond cleavage

Quite a few publications of the last several decades are devoted to cleavage of the C–N bond in heterocycles in the presence of metal-containing catalysts: palladium, rhodium, ytterbium, indium, mercury, copper, tin and sodium salts or complexes. In most cases, the reactions are intermolecular and involve one more reactant, which makes it possible to attain more complex structures of open-chain product **G** (Scheme 72). Transition metal catalysis is fairly attractive and promising, as these reactions have high selectivity and high yields and proceed under mild conditions, which is consistent with green chemistry principles.

Scheme 72

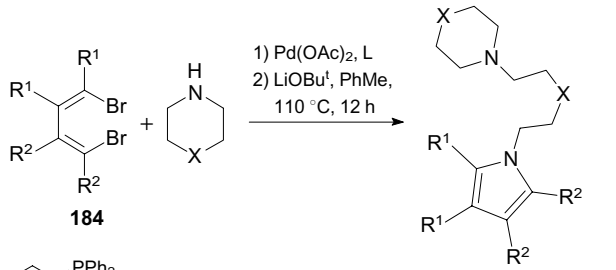


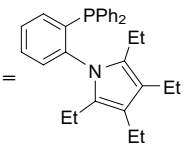
A **G**

Cat are transition metal complexes

Geng *et al.*[143] reported palladium(II) acetate-catalyzed cleavage of the C–N bond in cyclic amines (2 equiv.) under the action of dibromide **184**, resulting in the formation of pyrrole derivatives **185a–d** containing an aliphatic group at the nitrogen atom. The authors did not discuss the reaction mechanism in detail, but suggested that the products are formed upon the reaction of the Pd catalyst and amine with the dibromide followed by intramolecular cyclization of the intermediate metal complex (Scheme 73).

Scheme 73

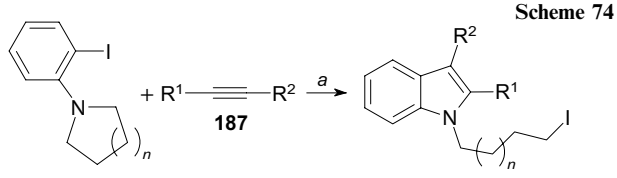




; X = CH_2: R^1 = R^2 = Et (**a**), Pr^n (**b**); R^1 = Et, R^2 = Ph (**c**); X = O, R^1 = R^2 = Et (**d**)

Hao *et al.*[144, 145] described the synthesis of indole-containing alkyl iodides **188a–h** from *o*-aminoiodobenzenes **186** and alkynes **187** (Scheme 74).

Scheme 74



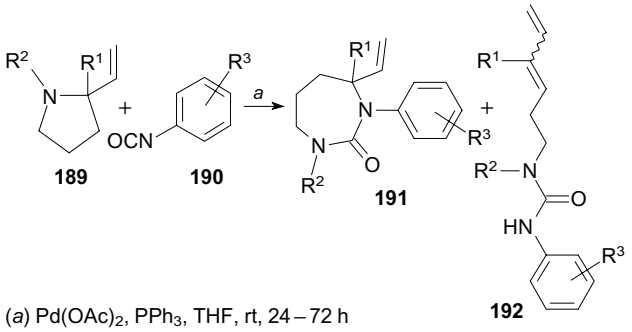
186 **188a–h** (62%–88%)

(*a*) $Pd(PPh_3)_4$, PPh_3, $LiOBu^t$, cyclohexane, 130 °C, 12 h

Compound **188**	*n*	R^1	R^2	Compound **188**	*n*	R^1	R^2
a	2	Et	Et	**e**	2	4-MeC_6H_4	4-MeC_6H_4
b	2	Pr^n	Pr^n	**f**	2	TMS	Ph
c	2	TMS	Me	**g**	2	4-FC_6H_4	4-FC_6H_4
d	2	Ph	Ph	**h**	1	Et	Et

Zhou and Alper[146] reported the ring expansion in 2-vinylpyrrolidines **189** upon the reaction with aryl isocyanates **190** catalyzed by a palladium salt and resulting in the formation of seven-membered heterocycles **191**. Depending on the nature of the substituent, the formation of conjugated diene **192** containing an urea moiety is also possible (Scheme 75, Table 1). The authors did not succeed in separating the geometric isomers of the diene, and their ratio was determined by ^{1}H NMR spectroscopy. It is noteworthy that most of products are isolated as mixtures of cyclic and open-chain ureas, which complicates the use of this method in laboratory practice.

Scheme 75



(*a*) $Pd(OAc)_2$, PPh_3, THF, rt, 24 – 72 h

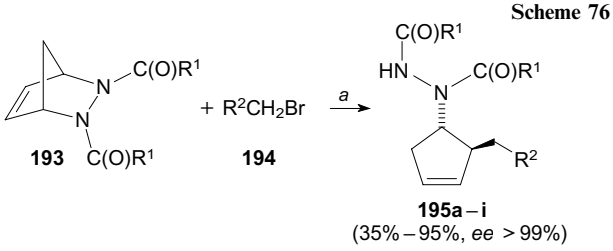
Using a palladium salt as the catalyst, it is possible to carry out the reaction of cyclic hydrazides **193** not only with alkenes, but also with benzyl bromides **194**. As a result, *trans*-3,4-disubstituted hydrazinocyclopentenes **195a – i** were obtained with high enantiomeric excess (Scheme 76).[147, 148]

The reaction of compounds **196** and **197** follows a rather unusual pathway, giving rise to betaines **198a – l** (Scheme 77).[149]

Crotti *et al.*[150] reported rhodium-catalyzed opening of bicyclic hydrazines **193** upon the reaction with boranes **199** carried out in the presence of ligand **200**. This method is suitable for the synthesis of *trans*-3,4-disubstituted hydrazinocyclopentenes **201a – f** containing the unsaturated five-membered ring (Scheme 78).

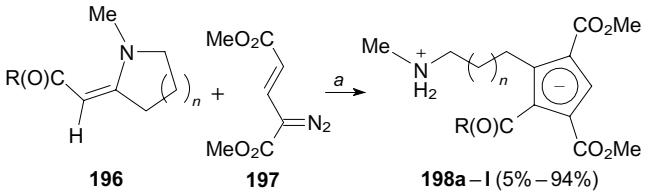
A similar transformation of bicyclic hydrazides **193** was accomplished using bis(pinacolate)diborane **203** in the presence of copper(I) chloride and phoshine **202** (Scheme 79).[151] It is noteworthy that this method provided stereoselective preparation of *trans*-3,4-disubstituted hydrazinocyclopentenes **204a – c** in high yields *via* intermediate formation of compounds **205**.

Scheme 76



(*a*) $(PdAllCl)_2$, In, dppe, $Yb(OTf)_3$, THF, 60 °C, 12 h;
R^2 = CH═CH_2: R^1 = OEt (**a**), OPr^i (**b**), OBu^t (**c**), OBn (**d**);
R^2 = Ph: R^1 = OPr^i (**e**), OBu^t (**f**), OBn (**g**);
R^2 = 4-$O_2NC_6H_4$: R^1 = OEt (**h**), OPr^i (**i**);
dppe is 1,2-bis(diphenylphosphino)ethane

Scheme 77



(*a*) $Rh_2(OAc)_4$, CH_2Cl_2, rt, 10 h;
n = 1: R = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-ClC_6H_4 (**c**), 2-Fu (**d**), 2-Th (**e**), MeO (**f**), Bu^tO (**g**);
n = 2: R = Ph (**h**), 4-ClC_6H_4 (**i**), 2-Th (**j**);
n = 3: R = 4-$MeOC_6H_4$ (**k**), 4-Th (**l**); Fu is furyl

Möhrle *et al.*[152, 153] reported ring opening in compounds **206a – h** on treatment with mercury(II) ethylenediaminetetraacetate in aqueous ethanol. The reaction gave carbonyl compounds **207a – h** (Scheme 80).

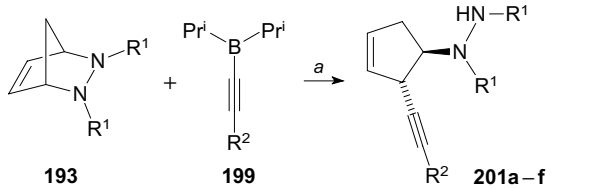
Ring opening in 1-benzylpyrrolidine-2-carbonitrile (**208**) is induced by trimethylsilyl azide in the presence of a catalytic amount of Bu^n_2SnO (Scheme 81).[154] The reaction mechanism proposed by the authors includes tin-catalyzed

Table 1. Products of reactions of 2-vinylpyrrolidines **189** with aryl isocyanates in the presence of $Pd(OAc)_2$ (see Scheme 75).

Compounds **191, 192**	R^1	R^2	R^3	Yield of **191** (%)	Yield of **192** (%)	Ratio of *trans*- to *cis*-isomers **192**
a	H	Bu^n	H	0	82	52 : 48
b	H	Bu^n	4-Br	24	27	50 : 50
c	H	Bu^n	2-Cl	60	0	
d	H	Bu^n	3-Cl	36	0	
e	H	Bu^n	4-Cl	22	26	52 : 48
f	H	Bu^n	2-NO_2	24	0	
g	H	Bu^n	4-NO_2	9	14	58 : 42
h	H	Bu^n	4-OMe	0	65	54 : 46
i	H	Cy	H	0	45	57 : 43
j	H	Cy	2-Cl	28	0	
k	Me	Bu^n	4-Cl	0	30	29 : 71

Note. Cy is cyclohexyl.

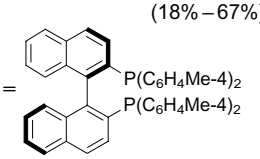
Scheme 78



193 **199** **201a – f** (18% – 67%)

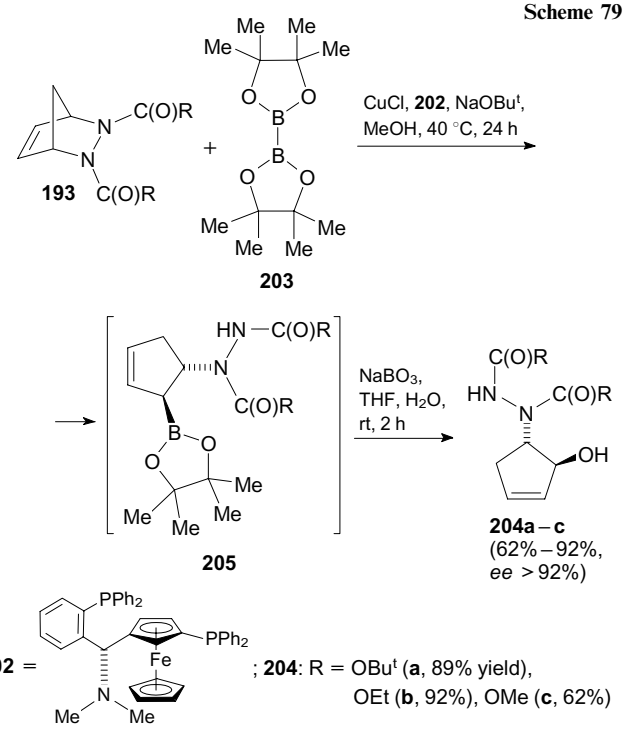
(*a*) $[Rh(C_2H_4)_2Cl]_2$, **200**, MeONa, MeOH, 65 °C, 18 h;

200 =



Compound **201**	R^1	R^2	*ee* (%)	Compound **201**	R^1	R^2	*ee* (%)
a	CO_2Bn	Ph	67	**d**	Boc	Ph	32
b	CO_2Bn	Bu^n	52	**e**	CO_2Bn	Bu^t	40
c	CO_2Et	Ph	52	**f**	CO_2Bn	TMS	58

Scheme 79



193 **203** **205** **204a – c** (62% – 92%, *ee* > 92%)

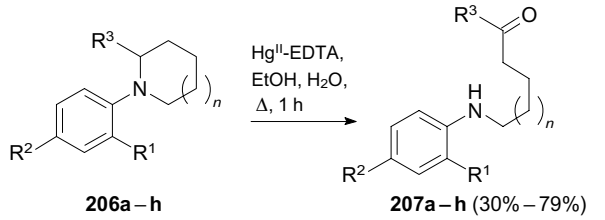
202 =

; **204**: R = OBu^t (**a**, 89% yield), OEt (**b**, 92%), OMe (**c**, 62%)

cycloaddition of the nitrile group to azide affording tetrazole **209**, which decomposes with evolution of two nitrogen molecules and gives alkyne **210**. However, this method is unsuitable for the preparative synthesis of alkynes containing an amino group, since the product is formed in a low yield as a mixture with tetrazole.

A Japanese research team [155] reported piperidine ring opening in the reaction of compound **211** with 3-bromoprop-1-ene in water in the presence of indium. However, the yield of product **212** in this reaction is only 34% (Scheme 82).

Scheme 80

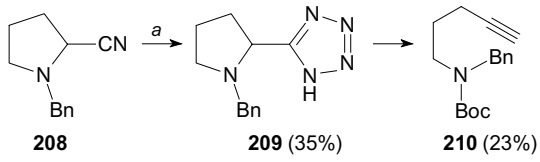


206a – h **207a – h** (30% – 79%)

EDTA is ethylenediaminetetraacetate

Compound	*n*	R^1	R^2	R^3	Compound	*n*	R^1	R^2	R^3
a	1	NO_2	H	Me	**e**	2	H	NO_2	H
b	1	NO_2	NO_2	Me	**f**	1	CHO	NO_2	Me
c	1	H	NO_2	Me	**g**	2	NO_2	H	H
d	1	NO_2	H	CH_2OH	**h**	1	Ac	H	H

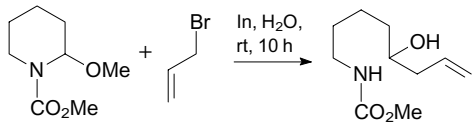
Scheme 81



208 **209** (35%) **210** (23%)

(*a*) 1) $TMSN_3$, Bu^n_2SnO, PhMe, 60 °C, 96 h; 2) Boc_2O, 1 h

Scheme 82



211 **212** (34%)

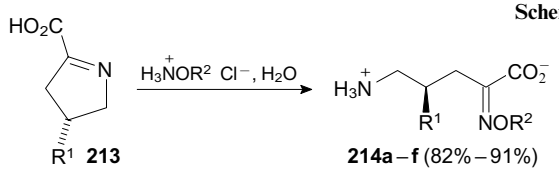
7. Miscellaneous C – N bond cleavage reactions

Below we present reactions accompanied by heterocyclic ring opening that were not covered in previous Sections. Many of these reactions are combinations of various methods: reduction, oxidation, acid, base or metal catalysis and enzymatic reactions. Among these reactions, mention should be made of mono- and bimolecular processes and spontaneous opening of nitrogen-containing rings. The wide diversity of reactions accompanied by C – N bond cleavage in heterocycles can serve for the synthesis of a broad range of polyfunctional open-chain compounds.

Häusler [156] studied ring opening in compounds **213**. The five-membered 1-pyrroline ring is cleaved under the action of N-nucleophiles, in particular, hydroxylamine salts. This results in good yields of derivatives of the amino acid ornithine **214a – f** (Scheme 83).

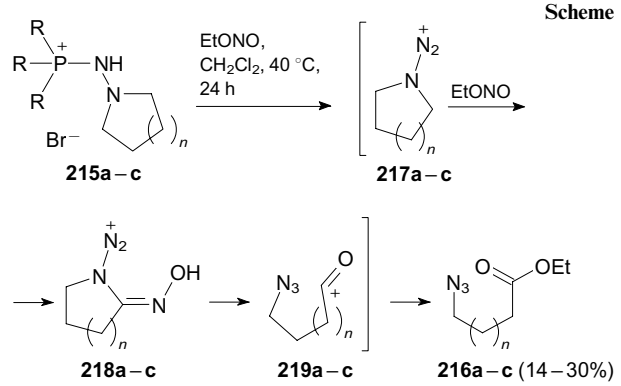
The diazotization of heterocycles **215a – c** containing a phosphorus moiety was reported to give ethyl 4-azidobutanoates **216a – c** with several reactive sites in the molecules. In the authors' opinion, the first step is elimination of phosphine and then the reaction advances towards azides **216a – c** *via* intermediates **217 – 219** (Scheme 84).[157]

Scheme 83



R^2 = H: R^1 = H (**a**), OH (**b**), OBu^t (**c**); R^1 = OH: R^2 = Me (**d**), All (**f**); R^1 = H, R^2 = Bu^t (**e**)

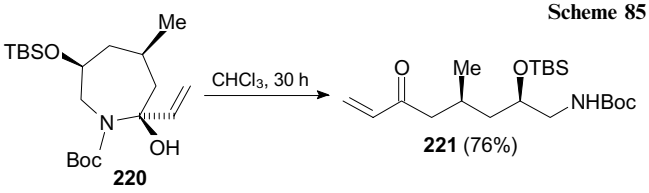
Scheme 84



n = 1 (**a**), 2 (**b**), 3 (**c**)

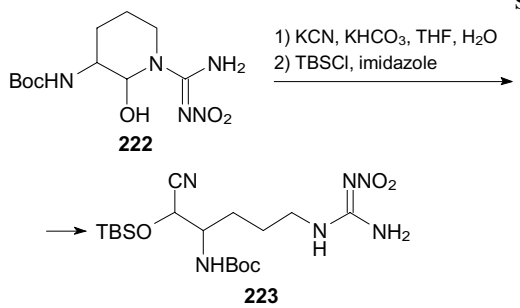
Spontaneous conversion of azacyclane **220** to acyclic product **221** takes place when the substrate is kept in chloroform (Scheme 85).[158]

Scheme 85



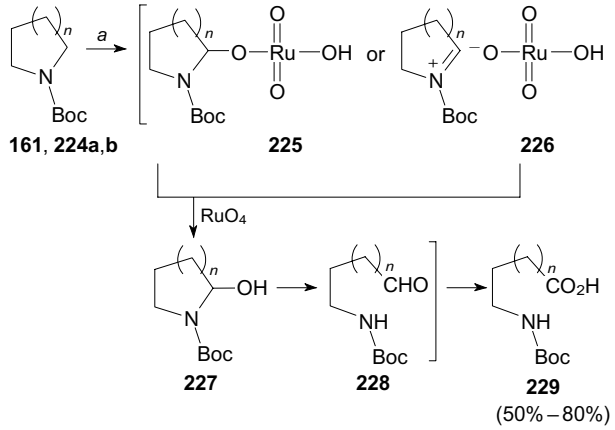
Compound **222** was converted to β-amino cyanide **223**, which was isolated as an 1 : 1 mixture of stereoisomers. Piperidine **222** was successively treated with potassium cyanide and *tert*-butyl(chloro)dimethylsilane. The target product was isolated in 67% yield (Scheme 86).[159]

Scheme 86



The oxidation of Boc-substituted cyclic amines **161** and **224a**,**b** with $NaIO_4$ in the presence of ruthenium tetroxide in aqueous 2-methylpropan-2-ol is accompanied by cleavage of the endocyclic C – N bond.[160] The authors assumed that the reaction initially gives intermediates **225** or *N*-acyliminium cations **226** as RuO_4 attacks position 2 of the cyclic amine. The subsequent transformations include hydrolysis to 2-hydroxylamines **227**, ring opening to give aldehydes **228** and oxidation of the aldehydes to amino acids **229a – c** (Scheme 87).

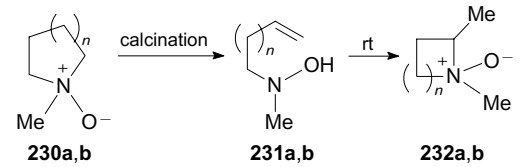
Scheme 87



(*a*) RuO_4, $NaIO_4$, Bu^tOH, H_2O; **229**: *n* = 1 (**a**), 2 (**b**), 3 (**c**)

Ciganek [161] and Cope and LeBel [162] studied thermal ring opening of *N*-methylazacycloalkane *N*-oxides **230a**,**b**, which are converted, on heating, to hydroxylamines **231a**,**b** containing a multiple bond. Compounds **231a**,**b** undergo quantitative cyclization at room temperature to yield oxides **232a**,**b** (Scheme 88).

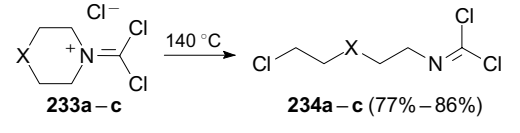
Scheme 88



n = 2 (**a**), 3 (**b**)

Thermolysis of cyclic phosgene iminium salts **233a – c** follows an unusual pathway and gives chlorolkyl isocyanide dichlorides **234a – c** in one step (Scheme 89).[163]

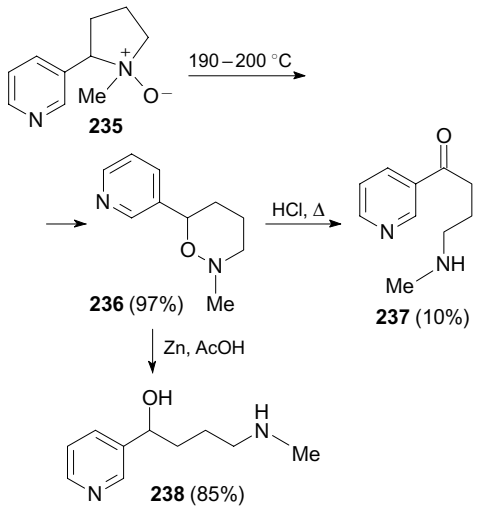
Scheme 89



X = CH_2 (**a**), O (**b**), CH_2CH_2 (**c**)

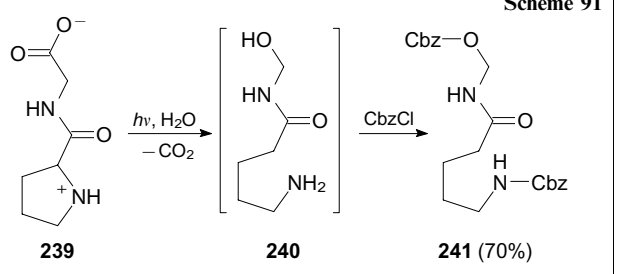
The rearrangement of nicotine oxide **235** accompanied by saturated ring opening was reported.[164, 165] Nicotine oxide is pyrolyzed to 2-methyl-6-(pyridin-3-yl)-1,2-oxazine (**236**), which is converted to ketone **237** on heating in hydrochloric acid. Reduction of compound **236** affords alcohol **238** (Scheme 90).

Scheme 90



An unusual transformation of prolylglycine **239** in a neutral aqueous solution was reported. The reaction was induced by UV irradiation at 254 nm and was accompanied by decarboxylation and ring opening. Treatment of the resulting compound **240** with benzyl chloroformate furnished amide **241** (Scheme 91).[166]

Scheme 91

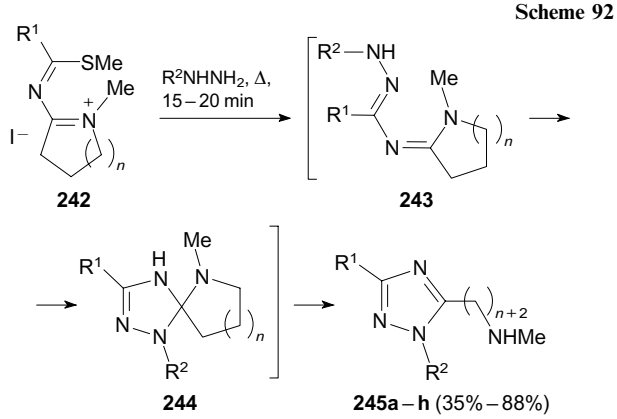


A series of studies[167 – 169] is devoted to the synthesis of various amines containing a 1*H*-1,2,4-triazole moiety. Compound **242** is refluxed in hydrazine or in arylhydrazines to give intermediates **243** and **244** and finally amines **245a – h** (Scheme 92). The authors noted that electron-withdrawing substituents in the hydrazine molecule lead to lower yields of the products.

Recently, the synthesis of pyrazole and isoxazole derivatives by the reaction of hydrazine, hydrazine derivatives, or hydroxylamine with pyrrolidine **246** in refluxing dioxane was reported.[170] The authors suggested that the pyrrolidine ring is converted to the pyrazole or isoxazole ring *via* nucleophilic attack by the amine with the intermediate formation of compounds **247**. Spiro intermediates **248** are formed upon the attack by the second dinucleophile atom on the nitrile group. The subsequent pyrrolidine ring opening promotes aromatization of azole and provides the formation of the aliphatic chain in compounds **249a – j** (Scheme 93, Table 2).

Indoline **250** reacts with α-chlorohydrazones **251a – d** in dichloromethane in the presence of triethylamine. Presumably, the reaction starts with the formation of spiro pyrazoline intermediates **252**, which then undergo ring opening (Scheme 94).[171, 172]

Scheme 92



Compound **245**	*n*	R^1	R^2	Compound **245**	*n*	R^1	R^2
a	1	4-$MeOC_6H_4$	4-$O_2NC_6H_4$	**e**	2	4-$MeOC_6H_4$	4-$O_2NC_6H_4$
b	1	4-ClC_6H_4	Ph	**f**	3	4-MeC_6H_4	Ph
c	1	NH_2	Ph	**g**	3	4-ClC_6H_4	4-$O_2NC_6H_4$
d	1	PhNH	H	**h**	3	PhNH	H

Scheme 93

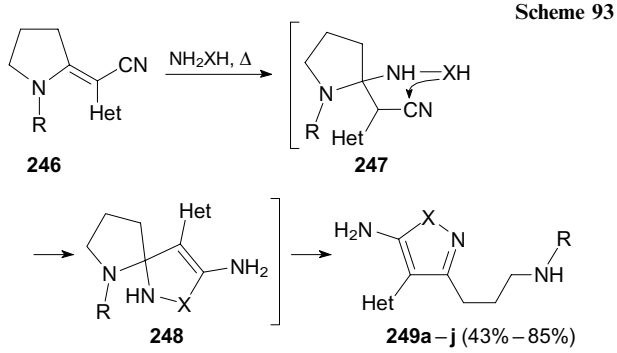
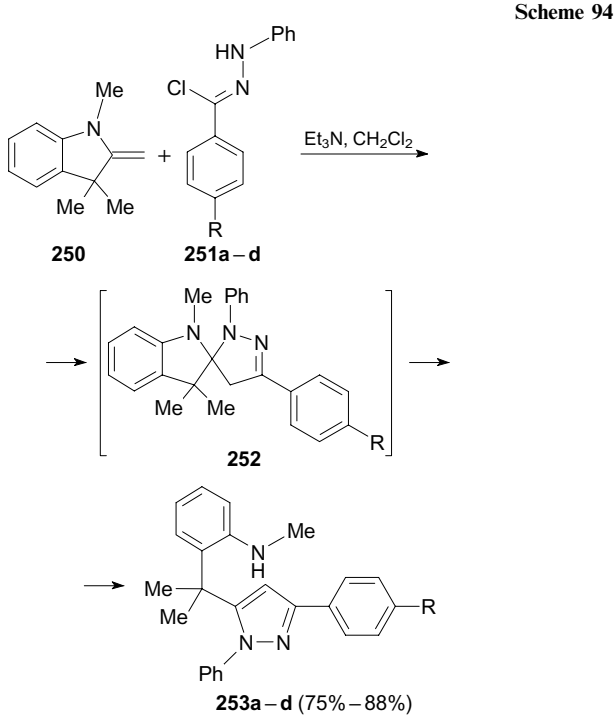


Table 2. Products of reaction of pyrrolidines **246** with NH_2XH (see Scheme 93).[170]

Compounds **249**	Het	X	R	Yield (%)
249a	Benzo[*d*]thiazol-2-yl	NMe	Me	85
249b	Benzo[*d*]thiazol-2-yl	NMe	Bn	70
249c	Benzo[*d*]thiazol-2-yl	NMe	cyclo-C_3H_5	62
249d	Benzo[*d*]thiazol-2-yl	NH	Me	56
249e	Benzo[*d*]thiazol-2-yl	NH	cyclo-C_3H_5	43
249f	1*H*-Benzo[*d*]imidazol-2-yl	NMe	Me	65
249g	Quinolin-2-yl	NMe	Bn	50
249h	Quinolin-2-yl	O	Bn	55
249i	Quinazolin-4(3*H*)-on-2-yl	NMe	Me	62
249j	Quinazolin-4(3*H*)-on-2-yl		Me	75

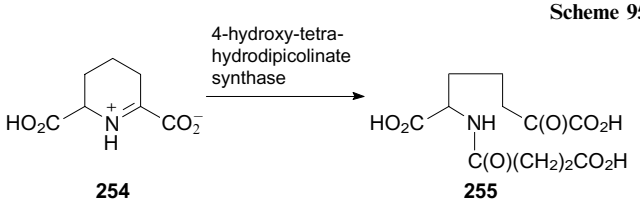
Couper *et al.*[173] investigated the enzymatic synthesis of L-lysine. One of its steps is enzyme-catalyzed ring opening in acid **254**, which leads to succinamide derivative **255** (Scheme 95). The authors do not indicate the product

Scheme 94



R = H (**a**), Br (**b**), Cl (**c**), OMe (**d**)

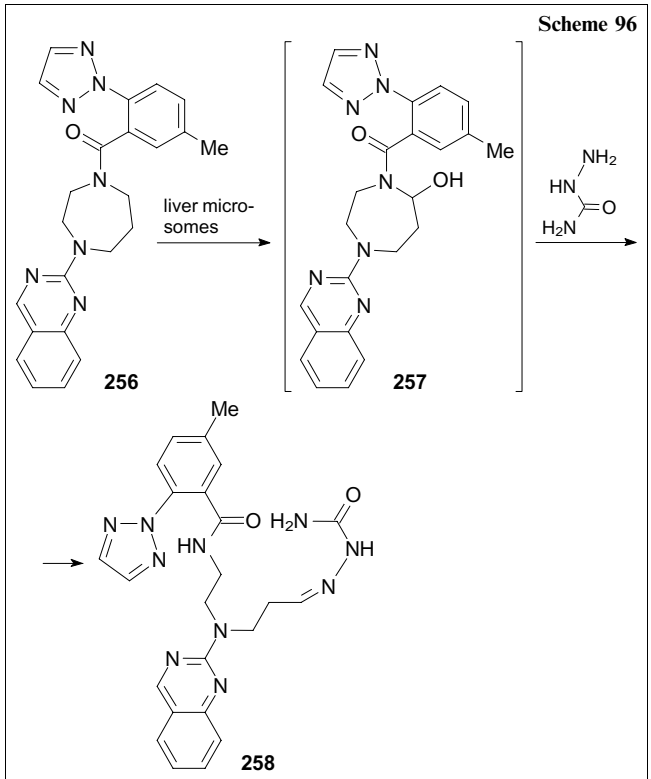
Scheme 95



yield, which complicates determination of the synthetic potential of this method.

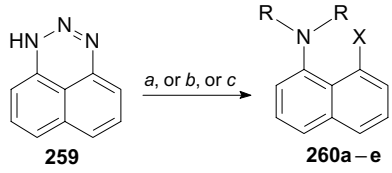
Cox *et al.*,[174] who studied the properties of compound **256**, an orexin receptor antagonist, found that heterocyclic ring opening takes place in microsomal preparations enriched with semicarbazide. The authors assumed that the ring opened takes place in intermediate **257** and yields aldehyde, which is trapped by semicarbazide to give compound **258**. However, this assumption was confirmed only by mass-spectrometry data (Scheme 96).

Scheme 96



Triazine **259** undergoes the Sandmeyer reaction in concentrated hydrohalic acids (method *a*), which gives 8-halonaphthalene-1-amines **260a – c**.[189] Also, compounds **260d**,**e** are formed in good yields in the presence of hydrogen fluoride and pyridine (methods *b* and *c*)[190, 191] (Scheme 97).

Scheme 97



(*a*) Cu, HX, rt, 12 h (48% – 81% yields); (*b*) HF · PyH (97%);
(*c*) 1) HF · PyH; 2) H_2SO_4, CH_2O; 3) $NaBH_4$ (80%);
R = H: X = Cl (**a**), Br (**b**), I (**c**); X = F: R = H (**d**), Me (**e**)

8. Ring opening in heterocycles containing several nitrogen atoms

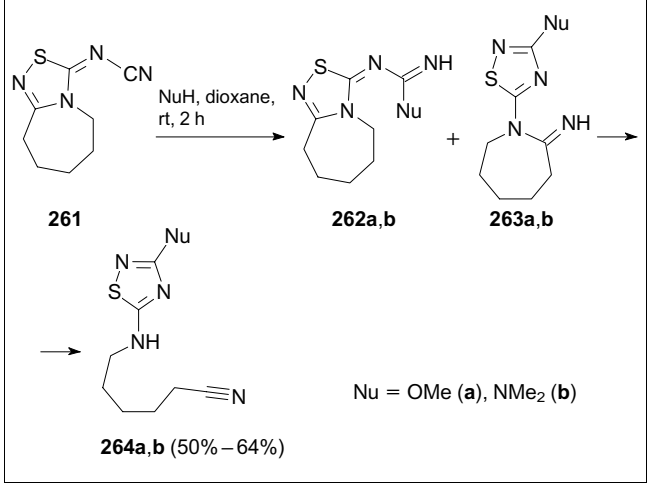
For five-membered heterocycles containing more than two nitrogen atoms (triazole and tetrazole derivatives), C – N bond cleavage is most often accompanied by elimination of a nitrogen molecule with retention of the ring.[175 – 183] We did not include retro-Diels – Alder reactions in the review, as they are exhaustively considered in the Rickborn's review,[184] which is devoted to this reaction and covers more than 900 papers. Other reviews[185 – 188] partially cover reactions accompanied by ring opening in triazole and tetrazole derivatives; therefore, examples of such reactions are not given here either.

The reaction of thiadiazole **261** with excess methanol or dimethylamine in dioxane at room temperature gives compounds **262a**,**b** and their isomers **263a**,**b**. When mixtures of these compounds are kept in dioxane, final products **264a**,**b** are formed (Scheme 98).[192]

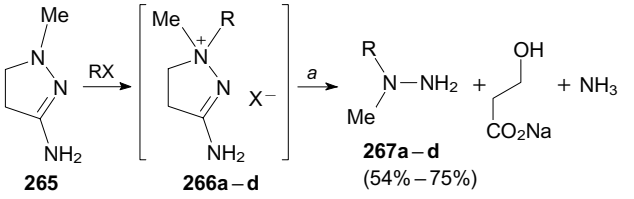
Smith *et al.*[193, 194] described a procedure for efficient synthesis of 1-alkyl-1-methylhydrazines from pyrazoline **265**. Advantages of this method include the ready accessibility of reactants, the possibility to conduct the reaction without isolation of intermediate salts **266a – d** and good yields of products **267a – d** (Scheme 99).

Maulide and co-workers[195] proposed a photoredox-catalytic synthetic route to bisindole derivatives **270a – f** based on the reaction of diazonium salts **268** with indoles

Scheme 98



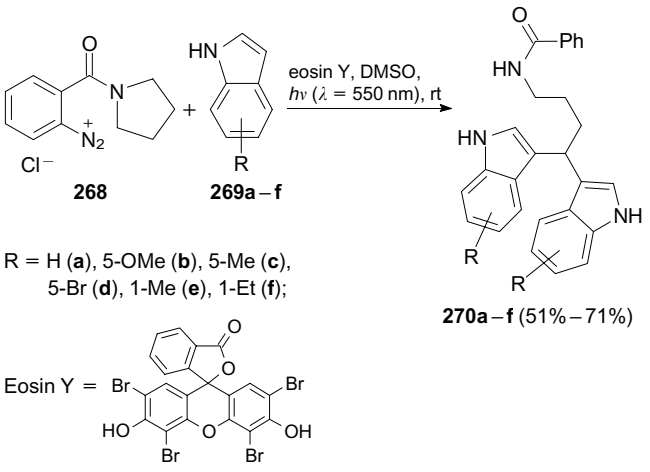
Scheme 99



(*a*) NaOH, H_2O; X = I (**266a – c**), Br (**266d**); R = Me (**a**), Et (**b**), Bu^n (**c**), Bn (**d**)

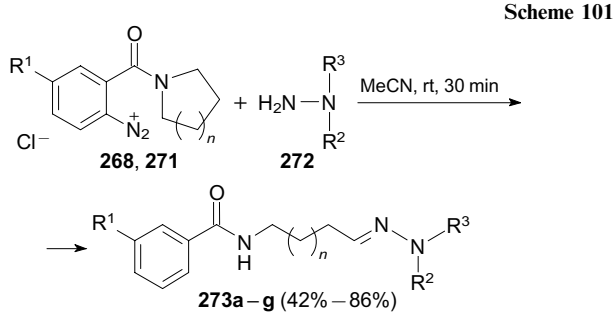
269a – f. The reaction was conducted in the presence of eosin Y photocatalyst. It was noted that indoles containing electron-donating substituents furnished the desired compound in good yields. When the starting indoles contained electron-withdrawing substituents, the yields of products were substantially lower (Scheme 100).

Scheme 100



The same group of authors[196] presented the redox opening of heterocycles **268** (n = 1) and **271** (n = 2). The reaction rapidly proceeds at room temperature with hydrazines **272**, functioning as both catalysts and nucleophiles, and affords acyclic products **273a – g** (Scheme 101).

Scheme 101



Compound **273**	n	R^1	R^2NR^3	Yield (%)
a	1	H	Piperidino	71
b	1	H	2,6-Dimethylpiperidino	81
c	1	H	4-Methylpiperazino	68
d	1	H	Me_2N	86
e	1	H	PhNEt	42
f	1	Br	Me_2N	59
g	2	Br	Me_2N	52

9. Conclusion

This review summarizes data on the reactions of various nitrogen-containing heterocycles accompanied by ring cleavage and applicable for the synthesis of polyfunctional open-chain compounds. It is noteworthy that methods based on C – N bond cleavage are widely used to obtain complex molecules often possessing biological activities. Therefore, achieving high stereoselectivity of these reactions is a relevant goal.

The reductive ring opening is catalyzed most often by platinum group metals, mainly palladium. However, in recent years samarium diiodide has been used more and more widely in organic synthesis. This single-electron reducing agent is more beneficial, because it ensures relatively fast cleavage of pyrrolidine and piperidine rings under mild conditions giving amides in good yields.

The photooxidative opening of the heterocyclic moiety is an equally promising (especially considering green chemistry principles) way for converting cyclic precursors to open-chain products. Currently, a reaction of this type is known only for indole derivatives. Nevertheless, an increase in the number of heterocycles that undergo photooxidation may expand the scope of applicability of this method. High promise of metal-catalyzed C – N bond cleavage in heterocyclic compounds also deserves mention, as these reactions are highly selective and give desired products in high yields.

Meanwhile, acid-catalyzed ring opening appears more attractive than metal-catalyzed reactions. Most acid-catalyzed processes take place at atmospheric pressure under rather mild conditions. Researchers' attention is focused on intramolecular types of these reactions. Publications considering the intermolecular reactions are less abundant, but the available published data attest to their high synthetic potential. An important advantage of these transformations is the possibility to functionalize a cyclic precursor in one step and thus to obtain polyfunctional acyclic products. Hence, the development of new approaches and improvement of known methods for heterocyclic ring opening seem to be highly promising for modern organic chemistry.

References

1. A.N.Kost, S.P.Gromov, R.S.Sagitullin. *Tetrahedron*, **37**, 3423 (1981)
2. J.Becher. *Synthesis*, 589 (1980)
3. W.-C.Cheng, M.J.Kurth. *Org. Prep. Proced. Int.*, **34**, 585 (2002)
4. B.Delpech. *Adv. Heterocycl. Chem.*, **111**, 1 (2014)
5. B.Iddon. *Bull. Soc. Chim. Belg.*, **99**, 673 (2010)
6. P.N.Confalone, E.M.Huie. In *Organic Reactions*. Vol. 36. (Ed. A.S.Kende). (New York: Wiley, 1988). P. 173
7. E.A.Chugunova, V.A.Samsonov, A.S.Gazizov, A.R.Burilov, M.A.Pudovik, O.G.Sinyashin. *Russ. Chem. Bull., Int. Ed.*, **67**, 1955 (2018)
8. M.Nonn, A.M.Remete, F.Fülöp, L.Kiss. *Tetrahedron*, **73**, 5461 (2017)
9. X.E.Hu. *Tetrahedron*, **60**, 2701 (2004)
10. P.Lu. *Tetrahedron*, **66**, 2549 (2010)
11. M.Andresini, S.De Angelis, A.Uricchio, A.Visaggio, G.Romanazzi, F.Ciriaco, N.Corriero, L.Degennaro, R.Luisi. *J. Org. Chem.*, **83**, 10221 (2018)
12. G.Casoni, E.Myers, V.Aggarwal. *Synthesis*, **48**, 3241 (2016)
13. F.Couty, O.David, F.Durrat. *Tetrahedron Lett.*, **48**, 1027 (2007)
14. G.S.Singh, M.D'hooghe, N.De Kimpe. *Tetrahedron*, **67**, 1989 (2011)
15. K.Hashimoto. *Prog. Polym. Sci.*, **25**, 1411 (2000)
16. X.Zhou, W.-J.Liu, J.-L.Ye, P.-Q.Huang. *Tetrahedron*, **63**, 6346 (2007)
17. J.Van Betsbrugge, W.Van Den Nest, P.Verheyden, D.Tourwé. *Tetrahedron*, **54**, 1753 (1998)
18. S.Louwrier, A.Tuynman, H.Hiemstra. *Tetrahedron*, **52**, 2629 (1996)
19. B.Zacharie, N.Moreau, C.Dockendorff. *J. Org. Chem.*, **66**, 5264 (2001)
20. H.Jiang, J.He, T.Liu, J.-Q.Yu. *J. Am. Chem. Soc.*, **138**, 2055 (2016)
21. J.Verduyckt, R.Coeck, D.E.De Vos. *ACS Sust. Chem. Eng.*, **5**, 3290 (2017)
22. A.P.Phillips. *J. Am. Chem. Soc.*, **76**, 2211 (1954)
23. F.Valdevenito, R.García, N.Escalona, F.J.Gil-Llambias, S.B.Rasmussen, A.López-Agudo. *Catal. Commun.*, **11**, 1154 (2010)
24. B.Ibeh, S.Zhang, J.M.Hill. *Appl. Catal. A: Gen.*, **368**, 127 (2009)
25. T.Honda, F.Ishikawa. *Chem. Commun.*, 1065 (1999)
26. C.-K.Tsung, J.N.Kuhn, W.Huang, C.Aliaga, L.-I.Hung, G.A.Somorjai, P.Yang. *J. Am. Chem. Soc.*, **131**, 5816 (2009)
27. C.J.Kliewer, M.Bieri, G.A.Somorjai. *J. Phys. Chem. C*, **112**, 11373 (2008)
28. H.Adkins, I.A.Wolff, A.Pavlic, E.Hutchinson. *J. Am. Chem. Soc.*, **66**, 1293 (1944)
29. J.L.Rainey, H.Adkins. *J. Am. Chem. Soc.*, **61**, 1104 (1939)
30. L.Hegedus. *Appl. Catal. A: Gen.*, **226**, 319 (2002)
31. L.Hegedüs, T.Máthé, A.Tungler. *Appl. Catal. A: Gen.*, **153**, 133 (1997)
32. S.P.Findlay. *J. Org. Chem.*, **21**, 644 (1956)
33. H.Huang, H.Li, P.Martásek, L.J.Roman, T.L.Poulos, R.B.Silverman. *J. Med. Chem.*, **56**, 3024 (2013)
34. S.Kang, W.Tang, H.Li, G.Chreifi, P.Martásek, L.J.Roman, T.L.Poulos, R.B.Silverman. *J. Med. Chem.*, **57**, 4382 (2014)
35. H.T.Do, H.-Y.Wang, H.Li, G.Chreifi, T.L.Poulos, R.B.Silverman. *J. Med. Chem.*, **60**, 9360 (2017)
36. D.M.Nason, S.D.Heck, M.S.Bodenstein, J.A.Lowe, R.B.Nelson, D.R.Liston, C.E.Nolan, L.F.Lanyon, K.M.Ward, R.A.Volkmann. *Bioorg. Med. Chem. Lett.*, **14**, 4511 (2004)
37. W.Zhang, W.Chen, H.Xiao, M.J.Krische. *Org. Lett.*, **19**, 4876 (2017)
38. J.I.Trujillo, W.Huang, R.O.Hughes, D.J.Rogier, S.R.Turner, R.Devraj, P.A.Morton, C.-B.Xue, G.Chao, M.B.Covington, R.C.Newton, B.Metcalf. *Bioorg. Med. Chem. Lett.*, **21**, 1827 (2011)
39. R.T.Blickenstaff, E.Foster, K.Gerzon, P.Young. *Steroids*, **48**, 223 (1986)
40. M.Nyerges, I.Fejes, L.Töke. *Synthesis*, 1823 (2002)
41. M.Nyerges, I.Fejes, L.Töke. *Tetrahedron Lett.*, **41**, 7951 (2000)
42. G.A.Cortez, R.R.Schrock, A.H.Hoveyda. *Angew. Chem., Int. Ed.*, **46**, 4534 (2007)
43. P.Liu, Y.Liu, E.L.-M.Wong, S.Xiang, C.-M.Che. *Chem. Sci.*, **2**, 2187 (2011)
44. A.M.Castaño, J.M.Cuerva, A.M.Echavarren. *Tetrahedron Lett.*, **35**, 7435 (1994)
45. R.Adams, N.J.Leonard. *J. Am. Chem. Soc.*, **66**, 257 (1944)
46. O.Onomura, S.S.Libendi, Y.Demizu, Y.Matsumura. *Heterocycles*, **77**, 311 (2009)
47. B.A.Czeskis. *J. Label. Compd. Radiopharm.*, **55**, 171 (2012)
48. D.L.Huang, D.J.Vinyard, J.D.Blakemore, S.M.Hashmi, R.H.Crabtree. *Organometallics*, **36**, 199 (2017)
49. T.J.Osberger, D.C.Rogness, J.T.Kohrt, A.F.Stepan, M.C.White. *Nature (London)*, **537**, 214 (2016)
50. G.Cocquet, C.Ferroud, A.Guy. *Tetrahedron*, **56**, 2975 (2000)
51. A.P.Davis, K.J.Dempsey. *Tetrahedron: Asymmetry*, **6**, 2829 (1995)
52. M.A.Convery, A.P.Davis, C.J.Dunne, J.W.MacKinnon. *Tetrahedron Lett.*, **36**, 4279 (1995)
53. C.Kashima, T.Maruyama, Y.Fujioka, K.Harada. *J. Chem. Soc., Perkin Trans. 1*, 1041 (1989)
54. A.Boto, R.Hernández, E.Suárez. *J. Org. Chem.*, **65**, 4930 (2000)
55. A.Boto, R.Hernández, Y.de León, E.Suárez. *J. Org. Chem.*, **66**, 7796 (2001)
56. S.Toumieux, P.Compain, O.R.Martin, M.Selkti. *Org. Lett.*, **8**, 4493 (2006)
57. T.Vidal, E.Magnier, Y.Langlois. *Tetrahedron*, **54**, 5959 (1998)
58. R.Ito, N.Umezawa, T.Higuchi. *J. Am. Chem. Soc.*, **127**, 834 (2005)
59. C.Zhang, S.Li, F.Bureš, R.Lee, X.Ye, Z.Jiang. *ACS Catal.*, **6**, 6853 (2016)
60. X.Ji, D.Li, Z.Wang, M.Tan, H.Huang, G.-J.Deng. *Eur. J. Org. Chem.*, 6652 (2017)
61. M.N.Dufour, A.L.Crumbliss, G.Johnston, A.Gaudemer. *J. Mol. Catal.*, **7**, 277 (1980)
62. M.S.B.Nayar, P.S.Callery. *J. Org. Chem.*, **46**, 1044 (1981)
63. F.D.King, S.Caddick. *Org. Biomol. Chem.*, **9**, 4361 (2011)
64. F.D.King, A.Aliev, S.Caddick, D.Tocher. *Tetrahedron*, **71**, 3411 (2015)
65. A.V.Smolobochkin, A.S.Gazizov, A.R.Burilov, M.A.Pudovik. *Russ. Chem. Bull., Int. Ed.*, **65**, 1377 (2016)
66. A.Gazizov, A.Smolobochkin, E.Anikina, A.Strelnik, A.Burilov, M.Pudovik. *Synlett*, **29**, 467 (2018)
67. A.S.Gazizov, A.V Smolobochkin, J.K.Voronina, A.R.Burilov, M.A.Pudovik. *Tetrahedron*, **71**, 445 (2015)
68. A.V.Smolobochkin, A.S.Gazizov, J.K.Voronina, A.R.Burilov, M.A.Pudovik. *Monatsh. Chem.*, **149**, 535 (2018)
69. P.B.White, S.S.Stahl. *J. Am. Chem. Soc.*, **133**, 18594 (2011)
70. T.Durst, J.A.Finke, R.Huisgen, R.Temme. *Helv. Chim. Acta*, **83**, 2363 (2000)
71. H.Harris, D.-S.Grierson, H.-P.Husson. *Tetrahedron Lett.*, **22**, 1511 (1981)
72. T.Nagasaka, Y.Koseki, H.Hayashi, Y.Yasuda, F.Hamaguchi. *Yakugaku Zasshi*, **109**, 823 (1989); *Chem. Abstr.*, **112**, 216668 (1990)
73. Z.Xing, H.-C.Wang, Y.Cheng, C.Zhu, T.D.James, J.Zhao. *Eur. J. Org. Chem.*, 1223 (2012)
74. T.C.Sanders, C.T.Seto. *J. Med. Chem.*, **42**, 2969 (1999)

75. X.Xiao, S.Antony, G.Kohlhagen, Y.Pommier, M.Cushman. *Bioorg. Med. Chem.*, **12**, 5147 (2004)
76. S.E.Choi, S.V.W.Weerasinghe, M.K.H.Pflum. *Bioorg. Med. Chem. Lett.*, **21**, 6139 (2011)
77. Y.Du, H.Ye, T.Gill, L.Wang, F.Guo, A.Cuconati, J.-T.Guo, T.M.Block, J.Chang, X.Xu. *Bioorg. Med. Chem. Lett.*, **23**, 2172 (2013)
78. C.B.Botta, W.Cabri, E.Cini, L.De Cesare, C.Fattorusso, G.Giannini, M.Persico, A.Petrella, F.Rondinelli, M.Rodriquez, A.Russo, M.Taddei. *J. Med. Chem.*, **54**, 2165 (2011)
79. M.A.Ramirez, M.V.Corona, M.M.Blanco, I.A.Perillo, W.Porcal, A.Salerno. *Tetrahedron Lett.*, **51**, 5000 (2010)
80. M.E.Hedrera, I.A.Perillo. *J. Heterocycl. Chem.*, **37**, 1431 (2000)
81. N.J.Leonard, E.W.Nommensen. *J. Am. Chem. Soc.*, **71**, 2808 (1949)
82. I.A.Hedrera, M.E.Salerno, A.López, J.Niemevz, F.Perillo. *Trends Org. Chem.*, **12**, 61 (2008)
83. F.Lindahl, H.N.Hoang, D.P.Fairlie, M.A.Cooper. *Chem. Commun.*, **51**, 4496 (2015)
84. S.Baktharaman, S.Selvakumar, V.K.Singh. *Org. Lett.*, **8**, 4335 (2006)
85. S.Selvakumar, S.Baktharaman, V.K.Singh. *J. Org. Chem.*, **72**, 10141 (2007)
86. R.C.Elderfield, H.A.Hageman. *J. Org. Chem.*, **14**, 605 (1949)
87. H.-J.Nitzscke, G.Faerber. *Chem. Ber.*, **87**, 1635 (1954)
88. M.Kawase, H.Miyamae, M.Narita, T.Kurihara. *Tetrahedron Lett.*, **34**, 859 (1993)
89. M.Kawase. *Tetrahedron Lett.*, **35**, 149 (1994)
90. M.Kawase, S.Saito, T.Kurihara. *Chem. Pharm. Bull.*, **48**, 1338 (2000)
91. M.Kawase, H.Sakagami, K.Kusama, N.Motohashi, S.Saito. *Bioorg. Med. Chem. Lett.*, **9**, 3113 (1999)
92. F.Ghotbi, M.M.Baradarani, D.Sheikh. *J. Sulfur Chem.*, **33**, 397 (2012)
93. C.Yu, M.A.Shoaib, N.Iqbal, J.S.Kim, H.-J.Ha, E.J.Cho. *J. Org. Chem.*, **82**, 6615 (2017)
94. K.Fröhlich, R.Wagemann, E.Vilsmaier. *Tetrahedron*, **54**, 13115 (1998)
95. M.G.Voronkov, I.P.Tsyrendorzhieva, V.I.Rakhlin. *Russ. J. Org. Chem.*, **46**, 794 (2010)
96. G.Zheng, L.P.Dwoskin, P.A.Crooks. *J. Org. Chem.*, **69**, 8514 (2004)
97. F.-X.Felpin, J.Lebreton. *J. Org. Chem.*, **67**, 9192 (2002)
98. D.Compère, C.Marazano, B.C.Das. *J. Org. Chem.*, **64**, 4528 (1999)
99. W.S.McCall, D.L.Comins. *Org. Lett.*, **11**, 2940 (2009)
100. W.S.McCall, T.A.Grillo, D.L.Comins. *J. Org. Chem.*, **73**, 9744 (2008)
101. W.S.McCall, T.A.Grillo, D.L.Comins. *Org. Lett.*, **10**, 3255 (2008)
102. T.Torigoe, T.Ohmura, M.Suginome. *Angew. Chem., Int. Ed.*, **56**, 14272 (2017)
103. E.D.Smith, F.C.Février, D.L.Comins. *Org. Lett.*, **8**, 179 (2006)
104. Y.Cheng, Y.-H.Zhan, O.Meth-Cohn. *Synthesis*, 34 (2002)
105. K.G.Nazarenko, K.V.Shvidenko, A.M.Pinchuk, A.A.Tolmachev. *Synth. Commun.*, **33**, 4241 (2003)
106. E.Desarbre, L.Savelon, O.Cornec, J.Mérour. *Tetrahedron*, **52**, 2983 (1996)
107. Z.Assaf, A.P.Larsen, R.Venskutonytė, L.Han, B.Abrahamsen, B.Nielsen, M.Gajhede, J.S.Kastrup, A.A.Jensen, D.S.Pickering, K.Frydenvang, T.Gefflaut, L.Bunch. *J. Med. Chem.*, **56**, 1614 (2013)
108. K.Nazarenko, S.Bova, V.Polovinko, A.Tolmachev. *Synthesis*, 3497 (2008)
109. S.Murahashi, T.Yano. *J. Am. Chem. Soc.*, **102**, 2456 (1980)
110. F.Acquadro, H.Oulyadi, P.Venturello, J.Maddaluno. *Tetrahedron Lett.*, **43**, 8759 (2002)
111. C.E.Neipp, J.M.Humphrey, S.F.Martin. *J. Org. Chem.*, **66**, 531 (2001)
112. I.Coldham, J.J.Patel, S.Raimbault, D.T.E.Whittaker, H.Adams, G.Y.Fang, V.K.Aggarwal. *Org. Lett.*, **10**, 141 (2008)
113. S.Chandrasekhar, M.V.Reddy, G.Rajaiah. *Tetrahedron Lett.*, **41**, 10131 (2000)
114. Y.Matsumura, T.Kinoshita, Y.Yanagihara, N.Kanemoto, M.Watanabe. *Tetrahedron Lett.*, **37**, 8395 (1996)
115. Y.Takeuchi, M.Oshige, K.Azuma, H.Abe, T.Harayama. *Chem. Pharm. Bull.*, **53**, 868 (2005)
116. M.A.Breuning, K.Harms, U.Koert. *Org. Lett.*, **13**, 1402 (2011)
117. M.V.Machado, G.Cenzi, M.F.A.Nascimento, R.C.de Paula, D.S.M.Guimaraes, A.C.Medeiros, R.B.Alves, R.P.Freitas, F.de P.Varotti, G.H.R.Viana. *J. Biol. Sci.*, **13**, 645 (2013)
118. T.Zincke, G.Weißpfenning. *Justus Liebigs Ann. Chem.*, **396**, 103 (1913)
119. T.Zincke, W.Würker. *Justus Liebigs Ann. Chem.*, **341**, 365 (1905)
120. W.König. *J. Prakt. Chem.*, **69**, 105 (1904)
121. T.Zincke, G.Heuser, W.Möller. *Justus Liebigs Ann. Chem.*, **333**, 296 (1904)
122. J.K.Lam, S.B.Joseph, C.D.Vanderwal. *Tetrahedron Lett.*, **56**, 3165 (2015)
123. A.M.Kearney, C.D.Vanderwal. *Angew. Chem., Int. Ed.*, **45**, 7803 (2006)
124. J.M.J.Nolsøe, M.Aursnes, J.E.Tungen, T.V.Hansen. *J. Org. Chem.*, **80**, 5377 (2015)
125. B.A.Trofimov, L.V.Andriyankova, K.V.Belyaeva, L.P.Nikitina, A.V.Afonin, A.G.Mal'kina. *Eur. J. Org. Chem.*, 7876 (2015)
126. N.O.Mahmoodi, M.Mamaghani, A.Ghanadzadeh, M.Arvand, M.Fesanghari. *J. Phys. Org. Chem.*, **23**, 266 (2010)
127. L.-H.Yan, A.Skiredj, Y.Dory, B.Delpech, E.Poupon. *Eur. J. Org. Chem.*, 4973 (2014)
128. A.Colombo, C.Dragonetti, S.Righetto, D.Roberto, A.Valore, T.Benincori, F.Colombo, F.Sannicolò. *J. Mater. Chem.*, **22**, 19761 (2012)
129. D.B.C.Martin, L.Q.Nguyen, C.D.Vanderwal. *J. Org. Chem.*, **77**, 17 (2012)
130. T.Nguyen, S.Peixoto, C.Ouairy, T.Nguyen, M.Bénéchie, C.Marazano, P.Michel. *Synthesis*, 103 (2010)
131. R.S.Paton, S.E.Steinhardt, C.D.Vanderwal, K.N.Houk. *J. Am. Chem. Soc.*, **133**, 3895 (2011)
132. S.E.Steinhardt, J.S.Silverston, C.D.Vanderwal. *J. Am. Chem. Soc.*, **130**, 7560 (2008)
133. J.Aleksić, M.Stojanović, M.Baranac-Stojanović. *Chem. – Asian J.*, **13**, 1811 (2018)
134. M.C.Bagley, C.Glover. *Molecules*, **15**, 3211 (2010)
135. M.C.Bagley, V.Fusillo, R.L.Jenkins, M.C.Lubinu, C.Mason. *Org. Biomol. Chem.*, **8**, 2245 (2010)
136. H.Andersson, X.Wang, M.Björklund, R.Olsson, F.Almqvist. *Tetrahedron Lett.*, **48**, 6941 (2007)
137. M.Ghandi, S.Sheibani, M.Sadeghzadeh, F.J.Daha, M.Kubicki. *J. Iran. Chem. Soc.*, **10**, 1057 (2013)
138. M.Ghandi, E.Babazadeh. *J. Iran. Chem. Soc.*, **12**, 379 (2015)
139. M.Ghandi, M.A.Kia, M.Sadeghzadegh, A.H.Bozcheloei, M.Kubicki. *J. Heterocycl. Chem.*, **52**, 1646 (2015)
140. I.A.Apple, O.Meth-Cohn. *ARKIVOC*, (vi), 4 (2002)
141. Y.R.Lee, T.V.Hung. *Tetrahedron*, **64**, 7338 (2008)
142. C.-K.Wu, D.-Y.Yang. *RSC Adv.*, **6**, 65988 (2016)
143. W.Geng, W.-X.Zhang, W.Hao, Z.Xi. *J. Am. Chem. Soc.*, **134**, 20230 (2012)
144. W.Hao, J.Wei, W.Geng, W.-X.Zhang, Z.Xi. *Angew. Chem., Int. Ed.*, **53**, 14533 (2014)

145. W.Hao, H.Wang, P.J.Walsh, Z.Xi. *Org. Chem. Front.*, **2**, 1080 (2015)
146. H.-B.Zhou, H.Alper. *J. Org. Chem.*, **68**, 3439 (2003)
147. J.John, S.Anas, V.S.Sajisha, S.Viji, K.V.Radhakrishnan. *Tetrahedron Lett.*, **48**, 7225 (2007)
148. K.V.Radhakrishnan, V.S.Sajisha, S.Anas, K.S.Krishnan. *Synlett*, 2273 (2005)
149. G.Maas, A.Müller. *Org. Lett.*, **1**, 219 (1999)
150. S.Crotti, F.Bertolini, F.Macchia, M.Pineschi. *Chem. Commun.*, 3127 (2008)
151. H.Lee, J.T.Han, J.Yun. *ACS Catal.*, **6**, 6487 (2016)
152. H.Möhrle, J.Mehrens. *Z. Naturforsch., Sect. B*, **53**, 37 (1998)
153. H.Möhrle, J.Gerloff. *Arch. Pharm.*, **312**, 219 (1979)
154. P.Quinodoz, K.Wright, B.Drouillat, O.David, J.Marrot, F.Couty. *Chem. Commun.*, **52**, 10072 (2016)
155. Y.Matsumura, O.Onomura, H.Suzuki, S.Furukubo, T.Maki, C.-J.Li. *Tetrahedron Lett.*, **44**, 5519 (2003)
156. J.Häusler. *Liebigs Ann. Chem.*, 1231 (1992)
157. E.Keschmann, E.Zbiral, J.Schweng. *Justus Liebigs Ann. Chem.*, 1508 (1977)
158. J.T.Bagdanoff, D.C.Behenna, J.L.Stockdill, B.M.Stoltz. *Eur. J. Org. Chem.*, 2101 (2016)
159. S.Y.Tamura, B.M.Shamblin, T.K.Brunck, W.C.Ripka. *Bioorg. Med. Chem. Lett.*, **7**, 1359 (1997)
160. M.Kaname, S.Yoshifuji, H.Sashida. *Tetrahedron Lett.*, **49**, 2786 (2008)
161. E.Ciganek. *J. Org. Chem.*, **55**, 3007 (1990)
162. A.C.Cope, N.A.LeBel. *J. Am. Chem. Soc.*, **82**, 4656 (1960)
163. N.Quillot, B.Martin, Z.Janousek, H.G.Viehe. *Synth. Commun.*, **19**, 2825 (1989)
164. P.G.Haines, A.Eisner. *J. Am. Chem. Soc.*, **72**, 1719 (1950)
165. C.H.Rayburn, W.R.Harlan, H.R.Hanmer. *J. Am. Chem. Soc.*, **72**, 1721 (1950)
166. J.D.Coyle, R.R.Hill, G.E.Jeffs. *Tetrahedron Lett.*, **28**, 2529 (1987)
167. J.Liebscher, M.Pätzel, Y.F.Kelboro. *Synthesis*, 672 (1989)
168. J.Bohrisch, M.Pätzel, C.Mügge, J.Liebscher. *Synthesis*, 1153 (1991)
169. M.Pätzel, A.Ushmajev, J.Liebscher. *Synthesis*, 525 (1993)
170. O.Kuleshova, O.Khilya, Y.Volovenko, S.Mallet-Ladeira, V.Dyakonenko, E.Gras. *ACS Omega*, **2**, 8911 (2017)
171. S.Dadiboyena, A.T.Hamme. *Eur. J. Org. Chem.*, 7567 (2013)
172. S.Dadiboyena, E.J.Valente, A.T.Hamme. *Tetrahedron Lett.*, **50**, 291 (2009)
173. L.Couper, D.J.Robins, E.J.T.Chrystal. *Tetrahedron Lett.*, **33**, 2717 (1992)
174. C.D.Cox, M.J.Breslin, D.B.Whitman, J.D.Schreier, G.B.McGaughey, M.J.Bogusky, A.J.Roecker, S.P.Mercer, R.A.Bednar, W.Lemaire, J.G.Bruno, D.R.Reiss, C.M.Harrell, K.L.Murphy, S.L.Garson, S.M.Doran, T.Prueksaritanont, W.B.Anderson, C.Tang, S.Roller, T.D.Cabalu, D.Cui, G.D.Hartman, S.D.Young, K.S.Koblan, C.J.Winrow, J.J.Renger, P.J.Coleman. *J. Med. Chem.*, **53**, 5320 (2010)
175. A.V.Aksenov, I.V.Aksenova, D.A.Lobach, A.M.Zhirov. *Chem. Heterocycl. Compd.*, **44**, 1022 (2008)
176. H.Al-Awadi, M.R.Ibrahim, H.H.Dib, N.A.Al-Awadi, Y.A.Ibrahim. *Tetrahedron*, **61**, 10507 (2005)
177. M.T.Migawa, L.B.Townsend. *Org. Lett.*, **1**, 537 (1999)
178. D.Simoni, R.Rondanin, G.Furnò, E.Aiello, F.P.Invidiata. *Tetrahedron Lett.*, **41**, 2699 (2000)
179. D.L.Lipilin, O.Y.Smirnov, A.M.Churakov, Y.A.Strelenko, S.L.Ioffe, V.A.Tartakovsky. *Eur. J. Org. Chem.*, 3435 (2002)
180. M.S.Klenov, A.A.Guskov, O.V.Anikin, A.M.Churakov, Y.A.Strelenko, I.V.Fedyanin, K.A.Lyssenko, V.A.Tartakovsky. *Angew. Chem., Int. Ed.*, **55**, 11472 (2016)
181. M.O.Ratnikov, D.L.Lipilin, A.M.Churakov, Y.A.Strelenko, V.A.Tartakovsky. *Org. Lett.*, **4**, 3227 (2002)
182. L.El Kaïm, L.Grimaud, P.Pravin. *Eur. J. Org. Chem.*, 4752 (2013)
183. T.L.Troyer, H.Muchalski, K.B.Hong, J.N.Johnston. *Org. Lett.*, **13**, 1790 (2011)
184. B.Rickborn. *The Retro – Diels – Alder Reaction. Part I. C – C Dienofiles. (Ser. Organic Reactions.* Vol. 52). (Hoboken, NJ: Wiley, 1998)
185. B.I.Buzykin. *Chem. Heterocycl. Compd.*, **46**, 1043 (2010)
186. B.I.Buzykin. *Chem. Heterocycl. Compd.*, **46**, 379 (2010)
187. T.L.Gilchrist, G.E.Gymer. *Adv. Heterocycl. Chem.*, **16**, 33 (1974)
188. A.R.Katritzky, X.Lan, J.Z.Yang, O.V.Denisko. *Chem. Rev.*, **98**, 409 (1998)
189. W.E.Noland, V.S.Narina, D.Britton. *J. Chem. Res.*, **35**, 694 (2011)
190. M.T.Scerba, C.M.Leavitt, M.E.Diener, A.F.DeBlase, T.L.Guasco, M.A.Siegler, N.Bair, M.A.Johnson, T.Lectka. *J. Org. Chem.*, **76**, 7975 (2011)
191. Z.Zhu, N.L.Colbry, M.Lovdahl, K.E.Mennen, A.Acciacca, V.G.Beylin, J.D.Clark, D.T.Belmont. *Org. Proc. Res. Dev.*, **11**, 907 (2007)
192. H.Sonnenschein, E.Schmitz, E.Gründemann, E.Schröder. *Liebigs Ann. Chem.*, 1177 (1994)
193. R.F.Smith, K.A.Brophy, G.Rodriguez, L.A.Dennis, W.J.Ryan. *Synth. Commun.*, **20**, 183 (1990)
194. R.F.Smith, L.A.Olson, W.J.Ryan, K.J.Coffman, J.M.Galante, T.S.Wojdan, P.A.Mallardi, T.P.Eckert. *Synth. Commun.*, **16**, 585 (1986)
195. S.Shaaban, A.Roller, N.Maulide. *Eur. J. Org. Chem.*, 7643 (2015)
196. S.Shaaban, J.Oh, N.Maulide. *Org. Lett.*, **18**, 345 (2016)