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Reactions of nitrogen-containing acetals with aromatic nucleophiles

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The data on the reactions of nitrogen-containing acetals with carbocyclic and heterocyclic aromatic nucleophiles published in the last decade are integrated and described systematically. It is shown that intermolecular reactions of this type result in diarylmethane derivatives or heterocyclic compounds — tryptamines and isoquinolines, as well as aryl-substituted imidazolidin-2-ones and 2-arylpyrrolidines. The intramolecular processes involving aromatic nucleophiles present as a part of the acetal molecule are considered. The transformations are classified in terms of the products formed.
The bibliography includes 156 references.

Contents

I. Introduction 75
II. Intermolecular reactions involving nitrogen-containing acetals 76
III. Intramolecular reactions involving nitrogen-containing acetals 82

I. Introduction

Nitrogen-containing acetals and aldehydes are widely used in organic chemistry. There are several reviews devoted to various aspects of the chemistry of these compounds (*e.g.*, Refs 1 – 3). However, numerous papers describing the chemical reactions of nitrogen-containing acetals and aldehydes with aromatic compounds have not yet been collected and described systematically. It should be noted that nitrogen-containing acetals are used in these reactions much more often than corresponding aldehydes. This is quite natural, especially in view of the fact that syntheses of most nitrogen-containing aldehydes are based either on modification of commercially available aminoacetals or on alkylation of nitrogen-containing substrates with acetals of haloacetaldehydes followed by hydrolysis of the acetal group; hence, acetals are intermediate compounds derived in the course of aldehyde synthesis. In this case, the chemical properties of the acetal and the aldehyde groups are not of particular importance as long as under conditions of acid catalysis, which is used most widely for this purpose, these groups are interconverted; therefore, they can be considered as synthetically equivalent.

In this review, the authors attempted to collate the data on the reactions of nitrogen-containing acetals with aromatic nucleophiles published in the literature over the last decade. Analysis of the available publications shows that all these reactions may be classified in two different groups: the intramolecular reactions (the aromatic nucleophile group is a part of the acetal molecule) and the intermolecular reactions (the nucleophile group and the acetal function belong to different compounds). Systematic description of the reactions according to the type of product appeared to be the most convenient method of systematization within each group. Nevertheless, in a number of cases, we had to deviate from the adopted classification in order to preserve the integrity of data presentation. It also should be noted that the review includes reactions of both carbocyclic and heterocyclic nucleophiles. Since the number of the latter is relatively small, we considered allocation of a separate section for such reactions to be inexpedient.

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II. Intermolecular reactions involving nitrogen-containing acetals

Intermolecular reactions of nitrogen-containing acetals with aromatic nucleophiles result in the formation of heterocyclic compounds or diarylmethane derivatives. The nitrogen-containing group may either be preserved within the product molecule or participate in the subsequent intramolecular reactions.

The heterocyclic compounds formed in these reactions include derivatives of tryptamine, isoquinoline and aryl-substituted imidazolidin-2-ones and 2-arylpyrrolidines. It should be noted that the reactions giving tryptamine and isoquinoline derivatives are variants of the well-known Fischer indole synthesis and comprehensively studied Pictet–Spengler reaction, respectively. The only difference between these reactions and the conventional variants is the use of nitrogen-containing acetals as a carbonyl component.

The route and the synthetic outcome of reactions of nitrogen-containing acetals with aromatic nucleophiles depend on the structure of initial compounds. If the amino or cyano group is present in the acetal molecule, the reaction products are diarylmethane derivatives. As for acetals containing urea moieties, the intermolecular reaction of acetal with aromatic nucleophile is accompanied by intramolecular processes resulting in the formation of imidazolidin-2-one and 2-arylpyrrolidine derivatives.

II.1. Synthesis of diarylmethane derivatives

The synthesis of diarylmethane derivatives by condensation of aminoacetaldehyde acetals with a variety of dihydric phenols was first described in the 1930s.[4–6] However, since the conclusions on the structure of reaction products were based on the elemental analysis data alone, nowadays these papers are rather a matter of historical interest.

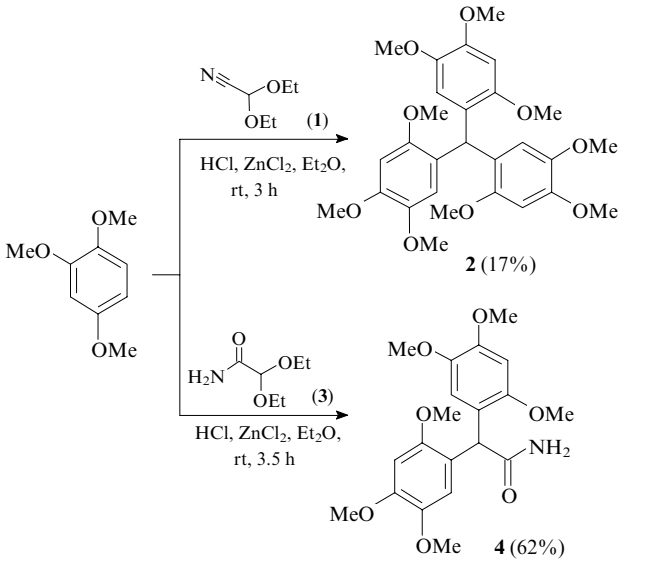
More recent publications dedicated to similar reactions are occasional.[7–11] The nucleophiles in these reactions are usually represented by polyhydric phenols or their alkyl ethers. Most examples of using phenols as nucleophiles in the reactions with nitrogen-containing acetals are associated exactly with the synthesis of diarylmethane derivatives.

An attempt to perform C-acylation of 1,2,4-trimethoxybenzene with diethoxyacetonitrile (**1**) according to the Hoesch reaction pattern gave tris(2,4,5-trimethoxyphenyl)-methane (**2**) in a low yield.[12] Note that in this reaction, the aryl moiety is substituted for the cyano group. The same publication describes the reaction of diethoxyacetamide (**3**) with 1,2,4-trimethoxybenzene to give bis(2,4,5-trimethoxyphenyl)acetamide (**4**) (Scheme 1). Unfortunately, the authors do not explain the low yield of triarylmethane **2** and do not discuss the possibility of formation of diaryl derivatives.

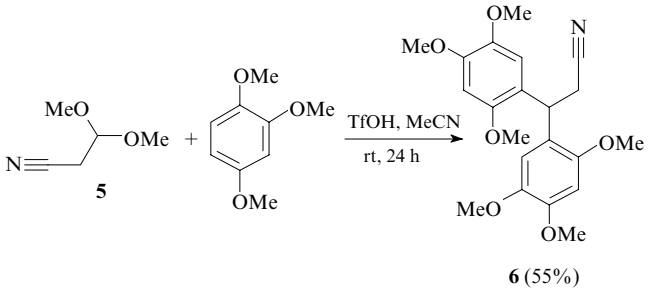
The reaction of the same 1,2,4-trimethoxybenzene with 3,3-dimethoxypropionitrile (**5**) in the presence of trifluoromethanesulfonic acid (TfOH) affords 3,3-bis-(2,4,5-trimethoxyphenyl)propionitrile (**6**) without any observed displacement of the cyano group (Scheme 2).[13]

A series of papers[14–18] are devoted to the condensation of aminoacetaldehyde acetals with polyhydric phenols. Thus acetals **7a–c** react with pyrocatechol to give polyphenols **8a–c** (Scheme 3). The yield of the reaction products is significantly affected by the presence of substituents at the nitrogen atom. Whereas polyphenol **8a** is obtained in a nearly quantitative yield (98%), in the case of compound **8c**, the product yield is only 59%. A similar reaction takes place between pyrocatechol and acetals **9a–c** containing the tetraalkylammonium moiety.[14] In this case, the strong dependence of target product yield on the substituent at the nitrogen atom is also observed. The increased length of the alkyl substituent leads to the rapid decrease in the target

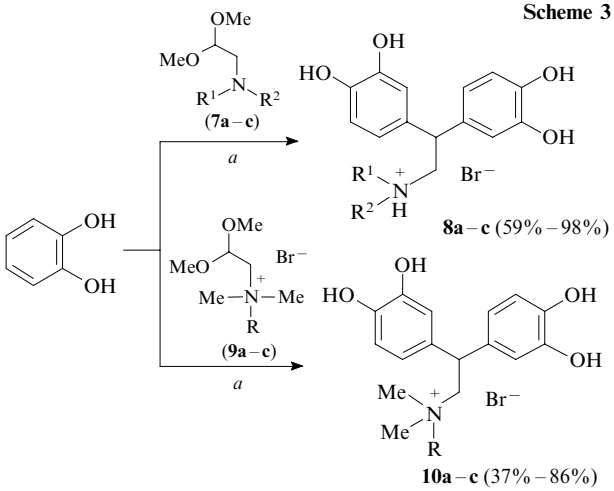
Scheme 1



Scheme 2



Scheme 3

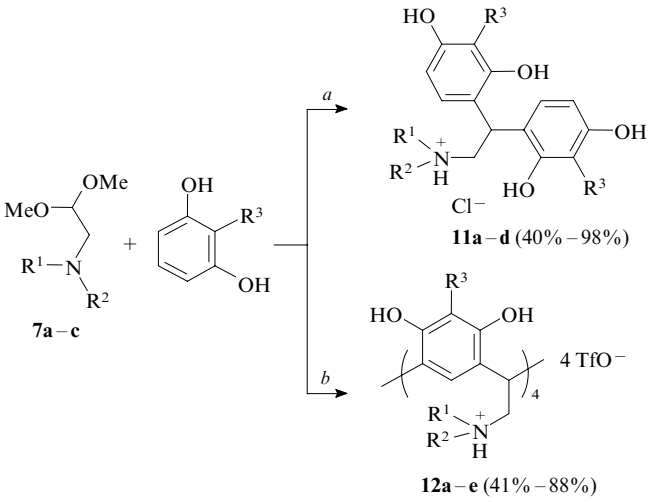


(*a*) HBr, H_2O, EtOH, Δ, 5 h; **7**, **8**: R^1 = H: R^2 = H (**a**), Me (**b**); R^1 = R^2 = Me (**c**); **9**, **10**: R = Me (**a**), Bu^n (**b**), n-$C_{10}H_{21}$ (**c**)

product yield from 86% for compound **10a** to 37% for polyphenol **10c**.

The reactions of other polyhydric phenols, in particular, resorcinol and 2-methylresorcinol, with acetals **7a–c** in aqueous ethanol in the presence of hydrochloric acid also afford diarylmethane derivatives **11a–d**.[15–17] In this case, unlike the pyrocatechol reaction, the increase in the number of N-substituents causes a significant increase in the product yield from 40% in the case of polyphenol **11a** to 98% in the case of polyphenol **11b**. It is notable that this reaction in anhydrous dioxane with trifluoromethanesulfonic acid as a catalyst results in the formation of macrocyclic compounds — calix[4]resorcinols **12a–e** modified with amino groups (Scheme 4).[15,17,18] Macrocycles **12** were formed in yields between 80% and 88%, except for compound **12c**, the yield of which was 41%.

Scheme 4



(*a*) HCl, H_2O, EtOH, Δ, 4 h; (*b*) TfOH, dioxane, Δ, 4 h;
11, **12**: R^3 = Me: R^1 = R^2 = H (**a**), Me (**b**); R^2 = Me: R^1 = R^3 = H (**c**); R^1 = H, R^3 = Me (**d**); R^1R^2 N is phthalimido, R^3 = H (**12e**)

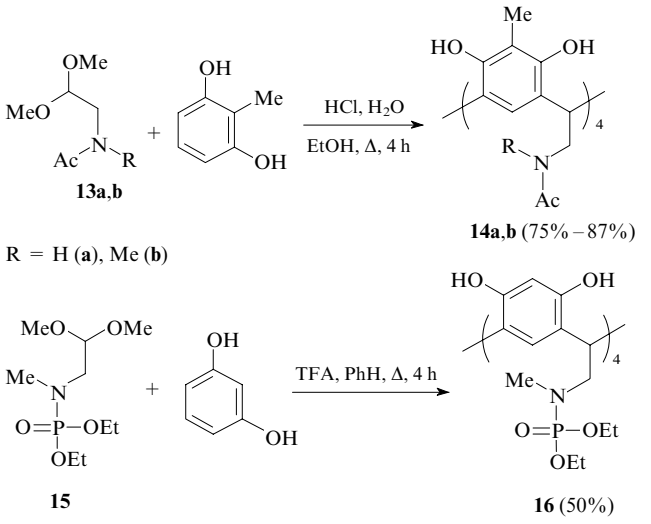
The same authors described the preparation of calix[4]-resorcinols modified with amide and phosphamide groups. It is interesting that the introduction of electron-withdrawing substituent to the nitrogen atom enabled convertion of acetals **13a,b** to macrocyclic compound **14a**,**b** in aqueous ethanol using hydrochloric acid as a catalyst (Scheme 5).[16] However, it should be noted that in the case of acetal **15** containing a phosphamide moiety, the reaction was followed by hydrolysis of the P–N bond, so target compound **16** could be prepared only with trifluoroacetic acid as a catalyst in anhydrous benzene.

Increasing the spacer length between the acetal and amine moieties also promotes the formation of macrocyclic compounds. 3-(Diethylamino)propanal diethylacetal (**17**) reacts with 2-methylresorcinol to give calix[4]resorcinol **18** (Scheme 6).[19]

In the case of reaction between 2-methylresorcinol and compounds **19a–c**, which contain four acetal groups rigidly attached to the calixarene matrix, calix[4]resorcinols **20a–c** with four diarylmethane moieties were obtained (Scheme 7).[20,21]

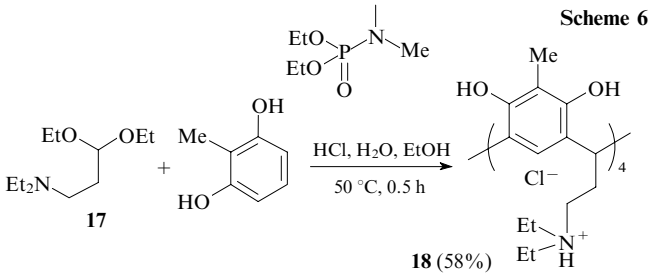
The reaction of 2-methylresorcinol with compounds **21a–c** resulting in calix[4]resorcinols **22a–c** has been described (Scheme 8).[20,22] In this case, the authors were able to introduce only two diarylmethane moieties to the

Scheme 5



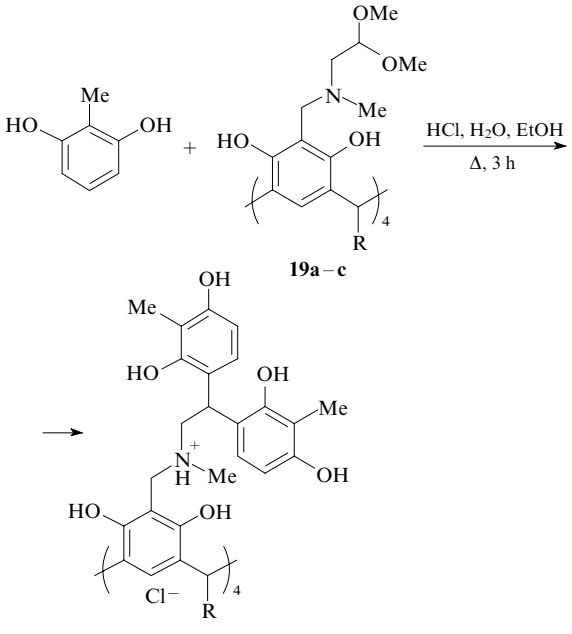
TFA is trifluoroacetic acid

Scheme 6



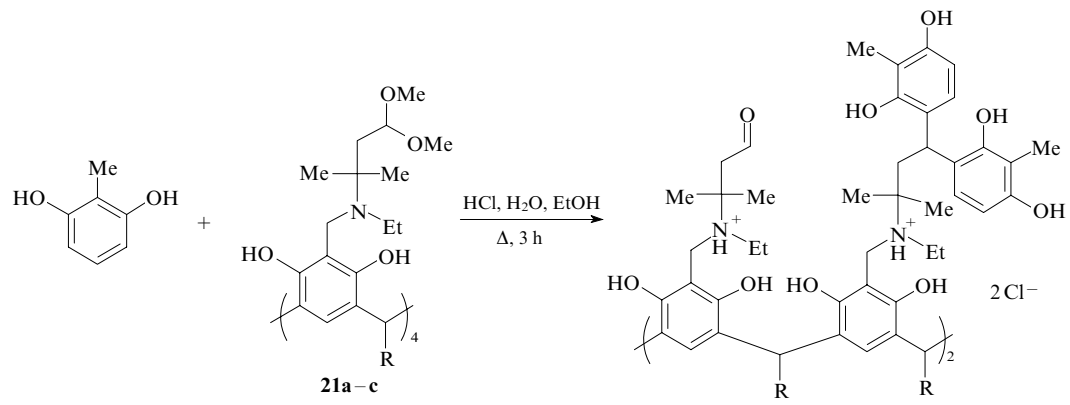
calixarene molecule, which is apparently explained by steric hindrance generated by methyl groups. The increase in the alkyl substituent length at the lower rim decreases the

Scheme 7



R = Me (**a**), Pr^n (**b**), n-C_5H_{11} (**c**)

Scheme 8



21a–c

22a–c (48%–78%)

R = Me (**a**), Pr^n (**b**), n-C_5H_{11} (**c**)

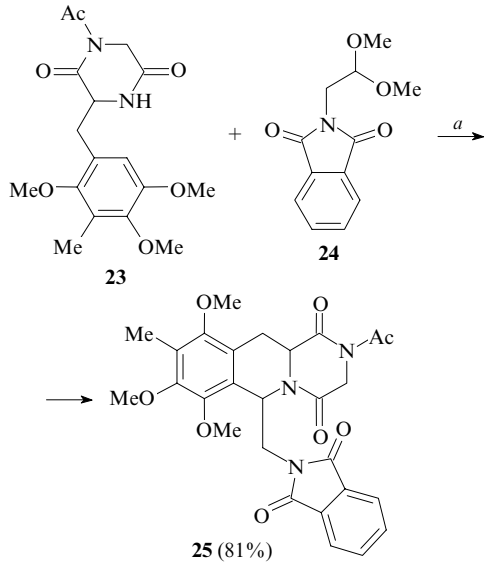
product yield, which equals 48% in the case of calixarene **22c**.

II.2. Synthesis of isoquinoline and isochroman derivatives (Pictet–Spengler reaction)

The Pictet–Spengler reaction (the reaction of aldehydes and their acetals with β-phenylethylamine derivatives) is described in many papers and is generally used for isoquinoline and isochroman synthesis.[23–26] However, examples of introduction of nitrogen-containing acetals as the carbonyl components in this reaction, which are included in the present review, are few in number.

For example, treatment of 2,5-diketopiperazine **23** with trimethylchlorosilane (TMSCl) followed by reaction with phthalimidoacetal **24** in the presence of trimethylsilyl triflate furnishes phthalascidin analogue — compound **25** possessing antiproliferative properties (Scheme 9).[27]

Scheme 9



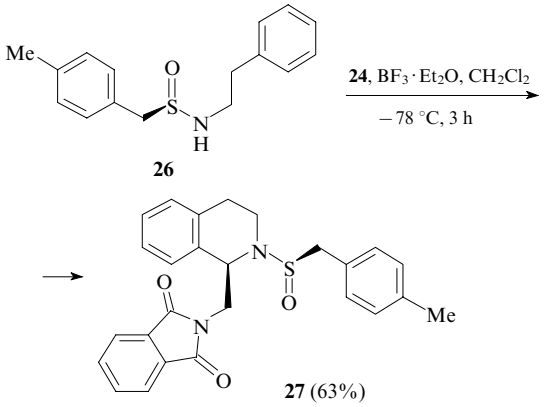
23 **24**

25 (81%)

(*a*) 1) TMSCl, Et_3N, CH_2Cl_2, rt, 2 h; 2) TMSOTf (5 equiv.), rt, 12 h

The condensation of the same acetal **24** with chiral sulfonamide **26** in the presence of boron trifluoride etherate produces tetrahydroisoquinoline **27** — an intermediate in the synthesis of the drug praziquantel (Scheme 10).[28]

Scheme 10

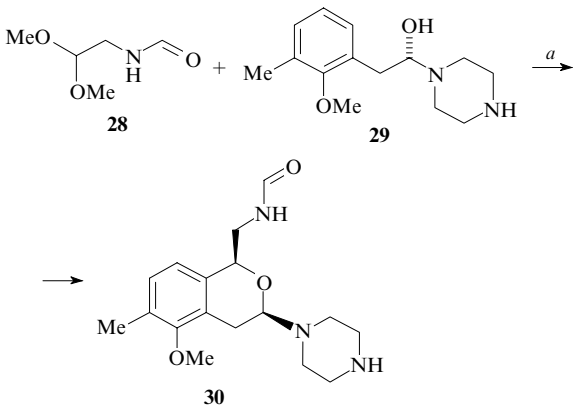


26

27 (63%)

It is also worth mentioning that the reaction of *N*-(2,2-dimethoxyethyl)formamide (**28**) with (*S*)-2-(3-methyl-2-methoxyphenyl)-1-(piperazino)ethanol (**29**) results in stereoselective synthesis of substituted isochroman **30** (Scheme 11).[29]

Scheme 11



28 **29**

30

(*a*) $BF_3 \cdot Et_2O$, CH_2Cl_2, Δ, 3 h

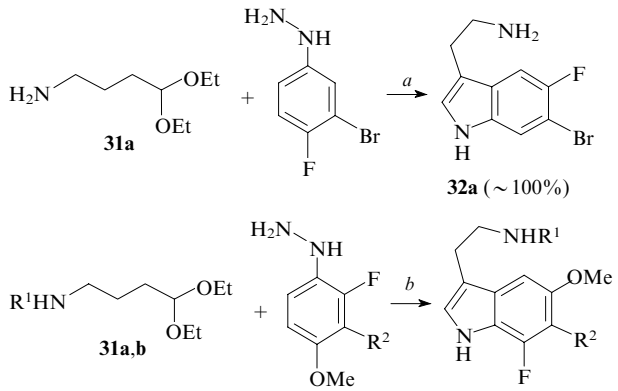
II.3. Synthesis of tryptamine derivatives (Fischer indole synthesis)

The synthesis of tryptamine derivatives described in this Section is a version of the well-known and comprehensively studied Fischer indole synthesis.[30–32] The only difference between these reactions and the conventional procedure is

the use of substituted 4,4-diethoxybutylamines (γ-aminoacetals), *e.g.*, compounds **31a**,**b**, as carbonyl components. It should be noted that no examples of introduction of other nitrogen-containing acetals into this reaction are available from the literature.

The compounds used most often as reactants are phenylhydrazines with a free amino group, the aromatic ring of which bears halogen atoms [33, 34] and methoxy groups (Scheme 12).[34] It is notable that the synthesis of compound **32a** was conducted without catalysts.[33] Nevertheless, the yield of the target compound was ~100%. Tryptamine derivatives **32b**–**d** were obtained in significantly lower yields, which is probably explained by mild conditions of the reaction.

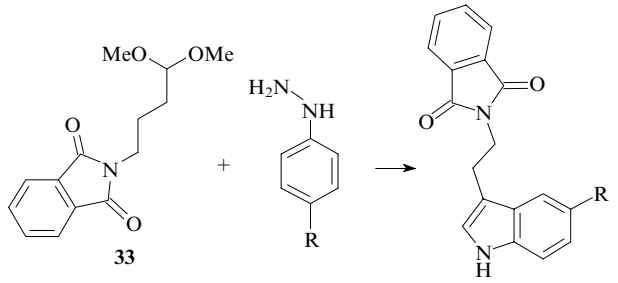
Scheme 12



(*a*) 1) 180 °C, 2.5 h; 2) MeOH, rt, 18 h; (*b*) HCl, EtOH, 40 °C, 12 h;
31: R^1 = H (**a**), HC(O) (**b**); **32**: R^1 = R^2 = H (**b**);
R^2 = F: R^1 = H (**c**), HC(O) (**d**)

Acetal **33,** in which the amino group is protected by a phthalamide moiety, was also introduced in the above-mentioned reaction.[35] The authors used a wide range of phenylhydrazines containing both electron-donating and electron-withdrawing substituents. As a result, the protected tryptamines **34a**–**j** were synthesized. It should be noted that the preparation of compound **34i** is the only example of this reaction involving a substituted phenol (Scheme 13).

Scheme 13

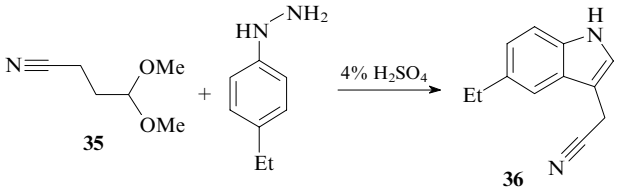


R = H (**a**), Me (**b**), Et (**c**), Pr^i (**d**), Ph (**e**), F (**f**), Cl (**g**), Br (**h**), HO (**i**), F_3CO (**j**)

A group of French authors [36] used 4,4-dimethoxybutanonitrile (**35**) as a carbonyl component and prepared indole derivative **36** (Scheme 14).

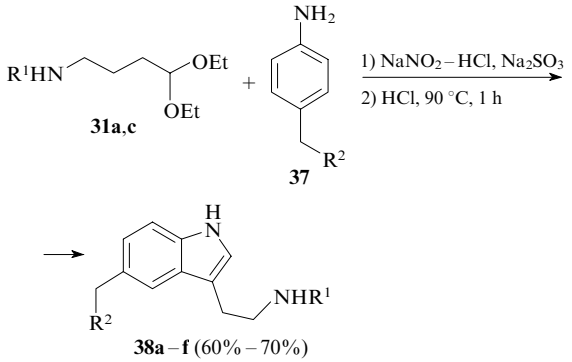
Noteworthy is also the use of aniline derivatives **37** in the reaction with acetals **31a**,**c** [R^1 = H (**a**), Me (**c**)]. Compounds **37** were converted *in situ* to respective arylhydrazines by diazotization followed by reduction with sodium

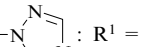
Scheme 14



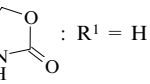
sulfite (Scheme 15).[37] The yields of tryptamine derivatives **38a**–**f** were not higher than 70%.

Scheme 15



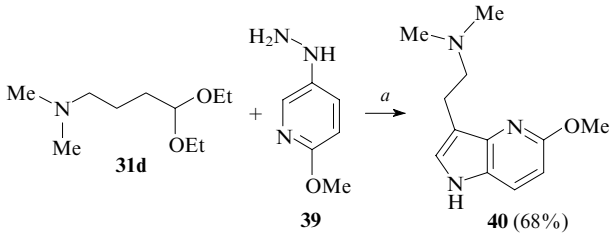
38: R^2 =  : R^1 = H (**a**), Me (**b**);

R^2 = SO_2NHMe: R^1 = H (**c**), Me (**d**);

R^2 =  : R^1 = H (**e**), Me (**f**)

Also worth noting is the reaction of acetal **31d** with pyridylhydrazine **39** described in a patent [38] of American authors; the reaction gave pyrrolopyridine derivative **40** in a good yield (Scheme 16).

Scheme 16



(*a*) H_2SO_4, H_2O, Δ, 2 h

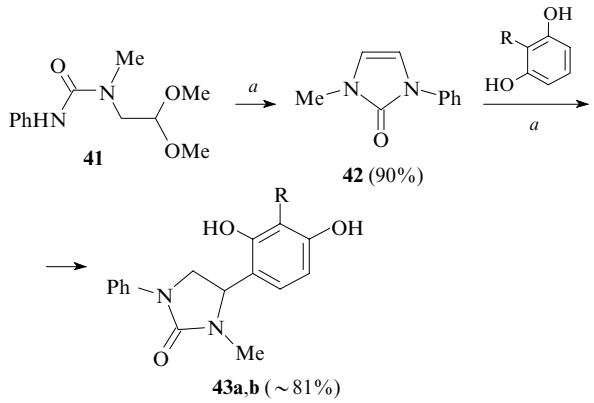
II.4. Synthesis of pyrrolidine and imidazole derivatives

Unlike the reactions described above, which are purely intermolecular, the reactions of aromatic nucleophiles with acetals containing the urea moiety are accompanied by intramolecular transformations. Depending on the number of methylene units between the acetal and urea groups, the reaction may result in aryl-substituted imidazolidin-2-ones or 2-arylpyrrolidines. The key stage in both cases is intramolecular cyclization of initial acetal with participation of the amide nitrogen atom.

Thus cyclization of 1-(2,2-dimethoxyethyl)-1-methyl-3-phenylurea (**41**) in the presence of trifluoroacetic acid for 4 h and subsequent reaction of the resulting imidazolinone **42** with 2-methylresorcinol or pyrogallol (30 h) resulted in

the synthesis of aryl-substituted imidazolidin-2-ones **43a**,**b** (Scheme 17).[39–41] Note the high regioselectivity of the reaction: only one of the two possible regioisomers is obtained in both cases. The authors also demonstrated the possibility of conducting the reaction without isolation of the intermediate imidazolinone.

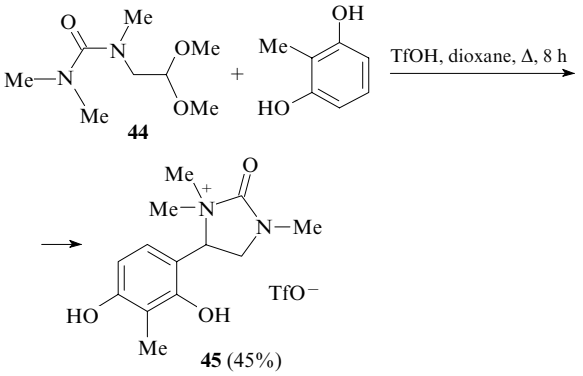
Scheme 17



(*a*) TFA, $CHCl_3$, 65 °C, 30 h; R = Me (**a**), HO (**b**)

The reaction between 1-(2,2-dimethoxyethyl)-1,3,3-trimethylurea (**44**) and 2-methylresorcinol produces imidazolin-2-one **45** containing the endocyclic onium nitrogen atom (Scheme 18).[42]

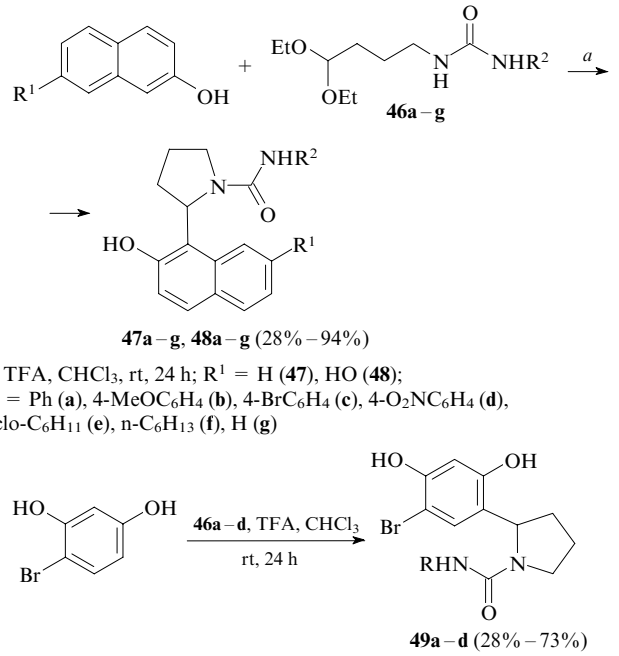
Scheme 18



The intramolecular cyclization of (4,4-diethoxybutyl)-ureas **46a**–**g** in the presence of 2-naphthol and naphthalene-2,7-diol catalyzed by trifluoroacetic acid results in 2-(1-naphthyl)pyrrolidines **47a**–**g** and **48 a**–**g** (Scheme 19).[43–46] It should be noted that despite the presence of two chemically reactive positions in the naphthalene-2,7-diol molecule, no 1,8-disubstituted products were detected. A similar reaction between acetals **46a**–**d** and 4-bromoresorcinol results in the production of compounds **49a**–**d** (see Scheme 19).[47] The yields of target products **47**–**49** were 62%–94%, the presence of aryl substituent at the nitrogen atom being favourable for higher yields. Exceptions are pyrrolidine derivatives **47d**, **48d** and **49d** with the electron-withdrawing nitro group in the aromatic moiety, the yields of which do not exceed 28%.

The reactions of acetals **46a**–**i** with resorcinol, 2-methylresorcinol and pyrogallol,[46,48,49] as well as with hydroquinone[47] resulted in the synthesis of bis(pyrrolidine-1-carboxamides) **50a**,**e**–**i**; **51a**,**e**–**i**; **52a**,**e**–**i** and compounds **53a**–**d** as a diastereoisomer mixture (Scheme 20). The yield of compounds **50**–**53** varies over a wide range depending on

Scheme 19

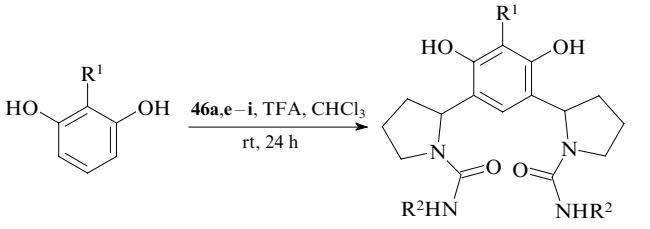


(*a*) TFA, $CHCl_3$, rt, 24 h; R^1 = H (**47**), HO (**48**);
R^2 = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-BrC_6H_4 (**c**), 4-$O_2NC_6H_4$ (**d**), cyclo-C_6H_{11} (**e**), n-C_6H_{13} (**f**), H (**g**)

R = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-BrC_6H_4 (**c**), 4-$O_2NC_6H_4$ (**d**)

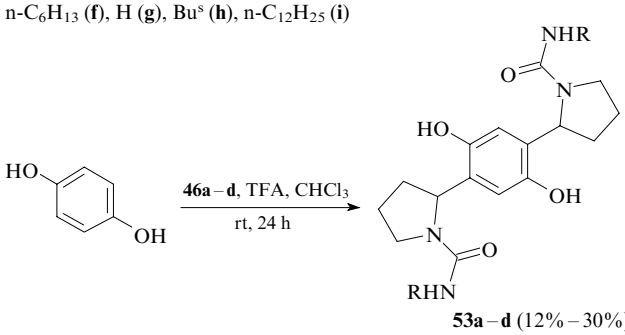
the nature of substituents at the nitrogen atom and the structure of phenol used. The highest yields (51%–74%) were obtained for compounds **50a**, **51a** and **52a** containing the phenyl group at the nitrogen atom. The replacement of the phenyl moiety by an alkyl one leads, most often, to decrease in the yields of the target compounds to 16%–35%. The yield of bis(pyrrolidine-1-carboxamides) **53 i**s also below 30%, which is probably explained by the lower chemical reactivity of hydroquinone as compared with resorcinol or pyrogallol and by its susceptibility to oxidation.

Scheme 20



50a,**e**–**i**; **51a**,**e**–**i**; **52a**,**e**–**i** (16%–74%)

R^1 = H (**50**), Me (**51**), HO (**52**); R^2 = Ph (**a**), cyclo-C_6H_{11} (**e**), n-C_6H_{13} (**f**), H (**g**), Bu^s (**h**), n-$C_{12}H_{25}$ (**i**)

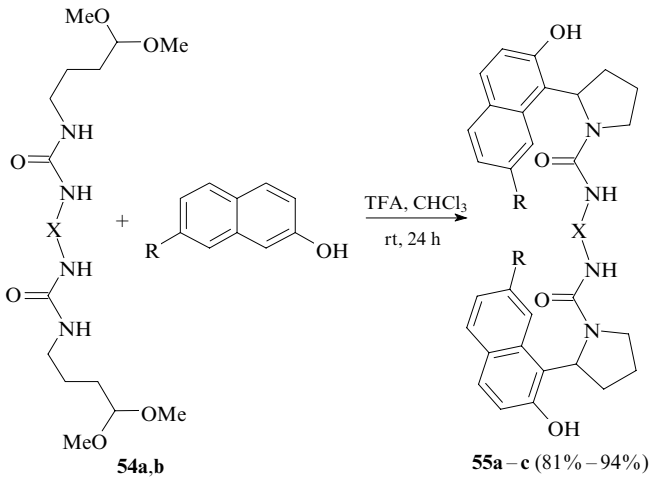


53a–**d** (12%–30%)

R = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-BrC_6H_4 (**c**), 4-$O_2NC_6H_4$ (**d**)

The reactions of diacetals **54a**,**b** containing two urea moieties with 2-naphthol and naphthalene-2,7-diol have been described (Scheme 21).[43,45] The reaction products are compounds **55a**–**c**, also formed as diastereoisomer mixtures. Note that in this case, the reaction also involves only one position of naphthalene-2,7-diol.

Scheme 21

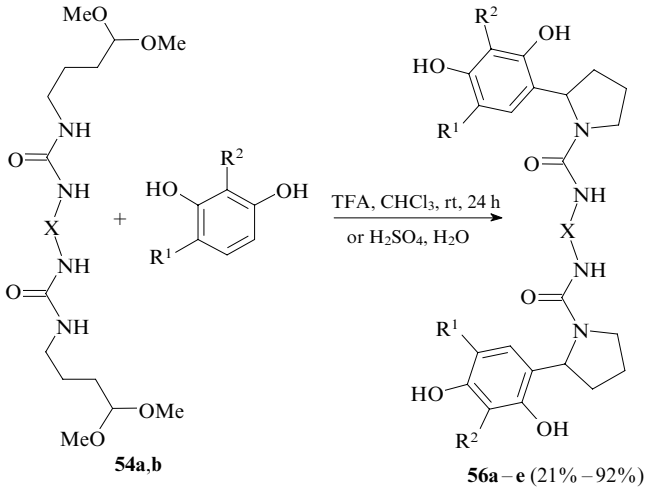


54a,**b** **55a**–**c** (81%–94%)

X = $(CH_2)_6$ (**54a**, **55a**), *p*-C_6H_4 (**54b**, **55b**, **55c**);
R = H (**55a**, **55b**), HO (**55c**)

A similar reaction takes place between acetals **54a**,**b** and 4-bromoresorcinol, resulting in the production of compounds **56a**,**b**.[47] The reaction between acetals **54a**,**b** and phenols having two chemically reactive positions, in particular, resorcinol, 2-methylresorcinol and pyrogallol, under the same conditions resulted in the formation of complex product mixtures, apparently of the polymer structure. The authors succeeded in obtaining target compounds **56c**–**e** by conducting the reaction in an aqueous solution in the presence of sulfuric acid (Scheme 22).[50] The yields of products **56** were 70%–92% except for compound **56a**, the yield of which was only 21%.

Scheme 22

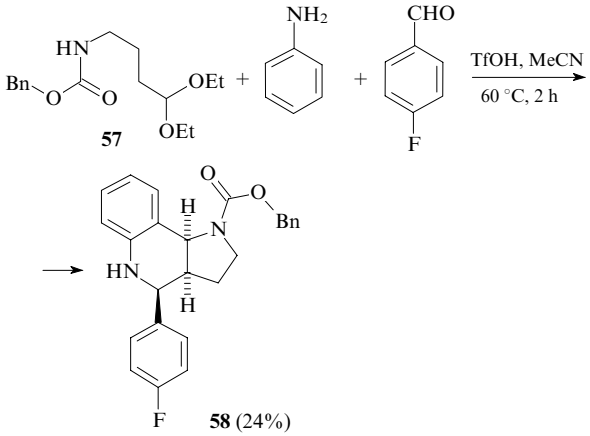


54a,**b** **56a**–**e** (21%–92%)

56: R^1 = Br, R^2 = H: X = $(CH_2)_6$ (**a**), *p*-C_6H_4 (**b**);
X = $(CH_2)_6$, R^1 = H: R^2 = H (**c**), Me (**d**), HO (**e**)

The three-component reaction involving benzyl(4,4-diethoxybutyl)carbamate (**57**), 4-fluorobenzaldehyde and aniline giving fused pyrrolidinoquinoline **58** pertains to the same type of reactions of acetals containing the urea moiety.[51] Probably, the first step of the reaction is the formation of the Schiff base as a result of aniline and 4-fluorobenzaldehyde condensation (Scheme 23).

Scheme 23



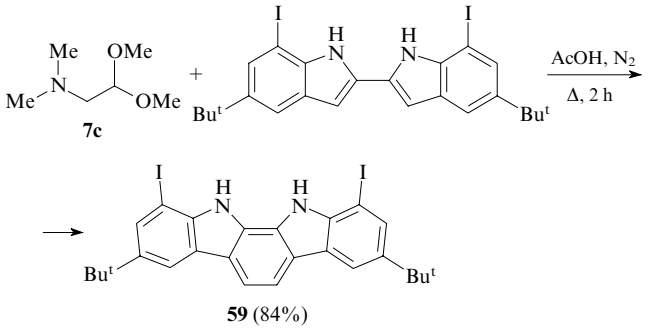
57 **58** (24%)

II.5. Reactions of nitrogen-containing acetals with indole derivatives

A number of papers are devoted to the reactions between aminoacetaldehyde acetals and indole derivatives that cannot be classified into any specific group within the classification adopted in the present review.

For instance, an original synthesis of substituted indolocarbazole **59** *via* the reaction between *N*,*N*-dimethylaminoacetaldehyde dimethylacetal (**7c**) and 2,2′-bisindole derivatives in an acid medium has been described[52,53] (Scheme 24). It of interest that this is the only example of reaction involving the elimination of dimethylamino group in the acetal **7c**.

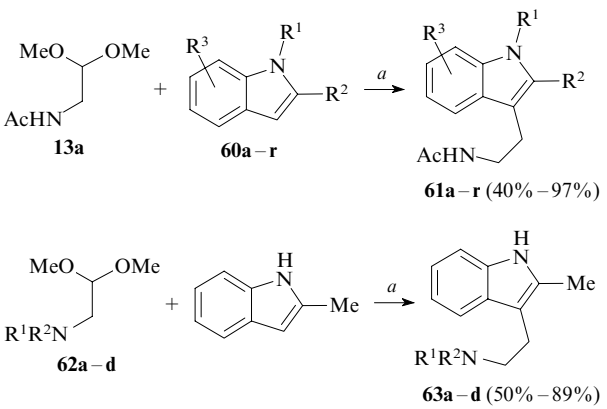
Scheme 24



7c **59** (84%)

Another research team[54] synthesized a wide range of tryptamine derivatives **61a**–**r** by reductive alkylation of substituted indoles **60a**–**r** with *N*-(2,2-dimethoxyethyl)acetamide (**13a**) in the presence of trifluoroacetic acid and triethylsilane (Scheme 25). The average yields of products **61** were 60%–87%. The presence of substituents at the nitrogen atom usually causes the yield to decrease: in the case of compounds **61m**,**p**–**r**, the yields are 40%–56%. The highest yields were obtained for tryptamines **61a**,**f**, namely, 90% and 97%, respectively. Similar products are formed when acetals **62a**–**d** are used (see Scheme 25). The yield of compounds **63** increases with increasing electron-withdrawing ability of the N-substituent from 50% for the tosyl moiety (compound **63b**) to 89% for the trifluoroacetyl group (compound **63c**).

Scheme 25



(*a*) TFA, Et_3SiH, CH_2Cl_2, Δ, 3 h;
61: $R^1 = R^3 = H$: $R^2 = Me$ (**a**), Bu^n (**b**), Bu^t (**c**), cyclo-C_5H_9 (**d**), Bn (**e**), Ph (**f**), $AcNH(CH_2)_2$ (**e**); $R^1 = H$, $R^2 = Me$: $R^3 = 5$-Me (**h**), 5-Cl (**i**), 5-(4,4,5,5-tetramethyldioxaborolan-2-yl) (**j**), 5-MeO (**k**), 6-MeO (**l**); $R^1 = Me$, $R^3 = H$: $R^2 = H$ (**m**), Me (**n**); $R^1 = Bn$, $R^2 = H$: $R^3 = H$ (**o**), 5-MeO (**p**); $R^2 = R^3 = H$: $R^1 = 4$-$MeOC_6H_4$ (**q**), All (**r**); All is allyl;
62, **63**: $R^1 = H$: $R^2 = BnO_2C$ (**a**), Ts (**b**), $F_3CC(O)$ (**c**);
R^1R^2N is phthalimido (**d**); Ts is *p*-toluenesulfonyl (tosyl)

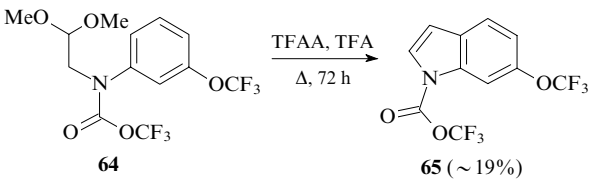
III. Intramolecular reactions involving nitrogen-containing acetals

The intramolecular reactions involving the acetal group occupy a prominent place in the chemistry of nitrogen-containing acetals. Therefore, it is not surprising that the most mentions of the nitrogen-containing acetal reactions with aromatic nucleophiles in the scientific literature relate exactly to this type of reactions. The nitrogen-containing moiety is most often represented by the amide group and may either participate in the reaction or remain unchanged. Since the aromatic nucleophile is a part of the acetal molecule, the products of these transformations are usually heterocycles annulated with an aromatic moiety, most often, benzene ring.

III.1. Indole synthesis

The successful indole synthesis through the intramolecular cyclization of 2-(arylamino)acetaldehyde acetals was first performed [55] in 1971 and is quite commonly used nowadays. In this review, we will consider only examples of reactions described in the last 10 years. It should be noted that the range of substituents in the acetal aromatic moiety is extremely wide and includes both electron-donating groups (alkyl, alkoxy and amino groups) and electron-withdrawing groups (halogen atoms and carbonyl and nitro groups), as well as their combinations. The presence of electron-withdrawing substituent at the nitrogen atom is usually needed to prevent the polymerization of the end product, indole. This substituent is usually represented by the trifluoroacetyl group. Cyclization of acetal **64** into indole **65** may be an example of such reaction (Scheme 26).[56, 57]

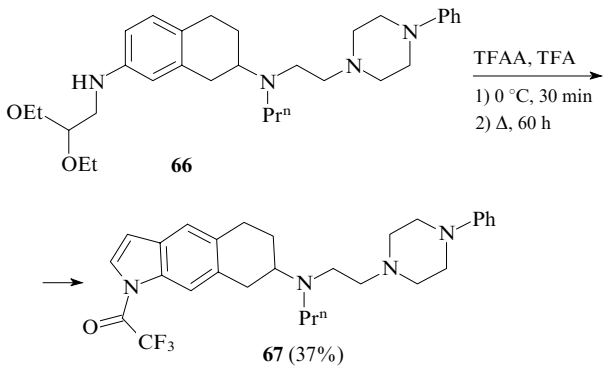
Scheme 26



TFAA is trifluoroacetic anhydride

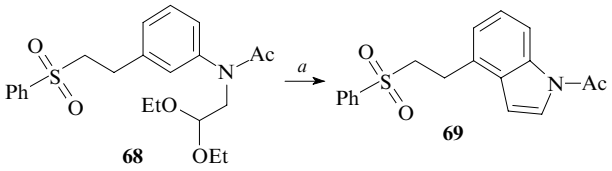
The reaction can also be performed for an acetal that does not contain any N-substituents, but a mixture of trifluoroacetic acid and trifluoroacetic anhydride should then be used as a solvent.[58] It is obvious that in this case, the *in situ* acylation of the nitrogen atom takes place, as, for example, in the case of conversion of compound **66** to tetrahydrobenzindole derivative **67** (Scheme 27).

Scheme 27



In another study,[59] the acetyl group was used for nitrogen atom protection and sulfuric acid served as the catalyst of cyclization of acetal **68** into indole **69** (Scheme 28).

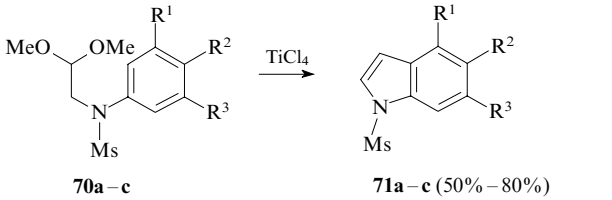
Scheme 28



(*a*) H_2SO_4, CH_2Cl_2, 75 °C

Several publications [60–62] describe the cyclization of acetals containing the methylsulfonyl (mesyl, Ms) substituent at the nitrogen atom (*e.g.*, compounds **70a–c**) (Scheme 29). The reaction proceeds under the action of Lewis acids, in particular, titanium tetrachloride, and affords indoles **71a–c**. This reaction was also used to prepare isotopicaly labelled indole.[60] The increase in the number of electron-donating substituents in the aromatic ring of the substrate apparently promotes the reaction. Thus 6-bromo-1-(methanesulfonyl)-5-methylindole (**71b**) was obtained in 50% yield. In the presence of additional methyl group (compound **71c**), the yield of the reaction product

Scheme 29

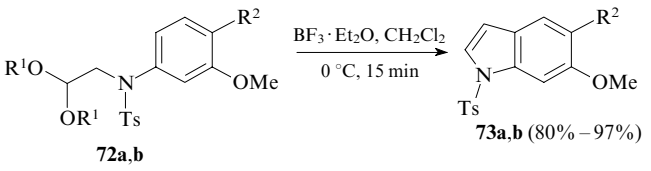


$R^1 = H$: $R^2 = R^3 = H$ (**a**), $R^2 = Me$, $R^3 = Br$ (**b**);
$R^1 = R^3 = Me$, $R^2 = Br$ (**c**)

increased up to 80%. The yield of the compound **71a** devoid of substituents in the benzene ring was 72%.

The synthesis of indoles with methoxy substituent in the benzene ring has been reported.[63–66] The researchers used the tosyl group as a protection for the nitrogen atom in compounds **72a**,**b** and boron trifluoride etherate as a catalyst. The products **73a**,**b** were formed in relatively high yields (Scheme 30).

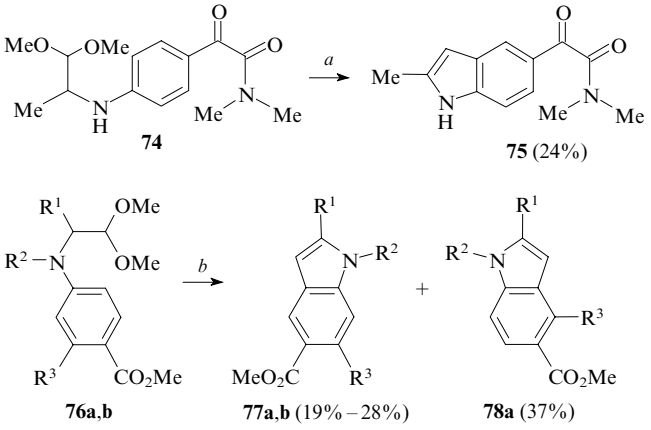
Scheme 30



R^1 = Et, R^2 = H (**a**); R^1 = Me, R^2 = MeO (**b**)

The cyclizations of N-unsubstituted and N-alkyl-substituted acetals have been reported [67, 68] (Scheme 31). In these cases, aluminium chloride served as the catalyst. For example, the cyclization of acetal **74** resulted in the synthesis of indole **75** containing 1,2-dicarbonyl substituent.[67] Note that when the chlorine atom is present in the aromatic ring of acetal **76a** in position 3, the reaction affords a mixture of isomeric indoles **77a** and **78a** in ~1 : 2 ratio in a total yield of 56%. At the same time, in the case of acetal **76b** with the methoxy group in the same position, only one regioisomer **77b** is formed in 28% yield.[68]

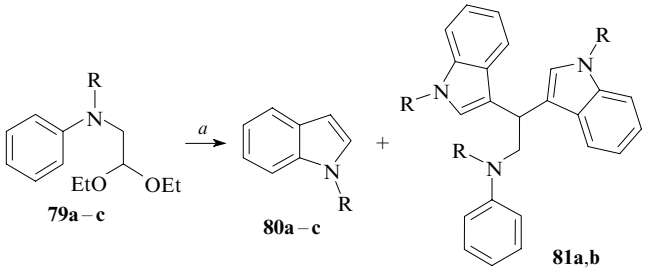
Scheme 31



(*a*) $AlCl_3$, CH_2Cl_2, 60 °C; (*b*) $AlCl_3$, $CHCl_3$, rt, 12 h;
R^1 = Me, R^2 = H, R^3 = Cl (**a**); R^1 = H, R^2 = Me, R^3 = MeO (**b**)

Unusual results were obtained in a study of intramolecular cyclization of acetals **79a**–**c** using molecular sieves with impregnated propanesulfonic acid (MCM-41-SO_3H) as a catalyst.[69] In addition to the target indoles **80a**–**c**, the reaction also gave bis(indolyl)methane derivatives **81a**,**b**, resulting from intramolecular reaction of indoles with initial acetals. It should also be noted that increasing the size of N-substituent decreases the proportion of compounds **81** in the mixture of reaction products. Thus in the case of acetal **79a** containing a methyl substituent at the nitrogen atom, the **80a** : **81a** ratio was 85 : 15 (82% yield) and for its isobutyl analogue, **80b** : **81b** = 90 : 10 (87% yield). In the case of diphenylmethyl substituent at the nitrogen atom, no dimer was formed (the yield of product **80c** was 22%). The authors suggest that bulky substituents prevent the indole molecule from penetration into the molecular sieve pores, thus inhibiting the efficient catalysis of the intermolecular reaction (Scheme 32).

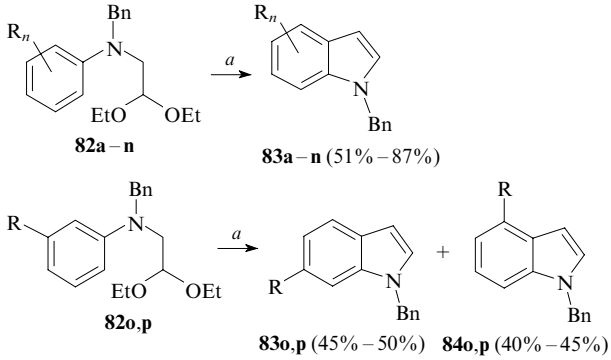
Scheme 32



(*a*) MCM-41-SO_3H, PhMe, Δ, 1–6 h; R = Me (**a**), Bu^i (**b**), Ph_2CH (**c**)

Subsequently, the same authors prepared a wide variety of indole derivatives by intramolecular cyclization of acetals **82a**–**n** with a benzyl substituent at the nitrogen atom (Scheme 33; positions of substituents in the initial acetal are indicated). The yields of compounds **83a**–**h**,**l**,**m** were 75%–97%, while the yields of **83i**–**k**,**n** were only 51%–68%. Thus, it is possible to conclude that the presence of strong electron-withdrawing substituents in the acetal aromatic moiety causes a decrease in the target indole yield except for fluorine-containing indoles **83g**,**h,** the yields of which were 93% and 80%, respectively. Note that in the case of acetals **82o**,**p,** cyclization follows two different pathways, which results in a mixture of regioisomeric indoles **83o**,**p** and **84o**,**p** in approximately equal amounts.

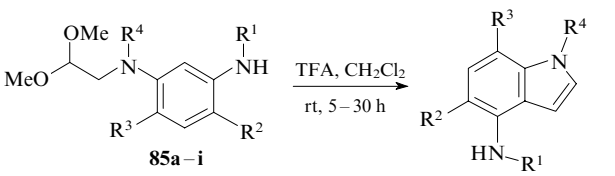
Scheme 33



(*a*) MCM-41-SO_3H, PhMe, Δ, 1–6 h; R_n = H (**a**), 4-OMe (**b**), 4-SMe (**c**), 4-Me (**d**), 4-Cl (**e**), 4-Br (**f**), 4-F (**g**), 4-CF_3 (**h**), 4-CN (**i**), 4-C(O)NMe_2 (**j**), 4-NO_2 (**k**), 3,5-Me_2 (**l**), 2-Me (**m**), 2-Cl (**n**), 3-Me (**o**), 3-Cl (**p**)

Special mention should be made of the paper [70] describing the cyclization of nitrophenyl-substituted acetals **85a**–**i** catalyzed by trifluoroacetic acid (Scheme 34). An important issue is that the reaction proceeds under mild conditions with a deactivated aromatic ring and no protection of the amino group in the initial acetal is required. The yield of products **86** is relatively high in most cases: 71%–94% for compounds **86a**,**b**,**d**,**f**,**h**, and 50%–64% for compounds **86c**,**g**,**i**. The only exception is indole **86e** formed in a yield of only 25% after prolonged refluxing of the reaction mixture.

Scheme 34

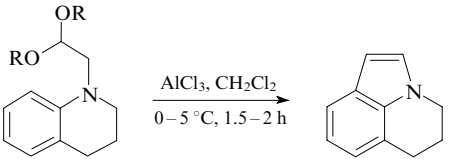


85a–i **86a–i** (25%–94%)

$R^2 = R^3 = O_2N$: $R^1 = Pr^i$, $R^4 = H$ (**a**); $R^1 = Pr^i$, $R^4 = Et$ (**b**); $R^1 = Pr^i$, $R^4 = 4\text{-}ClC_6H_4$ (**c**); $R^1 = R^4 = H$ (**d**); $R^1 = 4\text{-}ClC_6H_4$, $R^4 = H$ (**e**); $R^1 = MeO_2CCH(Me)$, $R^4 = H$ (**f**); $R^1 = Ph$, $R^2 = O_2N$, $R^3 = R^4 = H$ (**g**); $R^1 = cyclo\text{-}C_6H_{11}$, $R^2 = R^4 = H$, $R^3 = O_2N$ (**h**); $R^1 = R^4 = H$, $R^2 = Cl$, $R^3 = O_2N$ (**i**)

Of special note is the cyclization of acetals **87a**,**b** in which the nitrogen atom is incorporated into the saturated ring.[71] In this case, the reaction results in the formation of fused polycyclic compound **88** (Scheme 35).

Scheme 35

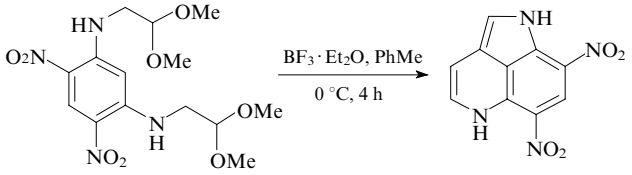


87a,**b** **88** (36%–43%)

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

Another example of synthesis of this type of compound is the cyclization of *m*-phenylenediamine derivative **89** containing two acetal moieties to give polycyclic compound **90** (Scheme 36).[72]

Scheme 36



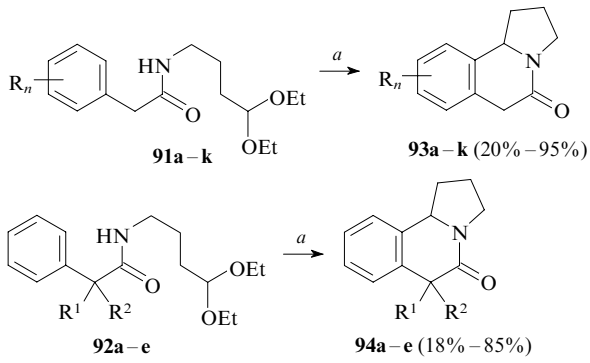
89 **90** (35%)

III.2. Synthesis of pyrrolidine derivatives. Cyclization of carboxylic acid amides

The examples of *N*-(4,4-diethoxybutyl)amide cyclization described in the present Section are much similar to the reactions of *N*-(4,4-diethoxybutyl)ureas (see Section II.4). In both cases, pyrrolidine ring is formed *via* intramolecular cyclization with participation of the amide nitrogen atom followed by reaction of the intermediate product with aromatic nucleophile. The difference is that in the case of *N*-(4,4-diethoxybutyl)amides, the nucleophile is incorporated into the acetal molecule and, therefore, the reaction furnishes fused heterocyclic compounds.

In a paper of UK researchers,[73] the intramolecular cyclization of acetals **91a–k** and **92a–e**, resulting in the synthesis of tetrahydropyrroloisoquinoline derivatives **93a–k** and **94a–e**, is described. Attention is attracted by fairly drastic reaction conditions, in particular, the reaction requires refluxing in the presence of trifluoroacetic acid. The yields of compounds **93a**,**b**,**g–k** are relatively high, namely, 71%–95%. With acetals **91c–f** containing electron-withdrawing substituents in the aromatic ring, the yields of tetrahydropyrroloisoquinolines **93c–f** are reduced to 20%–45%. In the case of acetals **92**, the yields of the target products **94** are relatively low, 18%–44%, except for compound **94b**, which is formed in a yield of 85%.

Scheme 37



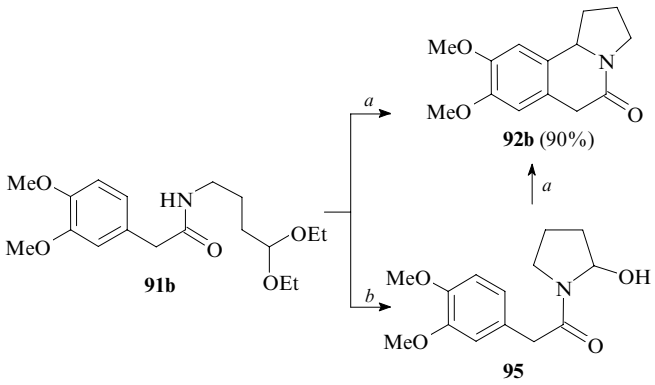
91a–k **93a–k** (20%–95%)

92a–e **94a–e** (18%–85%)

(*a*) TfOH, $CHCl_3$, Δ; **91**, **93**: R_n = H (**a**), 3,4-$(MeO)_2$ (**b**), 4-Cl (**c**), 4-Br (**d**), 3-Br (**e**), 2-Br (**f**), 4-Me (**g**), 3-Me (**h**), 2-Me (**i**), 2,3-Ph_2 (**j**), 3,4-Ph_2 (**k**); **92**, **94**: $R^1 = R^2 = Me$ (**a**), Ph (**d**); R^2 = H: R^1 is phthalimido (**b**), Ph (**c**), Bn (**e**)

The intramolecular cyclization of acetal **91b** catalyzed by aluminium chloride has been reported.[74] In this case, the authors were able to isolate the intermediate 2-hydroxypyrrolidine **95** (Scheme 38).

Scheme 38

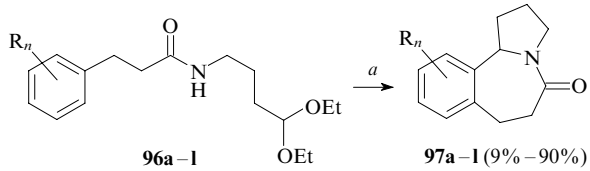


91b **95**

(*a*) $AlCl_3$, CH_2Cl_2, rt, 2 h; (*b*) 2 M HCl, Et_2O, rt, 0.5 h

In the study cited above,[73] acetals **96a–l** were converted to compounds **97a–l** with the tetrahydropyrrole ring annulated to the benzazepine moiety (Scheme 39). The yields of products were usually high — 75%–90%, except for those of benzazepines **97c**,**d**,**k**, which formed in 9%–15% yields.

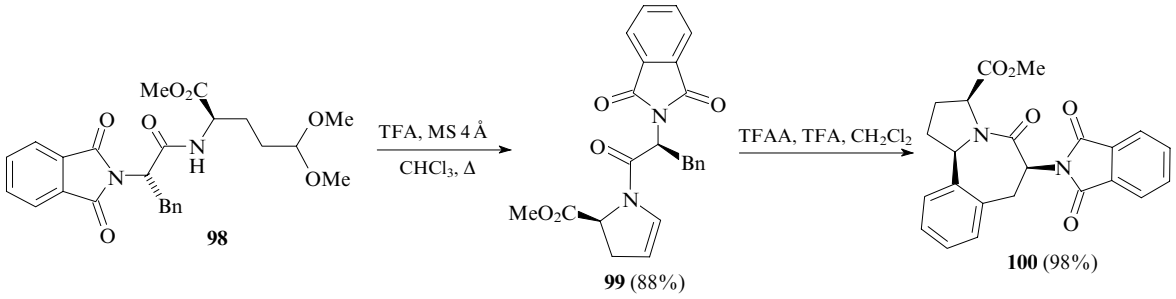
Scheme 39



96a–l **97a–l** (9%–90%)

(*a*) TfOH, $CHCl_3$, Δ; R_n = H (**a**), 2-MeO (**b**), 3-MeO (**c**), 4-MeO (**d**), 3,4-$(MeO)_2$ (**e**), 3,4,5-$(MeO)_3$ (**f**), 4-Me (**g**), 4-F (**h**), 3-Br (**i**), 4-Br (**j**), 3-Cl (**k**), 4-Cl (**l**)

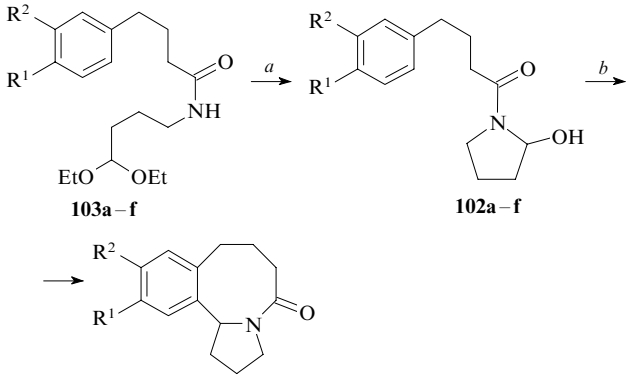
Scheme 40



Under the action of trifluoroacetic acid in the presence of molecular sieves (MS), acetal **98** is converted with high stereoselectivity to pyrroline derivative **99**, which then cyclizes to afford hydrogenated pyrrolobenzazepinone **100** (Scheme 40).[75]

The synthesis of hydrogenated pyrrolobenzazocinones **101a–f**, which also comprises two steps with isolation of intermediate 2-hydroxypyrrolidines **102a–f**, has been described.[76] Acetals **103a–f** were taken as the initial compounds. Note that tetrahydropyrrole ring closure requires milder conditions than the subsequent formation of the benzazocinone moiety (Scheme 41). Whereas halogen-substituted pyrrolobenzazocinones **103a**,**b**,**e** were formed in reasonable yields (55%–60%), the yield of compounds **103d**,**f** containing the methoxy group did not exceed 8%.

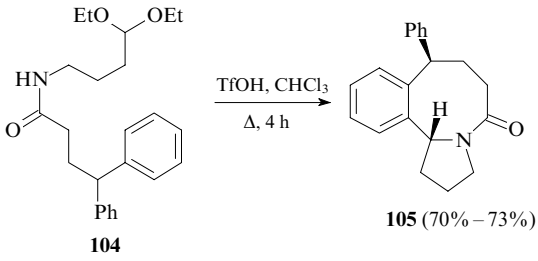
Scheme 41



(*a*) HCl, Me_2CO, rt, 0.5 h; (*b*) TfOH, $CHCl_3$, Δ, 1–21 h; R^2 = H: R^1 = Cl (**a**), Br (**b**), Ph (**c**), MeO (**d**); R^2 = Br: R^1 = H (**e**), MeO (**f**)

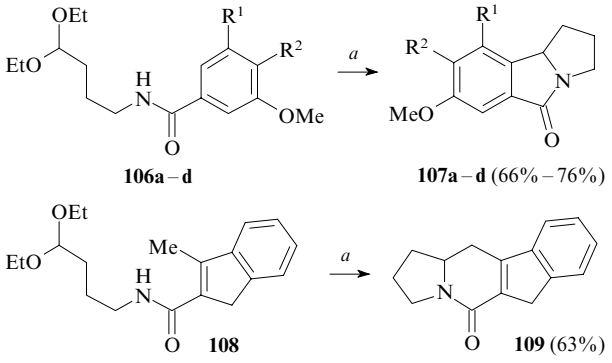
The same publication [76] presents an example of using acetal **104** in the stereoselective synthesis of pyrrolobenzazocinone **105**. Despite the fact that the authors did not use any asymmetric synthesis techniques, the ratio of diastereoisomers was 1 : 20 (Scheme 42).

Scheme 42



The intramolecular cyclization of *N*-(4,4-diethoxybutyl)-benzamides **106a–d** in the presence of trifluoromethanesulfonic acid resulted in tetrahydropyrroloisoquinoline derivatives **107a–d**.[77] Under the same conditions, *N*-(4,4-diethoxybutyl)amide of indene-2-carboxylic acid (**108**) cyclizes to afford indenoindolizine derivative **109** (Scheme 43). It should be noted that the authors used a large (25-fold) excess of the acid. Decrease in the acid quantity significantly reduced the product yield.

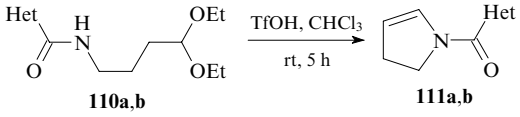
Scheme 43



(*a*) TfOH, $CHCl_3$, rt, 5 h; R^1 = R^2 = H (**a**), MeO (**b**); R^1 = H, R^2 = MeO (**c**); R^1 = MeO, R^2 = H (**d**)

Acetals **110a**,**b** containing thiophene or furan moiety form enamides **111a**,**b** rather than bicyclic products under similar conditions (Scheme 44).[77]

Scheme 44

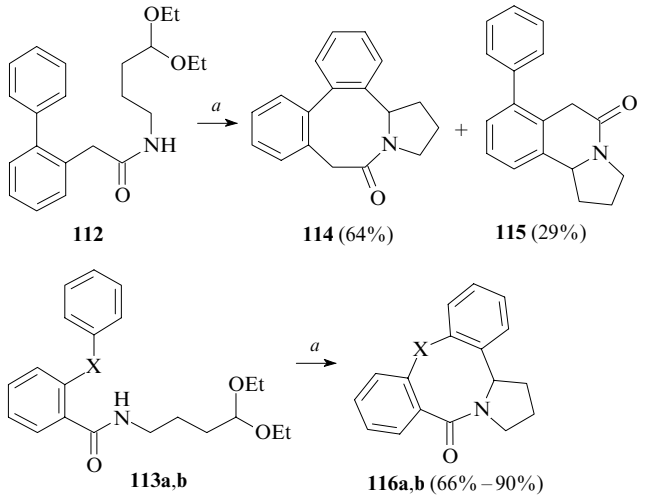


Het is 2-Th (**a**), 2,5-dimethyl-3-furyl (**b**); Th is thienyl

Owing to the presence of aryl substituent in the aromatic moiety of acetals **112** and 113a,b, it is possible to perform their cyclization with participation of two aromatic rings to give products **114–116** (Scheme 45).[76]

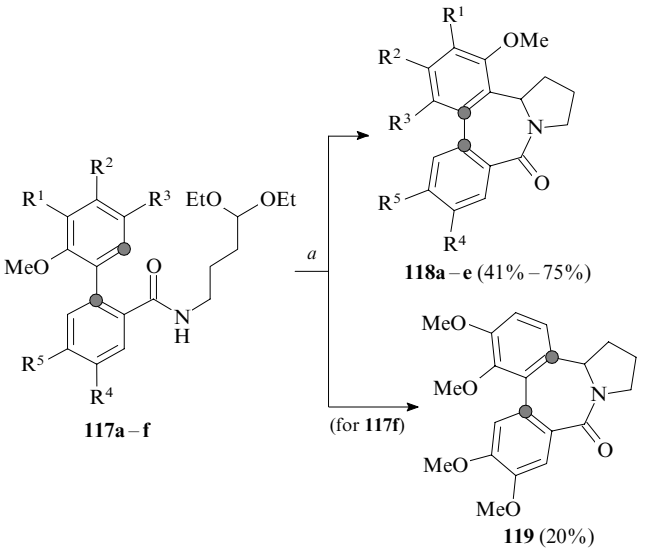
It is also necessary to mention the cyclization of 2-arylbenzoic acid *N*-(4,4-diethoxybutyl)amides **117a–e** on refluxung with TfOH; in this reaction, the authors observed unusual cationic 1,2-shift of the phenyl group (Scheme 46, two carbon atoms are marked for clarity).[78] The yields of products **118a–e** decreased with increasing number of methoxy groups in the initial acetal and were 62%–75% for compounds **118a**,**b**, 50%–51% for compounds **118c**,**d** and 41% for compound **118e**. The authors attributed the

Scheme 45



(*a*) TfOH, $CHCl_3$, Δ, 3 h; X = CH_2 (**a**), O (**b**)

Scheme 46



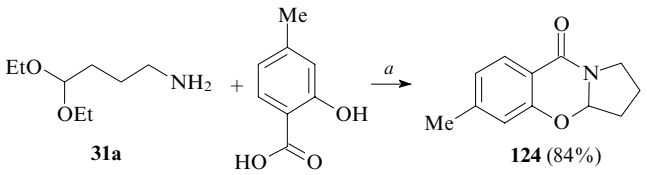
(*a*) TfOH, $CHCl_3$, Δ; $R^1 = R^2 = R^3 = R^4 = R^5 = H$ (**a**); $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = MeO$ (**b**); $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = MeO$ (**c**); $R^1 = R^2 = R^4 = R^5 = MeO$, $R^3 = H$ (**d**); $R^1 = R^2 = R^4 = MeO$, $R^3 = R^5 = H$ (**e**); $R^1 = R^4 = R^5 = MeO$, $R^2 = R^3 = H$ (**f**)

relatively small yield of product **118e** to the fact that it is demethylated under the reaction conditions. Meanwhile, acetal **117f** is converted to compound **119**, the conventional cyclization product, in a relatively small yield.

In a number of cases, *N*-(4,4-diethoxybutyl)amides were prepared *in situ*. Inded, there is an available description of the synthesis of benzoxazinone **120** and benzobisoxazinone **121** by heating diethyl 2,5-hydroxybenzene-1,4-dicarboxylate with 4,4-diethoxybutylamine (**31a**) followed by treating the reaction mixture with concentrated hydrochloric acid.[79] The authors optimized the reaction conditions in order to increase the yield of compound **120**. Benzoxazinone **122** and benzobisoxazinone **123** were obtained in a similar way (Scheme 47).

In an earlier patent,[80] the same authors described the synthesis of 6-methyl-1,2,3,3a-tetrahydro-9*H*-benzo[*e*]pyrrolo[2,1-*b*]-[1,3]oxazin-9-one (**124**). The reaction of 2-hydroxy-4-methylbenzoic acid with 4,4-diethoxybutylamine (**31a**) was performed in the presence of 1,1′-carbonyldiimidazole (CDI) with subsequent addition of a hydrochloric acid solution to the reaction mixture without isolation of the intermediate *N*-(4,4-diethoxybutyl)amide (Scheme 48).

Scheme 48

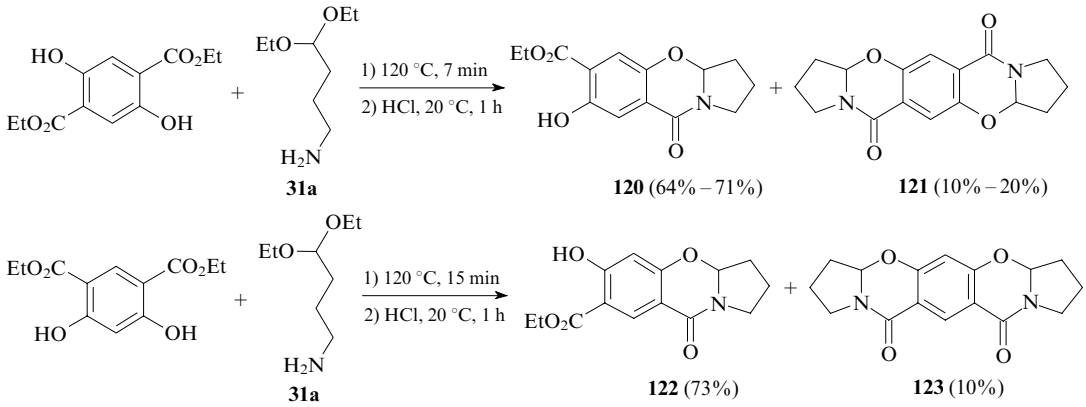


(*a*) 1) CDI, $CHCl_3$, 1 h; 2) 6 M HCl, 3 h

III.3. Synthesis of fused imidazole derivatives

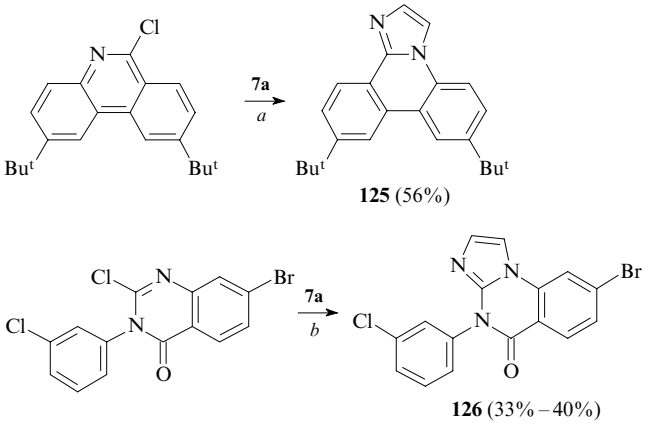
Only few examples of the synthesis of fused imidazole derivatives using nitrogen-containing acetals are available from the literature. Almost all of them are based on acid-catalyzed cyclization of aminoacetaldehyde acetals containing azine,[81,82] in particular, pyridine[83] substituent at the nitrogen atom. The imidazole ring is formed as a result of the intramolecular attack by the lone pair of the endocyclic nitrogen atom on the carbocation produced during the reaction. The initial acetal is obtained *in situ* by the reaction of aminoacetaldehyde dimethylacetal with the corresponding chloro-substituted heterocyclic compound; hydrogen chloride evolved in the reaction can catalyze the subsequent intramolecular cyclization. An example of such reaction is

Scheme 47



the synthesis of phenanthridine- (**125**) and quinazolinone- (**126**) fused imidazoles with participation of acetal **7a** (Scheme 49).[83]

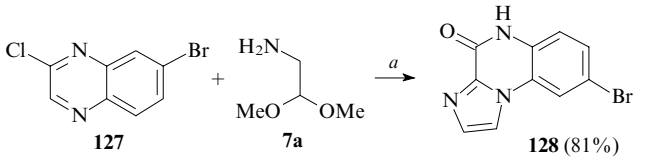
Scheme 49



(*a*) Diglyme, Δ, 96 h; (*b*) 1) Et_3N, EtOH, Δ, 0.5 h; 2) HCl, DMF, 80 °C, 1 h

These transformations can also be carried out under microwave radiation (MW). The reaction may be accompanied by electron density redistribution within the fused system. For example, on treatment with acetal **7a**, dihalo-substituted quinoxaline **127** forms product **128**, and this is accompanied by loss of aromaticity of the azine moiety (Scheme 50).[84]

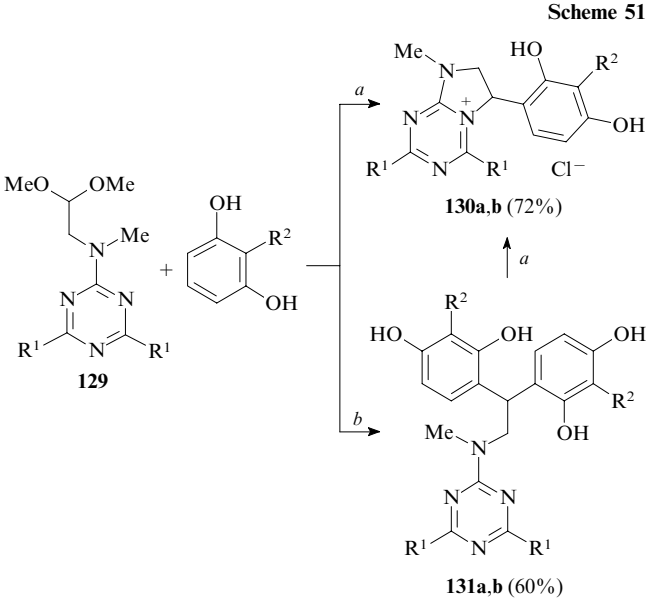
Scheme 50



(*a*) 1) MeOH, MW, 150 °C, 20 min; 2) 6 M HCl, MW, 120 °C, 20 min

Mention should be made of the paper[85] dedicated to the intramolecular cyclization of triazine-containing acetals **129**

Scheme 51



(*a*) HCl, Bu^{n}OH, Δ, 72 h; (*b*) HCl, Bu^{n}OH, 60 °C, 8 h;
R^1 is morpholino: R^2 = Me (**a**), HO (**b**)

in the presence of phenols (Scheme 51). The authors found that prolonged refluxing of the reaction mixture results in imidazotriazinium salts **130a**,**b** as the major reaction products, while lower temperature and shorter reaction time promote the predominant formation of diarylmethane derivatives **131a**,**b**. When products **131a**,**b** are refluxed in the presence of hydrochloric acid, this also results in imidazotriazinium salts **130a**,**b** (by aryl moiety elimination followed by cyclization of the resulting carbocation).

III.4. Synthesis of isoquinolines

III.4.a. Pomeranz–Fritsch reaction

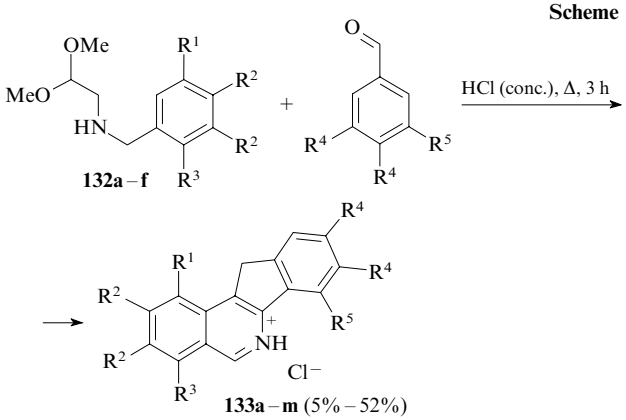
Numerous examples of isoquinoline synthesis by the Pomeranz–Fritsch reaction are surveyed in several reviews and monographs (*e.g.*, see[86–88]). Therefore, in the present review, we limited ourselves only to those reactions in which, simultaneously with isoquinoline ring formation, the C–C bond is formed in position 4 with participation of the carbonyl group.

It should be noted that in general, examples of the Pomeranz–Fritsch reaction giving rise to 4-substituted isoquinolines are relatively rare. There are only two papers[89,90] describing the reaction of *N*-benzylaminoacetaldehyde acetals **132a–f** with benzaldehyde derivatives resulting in fused indenoisoquinolines **133a–m** (Scheme 52). In the first step of the reaction, the intramolecular cyclization of acetals **132** gives intermediate 1,2-dihydroisoquinoline derivatives, which then react with benzaldehydes. It is difficult to elucidate the effect of substituents on the yield of target compounds **133**. Indeed, indenoisoquinolines **133b,d** were formed in yields not exceeding 52%, while the yield of compound **133a** with a similar structure was only 14%. The lowest yields were observed for products **133k–m** (5%–11%), while the yields of other compounds varied within the range of 18%–29%.

III.4.b. Cyclization of carboxamides

The reported[91] cyclization of *N*-(2,2-dimethoxyethyl)benzamide **134**, resulting in the formation of isoquinoline **135**,

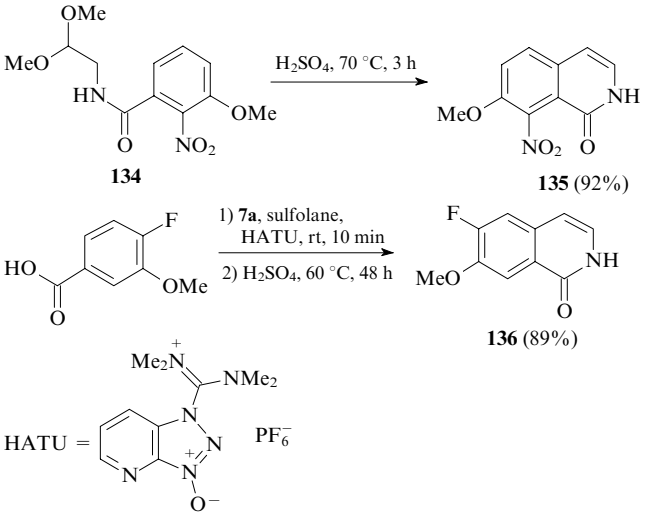
Scheme 52



R^1 = R^3 = H, R^2 = MeO (**132a**): R^4 = MeO, R^5 = H (**133a**);
R^4–R^4 = OCH_2O, R^5 = H (**133b**); R^1 = R^3 = MeO,
R^2 = H (**132b**): R^4 = MeO, R^5 = H (**133c**); R^4–R^4 = OCH_2O,
R^5 = H (**133d**); R^1 = R^3 = H, R^2 – R^2 = OCH_2O (**132c**): R^4 = MeO,
R^5 = H (**133e**); R^4–R^4 = OCH_2O, R^5 = H (**133f**);
R^4 = R^5 = MeO (**133g**); R^1 = R^2 = MeO, R^3= H (**132d**): R^4 = MeO,
R^5 = H (**133h**); R^4–R^4 = OCH_2O, R^5 = H (**133i**);
R^1 = R^2 = R^3 = MeO (**132e**): R^4 = MeO, R^5 = H (**133j**);
R^1 = H, R^2 = R^3 = MeO (**132f**): R^4 = MeO, R^5 = H (**133k**);
R^4–R^4 = OCH_2O, R^5 = H (**133l**); R^4 = R^5 = MeO (**133m**)

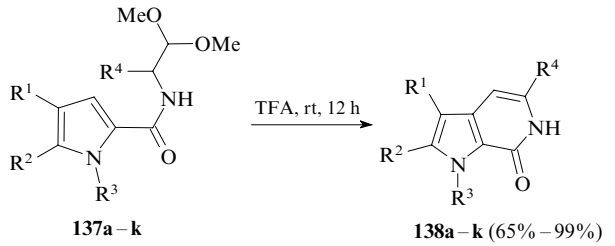
is very similar to the Pomeranz–Fritsch reaction. The possibility to prepare product **136** without preliminary isolation of the initial benzamide is noteworthy (Scheme 53).

Scheme 53



The cyclization of pyrrole-2-carboxylic acid *N*-(2,2-dimethoxyethyl)amides **137a–k** in the presence of trifluoroacetic acid giving pyrrolopyridones **138a–k** (Scheme 54) pertains to the same type of reactions.[92] The substituent at the nitrogen atom has a relatively small effect on the product yield. Thus the yields of compounds **138a–c** vary within the range of 65%–71%, while in the presence of benzyl substituent instead of the alkyl group, the yields of compounds **138d–g** somewhat increase (74%–82%). However, the introduction of even weak electron-donating substituents into the pyrrole moiety causes a significant increase in the yields of products **138h,i** up to 90% and 99%, respectively. High yields are also observed in the case of bromo-substituted pyrrolopyridones **138j,k** (84% and 86%).

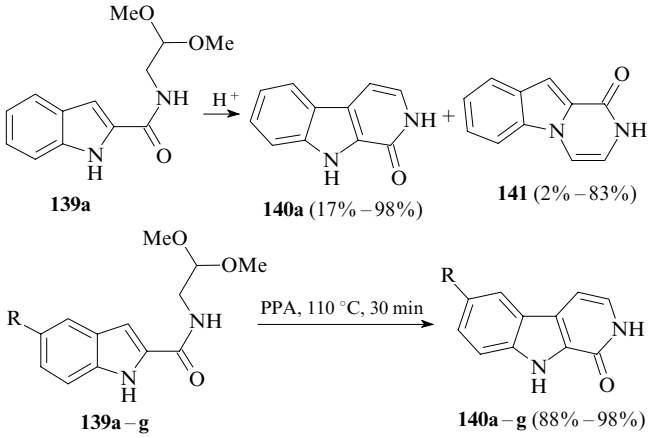
Scheme 54



$R^1 = R^2 = R^4 = H$: R^3 = Me (**a**), Et (**c**), Bn (**d**), 2-$FC_6H_4CH_2$ (**f**), 4-$MeOC_6H_4CH_2$ (**g**); $R^1 = R^2 = H$, R^4 = Me: R^3 = Me (**b**), Bn (**e**); $R^1 = R^4 = H$, R^3 = Me: R^2 = Me (**h**), Ph (**i**); R^1 = Br, $R^2 = H$, R^3 = Me: R^4 = H (**j**), Me (**k**)

Here, it is also necessary to mention the intramolecular cyclization of *N*-(2,2-dimethoxyethyl)amide of indole-2-carboxylic acid (**139a**), resulting in a mixture of two isomeric products — β-carbolinone **140a** and pyrazinoindole **141**.[93] The ratio of regioisomers depends on the reaction conditions and varies over a wide range. The authors were able to find the conditions for the preparation of β-carbolinone **140a** as the major product. Compounds **140b–g** were synthesized in a similar way in the presence of polyphosphoric acid (Scheme 55).

Scheme 55



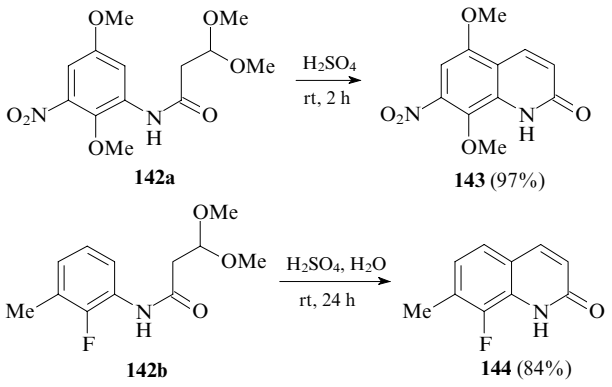
R = H (**a**), Me (**b**), F (**c**), Cl (**d**), Br (**e**), OMe (**f**), NO_2 (**g**);
PPA is polyphosphoric acid

III.5. Quinoline synthesis

Unlike the numerous isoquinoline derivatives obtained by the Pomeranz–Fritsch reaction, the number of quinolines synthesized using nitrogen-containing acetals is limited to only few examples.

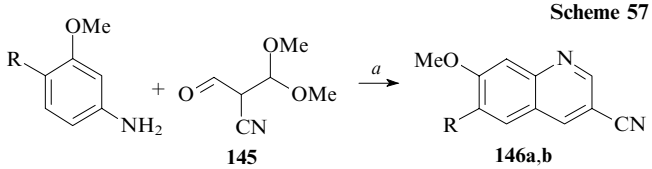
In particular, there is an available description of the intramolecular cyclization of N-aryl-substituted amides of 3,3-dimethoxypropionic acid **142a,b**, resulting in quinolines containing methoxy and nitro groups (compound **143**)[94] as well as a fluorine atom and a methyl group (compound **144**) in the aromatic moiety (Scheme 56).[95]

Scheme 56



Two sudies[96,97] are devoted to the reaction between 3,3-dimethoxy-2-formylpropionitrile (**145**) and aromatic amines to give substituted quinolines **146a,b** (Scheme 57). Probably, the reaction proceeds with the intermediate for-

Scheme 57

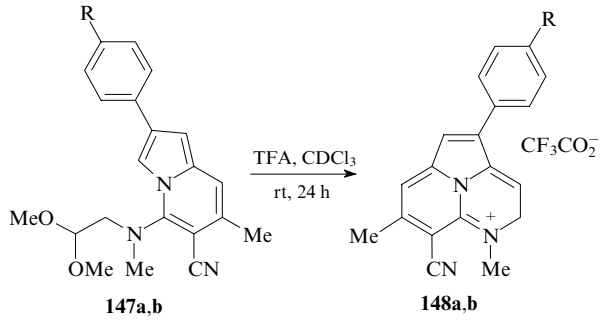


(*a*) 1) HCl, H_2O, MeOH, Δ, 2 h; 2) TsOH, PhMe, Δ, 16 h;
R = H (**a**), F (**b**)

mation of the Schiff base, which then undergoes an intramolecular cyclization in the acid medium. The yield of compound **146a** is 65%.

The intramolecular cyclization of acetals **147a**,**b** in the presence of trifluoroacetic acid results in pyrimidinioindolizine trifluoroacetates **148a**,**b** (Scheme 58).[98] However, the authors did not isolate the products, but only confirmed their formation by NMR.

Scheme 58



R = Me (**a**), O_2N (**b**)

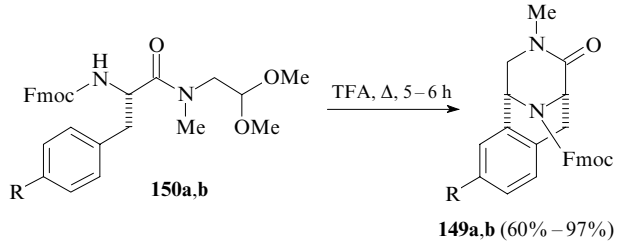
III.6. Synthesis of fused six-membered rings

The compounds with two saturated six-membered rings obtained by intramolecular cyclization of nitrogen-containing acetals may be divided into two major groups: bicyclic compounds with a bridging nitrogen atom and hexahydropyrazino[2,1-*a*]isoquinoline derivatives, analogues of the drug praziquantel. In all cases, one of the key steps of the synthesis is the intramolecular attack by the lone pair of the amide nitrogen atom on the carbocation formed in the reaction.

III.6.a. Compounds with a bridging heteroatom

This group of compounds is represented by derivatives of 3,9-diazabicyclo[3.3.1]nonan-2-one. A paper[99] describes the stereoselective synthesis of piperazinotetrahydroisoquinolines **149a**,**b** by the intramolecular cyclization of phenylalanine *N*-(2,2-dimethoxyethyl)-amides **150a**,**b** catalyzed by trifluoroacetic acid (Scheme 59).

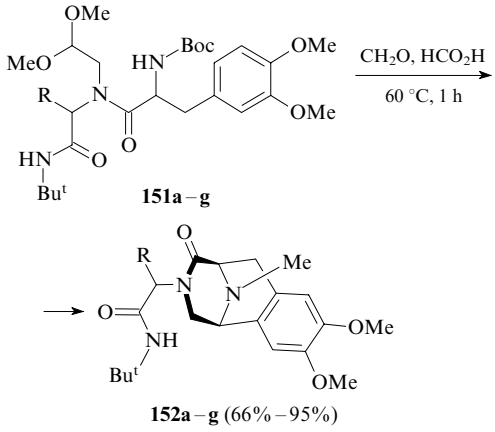
Scheme 59



R = H (**149a**, **150a**), HO (**149b**), Bu^tO (**150b**);
Fmoc is 9-fluorenylmethyloxycarbonyl

A similar transformation with the use of formic acid as a catalyst and a solvent has been described more recently[100] (Scheme 60). It should be noted that in this case, the reaction involves simultaneous elimination of the protective *tert*-butoxycarbonyl (Boc) group in compounds **151a**–**g**, intramolecular cyclization of the respective intermediates and reductive methylation of nitrogen, resulting in the formation of products **152a**–**g**.

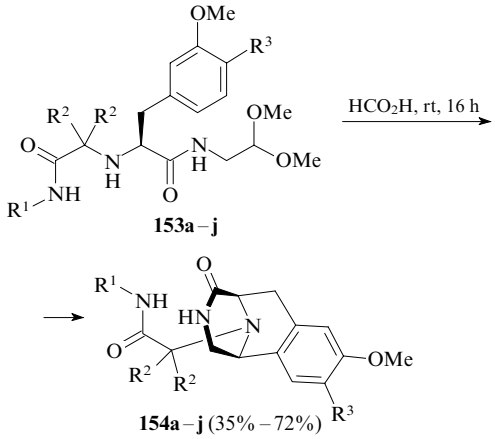
Scheme 60



R = H (**a**), Et (**b**), Ph (**c**), 4-$MeOC_6H_4$ (**d**), 4-ClC_6H_4 (**e**), 2-$O_2NC_6H_4$ (**f**), 3-O_2N-4-FC_6H_3 (**g**)

An approach to the synthesis of piperazinotetrahydroisoquinolines based on the intramolecular Pictet–Spengler reaction of acetals **153a**–**j** has been developed[101] (Scheme 61). Formic acid appeared to be the catalyst of choice for this transformation. It should be noted that the use of *p*-toluenesulfonic acid and camphorsulfonic acid as catalysts did not lead to target compounds **154a**–**j**. The presence of two methoxy groups in the aromatic moiety promoted the reaction: the corresponding compounds **154a**–**c**,**e**,**f**,**h**,**j** were formed in 52%–75% yields. The replacement of one methoxy group by a hydrogen atom decreases the yield of products **154d**,**g**,**i** to 35%–42%.

Scheme 61

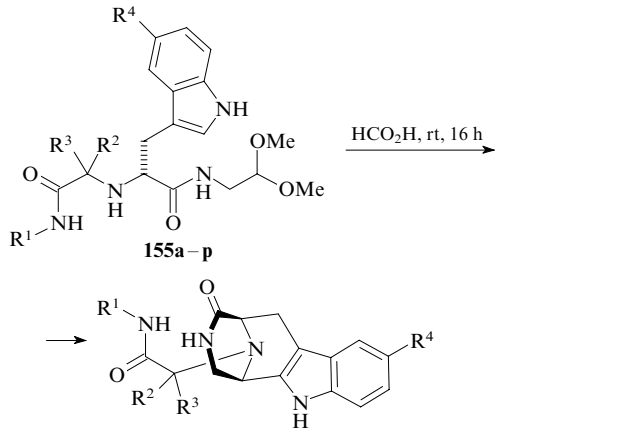


R^1 = $Ph(CH_2)_2$, R^3 = MeO: R^2–R^2 = $(CH_2)_3$ (**a**), $(CH_2)_2O(CH_2)_2$ (**b**); R^1 = 2-$MeOC_6H_4(CH_2)_2$, R^2–R^2 = $(CH_2)_3$, R^3 = MeO (**c**); R^1 = Bn: R^2–R^2 = $(CH_2)_6$, R^3 = H (**d**); R^2–R^2 = $(CH_2)_4$, R^3 = MeO (**e**); R^2–R^2 = $(CH_2)_2O(CH_2)_2$, R^3 = MeO (**f**); R^1 = 4-$FC_6H_4(CH_2)_2$, R^2 = Me, R^3 = H (**g**); R^1 = cyclo-C_6H_{11}: R^2–R^2 = $(CH_2)_4$, R^3 = H (**i**); R^2 = Me, R^3 = MeO (**j**)

In the same study,[101] a similar cyclization on indole-containing acetals **155a**–**p** was carried out, resulting in the synthesis of a number of polycyclic compounds **156a**–**p** with indole moiety (Scheme 62). No obvious dependence of the target product yield on the substituent nature was elucidated. In the case of compounds **156a**–**c**,**h**,**k**,**m**, the

yields were 40%–52%, while in the case of their analogues **156d–g**,**l**,**n**,**p**, the yields were 24%–35%. The highest yield (61%) was obtained for compound 156i, while the lowest one (19%) was observed for compound **156o**.

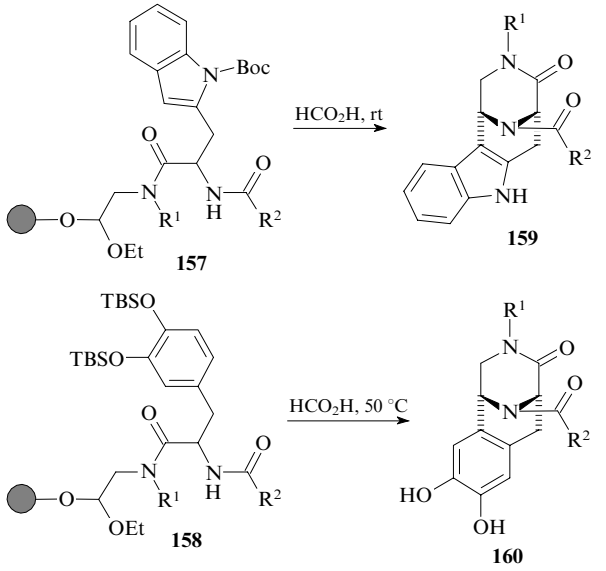
Scheme 62



R^1 = $Ph(CH_2)_2$, R^4 = H: R^2–R^3 = $(CH_2)_2NMe(CH_2)_2$ (**a**), $(CH_2)_6$ (**b**), $(CH_2)_5$ (**c**), $(CH_2)_4$ (**e**); R^2 = R^3 = H (**g**); R^1 = $Ph(CH_2)_2$, R^4 = HO: R^2–R^3 = $(CH_2)_5$ (**d**), $(CH_2)_3$ (**f**); R^1 = 2-$MeOC_6H_4(CH_2)_2$, R^2–R^3 = $(CH_2)_5$, R^4 = HO (**h**); R^1 = Bn, R^3 = H: R^2 = Ph, R^4 = H (**i**); R^2 = cyclo-C_5H_9, R^4 = HO (**j**); R^2 = R^3 = Me, R^4 = HO: R^1 = Ph_2CH (**l**), $TMSO(CH_2)_2$ (**m**); R^2–R^3 = $(CH_2)_5$: R^1 = 4-$FC_6H_4CH_2$, R^4 = HO (**k**); R^1 = $Et_2N(CH_2)_3$, R^4 = H (**n**); R^1 = $AllCH_2$, R^4 = H (**o**); R^1 = cyclo-C_6H_{11}, R^4 = HO (**p**)

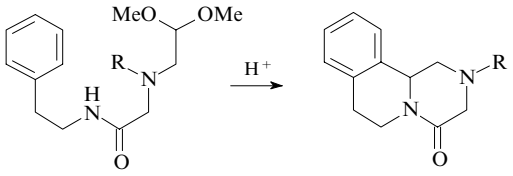
The solid-phase synthesis of the wide range of piperazinotetrahydroisoquinoline derivatives using formic acid as a catalyst and a solvent has been reported.[102] The high regio- and diastereoselectivity of the conversion of acetals **157** and **158** immobilized on a solid support to the corresponding heterocyclic compounds **159** and **160** should be noted (Scheme 63).

Scheme 63



R^1 = Alk: R^2 = Alk, AlkNH; ● is polymer; TBS is *tert*-butyldimethylsilyl

Scheme 64



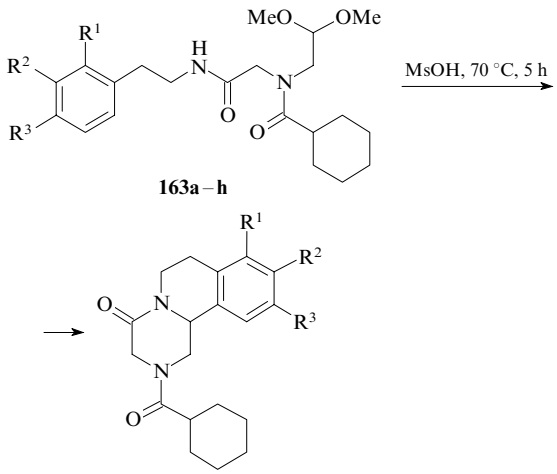
R = cyclo-$C_6H_{11}C(O)$ (**a**), H (**b**)

III.6.b. Praziquantel and related compounds

The discovery of the anthelmintic drug praziquantel [2-(cyclohexylcarbonyl)-1,2,3,7,11b-hexahydro-4*H*-pyrazino[2,1-*a*]-isoquinoline-4-one, **161a**] in 1975 led to the emergence of quite a number of papers devoted to the synthesis of this compound and its analogues. A method based on the intramolecular cyclization of nitrogen-containing acetals was also developed. In the overwhelming majority of cases, substituted *N*-(2,2-dimethoxyethyl)glycine amides were used as the initial acetals. Several papers describe the synthesis of pristine praziquantel[103, 104] and its N-substituted analogue **161b**[104–112] consisting in acid-catalyzed cyclization of *N*-(2,2-dimethoxyethyl)glycine *N*-phenetylamides **162a**,**b** (Scheme 64). Methanesulfonic acid,[103, 104, 110] *p*-toluenesulfonic acid[104] and sulfuric[105–109, 112] and phosphotungstic[111] acids were used as catalysts, and water[107–109] and dihaloalkanes[104, 110, 111] were employed as solvents.

The synthesis of praziquantel derivatives containing substituents in the aromatic nucleus has been reported.[113, 114] Electron-donating substituents present in position 3 of the aromatic rings of acetals **163a–c** are apparently beneficial for this reaction (Scheme 65). The corresponding polycyclic compounds **164a–c** were formed in the yields of 50%–56%, while in the case of acetals **163d**,**f–h**, the product yields were significantly lower, namely, 38%–46%. However, note that compound **164e**, which was obtained in the highest yield of 63%, is an exception to this trend.

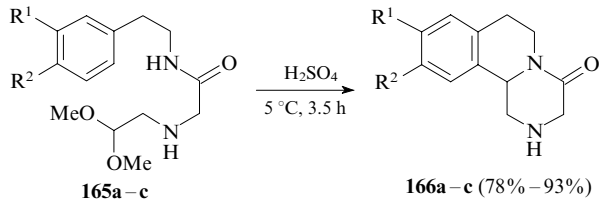
Scheme 65



R^1 = R^3 = H: R^2 = Br (**a**), Me (**b**), MeO (**c**); R^1 = R^2 = H: R^3 = Br (**d**), Me (**e**); R^2 = R^3 = H: R^1 = Br (**f**), Me (**g**), MeO (**h**)

Compounds **166a–c**, the molecules of which contain a free NH group, were prepared from acetals **165a–c** (Scheme 66).[112, 115]

Scheme 66



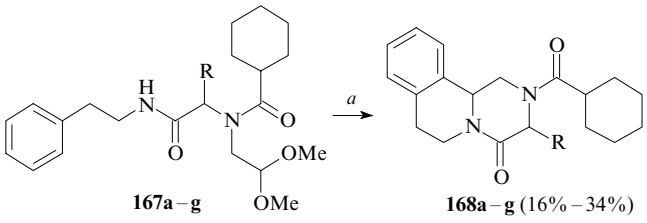
165a–c **166a–c** (78%–93%)

R^1 = R^2 = H (**a**), OMe (**b**); R^1 = H, R^2 = F (**c**)

A wide range of praziquantel derivatives were prepared by Liu *et al.*[116] The synthesis of the target compounds was performed in two steps, namely, the Ugi condensation of dimethylacetal of aminoacetaldehyde, formaldehyde, various isocyanides and carboxylic acids was followed by the cyclization of the acetals thus formed in the presence of magnesium sulfate and methanesulfonic acid. The possibility of conducting this reaction without isolation of the initial acetals was also demonstrated. This approach allowed the authors to vary substituents in the piperazine ring and the amide moiety and to insert the indole and thiophene rings into the molecule.

Using acetals **167a–g** as the initial compounds, piperazinoisoquinolines **168a–g** containing the alkyl or aryl group as substituents in the piperazine ring were synthesized by this method (Scheme 67).[116]

Scheme 67



167a–g **168a–g** (16%–34%)

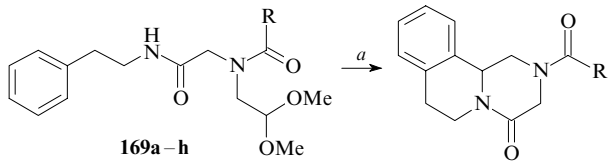
(*a*) MsOH, $MgSO_4$, DCE, 80 °C; R = Me (**a**), Pr^i (**b**), Bu^i (**c**), neo-C_5H_{11} (**d**), 4-FC_6H_4 (**e**), $HOCH_2$ (**f**), cyclo-C_3H_5 (**g**); DCE is 1,2-dichloroethane

The influence of substituents on the yield of piperazinoisoquinoline derivatives **168** was not unambiguously established. The highest yields (29%–34%) were obtained for compounds **168b**,**c**,**g** containing isopropyl, isobutyl and cyclopropyl substituents. Compound **168d** with the largest neopentyl substituent was formed in a yield of 23%. However, it is unlikely that the decrease in the yield is caused only by the steric factors, as the yield of compound **168a** containing the methyl substituent appeared to be almost the same — 21%. The lowest yields were found for products **168e**,**f** (16% and 17%, respectively).

A similar behaviour was observed for the conversion of acetals **169a–h** to piperazinoisoquinolines **170a–h**, in which the piperazine nitrogen atom was bound to the acetyl groups of various structure (Scheme 68).[116]

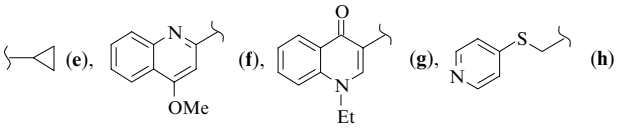
Among praziquantel derivatives **170**, the largest yield (58%) was obtained for compound **170e** containing the cyclopropyl substituent. Somewhat lower yields (42%–44%) were recorded for compounds **170a**,**c** containing phenyl and 2,4-dimethylphenyl substituents. The

Scheme 68



169a–h **170a–h** (10%–58%)

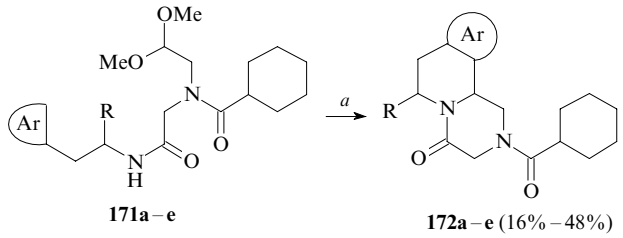
(*a*) MsOH, $MgSO_4$, DCE, 80 °C;
R = Ph (**a**), Bz (**b**), 2,4-$Me_2C_6H_3$ (**c**), 3-O_2N-4-FC_6H_3 (**d**),



increase of the electron-withdrawing ability of the substituent at the carboxamide group (compounds **170b**,**d**,**f**) resulted in decreasing the yields to 25%–29%. The lowest yields were found for products **170g**,**h** (10% and 19%, respectively).

The introduction of a methoxy group into the praziquantel aromatic ring and introduction of a methoxycarbonyl function into the piperazine ring, as well as replacement of the annulated benzene ring by indole or thiophene moieties were accomplished by the intramolecular cyclization of acetals **171a–e** (Scheme 69; the Ar substituents are specified for the initial acetals).[116]

Scheme 69



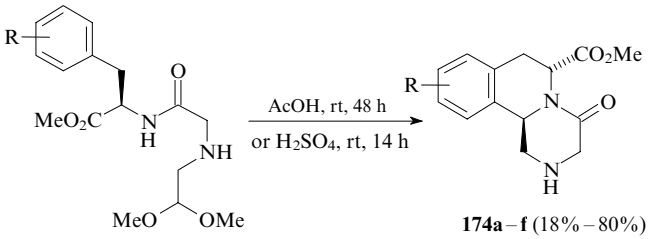
171a–e **172a–e** (16%–48%)

(*a*) MsOH, $MgSO_4$, DCE, 80 °C; R = H: Ar = 4-$MeOC_6H_4$ (**a**), 3,4-$(MeO)_2C_6H_3$ (**b**), 2-Th (**c**); R = MeO_2C: Ar = Ph (**d**), N-Boc-indol-3-yl (**e**)

The effect of substituents on the course of this reaction is rather pronounced. Indeed, an increase in the nucleophilicity of the aromatic moiety results in higher yield of derivative **172**. The highest product yield was observed for acetals **171a**,**b**,**e** containing *p*-methoxyphenyl, 3,4-dimethoxyphenyl and indole moieties (45%–48%). The presence of phenyl substituent in acetal **171d** results in decreasing the yield of compound **172d** to 34%. The lowest yield (16%) was obtained for compound **172c** containing the thiophene moiety, which is probably explained by its chemical instability in the acidic medium.

It is also interesting to consider the stereoselective cyclization of dipeptides **173a–f** to give methyl (6*R*,11b*R*)-4-oxo-1,3,4,6,7,11b-hexahydro-2*H*-pyrazino[2,1-*a*]isoquinoline-6-carboxylates **174a–f** with diastereomeric excess of 96%–99% described by Japanese researchers[117] (Scheme 70). The authors explain the high diastereoselectivity of the process by steric hindrances arising in the transition state from which the 6*R*,11b*S*-isomer is formed.

Scheme 70

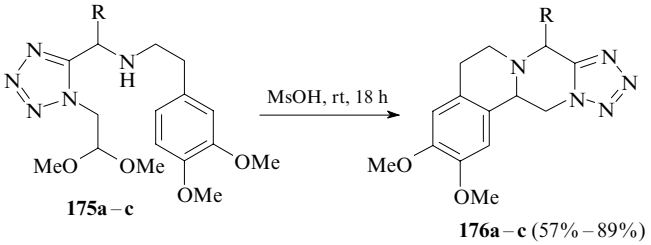


173a–f **174a–f** (18%–80%)

R = H (**a**), 4-Me (**b**), 4-MeO (**c**), 4-Cl (**d**), 3-Cl (**e**), 2-Cl (**f**)

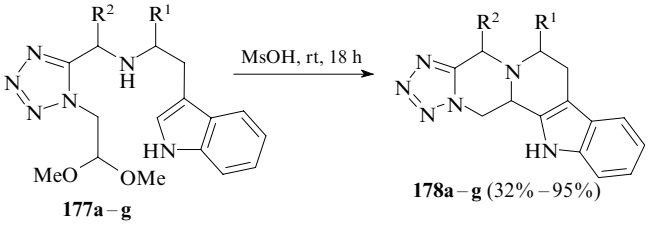
The intramolecular cyclization of acetals **175a–c** catalyzed by methanesulfonic acid, resulting in the formation of pyrazinoisoquinoline derivatives **176a–c** containing a tetrazole moiety, has been reported[118] (Scheme 71). Under similar conditions, acetals **177a–g** were converted to indole analogues **178a–g**. The product yield substantially depended on the nature of substituent in the piperazine ring. The highest yields of products (85%–95%) were achieved in the case of cyclization of acetals **175b**, **177b**,**f** containing *p*-chloro and *p*-nitrophenyl substituents. The introduction of 3,4,5-trimethoxyphenyl group into the same position led to a sharp decrease in the yield of pyrazinoisoquinoline **178d** (down to 32%). The compounds with alkyl substituents **176a**,**c** and **178a**,**c**,**e** as well as compound **178g** with a phenyl moiety were obtained in moderate yields (53%–77%).

Scheme 71



175a–c **176a–c** (57%–89%)

R = Pr^i (**a**), 4-ClC$_6$H$_4$ (**b**), cyclo-C$_6$H$_{11}$ (**c**)



177a–g **178a–g** (32%–95%)

R^1 = H: R^2 = cyclo-C$_6$H$_{11}$ (**a**), 4-O$_2$NC$_6$H$_4$ (**b**),
Bn[CH(CH$_2$CH$_2$)$_2$CH]-cyclo (**c**), 3,4,5-(MeO)$_3$C$_6$H (**d**);
R^1 = MeO$_2$C: R^2 = cyclo-C$_6$H$_{11}$ (**e**), 4-ClC$_6$H$_4$ (**f**), Ph (**g**)

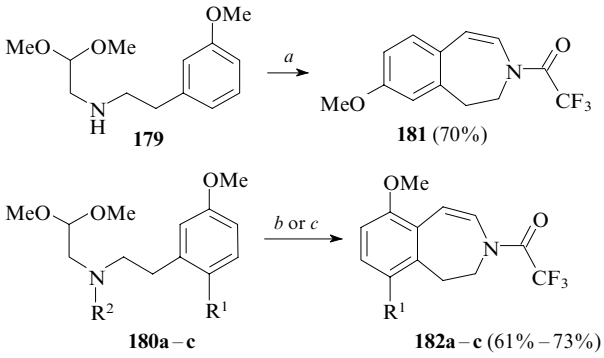
III.7. Synthesis of benzazepine derivatives

The reactions of nitrogen-containing acetals resulting in the preparation of benzazepine derivatives are much similar to the intramolecular cyclizations of acetals of 2-(arylamino)-acetaldehydes, *N*-(2,2-dimethoxyethyl)benzamides and 3,3-dimethoxypropionic acid N-aryl-substituted amides (see Sections III.1, III.4.b and III.5, respectively). All these reactions involve the intramolecular electrophilic substitution in the aromatic ring without participation of the acetal nitrogen-containing moiety in the reaction. The initial compounds are most often represented by acetals of substituted 2-(phenetylamino)acetaldehydes and *N*-(2,2-dimethoxyethyl)amides of phenylacetic acid. It should be noted that in the vast majority of cases, these reactions are related to the synthesis of benzo[*d*]azepines, including those annulated to other heterocycles.

III.7.a. Substituted benzazepines

Several papers[119–121] describe the synthesis of dihydrobenzo[*n*]azepine derivatives containing methoxy substituents in the aromatic moiety (Scheme 72). The initial compounds were represented by acetals with secondary (**179**, **180a**,**b**) or acylated (**180c**) amino groups. Phosphorus(V) oxide[120] or an excess of trifluoroacetic anhydride were used as catalysts.[119,121] In the latter case, the azepine ring closure was accompanied by amino group acylation to give products **181** and **182a**,**b**. It should be noted that in order to perform successful cyclization of acetal **180c** containing the electron-withdrawing substituent in the aromatic moiety along with the acylated nitrogen atom, it was necessary to conduct the reaction in trifluoroacetic acid with prolonged heating. Note also high regioselectivity of the reaction for acetal **179**; in this case, only the product of *para*-substitution of the aromatic ring was obtained.[119]

Scheme 72



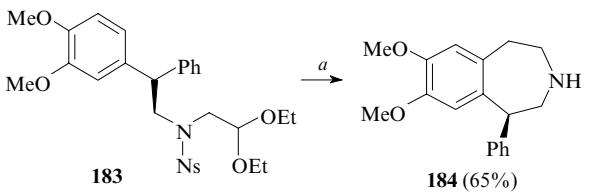
179 **181** (70%)

180a–c **182a–c** (61%–73%)

(*a*) TFAA, CH_2Cl_2, rt, 18 h; (*b*) TFAA, TFA, 40 °C, 18 h;
(*c*) P_2O_5, PhCl, 80 °C, 20 h; R^2 = H: R^1 = Br (**a**), F (**b**);
R^1 = F, R^2 = F$_3$CC(O) (**c**)

The intramolecular cyclization of chiral acetal **183** on treatment with acetic acid has been described.[122] The subsequent reduction of the intermediate dehydrobenzazepine and elimination of the protective *p*-nitrophenylsulfonyl (nosyl, Ns) group furnished compound **184** in a good yield (Scheme 73).

Scheme 73

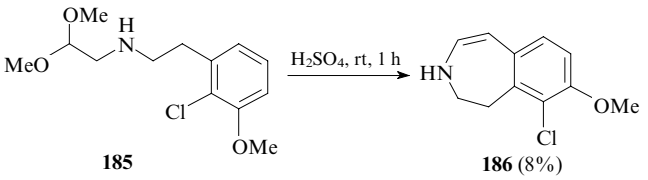


183 **184** (65%)

(*a*) 1) AcOH; 2) $NaBH_4$, TFA, CH_2Cl_2; 3) PhSH, K_2CO_3, DMF

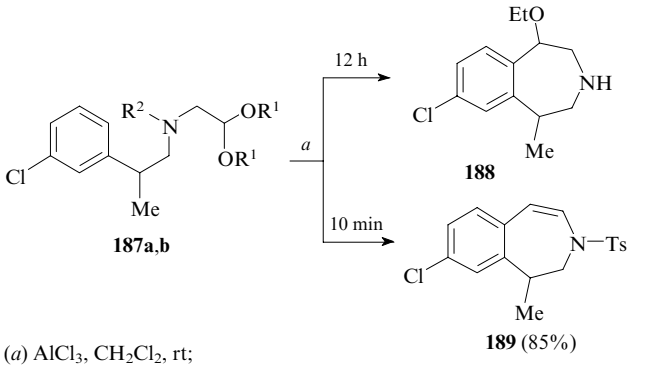
The cyclization of acetal **185** in concentrated sulfuric acid has been performed.[123] Benzazepine **186** was formed in a yield of only 8% (Scheme 74).

Scheme 74



2-{[2-(3-Chlorophenyl)propyl]amino}acetaldehyde acetals **187a**,**b** were cyclized in the presence of aluminium chloride.[124] The synthetic outcome of the reaction depended on the initial compound structure. In the case of N-substituted acetal **187a**, 7-chloro-1-ethoxy-5-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (**188**) formed as the only reaction product even after prolonged maintenance of the reaction mixture. Meanwhile, the intramolecular cyclization of its analogue **187b** containing a tosyl substituent at the nitrogen atom resulted rather rapidly in dihydrobenzazepine **189** (Scheme 75).

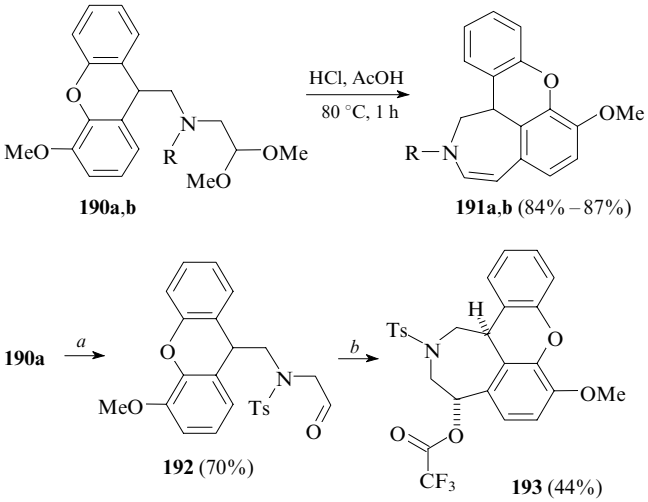
Scheme 75



(*a*) $AlCl_3$, CH_2Cl_2, rt;
R^1 = Et, R^2 = H (**a**); R^1 = Me, R^2 = Ts (**b**)

The cyclization of acetals **190a**,**b** has been investigated;[125] The reaction was found to give fused dihydrobenzazepines **191a**,**b** in high yields (Scheme 76). Mild hydrolysis of acetal **190a** followed by the intramolecular cyclization of aldehyde **192** in the presence of trifluoroacetic acid furnished tetrahydrobenzazepine **193**. Note that compound **193** occurs in the reaction mixture as a single diastereoisomer, as evidenced by ^{1}H NMR data.

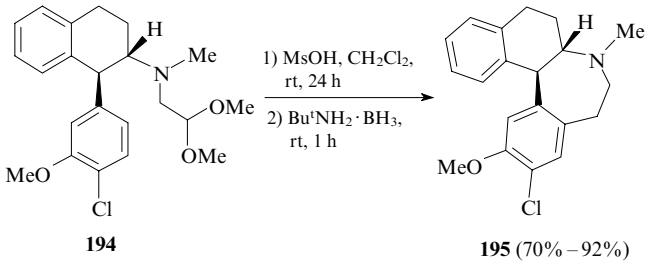
Scheme 76



(*a*) HCl, AcOH, rt, 1 h; (*b*) TFA, CH_2Cl_2, rt, 1 h; R = Ts (**a**), Tf (**b**)

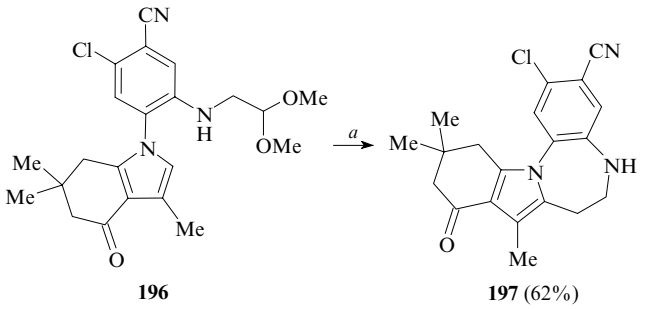
The intramolecular cyclization of chiral acetal **194** on treatment with methanesulfonic acid followed by reduction gives polycyclic compound **195** (Scheme 77).[126, 127]

Scheme 77



The conversion of acetal **196** to diazepine **197** with the pyrrole ring functioning as the nucleophile has been mentioned in the literature[128] (Scheme 78).

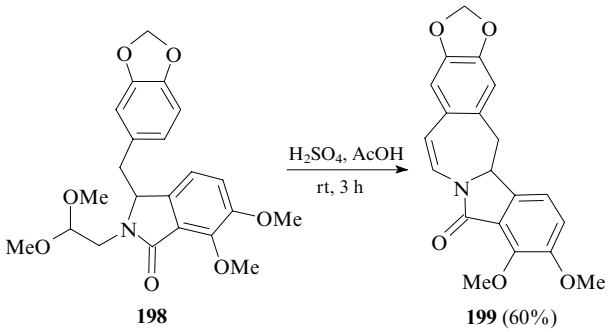
Scheme 78



(*a*) 1) TFA, CH_2Cl_2, 50 °C; 2) Et_3SiH, 5 °C

The cyclization of acetal **198** in a mixture of sulfuric and acetic acids yielding benzazepine **199** fused to an isoindoline moiety has been described by French researchers[129, 130] (Scheme 79).

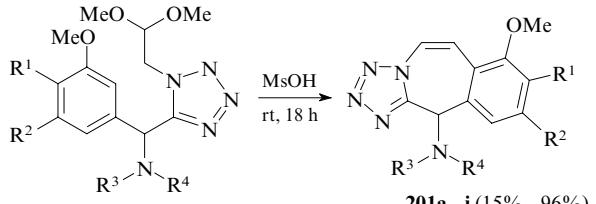
Scheme 79



Tetrazole-containing acetals **200a**–**j** have been successfully converted to a series of aminobenzazepine derivatives **201a**–**j** with annulated tetrazole ring[118] (Scheme 80). The yield of the target compounds was affected by substituents both in the aromatic moiety and at the nitrogen atom. The highest yields (83%–96%) were recorded for benzazepines **201e**–**g** containing two methoxy groups in the *meta*-position. Meanwhile, the yields of compounds **201i**,**j** containing these groups in the *ortho*-position were relatively

low — only 27% and 41%, respectively. Products **201a**,**c**,**d** occupy an intermediate position, being formed in 54%–62% yields; the yield of compound **201b** is somewhat higher (76%). The lowest yield (15%) was obtained for derivative **201h**, the only compound containing phenyl substituent at the nitrogen atom.

Scheme 80

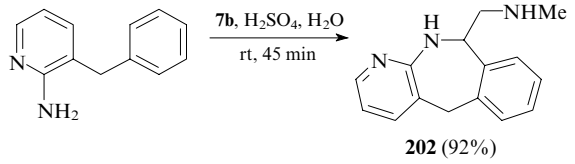


200a–j **201a–j** (15%–96%)

$R^1 = R^2 = MeO$, $R^4 = H$: $R^3 = Pr^i$ (**a**), 4-$ClC_6H_4CH_2$ (**c**), All (**d**);
$R^1 = R^2 = MeO$, $R^3 = R^4 = Pr^n$ (**b**); $R^2 = MeO$, $R^1 = R^4 = H$:
R^3 = All (**e**), 2-$ClC_6H_4(CH_2)_2$ (**f**), Ph (**h**),
Bn[$CH(CH_2CH_2)_2CH$]-cyclo (**g**); $R^1 = MeO$,
$R^2 = H$: R^3 = 2-$ClC_6H_4(CH_2)_2$, $R^4 = H$ (**i**);
$R^3 = R^4$ = Bn[$CH(CH_2CH_2)_2CH$]-cyclo (**j**)

An unusual example of synthesis of dihydrobenzopyridoazepine **202** by condensation of 2-amino-3-benzylpyridine with *N*-methylaminoacetaldehyde dimethylacetal (**7b**) in the presence of sulfuric acid is described in a patent [131] of American authors (Scheme 81).

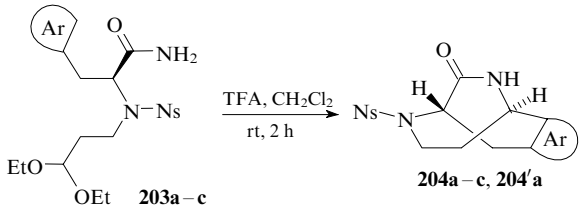
Scheme 81



202 (92%)

The intramolecular cyclization of (*S*)-3-aryl-2-[(3,3-diethoxypropyl)amino]propanamides **203a–c** results in bicyclic compounds.[132] In the case of acetal **203a**, the reaction products are regioisomeric benzazepines **204a** and **204′a** (Scheme 82). A high diastereoselectivity of this reaction should be noted, only the *S*,*R* isomers being formed in both cases.

Scheme 82

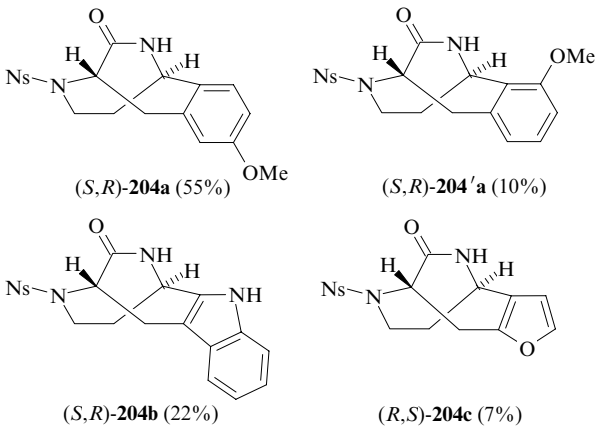


203a–c **204a–c**, **204′a**

203: Ar = 3-$MeOC_6H_4$ (**a**), 3-Ind (**b**), 2-Fu (**c**);
Ind is indolyl, Fu is furyl

Acetals **203b**,**c** containing the indole and furan rings, respectively, also cyclize with a high stereoselectivity. However, the yield of target compounds **204b**,**c** is relatively low due to their chemical instability in the strong acidic medium.

Structures 204

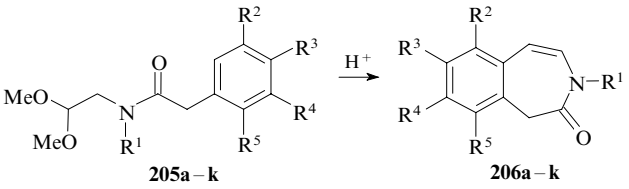


III.7.b. Benzazepine oxo derivatives

The intramolecular cyclization of phenylacetic acid *N*-(2,2-dimethoxyethyl)amides, resulting in the formation of benzo[*d*]azepin-2-ones, proceeds similarly to the reactions of substituted 2-(phenetylamino)acetaldehyde acetals described in the previous Section.

Various researchers have synthesized a wide range of 1,3-dihydrobenzo[*d*]azepin-2(2*H*)-one derivatives **206a–k** containing substituents in the aromatic moiety or at the nitrogen atom from acetals **205a–k** (Scheme 83). A solution of hydrogen chloride in acetic acid,[133–138] a mixture of sulfuric and acetic acids [139, 140] or formic acid were used as catalysts.[140] The yields of compounds **206** are summarized in Table 1.

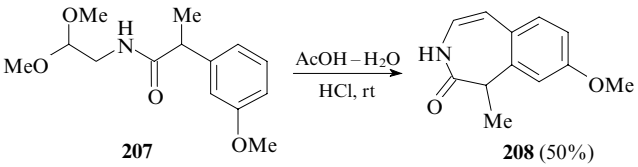
Scheme 83



205a–k **206a–k**

Acetal **207** served as the initial compound to prepare 1,3-dihydrobenzo[*d*]azepin-2(2*H*)-one **208** substituted in the benzene ring and in the azepine moiety (Scheme 84).[152]

Scheme 84



207 **208** (50%)

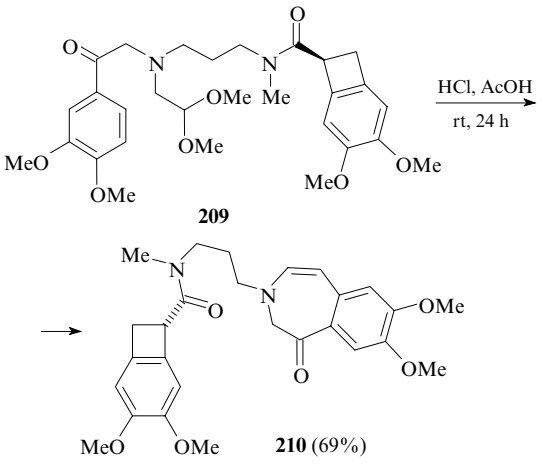
A similar reaction was successfully used [153, 154] to convert acetal **209** to benzazepinone **210**. The reaction was not prevented by the bulky substituent at the nitrogen atom (Scheme 85).

Table 1. Products of cyclization of acetals **205a–k** (see Scheme 83).

Compound **206**	R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
a	H	H	OCH_2O		H	56–59	133, 134, 141
b	see [a]	H	OCH_2O		H	85	141
c	Me	H	H	H	H	74	142
d	Me	H	MeO	MeO	H	84	143
e	H	H	H	MeO	H	51–84	144, 145
f	H	H	MeO	MeO	H	40–93	135, 139, 140, 146–151
g	H	H	H	MeO	Me	62	136
h	H	H	H	H	H	–	137
i	H	H	H	H	MeO	–	137
j	H	MeO	H	H	MeO	–	137
k	H	H	H	H	BnO	59	138

Note. The dash means that the yield was not specified in the original paper. [a] 2-bromo-5,6-dimethoxybenzoyl.

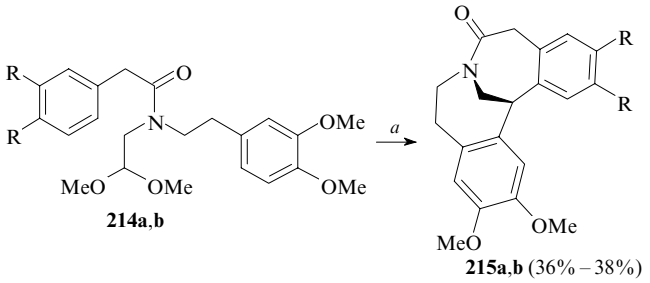
Scheme 85



The intramolecular cyclization of acetals **211a–c** gave rise to dihydrobenzazepinones **212a–c**, which subsequently reacted with various aromatic nucleophiles in the presence of trifluoromethanesulfonic acid to give compounds **213a–g** (Scheme 86).[155] The reaction can be accomplished for arenes both containing electron-donating and electron-withdrawing substituents. In the case of 2-chlorothiophene, compound **213g** was formed only when aluminium chloride was used as a catalyst, which is apparently caused by the chemical instability of both 2-chlorothiophene and the corresponding reaction product in a strong acid solution.

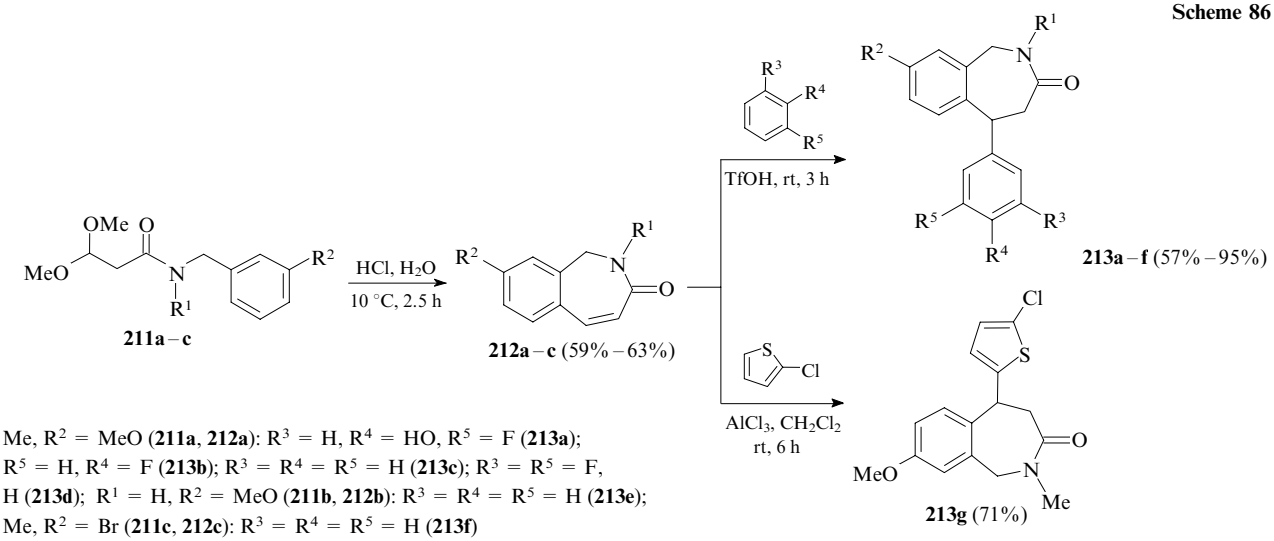
In the conversion of acetals **214a,b** to compounds **215a,b** with the bridgehead nitrogen atom, closure of two seven-membered rings takes place (Scheme 87).[156] The authors used formic acid or a solution of hydrogen chloride and sulfuric acid in acetic acid as catalysts. Although the catalyst nature did not significantly affect the target product yield, in the case of formic acid, duration of the reaction decreased from 17–20 hours to 4 hours.

Scheme 87



(*a*) HCO_2H, rt, 4 h; R = MeO (**a**), R–R = OCH_2O (**b**)

Scheme 86



R^1 = Me, R^2 = MeO (**211a**, **212a**): R^3 = H, R^4 = HO, R^5 = F (**213a**);
R^3 = R^5 = H, R^4 = F (**213b**); R^3 = R^4 = R^5 = H (**213c**); R^3 = R^5 = F,
R^4 = H (**213d**); R^1 = H, R^2 = MeO (**211b**, **212b**): R^3 = R^4 = R^5 = H (**213e**);
R^1 = Me, R^2 = Br (**211c**, **212c**): R^3 = R^4 = R^5 = H (**213f**)

* * *

To summarize the data surveyed in the present review, it is possible to draw the conclusion that the reactions of aromatic compounds with acetals functionalized with nitrogen-containing groups open up the way to a broad variety of products, mainly heterocyclic compounds, including those annulated to an aromatic ring. However, the key attention of researches is paid to the intramolecular types of these reactions. The intermolecular reactions of nitrogen-containing acetals with aromatic compounds are covered in considerably fewer publications and have been much less studied. Meanwhile, the available literature data attest to a significant synthetic potential of these reactions. An important advantage of these transformations over the intramolecular reactions is the possibility to vary both the acetal and aromatic components over wide ranges. This fact, together with the possibility of involvement of a heteroatomic group in the reactions makes further research in the field of nitrogen-containing acetal chemistry highly promising with an outlook for the synthesis of new classes of heterocyclic, macrocyclic and acyclic compounds, including those possessing practically valuable properties.

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