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Acid-Catalyzed Cascade Reaction of 4-Aminobutanal Derivatives with (Hetero)aromatic Nucleophiles: A Versatile One-Pot Access to 2-(Hetero)arylpyrrolidines.

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2-(Hetero)arylpyrrolidine fragment is found in a diverse array of biologically active molecules, both natural and unnatural. In recent years, a substantial increase in number of approved drugs featuring this scaffold is observed. Developing methods for the synthesis of such compounds has been essential for making progress in this field. Most of these methods require usage of metal catalysts and introduce additional chemical steps to obtain appropriately substituted starting compounds. This microreview details the one-pot approach for the synthesis of pyrrolidine derivatives possessing (hetero)aromatic substituent at the second position of pyrrolidine ring based on usage of readily available *N*-substituted 4,4-diethoxybutan-1-amines and (hetero)aromatics as starting compounds and Bronsted acids as catalysts.

Introduction

Pyrrolidine core is a structural motif of many biologically active compounds, both natural (such as nicotine, proline or hygrine) and synthetic.[1,2] According to the literature data,[3] the pyrrolidine ring is one of the most frequently occurring heterocyclic scaffolds in approved drugs. Taking this into account, it is not surprising that a significant amount of efforts is devoted to the search for novel methods of synthesis of pyrrolidine derivatives.[4–6]

In recent years, the number of 2-(hetero)arylpyrrolidine derivatives patented as drugs increased sharply, indicating growing interest in the practical application of such compounds. Examples are antiviral drugs Velpatasvir[7] and Daclatasvir[8] used in the treatment of hepatitis C infection, anticancer drugs Acalabrutinib[9] (approved by FDA in 2017) and Larotrectinib[10] (approved by FDA in 2018) (Figure 1).

However, despite the increasing number of research aimed at obtaining and study of 2-(hetero)arylpyrrolidines, a synthesis of these compounds meets certain difficulties. Approaches to these compounds can be divided into two main groups. The first one includes the modification of an existing pyrrolidine fragment. The most attractive pathway within this approach is the direct C–H bond functionalization. As a rule, these reactions are based on α-deprotonation of *N*-substituted pyrrolidines with organolithium compounds. Carbanions thus obtained are then involved into the Negishi cross-coupling via a transmetallation with zinc halides followed by interaction with aryl halides.[11–15] The other pathway within the same approach is a reaction of 2-hydroxy-, 2-alkoxy- or 2-acetoxypyrrolidines with organomagnesium or organolithium derivatives of aromatic compounds.[16,17] However, the serious limitation of these methods is the need in expensive metal catalysts and harsh reaction conditions.

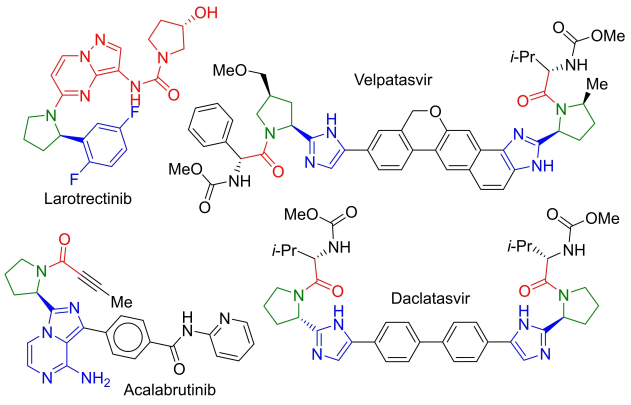

Figure 1. Approved drugs containing 2-(hetero)arylpyrrolidine moiety.

The second approach to the 2-(hetero)arylpyrrolidines is based on the formation of pyrrolidine ring from acyclic precursors. Within this approach, intermolecular cycloaddition reactions play a significant role,[18] [3 + 2] dipolar cycloadditions being the most used ones.[4,19,20] The methods based on the intramolecular cyclization of acyclic precursors are also widely used, especially in the case of polycyclic systems.[6,21,22] The essential drawback of these approaches is the need in preliminary synthesis of starting compounds with appropriate functional groups and desired (hetero)aryl fragment.

Hence, methods allowing simultaneous pyrrolidine ring closure and C–$C_{(hetero)aryl}$ bond formation are of a special interest. Most often this transformation is achieved by intramolecular

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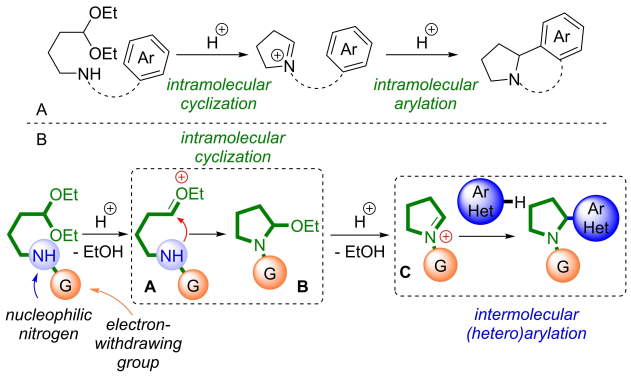
Pictet-Spengler reaction of 4-aminocarbonyl compounds or their acetals possessing aryl moiety (Scheme 1, A).[6,21,23] However, only polycyclic pyrrolidine derivatives are available via this approach. Intermolecular variants of such reactions allowing one-pot synthesis of 2-(hetero)arylpyrrolidines have received much less attention.

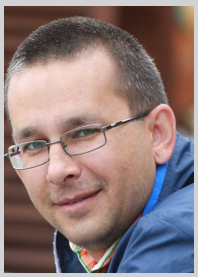


Scheme 1. A) Synthesis of polycyclic pyrrolidine derivatives via intramolecular Pictet-Spengler reaction; B) One-pot approach to 2-(hetero)arylpyrrolidines from *N*-substituted 4,4-diethoxybutan-1-amines.

Thus, the present microreview highlights the advances made towards the one-pot synthesis of 2-(hetero)arylpyrrolidines via consecutive intramolecular pyrrolidine ring closure / intermolecular (hetero)arylation reactions of 4,4-diethoxybutan-1-amine derivatives.

The general strategy for the synthesis of 2-(hetero) arylpyrrolidines via intramolecular cyclizations

The approach to 2-(hetero)arylpyrrolidines from *N*-substituted 4,4-diethoxybutan-1-amines includes two key stages (Scheme 1, B). The first one is the intramolecular attack of nitrogen lone pair on the oxonium cation **A** formed from starting acetal in acidic media. As a result of this intramolecular cyclization, a 2-ethoxypyrrolidine derivative **B** is formed. Further elimination of ethanol molecule provides 1-pyrrolinium cation



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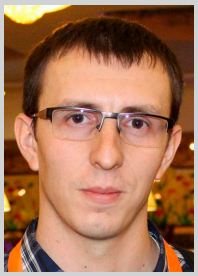

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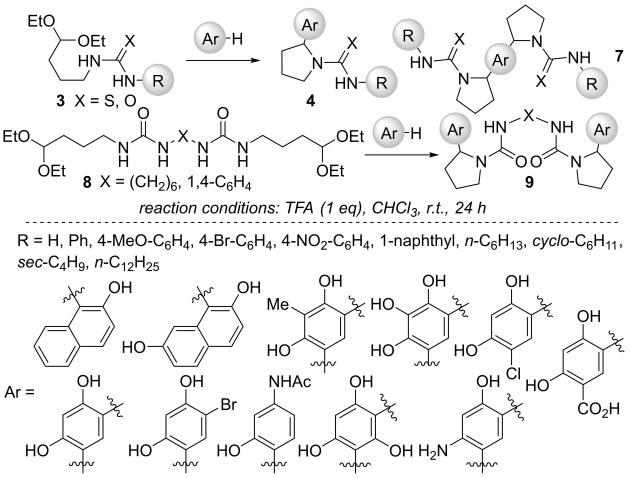
C. The second stage involves the intermolecular (hetero) arylation of this intermediate iminium ion via electrophilic substitution mechanism.

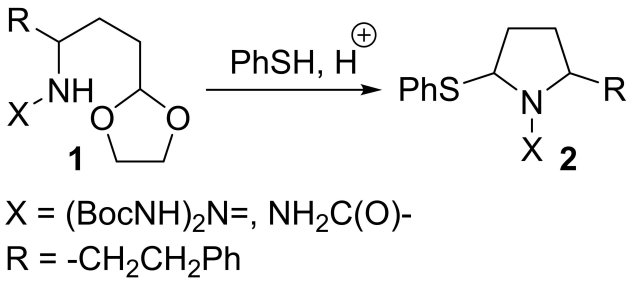
The substituent at the nitrogen atom of 4,4-diethoxybutan-1-amine derivatives plays crucial role in these reactions. Obviously, the nitrogen atom must have sufficient nucleophilicity for the first stage to proceed. At the same time, its basicity should be low enough to prevent its protonation in an acidic medium at least partially. Thus, the substituent must reduce the basicity of the nitrogen atom while keeping its nucleophilicity high enough for the reaction to proceed. Analysis of the data available for intramolecular cyclizations of 4-aminocarbonyl compounds reveals that an amide group is the most frequently occuring substituent. Carbamoyl, carboxyl and sulfonyl groups are used to a lesser extent.[6,21] Groups other than these are exceptionally rare, which may be attributed either to the complicated synthesis of the appropriate derivatives, or to the lack of research in this field, or to both of these reasons.



Scheme 3. Synthesis of *N*-carbamoyl-2-arylpyrrolidines.

Synthesis of 2-(hetero)arylpyrrolidines via intramolecular cyclization of *N*-(4,4-diethoxybutyl)ureas.

The first successful synthesis of 2-substituted pyrrolidine derivatives via intermolecular reaction of 4-aminobutanal acetals **1 a,b** containing guanidine and urea moieties with thiophenol was reported in 2001 by Overman and coworkers (Scheme 2).[24] Notably, only S-alkylated products **2 a,b** have been described.



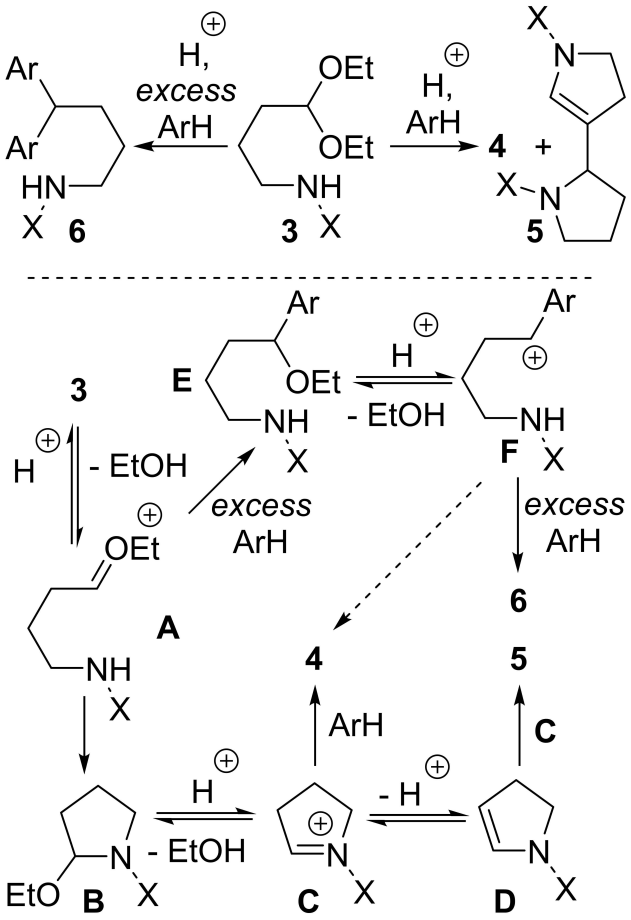
Scheme 2. Synthesis of 2-(phenylthio)pyrrolidines.

Inspired by this work, we developed a method of synthesis of 2-arylsubstituted *N*-carbamoylpyrrolidines **4** based on trifluoroacetic acid-catalyzed reaction of *N*-(4,4-diethoxybutyl) (thio)ureas **3** with aromatic nucleophiles (Scheme 3).[25–29] The reaction proceeds in mild conditions, and both aliphatic and aromatic substituents in ureas **3** are tolerated.

Yields vary widely depending on a substituent at the nitrogen atom. A presence of electron-withdrawing nitro or carboxyl group in phenyl fragment of ureas **3** lowers the yields of target compounds to 9–15%. On the contrary, electron-donating methoxy group increases the yield of corresponding pyrrolidines **4** up to 95%. This may be attributed to the fact that the phenyl ring, the π-electrons of the C=O bond, and the lone electron pairs of both nitrogen atoms form a conjugated system in phenyl-substituted ureas.[30,31] The presence of an electron-withdrawing group in the phenyl substituent causes a decrease of electron density on the nitrogen atoms, and thus hinders a formation of pyrrolidine ring. Vice versa, the electron donors promote the intramolecular cyclization resulting in increased yields of 2-arylpyrrolidines. An influence of alkyl substituents at the nitrogen atom is not so pronounced, and *N*-alkyl substituted pyrrolidines **4** were obtained with 50–60% yield.

The other factor influencing the reaction course is a nucleophilicity of aromatic compound used and urea-to-nucleophile ratio. Electron-rich hydroxybenzenes and naphthols reacted smoothly at room temperature, whereas less nucleophilic aromatics, such as benzene, failed to react even on prolonged heating. Bispyrrole derivatives **5** were the only products in this case (Scheme 4).[28,32] The same products **5** were observed when ureas **3** were used in excess. On the other hand, increasing the amount of aromatic nucleophile leads to the diarylbutane derivatives **6** formation.

A plausible mechanism of these reactions is depicted on Scheme 4.[32] The first stage of the reaction is the carboxonium ion **A** formation via protonation of oxygen atom and elimination of ethanol molecule from starting urea **3**. Subsequent intramolecular cyclization of this carbocation leads to the iminium ion **C** through the intermediate 2-ethoxypyrrolidine **B**. The cation **C** is a highly reactive species and may either react with aromatic nucleophile to give 2-arylpyrrolidine **4** or undergo deprotonation resulting in enamide **D**. Further reaction of this intermediate compound with another iminium cation **C** leads to the formation of bispyrrole derivative **5**. Obviously, the less a nucleophilicity of the aromatic compound, the more bispyrrole **5** is formed, and vice versa. In presence of excess of phenol, interaction of carbocation **A** with it becomes the major pathway. Further reaction of intermediate **E** with another phenol molecule leads to the formation of diarylbutane derivative **6** through the carbocation **F**. In principle,



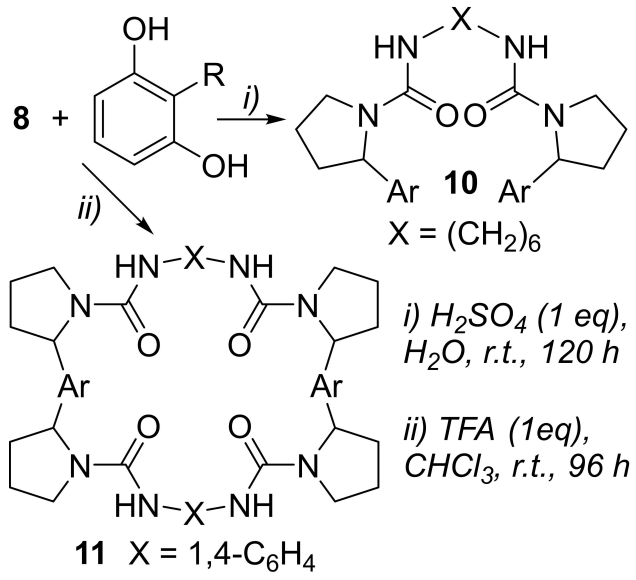
Scheme 4. Plausible mechanism of reaction of 4,4-diethoxybutan-1-amine derivatives with aromatic nucleophiles.

formation of 2-arylpyrrolidines **4** via intramolecular cyclization of cation **F** cannot be completely excluded from consideration. However, this cation seems unlikely to form without the excess of aromatic nucleophile due to high rate of cyclization of intermediate **A**. At the same time, when excess of aromatic nucleophile is used, interaction of carbocation **F** with it dominates over intramolecular cyclisation.

Reaction of ureas **3** with phenols possesing two reactive sites resulted in bis(pyrrolidines) **7** (Scheme 3).[33–37] Interestingly, no mono-substituted products were observed regardless of reactants ratio. When excess of urea **3** was used, the bispyrrole derivatives **5** were formed as byproducts, whereas the excess of phenol led to the diarylbutane derivatives **6** according to mechanism depicted on Scheme 4.

Due to the presence of two asymmetric carbon atoms compounds **7** were obtained mainly as diastereomeric mixtures. Diastereomeric ratio varies from 50 : 50 up to 15 : 85 depending on the structure of starting compounds. However, no unequivocal conclusions about the influence of particular substituents on diasteremiric ratio could be driven from data collected. We do not see any prerequisites for stereoselectivity of these reactions. Probably it is the different solubility of diastereomers in chloroform and solvents used for compounds purification, which affects a diastereomeric ratio. Similarly, a reaction of compounds **8** having two *N*-(4,4-diethoxybutyl)urea moieties connected via polymethylene or 1,4-phenylene spacer give diastereomeric bis(2-aryl)pyrrolidines **9** (Scheme 3)..[25–27]

The synthetic outcome of a reaction of bis(ureas) **8** with resorcinol derivatives depends on a structure of starting compound and reaction conditions (Scheme 5).[38,39] The reac-

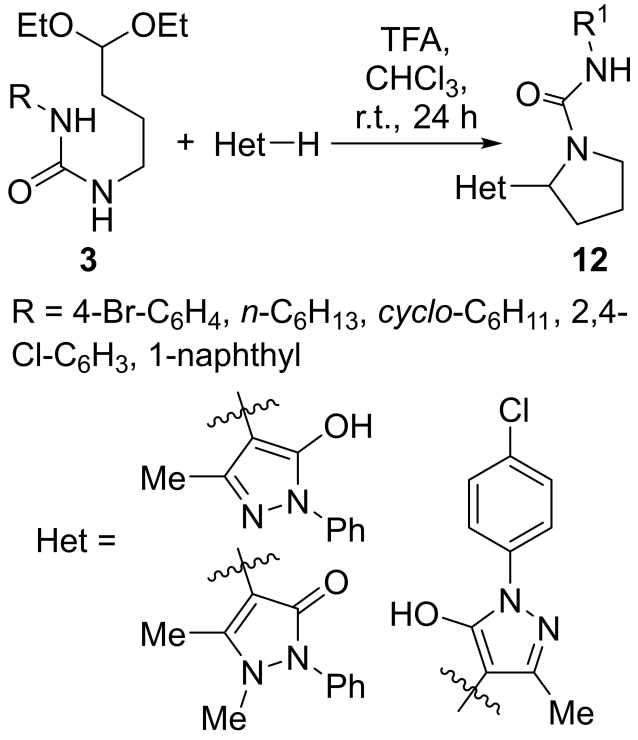


Scheme 5. Synthesis of bis(pyrrolidines) and pyrrolidine-containing macroheterocycles.

tion of urea **8** possessing hexamethylene spacer with two equivalents of resorcinol, 2-methylresorcinol, or pyrogallol in chloroform, benzene, or acetone in the presence of trifluoroacetic acid failed to produce the desired compounds. In all cases a complex mixture of polymeric products was formed. However, target bis(2-aryl)pyrrolidines **10** were successfully obtained using water as solvent and diluted sulfuric acid as catalyst.[38] Interestingly, in this case, only one of the two reactive sites of phenol was substituted. This may be due to precipitation of poorly water-soluble mono-substituted compounds **10**, which stops further reaction. Bis(urea) **8** having 1,4-phenylene spacer reacted with resorcinol, 2-methylresorcinol, and pyrogallol to give a new class of macroheterocyclic compounds **11**.[39] Notably, although the reactions were carried out without resorting to techniques specific to a synthesis of macrocyclic compounds (i.e., strong dilution of the reaction mixture), macrocycles **11** were isolated with more than 60% yield. This may be due to low solubility of the products **11** and starting bis(urea) **8** in chloroform, which ensured very low concentrations of reactants in solution.

We anticipated that the usage of heterocyclic nucleophiles instead of aromatics in these reactions should lead to the pyrrolidine derivatives bearing heterocyclic moiety at the 2nd position of pyrrolidine ring. As was already mentioned, this scaffold appears in many natural alkaloids and approved drugs,

thus representing an important synthetic target. Taking this into account, pyrazolones were chosen as substrates for this reaction. As a result, a series of previously unknown 2-(pyrazole-4-yl)pyrrolidines **12** were obtained with ~70% yield (Scheme 6).[40]



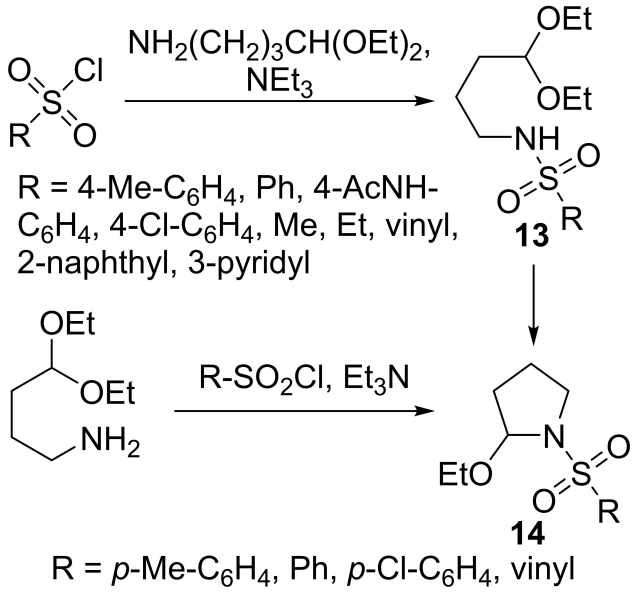
Scheme 6. Synthesis of *N*-carbamoyl-2-(pyrazol-4-yl)pyrrolidines.

Synthesis of 2-arylpyrrolidines via intramolecular cyclization of *N*-(4,4-diethoxybutyl)sulfonylamides.

Pyrrolidine derivatives containing sulfonamide group and aromatic moiety exhibit wide range of biological activity. 1-Sulfonyl-2-arylpyrrolidines are suggested for the treatment of thromboembolic[41] and neurodegenerative disorders, such as Huntington, Parkinson[42,43] and Alzheimer[44] deseases. These compounds also act as antagonists of chemokine receptor CCR4[45] and κ-opioid receptors.[46] There is evidence of the ability of these compounds to inhibit matrix metalloproteinase 2 (MMP2),[47] endothelin converting enzyme,[48] and carbonic anhydrase II.[49] ^{18}F-labeled phenylsufonylpyrrolidines can be used as contrast agents for positron emission tomography.[50]

Methods of synthesis of these compounds fall within two main approaches mentioned in introduction, with various inter- and intramolecular cyclizations being the most used ones. A cyclization of aryl substituted alkenes and alkynes containing sulfonamide group[51–55] and various [3+2] cycloadditions[18] can be given as examples. The most obvious and straightforward way of the synthesis of 1-sulfonyl-2-arylpyrrolidines is a reaction of 2-arylpyrrolidines with sulfonyl chlorides. Surprisingly, it is used only occasionally.[47,56] These methods also suffer from the above mentioned drawbacks, i.e. harsh reaction conditions, usage of expensive catalysts and reagents and a need in preliminary synthesis of appropriately substituted starting compounds.

Since amide and sulfonamide groups are isosteric and possess similar electronic characteristics, we supposed that *N*-(4,4-diethoxybutyl)sulfonylamides are able to react with electron-rich aromatics in acidic media similarly to *N*-(4,4-diethoxybutyl)ureas. This was further supported by syntheses of 2-hydroxy- or 2-methoxypyrrolidines from 4-(sulfonylamido)butanal derivatives in acidic media reported by King[57] and Wang with coworkers.[58] Additionally, during our studies we have also discovered that *N*-(4,4-diethoxybutyl)sulfonylamides **13** are prone to intramolecular cyclization in the presence of acids (Scheme 7). Based on these data, we have developed a one-pot

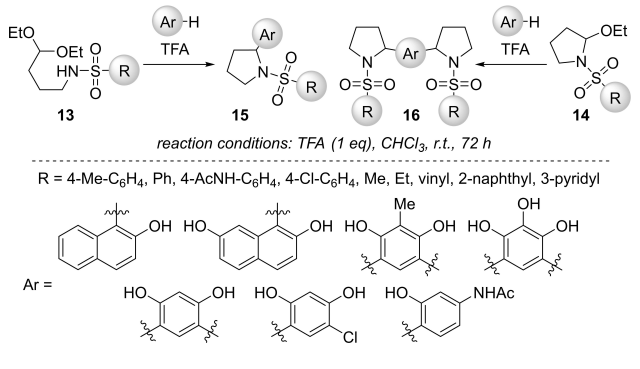


Scheme 7. One-pot synthesis of 1-sulfonyl-2-ethoxypyrrolidines.

approach to 1-sulfonyl-2-ethoxypyrrolidines **14** via a reaction of 4,4-diethoxybutan-1-amine with various sulfonyl chlorides (Scheme 7).[59–61] Notably, these compounds are valuable intermediates in the synthesis of various pyrrolidine derivatives.[62–68]

The reaction of sulfonylamides **13** with electron-rich aromatics actually led to the 1-sulfonyl-2-arylpyrrolidines **15** (Scheme 8).[59,69–71] Alkyl, alkenyl, aryl, hetero- and polyaromatic substituents in sulfonylamides **13** are well tolerated, and yields of target compounds are generally good. Notably, the influence of substituents on yield of pyrrolidines is not so distinct compared to ureas **3**. Apparently, this is due to the absence of conjugation between (hetero)aryl substituent and nitrogen lone pair, as in the case of compounds **3**.

The scope of aromatics is similar to that observed for the reaction with ureas. Again, the less a nucleophilicity of aromatic compounds, the less readily it undergoes the reaction and an absence of electron-donating substituent prevents the reaction



Scheme 8. Acid-mediated synthesis of 1-sulfonyl-2-arylpyrrolidines.

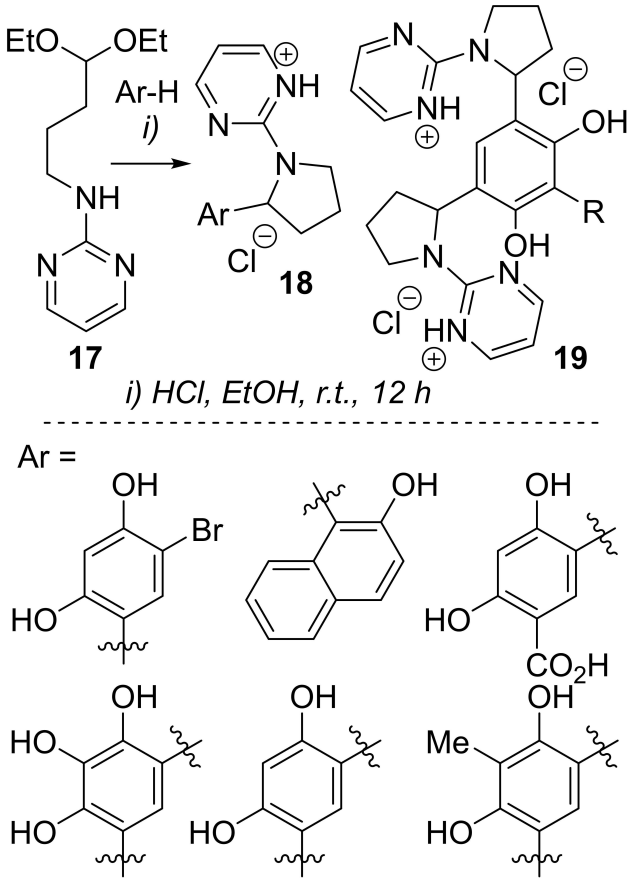
completely. Phenols possessing two reactive positions give bis (pyrrolidines) **16** as diastereomeric mixtures.[60,69,70] Remarkably, carrying out the same reactions in benzene instead of chloroform allowed to obtain some of target pyrrolidine derivatives as a single diastereomers.[60]

The mechanistic proposal for the target compounds formation is the same as for ureas **3** (Scheme 4). However, in case of *N*-(4,4-diethoxybutyl)sulfonylamides **13** the reaction stops at the 2-ethoxypyrrolidines **14** formation, and no bispyrroles similar to compounds **5** were observed. This may be attributed to the higher electron density on the nitrogen atom in sulfonylamides compared to ureas,[72,73] which stabilizes the iminium cation **B** and decreases its deprotonation rate (see Scheme 4). Interestingly, 1-sulfonyl-2-ethoxypyrrolidines **14** also react with phenols under the same conditions to give pyrrolidines **15** and **16**.[59–61] This fact, together with isolation of these compounds from the reaction mixtures, supports our proposal for the reaction mechanism.

Synthesis of 2-arylpyrrolidines via intramolecular cyclization of other 4,4-diethoxybutan-1-amine derivatives.

As was mentioned before, the role of substituent in 4,4-diethoxybutan-1-amine derivatives in these reactions is to balance the nucleophilicity and basicity of the nitrogen atom, thus preventing it from protonation in acidic media and keeping it reactive enough for the intramolecular cyclization to proceed. Analysis of literature shows that these substituents are electron-withdrawing amide, carbamoyl, carboxyl or sulfonyl groups, amide group being used the most often. Other derivatives of 4,4-diethoxybutan-1-amine are only scarcely used in spite of the fact that they may serve as promising starting compounds for the one-pot synthesis of *N*-substituted pyrrolidines. As an example, a cyclization of *N*-(4,4-diethoxybutyl) pyrido[2,3-d]pyrimidin-2-amine derivative leading to 2-ethoxypyrrolidine can be given.[74] This work, however, received no further attention.

The fruitfulness of this approach to various *N*-substituted 2-(hetero)arylpyrrolidine derivatives have been demonstrated by synthesis of 2-(2-arylpyrrolidin-1-yl)pyrimidines **18** and **19** via hydrochloric acid-catalyzed cyclization of *N*-(4,4-diethoxybutyl) pyrimidin-2-amine **17** in the presence of phenols (Scheme 9).[75]

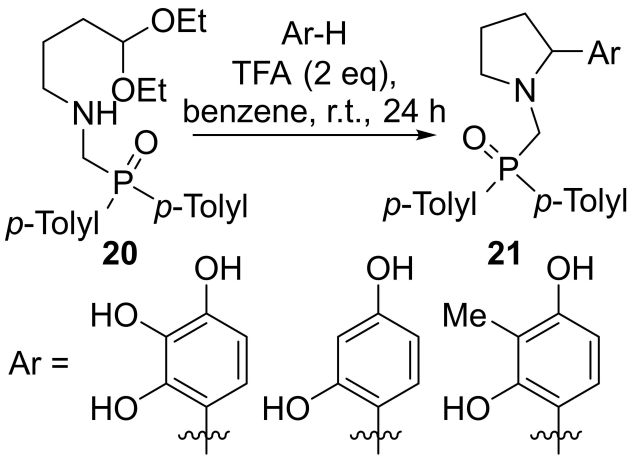


Scheme 9. Synthesis of 2-(2-arylpyrrolidin-1-yl)pyrimidines.

In principle, the mechanism of this reaction doesn't differ significantly from that proposed for ureas **3** and sulfonylamides **13** (see Scheme 4). Apparently, a π-electron-deficient pyrimidine moiety serves as electron-withdrawing group in this case. Additionally, a protonation of pyrimidine ring in acidic solution enhances its electron-withdrawing ability thus promoting intramolecular cyclization.

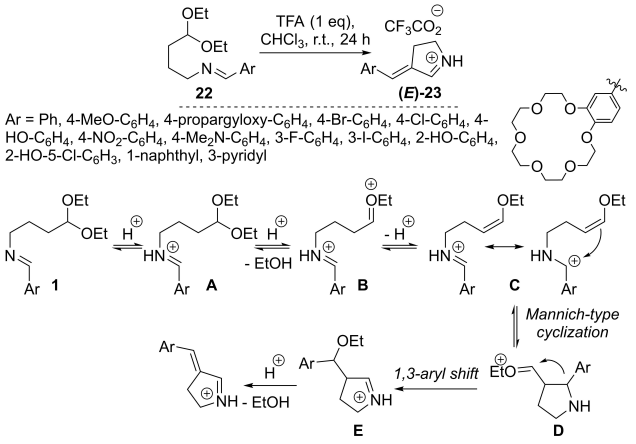
An excessive increase in this effect, however, may interfere with a cyclization, as exemplified by the reaction of *N*-(4,4-diethoxybutyl)-1,3,5-triazin-2-amine with phenols.[76] Only acyclic diarylbutane derivatives **6** are observed in this case, indicating that nucleophilicity of a nitrogen atom is too low for pyrrolidine ring closure.

Recently, a synthesis of phosphorus-containing 2-arylpyrrolidines **21** via acid-promoted reaction of phenols with (((4,4-diethoxybutyl)amino)methyl)di-p-tolylphosphine oxide **20** was reported (Scheme 10).[77] Notably, aminophosphine oxides (pK_a of conjugated acids ≈ 3…7[78,79]) are much stronger bases than ureas or sulfonylamides. Thus, phosphine oxide **20** in acidic media is likely to exist as ammonium salt mainly. Nonetheless, the electron-withdrawing effect of (diarylphosphoryl)methyl group appears to be sufficient to increase the concentration of a free base **20**, thus triggering intramolecular cyclization and pyrrolidine ring closure.



Scheme 10. Synthesis of phosphorus-containing 2-arylpyrrolidines.

The importance of nucleophilicity-basicity balance of nitrogen atom in reactions under consideration is demonstrated by behavior of *N*-(4,4-diethoxybutyl)arylimines **22** in the presence of acids.[80] An interaction of these compounds with various phenols leads to mixtures of unidentified products, whereas in the absence of aromatic nucleophiles they easily undergo intramolecular cyclization to pyrrolidine derivatives **23**. However, the plausible mechanism for this reaction differs from that proposed for cyclization of other 4,4-diethoxybutan-1-amine derivatives (Scheme 11). According to it, the formation of



Scheme 11. Acid-catalyzed intramolecular cyclization of *N*-(4,4-diethoxybutyl)-1-arylmethanimines.

iminium salt **A** is a first step of the reaction. Subsequent elimination of ethanol molecule leads to enol derivative **C** via oxonium ion **B**. Further intramolecular cyclization involving double C=C bond gives 2-arylpyrrolidine intermediate **D**. The combination of these steps can be considered as intramolecular Mannich reaction, similar to the previously described cyclization of γ-aminobutyric acid imines.[81] Next step is [1,3]-sigmatropic rearrangement leading to intermediate **E**. The driving force of this rearrangement is presumably the formation of more stable iminium cation. A final step of the reaction is (*E*)-3-arylidene-1-pyrroline **23** formation through the elimination of ethanol molecule. As seen from the above mechanism, a protonation of fairly basic imine nitrogen in *N*-(4,4-diethoxybutyl)arylimines **22** "turns off" its nucleophilicity and drives a reaction to a completely different pathway.

Conclusions

This minireview highlights the potential of 4-aminobutanal derivatives in synthesis of 2-(hetero)arylpyrrolidines. A general overview of the literature reveals that although a number of approaches to 2-(hetero)arylpyrrolidines have been developed, almost none of them allows simultaneous pyrrolidine ring closure and exocyclic carbon-carbon bond formation, thus providing one-pot synthesis of target compounds. In this context, reactions of *N*-substituted 4,4-diethoxybutan-1-amine derivatives provide straightforward and efficient access to a 2-(hetero)arylpyrrolidine scaffold. Another interesting features of this chemistry are mild reaction conditions and readily available starting materials / catalysts. We hope that this minireview will stimulate further research in this field. The application of the described reactions has not yet reached its full potential. For instance, an extension of a substrate scope towards the less reactive (hetero)aromatic and non-aromatic *C*-nucleophiles, search for other non-amidic substituents at nitrogen atom, as well as development of asymmetric variants of these reactions, seems worthwhile.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: arenes · cyclization · Mannich reaction · nitrogen heterocycles · synthetic methods

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