

NITROGEN AND PHOSPHORUS-CONTAINING ACETALS IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

A.S. Gazizov*, A.V. Smolobochkin, E.A. Anikina, A.S. Melyashova
L.I. Vagapova, Y.M. Sadykova, A.R. Burirov, M.A. Pudovik

¹Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center of RAS,
Kazan, Russia

Abstract. Herein we describe a novel approach to the aryl-substituted nitrogen heterocycles based on the acid-catalyzed intramolecular cyclization / intermolecular electrophilic aromatic substitution reaction sequence of nitrogen- and phosphorus-containing acetals with aromatic nucleophiles. The proposed approach benefits from usage of readily available starting materials, nontoxic / inexpensive catalysts and provides a convenient route to the C- and N-substituted imidazolidine, pyrrolidine and piperazine derivatives.

Keywords: nitrogen heterocycles, acetals, intramolecular cyclization, aromatic substitution

Corresponding Author: Prof. Almir S. Gazizov, Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center of RAS, 420088, Arbuzova str., 8, Kazan, Russian Federation, Tel.: +7-843-272-73-24, e-mail: agazizov@iopc.ru

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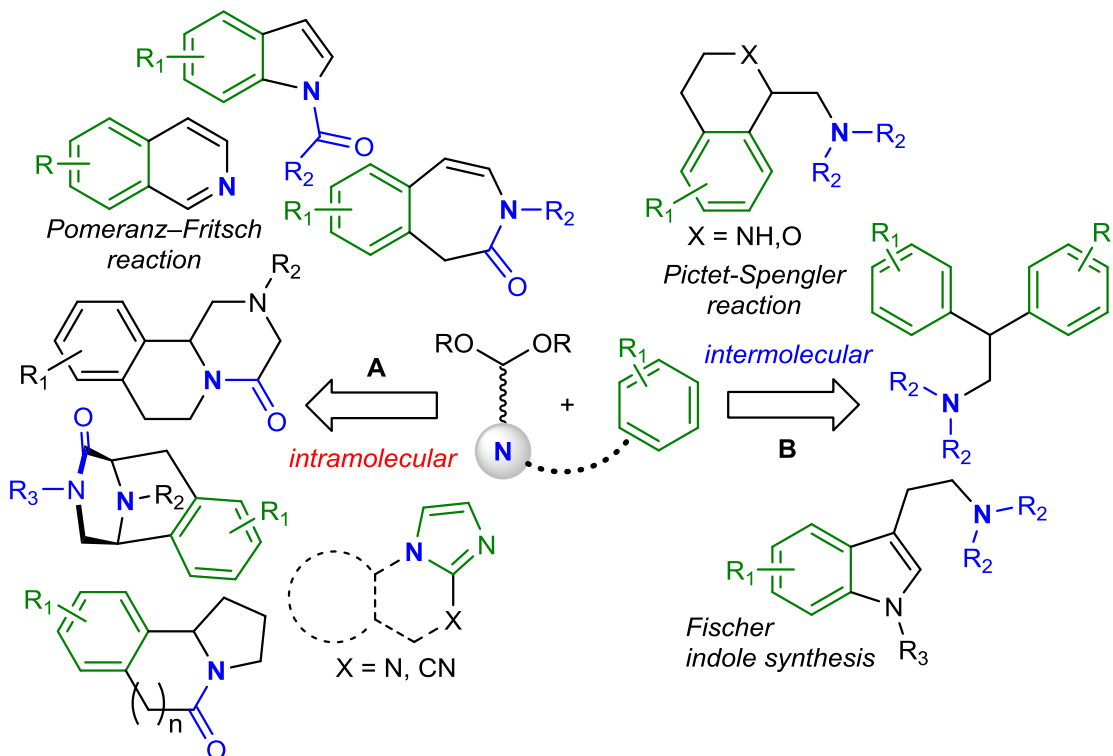
1. Introduction

Nitrogen-containing acetals serve as valuable synthetic blocks in various fields of organic chemistry because of their pronounced versatility due to the presence of both the masked formyl group and suitably protected amino functionality in the molecule (Gryko *et al.*, 2003; Jurczak and Golebiowski, 1989; Mann, 2001). The reactions of these compounds with various aromatic nucleophiles play an important role in the synthesis of various heterocycles and were reviewed by us previously (Chugunova and Burirov, 2017; Gazizov *et al.*, 2016; Gazizov *et al.*, 2017). Analysis of the literature data reveals two important facts (Scheme 1).

First of all, the intramolecular reactions of nitrogen-containing acetals with aromatics are limited in number and represented by only three pathways. Moreover, two of them, namely, the Fischer indole synthesis (Guzzo *et al.*, 2009) and Pictet-Spengler reaction (González *et al.*, 2005) are well known (Hughes, 1993; Stöckigt *et al.*, 2011). The only difference between these reactions and their classical variants is the use of nitrogen-containing acetals as the carbonyl source. The third pathway leading to the diarylmethane derivatives is mentioned in quite a few publications (Battersby and Binks, 1955; Humber *et al.*, 1966; Julia and Tilly, 1965; Klumpp *et al.*, 2002; Maryanoff *et al.*, 1987). Notably, the nitrogen-containing group is mainly an amino group and does not participate in the reaction (Scheme 1, B).

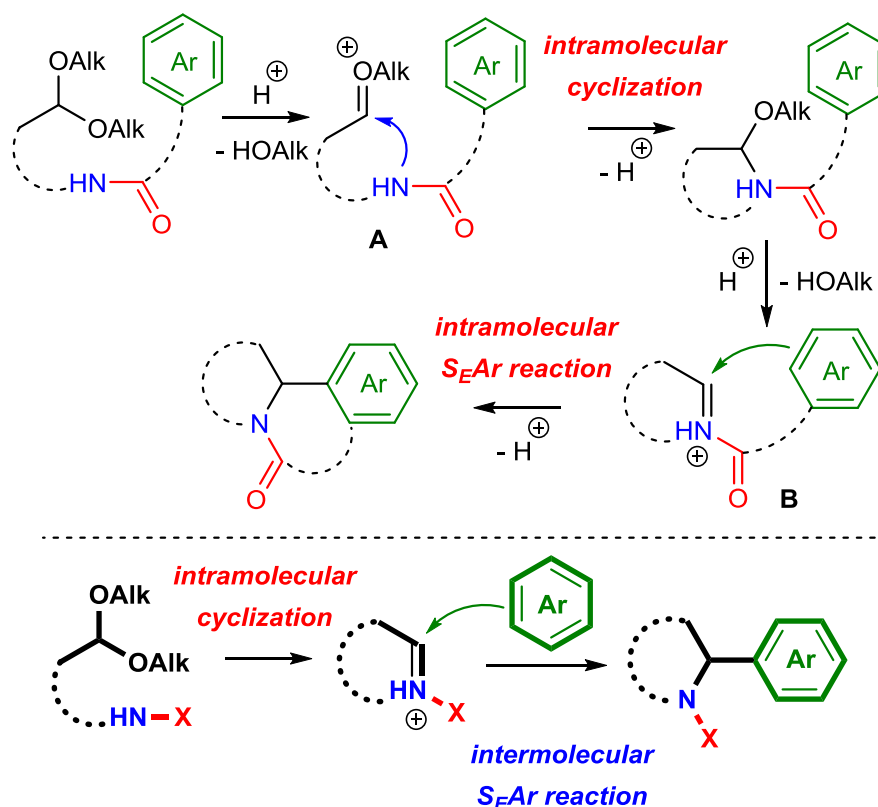
The vast majority of the reactions of nitrogen-containing acetals with aromatic nucleophiles are intermolecular, the nucleophile being the part of the acetal molecule. The range of products formed in these reactions is quite wide and includes derivatives

of benzazepine, indole, naphthalene, quinoline and isoquinoline, as well as polycyclic compounds. As a rule, the nitrogen atom in these cases is a part of amide group and participates in the reaction as a nucleophile (Scheme 1, B). It also should be noted that all of these reactions are acid-catalyzed, Bronsted acids being the most used ones.



Scheme 1. Reactions of nitrogen-containing acetals with aromatic nucleophiles

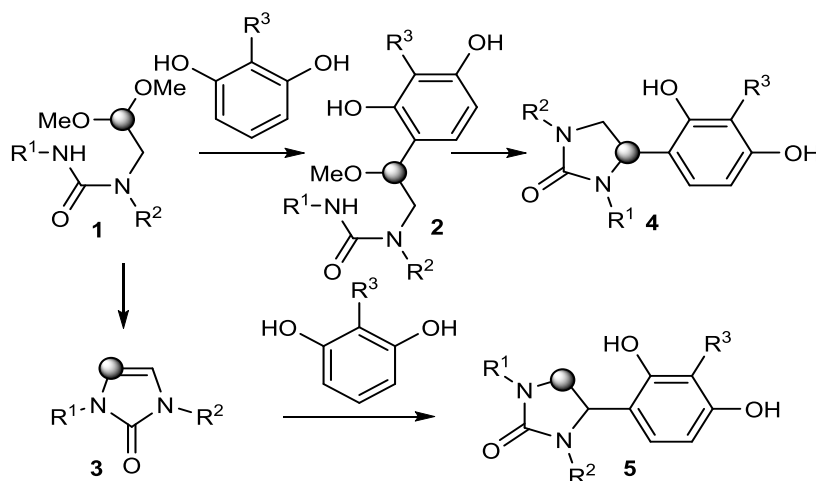
The necessity of the presence of a carbonyl substituent at the nitrogen atom becomes clear if one considers the mechanism of these reactions, which includes two key stages (Scheme 2). The first one is the nucleophilic attack of the nitrogen lone pair on the oxonium ion **A**, which leads to the first heterocyclic ring closure. At the next stage, the second ring is formed via the intramolecular S_{EAr} reaction of aromatic nucleophile with iminium ion **B**. Obviously, the nitrogen atom should be nucleophilic enough for the first stage to proceed. At the same time, its basicity should be low enough to prevent its protonation in an acidic environment. Thus, the electron-withdrawing carbonyl substituent plays the essential role in these reactions and maintains the required balance between the low basicity of the nitrogen atom and its sufficiently high nucleophilicity. Assuming all of the above, we have proposed the approach to the aryl substituted nitrogen heterocycles based on the intramolecular cyclization of nitrogen-containing acetals having the appropriate electron-withdrawing substituent at the nitrogen atom and subsequent intermolecular reaction of aromatic nucleophiles with intermediate iminium ion (Scheme 2). The key difference of this approach from the existing ones is the simultaneous closure of heterocyclic ring and formation of exocyclic carbon-carbon bond. Thus, it eliminates the tedious synthesis of appropriately substituted starting materials and opens the one-pot access of the target heterocycles. Additionally, both the aromatic nucleophile and substituent at the nitrogen atom can be varied easily hence giving the possibility to introduce the desired functionality into the molecule.



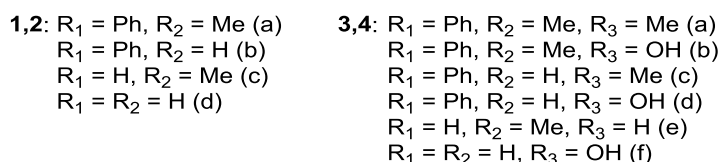
Scheme 2. Plausible mechanism of heterocycles formation and the proposed approach to the aryl substituted heterocycles.

2. Discussion

First, we have tried out the proposed approach using the (2,2-dimethoxyethyl)urea derivatives **1** as a model compounds. The phenols were chosen as the aromatic nucleophiles due to their high nucleophilicity as well as stability in strongly acidic media. The reaction proceeded smoothly in the presence of trifluoroacetic acid in refluxing chloroform and led to the formation of isomeric imidazolidine-2-ones **4** and **5** (Scheme 3) (Burilov *et al.*, 2008a; Burilov *et al.*, 2008b; Gazizov *et al.*, 2009; Khakimov *et al.*, 2009). We speculated that the formation of imidazolidines **4** proceeds via intermolecular alkylation of phenol with urea derivative **1** followed by intramolecular cyclization of intermediate benzyl ether **2**, whereas isomeric heterocycles **4** formed by the intramolecular cyclization of starting urea (Forrest *et al.*, 1974) **1** and subsequent alkylation of phenol with enamide derivative **3**. This hypothesis was further supported by the isolation of intermediates **3**. Interestingly, the reaction of these compounds with appropriate phenols led to imidazolidine-2-ones **5** solely, and no isomeric compounds **4** were detected in any case.

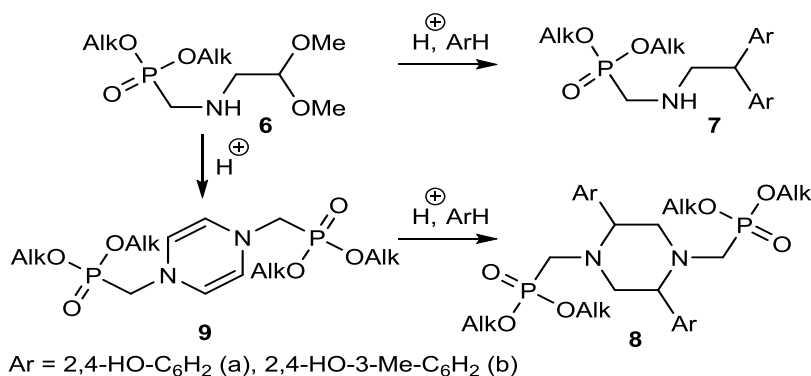


Reaction conditions: TFA, CHCl_3 , 4 h, reflux



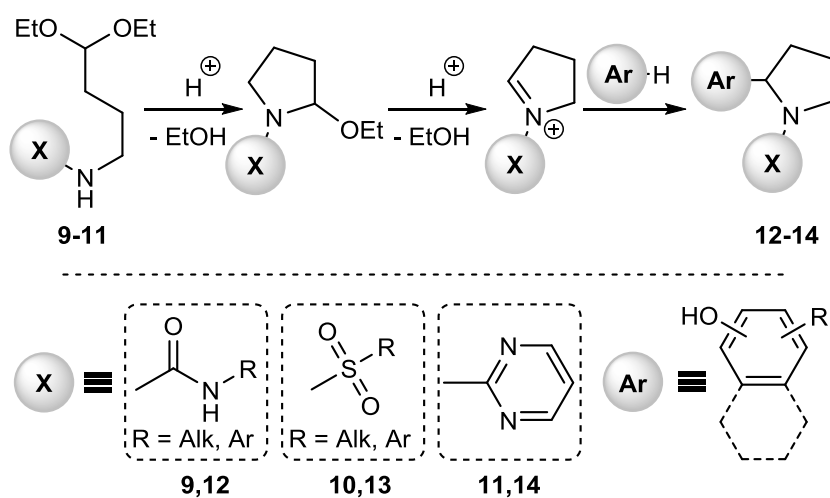
Scheme 3. Synthesis of aryl substituted imidazolidine-2-ones.

Next, we studied the reaction of phosphonates **6** with phenols in acidic media. It turned out that in this case the reaction leads to the mixture of the diarylmethane derivatives **7** and 2,5-diarylpyperazines **8** (Scheme 4). The formation of aryl-substituted piperazines **8** can be rationalized via initial condensation of two acetal molecules followed by two subsequent intermolecular $\text{S}_{\text{E}}\text{Ar}$ reactions of intermediate enamine **9** with phenol. Notably, similar reaction of 2,2-dialkoxyethan-1-amines with phenols led to the diarylmethane derivatives as the only products (Battersby and Binks, 1955; Buriilov *et al.*, 2005; Chugunova *et al.*, 2016a; Chugunova *et al.*, 2016b; Gazizov *et al.*, 2016; Gazizov *et al.*, 2013; Humber *et al.*, 1966; Julia and Tilly, 1965; Klumpp *et al.*, 2002; Maryanoff *et al.*, 1987). This is probably due to the protonation of nitrogen atom in the presence of acids, which inhibits formation of heterocyclic compounds as discussed above. Thus, one can speculate that the (dialkoxyphosphoryl)methyl moiety appears to be not electron-withdrawing enough to prevent fully the protonation of nitrogen atom so that the formation of diarylmethane derivatives **7** also becomes possible.



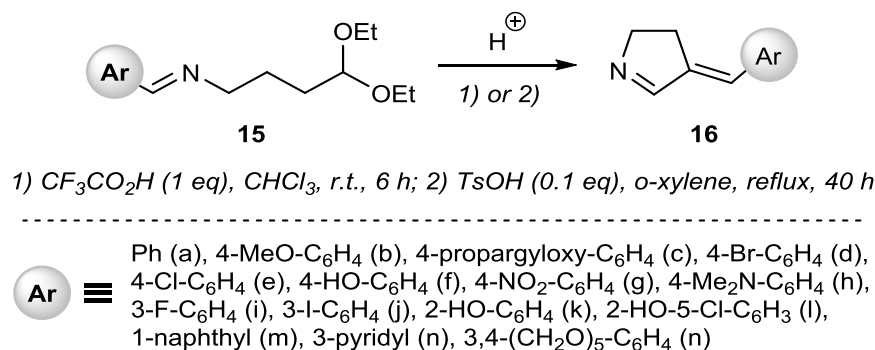
Scheme 4. Synthesis of diarylmethanes **7** and piperazines **8**

Further, we have increased the polymethylene spacer length between the acetal group and nitrogen-containing fragment. Thus, the reaction of (4,4-diethoxybutyl)ureas **9** with various phenols led to the formation of 2-arylpyrrolidines **12**. The reaction proceeds via intramolecular cyclization of urea to give cyclic iminium cation and its further interaction with aromatic nucleophile (Garifullin *et al.*, 2016; Gazizov *et al.*, 2014a, 2015; Gazizov *et al.*, 2014b; Gazizov *et al.*, 2015; Smolobochkin *et al.*, 2017). Both alkyl- and aryl-substituted ureas undergo this reaction. In case of aryl substituent, the presence of electron-withdrawing group decreases the yield of target pyrrolidine. This is probably due to the decrease of electron density on the nitrogen atom. Similarly, reaction of acetals possessing sulphonyl (Gazizov *et al.*, 2017; Smolobochkin, *et al.*, 2016a, 2017a; Smolobochkin, *et al.*, 2016b; Smolobochkin *et al.*, 2017b; Strobykina *et al.*, 2015) and pyrimidin-2-yl (Gazizov *et al.*, 2015) substituent led to the appropriate 2-arylpyrrolidine derivatives **13** and **14** (Scheme 5).



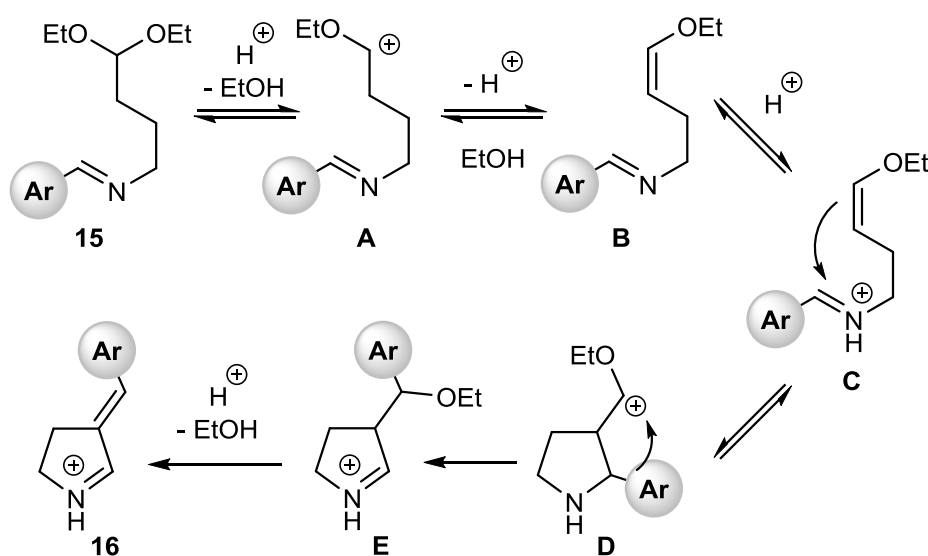
Scheme 5. Synthesis of 2-arylpyrrolidines **12-14**

Since imines are known to act as nucleophiles in the reactions involving cationic species, we proposed that the acetals containing imine moiety would also be subject to similar intramolecular cyclization. However, the acid-catalyzed reactions of acetals **15** appeared to be quite different from the abovementioned reactions. Surprisingly, the intramolecular cyclization of these compounds led to the formation of (*E*)-3-arylidene-1-pyrrolines **16** (Scheme 6) (Gazizov, *et al.*, 2017). Until recently, the only method for the synthesis of these compounds was the reaction of benzaldehyde derivatives with 1-pyrroline (Sampedro *et al.*, 2004) or pyrrolidine (Mandal *et al.*, 2015).



Scheme 6. Synthesis of 3-arylidene-1-pyrrolines **16**

In the next step, we studied the effect of aromatic substituent on the course of this reaction. The introduction of electron donor substituent at *p*-position of aromatic fragment slightly increases the yield of products. The presence of electron acceptor nitro groups at *p*-position or halogens gives a slight decrease in the yield of pyrrolines. As follows from the experimental data, the substituents at *p*- and *m*-positions of phenyl fragment affect weakly the yield of target compounds. The presence of substituents at *o*-position restricts the reaction, though in this case target compounds can be prepared in reasonable yields. However, with the substitution of hetero- and polyaromatic fragments for phenyl, target compounds are not observed. The exceptions are compounds (*E*)-**16m,n**, which were isolated in 31% and 84% yield, correspondingly. It should also be noted that exclusively (*E*)-isomers of compounds **16** were obtained and no (*Z*)-isomers were detected in either case.



Scheme 7. Proposed mechanism of formation of pyrrolines **16**

The proposed mechanism of the reaction is given in Scheme 7. According to scheme, the first step of the reaction is the protonation of nitrogen atom with the formation of oxonium ion **A**. Subsequent elimination of proton leads to enol derivative **B**. Further intramolecular cyclization involving π -electrons of double C=C bond gives cyclic intermediate **D**. The combination of these steps can be considered as intramolecular Mannich reaction, which is analogous to the previously described cyclization of imines of γ -aminobutyric acid under the action of Lewis acid (Suresh and Periasamy, 2004). In the next step of reaction, intermediate **E** is formed as a result of [1,3]-sigmatropic rearrangement, which is accompanied by the migration of aryl fragment. The driving force of this rearrangement is presumably the formation of more stable iminium cation. It should be noted that the reactions accompanied by 1,3-migration of phenyl group are quite rare. Until recently, only one example of 1,3-migration of phenyl group in pyrrole derivatives was known (Cheung and Sammes, 1991). In the final step of reaction, (*E*)-3-arylidene-1-pyrroline **16** is formed through the elimination of ethanol molecule.

3. Conclusion

In conclusion, we have successfully developed the approach to the various nitrogen heterocycles via acid-catalyzed intramolecular cyclization/aromatic electrophilic substitution reaction sequence of nitrogen-containing acetals and aromatic nucleophiles. The proposed approach benefits from usage of readily available starting materials, nontoxic / inexpensive catalysts and provides a convenient route to the C- and N-substituted imidazolidine, pyrrolidine and piperazine derivatives.

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