ACID-CATALYZED REACTION OF (4,4-DIETHOXYBUTYL)UREAS WITH PHENOLS AS A NOVEL APPROACH TO THE SYNTHESIS OF \( \alpha \)-ARYLPYRROLIDINES

Almir S. Gazizov, Andrey V. Smolobochkin, Julia K. Voronina, Alexander R. Burilov, and Michail A. Pudovik
A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, Kazan, Russian Federation

GRAPHICAL ABSTRACT

Abstract 1-(4,4-Diethoxybutyl)-3-alkylureas undergo intramolecular cyclization in the presence of trifluoroacetic acid and various phenols, leading to the new N-alkyl-2-arylpyrrolidine-1-carboxamides with moderate to excellent yields. It was found that these compounds undergo spontaneous solid-phase epimerization at room temperature. Advantages of the proposed approach are mild reaction conditions and no need for expensive reagents or catalysts.

Keywords 2-Arylpyrrolidine; cyclization; electrophilic aromatic substitution; phenols; ureas

INTRODUCTION

There are many known alkaloids, antibiotics, and synthetic drugs that contain pyrrolidine cores substituted at the \( \alpha \)-carbon atoms.[1–6] Among them, \( \alpha \)-arylpyrrolidines are of particular interest. These compounds are used as chiral catalysts[7] and organocatalysts.[8–10] Also \( \alpha \)-arylpyrrolidines possessing carboxamide substituent at

Received December 3, 2014.
Address correspondence to Almir S. Gazizov, A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, 8 Arbuzova str., Kazan 420088, Russian Federation. E-mail: agazizov@iopc.ru
the nitrogen atom have been patented as somatostatin receptor inhibitors,[11] glutamate receptors modulators,[12] histamine-H3 receptor antagonists,[13] anticancer drugs,[14] inhibitors of phosphoinositide 3-kinase,[15] and drugs for the treatment of neurological and neurodegenerative disorders such as Parkinson’s disease[16] and Alzheimer’s disease.[16,17]

Most of the strategies for the synthesis of substituted pyrrolidines employ intramolecular C–N bond-forming reactions for the construction of the heterocyclic ring.[18,19] However, very few methods allow for simultaneous intramolecular C–N bond formation and intermolecular formation of a α-C carbon–carbon bond.[20–23] Existing methods require harsh reaction conditions or toxic or expensive reagents, such as Pd complexes.[24] There is only one example of synthesis of α-substituted pyrrolidine via reaction of 1-(4-oxobutyl)urea derivative with thiophenol in acidic media.[25]

It should be noted that the vast majority of the published papers refer to 2-arylpyrrolidine-1-carboxamides having an aryl substituent at the nitrogen atom. 2-Arylpyrrolidine-1-carboxamides containing alkyl substituents received much less attention from the researchers. Methods of synthesis of such compounds include reactions of appropriate 2-arylpyrrolidines with isocyanates[26–28] or triphosgene followed by treatment of an intermediate product with amine[29] or interaction of amines with pyrrolidinecarbonylchloride.[12] There are virtually no methods allowing for the one-pot synthesis of N-alkyl-2-arylpyrrolidine-1-carboxamides, without the need to isolate intermediate 2-arylprrrolidines.

**DISCUSSION**

Earlier, we have reported a method of synthesis of 2-arylpyrrolidines based on intramolecular cyclization of 1-(4,4-diethoxybutyl)-3-arylureas in the presence of phenols and trifluoroacetic acid as catalyst.[30–32] The reaction proceeds smoothly at room temperature and allows wide variation in both aryl substituent of urea and structure of phenol. Herein, we report the application of this method to the one-pot synthesis of 2-arylpyrrolidine-1-carboxamides having an alkyl substituent at the nitrogen atom.

Starting 1-(4,4-diethoxybutyl)-3-alkylureas (γ-ureidoacetals) 1a–d were obtained via the reaction of aliphatic amines with 1,1’-carbonyldiimidazole (CDI) followed by treatment of intermediate N-alkyl-1H-imidazole-1-carboxamides with 4,4-diethoxybutan-1-amine (Scheme 1).

![Scheme 1. Synthesis of starting ureas 1.](image-url)
Interaction of compounds 1a–d with 2-naphthol in a 1:1 molar ratio in chloroform in the presence of trifluoroacetic acid leads to the formation of pyrrolidine derivatives 2a–d (Scheme 2). It should be noted that the compound 2a was isolated as a mixture of two diastereomers.

Structures of the compounds 2b,c were proved by x-ray analysis (Figs. 1 and 2). The crystal structures of both compounds represent the infinite chains oriented via 0a axis, which are formed by the classical O-H…O H-bonds. The chains are linked by the CH…O interactions.

Further investigations showed that the acid-catalyzed intramolecular cyclization of ureas 1a–d at the presence of diatomic phenols, namely, resorcinol, 2-methylresorcinol, and pyrogallol, gives rise to the bis(pyrrolidine-1-carboxamides) 3a–d, 4a–d, and 5a–d (Scheme 3).

All of the synthesized compounds were isolated as a mixture of diastereomers. Analysis of NMR data revealed that in the cases of compounds 3–5d containing

![Scheme 2. Reaction of ureas 1 with 2-naphthol.](image)

![Figure 1. Molecular structure of compound 2b in crystal. The minor component of the disordered hexyl chain and H-atoms are omitted for clarity.](image)
dodecyl substituent, and compound 3b, containing n-hexyl substituent, one of the
diastereomers predominates slightly [dr 40:60 (3d, 4d, 3b) and 35:65 (5d)]. Diastereomeric ratios for the compound 3c and compounds 4b and 5c are much greater and equal 15:85 and \( \approx 0:100 \) respectively. In all other cases, except for compounds 3–5a, products were isolated as equimolar mixtures of diastereomers (Table 1). Spectral data for bis(pyrrolidine-1-carboxamides) 3–5a having four chiral centers confirm the presence of multiple diastereomers; however, exact diastereomeric composition of these compounds could not be determined due to heavy signal overlapping in NMR spectra.

![Figure 2. Molecular structure of compound 2c in crystal.](image)

![Scheme 3. Reaction of ureas 1 with diatomic phenols.](image)
Interestingly, compounds 3c and 5c undergo spontaneous solid-phase epimerization upon standing at room temperature. According to NMR data, after 2 months, the amount of diastereomers was almost equal for both compounds (see spectra in Supplementary Material). Although solid-phase interconversion of stereoisomers is discussed in several papers,[33–35] we could not find examples of such transformations for pyrrolidine derivatives. We suggest that different diastereoselectivity of the abovementioned reactions, as well as failure of our attempts to isolate individual diastereomers, may be attributed to their easy interconversion.

In summary, we have successfully applied our method to the synthesis of 2-arylpyrrolidine-1-carboxamides containing various alkyl substituents at the nitrogen atom. The proposed approach allows for one-pot synthesis of target N-alkyl-2-arylpyrrolidine-1-carboxamides with simultaneous closure of the pyrrolidine ring and formation of C-C bond at the α-position, and compares favorably with the existing methods. Additional advantage of the method is the use of readily available trifluoroacetic acid as catalyst.

**EXPERIMENTAL**

To the solution of appropriate urea (I) (0.58 mmol) in dry chloroform (5 ml), 2-naphthol (0.15 g, 0.58 mmol) and trifluoroacetic acid (0.07 g, 0.58 mmol) were added. The reaction mixture was stirred at 20 °C for 3 days. Solvent was evaporated on a rotary evaporator, and the crude product washed thoroughly with diethyl ether and dried in vacuo (2 h, 0.01 torr, 20°C) to give desired compound 2.

**FUNDING**

This work was supported by the Russian Foundation for Basic Research (Grant Nos. 14-03-00191-a and 14-03-31740 mol_a).
SUPPORTING INFORMATION

Full experimental procedures, characterization data, and copies of NMR spectra for all synthesized compounds can be accessed on the publisher’s website.

Crystallographic data (excluding structure factors) for the structures in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1031375-1031376. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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