New method of synthesis of 2-arylpyrrolidines: reaction of resorcinol and its derivatives with γ-ureidoacetals

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Abstract
Method of synthesis of aryl substituted bis(pyrrolidine-1-carboxamides) has been developed based on acid-catalyzed reaction of γ-ureidoacetals with polyatomic phenols. Advantages of the method are high yield of target products, mild reaction conditions, and no need for expensive reagents.

Keywords: Acetals, phenols, heterocycles, cyclization, electrophilic aromatic substitution

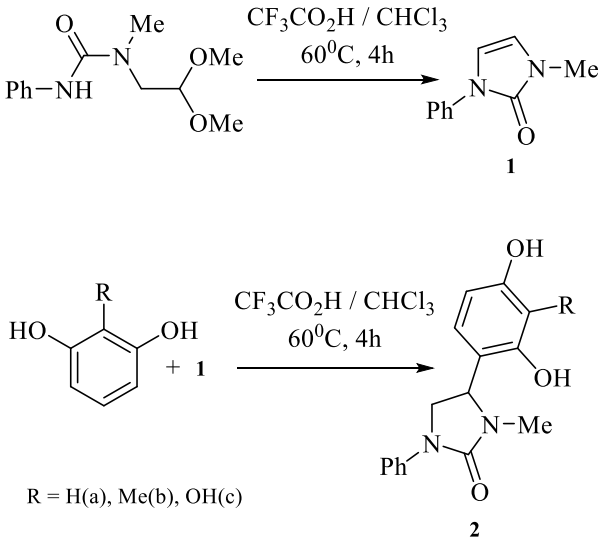
Introduction

Many known alkaloids, antibiotics, and synthetic drugs contain pyrrolidine ring substituted at α-carbon atom.[1–6] There are data on the use of α-arylpyrrolidines as chiral catalysts[7] and organocatalysts.[8–10] Particular attention is devoted to the α-arylpyrrolidines containing carboxamide substituent at nitrogen atom. The compounds involving this fragment were patented as inhibitors of somastatin receptors,[11] glutamate receptor modulators,[12] antagonists of histamine H_3-receptors,[13] anticancer drugs,[14] PI3-kinase inhibitors,[15] and drugs for the treatment of mental and neurophysiological disorders, more specifically, Parkinson[16] and Alzheimer diseases.[16,17]

Most approaches to the synthesis of these compounds are based on the intramolecular cyclization with the formation of pyrrolidine core.[18,19] However, few of them enable one to form carbon-carbon bond at the second position of heterocyclic ring together with the formation of C-N bond.[20–23] Existing methods require harsh reaction conditions and toxic or expensive reagents, namely, palladium complexes.[24] There is the only communication in published data,[25] where the synthesis of pyrrolidines via cyclization of γ-ureidoacetal in acidic medium with thiophenol was suggested. It should be noted that only S-substituted products are formed after this reaction with low yields.

Results and Discussion

Recently, in our group, reaction of resorcinol and its derivatives with α-ureidoacetals in the presence of trifluoroacetic acid as catalyst was studied.[26–28] It was determined that this reaction proceeds according to two steps. At the first step, initial α-ureidoacetal undergoes intramolecular cyclization resulting in imidazolinone **1**. At the second step, reaction of compound **1** with resorcinol or its derivatives takes place with the formation of new functionalized imidazolidine-2-ones **2**. It is essential to note that reaction proceeds with high degree of regioselectivity and leads to the formation of only one of two possible regioisomers (Scheme 1). Opportunity to perform this reaction in one step without the isolation of intermediate compound **1** was demonstrated as well.[27]



Scheme 1 Synthesis of imidazolidine-2-ones.

Based on these data, we suggested that reaction of resorcinol and its derivatives with γ-ureidoacetals can also give novel heterocyclic compounds.

Reaction of acetal **3** with resorcinol, 2-methylresorcinol, and pyrogallol was studied. Initial acetal **3** was synthesized by the reaction of phenylisocyanate with 1,1-diethoxybutylamine. In analogy with the procedure of cyclization of α-ureidoacetals developed by us,[26] reaction of acetal **3** with polyatomic phenols was performed in boiling chloroform with equimolar amount of trifluoroacetic acid. Compounds **4** containing two heterocyclic fragments were isolated from reaction mixture with the yields of 10-14%. The structure of the compounds synthesized was confirmed according to NMR spectroscopy. It should be noted that compounds **4** can exist as two diastereomers, NMR spectra of which should differ from each other. Nevertheless, there is only one set of signals in NMR spectra for the products **4** synthesized by us. Because we do not see any prerequisites for proceeding of stereoselective reaction in this case, this is most probably

determined by very small difference of chemical shifts of corresponding nuclei of both diastereomers.

The structure of compound **4b** was additionally confirmed by X-ray analysis (Figure 1). According to X-ray data, there is only one diastereomer in crystal of this compound and it has R,S-configuration of chiral centers.[29]

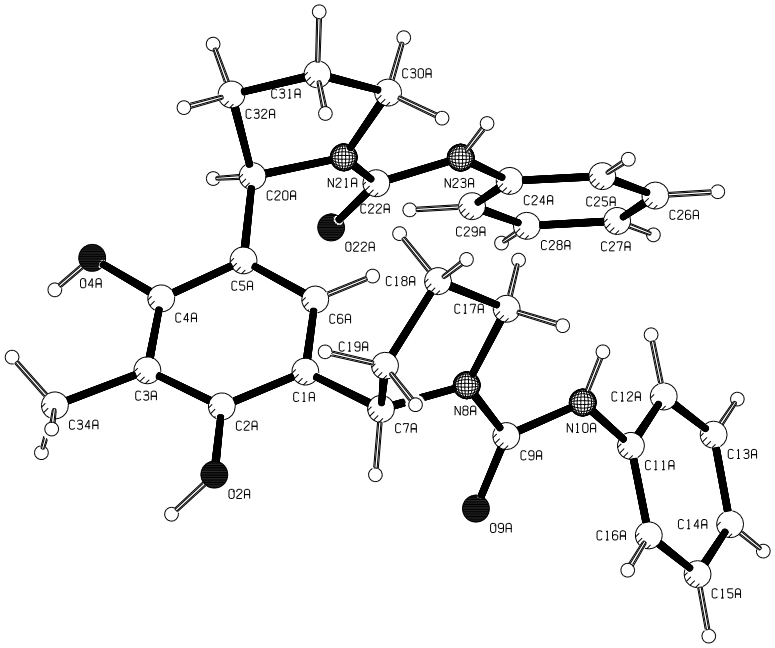
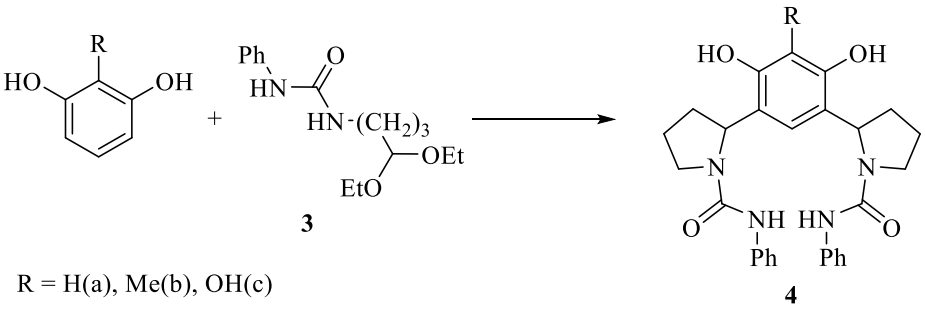


Figure 1 Molecular structure of compound **4b** in crystal.

DMSO and water molecules are present in the studied crystal besides compound **4b** (2:4:2 ratio). The geometry of the A and B molecules in crystal is the same within the deviation, the bond lengths, bond and torsion angles are in the ranges typical for every bond type. We have analyzed in more details the crystal structure and non-covalent interactions in crystal to explain the reason of the crystallization of the studied compound with two independent molecules in the unit cell. The crystal structure is mostly formed by the hydrogen bonds of different types, which is due to a big number of the functional groups capable of forming the hydrogen bonds (see Supporting Information). Analysis of the hydrogen bonds for every molecule of **4b** in crystal has shown that A and B molecules are bonded with each other by two pairs of symmetric OH…O interactions. Apart from that, both molecules are symmetrically bonded with the DMSO molecules via NH…O bonds. Thus, both molecules form NH…O bonds with water molecules, however oxygen atom of one of the carbonyl groups of molecule A acts as an acceptor of the OH…O hydrogen bond with another water molecule (O^{43}-H^{432}...O^{22A}). Similar bonding has not been found for the molecule B. Thus, the different binding of A and B molecules with the solvent molecules is the reason of the crystallization of the investigated crystal with z'=2.

In result, the structure of the investigated crystal consists of layers formed by the dimers of the A and B molecules, oriented via the main diagonal of the unit cell. The layers are united by the non-covalent interactions with the solvent molecules.

With an aim to improve the yields of compounds **4**, we optimized reaction conditions (Table 1).



Scheme 2. Synthesis of bis(pyrrolidine-1-carboxamides).

Table 1. Optimization of reaction conditions[a]

Entry	R	Catalyst	Solvent	Phenol : Acetal molar ratio	Yield[b] (%)
1	OH	CF_3CO_2H	$CHCl_3$	1 : 1	14
2	Me	CF_3CO_2H	$CHCl_3$	1 : 1	11
3	H	CF_3CO_2H	$CHCl_3$	1 : 1	10
4	OH	CF_3CO_2H	$CHCl_3$	1 : 2	74
5	Me	CF_3CO_2H	$CHCl_3$	1 : 2	67
6	H	CF_3CO_2H	$CHCl_3$	1 : 2	51
7	H	CF_3CO_2H	dioxane	1 : 2	20
8	OH	H_2SO_4	H_2O	1 : 2	0[c]
9	Me	H_2SO_4	H_2O	1 : 2	0[c]
10	H	H_2SO_4	H_2O	1 : 2	0[c]

[a]Reaction conditions: acetal **3** (1.78 mmol), catalyst (1.78 mmol), solvent (10 mL), phenol, 4 h, reflux. [b]Isolated yield of compound **4**. [c]Formation of hardly separable mixture of polymer products was observed

In particular, conduction of identical reaction at the reagent ratio of 1 : 2 (phenol : acetal **3**) enabled us to synthesize compounds **4** with the yields from 51 to 74% (see Table 1, entries 4, 5, 6). Conduction of reaction in less polar and having higher boiling point dioxane resulted in drastic decrease in the yield of target compound **4a**. And the main products of reaction presumably represented the products of polymer structure, which we did not succeed in isolating and characterizing (see Table 1, entry 7). As much as the methods of «green chemistry» recently assume greater importance, we attempted to perform this reaction with the use of water as solvent. However, in all cases, products of reaction represented hardly separable mixtures of

products. All attempts to isolate them individually failed. And the formation of target heterocyclic compounds was not observed (see Table 1, entries 8, 9, 10).

Table 2. Optimization of reaction conditions at 20 ºC[a]

Entry	R	Catalyst	Solvent volume, mL	Phenol : acetal : Catalyst molar Ratio	Yield[b]
1	OH	CF_3CO_2H	10	1 : 2 : 2	62
2	H	CF_3CO_2H	10	1 : 2 : 2	30
3	H	CF_3CO_2H	5	1 : 2 : 2	33
4	H	CF_3CO_2H	30	1 : 2 : 2	46
5	Me	CF_3CO_2H	10	1 : 2 : 0.1	0[c]
6	H	CF_3CO_2H	10	1 : 2 : 1	40
7	Me	CF_3CO_2H	10	1 : 2 : 1	69
8	OH	CF_3CO_2H	10	1 : 2 : 1	83

[a]Reaction conditions: acetal **3** (1.78 mmol), phenol (0.89 mmol), catalyst, $CHCl_3$, 20 ºC, 12 h. [b]Isolated yield of compound **4**. [c]Reaction did not proceed.

It also represented interest for us to study the opportunity of proceeding of this reaction under milder conditions. Experiments showed that the reaction of acetal **3** with polyatomic phenols at room temperature gives rise to remarkable decrease in the yields of target compounds **4** (see Table 1, entry 4 and Table 2, entry 1). Increase in concentration of reagents by two times did not influence substantially the yield of pyrrolidine derivatives **4** (see Table 2, entries 2, 3), while its decrease allowed us decreasing slightly the yield of product (see Table 2, entry 4). With the decrease in the amount of trifluoroacetic acid to 5 mol. % of the amount of γ-ureidoacetal, reaction did not proceed (see Table 2, entry 5). Conduction of reaction in the presence of trifluoroacetic acid taken at 50 mol. % of the amount of acetal leaded to the increase in the yields of target compounds, which were comparable with the yields achieved at reflux of reaction mixture (see Table 2, entries 6, 7, 8). It should be noted that the yield of target compounds decreases from pyrogallol to resorcinol regardless the temperature of reaction. This is presumably related to the decrease in electron donor ability of substituents in aromatic nucleus and, consequently, in reactivity of phenol.

Conclusions

Through the studies of the reaction of polyatomic phenols with γ-ureidoacetals, a convenient single-step method of synthesis of novel bis(pyrrolidine-1-carboxamides) containing aryl substituent at the 2 position of heterocyclic ring was developed. Advantages of method involve high yields of target products, mild reaction conditions, and no need for expensive reagents.

Experimental Section

General. Commercially available compounds were used without further purification. Solvents were purified according to standard procedures. The ^{1}H NMR spectra were recorded on an Avance 600 instrument with the working frequency of 600.13 MHz. The ^{13}C NMR spectra were recorded on an Avance 600 instrument with the working frequency of 150.90 MHz. Signals of residual protons of solvent in ^{1}H NMR spectra were used as references for the measurements of chemical shift. IR spectra were recorded on a Vector 22 (Bruker) spectrometer. All the melting points were uncorrected.

The X-Ray diffraction data were collected at 100 K on a Bruker AXS Smart Apex II CCD diffractometer in the ω and φ-scan modes using graphite monochromated MoK$_\alpha$ (λ 0.71073Å) radiation. The structure was solved by direct method and refined by the full matrix least-squares using SHELXTL[29] and WinGX[30] programs. All non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms were located from the Fourier electron density synthesis and were included in the refinement in the isotropic riding model approximation. All figures were made using PLATON.[31]

1-(4,4-Diethoxybutyl)-3-phenylurea (3). To the solution of 2.03 g (12.6 mmol) of (4,4-diethoxybutyl)amine in 10 mL of benzene 1.50 g (12.6 mmol) of phenylisocyanate was added dropwise at 5 ºC. Reaction mixture was stirred ad room temperature for 6 h. Solvent was removed and residue dried in vacuum (0.01 torr, 5 h) to give 1-(4,4-diethoxybutyl)-3-phenylurea **3** as white powder (3.00 g, 85.0%). mp 66-67 °C. IR (ν_{max}, cm^{-1}): 1598, 1637, 2726. ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 1.16 (6H, t, $^{3}J_{HH}$ 7.06 Hz), 1.46-1.62 (4H, m), 3.15 (2H, m); 3.44 (2H, q, $^{3}J_{HH}$ 7.04 Hz), 3.58 (2H, q, $^{3}J_{HH}$ 7.04 Hz), 4.39 (1H, t, $^{3}J_{HH}$ 5.45 Hz), 6.96 (1H, t, $^{3}J_{HH}$ 7.28 Hz), 7.20 (2H, t, $^{3}J_{HH}$ 8.12 Hz), 7.25 (2H, d, $^{3}J_{HH}$ 7.46 Hz). Anal.calcd for $C_{15}H_{24}N_2O_3$ (280.18): C, 64.26; H, 8.63; N, 9.99%. Found: C, 64.25; H, 8.65; N, 10.01%.

Synthesis of bis(pyrrolidine-1-carboxamides)

General procedure 1 (Table 1, entries 1-10). To the solution of 0.50 g (1.78 mmol) of 1-(4,4-diethoxybutyl)-3-phenylurea **3** in 10 mL of solvent appropriate amount of phenol and 1.78 mmol of catalyst were added. Reaction mixture was refluxed for 4 h. Precipitate formed was filtered off, washed with ethanol and dried in vacuum (0.01 torr, 5 h).

General procedure 2 (Table 2, entries 1-8). To the solution of 0.50 g (1.78 mmol) of 1-(4,4-diethoxybutyl)-3-phenylurea **3** in dry chloroform 0.89 mmol of phenol and appropriate amount of trifluoroacetic acid was added. Reaction mixture was stirred at 20ºC for 12 h. Precipitate formed was filtered off, washed with ethanol and dried in vacuum (0.01 torr, 5 h).

2,2'-(4,6-Dihydroxy-1,3-phenylene)bis(N-phenylpyrrolidine-1-carboxamide) (4a). White powder, yield 50.8%, 0.22 g, mp. 250-251 °C; IR (ν_{max}, cm^{-1}): 1596, 1652, 2726, 3151. ^{1}H NMR (600 MHz, d6-DMSO) δ_H 1.79-1.94 (6H, m), 2.07-2.20 (2H, m), 3.52-3.61, 3.62-3.74 (4H, m),

5.15-5.21 (2H, m), 6.37 (1H, s), 6.69 (1H, s), 6.86 (2H, t, $^3J_{HH}$ 7.24 Hz), 7.09 (4H, t, $^3J_{HH}$ 7.88 Hz), 7.30 (4H, d, $^3J_{HH}$ 7.88 Hz), 7.89 (2H, br. s), 9.50 (2H, br. s). ^{13}C NMR (150 MHz, d6-DMSO) δ_C 24.03, 33.69, 47.38, 55.95, 103.91, 120.71, 120.82, 122.45, 124.98, 128.99, 141.14, 154.27, 154.65. MALDI TOF: *m/z* = 486 $[M]^+$, 509 $[M + Na]^+$, 525 $[M + K]^+$. Anal.calcd for $C_{28}H_{30}N_4O_4$ (486.56): C, 69.12; H, 6.21; N, 11.51%. Found: C, 69.11; H, 6.21; N, 11.52%.

2,2'-(4,6-Dihydroxy-5-methyl-1,3-phenylene)bis(N-phenylpyrrolidine-1-carboxamide) (4b). White powder, yield 67.4%, 0.30 g, mp 203-204 °C; IR (ν_{max}, cm^{-1}): 1558, 1620, 2726, 3309. ^{1}H NMR (600 MHz, d6-DMSO) δ_H 1.91-2.04 (6H, m), 2.07 (3H, s), 2.18-2.27 (2H, m), 3.52-3.70 (4H, m), 5.20-5.24 (2H, m), 6.70 (1H, s), 6.94 (2H, t, $^3J_{HH}$ 7.29 Hz), 7.19 (4H, t, $^3J_{HH}$ 7.93 Hz), 7.38 (4H, d, $^3J_{HH}$ 7.61 Hz), 8.09 (2H, br. s), 9.12 (2H, br. s). ^{13}C NMR (150 MHz, d6-DMSO) δ_C 10.54, 24.76, 33.08, 47.30, 55.98, 113.91, 121.13, 121.95, 122.87, 129.07, 140.86, 152.85, 155.56. MALDI TOF: *m/z* = 500 $[M]^+$, 523 $[M + Na]^+$, 539 $[M + K]^+$. Anal.calcd (%) for $C_{29}H_{32}N_4O_4$ (500.59): C, 69.58; H, 6.44; N, 11.19%. Found: C, 69.57; H, 6.45; N, 11.17%.

2,2'-(4,5,6-Trihydroxy-1,3-phenylene)bis(N-phenylpyrrolidine-1-carboxamide) (4c). White powder, yield 74.1%, 0.331 g, mp 226-227 °C; IR(ν_{max}, cm^{-1}): 1594, 1654, 2726, 3336. ^{1}H NMR (600 MHz, d6-DMSO) δ = 1.89-2.02 (6H, m), 2.16-2.27 (2H, m), 3.52-3.68 (4H, m), 5.19-5.24 (2H, m), 6.37 (1H, s), 6.92 (2H, t, $^3J_{HH}$ 7.32 Hz), 7.16 (4H, t, $^3J_{HH}$ 7.86 Hz), 7.36 (4H, d, $^3J_{HH}$ 7.82 Hz), 7.99 (2H, br. s), 8.28 (1H, br. s), 8.98 (2H, br. s). ^{13}C NMR (150 MHz, d6-DMSO) δ_C 24.44, 33.27, 47.29, 55.99, 113.90, 120.94, 121.75, 122.69, 129.03, 134.71, 140.98, 143.09, 155.18. MALDI TOF: *m/z* = 502 $[M]^+$, 525 $[M + Na]^+$, 541 $[M + K]^+$. Anal.calcd for $C_{28}H_{30}N_4O_5$ (502.56): C, 66.92; H, 6.02; N, 11.15%. Found: C, 66.90; H, 6.05; N, 11.13%.

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