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An efficient synthesis of novel heterocycle-fused derivatives of 1-oxo-1,2,3,4-tetrahydropyrazine using Ugi condensation

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Abstract—We present a convenient synthesis of novel pyrrole- and indole-fused 1-oxo-1,2,3,4-tetrahydropyrazine heterocyclic structures using a novel modification of four-component Ugi condensation. We demonstrate the usefulness and versatility of the developed approach for the synthesis of variously substituted compounds, and discuss the scope and limitations of the chemistry involved.

3,4-Dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one fragment is present in a wide number of natural and synthetic biologically active agents. Among them are antineoplastic and antibacterial alkaloids longamide, longamide B, and phakellstatins isolated from marine organisms as well as their synthetic analogs,[1] antitrombotic agents,[2] potential antiprotozoal drugs,[3] and the insect feeding deterrents.[4] Aryl-fused analogs of 3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones, such as pyrazino[1,2-*a*]indoles, represent another group of compounds with interesting but still relatively little explored pharmaceutical properties described in a number of recent patent applications.[5] According to these examples, heterocycle-fused derivatives of 1-oxo-1,2,3,4-tetrahydropyrazine represent promising synthetic targets. Development of efficient synthetic approaches to the related scaffolds will provide a valuable source of novel physiologically active agents. In this paper, we communicate our success in developing a novel four-component Ugi-type reaction for the synthesis of novel 3-carboxamide derivatives of 3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and 3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which can be readily applied in combinatorial chemistry approaches.

In most of the reported synthetic approaches to pyrrole- and indole-fused 1-oxo-1,2,3,4-tetrahydropyrazines, key reaction is the intermolecular cyclization of the appropriate pyrrole- or indole-2-carboxylic acid derivatives leading to the desired heterocycles. For example, substituted pyrazino[1,2-*a*]indole-1-ones were obtained from the corresponding 1*H*-indole-2-carboxylic acid allyl amides[6] or 1*H*-indole-2-carboxylates.[7] However, the described synthetic strategies have found limitations mainly due to lack of versatility and a limited number of the appropriate initial reactants.

Recently, Ugi reaction was shown to be an effective approach to the assembly of differently substituted pyrazines.[8] One of important modifications of the classical four-component Ugi reaction includes the use of bifunctional reagents. Thus, modified versions of the Ugi four-component reaction using bifunctional aldehyde or keto acids, amine, and isocyanide as starting materials, have been reported.[9] In this work, we show first examples of a novel modification of the four-component Ugi reaction between isonitrile, amine, and a bifunctional azaheterocyclic reagent bearing a (2-oxoethyl)aminoacetic acid fragment. To illustrate our approach, we describe here the synthesis of a medium sized library of novel 1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **6**{*1–98*} and 1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]pyrroles **6**{*99–141*} (Scheme 1).

Key bifunctional reagents used in the four-component reaction were obtained from 2-pyrrole-2-carboxylates

Keywords: Ugi condensation; 3,4-Dihydropyrazino[1,2-*a*]indol-1(2*H*)-one; 3,4-Dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one; Library.
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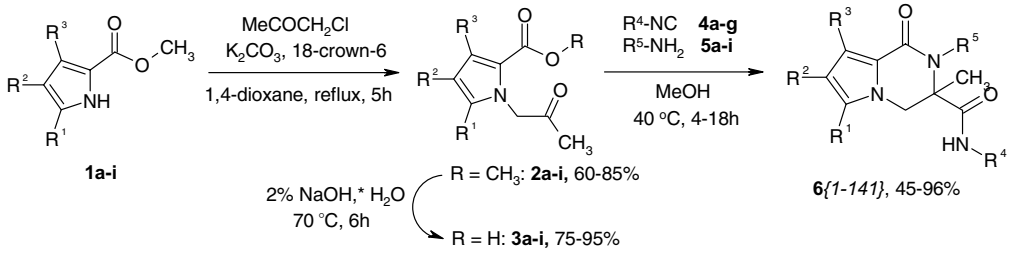


Scheme 1. Synthesis of 3-carboxamide derivatives of 3,4-dihydropyrazino[1,2-*a*]indol-1-(2*H*)-one **6**{*1–98*} and 3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one **6**{*99–141*}. *1% NaOH in the case of compound **2i** ($R^1 = R^3 = CH_3$, $R^2 = COOMe$).

1a–**i**, which were available from commercial sources or prepared as reported.[10,11] A solution of carboxylate **1a**–**i** in 1,4-dioxane was treated with chloroacetone under phase transfer conditions, in the presence of K_2CO_3 and 18-crown-6, to afford the desired product **2a**–**i** in a good yield (60–85%). Mild alkali hydrolysis of **2a**–**i** led to keto acids **3a**–**i** (yield 75–95%). Then we have found that the reaction of keto acids **3a**–**i** with isonitriles **4a**–**g** and amines **5a**–**i** led to the corresponding 3-carboxamide derivatives **6**{*1–141*}, which were not previously described in literature. The reaction smoothly proceeded in methanol at 40 °C to yield the desired products in 45–96% yield.[12] The reaction presumably follows the same initial course as the classical Ugi condensation[13] with an intermediate imine being attacked by the isonitrile to give a nitrilium intermediate, which then undergoes intramolecular cyclization.

As a synthetic tool for creating diverse compound libraries, the developed Ugi-type condensation offers a large number of potential input reactants (Fig. 1). We have observed that the nature of R^1–R^3 substituents does not substantially affect the reaction yield and time, and several differently substituted pyrrolo-2-carboxylate derivatives could be used. With respect to amine component, various aliphatic and aromatic primary amines, such as substituted anilines, linear, and branched aliphatic amines and nitrogen-containing compounds, were tolerated without any limitations. A restriction is the limited number of commercially or synthetically available isonitriles. In this work, we used seven different isonitriles **4a**–**g** available from ChemDiv.

Structures and yields of some representative compounds are shown in Tables 1 and 2. Isolated yields of **6**{*1–141*} were generally high (>60%, up to 96%), except for a few cases. All compounds were obtained as racemic mixtures of enantiomers. The assignment of these structures was made on the basis of ^{1}H NMR, ^{13}C NMR, and high-resolution mass-spectroscopy data.[14] The nonequivalent methylene protons of the pyrazinone ring are sometimes concealed by other signals, but usually can be seen as doublets in the range of δ 3.90–5.50 ppm with the geminal spin–spin coupling constants in the range of 5.6–8.2 Hz. In many cases, pure crystalline substances could be obtained, thus allowing firm relative and absolute stereochemical assignments to be made to the individual compounds through X-ray crystallography. Single crys-

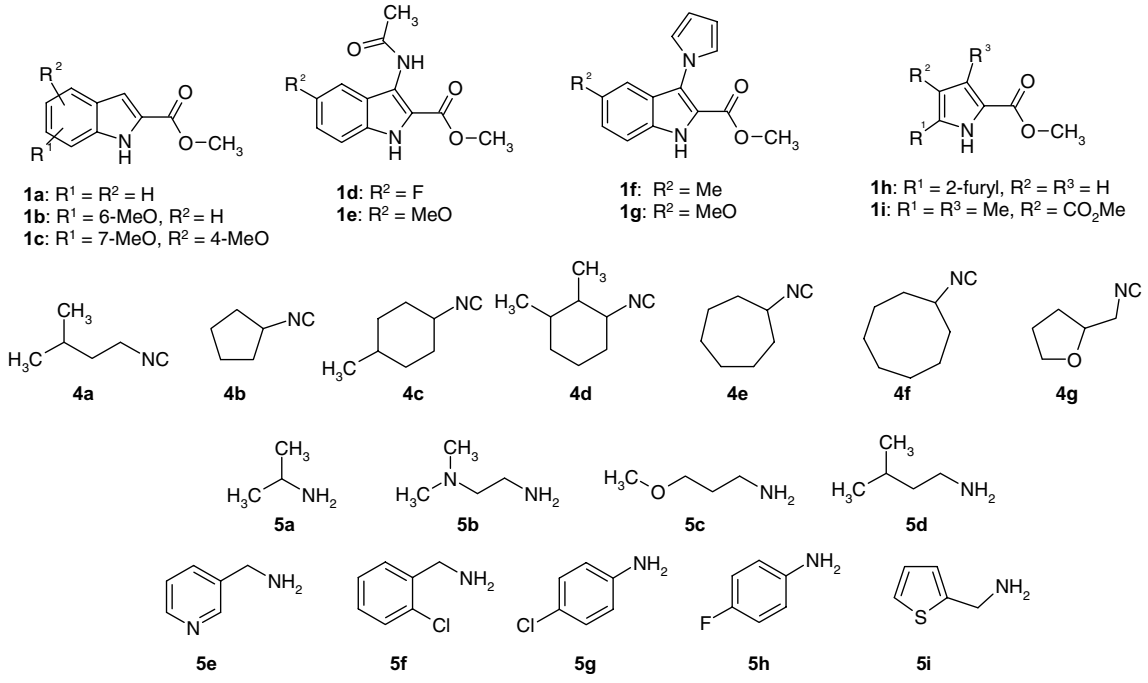
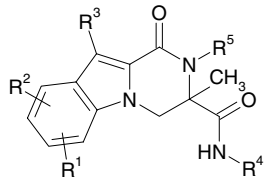


Figure 1. Evaluated building blocks.

Table 1. Structures and yields of representative 3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-ones



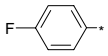
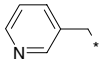
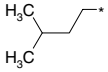
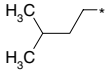
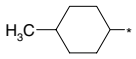
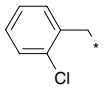
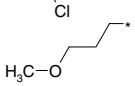
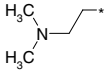
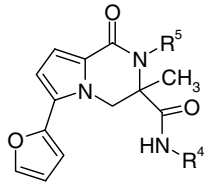
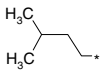
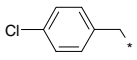
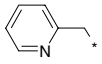
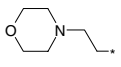
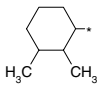
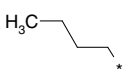
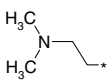
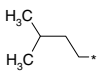
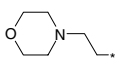
No	R^1	R^2	R^3	R^4	R^5	Yield, %	HRMS, exp.	HRMS, calcd
6{*1*}	H	H	H			85	443.2238	434.2238
6{*2*}	7-MeO	H	H			92	449.2185	449.2183
6{*3*}	H	H	1-Pyrrolyl			80	447.0321	447.0316
6{*4*}	H	8-F	AcNH			78	485.2009	485.2017
6{*5*}	H	8-CH_3O	AcNH			81	483.2958	483.2966
6{*6*}	H	8-CH_3	1-Pyrrolyl			64	565.2334	565.2341
6{*7*}	H	8-CH_3O	1-Pyrrolyl			68	507.2976	507.2966
6{*8*}	6-MeO	9-MeO	H			83	443.265	443.2653

Table 2. Structures and yields of representative 3,4-dihydropyrazino[1,2-*a*]pyrazin-1(2*H*)-ones (6-(2-furyl) derivatives)



No	R^4	R^5	Yield, %	HRMS, exp.	HRMS, calcd
6{*99*}			89	454.1891	454.18912
6{*100*}			78	433.0321	433.0317
6{*101*}			85	455.2650	455.2653
6{*102*}			62	426.1142	426.1147
6{*103*}			81	452.2010	452.2002
6{*104*}			68	441.2863	441.286
6{*105*}			64	443.5761	443.5758

tals of compounds suitable for X-ray analysis were grown from diethyl ether.

In summary, we have developed a novel synthetic approach to the assembly of the pyrrolo- and indole[1,2-*a*]pyrazin-1-one heterocycles based on a novel modification of the Ugi four-component reaction. A distinctive feature of our synthetic method is the use of bifunctional azaheterocyclic reagents bearing a (2-oxoethyl)amino-acetic acid fragment. Due to a wide spectrum of such reagents available, this reaction opens wide possibilities for synthesis of novel or poorly studied annelated heterocyclic systems such as 1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-3-carboxamide as well as other heterocyclic scaffolds, which were not previously described in literature.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.11.168. Spectral data for representative novel compounds and crystallographic data for compounds **6**{*3*} and **6**{*105*} is available. The supplementary data is available online with the paper in ScienceDirect.

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11. Hudkins, R. L. *Heterocycles* **1995**, *5*, 1045–1049.
12. General procedure for preparation of compounds **6**{*1–141*}. The equimolar amounts of keto acid **3**, the isonitrile **4**, and the amine **5** were dissolved in methanol to an approximate concentration of 1 M in each component. The reaction mixture was stirred at 40 °C for 4–18 h. The reaction was followed by TLC (5% MeOH in CH_2Cl_2). On completion, the reaction mixture was cooled to rt, the formed precipitate was filtered out and purified (if desired) by recrystallization from diethyl ether of by chromatography on silica gel, eluting with a gradient of 0–10% MeOH in CH_2Cl_2.
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14. Analytical spectral data for representative compounds **6**. Compound **6**{*5*}: ^{1}H NMR (DMSO + CCl_4, 400 MHz) δ 1.2–1.8 (m, 14H, cyclooctane), 1.5 (s, 9H, $3CH_3$), 2.2 (s, 3H, CH_3), 3.2–3.33 (m, 1H, CH), 2.8 (s, 3H, CH_3), 2.85–2.96 (m, 1H, CH), 6.89 (d, 1H, J = 7.0 Hz, ArH), 7.21 (d, 1H, J = 7.0 Hz, ArH), 7.62 (s, 1H, ArH), 7.9–8.0 (m, 1H, NH), 9.8 (s, 1H, NCO); ^{13}C NMR (100 MHz, DMSO) δ 21.4, 21.5, 21.7, 24.0, 24.1, 25.7, 27.2, 27.6, 31.8, 31.9, 49.9, 50.3, 51.2, 55.9, 64.8, 67.0, 104.9, 111.9, 116.5, 116.6, 128.2, 120.3, 130.3, 132.0, 169.1; HRMS *m/z* 483.2958 (M+). Compound **6**{*7*}: ^{1}H NMR (DMSO + CCl_4, 400 MHz) δ 1.1–2.0 (m, 14H, cycloheptane, CH_2), 1.6 (s, 3H, CH_3), 3.22 (s, 3H, CH_3), 3.26–3.48 (m, 3H, CH_2), 3.6–3.71 (m, 1H, CH), 3.72–3.8 (m, 1H, CH_2), 3.73 (s, 3H, CH_3), 4.0 (d, 1H, J = 5.4 Hz, CH_2), 4.83 (d, 1H, J = 5.4 Hz, CH_2), 6.16–6.19 (t, 2H, J = 1.2 Hz, ArH), 6.88 (d, 1H, J = 2.4 Hz, ArH), 6.91 (d, 1H, J = 2.8 Hz, ArH), 6.96 (d, 1H, J = 3.2 Hz, ArH), 6.98 (s, 1H, ArH), 7.35 (d, 1H, J = 7.4 Hz, ArH), 7.45 (d, 1H, J = 7.6 Hz, NH); ^{13}C NMR (100 MHz, DMSO) δ 20.6, 23.7, 23.8, 27.7, 29.5, 33.9, 34.0, 49.6, 50.6, 52.5, 54.6, 55.4, 57.9, 59.7, 70.2, 70.3, 99.4, 108.1, 109.3, 111.6, 112.2, 119.6, 119.9, 123.0, 123.1, 128.6, 129.6, 154.7, 159.2; HRMS *m/z* 507.2976 (M+). Compound **6**{*99*} : ^{1}H NMR (DMSO + CCl_4, 400 MHz) δ 0.7 (t, 3H, J = 8.2 Hz, CH_3), 1.0–1.13 (q, 2H, J = 8.3 Hz, CH_2), 1.15–1.2 (m, 1H, CH), 1.48 (s, 1H, CH), 2.97–3.11 (q, 2H, J = 7.8 Hz, CH_2), 3.95–4.2 (d, d, 2H, J = 7.4 Hz, CH_2), 4.9–5.0 (d, 1H, J = 7.5 Hz, CH_2), 5.33–5.49 (d, 1H, J = 7.5 Hz, CH_2) 6.4 (d, 1H, J = 8.2 Hz, ArH), 6.47 (2d, 1H, J = 8.4Hz, ArH), 6.52 (d, 1H, J = 8.1 Hz, ArH), 6.74 (d, 1H, J = 8.1 Hz, ArH), 7.2–7.36 (m, 4H, ArH), 7.6 (d, 1H, J = 8.2 Hz, ArH); HRMS *m/z* 454.1891 (M+).