AN EFFICIENT SYNTHESIS OF 3-OXO-1,2,3,4-TETRAHYDROPYRROLO[1,2-*a*]PYRAZINE-1-CARBOXAMIDES USING NOVEL MODIFICATION OF UGI CONDENSATION

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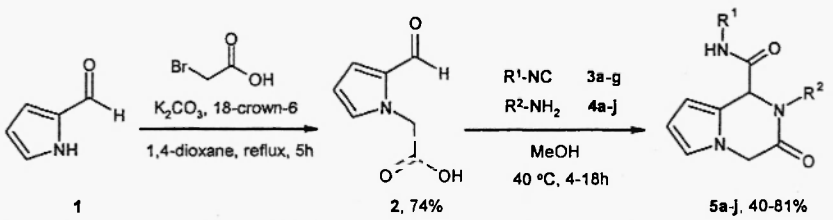
Abstract: We present a convenient synthesis of novel 3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamides using a modification of four-component Ugi condensation. According to this method, (2-formyl-1*H*-pyrrol-1-yl)acetic acid is used as a bifunctional coupling reagent in the reaction with isonitriles and amines to furnish the target structures. The reaction can be automated and is amenable to library production. The novel synthetic approach described herein can be elaborated further for the synthesis of a wide number of heterocycle-fused 6-oxopiperazine-2-carboxamides.

Introduction

1,2,3,4-Tetrahydropyrrolo[1,2-a]pyrazine fragment is present in a number of natural and synthetic physiologically 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 (3) and endocrine drugs (4). Specifically, the derivatives of 3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine represent promising, yet still little explored synthetic targets, and the development of efficient synthetic approaches to this scaffold will provide a valuable source of novel physiologically active agents. However, the described synthetic strategies have found limitations mainly due to lack of versatility and a limited number of the appropriate initial reactants (5, 6). In this paper, we communicate our success in developing a convenient synthetic approach to novel derivatives of 3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine.

Results

Ugi reaction was shown to be an effective approach to the assembly of differently substituted pyrazines (7, 8). One of important modifications of the classical four-component Ugi reaction includes the use of bifunctional reagents (9, 10). Recently, we developed a novel modification of classical four-component Ugi reaction, in which the heterocyclic keto acids were used as the bifunctional coupling partners in the reaction with isonitriles and amines (11, 12). Using this method, we efficiently synthesized several series of novel azaheterocyclic scaffolds including **pyrrolo[1,2-a][1,4]diazepines (11)**, 3,4-dihydropyrazino[1,2-a]indol-1(2H)-ones and 3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-ones (12). In this work, we have focused on broadening the scope of this useful synthetic methodology. Specifically, we show first example of utilization of (2-formyl-1H-pyrrol-1-yl)acetic acid as the key bifunctional reagent for the synthesis of a series of novel 3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-1-carboxamides (Scheme-1).

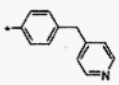


Synthesis of substituted 3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamides.

Scheme-1

(2-Formyl-1*H*-pyrrol-1-yl)acetic acid **2** used as a key bifunctional reagent in the developed reaction was obtained from 2-formyl-1*H*-pyrrole **1**. A solution of **1** in 1,4-dioxane was treated with bromoacetic acid under phase transfer conditions, in the presence of K_2CO_3 and 18-crown-6, to afford the desired product **2** in good yield. We have observed that the reaction of aldehyde acid **2** with isonitriles **3a-g** and amines **4a-j** led to the corresponding 1-carboxamide derivatives **5a-j** (Table 1), which were not previously described in literature. The reaction smoothly proceeded in methanol at 40 °C to yield the desired products in 40-81% yield. 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.

Table-1: R^1 and R^2 substituents and yields of 3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamides **5a-j** synthesized.

Entry	R^1	R^2	Yield, %
5a			49
5b			50
5c			54
5d			76
5e			81
5f			65
5g			45
5h			40
5i			79
5j			61

Discussions

As a synthetic tool for creating diverse compound libraries, the developed Ugi-type condensation offers a large number of potential input reactants. It can be envisaged that a wide variety of heterocyclic aldehyde acids containing the 2-oxoethylamino-acetic acid fragment can be used in this reaction. With respect to amine component, various aliphatic and aromatic primary amines, 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. Isolated yields of **5a-j** were generally good (>50%, up to 80%), 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 and high-resolution mass-spectroscopy data. The nonequivalent methylene protons of the pyrazinone ring 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.

Compounds synthesized in this work constitute interesting examples of conformationally rigid cyclic peptidomimetics, which are the subject of increasing interest as potential new small-

molecule therapeutics (14, 15). Specifically, the synthesized compounds represent examples of β-turn mimicks with an inherent potential for combinatorial exploration of functional diversity. Reverse β-turns are common secondary structures in biologically active peptides or proteins that often play an important role in their interactions with receptors, enzymes, or antibodies. Such peptide-protein or protein-protein interactions can be mimicked by small molecules bearing similar structural features. Syntheses of a putative peptide β-turn mimetic based on piperazinone fragment were reported (for example, (16)).

Conclusions

In summary, we have developed a novel synthetic approach to the assembly of 3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamides 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)aminoacetic acid fragment. The method can be readily applied in combinatorial chemistry approaches as a tool for rapid pharmaceutical lead finding and optimization.

Experimental

General Procedure for Preparation of Compounds 5a-j. The equimolar amounts of aldehyde acid 2, the isonitrile 3, and the amine 4 were dissolved in methanol to an approximate concentration of 1M 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.

Analytical spectral data for compounds **5a-j**.

Compound 5a: ^{1}H-NMR (400 MHz, DMSO-d_6+CCl_4): δ 8.1-8.0 (br s, 1H), 7.3-7.1 (m, 4H), 6.55 (s, 1H), 6.0-5.9 (d, J = 8.6 Hz, 2H), 5.06 (s, 1H), 4.7 (d, J = 5.4 Hz, 1H), 4.5 (d, J = 5.4 Hz, 1H), 3.81-3.74 (m, 1H), 3.2-3.08 (m, 3H), 3.0-2.8 (m, 1H), 2.8-2.6 (m, 1H), 1.65-1.5 (m, 1H), 1.38-1.22 (q, J = 4.6 Hz, 2H); HRMS (*m/z*): $[M]^+$ calcd for $C_{21}H_{26}ClN_3O_2$, 387.9133; found, 387.9138.

Compound 5b: ^{1}H-NMR (400 MHz, DMSO-d_6+CCl_4): δ 8.16 (d, J = 7.8 Hz, 1H), 7.4 ($q_{(F)}$, J = 7.6 Hz, 1H), 7.1-6.9 (m, 3H), 6.63 (s, 1H), 6.0-5.9 (d, J = 9.4 Hz, 2H), 5.4 (s, 1H), 4.9 (d, J = 5.4 Hz, 1H), 4.7 (d, J = 5.4 Hz, 1H), 4.01-3.85 (m, 1H), 2.0-1.2 (m, 8H); HRMS (*m/z*): $[M]^+$ calcd for $C_{19}H_{20}FN_3O_2$, 341.3886; found, 341.3879.

Compound 5c: ^{1}H-NMR (400 MHz, DMSO-d_6+CCl_4): δ 8.12 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 8.2 Hz, 1H), 7.0 (d, J = 8.2 Hz, 1H), 7.0-6.82 (t, J = 8.0 Hz, 1H), 6.58 (s, 1H), 6.0-5.9 (d, J = 5.9 Hz, 2H), 5.3 (d, J = 5.6 Hz, 1H), 5.1 (s, 1H), 4.75 (d, J = 5.6 Hz, 1H), 4.6 (d, J = 5.6 Hz, 1H), 4.1 (d, J = 5.6 Hz, 1H), 4.02-3.87 (m, 1H), 2.0-1.1 (m, 8H); HRMS (*m/z*): $[M]^+$ calcd for $C_{18}H_{21}N_3O_2S$, 343.4510; found, 343.4516.

Compound 5d: ^{1}H-NMR (400 MHz, DMSO-d_6+CCl_4): δ 8.2 (br s, 1H), 7.2 (d, J = 7.8 Hz, 1H), 7.0 (s, 1H), 6.7 (d, J = 7.8 Hz, 1H), 6.55 (s, 1H), 6.0-5.9 (d, J = 8.6 Hz, 2H), 5.1 (s, 1H), 4.8 (d, J = 5.4 Hz, 1H), 4.51 (d, J = 5.4 Hz, 1H), 3.83-3.79 (m, 2H), 3.2-3.03 (m, 2H), 3.0-2.8 (m, 1H), 1.9-1.0 (m, 10H); HRMS (*m/z*): $[M]^+$ calcd for $C_{22}H_{25}N_3O_4$, 395.4623; found, 395.4620.

Compound 5e: ^{1}H-NMR (400 MHz, DMSO-d_6+CCl_4): δ 8.02 (d, J = 7.6 Hz, 1H), 6.55 (s, 1H), 6.0-5.8 (d, J = 8.2 Hz, 2H), 5.1 (s, 1H), 4.72 (d, J = 5.4 Hz, 1H), 4.45 (d, J = 5.4 Hz, 1H), 3.6-3.5 (m, 1H), 3.5-3.4 (m, 1H), 3.4-3.3 (m, 2H), 3.3-3.15 (m, 2H), 3.1-2.9 (m, 1H), 2.22-1.13 (m, 16H); HRMS (*m/z*): $[M]^+$ calcd for $C_{21}H_{30}N_4O_2$, 386.4982; found, 386.4978.

Compound 5f: ^{1}H-NMR (400 MHz, DMSO-d_6+CCl_4): δ 8.10 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.1 (d, J = 8.4 Hz, 1H), 7.1-6.9 (t, J = 8.2 Hz, 1H), 6.53 (s, 1H), 6.0-5.88 (d, J = 5.8 Hz, 2H), 5.31 (d, J = 5.6 Hz, 1H), 5.11 (s, 1H), 4.73 (d, J = 5.6 Hz, 1H), 4.63 (d, J = 5.6 Hz, 1H), 4.1 (d, J = 5.6 Hz, 1H), 391-3.82 (m, 1H), 2.1-1.0 (m, 9H); 0.98 (d, J = 4.6 Hz, 2H), 0.93 (d, J = 4.6 Hz, 1H); HRMS (*m/z*): $[M]^+$ calcd for $C_{20}H_{25}N_2O_3$, 355.4423; found, 355.4416.

Compound 5g: ^{1}H-NMR (400 MHz, DMSO-d_6+CCl_4): δ 7.83 (br s, 1H), 6.52 (s, 1H), 6.0-5.89 (d, J = 7.4 Hz, 2H), 5.2 (s, 1H), 4.65 (d, J = 5.6 Hz, 1H), 4.46 (d, J = 5.6 Hz, 1H), 3.88-3.71 (m, 2H), 3.51-3.3 (m, 2H), 3.22 (s, 3H), 3.1-3.0 (m, 1H), 1.92-1.0 (m, 9H), 0.99 (d, J = 4.6 Hz, 2H), 0.95 (d, J = 4.6 Hz, 1H); HRMS (*m/z*): $[M]^+$ calcd for $C_{18}H_{27}N_3O_3$, 333.4342; found, 333.4340.

Compound 5h: ^{1}H-NMR (400 MHz, DMSO-d_6+CCl_4): δ 8.4 (s, 2H), 7.9-7.69 (m, 1H), 7.3-7.0 (m, 6H), 6.60 (s, 1H), 6.08-6.0 (d, J = 8.4 Hz, 2H), 5.4 (s, 1H), 4.8 (d, J = 5.6 Hz, 1H), 4.62 (d, J = 5.6 Hz, 1H), 4.0 (s, 2H), 3.18-3.03 (m, 1H), 1.8-1.0 (m, 9H), 0.8-0.63 (m, 3H); HRMS (*m/z*): $[M]^+$ calcd for $C_{27}H_{30}N_4O_2$, 442.5658; found, 442.5653.

Compound 5i: ^{1}H-NMR (400 MHz, DMSO-d_6+CCl_4): δ 7.8-7.68 (d, J = 6.4 Hz, 1H), 7.3 (d, J = 7.8 Hz, 2H), 7.2 (d, J = 7.8 Hz, 2H), 6.56 (s, 1H), 6.1-5.95 (d, J = 7.6 Hz, 2H), 5.23 (s, 1H), 4.72 (d, J = 5.4 Hz, 1H), 4.55 (d, J = 5.4 Hz, 1H), 3.2-3.11 (m, 1H), 2.0-0.6 (m, 8H), 0.8 (s, 3H), 0.68 (s, 3H); HRMS (*m/z*): $[M]^+$ calcd for $C_{22}H_{26}ClN_3O_2$, 399.9244; found, 399.9248.

Compound 5j: ^{1}H-NMR (400 MHz, DMSO-d_6+CCl_4): δ 8.03 (d, J = 7.8 Hz, 1H), 6.51 (s, 1H), 6.0-5.92 (d, J = 7.6 Hz, 2H), 5.1 (s, 1H), 4.68 (d, J = 5.4 Hz, 1H), 4.48 (d, J = 5.4 Hz, 1H), 4.1-3.92 (m, 1H), 3.81-3.67 (m, 1H), 1.91-1.31 (m, 14H), 1.00-0.5 (m, 4H); HRMS (*m/z*): $[M]^+$ calcd for $C_{19}H_{27}N_3O_2$, 329.4459; found, 329.4463.

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