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Report

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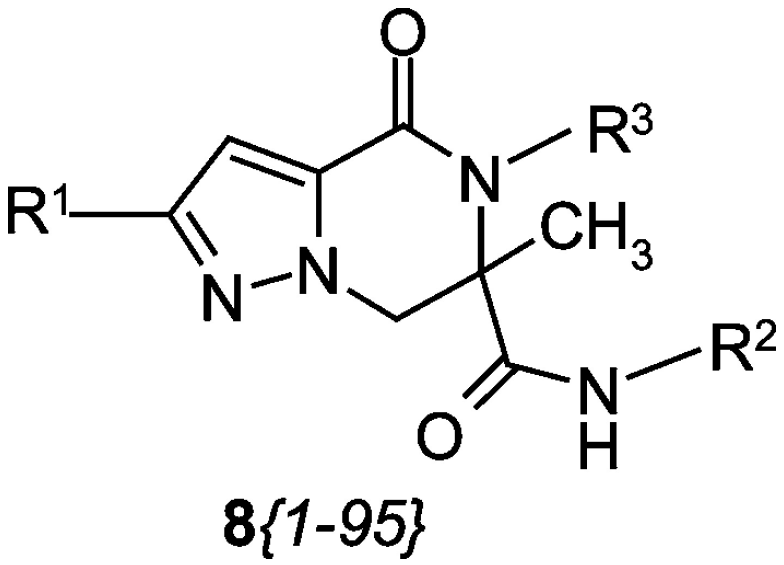

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Synthesis of 4-Oxo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-6-carboxamides Using a Modification of Ugi Condensation

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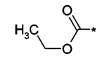
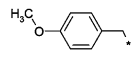
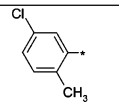
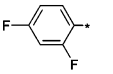
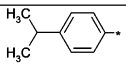
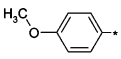
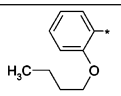
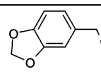
In the search for combinatorial methods which allow for the convenient synthesis of structurally diverse molecules, we focused our efforts toward the preparation of different heterocycle-fused pyrazinones. Among a variety of physiologically active compounds possessing these heterocyclic cores, the derivatives of 4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrazine-4-one represent a relatively little-explored group with interesting pharmaceutical properties. They have been described as vasodilators,[1] fibrinogen receptor antagonists with antiplatelet activity,[2] vitronectin-receptor antagonists,[3] and herbicidal agents.[4] According to these examples and due to bioisosteric similarity to physiologically active pyrrolo-[1,2-*a*]pyrazine-2-ones,[5] 4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrazine-4-ones represent promising synthetic targets. Development of efficient synthetic approaches to the related combinatorial scaffolds will provide valuable materials for pharmaceutical discovery.

In the reported synthetic approaches to pyrazolo[1,5-*a*]-pyrazine-4-ones,[2,3,6] a key reaction is the intermolecular cyclization of the appropriate pyrazole derivatives leading to the desired molecules. However, the described synthetic strategies have found limitations mainly due to lack of versatility and a limited number of the appropriate initial reactants. In addition, the described approaches have not provided a robust method suitable for the production of combinatorial libraries. The Ugi reaction[7] was shown to be an effective approach to the assembly of diverse compound libraries, which can be readily applied in combinatorial chemistry format. One of the 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.[8] Recently, we described an efficient synthetic route to novel 1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-3-carboxamides based on tethered Ugi reaction of bifunctional reagents bearing a (2-oxoethyl)aminoacetic acid fragment with isonitriles and amines.[9] In this work, we show the first examples of utilization of this useful synthetic strategy for the production of combinatorial libraries. Specifically, we describe here the synthesis of a series of novel 4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-6-carboxamides.

Table 1. R^1-R^3 Substituents and Yields of Representative Pyrazolo[1,5-*a*]pyrazine-6-carboxamides

	R^1	R^2	R^3	Yield from **4**, %
8{1}				61
8{2}				75
8{3}				65
8{4}				57
8{5}				84
8{6}				72
8{7}				45
8{8}				51
8{9}				54

We used the synthetic route depicted in Scheme 1. Key bifunctional reagents **4a** were obtained from the corresponding pyrazole-5-carboxylates **1a**−**h**. Upon the alkylation of initial carboxylates **1a**−**h** with chloroacetone under phase transfer conditions in the presence of K_2CO_3 and 18-crown-6, two isomers, **2a**−**h** and **3a**−**h**, were formed (ratios 1:1, as indicated by LC/MS analysis) in 60−85% yield. Mild alkali hydrolysis of the mixtures of **2a**−**h** and **3a**−**h** led to the corresponding keto acids **4a**−**h** and **5a**−**h** in good yields (90−95%). The mixes of isomers **4a**−**h** and **5a**−**h** were then reacted with isonitriles **6a**−**c** and primary amines **7a**−**i** under the conditions of Ugi condensation. We have found that the reaction of isomers **4a**−**h** with isocyanides and amines in methanol at 40 °C led to the generation of 6-carboxamide derivatives of 4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine **8**{*1*−*95*} (yield 45−85% from the isomers **4a**−**h**, which corresponds to 23−43% from the mixture of **4a**−**h** and **5a**−**h**),[10] which were previously not described in the literature. As indicated by LC/MS analysis of the reaction mixtures, the isomeric 1-(2-oxopropyl)-1*H*-pyrazole-3-carboxylates

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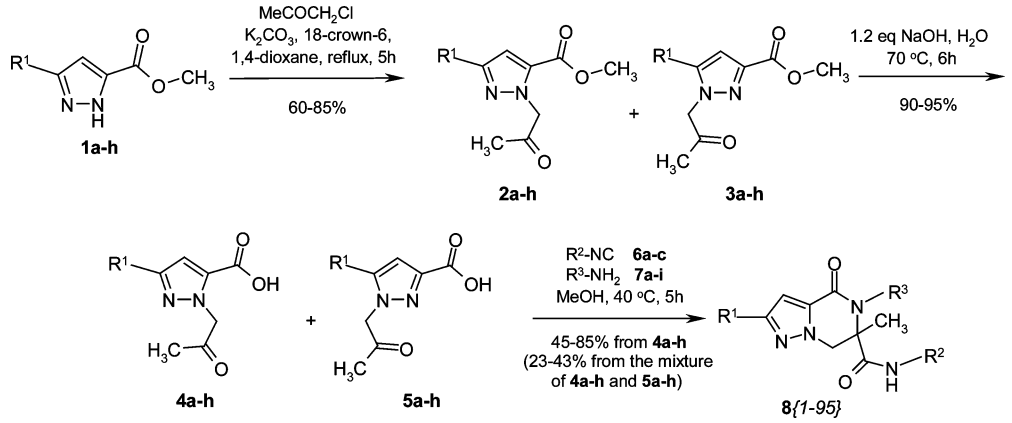
Scheme 1. Synthesis of 4-Oxo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-6-carboxamides **8**{*1*−*95*}



5a−**h** did not react under the described conditions. Only one major product of reaction of isomer **4** with isonitrile and amine was observed under the described conditions. The desired products **8**{*1*−95} usually precipitated from the reaction media, thus allowing their easy separation by filtration of the reaction mixtures. The reaction presumably follows the same initial course as the classical Ugi condensation,[7] 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 tethered Ugi condensation offers a large number of potential input reactants and resulting products (Figure 1). We have observed that the nature of the R^1 substituent does not substantially affect the reaction yield and time, and several differently substituted pyrazole-5-carboxylates **1a**−**h** could be used. With respect to the amine component, various aliphatic and aromatic primary amines **7a**−**i**, such as substituted anilines, benzylamines, 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 three different isonitriles **6a**−**c** available from ChemDiv.

Structures and yields of some representative compounds are shown in Table 1. Isolated yields of **8**{*1*−95} from isomers **4a**−**h** were generally high (>45%, up to 85%), 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 are sometimes concealed by other signals, but usually can be seen as doublets in the range of δ 4.12−5.28, with the geminal spin−spin coupling constants in the range of 7.0−7.6 Hz. In several cases, pure crystalline substances could be obtained, thus allowing their analyses through X-ray crystallography. The Supporting Information contains X-ray data for compound **8**{*4*}. Since the analyzed compound contains one stereogenic center and crystallize in the racemic space group *C*2/*c*, the exact stereochemical assignment was impossible. Single crystals of compounds suitable for X-ray analyses were grown from diethyl ether.

In summary, we have reported a new convenient approach to a variety of substituted 4-oxo-4,5,6,7-tetrahydropyrazolo-[1,5-*a*]pyrazine-6-carboxamides based on a novel modification of the Ugi four-component reaction. The developed methodology is suitable for rapid, parallel, automated synthesis of the corresponding combinatorial libraries for effective exploration of structural diversity around this promising pharmacophoric scaffold.

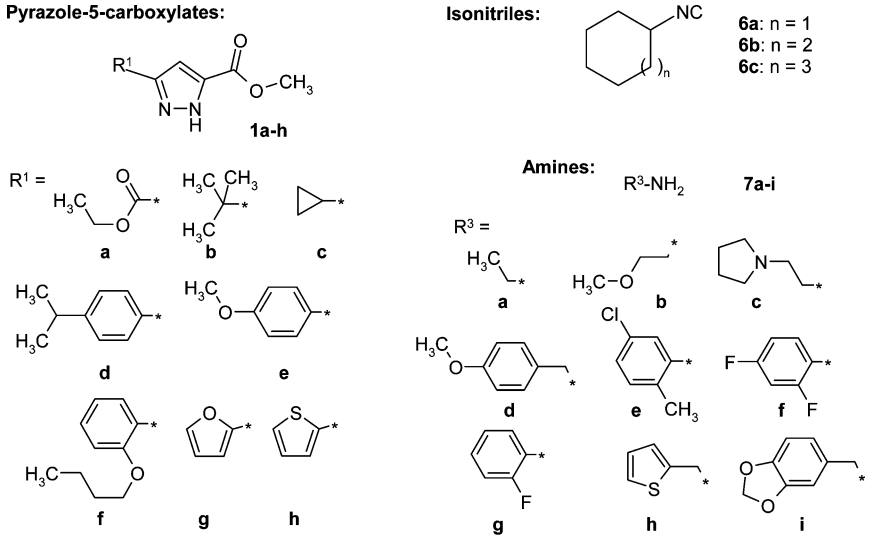


Figure 1. Building blocks evaluated in this work.

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Supporting Information Available. Analytical spectral data for selected compounds and X-ray crystallographic data for **8**{*4*}. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Nyeki, O.; Nogradi, K.; Chongor, E.-A.; Bartane Szalai, G.; Domany, G.; Demeter, A.; Galaambos, J.; Gizur, T.; Kassai, F.; Kiss, C.; Rill, A.; Schoen, I.; Trischler, F.; Torey, J.; Kyotani, Y.; Yokoyama, A. JP 2002255939, 2002; *Chem. Abstr*. **2002**, *137*, 232907.

(2) Askew, B. C.; McIntyre, C. J.; Hunt, C. A.; Claremon, D. A.; Baldwin, J. J.; Anderson, P. S.; Gould, R. J.; Lynch, R. J.; Chang, C. C−T.; Cook, J. J.; Lynch, J. J.; Holahan, M. A.; Sitko, G. R.; Stranieri, M. T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1531−1536.

(3) Wehner, V.; Stilz, H.-U.; Peyman, A.; Knolle, J.; Ruxer, J.-M.; Carniato, D.; Lefrancois, J.-M.; Gadek, T. R.; McDowell, R. DE Patent 19653647, 1998; *Chem. Abstr.* **1998**, *129*, 81970.

(4) Zimmerman, W. T. WO Patent 91-US23 19910109, 1994; *Chem. Abstr*. **1995**, *122*, 49104.

(5) For example, see: (a) Cafieri, F.; Fattorusso, E.; Taglialatela-Scafati, O. *J. Nat. Prod.* **1998**, *61*, 122−125. (b) Li, C.-J.; Schmitz, F. J.; Kelly-Borges, M. *J. Nat. Prod.* **1998**, *61*, 387−389. (c) Umeyama, A.; Ito, S.; Yuasa, E.; Arihara, S.; Yamada, T. *J. Nat. Prod*. **1998**, *61*, 1433−1434. (d) Cafieri, F.; Fattorusso, E.; Taglialatela-Scafati, O. *J. Nat. Prod.* **1998**, *61*, 122−125. (e) Li, C.-J.; Schmitz, F. J.; Kelly-Borges, M. *J. Nat. Prod.* **1998**, *61*, 387−389. (f) Umeyama, A.; Ito, S.; Yuasa, E.; Arihara, S.; Yamada, T. *J. Nat. Prod.* **1998**, *61*, 1433−1434. (g) Askew, B. C.; McIntyre, C. J.; Hunt, C. A.; Claremon, D. A.; Gould, R. J.; Lynch, R. J.; Armstrong, D. J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 475−480. (h) Tapia, R. A.; Prieto, Y.; Pautet, F.; Domard, M.; Sarciron, M.-E.; Walchshofer, N.; Fillion, H. *Eur. J. Org. Chem*. **2002**, *23*, 4005−4010. (i) Dumas, D. J. *J. Org. Chem.* **1988**, *53*, 4650−4653.

(6) Muehlstaedt, M.; Zschiedrich, J. *J. Prakt. Chem. (Leipzig)* **1969**, *311*, 363−369.

(7) (a) Ugi, I. *Isonitrile Chemistry*; Academic Press: London, 1971. (b) Ugi, I.; Doemling, A.; Hoerl, W. *Endeavour* **1994**, *18*, 115−122. For reviews see: (a) Armstrong, R. W.; Brown, D. S.; Keating, T. A.; Tempest, P. A. In *Combinatorial Chemistry Synthesis and Application*; Wilson, S., Czarnik, A. W., Eds.; John Wiley and Sons: New York, 1997, p 153. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res*. **1996**, *29*, 123−131.

(8) (a) Zhang, J.; Jacobson, A.; Rusche, J. R.; Herlihy, W. *J. Org. Chem*. **1999**, *64*, 1074−1076. (b) Lee, D.; Sello, J. K.; Schreiber, S. L.; *Org. Lett*. **2000**, *2*, 709−712. (c) Ley, S. V.; Taylor, S. J.; *Bioorg. Med. Chem. Lett*. **2002**, *12*, 1813−1816. (d) Marcaccini, S.; Pepino, R.; Torroba, T.; Miguel, D.; Garcia-Valverde, M. *Tetrahedron Lett*. **2002**, *43*, 8591−8593. (e) Marcaccini, D.; Miguel, T.; Torroba, M.; Garcia-Valverde, M. *J. Org. Chem*. **2003**, *68*, 3315−3318. (f) Short, K. M.; Mjalli, A. M. M. *Tetrahedron Lett.* **1997**, *38*, 359−362. (g) Harriman, G. C. B. *Tetrahedron Lett*. **1997**, *38*, 5591−5594. (h) Hanusch-Kompa, C.; Ugi, I. *Tetrahedron Lett*. **1998**, *37*, 2725−2728.

(9) Ilyn, A. P.; Kuzovkova, J. A.; Potapov, V. V.; Shkirando, A. M.; Kovrigin, D. I.; Tkachenko, S. E.; Ivachtchenko, A. V. *Tetrahedron Lett*. **2005**, *46*, 881−884.

(10) General procedure for preparation of 3-carboxamide derivatives of 4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-6-carboxamides **8**{*1*−95}. The equimolar amounts of keto acids **4a**−**h** and **5a**−**h** (as a 1:1 mixture of isomers), the isonitrile **6a**−**c**, and the amine **7a**−**i** 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 room temperature, and the formed precipitate was filtered out and purified (if desired) by recrystallization from diethyl ether or by chromatography on silica gel, eluting with a gradient of 0−10% MeOH in CH_2Cl_2.

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