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An Efficient and Versatile Synthesis of Piperazine-2-carboxamides

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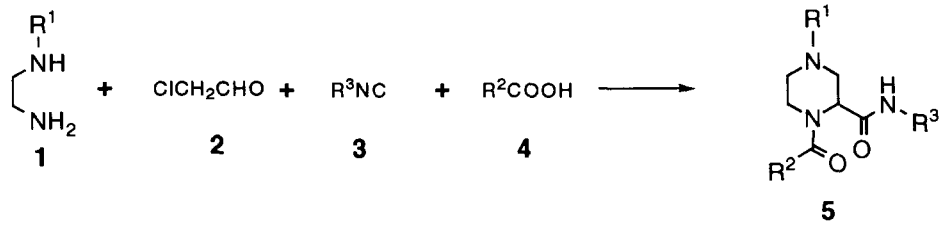
Abstract: An efficient and versatile synthesis of piperazine-2-carboxamides **5** is described. The preparation consists of a one-pot, 4-component Ugi condensation between an N-alkylethylenediamine **1**, chloroacetaldehyde (**2**), an isonitrile **3** and a carboxylic acid **4**. © 1997 Elsevier Science Ltd.

Piperazines and substituted piperazines are important pharmacophores that can be found in in many marketed drugs, such as the Merck HIV protease inhibitor Crixivan,[1] and drugs under development.[2] For this reason, the elaboration of substituted piperazines is an important field of study[3] and piperazine-2-carboxamides are especially attractive as assembly blocks in the synthesis of peptide mimetics.[4] Thus, direct approaches that allow the flexible assembly of these substrates by combining various components would be important, especially in view of the recent interest in multi-component condensations for the assembly of libraries of compounds.[5] This goal has been achieved using the 4-component Ugi condensation[6] as the key step in a one pot reaction between a mono-N-alkylethylenediamine **1**, chloroacetaldehyde (**2**), an isocyanide **3** and a carboxylic acid **4** to give the substituted piperazines **5**.

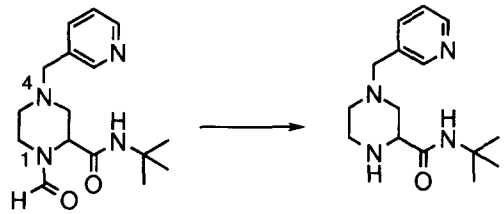


The reaction is operationally very easy to perform: an equimolar mixture of the the four components is stirred with 1 equivalent of $NaHCO_3$ in MeOH for 48 hours and the resulting piperazine carboxamide **5** is obtained after a standard workup with EtOAc and a SiO_2 flash chromatography.[7] It is equally possible to use the Na-salt of the acid instead of the acid and $NaHCO_3$ combination. The reaction works well with a wide range of substituted mono-N-alkylethylenediamines **1** (R^1: Me, benzyl, isopropyl and 3-picoloyl), carboxylic acids **3** (R^2: H, Me, Ph and $PhCH_2$) and isonitriles **4** (R^3: tert-butyl, n-butyl, benzyl and cyclohexyl) and gives the variously substituted piperazines **5a-j** in 34 to 66% isolated yield (Table 1).

Table 1

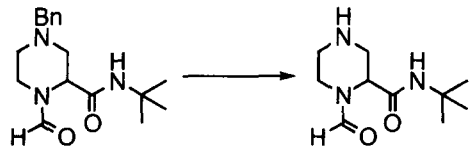
N-Alkylethylenediamine **1** R^1 =	Carboxylic acid **4** R^2 =	Isocyanide **3** R^3 =	Piperazine-2-carboxamide **5** Yield
a CH_2Ph	**a** H	**a** *tert*-butyl	**a** 60%
a CH_2Ph	**a** H	**b** CH_2Ph	**b** 55%
a CH_2Ph	**a** H	**c** *n*-butyl	**c** 66%
a CH_2Ph	**a** H	**d** cyclohexyl	**d** 65%
a CH_2Ph	**b** CH_3	**a** *tert*-butyl	**e** 47%
a CH_2Ph	**c** CH_2Ph	**a** *tert*-butyl	**f** 34%
a CH_2Ph	**d** Ph	**a** *tert*-butyl	**g** 39%
b Me	**a** H	**a** *tert*-butyl	**h** 50%
c isopropyl	**a** H	**a** *tert*-butyl	**i** 44%
d 3-picoloyl	**a** H	**a** *tert*-butyl	**j** 67%

The utility of the piperazine-2-carboxamides **5** would be enhanced if N1 and N4 could be selectively deprotected to allow for incorporation of the piperazine-2-carboxamide moiety into more complex systems. Indeed, this is readily accomplished for the formamide protected piperazines, such as **5j**, under acidic conditions (MeOH, 2N HCl) leading to the free N1 amine **6** (94 % yield).



5j **6**

Analogously, if N4 is benzyl as in **5e**, hydrogenolysis ($Pd(OH)_2$, EtOH, 3 atm H_2) of the N4 benzyl group is readily accomplished to produce the N4 free amine **7** (67% isolated yield).



5e **7**

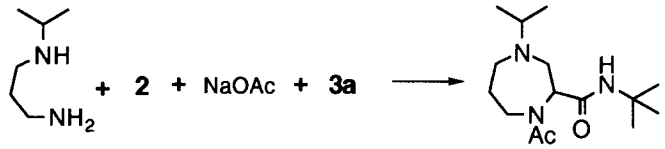
From the work of the Ugi group it is known that chiral acids don't lead to useful diastereoselectivity at the newly formed chiral center in the normal 4-component Ugi condensation. This also holds in this reaction as

50:50 mixtures of the two diastereomers were obtained using the chiral acids **4e-h**. The diastereomers of **5k-n** were readily separable by flash chromatography (Table 2), thus allowing simple and facile access to these systems.

Table 2

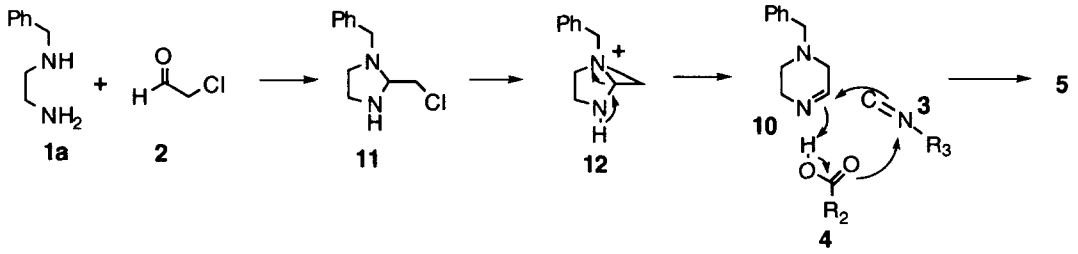
N-Alkylethylenediamine **1** R^1 =	Isocyanide **3** R^3 =	Carboxylic acid **4** R^4COOH =	Piperazine-2-carboxamide **5** Yield
a CH_2Ph	**a** *tert*-butyl	**e** (-)-2,3:4,6-Di-O-isopropylidene-2-keto-gulonic acid	**k** 13% +13%
a CH_2Ph	**a** *tert*-butyl	**f** N-Cbz-L-Serine	**l** 16% + 16%
a CH_2Ph	**a** *tert*-butyl	**g** (-) Camphanic acid	**m** 15% + 15%
a CH_2Ph	**a** *tert*-butyl	**h** (R)-Mandelic acid	**n** 25% + 25%

In an extension of this methodology, it is also possible to form the 7-membered 4-aza-azepin system **9** by using N-alkylpropylendiamines **8** instead of the the N-alkylethylenediamine **1**, although the yield for the formation of the seven membered ring system is dramatically reduced (17%).



8 **9**

The mechanism for the formation of **5** likely involves the addition of the isocyanide **3** and the acid **4** to the cyclic imine **10**. The reaction pathway to **10** was probed by combining N-benzylethylenediamine (**1a**) with chloroacetaldehyde (**2**) in CD_3OD. Examination of the reaction mixture by ^1H and ^{13}C NMR indicates essentially instantaneous formation of the cyclic aminal **11**.[8] Literature evidence[9] from analogous prolinol systems suggests that displacement of the halide by the tertiary amine with formation of the strained [3.1.0] system **12**, and its subsequent rearrangement will lead to the cyclic imine **10**.



1a **2** **11** **12** **4**

In summary, a highly flexible and operationally simple method is at hand for the preparation of piperazine-2-carboxamides **5** in a one pot procedure from N-alkylethylenediamine **1**, chloroacetaldehyde (**2**), isonitrile **4** and carboxylic acid **3**.

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7. (a) The following procedure for the preparation of **5j** is used analogously for the preparation of all piperazines. The ^{1}H, ^{13}C and MS data (Perkin Elmer SCIEX API 100) are in agreement with the proposed structures. (b) To a suspension of N-3-picolylethylene diamine (1.272g, 8.42 mmol) and sodium formate (0.605 g, 8.9 mmol) in 10 mL of MeOH is added *tert*-butylisocyanide (1.05 mL, 9.26 mmol) and aqueous chloroacetaldehyde solution (50 wt%, 1.1 mL). The reaction mixture is stirred at 23°C for 3 days. The reaction mixture is diluted with EtOAc, washed with 5% $NaHCO_3$ solution and brine, dried and evaporated. Flash chromatography gives 1.74 g of **5j** (67%) as a tan solid. Compound **5j** is a 52:48 rotameric mixture. **5j** ($CDCl_3$, 400 MHz Bruker AM) Major rotamer-^{1}H NMR δ 8.55-8.51 (om, 2H), 8.14 (s, 1H), 7.62 (br d, J=7.8, 1H), 7.30-7.25 (om, 1H), 6.85 (s, 1H), 4.28 (m, 1H), 3.93 (d, J=3.5, 1H), 3.54 (s, 2H), 3.40 (d, J=11.8, 1H), 2.94 (m, 1H), 2.90-2.81 (om, 1H), 2.27 (dd, J=11.8, 4.0, 1H), 2.15-2.05 (om, 1H), 1.33 (s, 9H). Minor rotamer-^{1}H NMR δ 8.55-8.51 (om, 2H), 8.15 (s, 1H), 7.70 (br d, J=7.8, 1H), 7.30-7.25 (om, 1H), 5.84 (s, 1H), 4.82 (d, J=3.5, 1H), 3.55 (s, 2H), 3.51-3.47 (om, 2H), 3.33 (d, J=11.8, 1H), 2.90-2.81 (om, 1H), 2.15-2.05 (om, 2H), 1.33$_2$ (s, 9H). Major rotamer-^{13}C NMR δ 167.5, 162.1, 150.4, 149.2, 136.8, 132.9, 123.5, 60.0, 58.1, 53.8, 52.1, 51.6, 37.6, 28.8. Minor rotamer-^{13}C NMR δ 167.2, 161.9, 150.0, 148.8, 136.7, 132.7, 123.5, 59.7, 52.9, 52.7, 52.2, 51.4, 28.7, 43.8.

8. NMR spectra of **11** (CD_3OD, Bruker AM 250): ^{1}H NMR δ 7.38-7.25 (om, 5H), 3.94 (d, J=12.9, 1H), 3.76 (dd, J=6.7, 3.3, 1H), 3.58 (d, J=12.9, 1H), 3.52 (dd, J=11.4, 3.3, 1H), 3.43 (dd, J=11.4, 6.8, 1H), 3.03-2.95 (om, 3H), 2.50 (m, 1H). ^{13}C NMR δ 140.1, 130.1, 129.5, 128.5, 80.8, 59.4, 54.6, 47.2, 44.3.

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