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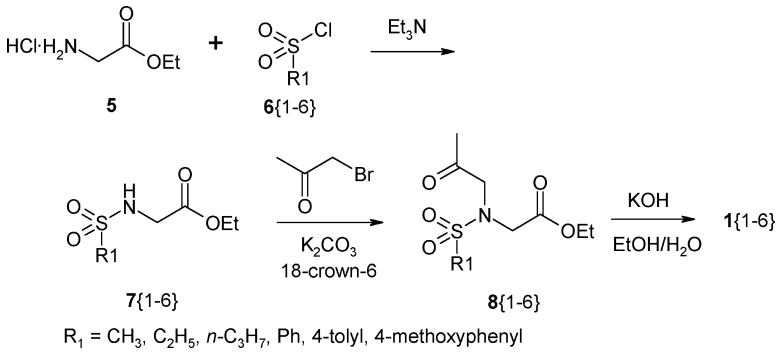

R_1 = CH_3, C_2H_5, *n*-C_3H_7, Ph, 4-tolyl, 4-methoxyphenyl

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One-Step Construction of Peptidomimetic 5-Carbamoyl-4-sulfonyl-2-piperazinones

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Piperazinones continue to attract considerable attention as principal scaffolds in the design of small-molecule modulators for peptidergic receptors.[1] These conformationally restricted structural motifs provide a favorable alternative to peptide analogues of endogenic receptor ligands due to their enhanced metabolic stability and better bioavailability. As a result, piperazinones are considered a common peptidomimetic tool in the development of longer-acting therapeutic agents as well as molecular probes for studying peptidergic biological systems.[2]

Building a piperazinone framework with a strictly defined substitution pattern often results in multistep reaction sequences. Commonly, the piperazinone nucleus is formed in a cyclization of substituted ethylenediamine synthon with an α-haloacid component or a dehydrative cyclization of a dipeptide.[3] Thus, the diversity of substituents in these traditional strategies is determined either by the structure of the precursors for cyclization or by the subsequent functional group manipulation.

Ugi multicomponent reactions (Ugi MCR[4]) have received a wide acceptance as a synthetic approach that allows us to build the piperazinone core and introduce the required diversity elements in the same step, thereby making Ugi MCR in many instances the method of choice[5] for production of combinatorial piperazinone libraries. Using bis-functional reagents further increases the synthetic utility of Ugi MCR and provides routes to substituted piperazinones otherwise difficult to access by traditional methods. For example, 2,5-diketopiperazinones were obtained by Ugi MCR of amines, aldehydes, isocyanides, and chloroacetic acid.[6] Formal five-component (U-5CR) reaction of various amines, glyoxalic ester, isocyanides, and α-amino acids led to the formation of 3,6-diketopiperazines, whereas the combination of 1-Boc-1,2-diaminoethanes with glyoxalic ester, isocyanides, and carboxylic acids in U-5CR furnished 2-carbamoyl-3-piperazinones.[7]

In our ongoing program[6,8] directed toward development of novel applications of Ugi MCR in combinatorial library synthesis, we became interested in developing a MCR-based protocol for preparation of 4-sulfonyl-2-piperazinones, the structural motif of high medicinal relevance. Indeed, these piperazinones have been reported to constitute an essential structural feature of tachykinin NK1 antagonists,[9] gene transcription inhibitors,[10] human Xa factor inhibitors,[11] and anticoagulant and antithrombotic agents[12] as well as inhibitors of squalene oxidase, an important enzyme in cholesterol biosynthesis.[13] The methods reported for preparation of 4-sulfonyl-2-piperazinones, however, are hardly amenable to the production of compound libraries in parallel or combinatorial fashion.[14]

Herein, we report the first example of using a Ugi reaction of sulfonamide ketoacids **1** with amines **2** and isocyanides **3** (formally, a U-4CR) to construct 5-carbamoyl-5-methyl-4-sulfonyl-2-piperazinones in a single step (Scheme 1). The notable feature of this type of cyclic framework is the high steric congestion around N-1, which is a likely reason for the lack of synthetic methods reported in the literature for construction of 1,4,5,5-tetrasubstituted piperazin-2-ones.

The crystalline *N*-sulfonyl-*N*-(2-oxopropyl)glycines **1** were reacted with equimolar amounts of primary amines and cycloalkyl isocyanides in methanolic solution to provide fair to good yields of the target piperazinones **4** requiring no chromatographic purification. The general procedure[15] proved to be suitable for parallel liquid-phase synthesis of a 218-member library of diverse 4,5-disubstituted 5-methyl-2-piperazinones. All synthesized compounds were characterized by LC/MS (with ELSD and UV_{254} detection) and ^1H NMR spectroscopy (Table 1 provides the data for selected library members) to confirm their identity and purity.

To obtain suitable bis-functional precursors **1**[16] for the U-4CR described above, we utilized a straightforward protocol[17] starting from ethyl glycinate involving sequential sulfonylation, alkylation, and ester hydrolysis (Scheme 2). Notably, in the sulfonamide alkylation step, the use of 18-crown-6 as phase-transfer catalysts offered a possibility of using a relatively mild base (K_2CO_3) and, thus, facilitated the reaction workup.

In summary, we have developed a convenient U-4CR protocol for one-step combinatorial preparation of 5-carbamoyl-2-piperazinones that utilizes readily available amines,

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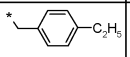
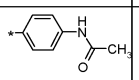
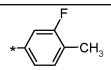
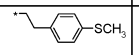
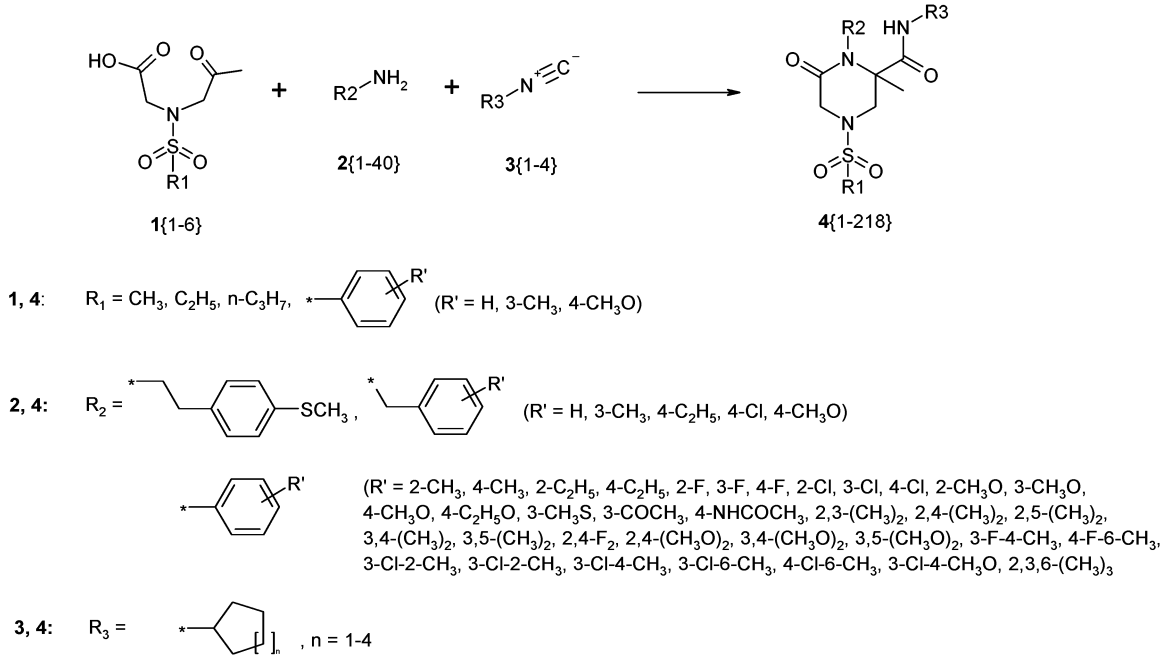
Table 1. Characterization Data for Selected 2-Piperazinones **4** Prepared in This Work

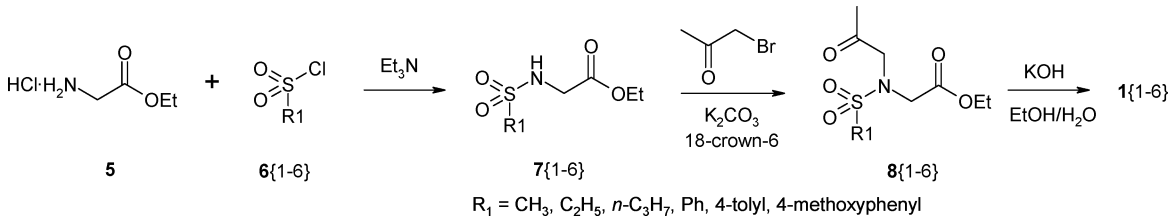
Compound	R_1	R_2	R_3	Mw	LC MS m/z (M+1)	Yield, %	^{1}H NMR data
4{1}	CH_3			463.6	464	53	δ 1.18 (t, 3H, $CH_2C\underline{H}_3$), 1.28 (s, 3H, $C\underline{H}_3C$), 1.39-1.77 (m, 14H, *c*-$C_8\underline{H}_{15}$), 2.58 (q, 2H, $C\underline{H}_2CH_3$), 3.11, 5.06 (dd, 2H,$C\underline{H}_2$Ar, *J* = 12.4Hz), 3.72-3.97 (m, 5H), 7.01, 7.07 (dd, 4H, $C_6\underline{H}_4$, *J* = 7.46Hz), 7.42 (br d, 1H, N<u>H</u>)
4{2}	CH_3			435.5	436	57	δ 1.05-1.4 (m, 5H, cyclohexyl), 1.2 (s, 3H, $C\underline{H}_3C$), 1.53-1.9 (m, 5H, cyclohexyl), 2.53 (s, 3H, $C\underline{H}_3CO$), 2.88 (s, 3H, $C\underline{H}_3SO_2$), 3.3, 4.7 (dd, 2H,$C\underline{H}_2$-ring, *J* = 11.8Hz), 3.52-3.68 (m, 1H, C<u>H</u>-N), 3.88, 3.96 (dd, 2H, $C\underline{H}_2$-ring, *J* = 16.8Hz), 7.36-7.53 (m, 2H), 7.68 (d, 1H, N<u>H</u>, *J* = 7.65Hz), 7.81 (s, 1H), 7.85 (d, 1H, *J* = 7.06Hz)
4{3}	C_2H_5			435.5	436	68	δ 1.05-1.42 (m, 5H, cyclohexyl), 1.08 (s, 3H, $C\underline{H}_3C$), 1.27 (t, 3H, $C\underline{H}_3CH_2$), 1.59-1.92 (m, 5H, cyclohexyl), 2.04 (s, 3H, $C\underline{H}_3$-Ar), 2.27 (s, 3H, $C\underline{H}_3$-Ar), 3.0 (q, 2H, $C\underline{H}_2SO_2$), 3.2, 4.15 (dd, 2H,$C\underline{H}_2$-ring, *J* = 11.95Hz), 3.58-3.72 (m, 1H, C<u>H</u>-N), 3.8-3.98 (m, 2H, $C\underline{H}_2$-ring), 6.94 (d, 1H, *J* = 7.9Hz), 7.03 (d, 1H, *J* = 7.9Hz), 7.11 (s, 1H), 7.54 (d, 1H, N<u>H</u>, *J* = 8.4Hz)
4{4}	n-C_3H_7			437.5	438	45	Amide rotation isomers: δ 1.03 (t, 3H, $C\underline{H}_3CH_2CH_2$), 1.23 (s, 3H, $C\underline{H}_3$-C), 1.34-2.1 (m, 10H), 2.92-3.11 (m, 2H, $CH_2C\underline{H}_2CH_3$), 3.17 (d, 0.8H, $C\underline{H}_2$-ring, *J* = 12.7Hz), 3.33 (d, 0.2H, $C\underline{H}_2$-ring, *J* = 12.7Hz), 3.64-4.21 (m, 7H), 6.71-7.4 (m, 4H, $C_6\underline{H}_3$), 7.66 (br d, 0.8H, N<u>H</u>), 7.9-7.96 (m, 0.2H, N<u>H</u>)
4{5}	n-C_3H_7			478.6	479	74	δ 0.87-1.33 (m, 11H), 1.5-1.87 (m, 7H), 1.99 (s, 3H, $C\underline{H}_3CO$), 2.95-3.05 (m, 2H, $C\underline{H}_2SO_2$), 3.25, 3.97 (dd, 2H, $C\underline{H}_2$-ring, *J* = 12.7 Hz), 3.48-3.6 (m, 1H, C<u>H</u>-N), 3.73-3.94 (m, 2H, $C\underline{H}_2$-ring), 7.02 (d, 2H, *J* = 7.3Hz), 7.48 (d, 2H, *J* = 7.3Hz), 7.58 (br d, 1H, N<u>H</u>), 9.78 (s, 1H, N<u>H</u>)
4{6}	Ph			490.0	491	61	δ 1.08 (s, 3H, $C\underline{H}_3$-C), 1.39-1.96 (m, 8H, *cyclo*-$C_5\underline{H}_9$), 1.98 (s, 3H, $C\underline{H}_3$-Ar), 2.83, 4.29 (dd, 2H, $C\underline{H}_2$-ring, *J* = 11.9Hz), 3.39, 3.93 (dd, 2H,$C\underline{H}_2$-ring, *J* = 16.2Hz), 4.06-4.17 (m, 1H, C<u>H</u>-N), 7.1 (t, 1H), 7.28 (d, 1H), 7.36 (d, 1H), 7.62, 7.79 (dd, 4H, *J* = 9.3Hz), 7.64-7.72 (m, 2H)
4{7}	4-Tolyl			487.5	488	52	δ 1.19 (s, 3H, $C\underline{H}_3$-C), 1.39-1.6 (m, 4H, *cyclo*-$C_5\underline{H}_9$), 1.63-1.92 (m, 4H, *cyclo*-$C_5\underline{H}_9$), 2.23 (s, 3H, $C\underline{H}_3$-Ar), 2.44 (s, 3H, $C\underline{H}_3$-Ar), 2.8, 4.07 (dd, 2H, $C\underline{H}_2$-ring, *J* = 11.5Hz), 3.31, 3.85 (dd, 2H, $C\underline{H}_2$-ring, *J* = 16.5Hz), 4.04-4.19 (m, 1H, C<u>H</u>-N), 6.83 (d, 1H), 6.91 (d, 1H), 7.11 (t, 1H), 7.41, 7.65 (dd, 4H, *J* = 8.0Hz), 7.7 (br d, 1H, N<u>H</u>);
4{8}	4-Tolyl			497.6	498	65	δ 1.09 (s, 3H, $C\underline{H}_3$-C), 1.39-1.95 (m, 12H, *cyclo*-$C_7\underline{H}_{13}$), 1.99 (s, 3H, $C\underline{H}_3$-Ar), 2.47 (s, 3H, $C\underline{H}_3$-Ar), 2.73, 4.27 (dd, 2H, $C\underline{H}_2$-ring, *J* = 11.9Hz), 3.32, 3.94 (dd, 2H, $C\underline{H}_2$-ring, *J* = 16.5Hz), 3.8-3.9 (m, 1H, C<u>H</u>-N), 7.14 (s, 3H), 7.34 (m, 1H), 7.42, 7.69 (dd, 4H, *J* = 8.5Hz), 7.67 (m, 1H, N<u>H</u>)
4{9}	4-$MeOC_6H_4$			559.7	560	75	δ 1.02-1.83 (m, 10H, *cyclo*-C_6H_{11}), 1.46 (s, 3H, $C\underline{H}_3C$), 2.4 (s, 3H, $C\underline{H}_3$-S), 2.61 (t, 1H), 2.79 (d, 1H, $C\underline{H}_2$-ring, *J* = 11.7Hz), 2.82-2.98 (m, 2H), 3.35 (d, 1H, $C\underline{H}_2$-ring, *J* = 16.7Hz), 3.48-3.7 (m, 4H), 3.9 (s, 3H, $C\underline{H}_3$-O), 7.04-7.2 (m, 6H), 7.62 (d, 1H, N<u>H</u>, *J* = 8.3Hz), 7.62 (d, 2H, *J* = 9.2Hz)

isocyanides, and easily synthesized ketoacids. Currently, we are in the process of exploring the scope of this novel transformation with respect to other N-tethered keto-carboxylic acids[18] as bis-functional partners in Ugi reactions. The results of these studies will be reported in due course.

Scheme 1



Scheme 2



Supporting Information Available. ^{1}H NMR spectra of selected 5-carbamoyl-4-sulfonyl-2-piperazinones **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The recently reported synthesis 4-arylsulfonyl-6-oxopiperazine-2-carboxylic acids included six linear steps: Nishida, H.; Mukaihira, T.; Saitoh, F.; Harada, K.; Fukui, M.; Matsusue, T.; Okamoto, A.; Hasaka, Y.; Matsumoto, M.; Shiromozu, I.; Ohnishi, S.; Mochizuki, H. *Chem. Pharm. Bull*. **2004**, *52*, 406−412, 459−462.

(15) The final 5-carbamoyl-4-sulfonyl-2-piperazinones **4** were prepared according to the following general procedure: A solution of an *N*-sulfonyl-*N*-(2-oxopropyl)glycine **1** (1 mmol), a primary aromatic or aliphatic amine **2** (1 mmol), and an isonitrile **3** (1 mmol) in anhydrous methanol (3−5 mL) was stirred at room temperature for 8 h. The precipitate formed was separated by filtration; washed with a small amount of cold methanol, followed by ether; and air-dried (in the cases when the product did not precipitate from the reaction mixture, the solvent was removed in vacuo, and the residue was then solidified upon addition of a small amount of ether prior to filtration). The yield of the obtained solid products was 45−75% with at least 95% purity, as demonstrated by LC/MS analysis.

(16) The keto acids **1** used in this study are commercially available from ChemDiv, Inc. (http://www.chemdiv.com).

(17) Ethyl glycinate was converted to the keto acid precursors for U-4CR according to the following three-step protocol: (i) Freshly distilled thriethylamine (0.50 mol) was added dropwise at 10−15 °C to a vigorously stirred suspension of ethyl glicinate hydrochloride **5** (0.20 mol) and an aryl or alkyl sulfonyl chloride **6** (0.21 mol) in anhydrous acetonitrile (250 mL). The mixture was then stirred at 45−50 °C for 4 h. After cooling to room temperature, the reaction mixture was filtered, and the solid was washed with anhydrous acetonitrile (2 × 50 mL). The combined filtrate and washings were concentrated in vacuo. The residue was crystallized from ethanol to provide ethyl *N*-sulfonyl glycinates **7** (65−92%). (ii) A mixture of a sulfonamide **7** (0.15 mol), freshly distilled chloroacetone (0.17 mol), finely powdered anhydrous potassium carbonate (0.2 mol), and a catalytic amount (∼100 mg) of 18-crown-6 in acetonitrile (150 mL, freshly distilled over P_2O_5) was heated at reflux with vigorous stirring until the reaction was complete by TLC analysis (SiO_2, 5% methanol in chloroform). The reaction mixture was concentrated to one-fourth of its original volume and poured into 5% aqueous potassium chloride (500 mL), and the resulting mixture was stirred for 15 min. It was then transferred into a separatory funnel and extracted with chloroform (3 × 200 mL). The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The product was crystallized from benzene to provide 60−80% yield of the esters **8**. (iii) A suspension of an ester **8** (0.1 mol) in 2% solution of KOH in ethanol−water (50% w/w) was stirred at 45−50 °C until the dissolution of the solid, followed by an additional 30 min of stirring. After the reaction mixture was cooled to room temperature, it was filtered and concentrated to olne-half of its original volume on a rotary evaporator. Aqueous HCl (2%) was added with stirring to pH 3, and the precipitate formed was filtered off, washed with water, and dried in vacuo over P_2O_5 to a constant weight (typically, at least 24 h). The yield obtained was 50−65%, and the product was judged to be at least 95% pure by ^{1}H NMR spectroscopy.

(18) Our preliminary results on similar multicomponent reactions involving ketocarboxylic acids derived from α-amino acids other than glycine indicated that such processes provide the desired products as mixtures of diastereomers. Because the latter were found difficult to separate, a possibility of attaining some degree of diastereocontol is being currently investigated.

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