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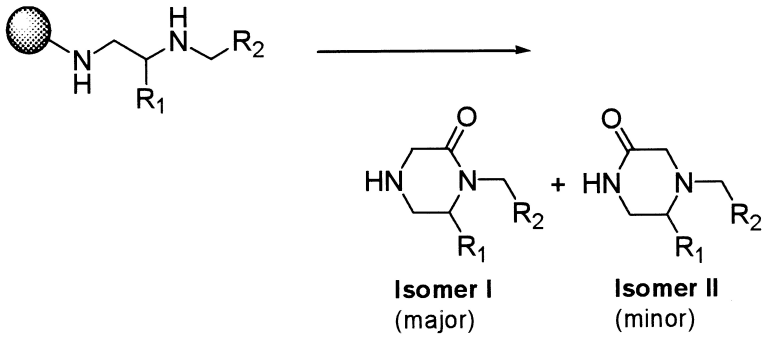

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Reports

Parallel Solid-Phase Synthesis of Disubstituted 1,6-Piperazine-2-ones

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Combinatorial chemistry is a powerful and well-established means of synthesizing large collections of organic compounds for the purpose of drug discovery. One major focus of this field is on the synthesis of small molecules on the solid phase. In particular, the synthesis of heterocycles has received much attention because of their interesting biological properties and prevalence in many bioactive compounds.[1] The monoketopiperazine heterocycle has shown a wide range of activities in such areas as GPIIb/IIIa antagonists,[2] enkephalin analogues,[3] and farnesyltransferase inhibitors.[4] A number of approaches have been reported for the solid-phase synthesis of monoketopiperazines. All of them involve synthesizing a linear carbonyl precursor and subsequently inducing an intramolecular cyclization.[5−7] We describe herein an efficient means for the synthesis of disubstituted 1,6-piperazine-2-ones from resin-bound diamines.

Starting with *p*-methylbenzhydrylamine (MBHA) resin (Scheme 1) and following amino acid coupling and acylation, the resin-bound acylated amino acid was reduced with borane−THF. The resulting diamine was treated with an excess of bromoacetic acid, diisopropylcarbodiimide, and diisopropylethylamine. The coupling of the bromoacetic acid to one of the secondary amines was followed by an in situ nucleophilic attack of the other amine on the brominated carbon, resulting in the formation of the monoketopiperazine. HF cleavage gave the final products in good yield and high purity

By use of the "tea-bag" method of parallel synthesis,[8] the parallel synthesis of individual monoketopiperazines was prepared as described in Scheme 1, using four different amino acids at R_1 and five different carboxylic acids at R_2. In all cases, one major isomeric form was observed with regioselectivity ranging from 70% to >99% (Table 1). To probe the observed regioselectivity, we purified several compounds for NMR analysis, in one case isolating the two separate isomers. As supporting proof of our assignment of the major isomer being the monoketopiperazine **4** having a secondary amine, we acylated a small amount of all of the compounds with acetic anhydride in the presence of DIEA in DCM solution. In all cases, we observed a shift of the major peak with an increase in mass of 42 Da, corresponding to the acyl group. The relative ratios of the isomers obtained were determined by HPLC and can be found in Table 1. An increase in the minor isomer was observed when both R_1 and R_2 are bulky groups.

When R_2 is sterically much smaller (−H), or in the absence of substituent, a different product is obtained in which the bromoacetic acid couples to both of the amines (Scheme 2). The N-methylated amino acids (R_2 = H) were cleanly obtained following reduction of resin-bound Boc-amino acids with borane in THF. We have described previously that carbamates are cleanly reduced in the presence of BH_3−THF to form the corresponding *N*-methyl derivatives.[9] The bis-*N*-bromoacetic compounds **6** were obtained in good yield and high purity (Table 2). The reaction conditions are the same as those for the monoketopiperazine formation. In all but one instance, only the bisbromoacyl product is observed. However, when R_1 = benzyl and R_2 = methyl, both the bisbromoacyl and the monoketopiperazine products are observed (see Table 2).

We developed a straightforward method for the solid-phase parallel synthesis of disubstituted monoketopiperazines. The chemistry allows the synthesis of a large number of individual compounds as well as mixture-based libraries.

Amino Acid Coupling. The amino acid (Boc-Xaa-OH, 6 equiv, 0.1 M) was coupled in DMF using the conventional coupling reagents diisopropylcarbodiimide (DIPCDI, 6 equiv) and hydroxybenzotriazole (HOBt, 6 equiv) for 1 h. After removal of the Boc group with 55% trifluoroacetic acid in DCM (30 min) and washing with DCM (6×), the resin was neutralized with 5% DIEA in DCM (3×).

Acylation. The free amine was N-acylated with a carboxylic acid (10 equiv) in the presence of DIPCDI (10 equiv) and HOBt (10 equiv) in DMF overnight.

Exhaustive Reduction of the Amide Groups. The reduction was performed in 50 mL Kimax tubes under a blanket of nitrogen. The resin packet and boric acid (15-fold excess over each amide bond) were added to each tube, followed by trimethyl borate (15-fold excess over each amide bond) and 1 M BH_3−THF (40-fold excess over each amide bond). The tubes were then heated to 65 °C for 86 h, followed by quenching with MeOH. The resin was washed with methanol (4×), and the borane was disproportionated by treatment with neat piperidine at 65 °C overnight. The resin was then washed with methanol (2×) and DMF (6×)

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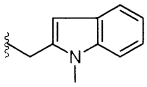
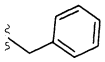
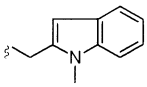
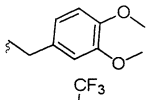
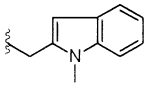
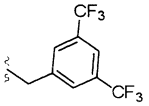
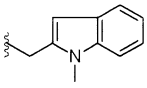
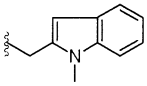
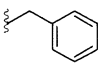
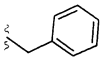
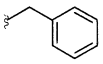
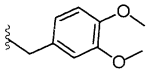
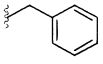
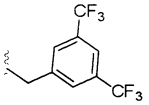
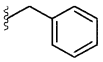
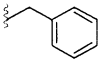
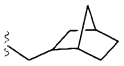
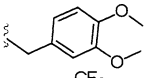
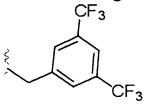
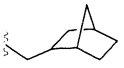
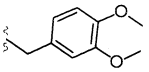
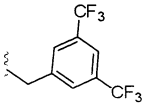
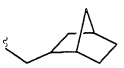
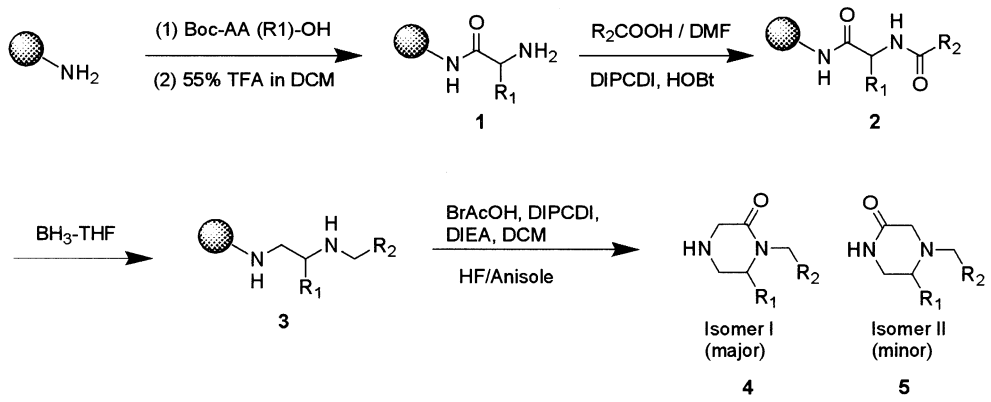
Table 1. Individual Monoketopiperazines

Entry	R_1	R_2	MW (calculated)	MW (found)	% Isomer I (4)	% Isomer II
4a			347.4	348.4 (MH+)	87	13
4b			407.5	408.4 (MH+)	82	18
4c			483.4	484.4 (MH+)	71	29
4d			299.4	300.0 (MH+)	83	17
4e			365.5	366.4 (MH+)	85	15
4f			294.3	294.9 (MH+)	96	4
4g			354.4	355.4 (MH+)	96	4
4h			430.3	431.3 (MH+)	> 99	—
4i			246.3	247.2 (MH+)	> 99	—
4j			312.4	313.3 (MH+)	> 99	—
4k			278.3	278.9 (MH+)	> 99	—
4l			354.2	354.7 (MH+)	> 99	—
4m			170.2	170.8 (MH+)	> 99	—
4n			236.3	237.0 (MH+)	> 99	—
4o			306.4	307.0 (MH+)	71	29
4p			382.3	383.7 (MH+)	70	30
4q			198.3	198.8 (MH+)	98	2
4r			264.4	265.0 (MH+)	97	3

and dried. The completeness of the reduction was verified by cleavage and analysis of a reduction control.

Monoketopiperazine Formation. The resin-bound amines were reacted with bromoacetic acid (5 equiv per amine),

Scheme 1. Solid-Phase Synthesis of Disubstituted Monoketopiperazines



Scheme 2. Solid-Phase Synthesis of Bis-*N*-bromoactyl Compounds

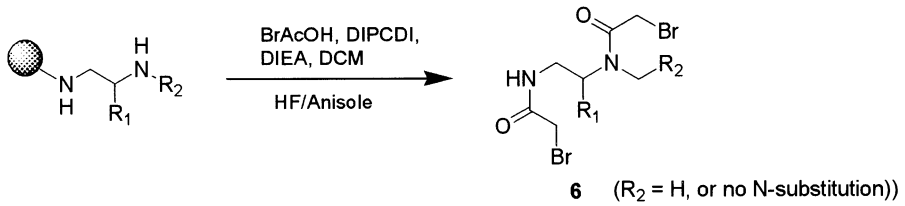
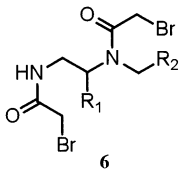


Table 2. Individual Bisbromoacyl Compounds



entry	R_1	R_2	MW (calcd)	MW (found)	% bisbromoacyl	% monketopiperazine
6a	CH_3	H	330.0	331.0 (MH^+)	>99	
6b	$CH_2C_6H_5$	H	406.1	407.0 (MH^+)	69	31
6c	$CH(CH_3)_2$	H	358.0	359.0 (MH^+)	>99	
6d	CH_3	NA	344.0	316.7 (MH^+)	>99	
6e	$CH_2C_6H_5$	NA	392.0	393.1 (MH^+)	>99	
6f	$CH(CH_3)_2$	NA	344.0	344.8 (MH^+)	>99	

DIPCDI (5 equiv per amine), and DIEA (2.5 equiv per amine) in DCM (0.1 M) for 36 h at room temperature. The resin was then washed with DCM (6×) and dried. Following cleavage from the resin with anhydrous HF in the presence of anisole at 0 °C for 7 h, the desired products were extracted with acetonitrile−water (50:50), lyophilized, and characterized.

1-(2-Bicyclo[2.2.1]hept-2-ylethyl)-6-methylpiperazin-2-one (4e): ^{1}H NMR δ 9.42 (m, 2H), 3.77 (m, 1H), 3.59 (m, 1H), 3.44 (dd, J = 4.3 Hz, J = 12.8 Hz, 1H), 3.17 (dd, J = 6.5 Hz, J = 12.9 Hz, 1H), 2.97 (m, 1H), 1.52 (m, 1H), 1.33 (m, 5H), 1.24 (d, J = 6.6 Hz, 3H), 1.10 (m, 6H), 161.33, 48.10, 48.03, 45.03, 44.36, 41.80, 41.68, 40.46, 40.01, 37.57, 35.94, 34.97, 33.85, 29.50, 28.30, 17.4.

1-{2-[3,5-Bis(trifluoromethyl)phenyl]ethyl}-6-(1-phenylethyl)piperazin-2-one (4h): ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.51 (s, 2H), 7.98 (s, 2H), 7.95 (s, 1H), 7.35 (m, 5H), 3.98 (m, 1H), 3.87 (m, 1H), 3.80 (d, J = 16.7 Hz, 1H), 3.72 (d, J = 16.6 Hz, 1H), 3.33 (m, 1H), 3.26 (dd, J = 4.8 Hz, J = 13.7 Hz, 1H), 3.13 (m, 2H), 3.07 (m, 1H), 2.90 (m, 1H), 2.87 (dd, J = 10.1 Hz, J = 13.6 Hz, 1H).

1-[2-(3,4-Dimethoxyphenyl)ethyl]-6-isopropylpiperazin-2-one (4o). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.49 (s,2H), 6.85 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 1.6 Hz, 1H), 6.71 (dd, J = 1.5, J = 7.8 Hz, 1H), 3.97 (m, 1H), 3.82 (d, J = 16.4 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.65 (d, J = 16.4 Hz, 1H), 3.54 (m, 1H), 3.27 (m, 1H), 3.17 (m, 1H), 3.10 (m, 1H), 2.78 (m, 1H), 2.62 (m, 1H), 2.22 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H).

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Supporting Information Available. LC−MS of representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Gallop, M. A.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233. (b) Gordon, E. M.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1385. (c) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555.

(d) Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 17. (e) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527. (f) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev*. **1997**, *97*, 449.

(2) Sugihara, H.; Fukushi, H.; Miyawaki, T.; Imai, Y.; Terashita, Z.-i.; Masaki, K.; Yukio, F.; Shunbun, K. *J. Med. Chem.* **1998**, *41*, 489−502.

(3) Dinsmore, C. J.; Bergman, J. M.; Wei, D. D.; Zartman, C. B.; Davide, J. P.; Greenberg, I. B.; Liu, D.; O'Neill, T. J.; Gibbs, J. B.; Koblan, K. S.; Kohl, N. E.; Lobell, R. B.; Chen, I. W.; McLoughlin, D. A.; Olah, T. V.; Graham, S. L.; Hartman, G. D.; Williams, T. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 537−540.

(4) Piercy, M. F.; Moon, M. W.; Blinn, J. R.; Dobry-Scheur, P. J. K. *Brain Res.* **1986**, *74*, 385.

(5) Vojkovsk, T.; Weichsel, A.; Patek, M. *J. Org. Chem.* **1998**, *63*, 3162−3163.

(6) Shreder, K.; Zhang, L.; Gleeson, J. P.; Ericsson, J. A.; Yalamoori, V. V.; Goodman, M. *J. Comb. Chem.* **1999**, *1*, 383−387.

(7) (a) Goff, D. A. *Tetrahedron Lett.* **1998**, *39*, 1473−1476. (b) Mohamed, N.; Bhatt, U.; Just, G. *Tetrahedron Lett.* **1998**, *39*, 8213−8216. (c) Zhu, Z.; Mckittrick, B. *Tetrahedron Lett.* **1998**, *39*, 7479−7482. (d) Hulme, C.; Ma, L.; Kumar, N. V.; Krolikowski, P. H.; Allen, A. C.; Labaudiniere, R. *Tetrahedron Lett.* **2000**, *41*, 1509−1514. (e) Hulme, C.; Ma, L.; Cherrier, M. P.; Romano, J. J.; Morton, G.; Duquenne, C.; Salvino, J.; Labaudiniere, R. *Tetrahedron Lett.* **2000**, *41*, 1883−1887.

(8) Houghten, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5131−5134.

(9) Nefzi, A.; Ostresh, J. M.; Giulianotti, M.; Houghten, R. A. *J. Comb. Chem*. **1999**, *1*, 195−198.

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