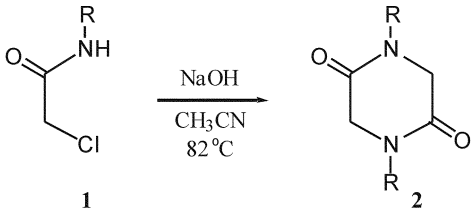
One-pot Synthesis of Symmetrical 1,4-Disubstituted Piperazine-2,5-diones

Su-Dong Cho,* Sang-Yong Song, Kyung-Hyun Kim, Bao-Xiang Zhao, Chuljin Ahn, Woo-Hong Joo, Yong-Jin Yoon,† J. R. Falck,‡ and Dong-Soo Shin*

Departments of Chemistry & Biology, Changwon National University, Changwon 641-773, Korea
†Department of Chemistry & Research Institute of Natural Science, Gyeongsang National University, Chinju 660-701, Korea
‡Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, TX 75390, U.S.A.
Received December 9, 2003

Key Words : One-pot synthesis, Piperazine, Symmetrical, 1,4-Disubstituted piperazine-2,5-dione

The piperazine-2,5-dione moiety occurs in a variety of drugs and natural products which span a wide spectrum of biological activities, *e.g*., roquefortine,[1,2] bicyclomycin,[3] dipodazine,[4] neihumicin,[5] phomamide,[6] and dihydrodysamide C.[7] Additionally, this heterocyclic system has found unique applications as an acceptor for organic anions or metal cations[8] and in material sciences.[9] While numerous approaches[10-14] to piperazine-2,5-diones have been reported, there is still considerable demand for more economic and versatile syntheses. Herein, we report a convenient, one-pot synthesis of 1,4-disubstituted piperazine-2,5-diones (**2**) based on the mild homoannulation of *N*-substituted 2-chloroamides (**1**, eq. 1).



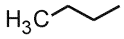
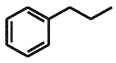
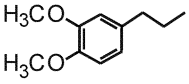
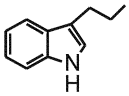
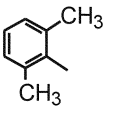
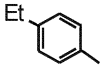
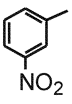
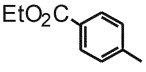
1 **2** (1)

The key precursor **1** was readily prepared in excellent yield by addition of the appropriate amine to 2-chloroacetyl chloride in CH_2Cl_2 (Table 1).[15] Homoannulation, *i.e*., cyclization between two molecules of **1**, in the presence of strong base such as NaOH (or KOH, NaH, and *t*-BuOK) in CH_3CN (or DMF) gave the corresponding piperazine-2,5-diones **2** in good yield. In contrast, K_2CO_3 failed to give any **2** even at reflux temperature overnight.

The influence of the nitrogen substituent on the yield of piperazine-2,5-dione **2** was also systematically investigated. The results are summarized in Table 1. Acetamides **1** bearing simple alkyl (Entry 1), cycloalkyl (Entries 2, 3), and heterocyclic (Entry 4) groups reacted smoothly. Cyclizations with benzylic (Entries 5, 6), phenethyl (Entries 7, 8), indolylene (Entry 9) moieties also gave good yields. Aryl (Entry 10) functionality, even sterically hindered examples (Entry 11) as well as those with alkyl (Entry 12) and halogen substituents (Entry 13), were well tolerated. However, strong

*Corresponding Author. Tel: +82-55-279-7433; Fax: +82-55-279-7439; e-mail: sdcho64@hanmail.net or dsshin@changwon.ac.kr

Table 1. Synthesis of chloroacetamides **1** and piperazines **2**

Entry	R-	**1** Yield[a] (%)	**2** Yield (%)
1		89	62
2		92	67
3		93	71
4		87	58
5		90	83
6		92	87
7		94	85
8		95	87
9		93	61
10		95	78
11		93	83
12		96	53
13		94	76
14		96	0
15		92	0

[a]Isolated yield based on amine.

electron withdrawing substituents on the aromatic ring (Entries 14 and 15) proved unsatisfactory.

In conclusion, we describe a mild, convenient and simple methodology for the synthesis of 1,4-disubstituted piperazine-2,5-diones. This strategy will be useful for preparing the building blocks in complex natural product synthesis and combinatorial applications.

Representative Procedures

2-Chloro-*N*-phenethylacetamide (Entry 7): 2-Chloroacetyl chloride (6.26 g, 55.5 mmol) was added over 30 min at room temperature to a mixture of phenethylamine (6.11 g, 50.4 mmol) and powdered K_2CO_3 (8.0 g, 58.0 mmol) in dichloromethane (100 mL). After 30 min, the mixture was refluxed for 4 h and then stirred for an additional 30 min at room temperature. The reaction mixture was poured into cold water (200 mL) and extracted with dichloromethane (2 × 100 mL). The combined organic extracts were washed with water and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane:ethyl acetate (1/1, v/v) as eluent affording 2-chloro-*N*-phenethylacetamide (9.37 g, 94% yield) as a white solid, mp 64-65 ºC (lit.[16] mp 67 ºC) ; IR (KBr) 3327, 3026, 2940, 1654, 1551, 1293, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.85 (t, 2H), 3.56 (q, 2H), 4.01 (s, 2H), 6.64 (bs, NH, D_2O exch.), 7.19-7.35 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 35.52, 41.05, 42.69, 126.72, 128.76, 138.77, 169.92; MS (m/z) 197.66.

1,4-Phenethylpiperazine-2,5-dione: A solution of 2-chloro-*N*-phenethylacetamide (3 g, 15.2 mmol) and NaOH (1.3 g, 33.4 mmol) in CH_3CN (60 mL) was refluxed for 6 h, then stirred at 20 ºC for 30 min. The resulting mixture was filtered, concentrated *in vacuo*, and diluted with CH_2Cl_2 (100 mL). The solution was washed three times with water (100 mL), dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by chromatography on silica gel using ethyl acetate as eluent affording piperazine-2,5-dione as a white solid (4.16 g, 85% yield), mp 204-206 ºC (Et_2O); IR (KBr) 2934, 3024, 1654, 1492, 1341 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) d 7.19-7.38 (m, 5H), 3.79 (s, 2H), 3.57-3.62 (t, 2H, J = 7.5 Hz), 2.85-2.90 (t, 2H, J = 7.5 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 163.02, 137.67, 133.17, 128.38, 128.34, 126.43, 50.28, 47.51, 32.77; MS (m/z) 322.40.

Acknowlegments. This work was financially supported by the Korea Research Foundation (KRF2000-015-DP0257).

References and Notes

1. Chen, W. C.; Joullie, M. M. *Tetrahedron Lett.* **1998**, *39*, 8401-8404.
2. Ohmomo, S.; Oguma, K.; Ohashi, T.; Abe, M. *Agric. Biol. Chem.* **1978**, *42*, 2387-2389.
3. Bradley, E. L.; Herbert, R. B.; Lawrie, K. W. M.; Khan, J. A.; Moody, C. M.; Young, D. W. *Tetrahedron Lett.* **1996**, *37*, 6935-6938.
4. Sorensen, D.; Larsen, T. O.; Christophersen, C.; Nielsen, P. H.; Anthoni, U. *Phytochem.* **1999**, *51*, 1181-1183.
5. Yokoi, T.; Yang, L. M.; Yokoi, T.; Wu, R. Y.; Lee, K. H. *J. Antibiot.* **1988**, *41*, 494-501.
6. Ferezou, J. P.; Quesneau-Thierry, A.; Barbier, M.; Kollmann, A.; Bousquet, J. F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 113-115.
7. Dumdei, E. J.; Simpson, J. S.; Garson, M. J.; Byriel, K. A.; Kennard, C. H. L. *Australian J. Chem.* **1997**, *50*, 139-144.
8. Fuji, K.; Takasu, K.; Miyamoto, H.; Tanaka, K.; Taga, T. *Tetrahedron Lett.* **1996**, *37*, 7111-7114.
9. Li, W.-R.; Kao, K.-C.; Yo, Y.-C.; Lai, C. K. *Helv. Chim. Acta* **1999**, *82*, 1400-1407.
10. Marcaccini, S.; Pepino, R.; Pozo, M. C. *Tetrahedron Lett.* **2001**, *42*, 2727-2728.
11. Loughlin, W. A.; Marshall, R. L.; Carreiro, A.; Elson, K. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 91-94 and cited references.
12. Bossio, R.; Fernandez Marcos, C.; Marcaccini, S.; Pepino, R. *Tetrahedron Lett.* **1997**, *38*, 2519-2510.
13. Yates, P.; Hoare, J. H. *Can. J. Chem.* **1983**, *61*, 519-528.
14. Okawara, T.; Noguchi, Y.; Matsuda, T.; Furukawa, M. *Chem. Lett.* **1981**, 185-188.
15. Cho, S.-D.; Choi, W.-Y.; Yoon, Y.-J. *J. Heterocyclic Chem.* **1996**, *33*, 1579-1582.
16. Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *J. Org. Chem.* **1995**, *60*, 7149-7152.