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One-step diketopiperazine synthesis using phase transfer catalysis

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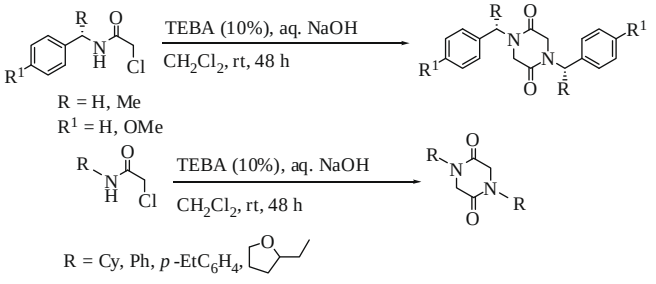
ABSTRACT

A simple and efficient one-step procedure is described for the synthesis of a number of symmetrical 1,4-disubstituted piperazine-2,5-diones under phase transfer conditions. The reactions are carried out at room temperature, starting from a suitable *N*-chloroacetamide in the presence of an aqueous solution of sodium hydroxide. Piperazine-2,5-diones were obtained with excellent selectivity in yields of up to 90%.

Diketopiperazines (DKPs) are a class of compounds which are of significant interest in biology and drug discovery.[1,2] These compounds are present in biologically active natural products[2], and because of their embedded amino acid structures, they represent an important alternative to common peptides. The synthesis of DKPs is described extensively in the literature.[3] Here we report the synthesis of 1,4-disubstituted piperazine-2,5-diones by direct cyclization of N-substituted chloroacetamides in a two-phase medium (CH_2Cl_2/alkaline solution) in the presence of the phase transfer catalyst, triethylbenzylammonium chloride (TEBA) (Scheme 1).

Phase transfer catalysis (PTC) is a convenient method which generally allows for the rate increase of a reaction under mild conditions. The catalytic amount of base which is transferred into the organic layer at any given time appears to be totally selective towards the cyclization rather than polymerization of the chloroacetamides. Bifunctional molecules such as chloroacetamides or amino acids are known to polymerize in highly concentrated solutions, and cyclization is merely a side reaction.[4] Quaternary ammonium salts have been investigated widely and successfully used in several areas of organic chemistry since their discovery as PT catalysts.[5,6] A single example of their use in the synthesis of DKPs was reported in 1981.[7] Compound **4b** was prepared using this methodology in only 50% yield and no other example was reported.[7] Considering the rising demand for peptide alternatives such as DKPs, due to their potential industrial and medical applications,[8] there is great interest in the development of efficient routes to the synthesis of peptide precursors, such as the synthesis of symmetrical disubstituted piperazine-2,5-diones as presented here. In contrast to the most common step-wise procedures which consist of construction of head-to-tail dipeptides, followed by their cyclization at elevated temperatures,[9,10] the one-step synthesis reported here is carried out at room temperature and in the presence of a catalytic amount of TEBA. Following this procedure, a series of symmetrical 1,4-disubstituted piperazine-2,5-diones was synthesized (Table 1).

The chiral DKP **3b** has been employed extensively in the asymmetric synthesis of both enantiomers of 2,6-diaminopimelic acid and its derivatives as well as non natural amino acids.[11–13] As a result, it can be considered an important building block in the synthesis of various molecules. Under PT conditions, compound **3b** was isolated successfully in 90% yield. Similar results were obtained for the chiral derivative **5b** (88%). This molecule is currently under investigation as a precursor in the synthesis of non-natural amino acids. Cyclization of aromatic, non-chiral chloroacetamides **1a** and **4a** afforded the corresponding diketopiperazine products **1b** and **4b**, both in 85% yield. 2-Chloro-*N*-(1-ethylphe-



Scheme 1.

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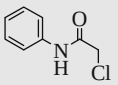
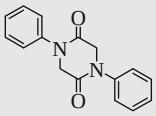
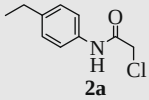
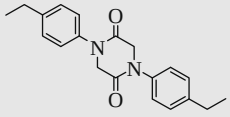
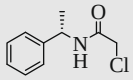
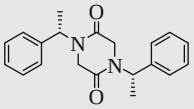
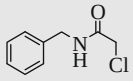
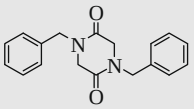
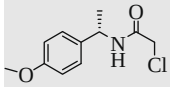
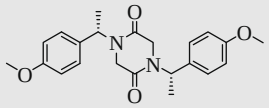
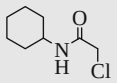
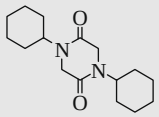
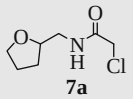
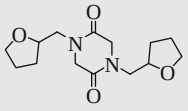
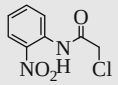
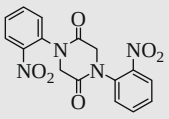
Table 1
Cyclization of N-substituted chloroacetamides under phase transfer conditions to give the corresponding diketopiperazine[a,b]

Amide	Diketopiperazine	Yield (%)
 **1a**	 **1b**	85
 **2a**	 **2b**	70
 **3a**	 **3b**	90
 **4a**	 **4b**	85
 **5a**	 **5b**	88
 **6a**	 **6b**	70
 **7a**	 **7b**	80
 **8a**	 **8b**	—

[a] Catalyst loading (10%) in each case was in wt/% based on the weight of the amide. Reaction time was 48 h.
[b] Compound **7a** afforded the corresponding diketopiperazine **7b** in 80% crude yield as a mixture of isomers. The *meso* isomers were purified by chromatography and characterized. The other isomers however, co-eluted on silica gel with unreacted starting material **7a**, hence full characterization of these is not provided.

nyl)acetamide **2a** afforded the corresponding diketopiperazine **2b** in 70% yield.

Cyclization of the non-aromatic chloroacetamides **6a** and **7a** was also investigated. It was found that these amides also underwent cyclization under PT conditions, affording the desired products **6b** and **7b** in good yields. Specifically, reaction of **6a** gave the corresponding diketopiperazine **6b** in 70% yield. The racemic 2-chloro-*N*-[(tetrahydrofuran-2-yl)methyl] acetamide **7a** afforded the corresponding diketopiperazine **7b** in 80% crude yield, which is substantially higher than that previously reported in homophase conditions.[14]

Among the various amides tested, 2-chloro-*N*-(2-nitrophenyl)acetamide **8a** was the only example which did not undergo cyclization under these conditions. This is likely to be due to the electron withdrawing effect of the nitro group.

In conclusion, we have developed an efficient one-step procedure for the synthesis of 1,4-disubstituted piperazine-2,5-diones[15,16] employing a phase transfer catalyst. This method results in good to very good yields in most cases, and in complete selectivity towards cyclization even in the presence of a high concentration of reactants. Generally, high dilution favours cyclization, whereas high concentrations favour polymerization of polymerizable monomers.[17] In our case, the selectivity towards cyclization can be attributed to the low concentration of base which reacts with the chloroacetamide at any given time due to the PTC employed.

The ratio of TEBA/chloroacetamide was also investigated, and optimal results were achieved with the addition of 10% wt/wt of catalyst/amide. This study has demonstrated that slow addition of the catalyst, ideally over a 48-h period, gives high, reproducible yields.

Acknowledgements

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References and notes

1. Gomez-Monterrey, I.; Campiglia, P.; Carotenuto, A.; Stiuso, P.; Bertamino, A.; Sala, M.; Aquino, C.; Grieco, P.; Morello, S.; Pinto, A.; Ianelli, P.; Novellino, E. *J. Med. Chem.* **2008**, *51*, 2924–2932.
2. Boger, D. L.; Zhou, J. *J. Am. Chem. Soc.* **1993**, *115*, 11426–11433.
3. (a) Martins, M. B.; Carvalho, I. *Tetrahedron* **2007**, *63*, 9923–9932; (b) Dinsmore, C. J.; Beshore, D. C. *Tetrahedron* **2002**, *58*, 3297–3312.
4. Remias, J. E.; Elia, C.; Grove, L. E.; Sen, A. *Inorg. Chim. Acta* **2006**, *359*, 2956–2965.
5. Takashi Ooi, K. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222–4266.
6. Aggarwal, V. K.; Lopin, C.; Sandrinelli, F. *J. Am. Chem. Soc.* **2003**, *125*, 7596–7601.
7. Okawara, T.; Noguchi, Y.; Matsuda, T.; Furukawa, M. *Chem. Lett.* **1981**, 185–188.
8. Borthwick, A. D.; Davies, D. E.; Exall, A. M.; Hatley, R. J. D.; Hughes, J. A.; Irving, W. R.; Livermore, D. G.; Sollis, S. L.; Nerozzi, F.; Valko, K. L.; Allen, M. J.; Perren, M.; Shabbir, S. S.; Woollard, P. M.; Price, M. A. *J. Med. Chem.* **2006**, *49*, 4159–4170.
9. Estevez, J. C.; Burton, J. W.; Estevez, R. J.; Ardron, H.; Wormald, M. R.; Dwek, R. A.; Brown, D.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2137–2154.
10. Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1992**, *57*, 6532–6536.
11. Paradisi, F.; Porzi, G.; Rinaldi, S.; Sandri, S. *Tetrahedron: Asymmetry* **2000**, *11*, 1259–1262.
12. Paradisi, F.; Porzi, G.; Rinaldi, S.; Sandri, S. *Tetrahedron: Asymmetry* **2000**, *11*, 4617–4622.
13. Paradisi, F.; Piccinelli, F.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **2002**, *13*, 497–502.
14. Cho, S. D.; Song, S. Y.; Kim, K. H.; Zhao, B. X.; Ahn, C.; Joo, W. H.; Yoon, Y. J.; Falck, J. R.; Shin, D. S. *Bull. Korean Chem. Soc.* **2004**, *25*, 415–416.
15. Compounds **1a**–**4a** and **6a**–**8a** are commercially available.
(S)-2-Chloro-N-(1-(4-methoxyphenyl)ethyl)acetamide **5a**: Off-white solid: mp: 243–245 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29–7.21 (m, 2H), 6.93–6.86 (m, 2H), 6.70 (s, 1H), 5.09 (p, J = 7.0 Hz, 1H), 4.04 (q, J = 15.2 Hz, 2H), 3.80 (s, 3H), 1.52 (d, J = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.80, 159.06, 134.42, 127.31, 114.15, 55.29, 48.70, 42.63, 21.51; HRMS (EI): m/z calcd for $C_{11}H_{14}ClNO_2$: 227.0713, found: 227.0711; $[\alpha]_D^{20}$ −89 (c 0.35, $CHCl_3$).
16. General procedure for the synthesis of 1,4-disubstituted piperazine-2,5-diones (**1b**–**8b**).
Chloroacetamides **1a**–**8a** (18 mmol) were dissolved in CH_2Cl_2 (23 mL) and a 50% aqueous NaOH solution (8 equiv, 144 mmol, 11.5 mL) was added at room temperature. TEBA was added gradually over a 48-h period to a total of 10% (based on starting chloroacetamide weight), under vigorous stirring. The reaction was quenched, firstly with H_2O (20 mL) and then with 6 M HCl (45 mL). The CH_2Cl_2 was removed in vacuo and the aqueous phase extracted with EtOAc (3 × 15 mL). The organic layers were combined, washed with brine and dried over $MgSO_4$. After removal of the solvent in vacuo, the resulting solid was purified by column chromatography using silica gel (cyclohexane/ethyl

acetate = 2:1), affording the 1,4-disubstituted piperazine-2,5-dione in the specified yield.

1,4-Diphenylpiperazine-2,5-dione (**1b**): White solid; mp: 267–268 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 10H), 4.55 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.96, 139.58, 129.47, 127.57, 124.97, 53.48; Anal. Calcd for $C_8H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.36, H, 5.26, N, 10.14.

1,4-Bis(4-ethylphenyl)piperazine-2,5-dione (**2b**): White solid; mp: 243–245 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17–7.23 (m, 8H), 4.44 (s, 4H), 2.60 (q, J = 7.6 Hz, 4H), 1.18 (t, J = 7.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 143.8, 137.1, 128.9, 124.9, 53.5, 28.5, 15.5; Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.71; H, 6.79; N, 8.53.

1,4-Bis[(S)-1-phenylethyl]piperazine-2,5-dione (**3b**): Off-white solid; mp: 109–110 °C (lit. mp: 109–110);[18] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.16 (m, 10H), 5.95 (q, J = 7.1 Hz, 2H), 3.86 (d, J = 16.7 Hz, 2H), 3.52 (d, J = 16.7 Hz, 2H), 1.54 (d, J = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.81, 138.27, 128.78, 128.05, 127.32, 50.14, 44.67, 15.10; Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.02; H, 7.05; N, 8.66. $[\alpha]_D^{20}$ −318.2 (c 2.1, $CHCl_3$) (lit. $[\alpha]_D^{20}$ −323.2).[18]

1,4-Dibenzylpiperazine-2,5-dione (**4b**): White solid; mp: 175–176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 10H), 4.58 (s, 4H), 3.93 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 134.9, 128.9, 128.5, 128.2, 49.3, 49.2; Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.38; H, 6.27; N, 9.43.

1,4-Bis[(S)-1-(4-methoxyphenyl)ethyl]piperazine-2,5-dione (**5b**): Off-white solid; mp: 98–99 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.15 (m, 4H), 6.89–6.82 (m, 4H), 5.88 (q, J = 7.1 Hz, 2H), 3.81 (d, J = 16.5 Hz, 2H), 3.78 (s, 6H), 3.49 (d, J = 16.5 Hz, 2H), 1.50 (d, J = 7.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.67, 159.25, 130.19, 128.52, 114.05, 55.20, 49.61, 44.45, 15.21; Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.95; H, 6.93; N, 7.13. $[\alpha]_D^{20}$ −383.5 (c 0.65, $CHCl_3$).

1,4-Dicyclohexylpiperazine-2,5-dione (**6b**): White solid; mp: 227–228 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (m, 2H), 3.88 (s, 4H), 1.82 (m, 4H), 1.67 (m, 6H), 1.39 (m, 8H), 1.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 52.2, 45.2, 29.3, 25.4, 25.3; HRMS (EI): m/z calcd for $C_{16}H_{27}N_2O_2$: 278.1194, found: 279.2074 $[M+H]^+$.

1,4-Bis[(tetrahydrofuran-2-yl)methyl]piperazine-2,5-dione (**7b**): Beige waxy solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (dd, J = 17.1, 5.9 Hz, 2H), 4.18–3.98 (m, 4H), 3.86 (dd, J = 14.6, 7.4 Hz, 2H), 3.80 (ddd, J = 13.9, 5.7, 2.9 Hz, 2H), 3.73 (dd, J = 14.5, 7.5 Hz, 2H), 3.19–3.06 (m, 2H), 2.07–1.97 (m, 2H), 1.95–1.82 (m, 4H), 1.59–1.47 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.05, 164.02, 77.42, 77.40, 67.92, 51.58, 49.88, 49.85, 29.07, 29.05, 25.38. Anal. Calcd for $C_{14}H_{22}N_2O_4$: C. 59.56; H, 7.85; N, 9.92. Found: C, 59.54; H, 7.82; N, 9.71.

17. Sundarrajan, S.; Sabdham, K.; Srinivasan, V. *Macromol. Rapid Commun.* **2004**, *25*, 1406–1409.
18. Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **1994**, *5*, 453–464.