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From amines to diketopiperazines: a one-pot approach

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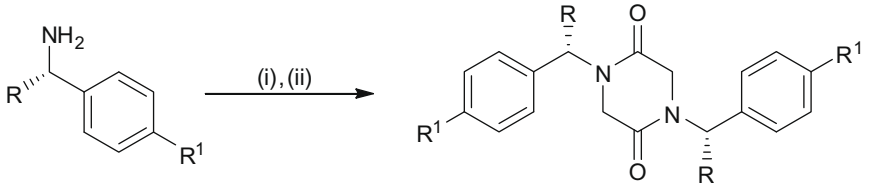
ABSTRACT

An efficient one-pot synthesis is described for the preparation of 1,4-disubstituted piperazine-2,5-diones starting from a suitable amine and chloroacetyl chloride in the presence of an aqueous base. The resulting chloroacetamide is cyclised in situ by employing the phase-transfer (PT) catalyst, benzyltriethylammonium chloride (TEBA). The products are isolated in excellent yields of up to 90%.

Diketopiperazines (DKPs) are the smallest cyclic peptides known and represent an important alternative to common peptides. These secondary metabolites have been isolated from micro-organisms[1] and plants.[2] As with many compounds resulting from microbial secondary metabolic pathways, DKPs are known to display antimicrobial activity against a range of organisms.[3,4] Synthetic strategies for the construction of DKPs often rely on readily available natural and unnatural amino acids. Although there have been a number of effective routes reported for the synthesis of 2,5-DKPs,[5–8] efficient routes for the preparation of 1,4-disubstituted piperazine-2,5-diones are less common. Recently, we reported the one-step synthesis of a series of 1,4-disubstituted piperazine-2,5-diones under phase-transfer (PT) conditions starting from a suitable chloroacetamide, with complete selectivity towards cyclisation rather than polymerisation of this bi-functional molecule.[9]

When chloroacetamides are not commercially available, they can be easily prepared from the corresponding amine. This simple step often requires purification before the chloroacetamide can be carried through to the next step,[10] which lengthens the overall synthetic process and inevitably affects the overall yield.

We have now extended our original method to incorporate the synthesis of the chloroacetamide and its selective cyclisation in one-pot under PT conditions (Schemes 1 and 2).[11] This method can be considered as an effective and general route to a wide range of aromatic and aliphatic 1,4-disubstituted DKPs.



1 **2**

a R = H, R^1 = H
b R = Me, R^1 = H
c R = Me, R^1 = OMe

Scheme 1. Reagents and conditions: (i) $C_2H_2Cl_2O$, CH_2Cl_2, aq NaOH (50%); (ii) TEBA (10 mol %).

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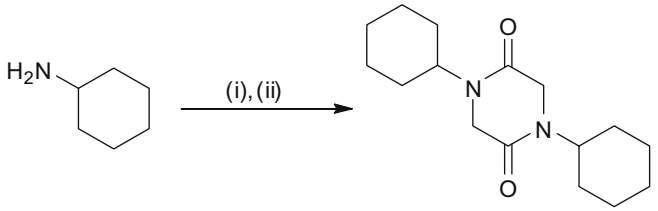

Scheme 2. Reagents and conditions: (i) $C_2H_2Cl_2O$, CH_2Cl_2, aq NaOH (50%); (ii) TEBA (10 mol %).

The chloroacetamide was formed initially via the Schotten–Baumann reaction of amine **1a–c** or **3** with chloroacetyl chloride in aqueous NaOH. The addition of the PT catalyst, TEBA, resulted in the selective in situ cyclisation of the chloroacetamide, affording the 1,4-disubstituted DKPs **2a–c** or aliphatic DKP **4** in high yields.

In summary, we have developed a one-pot strategy for the synthesis of an important class of DKPs starting from a suitable amine and chloroacetyl chloride, under PT conditions. The one-pot preparation of important molecules is a fundamental goal in organic synthesis as it avoids the expensive purification that follows a step-by-step synthesis. Specifically, this method avoids purification of the chloroacetamide, allowing a direct and selective cyclisation under PT conditions. There is also a scope for the synthesis of a variety of 1,4-disubstituted piperazines using this method, with the ready availability of a wide range of starting amines.

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11. General procedure for the one-pot synthesis of 1,4-disubstituted piperazine-2,5-diones **2a–c** and **4**.
Amine **1a–c** or **3** (13.23 mmol, 1 equiv) was dissolved in CH_2Cl_2 (20 mL) and a 50% aqueous NaOH solution (105.8 mmol, 8 equiv) was added. The stirred solution was cooled to 0 °C and chloroacetyl chloride (13.23 mmol, 1 equiv) was added dropwise. The solution was allowed to warm slowly to room temperature. The formation of the amide was monitored by thin layer chromatography and once the amine had been consumed, TEBA (1.32 mmol, 10 mol %) was added gradually over 48 h to the vigorously stirred solution. The reaction was quenched, firstly with H_2O (20 mL) and then brought to pH 7.0 by the addition of 10% HCl. CH_2Cl_2 was removed in vacuo and EtOAc (30 mL) was added. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated. The resulting solids were purified by silica gel column chromatography (hexane/EtOAc, 2:1) to afford the pure DKPs in the yields specified.
1,4-Dibenzylpiperazine-2,5-dione (**2a**). White solid; 90% yield; mp: 175.5–176.5 °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; HRMS (EI): *m*/*z* calcd for $C_{18}H_{18}N_2O_2$: 294.1368, found: 294.1362 $[M]^+$.
1,4-Bis[(S)-1-phenylethyl]piperazine-2,5-dione (**2b**). Off-white solid; 90% yield; mp: 108–110 °C; ^{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 163.8, 138.3, 128.8, 128.1, 127.3, 50.1, 44.7, 15.1; HRMS (EI): *m*/*z* calcd for $C_{20}H_{22}N_2O_2$: 322.1681, found: 322.1693 $[M]^+$; $[\alpha]_D^{20}$ −319.1 (*c* 2.2, $CHCl_3$).
1,4-Bis[(S)-1-(4-methoxyphenyl)ethyl]piperazine-2,5-dione (**2c**). White solid; 86% yield; mp: 97.5–99 °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* = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.7, 159.3, 130.2, 128.5, 114.1, 55.2, 49.6, 44.5, 15.2; HRMS (CI): *m*/*z* calcd for $C_{22}H_{27}N_2O_4$: 383.1971, found: 383.1985 $[M+H]^+$; $[\alpha]_D^{20}$ −380.5 (*c* 0.68, $CHCl_3$).
1,4-Dicyclohexylpiperazine-2,5-dione (**4**). White solid; 68% yield; 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 $C_{16}H_{26}N_2O_2$: 278.1994, found: 278.2003 $[M]^+$.