Application of Polymer Supported Base in Solid Phase Synthesis: Convenient Synthesis of *N*-Aryl-*N'*-benzyl Piperazine Derivatives

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N-Aryl-*N'*-benzyl piperazine derivatives were synthesized using REM resin. In cleavage step, the piperazine derivatives were successfully prepared in a good yield and excellent purity by treatment with novel polymer supported base in the absence of any base.

Rapid preparation of small molecule libraries using solid phase chemistry or liquid phase chemistry accelerate lead generation and optimization in drug discovery. Recently, many research groups have been studying how to apply solid supported reagents for rapid preparation of small molecule libraries.[1] In our previous paper, we reported that resin-bound piperazine (**1**) was obtained readily by reaction of Wang resin-bound benzoate with piperazine (130 °C, 5 h).[2] We designed novel solid supported base (**2**) in order to demonstrate the new aspect of polymer supported piperazine derivatives.

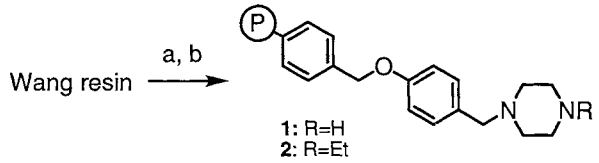

Figure 1. Synthetic scheme of polymer supported base. a) benzoyl chloride (x3), DIEA (x3)/CH_2Cl_2, rt, 10 h; b) piperazine (neat), 130 °C, 5 h or ethylpiperazine (neat), 140 °C, 30 h.

Morphy and coworkers demonstrated that REM resin, a kind of traceless linkers, was very useful for rapid preparation of tertiary amines from the resin-bound quaternary ammonium salt.[3] In their study, diisopropylethylamine (DIEA) induced Hofmann elimination was utilized to release the desired tertiary amines from the resin. For rapid preparation of the amines, an excess of DIEA and DIEA HBr salt were removed by the solid phase extraction method. Very recently, IRA-95 basic ion-exchange resin combination with catalytic amount of Et_3N were employed in the elimination step to generate tertiary amines.[4] After simple filtration of reaction mixture and condensation of the filtrate, the amines were obtained in a high yield. However, in this cleavage step, the use of catalytic amount of Et_3N is crucial to attain high chemical yield.

It is considered that the novel polymer supported base (**2**) can be used in cleavage step instead of ion-exchange resin for rapid synthesis of aryl piperazine derivatives in high purity, of which pharmaceutically interesting activities were anticipated. Herein, we describe preparation of the novel polymer supported base (**2**) and release of *N*-aryl-*N'*-benzyl piperazine derivatives from REM resin by the use of solid supported base (**2**) without any base.

In Figure 1, a scheme for preparation of the novel polymer supported base (**2**) is shown. Conversion of Wang resin-bound benzoate to a novel base (**2**) was achieved using a large amount of ethyl piperazine (neat) at 140 °C for 30 h. A small amount of **2** was treated with 65% trifluoroacetic acid (TFA) at room temperature (rt) for 3 h to determine loading ratio of piperazine derivatives. It was found to be 1.62 mmol/g.

Preparation of REM resin-bound aryl piperazine (**4**) from hydroxymethyl resin (**3**) was carried out in the same manner as described Ref. 3. Aryl piperazine (**4**) was treated with benzyl bromide derivative in *N*-methylpyrrolidone (NMP) to give quaternary ammonium salt (**5**) (Figure 2). Use of the NMP instead of the more common *N*,*N*-dimethylformamide (DMF) in this reaction resulted in a higher yield.

Hofmann elimination of **5** for releasing the desired

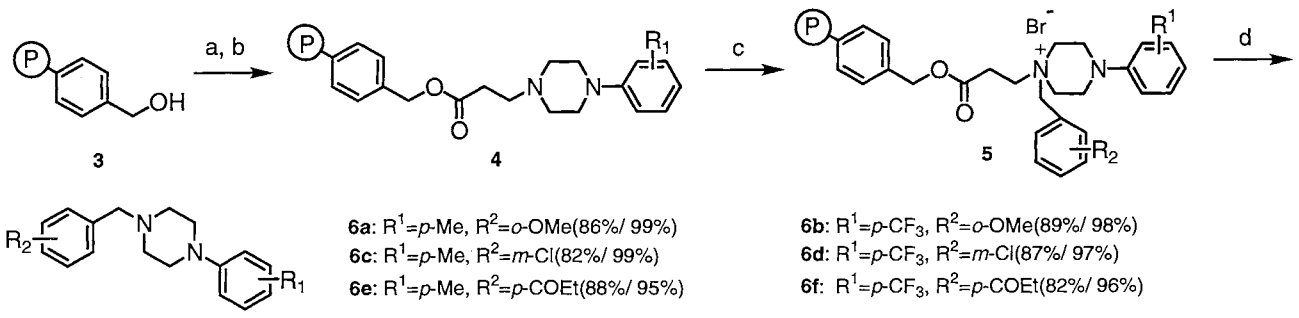

Figure 2. Synthetic scheme of *N*-aryl-*N'*-benzyl piperazine derivatives (% yield*/% HPLC purity**). a) acryloyl chloride (x10), DIEA (x10)/CH_2Cl_2, rt, 10 h; b) aryl piperazines (x10)/DMF, rt, 16 h; c) benzyl bromides (x10)/ NMP, rt, 36 h; d) polymer supported base(**2**) (x2)/CH_2Cl_2, rt, 16 h. *calculated from **3**. **UV detection at 254 nm.

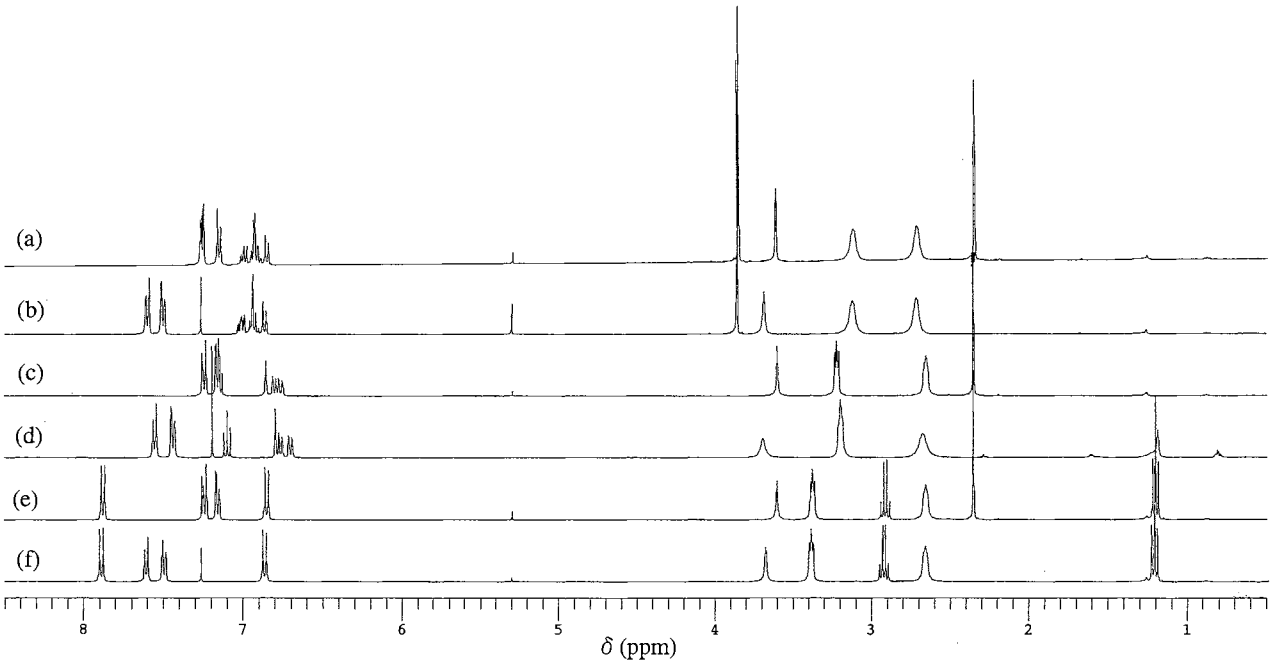

Figure 3. ^{1}H NMR spectra of crude product **6a** (a), **6b** (b), **6c** (c), **6d** (d), **6e** (e), and **6f** (f) in $CDCl_3$ (400 MHz).

compounds (**6a-6e**) was achieved by polymer supported base (**2**) in CH_2Cl_2 at rt for 16 h.[5] After the reactions were completed, highly pure **6a-6e** were obtained by simple filtration followed by condensation. Isolated yield and HPLC purity of these piperazine derivatives are shown in Figure 2. In Figure 3, we also show ^{1}H NMR spectra of crude products (**6a-6f**). This procedure with the novel polymer supported base (**2**) is very convenient for rapid preparation of piperazine derivatives.

References and Notes

1 W. Xu, R. Mohan, and M. M. Morrissey, *Tetrahedron Lett.*, **38**, 7337 (1997); *J. Am. Chem. Soc.*, **119**, 4882 (1997); S. Kobahashi and S. Nagayama, *J. Am. Chem. Soc.*, **118**, 8977 (1996); S. W. Kaldor, M. G. Siegel, J. E. Fritz, B. A. Dressman, and P. J. Hahn, *Tetrahedron Lett.*, **37**, 7193 (1996).

2 Y. Yamamoto, K. Ajito, and Y. Ohtsuka, *Chem. Lett.*, **1998**, 379.

3 A. R. Brown, D. C. Rees, Z. Rankovic, and R. Morphy, *J. Am. Chem. Soc.*, **119**, 3288 (1997).

4 X. Ouyang, R. W. Armstrong, and M. M. Murphy, *J. Org. Chem.*, **63**, 1027 (1998).

5 **6a**: ^{1}H NMR ($CDCl_3$) δ 2.34 (3H, s), 2.65 (4H, bs), 3.08 (4H, bs), 3.55 (2H, s), 3.85 (3H, s), 6.84 (1H, dd, J = 8.2, 1.6 Hz), 6.88-6.95 (2H, complex), 6.97 (1H, ddd, J = 8.0, 6.8, 2.4 Hz), 7.14 (2H, d, J = 7.6 Hz), 7.24 (2H, d, J = 8.0 Hz); mp 70-71°C; HR FABMS(m/z) Found $C_{19}H_{25}ON_2$ 297.1964 $(M+H)^+$. Calcd 297.1967; IR (KBr, cm-1) 2850, 1500, 1240. **6b** : ^{1}H NMR ($CDCl_3$) δ 2.66 (4H, bs), 3.10 (4H, bs), 3.63 (2H, s), 3.86 (3H, s), 6.86 (1H, dd, J = 8.2, 1.2 Hz), 6.89-6.96 (2H, complex), 7.0 (1H, ddd, J = 8.0, 6.6, 2.8 Hz), 7.49 (2H, d, J = 8.0 Hz), 7.58 (2H, d, J = 8.0 Hz); mp 75-77°C; HR FABMS(m/z) Found $C_{19}H_{22}ON_2F_3$ 351.1686 $(M+H)^+$. Calcd 351.1684; IR (KBr, cm-1) 2850, 1500, 1320, 1120. **6c**: ^{1}H NMR ($CDCl_3$) δ 2.34 (3H, s), 2.57 (4H, t, J = 4.9 Hz), 3.18 (4H, t, J = 4.9 Hz), 3.52 (2H, s), 6.75-6.80 (2H, complex), 6.85 (1H, t, J = 2.0 Hz), 7.14 (1H, t, J = 8.0 Hz), 7.14 (2H, d, J = 8.0 Hz), 7.23 (2H, d, J = 8.0 Hz); mp 69-70°C; HR FABMS(m/z) Found $C_{18}H_{22}N_2C$ 301.1462 $(M+H)^+$. Calcd 301.1471; IR (KBr, cm-1) 1590, 1410, 1240, 1140. **6d**: ^{1}H NMR ($CDCl_3$) δ 2.60 (4H, t, J = 5.1 Hz), 3.20 (4H, t, J = 5.1 Hz), 3.61 (2H, s), 6.76-6.80 (2H, complex), 6.87 (1H, t, J = 2.0 Hz), 7.16 (1H, t, J = 8.0 Hz), 7.48 (2H, d, J = 8.0 Hz), 7.59 (2H, d, J = 8.0 Hz); mp 68°C; HR FABMS(m/z) Found $C_{18}H_{19}N_2ClF_3$ 355.1185 $(M+H)^+$. Calcd 355.1189; IR (KBr, cm-1) 1600, 1320, 1125. **6e**: ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, t, J = 7.3 Hz), 2.35 (3H, s), 2.57 (4H, t, J = 5.1 Hz), 2.57 (4H, t, J = 5.1 Hz), 2.91 (2H, q, J = 7.3 Hz), 3.35 (4H, t, J = 5.1 Hz), 3.53 (2H, s), 6.85 (2H, d, J = 9.2 Hz), 7.14 (2H, d, J = 8.0 Hz), 7.23 (2H, d, J = 8.0 Hz), 7.88 (2H, d, J = 9.2 Hz); mp 129-130°C; HR FABMS(m/z) Found $C_{21}H_{27}ON_2$ 323.2104 $(M+H)^+$. Calcd 323.2123; IR (KBr, cm-1)1670, 1590, 1220. **6f**: ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, t, J = 7.3 Hz) 2.60 (4H, t, J = 4.9 Hz), 2.91 (2H, q, J = 7.3 Hz), 3.36 (4H, t, J = 5.1 Hz), 3.62 (2H, s), 6.86 (2H, d, J = 8.8 Hz), 7.48 (2H, d, J = 8.0 Hz), 7.59 (2H, d, J = 7.6 Hz), 7.88 (2H, d, J = 9.2 Hz); mp 148-149°C; HR FABMS(m/z) Found $C_{21}H_{24}ON_2F_3$ 377.1856 $(M+H)^+$. Calcd 377.1840; IR (KBr, cm-1) 1670, 1605, 1320, 1235.