Model Study for Preparation of Asymmetric *N,N'*-Disubstituted Piperazine Library: Efficient Synthesis of Aryl Piperazine and Benzyl Piperazine Derivatives on the Solid Support

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(Received December 25, 1997; CL-970973)

Several classes of asymmetrical *N,N'*-disubstituted aryl piperazine and benzyl piperazine derivatives were successfully synthesized by the solid phase method from the same intermediate.

An asymmetrical aryl piperazine and an asymmetrical benzyl piperazine derivatives often have pharmaceutically interesting activities and the synthetic and biological studies of these compounds have been carried out in many research groups.[1]

For preparation of the targeted asymmetrical piperazine derivatives using solution method, it is necessary to use either excess piperazine or suitable protected piperazine. Therefore removal of undesired symmetrical disubstituted piperazine or excess piperazine and removal of protecting groups is required.[1,2] In contrast, solid phase reaction is very efficient for rapid synthesis of asymmetric *N,N'*-disubstituted piperazine derivatives.[1c,3]

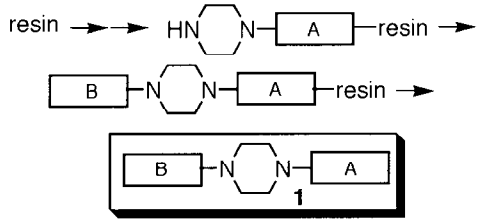

Figure 1. Scheme for preparation of asymmetric piperazine library.

Recently, we found that both *N*-substituted aryl and benzyl piperazine derivatives could be synthesized from a common intermediate on the solid support. We tried to apply our methodology to the preparation of a pharmaceutically interesting asymmetrical piperazine library (**1**) as shown in Figure 1. In order to prepare the library (**1**) as a model case, the piperazine derivatives were synthesized by the solid phase method *via* resin-bound *N*-substituted piperazine.

In this report, we have described the solid phase synthesis of asymmetrical aryl piperazine derivatives using unprotected piperazine with Wang resin. In addition, we present a new application of solid phase synthesis of asymmetrical benzyl piperazine derivatives from a resin-bound *p*-fluorobenzoate (**2**) which is also an intermediate of aryl piperazine derivatives.

In Figure 2, a scheme for the synthesis of piperazine derivatives are shown. Wang resin and *p*-fluorobenzoic acid were coupled with *N,N'*-diisopropylcarbodiimide (DIC) in the presence of 4-dimethylaminopyridine (DMAP) to obtain **2.** Conversion of **2** to **3** was performed with excess piperazine (45 eq.) in *N*-methylpyrrolidone (NMP) at 110°C for 10 h.[1c] A small amount of **3** was treated with 30% trifluoroacetic acid (TFA)/CH_2Cl_2 to confirm the formation of mono *N*-aryl piperazine by MS and NMR. For the preparation of a resin-bound benzyl piperazine derivative (**4**), we applied the Loubinoux' method[4] to a solid phase reaction. A resin-bound benzyl piperazine derivative (**4**) was synthesized by the treatment of piperazine (neat) at 130°C for 20 h. Under these conditions, the presence of aryl piperazine

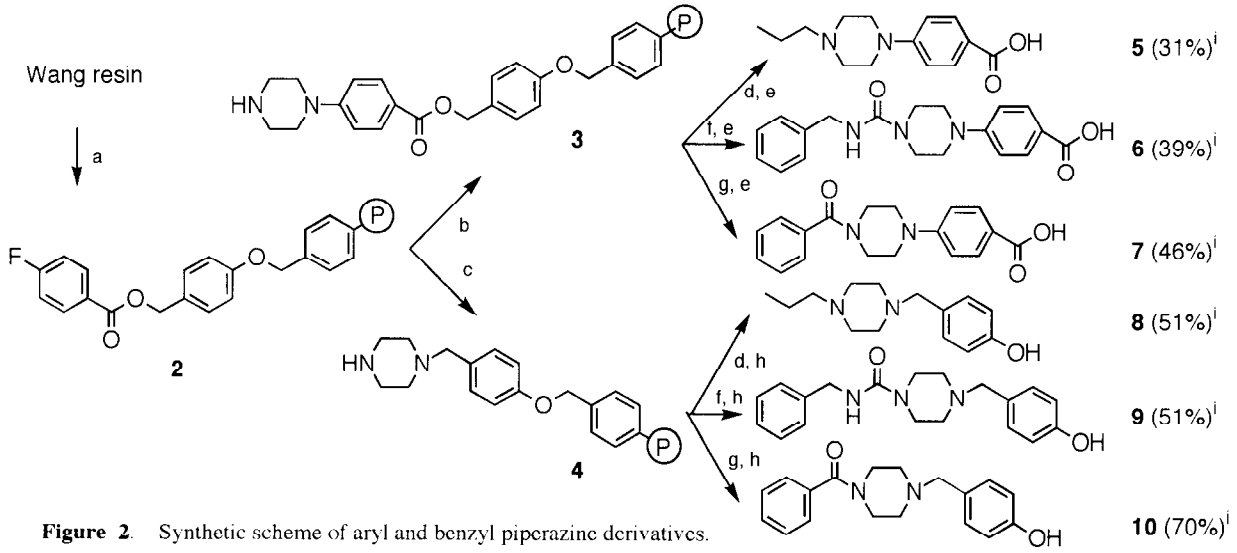

Figure 2. Synthetic scheme of aryl and benzyl piperazine derivatives.

a) 4-fluorobenzoic acid (x3), DIC (x3), DMAP (x0.3)/DMF-CH_2Cl_2 (2/1), rt, 16 h; b) piperazine (x45)/NMP, 110 °C, 10 h; c)piperazine (neat), 130 °C, 20 h; d) propionaldehyde (x10), $NaBH(OAc)_3$ (x10)/CH_2Cl_2-MeOH (1/1), rt, 16 h; e) 30%TFA/CH_2Cl_2, rt, 1h ; f) 1) triphosgene (x0.5), Et_3N (x3)/CH_2Cl_2, rt, 5 h; 2) benzylamine (x10)/CH_2Cl_2, rt, 16 h; g) benzoyl chloride (x3), DIEA (x1.5), rt, 16 h; h) 65%TFA/CH_2Cl_2, rt, 3 h; i) calculated from Wang resin.

derivative was still observed in shorter reaction time (less than 20 h) after TFA cleavage. This result suggests that piperizine attacks an aromatic ring easier than a benzylic position in the resin.

In the case of piperazine treatment (neat) with Wang resin-bound acetate or benzoate, **4** was smoothly obtained at 130°C for 5 h. During the formation of aryl or benzyl piperizine, no symmetrical disubstituted piperizine derivatives were detected as expected.

N-Alkylation of **3** using a reductive alkylation reaction[5] was carried out by the treatment of propionaldehyde and $NaBH(OAc)_3$ in $MeOH/CH_2Cl_2$ (1:1) at room temperature (rt) for 16 h. Cleavage from the solid support with 30% TFA/CH_2Cl_2 afforded the propyl piperazine derivative (**5**)[6] in high purity (Figure 3a). Preparation of a precursor of urea (**6**), carbamoyl chloride[7], from **3** was carried out by the use of triphosgene and Et_3N at rt for 5 h. Coupling between the precursor and benzylamine was attained in CH_2Cl_2 at rt for 16 h followed by 30% TFA/CH_2Cl_2 treatment to obtain **6**.[6] Resin-bound aryl piperizine derivative (**3**) was treated with benzoyl chloride in the presence of N,N-diisopropylethyl-amine (DIEA) and then treated with 30% TFA/CH_2Cl_2 to give amide (**7**).[6]

Three benzyl piperazine derivatives **8**, **9**, and **10** were successfully synthesized in the same route for **5**, **6**, and **7** respectively, except the final cleavage step (Figure 2).[6] The cleavage was achieved by treatment of 65% TFA/CH_2Cl_2 at rt for 3 h. The NMR spectrum of the crude product **8** is shown in Figure 3b.

In summary, we synthesized six different types of compounds which have an aryl and a benzyl piperazine moiety from a single intermediate (**2**) in high purity by the use of solid phase synthesis technique. In addition, we demonstrated that this technique had an advantage over the known methods for its ability to achieve rapid preparation of an asymmetric *N*, *N*'-disubstituted piperazine library.

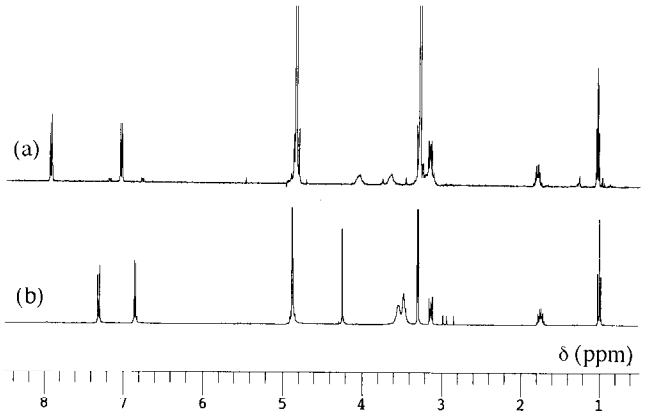

Figure 3. ^1H NMR spectra of crude product **5** (a) and **8** (b) in CD_3OD (400 MHz).

References and Notes

1 a)C. L. E. Broekkamp, D. Leysen, B. W. M. M. Peeters, and R. M. Pinder, *J. Med. Chem.*, **38**, 4615 (1995). b)M. Perez, C. Fourrier, I. Sigogneau, P. J. Pauwels, C. Palmier, G. W. John, J. P. Valentin, and S. Halazy, *J. Med. Chem.*, **38**, 3602 (1995). c)A. A. MacDonald, S. H. DeWitt, E. M. Hogan, and R. Ramage, *Tetrahedron Lett.*, **37**, 4815 (1996). d)H. Ohtaka, K. Yoshida, K. Suzuki, K. Shimohara, S. Tajima, and K. Ito, *Chem. Pharm. Bull.*, **36**, 3948 (1988).

2 a)J. P. Wolfe, and S. L. Buchwald, *J. Org. Chem.*, **61**, 1133 (1995). b)M. Perez, P. Potier, and S. Halazy, *Tetrahedron Lett.*, **37**, 8487 (1996).

3 S. M. Dankwardt, S. R. Newman, and J. L. Krstenansky, *Tetrahedron Lett.*, **36**, 4923 (1995).

4 B. Loubinoux, J. Miazimbakana, and P. Gerardin,*Tetrahedron Lett.*, **30**, 1939 (1989).

5 D. W. Gordon and J. Steele, *Bioorg. Med. Chem. Lett.*, **5**, 47 (1995).

6 **5:** H. Tatsuta, T. Ohtsuka, S. Takenaka, and S. Kusabayashi. JP 57-206672. **6:** ^1H NMR ($CDCl_3/CD_3OD$ = 10/1) δ 3.38 (4H, complex), 3.58 (4H, complex), 4.43 (2H, s), 6.85 (2H, d, J = 8.8Hz), 7.26-7.37 (5H, Bn), 7.94 (2H, d, J = 8.8Hz); mp 189°C(dec); HR FABMS(m/z) found $C_{19}H_{22}N_3O_3$ 340.1638 $(M+H)^+$; calcd 340.1661; IR (KBr, cm^{-1}) 2810, 1665, 1605, 1430, 1335. **7:** A. Stuetz and H. Egger, Ger. Offen. DE 3,408,127. **8:** ^1H NMR ($CDCl_3/CD_3OD$ = 10/1) δ 0.89 (3H, t, J = 7.6Hz), 1.52 (1H, m), 2.33 (2H, t, J = 8Hz), 2.68 (4H, bs), 2.86 (4H, bs), 3.34 (2H, s), 6.75 (2H, d, J = 8.4Hz), 7.13 (2H, d, J = 8.4Hz); mp 156-158°C; HR FABMS(m/z) found $C_{14}H_{23}N_2O$ 235.1815 $(M+H)^+$; calcd 235.1811; IR (KBr, cm^{-1}) 2950, 2810, 1615, 1600, 1515, 1250. **9:** ^1H NMR ($CDCl_3/CD_3OD$ = 10/1) δ 2.42 (4H, t, J = 5.2Hz), 3.38 (4H, t, J = 5.2Hz), 3.44 (2H, s), 4.39 (2H, d, J = 4.0Hz), 6.77 (2H, d, J = 8.4Hz), 7.12 (2H, d, J = 8.4Hz), 7.26-7.34 (5H, Bn); mp 57-58°C; HR FABMS(m/z) found $C_{19}H_{24}N_3O_2$ 326.1877 $(M+H)^+$; calcd 326.1868; IR (KBr, cm^{-1}) 2900, 2480, 1620, 1520, 1490, 1250. **10** (oil): ^1H NMR ($CDCl_3/CD_3OD$ = 10/1) δ 2.37 (2H,bs), 2.53 (2H, bs), 3.37 (2H, bs), 3.46 (2H, bs), 3.43 (2H, s), 3.70 (2H, bs), 6.77 (2H, d, J = 8.4Hz), 7.11 (2H, d, J = 8.4Hz), 7.42-7.37 (5H, Bz); HR FABMS(m/z) found $C_{18}H_{21}N_2O_2$ 297.1591 $(M+H)^+$; calcd 297.1603; IR (neat, cm^{-1}) 2810, 1615, 1520, 1440.

7 G. T. Wang, Y. C. Wang, R. Sciotti, and T. Sowin, *Tetrahedron Lett.*, **38**, 1895 (1997). In this work, they used 20% phosgene/ toluene for carbamoyl chloride preparation.