

## A Novel Synthesis of 1,4-Diarylpiperazines

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1,4-Diarylpiperazines are readily prepared, generally in good yields, by the reaction of substituted aromatic amines with two thirds of an equivalent of tris(2-chloroethyl)phosphate.

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## Results and Discussion

1,4-Diarylpiperazines are of interest for several medicinal applications (1-3). They are generally prepared by one of four methods: 1) condensation of aryl amines with ethylene dibromide (3-7); 2) alkylation of piperazine with an aromatic or heterocyclic halide (1,8-10); 3) dehydration of an aryl bis(hydroxyethyl)amine (11); or 4) thermal decomposition of a bis(2-aminoethyl)phenylphosphonite (12,13), an azirdine (14), or an *N*-arylformimino chloroethyl ether (15). This report describes another simple one-step procedure for making many of these interesting piperazine derivatives.

Alkyl phosphates readily react with aromatic amines to produce alkylarylamines (16-19); the chlorine of tris(2-chloroethyl)phosphate is also reactive towards amines. Thus, heating an aromatic amine with 0.67 equivalents of this phosphate results in the formation, generally in good yields, of symmetrical 1,4-diarylpiperazines. The experimental procedure is simple and the products can usually be purified by simple recrystallization. The reaction fails with amines that are substituted with electron withdrawing groups (e.g., *o*-, *m*-, or *p*-nitroaniline) or with amines substituted with groups that could react with phosphoric acid (e.g., *m*-aminophenol, *p*-aminobenzoic acid, or *p*-aminoacetophenone). *o*-Phenylenediamines should yield 1,2,3,4-tetrahydro-1,4-naphthyridines and polymers, and *m*- and *p*-phenylenediamines should yield polymers. Otherwise the reaction appears to be quite general. The compounds that have been prepared by this method are given in the experimental section. Two of these, 1,4-bis(2-fluorophenyl)piperazine and 1,4-bis(3-bromophenyl)piperazine, have not been reported previously.

## EXPERIMENTAL

Nuclear magnetic resonance (nmr) spectra were obtained in carbon tetrachloride solutions on a Varian EM360 instrument (20). In the nmr listings, S = singlet, M = a complex multiplet

centered at the  $\delta$  indicated, T = triplet, Q = quartet. Shifts are measured relative to internal tetramethylsilane and are given in ppm. The number in parentheses is the relative area. Melting points were taken on a Mettler FPI at a heating rate of 2°/minute and are corrected. Microchemical analyses were performed by Midwest Microlab Ltd., Indianapolis, Indiana.

## 1,4-Diphenylpiperazine.

Aniline (9.3 g., 0.1 mole) and tris(2-chloroethyl)phosphate (19.1 g., 0.067 mole) were heated together under reflux for 10 hours. The reaction mixture was poured with good stirring into 300 ml. of 0.8*N* aqueous sodium hydroxide. The precipitated solid was filtered off, washed with 95% ethanol, and dried under vacuum at room temperature. The yield was 8.9 g. (74%). After one recrystallization from ethanol, the solid melted at 164.3° (lit. (7) 164°); nmr:  $\delta$  (CH<sub>2</sub>) 3.26 S (8);  $\delta$  (ArH) 7.05 M (10).

## 1,4-Bis(3-methoxyphenyl)piperazine.

*m*-Anisidine (12.3 g., 0.1 mole) was treated as above. The yield of crude product was 10.9 g. (73%). Recrystallization from ethanol gave pure material melting at 143.7° (lit. (10) 142°); nmr:  $\delta$  (CH<sub>2</sub>) 3.28 S (8);  $\delta$  (OCH<sub>3</sub>) 3.77 S (6);  $\delta$  (ArH) 6.4 M (6), 7.1 M (2).

## 1,4-Bis(2-ethoxyphenyl)piperazine.

Treatment of 13.7 g. (0.1 mole) of *o*-phenetidine as above gave 14.8 g. (91%) of crude product, which, after two recrystallizations from ethanol, melted at 161.8° (lit. (11) 160°); nmr:  $\delta$  (CH<sub>3</sub>) 1.48 T (6), J = 8;  $\delta$  (CH<sub>2</sub>) 3.20 S (8), 4.06 Q (4), J = 8;  $\delta$  (ArH) 6.82 S (8).

## 1,4-Bis(2-fluorophenyl)piperazine.

2-Fluoroaniline by the above procedure yielded 88% of the 2-fluoro derivative, which after three recrystallizations from ethanol followed by sublimation at 150° and 10  $\mu$  pressure, melted at 162.4°; nmr:  $\delta$  (CH<sub>2</sub>) 3.25 S (8);  $\delta$  (ArH) 6.90 S, 7.00 S (8).

Anal. Calcd. for C<sub>16</sub>H<sub>16</sub>F<sub>2</sub>N<sub>2</sub>: C, 70.06; H, 5.58; N, 10.21. Found: C, 69.84; H, 5.86; N, 10.62.

## 1,4-Bis(4-fluorophenyl)piperazine.

4-Fluoroaniline by the above procedure yielded 71% of the 4-fluoro derivative, m.p. 175.0° (lit. (15) 174-175°); nmr:  $\delta$  (CH<sub>2</sub>) 3.20 S (8);  $\delta$  (ArH) 6.85 S, 6.98 S (8).

## 1,4-Bis(2-methylphenyl)piperazine.

*o*-Toluidine yielded 81% of the 2-methyl derivative, m.p.

174.5° (lit. (11) 174°); nmr:  $\delta$  (CH<sub>3</sub>) 2.32 S (6);  $\delta$  (CH<sub>2</sub>) 3.05 S (8);  $\delta$  (ArH) 7.08 M (8).

1,4-Bis(3-methylphenyl)piperazine.

*m*-Toluidine yielded 65% of the 3-methyl derivative, which was recrystallized from aqueous ethanol, m.p. 126.2° (lit. (11) 126°). This derivative was more soluble in ethanol than the others, and the lower yield may be a result of losses occurring during the washing of the crude product with 95% ethanol; nmr:  $\delta$  (CH<sub>3</sub>) 2.30 S (6);  $\delta$  (CH<sub>2</sub>) 3.25 S (8);  $\delta$  (ArH) 6.68 M (6), 7.05 M (2).

1,4-Bis(4-methylphenyl)piperazine.

*p*-Toluidine yielded 79% of the 4-methyl derivative, m.p. 189.3° (lit. (11) 190°); nmr:  $\delta$  (CH<sub>3</sub>) 2.30 S (6);  $\delta$  (CH<sub>2</sub>) 3.22 S (8);  $\delta$  (ArH) 6.88 M (8).

1,4-Bis(3-bromophenyl)piperazine.

*m*-Bromoaniline, treated as above, gave a black tarry product, which was separated from the aqueous base by decantation and recrystallized from 95% ethanol. The yield was only 9% due in large part to the difficulty of purification, m.p. 122.4°; nmr:  $\delta$  (CH<sub>2</sub>) 3.30 S (8);  $\delta$  (ArH) 6.85 M (8).

*Anal.* Calcd. for C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>Br<sub>2</sub>: C, 48.51; H, 4.07; N, 7.07. Found: C, 48.80; H, 4.02; N, 6.91.

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#### REFERENCES AND NOTES

- (1) K. E. Hamlin, A. W. Weston, F. E. Fisher, and R. J. Michaels, Jr., *J. Am. Chem. Soc.*, **71**, 2734 (1949).
- (2) P. C. Jain, V. Kapoor, N. Anand, A. Ahmad, and G. K. Patnaik, *J. Med. Chem.*, **10**, 812 (1967).
- (3) L. Zhelyakov and M. Agova, *Farmatsiya (Sofia)*, **7**, 17 (1957).
- (4) Hoffman, *Jahresber. Fortschr. Chem.*, **353** (1858); 388 (1859).
- (5) C. A. Bischoff, *Ber.*, **22**, 1777 (1889); *ibid.*, **25**, 2942 (1892).
- (6) C. A. Bischoff and C. Trapesonjanz, *Ber.*, **23**, 1977 (1890).
- (7) A. E. Schouten, *Rec. Trav. Chim.*, **56**, 863 (1937).
- (8) M. E. Hultquist and K. L. Howard, US Patent No. 2,606,906 (Aug. 12, 1952).
- (9) J. J. Denton and K. L. Howard, US Patent No. 2,459,367 (Jan. 18, 1949).
- (10) J. Munder and H. Schlesinger, German Patent No. 1,239,940 (May 3, 1967).
- (11) L. Armand and V. Alain, *Bull. Soc. Chim. France*, 2044 (1965).
- (12) O. Mitsunobu, T. Ohashi, M. Kikuchi, and T. Makaiyama, *Bull. Chem. Soc., Japan*, **40**, 2964 (1967).
- (13) M. Kikuchi, T. Ohashi, H. Mitsunobu, M. Makaiyama, and N. Kubota, *Japan*, **68**, 07,542; *Chem. Abstr.*, **70**, p28947h (1969).
- (14) A. P. Simeonov, F. N. Gladysheva, V. S. Etlis, and V. S. Kutyreva, *Khim. Geterotsikl. Soedin.*, 475 (1970).
- (15) W. I. Awad, F. A. Hussein, and M. T. A. Bushi, *J. Chem. UAR*, **10**, 153 (1967).
- (16) J. H. Billman, A. Radike, and B. W. Mundy, *J. Am. Chem. Soc.*, **64**, 2977 (1942).
- (17) D. G. Thomas, J. H. Billman, and C. E. Davis, *ibid.*, **68**, 895 (1946).
- (18) K. Yamauchi and M. Kinoshita, *J. Chem. Soc., Perkin Trans. I*, 391 (1973).
- (19) E. R. Bissell, *J. Fluorine Chem.*, **9**, 5 (1977).
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