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A Convenient Procedure for the Synthesis of Phenothiazine Drugs

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Alkylation of phenothiazines to prepare chlorpromazine and analogous compounds was achieved by solid–liquid phase-transfer catalysis in the presence of Aliquat 336 in the absence of any organic solvent. This simple procedure is easy and rapid.

Keywords——phenothiazine; chlorpromazine; alkylation; phase-transfer catalysis

The study of the biological activity of phenothiazine derivatives led to the discovery of the first neuroleptic agents and to the development of major antihistaminic and anti-parkinsonian drugs. These compounds are in most cases prepared by alkylation of the parent heterocycle. Since the proton on the nitrogen is only weakly acidic, the anionic activation requires strong bases such as alkali metal amides[1-3] or organometallic compounds.[4,5]

Very recently, phase-transfer catalysis was used successfully in the preparation of chlorpromazine[6] and alkylphenothiazines.[7] We have previously shown that anionic alkylation of indole,[8] purine and pyrimidine[9] anions can be performed with simple halides in the presence of a catalytic quantity of tetra-alkyl ammonium salts without any organic solvent. When we attempted to apply this approach to the alkylation of phenothiazine, we found that a very simple procedure worked efficiently, *i.e.*, phenothiazine was directly heated with the commercially available hydrochloride of the alkylating agent, potassium hydroxide and a catalytic quantity of Aliquat 336.[10] The reaction also proceeded at room temperature, but the yields were lower. Neither fresh distillation of the chloroalkylamine nor formation of the anion of the heterocycle was necessary before adding the alkylating agent. In contrast to previous observations[11] bulky substituents such as an isopropyl group on the nitrogen did not affect the yield.

1a

1a:	R_1=Cl,	R_2=$(CH_2)_3N(Me)_2$	**1d**:	R_1=H,	R_2=$CHCH_2N(Me)_2$ (Me)
1b:	R_1=H,	R_2=$(CH_2)_2N(Me)_2$			
1c:	R_1=H,	R_2=$CH_2CHN(Me)_2$ (Me)	**1e**:	R_1=H,	R_2=$(CH_2)_2N(iso\text{-}Pr)_2$
			1f:	R_1=Cl,	R_2=$(CH_2)_2N(iso\text{-}Pr)_2$

This technique is characterized by a very easy work-up, and it avoids the use of any expensive and polluting solvent. It requires smaller amounts of catalyst, a lower reaction temperature and a much shorter reaction time (1 h instead of 18 h) as compared to the most recently reported method.[6]

Experimental

Melting points were taken on a Kofler apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian EM 390 spectrometer.[12]

2-Chloro-10-(3-dimethylaminopropyl)phenothiazine (1a, Chlorpromazine)——2-Chlorophenothiazine (2.33 g, 0.01 mol), KOH (1.40 g, 0.025 mol), 3-chlorodimethylaminopropyl hydrochloride (1.62 g, 0.01 mol) and Aliquat 336 (0.120 g, 0.0003 mol) were heated for 1 h at 80 °C. After the mixture had cooled to room temperature 1 g of silica gel was added to retain the catalyst. The mixture was extracted three times with 50 ml of diethyl ether. The crude chlorpromazine was purified by column chromatography (silica gel, ethyl acetate), or the hydrochloride was directly obtained by bubbling hydrogen chloride gas into the ethereal solution. The salt, which separated as an oil, was crystallized by trituration in ethyl acetate. Yield 3.02 g (85%), mp 170 °C. *Anal.* Calcd for $C_{17}H_{20}Cl_2N_2S$: C, 57.46; H, 5.63; N, 7.89. Found: C, 57.31; H, 5.55; N, 8.12. ^{1}H-NMR ($CDCl_3$) δ: 1.90 (2H, m, J=5 Hz), 2.20 (6H, s), 2.35 (2H, t, J=5 Hz), 3.80 (2H, t, J=5 Hz), 6.63—7.15 (7H, m).

The following compounds were prepared in a similar fashion.

10-(2-Dimethylaminoethyl)phenothiazine (1b)——Yield: 78% or 71% after 24 h at 20 °C. Hydrochloride, mp 200 °C. *Anal.* Calcd for $C_{16}H_{19}ClN_2S$: C, 62.64; H, 6.20; N, 9.14. Found: C, 62.53; H, 6.12; N, 9.21. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (6H, s), 2.60 (2H, t, J=5 Hz), 3.95 (2H, t, J=5 Hz), 6.60—7.15 (8H, m).

10-(2-Dimethylamino-2-methylethyl)phenothiazine (1c, Promethazine)[13]——Yield: 71 %. Hydrochloride, mp 230 °C. *Anal.* Calcd for $C_{17}H_{21}ClN_2S$: C, 63.65; H, 6.24; N, 8.73. Found: C, 63.55; H, 6.10; N, 8.91. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, d, J=4 Hz), 2.20 (6H, s), 3.00 (1H, m), 3.61 (1H, m, J_{AB}=8 Hz, J_{AX}=6 Hz), 3.95 (1H, m, J_{AB}=8 Hz, J_{BX}=2 Hz), 6.66—6.81 (8H, m).

10-(2-Dimethylamino-1-methylethyl)phenothiazine (1d, Isopromethazine)——Yield: 12%. Hydrochloride, mp 190 °C. *Anal.* Calcd for $C_{17}H_{21}ClN_2S$: C, 63.65; H, 6.24; N, 8.73. Found: C, 63.61; H, 6.11; N, 8.91. ^{1}H-NMR ($CDCl_3$) δ: 1.58 (3H, d, J=5 Hz), 2.03 (6H, s), 2.66 (1H, m, J_{AB}=8 Hz, J_{AX}=4 Hz).

10-(2-Diisopropylaminoethyl)phenothiazine (1e)——Yield: 84% or 50% after 24 h at 20 °C. Hydrochloride, mp 197 °C. *Anal.* Calcd for $C_{20}H_{27}ClN_2S$: C, 66.20; H, 7.45; N, 7.72. Found: C, 66.05; H, 7.31; N, 7.78. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (6H, d, J=5 Hz), 2.83 (2H, t, J=5.5 Hz), 3.08 (1H, m, J=5 Hz), 3.96 (2H, t, J=5.5 Hz), 6.80—7.26 (8H, m).

2-Chloro-10-(2-diisopropylaminoethyl)phenothiazine (1f)——Yield: 79%. Hydrochloride, mp 170 °C. *Anal.* Calcd for $C_{20}H_{26}Cl_2N_2S$: C, 64.72; H, 5.84; N, 6.29. Found: C, 64.65; H, 5.75; N, 6.37. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (6H, d, J=5 Hz), 2.76 (2H, t, J=5.5 Hz), 3.03 (1H, m, J=5 Hz), 3.80 (2H, t, J=5.5 Hz), 6.70—7.13 (7H, m).

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