N-Dimethylaminopropylation in a Solid-Liquid Two Phase System: Synthesis of Chlorpromazine, its Analogs, and Related Compounds*

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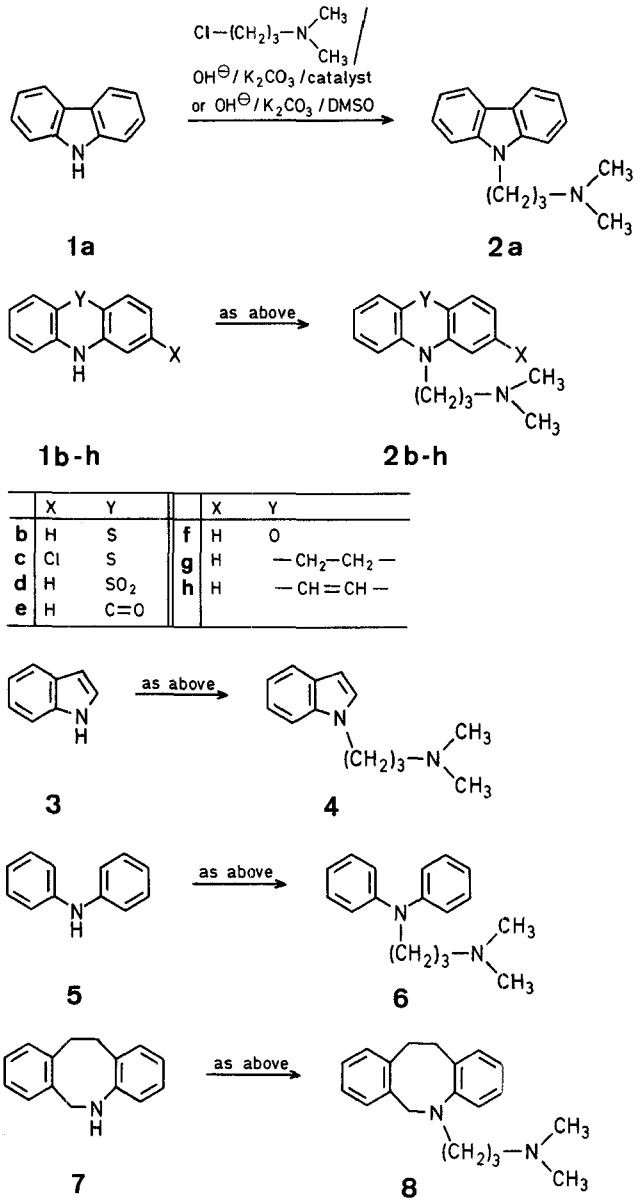
Phase-transfer catalysis (PTC) in the *N*-alkylation with simple alkyl halides of carbazole[1], 2-chlorophenothiazine[2], acridanone[3], and indole[4] proceeds well. Standard preparative procedures for these alkylations require such bases as sodium amide, sodium hydride, or alkylmetal derivatives. While alkylation with simple alkyl halides in a liquid-liquid two phase system was facile, alkylations using 3-dimethylaminopropyl chloride were unsuccessful[2]. Similarly, alkylation of acridanone with 3-diethylaminopropyl chloride proceeded slowly and gave only 43% yield[3].

Although the use of 50% aqueous sodium hydroxide and dimethyl sulfoxide has been reported for the alkylation of pyrrole, indole, carbazole, and diphenylamine with simple alkyl halides[1], the utilization of aqueous hydroxide with haloamines, as previously mentioned, has given mixed results. Alkylation of pyrroles[5] and indoles[5,6] with simple alkyl halides/solid potassium hydroxide/dimethyl sulfoxide gave good yields of the *N*-alkyl derivatives.

While use of fluoride ion as a base in organic synthesis is well-known[7], its application to the *N*-alkylation of amines is not routine. Published reports are limited to *N*-methylaniline, aniline, pyrrolidine, and piperidine using potassium fluoride (neat)[8] and aniline and piperidine using potassium fluoride/Celite/acetonitrile[9]. The importance of the dialkylaminoalkyl structural moiety in various therapeutic agents (i.e., chlorpromazine and imipramine) coupled with the technical problems encountered when using bases such as sodium amide on a large scale suggest alternative conditions of alkylation involving haloamines under phase-transfer catalysis would be beneficial.

Using a solid base/organic liquid two-phase system, benzamides and formamides were *N*-alkylated in good yield[10]. Use of a mixture of solid sodium hydroxide and potassium carbonate with 10 mol% of tetra-*n*-butylammonium hydrogen sulfate in benzene afforded the sodium salt of the amide. The high efficiency of this base in solid-liquid PTC alkylation was attributed to the limited amount of water in the system, thereby enhancing the reaction rate by effective solvation control[11]. The potassium carbonate apparently prevents aggregation of hydroxide particles in the presence of the by-product water.

For the heterocyclic amine phenothiazine and its analogs, we report conditions allowing effective alkylation with 3-dimethylaminopropyl chloride under phase transfer conditions (Scheme). First, only 1.1 equivalents of sodium hydroxide are employed. Second, the sodium salt of the amine was generated at ambient temperature. Finally, the alkylations were found to proceed efficiently in refluxing toluene. Thus, the heterocyclic amine was stirred with a slight excess of a pulverized mixture of sodium hydroxide and potassium carbonate in toluene containing either tetra-*n*-butylammonium hydrogen sulfate or a crown ether at room temperature for several hours. A toluene solution of 3-dimethylaminopropyl chloride, freshly generated from the hydrochloride salt, was then added and the resulting mixture was heated at reflux for 18 h. For both 5*H*-dibenz[*b*,*f*]azepines (**1g** and **1h**) and diphenylamine (**5**), the hydroxide ion/quaternary ammonium salt/toluene method failed to produce the desired products. While no published precedent exists for the *N*-alkylation of compounds **1g** and **1h** under phase-transfer catalysis, owing to the importance of imipramine (**2g**) as a tricyclic antidepressant, alkylation in various solid-liquid two phase systems was examined.



Attempts at the alkylations of compounds **1g**, **1h**, and **5** in the presence of potassium fluoride/*N*,*N*-dimethylformamide failed. However, the application of the sodium hydroxide/potassium carbonate/dimethyl sulfoxide method was found to provide an efficient, simple, and inexpensive route for the al-

kylation of the dibenz[*b,f*]azepines and diphenylamine with haloamines. Thus, the sodium salts of amines **1g**, **1h**, and **5** were generated at ambient temperature, the haloamine in dimethyl sulfoxide added, and the reaction mixture was vigorously stirred for 18 h at elevated temperature.

The yields of these alkylation reactions in a solid-liquid two phase system are generally equivalent to or higher than the yields from those reactions run under the standard conditions using sodium amide (Table). The choice of tetra-*n*-butylammonium hydrogen sulfate as the catalyst was based upon its stability, good activity, balanced lipophilicity, low toxicity, and ease of recovery[12]. In those cases where 18-crown-6 was used as the catalyst, the toxicity and cost of the more expensive crown ether may present certain drawbacks.

While it is possible to also recover the 18-crown-6[13], in order to avoid the toxicity of crown ethers as well as their high cost, linear oligo-polyethylene glycols[14,15] as an alternative choice of catalyst for the *N*-alkylations were used for our systems. Attempts using PEG-400 (polyethylene glycol-average molecular weight of 400) alone, PEG-400 immobilized onto silica gel[16,17], or PEG-400 as the solvent failed to yield the desired *N*-alkylation products.

This work has demonstrated the feasibility to synthesize chlorpromazine and certain of its analogs in a facile and cost-effective manner using a solid-liquid two phase system.

Alkylation of 2-Chlorophenothiazine (1c) with 3-Dimethylaminopropyl Chloride; General Procedure A:

In a 250 ml three-neck flask equipped with nitrogen inlet, water-cooled condenser, and pressure-equalizing addition funnel is placed 2-chlorophenothiazine (**1c**; 2.34 g, 10 mmol), powdered anhydrous potassium carbonate (0.83 g, 6 mmol), powdered sodium hydroxide (0.44 g, 11 mmol), and tetra-*n*-butylammonium hydrogen sulfate (0.34 g, 1 mmol) in toluene (80 ml). The mixture is stirred under nitrogen at room temperature for 2 h. Freshly prepared 3-dimethylaminopropyl chloride, generated from its hydrochloride salt (1.74 g, 11 mmol), is dissolved in toluene (5 ml) and added dropwise. The mixture is stirred for 18 h at reflux. After cooling to room temperature, the inorganic salts are filtered off and washed with toluene (2 × 20 ml). The combined toluene solutions are water washed (3 × 40 ml) to remove the catalyst. The organic phase is extracted with 15% hydrochloric acid (1 × 60 ml). The acidic phase is basified (pH 7–8) cautiously with saturated sodium carbonate solution. The oily liquid product is extracted with dichloromethane (3 × 30 ml) and the dichloromethane solution is dried over anhydrous sodium sulfate. Evaporation of dichloromethane gives an oily residue which is distilled and chromatographed on basic alumina with chloroform to yield pure **2c**.

Alkylation of Carbazole (1a) with 3-Dimethylaminopropyl Chloride; General Procedure B:

In a 250 ml three-neck flask equipped with nitrogen inlet, water-cooled condenser, and pressure-equalizing addition funnel is placed carbazole (**1a**; 1.67 g, 10 mmol), powdered anhydrous potassium carbonate (0.83 g, 6 mmol), powdered 85% potassium hydroxide (0.73 g, 11 mmol), and 18-crown-6 (0.26 g, 1 mmol) in toluene (80 ml). The

Table. Phase-Transfer-Catalyzed *N*-(3-Dimethylaminopropylation) of Compounds **1a–h**, **3**, **5**, and **7**

Product	Procedure	Yield [%][a]		b.p. [°C]/torr[b]		M.S. for M^+ observed[c] (calc. for M^+)	^{1}H-N.M.R. ($CDCl_3$/TMS)[d] δ [ppm]
		observed	reported	observed	reported		
2a	B	90	76[18]	165–168°/0.58	152–155°/0.3[18]	252.1622 (252.1626)	1.78–1.88 (p, 2H); 2.07–2.12 (t, 2H); 2.09 (s, 6H); 4.19 (t, 2H); 7.13–7.19 (m, 2H); 7.32–7.41 (m, 4H); 8.02 (d, 2H)
2b	A	75	—[e, 19]	190–198°/0.2	203–210°/0.3[20]	284.1346 (284.1348)	1.81–1.91 (p, 2H); 2.13 (s, 6H); 2.30 (t, 2H); 3.81 (t, 2H); 6.80–6.86 (m, 4H); 7.04–7.11 (m, 4H)
2c	A	78	—[e, 21]	195–200°/0.68	202–205°/0.8[22]	318.0930 (318.0958)	1.79–1.90 (p, 2H); 2.14 (s, 6H); 2.30 (t, 2H); 3.78 (t, 2H); 6.78–6.94 (m, 2H); 7.04–7.12 (m, 5H)
2d	A	55	—[e, 24]	m.p. 98–100°	m.p. 98°[23]	316.1219 (316.1246)	1.98–2.06 (p, 2H); 2.24 (s, 6H); 2.39 (t, 2H); 4.26 (t, 2H); 7.23–7.28 (m, 2H); 7.43 (d, 2H); 7.57–7.63 (m, 2H); 8.1 (dd, 2H)
2e	B	85	78[24]	m.p. 87–88°	—[e, 24]	280.1579 (280.1575)	2.0–2.1 (p, 2H); 2.32 (s, 6H); 2.45 (t, 2H); 4.45 (t, 2H); 7.25–7.32 (m, 2H); 7.62–7.76 (m, 4H); 8.58 (d, 2H)
2f	A	79	58[25]	180–185°/0.35	190°/0.5[25]	268.1559 (268.1576)	1.70–1.78 (p, 2H); 2.20 (s, 6H); 2.29 (t, 2H); 3.48 (t, 2H); 6.48 (d, 2H); 6.57 (dd, 4H); 6.70–6.77 (m, 2H)
2g	C	43	—[e, 26]	180–185°/0.4	160°/0.1[26]	280.1939 (280.1939)	1.62–1.71 (p, 2H); 2.07 (s, 6H); 2.23 (t, 2H); 3.10 (s, 4H); 3.70 (t, 2H); 6.81–6.87 (m, 2H); 7.01–7.09 (m, 6H)
2h	C	75	75[27]	160–170°/0.4	155–165°/0.3[18]	278.1773 (278.1782)	1.62–1.72 (p, 2H); 2.09 (s, 6H); 2.30 (t, 2H); 3.70 (t, 2H); 6.67 (s, 2H); 6.89–7.02 (m, 6H); 7.17–7.22 (m, 2H)
4	B	80	75[28]	108–112°/0.3	112–114°/0.4[28]	202.1457 (202.1470)	1.84–1.93 (p, 2H); 2.12–2.17 (t, 2H); 2.15 (s, 6H); 4.1 (t, 2H); 6.45 (d, 1H); 7.04–7.19 (m, 3H); 7.32 (d, 1H); 7.60 (d, 1H)
6	C	79	77[18]	125–130°/0.3	122–125°/0.2[18]	254.1808 (254.1783)	1.74–1.81 (p, 2H); 2.14 (s, 6H); 2.24 (t, 2H); 3.72 (t, 2H); 6.83–6.89 (m, 2H); 6.98 (dd, 4H); 7.14–7.21 (m, 4H)
8	C	0	70[29]	—	163–168°/1.4[29]	—	—

[a] The observed yields are of pure chromatographed products.
[b] Kugelrohr bulb to bulb distillation.
[c] Recorded on a Kratos MS-80 mass spectrometer. (NSF grant PCM-82-19912.)
[d] Measured at 300 MHz on a Nicolet NT 300 spectrometer (NSF grant CHE-8102974).
[e] Data unavailable.

mixture is stirred under nitrogen at room temperature for 2 h. Freshly prepared 3-dimethylaminopropyl chloride, generated from its hydrochloride salt (1.74 g, 11 mmol), is dissolved in toluene (5 ml) and added dropwise. The mixture is stirred for 18 h at reflux. After cooling to room temperature, the inorganic salts are filtered off and washed with toluene (2 × 20 ml). The toluene solution is washed with saturated potassium chloride solution (3 × 40 ml) to remove the catalyst. Work up of the reaction mixture is continued as in Procedure A to give pure **2a**.

In the case of acridone (**1e**) the product **2e** could not be distilled due to decomposition.

Alkylation of Diphenylamine (5) with 3-Dimethylaminopropyl Chloride; General Procedure C:

In a 250 ml three-neck flask equipped with nitrogen inlet, water-cooled condenser, and pressure-equalizing addition funnel is placed diphenylamine (**5**; 1.69 g, 10 mmol), powdered anhydrous potassium carbonate (0.83 g, 6 mmol), and powdered sodium hydroxide (0.44 g, 11 mmol) in dimethyl sulfoxide (80 ml). The mixture is stirred under nitrogen at room temperature for 2 h. Freshly prepared 3-dimethylaminopropyl chloride, generated from its hydrochloride salt (1.74 g, 11 mmol), is added dropwise. The mixture is stirred for 18 h at 110°C. After cooling to room temperature, the mixture is poured onto a large excess of water (350 ml). The aqueous solution is extracted with benzene (3 × 60 ml). After washing the benzene solution with water (3 × 50 ml) to remove any remaining dimethyl sulfoxide, work up of the reaction mixture is continued as in Procedure A to give pure **6**.

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