Phase Transfer Catalysis in *N*-Alkylation of the Pharmaceutical Intermediates Phenothiazine and 2-Chlorophenothiazine

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The *N*-alkylation of the two title compounds was studied, utilizing phase transfer catalysis (PTC) methods. Very mild reaction conditions were developed, especially for three-carbon *N*-alkylation. Of special interest is the high-yield synthesis of *N*-(3-chloropropyl)-2-chlorophenothiazine. The results are discussed in terms of the classical PTC/OH^- mechanisms.

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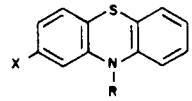
We have recently reported in this Journal very mild phase-transfer-catalysis (PTC) reaction procedures for the *N*-alkylation of the pharmaceutical intermediates 5*H*-dibenz[*b*,*f*]azepine and 5*H*-10,11-dihydrodibenz[*b*,*f*]azepine [1]. As part of our on-going interest in the alkylations of heterocyclic *N*-nucleophiles, especially those of interest to the pharmaceutical industry, we continued to explore our PTC techniques on phenothiazine (**1**) and on 2-chlorophenothiazine (**2**). These two heterocyclic systems are found in a large number of drugs [2] especially in psychotropic agents such as chlorpromazine (**3**). We wish to report that the mild, energy saving non-hazardous conditions previously developed by us [1] are applicable with moderate to high yields for the heterocycles **1** and **2**. In particular, we succeeded in the synthesis of the 3-chloro-



	X	R
1	H	H
2	Cl	H
3	Cl	$CH_2CH_2CH_2N(CH_3)_2$
4	Cl	$CH_2CH_2CH_2Cl$
5	Cl	$CH_2CH_2CH_2N<$
6	Cl	$CH_2CH_2CH_2-N\quad N-CH_2CH_2-OH$
7	Cl	$CH_2CH=CH_2$
8	H	$CH_2CH=CH_2$
9	Cl	$CH_2CH_2CH_2Br$
10	H	$CH_2CH_2CH_2Cl$
11	H	$CH_2CH_2CH_2Br$

Table

PTC *N*-Alkylation of **1** and **2**

Experiment No.	Alkylating Agent	Equimolars [a] of alkylating agent	Nucleophile Y = H, Cl	Solvent [b]	Reaction Time (hours)	Yield % [c]	Conversion %
1	CH_3CH_2Br	3	H	MC	23	47	79
2		3	H	MIK	23	100	90
3	$BrCH_2CH_2CH_2Br$	4	H	MC	24	38 [f], 52 [e]	95
4		4	H	MIK	20	16 [f], 64 [e]	100
5		4	Cl	MC	17	56 [f], 31 [e]	87
6		4	Cl	MC	23	44 [f], 40 [e]	93
7		4	Cl	MIK	23	30 [f], 64 [e]	95
8	$BrCH_2CH_2CH_2Cl$	3	H	MC	23	50 [d], 5 [e]	98
9		3	H	MIK	24	74 [d], 22 [e]	100
10		3	Cl	MC	19	97 [d], 2 [e]	84
11		3	Cl	MIK	19	66 [d], 26 [e]	100
12	$CH_2=CHCH_2Br$	1.5	H	MC	3	90	100
13		1.5	H	MIK	2.5	100	100
14		1.7	Cl	MC	2	90	100
15		1.7	Cl	MIK	2	100	100
16	$CH_3CH_2CH_2CH_2Cl$	3.0	H	MC	19	18	57

[a] Relative to **1** or **2**. [b] MC = methylene chloride, MIK = methylisobutyl ketone. [c] Based on reacted **1** or **2**. [d] *N*-(3-chloropropyl) product. [e] Allyl product. [f] *N*-(3-Bromopropyl) product.

propyl derivative **4**, which is a key intermediate in the synthesis of drugs of the type **5**, such as **3** and perphenazine (**6**). Previous attempts to PTC-alkylate **2** resulted in elimination to form the allyl product **7** [3]; we could alkylate **2** to 97% of **4** and only 2% of **7** in 84% conversion in the system **2**/1-bromo-3-chloropropane/50% aqueous sodium hydroxide/*n*-tetrabutylammonium hydrogen sulfate (TBAH)/methylene chloride (MC), at room temperature, after 19 hours. Other experiments and results, are summarized in the Table. The crucial role of the PT-catalyst was demonstrated in a control reaction for experiment 1 (Table): in the presence of all reactants, but without the catalyst, no reaction occurred. Most of our attention, as evident from the Table, was directed towards the introduction of a three-carbon side chain, capable of serving as starting material for type-**5** drugs. We conducted a number of experiments in order to clarify some of the mechanistic aspects of the problematic halopropylation with the purpose of attaining selectivity of this reaction, *i.e.*, avoiding the competing dehydrohalogenations forming **7** and **8** as by-products to **4**, **9** and **10**, **11**, respectively. First, 1,3-dibromopropane and 1-bromo-3-chloropropane were subjected to the standard reaction mixture, excluding the heterocyclic substrates. When the organic solvent was methylisobutyl ketone (MIK), hydrogen bromide was rapidly eliminated from the two alkylating agents, yielding allylbromide and allylchloride, respectively. As expected, hydrogen chloride elimination occurred only to a negligible extent. In sharp contrast, when the less-polar MC was used, elimination from both alkylating reagents was almost completely suppressed even after 17 hours ($\leq$ 5%). Second, when the final product **10** was subjected to the standard reaction conditions, no elimination of hydrogen chloride occurred either in MC, or in MIK. Interestingly elimination of hydrogen bromide did occur from the product **9** even in MC (experiments 5, 6).

These results indicate that when the reaction is carried out in MIK, elimination of hydrogen halide from the dihalopropane occurs prior to alkylation, but in MC alkylation preceeds elimination. The results obtained in MC may be explained in terms of the classical PTC/OH^- mechanisms [4,5]. Dehydrohalogenation of the non-activated compounds, 1-bromo-3-chloropropane and 1,3-dibromopropane (in the absence of the *N*-nucleophile) must occur *via* the OH^- extraction mechanism as no carbanionic intermediate may be formed. Due to leaving group ability, hydrogen bromide is preferably eliminated in both cases. As in the other PTC/OH^- eliminations [6,7] the TBAH catalyst is "poisoned" by the bromide ion liberated, preventing hydroxide ion extraction into the organic phase, and subsequently suppressing elimination. In the presence of a deactivated secondary amine (*i.e.* **1** or **2**), an *N*-anion is formed by interfacial deprotonation. This organophilic anion (more so than bromide) is preferably drawn into the bulk organic phase by the quaternary ammonium ion and may act as a base in the elimination of hydrogen chloride, in addition to its ability to be alkylated. In any case, (MIK, MC or aromatic hydrocarbons) elimination of hydrogen chloride from compounds **4** and **10** requires more elevated temperatures [3]. The rapid elimination of hydrogen bromide in MIK even in the absence of the heterocyclic substrates, may be due to the presence of a base either in the enolate form of the deprotonated solvent or as a result of the partial solubility of the aqueous MIK.

Finally, when **1** was alkylated with a 1:1 mixture of allyl bromide and allyl chloride and the reaction stopped after 15 minutes, 24% of the former and 4% of the latter reacted, indicating a 6:1 reactivity ratio in favor of the allyl bromide.

The alkylating procedure is described in detail for the synthesis of **10**. Other alkylations were carried out similarly. In conclusion, PTC is a convenient and efficient method for *N*-alkylating phenothiazine derivatives, and selective introduction of the important halopropyl chain on the nitrogen atom is feasible only when the halogen is chlorine and when working at ambient temperatures.

EXPERIMENTAL

N-(3-Chloropropyl)phenothiazine.

A solution of 0.50 g (2.5 mmoles) of **1**, 85 mg (0.25 mmole) of TBAH and 0.70 ml (7.1 mmoles) of 1-bromo-3-chloropropane in 10 ml of MIK was stirred vigorously with 10 ml of 50% aqueous sodium hydroxide for 24 hours. The reaction was followed by tlc (silica gel, MC:petrol-ether 40-60° = 3:7). The reaction was stopped when all **1** was consumed by pouring the mixture to 50 ml of water and 10 ml of MIK. The organic layer was separated and the aqueous layer washed with MIK. The combined organic extracts were washed with water, and the wet solvent then removed under vacuum (water/MIK forms an azeotrope). The oily residue was dissolved in 10 ml of MIK, the solution dried over magnesium sulfate, the solvent evaporated, and the resulting crude products separated by flash-chromatography [8] (silica gel, MC:petrol-ether 40-60° = 3:7) to yield 0.51 g (1.85 mmoles, 74%) of pure **10**, mp 62° (lit 64-66° [3b]); nmr of **10** (deuteriochloroform): 2.18-2.27 (q, $-CH_2-$, 2H), 3.64-3.68 (t, $-CH_2-$, 2H), 4.03-4.07 (t, $-CH_2-$, 2H), 6.86-7.21 (m, aromatic, 8H); 0.13 g (0.55 mmole, 22%) of the allyl product **8** (colorless oil) was eluted from the column.

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