Research Article

A Novel and Chemoselective Process of *N*-Alkylation of Aromatic Nitrogen Compounds Using Quaternary Ammonium Salts as Starting Material

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The process of *N*-alkylation of several pyrroles, indoles, and derivative heterocycles is herein described, using quaternary ammonium salts as the source of an alkylating agent. These reactions were carried out on several heterocyclic rings with triethylbenzylammonium chloride or tetradecyltrimethylammonium bromide and an NaOH solution at 50%, leading to a chemoselective *N*-alkylated product and an average yield of 73%. This is an alternative process to the traditional benzylation and methylation of *N*-heterocycles with direct handling of alkyl halides.

1. Introduction

Quaternary ammonium salts are one of the most widely used reagents in the synthesis of organic compounds when seeking to develop certain vital products, including drugs, pesticides, monomers, and cleaning agents [1, 2]. In the area of materials development, they have been employed in recent years as surfactants, template agents, and alkaline anion exchange membranes (AAEM) [3, 4].

In organic chemistry, these salts have various applications in situations where inorganic and organic anions react with organic substrates that are separated into distinct phases known as phase-transfer catalysis. These anions need to be introduced in the organic phase as a lipophilic ion pair provided by a catalyst. Among the most commonly used catalysts are quaternary ammonium salts. Although there are a variety of articles about phase-transfer catalysts, little has

been reported about them as an alkylating agent of nitrogen heterocyclic rings [5].

During one of our current research programs involving experiments with nitrogen heterocycles, utilizing reactions under conditions of phase-transfer catalysis between triethylbenzylammonium chloride (TEBAC) and a pyrrole ring, it was observed that the catalyst participated as an *N*-alkylating agent providing a benzylated product. By tracking this observation, we discovered that if the original alkylating agent was omitted from the reaction, employing instead more than a stoichiometric amount of TEBAC, a clean transfer of a unique benzyl group took place. We did not detect the transfer of an ethyl group from the TEBAC salt nor any long-chain alkylation in the case of tetradecyltrimethylammonium bromide. Therefore, we conducted a series of experiments with two quaternary ammonium salts (TEBAC and tetradecyltrimethylammonium bromide) and a series of nitrogenous
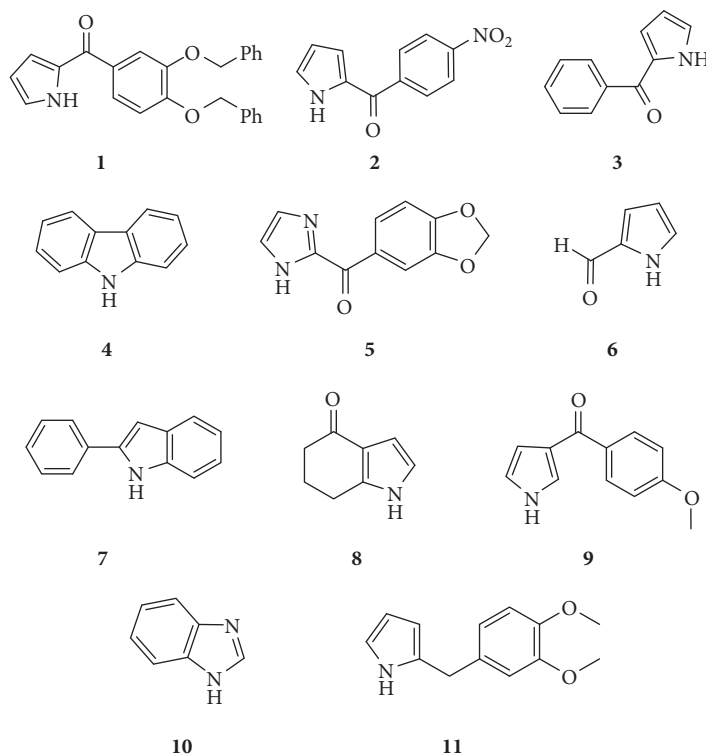
Figure 1

Table 1: Chemoselective alkylation of nitrogen heterocyclic rings with TEBAC.

	Starting material	Product	Time (h)	Yield* (%) R = Bn
	1	**1a**	18	84
	2	**2a**	6	90
	3	**3a**	2	98
	4	**4a**	17	88
	5	**5a**	4	61
	6	**6a**	3	86
	7	**7a**	4	75
	8	**8a**	8	52
	9	**9a**	8	50
	10	**10a**	2	64

*Yields refer to chromatographically pure isolated compounds.

aromatic heterocycles (Figure 1), obtaining the *N*-alkylation of these compounds as the main product (Table 1).

The transfer of an alkyl group from a quaternary ammonium salt has been briefly mentioned in the case of 2-chlorophenothiazine [6]. A study of the stability of three phase-transfer catalysts to afford five different nucleophiles suggests the feasibility of quaternary ammonium salts acting as alkylating agents for certain carbon and sulfur nucleophiles [7] and demonstrates the reaction of thiolate nucleophiles with a catalyst in preference to the substrate. However, there are no previous studies with aromatic nitrogen compounds

which in comparison with the ones mentioned above are less acid.

2. Results and Discussion

In several TEBAC-promoted benzylation reactions, we observed the formation of diethylbenzylamine as a substantial side-product. Although its presence was not troubling insofar as the purification of the principal product was concerned, it did raise several mechanistic questions. The fact

TABLE 2: Chemoselective alkylation of nitrogen heterocyclic rings with tetradecyltrimethylammonium bromide.

	Starting material	Product	Time (h)	Yield* (%) R = CH$_3$
	1	**1b**	3	73
	2	**2b**	4	78
	3	**3b**	5	76
	4	**4b**	5	97
	5	**5b**	18	74
	6	**6b**	5	46
	7	**7b**	3	73
	11	**11b**	6	43

*Yields refer to chromatographically pure isolated compounds.

that no ethylated heterocycle was ever found argued against the attack of a heterocycle on the ethyl group.

Upon examining the behavior and stability of the catalyst at reaction temperature and in the absence of the heterocycle, it was found that diethylbenzylamine formed in high yield (76%) after only 4 hours, suggesting competitive catalyst/substrate decomposition under specific reaction conditions. The latter include the use of an aqueous NaOH solution at 50% in toluene, which means that the organic solvent does not need to be in an anhydrous condition, as would be necessary for a conventional alkylation reaction [8]. Two more reactions led to mechanistic information. First, when benzyltriethylammonium tetrafluoroborate was employed instead of the chloride salt, the yield of benzylated heterocycle in the case of 2-phenylindole (7) rose from 75% to 89% in less reaction time (3 h). In the same period, less than 2% formation of diethylbenzylamine was observed when the heterocycle was omitted from the reaction. This observation rules out the possibility that the quaternary ammonium chloride merely acted as an in situ source of benzyl chloride by chloride displacement of trimethylamine. Second, a predictably poor alkylating agent, isopropyl iodide, gave only N-isopropyl-2-phenylindole in low yield when a normal quantity (25% mole) of TEBAC was used in conjunction with 1 eq. of alkylating agent. When the quantity of TEBAC was increased from 1 to 2 eq. of alkylating agent, the N-isopropyl and N-benzyl products were formed in a 67 : 33 ratio. These observations led us to conclude that an S_N2 attack on the quaternary ammonium salts is more likely than the reverse Menschutkin forming benzyl chloride [9, 10].

According to these results, a plausible mechanism is proposed in Scheme 1, in which the first step of phase-transfer catalysis proceeds to a nucleophilic attack by the pyrrolyl anion on the quaternary salt. Conditions for S_N2 occurred in the case of TEBAC, attacking exclusively the methylene of the benzyl group. Chempath et al. described the degradation of trimethylbenzylammonium hydroxides, showing how a base extracts a proton from the methylene. They explained that the intrinsic stability of the benzyl cations is very close to that of $N(CH_3)_4^+$ [3]. Thus, N-benzylation was herein carried out on the pyrrole ring. Similarly, conditions for S_N2 probably occurred with bromide tetradecyltrimethylammonium.

Since it would be very difficult to carry out the attack on the long chain due to steric effects, the pyrrolyl anion would proceed to attack the less hindered electrophilic carbon, leading to N-methylation in the methyl group [11, 12].

Tables 1 and 2 indicate that the quaternary ammonium salts are the main substrate in the reaction that results in N-alkylation and the formation of a tertiary amine. Furthermore, in cases where TEBAC and tetradecyltrimethylammonium bromide acted as alkylating agents, N-substituted compounds were obtained by benzyl and methyl groups, respectively, as can be appreciated. Also, there was reduced performance with substrates that have low reactivity (those having electron-groups at position 3 on the ring), because they do not carry out the alkylation well. The present technique proved to be chemoselective, reacting specifically with only one substituent of the quaternary salt. One possible mechanism for these reactions of N-alkylation that take place through one of the two quaternary ammonium salts is shown in Scheme 1.

When comparing the conventional technique of homogeneous alkylation to that utilizing a quaternary ammonium salt, similar results are obtained. However, the benefit of the latter is the avoidance of an anhydrous solution that requires meticulous care. From the economic point of view, the use of anhydrous solutions in industry is generally seen as disadvantageous because of requiring greater investment. Additionally, the method herein employed does not require direct handling of an alkyl halide or dimethyl sulfate, therefore eliminating the respective health risks. We demonstrate that quaternary ammonium salts allow for feasible and simple alkylation reactions in organic synthesis [13, 14].

3. Conclusions

This method offers a convenient alternative to the traditional benzylation and methylation of N-heterocycles with alkyl halides. It is particularly useful in cases such as pyrroles which have a substantially more reactive anion compared to phenothiazine. Commercially available TEBAC and tetradecyltrimethylammonium bromide are considerably more convenient to handle than alkyl halides, the latter of which are lachrymators and carcinogenic reagents.
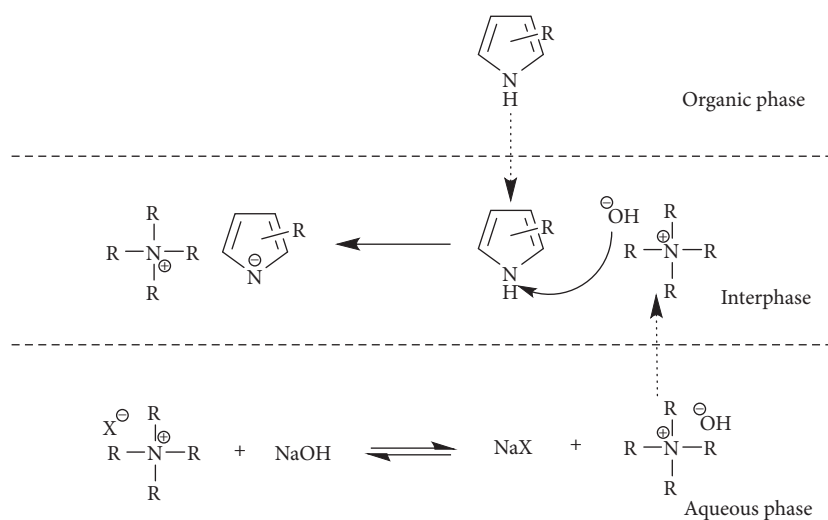
(a) General mechanism of phase-transfer catalysis
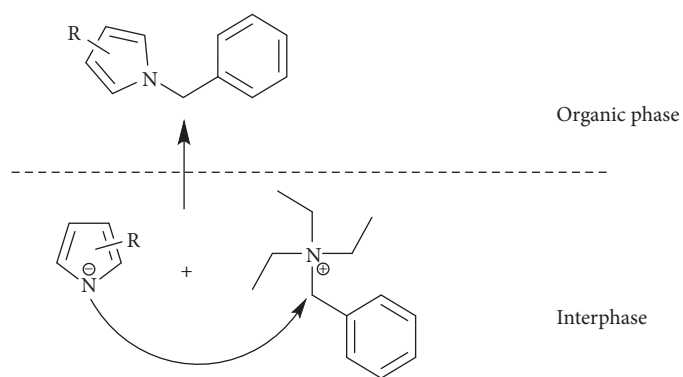
(b) Possible mechanism of *N*-benzylation
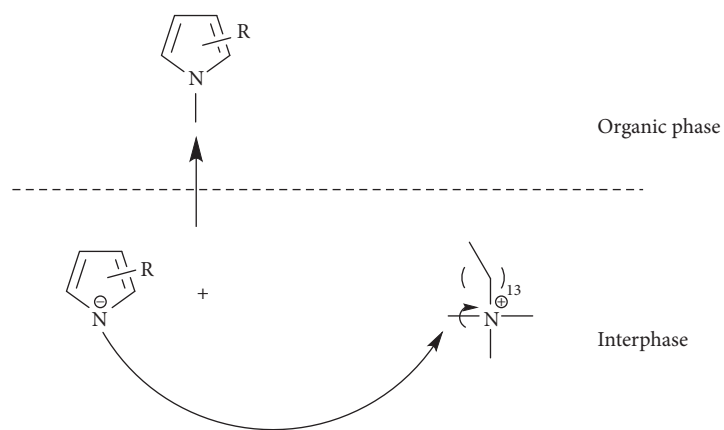
(c) Possible mechanism of *N*-methylation

Scheme 1

4. Material and Methods

General Details. The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. Flash column chromatography was performed with silica gel 60 (230–400 mesh). Thin layer chromatography was carried out on silica plates of 0.20 mm thickness and visualized by UV light at 254 nm or by revelation with iodine. Melting points were determined on a Fischer-Johns Scientific melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Avance 300 MHz and a Varian 500 MHz. The chemical shifts (δ) are given in ppm relative to TMS as internal standard (0.00). For analytical purposes, the mass spectra were recorded on a Shimadzu GCMS-QP2010 Plus.

*4.1. General Procedure for the Synthesis of **1a–10a**.* A 100 mL round-bottom flask was equipped with a magnetic stir bar and a reflux condenser. To xylene (10.0 mL), TEBAC (1.1 mmol) and a heterocyclic compound (1.0 mmol) were added, followed by a solution of NaOH 50% (5.0 mL). The mixture was stirred at reflux temperature for 2–18 h. After completion of the reaction, the mixture was air-jet cooled to 25°C and TLC evidenced the disappearance of the starting material. The reaction mix was treated with AcOEt (4 × 20 mL), and the organic phase separated and removed under reduced pressure. The residue was purified to analytical purity by column chromatography.

*4.2. General Procedure for the Synthesis of **1b–7b** and **11b**.* A 100 mL round-bottom flask was equipped with a magnetic stir bar and a reflux condenser. To xylene (10.0 mL), tetradecyltrimethylammonium bromide (1.1 mmol) and a heterocyclic compound (1.0 mmol) were added, followed by a solution of NaOH 50% (5.0 mL). The mixture was stirred at reflux temperature for 2–18 h. After completion of the reaction, the mixture was air-jet cooled to 25°C and TLC indicated the disappearance of the starting material. The reaction mix was treated with AcOEt (4 × 20 mL), and the organic phase separated and removed under reduced pressure. The residue was purified to analytical purity by column chromatography.

(3a) (1-Benzyl-1H-pyrrol-2-yl)(phenyl)methanone [15]. Using the standard procedure, to xylene (10.0 mL), 0.5003 g of TEBAC (1.1 Eq) and 0.2996 g of methanone **(3a)** (1.0 Eq) were added, followed by a solution of NaOH 50% (5.0 mL). The mixture was stirred at reflux temperature for 2 h. After cooling to r.t., TLC revealed the disappearance of the starting material. The reaction mix was treated with AcOEt (4 × 20 mL), and the organic phase separated and removed under reduced pressure. The compound was isolated as an off-yellow solid: ^{1}H NMR: (300 MHz, CDCl$_3$) δ = 7.81–7.68 (m, 2H), 7.53–7.34 (m, 3H), 7.34–7.10 (m, 5H), 7.00 (t, J = 2.1 Hz, 1H), 6.76 (dd, J = 4.1, 1.7 Hz, 1H), 6.19 (dd, J = 4.1, 2.6 Hz, 1H), 5.65 (s, 2H). ^{13}C NMR: (126 MHz, CDCl$_3$) δ = 186.20, 171.26, 139.83, 138.28, 131.46, 130.04, 129.24, 128.62, 128.42, 127.34, 127.16, 123.70, 108.73, 69.67, 60.44, 52.37. MS [EI$^+$] m/z (%): 306 (M$^+$), 289 (28), 259 (14), 229 (4), 156 (22), 91 (100), 65 (17).

Conflicts of Interest

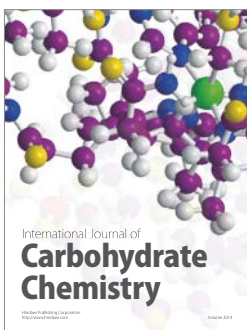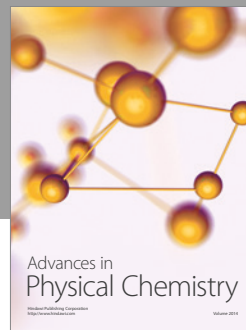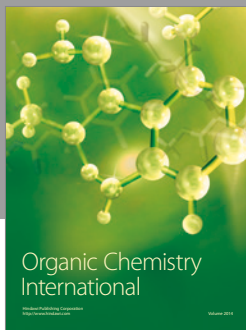The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

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