

Quaternary Ammonium Salts as Highly Efficient and Green Alkylating Agents for *N*-Alkylation of Azaheterocycles under Microwave Irradiation

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This paper is dedicated to Professor Habib Firouzabadi on the occasion of his retirement for his great efforts and contribution in the field of organic chemistry.

An efficient, simple and green procedure for *N*-alkylation of azaheterocycles by quaternary ammonium salts in the presence of K_2CO_3 under microwave irradiation is described. Using this method, *N*-alkyl derivatives of azaheterocycles are obtained in good to excellent yields and short reaction times.

Keywords: Quaternary ammonium salt, *N*-Alkylation, Azaheterocycle, Microwave, Green chemistry

INTRODUCTION

N-Alkyl derivatives of azaheterocycles have been widely used in medicinal chemistry [1-5]. For example, some *N*-alkyl phthalimides have been applied as antipsychotic [1], anti-inflammatory agents [2], and receptors [3]. *N*-Alkylated azoles have also various biological activities, such as anti-cancer [4], anti-AIDS [4], antifungal [4], and acaricides properties [5]. Moreover, some *N*-alkyl derivatives of azaheterocycles have been used as starting materials in several organic transformations [6]. The most common route for the synthesis of these compounds is *N*-alkylation of azaheterocycles by alkylating agents, such as alkyl halides [7]. The methods have been established for *N*-alkylation of azaheterocycles are associated with one or more of the following drawbacks: (i) long reaction time, (ii) moderate yield, (iii) the use of solvents such as DMSO and DMF that the workup of reaction is not

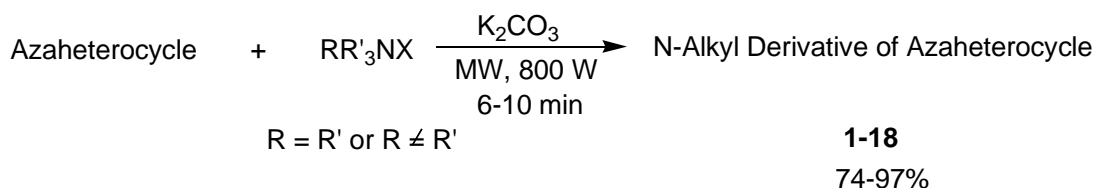
only cumbersome, but also the green aspect of reaction is annihilated using these solvents. In addition, these reactions often are performed at high temperature, thus, the use of low boiling point alkylating agents (methyl, ethyl and propyl halides, etc.) in the reaction is difficult. Therefore, it is necessary to find alkylating agents with high boiling points for the preparation of *N*-alkyl derivatives of azaheterocycles, especially when a short chain alkyl group is combined to heterocyclic compound.

Potassium carbonate (K_2CO_3) is a cheap, commercially available, and green base which has been used frequently in *N*-[8], *C*-[9], and *O*-alkylation reactions [10].

Microwave-assisted organic synthesis has been known since 1986 [11]. This "non-conventional" synthetic method has shown broad applications as a very efficient way to accelerate many organic reactions, giving better yields and higher selectivity, lower quantities of side products, and consequently, easier work-up and purification of the products [11,12].

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Scheme 1

Having the above subjects in mind and also in continuation of our previous studies on *N*-alkylation reactions [8a,13] as well as green organic synthesis [8a,13a-h,14], we report here a green, facile, and rapid solventless method for *N*-alkylation of azaheterocycles by quaternary ammonium salts as high boiling point alkylating agents in the presence of K_2CO_3 as a cheap base under microwave conditions (Scheme 1).

EXPERIMENTAL

All chemicals were purchased from Merck or Fluka chemical companies. All compounds were identified by comparison of their melting points and ^1H NMR data with the authentic samples. All reactions were carried out using domestic microwave oven (MB 245, Butan Industrial Co., Iran). The ^1H NMR (250 MHz) spectra were run on a Bruker Avance DPX-250, FT-NMR spectrometer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

General Procedure for *N*-Alkylation of Azaheterocycles

In a mortar, a mixture of compounds including azaheterocycle (5 mmol), quaternary ammonium salt (6 mmol) and K_2CO_3 (0.69 g, 5 mmol) was powdered to give a homogeneous mass. The mixture was transferred into a test tube and irradiated in a microwave oven at 800 W for the times reported in Table 2. The reaction mixture was cooled to room temperature and was suspended in chloroform (200 mL), filtered and the filtrate was washed with water (2×100 mL), and dried with MgSO_4 . The solvent was evaporated and the crude product was purified by short column chromatography on silica gel eluted with EtOAc/*n*-hexane (1/3).

Selected ^1H NMR Data

2-Butyl-isoindole-1,3-dione (1). Colorless solid; ^1H NMR (CDCl_3): δ 0.94 (t, $J = 7.7$ Hz, 3H), 1.36 (m, 2H), 1.66 (m, 2H), 3.68 (t, $J = 7.8$ Hz, 2H), 7.74 (m, 2H), 7.86 (d, $J = 5.3$ Hz, 2H).

1-Benzyl-1H-indole (11). Colorless solid; ^1H NMR (CDCl_3): δ 5.31 (s, 2H), 6.65 (d, $J = 2.8$ Hz, 1H), 6.96 (d, $J = 2.8$ Hz, 1H), 7.16-7.31 (m, 5H), 7.37-7.63 (m, 4H).

1-Benzyl-1H-imidazole (14). Colorless solid; ^1H NMR (CDCl_3): δ 4.95 (s, 2H), 6.75 (d, $J = 1.3$ Hz, 1H), 6.99-7.22 (m, 6H), 7.42 (s, 1H).

9-Benzyl-9H-carbazole (15). Colorless solid; ^1H NMR (CDCl_3): δ 5.37 (s, 2H), 7.00-7.17 (m, 5H), 7.18-7.36 (m, 6H), 8.04 (m, 2H).

7-Benzyl-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (18). Pale yellow solid; ^1H NMR (CDCl_3): δ 3.32 (s, 3H), 3.74 (s, 3H), 5.11 (s, 2H), 7.10-7.23 (m, 5H), 7.49 (s, 1H).

RESULTS AND DISCUSSION

As previously mentioned there is a great need to find a green high boiling point alkylating agent. In our attempts to find this reagent, we found that quaternary ammonium salts can successfully applied as high boiling point alkylating agents for *N*-alkylation of azaheterocycles under microwave irradiation. Moreover, K_2CO_3 has been frequently applied in alkylation reactions [8-10]. These subjects encouraged us to use quaternary ammonium salts in the presence K_2CO_3 for *N*-alkylation of azaheterocycles. Thus, at first, we used tetrabutylammonium bromide (TBAB) for *N*-alkylation of phthalimide in the presence of K_2CO_3 under microwave irradiation in the range 100-900 W of microwave power. The results are summarized in Table 1. As Table 1 indicates, this reaction was not efficient at 100-200 W even by prolonging the reaction time. The range of 300-500 W afforded the product in low to moderate yields. Performing the reaction at 600-700 W gave good yields in relatively long reaction times. The best results were obtained at 800 W. Thus, all reactions were carried out at this power. At 900 W, lower reaction yield was obtained in comparison with the condition using 800 W irradiation power.

Table 1. The Effect of Different Microwave Powers on *N*-Alkylation of Phthalimide by TBAB in the Presence of K_2CO_3

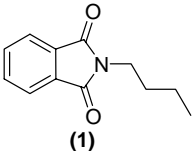
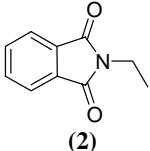
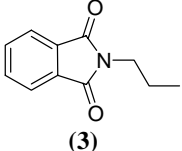
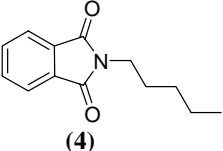
Entry	MW Power (W)	Time (min)	Yield ^a (%)
1	100	30	14
2	200	25	21
3	300	20	32
4	400	20	39
5	500	20	48
6	600	15	75
7	700	13	83
8	800	6	97
9	900	4	86

^aIsolated yield

To recognize the generality and scope of our method, different azaheterocycles were alkylated by various quaternary ammonium salts (Table 2). As it is shown in Table 2, all reactions proceeded efficiently and the desired products were obtained in good to excellent yields and short reaction times.

It has been observed that the length of alkyl group of quaternary ammonium salts had no significant effect on the yields and the reaction times (Table 2). Moreover, the kind of halide (Br and Cl) of quaternary ammonium salts did not affect on the results of reactions (Table 2). Interestingly, when benzyltriethylammonium chloride, allyltriethylammonium and triethylpropargylammonium bromide were applied as alkylating agents, only *N*-benzyl, *N*-allyl and *N*-propargyl derivatives of azaheterocycles were produced respectively (Table 2).

Table 2. *N*-Alkylation of Azaheterocycles by Quaternary Ammonium Salts in the Presence of K_2CO_3 under Microwave Irradiation (800 W)

Entry	RR'_3NX	Product	Time (min)	Yield ^a (%)	M.p. °C (Lit.)
1	$(n-C_4H_9)_4NBr$	 (1)	6	97	29-31 (31-32) [15]
2	$(C_2H_5)_4NCl$	 (2)	6	97	71-73 (71-72) [16]
3	$(n-C_3H_7)_4NCl$	 (3)	6	97	63-65 (64) [16]
4	$(n-C_5H_{11})_4NBr$	 (4)	6	96	Oil (17-18) [8d]

Quaternary Ammonium Salts as Highly Efficient

Table 2. Continued

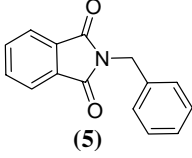
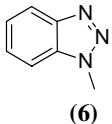
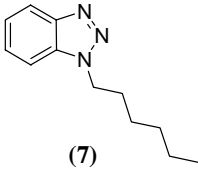
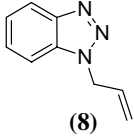
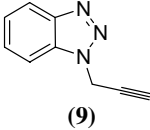
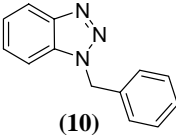
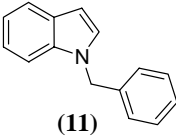
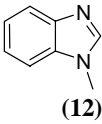
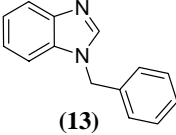
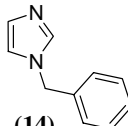
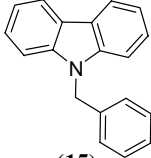
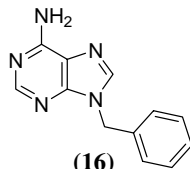
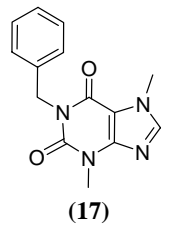
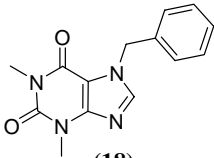
Entry	RR'_3NX	Product	Time (min)	Yield ^d (%)	M.p. °C (Lit.)
5	$\text{PhCH}_2\text{N}(\text{C}_2\text{H}_5)_3\text{Cl}$	 (5)	6	97	114-115 (114-116) [17]
6	$(\text{CH}_3)_4\text{NBr}$	 (6)	7	96	62-63 (64-65) [7f]
7	$(n\text{-C}_6\text{H}_{13})_4\text{Br}$	 (7)	7	95	Oil (Oil) [7g]
8	$\text{H}_2\text{C}=\text{CHCH}_2\text{N}(n\text{-C}_4\text{H}_9)_3\text{Br}$	 (8)	7	96	Oil (Oil) [7g]
9	$\text{HC}\equiv\text{CCH}_2\text{N}(n\text{-C}_4\text{H}_9)_3\text{Br}$	 (9)	7	95	57-58 (57) [7g]
10	$\text{PhCH}_2\text{N}(\text{C}_2\text{H}_5)_3\text{Cl}$	 (10)	7	96	113-114 (114-116) [7h]
11 ^b	$\text{PhCH}_2\text{N}(\text{C}_2\text{H}_5)_3\text{Cl}$	 (11)	10	74	39-40 (41-43) [18]
12	$(\text{CH}_3)_4\text{NBr}$	 (12)	7	97	244-246 (247-149) [19]
13	$\text{PhCH}_2\text{N}(\text{C}_2\text{H}_5)_3\text{Cl}$	 (13)	7	97	113-115 (115-117) [18]

Table 2. Continued

Entry	RR'_3NX	Product	Time (min)	Yield ^a (%)	M.p. °C (Lit.)
14	$\text{PhCH}_2\text{N}(\text{C}_2\text{H}_5)_3\text{Cl}$	 (14)	8	92	69-71 (71-73) [18]
15 ^b	$\text{PhCH}_2\text{N}(\text{C}_2\text{H}_5)_3\text{Cl}$	 (15)	10	79	116-118 (117-119) [18]
16	$\text{PhCH}_2\text{N}(\text{C}_2\text{H}_5)_3\text{Cl}$	 (16)	10	94	226-228 (230-232) [20]
17	$\text{PhCH}_2\text{N}(\text{C}_2\text{H}_5)_3\text{Cl}$	 (17)	10	89	138-139 140-142 [20]
18	$\text{PhCH}_2\text{N}(\text{C}_2\text{H}_5)_3\text{Cl}$	 (18)	10	93	150-152 (153-156) [20]

^aIsolated yield. ^bIn this reaction, the mole ratio of azaheterocycle/quaternary ammonium salt was 1.5/1.

CONCLUSIONS

In summary, we have introduced the quaternary ammonium salts as efficient alkylating agents for *N*-alkylation of azaheterocycles. The advantages of the present method are high yields, short reaction times, simplicity, low cost and also the green nature of the protocol.

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