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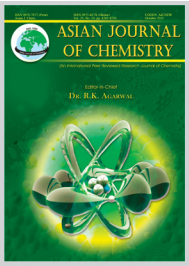

NOTE

A Green and Simple Synthesis of *N*-Alkyl-2-acetylbenzimidazoles

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A green and simple synthesis of *N*-alkyl-2-substituted benzimidazoles has been developed. In this method, 2-acetyl benzimidazole compound (**1**) was alkylated with reagents such as dimethyl sulfate/diethyl sulfate/benzyl chloride under green conditions *i.e.*, by physical grinding in presence of a mild base like K_2CO_3 or by using green solvents like PEG-600, ethanol *etc*. or by using micro-wave irradiation technique to obtain *N*-alkyl-2-acetylbenzimidazoles compound (**2**)

Key Words: 2-Acetyl benzimidazole, Alkylating agent (DMS/DES/PhCH$_2$Cl), K_2CO_3, PEG-600.

Benzimidazole derivatives are useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest[1,2]. Substituted benzimidazoles have found applications in diverse therapeutic areas as antiulcer agents, anticancer agents, antimicrobial agents and anthelmintic agents, *etc.*[3-6]. Some of them exhibited activities against several viruses including HIV, influenza and human cytomegalovirus[7]. Accordingly, the synthesis of benzimidazoles has received much attention and several studies have been developed in recent years to uncover a variety of synthetic methods and new reagents for the preparation of novel benzimidazole derivatives[8-14]. In continuation of our earlier work on synthesis of 2-substituted benzimidazoles, we now wish to report our results on alkylation of 2-acetylbenzimidazole under green conditions.

Preparation of *N*-alkyl-2-acetylbenzimidazoles (2) from 2-acetyl benzimidazole (1)

Physical grinding method: A mixture of compound **1** (1.60 g, 10 mM), K_2CO_3 (2.76 g, 20 mM) and alkylating agent (10 mM) were ground together for about 10-15 min in a mortar and pestle at room temperature to obtain a homogeneous mixture. The mixture was then treated with ice-cold water (*ca.* 30-40 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried to obtain crude compound **2**. Recrystallization of the crude product from a suitable solvent gave pure compound **2 (Scheme-I)**. Yields are given in Table-1.

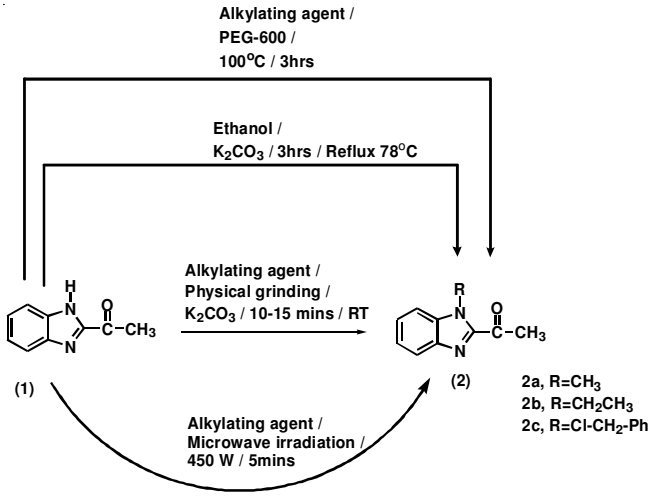
In PEG-600: A mixture of compound **1** (1.60 g, 10 mM), alkylating agent (10 mM) and PEG-600 (20 mL) was heated on a steam-bath at 100 ºC for 3 h. At the end of this period, the mixture was cooled to room temperature and poured into ice-cold water (*ca.* 50 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The crude product was recrystallized from a suitable solvent to obtain pure compound **2 (Scheme-I)**. Yields are given in Table-1.

TABLE-1
PREPARATION OF COMPOUND **2** FROM COMPOUND **1** UNDER DIFFERENT CONDITIONS

S. No.	Green conditions	Substrate	Reagent	Product	Time (Min)	Yield (%)
1	Physical grinding	**1**	DMS	**2a**	10-15	70
			DES	**2b**	10-15	90
			PhCH$_2$Cl	**2c**	10-15	90
2	PEG-600	**1**	DMS	**2a**	180	65
			DES	**2b**	180	60
			PhCH$_2$Cl	**2c**	180	70
3	Ethanol	**1**	DMS	**2a**	180	70
			DES	**2b**	180	60
			PhCH$_2$Cl	**2c**	180	60
4	Microwave irradiation	**1**	DMS	**2a**	5	80
			DES	**2b**	5	70
			PhCH$_2$Cl	**2c**	5	85

In ethanol: To a suspension of K_2CO_3 in ethanol was added compound **1** (1.60 g, 10 mM) and the mixture stirred at room temperature for 10 min. To this mixture was added a solution of alkylating agent (10 mM) and refluxed on water bath for 3 h. The progress of the reaction was monitored on TLC for the disappearance of compound **1**. After the completion of the reaction (*ca.* 3 h) the excess ethanol was rotary evaporated and the residual reaction mixture poured into ice-cold water

(2 × 10 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The crude product was recrystallized from a suitable solvent to obtain pure compound **2 (Scheme-I)**.



Scheme-I

Under microwave condition: Mixture of compound **1** and alkylating agent was taken in Erlenmeyer flask capped with a funnel. The mixture was kept in a domestic microwave oven for microwave irradiation at 450 watts for 5 min. The completion of the reaction was monitored by the TLC technique. After the completion of the reaction, the mixture was cooled to room temperature and poured into ice-cold water (2 × 10 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried **(Scheme-I)**.

RESULTS AND DISCUSSION

Reaction of compound **1** independently with each of dimethyl sulphate (DMS), diethyl sulphate (DES) and benzyl chloride ($PhCH_2Cl$) in the presence of K_2CO_3 as a mild base, by a simple physical grinding of the reaction mixture in a mortar and pestle under solvent-free conditions for 10-15 min at room temperature, followed by processing, gave respectively 1-methyl-2-acetyl benzimidazole (compound **2a**, *i.e.*, R = CH_3), 1-ethyl-2-acetyl benzimidazole (compound **2b**, *i.e.*, R = C_2H_5), 1-phenyl-2-acetyl benzimidazole (compound **2c**, *i.e.*, R = $PhCH_2Cl$), as the products identical with the ones reported in the earlier methods[15,16] in all respects (m.p., m.m.p. and co-TLC analysis).

The reaction was also carried out in PEG-600 as a solvent. Thus, heating a mixture of compound **1**, independently with each of dimethyl sulphate, diethyl sulphate and benzyl chloride ($PhCH_2Cl$) in PEG-600 at 100 ºC for 3 h without the use of any added base, followed by simple processing, gave respectively compound **2a** (*i.e.*, **2**, R = CH_3), compound **2b** (*i.e.*, **2**, R = CH_2CH_3) and compound **2c** (*i.e.*, 2, R = $PhCH_2$) identical with the same products obtained above.

The reaction of compound **1** independently with each of dimethyl sulphate, diethyl sulphate and benzyl chloride was also carried out in ethanol in the presence of a mild base like K_2CO_3. The reaction mixture was refluxed on a water-bath for 3 h, followed by simple processing, gave respectively compound **2a** (*i.e.*, **2**, R = CH_3), compound **2b** (*i.e.*, **2**, R = CH_2CH_3) and compound **2c** (*i.e.*, **2**, R = $PhCH_2$) identical with the same products obtained above.

Compound **2** could also be prepared by an alternative method. Thus, compound **1** on treating independently, with each of dimethyl sulphate, diethyl sulphate and benzyl chloride under microwave irradiation conditions for 5 min and subsequent processing, gave respectively compound **2a** (*i.e.*, **2**, R = CH_3), compound **2b** (*i.e.*, **2**, R = CH_2CH_3), compound **2c** (*i.e.*, **2**, R = $PhCH_2$) identical with the products obtained earlier above.

Conclusion

In conclusion, green and simple syntheses of *N*- alkyl-2-acetyl benzimidazoles (**2**) from 2-acetyl benzimidazole (**1**) are described. It appears from this study that green syntheses such as solid phase synthesis (physical grinding) and microwave irradiation give better yields, quality and in less reaction time the products over conventional methods.

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