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Der Pharma Chemica, 2013, 5(6):69-72
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

A facile and green synthesis of N-substituted-2-chlorobenzimidazoles

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ABSTRACT

*A facile and green synthesis of N-substituted-2-chlorobenzimidazoles (**4**) under different conditions has been developed. In this method, 2-chlorobenzimidazole (**3**) was treated with an alkylating agent such as DMS/DES/PhCH$_2$Cl under green conditions i.e., by physical grinding in the presence of K$_2$CO$_3$ at RT or by heating in PEG-600 as green solvent at 100^{0}C or by irradiation with micro-wave at RT to obtain N-alkyl-2-chlorobenzimidazoles (**4**).*

Keywords: Benzimidazole, N-alkyl-2-chlorobenzimidazole, Green synthesis, Grinding.

INTRODUCTION

Benzimidazoles are very important class of compounds due to their wide spectrum of biological activity [1]. Benzimidazole derivatives play an important role with diverse types of pharmacological actions [2-8].

Yu et al reported [9] the reaction of 2-chlorobenzimidazole with methyl iodide in the presence of sodium hydride as a base and DMF as a solvent at RT giving N-methyl-2-chlorobenzimidazole in 53% yield. Tim et al reported [10] the reaction of 2-chlorobenzimidazole with methyl iodide in the presence of aq. NaOH and acetonitrile as a solvent at RT giving N-methyl-2-chlorobenzimidazole in 88% yield. The reaction of N-methyl-2-hydroxybenzimidazole with POCl$_3$ under reflux for 12 hrs giving N-methyl-2-chlorobenzimidazole was reported [11] by Baburao et al. Lajos et al carried out [12] the reaction of 2-chlorobenzimidazole with dimethylsulfate in aq.NaOH for 2 hrs at RT to get N-methyl-2-chlorobenzimidazole. Steven et al [13] reported the reaction of 2-chlorobenzimidazole with methyl iodide in the presence of sodium hydride as a base and THF as a solvent for 1 hr at 80^{0}C resulting in N-methyl-2-chlorobenzimidazole in 64% yield. Frank et al [14] found out a very efficient (81%) alkylation of 2-chlorobenzimidazole with dimethylsulfate in aq.NaOH for 2 hrs at RT to get N-methyl-2-chlorobenzimidazole. Guida et al reported [15] that 2-chlorobenzimidazole with methyl iodide in the presence of KOH as a base and acetone as a solvent for 2 hr at RT gave N-methyl-2-chlorobenzimidazole.

It is obvious from the literature survey given above, that there seems to be **not** much information on use of Green methods for the alkylation of 2-chlorobenzimidazole. In continuation of our earlier studies on alkylation of 2-acetylbenzimidazole [16] and thiolation of N-methyl-2-chlorobenzimidazole [17], we now wish to report our studies on alkylation of 2-chlorobenzimidazole using Green methods.

MATERIALS AND METHODS

Melting points were determined in open capillaries in sulfuric acid bath and are uncorrected. Thin-layer chromatography (TLC) analyses were done on glass plates coated with silica gel GF-254 and spotting was done using Iodine or UV lamp.

Preparation of 4 from 3:

1) Physical grinding method:

A mixture of **3** (1.45gms, 10mM), K_2CO_3 (2.76gms, 20mM) and alkylating agent(10mM) was ground together for about 10-15 min in a mortar with a pestle at RT to obtain a homogeneous mixture. The completion of the reaction was monitored by TLC on prepared silica gel-G Plates using authentic samples of the starting material and the target compounds as references. The mixture was then treated with ice-cold water (≈30-40ml). The separated solid was filtered, washed with water (2x10ml) and dried to obtain crude **4a-c**. For yields please see **Table-1.** Recrystallization of the crude product from a suitable solvent gave pure **4a-c**. IR, ^{1}H-NMR and LC-MS spectra for the compounds **4a-c** were found to be in agreement with the structures assigned to them.

2) In PEG-600:

A mixture of **3** (1.45gms, 10 mM), alkylating agent (10mM) and PEG-600 (20 ml) was heated on a steam-bath at 100°C for 3hrs. At the end of this period, the mixture was cooled to RT and poured into ice-cold water (≈50ml).The separated solid was filtered, washed with water (2x10ml) and dried. The crude products were recrystallized from a suitable solvent to obtain pure **4a-c,** identical with the same products obtained above**.** For yields please see **Table-1.**

3) Under microwave condition:

A mixture of **3** (1.45gms, 10 mM) and alkylating agent (10mM) was taken in a 10 mL CEM-reaction tube sealed by rubber stopper and subjected to microwave irradiation for 2 mins in the commercial micro-wave reactor. After that, the tube was cooled and the completion of reaction was checked by TLC. Then, the reaction mixture was poured into ice-cold water (50 mL). The separated solid was filtered, washed with water (2x10ml) and dried. The crude products were recrystallized from a suitable solvent to obtain pure **4a-c,** identical with the same products obtained above. For yields, please see **Table-1.**

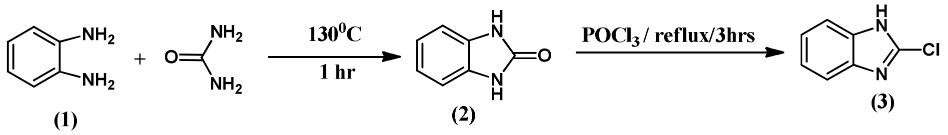
RESULTS AND DISCUSSION

Condensation of o-Phenylenediamine (**1**) with urea by dry fusion of reactants at 130^{0}C gives the known benzimidazole-2-one (**2**), which on treatment with $POCl_3$, in the presence of catalytic amount of phenol, yields the previously reported[16] 2-chlorobenzimidazole (**3**). Reaction of **3,** 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 with a pestle under solvent-free conditions for 10-15 min at RT, followed by processing, gave respectively 1-methyl-2-chlorobenzimidazole (**4a**, i.e., $R=CH_3$) , 1-ethyl-2-chlorobenzimidazole (**4b**, i.e., $R=C_2H_5$), 1-benzyl-2-chlorobenzimidazole (**4c**, i.e., $R=PhCH_2$), as the products identical with the ones reported in the earlier methods[7,8] in all respects (m.p. m.m.p. and co-tlc analysis).

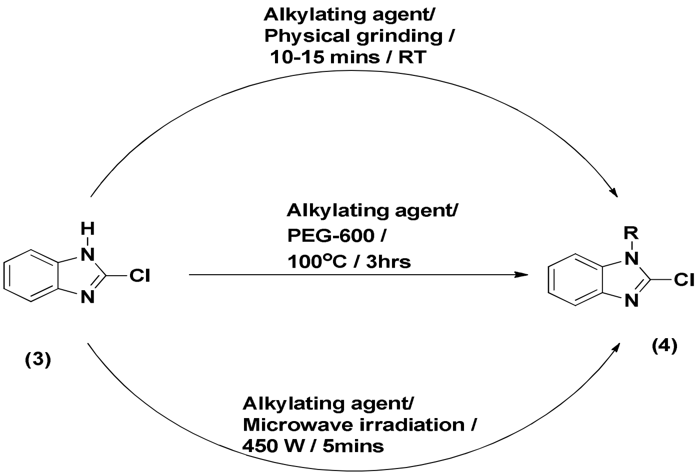
The reaction was also carried out in PEG-600 as a solvent. Thus, heating a mixture of **3,** independently, with each of dimethylsulphate (DMS), diethylsulphate (DES) and benzyl chloride ($PhCH_2Cl$) in PEG-600 at 100°C for 3hrs without the use of any added base, followed by simple processing, gave respectively **4a** (i.e.**, 4,** $R=CH_3$)**, 4b** (i.e., **4**, $R=CH_2CH_3$) and **4c** (i.e., **4** $R=PhCH_2$) identical with the same products obtained above.

4 could also be prepared by an alternative method. Thus, **3** on treating independently, with each of dimethyl sulphate (DMS), diethyl sulphate (DES) and benzyl chloride ($PhCH_2Cl$) under microwave irradiation conditions for 5 min and subsequent processing, gave respectively **4a** (i.e., **4,** $R=CH_3$) **4b** (i.e., **4,** $R=CH_2CH_3$) **, 4c** (i.e., **4,** $R=PhCH_2$) identical with the products obtained earlier above.

SCHEME: 1



SCHEME: 2



*(**4a**, R = CH_3; **4b**, R = C_2H_5; **4c**, R = CH_2Ph)*

Table -1: Preparation of 4 from 3 under different green conditions

S.No.	SM	Reagent	Product	Methods								
				Physical grinding			Green solvent PEG-600			Microwave irradiation		
				Time (Min)	Temp (^{0}C)	Yield* (%)	Time (Min)	Temp (^{0}C)	Yield* (%)	Time (Min)	Temp (^{0}C)	Yield* (%)
1.	**1**	DMS	**4a**	10-15	RT	88	180	100	69	2	RT / 450 W	89
	2	DES	**4b**	10-15	RT	86	180	100	73	2	RT / 450 W	87
	3	$PhCH_2Cl$	**4c**	10-15	RT	82	180	100	64	2	RT / 450 W	85

*M.P. of **4a:** 192-96^{0}C (Lit.$^{(7,8)}$ m.p. 193-97^{0}C)* **Yield refers to isolated crude product only.*
*M.P. of **4b:** 174- 78^{0}C (Lit.$^{(7,8)}$ m.p. 172-75^{0}C)*
*M.P. of **4c:** 212- 215^{0}C (Lit.$^{(7,8)}$ m.p. 213-216^{0}C)*

CONCLUSION

In conclusion, we have developed simple and green synthesis of N-alkyl-2-chlorobenzimidazole under different conditions.

Acknowledgement
The authors are indebted to the authorities of Jawaharlal Nehru Technological University Hyderabad for providing facilities.

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