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AN ECO-FRIENDLY SYNTHESIS OF N-ALKYL-2-AMINO BENZIMIDAZOLE

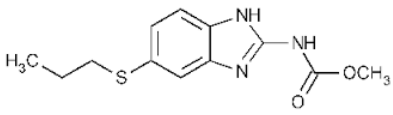
Sadhu Srinivas Rao

Department of Chemistry, Vidya Jyothi Institute of Technology (Autonomous)
Himayatnagar (Vill.), C.B.Post, Hyderabad, India – 500 075.
E-mail: seenu604@gmail.com

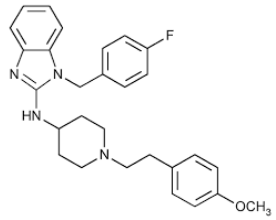
ABSTRACT
A green approach for the synthesis of N-alkyl-2-aminobenzimidazoles **2** (R^1= CH_3, C_2H_5, CH_2Ph) under, different conditions has been developed from 2-aminobenzimidazole **1** by reaction with an alkylating agent by physical grinding or by using green solvent like PEG-600 or by using micro-wave irradiation technique.

KEYWORDS Green synthesis, benzimidazole, grinding, microwave, 2-amino benzimidazole.

INTRODUCTION
Benzimidazoles are very useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest[I]. Benzimidazoles are an important class of bioactive molecules in the field of drugs and pharmaceuticals[II]. 2-Mercaptobenzimidazole derivatives having substitution at either the nitrogen or sulfur are reported to exhibit a broad spectrum of biological activity. [III-VII]
Moreover, 2-amino benzimidazoles[VIII-IX] occurs in broad spectrum of drugs and pharmacological agents with anticancer, antiviral, analgesic and antidiabetic properties. For example, mebendazole represents a big group of antiparasitic drugs and astemizole represents an antihistaminic group II generation drug with selective activity toward H1 receptors.



MEBENDAZOLE



ASTEMIZOLE

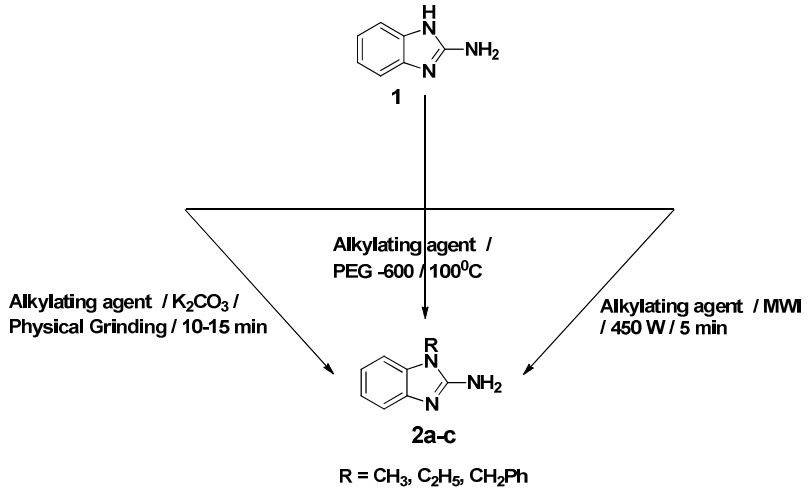
RESULTS AND DISCUSSION
Condensation of o-phenylene diamine with urea by dry fusion of reactants at 130^0C gives the known benzimidazole-2-one, which on treatment with $POCl_3$ in the presence of catalytic amount of phenol, yields the previously reported[X] 2-chloro benzimidazole. The latter on alkylation with alkylating agent such as dimethyl sulphate in the presence of K_2CO_3 in

CH_3CN medium using tetra-n-butylammonium bromide (TBAB) as phase transfer catalyst at RT for 3hr gave the previously reported[X] N-methyl-2-chlorobenzimidazole.

Reaction of **1,** independently, with each of dimethyl sulphate (DMS), diethyl sulphate (DES) and benzyl chloride ($PhCH_2Cl$) in the presence of K_2CO_3, 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 N-methyl-2-aminobenzimidazole **2a** (*i.e.*, **2,** R=CH_3**),** N-ethyl-2-aminobenzimidazole **2b** (*i.e.*, **2,** R=CH_2CH_3) and N-benzyl-2-aminobenzimidazole **2c** (*i.e.*, **2**, R=$PhCH_2$), as the products identical with the ones reported in the earlier methods[XI] in all respects (m.p. m.m.p. and co-tlc analysis).

The reaction was also carried out in PEG-600 as the green solvent. Thus, heating a mixture of **1** with an alkylating agent in PEG-600 for 3h without the use of any added base, followed by simple processing, gave respectively 2**a** (*i.e.*, **2,** R=CH_3**), 2b** (*i.e.*, **2,** R=CH_2CH_3**)** and **5c** (*i.e.*, **5,** R= CH_2Ph**)** identical with the same products obtained above (**Scheme I**).

Compound **2** could also be prepared by an alternative, green method. Thus, **1** with an alkylating agent and K_2CO_3 as a base under microwave irradiation at RT conditions for 2 min and subsequent processing, gave respectively 2**a** (*i.e.*, **2,** R= CH_3**), 2b** (*i.e.*, **2,** R= CH_2CH_3) **, 2c** (*i.e.*, **2,** R= CH_2Ph**)** identical with the products obtained above (**Scheme I**).



Scheme-1 Synthesis of N-alkyl-2-aminobenzimidazole

EXPERIMENTAL

Melting points were determined in open capillaries in sulfuric acid bath and are uncorrected. IR Spectra were recorded with Jasca FT-IR 5300. ^1H NMR and spectra were recorded in $CDCl_3$ / DMSO using Varian 400-MHz instrument. Mass spectra were recorded on an Agilent LC-MS instrument giving only M^+ values in Q+1 mode. Thin-layer chromatography (TLC) analyses were carried out on glass plates coated with silica gel GF-254 and visualization was achieved using iodine vapours or UV lamp. Experiments under microwave irradiation were carried out by using the commercially available CEM Discover Microwave Reactor.

Preparation of 2 from 1:

(i) Physical grinding method

A mixture of **1** (10 mM), alkylating agent (10 mM) and K_2CO_3 (1.38g, 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 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 (≈30-40 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried to obtain crude 2**a-c**. Recrystallization of the crude product from ethyl acetate gave pure **2a-c**. IR, ^{1}H NMR and LC-MS spectra for the compounds **2a-c** were found to be in agreement with the structures assigned to them. Yields are shown in **Table I.**

(ii) In PEG-600

A mixture of **1** (10 mM), alkylating agent (10 mM) and PEG-600 (20 mL) was heated on a steam-bath at 100^{o}C for 3hr. At the end of this period, the mixture was cooled to RT and poured into ice-cold water (≈50 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The crude products were purified by recrystallization from ethyl acetate to obtain pure **2a-c**, identical with the same products obtained above. Yields are shown in **Table I.**

(iii) Under Microwave condition

A mixture of **1** (10 mM) and alkylating agent (10 mM) was taken in a 10 mL CEM-reaction tube sealed by rubber stopper and subjected to microwave irradiation for 2 min in a 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 (2 × 10 mL) and dried. The crude products were purified by recrystallization from ethyl acetate to obtain pure **2a-c,** identical with the same products obtained above. Yields are shown in **Table I.**

Table -I

Preparation of **2** from **1** under different green conditions

S.No.	SM	Reagent	Product	Physical grinding			Green solvent irradiation PEG-600			Microwave		
				Time (Min)	Temp (^{0}C)	Yield* (%)	Time (Min)	Temp (^{0}C)	Yield* (%)	Time (Min)	Temp (^{0}C)	Yield* (%)
1.	**1**	DMS	**2a**	10-15	RT	84	180	100	70	2	RT / 450 W	86
		DES	**2b**	10-15	RT	87	180	100	73	2	RT / 450 W	84
		$PhCH_2Cl$	**2c**	10-15	RT	80	180	100	64	2	RT / 450 W	74

*Yield refers to isolated crude product only.

M.P. of **2a:** 232- 35^{0}C (Lit.[XI] m.p. 235-38^{0}C)

M.P. of **2b:** 248-54^{0}C (Lit.[XI] m.p. 250-52^{0}C)

M.P. of **2c:** 185- 87^{0}C (Lit.[XI] m.p. 187-89^{0}C)

CONCLUSION

In conclusion, the use of solvents like DMF / CH_3CN for N-alkylation are not green and hence we have developed a green approach for the synthesis of N-alkyl-2-aminobenzimidazoles under different conditions.

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References

I. (a) G L Gravatt, B C Baugley , W R Wilson W.A.Denny, *J Med Chem,* 37, 4338 (1994),
(b) J. S. Kim, B. Gatto and L. F .Liu, *Eur J Med Chem*, 39, 992 (1996); (c) T Roth,M L Morningstr, P L Boyer, S H Hughes, R W Buckheit and C J Michejda, *J Med Chem*,40, 4199 (1997); (d) D A Horton, G T Bourne and M L Smythe, *Chem Rev,* 893 (2003),.

II. (a) G L Gravatt, B C Baugley , W R Wilson and Denny W A, *J Med Chem,* 37, 4338 (1994); b) B Jayasankara and K M L Rai, *Arkivoc* 75 (2008); (c) T Roth, M L Morningstar,P L Boyer, S H Hughes, R W Buckheit and C J Michejda, *J Med Chem*, 40, 4199 (1997).

III. H Hasegawa, N Tsuda and M Hasoya, *Japanese Pat,* 198 (1974); *Chem Abstr*, (1975), 156308.

IV. G Rovnyak, V L Narayana, R D Haugwitz and C M Cimarusti, *US Pat*, 014, (1973); *Chem Abstr*, 1974, 105596.

V. S C Bell and P H Wei, *J Med Chem,* 19, 524 (1976).

VI. D R Graber, R A Morge and Raenko, *J Org Chem,* 52, 4620 (1987).

VII. N I Korotkikh, G F Raenko and O P Shavaika, *Chem Heterocycl compd,* 31, 359 (1995).

VIII. V Andre, A Hardeman, I Halasz, RS Stein, GJ Jackson and DG Reid, *Angew. Chem. Int.Ed*, 50, 7858 (2011).

IX. M B J Atkinson, D K Bucar, A N Sokolv, T Fricscic, C N Robinson, M Y Bilai, *Chem.Commun*, 14, 10570 (2008).

X. P K Dubey, A Naidu, V Anandam, *Indian J. Chem,* 44, 417 (2005).

XI. T Anelia, P D Mavrova, A Yordan, K Tsenov, *Bioorganic & Medicinal Chemistry*, 15, 6291(2007).

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