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PEG-600 Mediated Phase Transfer Catalyst Free *N*-Alkylations of 2-Butyl-5-chloro-1*H*-imidazole-4-carbaldehyde

A.V. Hanumantha Rao*, P.N. Kishore Babu, V. Lakshman Rao and A. Jaya Shree

Centre for Chemical Sciences and Technology, Institute of Science and Technology, Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad-500 085, India

*Corresponding author: E-mail: avhanumantharao@gmail.com

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A convenient, rapid, efficient and environmentally benign route has been developed for the synthesis of *N*-alkyl-2-butyl-5-chloro-1*H*-imidazole-4-carbaldehydes **3(a-g)** using PEG-600 as solvent as well as phase transfer catalyst, where the reaction of 2-butyl-5-chloro-1*H*-imidazole-4-carbaldehyde **(1)** was done with alkylating agents **2** using PEG-600 as solvent.

Keywords: PEG-600, Green synthesis, Phase transfer catalyst free *N*-alkylations.

INTRODUCTION

2-Butyl-5-chloro-1*H*-imidazole-4-carbaldehyde (**1**) and its chemistry is considered to be an important class of *N*-heterocyclic compounds with various active sites serving as synthons for the synthesis of several new compounds with useful biological properties. Weinstock *et al.*[1] reported the use of **1** and its derivatives to exhibit potent and selective angiotension II receptor antagonists, Kantevari *et al.*[2] reported that, *N*-alkyl chalcone derivatives can be used as angiotension converting enzyme (ACE) inhibitors, Salimbeni *et al.*[3] reported the *N*-alkyl derivatives can act as nonpeptide angiotension II receptor antagonists and several reports reveal the use of **1** with various biological activities[4-7].

Although there are numerous reports on *N*-alkylations of various compounds using various solvents but most of them suffer due to hazardous use of solvents, harsh reaction conditions, use of external phase transfer catalysts and longer reaction times. Hence, there is a need for the development of new techniques which are environmentally benign in nature. Use of polyethylene glycol as solvent has attracted the attention of many researchers in the present context of green synthesis. PEG has been considered as green and efficient solvent for carrying various organic reactions. In present work, choose of PEG-600 as solvent provoked by being thermally labile, availability, inexpensive, easy work-up and recyclability. PEG-600 has unique solvent property which has excellent cataionic coordination capability which render it a perfect proton abstracter facilitating *N*-alkylations.

Conventional *N*-alkylations mostly requires base like K_2CO_3 which neutralize the acid liberated from the reaction and also requires phase transfer catalysts like TBAB, TEBAC, D-glucose[8-10], *etc*. which enhances the reaction. Present work deals with the use of PEG-600 as green solvent and phase transfer catalyst free conditions for *N*-alkylation of 2-butyl-5-chloro-1*H*-imidazole-4-carbaldehyde (**1**) using various alkylating agents.

EXPERIMENTAL

Melting points are uncorrected and are determined in open capillary tubes in sulphuric acid bath. TLC was performed on silica gel-G and spotting was done using iodine or UV light. IR spectra were recorded using Perkin-Elmer 1000 instrument in KBr phase, ^{1}H NMR on VARIAN 400 MHz instrument, ^{13}C NMR on Bruker Avance 75 MHz and Mass spectra on Agilent-LC-MS instrument giving only $M^{+\bullet}+1$ or $M^{+\bullet}-1$ values. Methanol, ethanol, glycerol, ethylene glycol and PEG-600 were purchased from Finar reagents, India. K_2CO_3 and TBAB was purchased from S.D. Fine chemicals Ltd., India.

Preparation of 3a from 1 and 2a under conventional method: A mixture of tetrabutylammonium bromide (PTC, 0.2 g), K_2CO_3 (1.4 g, 10 mM) and **1** (1.85 g, 10 mM) in methanol (20 mL), alkylating agent dimethylsulphate (1.2 mL, 11 mM) was added and continued stirring for 4 h at room temperature. After completion of the reaction (monitored by TLC), the mixture was filtered and the insoluble material washed with CH_3OH (2 × 5 mL). The filtrate was evaporated to dryness and the residue treated with chloroform (25 mL), the chloroform layer was washed with water (3 × 30 mL) and evaporated to dryness to give **3a**.

Preparation of 3a from 1 and 2a using PEG-600 as solvent as well as phase transfer catalysts: A mixture of **1** (1.85 gm, 10 mM) in PEG-600 (20 mL) and dimethylsulphate (1.2 mL, 11 mM) stirred for 15 min. at 50 °C. After completion of the reaction (monitored by TLC), the mixture was poured into crushed ice (30 gms). A white coloured solid separated was filtered, dried to obtain crude **3a**. Recrystallization was done using chloroform to obtain pure product.

2-Butyl-5-chloro-1-methyl-1*H*-imidazole-4-carbaldehyde (3a): Yield: 1.62 g (81 %); m.p. = 45-47 °C; IR (KBr, ν_{max}, cm^{-1}): 1673 (C**HO**); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 9.24 (s, 1**H**, C**H**O), 4.26 (s, 3H, N-C**H**$_3$), 2.71 (t, 2H, -C**H**$_2$), 1.61 (m, 2H, -C**H**$_2$), 1.30 (m, 2H, -C**H**$_2$), 0.84 (t, 3H, C**H**$_3$); LC-MS: *m/z*: 201 (M^+ + 1).

2-Butyl-5-chloro-1-ethyl-1*H*-imidazole-4-carbaldehyde (3b): Yield: 1.70 g (80 %); m.p. = 68-70 °C; IR (KBr, ν_{max}, cm^{-1}): 1676 (CHO); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 9.37 (s, 1**H**, C**H**O), 4.52 (q, 2H, N-C**H**$_2$), 2.65 (t, 2H, -C**H**$_2$), 1.56 (m, 2H, -C**H**$_2$), 1.21 (m, 2H, -C**H**$_2$), 1.04 (t, 3H, C**H**$_3$), 0.84 (t, 3H, C**H**$_3$); LC-MS: *m/z*: 215 (M^+ + 1).

2-Butyl-5-chloro-1-propyl-1*H*-imidazole-4-carbaldehyde (3c): Yield: 1.92 g (84 %); m.p. = 75-78 °C; IR (KBr, ν_{max}, cm^{-1}): 1669 (CHO); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 9.44 (s, 1**H**, C**H**O), 3.89 (t, 2H, N-C**H**$_2$), 2.78 (t, 2H, -C**H**$_2$), 2.45 (m, 2H, -C**H**$_2$), 1.44 (m, 2H, -C**H**$_2$), 1.12 (m, 2H, -C**H**$_2$), 1.05 (t, 3H, C**H**$_3$), 0.94 (t, 3H, C**H**$_3$); LC-MS: *m/z*: 230 (M^+ + 1).

1-Benzyl-2-butyl-5-chloro-1*H*-imidazole-4-carbaldehyde (3d): Yield: 2.31 g (88 %); m.p. = 155-158 °C; IR (KBr, ν_{max}, cm^{-1}): 1665 (CHO); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 9.21 (s, 1**H**, C**H**O), 7.85-8.04 (m, 5**H**, Ar-H), 5.11 (s, 2H, N-C**H**$_2$), 2.61 (t, 2H, -C**H**$_2$), 2.21 (m, 2H, -C**H**$_2$), 1.36 (m, 2H, -C**H**$_2$), 1.15 (t, 3H, C**H**$_3$); LC-MS: *m/z*: 278 (M^+ +1).

2-Butyl-5-chloro-1-(phenylsulfonyl)-1*H*-imidazole-4-carbaldehyde (3f): Yield: 1.91 g (85 %); m.p. = 142-144 °C; IR (KBr, ν_{max}, cm^{-1}): 1660 (CHO); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 9.36 (s, 1**H**, C**H**O), 7.76-8.11 (m, 5**H**, Ar-H), 2.34 (t, 2H, -C**H**$_2$), 2.11 (m, 2H, -C**H**$_2$), 1.24 (m, 2H, -C**H**$_2$), 0.96 (t, 3H, C**H**$_3$); LC-MS: *m/z*: 228 (M^+ + 1).

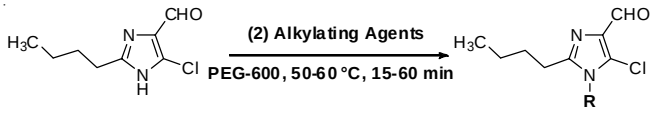
2-Butyl-5-chloro-1-tosyl-1*H*-imidazole-4-carbaldehyde (3g): Yield: 2.6 g (77 %); m.p. = 148-150 °C; IR (KBr, ν_{max}, cm^{-1}): 1666 (CHO); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 9.42 (s, 1**H**, C**H**O), 7.55-7.88 (m, 4**H**, Ar-H), 3.89 (t, 3H, C**H**$_3$), 2.62 (t, 2H, -C**H**$_2$), 2.00 (m, 2H, -C**H**$_2$), 1.12 (m, 2H, -C**H**$_2$), 1.11 (t, 3H, C**H**$_3$); LC-MS: *m/z*: 282 (M^+ + 1).

2-Butyl-5-chloro-1-(methylsulfonyl)-1*H*-imidazole-4-carbaldehyde (3h): Yield: 2.4 g (90 %); m.p. = 96-98 °C; IR (KBr, ν_{max}, cm^{-1}): 1685 (CHO); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 9.21 (s, 1**H**, C**H**O), 4.47 (t, 3H, C**H**$_3$), 2.58 (t, 2H, -C**H**$_2$), 2.05 (m, 2H, -C**H**$_2$), 1.02 (m, 2H, -C**H**$_2$), 0.80 (t, 3H, C**H**$_3$); LC-MS: *m/z*: 266 (M^+ + 1).

RESULTS AND DISCUSSION

Under conventional method *N*-methylation of 2-butyl-5-chloro-1*H*-imidazole-4-carbaldehyde (**1**) was done using TEBAC as phase transfer catalysts (PTC), K_2CO_3 as base, dimethylsulfate (**2a**) as alkylating agent and methanol as solvent with a reaction time of 4 h to yield 2-butyl-5-chloro-1-methyl-1*H*-imidazole-4-carbaldehyde (**3a**) in 60 % yield. When the same reaction attempted using PEG-600 as solvent and TEBAC as PTC, K_2CO_3 as base, dimethylsulfate (**2a**) as alkylating agent with 0.5 h reaction time at 50 °C yielded **3a** in 90 % yield.

To check whether the reaction accelerated by phase transfer catalysts or by solvent, attempt was done using PEG-600 as solvent and also as phase transfer catalysts at 50 °C for 15 min. yielded **3a** in 90 % yield. It was obvious by the result that the reaction was self catalysed by the slight basic nature of PEG-600.



(1) **3(a-g)**

By the results obtained, to check the role of solvent a variety of green solvents were used like glycerol, ethylene glycol, methanol, ethanol and water. Among them PEG-600 proved to be the best as solvent as well as phase transfer catalysts. The results obtained were summarized in Table-I.

The above reaction was found to be general and has extended to other alkylating agents yielding **3(b-g)**. Yields and time were summarized in Table-II.

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TABLE-1
REACTION OF **1** WITH **2A** WITHOUT USE OF PHASE TRANSFER CATALYST IN GREEN SOLVENTS

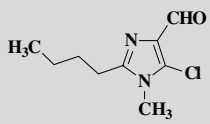
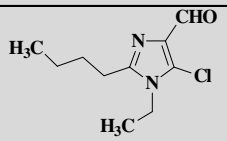
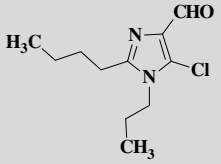
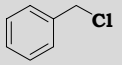
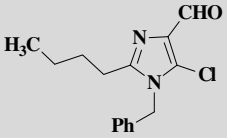
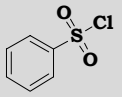
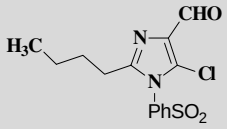
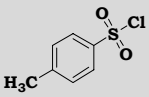
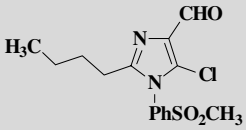
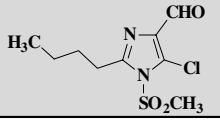
S. no.	Solvent	Product	Time (min)	Yield (%)
1	PEG-600		15	90
2	Glycerol		40	85
3	Ethylene glycol		55	85
4	Methanol		180	No reaction
5	Ethanol		120	30
6	Water		180	No reaction

TABLE-2
REACTION OF **1** WITH DIFFERENT ALKYLATING AGENTS USING PEG-600 AS SOLVENT AT 50-55 °C

S. no.	Entry	Reagent	Time (min)	Yield (%)	Product
1	3b	Diethyl sulphate	20	85	
2	3c	Propylchloride	25	80	
3	3d		30	75	
4	3e		30	70	
5	3f		55	70	
6	3g	Methane sulphonyl chloride	30	80	

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