*Iranian Journal of Organic Chemistry Vol. 10, No. 2 (2018) 2325-2331*

# An efficient room temperature synthesis of $N^1$-(4-substitutedbenzyl)-2-methyl-4-nitro-1*H*-imidazoles and $N^1$-butyl-2-methyl-4-nitro-1*H*-imidazoles

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Received: February 2018; Revised: March 2018; Accepted: April 2018

**Abstract:** $N^1$-(4-substitutedbenzyl)-2-methyl-4-nitro-1*H*-imidazoles (3a-i) were successfully synthesized by treating 2-methyl-4(5)-nitroimidazole (1a) with benzyl/butyl halides (2a-i) in the presence of solid-liquid phase transfer catalyst at room temperature. All the synthesized compounds were characterized by elemental analysis, FT-IR, $^1$H-NMR and $^{13}$C-NMR spectral studies. The methodology involves simple work up procedure, highly regioselective and mild conditions for the $N^1$-alkylation of a hindered imidazole with excellent yield of 4-nitroimidazoles.

**Keywords:** *C-N* formation, *N*-alkyl-4-nitroimidazoles, *N*-alkylation, Phase transfer catalysis, Room temperature reaction.

## Introduction

Nitroimidazoles are obtained as essential intermediates in several organic syntheses. *N*-alkylated nitroimidazoles are the valuable structural motifs of plentiful medicinally important compounds and other fine chemicals [1-3]. The regiospecific *N*-alkylation of 4(5)-Nitro-1*H*-imidazoles has been a problem of incredible interest due to the chemotherapeutic and pharmacological viability of $N^1$-alkyl-5-nitro- and $N^1$-alkyl-4-nitro-1*H*-imidazoles [4-13]. The problem encountered in the synthesis of *N*-alkyl imidazoles is the ascendancy of the regioselectivity. To be sure, *N*-alkylation gives a mixture of isomers wherein the major product is the sterically beneath hindered 1,4-isomer (Scheme **1**) [10-13].

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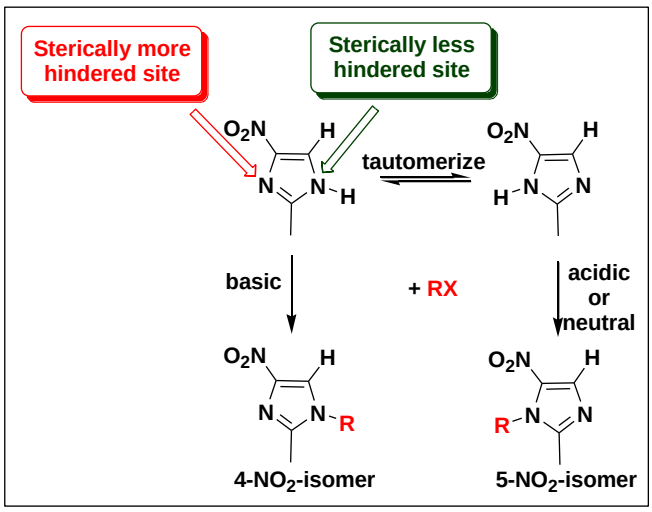
This perceived poor regioselectivity is owing to a prompt tautomeric equilibrium of (*NH*)-derivatives, and the moderately faster alkylation of the beneath hindered nitrogen.

In spite of the facts that neutral or acidic media procures 5-Nitroimidazole derivative as the predominant product, and the basic media forms 4-Nitro-1*H*-imidazole derivative as the major product during the *N*-alkylation of 4(5)-Nitro-1*H*-imidazoles with alkylating agents like alkyl halides or sulfates [14-18], there is a poor yield and lack of regioselectivity of either 4- and 5-Nitro-1*H*-imidazoles. Usually excellent yields of $N^1$-alkyl-4-nitro-1*H*-imidazoles could be obtained by reacting 4(5)-Nitro-1*H*-imidazoles with alkyl halides in basic media [19-21].

From the extensive literature reviews, it is understood that the reaction of $N^1$-alkylation of 2-Methyl-4(5)-nitro-1*H*-imidazoles was executed in the presence of sodium alcoholate in protic solvents [22-24]. The intermediate tetraalkylammonium salts of

nitroimidazoles were obtained through reaction between 4(5)-Nitro-1*H*-imidazoles and equivalent amount of a variety of tetraalkylammonium halides.




**Scheme 1.** $N^1$-alkylation of 2-methyl-4(5)-nitro-1*H*-imidazole

$N^1$-alkylations were carried out by employing tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst in the binary system consisting potassium hydroxide (aqueous phase) and benzene (organic phase) [25]. These methods suffer from serious problems like poor yield and the formation of undesired by-products. To overcome these problems, Rao *et al.* carried out $N^1$-alkylation using $K_2CO_3$ in DMF solvent at 110-120ºC [19]. This method of synthesis affords to give higher yields of regioselective products in lesser reaction time than the conventional methods. Usage of less expensive solvents and lesser reaction temperature (for low boiling alkyl halides) are the added advantages of this method.

In attention of the high activity of imino-hydrogen, phase-transfer catalysis promise to be probably a right approach for the nucleophilic substitution reaction of 4(5)-Nitro-1*H*-imidazoles. Yet, the inability of a few alkyl halides and the prevalence of other unwanted reactions cannot be avoided as a result of the contact with aqueous alkali within the liquid-liquid-transfer system. With the intention to get rid of this hassle, $N^1$-alkyl-4-nitro-1*H*-imidazoles have been suggested in solid-liquid-transfer system exploiting $K_2CO_3$ (a mild base), acetonitrile or ethyl acetate (solvent) and TBAB as phase-transfer catalyst at 70-80ºC [26].

An assay of assorted appear examples of alkylation of 4(5)-Nitro-1*H*-imidazoles in basic media appear that an acceptable amount of aberrant cases, such as benzylation and alkylation, bare explanation. From the extensive literature survey, it is vividly known that mostly 4-Nitro isomers are procured only in the temperature range of 110-140ºC. However, Liu *et al.* have produced 4-Nitro isomers at 70-80°C [26]. In the present investigation, the same was obtained at room temperature itself. This is considered to be one of the major advantages of this method. In the present work, alkyl halides of differing reactivity were utilized as part of the alkylation reactions of 4(5)-Nitro-1*H*-imidazole using $K_2CO_3$ (a mild alkali), acetonitrile (solvent) and TBAB as phase-transfer catalyst at room temperature. We accomplished $N^1$-alkyl-4-nitro-1*H*-imidazoles with excellent yields.

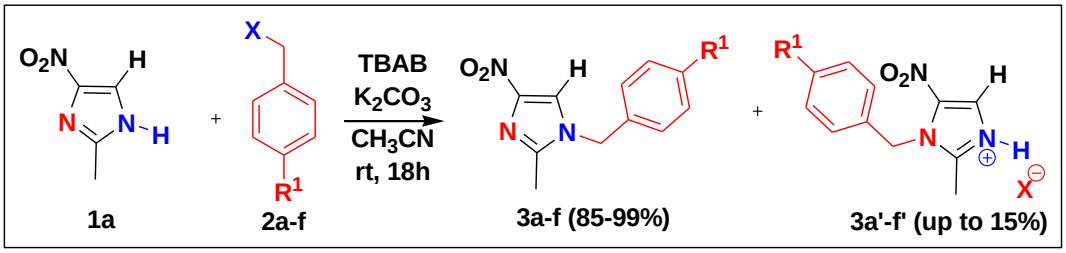
## Results and discussion

The studies on the alkylation of 4(5)-Nitro-1*H*-imidazole were carried out on a representative substrate 2-Methyl-4(5)-nitro-1*H*-imidazole **1a**. The reactive alkylating agents chosen for the study were 4-substitutedbenzyl halides **2a-f** and butyl halides **2g-i** at room temperature in the presence of phase transfer catalyst TBAB, $K_2CO_3$ and acetonitrile. The alkylation reactions were studied at room temperature and isolated product in each case was analyzed by $^1$H-NMR to ascertain the 4-Nitroimidazoles **3a-i** and 5-Nitro-imidazolium salts **3a´-i´** (slightly isolated, Table **1**) distribution. Typically, the experiments with the 1:1.2 ratio of 2-Methyl-4(5)-nitro-1*H*-imidazole **1a**: alkylating agents **2a-i** in room temperature was carried out for 18 h.

The $N^1$-benzylation of **1a** with **2a-f** at room temperature showed varying degrees of regioselectivity with the preferential formation of 4-Nitroimidazoles **3a-f.** The reaction of **2a** with **1a** at room temperature, the product **3a** was the exclusive one observed in the ratio >99:1 (Table **1**: Entry-1) with 5-Nitroimidazolium salt **3a´**. Benzylation of **1a** with **2b** and **2f** produced the 4-Nitroimidazoles **3b, 3b´** and **3f, 3f´** in the ratio of almost 92:8 (Table **1**: Entry-2 & 6). The 4-Nitro imidazoles **3d, 3d´** and **3e, 3e´** were obtained from the reaction of **2d** and **2e** with **1a** in the ratio of almost 94:6 (Table **1**: Entry-4 & 5). The reaction of **2c** produced **3c, 3c´** in the ratio of 85:15 (Table **1**: Entry-3). The total yield of the $N^1$-(4-benzylatedbenzyl)-2-methyl-4-nitroimidazoles **3a-f** was achieved in excellent yield at room temperature.

$N^1$-butylation of **1a** with **2g-h** in the presence of phase transfer catalyst TBAB, $K_2CO_3$ and acetonitrile at room temperature produced 4-Nitroimidazoles **3g, 3g´** and **3h, 3h´** as predominant products with similar regioselectivity in the ratio >99:1 (Table **2**: Entry-1 &

2). The reaction of **3i** at room temperature yielded 4-Nitroimidazoles **3i, 3i´** in the ratio of 93:7 (Table **2**: Entry-3).

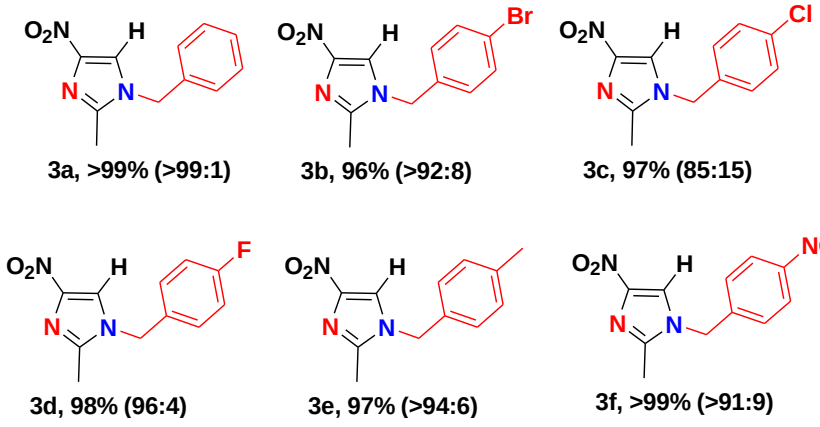



**Scheme 2.** *N*-Benzylation of 4(5)-Nitro-1H-imidazole[a]

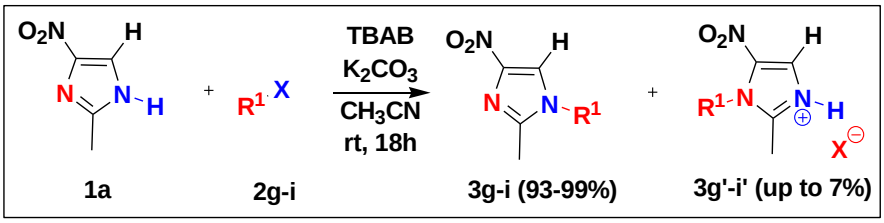
[a]Reaction conditions: 1.0 equiv. of 1a, 1.2 equiv. of 4-$R^1$- $C_6H_4CH_2$-X ($C_6H_5CH_2Cl$ **2a**, 4-Br-$C_6H_4CH_2Br$ **2b**, 4-Cl-$C_6H_4CH_2Cl$ **2c**, 4-F-$C_6H_4CH_2Cl$ **2d**, 4-$CH_3$-$C_6H_4CH_2Br$ **2e**, 4-$NO_2$-$C_6H_4CH_2Br$ **2f**), 0.02 equiv. of TBAB, 2 equiv. of $K_2CO_3$, 12mL $CH_3CN$, rt.

**Table 1:** $N^1$-Benzylation of 4(5)-Nitro-1H-imidazole

| Entry | Product mixture | Yield (%) | Product composition[b] | |
|---|---|---|---|---|
| | | | 4-$NO_2$ | 5-$NO_2$ |
| 1 | 3a+3a´ | >99 | >99 | trace |
| 2 | 3b+3b´ | 96 | 92 | 8 |
| 3 | 3c+3c´ | 97 | 85 | 15 |
| 4 | 3d+3d´ | 98 | 96 | 4 |
| 5 | 3e+3e´ | 97 | 94 | 6 |
| 6 | 3f+3f´ | >99 | >91 | 9 |




[b]Determined by $^1$H NMR integration of the >N$CH_2$Ph resonance:[15] **3a** $\delta_H$ 5.09 (s), **3a´** $\delta_H$ 5.59 (s), **3b** $\delta_H$ 5.27 (s), **3b´** $\delta_H$ 5.76, 5.55 (s), **3c** $\delta_H$ 5.28 (s), **3c´** $\delta_H$ 5.53, 4.66 (s), **3d** $\delta_H$ 5.08 (s), **3d´** $\delta_H$ 5.53 (s), **3e** $\delta_H$ 5.07 (s), **3e´** $\delta_H$ 5.52 (s), **3f** $\delta_H$ 5.47 (s), **3f´** $\delta_H$ 5.73(s).

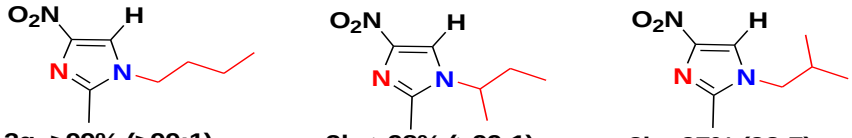



**Scheme 3.** $N^1$-Butylation of 4(5)-nitro-1H-imidazole[a]

[a]Reaction conditions: 1.0 equiv. of 1a, 1.2 equiv. of R-X (*n*-$C_4H_9Br$ **2g**, *sec*-$C_4H_9Br$ **2h**, *i*-$C_4H_9Br$ **2i**), 0.02 equiv. of TBAB, 2 equiv. of $K_2CO_3$, 12mL $CH_3CN$, rt.

**Table 2.** $N^1$-Alkylation of 4(5)-nitro-1*H*-imidazole

| Entry | Product mixture | Yield (%) | Product composition[b] | |
|---|---|---|---|---|
| | | | 4-$NO_2$ | 5-$NO_2$ |
| 1 | 3g+3g′ | .>99 | >99 | Trace |
| 2 | 3h+3h′ | >98 | >99 | trace[c] |
| 3 | 3i+3i′ | 97 | 93 | 7 |




[b]Determined by integration of the >N$CH_2$R (R = n-$C_3H_7$-; **3g**, i-$C_3H_7$-; **3i**) resonance: [15] (**3g** + **3g′**): $\delta_H$ 3.98, 3.97, 3.95 (t), **3i** $\delta_H$ 3.81, 3.80 (d), **3i′** $\delta_H$ 4.10, 4.13 (d) . [c]Determined by $^1$H NMR integration of the >N$CH$($R^1$)$R^2$ ($R^1$ = -$CH_3$, $R^2$ = -$C_2H_5$; **3h**) resonance: (**3h** + **3h′**): $\delta_H$ 4.24, 4.23, 4.22, 4.20, 4.19, 4.18 (sext.).

## Conclusion

To the best of our knowledge, $N^1$-alkylation of 4(5)-Nitroimidazoles has not been attempted so far to yield predominant and highly regioselective 4-Nitroimidazoles at room temperature. In the present method, we have developed a simple, highly regioselective $N^1$-alkylation of 2-Methyl-4(5)-nitroimidazole under milder conditions than the conventional ones. The interest of our methodology does not only reside in the excellent observed regioselectivity but also the attainability of regioisomer as a predominant product at room temperature. Cost effectiveness (as it involves less expensive chemicals) and eco-friendliness (as it utilizes green chemicals like ionic liquids and recomended greener solvents like Acetonitrile, Ethyl acetate) are the other added advantages of the present method. We strongly hope that this methodology will be an eye opener for the researchers to pursue this kind of research in the future, short reaction time, availability and low cost of the catalyst, easy and clean work-up, and high yields of products, we believe that this new procedure could be a useful addition to the available methodologies.

## Experimental

**Synthetic procedure for the synthesis of compounds 3a-g:** A mixture of 2-Methyl-4(5)-nitroimidazole **1a** (15.7mmol, 2.0g, 1.0eq), $K_2CO_3$ (31.4mmol, 4.339g, 2.0eq), tetrabutylammonium bromide **TBAB** (0.31mmol, 0.1g, 0.1eq) and acetonitrile (12mL) in a tightly closed RB-flask to prevent solvent evaporation and the reaction mixture was stirred vigorously at room temperature for 15mins. Then 4-substituted benzyl halides **2a-f**/*n*-butyl bromide **2g** (18.84mmol, 1.2eq) was added to this mixture and

continuously stirred for 18h. After the reaction was completed, then the inorganic salts were filtered off and washed with acetonitrile (3x2mL). The combined acetonitrile solution was allowed to evaporate slowly which then yielded residue of **3a-g** crystallized from ethyl acetate: ethanol (4:1).

**1-Benzyl-2-methyl-4-nitro-1*H*-imidazole (3a):** [19,26-27]: pale yellow crystals, yield (3.3918g, >99%), 104-106°C (*Lit.*[19]: 104-106°C, *Lit.*[26]: 106-107°C *Lit.*[27]: 104-105°C), Anal. calc. for $C_{11}H_{11}N_3O_2$, (217.23 g $mol^{-1}$): C, 60.82; H, 5.10; N, 19.34; O, 14.73, found: C, 59.40; H, 5.05; N, 19.37; O, 14.70%. IR (KBr, υ, $cm^{-1}$): 3096 (>C-H), 1604 (>C=C<), 1538, 1291, 831 (>C=N-), 1496, 1291 (-$NO_2$), 1143, 757 (>C-N). **$^1$H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.65 (s, 1H, C**H**$_{\text{Imidazole ring}}$), 7.39-7.37 (m, 3H, -C**H**$_{\text{phenyl ring}}$), 7.14, 7.12 (dd, 2H, -C**H**$_{\text{phenyl ring}}$), 5.58 (s, 2H, Ph-C**H**$_2$-N$^3$**<,** 5-$NO_2$-isomer**)**, 5.09 (s, 2H, Ph-C**H**$_2$-N$^1$**<)**, 3.37 (bs, >N**H**$^+$, 5-$NO_2$-isomer ), 2.39 (s, 3H, Im-C**H**$_3$). **$^{13}$C NMR** (400 MHz, $CDCl_3$, δ in ppm): 145.15 (Im-**$C_2$** + Im-**$C_4$**), 133.89 (Ph-**$C_1$**), 129.47 (Ph-**$C_3$** & Ph-**$C_5$**), 128.99 (Ph-**$C_2$** & Ph-**$C_6$**), 127.29 (Ph-**$C_4$**), 120.24 (Im-**$C_5$**), 51.05 (Ph-**C**H$_2$-N$^1$), 13.40 (Im–**C**H$_3$).

**1-(4-Bromobenzyl)-2-methyl-4-nitro-1*H*-imidazole (3b)**: reddish brown crystals, yield (4.4721g, 96%), 179-181°C, Anal. calc. for $C_{11}H_{10}BrN_3O_2$, (296.12 g $mol^{-1}$): C, 44.62; H, 3.40; N, 14.19; O, 10.81, found: C, 44.08; H, 3.95; N, 14.05; O, 10.76. IR (KBr, υ, $cm^{-1}$): 3131 (>C-H), 1598 (>C=C<), 1543, 1292, 840 (>C=N-), 1495, 1292 (-$NO_2$), 1150, 754 (>C-N). **$^1$H NMR** (500 MHz, DMSO-d$^6$, δ in ppm): 8.44 (s, 1H, C**H**$_{\text{Imidazole ring}}$, 4-$NO_2$-isomer), 8.31 (s, 1H, C**H**$_{\text{Imidazole ring}}$, 5-$NO_2$-isomer), 7.59-7.57 (m, 2H, -C**H**$^{3,5}_{\text{phenyl ring}}$), 7.24-7.22 (m, 2H, -CH$^{2,6}_{\text{phenyl ring}}$), 5.27 (s, 2H, Ph-C**H**$_2$-N$^1$**)**, 3.34 (bs, >N**H**$^+$, 5-$NO_2$-isomer ), 2.27 (s, 3H, Im-C**H**$_3$). **$^{13}$C NMR** (500 MHz, DMSO-d$^6$, δ in ppm): 145.43 (Im-**$C_4$**), 145.05 (Im-**$C_2$**), 135.04 (Ph-**$C_1$**), 131.82 (Ph-**$C_3$** & Ph-**$C_5$**), 129.66 (Ph-**$C_2$** & Ph-**$C_6$**), 122.49 (Ph-**$C_4$**), 121.31 (Im-**$C_5$**), 48.99 (Ph-**C**H$_2$-N$^1$<), 12.77 (Im–**C**H$_3$).

**1-(4-Cholorobenzyl)-2-methyl-4-nitro-1*H*-imidazole (3c)** [19]: yellowish brown crystals, yield (3.8412g, 97%), 178-180°C (*Lit.*[19]: not reported), Anal. calc. for $C_{11}H_{10}ClN_3O_2$, (251.67 g $mol^{-1}$): C, 52.50; H, 4.01; N, 16.70; O, 12.71, found: C, 53.07; H, 4.38; N, 16.91; O, 12.67. IR (KBr, υ, $cm^{-1}$): 3131 (>C-H), 1622 (>C=C<), 1537, 1292, 839 (>C=N-), 1493, 1292 (-$NO_2$), 1152, 754 (>C-N). **$^1$H NMR** (500 MHz, DMSO-d$^6$, δ in ppm): 8.44 (s, 1H, C**H**$_{\text{Imidazole ring}}$, 4-$NO_2$-isomer), 8.31 (s, 1H, C**H**$_{\text{Imidazole ring}}$, 5-$NO_2$-isomer), 7.46-7.44 (m, 2H, -C**H**$^{3,5}_{\text{phenyl ring}}$), 7.31-7.28 (m, 2H, -CH$^{2,6}_{\text{phenyl ring}}$), 5.28 (s, 2H, Ph-C**H**$_2$-N$^1$**)**, 3.33 (bs, >N**H**$^+$, 5-$NO_2$-isomer ), 2.27 (s, 3H, Im-C**H**$_3$). **$^{13}$C NMR** (500 MHz, DMSO-d$^6$, δ in ppm): 145.43 (Im-**$C_4$**), 145.04 (Im-**$C_2$**), 134.62 (Ph-**$C_1$**), 132.76 (Ph-**$C_4$**), 129.37 (Ph-**$C_3$** & Ph-**$C_5$**), 128.90 (Ph-**$C_2$** & Ph-**$C_6$**), 122.49 (Im-**$C_5$**), 48.93 (Ph-**C**H$_2$-N$^1$<), 12.77 (Im–**C**H$_3$).

**1-(4-Fluorobenzyl)-2-methyl-4-nitro-1*H*-imidazole (3d)**: yellowish brown crystals, yield (3.6304g, 98%), 104-106°C, Anal. calc. for $C_{11}H_{10}FN_3O_2$, (235.21 g $mol^{-1}$): C, 56.17; H, 4.29; N, 17.86; O, 13.60, found: C, 56.05; H, 4.06; N, 17.65; O, 13.67. IR (KBr, υ, $cm^{-1}$): 3099 (>C-H), 1542 (>C=C< + >C=N-), 1291, 822 (>C=N-), 1495, 1291 (-$NO_2$), 1141, 757 (>C-N). **$^1$H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.64 (s, 1H, C**H**$_{\text{Imidazole ring}}$), 7.15-7.06 (m, 2H, -C**H**$^{3,5}_{\text{phenyl ring}}$), 7.02-7.01 (d, 2H, -C**H**$_{\text{phenyl ring}}$), 5.53 (s, 2H, Ph-C**H**$_2$-N$^3$**<,** 5-$NO_2$-isomer**)**, 5.08 (s, 2H, Ph-C**H**$_2$-N$^1$**<,** 4-$NO_2$-isomer**)**, 2.39 (s, 3H, Im-C**H**$_3$). **$^{13}$C NMR** (400 MHz, $CDCl_3$, δ in ppm): 146.64 (Im-**$C_4$**), 145.04 (Im-**$C_2$**), 129.77, 129.74 (Ph-**$C_4$**), 129.32 (Ph-**$C_1$**), 129.24 (Ph-**$C_2$** & Ph-**$C_6$**), 116.76, 116.54 (Ph-**$C_3$** & Ph-**$C_5$**), 120.01 (Im-**$C_5$**), 50.36 (Ph-**C**H$_2$-N), 13.77, 13.41 (Im–**C**H$_3$).

**2-Methyl-1-(4-methylbenzyl)-4-nitro-1*H*-imidazole (3e)**: pale yellow crystals, yield (3.5217g, 97%), 115-117°C, Anal. calc. for $C_{12}H_{13}N_3O_2$, (231.25 g $mol^{-1}$): C, 62.33; H, 5.67; N, 18.17; O, 13.84, found: C, 61.91; H, 5.47; N, 18.34; O, 13.63. IR (KBr, υ, $cm^{-1}$): 3125 (>C-H), 1604 (>C=C<), 1538, 1291, 828 (>C=N-), 1495, 1291 (-$NO_2$), 1142, 756 (>C-N). **$^1$H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.61 (s, 1H, C**H**$_{\text{Imidazole ring}}$), 7.19-7.17 (d, 2H, -C**H**$^{2,6}_{\text{phenyl ring}}$), 7.03-7.01 (m, 2H, -C**H**$^{3,5}_{\text{phenyl ring}}$), 5.03 (s, 2H, Ph-C**H**$_2$-N$^1$**<)**, 2.39 (s, 3H, Im-C**H**$_3$), 2.34 (s, 3H, PhC$^4$-C**H**$_3$). **$^{13}$C NMR** (400 MHz, $CDCl_3$, δ in ppm): 145.06 (Im-**$C_2$** + Im-**$C_4$**), 139.07 (Ph-**$C_1$** + Ph-**$C_4$**), 130.80, 130.16 (Ph-**$C_3$** & Ph-**$C_5$**), 127.41 (Ph-**$C_2$** & Ph-**$C_6$**), 120.15 (Im-**$C_5$**), 50.87 (Ph-**C**H$_2$-N$^1$<), 21.21 (PhC$^4$-**C**H$_3$), 13.29 (Im–**C**H$_3$).

**2-Methyl-4-nitro-1-(4-nitrobenzyl)-1*H*-imidazole (3f)**: brown crystals, yield (4.0931g, >99%), 130-132°C, Anal. calc. for $C_{11}H_{10}N_4O_4$, (262.22 g $mol^{-1}$): C, 50.38; H, 3.84; N, 21.37; O, 24.40, found: C, 50.59; H, 3.45; N, 21.68; O, 24.67. IR (KBr, υ, $cm^{-1}$): 3113 (>C-H), 1604 (>C=C<), 1543, 1291, 829 (>C=N-), 1493, 1291 (-$NO_2$), 1141, 756 (>C-N). **$^1$H NMR** (400 MHz, DMSO-d$^6$, δ in ppm): 8.49 (s, 1H, C**H**$_{\text{Imidazole ring}}$, 4-$NO_2$-isomer), 8.31 (s, 1H, C**H**$_{\text{Imidazole ring}}$, 5-$NO_2$-isomer), 8.25-8.23 (m, 2H, -C**H**$^{3,5}_{\text{phenyl ring}}$), 7.51, 7.49

(m, 2H, -$CH^{2,6}_{\text{phenyl ring}}$), 5.46 (s, 2H, Ph-C**H**$_2$-N$^1$**)**, 3.35 (bs, >N**H**$^+$, 5-$NO_2$-isomer ), 2.27 (s, 3H, Im-C**H**$_3$). **$^{13}$C NMR** (400 MHz, DMSO-d$^6$, δ in ppm): 147.67 (Ph-**C$_4$**), 146.05 (Im-**C$_4$**), 145.73 (Im-**C$_2$**), 143.61 (Ph-**C$_1$**), 128.99 (Ph-**C$_2$** & Ph-**C$_6$**), 124.54 (Ph-**C$_3$** & Ph-**C$_5$**), 123.18 (Im-**C$_5$**), 49.48 (Ph-**C**H$_2$-N$^1$<), 13.21 (Im–**C**H$_3$).

**1-Butyl-2-methyl-4-nitro-1*H*-imidazole (3g)** [26]: pale yellow crystals, yield (2.8586g, >99%), 58-60°C (*Lit.*[26]: 58-59°C), Anal. calc. for $C_8H_{13}N_3O_2$, (183.21 g mol$^{-1}$): C, 52.45; H, 7.15; N, 22.94; O, 17.47, found: C, 52.22; H, 6.93; N, 23.11; O, 17.16. **$^1$H NMR** (DMSO-d$^6$, δ in ppm): 8.32 (s, 1H, C**H**$_{\text{Imidazole ring}}$), 3.98, 3.97, 3.95 (t, 2H, -C**H**$_2$-N**)**, 3.35 (bs, >N**H**$^+$, 5-$NO_2$-isomer ), 2.35 (s, 3H, Im-C**H$_3$**), 1.71-1.65 (quint., 2H, -$CH_2$-C**H**$_2$-$CH_2$-N$^1$<), 1.30-1.23 (sext., 2H, -$CH_3$-C**H**$_2$-$CH_2$-), 0.90-0.88 (t, 3H, C**H**$_3$-$CH_2$-). **$^{13}$C NMR** (DMSO-d$^6$, δ in ppm): 145.30 (Im-**C$_4$**), 144.85 (Im-**C$_2$**), 122.06 (Im-**C$_5$**), 46.15 (-**C**H$_2$-N$^1$), 31.52 (-$CH_2$-**C**H$_2$-$CH_2$N$^1$), 19.22, 19.05 (-**C**H$_2$-$CH_2$-$CH_2$N$^1$), 13.47, 13.40 (**C**H$_3$-$CH_2$-$CH_2$-$CH_2$N$^1$), 12.56 (Im–**C**H$_3$).

**Synthetic procedure for the synthesis of compounds 3h-i:**

A mixture of 2-Methyl-4(5)-nitroimidazole **1a** (15.7mmol, 2.0g, 1.0eq), $K_2CO_3$ (31.4mmol, 4.339g, 2.0eq), tetrabutylammonium bromide **TBAB** (0.31mmol, 0.1g, 0.1eq) and acetonitrile (12mL) in a tightly closed RB-flask to prevent solvent evaporation and the reaction mixture was stirred vigorously at room temperature for 15mins. Then 2-Bromobutane **2h** / 1-Bromo-2-methylpropane **2i** (18.84mmol, 1.2eq) was added to this mixture and continuously stirred for 18h. After the reaction was completed, then the inorganic salts were filtered off and washed with acetonitrile (3x2mL). The combined acetonitrile solution was allowed to evaporate slowly which yielded **3h-i.**

**1-*sec*-Butyl-2-methyl-4-nitro-1*H*-imidazole (3h):** light brown liquid, yield (>98%), Anal. calc. for $C_8H_{13}N_3O_2$, (183.21 g mol$^{-1}$): C, 52.45; H, 7.15; N, 22.94; O, 17.47, found: C, 52.59; H, 6.90; N, 22.75; O, 17.59. **$^1$H NMR** (DMSO-d$^6$, δ in ppm): 8.44 (s, 1H, C**H**$_{\text{Imidazole ring}}$), 8.02, 7.80 (s, 1H, C**H**$_{\text{Imidazole ring}}$, 5-$NO_2$-isomer), 4.24-4.18 (sext., 1H, -C**H**-N**)**, 3.43 (bs, >N**H**$^+$, 5-$NO_2$-isomer ), 2.17 (s, 3H, Im-C**H$_3$**), 1.79-1.71 (quint., 2H, $CH_3$-C**H**$_2$-CH-N$^1$<), 1.39, 1.38 (d, 3H, C**H**$_3$-CH-N$^1$<), 0.94-0.91, 0.76-0.73 (t, 3H, **C**H$_3$-$CH_2$-). **$^{13}$C NMR** (DMSO-d$^6$, δ in ppm): 146.02 (Im-**C$_4$**), 144.70 (Im-**C$_2$**), 119.03 (Im-**C$_5$**), 54.29 (-**C**H-N$^1$), 29.29 ($CH_3$-**C**$H_2$-CHN$^1$), 20.68 (**C**$H_3$-CHN$^1$), 12.85 (Im–**C**$H_3$), 10.22 (**C**$H_3$-$CH_2$-).

**1-Isobutyl-2-methyl-4-nitro-1*H*-imidazole (3i):** brown viscous oil, yield (97%), Anal. calc. for $C_8H_{13}N_3O_2$, (183.21 g mol$^{-1}$): C, 52.45; H, 7.15; N, 22.94; O, 17.47, found: C, 51.98; H, 7.79; N, 22.52; O, 17.38. **$^1$H NMR** (DMSO-d$^6$, δ in ppm): 8.29 (s, 1H, C**H**$_{\text{Imidazole ring}}$), 8.03 (s, 1H, C**H**$_{\text{Imidazole ring}}$, 5-$NO_2$-isomer), 3.81, 3.80 (d, 2H, -C**H**$_2$-N**)**, 3.50 (bs, >N**H**$^+$, 5-$NO_2$-isomer ), 2.34 (s, 3H, Im-C**H$_3$**), 2.07-1.97 (n, 1H, -C**H**- $CH_2$N$^1$<), 0.93, 0.91 (d, 6H, **C**$H_3$-CH-). **$^{13}$C NMR** (DMSO-d$^6$, δ in ppm): 145.31 (Im-**C$_4$**), 145.02 (Im-**C$_2$**), 122.35 (Im-**C$_5$**), 53.21 (-**C**$H_2$-N$^1$), 28.76 ($CH_3$-**C**H-$CH_2$N$^1$), 19.23 (**C**$H_3$-CH-), 12.67 (Im–**C**$H_3$).

**Acknowledgements**

The authors thank the Principal and the management of the Sir Theagaraya College, Chennai-21 and L. N. Government College, Ponneri for the constant support and encouragement rendered. The authors also thank the Department of Physics, Alagappa University, Karaikudi for FT-IR spectral studies. The authors wish to thank the SAIC, Tezpur University, Tezpur, Assam and SAIF, IIT Bombay, Mumbai for elemental analysis and NMR spectral studies.

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