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Synthesis, Spectroscopic and Structural Studies of New 2-Substituted 4-Nitroimidazoles

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Abstract: This study describes the synthesis of novel 4-nitro-2-substitutedimidazole derivatives *via* a transposition reaction of nitro group. Conversion of 5-nitro-2-phenylethanol (styryl) imidazole derivatives into the corresponding 4-nitroisomers was achieved in good yields in nitrobenzene using a catalytic amount of methyl iodide. Spectroscopic study and single crystal X-ray structures are reported for five compounds to understand the conformational structures of these compounds.

Keywords: Transposition reaction, 4-nitroimidazole, 5-nitroimidazole, crystal structure.

INTRODUCTION

Nitroimidazoles and their derivatives have drawn a continuing interest over the years due to their varied biological activities. 5-Nitroimidazoles are commonly used in medicine, and some of them have been extensively investigated for hypoxia-selective cytotoxicity and hypoxic cell radiosensitization in *in vitro* and *in vivo* studies [1].

The 5-nitroimidazole derivatives generally possess a significant biological activity. However, only few properties of 4-nitroimidazole derivatives have been reported [2]. This could be the result of the few available synthetic methods of 4-nitroimidazole derivatives.

Nitration of 1, 2-disubstitutedimidazoles leads to a mixture of 4-nitro and 5-nitro derivatives, [3] and the presence of various substituents at second position does not change the direction of nitration [4]. For example, the nitration of 2-ethylimidazole, [5] 2-isopropylimidazole, [6] and 2-styrylimidazole [7] takes place similarly.

The transposition of nitro group in 5-nitroimidazoles is described in the literature and represents an efficient synthetic procedure of 4-nitroisomer [8]. However, only few examples of this reaction are described using methyl iodide [8b].

In order to enlarge the known transposition reaction of nitro group to other substituted 5-nitroimidazole derivatives, we describe herein an efficient and selective procedure for the preparation of 4-nitro-2-phenylethanol (styryl) imidazole by a transposition reaction. The structures of prepared compounds were established and examined by NMR spectroscopy and by X-ray diffraction.

Initially, 2-(1-methyl-5-nitro-1*H*-imidazol-2-yl)-1-phenyl ethanol **2a** was prepared by reacting 1,2-dimethyl-5-nitro-1*H*-imidazole **1** with benzaldehyde, as preferred aromatic aldehyde in condensation reaction, in the presence of potassium hydroxide in ethanol at room temperature. The (*E*)-1-methyl-5-nitro-2-styryl-1*H*-imidazole **3a** was easily obtained by acid catalyzed dehydration of the corresponding compound **2a**, in glacial acetic acid (Scheme **1**) [9].

The transposition reaction of 2-(phenylethanol)-5-nitroimidazole **2a** and 2-styryl-5-nitroimidazole **3a**, realized in nitrobenzene in the presence of catalytic amount of methyl iodide, was selected as a model reaction for catalyst evaluation (Scheme **1**).

The results showed that no reaction took place at room temperature. However, after 24h at 160 °C, in minimum volume of nitrobenzene, the starting material **2a** or **3a** had been consumed (TLC) and quantitative yields of products **4a** or **5a** were obtained without the need of chromatographic separation. The 4-nitroimidazoles **4a** and **5a** are isolated, by simple filtration after addition of hexane/Et_2O mixture, in 89 and 94%, respectively.

Note that this method furnishes compound **5a** in high yield compared to the previously reported reaction involving the addition of $\dot{C}Br_3$ radical as catalyst (65%) [8b].

The proposed mechanism is similar to the previously reported one for the transposition of 1,2-dimethyl-5-nitroimidazole using methyl iodide as catalyst. It is clear that the thermal decomposition of the 1,2,3-trimethyl-5-nitroimidazolium entity during the transformation with elimination of a

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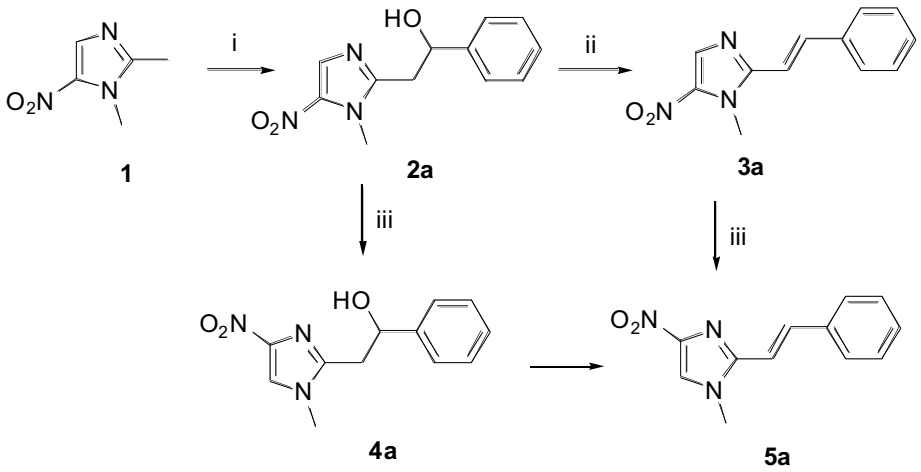
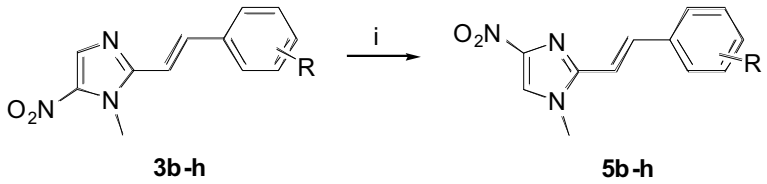


Scheme 1. Reagents and conditions: (i) benzaldehyde (3 equiv), KOH, EtOH, rt, 48h; (ii) AcOH, H_2SO_4, 110 °C, 18h; (iii) methyl iodide (0.1 equiv), nitrobenzene, 160 °C, 24h.



Scheme 2. Reagents and conditions: (i) methyl iodide (0.1 equiv), nitrobenzene, 160 °C, 24h.

methyl group leads to the formation of the 4-nitroimidazole structure [8b].

Encouraged by these results, and to demonstrate the efficiency and the scope of the present method, we performed the intramolecular transposition reaction using various substitutions on the aromatic phenyl ring.

As shown in (Table **1**), substrates **3b-h** containing aromatic nucleus with electron-withdrawing groups (such as halide) or electron-donating groups (such as methoxy or methyl), gave the corresponding products **5** in good to high yields under the same reaction conditions. No obvious effects resulting from the electronic or steric nature of the aromatic ring substituents were observed.

Most studies of nitroimidazoles are focused on the synthesis and biological activity, but only a few studies are concentrated to understand the conformational structures of these compounds.

Structures of products **2a**, **3a**, **4a**, and **5a** were confirmed by means ^{1}H, ^{13}C-NMR spectroscopy and X-ray single crystal diffraction. Spectroscopic results were in full agreement with literature report [10] and chemical shifts data of selected atoms in 1-methyl-2-substituted-4- and 5-nitroimidazoles are summarized in (Tables **2** and **3**).

The analysis shows that the values for the ring carbon atoms and protons are definitive for the groups of compounds and can be used to assign unambiguously the position of the nitro group.

In ^{1}H NMR spectroscopy, the 1-methyl group protons appeared, for 5-nitroimidazole derivatives **2a** and **3a** at low field (Table **2**) relative to the corresponding 4-nitroimidazole **4a** and **5a** respectively (Table **3**). This can be explained by the greater de-shielding effect of the 5-nitro group as compared with 4-position. However, in ^{13}C NMR, no significant differences were observed in the chemical shifts of the methyl carbon atom for the two isomers.

Chemical shifts of carbon C_5 are about 124 ppm for the 4-nitro derivatives (compounds **4a** and **5a**) and 139 ppm for the 5-nitro isomers (**2a** and **3a**), whereas chemical shifts for carbon C_4 are around 146 ppm for the 4-nitro and 133 ppm for the corresponding 5-nitro isomer. The chemical shift of C_2 atom is also dependent on the location of the nitro substituent. Thus in 5-nitroimidazole series (Table **2**), it is at some 5-7 ppm more downfield than that in the corresponding 4-nitroimidazole (Table **3**).

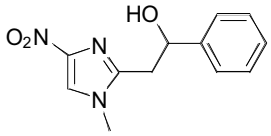
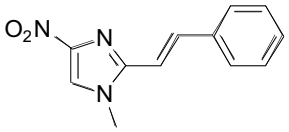
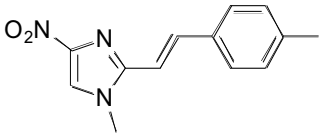
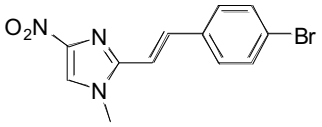
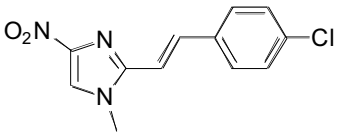
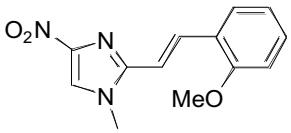
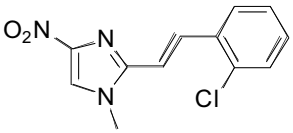
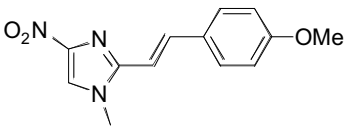
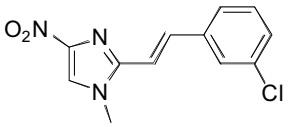
X-ray crystallographic analyses of compounds **2a**, **3a**, **4a** and **5a** were carried out to examine the influence of the nitro substituent on the molecular structure of the imidazole ring. Moreover, the structures of nitroimidazoles have been studied more thoroughly and can explain wide applications of these compounds, especially in medicine.

Suitable crystals for X-ray experiments of compounds **1**, **2a**, **3a**, **4a** and **5a** were obtained by slow evaporation from a water/methanol or isopropanol solution at room temperature. X-ray single-crystal structures of compounds **1** have been shown in (Fig. **1**), those of compounds **2a** and **3a**, in (Fig. **2**) and those of **4a** and **5a** in (Fig. **3**) [11].

Selected geometry details of compounds **1**, **2a**, **3a**, **4a** and **5a** are presented in (Table **4**). Compound **1** is composed of 1-methylimidazole bearing at C2 a methyl group and a nitro group at C5 atom.

The bond lengths of 1,2-dimethyl-5-nitroimidazole **1** have been compared with the corresponding ones of Bis(2-methylimidazol-1-yl)methane[12]. This examination shows that the bond lengths of N1-C2, N3-C4 and N1-C1 in the

Table 1. Methyl Iodide Catalyzed Transposition of Nitro Group

Compounds	Product	Yield (%)[a]
4a		89
5a		94
5b		94
5c		96
5d		97
5e		83
5f		95
5g		88
5h		94

[a] Yields of isolated pure products from transposition reaction of **2a** and **3a-h**

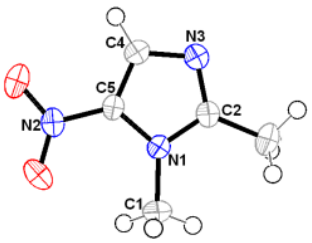
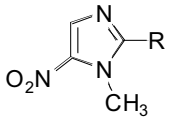


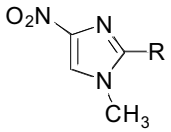
Fig. (1). ORTEP plot of the X-ray crystal structure of **1**. Displacement ellipsoids are drawn at the 50% probability level [11].

Table 2. ^{13}C (^{1}H) NMR Chemical Shifts of 2-substituted-5-nitroimidazole



Compound	R	Chemical Shifts (δ) Values			
		1-CH_3	C_2	C_4	C_5
2a	$CH_2CH(OH)Ph$	33.7(3.75)	152.3	132.9	139.1
3a	CH=CH-Ph	33.2(4.04)	150.2	134.6	139.5

Table 3. ^{13}C (^{1}H) NMR Chemical Shifts of 2-substituted-4-nitroimidazole



Compound		Chemical shifts (δ) values			
	R	1-CH_3	C_2	C_4	C_5
4a	$CH_2CH(OH)Ph$	33.9(3.58)	147.0	145.6	123.5
5a	CH=CH-Ph	33.9(3.86)	145.4	146.4	124.2

imidazole ring are practically unchanged when the nitro group is introduced into position 5.

The incorporation of an NO_2 group affects the valence angles of the imidazole cycle [13]. This variation is caused by electron-acceptor effect of the nitro group (see Table **4**). The examination of valence angles of compound **1** shows an increasing of the angle C4-C5-N1 as well as a decreasing of the adjacent angle N3-C4-C5 compared with Bis(2-methylimidazol-1-yl)methane.

Series of compounds **2a (4a)** and **3a (5a)** are composed of 1-methylimidazole bearing at C2 a phenylethanol or a styryl fragment, and a nitro group at C5 (C4) atom. X-ray analysis data of the compounds **2a**, **3a**, **4a** and **5a** given in (Table **4**) indicate that the five-membered ring of 4 or 5-nitroimidazole is planar, while the nitro group is slightly rotated by 2.15(1)°, 5.03(12)°, 6.06(1)° and 1.33(9)°, respectively with respect to the imidazole cycle.

The bond lengths of 4 or 5-nitroimidazole unit have been compared with the corresponding ones of Bis(2-methylimidazol-1-yl)methane. The bond lengths of C4-C5, C2-N3 of both 5-nitro-2-substitutedimidazoles (**2a** and **3a**) or their 4-isomers (**4a** and **5a**), are longer than that in Bis(2-methylimidazol-1-yl)methane. Similarly, the location of nitro group influences the bond length of C_5-N_1. Indeed, the C5-N1 bond length in the Bis(2-methylimidazol-1-yl)methane is 1.374(3)Å, which is longer than the corresponding one in 4-nitroimidazole derivatives (for **4a**, 1.3559(16)Å and 1.3595(16)Å for **5a**), but shorter than that in 5-isomers (for **2a**, 1.3848(16)Å and 1.376(2)Å for **3a**).

Fig. (2). ORTEP plot of the X-ray crystal structure of 5-nitroimidazoles **2a** and **3a**. Displacement ellipsoids are drawn at the 50% probability level [11].

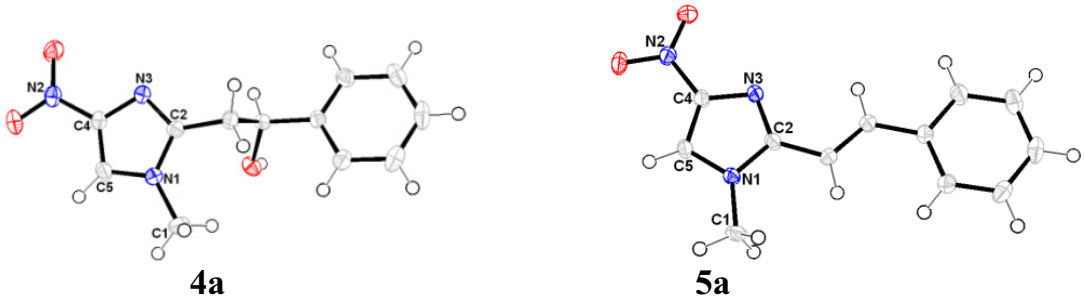


Fig. (3). ORTEP plot of the X-ray crystal structure of 4-nitroimidazoles **4a** and **5a**. Displacement ellipsoids are drawn at the 50% probability level [11].

Table 4. Selected Bonds and Angles for Characterized Compounds

Bonds Lengths	1	2a	3a	4a	5a	Bis(2-methylimidazol-1-yl)methane
N1-C2	1.3571(19)	1.3524(15)	1.358(2)	1.3680(17)	1.3752(15)	1.362(2)
C2-N3	1.3367(19)	1.3409(16)	1.345(2)	1.3225(16)	1.3272(16)	1.309(3)
N3-C4	1.361(2)	1.3545(17)	1.348(2)	1.3649(16)	1.3570(15)	1.368(3)
C4-C5	1.3679(19)	1.3647(18)	1.370(2)	1.3561(18)	1.3736(17)	1.341(3)
C5-N1	1.3824(18)	1.3848(16)	1.376(2)	1.3559(16)	1.3595(16)	1.374(3)
N1-C1	1.4712(18)	1.4724(16)	1.466(2)	1.4656(16)	1.4631(15)	1.445(2)
Bands Angles						
N1-C2-N3	112.22(14)	111.97(10)	111.69(16)	111.08(11)	111.49(10)	110.62(16)
C2-N3-C4	105.68(12)	105.95(10)	105.67(14)	103.90(10)	103.81(10)	105.69(15)
N3-C4-C5	109.40(13)	109.29(11)	109.86(15)	112.59(11)	112.89(11)	111.0(2)
C4-C5-N1	107.51(13)	107.65(11)	107.28(15)	104.42(11)	104.11(11)	105.35(17)
C5-N1-C2	105.19(12)	105.14(10)	105.49(14)	108.01(11)	107.70(10)	107.29(15)

It is interesting to note that the bond lengths of both C4-C5 and N1-C1 are practically equal in the two isomers series. However, the N1-C2 and N3-C4 are longer in 4-nitro-2-substitutedimidazoles than in 5-isomers, for the two series.

The others two C-N bond lengths in both for 5-nitroimidazole, C2-N3 (1.3409(16)Å), and C5-N1 (1.3848(16)Å) for **2a**, and for **3a**, C2-N3 (1.345(2)Å), C5-N1 (1.376(2)Å) are longer than the corresponding bonds in 4-nitroimidazoles (for **4a**, C2-N3 1.3225(16)Å, C5-N1 1.3559(16)Å, and C2-N3 1.3272(16)Å, C5-N1 1.3595(16)Å for **5a**).

An increase of the valence angle in the 4 or 5-nitroimidazole ring of the carbon atom bearing the nitro group (C4 or C5, respectively) as well as a decrease of the adjacent angles (C5 or C4, respectively), were observed for the 2-substituedimidazole derivatives **4a** and **5a** compared with Bis(2-methylimidazol-1-yl)methane. Consequently, the two adjacent angles to C4 and C5 (C5-N1-C2 and C4-N3-C2) are affected. Similar effect was observed in others nitro-imidazoles [14]. However, the valence angles N1-C2-N3 in 5 or 4-nitro-2-substitutedimidazole derivatives are not changed and are similar to those observed in Bis(2-methylimidazol-1-yl)methane. In summary, these spectroscopic data provide a

direct indication of the location effect of the nitro group on the structural features of the imidazole nucleus.

In conclusion, we have elaborated an effective synthetic pathway toward unknown 4-nitro-2-phenylethanol or styryl imidazole derivatives by reaction of methyl iodide with the corresponding 5-nitroisomers, which could be prepared independently by simple methods in high yields. ^{1}H, and ^{13}C-NMR and X-ray crystallographic analysis of the nitrated compounds revealed that their molecular structures were affected by the position of the nitro group. These routes may contribute to the synthesis of novel 4-nitroisomer derivatives and may open new ways for their utilization in bioorganic science. The structural information is potentially useful for a further derivatization of these compounds.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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[11] Crystal structure analysis for **1:** $C_5H_7N_3O_2$, Mr = 141.14 g.mol^{-1}, orthorhombic, space group P m c n, a = 6.4401(4) Å, b = 9.2017(8) Å, c = 10.8633(7) Å, α = 102.732(3)°, V = 643.76(8) Å^3, Z = 4, ρ_c= 1.456 g.cm^3, F(000) = 296, crystal size: 0.34 x 0.24 x 0.13 mm. Crystal structure analysis: for **2a**: $C_{12}H_{13}N_3O_3$, Mr = 247.25 g.mol^{-1}, monoclinic, space group P 2_1/n, a = 7.5076(5) Å, b = 10.1643(6) Å, c = 15.2589(9) Å, β = 95.080(2)°, V = 1159.83(12) Å^3, Z = 4, ρ_c= 1.416 g.cm^3, F(000) = 520, crystal size: 0.38 x 0.29 x 0.15 mm. Crystal structure analysis for **3a:** $C_{12}H_{11}N_3O_2$, Mr = 229.24 g.mol^{-1}, monoclinic, space group P 2_1/n, a = 6.4969(5) Å, b = 12.3713(10) Å, c = 13.7871(8) Å, β = 102.732(3)°, V = 1080.89(14)Å^3, Z = 4, ρ_c= 1.409 g.cm^3, F(000) = 480, crystal size: 0.38 x 0.16 x 0.11 mm. Crystal structure analysis: for **4a**: $C_{12}H_{13}N_3O_3$, Mr = 247.25 g mol^{-1}, monoclinic, space group P 2_1/c, a = 9.5950(9) Å, b = 12.0748(14) Å, c = 10.5260(8) Å, β = 99.555(3)°, V = 1202.6(2) Å^3, Z = 4, ρ_c=1.366 g.cm^3, F(000) = 520, crystal size: 0.33 x 0.3 x 0.3 mm. Crystal structure analysis: for **5a**: $C_{12}H_{11}N_3O_2$, Mr = 229.24 g mol^{-1}, triclinic, space group P -1, a = 6.7430(3) Å, b = 7.2223(3) Å, c = 11.6924(5) Å, α = 94.535(2)°, β = 104.866(2)°, γ = 98.808(2)°,V = 539.68(4) Å^3, Z = 2, ρ_c=1.411 g.cm^3, F(000) = 240, crystal size: 0.34 x 0.19 x 0.07 mm. Crystallographic data (excluding structure factors) for these compounds have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 920910 for **1**, CCDC 901753 for **2a**, CCDC 901751 for **3a**, CCDC 901752 for **4a** and CCDC 901754 for **5a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif./cif.

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