Isomerization of 4-Bromo-2-methyl-5-nitro-1-phenacylimidazoles into 5-Bromo-2-methyl-4-nitro-1-phenacylimidazoles

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Received February 18th, 1998, respectively November 1st, 1998

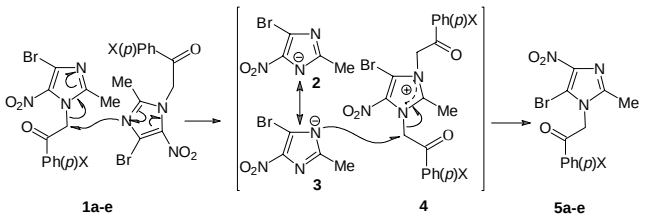
Keywords: Heterocycles, Isomerizations, Nitrogen heterocycles, Rearrangement, Imidazoles

Abstract. 4-Bromo-2-methyl-5-nitro-1-phenacylimidazoles (**1a**–**e**) dissolved in EtOH in presence of sodium bicarbonate (or without it) heated under reflux were isomerized into 5-bromo-2-methyl-4-nitro-1-phenacylimidazoles (**5a**–**e**). The structures of **5a**–**e** were assigned using SFORD (Single Frequency Off Resonance Decoupling) and COLOC (Correlation Spectroscopy for Long Range Coupling) NMR techniques. A conceivable mechanism of isomerization is discussed.

Nitroimidazoles have been widely applied, particularly as antibacterial agents [1–2].

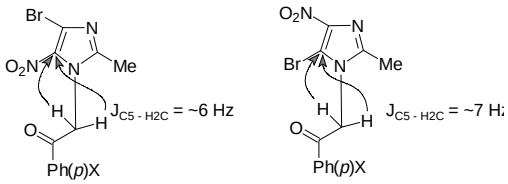
Metronidazole [3] [1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole] and Tinidazole [4] {1-[2-(ethylsulfonyl)ethyl]-2-methyl-5-nitroimidazole} are used as a clinical effective trichomon-acides.The 4-nitroisomers have gained pharmacological significance as immunosuppressants [5], aldehyde dehydrogenase inhibitors [6], potential radiosensitizers [7], and radiotherapy synergists [8, 9].

In the previous paper [10] we presented a synthesis of some 4-bromo-2-methyl-5-nitro-1-phenacylimidazoles and 5-bromo-2-methyl-4-nitro-1-phenacylimidazoles. After separation by column chromatography, isomers were crystallized from ethanol. On crystallization of 4-bromo-2-methyl-5-nitro-1-phenacylimidazoles (chromatographically pure) we observed some 5-bromo-4-nitroisomers. In the present paper the rearrangement of 4-bromo-2-methyl-5-nitro-1-phenacylimidazoles to 5-bromo-2-methyl-4-nitro-1-phenacylimidazoles is shown.



Compounds **1a**–**e** were heated under reflux in ethanol (90% v/v) with or without catalytic amounts of a base (sodium hydrogen carbonate). Under these conditions 4-nitro isomers **5a**–**e** were formed with good yields (over 80%, see Table 1).

The structures of the isomers thus obtained were confirmed by comparison with authentic samples reported earlier [10]. The ^{13}C NMR spectra of compounds **1a**–**e** and **5a**–**e** revealed significantly different chemical shift values for the imidazole carbons [11]. The values of chemical shifts of carbon atoms substituted with the nitro group were 150 and 143 ppm, respectively, and lower for the substitution with bromine atom: 119 ppm and 107 ppm, respectively. The differences alone did not allowns to assign the structures of **1a**–**e** and **5a**–**e**. The structural assignments are based on SFORD (Single Frequency Off Resonance Decoupling) and COLOC (Correlation Spectroscopy for Long Range Coupling) techniques. Also X-ray diffraction studies were performed for selected compounds (**1c** and **5c**). The results were reported in ref. [12]. The coupling constants for the C**H**$_2$ phenacyl moiety and C-5 of the imidazole ring determined by the SFORD method were: ~ 7 Hz for compounds **1a-e** and ~ 6 Hz for **5a**–**e**. No coupling of the C**H**$_2$ group protons with C-4 imidazole rings were detected.



A similar isomerization of 1-[2-(alkylsulfonyl)ethyl]-2-methyl-5-nitroimidazole (*e.g.* Tinidazole) into the 4-nitroisomer was reported by Rao *et al*. [13]. According to the literature, the 4-nitro isomer is thermodynamically more stable [14–16] than the corresponding 5-nitro isomer. The isomerization of **1a**–**e** to **5a**–**e** is suggested to proceed *via N*-dealkylation of phenacyl moiety, followed by *N*-realkylation on the other nitrogen. The suggested mechanism of isomerization is will be subject to further examinations.

Experimental

The structures of the isolated compounds were confirmed by a comparison of TLC, melting points, and NMR data with the data for the compounds obtained earlier [10]. Melting points were taken on a Boëtius apparatus and are corrected. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 300VT spectrometer. Chemical shifts (δ) are given in ppm relative to TMS. All reactions were monitored by TLC car-

  1436-9966/99/3410X-179 $ 17.50 + .50/0

Table 1 4-Bromo-2-methyl-5-nitro-1-phenacylimidazoles (**1a–e**) and 5-Bromo-2-methyl-4-nitro-1-phenacylimidazoles (**5a–e**)

Entry	X	lit. *m.p.*(°C) *m.p.* (°C)	Yield (%) method **a**	 **b**	R_F Lit. R_F[a]) ($CHCl_3$)	^{1}H NMR (300 MHz,DMSO-6d) ^{13}C NMR (75 MHZ,DMSO-6d) , δ(ppm):
1a	H	138–139 [a])	–	–	0.48 [a])	^{1}H: 8.87–7.71 (m, 5H, ArH), 5.86 (s, 2H, **C**H$_2$), 2.27 (s, 3H, C**H**$_3$); ^{13}C: 191.38 (C=O), 147,41 (C5 Im), 140.73 (C4 Ph), 133.63 (C2 Im),132.34 (C1 Ph) 130.94 (C2 and C6 Ph), 129.92 (C3 and C5 Ph), 118.96 (C4 Im), 53.32 (CH$_2$), 13.81 (CH$_3$).
1b	F	142–143 [a])	–	–	0.40 [a])	^{1}H: 8.21–7.31 (m, 4H, ArH), 5.59 (s, 2H, **C**H$_2$), 2.32 (s, 3H, C**H**$_3$); ^{13}C: 190.41 (C=O), 165.95 (C4 Ph), 149.80 (C5 Im), 134.17 (C2 Im), 131.37 (C2 and C6 Ph), 130.85 (C1 Ph), 116.35 (C3 and C5 Ph), 115. 91 (C4 Im), 53.25 (CH$_2$), 13.58 (CH$_3$).
1c	Cl	156–157 [a])	–	–	0.42 [a])	^{1}H: 8.18-7.72 (m, 4H, ArH), 5.97 (s, 2H, (**C**H$_2$), 2.39 (s, 3H, C**H**$_3$); ^{13}C: 190.26 (C=O), 150.21 (C5 Im), 139.35 (C4 Ph), 134.99 (C2 Im), 132.60 (C1 Ph), 130.16 (C2 and C6 Ph), 129.15 (C3 and C5 Ph), 119.74 (C4 Im), 53.48 (CH$_2$), 13.72 (CH$_3$).
1d	Br	172–173 [a])	–	–	0.41 [a])	^{1}H: 8.07–7.46 (m, 4H, ArH), 5.78 (s, 2H, **C**H$_2$), 2.28 (s, 3H, C**H**$_3$); ^{13}C: 190.43 (C=O), 149.84 (C5 Im), 135.21 (C2 Im), 132.77 (C1 Ph), 132.15 (C3 and C5 Ph), 130.47 (C2 and C6 Ph), 128.69 (C4 Ph), 119.67 (C4 Im), 53.38 (CH$_2$), 13.69 (CH$_3$).
1e	I	182–183 [a])	–	–	0.39 [a])	^{1}H: 8.23–7.81 (m, 4H, ArH), 5.43 (s, 2H, **C**H$_2$), 2.25 (s, 3H, C**H**$_3$); ^{13}C: 190.47 (C=O), 150.32 (C5 Im), 138.00 (C3 and C5 Ph), 134.98 (C2 Im), 132.97 (C1 Ph), 130.03 (C2 and C6 Ph), 119.49 (C4 Im), 103.74 (C4 Ph) 53.38 (CH$_2$), 13.69 (CH$_3$);
5a	H	189–190 [a]) 189–190	86	72	0.35 [a]) 0.35	^{1}H: 8.76–7.64 (m, 5H, ArH), 5.97 (s, 2H, **C**H$_2$), 2.27 (s, 3H, C**H**$_3$); ^{13}C: 191.62 (C=O), 146.72 (C2 Im), 143.36 (C4 Im), 140.12 (C4 Ph), 132.70 (C1 Ph), 130.86 (C2 and C6 Ph), 129.96 (C3 and C5 Ph), 107.22 (C5 Im), 54.48 (CH$_2$), 13.75 (CH$_2$).
5b	F	194–195 [a]) 194–195	83	74	0.27 [a]) 0.27	^{1}H: 8.21–7.31 (m, 4H, ArH), 5.59 (s, 2H, **C**H$_2$), 2.32 (s, 3H, C**H**$_3$); ^{13}C: 190.63 (C=O), 165.75 (C4 Ph), 146.21 (C2 Im), 143.64 (C4 Im), 131.27 (C2 and C6 Ph), 130.87 (C1 Ph) 116.49 (C3 and C5 Ph), 107.32 (C5 Im), 52.45 (CH$_2$), 13. 69 (CH$_3$).
5c	Cl	212–213 [a]) 211–212	91	81	0.32 [a]) 0.32	^{1}H:8.11–7.08 (m, 4H, ArH), 6.02 (s, 2H, **C**H$_2$), 2.44 (s, 3H, C**H**$_3$); ^{13}C: 190.36 (C=O), 146.97 (C2 Im), 142.76 (C4 Im), 139.61 (C4 Ph), 132.64 (C1), 130.29 (C2 and C6 Ph), 129.11 (C3 and C5 Ph), 107.63 (C5 Im), 52.67 (CH$_2$), 13.70 (CH$_3$).
5d	Br	221–223 [a]) 221–222	88	79	0.24 [a]) 024	^{1}H: 8.02–7.38 (m, 4H, ArH), 5.93 (s, 2H, **C**H$_2$), 2.34 (s, 3H, C**H**$_3$); ^{13}C: 190.91 (C=O), 146.56 (C2 Im), 143.29 (C4 Im), 132.79 (C1 Ph), 132.11 (C3 and C5 Ph), 130.52 (C2 and C6 Ph), 128.66 (C4 Ph), 107.34 (C5 Im), 52.36 (CH$_2$), 13.71 (CH$_3$).
5e	I	131–132 [a]) 132–133	72	68	0,21 [a]) 0.21	^{1}H: 8.26–7.85 (m, 4H, ArH), 5.48 (s, 2H, **C**H$_2$), 2.29 (s, 3H, C**H**$_3$); ^{13}C: 190.11 (C=O), 146.60 (C2 Im), 143.31 (C4 Im), 138.13 (C3 and C5 Ph), 132.93 (C1 Ph), 130.04 (C2 and C6 Ph), 107.74 (C5 Im), 103.72 (C4 Ph), 53.38 (CH$_2$), 13.69 (CH$_3$).

[a]) Ref. [10]

ried out on Merck Kieselgel 60 F_{254} on aluminium. Visualization was accomplished by UV light. All reagents and solvents were purchased from Aldrich and were used without additional purification.

5-Bromo-2-methyl-4-nitro-1-phenacylimidazoles (5a–e) (General Procedure)

Method a: 4-Bromo-2-methyl-5-nitro-1-phenacylimidazoles **1a–e** (0.5 mmole) were refluxed in ethanol (100 ml – 90%) for 3 h. About 70% of the solvent was evaporated under reduced pressure. The concentrated solution was kept overnight in a refrigerator. After filtration the solid material was recrystallized from ethanol to yield products **5a–e.**

Method b: To a solution of 4-bromo-2-methyl-5-nitro-1-phenacylimidazoles **1a–e** (0.5 mmole) in ethanol (10 ml – 90%) sodium bicarbonate (0.001 g, 0.012 mmole) was added, and the mixture was refluxed for 2 h with stirring. Ethanol was evaporated to dryness *in vacuo*. The residue was recrystallized from ethanol to yield products **5a–e**. Analytical data and yields are shown in the Table 1.

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