

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

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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

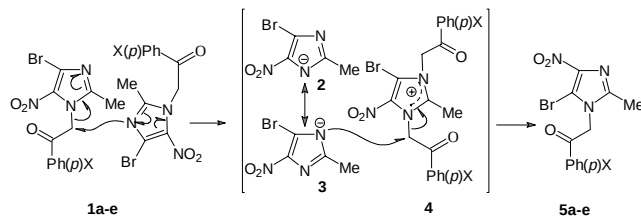
Frequency Off Resonance Decoupling) and COLOC (Correlation Spectroscopy for Long Range Coupling) NMR techniques. A conceivable mechanism of isomerization is discussed.

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].

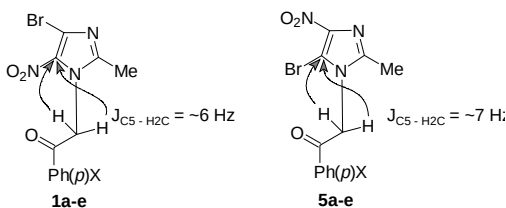
In the previous paper [10] we presented a synthesis of some 4-bromo-2-methyl-5-nitro-1-phenacylimidazoles and 5-bromo-2-methyl-4-nitro-1-phenacylimidazoles. After separation by column chromatography, isomers were crystallized from ethanol. On crystallization of 4-bromo-2-methyl-5-nitro-1-phenacylimidazoles (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.

119 ppm and 107 ppm, respectively. The differences alone did not allow 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 CH₂ 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 CH₂ group protons with C-4 imidazole rings were detected.



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 ¹³C 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:



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. ¹H and ¹³C 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-

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. <i>m.p.</i> (°C)	Yield (%)		<i>R_F</i> Lit. <i>R_F</i> ^{a)} (CHCl ₃)	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) ¹³ C NMR (75 MHz, DMSO- <i>d</i> ₆) , δ (ppm):
		<i>m.p.</i> (°C)	a	b		
1a	H	138–139 ^{a)}	–	–	0.48 ^{a)}	¹ H: 8.87–7.71 (m, 5H, ArH), 5.86 (s, 2H, CH ₂), 2.27 (s, 3H, CH 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, CH ₂), 2.32 (s, 3H, CH 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, CH ₂), 2.39 (s, 3H, CH ₃); ¹³ C: 190.26 (C=O), 150.21 (C5 Im), 139.35 (C4 Ph), 134.99 (C2 Im), 132.60 (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, CH ₂), 2.28 (s, 3H, CH 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, CH ₂), 2.25 (s, 3H, CH 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, CH ₂), 2.27 (s, 3H, CH 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 ₃).
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, CH ₂), 2.32 (s, 3H, CH 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, CH ₂), 2.44 (s, 3H, CH 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)} 0.24	¹ H: 8.02–7.38 (m, 4H, ArH), 5.93 (s, 2H, CH ₂), 2.34 (s, 3H, CH 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, CH ₂), 2.29 (s, 3H, CH 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 F₂₅₄ 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 recrystal-

lized from ethanol to yield products **5a–e**. Analytical data and yields are shown in the Table 1.

References

- [1] K. Maeda, T. Osato, H. Umezawa, J. Antibiot. **1953**, 6A, 182
- [2] H. Nakamura, Pharm. Bull. **1995**, 3, 379
- [3] D. Cosar, L. Julon, M. Benazet, Ann. Inst. Pasteur **1959**, 96, 238
- [4] C. E. Nord, Antimicrob. Chemother. (Suppl. A.) **1982**, 10, 35
- [5] P. Galanaud, Pharmacologie Clinique. Bases de la thérapeutique; P. J. Giroud, G. Mathe, Meyniel Expansion Scientifique, Paris 1978, p. 1781, Chem. Abstr. **1979**, 90, 81101s
- [6] R. Klink, K. G. R. Pachler, R. Gottschlich, Arzneim.-Forsch. **1985**, 35, 1220
- [7] J. Morgenstern, R. Otto, S. Scheithauer, Ger. (East) DD 260, 062, 14 Sept. 1988; Chem. Abstr. **1989**, 110, 231634r
- [8] S. Dische, M. I. Lee, I. R. Flockhart, Br. J. Cancer **1977**, 35, 567
- [9] T. H. Wasserman, J. Stetz, T. L. Phillips, Radiation sensitiz-

- ers – Their use in the Clinical Management of Cancer, Masson Publishing: New York, USA 1980, p. 387
- [10] S. Sobiak, Polish J. Chem. **1998**, 72, 78
- [11] D. E. Ewing, Org. Magn. Reson. **1979**, 12, 499
- [12] T. Borowiak, I. Wolska, M. Barylas, S. Sobiak, Acta Cryst. **1989**, C45, 449
- [13] A. K. S. B. Rao, R. S. Prasad, C. G. Rao, B. B. Singh, J. Chem. Soc., Perkin Trans. I **1989**, 1352
- [14] K. Hofman, Imidazole and its Derivatives, Part I, Interscience, New York, NY, 1953, p.132
- [15] A. R. Katritzky, C. W. Rees, E. F. V. Scrin, Comprehensive Heterocyclic Chemistry, Elsevier Science Inc. NY, 1996, p. 108
- [16] Schofield, M. R. Grimmet, M. R. Keene, Azoles, Cambridge University Press, 1977, p. 27

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