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Azoles 48 [1]: Synthesis of Some 4-Amino-2-methyl-5-nitro-1-phenacylimidazoles

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Summary. Reactions of 1-phenacyl derivatives of 2-methyl-4,5-dinitroimidazole with primary or secondary amines (aniline, morpholine, piperidine, pyrrolidine) yielded the 4-amino-5-nitroimidazole derivatives only.

Keywords. Nitroimidazoles; Isomers; NMR spectroscopy; Nucleophilic substitution.

Introduction

Imidazole and its nitro derivatives are known to show pharmacological activity. Numerous compounds from this group have been identified as antibacterial, antiprotozoic, antimycotic, immunosuppresive, and radiosensitizing agents [2]. It has been established that 5-nitro derivatives usually are more active than 4-nitro isomers. Our earlier investigations have been devoted to synthesis and antifungal as well as antibacterial properties of *N*-phenacyl-4,5-dinitroimidazole derivatives [3, 4]. In continuation of our studies, this work reports a convenient and general synthesis of 4-amino-5-nitroimidazoles with the phenacyl group at the 1-position using appropriate 4,5-dinitroimidazoles as substrates. The simple substitution of the nitro by the amino group is known for a long time. Thus, the reaction of 1,2-dimethyl-4,5-dinitroimidazole with amines in alcoholic solutions has been described [5]. However, its only products were derivatives of 5-amino-4-nitroimidazole. Products of similar kind were also formed in the reaction of both 4-bromo-5-nitro- and 5-bromo-4-nitro-1-phenacyl derivatives of imidazole [6, 7]. Accordingly, the isomeric 4-amino-5-nitroimidazole derivatives can only be obtained on the route described here.

Results and Discussion

In this paper the reactions of 1-phenacyl or *p*-chlorophenacyl substituted 2-methyl-4,5-dinitroimidazole **1** and **2** with cyclic secondary amines as morpholine,

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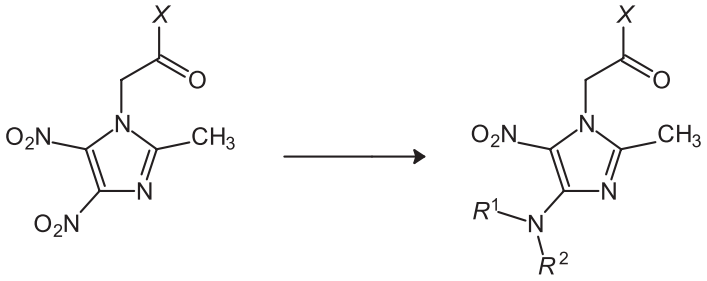

1 $X = Ph$
2 $X = 4\text{-Cl-}Ph$

3 $X = Ph$, $R^1R^2 = -(CH_2)_2O(CH_2)_2-$
4 $X = Ph$, $R^1R^2 = -(CH_2)_5-$
5 $X = Ph$, $R^1R^2 = -(CH_2)_4-$
6 $X = Ph$, $R^1 = H$, $R^2 = Ph$
7 $X = 4\text{-Cl-}Ph$, $R^1R^2 = -(CH_2)_2O(CH_2)_2-$
8 $X = 4\text{-Cl-}Ph$, $R^1R^2 = -(CH_2)_5-$
9 $X = 4\text{-Cl-}Ph$, $R^1R^2 = -(CH_2)_4-$
10 $X = 4\text{-Cl-}Ph$, $R^1 = H$, $R^2 = Ph$

Scheme 1

piperidine, and pyrrolidine or with the primary amine aniline are reported. The treatment of **1** and **2** with the above-mentioned amines, even at the molar ratio 1:5 led to the 4-amino-5-nitroimidazole derivatives **3**–**10** only (Scheme 1).

A comparison of the NMR spectra of 4-nitro-5-aminoimidazoles reported in literature [6, 7] with the spectra of the compounds studied in this work reveals significant differences allowing the empirical differentiation of the isomeric compounds. In the ^{1}H NMR spectra of the isomers of 5-amino-4-nitroimidazoles, the signals of the CH_2 protons are in the range of 5.93–6.04 ppm, with the higher values assigned to the phenylamine derivatives, whose isomeric correspondents have not been earlier described. The signals of the other H atoms are similar and could not be related to structure. In the ^{13}C NMR spectra the well resolved signal of the methyl group at C-2 of the imidazole ring is of greatest analytical importance. The CH_3- signal for all 5-amino-4-nitro isomers is at $\delta = 13.71$ ppm [6, 7], whereas for 4-amino-5-nitro isomers it was found in the range of 14.16–14.30 ppm.

The X-ray structure determination of **6** was carried out in order to facilitate the interpretation of ^{1}H and ^{13}C NMR data and to determine the position of the nitro and phenylamine residues in the imidazole moiety and also to study the nature of the hydrogen-bond formation in the crystalline state.

The geometry of the molecule is illustrated in Fig. 1. The nitro and phenylamine moieties are connected at C-5 and C-4.

The C(5)-nitro and C(4)-phenylamino groups on the one hand and the *N*(1)-phenacyl residue on the other hand subtend very different interplanar angles to the imidazole ring. The dihedral angles between the planar C(4)-phenylamino- and C(5)-nitro groups and the imidazole ring are 8.82(7) and 3.77(11)°, respectively, showing conjugation between these groups and the imidazole moiety. The resonance interaction is reflected in a significant shortening of the C(5)–N(23) bond length [1.3577(19) Å], compared with the regular single bond Csp^2–NO_2

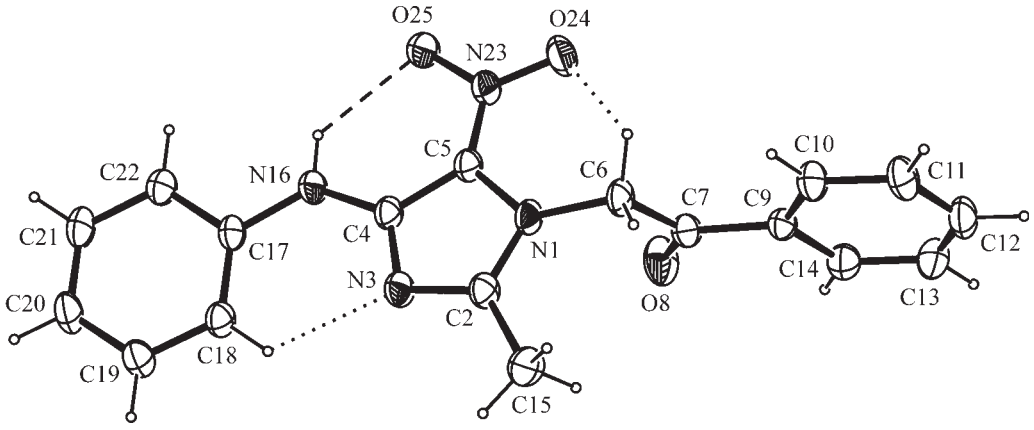

Fig. 1. The molecular structure of **6** with displacement ellipsoids drawn at the 30% probability level; H atoms, treated as isotropic, are on an arbitrary scale; the hydrogen bonds are indicated with dashed and dotted lines

(1.468(1) Å [8]), whereas the C(4)–N(16) bond length (1.3556(18) Å) is consistent with the value for a regular C_{ar}–NH(–C) bond (1.353(2) Å [8]). The almost planar phenacyl group is nearly perpendicular to the imidazole moiety (dihedral angle 87.84(6)°). The torsion angle C(5)–N(1)···C(7)–O(8), −61.59(15)°, indicates a synperiplanar (*−sp*) conformation of the C=O group in the phenacyl residue with respect to the N(1)–C(5) bond.

The conformation adopted by the molecule in the solid state is stabilized by three intramolecular hydrogen bonds, N(16)–H(16)···O(25), C(6)–H(6B)···O(24), and C(18)–H(18)···N(3) (N(16)···O(25), 2.7476(18) Å, C(6)···O(24), 2.871(2) Å, and C(18)···N(3), 2.906(2) Å). The crystal packing involves the close contacts C(6)–H(6B)···O(25)^{i} (C(6)···O(25)^{i}, 3.332(2) Å; (i): $2-x, -y, 1-z$).

The substitution reaction described above can occur in different solvents, *e.g.* ethanol, acetonitrile, methylene chloride, benzene, or *THF*. From among them, *THF* favours the formation of 4-amino-5-nitro isomers, but ethanol is more convenient for the production of a mixture of both possible isomers. The optimum for the reactions is room temperature, because elevated temperatures favour formation of impurities and by-products. The molar ratio of dinitroimidazole and amine can be changed from 1:2.2 to 1:5 and has no essential influence on the kind and quantity of the product obtained. Irrespective of the reaction conditions, the 4-amino-5-nitroimidazole derivatives were the main or even sole products. Under the conditions applied the 5-nitro isomers were formed with better than 80% yields and no 4-nitro isomers were present in the reaction mixture. These new compounds are conveniently obtainable in the described manner and they are presently inaccessible by any other way.

Experimental

The structures of **3**–**10** were confirmed by means of spectroscopic methods and X-ray crystallography. ^{1}H and ^{13}C NMR spectra were recorded using a Varian Gemini 300VT spectrometer (300 MHz and 75 MHz, $CDCl_3$ solutions). Chemical shifts (δ) are given in ppm relative to *TMS* as internal standard.

MS and HRMS spectra were obtained on an AMD 402 instrument. Progress of the reaction was monitored by TLC on plates covered with Kieselgel. Visualisation was accomplished by I_2 vapours. Melting points were determined on a Boetius apparatus and are uncorrected. The *THF* and amines used in the reactions were distilled freshly. The starting materials **1** and **2** were prepared according to Ref. [3].

General Procedure

To a solution of 1 mmol of 2-methyl-4,5-dinitro-1-phenacylimidazole (**1**) or its *p*-chloro derivative **2** in 5 cm^3 of *THF* 5 mmol of secondary amine (morpholine, piperidine, or pyrrolidine) or primary amine (aniline) were added slowly and dropwise at room temperature. After standing for 2–4 h, the precipitate was filtered off, washed with a small quantity of cold *THF* and dried. The precipitate was crystallised from methanol:H_2O (9:1) to yield **3**–**10**.

2-Methyl-4-morpholino-5-nitro-1-phenacylimidazole (**3**, $C_{16}H_{18}N_4O_4$)

Yellow fine threads, yield 84%, mp 210–211°C; ^{1}H NMR: $\delta = 8.02$–7.99 (m, 2,6-Ph), 7.66–7.64 (m, 4-Ph), 7.56–7.51 (m, 3,5-Ph), 5.73 (s, CH_2), 3.86–3.83 (m, $2CH_2$, 3,5-morph.), 3.65–3.62 (m, $2CH_2$, 2,6-morph.), 2.33 (s, CH_3) ppm; ^{13}C NMR: $\delta = 191.05$ (>C=O), 153.63 (4-Im), 151.15 (5-Im), 134.27 (4-Ph), 134.24 (1-Ph), 134.06 (2-Im), 128.96 (2,6-Ph), 128.11 (3,5-Ph), 66.75 (3,5-morph.), 52.31 (CH_2), 49.76 (2,6-morph.), 14.22 (CH_3) ppm; HRMS: calcd. 330.13281, found 330.13220.

2-Methyl-5-nitro-1-phenacyl-4-piperidinoimidazole (**4**, $C_{17}H_{20}N_4O_3$)

Yellow needles, yield 96%, mp 166–168°C; ^{1}H NMR: $\delta = 8.02$–7.99 (m, 2,6-Ph), 7.68–7.62 (m, 4-Ph), 7.55–7.50 (m, 3,5-Ph), 5.73 (s, CH_2), 3.59–3.55 (m, $2CH_2$, 2,6-pip.), 2.31 (s, CH_3), 1.74–1.68 (m, $3CH_2$, 3,4,5-pip.) ppm; ^{13}C NMR: $\delta = 191.43$ (>C=O), 154.74 (4-Im), 151.97 (5-Im), 134.25 (2-Im), 134.18 (4-Ph), 134.18 (1-Ph), 128.95 (2,6-Ph), 128.17 (3,5-Ph), 52.25 (CH_2), 50.86 (2,6-pip.), 25.93 (3,5-pip.), 24.23 (4-pip.), 14.20 (CH_3) ppm; HRMS: calcd. 328.15354, found 328.15330.

2-Methyl-5-nitro-1-phenacyl-4-pyrrolidinoimidazole (**5**, $C_{16}H_{18}N_4O_3$)

Yellow needles, yield 95%, mp 183–186°C; ^{1}H NMR: $\delta = 8.03$–7.99 (m, 2,6-Ph), 7.67–7.62 (m, 4-Ph), 7.54–7.50 (m, 3,5-Ph), 5.73 (s, CH_2), 3.71–3.64 (m, $2CH_2$, 2,5-pyrr.), 2.30 (s, CH_3), 1.99–1.94 (m, $2CH_2$, 3,4-pyrr.) ppm; ^{13}C NMR: $\delta = 191.51$ (>C=O), 152.01 (4-Im), 151.78 (5-Im), 134.20 (2-Im), 134.09 (4-Ph), 134.09 (1-Ph), 128.87 (2,6-Ph), 128.12 (3,5-Ph), 52.08 (CH_2), 51.00 (2,5-pyrr.), 25.55 (3,4-pyrr.), 14.27 (CH_3) ppm; HRMS: calcd. 314.13788, found 314.13716.

2-Methyl-5-nitro-1-phenacyl-4-phenylaminoimidazole (**6**, $C_{18}H_{16}N_4O_3$)

Light orange needles, yield 81%, mp 213–214°C; ^{1}H NMR: $\delta = 9.48$ (s, N–H), 8.03–8.00 (m, 2,6-Ph), 7.75–7.70 (m, 2,6-Ph-NH), 7.68–7.65 (m, 4-Ph), 7.57–7.52 (m, 3,5-Ph), 7.41–7.35 (m, 3,5-Ph-NH), 7.15–7.08 (m, 4-Ph-NH), 5.79 (s, CH_2), 2.40 (s, CH_3) ppm; ^{13}C NMR: $\delta = 190.71$ (>C=O), 152.99 (4-Im), 149.32 (5-Im), 138.33 (2-Im), 134.41 (4-Ph), 133.97 (1-Ph), 129.17 (3,5-Ph-NH), 129.03 (2,6-Ph), 128.18 (3,5-Ph), 123.79 (1-Ph-NH), 119.60 (2,6- and 4-Ph-NH), 51.64 (CH_2), 14.30 (CH_3) ppm; HRMS: calcd. 336.12224, found 336.12261.

1-(4-Chlorophenacyl)-2-methyl-4-morpholino-5-nitroimidazole (**7**, $C_{16}H_{17}ClN_4O_4$)

Yellow fine plates, yield 90%, mp 215–219°C; ^{1}H NMR: $\delta = 7.97$–7.92 (m, 2,6-Ph), 7.53–7.47 (m, 3,5-Ph), 5.66 (s, CH_2), 3.86–3.82 (m, $2CH_2$, 3,5-morph.), 3.65–3.62 (m, $2CH_2$, 2,6-morph.),

2.33 (s, CH_3) ppm; ^{13}C NMR: $\delta = 190.02$ (>C=O), 153.59 (4-Im), 151.15 (5-Im), 140.84 (4-Ph), 132.40 (1-Ph), 129.52 (2,6-Ph), 129.32 (2-Im), 129.32 (3,5-Ph), 66.73 (3,5-morph.), 52.14 (CH_2), 49.73 (2,6-morph.), 14.21 (CH_3) ppm; HRMS: calcd. 364.09383, found 364.09311.

1-(4-Chlorophenacyl)-2-methyl-5-nitro-4-piperidinoimidazole (**8**, $C_{17}H_{19}ClN_4O_3$)

Yellow fine plates, yield 86%, mp 198–201°C; ^1H NMR: $\delta = 7.96$–7.92 (m, 2,6-Ph), 7.52–7.47 (m, 3,5-Ph), 5.66 (s, CH_2), 3.59–3.55 (m, $2CH_2$, 2,6-pip.), 2.31 (s, CH_3), 1.74–1.70 (m, $3CH_2$, 3,4,5-pip.) ppm; ^{13}C NMR: $\delta = 190.28$ (>C=O), 154.56 (4-Im), 151.86 (5-Im), 140.63 (4-Ph), 132.50 (1-Ph), 129.49 (2-Im), 129.49 (2,6-Ph), 129.23 (3,5-Ph), 52.09 (CH_2), 50.84 (2,6-pip.), 25.94 (3,5-pip.), 24.23 (4-pip.), 14.25 (CH_3) ppm; HRMS: calcd. 362.11457, found 362.11401.

1-(4-Chlorophenacyl)-2-methyl-5-nitro-4-pyrrolidinoimidazole (**9**, $C_{16}H_{17}ClN_4O_3$)

Yellow needles, yield 86%, mp 189–191°C; ^1H NMR: $\delta = 7.97$–7.92 (m, 2,6-Ph), 7.51–7.47 (m, 3,5-Ph), 5.66 (s, CH_2), 3.70–3.65 (m, $2CH_2$, 2,5-pyrr.), 2.30 (s, CH_3), 2.01–1.92 (m, $2CH_2$, 3,4-pyrr.) ppm; ^{13}C NMR: $\delta = 190.52$ (>C=O), 151.94 (4-Im), 151.76 (5-Im), 140.62 (4-Ph), 132.58 (1-Ph), 129.54 (2-Im), 129.54 (2,6-Ph), 129.24 (3,5-Ph), 51.94 (CH_2), 51.02 (2,5-pyrr.), 25.56 (3,4-pyrr.), 14.27 (CH_3) ppm; HRMS: calcd. 348.09892, found 348.09856.

1-(4-Chlorophenacyl)-2-methyl-5-nitro-4-phenylaminoimidazole (**10**, $C_{18}H_{15}ClN_4O_3$)

Orange needles, yield 82%, mp 202–204°C; ^1H NMR: $\delta = 9.47$ (s, N–H), 7.98–7.94 (m, 2,6-Ph), 7.75–7.71 (m, 2,6-Ph-NH), 7.54–7.50 (m, 3,5-Ph), 7.41–7.36 (m, 3,5-Ph-NH), 7.15–7.10 (m, 4-Ph-NH), 5.73 (s, CH_2), 2.40 (s, CH_3) ppm; ^{13}C NMR: $\delta = 189.87$ (>C=O), 153.01 (4-Im), 149.41 (5-Im), 141.12 (4-Ph), 138.45 (2-Im), 132.50 (1-Ph), 129.64 (3,5-Ph-NH), 129.49 (2,6-Ph), 129.25 (3,5-Ph), 123.91 (1-Ph-NH), 119.69 (2,6- and 4-Ph-NH), 51.45 (CH_2), 14.16 (CH_3) ppm; HRMS: calcd. 370.08327, found 370.08383.

Crystal Structure Determination of **6**

Crystal data: $C_{18}H_{16}N_4O_3$, $M = 336.35$, monoclinic, space group $P2_1/n$, $a = 7.871(2)$, $b = 21.074(4)$, $c = 10.030(2)$ Å, $\beta = 107.54(3)°$; $V = 1586.4(6)$ Å^3, $Z = 4$, $T = 293(2)$ K.

Data collection: A crystal of $0.53 \times 0.16 \times 0.12$ mm was used to record 3114 (Cu$K\alpha$ radiation, $\theta_{max} = 70.16°$) intensities on a Kuma KM-4 diffractometer [9]. Accurate unit cell parameters were determined by least squares techniques from the θ values of 57 reflections, θ range 15.3–30.2°. The intensities were collected in the ω-2θ scan mode with graphite-monochromatized Cu$K\alpha$ radiation. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption (μ(Cu$K\alpha$) = 0.815 mm^{-1}). The 2945 total unique reflections (R(int) = 0.0146) were used for further calculations.

Structure solution and refinement: The structure was solved by the direct methods using the program SHELXS-97 [10], and refinement was done against F^2 for all data using SHELXL-97 [10]. The positions of the H atoms were obtained from difference *Fourier* maps and refined freely. The final refinement converged with $R = 0.0361$ (for 2378 data with $F^2 > 4\sigma(F^2)$), $wR = 0.1081$ (on F^2 for all data), and $S = 1.021$ (on F^2 for all data). The minimum and maximum peaks in the final difference *Fourier* map were -0.19 and 0.17 eÅ^{-3}. The molecular illustration was drawn using ORTEP-3 for Windows [11]. Software used to prepare material for publication was PLATON [12] and SHELXL-97 [10].

The data have been deposited at the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ (UK), Tel.: (+44) 1223/336-408, Fax: (+44) 1223/336-033, E-mail: deposit@ccdc.cam.ac.uk, World Wide Web: http://www.ccdc.cam.ac.uk (deposition No. CCDC 209346).

References

[1] Part 47: Gzella A, Wrzeciono U (2001) Acta Cryst C**57**: 1189
[2] Boyer JH (1986) Nitroazoles. VCH Publishers Inc, Deerfield Beach FL, p 165 and references cited therein
[3] Zaprutko L, Gajdziński M, Michalska W, Pietkiewicz K, Lutomski K, Łukaszewski Z, Wrzeciono U (1989) Pharmazie **44**: 817
[4] Zaprutko L, Wrzeciono U, Gajdziński M, Bartkowiak M, Lutomski K, Michalska W, Pietkiewicz K (1992) Pharmazie **47**: 258
[5] Suwiński J, Król W, Pacocha C (1985) Zeszyty Naukowe Politechniki Śląskiej, s Chemia 13; (1988) Chem Abstr **109**: 110323j
[6] Sobiak S (1998) Polish J Chem **72**: 78
[7] Sobiak S (1998) Synth Commun **28**: 2703
[8] Allen FH, Kennard O, Watson DG, Brammer L, Orpen AG, Taylor R (1987) J Chem Soc Perkin Trans II, S1–19
[9] Kuma Diffraction (1991) Version 1991t Kuma KM-4 User's Guide, Wrocław, Poland
[10] Sheldrick GM (1997) *SHELXS97* and *SHELXL-97*, Release 97-2, University Göttingen, Germany
[11] Farrugia LJ (1997) J Appl Cryst **30**: 565
[12] Spek AL (1990) Acta Cryst A**46**: C-34