Selective Reduction of 2,4-Dinitro- and 4,5-Dinitroimidazole Derivatives Using Iron Dust

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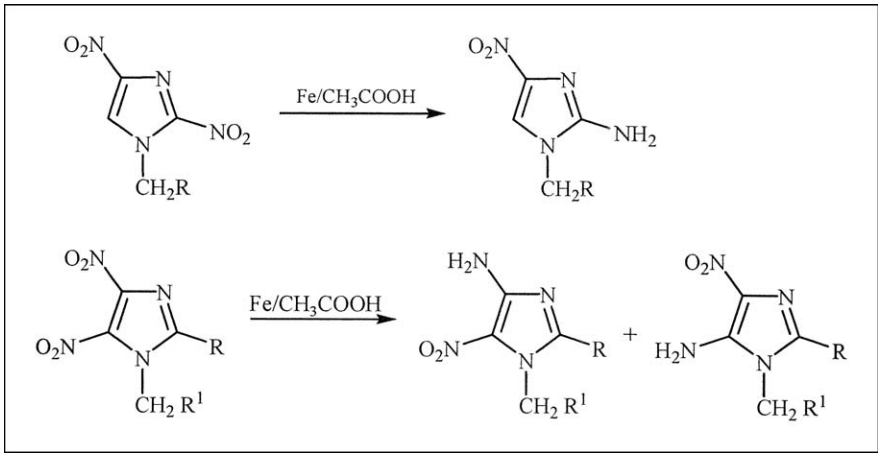

A series of *N*-substituted 2,4-dinitroimidazoles, 4,5-dinitroimidazoles, and 2-methyl-4,5-dinitroimidazoles have been selectively reduced to the corresponding aminonitroimidazole derivatives, using iron dust in glacial acetic acid at room temperature. 2,4-Dinitroimidazoles have been reduced to the 2-amino-4-nitro-derivatives only but 4,5-dinitroimidazoles have given 4-amino-5-nitro- or 5-amino-4-nitro-derivatives depended on the structure of the *N*-substituent.

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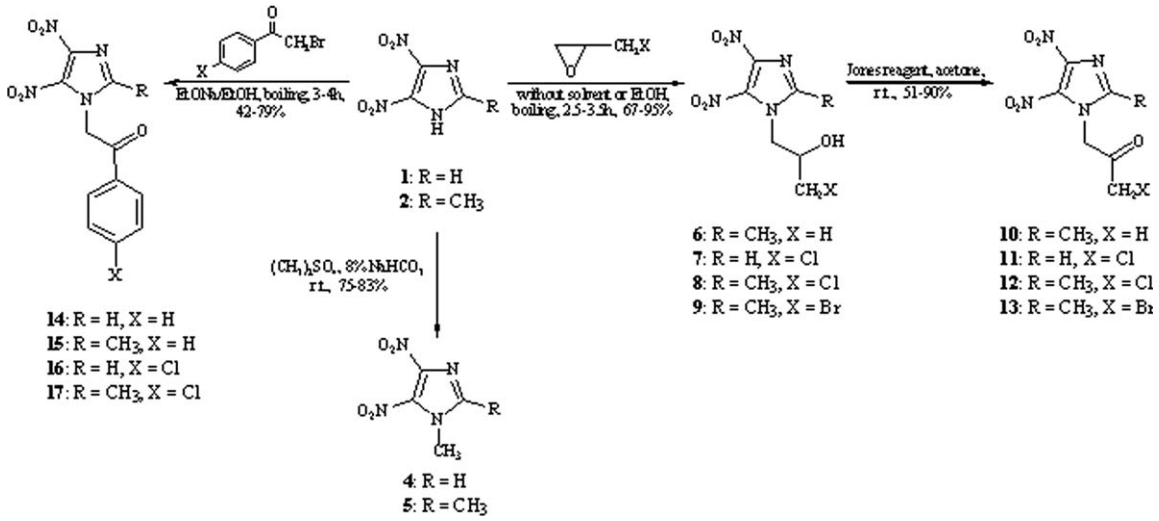
INTRODUCTION

Imidazoles and their derivatives are very important group of compounds for their pharmacological properties [1,2]. Particularly, the nitroimidazole class of medicines mainly shows activity against bacteria [3,4]. Also, these drugs have become the important agents for treatment of serious infections caused by protozoa. Some of them have been tested against HIV [5]. 2-Nitroimidazoles played a major role as bioreductive markers for tumour hypoxia [6] and as radiosensitizers [7,8]. Our earlier investigations have been devoted to synthesis and antifungal as well as antibacterial properties of *N*-phenacyl-4,5-dinitroimidazole and 4-substituted amino-5-nitroimidazole derivatives, which have been prepared by nucleophilic displacement of the nitro group in 4,5-dinitroimidazole derivatives by primary or secondary amines [9,10].

Reduction of the nitro compounds has been one of the most important reactions in organic chemistry used as a routine method for the preparation of various nitrogen derivatives such as amines, nitrosocompounds, or hydroxylamines. The reported reduction methods of aromatic nitro compounds to prepare amino derivatives are very numerous. The reduction of the nitroazoles is readily achieved by using of one of many possible reagents like for instance iron in an acidic medium [11,12], hydrogen in the presence of palladium [13,14], Raney nickel [15] sodium borohydride [16]. Only limited number of all reduction methods have described the selective reduction of one nitro group in dinitro-compounds with remain unchanged of other functional groups. For example, reduction of 2,4-dinitrophenol using sodium sulfide has led to 2-amino-4-nitrophenol [17], but 4-amino-2-nitro-carboxamide mustard have been obtained by selective 4-nitro group reduction of 2,4-dinitrobenzamide derivative with $SnCl_2$ in concentrated HCl [18]. Lin and Sun [17] have found that using either Zn in $HCOONH_4$ or tin (II) chloride dihydrate can deliver traceless synthesis of 2-quinoxalinone analogues, an *o*-nitroaniline intermediate without further reduction of another nitro group under microwave irradiation or by conventional heating.

Products of reductions of nitroimidazole derivatives exhibit potential biological significance and are intermediates in syntheses of a variety of biologically active imidazoles. The compounds containing amino group in azoles ring can show good antimicrobial activity. In particular, the introduction of a bromine or two chlorine atoms or one phenyl group to the phenyl ring, except for the amino group in 2-amino-4(5)-arylimidazoles

Scheme 1



leads to compounds provided some antimicrobial activity [19]. Moreover, compound with the amino and the nitro groups have played important role as potent inhibitor of Coxackie virus B3 replication [20]. Synthetic 2-aminoimidazole derivatives including 2-aminohistamine have shown to have H_1 and H_2 receptor agonist and antagonist activity. Other 2-aminoimidazole derivatives are selective 5-HT_3 receptor antagonists, which may be potentially useful in the treatment of chemotherapy induced emesis [21]. Imidazole alkaloids containing the amino group at *C*-2 position in the heterocyclic ring also show interesting biological property such as anthelminthic activity (dorimidazole A, preclathridine A) [1].

RESULTS AND DISCUSSION

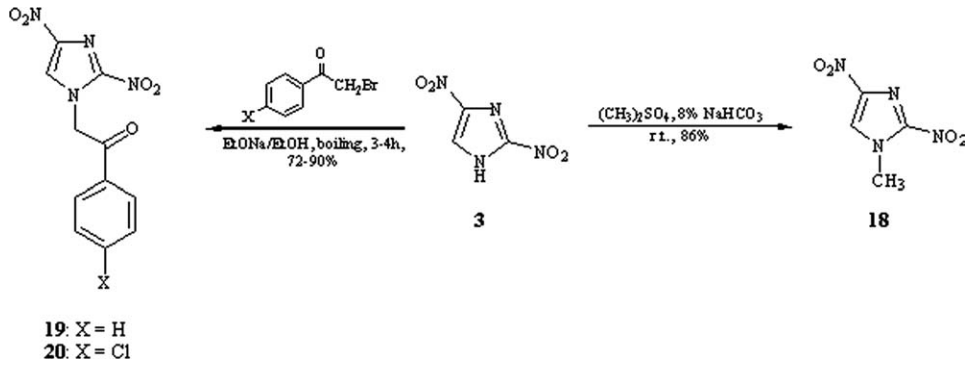
The reduction of *N*-substituted 2,4-dinitroimidazole, 4,5-dinitroimidazole, and 2-methyl-4,5-dinitroimidazole to the corresponding aminonitroderivatives by use of iron dust in glacial acetic acid at room temperature exhibits high selectivity. It is very surprising that iron dust in an acidic medium is capable of reducing one nitro group without further reduction of second nitro group. It is known that iron in the presence of acid is not selective agent [11]. In our experiments, treatment of dinitroimidazole derivatives with iron dust afforded, after purification, the crystalline aminonitro-compounds. Stability of these compounds depended on the position of the amino group, decreased in a series of 2-amino, 5-amino and 4-amino compounds.

The starting 4,5-dinitroimidazole (**1**), 2-methyl-4,5-dinitroimidazole (**2**), and 2,4-dinitroimidazole (**3**) were prepared according to the methods described in the literature [22,23]. The *N*-substituted derivatives of 4,5-dinitroimidazoles (**4–17**) were obtained in the reaction of **1** or **2** with $(CH_3)_2SO_4$, epoxypropane, epichlorohydrin, or phenacyl bromides in accordance with the method described in the literature [9,23,24]. The *N*-(2-hydroxypropyl) and *N*-(3-chloro-2-hydroxypropyl) compounds (**6–8**) were oxidized by Jones reagent to the desired carbonyl derivatives (**10–12**) [24]. Additionally, 2-methyl-4,5-dinitroimidazole was alkylated with epibromohydrin according to the method described for prepared epichlorohydrin derivatives [9]. The treatment of **2** with an excess of epibromohydrin (1:2) under reflux without solvent for about 3 h led to new 1-(3-bromo-2-hydroxypropyl)-2-methyl-4,5-dinitroimidazole (**9**). This new derivative was oxidized by Jones reagent to the 1-(3-bromo-2-oxopropyl)-2-methyl-4,5-dinitroimidazole (**13**) in accordance with the method described earlier [24]. Synthesis of *N*-substituted 4,5-dinitroimidazole derivatives **4–17** is shown in the Scheme 1.

Also, the 2,4-dinitroimidazole (**3**) was put on the reactions with $(CH_3)_2SO_4$ and phenacyl bromides according to the methods described in the literature [9,23,25]. The reactions of **3** with appropriate reagents resulted in the formation of *N*-substituted derivatives of 2,4-dinitroimidazole (**18–20**), as shown in the Scheme 2.

The *N*-methyl (**18**) and *N*-phenacyl derivatives of 2,4-dinitroimidazole (**19,20**) in the reduction gave only respective 2-amino-4-nitroimidazole with yield 54–82% (Scheme 3). When the reaction was complete, the excess of iron and its oxidation products were filtered off and the reaction mixture was diluted with water. The 2-amino-1-methyl-4-nitroimidazole (**21**) was isolated by extraction. After removal of the solvent, the crude product was crystallized. The precipitated crude reduction products (**22, 23**) were filtered off. A large, lipophilic phenacyl group facilitated obtaining the aminonitroderivatives. Reduction

Scheme 2



of *N*-substituted 2,4-dinitroimidazole derivatives **18**–**20** is shown in the Scheme 3.

The structures of **21–23** were confirmed by full spectral data. The infrared spectra showed absorptions at about 3400 and 3265 cm^{-1} and also 1560 and 1300 cm^{-1} indicative for the N—H and NO_2 resonances, respectively. The mass spectra exhibit strong molecular ions at 142, 246, and 280, respectively. In addition to the molecular ions, in spectra of compounds **22** and **23** strong signal (rel. int. 100%) corresponding to ion from phenacyl (*m*/*z* 105) or *p*-chlorophenacyl group (*m*/*z* 139) was observed. In the ^1H NMR spectra, the signals of the amino groups are as singlets at about 6.30 ppm, CH_2 protons of the phenacyl groups resonated as singlet at 5.56 and 5.54 ppm. The aromatic protons at *C*-5 position of the imidazole ring were observed at about 7.84 ppm.

Reduction of 4,5-dinitroimidazole alkyl derivatives led to *N*-alkylaminonitroimidazoles, as well. The iron dust in glacial acetic acid reduced with facility one nitro group but the second remained unreactive. In the same conditions, mixture of two isomers: 4-amino-5-nitro- and 5-amino-4-nitro- with predomination of the latter mentioned were formed (Scheme 4). The 4,5-diaminoimidazoles were not observed in the reaction mixtures. Formation of the aminonitroimidazoles depended on the position of the new formed amino group and yielding of 4-amino-compounds was the poorest. The low efficiency in reduction reactions of 4,5-dinitroimidazole alkyl derivatives probably is connected with structures and stability of compounds obtained. Moreover, the isolation of pure, definite, aminonitroderivatives was very inconvenient. Some of them were obtained after complex extraction, then purification by column chromatography and additional crystallization.

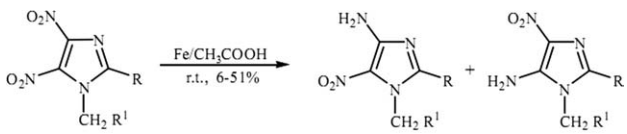
Reduction of *N*-substituted 4,5-dinitroimidazole derivatives **4**,**5**,**7–17** is shown in the Scheme 4.

Reaction of the compounds containing *N*-methyl group (**4, 5**) with iron dust afforded 4-amino-5-nitroimidazoles (**24, 25**) only that were separated after extraction with chloroform. In the reduction of the *N*-halohydroxypropyl derivatives (**7–9**) were formed 5-amino-4-nitro-compounds (**26–28**). These substances were obtained as solid products. Other 4,5-dinitroimidazoles (**10–17**) containing the carbonyl group in the chain

Scheme 3

Substrate	R	Product
18	H	**21**
19	$C(O)C_6H_5$	**22**
20	$C(O)C_6H_4$(*p*-Cl)	**23**

Scheme 4



Substrate	R	R^1	4-Amino derivatives	5-Amino derivatives
4	H	H	24	
5	CH_3	H	25	
7	H	$CH(OH)CH_2Cl$		26
8	CH_3	$CH(OH)CH_2Cl$		27
9	CH_3	$CH(OH)CH_2Br$		28
10	CH_3	$C(O)CH_3$	29	
11	H	$C(O)CH_2Cl$	30	
12	CH_3	$C(O)CH_2Cl$	31	
13	CH_3	$C(O)CH_2Br$	32	
14	H	$C(O)C_6H_5$	33	
15	CH_3	$C(O)C_6H_5$	34	35
16	H	$C(O)C_6H_4$(*p*-Cl)	36	
17	CH_3	$C(O)C_6H_4$(*p*-Cl)	37	38

at *N*-1 position of the imidazole ring provided mainly 4-amino-5-nitro- derivatives, after extraction **(29–34, 36, 37**). Only in the reduction of 2-methyl-4,5-dinitro-1-phenacylimidazole (**15**) and (**17**), the mixtures of two products were obtained. After reduction of **15**, isomers: 4-amino-2-methyl-5-nitro-1-phenacylimidazole (**34**) and 5-amino-2-methyl-4-nitro-1-phenacylimidazole (**35**) were obtained. Compound **35** was separated by the filtration and purified by crystallization. Dominating product, **34**, was obtained after extraction and was purified by column chromatography. Similarly, the 4-amino-1-(*p*-chlorophenacyl)-2-methyl-5-nitroimidazole **(37**) and 5-amino-1-(*p*-chlorophenacyl)-2-methyl-4-nitroimidazole **(38**) were obtained as products of the reduction of 1-(*p*-chlorophenacyl)-2-methyl-4,5-dinitroimidazole (**17**). These derivatives were separated by column chromatography. In all cases, 4,5-diamino derivatives were not observed.

The infrared spectra of **24–38** showed absorptions at about 3400 and 3260 cm^{-1} and also 1560 and 1300 cm^{-1} indicative for the N—H and NO_2 resonances, respectively. The mass spectra confirmed that only one nitro group in the dinitroimidazoles was reduced. The ^1H NMR spectra of new products provided evidence for the presence of the amino group. The NH_2 protons were observed as a singlet at about 7.40 ppm (**24, 25**) or within the range of 7.57–7.71 ppm (**26–38**). In the ^{13}C NMR spectra of **26–28**, signal for the carbon jointed with hydroxyl group was near 67 ppm. Moreover, the signal corresponded to the C=O group of **29–38** resonated in the range of 190.88–201.22 ppm. The position of the amino group in **26–38** was connected with the place of a signal of a methylene group at *N*-1 position of the heterocylic ring. In the ^{13}C NMR of **26–28**, the signal in the range 46.29–47.09 ppm was assigned to the CH_2 group. It is also observed that in the ^{13}C NMR of **29–32**, the resonances due to CH_2 occurred in the range 52.21–54.40 ppm. It is very interesting that the signals of the methylene groups of the pairs **34, 35** and **37, 38** occurred at different values: 52.01 and 50.27 ppm or 51.96 and 49.65 ppm, respectively. In the spectra of 5-amino-4-nitro-products, the signals of the carbons in the imidazole ring appeared in lower values, too. Additionally, the X-ray structures determination of the pair of isomers (**34,35**) facilitated the interpretation of NMR data and to determine the position of the amino group. The geometry of the molecules confirmed that the compound **35** is 5-amino-4-nitro- derivative but the second is 4-amino-5-nitro-isomer (**34**). The results obtained were in agreement with our interpretation of NMR spectra. The signals of the methylene group and carbon atoms of the imidazole ring of the all 5-amino-4-nitro compounds were shifted toward the lower field.

In conclusion, we have demonstrated very selective nitro group reduction method in the dinitroimidazole derivatives using iron dust in the acetic acid solution at room temperature. This method provided the products with the amino and the nitro group simultaneously. The presence of an electron-donating amino group at a position neighbouring to the nitro group can have influence on the many biological properties, which depended on the kind of substituents at positions *N*-1 and *C*-2 in the heterocyclic ring, as well.

To recapitulate, the *N*-derivatives of 2,4-dinitroimidazoles were reduced only to the 2-amino-4-nitro compounds. It was found that the reduction process among the *N*-derivatives of 4,5-dinitroimidazoles is more complicated, but it concerns mainly the 4-NO_2 group. Nitro group at *C*-5 position of imidazole ring is susceptible to reduction when there is a hydroxy group in the *N*-1 alkyl chain connected with tetrahedral carbon atom. Probably, some specific trigonal arrangements have the influence on the direction of nitro group reduction process.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and were uncorrected. The ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 300 VT spectrometer (300 and 75 MHz respectively). Chemical shifts (δ) are expressed in ppm, relative to tetramethylsilane (TMS) as an internal standard, using DMSO–d_6 as solvents. Coupling constants (*J* values) are expressed in Hertz (Hz). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet. MS spectra were recorded on a 402 AMD INTECTRA apparatus by the electron impact technique, operating at 75 eV. The infrared (IR) spectra were recorded in KBr tablets using a Specord 75–IR spectrophotometer and were expressed in cm^{-1} scale. Elemental analysis was performed on a Vario EL III model of elemental analyzer and data of C, H, and N were within ±0.4% of calculated values. The progress of reactions and purity of products were controlled with thin-layer chromatography method (TLC) on silica gel plates (60 F_{254} from Merck) in a $CHCl_3$/MeOH (9:1, v/v) as a developing system. The spots on the plates were observed in the UV light (λ = 254nm). Solid products of amino-nitro-derivatives were purified in the crystallization process using acetonitrile. Crude, oily products were purified by column chromatography on silica gel using the mixture of chloroform and methanol (50:0 → 50:5) as eluent. Among substances, which were used as substrates, the epichlorohydrin, epoxypropane, epibromohydrin, phenacyl bromides, and iron dust were commercial products. Compounds **4–8, 10–12**, and **14–18** were obtained according to the literature method [9,23–25].

1-(3-Bromo-2-hydroxypropyl)-2-methyl-4,5-dinitroimidazole (9). The 2-methyl-4,5-dinitroimidazole (3.44 g, 20 mmol) was added to epibromohydrin (3.42 mL, 40 mmol). The mixture was heated under reflux for about 3 h. Then, cooled and poured into the water. The precipitate was filtered off, washed with water, air-dried and crystallized from 40% EtOH as yellow needles; 5.40 g (87.5%); mp 103–105°C; R_f = 0.64; IR: 3380, 1520, 1340; ^1H NMR (300 MHz, DMSO–d_6): δ = 5.92 (m, 1H, OH), 4.49 (m, 1H, CH), 4.21 and 4.00 (2 m, 2H,

CH_2Br), 3.59 (m, 2H, N-CH_2), 2.49 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 145.42, 139.29, 130.68, 67.97, 50.09, 35.81, 13.72; ms: m/z 308 (2) and 310 (2) (M^+), 182 (100.0); Anal. calc. for $C_7H_9N_4O_5Br$: C, 27.29; H, 2.94; N, 18.19; found: C, 27.25; H, 2.98; N, 18.22.

1-(3-Bromo-2-oxopropyl)-2-methyl-4,5-dinitroimidazole (13). To a solution of **9** (3.10 g, 10 mmol) in acetone (50 mL), at room temperature was dropped Jones reagent (10 mL). After 24 h, *i*-PrOH (10 mL) was added. The dark green precipitate was filtered and washed with a small volume of acetone. The combined filtrates were poured into the water (200 mL) and the solution was held 2–3 days to afford the crystalline solid. The precipitate was filtered off, washed with water, air-dried, and crystallized from MeOH as yellow needless; 2.32 g (76.0%); mp 117–119°C; R_f = 0.64; IR: 1720, 1510, 1380; ^1H NMR (300 MHz, DMSO–d_6): δ = 5.54 (s, 2H, CH_2), 4.59 (s, 2H, CH_2Br), 2.43 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 193.95, 146.10, 140.06, 129.42, 53.28, 33.62, 13.31; ms: m/z 308 (15) and 306 (16) (M^+), 156 (100); Anal. calc. for $C_7H_7N_4O_5Br$: C, 27.47; H, 2.92; N, 18.31; found: C, 27.52; H, 2.97; N, 18.28.

General procedure for synthesis of *N*-phenacyl-2,4-dinitroimidazole derivatives (19–20). The solution of Na (1.38 g, 60 mmol) in absolute EtOH (40 mL) was added dropwise under stirring to a solution of 2,4-dinitroimidazole (**3**) (7.90 g, 50 mmol) in absolute ethanol (50 mL). Subsequently, a solution of phenacyl bromide or *p*-chlorophenacyl bromide (50 mmol) in absolute ethanol (100 mL) was dropped and heated under reflux for 4 h. The mixture was cooled and the precipitate was filtered off, air-dried, and crystallized from EtOH.

2,4-Dinitro-1-phenacylimidazole (19). This compound was obtained as cream needles (EtOH), 12.50 g (90.6%); mp 123–125°C; R_f = 0.64; IR: 1680, 1526, 1320; ^1H NMR (300 MHz, DMSO–d_6): δ = 8.72 (s, 1H, 5-Im), 8.09 (m, 2H, 2,6-Ph), 7.76 (m, 1H, 4-Ph), 7.66 (m, 2H, 3,5-Ph), 6.27 (s, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 190.84, 142.30, 141.69, 134.87, 133.34, 129.27, 128.27, 126.86, 57.24; ms: *m*/*z* 276 (28) (M^+), 105 (100); Anal. calc. for $C_{11}H_8N_4O_5$: C, 47.86; H, 2.92; N, 20.29; found: C, 47.90; H, 2.94; N, 20.32.

1-(*p*-Chlorophenacyl)-2,4-dinitroimidazole (20). This compound was obtained as cream needles (EtOH), 11.20 g (72.2%); mp 154–156°C; R_f = 0.62; IR: 1680, 1526, 1320; ^1H NMR (300 MHz, DMSO–d_6): δ = 8.71 (s, 1H, 5-Im), 8.12 (m, 2H, 2,6-Ph), 7.74 (m, 2H, 3,5-Ph), 6.26 (s, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 190.02, 142.29, 141.65, 139.80, 132.05, 130.18, 129.42, 126.85, 57.16; ms: m/z 312 (11), 310 (32) (M^+), 139 (100); Anal. calc. for $C_{11}H_7N_4O_5Cl$: C, 42.61; H, 2.27; N, 18.07; found: C, 42.58; H, 2.24; N, 18.10.

General procedure for synthesis of Aminonitroimidazoles (21–38). Appropriate *N*-substituted 2,4-dinitro-, 4,5-dinitro-, or 2-methyl-4,5-dinitroimidazole derivatives (2 mmol) were dissolved in glacial AcOH (25 mL), and the excess of iron dust (0.37 g, 6.60 mmol) was added. The resulting mixtures were then left for about 3 days at room temperature shaking them from time to time. Upon completion reaction, the excess of iron and its oxidation products were filtered off, and the reaction mixtures were diluted with water (75 mL). The precipitated crude products were filtered off. If products not solidified, then the filtrate was extracted with $CHCl_3$ (4 × 5 mL) and the combined organic phases were dried ($MgSO_4$), filtered off. After removal of the solvents, the crude product was purified by column chromatography on silica gel. All new products were crystallized from MeCN.

2-Amino-1-methyl-4-nitroimidazole (21). This compound was obtained as yellow needles (MeCN), 0.15 g (53.6%); mp 216–218°C; R_f = 0.18; IR: 3425, 3265, 1627, 1554, 1300; ^1H NMR (300 MHz, DMSO–d_6): δ = 7.88 (s, H, 5-Im), 6.23 (s, 2H, NH_2), 3.44 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 149.38, 143.29, 119.93, 32.30; ms: m/z 142 (68) (M^+), 42 (100); Anal. calc. for $C_4H_6N_4O_2$: C, 33.82; H, 4.25; N, 39.44; found: C, 33.86; H, 4.20; N, 39.42.

2-Amino-4-nitro-1-phenacylimidazole (22). This compound was obtained as yellow needles (MeCN), 0.40 g (81.3%); mp 243–245°C; R_f = 0.41; IR: 3400, 3270, 1680, 1627, 1560, 1295; ^1H NMR (300 MHz, DMSO–d_6): δ = 8.03 (m, 2H, 2,6-Ph), 7.84 (s, H, 5-Im), 7.73 (m, H, 4-Ph), 7.60 (m, 2H, 3,5-Ph), 6.31 (s, 2H, NH_2), 5.56 (s, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 192.16, 149.51, 143.63, 134.34, 134.06, 128.92, 128.11, 119.67, 51.83; ms: m/z 246 (14) (M^+), 105 (100); Anal. calc. for $C_{11}H_{10}N_4O_3$: C, 53.68; H, 4.09; N, 22.76; found: C, 53.73; H, 4.11; N, 22.81.

2-Amino-1-(*p*-chlorophenacyl)-4-nitroimidazole (23). This compound was obtained as yellow needles (MeCN), 0.42 g (75.0%); mp 260–262°C; R_f = 0.43; IR: 3375, 3265,1675, 1634, 1565, 1285; ^1H NMR (300 MHz, DMSO–d_6): δ = 8.05 (m, 2H, 2,6-Ph), 7.82 (s, H, 5-Im), 7.70 (m, 2H, 3,5-Ph), 6.33 (s, 2H, NH_2), 5.54 (s, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 191.33, 149.48, 143.64, 138.87, 133.03, 130.00, 129.05, 119.54, 51.83; ms: m/z 282 (6) and 280 (18) (M^+), 139 (100); Anal. calc. for $C_{11}H_9N_4O_3Cl$: C, 47.17; H, 3.23; N, 20.00; found: C, 47.15; H, 3.26; N, 20.05.

4-Amino-1-methyl-5-nitroimidazole (24). This compound was obtained as yellow needles (MeCN), 0.03 g (10.7%); mp 157–160°C; R_f = 0.18; IR: 3405, 3265, 1620, 1540, 1350; ^1H NMR (300 MHz, DMSO–d_6): δ = 7.72 (s, 1H, 2-Im), 7.40 (s, 2H, NH_2), 3.76 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 153.23, 143.56, 121.09, 34.83; ms: m/z 142 (51) (M^+), 42 (100); Anal. calc. for $C_4H_6N_4O_2$: C, 33.82; H, 4.25; N, 39.44; found: C, 33.86; H, 4.26; N, 39.45.

4-Amino-1,2-dimetylo-5-nitroimidazole (25). This compound was obtained as yellow needles (MeCN), 0.09 g (29.0%); mp 265–268°C; R_f = 0.43; IR: 3405, 3265, 1625, 1555, 1380; ^1H NMR (300 MHz, DMSO–d_6): δ = 7.47 (s, 2H, NH_2), 3.70 (s, 3H, N-CH_3), 2.27 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 153.20, 152.66, 120.32, 32.88, 13.84; ms: m/z 156 (100) (M^+); Anal. calc. for $C_5H_8N_4O_2$: C, 38.47; H, 5.16; N, 35.89; found: C, 38.51; H, 5.21; N, 35.93.

5-Amino-1-(3-chloro-2-hydroxypropyl)-4-nitroimidazole (26). This compound was obtained as dark yellow pales (MeCN), 0.14 g (31.9%); mp 160–162°C; R_f = 0.05; IR: 3360, 3325, 3225, 1625, 1560, 1340; ^1H NMR (300 MHz, DMSO–d_6): δ = 7.57 (s, 2H, NH_2), 7.20 (s, 1H, 2-Im), 5.71 (s, 1H, OH), 3.90 (m, 2H, N-CH_2), 3.68 (m, 2H, CH_2Cl), 3.58 (m, 1H, CH); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 143.39, 132.56, 128.06, 67.80, 47.34, 47.19; ms: m/z 222 (19) and 220 (44) (M^+), 70 (100); Anal. calc. for $C_6H_9N_4O_3Cl$: C, 32.75; H, 4.12; N, 25.46; found: C, 32.80; H, 4.15; N, 25.47.

5-Amino-1-(3-chloro-2-hydroxypropyl)-2-methyl-4-nitroimidazole (27). This compound was obtained as light yellow pales (MeCN), 0.16 g (34.1%); mp 206–208°C; R_f = 0.25; IR: 3360, 3325, 3300, 1625, 1560, 1400; ^1H NMR (300 MHz, DMSO–d_6): δ = 7.61 (s, 2H, NH_2), 5.72 (s, 1H, OH), 3.91 (m, 2H, N-

CH_2), 3.78 (m, 2H, CH_2Cl), 3.64 (m, 1H, CH), 2.23 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 144.61, 140.30, 126.80, 67.78. 47.56, 46.29, 13.44; ms: m/z 236 (16) and 234 (45) (M^+), 55 (100); Anal. calc. for $C_7H_{11}N_4O_3Cl$: C, 35.91; H, 4.73; N, 23.93; found: C, 35.92; H, 4.75; N, 23.96.

5-Amino-1-(3-bromo-2-hydroxypropyl)-2-methyl-4-nitroimidazole (28). This compound was obtained as yellow needles (MeCN), 0.14 g (25.4%); mp 195–197°C; R_f = 0.19; IR: 3380, 3350, 3250, 1625, 1565, 1345; ^1H NMR (300 MHz, DMSO–d_6): δ = 7.61 (s, 2H, NH_2), 5.74 (m, 1H, OH), 3.70 (m, 5H, $CH_2CH(OH)CH_2Br$), 2.23 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 144.40, 140.09, 126.64, 67.34, 47.09, 37.23, 13.50; ms: m/z 280 (7) and 278 (7) (M^+), 80 (100); Anal. calc. for $C_7H_{11}N_4O_3Br$: C, 30.24; H, 3.98; N, 20.15; found: C, 30.22; H, 4.03; N, 20.18.

4-Amino-2-methyl-5-nitro-1-(2-oxopropyl)-imidazole (29). This compound was obtained as yellow pales (MeCN), 0.20 g (51.3%); mp 232–234°C; R_f = 0.26; IR: 3420, 3350, 1720, 1620, 1520, 1340; ^1H NMR (300 MHz, DMSO–d_6): δ = 7.60 (s, 2H, NH_2), 5.13 (s, 2H, CH_2), 2.20 (s, 6H, 2xCH_3); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 201.22, 153.16, 153.09, 120.29, 107.08, 54.40, 26.83, 13.59; ms: m/z 198 (100.0) (M^+); Anal. calc. for $C_7H_{10}N_4O_3$: C, 42.44; H, 5.08; N, 28.28; found: C, 42.48; H, 5.05; N, 28.30.

4-Amino-1-(3-chloro-2-oxopropyl)-5-nitroimidazole (30). This compound was obtained as yellow needles (MeCN), 0.08 g (18.2%); mp 215°C; R_f = 0.23; IR: 3405, 3360, 1710, 1610, 1500, 1300; ^1H NMR (300 MHz, DMSO–d_6): δ = 7.71 (s, 1H, 2-Im), 7.61 (s, 2H, NH_2), 5.25 (s, 2H, N—CH_2), 4.68 (s, 2H, CH_2Cl); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 195.94, 153.11, 144.29, 119.96, 53.57, 46.98; ms: m/z 220 (26) and 218 (75) (M^+), 68 (100); Anal. calc. for $C_6H_7N_4O_3Cl$: C, 33.05; H, 3.23; N, 25.69; found: C, 33.09; H, 3.26; N, 25.69.

4-Amino-1-(3-chloro-2-oxopropyl)-2-methyl-5-nitroimidazole (31). This compound was obtained as yellow needles (MeCN), 0.20 g (43.5%); mp 270°C; R_f = 0.20; IR: 3395, 3260, 1725, 1625, 1540, 1390; ^1H NMR (300 MHz, DMSO–d_6): δ = 7.65 (s, 2H, NH_2), 5.24 (s, 2H, N—CH_2), 4.68 (s, 2H, CH_2Cl), 2.23 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 195.73, 153.44, 153.12, 120.12, 52.21 46.99, 13.62; ms: m/z 234 (18), 232 (50) (M^+), 67 (100); Anal. calc. for $C_7H_9N_4O_3Cl$: C, 36.23; H, 3.90; N, 24.14; found: C, 36.20; H, 3.89; N, 24.15.

4-Amino-1-(3-bromo-2-oxopropyl)-2-methyl-5-nitroimidazole (32). This compound was obtained as yellow crystals (MeCN), 0.21 g (38.5%); mp 186–189°C; R_f = 0.29; IR: 3395, 3260, 1725, 1625, 1540, 1360; ^1H NMR (300 MHz, DMSO–d_6): δ = 7.65 (s, 2H, NH_2), 5.23 (s, 2H, N—CH_2), 4.68 (s, 2H, CH_2Br), 2.24 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 195.72, 153.44, 153.11, 120.11, 52.21, 46.98, 13.61; ms: m/z 278 (7), 276 (7) (M^+), 67 (100); Anal. calc. for $C_7H_9N_4O_3Br$: C, 30.46; H, 3.28; N, 20.30; found: C, 30.42; H, 3.26; N, 20.27.

4-Amino-5-nitro-1-phenacylimidazole (33). This compound was obtained as dark yellow pales (MeCN), 0.10 g (20.4%); mp 219–221°C; R_f = 0.30; IR: 3400, 3250, 1670, 1626, 1510, 1350; ^1H NMR (300 MHz, DMSO–d_6): δ = 8.01 (m, 2H, 2,6-Ph), 7.65 (m, 3H, 3,4,5-Ph), 7.69 (s, 2H, NH_2), 7.23 (s, 1H, 2-Im), 5.64 (s, 2H, CH_2); ^{13}C NMR NMR (75 MHz, DMSO–d_6): δ = 191.49, 153.65, 144.06, 134.18, 133.75, 129.01, 128.32, 120.42, 50.55; ms: m/z 246 (6) (M^+), 105 (100); Anal. calc. for $C_{11}H_{10}N_4O_3$: C, 53.69; H, 4.09; N, 22.77; found: C, 53.72; H, 4.10; N, 22.74.

4-Amino-2-methyl-5-nitro-1-phenacylimidazole (34). This compound was obtained as light yellow pales (MeCN), 0.16 g (30.1%); mp 227–229°C; R_f = 0.45; IR: 3400, 3250, 1680, 1620, 1500, 1340; ^1H NMR (300 MHz, DMSO–d_6): δ = 8.06 (m, 2H, 2,6-Ph), 7.68 (m, 5H, 3,4,5-Ph, NH_2), 5.84 (s, 2H, CH_2), 2.28 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 192.52, 153.66, 153.28, 134.06, 133.94, 128.80, 128.07, 120.42, 52.01, 13.70; ms: m/z 260 (27) (M^+), 105 (100); Anal. calc. for $C_{12}H_{12}N_4O_3$: C, 55.41; H, 4.65; N, 21.54; found: C, 55.42; H, 4.62; N, 21.54.

5-Amino-2-methyl-4-nitro-1-phenacylimidazole (35). This compound was obtained as yellow needles (MeCN), 0.03 g (5.8%); mp 265–267°C; R_f = 0.28; IR: 3495, 3265, 1665, 1625, 1555, 1355; ^1H NMR (300 MHz, DMSO–d_6): δ = 8.06 (m, 2H, 2,6-Ph), 7.69 (m, 5H, 3,4,5-Ph, NH_2), 5.63 (s, 2H, CH_2), 2.10 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 192.80, 146.08, 142.11, 135.40, 134.40, 129.83, 129.06, 127.17, 50.27, 13.44; ms: m/z 260 (53) (M^+), 105 (100); Anal. calc. for $C_{12}H_{12}N_4O_3$: C, 55.41; H, 4.65; N, 21.54; found: C, 55.40; H, 4.67; N, 21.50.

4-Amino-1-(*p*-chlorophenacyl)-5-nitroimidazole (36). This compound was obtained as yellow pales (MeCN), 0.12 g (21.4%); mp 245–248°C; R_f = 0.23; IR: 3440, 3255, 1680, 1625, 1565, 1300; ^1H NMR (300 MHz, DMSO–d_6): δ = 8.06 (m, 2H, 2,6-Ph), 7.73 (s, 1H, 2-Im), 7.69 (m, 2H, 3,5-Ph), 7.61 (s, 2H, NH_2), 5.85 (s, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 191.78, 153.16, 144.22, 138.90, 132.57, 129.79, 129.05, 120.33, 53.39; ms: m/z 282(3), 280 (10) (M^+), 139 (100); Anal. calc. for $C_{11}H_9N_4O_3Cl$: C, 47.18; H, 3.24; N, 20.01; found: C, 47.20; H, 3.28; N, 19.98.

4-Amino-1-(*p*-chlorophenacyl)-2-methyl-5-nitroimidazole (37). This compound was obtained as dark yellow pales (MeCN), 0.06 g (10.2%); mp 270–272°C; R_f = 0.43; IR: 3440, 3255, 1680, 1625, 1565, 1300; ^1H NMR (300 MHz, DMSO–d_6): δ = 8.07 (m, 2H, 2,6-Ph), 7.70 (m, 4H, 3,5-Ph, NH_2), 5.82 (s, 2H, CH_2), 2.27 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 191.70, 153.64, 153.24, 138.80, 132.76, 129.97, 128.92, 120.36, 51.96, 13.68; ms: m/z 296 (10), 294 (32) (M^+), 139 (100); Anal. calc. for $C_{12}H_{11}N_4O_3Cl$: C, 49.01; H, 3.77; N, 19.05; found: C, 49.04; H, 3.78; N, 19.09.

5-Amino-1-(*p*-chlorophenacyl)-2-methyl-4-nitroimidazole (38). This compound was obtained as cream needles (MeCN), 0.08 g (13.5%); mp 220°C; R_f = 0.25; IR: 3420, 3250, 1680, 1625, 1540, 1320. ^1H NMR (300 MHz, DMSO–d_6): δ = 8.06 (m, 2H, 2,6-Ph), 7.71 (m, 4H, 3,5-Ph, NH_2), 5.61 (s, 2H, CH_2), 2.10 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO–d_6): δ = 190.88, 144.91, 139.65, 138.78, 132.75, 130.05, 128.76, 126.58, 49.65, 12.84; ms: m/z 296 (10), 294 (31) (M^+), 139 (100); Anal. calc. for $C_{12}H_{11}N_4O_3Cl$: C, 49.01; H, 3.77; N, 19.05; found: C, 49.03; H, 3.75; N, 19.09.

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