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TRANSFORMATIONS OF THE IMIDAZOLE RING IN 1-ALKYL- AND 1-ARYL-4-NITROIMIDAZOLES FOLLOWING THE ATTACK OF HYDROXYLAMINE OR 4-AMINO-1,2,4-TRIAZOLE

Jerzy Suwinski and Krzysztof Swierczek

Novel imidazole-oxadiazole ring interconversions (transformations) accompanying nucleophilic amination of 4-nitroimidazoles by hydroxylamine or 4-amino-1,2,4-triazole are described with suggestions concerning mechanisms of the reactions.

The imidazole ring is characterized by high values of aromatic indices [1]. Due to that, it remains unchanged in most reactions. There are many examples of transformations of other heteroaromatic compounds into imidazole derivatives [2] and only a few of the transformation or decomposition of the imidazole ring. They concern some of the reactions of imidazolium salts or imidazole derivatives containing strong electron-withdrawing groups with nucleophiles [2, 3].

1-Substituted 4-nitroimidazoles constitute a good subject for investigations on the imidazole ring transformation. We have already provided information on the reactions of imidazole ring transformation in 1-arenesulfonyl-4-nitroimidazoles [4] and 1,4-dinitroimidazoles [5] under the action of primary amines, and in 1-aryl-4-nitroimidazoles affected by hydroxylamine [6] or 4-amino-1,2,4-triazole [6, 7]. The present paper presents new results obtained from the latter reactions continued in the group of 1-aryl-4-nitroimidazoles, and additionally in the group of 1-alkyl-4-nitroimidazoles, in which the ring transformations have not been investigated so far. The results obtained during the experiments should be helpful in proposing or specifying the mechanisms of imidazole ring transformation in 4-nitroimidazoles subjected to the reactions with nucleophilic aminating reagents.

In spite of the fact that 1-alkyl-4-nitroimidazoles are easily obtainable (by alkylation of 4(5)-nitroimidazoles in the presence of alkalis [8], or by the reaction of 1,4-dinitroimidazoles with compounds containing primary amino group [5]) and have been for a long time intensely investigated as potential drugs [9], the literature provides no information on transformations of the imidazole ring in these compounds subjected to the reactions with nucleophiles. It was another incentive to begin the investigations in question.

According to the work of Sunjic et al. [10] (often quoted in the chemical literature), the reaction of 1,2-dimethyl-4-nitroimidazole (Ia) with hydroxylamine hydrochloride in the methanol–ethanol mixture containing potassium hydroxide, leads to the formation of 5-amino-1,2-dimethyl-4-nitroimidazole (IIa). While retesting this amination of 1,2-dimethyl-4-nitroimidazole, and, additionally, 1-benzyl-2-methyl-4-nitroimidazole (Ib), we observed that, apart from the expected products of 5-amination (IIa, b), compounds isomeric with them were also formed as by-products in comparatively low yields. We have already proved [6] that, under similar conditions, 1-aryl-2-methyl-4-nitroimidazoles undergo a novel ring transformation to give usually high yields of 4-acetylamino-2-aryl-1-oxy-2H-1,2,3-triazoles (isomeric with 5-amino-1-aryl-2-methyl-4-nitroimidazoles, prepared in these cases in a different reaction). The products (isomeric with aminonitroimidazoles), obtained by the treatment of 4-nitroimidazole Ia, b with hydroxylamine had, however, different structures. They contained neither the triazole ring, nor the imidazole one, though they also were the products of its transformation. Based on the results of elemental analysis and MS and ^{1}H NMR spectra, we suggest for them the structure of 1,2,5-oxadiazole derivatives (IIIa, b) (Scheme 1).

Institute of Organic Chemistry and Technology Silesian Technical University, Krzywoustego 4, 44-100 Gliwice, Poland. Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1214-1221, September, 1996. Original article submitted May 20, 1996.

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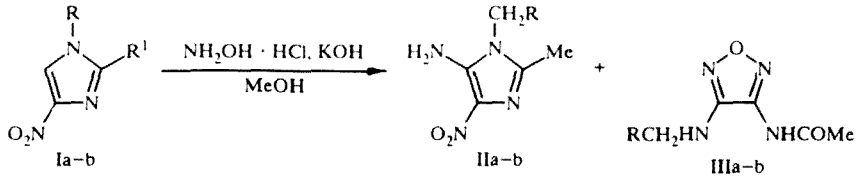
Scheme 1



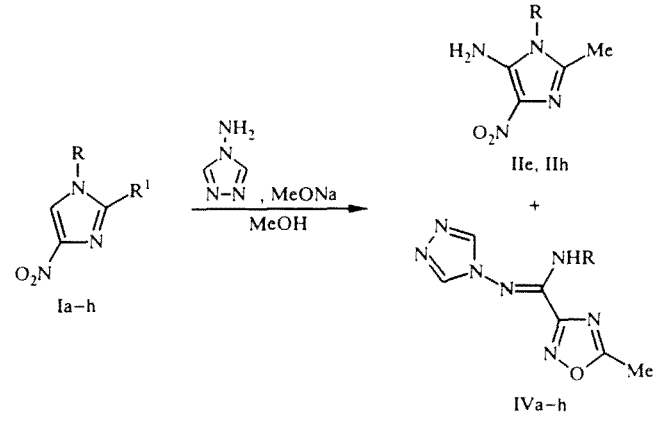
Ia–b IIa–b IIIa–b

a R = Me, b R = CH_2Ph; R^1 = Me

Apart from hydroxylamine, another known nucleophilic aminating agent is 4-amino-1,2,4-triazole [11]. Recently we have given evidence that 2-methyl-4-nitro-1-phenylimidazole (Ic) subjected to the reaction with 4-aminotriazole undergoes both amination (in dimethylsulfoxide) [6] and ring transformation (in methanol into 1,2,4-oxadiazole derivatives) reactions [7]. Thus the preferred course of the reaction depended on the solvent. The aim of the investigations described in this paper was, however, to determine the effect of substituents at position 1 and the possible absence of methyl group at position 2 of the starting 4-nitroimidazoles Ia-m on the course of the reaction with aminotriazole.

It turned out that 1,2-dimethyl-4-nitroimidazole (Ia), 1-benzyl-2-methyl-4-nitroimidazole (Ib), and 1-aryl-2-methyl-4-nitroimidazoles (Ic-h), when subjected to the reaction with 4-amino-1,2,4-triazole in methanol, in the presence of sodium methoxide, underwent transformations into respective derivatives of 1,2,4-oxadiazole (IVa-h). Some of the 1-aryl-2-methyl-4-nitroimidazoles yield additionally small quantities of products of amination at the position 5 (IIe, h) (which have been the only products of the reaction carried out in dimethylsulfoxide [6]) (Scheme 2).

Scheme 2

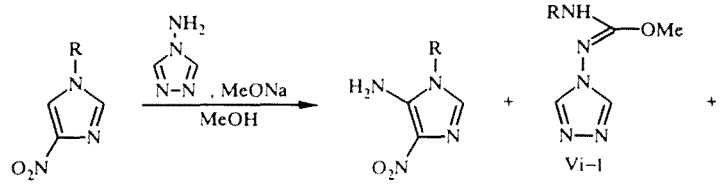


Ia–h IIe, IIh IVa–h

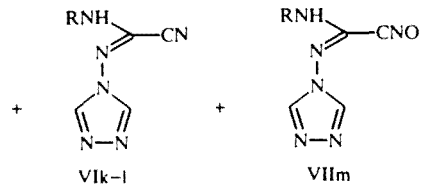
I, II R^1 = Me; IV a R = Me, b R = $CH_2C_6H_5$, c R = Ph, d R = 3-MeC_6H_4, e R = 4-$MeOC_6H_4$, f R = 4-FC_6H_4, g R = 3-ClC_6H_4, h R = 4-BrC_6H_4

The absence of methyl group at position 2 of the imidazole ring in 1-alkyl and 1-aryl-4-nitroimidazoles considerably complicates the reaction with aminotriazole. 1-Methyl-4-nitroimidazole (Ii) and 1-benzyl-4-nitroimidazole (Ij) yield neither the amination products nor oxadiazole derivatives, but they form N,O-dimethyl-N′-(1,2,4-triazol-4-yl)isourea (Vi) and N-benzyl-O-methyl-N′-(1,2,4-triazol-4-yl)isourea (Vj) respectively. 5-Amino derivatives (IIk-*l*), apart from O-methylisourea (Vk, *l*) and amidinecarbonitrile (Vlk, *l*) and, possibly, amidinecarbonitrile oxide (VIIm) derivatives are, however, the main products of the reaction of aminotriazole with 1-aryl-4-nitroimidazoles (Scheme 3).

Scheme 3



Ii–m IIk–l Vi–l



VIk–l VIIm

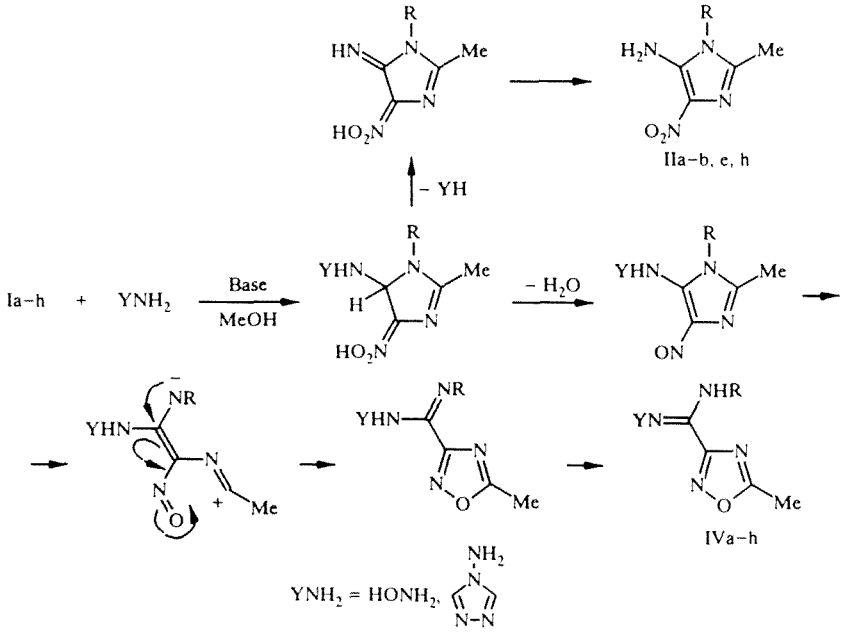
i R = Me; j R = $PhCH_2$; k R = Ph; l R = 4-$MeOC_6H_4$; m R = 3-ClC_6H_4

We were not able to obtain the products VI and VII (Scheme 3) in pure form. Attempts to separate the resulting mixtures, both through crystallization and chromatography, were unsuccessful due to the very weak solubility of the products. In some cases the differences in volatility made it possible to separate the mixtures directly in the mass spectrometer, and hence, to obtain separate MS spectra. Furthermore, high concentration of isourea derivatives in the mixtures made it possible to obtain clear pictures of their ^1H NMR spectra. Prolonging the reaction time, increasing the concentration of sodium methoxide or raising the reaction temperature resulted only in formation of tars. It also applies to other reactions described in the present paper.

Despite the fact that the yields of some products were sometimes low, and that there were difficulties in isolating some of them, the results obtained in the present work allow us to formulate rational hypotheses concerning the mechanisms of observed transformations, as well as hypotheses concerning the effect of 2-methyl substituent in starting 4-nitroimidazoles on the reaction course and the structure of final products.

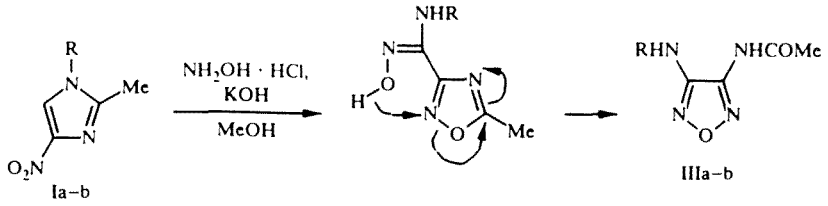
In our opinion, the reactions of hydroxylamine and of 4-amino-1,2,4-triazole (both marked on Scheme 4 with the common symbol YNH_2) with 1-alkyl- and 1-aryl-4-nitroimidazoles (independently of the presence or absence of 2-methyl group in the substrate) occur in the initial phase according to similar mechanisms. The reactions start with the attack of a nucleophile on the carbon atom 5 of the nitroimidazole. The created Meisenheimer's adducts stabilize to amino derivatives, according to the known vicarious nucleophilic substitution, or, when subjected to the attack of sodium methoxide in methanol, their nitro group is reduced to the nitroso one. The mechanism of nitro- to nitroso-group reduction in the presence of nucleophile (e.g., hydride anion) and sodium methoxide–methanol system has been investigated and presented by us in detail in another work [12]. After the N(1)–C(2) bond break, nitrosoimidazole transforms into 1,2,4-oxadiazole (Scheme 4). Further possible transformations of 1,2,4-oxadiazole derivatives depend on the substituents present (or absent) therein.

Scheme 4



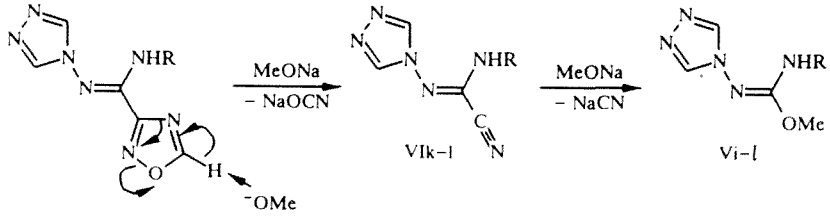
As to the reaction of 1-alkyl-2-methyl-4-imidazoles Ia, b with hydroxylamine, the forming 1,2,4-oxadiazole derivative, which is analogous to products IV, due to the presence in the alkaline medium of the strongly nucleophilic oxime oxygen atom undergoes in turn Boulton–Katritzky's transformation into 1,2,5-oxadiazole derivative IIIa, b (Scheme 5).

Scheme 5



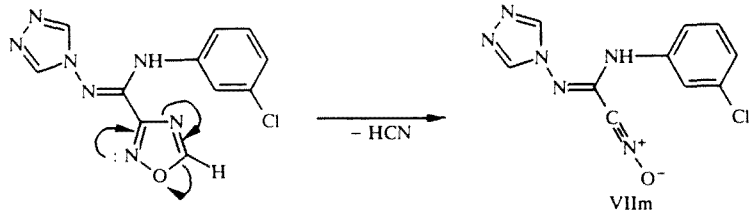
We assume that derivatives of 1,2,4-oxadiazole are also formed as intermediate products, in the reactions of 1-alkyl and 1-aryl-4-nitroimidazoles without methyl group at the position 2, but after that, the oxadiazole ring undergoes decomposition. The formation of amidinecarbonitrile derivatives VIk, *l* can be explained by a generally known fact that in an alkaline medium 1,2,4-oxadiazoles with the free 5-position eliminate cyanic acid and form cyanides [13]. Amidinecarbonitriles VIk, *l* subjected to the sodium methoxide-methanol system undergo the replacement of cyanide group by methoxy one to form isourea derivatives Vi, *l* (Scheme 6).

Scheme 6



Possible presence of amidinecarbonitrile oxide VIIm (not isolated in a pure form) among the reaction products of 1-(3-chlorophenyl)-4-nitroimidazole Im with aminotriazole can be explained by 1,3-dipolar cycloelimination of the hydrogen cyanide particle from the respective 1,2,4-oxadiazole (Scheme 7), although the probability of such a reaction under the experimental conditions is rather low.

Scheme 7



Since the investigated reactions took course in many directions, and the experiments did not have quantitative character, their results do not make it possible to evaluate without doubt the effect of a substituent at the position 1 of the starting 4-nitroimidazoles on the tendency to transform the imidazole ring in reactions with aminating nucleophilic reagents. Dramatic differences in the structure of the reaction products of 1-alkyl-2-methyl-4-nitroimidazoles (5-amino-4-nitroimidazoles) and 1-aryl-2-methyl-4-nitroimidazoles (1,2,3-triazole N-oxides) with hydroxylamine indicate that at least in some cases the effect can be dominant.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded in DMSO-D_6 with TMS as the internal standard. TLC was performed on plates with silica gel, developed with benzene–ethyl acetate (1:2) or acetone and observed under UV light.

Reactions of 1-Alkyl-2-methyl-4-nitroimidazoles (Ia, b) with Hydroxylamine (general procedure). To a suspension of nitroimidazole and hydroxylammonium chloride in methanol, an 11 M potassium hydroxide solution in methanol

was added dropwise while stirring at < 5°C. The mixture was stirred several hours at 25°C and then neutralized with conc. hydrochloric acid. Methanol was removed under reduced pressure and the residue was diluted with water. The precipitations were collected and extracted with boiling water. Insoluble crude oxadiazole was filtered off. The hot filtrate was evaporated to yield crude aminonitroimidazole. The crude products were recrystallized and analyzed.

5-Amino-1,2-dimethyl-4-nitroimidazole (IIa) and 3-Acetylamino-4-methylamino-1,2,5-oxadiazole (IIIa). 4-Nitroimidazole Ia (10 g, 0.071 mole), hydroxylammonium chloride (30 g, 0.43 mole) in methanol (150 ml) and the potassium hydroxide solution (100 ml) gave compounds IIa (7.95 g, 71.9%) and IIIa (0.82 g, 7.4%). IIa, mp 284-285°C (from water, dec.). ^{1}H NMR: 2.20 (s, 3H), 3.39 (s, 3H), 7.60 (s, 2H). MS: 156 (M^+, 38.7), 140 (2.4), 139 (1.6), 122 (1.7), 110 (5.3), 109 (3.0), 108 (1.8), 93 (1.8), 83 (13.1), 67 (19.3), 56 (100.0), 43 (24.6), 42 (28.5). Found, %: C 37.91; H 5.31; N 35.46. $C_5H_8N_4O_2$. Calculated, %: C 38.46; H 5.16; N 35.88. IIIa, mp 257°C (from acidified alkaline solution, dec.). ^{1}H NMR: 2.22 (s, 3H), 3.11 (s, 3H), 11.11 (s, 1H), 11.28 (s, 1H). MS: 156 (M^+, 21.3), 140 (2.3), 126 (21.1), 122 (2.9), 108 (13.9), 96 (29.6), 85 (8.9), 83 (6.0), 81 (6.7), 72 (11.2), 67 (62.0), 56 (59.9), 43 (23.3), 42 (73.3). Found, %: C 38.37; H 5.19; N 35.08. $C_5H_8N_4O_2$. Calculated, %: C 38.46; H 5.16; N 35.88.

5-Amino-1-benzyl-2-methyl-4-nitroimidazole (IIb) and 3-Acetylamino-4-benzylamino-1,2,5-oxadiazole (IIIb). 4-Nitroimidazole Ib (5g, 0.023 mole), hydroxylammonium chloride (15 g, 0.22 mole) in methanol (75 ml) and the potassium hydroxide solution (50 ml) gave compounds IIb (3.02 g, 56.4%) and IIIb (0.18 g, 3.4%); IIb mp 184.5-186°C (from water). ^{1}H NMR: 2.15 (s, 3H), 5.20 (s, 2H), 6.8-7.5 (m, 5H), 7.70 (s, 2H). Found, %: C 56.55; H 5.18; N 24.04. $C_{11}H_{12}N_4O_2$. Calculated, %: C 56.89; H 5.21; N 24.13; IIIb, mp 220°C (from acidified alkaline solution, dec.), ^{1}H NMR: 2.22 (s, 3H), 4.80 (s, 2H), 7.20 (s, 5H), 11.00 (s, 1H), 11.25 (s, 1H). Found, %: C 56.71; H 5.15; N 24.05, $C_{11}H_{12}N_4O_2$. Calculated, %: C 56.89; H 5.21; N 24.13.

Reactions of 1-Alkyl (Ia, b) or 1-aryl-2-methyl-4-nitroimidazoles (Ic-h) with 4-amino-1,2,4-triazole (a general procedure). Sodium methoxide solution (prepared by dissolution of sodium in methanol), 1-alkyl- or 1-aryl-2-methyl-4-nitroimidazole and 4-amino-1,2,4-triazole in methanol were left at 25°C until full conversion of the nitroimidazole. The reaction progress was monitored by TLC. The reaction mixture was then neutralized with conc. hydrochloric acid; methanol was removed under reduced pressure; the residue was diluted with water and forming precipitations were collected. Further work-up, slightly different for each reaction, is given below.

N^1-Methyl-N^2-(1,2,4-triazol-4-yl)-5-methyl-1,2,4-oxadiazole-3-carboxamidine (IVa). From sodium (4 g, 0.174 mole), Ia (2 g, 14.2 mmole), 4-amino-1,2,4-triazole (4 g, 47.6 mmole) in methanol (200 ml) after 12 days of reacting no precipitation was observed. Thus the aqueous solution was extracted with chloroform; the organic layer was separated and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to leave crude solid oxadiazole IVa (1.19 g, 40.5%), mp 186-188°C (from acetone). ^{1}H NMR: 2.60 (s, 3H), 2.90 (d, 3H), 8.30 (s, 2H). MS: 207 (M^+, 27.1), 136 (4.1), 124 (33.9), 110 (38.6), 95 (6.8), 83 (32.4), 82 (44.9), 69 (30.7), 68 (15.5), 56 (13.0), 55 (20.2), 53 (22.5), 43 (100.0), 42 (60.3). Found, %: C 40.24; H 4.33; N 47.04. $C_7H_9N_7O$. Calculated, %: C 40.58; H 4.37; N 47.33.

N^1-Benzyl-N^2-(1,2,4-triazol-4-yl)-5-methyl-1,2,4-oxadiazole-3-carboxamidine (IVb). From sodium (4 g, 0.174 mole), Ib (2 g, 9.22 mmole), 4-amino-1,2,4-triazole (4 g, 47.6 mmole) and methanol (200 ml) after 21 days oxadiazole IVb (1.98 g, 75.9%) was obtained. It was recrystallized from aqueous methanol to give white crystals of mp 208-209°C. ^{1}H NMR: 2.55 (s, 3H), 4.60 (s, 2H), 7.30 (s, 5H), 8.25 (s, 2H), 8.82 (s, 1H). MS: 287 (M^+, 19.6), 246 (1.8), 245 (1.9), 216 (36.7), 204 (68.9), 163 (39.5), 162 (17.8), 135 (17.2), 122 (30.6), 121 (38.1), 95 (38.3), 83 (53.6), 75 (26.3), 43 (100.0). Found, %: C 54.54; H 4.52; N 34.38. $C_{13}H_{13}N_7O$. Calculated, %: C 55.11; H 4.63; N 34.61.

N^1-Phenyl-N^2-(1,2,4-triazol-4-yl)-5-methyl-1,2,4-oxadiazole-3-carboxamidine (IVc). From sodium (1.2 g, 52 mmole), Ic (0.5 g, 2.46 mmole), 4-amino-1,2,4-triazole (1.1 g, 13.1 mmole) and methanol (50 ml) after 3 days oxadiazole IVc (0.5 g, 74%) was obtained. It was recrystallized from aqueous methanol to give needles decomposing at 215°C. ^{1}H NMR: 2.65 (s, 3H), 7.1-7.9 (m, 5H), 8.40 (s, 2H), 10.40 (s, 1H). HRMS (%, formula, Δ): 269.1016 (37, $C_{12}H_{11}N_7O$, 3.3), 198.0756 (37, $C_{10}H_8N_5$, 11.9), 186.0682 (100, $C_{10}H_8N_3O$, 8.1). ^{13}C NMR: 11.7, 120.9, 124.5, 128.8, 138.2, 140.7, 153.5, 160.7, 178.1. Found, %: C 53.80; H 4.18; N 35.92. $Cl_{12}H_{11}N_7O$. Calculated, %: C 53.53; H 4.12; N 36.40.

N^1-(3-Methyl)-N^2-(1,2,4-triazol-4-yl)-5-methyl-1,2,4-oxadiazole-3-carboxamidine (IVd). From sodium (1.2 g, 52 mmole), nitroimidazole Id (0.5 g, 2.30 mmole), 4-amino-1,2,4-triazole (1.1 g, 13.1 mmole) and methanol (50 ml) after 6 days oxadiazole IVd (0.46 g, 78.4%) was separated. Recrystallization from ethanol afforded decomposition of needles at 224°C. ^{1}H NMR: 2.32 (s, 3H), 2.65 (s, 3H), 6.9-7.7 (m, 4H), 8.40 (s, 2H), 10.33 (s, 1H). MS: 283 (M^+, 58.2), 212 (29.5), 200 (95.1), 171 (17.8), 131 (24.0), 118 (21.1), 77 (35.8), 65 (43.9). Found, %: C 54.99; H 4.53; N 34.52. $C_{13}H_{13}N_7O$. Calculated, %: C 55.12; H 4.63; N 34.61.

N^1-(4-Methoxyphenyl)-N^2-(1,2,4-triazol-4-yl)-5-methyl-1,2,4-oxadiazole-3-carboxamidine(IVe)and5-Amino-1-(4-methoxyphenyl)-2-methyl-4-nitroimidazole (IIe). From sodium (4 g, 0.174 mole), nitroimidazole Ie (2 g, 8.58 mmole), 4-amino-1,2,4-triazole (4 g, 47.6 mmole) and methanol (200 ml) after 14 days a mixture of IIe and IVe (2.22 g) was obtained. The mixture was stirred with diluted (1:5) hydrochloric acid (120 ml) for 0.5 hour. The obtained suspension was filtered. The filtrate was neutralized with concentrated sodium hydroxide solution to afford yellow precipitations that after rinsing with water and drying gave aminonitroimidazole IIe (0.15 g, 7%), mp, and MS spectrum identical with those given in the literature [6]. Solid insoluble in acid was combined with the neutral filtrate and alkalized with concentrated sodium hydroxide solution to yield white solid oxadiazole IVe (1.68 g, 65.5%). It was recrystallized twice from methanol to afford needles decomposing at 212°C. ^{1}H NMR: 2.65 (s, 3H), 3.79 (s, 3H), 7.0-7.7 (m, 4H), 8.40 (s, 1H). MS: 299 (M, 45.6), 281 (22.4), 257 (13.6), 216 (53.0), 188 (8.6), 175 (17.6), 147 (36.8), 133 (28.0), 108 (11.9), 92 (14.0), 43 (100.0). Found, %: C 52.20; H 4.27; N 32.70. $C_{13}H_{13}N_7O_2$. Calculated, %: C 52.17; H 4.38; N 32.76.

N^1-(3-Fluorophenyl)-N^2-(1,2,4-triazol-4-yl)-5-methyl-1,2,4-oxadiazole-3-carboxamidine (IVf). Sodium (1.2 g, 52 mmole) nitroimidazole If (0.5 g, 2.26 mmole), 4-amino-1,2,4-triazole (1.1 mmole) reacting in methanol (50 ml) for 4 days afforded oxadiazole IVf (0.55 g, 87%) that after recrystallization from methanol decomposed at 241°C. ^{1}H NMR: 2.65 (s, 3H), 7.2-7.9 (m, 4H), 8.41 (s, 2H), 10.46 (s, 1H). MS: 287 (M^+, 19.6), 246 (1.8), 245 (1.9), 216 (36.7), 204 (68.9), 163 (39.5), 162 (17.8), 135 (17.2), 122 (30.6), 121 (38.1), 95 (38.3), 83 (33.6), 75 (26.3), 43 (100.0). Found, %: C 50.44; H 3.51; N 34.16. $C_{12}H_{10}FN_7O$. Calculated, %: C 50.16; H 3.51; N 34.14.

N^1-(3-Chlorophenyl)-N^2-(1,2,4-triazol-4-yl)-5-methyl-1,2,4-oxadiazole-3-carboxamidine (IVg). Sodium (1.2 g, 52.2 mmole), nitroimidazole Ig (0.5 g, 2.11 mmole), 4-amino-1,2,4-triazole (1.1 g, 13.1 mmole) reacting in methanol (50 ml) for 3 days yielded oxadiazole IVg (0.52 g, 81.3%) that after recrystallization from aqueous methanol decomposed at 235°C, ^{1}H NMR: 2.65 (s, 3H), 7.1-9.0 (m, 4H), 8.45 (s, 2H), 10.60 (s, 1H). MS: 303 (M^+, 16.9), 262 (4.7), 232 (47.1), 220 (90.0), 179 (27.1), 152 (19.6), 137 (35.6), 111 (38.8), 75 (45.0), 43 (100.0). Found, %: C 47.41; H 3.21; N 32.28. $C_{12}H_{10}ClN_7O$. Calculated, %: C 47.46; H 3.32; N 32.28.

N^1-(4-Bromophenyl)-N^2-(1,2,4-triazol-4-yl)-5-methyl-1,2,4-oxadiazole-3-carboxamidine (IVh) and 5-Amino-1-(4-bromophenyl)-2-methyl-4-nitroimidazole (IIh). Sodium (4 g, 174 mmole), nitroimidazole Ih (2 g, 7.1 mmole), 4-amino-1,2,4-triazole (4 g, 47.6 mmole) reacting in methanol (200 ml) for 3 days afforded a mixture of IIh and IVh (2.17 g). The mixture was treated with concentrated hydrochloric acid (25 ml). Insoluble white solid was collected. The filtrate was neutralized with concentrated sodium hydroxide solution. Forming yellow solid was filtered off and rinsed with water to give after drying aminonitroimidazole IIh (0.14 g, 6.6%), mp 250°C (dec.). MS: 298 (M^+, 97.9), 296 (M^+, 96.8), 281 (6.2), 279 (5.9), 266 (3.7), 264 (4.1), 240 (3.7), 238 (4.4), 226 (21.9), 224 (32.2), 198 (88.8), 196 (84.4), 157 (78.4), 155 (79.2), 83 (28.0), 76 (100.0), 75 (80). Found, %: C 40.38; H 3.03; N 18.83. $C_{10}H_9BrN_4O$. Calculated, %: C 40.13; H 3.05; N 18.86. Solid insoluble in acid was treated with water and dried then to yield oxadiazole IVh (0.83 g, 46.6%) that after recrystallization from methanol decomposed at 247°C. ^{1}H NMR: 2.64 (s, 3H), 7.5-7.85 (m, 4H), 8.42 (s, 2H), 10.55 (s, 1H). MS: 349 (M^+, 38.8), 347 (M, 38.4), 306 (3.6), 278 (61.8), 276 (60.9), 266 (97.6), 264 (100.0), 225 (43.3), 223 (43.8), 198 (32.4), 197 (34.2), 196 (23.7), 195 (25.0), 184 (36.9), 183 (40.0), 182 (38.5), 181 (37.5), 157 (52.0), 155 (47.0), 144 (34.6), 102 (62.8), 91 (50.1), 90 (49.8), 77 (38.2), 76 (77.0). Found, %: C 41.58; H 2.73; N 28.37. $C_{12}H_{10}BrN_7O$. Calculated, %: C 41.40; H 2.90; N 28.16.

Reactions of 1-Alkyl- (Ii, j) or 1-Aryl-4-nitroimidazoles (Ik-m) with 4-Amino-1,2,4-triazole (general procedure). The reactions were performed similarly to the reactions of 2-methyl-4-nitroimidazoles described earlier. After completion of the reaction, aminonitroimidazoles (II) were filtered off. The filtrate was neutralized with conc. hydrochloric acid, then methanol was evaporated under reduced pressure and water was added to the residue. The precipitations were collected and analyzed.

N,O-Dimethyl-N′-(1,2,4-triazol-4-yl)isourea (Vi). Sodium (4 g, 174 mmole), nitroimidazole Ii (2 g, 15.7 mmole), 4-amino-1,2,4-triazole (4 g, 47.6 mmole) reacting in methanol (200 ml) for 30 days afforded clear solution only. The solution was extracted with chloroform (4 × 20 ml). The organic layer was separated, dried over magnesium sulfate, and condensed to yield isourea Vi (0.45 g, 18.4%) of mp 192-195°C (from acetone). ^{1}H NMR: 2.58 (d, 3H), 3.85 (s, 3H), 6.52 (q, 1H), 8.30 (s, 2H). Found, %: C 38.46; H 5.82; N 45.01. $C_5H_9N_5O$. Calculated, %: C 38.70; H 5.84; N 45.14.

N-Benzyl-O-methyl-N′-(1,2,4-triazol-4-yl)isourea (Vj). From sodium (4 g, 174 mmole), nitroimidazole Ij (2 g, 9.85 mmole), 4-amino-1,2,4-triazole (4 g, 47.6 mmole) in methanol (200 ml) after 20 days isourea Vj (1.46 g, 64.1%) was obtained. It was recrystallized from methanol to give white crystals of mp 183-185°C. ^{1}H NMR: 3.76 (s, 3H), 4.12 (d, 2H), 7.20 (s, 5H), 8.35 (s, 2H). Found, %: C 56.68; H 5.61; N 30.68. $C_{11}H_{13}N_5O$. Calculated, %: C 57.13; H 5.67; N 30.29.

5-Amino-4-nitro-1-phenylimidazole (IIk), O-Methyl-N-phenyl-N′-(1,2,4-triazol-4-yl)isourea (Vk) and N-phenyl-N′-(1,2,4-triazol-4-yl)amidinecarbonitrile (VIk). From sodium (2g, 87 mmole), nitroimidazole Ik (1g, 5.29 mmole), 4-amino-1,2,4-triazole (2 g, 23.8 mmole) and methanol (100 ml) reacting for 5 days known [6] aminonitroimidazole IIk (0.35 g, 32.4%) and a mixture (0.54 g) of isourea Vk and nitrile VIk was obtained. The mixture decomposing at 165°C was analyzed producing the following data. ^{1}H NMR: 3.88 (s), 6.9-7.9 (m), 8.45 (s), 8.80 (s), 8.85 (s), 11.35 (s). MS: 217 (M^+ Vk, 74.6, 212 (M^+ VIk, 7.0), 161 (6.7), 160 (9.1), 134 (27.7), 133 (6.9), 120 (40.1), 119 (42.2), 118 (22.0), 106 (8.2), 104 (16.0), 103 (18.6), 92 (42.1), 91 (53.1), 77 (97.9), 65 (52.1), 51 (50.2), 39 (42.3), 27 (100.0). Found, %: C 56.17; H 4.50; N 35.71.

5-Amino-1-(4′-methoxyphenyl-4-nitroimidazole (III), N-(4′-Methoxyphenyl-O-methyl-N′-(1,2,4-triazol-4-yl)isourea (V*l*) and N-(4′-methoxyphenyl-N′-(1,2,4-triazol-4-yl)amidinecarbonitrile (VII) [sic]. From sodium (2 g, 87 mmole), nitroimidazole Il (1 g, 4.57 mmole), 4-amino-1,2,4-triazole (2 g, 23.8 mmole) and methanol (100 ml) reacting for 5 days known [6] aminonitroimidazole III (0.3 g, 28.1%) and a mixture (0.76 g) of isourea V*l* and nitrile VII was obtained. The mixture decomposing at 185°C was analyzed, producing the following data. ^{11}H NMR: 3.70 (s), 3.75 (s), 385 (s), 6.6-7.7 (m), 8.45 (s), 8.60 (s), 8.70 (s), 11.20 (s). MS: 247 (M^+ V*l*, 33.1), 242 (M^+ VII, 90.6), 215 (20.1), 201 (12.9), 159 (100.0), 147 (44.1), 134 (73.2), 133 (63.6), 122 (25.0), 107 (38.4), 92 (32.6), 90 (31.6), 77 (54.0), 64 (49.0), 63 (51.4), 53 (49.3), 39 (38.3), 27 (56.9). Found, %: 52.69; H 4.96; N 30.54.

N-(3′-Chlorophenyl-N′-(1,2,4-triazol-4-yl)amidinecarbonitrile (VIm) and (N-3′-Chlorophenyl-N′-(1,2,4-triazol-4-yl)amidinecarbonitrile N-Oxide (VIIm) [sic]. From sodium (1.2 g, 52.2 mmole), nitroimidazole Il (0.5 g, 2.24 mmole), 4-amino-1,2,4-triazole (1.1 g, 13.1 mmole) and methanol (50 ml) reacting for 2 days a mixture (0.26 g) of nitrile VIm and nitrile N-oxide VIIm was obtained. The mixture decomposing at 202-228°C was analyzed producing the following data. ^{1}H NMR: 7.1-8.0 (m, 4H), 8.80 (s, 2H), 11.50 (s, 1H). MS: 262 (M^+ VIIm, 22.7), 246 (M^+ VIk, 7.2), 219 (44.6), 201 (3.2), 177 (3.1), 163 (10.4), 152 (36.9), 137 (36.4), 125 (22.5), 111 (26.3), 99 (37.3), 85 (33.3), 75 (42.4), 71 (66.4), 69 (50.1), 57 (100), 43 (98.0). Found, %: C 48.25; H 2.69; N 33.72.

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