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NUCLEOPHILIC ALKYLATION AND RING TRANSFORMATION IN 4-NITROIMIDAZOLES

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Novel imidazole-oxadiazole ring transformation and oxidative nucleophilic substitution of hydrogen in 4-nitroimidazoles following attack by carbanions are described with suggestions concerning the mechanisms of the reactions.

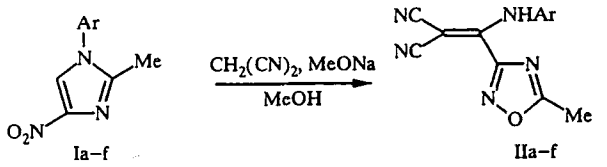
In the chemical literature one can find many examples of heteroarene ring transformations into imidazole derivatives [1] while only few polar inverse transformations are known. Most of them refer to the reactions of imidazole salts or derivatives containing strong electron-withdrawing groups with nucleophiles [1, 2]. In other compounds the imidazole ring is highly aromatic [3] and not susceptible to attack by nucleophiles.

In the previous studies we have shown that 1-substituted 4-nitroimidazoles provide convenient subjects to investigate imidazole ring transformations following nucleophilic attack of primary amines [4, 5], hydroxylamine [6], 4-amino-1,2,4-triazole [6-8], and sulfide ions [7].

This work shows the preliminary results of reactions of relatively stable carbanions (not containing a nucleofugal group at the nucleophilic center, to avoid probable vicarious nucleophilic substitution [9]) with selected 1-alkyl- and 1-aryl-4-nitroimidazoles. The reactions were carried out under conditions similar to those used previously [6-8], i.e., in methanol in the presence of sodium methoxide at 25°C.

Under these conditions malononitrile reacting with 1-aryl-2-methyl-4-nitroimidazoles (Ia-f) gave derivatives of 1,2,4-oxadiazole IIa-f (Scheme 1).

Scheme 1

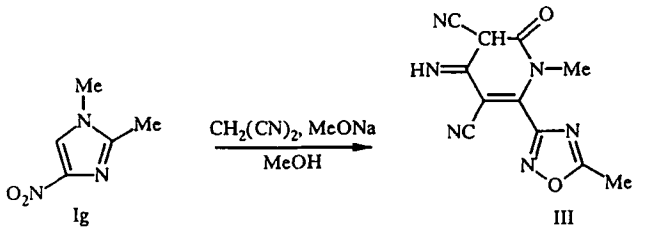


Ia–f IIa–f

a Ar = C_6H_5, b Ar = 4-$MeOC_6H_4$, c Ar = 3-ClC_6H_4, d Ar = 4-BrC_6H_4, e Ar = 4-FC_6H_4, f Ar = 4-MeC_6H_4

The use of 1,2-dimethyl-4-nitroimidazole (Ig) also led to 1,2,4-oxadiazole (III), but with a different kind of substituent at the 3-position (Scheme 2).

Scheme 2



Ig III

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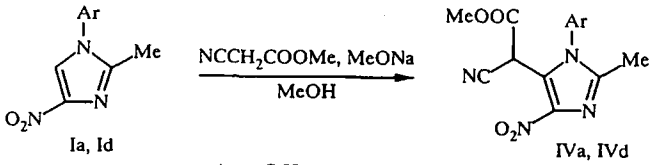
Methyl cyanoacetate reacting with 1-aryl-2-methyl-4-nitroimidazoles afforded products unlike those described until now. In these reactions the imidazole ring remained unchanged. The compounds obtained have been identified as the products of substitution of the 5-H atom in 4-nitroimidazoles with the methyl cyanoacetate group (Scheme 3).

Scheme 3

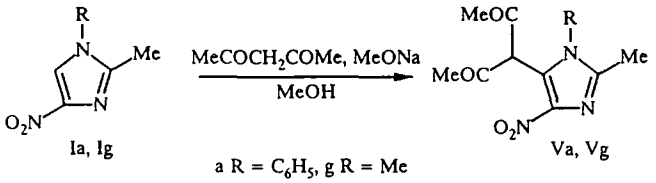


Ia, Id — IVa, IVd

a Ar = C_6H_5, d Ar = 4-BrC_6H_4

Reactions of acetylacetone with 2-methyl-4-nitro-1-phenylimidazole (Ia) or 1,2-dimethyl-4-nitroimidazole (Ig) took a similar course as the reaction of methyl cyanoacetate with the same nitroimidazoles, though only low yields of the products were obtained (Scheme 4). The products were isolated and purified by repeated recrystallization because of difficultly removable impurities. This doubtless considerably reduced the final yields.

Scheme 4



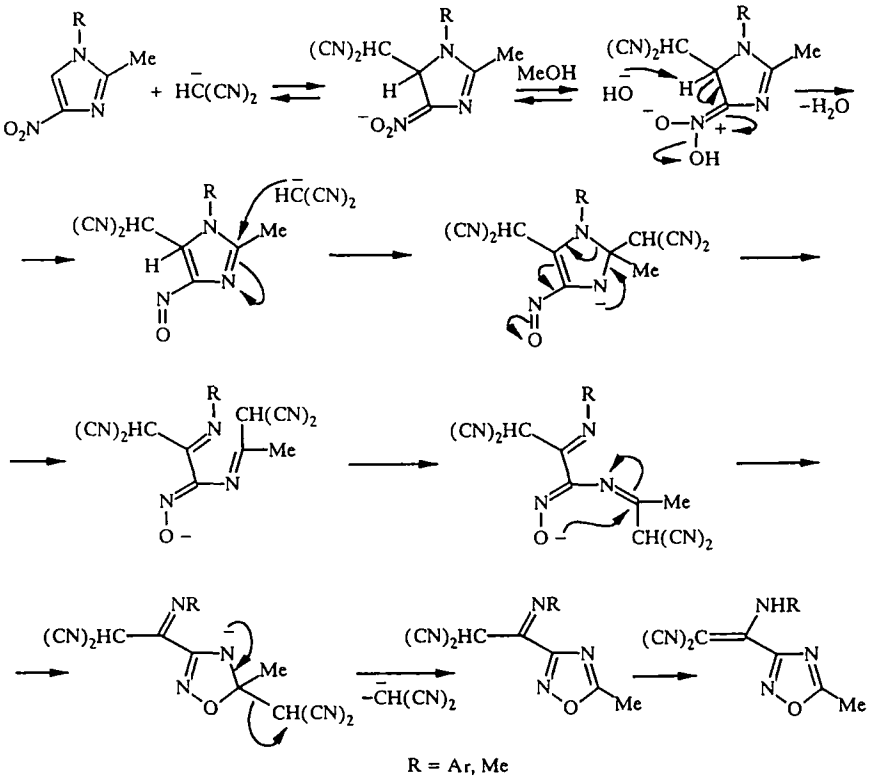
Ia, Ig — Va, Vg

a R = C_6H_5, g R = Me

Reactions of malononitrile with 1-alkyl- and 1-aryl-4-nitroimidazoles (without the methyl group in the 2-position) and reactions of methyl cyanoacetate with 1,2-dimethyl-4-nitroimidazole (Ig) produced only mixtures of unidentified substances.

The structure of 1,2,4-oxadiazoles (formed in the reaction of malononitrile with imidazole I) is similar to that of products we obtained earlier in the reaction of compound I with 4-amino-1,2,4-triazole [7, 8]. Thus, we suppose that the mechanisms of both reactions are similar (Scheme 5).

Scheme 5



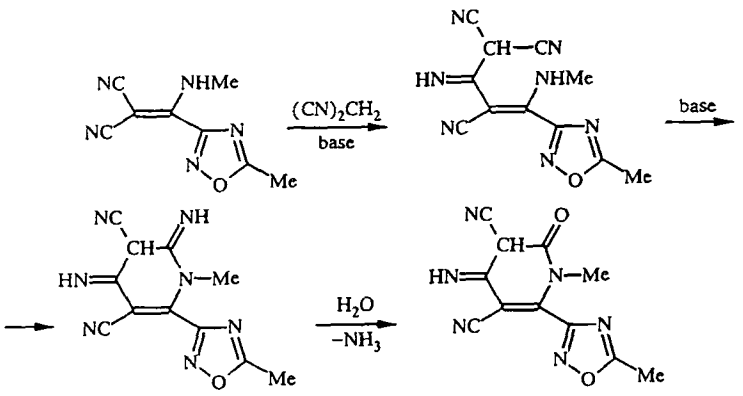
R = Ar, Me

The reaction begins with the nucleophilic attack of malononitrile carbanion on the $C_{(5)}$ atom in the starting nitroimidazole. The forming σ^H-complex cannot be stabilized according to the mechanism of vicarious substitution of hydrogen atom (lack of a nucleofugal group at the nucleophilic center). Instead, the known reduction of the nitro to the nitroso group [10] proceeds under the action of sodium methoxide in methanol. Then the nitrosoimidazole formed rearranges to 1,2,4-oxadiazole. Probably the rearrangement is catalyzed by any active nucleophile present in the reaction mixture. The nucleophilic catalyst attacks the position 2, the $N_{(1)}-C_{(2)}$ bond breaks, rotation around the $N_{(3)}-C_{(4)}$ bond occurs, and finally the 1,2,4-oxadiazole ring is formed, reproducing the nucleophilic catalyst.

Most probably, a compound of structure similar to II is formed as an intermediate in the reaction of malononitrile with 1,2-dimethyl-4-nitroimidazole (Ig). However, the intermediate is subjected to further reactions. We assume base-catalyzed addition of the second molecule of malononitrile to the cyanide group of the intermediate oxadiazole. This is followed by six-membered ring closure (as a result of intramolecular addition) and, finally, hydrolysis of imine (Scheme 6). Most likely, a similar reaction of IIa-f with malononitrile is impeded by the reduced nucleophilic properties of the nitrogen atom in the arylamino group (compared with the methylamino group in Ig).

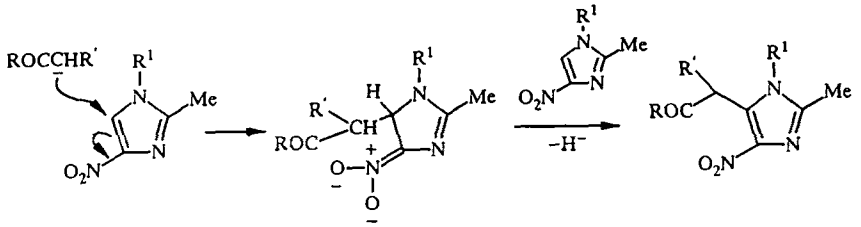
The reactions of methyl cyanoacetate or acetylacetone with 1-alkyl- and 1-aryl-2-methyl-4-nitroimidazoles occur according to the mechanism of the so-called oxidative aromatic nucleophilic substitution of the hydrogen atom. It involves the "spontaneous" oxidation of the σ^H-complex by the second molecule of the starting nitroimidazole (Scheme 7). The nitroimidazole reduction products have not been isolated, but this is understood in the light of their known instability [11].

Scheme 6



The σ^H-complexes from acetylacetone or methyl cyanoacetate and 4-nitroimidazoles are not converted to nitroso derivatives (which would rearrange to 1,2,4-oxadiazoles). This is probably related to the interaction of the carbonyl groups present in the substituents at position 5 with an oxygen atom from the nitro group. Explanation of these interactions is the subject of our present investigations.

Scheme 7



R = MeO, R' = CN; R = Me, R' = MeCO; R^1 = Ar, Me

The results of this work confirm our earlier observations that 1-aryl-2-methyl-4-nitroimidazoles I (from those being examined here) are the best models for the investigation of imidazole ring transformations following attack by anionic nucleophiles. It concerns nucleophiles carrying the hydrogen atom at the nucleophilic center. Replacement of the aryl substituent

(at position 1 of I) with an alkyl substituent, or the methyl group (at position 2) with hydrogen atom, does not change substantially the direction of the nitroimidazole reactions with nucleophiles. The changes in structure of the starting imidazoles considerably reduce the stability of intermediates and final products, frequently leading to production of mixtures that are difficult to separate. This explains the lack of identified reaction products of 1-alkyl- and 1-aryl-4-nitroimidazoles with the tested carbanions.

In the previous work [8] we suggested 1,2,5-oxadiazole derivative structures for the by-product reactions of 1,2-dimethyl-4-nitroimidazole or 1-benzyl-2-methyl-4-nitroimidazole with hydroxylamine, while assuming they are produced due to Boulton–Katritzky rearrangement of the intermediately formed 1,2,4-oxadiazoles. From repeated examination of the spectral data of these by-products we are inclined to conclude that our suggestion relating to the structures may be improper since it cannot be ruled out that the compounds described by us as 1,2,5-oxadiazoles are, in fact, isomeric to them. Also, the structure of compound III from the reaction of malononitrile with Ig, as suggested in this study, requires additional investigations using the X-ray diffraction method.

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 or 1-Aryl-2-methyl-4-nitroimidazoles with Malononitrile (general procedure). Sodium methoxide solution prepared by dissolution of sodium (1.2 g, 52 mmole) in methanol, 1-alkyl or 1-aryl-2-methyl-4-nitroimidazole, and malononitrile in methanol (50 ml) were left at 25°C until full conversion of the nitroimidazole. The progress of the reaction 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 the precipitate formed was collected, dried, and crystallized from water–methanol mixture. Further work-up, slightly different for each reaction, is given below.

3-(3,5-Dicyano-4-imino-1-methyl-6-oxo-pyridin-2-yl)-5-methyl-1,2,4-oxadiazole (III). From 1,2-dimethyl-4-nitroimidazole Ig (2 g, 14.2 mmole), malononitrile (2.06 g, 31 mmole), sodium (4 g, 174 mmole), and methanol (200 cm^3), after 24 hours crude oxadiazole III (0.97 g, 26.7%) was obtained; mp 245-247°C (dec.). ^1H NMR: 2.75 (s, 3H, C–CH_3), 4.00 (s, 3H, –CH_3), 8.2 (broad s). ^{13}C NMR: 12.0, 55.0, 82.4, 82.9, 113.6, 114.1, 144.2, 161.2, 163.4, 165.8, 178.7. MS: 256 (M^+, 76.4), 241 (24.9), 227 (7.4), 215 (11.9), 186 (17.2), 185 (19.3), 130 (11.0), 69 (10.7), 43 (100). Found, %: C 51.49; H 3.06; N 32.66. $C_{11}H_8N_6O_2$. Calculated, %: C 51.56; H 3.15; N 32.80.

3-(2,2-Dicyano-1-phenylaminovinyl)-5-methyl-1,2,4-oxadiazole(IIa). From2-methyl-4-nitro-1-phenylnitroimidazole Ia (0.5 g, 2.46 mmole) and malononitrile (0.2 g, 2.96 mmole) after 5 days crude oxadiazole IIa (0.4 g, 64.7%) was obtained; mp 175-176°C. ^1H NMR: 2.70 (s, 3H, CH_3), 7.2-7.7 (m, 5H, Ph), 11.45 (broad s, 1H, NH). ^{13}C NMR: 11.9, 113.0, 115.0, 125.0, 127.7, 129.0, 136.6, 152.8, 162.9, 178.9. MS: 251 (M^+, 19), 236 (7), 209 (60), 182 (4), 167 (31), 144 (5), 102 (4), 77 (100), 65 (9), 51 (51), 43 (82). Found, %: C 62.11; H 3.53; N 27.54. $C_{13}H_9N_5O$. Calculated, %: C 62.15; H 3.61; N 27.87.

3-[2,2-Dicyano-1-(4-metoxyphenylamino)vinyl]-5-methyl-1,2,4-oxadiazole (IIb). From 1-(4-methoxyphenyl)-2-methyl-4-nitroimidazole Ib (0.5 g, 2.15 mmole) and malononitrile (0.17 g, 2.58 mmole) after 3 days crude oxadiazole IIb (0.32 g, 53.1%) was obtained; mp 157-158°C. ^1H NMR: 2.72 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 6.8-7.4 (m, 4H, Ph), 11.20 (broad s, 1H, NH). MS: 281 (M^+, 31), 266 (9), 239 (24), 224 (23), 209 (12), 197 (72), 182 (10), 171 (4), 154 (5), 149 (6), 140 (3), 133 (15), 127 (4), 107 (13), 92 (24), 77 (40), 64 (24), 52 (18), 43 (100). Found, %: C 60.07; H 3.94; N 24.65. $C_{14}H_{11}N_5O_2$. Calculated, %: C 59.78; H 3.94; N 24.90.

3-[1-(3-Chlorophenylamino)vinyl-2,2-dicyano]-5-methyl-1,2,4-oxadiazole (IIc). From1-(3-chlorophenyl)-2-methyl-4-nitroimidazole Ic (0.5 g, 2.11 mmole) and malononitrile (0.17 g, 2.53 mmole) after 3 days crude oxadiazole IIc (0.38 g, 63.3%) was obtained; mp 174-176°C. ^1H NMR: 2.72 (s, 3H, CH_3), 7.0-7.5 (m, 4H, Ph), 11.40 (broad s, 1H, NH). MS: 285 (M^+, 15), 270 (4), 243 (10), 235 (3), 208 (69), 201 (18), 152 (4), 111 (41), 75 (25), 63 (6), 50 (9), 43 (100). Found, %: C 54.54; H 2.70; N 24.29. $C_{13}H_8ClN_5O$. Calculated, %: C 54.65; H 2.82; N 24.51.

3-[1-(4-Bromophenylamino)vinyl-2,2-dicyano]-5-methyl-1,2,4-oxadiazole (IId). From 1-(4-bromophenyl)-2-methyl-4-nitroimidazole Id (0.5 g, 1.8 mmole) and malononitrile (0.14 g, 2.1 mmole) after 4 days crude oxadiazole IId (0.36 g, 61.5%) was obtained; mp 179-181°C. ^1H NMR: 2.70 (s, 3H, CH_3), 7.0-7.7 (m, 4H, Ph), 11.35 (broad s, 1H, NH). MS: 331 and

329 (M^+, 10), 247 and 245 (19), 208 (73), 181 (16), 157 and 155 (27), 76 (24), 63 (11), 50 (20), 43 (100). Found, %: C 47.18; H 2.33; N 20.95. $C_{13}H_8BrN_5O$. Calculated, %: C 47.29; H 2.44; N 21.21.

3-[2,2-Dicyano-1-(4-fluorophenylamino)vinyl]-5-methyl-1,2,4-oxadiazole (IIe). From 1-(4-fluorophenyl)-2-methyl-4-nitroimidazole Ie (0.5 g, 2.26 mmole) and malononitrile (0.18 g, 2.71 mmole) after 4 days crude oxadiazole IIe (0.32 g, 52.6%) was obtained; mp 188-190°C. ^1H NMR: 2.70 (s, 3H, CH_3), 7.2-7.4 (m, 4H, Ph), 11.38 (broad s, 1H, NH). MS: 269 (M^+, 16), 254 (3), 227 (57), 185 (42), 95 (76), 75 (27), 57 (12), 43 (100). Found, %: C 57.98; H 2.91; N 25.30. $C_{13}H_8FN_5O$. Calculated, %: C 57.98; H 3.00; N 26.02.

3-[2,2-Dicyano-1-(4-methylphenylamino)vinyl]-5-methyl-1,2,4-oxadiazole (IIf). From 2-methyl-(4-methylphenyl)-4-nitroimidazole If (0.5 g, 2.3 mmole) and malononitrile (0.18 g, 2.76 mmole) after 4 days crude oxadiazole IIf (0.47 g, 77.0%) was obtained; mp 179-180°C. ^1H NMR: 2.30 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 7.0-7.3 (m, 4H, Ph), 11.40 (broad s, 1H, NH). MS: 265 (M^+, 33), 250 (10), 223 (74), 208 (10), 181 (47), 91 (100), 77 (14), 65 (49), 51 (14), 43 (99). Found, %: C 62.67; H 4.18; N 25.61. $C_{14}H_{11}N_5O$. Calculated, %: C 63.39; H 4.18; N 26.40.

Reactions of 1-Aryl-2-methyl-4-nitroimidazoles with Methyl Cyanoacetate. The reactions were performed similarly to the reactions of 4-nitroimidazoles I described above.

Methyl (2-methyl-4-nitro-1-phenylimidazo-5-yl)cyanoacetate (IVa). From 2-methyl-4-nitro-1-phenylimidazole Ia (0.5 g, 2.46 mmole), sodium metal (1 g, 43 mmole), and methyl cyanoacetate (0.29 g, 0.26 cm^3, 3 mmole) in methanol (50 cm^3) after 7 days crude acetate IVa (0.34 g, 46%) was obtained; mp 178-181°C (methanol, dec.). ^1H NMR: 2.20 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.87 (s, 1H, CH), 7.4-7.8 (m, 5H, Ph). ^{13}C NMR: 13.4, 34.4, 53.9, 113.1, 123.3, 127.6, 128.8, 130.3, 130.8, 132.0, 143.1, 145.9, 162.7. MS: 300 (M^+, 13.4), 254 (3.1), 241 (9.1), 226 (9.0), 225 (9.7), 211 (5.2), 195 (14.5), 169 (8.3), 142 (30.5), 129 (11.0), 118 (39.9), 103 (15.7), 77 (100). Found, %: C 55.91; H 4.03; N 18.53. $C_{14}H_{12}N_4O_4$. Calculated, %: C 56.00; H 4.03; N 18.66.

Methyl [1-(4-bromophenyl)-2-methyl-4-nitroimidazo-5-yl]cyanoacetate (IVd). From 1-(4-bromophenyl)-2-methyl-4-nitroimidazole Id (0.5 g, 1.77 mmole) and methyl cyanoacetate (0.21 g, 0.19 cm^3, 2.13 mmole) crude acetate IVd (0.49 g, 72.9%) was obtained; mp 170-171°C (methanol, dec.). ^1H NMR: 2.20 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.92 (s, 1H, CH), 7.3-8.0 (m, 4H, Ph). MS: 380 and 378 (M^+, 13.5), 319 (8.0), 306 and 304 (10.4), 305 and 303 (9.0), 275 and 273 (9.0), 222 and 220 (18.0), 209 and 207 (10.0), 198 (25.3), 196 (28.2), 194 (11.2), 184 and 182 (6.0), 183 and 181 (6.0), 157 (38.0), 155 (39.6), 102 (13.6). Found, %: C 44.37; H 2.85; N 14.73. $C_{14}H_{11}BrN_4O_4$. Calculated, %: C 44.35; H 2.92; N 14.78.

Reactions of 1-Alkyl or 1-Aryl-2-methyl-4-nitroimidazoles with Acetylacetone. The reactions were performed similarly to the reactions of 4-nitroimidazoles I described above. Further work-up, slightly different for each reaction, is given below.

3-(1,2-Dimethyl-4-nitroimidazo-5-yl)-2,4-pentanedione (Vg). From 1,2-dimethyl-4-nitroimidazole Ig (2 g, 14.2 mmole), sodium metal (4 g, 174 mmole), and acetylacetone (3.1 g, 3.2 cm^3, 31 mmole) in methanol (200 cm^3) after 30 days and the usual work-up procedure no precipitate was obtained. 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 diketone Vg, containing a little bit of starting material. After crystallization twice from water, pure product (0.14 g, 4.1%) was obtained; mp 178-180°C. ^1H NMR: 1.90 (s, 6H, $COCH_3$), 2.40 (s, 3H, C−CH_3), 3.42 (s, 3H, N−CH_3). MS: 239 (M^+, 11.2), 209 (1.3), 196 (2.8), 193 (31.8), 180 (1.8), 151 (5.7), 124 (5.8), 67 (17.2), 56 (54.7), 43 (100), 42 (89.1). Found, %: C 49.72; H 5.54; N 16.99. $C_{10}H_{13}N_3O_4$. Calculated, %: C 50.21; H 5.48; N 16.99.

3-(2-Methyl-4-nitro-1-phenylimidazo-5-yl)-2,4-pentanedione (Va). From 1-phenyl-2-methyl-4-nitroimidazole Ia (0.5 g, 2.46 mmole), sodium metal (1.2 g, 52 mmole) and acetylacetone (0.27 g, 0.28 cm^3, 2.71 mmole) in methanol (50 cm^3) after 18 days crude diketone Va (0.21 g, 28.3%) was obtained; mp 244-245°C (acetone). ^1H NMR: 1.95 (s, 6H, $COCH_3$), 2.25 (s, 3H, CH_3), 7.50 (s, 5H, Ph). MS: 301 (M^+, 5.1), 271 (1.2), 255 (31.2), 242 (1.4), 213 (5.0), 186 (4.8), 118 (21.3), 104 (22.5), 77 (74.9), 51 (27.1), 43 (100). Found, %: C 59.50; H 4.98; N 13.94. $C_{15}H_{15}N_3O_4$. Calculated, %: C 59.80; H 5.01; N 13.95.

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