

RING TRANSFORMATION REACTIONS IN 4-NITROIMIDAZOLES FOLLOWING AN ATTACK OF NUCLEOPHILES

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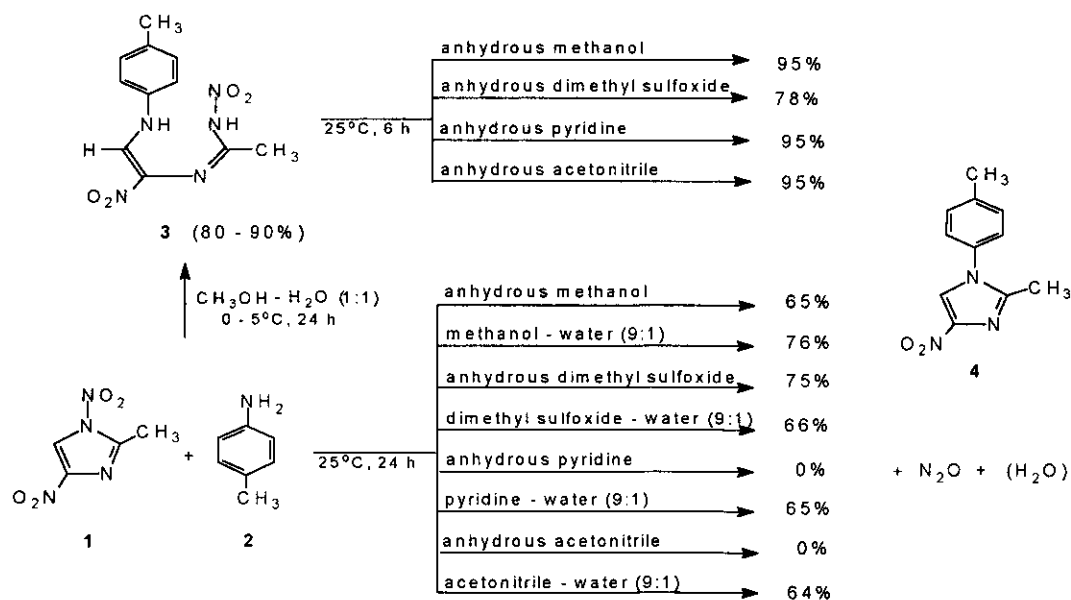
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Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

Abstract - It was proved that 4-nitroimidazoles substituted at the nitrogen atom 1 with electron acceptor groups (aryl, arenesulfonyl, nitro) in reactions with some nucleophiles yield the products of ordinary or degenerated imidazole ring transformation (oxadiazoles, triazoles, imidazoles).

The imidazole ring characterizes in high aromaticity indices¹ and is resistant to an attack of nucleophiles.² The stability and resistance deteriorate in imidazolium cation³ and in imidazole derivatives containing strong electron-withdrawing substituents. Nucleophilic substitution of the good leaving groups⁴ and even of the hydrogen atom (vicarious substitution^{5,6}) can be observed then. Only a few reports on imidazole ring opening or its transformation following an attack of nucleophiles have appeared.⁷⁻¹⁰ We have observed that the ring opening in 4-nitroimidazoles shall be enhanced by arenesulfonyl, aryl or nitro group at the position 1. The most reactive 1,4-dinitroimidazoles under action of secondary amines underwent *cine* nucleophilic substitution¹¹ and ring opening, whereas in reactions with primary amines the degenerated imidazole ring transformation occurred to yield 1-alkyl (or aryl)-4-nitroimidazoles.¹²⁻¹⁴ Also 4-nitro-1-(*p*-toluenesulfonyl)imidazole with aniline yielded

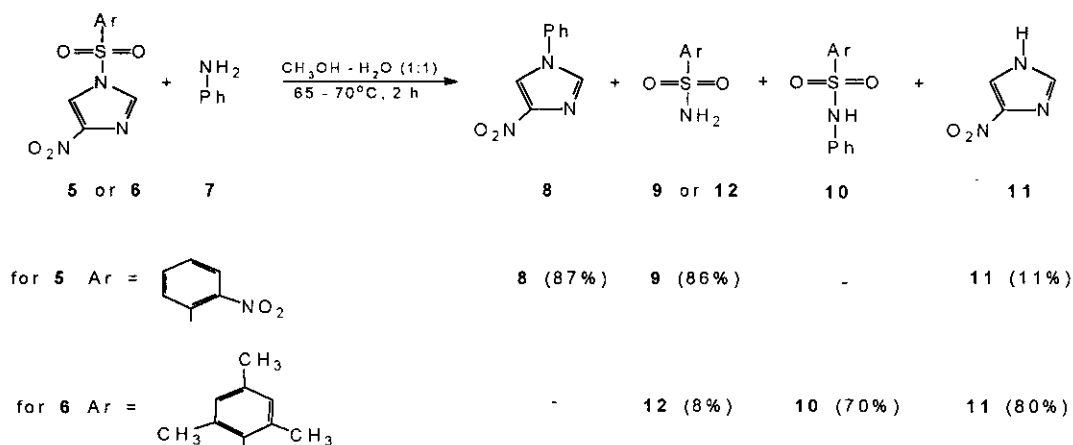
4-nitro-1-phenylimidazole.¹⁵ The above transformations proceeded in aqueous methanol and were accompanied by hydrolysis of the starting nitroimidazoles. 1-Aryl-4-nitroimidazoles are resistant to hydrolysis. Hence, they are excellent compounds to study imidazole ring transformation reactions under the influence of nucleophiles.¹⁶ In this paper, we present the hitherto unpublished results concerning the reactions of 1,4-dinitro-2-methylimidazole with *p*-toluidine in different solvents, of 4-nitro-1-(*o*-nitrobenzenesulfonyl)imidazole and 1-(mesitylene-2-sulfonyl)-4-nitroimidazole with aniline in aqueous methanol solution, and of 2-methyl-4-nitro-1-phenylimidazole with 4-amino-1,2,4-triazole, hydroxylamine or sodium sulfide in aqueous methanol solution. The Scheme 1 shows the results of our preparative studies on the effect of a solvent on yields of **4** obtained



Scheme 1

in reaction of **1** with **2**. The compound (**1**) when reacted with **2** in aqueous methanol suspension at 0-5°C yielded a coloured adduct (**3**), containing no imidazole ring, insoluble under reaction conditions.¹⁷ This adduct in dehydrated organic solvents like methanol, dimethyl sulfoxide, pyridine or acetonitrile at 25°C underwent a transformation to **4** with high yields. Nitrous oxide and water were eliminated in this reaction. In anhydrous

pyridine or acetonitrile **1** with **2** did not form **4** but underwent *N*-denitration reaction. In dehydrated methanol or dimethyl sulfoxide the product (**4**) was obtained with yields slightly lower than in reactions *via* adduct (**3**). In solutions containing 10 vol.% water **4** was obtained with yields of over 60% irrespective of an organic solvent type. The Scheme 2 shows the reaction between **5** or **6** and **7** carried out at 65-70°C in aqueous

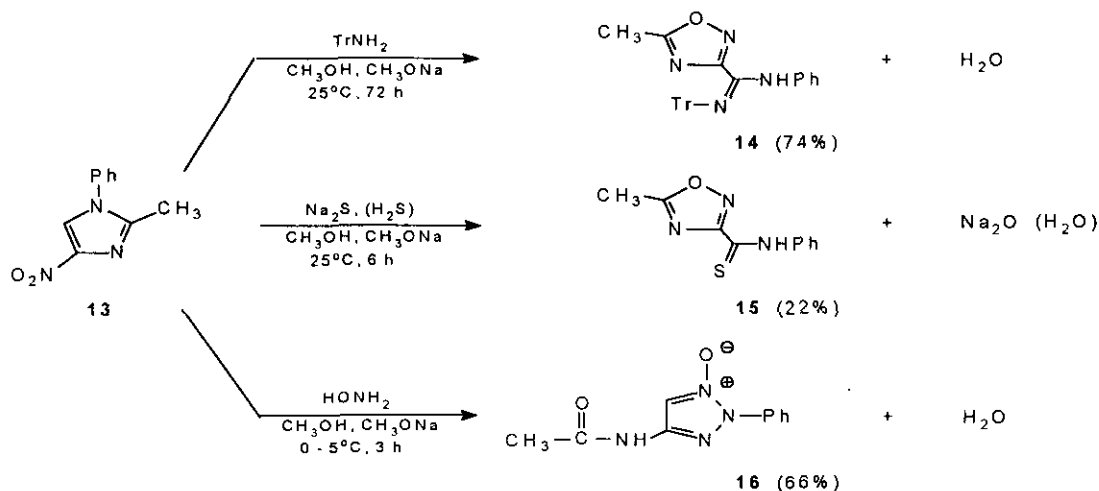


Scheme 2

methanol solution. The reaction of **5** with **7** under these conditions yielded **8** and **9** with practical yields of about 90%. Also, a small quantity of **11** was obtained in this reaction. The reaction of **6** with **7** gave **10**, **11** and a small quantity of **12**. No traces of **8** were found in the post-reaction mixture. The reaction of 1-arenesulfonyl-4-nitroimidazoles with aniline was effected not only by the substituents in arenesulfonyl group but also a solvent. For example, a reaction of 4-nitro-1-(*p*-toluenesulfonyl)imidazole with aniline carried out in aqueous methanol at 65-70°C produced **8** and *p*-toluenesulfonamide with yields exceeding 45%,¹⁵ whereas that performed in pyridine yielded **11** and *p*-toluenesulfonanilide as main products.

The Scheme 3 presents the results obtained in reactions of **13** with 4-amino-1,2,4-triazole (TrNH_2), sodium sulfide or hydroxylamine carried out in methanol in the presence of sodium methoxide at 0-25°C. The reaction of **13** with TrNH_2 yielded 1,2,4-oxadiazole derivative (**14**). Other 1,2,4-oxadiazole derivative (**15**) was obtained in reaction of **13** with sodium sulfide. Under similar conditions, **13** reacted with hydroxylamine yielding 1,2,3-triazole derivative (**16**). It was tried to react **13** with methoxyamine in place of hydroxylamine but **13** left un-

changed. The reactions of 1-aryl-4-nitroimidazoles with TrNH_2 , sodium sulfide and hydroxylamine in presence

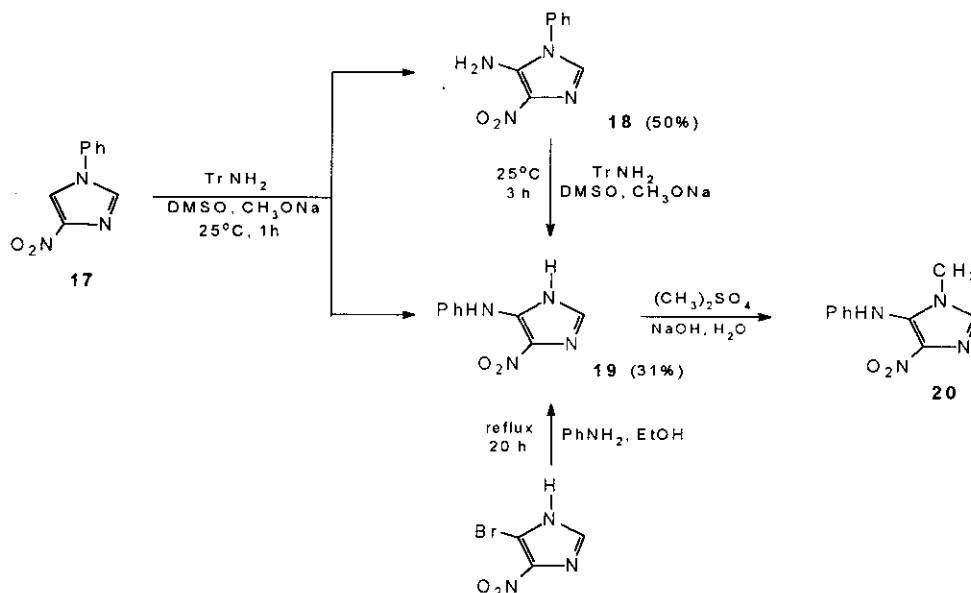


Scheme 3

of sodium methoxide were carried out also in dimethyl sulfoxide solution. The determinable products were obtained only in case of a reaction with TrNH_2 . The reaction products included 5-amino-1-aryl-4-nitroimidazoles¹⁶ obtained in the vicarious nucleophilic substitution of the hydrogen atom¹⁸ in the reaction proposed by Katritzky.¹⁹ However, we have found that the amination reaction of **17** to **18** is accompanied with formation of **19**. The compound (**19**) could be also obtained (as shown in the Scheme 4) in reaction of **18** with TrNH_2 in dimethyl sulfoxide in the presence of sodium methoxide. In the absence of TrNH_2 , the reaction of **18** to **19** did not proceed. The structure of **19** was confirmed by its independent synthesis and methylation of **19** to the known **20**.

In the examined 1-substituted 4-nitroimidazoles there are three centres susceptible to an attack of nucleophiles: annular carbon atoms 2 and 5 of the imidazole ring and possibly a substituent at nitrogen 1. The attack on that third center in 1-aryl-4-nitroimidazoles should be taken into consideration only in special cases.²⁰ In 1,4-dinitroimidazoles and 1-arenesulfonyl-4-nitroimidazoles the attack of nucleophiles on a substituent at nitrogen 1 is especially preferred in such solvents like pyridine or acetonitrile. The nucleophilic attack of primary aromatic amines on the imidazole ring carbon atoms in 1,4-dinitroimidazoles and 1-arenesulfonyl-4-nitroimidazoles

undergoes very easily in water-containing solutions. Not only 1,4-dinitroimidazole but also its 2-methyl or



Scheme 4

5-methyl derivative reacts with anilines towards a formation of 1-aryl-4-nitroimidazoles.¹² Among 1-arene-sulfonyl-4-nitroimidazoles only certain compounds with free 2 and 5 positions react with aniline to 4-nitro-1-phenylimidazoles.²¹ In the *cine* substitution of 1,4-dinitroimidazoles¹¹ and in vicarious amination of 1-aryl-4-nitroimidazoles²⁰ the substituent takes a 5 position. We believe that in 1-substituted 4-nitroimidazoles having free positions 2 and 5 the first nucleophilic attack is directed to the carbon atom 5. In the presence of water, a bond $\text{N}(1)\text{-C}(5)$ can be broken and a non-cyclic product is formed. As we stated in¹⁷ the recyclization step is also accelerated in the presence of water. The transformation of **1** to **4** in the presence of **2** in aprotic dimethyl sulfoxide is attributed by us rather to the difficulties in its complete dehydration and water formation than to a great acceleration of nucleophilic reaction, frequently observed, in this solvent.²² A high yield of **8** (and of **9**) achieved in a reaction of **5** with **7** in aqueous methanol solution at an elevated temperature and no formation of **8** from **6** and **7** under similar condition we explain by differences in nature of the arenesulfonyl substituents.

The *o*-nitro group in **5**, owing to its strong electron acceptor effect, facilitates the nucleophilic attack on imidazole and sterically protects the sulfur atom.²³ The mesitylene-2-sulfonyl substituent promotes a S-N(1) bond ionization and a formation of **10** from **6** and **7** according to the mechanism, close to S_N1.²³

In the absence of strong alkalies, 1-aryl-4-nitroimidazoles do not react with neutral molecules containing a primary amine group. They undergo reactions with TrNH₂, hydroxylamine (and also with sodium sulfide) in the presence of sodium methoxide. In these conditions, 1,2,4-oxadiazole derivatives are obtained from **13** and TrNH₂ or sodium sulfide. In our opinion, a reaction also commences with an attack of nucleophile on the carbon atom 5. In the formed adduct, in the presence of sodium methoxide a reduction of nitro group to nitroso one occurs. Similar reductions have been recently described.²⁴ In the formed nitroso derivative of reduced aromaticity, the carbon atom 2 is attacked by the nucleophile as the position 5 is masked with strongly electron donor group. A cleavage of imidazole N(1)-C(2) bond after the attack of a nucleophile, followed by the rotation around N(3)-C(4) bond, enables a formation of 1,2,4-oxadiazole arrangement. Literature describes a transformation reaction of 2-amino-5-aryl-4-nitrosoimidazoles to 5-amino-5-aryl-1,2,4-oxadiazoles by heating the substrates in water.¹⁰ We assume that 1,2,4-oxadiazole derivative is also the intermediate product in transformation reaction of **13** to **16** in the presence of hydroxylamine.¹⁶ In this intermediate (anilidoxime), in result of oxime-nitroso tautomerism and addition of aniline nitrogen to a nitroso group, 1-hydroxy-2-phenyldiaziridine derivative of 1,2,4-oxadiazole can be formed, followed by a cleavage of the aziridine ring due to a hydroxyl group deprotonation. The highly reactive intermediate product will undergo the known Boulton-Katritzky rearrangement reaction²⁵ to 1,2,3-triazole derivative.

The Dimroth rearrangement of **18** into **19** described here proves a possible attack of nucleophile on the carbon atom 2 not only in 4-nitrosoimidazoles but also in 4-nitroimidazoles (with the position 5 masked by electron donor substituent). The behaviour of 1-substituted 4-nitroimidazoles, examined by us, under the influence of amine and sulfur nucleophiles, reminds the untypical behaviour of 3,4-dinitroderivatives of thiophene^{26,27} or pyrrole^{28,29} known from literature. This fact confirms once again that a "pyridine" nitrogen atom in the five-member ring causes a similar while weaker effect like in case of substitution of a hydrogen atom at the annular carbon atom by nitro group.

EXPERIMENTAL

^1H and ^{13}C nmr spectra were recorded on a Tesla BS-587 (80 and 20 MHz) spectrometer with TMS as the internal standard. Ms spectra were taken on a LKB-2091 GC-MS instrument. Accurate mass measurements were carried out using a Finnigan MAT 95 spectrometer. Uv spectra were run on a Specord M 40 spectrophotometer. The purity of compounds was monitored by mp's, tlc and microanalyses.

2-Methyl-4-nitro-1-(*p*-tolyl)imidazole (4).

a) A solution of **1**³⁰ (0.86 g, 5 mmol) and **2** (0.53 g, 5 mmol) in adequate solvent (10 ml, see Scheme 1) was stirred in a closed vessel at 25°C for 24 h and then poured into water. The precipitated sediment was separated and crystallized from methanol. b) A suspension or solution of the adduct (**3**)¹⁷ (1.39 g, 5 mmol), dried to a constant weight, was stirred in adequate solvent (10 ml) at 25°C for 6 h. The post-reaction mixture was handled as described above. Compound (**4**) was obtained with yields given in the Scheme 1; mp 136-139°C; ^1H nmr [$(\text{CD}_3)_2\text{CO}$] δ : 2.30 (3H, s, $\text{CH}_3\text{-Im}$), 2.43 (3H, s, $\text{CH}_3\text{-Ph}$), 7.39 (4H, br s, CH-phenyl), 8.08 (1H, s, CH-imid); ^{13}C nmr (CDCl_3) δ : 13.58 (q, $\text{CH}_3\text{-Im}$), 21.07 (q, $\text{CH}_3\text{-Ph}$), 120.11 (d, 5-C), 124.80 (d, 2'-C, 6'-C), 130.08 (d, 3'-C, 5'-C), 132.75 (s, 1'-C), 139.69 (s, 4'-C), 144.46 (s, 2-C), 146.32 (s, 4-C); uv (MeOH) λ (ϵ): 309 (10 500); ms m/z : 217 (M^+ , 20%); Anal. Calcd for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.8; H, 5.50; N, 19.3.

4-Nitro-1-(*o*-nitrobenzenesulfonyl)imidazole (5).

Triethylamine (1.26 g, 12.5 mmol) and *o*-nitrobenzenesulfonyl chloride (2.76 g, 12.5 mmol) were successively added to a stirred suspension of 4(5)-nitroimidazole (1.13 g, 10 mmol) in dichloromethane (20 ml). After mixing for 2 h at 25°C, the suspension was left overnight. The solvent was removed under reduced pressure at 25°C and the residue was shaken twice with methanol (2 x 10 ml) to obtain **5** (2.7 g, 90%), mp 176-178°C. After crystallization from ethyl acetate, **5** showed mp 177-178°C; ^1H nmr [$(\text{CD}_3)_2\text{CO}$] δ : 7.93-8.65 (4H, m, CH-phenyl), 8.49 (1H, d, $J=1.6$ Hz, CH-imid), 8.62 (1H, d, $J=1.6$ Hz, CH-imid); uv (CH_3OH) λ (ϵ): 213 (20 000), 271 (10 300); Anal. Calcd for $\text{C}_9\text{H}_6\text{N}_4\text{O}_6\text{S}$: C, 36.25; H, 2.03; N, 18.79. Found: C, 36.14; H, 1.91; N, 18.78.

4-Nitro-1-phenylimidazole (8) and *o*-nitrobenzenesulfonamide (9).

A suspension of **5** (0.745 g, 2.5 mmol) and **7** (1 g, 11 mmol) in a water/methanol mixture (1:1, 20 ml) was

stirred and heated on a water bath at about 70°C for 2 h. Then, the mixture was water-steam distilled. The distillate was rejected and **8** (0.41 g, 87%) was hot separated from the residue, and after cooling **9** (0.42 g, 86%) was collected. The aqueous filtrate was evaporated yielding **11** (0.03 g, 11%) slightly contaminated with **9** (tlc). Compound (**8**), mp 185-187°C; ¹H nmr [(CD₃)₂CO] δ: 7.46-7.83 (5H, m, CH-phenyl), 8.14 (1H, d, J=1.6 Hz, CH-imid), 8.53 (1H, d, J=1.6 Hz, CH-imid); ms m/z (% formula, Δ): 189.0533 (100, C₉H₇N₃O₂, 0.5); Anal. Calcd for C₉H₇N₃O₂: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.1; H, 4.0; N, 22.2.

5-Methyl-3-[N²(1,2,4-triazol-4-yl)-N¹-phenylcarbamidoyl]-1,2,4-oxadiazole (14**).**

Sodium methoxide, prepared by dissolution of sodium (1.2 g, 52 mmol) in methanol (20 ml), was added into the solution of **13**¹² (0.5 g, 2.5 mmol) and 4-amino-1,2,4-triazole (1.1 g, 12.5 mmol) in methanol (30 ml) at 25°C. After 72 h the solution was acidified with concentrated hydrochloric acid to pH about 5. Solvents were evaporated under reduced pressure at about 25°C and then water (25 ml) was added to the residue. A solid was collected and recrystallized from aqueous methanol to give the product (**14**) (0.50 g, 74%), mp 215°C (decomp.); ¹H nmr [(CD₃)₂SO] δ: 2.59 (3H, s, CH₃), 7.1-7.9 (5H, m, CH-phenyl), 8.38 (2H, s, CH-triazole), 10.30 (1H, s, NH); ms m/z (% formula, Δ): 269.1016 (37, C₁₂H₁₁N₇O, 3.3), 268.0933 (3, C₁₂H₁₀N₇O, 3.3), 198.0756 (37, C₁₀H₈N₅, 11.9), 186.0682 (100, C₁₀H₈N₃O, 8.1), 144.0557 (19, C₈H₆N₃, 3.5), 142.0825 (17), 104.0503 (15, C₇H₆N, 2.9), 103.0418 (23, C₇H₅N, 3.9), 77.0380 (37, C₆H₅, 14.3); Anal. Calcd for C₁₂H₁₁N₇O: C, 53.53; H, 4.12; N, 36.40. Found: C, 53.80; H, 4.18; N, 35.92.

5-Methyl-3-(N-phenylcarbamathioyl)-1,2,4-oxadiazole (15**).**

Sodium sulfide Na₂S·10H₂O (10 g, 42 mmol) was added to the solution of **13** (1.0 g, 5 mmol) and potassium hydroxide (2.0 g, 36 mmol) in methanol (50 ml). The mixture was stored at 25°C for 24 h and then acidified with concentrated hydrochloric acid (about 8 ml) to pH about 5. Solvents were evaporated under reduced pressure at 25°C and water (50 ml) added to the residue. The sediment was filtered off and extracted with chloroform. The chloroform extract was chromatographed on a silica gel yielding **15** (0.16 g, 15%) as a crystalline substance of mp 104-106°C; ¹H nmr (CDCl₃) δ: 2.68 (3H, s, CH₃), 7.2-8.0 (5H, m, CH-phenyl), 10.40 (1H, br s, NH); ms m/z (% formula, Δ): 219.0466 (100, C₁₀H₉N₃OS, 0.5), 218.0370 (61, C₁₀H₈N₃OS, 8.2), 186.0679 (56, C₁₀H₈N₃O, 6.5), 177.0348 (16, C₈H₇N₃S, 7.3), 176.0299 (69, C₈H₆N₃S, 9.1), 149.0168

(12, $C_7H_5N_2S$, 4), 145.0411 (11, $C_8H_5N_2O$, 6.2), 135.0183 (62, C_7H_5NS , 30), 119.0366 (32, C_7H_5NO , 4.2), 110.0203 (17, C_6H_6S , 11), 109.0090 (12, C_6H_5S , 20), 104.0503 (19, C_7H_6N , 2.9), 103.0415 (6, C_7H_5N , 6.8), 91.0406 (11, C_6H_5N , 17.6), 77.0381 (100, C_6H_5 , 13); Anal. Calcd for $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16. Found: C, 55.10; H, 4.23; N, 18.78.

4(5)-Nitro-5(4)-phenylaminoimidazole (19).

A solid sodium methoxide (0.28 g, 52 mmol) in dimethyl sulfoxide (2 ml) was added to the solution of **18**²⁰ (0.1g, 0.5 mmol) and 4-amino-1,2,4-triazole (0.2 g, 24 mmol) in dimethyl sulfoxide (2 ml) and stirred at 25°C for 3 h. The post-reaction mixture was poured into a concentrated aqueous ammonium chloride solution (25 ml). The sediment of initial **18** was filtered off and the filtrate was acidified with concentrated hydrochloric acid. The precipitated sediment was filtered off and crystallized from ethanol with active coal yielding **19** (0.22 g, 22%), mp 204-205°C (decomp.); ¹H nmr [(CD₃)₂SO] δ: 6.8-7.8 (6H, m, CH-arom), 9.21 (1H, s, NH), 13.74 (1H, br s, NH); ms m/z: 204 (M⁺, 100%); uv (CH₃OH) λ (ε): 422 (14 700); Anal. Calcd for $C_9H_8N_4O_2$: C, 52.94; H, 3.95; N, 27.44. Found: C, 53.02; H, 3.97; N, 27.28.

ACKNOWLEDGEMENT

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