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REACTIONS OF 4,5-DINITROIMIDAZOLE AND 4(5)-NITROIMIDAZOLE-5(4)-SULFONIC ACID WITH NUCLEOPHILES

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UDC 547.781.5'782.9.07:543.422

The reactions of 4,5-dinitroimidazole and 5(4)-nitroimidazole-4(5)-sulfonic acid with nucleophilic agents were studied. Mercapto-, alkoxy-, and aminonitroimidazoles were synthesized. In the reaction of dinitroimidazole with sodium alkoxides 5(4)-nitroimidazole was obtained in addition to alkoxynitroimidazoles. It is shown that in the formation of salts of the starting imidazoles with bases nucleophilic-substitution reactions take place only with "soft" reagents.

The aim of the present research was to study the reactivities of 4,5-dinitroimidazole (I) and 4(5)-nitroimidazole-5(4)-sulfonic acid (II) in nucleophilic-substitution reactions.

As in the case of 4(5)-bromo-5(4) nitroimidazole (III) [1], 4(5)-mercapto-5(4)-nitroimidazole (IV) is formed in almost quantitative yield in the reaction of dinitroimidazole I with sodium sulfide at room temperature. At the same time, in contrast to imidazole III [2], I reacts with sodium sulfite even at room temperature to give sodium 4(5)-nitroimidazole-5(4)-sulfonate (II). Under the same conditions 4(5)-ethoxy- (VI) and 4(5)-methoxy-5(4)nitroimidazole (V) were obtained from imidazole I with sodium ethoxide and methoxide in the corresponding alcohol. It should be noted that, in addition to V and VI, we also isolated 4(5)-nitroimidazole (VII). By means of PMR spectroscopy we found that the ratio of imidazoles VI and VII in the reaction mixture prior to crystallization is 9:1. The formation of nitroimidazole VII constitutes indirect evidence for an anion-radical mechanism for this reaction. The reaction of dinitroimidazole I with aqueous alkali without heating leads to destruction of the imidazole ring. Compound I does not react with "harder" anionic nucleophiles such as sodium azide, acetate, and phenoxide in water, alcohol, and dimethylformamide (DMF) even at elevated temperatures. Attempts to carry out the reaction of the ammonium salt of imidazole I with potassium thiocyanate in water were also unsuccessful. However, bis[5(4)-nitro-4(5)-imidazolyl]disulfide (VIII) was obtained from dinitro compound I in the reaction with potassium thiocyanate in dilute sulfuric acid. The 4(5)-nitro-5(4)thiocyanatoimidazole formed under these conditions probably undergoes decomposition, since cyanogen is liberated during the process.

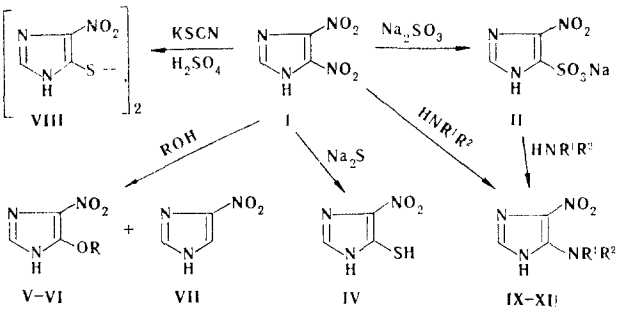
Methylamine and dimethylamine react with I in the same way as strong anionic nucleophiles and 4(5)-methylamino- (IX) and 4(5)-dimethylamino-5(4)-nitroimidazole (XII). The reaction of ammonia and aniline takes place only at 70-100°C to give 4(5)-amino- (XI) and 4(5)-phenylamino-5(4)-nitroimidazole (XII). The reaction of dinitroimidazole I with an equimolar amount of hydrazine hydrate in both water and alcohol proceeds very vigorously even with cooling. Four to five unidentified compounds with close chromatographic mobilities were detected in

S. M. Kirov Ural Polytechnic Institute, Sverdlovsk 620002. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 808-810, June, 1983. Original article submitted August 2, 1982.

 0009-3122/83/1906-0650$07.50

the reaction mixture. An increase in the amount of hydrazine hydrate leads to destruction of the imidazole ring.

When the temperature of the reaction of I with sodium sulfide, methylamine, and dimethylamine is raised to 40-60°C, the yields of the final products decrease, and cleavage of the imidazole ring is observed in the case of sodium methoxide and ethoxide in refluxing alcohol solution. Just as in the case of dinitro compound I, sulfonic acid II reacts only with "soft" nucleophiles. Thus imidazoles IX and X were obtained in good yields in the reaction of II with methylamine and dimethylamine, while the sodium salt of nitro sulfonic acid II was isolated in unchanged form in the attempted reaction with sodium phenoxide.



V $R=CH_3$; VI $R=C_2H_5$; IX $R^1=H$, $R^2=CH_3$; X $R^1=R^2=CH_3$; XI $R^1=R^2=H$; XII $R^1=H$, $R^2=C_6H_5$

Thus we have obtained the previously inaccessible 4(5)-nitroimidazole derivatives. We have shown that for I and II in the case of the formation of salts with bases nucleophilic-substitution reactions take place only with "soft" reagents.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with UR-20 and Beckman IR-4260 spectrometers. The UV spectra of solutions in water were recorded with a Beckman UV-5270 spectrophotometer. The individuality of the substances were verified by thin-layer chromatography (TLC) on Silufol UV-254 plates in propanol—3% ammonium hydroxide (3:1) (R_f') and butanol—acetic acid—water (4:1:1) (R_f'') systems.

4(5)-Mercapto-5(4)-nitroimidazole (IV). A solution of 1.0 g (6.3 mmole) of I in 15 ml of water was added with stirring at room temperature to a solution of 2.7 g of $Na_2S \cdot 9H_2O$ in 20 ml of water. After 20 min, the solution was filtered with charcoal, and the filtrate was acidified to pH 3-4 with concentrated HCl. The resulting precipitate was removed by filtration and washed with water and acetone to give 0.85 g (92%) of a product with mp > 300°C, R_f' 0.6, and R_f'' 0.69. IR spectrum: 1355, 1505 (NO_2); 3115 cm^{-1} (CH). UV spectrum, λ_{max} (log ε): 217 (4.47) and 372 nm (4.14). Found: C 24.8; H 2.2; N 28.5; S 21.3%. $C_3H_3N_3O_2S$. Calculated: C 24.9; H 2.1; N 28.3; S 21.1%.

Sodium 4(5)-Nitro-5(4)-imidazolesulfonate (II). A solution of 1.0 g (6.3 mmole) of dinitroimidazole I in 40 ml of 6.5% Na_2SO_3 solution was maintained at room temperature for 30 h, after which it was acidified to pH 3-4 with 50% H_2SO_4. It was then evaporated in vacuo to a volume of 5-10 ml, and the resulting precipitate was removed by filtration and crystallized from water to give 0.70 g (51%) with mp > 300°C (dec.), R_f' 0.33, and R_f'' 0.3. IR spectrum: 1390, 1537 (NO_2); 3178 cm^{-1} (CH). UV spectrum, λ_{max} (log ε): 220 (3.79) and 293 nm (3.93). Found: C 16.5; H 0.8; N 18.8; S 15.0%. $C_3H_2N_3O_5S \cdot Na$. Calculated: C 16.7; H 0.8; N 19.5; S 14.9%.

4(5)-Nitro-5(4)-methoxyimidazole (V). A 1.0-g (6.3 mmole) sample of I was added to a solution of sodium methoxide, obtained from 2 g of Na in 50 ml of absolute methanol, and the mixture was stirred until all of the solid material dissolved, after which the solution was maintained at room temperature for 10 h. The mixture was then neutralized to pH 5-6 with concentrated HCl and evaporated to dryness. The residue was crystallized from water with charcoal. The resulting precipitate was removed by filtration, dried, and heated in 50 ml of alcohol. The undissolved nitroimidazole VII was removed by filtration. The filtrate was then evaporated to dryness. The yield of V, with mp 212-213°C, R_f' 0.54, and R_f'' 0.68, was 0.48 g (53%). IR spectrum: 1330, 1570 cm^{-1} (imidazole ring CH). UV spectrum, λ_{max} (log ε): 225 (3.75) and 387 nm (4.11). Found: C 33.7; H 3.4; N 29.5%. $C_4H_5N_3O_3$. Calculated: C 33.6;

H 3.5; N 29.4%. The yield of VII was 0.05 g (7%). The product was identical to the nitroimidazole obtained by the method in [3].

4(5)-Nitro-5(4)-ethoxyimidazole (VI). This compound, with mp 184-185°C, R'_f 0.56, and R''_f 0.73, was obtained in a yield of 0.55 g (56%) by the method used to prepare V. IR spectrum: 1341, 1570 cm^{-1} (NO). UV spectrum, λ_{max} (log ε): 230 (3.62) and 390 nm (4.10). Found: C 38.2; H 4.56; N 26.7%. $C_5H_7N_3O_3$. Calculated: C 38.2; H 4.5; N 26.8%. The yield of VII was 0.03 g (4%).

Bis-5(4)-nitro-4(5)-imidazolyl Disulfide (VIII). A solution of 1.3 g of KSCN in 5 ml of H_2O and 4 ml of concentrated H_2SO_4 was added to a solution of 1 g (6.3 mmole) of I in 15 ml of H_2O, and the mixture was refluxed for 30 min. It was then cooled, and the resulting precipitate was removed by filtration, washed with water, and crystallized from DMF to give 0.85 g (93%) of VIII with mp > 300°C, R'_f 0.60, and R''_f 0.67. UV spectrum, λ_{max} (log ε): 357 nm (4.03). Found: C 25.1; H 1.4; N 29.4; S 22.5%. $C_6H_4N_6O_4S_2$. Calculated: C 25.0; H 1.4; N 29.2; S 22.2%.

4(5)-Nitro-5(4)-methylaminoimidazole (IX). A) A solution of 1.0 g (6.3 mmole) of dinitroimidazole I in 50 ml of 25% CH_3NH_2 was maintained at room temperature for 24 h, after which it was evaporated to the minimum volume in vacuo, and the resulting precipitate was removed by filtration and crystallized from a large volume of methanol to give 0.50 g (56%) of a product with mp > 300°C, R'_f 0.50, and R''_f 0.45. IR spectrum: 1365, 1542 (NO_2); 3173 cm^{-1} (imidazole ring CH). UV spectrum, λ_{max} (log ε): 209 (4.06) and 382 nm (4.18). Found: C 34.2; H 4.5; N 39.8%. $C_4H_6N_4O_2$. Calculated: C 33.8; H 4.2; N 39.5%.

B) A solution of 1.0 g (4.65 mmole) of II in 30 ml of 25% CH_3NH_2 was maintained at room temperature for 4 days, after which it was evaporated to the minimum volume in vacuo, and the resulting precipitate was removed by filtration and crystallized from methanol to give 0.56 g (63%) of a product that was identical to imidazole IX obtained from I with respect to its melting point, chromatographic mobility, and UV and IR spectra.

4(5)-Nitro-5(4)-dimethylaminoimidazole (X). A) A solution of 1.0 g (6.3 mmole) of dinitroimidazole I in 30 ml of 33% $(CH_3)_2NH$ was maintained at room temperature for 20 h, after which it was evaporated to dryness in vacuo, and the residue was crystallized from ethanol with charcoal to give 0.51 g (52%) of a product with mp 174-175°C, R'_f 0.56, and R''_f 0.53. IR spectrum: 1383, 1520 (NO_2); 3172 cm^{-1} (CH). UV spectrum, λ_{max} (log ε): 211 (4.05) and 398 nm (4.06). Found: C 38.5; H 5.4; N 36.0%. $C_5H_8N_4O_2$. Calculated: C 38.4; H 5.1; N 35.9%.

B) A solution of 1.0 g (4.65 mmole) of II in 20 ml of 33% $(CH_3)_2NH$ was maintained at room temperature for 3 days, after which it was evaporated in vacuo, and the residue was crystallized from ethanol to give 0.31 g (42%) of a product that was identical to imidazole X obtained from I with respect to its melting point, chromatographic mobility, and UV and IR spectra.

4(5)-Nitro)5(4)-aminoimidazole (XI). A solution of 1.0 g of I in 50 ml of 25% NH_4OH was heated in an autoclave at 100°C for 15 h, after which it was evaporated to the minimum volume in vacuo, and the resulting precipitate was removed by filtration and crystallized from water to give 0.32 g (39%) of a product that was identical to XI obtained by the method in [4] with respect to its melting point, chromatographic mobility, and UV spectrum.

4(5)-Nitro-5(4)-phenylaminoimidazole (XII). A 1.0-g (6.3 mmole) sample of I was added to a solution of 3 ml of aniline in 30 ml of ethanol, and the mixture was refluxed for 3 h. The hot solution was filtered with charcoal, and the filtrate was cooled. The resulting precipitate was removed by filtration and crystallized from ethanol to give 0.45 g (61%) of a product with mp 224-225°C, R'_f 0.71 and R''_f 0.84. IR spectrum: 1347, 1534 (NO_2). UV spectrum, λ_{max} (log ε): 242 (4.05) and 392 nm (4.15). Found: C 52.8; H 3.8; N 27.5%. $C_9H_8N_4O_2$. Calculated: C 52.9; H 3.9; N 27.5%.

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