SYNTHESIS OF 2-AMINO-5-CYANO-1,3,4-OXADIAZOLE AND SOME OF ITS DERIVATIVES

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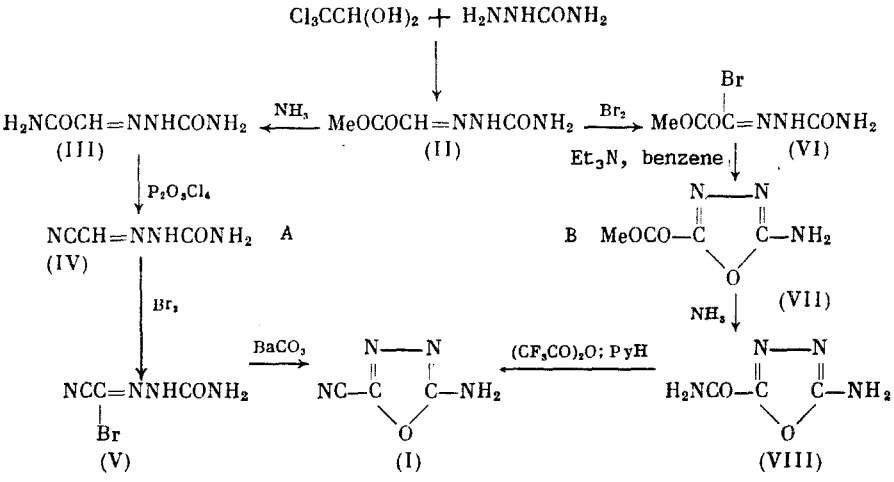
Preparative syntheses have been developed for 2-amino-5-cyano-1,3,4-oxadiazole from the semicarbazone of methyl glyoxylate and some of its transformations were studied. This product is an important intermediate in the preparation of its derivatives.

Bifunctional derivatives of 1,3,4-oxadiazole hold significant interest in the synthesis of physiologically active compounds, photoconductors, and heat stable polymers. 2-Amino-1,3,4-oxadiazole derivatives have bactericidal [1], fungicidal [2], herbicidal [3], antihelminthic [4], and other physiological activity [5]. These compounds are used in the synthesis of electrophotographic [6] and other polymer materials [7].

The synthesis of 2-amino-5-cyano-1,3,4-oxadiazole (I), which is necessary for the solution of several practical problems, was carried out from the semicarbazone of methyl glyoxylate (II) through the two pathways shown in Scheme 1. In pathway A, semicarbazone (II) was converted by the action of NH_3 into the semicarbazone of glyoxamide (III), which could be dehydrated to the nitrile of the semicarbazone of glyoxalic acid (IV) only by the action of pyrophosphoryl chloride.

Scheme 1



The action of bromine on (IV) in acetic acid gave bromide (V), which was cyclized to aminonitrile (I) in the presence of $BaCO_3$. The cyclization also proceeds in aqueous $NaHCO_3$ and with magnesium and calcium carbonates but more stable and higher yields are obtained with $BaCO_3$.

The bromination of semicarbazone (II) by bromine in acetic acid (pathway B) gave bromide (VI), which was cyclized to 5-carbomethoxy-2-amino-1,3,4-oxadiazole (VII) upon treatment with triethylamine in benzene solution. The action of ammonia on (VII) gave amide (VIII), whose conversion to (I) was very difficult. The dehydration of (VIII) did not proceed upon reaction with $TiCl_4$ and Et_3N in THF-CCl_4 [8], with $PhSO_2Cl$ in pyridine [9], with DMF and $SOCl_2$, with pyrophosphoryl chloride, and with other dehydrating agents. This

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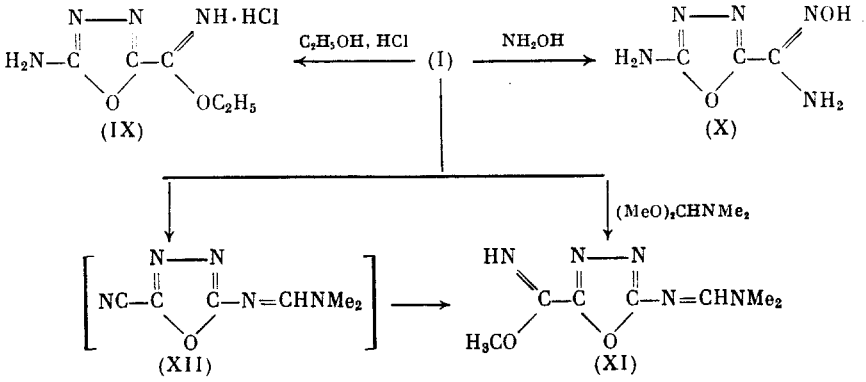
transformation was achieved by the action of trifluoroacetic anhydride in dioxane in the presence of pyridine [10] with a suitable yield.

The overall yield was 27% through pathway A and 29% through pathway B (relative to methyl glyoxylate semicarbazone). The two pathways have the same number of steps.

Scheme 2



2-Amino-5-cyano-1,3,4-oxadiazole (I) readily reacts at the C≡N group with HCl and ethanol to give the hydrochloride salt of iminoester (IX) and with hydroxylamine to give amidoxime (X) but is not acylated at the amino group by the action of ordinary acetylating agents such as RCOCl and acetic anhydride. The reaction of (I) with the dimethylacetal of dimethylformamide gives iminoester (XI) (Scheme 2). This reaction apparently begins with the formation of formamidine (XII), which reacts at the C≡N group with methanol, formed as a result of the reaction, to give the final product.

EXPERIMENTAL

The melting points were determined on a Boetius microscopic instrument. The mass spectra were taken on a Varian MAT CH-6 mass spectrometer. The ionizing potential was 60 eV. The temperature of the ionization chamber was 50-150°C. The ^{13}C, ^{15}N, and ^{1}H NMR spectra were taken on a Bruker WM-250 spectrometer at 250 MHz. The IR spectra were taken for KBr pellets on a UR-20 spectrometer at 400-4000 cm^{-1}.

Semicarbazone of Glyoxamide (III). Ammonia was passed through a mixture of 20.0 g (138 mmoles) semicarbazone of methyl glyoxylate (II) [11] in 1000 ml methanol at reflux with stirring for 1.5 h. The precipitate formed upon cooling was filtered off and the filtrate was evaporated to 100 ml residual volume and an additional amount of product separated. The yield of the monohydrate of (III) was 18.9 g (83.5%), mp 222-224°C [11]. Colorless (III) was obtained by drying at 100°C (3 mm) for 8 h. IR spectrum (ν, cm^{-1}): 3400, 3200 (NH_2), 1730, 1700 (C=O), 1600 (C=N).

Semicarbazone of the Nitrile of Bromoglyoxalic Acid (V). A sample of 17.96 g (112 mmoles) bromine in 60 ml acetic acid was added over 50 min to a stirred suspension of 12.2 g (109 mmoles) semicarbazone of the nitrile of glyoxalic acid (IV) obtained according to Uchitylova and But [11] and stirred for 30 min. The mixture was poured into water and the precipitate formed was filtered off. The filtrate was extracted with ethyl acetate. The extract was washed with a small amount of water, aqueous thiosulfate, and brine and dried over $MgSO_4$. The residue after removal of the solvent was combined with the initial precipitate to give 14.85 g (71%) (V), mp 184-186°C (from ethyl acetate). Found: C, 18.92; H, 1.90; Br, 41.59; N, 29.13%. Calculated for $C_3H_3BrN_4O$: C, 18.84; H, 1.59; Br, 41.88; N, 29.31%.

2-Amino-5-cyano-1,3,4-oxadiazole (I). A suspension of 5.74 g (30 mmoles) bromide (V) and 7.09 g (36 mmoles) $BaCO_3$ in 600 ml water was stirred for 1.5 h at 20°C. The reaction mixture was filtered to remove the unreacted reagents. The filtrate was saturated with NaCl and extracted with six 20-ml portions of ethyl acetate. The filtrate was dried over $MgSO_4$ and evaporated in vacuum. The residue (2.1 g) was reprecipitated from THF solution by the addition of pentane to give 1.82 g (55%) (I), mp 189-190°C. Found: C, 32.86; H, 2.02; N, 50.64%, M^+ = 110. Calculated for $C_3H_2N_4O$: C, 32.72; H, 1.81; N, 50.94%. IR spectrum (ν, cm^{-1}): 3430, 3150 (NH_2), 2260 (C≡N), 1670 (C=N). PMR spectrum in $(CD_3)_2CO$ (δ, ppm): 8.12 s (NH_2). ^{13}C NMR spectrum (δ, ppm, J, Hz): 107.9 s (C≡N), 134.7 s (C^5), 165.2 t (C^2, $J_{C^2-NH_2}$ = 1.1 Hz). ^{15}N NMR spectrum (δ, ppm, J, Hz): -321.3 t (NH_2, J_{NH_2} = 1.1 Hz).

Methyl Ester of 5-Amino-1,3,4-oxadiazole-2-carboxylic Acid (VII). A sample of 5.5 ml (40 mmoles) triethylamine was added to a benzene suspension of 4.45 g (20 mmoles) semicarbazone of methyl α-bromoglyoxylate (VI) obtained in 55% yield according to Werber et al. [12] and the mixture was heated at reflux for 1.5 h. The precipitate was filtered off, treated with water, and again filtered to give 2.33 g (82%) (VII), mp 206°C (dec.) [12]. PMR spectrum (δ, ppm): 3.85 s (3H, MeO), 7.76 s (2H, NH_2). ^{13}C NMR spectrum (δ, ppm, J, Hz): 52.83 q ($O\underline{C}H_3$, J_{C-H} = 148.8), 150.2 s (C^2), 154.5 q (C=O, J_{C-OCH_3} = 4.0), 165.1 t (C^5, $J_{\underline{C}^5-NH_2}$ = 1.1). ^{15}N NMR spectrum (δ, ppm, J, Hz): −324.5 t (NH_2, J = 89.3).

Amide of 5-Amino-1,3,4-oxadiazole-2-carboxylic Acid (VIII). Ammonia was passed for 30 min through a suspension of 2.23 g (15.5 mmoles) (VII) in 20 ml methanol. The precipitate was filtered off and washed with water and acetone to give 1.9 g (95.5%) amide (VIII), which does not melt up to 380°C. Found: C, 28.48; H, 2.82%. Calculated for $C_3H_4N_4O_2$: C, 28.12; H, 3.12%. IR spectrum (ν, cm^{-1}): 3340, 3140 (NH_2), 1725 (C=O), 1665 (C=N).

2-Amino-5-cyano-1,3,4-oxadiazole (I) from Amide (VIII). A sample of 0.83 ml (5.94 mmoles) trifluoroacetic anhydride was added with stirring to 0.7 g (5.4 mmoles) amide (VIII) in 25 ml anhydrous dioxane and 0.87 ml (10.8 mmoles) pyridine at a rate such that the temperature did not rise above +5°C, stirred for 3 h at 20°C, and then, the same amounts of pyridine and trifluoroacetic anhydride were added at 0°C. The reaction mixture was stirred for an additional 1 h, poured into water, saturated with NaCl, and extracted with ethyl acetate. The dried extract was evaporated in vacuum to give 0.4 g (67%) (I), mp 189-190°C. This product was identical in its physical and spectral data to the sample described above.

Hydrochloride Salt of the Ethyl Ester of Imino[5-amino-1,3,4-oxadiazol-2-yl]carboxylic Acid (IX). Anhydrous HCl was introduced through a solution of 1 g (9.1 mmoles) (I) in 20 ml anhydrous ether containing 0.57 ml (9.9 mmoles) ethanol. The hydrochloride salt precipitate was separated and washed with ether to give 1.7 g (97%) (IX). Upon heating above 150°C, (IX) is converted to amide (VIII). Found: C, 30.82; H, 4.50; Cl, 18.07; N, 28.93%, M^+ = 194.192, M^+ − HCl = 156. Calculated for $C_5H_9ClN_4O_2$: C, 31.17; H, 4.67; Cl, 18.44; N, 29.09%.

Amide of 5-Amino-1,3,4-oxadiazole-2-hydroxamic Acid (X). A solution of NH_2OH obtained from 6.25 g (90 mmoles) $NH_2OH \cdot HCl$ and 3.75 g (67 mmoles) KOH in 100 ml methanol was added to a solution of 5 g (45 mmoles) (I) in 50 ml methanol and stirred for 1 h. The precipitate formed was filtered off to give 6.4 g (98%) (X), mp 220°C (dec.). Found: C, 24.72; H, 3.37; N, 48.90%. M^+ = 143. Calculated for $C_3H_5N_5O_2$: C, 25.17; H, 3.49; N, 48.95%. PMR spectrum (δ, ppm): 5.79 s (2H, NH_2), 7.24 s (2H, C^5-NH_2), 10.19 s (1H, OH). ^{15}N NMR spectrum (δ, ppm, J, Hz): −329.1 t (NH_2, J = 88.5).

N,N-Dimethyl-N′-[5-methoxycarbimido-2-(1,3,4-oxadiazolyl)formamidine (XI). A sample of 1.6 g (14.5 mmoles) (I) was added with stirring to 2.88 g (24 mmoles) dimethylacetal of dimethylformamide. The mixture turned yellow and heat was evolved. After stirring for 1 h at 20°C and standing in a refrigerator, the crystalline precipitate was filtered off to give 2.43 g (85%) (XI), mp 108.5-109.5°C (from ethanol). Found: C, 42.99; H, 5.84; N, 35.69%, M^+ = 197. Calculated for $C_7H_{11}N_5O_2$: C, 42.63; H, 5.62; N, 35.52%. PMR spectrum (δ, ppm): 3.09 s (3H) and 3.27 s (3H) ($N(CH_3)_2$), 3.92 s (3H, OCH_3), 8.46 and 8.83 s (−CH= and −NH−). ^{13}C NMR spectrum (δ, ppm, J, Hz): 34.8 q and 41.1 q (J_{CH_3} = 137 and 139) ($N(CH_3)_2$), 53.6 q (OCH_3, J_{CH_3} = 148), 154.0 s, 156.6 s, 169.7 s (C=NH(OCH)₃), C^2 and C^5), 159.7 d (−CH=N−, J_{CH} = 179).

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