The Reaction of *N*-Cyanocarbonimidate and Related Compounds with Hydroxylamine

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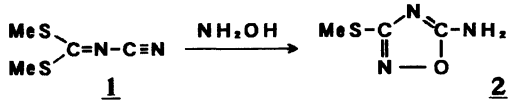
Synopsis. *O*-ethyl *S*-methyl *N*-cyanocarbonimidothioate reacted with hydroxylamine to give 5-amino-3-ethoxy-1,2,4-oxadiazole, whereas diethyl *N*-cyanocarbonimidate reacted to give 3-amino-5-ethoxy-1,2,4-oxadiazole. The reaction of ethyl *N*-cyanocarbamate or *S*-methyl *N*-cyanothiocarbamate with hydroxylamine afforded 3-amino-1,2,4-oxadiazol-5(4*H*)-one.

The synthesis of oxadiazoles substituted by an amino, alkoxyl or hydroxyl group at both the 3- and 5-positions is rather difficult.[1—3] Dimethyl *N*-cyanocarbonimidodithioate (**1**) has been known to react with hydroxylamine to produce 5-amino-3-methylthio-1,2,4-oxadiazole (**2**) (Chart 1).[4] We report on the reactions of other related *N*-cyanocarbonimidates (or carbamates).

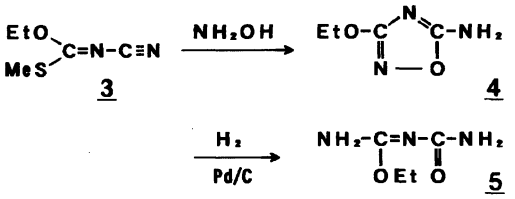
The reaction of *O*-ethyl *S*-methyl *N*-cyanocarbonimidothioate (**3**) with hydroxylamine afforded 5-amino-3-ethoxy-1,2,4-oxadiazole (**4**) in good yield (Chart 2). The structural assignment of **4** was accomplished by its mass spectrum, which showed a fragment at m/z 43 (HOCN), and by catalytic hydrogenation to 3-carbamoyl-2-ethylisourea (**5**). The oxadiazole **4** was stable in a 1 M (1 mol dm^{-3}) aqueous alkaline solution, but was hydrolyzed in 2 M sodium hydroxide to give the sodium salt of 3-ethoxy-1,2,4-oxadiazol-5(4*H*)-one (**6**), which gave a dioxane-containing crystal from the same solvent (Chart 3). The structure of **6** was confirmed by leading it into the known free base[3] and by catalytic hydrogenation to 2-ethylisourea (**7**).

The carbonimidate moiety of **1** or **3** is attacked by the amino group of hydroxylamine to produce the corresponding oxadiazole, **2**, or **4**, whereas Fritz[5] reported that the reaction product of diethyl *N*-cyanocabonimidate (**8**) with hydroxylamine was 3-amino-5-



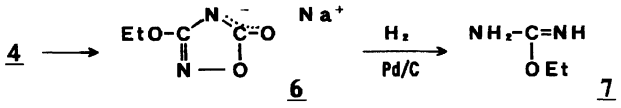
1 2

Chart 1.



3 4 5

Chart 2.



6 7

Chart 3.

ethoxy-1,2,4-oxadiazole (**9**). However, he assumed the structure of **9** merely by a ^{15}N NMR analysis, and the method of preparation and other physical data, such as the melting point, were not reported. We therefore reinvestigated the reaction of **8**.

Compound **8** had been synthesized by a complicating method;[6] however, it could be simply obtained by a treatment of readily available **1** or **3**[7] with sodium ethoxide. When compound **8** was reacted with hydroxylamine, a single product **9** was obtained in 78% yield (Chart 4). It showed a distinction from **4** regarding physical data, and the catalytic reduction afforded ethoxycarbonylguanidine **10**, thus confirming the original assignment of **9**.

Likewise, the potassium salt of ethyl *N*-cyanocarbamate (**11**) or *S*-methyl *N*-cyanothiocarbamate (**12**) was made to react with hydroxylamine hydrochloride; 3-amino-1,2,4-oxadiazol-5(4*H*)-one (**13**) was obtained (Chart 5). The structure of **13** was confirmed by catalytic hydrogenation, giving guanidine.

Experimental

Commercially available reagent-grade solvents were used

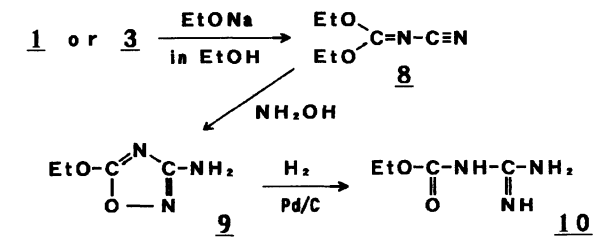


Chart 4.

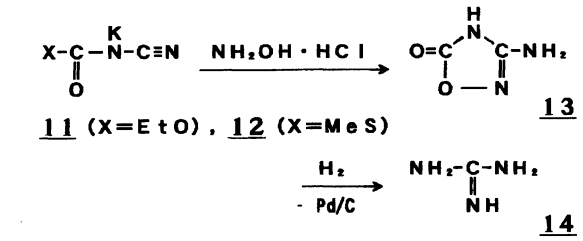


Chart 5.

without further purification. The melting points were uncorrected. The ^{1}H NMR, IR, and mass spectra were recorded on JEOL JNM-PMX60SI, Hitati 260-10, and Shimadzu GCMS-QP 1000A spectrophotometers.

Preparation of 4. To a solution of hydroxylamine hydrochloride (6.95 g, 0.10 mol) in water (15 ml) was added a solution of 95% sodium hydroxide (4.17 g, 0.10 mol) in ethanol (80 ml). After stirring for 15 min, the precipitated sodium chloride was filtered off. To the filtrate was added **3**[7] (14.4 g, 0.10 mol) and the mixture was stirred for 1.5 h below 10 °C and for 0.5 h at room temperature. After evaporation of the solvent, the residue was recrystallized from toluene to afford oxadiazole **4**. Yield: 11.56 g (89.5%); mp 114.0—114.5 °C; IR (KBr) 3470, 3150, 1695, 1660, 1599 and 1565 cm^{-1}; MS (70 eV) m/z 129 (M^+), 43 ($HOCN^+$). Found: C, 37.56; H, 5.58; N, 32.39%. Calcd for $C_4H_7N_3O_2$: C, 37.21; H, 5.47; N, 32.54%.

Catalytic Hydrogenation of 4. A solution of **4** (1.29 g, 10 mmol) in methanol (50 ml) containing 1 M hydrochloric acid (10 ml) was hydrogenated over 10% Pd/C (1.30 g) at atmospheric pressure for 4 h. After filtration, the filtrate was neutralized with 2 M sodium hydroxide and dried up. Extraction with ethyl acetate and recrystallization from toluene gave **5**. Yield: 0.93 g (72%); mp 125—126 °C (lit,[8] 129 °C).

Preparation of 6. Oxadiazole **4** (2.58 g) in 2 M sodium hydroxide (30 ml) was refluxed for 2.5 h; the resulting solution was cooled to room temperature, neutralized with carbon dioxide, and dried up. The residue was extracted with ethanol. A white semi-solid, thus obtained, was triturated with dioxane to crystallize. Recrystallization from dioxane gave a pure sodium salt of **6**, whose crystal contained one mol of dioxane. Yield: 3.68 g (76.7%); mp 86.0—86.5 °C (mp varies depending upon the rate of heating); IR (KBr) 3400, 1690, 1560, 1480, 1360, and 795 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=3.99 (2H, q, CH_2), 3.57 (8H, s, CH_2), 1.21 (3H, t, CH_3).

The dioxane-containing sodium salt of **6** (1.0 g, 4.2 mmol) was hydrogenated in the same manner as described for **4**. A crude product was obtained after filtration, evaporation and extraction with ethanol, and was recrystallized from acetonitrile to give **7**. Yield: 0.38 g (73.1%); mp 121—121.5 °C (lit,[9] 123—124 °C).

The solution of dioxane-containing sodium salt of **6** (1.2 g, 5 mmol) in 1 M hydrochloric acid (5 ml) was dried up. Extraction of the residue with ethyl acetate afforded free acid of **6**. Yield: 0.62 g (95.4%); mp 105.5—106 °C (lit,[3] 106—108 °C).

Preparation of 8. To the sodium ethoxide solution formed from sodium (1.15 g) in absolute ethanol (60 ml) was added 7.20 g (50 mmol) of **3**; the mixture was then stirred for 0.5 h below 10 °C. Pyridinium nitrate (10.83 g, 76 mmol) was added and the mixture was stirred for 1 h. The resulting precipitate was filtered off and the filtrate was dried up. The residue was partitioned between carbon tetrachloride (100 ml) and water (100 ml). The organic layer was dried (Na_2SO_4) and evaporated to give **8**. Its infrared spectrum completely agreed with that reported in the literature;[6] it was used for the next step. Yield: 6.10 g (85%); MS (70 eV) m/z 142 (M^+); ^{1}H NMR (CCl_4) δ=1.39 (3H, t, CH_3), 4.36 (2H, q, CH_2).

Compound **8** was also obtained in the same manner using one mol of **1**, 2 mol of sodium and a slight excess of pyridinium nitrate.

Preparation of 9. Oxadiazole **9** was obtained from 2.84 g (20 mmol) of **8** according to the same procedure used for the preparation of **4**, and recrystallized from water. Yield: 2.01 g (77.9%); mp 128—129 °C; IR (KBr) 3380, 3220, 1670, 1615, 1590, and 1470 cm^{-1}; MS (70 eV) m/z 129 (M^+), 101 ($M^+-C_2H_4$), 44 (CO_2^+); ^{1}H NMR (DMSO-d_6) δ=1.37 (3H, t, CH_3), 4.41 (2H, q, CH_2), 5.91 (2H, s, NH_2). Found: C, 37.40; H, 5.19; N, 32.25%. Calcd for $C_4H_7N_3O_2$: C, 37.21; H, 5.47; N, 32.54%.

Oxadiazole **9** (0.65 g, 0.005 mol) was hydrogenated in the same manner as that described for **4**, and compound **10** was obtained as picrate. Yield: 0.98 g (54%); mp 221 °C (lit,[10] 222—223 °C).

Preparation of 13. Compound **12** (3.08 g, 20 mmol) and hydroxylamine hydrochloride (1.5 g, 20 mmol) in ethanol (30 ml) was refluxed for 1 h, and some insoluble impurities were filtered off. Upon cooling, 0.51 g of **13** precipitated and was collected by filtration. The filtrate was dried up. The residue was dissolved in 2 M sodium hydroxide, and carbon dioxide was bubbled into this solution. *S*-methyl *N*-carbamoylthiocarbamate[11] (0.04 g, 1.5%) precipitated was filtered off. The filtrate was acidified with dilute hydrochloric acid to precipitate **13** (0.35 g). The total yield of **13** was 42.5%. Recrystallization from water afforded pure **13**. Mp 195—196 °C; MS (70 eV) m/z 101 (M^+), 44 (CO_2^+), 43 ($HOCN^+$). Found: C, 24.01; H, 3.08; N, 41.39%. Calcd for $C_2H_3N_3O_2$: C, 23.77; H, 2.99; N, 41.58%. The same procedure using **11** afforded 44.4% of **13** and 4.1% of *N*-carbamoylcarbamate.

The analogous hydrogenation of **13** as that described for **9** afforded 55% of guanidine picrate, mp 323 °C.

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