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Ring Transformation of 1-Substituted 3,5-Dinitro-4-pyridones to 4-Nitro-5(2*H*)-isoxazolone by Hydroxylamine[1]

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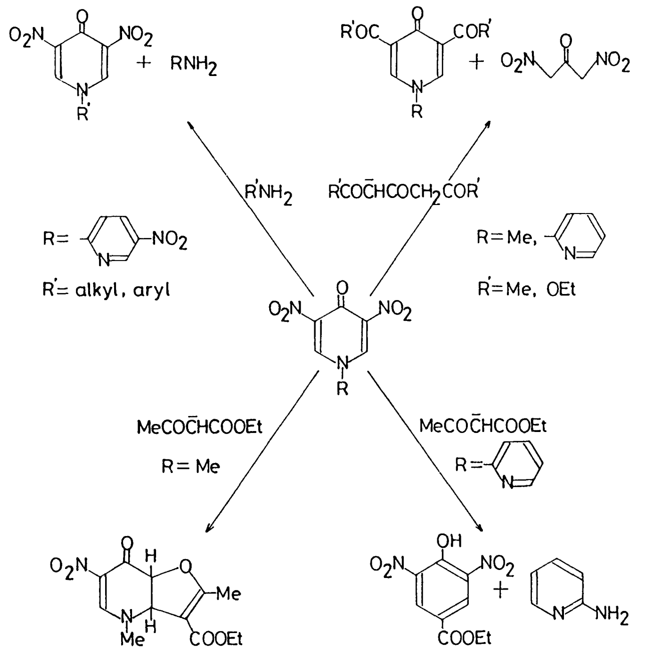
New ring transformations of 3,5-dinitro-1-(4-nitrophenyl)-4-pyridone and its homologues with hydroxylamine were found to give 4-nitro-5(2*H*)-isoxazolone. These results were rationalized by double ring transformations in sequence. The fact that the 4-position of the 4-pyridone behaved as an electrophlic site was the first example in this series of ring transfomations, and was caused by the alpha-effect of the reagent. Some reactions of the isoxazolone were carried out.

In this series of nucleophilic reactions of elctron-deficient pyridones, we have reported ring transformations of 1-substituted 3,5-dinitro-4-pyridones with either enolate anions or primary amines. Several types of ring transformations were observed depending on the combination of the enolate anion and the 1-substituent of the pyridone used.[2] Reaction with a primary amine resulted in the exchange of the ring nitrogen moiety of the pyridone with that of the primary amine.[3] This reaction developed the utility of the 4-pyridone as a protecting group for primary amines. Thus, a variety of amino acids were protected and deprotected by 3,5-dinitro-1-(4-nitrophenyl)-4-pyridone (**1a**) without racemization throughout the sequence.[4] This replacement of the ring nitrogen moiety was caused by a small difference in the basicity between the primary amine used for the reagent and the liberated one.

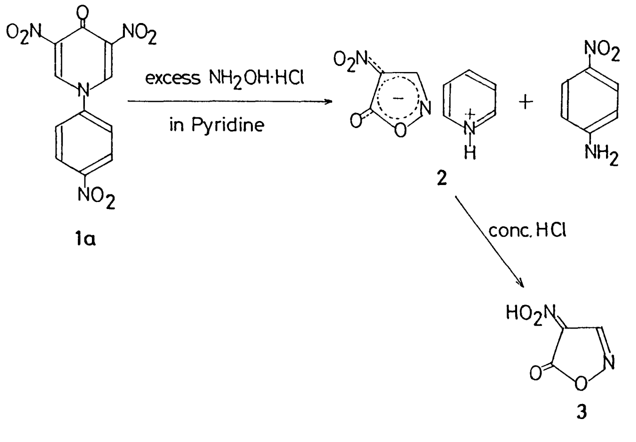
These results prompted us to investigate the behavior of hetero bidentate nucleophilic reagents such as hydroxylamine or hydrazine toward the pyridone. The carbonyl carbon of the pyridone did not act as an electrophilic center in our previous studies of this series, but such ambident reagents were anticipated to attack the carbonyl carbon of the pyridone, because of their strong nucleophilicity caused by the alpha-effect.



In this paper we wish to report a new type of ring transformation of 1-substituted 3,5-dinitro-4-pyridones with hydroxylamine.

Results and Discussion

Reaction of 3,5-dinitro-1-(4-nitrophenyl)-4-pyridone (**1a**) with a twofold excess of hydroxylamine hydrochloride in pyridine occurred smoothly at room temperature. The dark red color of the reaction mixture faded to yellow within an hour, and product (**2**) was obtained as colorless needles together with 4-nitroaniline. Treatment of **2** with concd hydrochloric acid gave a free acid, 4-aci-nitro-5(4*H*)-isoxazolone (**3**), liberating a pyridine molecule. The pyridinium salt of **3** was identical to **2** as confirmed by mixing **3** with pyridine to give **2** quantitatively. The ^{1}H NMR spectrum of **3** showed two singlets at 8.40 and 11.0 ppm; the latter disappeared on addition of D_2O. The broad absorption with its center at about 2300 cm^{-1} (hydrogen bonded O–H) and the strong absorption at 1770 cm^{-1} (C=O) in the IR spectrum



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suggested that **3** was the aci-nitro form. These spectral characteristics of **3** were very similar to those of 3-methyl-4-aci-nitro-5(4*H*)-isoxazolone as reported by R. Nesi et al.[5]

The structure of **3** was also confirmed by independent synthesis of **3** from the reaction of methyl 2-nitro-3-ethoxypropenoate and hydroxylamine hydrochloride in the presence of pyridine.

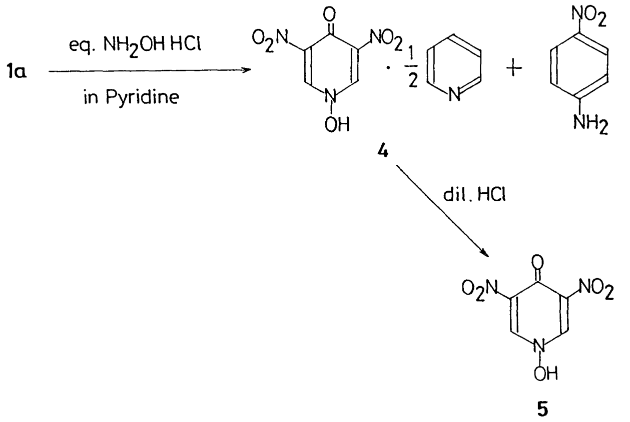
The results apparently showed that the N and O atoms of hydroxylamine attacked at the 2- and 4-positions of the 4-pyridone ring, respectively. Concurrent formation of 4-nitroaniline, however, showed that cleavage of the N(1)–C(2) bond and the N(1)–C(6) bond of the pyridone had occurred. That is, double ring transformations in sequence were suggested to occur, and 2-nitroacetaldehyde oxime must have been produced in addition to **2** and 4-nitroaniline.

The following two reactions were examined from the above viewpoint.

The reaction of **1a** with 1.1 equimolar amounts of the reagent in pyridine yielded the complex of 1-hydroxy-3,5-dinitro-4-pyridone and pyridine in a molar ratio of 2:1 (**4**) as red columns in addition to 4-nitroaniline (Table 1, Entry 2). Product **4** easily gave 1-hydroxy-3,5-dinitro-4-pyridone (**5**) by treating with dil hydrochloric acid, and was regenerated reversibly by treating **5** with pyridine. This fact showed that hydroxylamine acted as a primary amine, and attacked at the 2- and 6-positions of the 4-pyridone to result in exchange of the *N*-substituent moiety of the 4-pyridone as reported in the previous paper.[3]

Treatment of **4** with a slight excess of hydroxylamine hydrochloride in pyridine at room temperature gave **2** in a good yield (Table 1, Entry 3). 2-Nitroacetaldehyde oxime which should supposedly have been derived from the rest of **4** in the ring transformation was not isolated directly under these conditions, but its formation was evidently confirmed by the fact that 2-nitro-2-(phenylhydrazono)acetaldehyde oxime (**6**) was isolated when the filtrate from which **2** had been filtered off was treated with aqueous benzenediazonium chloride. The oxime **6** was independently obtained from authentic 2-nitroacetaldehyde oxime[6] with benzenediazonium chloride.

A provable reaction course matching the above observations may be proposed as follows. Formation of the σ-addut was followed by ring opening to give an intermediate **7**, and the cyclization of **7** with elimination of 4-nitroaniline gave **5**. Pyridone **5** was then easily subject to attack by excess hydroxylamine to give ring-opened intermediate **8**. In the symmetrical intermediate **8**, an intramolecular attack of either oxygen atom of the two hydroxylamino functions at the carbonyl carbon atom lead to 4-aci-nitro-5(4*H*)isoxazolone **3** with liberation of 2-nitroacetaldehyde oxime. Even though either of the more nucleophilic nitrogen atoms of these hydroxylamino groups attacked at the *β*-position of the nitroolefin part of **8**, the intramolecular reaction resulted in



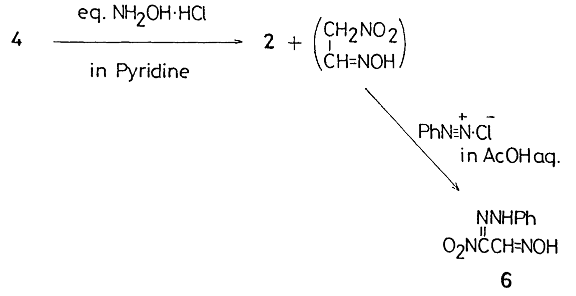
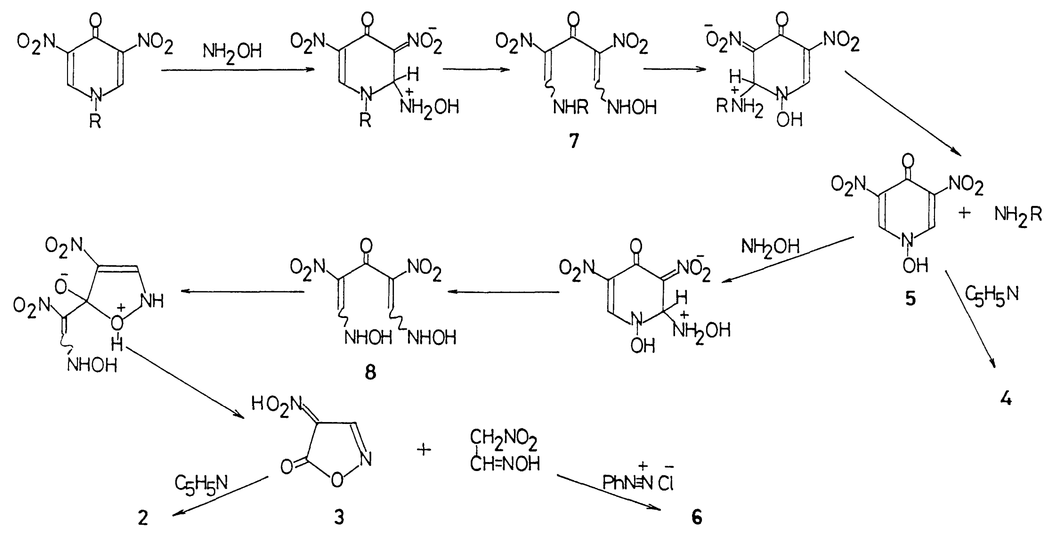


Table 1. Ring Transformations of 1-Substituted 3,5-Dinitro-4-pyridones with Hydroxylamine

Entry	4-Pyridone 1-Substituent	Reaction conditions			Products (Yield/%)		
		$NH_2OH \cdot HCl$ mol ratio	Temp °C	Time h	**2**	**4**	**1**(recovery)
1	**1a** $-C_6H_4-NO_2-4$	3.0	20	2	88	—	—
2	**1a** $-C_6H_4-NO_2-4$	1.1	20	2	—	83	—
3	**4** -OH	1.1	20	2	80	—	—
4	**1b** -2-Pyridyl	3.0	20	2	83	—	—
5	**1c** $-C_6H_5$	3.0	20	2	21	—	78
6	**1c** $-C_6H_5$	3.0	50	2	71	—	16
7	**1c** $-C_6H_5$	3.0	20	5	62	—	27
8	**1d** $-CH_3$	3.0	20	5	Trace	—	93
9	**1d** $-CH_3$	3.0	50	5	26	—	65
10	**1d** $-CH_3$	1.1	50	5	16	—	73



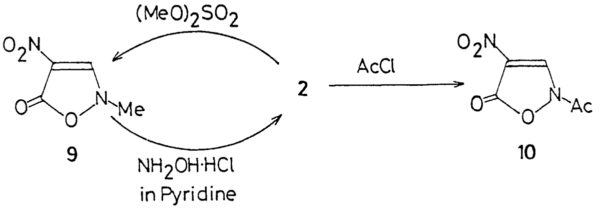
regeneration of **5**.

In order to prove the generality and limitation of the reaction, some 1-substituted 3,5-dinitro-4-pyridones (**1b**, **1c**, and **1d**) were investigated.

The order of reactivity of these pyridones in the ring transformation appeares to be **1a**≈**1b**>**1c**>**1d** from the results of the reactions shown in Table 1. The 1-methyl homologue **1d**, which was the least reactive among the four, however, gave a satisfactory result under modified reaction conditions. These results are reasonably acceptable upon reflection of the electronic effects of the 1-substituent. The electron-releasing effect of the methyl group might have suppressed the reactivity of the pyridone ring. In the case of the reactions of **1a** and **1b**, the color of the reaction mixture turned immediately to dark red when the reactants were mixed, then faded away within an hour. On the other hand, **1c**, and **1d** showed moderate or no evident change in color of the reaction mixture during the reactions. These facts show that the more basic the liberated amine moiety is the smaller the rate of the formation of **5** is. The fact that **2** rather than **4** is obtained as a product with recovery of substrate from the reaction of **1d** with equimolar hydroxylamine (Table 1, Entry 10) contrasts to the result of the reaction of **1a** (Entry 2). The reaction rate of the first step ring transformation of **1a** and **1b** appears to be larger than that of the second step ring transformation, but the rate of **1d** appears to be just the opposite.

Although, 3-methyl[5] and 3-phenyl[7] analogs of **3** have been reported, to our knowledge 3-unsubstituted 4-nitro-5(2*H*)-isoxazolones, **3** and **2**, are unknown compounds. Some reactions of the isoxazolones were carried out to examine their particular chemical properties.

The *N*-methylation of **3** was accomplished by direct treatment of **2** with dimethyl sulfate to give 2-methl-4-nitro-5(2*H*)-isoxazolone (**9**) in a good yield. Acetylation could be performed by heating **2** in excess acetyl chloride at 50 °C to give 2-acetyl-4-nitro-5(2*H*)-isoxazolone (**10**). Reaction of **9** with hydroxylamine hydrochloride in pyridine reproduced **2** quantitatively.



We were able to draw out a new reactivity of the 4-pyridone by the ring transformation with hydroxylamine giving 4-nitro-5(2*H*)-isoxazolone with elimination of the 2-nitroacetaldehyde derivative. The product and its derivatives, especially the *N*-methyl derivative **9**, have a variety of functionalities, such as β-nitro enamine, heterodiene and α-nitro lactone, in its ring, and are anticipated to demonstrate various types of reactivity including ring transformation. New ring transformations of **9** on the basis of this idea are currently under study.

Experimental

All melting points were measured on a Yanako melting point apparatus and were uncorrected. IR spectra were obtained on a Hitachi 260-10 spectrometer as Nujol mull, and ^{1}H NMR spectra were recorded on a Hitachi R-20B spectrometer with TMS as an internal standard.

Reaction of 3,5-Dinitro-1-(4-nitrophenyl)-4-pyridone (1a) with Excess Hydroxylamine Hydrochloride. Hydroxylamine hydrochloride (0.690 g, 10.0 mmol) was added with stirring by a magnetic stirrer to a solution of **1a** (1.00 g, 3.27 mmol) in pyridine (50 ml). The reaction mixture was allowed to stand at room temperature for 2 h. The pyridine was evaporated under reduced pressure at 35—40 °C, water (50 ml) was added to the residual solid, and the yellow precipitates were collected on a filter to give 4-nitroaniline (0.420 g, 3.04 mmol, 93% yield). The filtrate was concentrated to dryness under reduced pressure. The residual mass was dissolved in ethanol

(20 ml), and the resulting solution was cooled in an ice bath. The crystalline precipitates were collected by filtration to give **2** (0.602 g, 2.88 mmol, 88% yield) as colorless needles (recrystallized from ethanol), mp 136.0—137.0 °C (decomp). IR 2500—1950 (broad) (N–H), 1680 (C=O), 1520, and 1325 cm^{-1} (NO_2). ^1H NMR (DMSO-d_6) δ=8.2 (m, 2H), 8.41 (s, 1H), 9.0 (m, 2H), and 10.4 (broad s, 1H). Found: C, 45.93; H, 3.39; N, 20.20%. Calcd for $C_8H_7N_3O_4$: C, 45.94; H, 3.37; N, 20.09%.

Reaction of 1a with 1.1 Equimolar Amounts of Hydroxylamine Hydrochloride. One gram (3.27 mmol) of **1a** was treated with hydroxylamine hydrochloride (0.250 g, 3.60 mmol) as described above, in this case, the dark red color of the reaction mixture remained during the reaction time. After the solvent was evaporated off, the residual solid was extracted with chloroform. From the extraction, 4-nitroaniline (0.425 g, 3.08 mmol, 94% yield) was obtained. The residual solid was rinsed with a small amount of ethanol to give **4** (0.650 g, 2.70 mmol, 83% yield) as red columns (recrystallized from water), mp 202.0—203.0 °C (decomp). ^1H NMR (DMSO-d_6) δ=7.5 (m, 1H), 7.9 (m, 0.5H), 8.6 (m, 1H), 9.16 (s, 2H), and 9.5 (broad s, 1H). Found: C, 37.16; H, 2.30; N, 20.37%. Calcd for $C_{15}H_{11}N_7O_{12}$: C, 37.43; H, 2.30; N, 20.37%.

Reaction of 4 with Hydroxylamine Hydrochloride. A mixture of **4** (0.500 g, 2.08 mmol) and hydroxylamine hydrochloride (0.175 g, 2.88 mmol) in pyridine (50 ml) was allowed to stand at room temperature for 2 h. The pyridine was evaporated to dryness, ethanol (10 ml) was added to the residue, and the crystalline precipitates were collected on a filter to give **2** (0.350 g, 1.67 mmol, 80% yield). The filtrate was concentrated and the residue was dissolved in water (10 ml), then the resulting aqueous solution was cooled in an ice bath. To the solution was added an aqueous solution of benzenediazonium chloride prepared from aniline (0.250 g, 2.69 mmol) and sodium nitrite (0.220 g, 3.19 mmol) in 1 M (1 M=1 mol dm^{-3}) hydrochloric acid (10 ml) at 0 °C. The precipitates were recrystallized from water to give **5** (0.210 g, 1.01 mmol, 49% yield) as orange needles, mp 186.0—187.0 °C (decomp). ^1H NMR (DMSO-d_6) δ=7.4 (m, 5H), 8.56 (s, 1H), 12.3 (broad s, 1H), and 12.53 (s, 1H). Found: C, 46.72; H, 4.03; N, 27.04%. Calcd for $C_8H_8N_4O_3$: C, 46.15; H, 3.87; N, 25.97%.

Alternate Synthesis of 2. A mixture of methyl 3-ethoxy-2-nitropropenoate[8] (3.50 g, 20.0 mmol), hydroxylamine hydrochloride (1.81 g, 26.0 mmol), and pyridine (5.40 g, 50.6 mmol) in ethanol (75 ml) was heated at 50—60 °C for 2 h. The reaction mixture was cooled in an ice bath, and the crystalline precipitates were collected by filtration giving **2** (3.60 g, 17.2 mmol, 86% yield).

Preparation of 6 from Authentic 2-Nitroacetaldehyde Oxime. A solution of benzenediazonium chloride prepared just as described above was added to a solution of 2-nitroacetaldehyde oxime (0.200 g, 1.92 mmol) in 1 M hydrochloric acid (10 ml) at 0 °C. Yellow precipitates were recrystallized from water to give **6** (0.220 g, 1.06 mmol, 55% yield).

4-Aci-nitro-5(4*H*)-isoxazolone (3). A mixture of **2** (1.00 g, 4.78 mmol) in concd hydrochloric acid (10 ml) was heated at 50—60 °C until **2** dissolved, and then cooled in an ice bath. The precipitates were collected by filtration, rinsed with a small amount of cold water and then with diethyl ether, and were dried in a desiccator over sodium hydroxide to give **3** (0.510 g, 3.92 mmol, 82% yield) as colorless needles, mp 145.0—146.0 °C. IR 2600 (broad) (O–H) and 1700 cm^{-1} (C=O). ^1H NMR (DMSO-d_6) δ=8.40 (s, 1H) and 11.0 (s, 1H). Found: C, 27.86; H, 1.65; N, 21.33%. Calcd for $C_3H_2N_2O_4$: C, 27.70; H, 1.55; N, 21.54%.

Reaction of 1b, 1c, and 1d with Hydroxylamine Hydrochloride. One gram of 4-pyridone was treated with 3 equimolar amounts of hydroxylamine hydrochloride under the conditions shown in Table 1 according to the reaction of **1a**. The solvent was evaporated off, and the residual solid was treated with a small amount of benzene. After removal of the benzene by decantation, the residual mass was extracted with hot chloroform (30 ml×3). The combined extractions were evaporated and the residual solid was rinsed with a small portion of ethanol to give **3**.

2-Methyl-4-nitro-5(2*H*)-isoxazolone (9). A mixture of **2** (1.00 g, 4.78 mmol) and dimethyl sulfate (0.900, 7.14 mmol) was gently heated at 50—60 °C for 100 m. Water (10 ml) was added to the cold reaction mixture, and the precipitates were collected by filtration then rinsed with a small amount of cold ethanol to give **6** (0.585 g, 4.06 mmol, 85% yield) as colorless needles (recrystallized from etrhanol), mp 136.0—137.0 °C (decomp). IR 1775 (C=O), 1615 (C=N), 1510, and 1375 cm^{-1} (NO_2). ^1H NMR (DMSO-d_6) δ=3.79 (s, 3H), and 9.63 (s, 1H). Found: C, 33.44; H, 2.87; N, 19.45%. Calcd for $C_4H_4N_2O_4$: C, 33.44; H, 2.80; N, 19.44%.

2-Acetyl-4-nitro-5(2*H*)-isoxazolone (10). A mixture of **2** (0.500 g, 2.39 mmol) and acetyl chloride (3.0 g, 38.2 mmol) was heated at 50 °C for 30 min. After the acetyl chloride was evaporated, crushed ice (2 9) was added to the residue, and the crystalline precipitates were collected on filter and rinsed with a small amount of cold water to give **10**, (0.281 g, 1.50 mmol, 63% yield), mp 132.0—134.0 °C (decomp). IR 1810 (C=O), 1760 (C=O), 1570, and 1350 cm^{-1} (NO_2). ^1H NMR (DMSO-d_6) δ=1.91 (s, 3H) and 8.43 (s, 1H). Found: C, 35.09; H, 2.41; N, 16.50%. Calcd for $C_5H_4N_2O_5$: C, 34.89; H, 2.34; N, 16.28%.

Reaction of 9 with Hydroxylamine Hydrochloride. A mixture of **9** (0.500 g, 3.47 mmol) and hydroxylamine hydrochloride (0.290 g, 4.17 mmol) in pyridine (20 ml) was heated at 50 °C for 1 h. After the solvent was evaporated in vacuo, ethanol (10 ml) was added to the residue, and the crystalline precipitates were collected by filtration to give **3** (0.690 g, 3.30 mmol, 95% yield).

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