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The Nucleophilic Reaction upon Electron-Deficient Pyridone Derivatives. VIII.[1] Novel Fragmentation of 3,5-Dinitro-2-pyridone by Primary Amine

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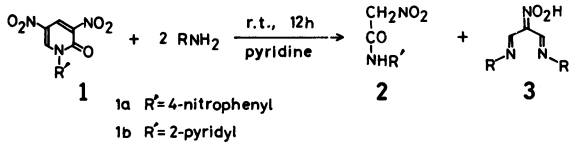
Fragmentation of 3,5-dinitro-2-pyridone (**1**) by primary amine gave nitroacetamide (**2**) and nitromalonaldehyde diimine. In the case of *N*-methyl derivative (**1c**), the reaction was completely suppressed by the product **2** to give an anionic σ-adduct of **1c** with **2**. The mechanism of the reaction was discussed.

In previous papers, we reported a ring transformation of 3,5-dinitro-2-pyridone (**1**) with various ketones into *p*-nitrophenols[2] or *p*-nitroanilines.[3] Three types of the intermediates were isolated and characterized, i.e., an anionic σ-adduct,[4] a 2-azabicyclo[3.3.1]nonane derivative,[2,3] and an α-nitro-α-(2-nitro-2,4-hexadienyl)acetamide derivative.[3] (Scheme 1) The reaction of **1** is unusual in the reactions of heteroaromatic compounds, because most ring transformations of electron-deficient heterocyclic compounds with ketones or other nucleophiles proceed through open chain intermediates rather than through such bicyclic compounds.[5] It is analogous to the reaction of 1,3,5-trinitrobenzene with acetone and diethylamine to give *N,N*-diethyl-*p*-nitroaniline,[6] because an anionic σ-adduct[7] and a bicyclo[3.3.1]nonane derivative[8] were recognized as the intermediates.

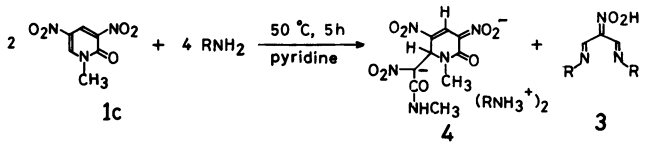
In our study on electron-deficient pyridone derivatives, we found a novel fragmentation of 3,5-dinitro-2-pyridone (**1**) by primary amine. The mechanism of the reaction which appears to be closely related to those of the above reactions will be discussed.

Results and Discussion

The reaction of 3,5-dinitro-1-(4-nitrophenyl)-2-pyridone (**1a**) with excessive aliphatic or aromatic primary amine in pyridine at room temperature gave a nitroacetamide (**2a**) and nitromalonaldehyde diimine (**3**) (Eq. 1). The aliphatic amines reacted faster and gave better yields of **2** and **3** than the aromatic amines. The reaction of **1a** with cyclohexylamine was completed within 5 min. Similarly, 1-(2-pyridyl) derivative (**1b**) reacted with these amines according to Eq. 1. On the other hand, 1-methyl derivative (**1c**) reacted with excess of the aliphatic primary amines at 50 °C to give **3** and a Michael-type adduct (**4**) as indicated in Eq. 2. No aromatic primary amines reacted with **1c** at 50 °C due to their low basicity. The results are summarized in Table 1. The structure of **3** was confirmed by comparing **3b** with an authentic sample prepared by the reaction of sodium salt of nitromalonaldehyde with *p*-anisidine. The product **4** showed characteristics of anionic σ-adduct of **1c** by the UV and ^{1}H NMR spectra.[4] The addition site of nucleophilic carbon or nitrogen is C-6 of **1c**. Chemical shifts of H-6 of **4a** (cyclohexylammonium salt) or **4b** (*t*-butylammonium salt) were found at δ of 6.2. The values are about 1 ppm lower than those of anionic σ-adducts of **1c** with usual carbon nucleophiles. This is attributed to strong diamagnetic anisotropic effect of anionic part of α-(*N*-methyl-carbamoyl)-α-nitromethylene of **4**. Coupling between H-4 and H-6 was not observed. Treatment of **4a** with hydrochloric acid gave **1c**, *N*-methyl-α-nitroacetamide (**2c**), and cyclohexylammonium chloride in 85, 45, and 90% yields, respectively. An authentic sample of **4a** was obtained by mixing its components in pyridine at room temperature. From these facts, **4** were identified as dianionic salts as indicated in Eq. 2.



(1)



(2)

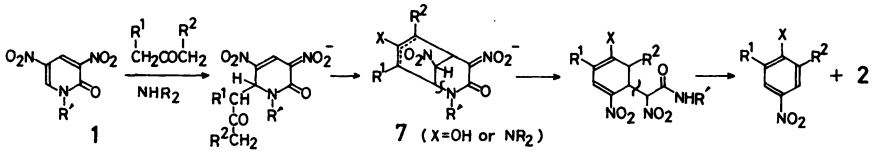
The different results between **1a**, **1b**, and **1c** can be interpreted by the hard-soft concept. **1c** is a softer electrophile than **1a** and **1b**, because **1c** is a weaker electrophile for hard amines but has stronger affinity for soft nucleophilic carbon of nitroacetamide (**2**) than **1a** and **1b**. In the case of **1c**, the reaction indicated by Eq. 1 is completely suppressed by the product **2c** which gives adduct **4** by addition to **1c**. The difference in reactivity between **1a** and **1c** explains the following facts. In the presence of excess acetone, the reaction of **1c** with cyclohexylamine at 70 °C gave *N*-cyclohexyl-*p*-nitroaniline quantitatively. The fragmentation in Eqs. 1 and 2 is thus completely suppressed by acetone nucleophile. On the other hand, in the case of the reaction of **1a** under similar conditions, competitive reactions between the fragmentation and the ring transformation occurred to give a mixture of **3a** and *N*-cyclohexyl-*p*-nitroaniline in 41 and 19% yields, respectively.

When the reaction of a mixture of **1c** and excess of cyclohexylamine (1:6 mol ratio) in pyridine-d_5 was monitored at 37 °C by ^{1}H NMR spectra, the first observable species was only an anionic σ-adduct (**5**) of **1c** with the amine; δ=3.18 (s, NCH_3), 5.68 (d, H-6, J=1.0 Hz), and 9.37 (d, H-4, J=1.0 Hz). The chemical shifts and coupling patterns were similar to those of the secondary amine adducts of **1c**.[4] As the peaks of **5** decreased slowly, the peaks of the products **3a** and **4a** increased. The change did not obey the first-order kinetics as expected from the mechanism. Neither other intermediate nor by-product was detected. Transformation of **5** to an intermediate is the rate-determining step. The pyridone **1c** also reacted with strong secondary amines such as pyrrolidine and diethylamine in pyridine-d_5 to give anionic σ-adducts immediately, but the further fragmentation did not occur under the similar conditions. On the other hand, the reactive pyridone **1a** was rapidly decom-

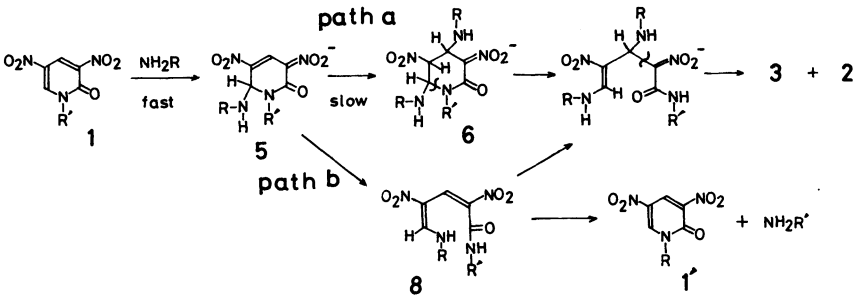
Table 1. Fragmentation of 3,5-Dinitro-2-pyridone (**1**) by Primary Amine

Substrate[a]	Amine	Reaction Temperature	Products	(Yields/%)[c]
1a	Cyclohexylamine	r.t.	**2a** (80)	**3a** (88)
1a	*p*-Anisidine	r.t.	**2a** (15)	**3b** (73)
1a	Aniline	r.t.	**2a** (0)	**3c** (59)
1b	Cyclohexylamine	r.t.	**2b'**[b] (75)	**3a** (86)
1b	*p*-Anisidine	r.t.	**2b** (56)	**3b** (82)
1b	Aniline	r.t.	**2b** (0)	**3c** (58)
1c	Cyclohexylamine	50 °C	**4a** (94)	**3a** (88)
1c	*t*-Butylamine	50 °C	**4b** (92)	**3d** (88)
1c	*p*-Anisidine	100 °C	—	**3c** (6)

a) Notations of the compounds are described in Eqs. 1 and 2. b) Isolated as a cyclohexylammonium salt. c) In the reaction of **1a** and **1b**, yields are based on Eq. 1. In the reaction of **1c**, yields are based on Eq. 2.



Scheme 1.



Scheme 2.

posed to unidentifiable products by pyrrolidine.

There are two possible courses of the reaction. The one involves a complex (**6**) formed by twofold addition of the primary amine. (Scheme 2, path a) The complex **6** corresponds to the bicyclic intermediate (**7**) in the ring transformation (Scheme 1).[2,3] Although diadduct formation such as **6** has been exemplified in the reaction of 1,3,5-trinitrobenzene and other electron-deficient aromatic systems,[9] this type of fragmentation has not been reported. Easy heterolysis of C_6–N_1 bond of **6** explains the fragmentation of **1**, whereas lack of such a bond in the diadduct of trinitrobenzene would result no fragmentation.

The alternative course which involves an open-chain intermediate (**8**) can be considered. (path b) The similar intermediate has been postulated in the reactions of 3,5-dinitro-4-pyridone with sodium salt of ethyl acetoacetate[10] or with primary amine.[11] In the latter reaction, recyclization of the open-chain intermediate gives another 4-pyridone, in which an original *N*-substituent is exchanged for the primary amine. Since such a substitution product (**1'**) was not found in the present reaction, path a is more probable than path b.

Thus the fragmentation is a characteristic reaction of 3,5-dinitro-2-pyridone (**1**) and unique reaction of electron-deficient aromatic compounds.

Experimental

The infrared spectra were measured in nujol by means of a Hitachi 260-10 spectrophotometer, ^{1}H NMR spectra by a Hitachi R-20 B spectrometer, and ultraviolet spectra by a Shimadzu UV-240 spectrophotometer.

3,5-Dinitro-(4-nitrophenyl)-2-pyridone (1a). Nitration of 1-(4-nitrophenyl)-2-pyridone with fuming nitric acid (d 1.42) at 130 °C for 7 h gave **1a** in 65% yield. Pale yellow needles (AcOH–H_2O 3:1); mp 221.5—222 °C. ^{1}H NMR (DMSO-d_6) δ=7.91 (d, 2H, J=9.1 Hz), 8.46 (d, 2H, J=9.1 Hz), 9.17 (d, 1H, J=3.1 Hz), 9.51 (d, 1H, J=3.1 Hz), IR: 1710 cm^{-1} (C=O), 1577, 1530, 1346, 1324 cm^{-1} (NO_2). Found: C, 43.10; H, 2.05; N, 18.27%. Calcd for $C_{11}H_6N_4O_7$: C, 43.15; H, 1.98; N, 18.30%.

Reaction of 1a with Cyclohexylamine. To a solution of 0.61 g of **1a** in 15 ml of pyridine 1.21 g of cyclohexylamine in 5 ml of pyridine was added at 0 °C. The mixture was allowed to stand at room temperature for 12 h. After removal of the solvent in vacuo, residual oil was extracted with hexane to give 0.49 g of the diimine **3a**; colorless needles (hexane); mp 86—87 °C. ^{1}H NMR ($CDCl_3$) δ=1.0—2.2 (m, 20H), 3.0—3.5 (m, 2H), 8.70 (s, 2H), 11.0 (broad, 1H). IR: 1650, 1600 cm^{-1} (C=N). Found: C, 64.74; H, 9.00; N, 14.99%. Calcd for $C_{15}H_{25}N_3O_2$: C, 64.48; H, 9.02; N, 15.04%. The residue was dissolved in water and slightly excess hydrochloric acid was added to the solution. Precipitates were recrystallized from ethanol to give 0.36 g of α-nitro-*N*-(4-nitrophenyl)acetamide (**2a**); pale yellow needles; decomp 177—179 °C. ^{1}H NMR (DMSO-d_6) δ=5.59 (s, 2H), 7.83 (d, 2H, J=9.2 Hz), 8.23 (d, 2H, J=9.2 Hz), 11.07 (broad s, 1H). IR: 3360 cm^{-1} (N–H), 1703 cm^{-1} (C=O). Found: C, 42.90; H, 3.17; N, 18.69%. Calcd for $C_8H_7N_3O_5$: C, 42.67; H, 3.13; N, 18.66%.

Reaction of 3,5-Dinitro-1-(2-pyridyl)-2-pyridone (1b) with *p*-Anisidine. To a solution of 0.52 g of **1b** in 15 ml of pyridine was added 0.74 g of *p*-anisidine in 5 ml of pyridine at 0 °C. The mixture was allowed to stand at room temperature for 12 h. Water was added to the mixture and resulted precipitates were recrystallized from ethanol to give 0.54 g of **3b**. Yellow needles; mp 133—135 °C. ^{1}H NMR ($CDCl_3$) δ=3.82 (s, 6H), 6.94 (d, 4H, J=9.1 Hz), 7.19 (d, 4H, J=9.1 Hz), 8.99 (s, 2H), 13.5 (broad, 1H). IR: 1642, 1563 cm^{-1} (C=N). Found: C, 62.50; H, 5.36; N, 12.74%. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.37; H, 5.24; N, 12.84%. After the solvent was removed in vacuo, the residue was recrystallized from chloroform to give 0.21 g of **2a**.[2]

Similarly, nitromalonaldehyde dianil (**3c**) was obtained. Yellow needles; mp 93—95 °C. ^{1}H NMR ($CDCl_3$) δ=7.0—7.6 (m, 10H), 9.10 (s, 2H), 13.5 (broad, 1H). IR: 1650, 1567 cm^{-1} (C=N). Found: C, 67.54; H, 4.88; N, 15.47%. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72%.

Reaction of 1-Methyl-3,5-dinitro-2-pyridone (1c) with Cyclohexylamine. To a solution of 0.40 g of **1c** in 15 ml of pyridine 1.21 g of cyclohexylamine in 5 ml of pyridine was added. The mixture was heated at 50 °C for 3 h. After the solvent was removed in vacuo, residual oil was extracted with hexane. The extract was recrystallized from hexane to give 0.25 g of **3a**. The residue was dissolved in hot ethanol containig a few drops of cyclohexylamine. After cooling, 0.43 g of **4a** was obtained as orange powder; decomp 118—123 °C. ^{1}H NMR (DMSO-d_6) δ=0.9—2.2 (m, 20H), 2.71 (s, 3H), 2.71 (d, 3H, J=5.2 Hz), 2.4—3.2 (m, 2H), 6.20 (s, H-6), 5.8—7.0 (broad, 8H), 8.60 (s, H-4), 10.04 (broad q, 1H, J=5.2 Hz). IR: 3260, 2650, 2550 cm^{-1} (NH_3^+), 1626 cm^{-1} (C=O). UV (MeOH, 8.38×10^{-5} mol l^{-1}, ε depends on the concentration of **4a**): λ_{max} (ε) 489 nm (1.96×10^4), 302 nm (1.37×10^4). Found: C, 47.27; H, 7.30; N, 18.42%. Calcd for $C_{21}H_{39}N_7O_9$ (monohydrate): C, 47.27; H, 7.37; N, 18.38%.

Similarly **3d** and **4b** were obtained from reaction of **1c** with *t*-butylamine.

3d: Colorless needles (hexane); mp 142—143 °C. ^{1}H NMR ($CDCl_3$) δ=1.34 (s, 18H), 8.73 (s, 2H), 12.6 (broad, 1H). IR: 1640, 1592 cm^{-1} (C=N). Found: C, 58.02; H, 9.29; N, 18.43%. Calcd for $C_{11}H_{21}N_3O_2$: C, 58.12; H, 9.31; N, 18.49%.

4b: Orange powder (ethanol-*t*-butylamine); decomp 120—127 °C. ^{1}H NMR (DMSO-d_6) δ=1.24 (s, 18H), 2.70 (s, 3H), 2.71 (d, 3H, J=4.9 Hz), 6.28 (s, H-4), 6.7 (broad, 9H), 8.61 (s, H-6), 10.04 (broad q, 1H, J=4.9 Hz). IR: 2610, 2500 cm^{-1} (NH_3^+), 1627 cm^{-1} (C=O). UV (MeOH, 8.38×10^{-5} mol l^{-1}): λ_{max} (ε) 489 nm (1.71×10^4), 301 nm (1.61×10^4). Found: C, 41.83; H, 7.10; N, 20.22%. Calcd for $C_{17}H_{36}N_7O_{9.5}$ (1.5 hydrate): C, 41.63; H, 7.40; N, 19.99%.

Reaction of 1a with Cyclohexylamine in the Presence of Acetone. A solution of 0.31 g of **1a**, 0.61 g of cyclohexylamine, and 0.58 g of acetone in 20 ml of pyridine was heated at 70 °C for 3 h. The solvent was removed in vacuo and residue was treated by column-chromatograph with silica gel. Benzene elute gave 42 mg of *N*-cyclohexyl-*p*-nitroaniline; mp 99 °C; yellow needles (hexane). Chloroform elute gave 82 mg of 3-cyclohexylamino-2-nitro-2-propenal; mp 130—131 °C; pale yellow needles (hexane). Found: C, 54.58; H, 7.12; N, 14.35%. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13%. This compound was quantitatively obtained by treatment of **3a** with silica gel.

References

1) For the preceding paper: M. Ariga, Y. Tohda, and E. Matsumura, *Bull. Chem. Soc. Jpn.*, **58**, 393 (1985).
2) E. Matsumura, M. Ariga, and Y. Tohda, *Bull. Chem. Soc. Jpn.*, **52**, 2413 (1979).
3) E. Matsumura, Y. Tohda, and M. Ariga, *Bull. Chem. Soc. Jpn.*, **55**, 2174 (1982).
4) Y. Tohda, M. Ariga, T. Kawashima, and E. Matsumura, *Chem. Lett.*, **1983**, 715.
5) For example in pyridine system: A. N. Kost, S. P. Gromov, and R. S. Sagitullin, *Tetrahedron*, **37**, 3423 (1981).
6) T. Abe, *Bull. Chem. Soc. Jpn.*, **32**, 997 (1959).
7) R. Foster and C. A. Fyfe, *Tetrahedron*, **22**, 1831 (1966).
8) M. J. Strauss and H. Schran, *J. Am. Chem. Soc.*, **91**, 3974 (1969); H. Schran and M. J. Strauss, *J. Org. Chem.*, **36**, 856 (1971); L. M. Gnanadoss and D. Kalaivani, *ibid.*, **50**, 1174 (1985); *idem, ibid.*, **50**, 1178 (1985).
9) M. J. Strauss, *Chem. Rev.*, **70**, 688 (1970).
10) E. Matsumura, M. Ariga, and Y. Tohda, *Bull. Chem. Soc. Jpn.*, **53**, 2891 (1980).
11) E. Matsumura, M. Ariga, Y. Tohda, and T. Kawashima, *Tetrahedron Lett.*, **22**, 757 (1981); E. Matsumura, H. Kobayashi, T. Nishikawa, M. Ariga, Y. Tohda, and T. Kawashima, *Bull. Chem. Soc. Jpn.*, **57**, 1961 (1984).