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Ring Transformation of 1,4 (or 1,6)-Disubstituted 3,5-Dinitro-2-pyridones with Sodio *β*-Keto Esters[1]

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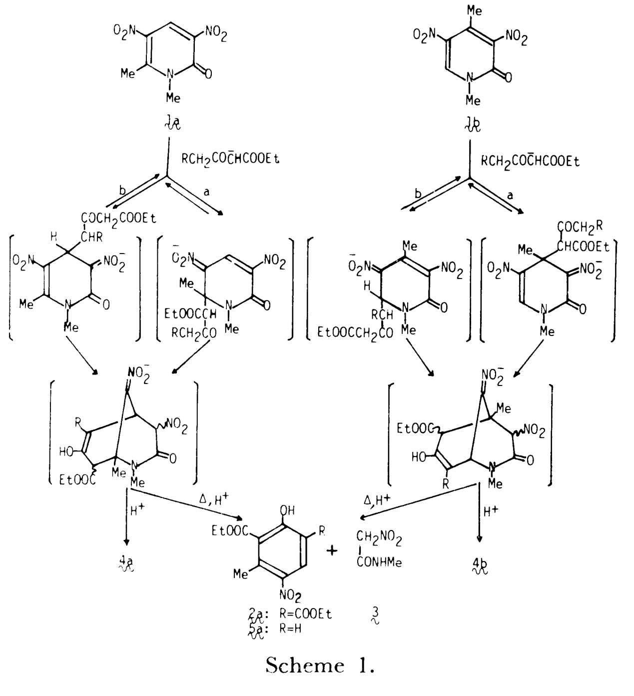
Synopsis. The ring transformation of 1,6-dimethyl-, 1,4-dimethyl- and 4-methoxy-1-methyl-3,5-dinitro-2-pyridones with sodio *β*-keto esters to nitrosalicylic esters was investigated concerning the electronic effects of 4 and 6-substituents. The results were explained by the HSAB principle.

In the previous paper of this series,[2] we reported the nucleophilic ring transformation of 1-substituted 3,5-dinitro-2-pyridones with some sodio *β*-keto esters to give nitrophenol derivatives together with *N*-substituted 2-nitroacetamides, and proposed a plausible reaction course including the stepwise formation of a bicyclic intermediate. Our interests have been directed to the investigation of the scope and limitation of these reactions. In this paper we describe the effects of the electron-donating substituents at the 4 or 6-position of 3,5-dinitro-2-pyridone on the nucleophilic attack of enolate ions of the *β*-keto esters.

Results and Discussion

As substrates 1,6-dimethyl- (**1a**), 1,4-dimethyl- (**1b**) and 4-methoxy-1-methyl- (**1c**) 3,5-dinitro-2-pyridones were employed, and diethyl sodio-3-oxopentanedioate (Na.DOPD) and ethyl sodioacetoacetate (Na. EAA) were used as the uncleophiles.

Treatment of **1a** with Na.DOPD at 50 °C in pyridine gave diethyl 2-hydroxy-4-methyl-5-nitro-1,3-benzenedicarboxylate (**2a**)[3] and *N*-methyl-2-nitroacetamide (**3**) in 94.3 and 25.9%, respectively. Under somewhat milder conditions (25 °C) a colorless crystalline product (**4a**) was obtained in addition to **2a** and **3**. The product **4a** was easily converted to **2a** and **3** by the treatment with bases at 70 °C, and the ^{1}H-NMR spectrum of **4a** (see Experimental) behaved analogously to the bicyclic compounds reported in the previous paper.[2] On the bases of these data **4a** was assigned to be diethyl 7-hydroxy-1,2-dimethyl-4,9-dinitro-3-oxo-2-azabicyclo[3.3.1]non-6-ene-6,8-dicarboxylate, an adduct of **1a** and DOPD.



Scheme 1.

From the reaction of **1b** with Na.DOPD, **2a**, **3**, and bicyclic compound, **4b**, were obtained. The similar reaction of **1c** with Na.DOPD gave diethyl 2-hydroxy-4-methoxy-5-nitro-1,3-benzenedicarboxylate (**2c**) together with **3** and bicyclic compound, **4c**.

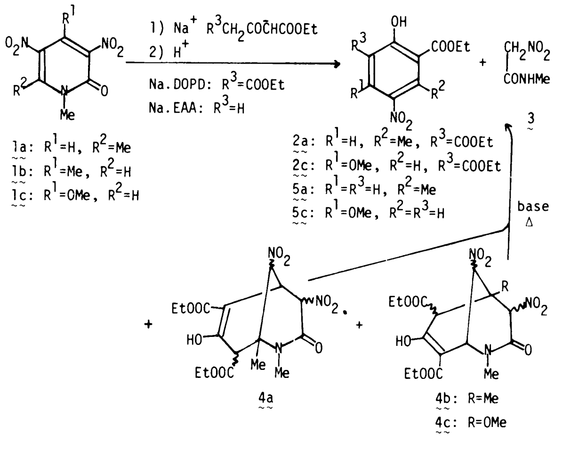
From both the reactions of **1a** and **1b** with Na.EAA, ethyl 6-hydroxy-2-methyl-3-nitrobenzoate (**5a**)[4] was solely yielded in addition to **3**; ethyl 2-hydroxy-4-methyl-5-nitrobenzoate which was anticipated as the alternative product was not obtained.

These facts suggest a probable course involving a preferential attack of the somewhat softer C-2 anion of EAA at the softer methyl-substituted 6 and 4-position of **1a** and **1b**, respectively. The subsequent intramolecular nucleophilic attack of the C-4 anion of EAA at the harder methyl-unsubstituted 4 or 6-position of the parent pyridone may lead to the same products, **4a** and **3** *via* the bicyclic intermediates.[5] (Scheme 1, course a) The alternative course (b), however, is not to be discounted. Thus, the attack of the harder nucleophilic center of EAA, C-4 anion, at the harder methyl-unsubstituted position was followed by attack of the softer C-2 anion of EAA at the other position.[6]

From the above results, it is difficult to decide which of the courses is more plausible.

On the other hand, from the reaction of **1c** with Na.EAA ethyl 2-hydroxy-4-methoxy-5-nitrobenzoate (**5c**) and **3** were obtained. The structure of **5c** was supported by the ^{1}H-NMR data and by the hydrolysis to 2-hydroxy-4-methoxy-5-nitrobenzoic acid.[7]

This fact is interpreted as follows: The resonance effects of the nitro groups are decreased by the steric



hydrance of the 4-methoxyl group, and the inductive effect of the 4-methoxyl group makes the C-4 position of the pyridone harder than the C-6 position, so the C-2 anion of Na.EAA attacks at the C-6 of the pyridone and C-2 of EAA at the C-4 of the pyridone.

Consequently, the sequence of the reaction steps could not be decided, neverthless the regiochemistry of the reaction could be explained by the HSAB principle, considering the electronic effects of the substituents.

Experimental

Substrates, 1a, 1b, and 1c. These compounds were obtained from corresponding *N*-methyl-2-pyridones by the nitration with fuming nitric acid in acetic anhydride at room temperature.

1,6-Dimethyl-3,5-dinitro-2-pyridone (1a). Mp 135.5—136.0 °C. IR: 1695 cm^{-1} (C=O), 1570, 1340 (NO_2). NMR (acetone-d_6): δ=2.94 (3H, s), 3.78 (3H, s), 8.87 (1H, s).

1,4-Dimethyl-3,5-dinitro-2-pyridone (1b). Mp 155.0—156.0 °C. IR: 1695 cm^{-1} (C=O), 1570, 1340 (NO_2). NMR (acetone-d_6): δ=2.47 (3H, s), 3.74 (3H, s), 9.12 (1H, s).

4-Methoxy-1-methyl-3,5-dinitro-2-pyridone (1c). Mp 114.5—115.5 °C. IR: 1690 cm^{-1} (C=O), 1570, 1340 (NO_2). NMR (acetone-d_6): δ=3.72 (3H, s), 4.02 (3H, s), 9.12 (1H, s).

The Reaction of 1 with Sodium Salts. The method used here was the same as that described ealier.[2] Poor yield of **3** in all cases would be caused by acidity and lability of **3** to decompose under the reaction conditions.

Diethyl 2-Hydroxy-4-methyl-5-nitro-1,3-benzenedicarboxylate (2a). Colorless prisms (petroleum benzine), mp 69.0—70.0 °C. IR: 3100 cm^{-1} (O–H), 1745 (C=O), 1530, 1340 (NO_2). NMR ($CDCl_3$): δ=1.30 (3H, t, J=7 Hz), 1.44 (3H, t, J=7 Hz), 2.54 (3H, s), 4.44 (2H, q, J=7 Hz), 4.55 (2H, q, J=7 Hz), 8.49 (1H, s), 11.55 (1H, s).

Diethyl 2-Hydroxy-4-methoxy-5-nitro-1,3-benzenedicarboxylate (2c). Colorless needles (petroleum benzine), mp 100.0—100.5 °C. IR: 3200 cm^{-1} (O–H), 1740 (C=O), 1540, 1340 (NO_2). NMR ($CDCl_3$): δ=1.36 (3H, t, J=7 Hz), 1.39 (3H, t, J=7 Hz), 3.95 (3H, s), 4.39 (2H, q, J=7 Hz), 4.40 (2H, q, J=7 Hz), 8.57 (1H, s), 11.74 (1H, s).

Diethyl 7-Hydroxy-1,2-dimethyl-4,9-dinitro-3-oxo-2-azabicyclo[3.3.1]non-6-ene-6,8-dicarboxylate (4a). Colorless prisms (ethanol), mp 170.0—171.0 °C. IR: 1735 cm^{-1} (C=O), 1690 (C=O), 1550, 1320 (NO_2). NMR ($CDCl_3$): δ=1.28 (3H, t, J=7 Hz), 1.35 (3H, t, J=7 Hz), 1.53 (3H, s), 3.05 (3H, s), 3.72 (1H, s, H-8), 4.27 (4H, q, J=7 Hz), 4.37 (1H, dd, J=4 and 6 Hz, H-5), 5.59 (1H, *d*, J=6 Hz, H-9), 5.77 (1H, d, J=4 Hz, H-4), 12.64 (1H, s, 7-OH).

Diethyl 3,7-Dihydroxy-2,5-dimethyl-4,9-dinitro-2-azabicyclo[3.3.1]nona-3,7-diene-6,8-dicarboxylate (4b). Colorless prisms (ethanol), mp 151.0—152.0 °C. IR: 1750 cm^{-1} (C=O), 1670 (C=O), 1570, 1360 (NO_2). NMR ($CDCl_3$): δ=1.35 (3H, t, J=7 Hz), 1.41 (3H, t, J=7 Hz), 1.65 (3H, s), 3.16 (3H, s), 4.24 (1H, s, H-6), 4.27 (2H, q, J=7 Hz), 4.38 (2H, q, J=7 Hz), 4.85 (1H, d, J=3 Hz, H-1), 5.82 (1H, d, J=3 Hz, H-9), 12.41 (1H, s, 7-OH), 19.01 (1H, s, 3-OH, enol form).

Diethyl 7-Hydroxy-5-methoxy-2-methyl-4,9-dinitro-3-oxo-2-azabicyclo[3.3.1]non-7-ene-6,8-dicarboxylate (4c). Colorless prisms (ethanol), mp 198.0—199.0 °C. IR: 1750 cm^{-1} (C=O), 1690 (C=O), 1560, 1330 (NO_2). NMR ($CDCl_3$): δ=1.32 (3H, t, J=7 Hz), 1.45 (3H, t, J=7 Hz), 3.16 (3H, s), 3.60 (3H, s), 3.90 (1H, s, H-6), 4.30 (2H, q, J=7 Hz), 4.39 (2H, q, J=7 Hz), 4.93 (1H, d, J=4 Hz, H-1), 6.09 (1H, d, J=4H, H-9), 6.17 (1H, s, H-4), 12.38 (1H, s, 7-OH).

Treatment of 4 with Sodium Ethoxide. The raction was carried out according to the procedure described in Lit 2. From 208 mg of **5a** were obtained 112 mg (76.2%) of **2a** and 21 mg (41.3%) of **3**. Similarly, **2a** and **3** were yielded from **4b** in 58.7% and 28.8% yield, respectively, and **2c** in 27.9% and trace of **3**.

Ethyl 6-Hydroxy-2-methyl-3-nitrobenzoate (5a). Colorless needles (petroleum benzine), mp 58.0—58.5 °C. IR: 3200 cm^{-1} (O–H), 1670 (C=O), 1530, 1340 (NO_2). NMR ($CDCl_3$): δ=1.43 (3H, t, J=7 Hz), 2.60 (3H, s), 4.47 (2H, q, J=7 Hz), 6.85 (1H, d, J=9.5 Hz, H-5), 7.76 (1H, d. J=9.5 Hz, H-4), 11.33 (1H, s, 6-OH).

Ethyl 2-Hydroxy-4-methoxy-5-nitrobenzoate (5c). Colorless needles (petroleum benzine), mp 137.5—138.5 °C. IR: 3200 cm^{-1} (O–H), 1670 (C=O), 1540, 1340 (NO_2). NMR ($CDCl_3$): δ=1.41 (3H, t, J=7 Hz), 3.95 (3H, s), 4.31 (2H, q, J=7 Hz), 6.51 (1H, s, H-3), 8.48 (1H, s, H-6), 11.49 (1H, s, 2-OH).

Table 1. Reaction of 1,4- (or 1,6)-disubstituted 3,5-dinitro-2-pyridones with sodio β-keto esters*

Substrate	Reaction Conditions			Products (Yield/%)		
	Reagent	Mol. ratio	Temp			
1a	Na.DOPD	1.5	50 °C	**2a**(94.3)	**3**(25.9)	—
1a	Na.DOPD	1.5	25	**2a**(34.6)	**3**(7.8)	**4a**(46.9)
1b	Na.DOPD	1.5	50	**2a**(63.9)	**3**(17.2)	**4b**(23.6)
1b	Na.DOPD	3.0	70	**2a**(62.7)	**3**(16.9)	**4b**(23.6)
1b	Na.DOPD	1.5	25	**2a**(3.8)	—	**4b**(86.7)
1c	Na.DOPD	1.5	50	**2c**(62.2)	**3**(8.5)	**4c**(24.5)
1c	Na.DOPD	3.0	70	**2c**(64.2)	**3**(7.1)	**4c**(22.1)
1a	Na.EAA	3.0	70	**5a**(51.4)	**3**(11.3)	
1b	Na.EAA	3.0	70	**5a**(48.3)	**3**(8.3)	
1c	Na.EAA	3.0	70	**5c**(36.9)	**3**(8.5)	

* All the reactions were carried out in pyridine for 5 h.

Table 2. Analytical data of the substrates and products

Compound	Found(%)			Calcd(%)		
	C	H	N	C	H	N
1a	39.25	3.18	19.63	39.44	3.29	19.72
1b	39.16	3.09	19.82	39.44	3.29	19.72
1c	36.60	3.23	18.56	36.69	3.08	18.34
2a	52.47	4.95	4.95	52.52	5.09	4.71
2c	49.65	4.61	4.71	49.84	4.83	4.47
4a	46.05	4.81	10.11	46.26	5.10	10.12
4b	45.98	4.93	9.99	46.26	5.10	10.12
4c	44.56	5.14	9.61	44.55	4.90	9.74
5a	53.45	4.77	6.19	53.33	4.92	6.22
5c	49.70	4.68	5.51	49.80	4.95	5.80

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