Diels-Alder Reactions of 2-Pyrones with Acyclic Dienophiles and Hydrolyses of the Mono-adducts

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Diels-Alder reactions of 2-pyrone (**1**) with fumaronitrile and maleonitrile afforded regio- and stereo-specific mono-adducts **3a** and **3b**, respectively. The reaction of **1** with acrylonitrile gave a bis-adduct. The reaction of 4,6-dimethyl-2-pyrone (**7**) with dimethyl fumarate and dimethyl maleate at higher temperature gave benzene derivatives. The low reactivity of **7** and the instability of the mono-adducts with **7** were considered from the existence of back reaction and easy elimination of methyl formate, respectively. Hydrolyses of the mono-adducts of 2-pyrones gave polyfunctionalized cyclohexenes and elimination products generated from the preferencial *trans*-elimination of the leaving groups.

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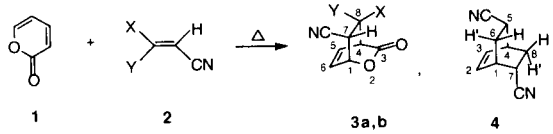
Diels-Alder (DA) reactions of 2-pyrones and the continuous decarboxylations of the mono-adducts were used as key steps to synthesize such interesting compounds as chorismic acid [1], colchicine [2] and barrelene [3]. The utilization is limited, however, because the DA reactions occur with difficulty owing to the aromaticity of 2-pyrones, and the resulting mono-adducts are thermally susceptible to decarboxylation to give bis-adducts [4] and benzene derivatives [5].

We previously reported the DA reactions of 2-pyrones with electron-poor and electron-rich dienophiles to afford mono- and/or bis-adducts [6]. The present paper describes the DA reactions of 2-pyrone and 4,6-dimethyl-2-pyrone with electron-poor acyclic dienophiles, and the hydrolyses of the mono-adducts including previously reported ones [6b].

2-Pyrone (**1**) reacted with fumaronitrile at 120° in a sealed tube to afford a mono-adduct **3a** in 15% yield. Similar reaction of **1** with maleonitrile gave a mono-adduct **3b** in 27% yield. On the other hand, the reaction of **1** with acrylonitrile at 140° gave a bis-adduct **4** in 23% yield (Scheme 1). These reactions did not occur in another mild conditions, and the reactions of **1** with dimethyl fumarate and dimethyl maleate at 160° resulted in quantitative recoveries of **1**, respectively.

Scheme 1



1 **2** **3a,b** **4**

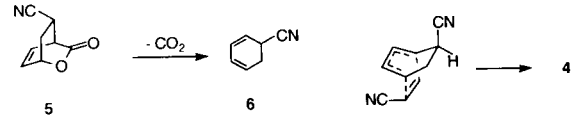
a: X=CN, Y=H
b: X=H, Y=CN
c: X=Y=H

The structure of **3a** was assigned as 3-oxo-2-oxabicyclo-[2.2.2]oct-5-ene-*endo*-7,*exo*-8-dicarbonitrile from the spectral evidence that showed β,γ-unsaturated carbonyl absorption (1750 cm^{-1}) in the ir data and a long-range coupling between 6-H and 7-H (J = 0.8 Hz) in the ^1H nmr data which was found in bicyclo[2.2.2]octene system [7]. Compound **3b** was also confirmed to be 3-oxo-2-oxabicyclo[2.2.2]oct-5-ene-*endo*-7,*endo*-8-dicarbonitrile because of showing another long-range coupling between 5-H and 8-H in addition with 6-H and 7-H ($J_{5,8} = J_{6,7} = 1.0$ Hz). The addition-regioselectivity of cyanoethylenes 2a, 2b is reasonable by considering the Alder rule.

The structure of **4** was assigned as bicyclo[2.2.2]oct-2-ene-*endo*-5,*endo*-7-dicarbonitrile on the basis of the spectral data. The skeleton was suggested from the absence of carbonyl group in the ir data. The positions and the stereochemistry of the two cyano groups were estimated as *endo*-5 and *endo*-7 positions from the ^1H nmr data because of showing the same chemical shift and the symmetrical pattern of 2-H and 3-H (δ = 6.52 ppm). The *endo* positions of the two cyano groups were assigned from the long-range coupling between 3-H (2-H) and 5-H (7-H) ($J_{3,5} = J_{2,7} = 2.0$ Hz).

It seemed reasonable to assume that 2-pyrone undergoes DA reaction by inverse electron demand manner [6b] (2-pyrone (LUMO)-acrylonitrile (HOMO) to give **5**, and to be followed by decarboxylation of **5** and addition of another molecule of the acrylonitrile (Scheme 2).

Scheme 2

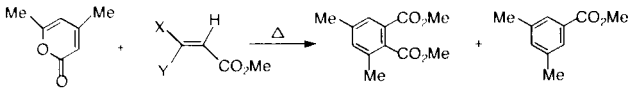


5 **6**

4,6-Dimethyl-2-pyrone (**7**) reacted with dimethyl fumarate at 160° in sealed tube to give dimethyl 3,5-dimethylphthalate (**10**) and methyl 3,5-dimethylbenzoate (**11**) in 15% and 8% yields, respectively, whose compounds were formed *via* decarboxylation of the mono-adducts and fol-

lowed by additional dehydrogenation or elimination of methyl formate. The similar reaction of **7** with dimethyl maleate gave **10** (14%) and **11** (8%), respectively. The DA reactions of 2-pyrone **7**, which was more electron-rich diene than **1**, with fumaronitrile and acrylonitrile were expected to occur, but **7** was recovered quantitatively. On the basis of these results, it was considered that the lower DA reactivity of **7** with electrophilic acyclic dienophiles was caused by the easy and fast back reaction leading to the 2-pyrone **7** by the aromatization. The instability of the mono-adducts of **7** with dimethyl fumarate and dimethyl maleate was estimated from the consideration that the mono-adducts **9d** and **9e** were more unstable than mono-adducts **9a** and **9b** because of the rotational hindrance of the methoxycarbonyl groups to give intermediates **A**. The intermediates **A** were stabilized by the hyperconjugation of methyl group [6a] and followed by the easy elimination of carbon dioxide and to hydrogen to give **10**, or carbon dioxide to give **11** (Scheme 4). These results reveal that the elimination of hydrogen cyanide is more difficult to occur than that of methyl formate.

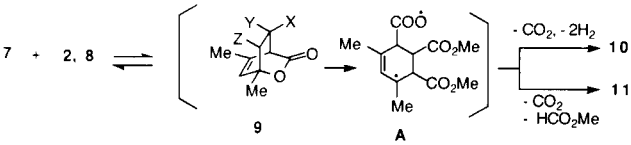
Scheme 3



7 8 10 11

d: X=CO$_2$Me, Y=H
e: X=H, Y=CO$_2$Me

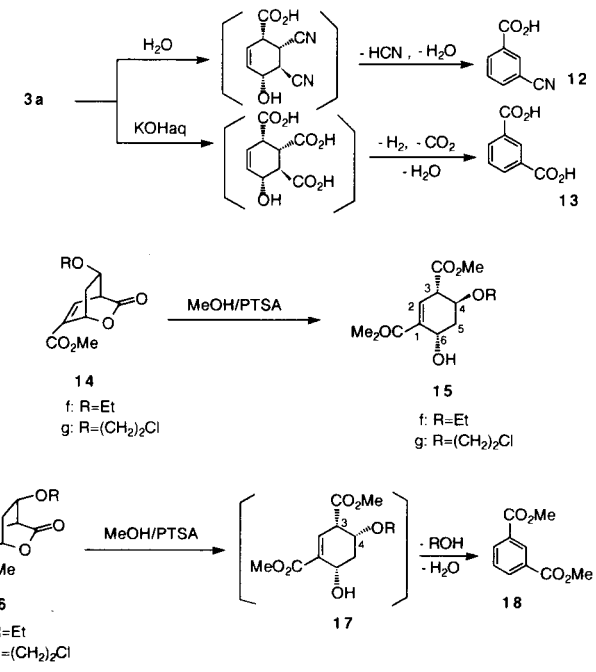
Scheme 4



a: X=Z=CN, Y=H
c: X=Z=H, Y=CN
d: X=Z=CO$_2$Me, Y=H
e: X=H, Y=Z=CO$_2$Me

We next investigated the hydrolyses of the mono-adduct **3a** and previously reported ones, **14** and **16** [6b], leading to the formation of benzene derivatives or polyfunctionalized cyclohexenes (Scheme 5). The hydrolysis of **3a** with water and 10% potassium hydroxide solution afforded *m*-cyanobenzoic acid (36%) and isophthalic acid (43%), respectively, whose products were formed from the cyclohexenes by way of preferential *trans*-elimination. The treatment of **3a** with concentrated hydrochloric acid gave complex mixture. On the other hand, acid hydrolysis of the *endo*-adducts **14f** and **14g** in the presence of *p*-toluenesulfonic acid in methanol afforded stable cyclohexenes **15f** and **15g**, 66% and 64% yields, respectively.

Scheme 5



The structures of **15f** and **15g** were assigned from the spectral data. For instance, the stereochemistry of **15f** was confirmed from the ^{1}H nmr data showing $J_{3,4}$ = 7.5 Hz which was in good agreement with *trans*-related positions in the similar cyclohexene system [8]. This assignment was confirmed by the resistance for the elimination of ROH as shown in the next description.

The similar treatment of the *exo*-adducts **16f** and **16g** under reflux gave dimethyl isophthalate (**18**) in 51% and 83% yields, respectively. The reaction did not proceed at 50°. As the nucleophilic attack of methanol to the bicyclolactones **16** was controlled by the streic hindrance of *exo*-OR group, severe condition was required in the methanolysis of *exo*-adducts **16**, compared to that of *endo*-adducts **12**. The difference of the methanolysis products between **14** and **16** is concluded to be dependent upon the configuration difference at the 3- and 4-positions of the cyclohexenes **15** and **17**. The trans-elimination of ROH causes the elimination of water and aromatization to give **18**.

EXPERIMENTAL

All the melting points were measured on a Yanagimoto Meltemp apparatus and are uncorrected. The ir, ^{1}H nmr and mass spectra were recorded on JASCO A-3, JEOL JNM-MH-100 (100 MHz), and JEOL JMSOISG spectrometers, respectively. The ^{1}H nmr spectra were recorded with TMS as an internal standard.

2-Pyrone (**1**) [9] and 4,6-dimethyl-2-pyrone (**7**) [10] were prepared according to methods previously described in the literature.

3-Oxo-2-oxabicyclo[2.2.2]oct-5-ene-*endo*-7,*exo*-8-dicarbonitrile (**3a**).

A mixture of **1** (1.0 g, 10 mmoles) and fumaronitrile (0.83 g, 11 mmoles) was heated at 120° for 5 hours in a sealed tube. The reaction mixture was recrystallized from acetonitrile to give **3a** (0.26 g, 15%).

Compound **3a** had mp 140° dec; ir (potassium bromide): 2240, 1750, 1613 cm^{-1}; ^1H nmr (acetonitrile): δ = 3.30 (dd, 1H, 8-H, $J_{8,4}$ = 2.0, $J_{8,7}$ = 4.4 Hz), 3.83 (ddd, 1H, 7-H, $J_{7,1}$ = 3.0, $J_{7,6}$ = 0.8, $J_{7,8}$ = 4.4 Hz), 3.92 (q, 1H, 4-H, $J_{4,8}$ = $J_{4,5}$ = $J_{4,6}$ = 2.0 Hz), 5.42 (q, 1H, 1-H, $J_{1,7}$ = $J_{1,6}$ = $J_{1,5}$ = 3.0 Hz), 6.50 (m, 2H, 5-H, 6-H); ms: m/z (relative intensity) 130 ($M-CO_2$, 72), 103 (100).

Anal. Calcd. for $C_9H_6N_2O_2$: C, 62.06; H, 3.45; N, 16.09. Found: C, 62.25; H, 3.52; N, 15.94.

3-Oxo-2-oxabicyclo[2.2.2]oct-5-ene-*endo*-7,*endo*-8-dicarbonitrile (**3b**).

A mixture of **1** (0.20 g, 2.1 mmoles) and maleonitrile (0.16 g, 2.1 mmoles) was heated at 120° for 6 hours in a sealed tube. The reaction mixture was recrystallized from acetonitrile to give **3b** (0.10 g, 27%).

Compound **3b** had mp 217-220°; ir (potassium bromide): 2240, 1760, 1624 cm^{-1}; ^1H nmr (acetonitrile): δ = 3.52 (ddd, 1H, 8-H, $J_{8,7}$ = 8.0, $J_{8,4}$ = 2.0, $J_{8,5}$ = 1.0 Hz), 3.64 (ddd, 1H, 7-H, $J_{7,8}$ = 8.0, $J_{7,1}$ = 2.0, $J_{7,6}$ = 1.0 Hz), 3.68 (m, 1H, 4-H), 5.02 (m, 1H, 1-H), 6.09 (m, 2H, 5-H, 6-H).

Anal. Calcd. for $C_9H_6N_2O_2$: C, 62.06; H, 3.45; N, 16.09. Found: C, 61.87; H, 3.48; N, 15.80.

Bicyclo[2.2.2]oct-2-ene-*endo*-5,*endo*-7-dicarbonitrile (**4**).

A mixture of **1** (2.88 g, 3.0 mmoles) and acrylonitrile (4.77 g, 90 mmoles) was heated at 140° for 60 hours in a sealed tube. To the reaction mixture was added ethanol and the filtrate was chromatographed on a silica gel (Wakogel C-200) using petroleum ether-diethyl ether 1:1 v/v mixture as the eluent to give 4 (1.1 g, 23%).

Compound **4** had mp 122-123°; ir (potassium bromide): 2250, 1650 cm^{-1}; ^1H nmr (deuteriochloroform): δ = 1.60 (ddd, 2H, 6'-H, 8'-H, $J_{6',6}$ = $J_{8',8}$ = 14.0, $J_{6',5}$ = $J_{8',7}$ = 4.5, $J_{6',1}$ = $J_{8',4}$ = 4.0 Hz), 1.92 (ddd, 2H, 6-H, 8-H, $J_{6,6'}$ = $J_{8,8'}$ = 14.0, $J_{6,5}$ = $J_{8,7}$ = 8.0, $J_{6,1}$ = $J_{8,4}$ = 2.5 Hz), 2.66 (ddt, 2H, 5-H, 7-H, $J_{5,6}$ = $J_{7,8}$ = 9.0, $J_{5,6'}$ = $J_{7,8'}$ = $J_{5,4}$ = $J_{7,1}$ = 5.0, $J_{5,3}$ = $J_{7,2}$ = 2.0 Hz), 3.12 (m, 2H, 1-H, 4-H), 6.52 (m, 2H, 2-H, 3-H); ms: m/z (relative intensity) 158 (M^+, 54), 105 (100).

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.98; H, 6.37; N, 17.71. Found: C, 75.74; H, 6.52; N, 17.60.

Reactions of **7** with Dimethyl Fumarate and Dimethyl Maleate.

A mixture of **7** (0.19 g, 1.5 mmoles) and dimethyl fumarate (0.22 g, 1.5 mmoles) was heated at 160° for 48 hours in a sealed tube. The usual workup afforded dimethyl 3,5-dimethylphthalate (**10**) and methyl 3,5-dimethylbenzoate (**11**) in 15% and 8% yields, respectively. The same reaction of **7** with dimethyl maleate gave **10** and **11** in 14% and 8% yields, respectively.

Hydrolysis of **3a**.

After refluxing a mixture of **3a** (0.20 g, 1.1 mmoles) and water (2 ml) for 7 hours, resulting solid was recrystallized from acetone-water 1:1 v/v mixture to give *m*-cyanobenzoic acid (0.06 g, 36%). A mixture of **3a** (1.0 g, 5.7 mmoles) and potassium hydroxide (3.0 g) in ethanol (27 ml) was refluxed for 12 hours. The solution was neutralized with hydrochloric acid to give isophthalic acid (0.41 g, 43%).

Dimethyl 4-Methoxy-6-hydroxy-1-cyclohexene-1,3-dicarboxylate (**15f**) and Dimethyl 4-(2-Chloroethoxy)-6-hydroxy-1-cyclohexene (**15g**).

A solution of **14f** (0.3 g, 1.4 mmoles) in methanol (5 ml) in the presence of *p*-toluenesulfonic acid (10 mg) was refluxed for 3 hours. The solvent was removed *in vacuo* and the resulting solid was recrystallized from petroleum ether to give **15f** (0.22 g, 66%). The similar treatment of **14g** (0.22 g, 0.84 mmole) at 50° for 2 hours afforded **15g** (0.16 g, 64%) from the chromatography using benzene-acetone 10:1 v/v mixture.

Compound **15f** had mp 53-55°; ir (potassium bromide): 3550, 1745, 1720, 1650 cm^{-1}; ^1H nmr (deuteriochloroform): δ = 1.18, 3.56 (OCH_2CH_3), 1.80 (ddd, 1H, 5-H', $J_{5',4}$ = 10.0, $J_{5',6}$ = 4.0, $J_{5',5}$ = 13.0 Hz), 2.20 (ddd, 1H, 5-H, $J_{5,4}$ = 3.5, $J_{5,6}$ = 4.0, $J_{5,5'}$ = 13.0 Hz), 3.75 (s, 3H, CO_2Me), 3.78 (s, 4H, CO_2Me, OH), 4.08 (ddd, 1H, 4-H, $J_{4,3}$ = 7.5, $J_{4,5}$ = 3.5, $J_{4,5'}$ 10.0 Hz), 4.68 (t, 1H, 6-H, $J_{6,5}$ = $J_{6,5'}$ = 4.0 Hz), 6.84 (d, 1H, 2-H, $J_{2,3}$ = 3.5 Hz); ms: m/z (relative intensity) 358 (M^+, 0.3), 186 (100).

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.81; H, 6.98. Found: C, 55.74; H, 6.97.

Compound **15g** was obtained as an oil; ir (neat): 3500, 1730, 1650, 670 cm^{-1}; ^1H nmr (deuteriochloroform): δ = 1.86 (m, 1H, 5'-H), 2.28 (m, 1H, 5-H), 3.36 (dd, 1H, 3-H, $J_{3,2}$ = 3.5, $J_{3,4}$ = 7.5 Hz), 3.64, 4.16 (each m, 2H, OCH_2CH_2Cl), 3.82 (s, 6H, CO_2Me), 3.87 (m, 1H, 4-H), 4.20 (s, 1H, OH), 4.77 (t, 1H, 6-H, $J_{6,5}$ = $J_{6,5'}$ = 4.0 Hz), 6.98 (d, 1H, 2-H, $J_{2,3}$ = 4.0 Hz); ms: m/z (relative intensity) 293 (M + 1, 0.4), 186 (100).

Anal. Calcd. for $C_{12}H_{17}ClO_6$: C, 49.24; H, 5.85. Found: C, 49.55; H, 5.71.

Methanolysis of **16f** and **16g**.

A solution of **16f** (0.16 g, 0.69 mmole) in methanol (3 ml) in the presence of *p*-toluenesulfonic acid (7 mg) was refluxed for 6 hours. After removing the solvent, the resulting solid was recrystallized from petroleum ether to afford dimethyl isophthalate (**18**) (0.07 g, 51%). The similar treatment of **16g** gave **18** in 83% yield.

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