Preparations of 2-Azabicyclo[2.2.2]octa-5,7-dien-3-ones and 7-Azabicyclo[4.2.0]octa-2,4-dien-8-ones from Addition Reactions of 2-Pyridones

Kenichi Somekawa*, Yasuo Okumura, Kunitomi Uchida and Tetsuro Shimo

Department of Applied Chemistry, Faculty of Engineering, Kagoshima University, Korimoto, Kagoshima 890, Japan

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The low temperature photoaddition of 2-pyridone with dimethyl acetylenedicarboxylate gave a [4+2]-cycloadduct and a [2+2]-cycloadduct across the 5,6-position of 2-pyridone. Their formations were competing with a Michael reaction of the two substrates at the room temperature reaction. The reactions of other pyridones with dimethyl acetylenedicarboxylate gave [2+2]- and/or [4+2]-cycloadducts. The [2+2]-cycloadducts underwent an intriguing rearrangement to fused β-lactams.

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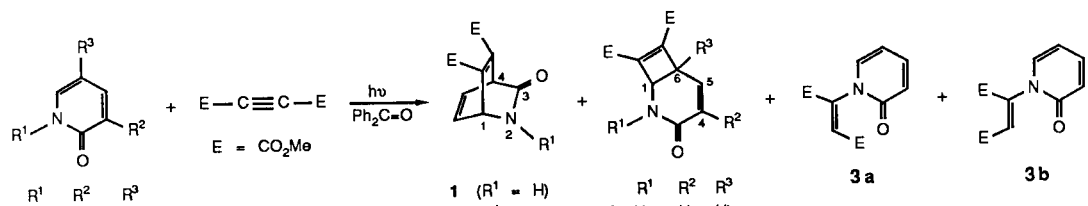
Since 2-pyridone was estimated to have the aromaticity and conjugated diene properties possible for Diels-Alder reactions [1a], many thermal reactions with several 2-pyridones have been examined. The early examinations did not give Diels-Alder adducts [1]. Later results showed that *N*-substituted 2-pyridones gave Diels-Alder adducts under the proper reaction conditions or decomposed products from the adducts [2], but that 2-pyridones without *N*-substituents gave a Michael-type of or more complex products [3]. Diels-Alder reactions between 2-pyridones and acetylenic compounds may yield interesting azabarrelenes. For that purpose, namely for preparation of Diels-Alder adducts between *N*-alkyl-2-pyridones and dimethyl acetylenedicarboxylate, a high-pressure technique was used [2c]. Similar 2-azabicyclo[2.2.2]octadienes were also obtained *via* several steps including electrolytic decarboxylation though the product yields were low [4]. We have clarified the photoreactions of 2-pyridones [5], or 2-pyrones [6] with olefins. The reactions of 2-pyridones gave ring-expansion products together with two types of [2+2]-cycloadducts, while the reactions of 2-pyrones afforded stable [4+2]-cycloadducts or benzene derivatives with concurrent decarboxylation, together with two types of [2+2]-cycloadducts, depending upon substituents on the two substrates. We also derived intriguing β-lactams *via* dechlorination and valence-isomerization from [2+2]-cycloadducts between 2-pyridones and chloroethylenes [7]. Meyers *et al.* showed photocycloaddition of di- or tri-substituted 2-pyridones with diphenylacetylene to give quadricyclic δ-lactams and the valence isomer, a [4+2]-cycloadduct [8].

Surprisingly, just 2-pyridone has never directly produced the [4+2]-cycloadducts and [2+2]-cycloadducts in the reaction with acetylenic compounds. Low-temperature photoreactions of 2-pyridone with electron-deficient acetylenes seems to give [4+2]-cycloadducts and [2+2]-cycloadducts being expected to be directly converted to β-lactams. We now report the results of observant photoadditions of 2-pyridones with dimethyl acetylenedicarboxylate and the thermal isomerization of the one [2+2]-cycloadduct.

Photochemical Cycloadditions.

Photoirradiation of a mixture of 2-pyridone and dimethyl acetylenedicarboxylate in the presence of benzophenone in acetonitrile at room temperature gave a [4+2]-cycloadduct **1**, a [2+2]-cycloadduct **2** across the 5,6-bond of 2-pyridone and a Michael-type of adducts, **3a**, **3b** as shown in Scheme 1 and Table 1. The photoreaction at low temperature in a bath at −35° afforded only **1** and **2**. The results show that **1** and **2** were from the sensitized triplet photoreaction of 2-pyridone and **3a** and **3b** came from the thermal reactions. Similar reactions between *N*-methyl-2-pyridone and dimethyl acetylenedicarboxylate at room temperature or in a bath at −35° gave a [4+2]-cycloadduct **4** and a [2+2]-cycloadduct **5** as shown in Scheme 1 and Table 1.

Scheme 1



R^1	R^2	R^3
H	H	H
Me	H	H
H	OMe	H
H	H	Me

Table 1

Reaction Products of 2-Pyridones with Dimethyl Acetylenedicarboxylate

2-Pyridones			Reaction	Products (%)		
R^1	R^1	R^3	Temp	[4+2] Adduct	[2+2] Adduct	Michael Adduct
H	H	H	room temp	**1** (18)	**2** (15)	**3a** (15), **3b** (12)
			−20 - −10°	**1** (12)	**2** (13)	
Me	H	H	room temp	**4** (11)	**5** (3)	
			−20 - −10°	**4** (11)	**5** (5)	
H	OMe	H	room temp		**6** (10)	
H	H	Me	room temp		**7** (9)	

The reactions with 3-methoxy- or 5- methyl-2-pyridones at room temperature, however, afforded only [2+2]-cycloadducts, **6** and **7**, respectively. That with 1,6-dimethyl-2-pyridone gave no adducts and products **4**, **5**, **6** and **7** were not given without the triplet sensitizers. We have already reported the results of site-selectivity and regio-selectivity in the triplet photoaddition reactions of 2-pyridones [6] or 2-pyrones [7] with substituted ethylenes. We can now provide the following suggestions for this reactions with dimethyl acetylenedicarboxylate. The first steps in the triplet addition-reactions of 2-pyridones are radical additions at the favored 6-position in the LUMO-LUMO interactions but hindered by substituents at the 6-position. The reactions of 3-methoxy- or 5-methyl-2-pyridones possessing electron-donating groups are thought to be more effective for [2+2]-cycloadditions across the 5,6-positions than for [4+2]-cycloadditions [5a].

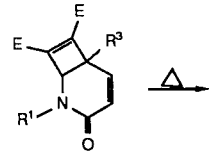
The [4+2]-cycloadducts, **1** and **4**, 2-azabicyclo[2.2.2]-octa-5,7-dien-3-ones were characterized as possessing the same and low field ^{1}H nmr signals (δ 6.8-6.9 ppm) of the 7-H and 8-H, and also those (δ *ca.* 5.2 and *ca.* 4.5 ppm) of the 1-H and 4-H. These are similar to the Diels-Alder adducts of *N*-alkyl-2-pyridones and maleimides [2b]. The mass spectral patterns of the [4+2]-cycloadducts are also characteristic. They hardly have the parent-signals but large signals related to dimethyl phthalates given from the characteristic decomposition.

The chemical shifts and spin-spin coupling patterns in ^{1}H nmr spectra of **2**, **5**, **6** and **7** possessed a distinctive feature of the [2+2]-cycloadducts across the 5,6-positions of the 2-pyridones [5]. The mass spectra had relatively large parent-signals with the 2-pyridone's signals being almost base peaks. Namely, **2**, **5**, **6** and **7** were assigned to be 7,8-bismethoxycarbonyl-2-azabicyclo[4.2.0]octa-4,7-dien-3-ones. Compounds **3a** and **3b** were confirmed to be a Michael-type of adducts from the ^{1}H nmr spectra. Compound **3a** was known as the *Z*-isomer [1d] and **3b** was analysed to be the the *E*-isomer which was isomerized to **3a** at elevated temperature. These two were also produced by a prolonged dark reaction between 2-pyridone and dimethyl acetylenedicarboxylate at room temperature.

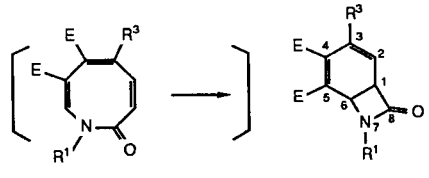
Valence Isomerization of 7,8-Bismethoxycarbonyl-2-azabicyclo[4.2.0]octa-4,7-dien-3-ones.

The heating of **2** at 70° and that of **5** and **7** at 90-100° in solvents directly produced bismethoxycarbonyl-7-azabicyclo[4.2.0]octa-2,4-dien-8-ones, **8** (38%), **9** (48%) and **10** (73%), respectively. They are a type of β-lactams as shown in Scheme 2. The structural assignments were easy because patterns of their ir, ^{1}H nmr and mass spectra were similar to those of chlorinated 7-azabicyclo[4.2.0]octa-2,4-dien-8-ones from our previous report [5]. Namely, **8**, **9** and **10** are simple valence-isomers **via** the intermediates, 2(1*H*)-azocinons as illustrated in Scheme 2 from **2**, **5** and **7** respectively. Compound **8** in DMSO-d_6 was decomposed to dimethyl phthalate at 90° but **9** in DMSO-d_6 was stable even after heating at 150°. Compound **9** slowly changed to dimethyl phthalate at 170°. These results suggest that the *N*-methylation of the β-lactams produces their thermal stability. This property will be utilized for further derivation of the β-lactams.

Scheme 2



2, R^1 = R^3 = H
5, R^1 = Me, R^3 = H
7, R^1 = H, R^3 = Me



E = CO_2Me

8, R^1 = R^3 = H
9, R^1 = Me, R^3 = H
10, R^1 = H, R^3 = Me

EXPERIMENTAL

All the melting points were measured on a Yanagimoto Mel-temp 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 JMS-OISG spectrometers, respectively. The ^{1}H nmr spectra were recorded with TMS as an internal standard. The reported values for ir are cm^{-1} and for ^{1}H nmr are δ (ppm). All the photo-addition and isomerization reactions were monitored by the use of gc, which was performed on a Yanagimoto G80 instrument using a column of Silicone SE-30 (10%) or by tlc on silica-gel plates.

Dimethyl 2-Azabicyclo[2.2.2]octa-5,7-dien-3-one-5,6-dicarboxylate (**1**), Dimethyl 2-Azabicyclo[4.2.0]octa-4,7-dien-3-one-7,8-dicarboxylate (**2**) and *N*-[*E*-1',2'-Bis(methoxycarbonyl)ethenyl]-2-pyridone (**3b**).

1) A mixture of 2-pyridone (1.0 g, 10 mmoles), dimethyl acetylenedicarboxylate (7.6 g, 50 mmoles) and benzophenone (1.2 g) in acetonitrile (200 ml) was irradiated under nitrogen with a 400W high-pressure mercury lamp through a Pyrex jacket for 3 hours at room temperature. The solvent was then removed under reduced pressure and the residue was chromatographed on a silica-gel column (Wakogel C-200) using diethyl ether and acetone as the eluents to give products **1** (18%), **3** (**3a** and **3b**) and **2** (15%) in this order. Compound **3a**, *N*-[*Z*-1',2'-bis(methoxycarbonyl)-ethenyl]-2-pyridone [1d] (17%) and **3b** (12%) were separated from each other by recrystallization with acetone in this order. 2) A similar mixture of 2-pyridone, dimethyl acetylenedicarboxylate, benzophenone and acetonitrile in a bath at −35° was irradiated under nitrogen for 3 hours. The similar work-up and chromatography using diethyl ether gave only **1** (12%) and **2** (13%) in this order. Compound **1** had mp 130-132°; ir (potassium bromide): 1715, 1685 cm^{-1}; ^1H nmr (deuteriochloroform): δ = 3.79 (s, 3H), 3.83 (s, 3H), 6.29 (s and d, 2H), 6.51 (d, 1H), 7.29 (m, 2H); ms: m/z (relative intensity) 194 (M^+-C_2H_4NO, 100).

Anal. Calcd. for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.91. Found: C, 55.55; H, 4.70; N, 5.93.

Compound **2** had mp 121-122°; ir (potassium bromide) 1735, 1720, 1685 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 3.71 (s, 3H), 3.76 (s, 3H), 3.88 (t, 1H, 6-H, J = 4 Hz), 4.62 (t, 1H, 1-H), 5.70 (d, 1H, 4-H, J = 10 Hz), 6.73 (dd, 1H, 5-H), 7.96 (bs, N-H); ms: m/z (relative intensity) 237 (M^+, 11), 95 ($C_5H_5NO^+$, 100).

Anal. Calcd. for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.91. Found: C, 55.69; H, 4.75; N, 5.93.

Compound **3b** had mp 115-117°; ir (potassium bromide): 1727, 1668, 1650 cm^{-1}; ^1H nmr (deuteriochloroform): δ = 3.79 (s, 3H), 3.83 (s, 3H), 6.29 (s and d, 2H), 6.51 (d, 1H), 7.29 (m, 2H); ms: m/z (relative intensity) 237 (M^+, 2), 178 (M^+ -$C_2H_3O_2$, 100).

Anal. Calcd. for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.91. Found: C, 55.28; H, 4.80; N, 5.98.

Dimethyl 2-Methyl-2-azabicyclo[2.2.2]octa-5,7-dien-3-one-5,6-dicarboxylate (**4**) and Dimethyl 2-Methyl-2-azabicyclo[4.2.0]octa-4,7-dien-3-one-7,8-dicarboxylate (**5**).

A mixture of *N*-methyl-2-pyridone (10.9 g, 100 mmoles), dimethyl acetylenedicarboxylate (29.5 g, 210 mmoles) and benzophenone (3.75 g) in acetonitrile (400 ml) was similarly irradiated for 20 hours at room temperature. A crystalline dimer of *N*-methyl-2-pyridone (11%) [9] was separated and the residue was similarly chromatographed using diethyl ether and acetone as the solvents to give products, a [4+2]-cycloadduct, **4** [2c] (11%) and a [2+2]-cycloadduct, **5** (3%). The low-temperature photoreaction similar to the case of 2-pyridone also gave **4** (11%) and **5** (5%).

Compound **5** was obtained as a liquid; ir (liquid): 1740, 1720, 1687 cm^{-1}; ^1H nmr (deuteriochloroform): δ = 3.01 (s, 3H), 3.73, 3.81 (s, 3H), 4.51 (d, 1-H, $J_{1,6}$ = 5 Hz), 5.77 (d, 4-H, $J_{4,5}$ = 10 Hz), 6.56 (dd, 5-H); ms: m/z (relative intensity) 251 (M^+, 5), 163 (M^+ -$C_3H_6NO_2$, 100).

Anal. Calcd. for $C_{12}H_{13}NO_5$: C, 57.39; H, 5.22; N, 5.58. Found: C, 57.36; H, 5.22; N, 5.58.

Dimethyl 4-Methoxy-2-azabicyclo[4.2.0]octa-4,7-dien-3-one-7,8-dicarboxylate (**6**).

A mixture of 3-methoxy-2-pyridone (2.0 g, 16 mmoles), dimethyl acetylenedicarboxylate (12.1 g, 80 mmoles) and benzophenone (1.0 g) in acetonitrile (200 ml) was photoirradiated for 3 hours at room temperature. After evaporation of the solution *in vacuo*, the residue was similarly chromatographed using benzene-acetone to give a [2+2]-cycloadduct, **6**, (10%). This compound had mp 139-140°; ir (potassium bromide): 1752, 1710, 1685, 1640 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 3.50 (s, 3H), 3.74 (s, 6H), 3.96 (t, 6-H, J = 4 Hz), 4.58 (t, 1-H), 5.56 (d, 5-H, J = 4 Hz), 8.14 (bs, N-H); ms: m/z (relative intensity) 267 (M^+, 6), 125 (M^+ -DMAD, 100).

Anal. Calcd. for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.93; H, 4.92; N, 5.21.

Dimethyl 6-Methyl-2-azabicyclo[4.2.0]octa-4,7-dien-3-one-7,8-dicarboxylate (**7**).

A mixture of 5-methyl-2-pyridone (1.4 g, 10 mmoles), dimethyl acetylenedicarboxylate (10.1 g, 50 mmoles) and benzophenone (0.7 g) in acetonitrile (150 ml) was photoirradiated for 3 hours at room temperature. The similar work-up and chromatography for **6** gave a [2+2]-cycloadduct, **7** (9%). This compound had mp 114-116°; ir (potassium bromide): 1710, 1675, 1645 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.20 (s, 3H), 3.76 (s, 7H, 1-H and OCH_3 x 2), 5.66 (d, 4-H, J = 10 Hz), 6.62 (d, 5-H), 8.02 (bs, N-H); ms: m/z (relative intensity) 251 (M^+, 5), 192 (100).

Anal. Calcd. for $C_{12}H_{13}NO_5$: C, 57.39; H, 5.22; N, 5.58. Found: C, 57.22; H, 5.23; N, 5.52.

Dimethyl 7-Azabicyclo[4.2.0]octa-2,4-dien-8-one-4,5-dicarboxylate (**8**).

After the heating of **2** (150 mg, 0.6 mmole) in acetonitrile (4 ml) at 70° for 14 hours, the residue was chromatographed on a silica-gel column with benzene-diethyl ether as the eluent to give a valence isomer, **8** (38%). Compound **8** was slowly decomposed by heating at 90° in a glass tube to give dimethyl phthalate. This compound had mp 115-120° dec; ir (potassium bromide): 1780, 1755-1710 cm^{-1}; ^1H nmr (deuteriochloroform): δ = 3.80 (s, 3H), 3.86 (s, 3H), 4.28 (br t, 1-H, J = 5 Hz), 4.66 (d, 6-H), 6.23 (m, 2H), 6.76 (bs, N-H); ms: m/z (relative intensity) 237 (M^+, 3), 163 ($C_9H_7O_3^+$, 100).

Anal. Calcd. for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.63; H, 4.60; N, 5.87.

Dimethyl 7-Methyl-7-azabicyclo[4.2.0]octa-2,4-dien-8-one-4,5-dicarboxylate (**9**).

After heating of **5** (170 mg, 0.7 mmole) in *p*-xylene (2 ml) at 90° for 1 hour, the residue was similarly chromatographed with benzene-diethyl ether to give a valence isomer, **9** (48%).

Compound **9** was relatively stable to heating. Namely, behaviors of **5** and **9** in DMSO-d_6 by heating were analysed by the use of the ^1H nmr spectrometer, and it was apparent that **5** rapidly changed to **9** at 80°, but **9** was laboriously decomposed at 170° to give dimethyl phthalate. This compound had mp 264-270° dec; ir (potassium bromide): 1775, 1760-1710 cm^{-1}; ^1H nmr (deuteriochloroform): δ = 2.93 (s, 3H), 3.91 (s, 3H), 4.28 (br t, 1-H, J = 6 Hz), 4.69 (d, 6-H), 6.26 (d, 3-H, J = 9.5 Hz), 6.50 (dd, 2-H); ms: m/z (relative intensity) 251 (M^+, 5), 163 ($C_9H_7O_3^+$, 100).

Anal. Calcd. for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.48; H, 5.18; N, 5.44.

Dimethyl 3-Methyl-7-azabicyclo[4.2.0]octa-2,4-dien-8-one-4,5-dicarboxylate (**10**).

After heating **7** (103 mg, 0.41 mmole) in toluene (5 ml) at 100° for 11 hours, similar chromatography of the residue with diethyl ether gave a valence isomer, **10** (73%). This compound had mp 161.5-163°; ir (potassium bromide): 1780, 1720, 1710 cm^{-1}; ^1H nmr (deuteriochloroform): δ = 1.80 (s. 3H), 3.71 (s, 3H), 3.82 (s, 3H), 4.16 (dd, 1-H), 4.58 (d, 6-H, J = 6 Hz), 5.92 (d, 2-H, J = 4 Hz), 6.42 (bs, N-H); ms: m/z (relative intensity) 251 (M^+, 2), 176 (100).

Anal. Calcd. for $C_{12}H_{13}NO_5$: C, 57.39; H, 5.22; N, 5.58. Found: C, 57.77; H, 5.23; N, 5.35.

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