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Reaction of Diketene-Acetone Adduct with Enamines, Ketene Acetals, Vinyl Ethers, and β -Diketones

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Diketene-acetone adduct (**1**) generates acetylketene (**2**) under heating. In order to compare the reactivity of **2** with that of diketene, the reaction of **1** with electron-rich olefins was investigated.

On heating with **1**, primary enamines (**3a—d**) produced the corresponding 3-substituted 2,6-dimethyl-4(1*H*)-pyridones (**4a—d**), while the tertiary enamine **3e** gave the 4-pyrone derivative (**7**). The reaction of **1** with ketene acetals (**8**) gave the 2,2-diethoxy-2,3-dihydro-4-pyrone derivatives (**9**). The vinyl ether derivatives **13** similarly reacted with **1** to give the 4-pyrone derivative **15** or **16** as the major product. The result shows that both diketene and **2** react with electron-rich olefins in a similar manner.

Keywords—diketene; acetylketene; diketene-acetone adduct; enamine; ketene acetal; vinyl ether; 1,3-dioxin-4-one; 4-pyridone; 4-pyrone; cycloaddition

Diketene-acetone adduct (**1**)¹⁾ shows a remarkable reactivity under heating. The adduct **1** reacts with amines, alcohols,¹⁾ and amides²⁾ to produce acetoacetylated compounds, and it also reacts with compounds having a C=N or C $\equiv$ N group to produce 1,3-oxazin-4-ones.³⁾ Such a reactivity, which is analogous to that of diketene⁴⁾ itself, can be rationalized in terms of thermal fragmentation of **1** to acetylketene (**2**).^{3a)} We recently obtained evidence that strongly supports the involvement of an intermediary acetylketene.^{3d)}

In order to compare acetylketene with diketene in terms of reactivity, we studied the reaction of **1** with enamines, ketene acetals, vinyl ethers, and β -diketones.

Reaction with Enamines

On treatment with diketene, tertiary enamines produce 4-pyrones,⁵⁾ while primary and secondary enamines usually produce 4-pyridones.⁶⁾

When **1** was heated with primary enamines (**3a—d**), 4-pyridones (**4a—d**) were obtained. The enamine **3c** gave the *N*-acylated product **5c** as a by-product. Compound **4** is presumably formed *via* the *C*-acetoacetylated intermediate **6**. The tertiary enamine **3e**, on treatment with **1**, gave the chromone derivative **7** and *N*-acetoacetylmorpholine.

The products **4**, **5**, and **7** are also formed by the use of diketene and the yields are comparable to that from the adduct **1**. Therefore, it can be concluded that acetylketene and diketene both show similar reactivity towards enamines.

Reaction with Ketene Acetals

Previously, we have reported that diketene adds to ketene acetals (**8a** and **8b**) to give 2,2-diethoxy-2,3-dihydro-4-pyrones (**9a** and **9b**).⁷⁾ Thus, we tried the reaction of adduct **1** with ketene acetals under heating, and obtained the same products **9** in better yields (51—70%). In addition, the less reactive acetal **8c** also afforded the product **9c** which was not obtained from diketene. When the reaction was conducted without any solvent, the acetal **8a** gave the

Chart 1

benzene derivative **10** as a by-product.

The most reasonable pathway to the products is shown in Chart 2. Though cycloaddition of acetylketene **2** with **8** to give **9** can be explained either by a stepwise mechanism which involves the intermediate **11** or by a concerted mechanism, the former is better able to explain the formation of **10**. Namely, further addition of **8a** to the intermediate **11** gives the intermediate **12**, which produces **10** with elimination of ethanol.

Chart 2

Reaction with Vinyl Ethers

Next, we examined the reaction of **1** with vinyl ethers. When α -ethoxystyrene (**13a**) was heated with two equivalents of **1**, 2-methyl-6-phenyl-4-pyrone (**15a**) was obtained in 30% yield. On similar treatment, butyl vinyl ether (**13b**) gave 2-methyl-4-pyrone (**15b**) together with a small amount of the 2,6-dimethyl-4-pyrone derivative (**16b**), while 3,4-dihydropyran (**13c**) gave only the 2,6-dimethyl-4-pyrone (**16c**) in 42% yield.

When the reaction of **13a** with **1** was conducted under milder conditions, the dihydropyrone derivative (**14a**) was obtained in low yield together with **15a**.

The 1,4-cycloadduct that corresponds to **14a** is probably formed in every case. However, the cycloadduct (**14**) is transformed to **15** with the elimination of the alcohol during the reaction. Addition of acetylketene **2** to a zwitterionic intermediate **17** would give the tetraketone **18**, which spontaneously cyclized to **16**.

Reaction of diketene with vinyl ethers has not been reported. Reaction of **13a** with diketene even in the presence of a catalyst such as triethylamine or *p*-toluenesulfonic acid resulted in the recovery of the starting material **13a**.

Chart 4

Reaction with β -Diketones

In the presence of a basic or acidic catalyst, diketene reacts with β -diketones to yield the 4-pyrone derivative.⁸⁾ In connection with this fact, the reaction of **1** with β -diketone was studied.

The reaction of **1** with acetylacetone (**19a**) and benzoylacetone (**19b**) proceeded without any catalyst to yield the corresponding 4-pyrones (**20a** and **20b**). The yield was slightly better than that from diketene. In contrast to the reaction of diketene, the use of catalysts such as triethylamine and *p*-toluenesulfonic acid resulted in a significant decrease of the yield.

The reaction of **19a** with **1** afforded the 1,3-dioxin-4(2*H*)-one derivative (**21**) as a by-product. A similar compound (**22**) was obtained from cyclohexanone in a good yield on treatment with **1**. Compounds **21** and **22** are the 1,4-cycloadducts of the ketones with acetylketene.

Conclusion

Most reactions of diketene fall into the category of addition reactions to produce acetoacetyl compounds or heterocyclic compounds.⁴⁾ The results of this work and our previous studies on the adduct **1** show that **1** is equally useful for preparation of such compounds, and **1** often gives better results due to the higher reactivity of the intermediary acetylketene. Moreover, the results suggest that the dioxinone **23** may react analogously to the mixed diketene **24**, which is not easily accessible.⁹⁾

Experimental

All melting and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO A-102 spectrometer. Nuclear magnetic resonance (NMR) spectra were measured on a JEOL JNM-PMX 60 spectrometer and data are reported as δ values (ppm) relative to tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a Hitachi M-52G mass spectrometer. Unless otherwise noted, all known compounds were identified by comparison of the IR spectra with those of authentic samples prepared according to the literature.

Reaction of Adduct 1 with Primary Enamines: General Procedure—Enamines **3a**,¹⁰⁾ **3b**,¹¹⁾ **3c**,¹²⁾ and **3d**¹³⁾ were prepared according to the literature. A mixture of **1**¹⁾ (40 mmol) and **3** (20 mmol) was heated in a flask, directly attached to a tube of calcium chloride, at 120–130 °C (bath temperature) for 1 h. Products were isolated in the following manner.

3-Acetyl-2,6-dimethyl-4(1*H*)-pyridone (4a)—Ether (10 ml) was added to the reaction mixture. Crystals were collected by suction and recrystallized from ethanol to give **4a** as needles of mp 234–235 °C (lit.^{6b)} mp 240 °C). Yield, 1.47 g (44%).

Ethyl 2,6-Dimethyl-4(1*H*)-pyridone-3-carboxylate (4b)—The crude crystals obtained in the above manner were recrystallized from acetone to give **4b** as needles of mp 168 °C (lit.^{6b)} mp 167 °C). Yield, 1.56 g (40%).

3-Cyano-2,6-dimethyl-4(1*H*)-pyridone (4c) and 3-acetoacetamidocrotononitrile (5c)—Ethyl acetate (10 ml) was added to the reaction mixture. Crystals were collected by suction and recrystallized from ethanol to give **4c** as prisms of mp 104–106 °C (lit.^{6b)} mp 105–107 °C). Yield, 1.94 g (66%). The ethyl acetate-soluble fraction was concentrated and crystallized from ether. Recrystallization from benzene gave **5c** as plates of mp 78–81 °C (lit.^{6b)} mp 85 °C). Yield, 0.66 g (20%).

3-Benzoyl-2,6-dimethyl-4(1*H*)-pyridone (4d)—Ether (10 ml) was added to the reaction mixture. Crystals were collected by suction and recrystallized from ethanol to give **4d** as needles of mp 290 °C (dec.) [lit.^{6a)} mp 301 °C (dec.)]. Yield, 1.0 g (22%).

2-Methyl-5,6,7,8-tetrahydrochromone (7)—A mixture of **1** (2.84 g) and **3e**¹⁴⁾ (1.67 g) was heated at 120–130 °C for 90 min. The reaction mixture was dissolved in chloroform (150 ml) and extracted with 150 ml of 10% sodium hydroxide solution which was saturated with sodium chloride. The organic layer was dried over sodium sulfate and then concentrated. The residue on recrystallization from hexane gave **7** as prisms of mp 95–96 °C (lit.^{6a)} mp 97–98 °C). Yield, 1.16 g (71%). The above aqueous layer was neutralized with dil. hydrochloric acid and extracted with chloroform. Concentration of the organic layer gave an oil, which was distilled to give *N*-acetoacetylmorpholine as an oil of bp 98–103 °C (0.6 mmHg). Yield, 0.68 g (40%).

Reaction of 1 with Ketene Diethylacetal (8a)—a) A mixture of **1** (2.13 g), **8a**¹⁵⁾ (1.75 g), and dry toluene (16 ml) was heated under reflux for 40 min. Distillation of the mixture gave 2,2-diethoxy-2,3-dihydro-6-methyl-4-pyrone (**9a**)

as an oil of bp 80–83 °C (0.3 mmHg) [lit.⁷⁾ bp 83–84 °C (3 mmHg)]. Yield, 2.1 g (70%).

b) A mixture of **1** (6.15 g) and **8a** (2.52 g) was heated at 110 °C for 30 min. Distillation of the mixture gave 1.55 g (28%) of **9a** and a residue (1.4 g). The residue was purified by silica gel column chromatography using ether as an eluent to give 2,4-diethoxy-6-hydroxyacetophenone (**10**) as needles of mp 83 °C (lit.¹⁶⁾ mp 85 °C). Yield, 0.53 g (22%).

Reaction of 1 with Methylketene Diethylacetal (8b)—A mixture of **1** (1.42 g), **8b**¹⁷⁾ (1.34 g), and dry toluene (10 ml) was heated under reflux for 30 min. Purification by distillation gave 2,2-diethoxy-2,3-dihydro-3,6-dimethyl-4-pyrone (**9b**) as an oil of bp 70 °C (0.15 mmHg) [lit.⁷⁾ bp 95–96 °C (3 mmHg)]. Yield, 1.29 g (60%).

Reaction of 1 with Phenylketene Diethylacetal (8c)—A mixture of **1** (1.42 g), **8c**¹⁸⁾ (1.96 g), and dry toluene (10 ml) was heated under reflux for 30 min. The reaction mixture was chromatographed on a silica gel (60 g) column. Elution with a mixture of hexane–ether (1:1) gave 2,2-diethoxy-2,3-dihydro-6-methyl-3-phenyl-4-pyrone (**9c**) as prisms of mp 98–101 °C (from ether–hexane). Yield, 1.4 g (51%). *Anal.* Calcd for C₁₆H₂₄O₄: C, 69.54; H, 7.30. Found: C, 69.24; H, 7.58. IR (CHCl₃): 1670 (C=O), 1630 (C=C) cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.87, 1.00 (each 3H, t, *J*=7 Hz, 2 × OCH₂CH₃), 1.97 (3H, s, C₆-Me), 3.30–4.00 (4H, m, 2 × OCH₂CH₃), 3.93 (1H, s, C₃-H), 5.20 (1H, s, C₅-H), 7.15 (5H, s, Ph).

Reaction of 1 with α-Ethoxystyrene (13a)—a) A mixture of **1** (2.84 g) and **13a**¹⁹⁾ (1.48 g) was heated at 130 °C for 5 h. The reaction mixture was chromatographed on a silica gel (40 g) column. Elution with hexane–ethyl acetate (1:1) gave unreacted **13a**. Elution with ethyl acetate gave crude **15a**. Recrystallization from ether–hexane gave needles of mp 86–87 °C (lit.²⁰⁾ mp 87–88 °C). Yield, 0.5 g (30%).

b) A mixture of **1** (2.13 g) and **13a** (4.44 g) was heated at 120 °C for 2 h. Excess **13a** was distilled off under reduced pressure. The residue was purified by medium pressure column chromatography (Kieselgel H 60, Merck). Elution with hexane–ethyl acetate (1:1) gave 2-ethoxy-2,3-dihydro-6-methyl-4-pyrone (**14a**) as an oil.²¹⁾ Yield, 0.43 g (12%). IR (CHCl₃): 1655 (C=O), 1610 (C=C) cm⁻¹. ¹H-NMR (CCl₄) δ: 1.00 (3H, t, *J*=7 Hz, OCH₂CH₃), 2.02 (3H, s, C₆-Me), 2.35 and 2.63 (each 1H, d, *J*=9 Hz, C₃-H₂), 3.23 (2H, q, *J*=7 Hz, OCH₂CH₃), 5.30 (1H, s, C₅-H), 7.0–7.6 (5H, m, Ph). MS *m/e*: 232 (M⁺). Further elution with ethyl acetate gave **15a**. Yield, 0.64 g (23%).

Reaction of 1 with Butyl Vinyl Ether (13b)—A mixture of **1** (4.26 g) and **13b** (1.0 g) was heated at 130 °C for 30 h. The reaction mixture was chromatographed on a silica gel (60 g) column. Elution with hexane–ethyl acetate (2:1) gave butyl acetoacetate (0.8 g). Further elution with ethyl acetate gave 2,6-dimethyl-3-(3-butoxypropenyl)-4-pyrone (**16b**) as an oil. Yield, 0.17 g (7%). *Anal.* Calcd for C₁₄H₁₈O₄: C, 67.18; H, 7.25. Found: C, 66.99; H, 7.22. IR (CHCl₃): 1660 (C=O), 1610 (C=C) cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.7–2.0 (7H, m, C₃H₇), 2.25 (3H, s, C₆-Me), 2.30 (3H, s, C₂-Me), 3.87 (2H, t, *J*=6 Hz, OCH₂), 5.90 (1H, d, *J*=13 Hz, CH=CHO–), 6.10 (1H, s, C₅-H), 7.50 (1H, d, *J*=13 Hz, CH=CHO–). MS *m/e*: 251 (M⁺), 193, 177, 151. Further elution with ethyl acetate gave 2-methyl-4-pyrone (**15b**) as an oil. Yield, 0.28 g (26%). The ¹H-NMR data were identical with those given in the literature.²²⁾

Reaction of 1 with 3,4-Dihydro-2H-pyran (13c)—A mixture of **1** (5.68 g) and **13c** (1.68 g) was heated at 130 °C for 14 h. The reaction mixture was concentrated *in vacuo*. The residue was chromatographed on a silica gel (70 g) column. Elution with ethyl acetate gave crystals. Recrystallization from ethyl acetate–hexane gave 3,4-dihydro-2H-pyran-5-yl 2,6-dimethyl-4-oxo-4H-pyran-3-yl ketone (**16c**) as needles of mp 153–155 °C. *Anal.* Calcd for C₁₃H₁₄O₄: C, 66.65; H, 6.02. Found: C, 66.41; H, 6.19. IR (CHCl₃): 1660 (C=O), 1600 (C=C) cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.17 (3H, s, pyran C₆-Me), 2.23 (3H, s, pyran C₂-Me), 1.60–2.57 (4H, m, CH₂CH₂CH₂O), 4.13 (2H, t, *J*=5 Hz, CH₂O), 6.08 (1H, s, pyran C₅-H), 7.35 (1H, s, =CHO).

Reaction of 1 with Acetylacetone—A mixture of **1** (8.52 g) and acetylacetone (3.0 g) was heated at 120–130 °C for 1 h. The reaction mixture was distilled to give 0.93 g of acetylacetone. The residue was chromatographed on a silica gel (140 g) column. Elution with hexane–ethyl acetate (4:1) gave **1** (1.62 g). Successive elution with hexane–ethyl acetate (2:1) gave an oil, which on distillation afforded 2-acetonil-2,4-dimethyl-1,3-dioxin-4(2H)-one (**21**) as an oil of bp 100 °C (0.001 mmHg). Yield, 0.67 g (12%). *Anal.* Calcd for C₉H₁₂O₄: C, 58.69; H, 6.57. Found: C, 58.80; H, 6.74. IR (CHCl₃): 1710 (C=O), 1630 (C=C) cm⁻¹. ¹H-NMR (CCl₄) δ: 1.72 (3H, s, C₂-Me), 2.00 (3H, s, C₆-Me), 2.18 (3H, s, acetyl), 3.02 (2H, s, CH₂), 5.16 (1H, s, C₅-H). Further elution with hexane–ethyl acetate (1:1) gave 3-acetyl-2,6-dimethyl-4-pyrone (**20a**) as an oil of bp 85–92 °C (0.3 mmHg) [lit.^{8a)} bp 100–105 °C (3 mmHg)]. Yield, 1.15 g (23%).

When the period of heating in this reaction was extended to 2 h, only **20a** was obtained. Yield, 3.12 g (63%).

Reaction of 1 with Benzoylacetone—A mixture of **1** (8.52 g) and benzoylacetone (4.86 g) was heated at 120–130 °C for 4 h. The reaction mixture was chromatographed on a silica gel (160 g) column. Elution with hexane–ether (9:1) gave 2.22 g of benzoylacetone. Elution with hexane–ether (3:1) gave dehydroacetic acid (0.49 g). Elution with ether gave 3-benzoyl-2,6-dimethyl-4-pyrone (**20b**) as needles of mp 97–98 °C (lit.^{8b)} mp 97–98 °C) (recrystallized from ether–hexane). Yield, 2.36 g (36%).

Reaction of 1 with Cyclohexanone—A mixture of **1** (2.84 g) and cyclohexanone (5.88 g) was heated at 120 °C for 1 h. Distillation of the mixture gave **22** as an oil of bp 81 °C (0.1 mmHg) [lit.²³⁾ bp 117–122 °C (0.4 mmHg)]. Yield, 2.51 g (69%).

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References and Notes

- 1) M. F. Carroll and A. R. Bader, *J. Am. Chem. Soc.*, **74**, 6305 (1952).
- 2) M. Sato, N. Kanuma, and T. Kato, *Chem. Pharm. Bull.*, **30**, 1315 (1982).
- 3) a) G. Jäger and J. Wenzelburger, *Justus Liebigs Ann. Chem.*, **1976**, 1689; b) M. Sato, H. Ogasawara, E. Yoshizumi, and T. Kato, *Heterocycles*, **17**, 297 (1982); c) M. Sato, N. Kanuma, and T. Kato, *Chem. Pharm. Bull.*, **30**, 4359 (1982); d) M. Sato, H. Ogasawara, E. Yoshizumi, and T. Kato, *Chem. Pharm. Bull.*, **31**, 1902 (1983).
- 4) T. Kato, *Acc. Chem. Res.*, **7**, 265 (1976).
- 5) a) B. Milward, *J. Chem. Soc.*, **1960**, 26; b) S. Hünig, E. Benzing, and K. Hübner, *Chem. Ber.*, **94**, 486 (1961).
- 6) a) E. Ziegler, I. Herbst, and Th. Kappe, *Monatsh. Chem.*, **100**, 132 (1969); b) T. Kato, H. Yamanaka, and T. Hozumi, *Yakugaku Zasshi*, **91**, 740 (1971); c) P. Caramella and A. Querci, *Synthesis*, **1972**, 42.
- 7) T. Kato, Y. Yamamoto, and S. Takeda, *Chem. Pharm. Bull.*, **21**, 1047 (1973).
- 8) a) K. Hamamoto, T. Isoshima, and M. Yoshioka, *Nippon Kagaku Zasshi*, **79**, 840 (1958); b) T. Kato and T. Hozumi, *Chem. Pharm. Bull.*, **20**, 1574 (1972).
- 9) H. W. Moore and D. S. Wilbur, *J. Org. Chem.*, **45**, 4483 (1980).
- 10) A. Combes and C. Combes, *Bull. Soc. Chim. Fr.*, **7**, 779 (1892).
- 11) A. Michaelis, *Justus Liebigs Ann. Chem.*, **1909**, 337.
- 12) J. Moir, *J. Chem. Soc.*, **81**, 101 (1902).
- 13) C. Beyer and L. Claisen, *Chem. Ber.*, **20**, 2180 (1887).
- 14) S. Hünig, E. Benzing, and E. Lucke, *Chem. Ber.*, **90**, 2833 (1957).
- 15) S. M. McElvain and D. Kundiger, "Organic Syntheses," Coll. Vol. III, ed. by A. H. Blatt, John Wiley and Sons, Inc., New York, 1943, p. 506.
- 16) S. Kostancecki and J. Tambor, *Chem. Ber.*, **32**, 2263 (1899).
- 17) P. M. Walters and S. M. McElvain, *J. Am. Chem. Soc.*, **62**, 1482 (1940).
- 18) S. M. McElvain and C. L. Stevens, *J. Am. Chem. Soc.*, **68**, 1917 (1946).
- 19) Y. Ogata, A. Kawasaki, and K. Tsujimura, *Tetrahedron*, **27**, 2765 (1971).
- 20) M. Rolla, M. Sanesi, and G. Traverso, *Ann. Chim. (Roma)*, **44**, 430 (1954).
- 21) Analytically pure **14** was not obtainable, since **14** partially decomposed during chromatography.
- 22) L. C. Dorman, *J. Org. Chem.*, **32**, 4105 (1967).
- 23) E. V. Dehmlow and A. R. Shamout, *Justus Liebigs Ann. Chem.*, **1982**, 1753.