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A New Aromatic Annelation Reaction with Two Synthons, Enaminones and 3-Oxoglutarate.[1] Studies on the *β*-Carbonyl Compounds Connected with *β*-Polyketides. VIII[2]

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Reactions of the enaminones **1** with dimethyl 3-oxoglutarate in the presence of KF–AcOH or AcONa–AcOH and 18-crown-6 gave the dimethyl 2-hydroxy-1,3-benzenedicarboxylates **3**, providing a new aromatic annelation reaction.

Keywords——enaminone; dimethyl 3-oxoglutarate; buffer catalysis; aromatic annelation; dimethyl 2-hydroxy-1,3-benzenedicarboxylate

Currently, there is considerable interest in the reactions of enaminones because of their potential use in synthetic chemistry.[3] Although numerous investigations of intra- and intermolecular condensation reactions leading to aromatic ring formation have been reported,[4] only a few attempts to use enaminones as an equivalent synthon of *β*-dicarbonyl compounds for the construction of aromatic ring compounds have been reported, namely, the self-condensation reactions of enamino esters,[5] and the condensation reactions of enamine aldehydes with the dianions of *β*-dicarbonyl compounds,[6] *etc.* Herein we report a new aromatic annelation reaction by a straight forward reaction of enaminones and 3-oxoglutarate.

Renewed interest in the area of aromatic annelations has resulted in some progress in the synthesis of phenols, pyridines and benzene rings from non-aromatic precursors.[7] Our present interest is to determine whether annelation products such as **3** can be obtained from the enaminones **1** and dimethyl 3-oxoglutarate (**2**) under suitable reaction conditions in reasonable yield.

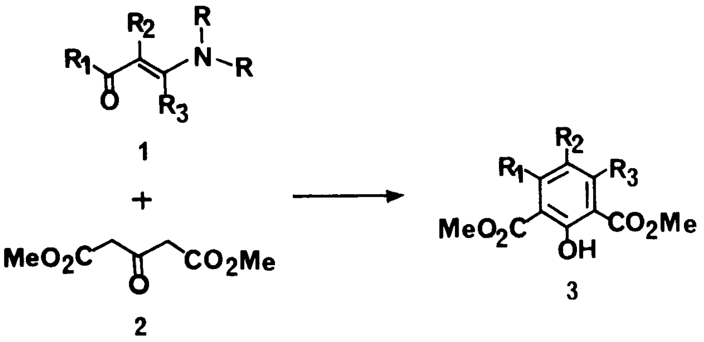


Chart 1

The following enaminones, namely, 3-dimethylamino-2-propenal (**4**), 4-diethylamino-3-buten-2-one (**5**), 4-dimethylamino-3-penten-2-one (**6**), 3-dimethylamino-1-phenyl-2-propenone (**7**), 5-dimethylamino-1-phenyl-1,4-pentadien-3-one (**8**), 2-dimethylaminomethylenecyclohexanone (**9**), and 5,5-dimethyl-2-dimethylaminomethylene-1,3-cyclohexadione (**10**), were selected for the present purpose. The enaminones **4**, bp 80—107 °C (0.45 mmHg), **7**, mp 89—90 °C, **8**, oil, **9**, oil, and **10**, mp 80—81 °C, were prepared by the reactions of bis-dimethylaminomethoxymethane[8] and the corresponding carbonyl compounds in yields of 25, 50, 73.5, 80, and 73.3%, respectively. The enaminones **5** and **6** were synthesized by the known methods as shown in Chart 2.

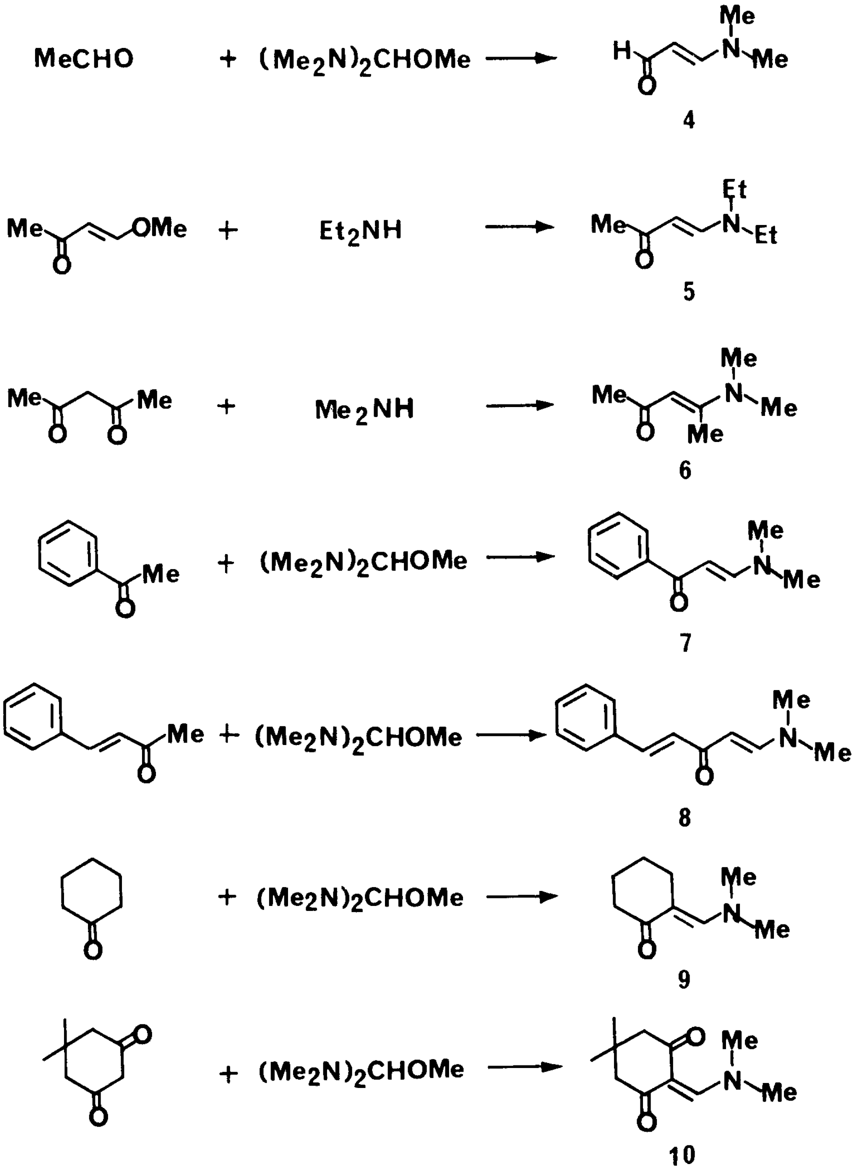
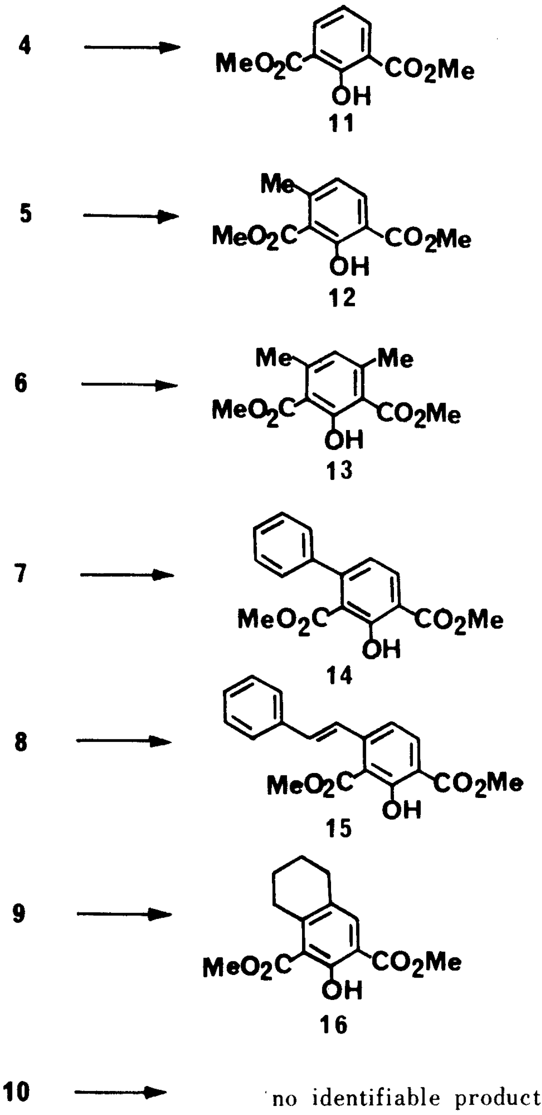


Chart 2

Although several attempts at the annelation reaction of the enaminones **1** with dimethyl 3-oxoglutarate in the presence of bases and acids were unsuccessful,[9] the annelation products **3** were obtained by heating in dioxane in the presence of KF–AcOH (method A) or in toluene in the presence of AcONa–AcOH and 18-crown-6 (method B). The dimethyl 2-hydroxy-1,3-benzenedicarboxylates, namely, dimethyl 2-hydroxy-1,3-benzenedicarboxylate (**11**), mp 69—70 °C, dimethyl 2-hydroxy-4-methyl-1,3-benzenedicarboxylate (**12**), mp 53—54 °C, dimethyl 2-hydroxy-4,6-dimethyl-1,3-benzenedicarboxylate (**13**), mp 110—111 °C, dimethyl 2-hydroxy-4-phenyl-1,3-benzenedicarboxylate (**14**), mp 85—87 °C, dimethyl 2-hydroxy-4-(2-phenylethenyl)-1,3-benzenedicarboxylate (**15**), mp 151—152 °C, and dimethyl 5,6,7,8-tetrahydro-2-hydroxy-1,3-naphthalenedicarboxylate (**16**), mp 82—84 °C, were obtained in reasonable yields by the two methods as shown in Chart 3. Reaction of **10** with methyl oxoglutarate by the above methods gave no identifiable products.



		Yield (%)	
		method A	method B
4 →	**11**	48.5	16.0
5 →	**12**	53.2	34.1
6 →	**13**	49.1	2.2
7 →	**14**	56.7	44.2
8 →	**15**	63.0	45.1
9 →	**16**	30.8	16.8
10 →	no identifiable products		

Chart 3

The Aromatic Annelation Reactions of Enaminones with Methyl 3-Oxoglutarate

These results provide a new aromatic annelation method and indicate the potential utility of this method in the synthesis of *β*-polyketide derived natural products, in particular, in the synthesis of naturally occurring stilbene derivatives in view of the result of **8** to **15**.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 215 spectrometer, nuclear magnetic resonance (NMR) spectra with a Varian T-60 spectrometer at 60 MHz with tetramethylsilane as an internal standard ($CDCl_3$), and mass spectrum (MS) with a Hitachi RMS-4 spectrometer at 70 eV using the direct insertion technique. Elementary analyses were done by Ms. M. Nishizawa and Ms. M. Takeda, Kissei Pharmaceutical Company, Matsumoto, Japan. Mallinckrodt silica gel (100 mesh) and Merck Kieselgel G nach Stahl were used for column chromatography and thin-layer chromatography (TLC), respectively.

3-Dimethylamino-2-propenal (4)——Acetaldehyde (10 g) was added to bisdimethylaminomethoxymethane (34.8 g) at 0 °C and the whole was stirred at 0 °C for 1 h. The reaction mixture was distilled to give 5.5 g (24.4%) of **4** as an oil, bp 80—107 °C (0.5 mmHg). IR (film): 1600 cm^{-1}. NMR ($CDCl_3$) δ: 2.95 (6H, br, $-NMe_2$), 5.00 (1H, dd, $J=$ 12.6 and 7.8 Hz, olefinic H), 6.93 (1H, d, $J=12.6$ Hz, olefinic H), 8.93 (1H, d, $J=7.8$ Hz, –CHO).

3-Dimethylamino-1-phenyl-2-propenone (7)——Bisdimethylaminomethoxymethane (2.7 g) was added to a solution of acetophenone (2 g) in abs. ethanol (15 ml), and the whole was heated overnight at 80 °C under stirring. The reaction mixture was concentrated under a vacuum, and the residue was recrystallized from ether–*n*-hexane to yield 1.5 g (50%) of **7** as yellow crystals, mp 89—90 °C. IR (Nujol): 1640, 1580, 1550 cm^{-1}. NMR ($CDCl_3$) δ: 3.00 (6H, s, $-NMe_2$), 5.70 (1H, d, $J=12$ Hz, olefinic H). MS *m/e*: 175 (M^+).

Compounds **8**, **9**, and **10** were prepared in a similar manner.

5-Dimethylamino-1-phenyl-1,4-pentadien-3-one (8)——As an oil (73.5%). IR (film): 1650, 1640, 1615 cm^{-1}. NMR ($CDCl_3$) δ: 2.85 (6H, s. $-NMe_2$), 5.12 (1H, d, $J=12.6$ Hz, olefinic H), 6.57 (1H, d, $J=16$ Hz, olefinic H), 7.37 (1H, d, $J=16$ Hz, olefinic H), 7.52 (1H, d, $J=12.6$ Hz, olefinic H). Compound **8** was used in the next step without purification.

2-Dimethylaminomethylenecyclohexanone (9)——As an oil (80%). IR (film): 1680, 1640 cm^{-1}. NMR ($CDCl_3$) δ: 1.72 (4H, m, $2\times -CH_2-$), 2.27 (4H, m, $2\times -CH_2-$), 3.07 (6H, s, $-NMe_2$), 7.50 (1H, s, olefinic H). Compound **9** was used in the next step without purification.

5,5-Dimethyl-2-dimethylaminomethylene-1,3-cyclohexadione (10)——As yellow crystals, mp 80—81 °C (73.3%). IR (KBr): 1650, 1580 cm^{-1}. NMR ($CDCl_3$) δ: 0.95 (6H, s, $2\times$ Me), 2.22 (4H, s, $2\times -CH_2-$), 3.05 (3H, s, $=NMe$), 3.23 (3H, s, $=NMe$), 7.80 (1H, s, olefinic H). MS *m/e*: 195 (M^+).

Reactions of Enaminones with Dimethyl 3-Oxoglutarate (2)——Method A: Acetic acid (0.5 ml) and potassium fluoride (230 mg) were added to a solution of the enaminone (0.1 mmol) and **2** (0.2 mmol) in dry dioxane (5 ml) and the whole was refluxed overnight. The reaction mixture was concentrated under a vacuum, acidified with 5% HCl and then extracted with chloroform. The chloroform layer was washed with sat. $NaHCO_3$ and water, then dried and concentrated. The residue was subjected to silica gel chromatography. The benzene eluate gave the condensation product as crystals (ether–*n*-hexane).

Method B: Acetic acid (0.1 ml), dry sodium acetate (50 mg) and 18-crown-6 (100 mg) were added to a solution of the enaminone (0.1 mmol) and **2** (0.2 mmol) in dry toluene (10 ml), and the whole was refluxed for 3 h. The reaction mixture was worked up as described in Method A.

Dimethyl 2-Hydroxy-1,3-benzenedicarboxylate (11)——As crystals, mp 69—70 °C. IR (KBr): 1725, 1665, 1610 cm^{-1}. NMR ($CDCl_3$) δ: 3.88 (6H, s, $2\times -CO_2Me$), 6.78 (1H, t, $J=8.0$ Hz, aromatic H), 7.88 (2H, d, $J=8.0$ Hz, aromatic H), 11.60 (1H, s, –OH). MS *m/e*: 210 (M^+). *Anal.* Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 57.26; H, 4.88.

Dimethyl 2-Hydroxy-4-methyl-1,3-benzenedicarboxylate (12)——As crystals, mp 53—54 °C. IR (KBr): 1725, 1663, 1620 cm^{-1}. NMR ($CDCl_3$) δ: 2.20 (3H, s, –Me), 3.78 (6H, s, $2\times -CO_2Me$), 6.53 (1H, d, $J=7.8$ Hz, aromatic H), 7.56 (1H, d, $J=7.8$ Hz, aromatic H), 10.91 (1H, s, –OH). MS *m/e*: 224 (M^+). *Anal.* Calcd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 58.96; H, 5.43.

Dimethyl 2-Hydroxy-4,6-dimethyl-1,3-benzenedicarboxylate (13)——As crystals, mp 110—111 °C. IR (KBr): 1715, 1655, 1608 cm^{-1}. NMR ($CDCl_3$) δ: 2.35 (6H, s, $2\times$ –Me), 3.86 (6H, s, $2\times -CO_2Me$), 6.45 (1H, s, aromatic H), 11.71 (1H, s, –OH). MS *m/e*: 238 (M^+). *Anal.* Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.73; H, 6.01.

Dimethyl 2-Hydroxy-4-phenyl-1,3-benzenedicarboxylate (14)——As crystals, mp 108—110 °C. IR (KBr): 1725, 1668, 1610 cm^{-1}. NMR ($CDCl_3$) δ: 3.53 (3H, s, $-CO_2Me$), 3.85 (3H, s, $-CO_2Me$), 6.77 (1H, d, $J=7.8$ Hz, aromatic H), 7.22 (5H, s, $5\times$ aromatic H), 7.75 (1H, d, $J=7.8$ Hz, aromatic H), 11.00 (1H, s, –OH). MS *m/e*: 286 (M^+). *Anal.* Calcd for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93. Found: C, 67.20; H, 5.03.

Dimethyl 2-Hydroxy-4-(2-phenylethenyl)-1,3-benzenedicarboxylate (15)——As crystals, mp 151—152 °C. IR (Nujol): 1713, 1664, 1635, 1613 cm^{-1}. NMR ($CDCl_3$) δ: 3.93 (3H, s, –Me), 3.96 (3H, s, –Me), 7.03 (2H, s, $2\times$ olefinic H), 7.74 (1H, d, $J=8.0$ Hz, aromatic H), 11.00 (1H, br, –OH). MS *m/e*: 312 (M^+). *Anal.* Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.38; H, 5.16.

Dimethyl 5,6,7,8-Tetrahydro-2-hydroxy-1,3-naphthalenedicarboxylate (16)——As crystals, mp 82—84 °C. IR (Nujol): 1720, 1680, 1615 cm^{-1}. NMR ($CDCl_3$) δ: 1.74 (4H, m, $2\times -CH_2-$), 2.70 (4H, m, $2\times -CH_2-$), 3.95 (6H, s, $2\times -CO_2Me$), 7.60 (1H, s, aromatic H), 11.10 (1H, s, –OH). MS *m/e*: 264 (M^+). *Anal.* Calcd for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10. Found: C, 63.85; H, 6.33.

References and Notes

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9) These annelation reactions were unsuccessful with acids and bases such as BF_3–ether, $SnCl_4$, NaOEt, and *n*-BuLi alone.