Annelation Reactions of Enaminones with Ethyl Acetoacetate. Studies on the β-Carbonyl Compounds Connected with the β-Polyketides. XI[1)]

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Though condensation at either the carbonyl oxygen or the unsaturated carbon adjacent to nitrogen of enaminones can occur in the reaction with the active methylene of ethyl acetoacetate, the results obtained in the condensation reactions of the enaminones 1 and 2 with ethyl acetoacetate in the presence of Knoevenagel catalysts to give the α-pyranones 3 and 4 and with the dianion of ethyl acetoacetate to give the ethyl salicylates 6 and 19 show that these reactions proceed at the latter position.

Keywords condensation reaction; enaminone; ethyl acetoacetate; Knoevenagel catalyst; dianion; α-pyranone; ethyl salicylate

Enaminones are useful synthons in synthetic organic chemistry,[2)] and we have reported an aromatic annelation reaction by the reaction of an enaminone with dimethyl 3-oxoglutarate[3)] and an application of this reaction for the synthesis of *d,l*-phyllodulcin,[4,5)] a sweet dihydroisocoumarin.[6)] In the present paper, we describe the annelation reactions of enaminones with ethyl acetoacetate, investigated in connection with a previous report,[3)] to give several annelation products.

Two condensation patterns, namely, A and B, are possible in the condensation of the enaminones with the active methylene of ethyl acetoacetate, as shown in Chart 1.

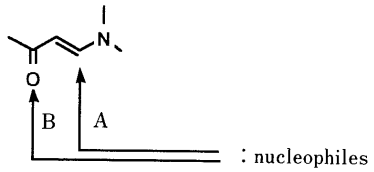
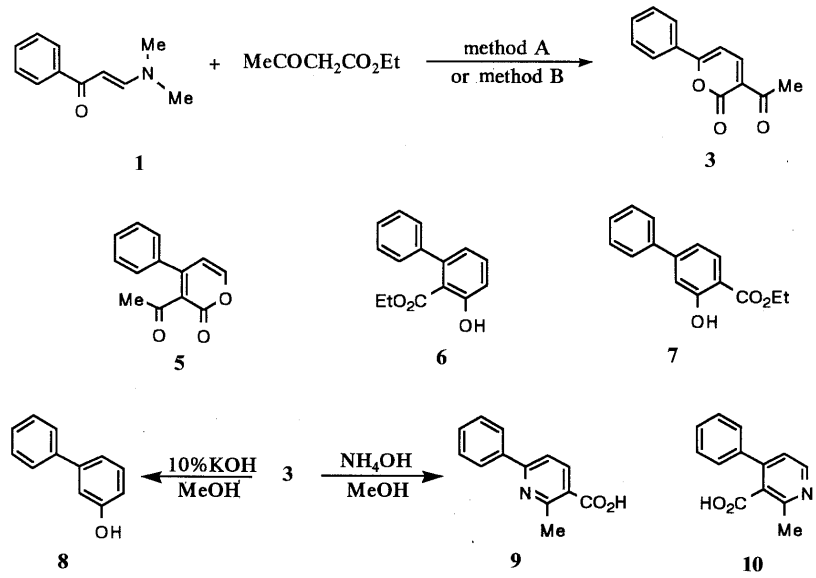


Chart 1

Two enaminones, 3-dimethylamino-1-phenyl-2-propenone (**1**)[3)] and 5-dimethylamino-1-phenyl-1,4-pentadien-3-one (**2**),[3)] were selected for the studies on the reactivity with ethyl acetoacetate. First, the condensation reactions in the presence of Knoevenagel catalysts were investigated by two methods. Reactions of the enaminone **1** with ethyl acetoacetate in the presence of AcONa, AcOH, and 18-crown-6 (method A) or in the presence of KF–AcOH (method B) afforded a condensation product **3** in a yield of 50.3 or 32.1%, respectively. Similar condensation reaction with the enaminone **2** by method A or B gave a condensation product **4** in 28.4 or 14.4% yield, respectively.

Four condensation products, namely, **3**, **5**, **6**, and **7**, are possible in the reaction of the enaminone **1** with ethyl acetoacetate (Chart 1). The following chemical transformations were performed to confirm the structure of 3-acetyl-6-phenyl-2-pyranone (**3**). Treatment of **3** with 10% KOH–MeOH (1 : 1) gave 3-phenylphenol (**8**)[7)] and reaction with NH_4OH in MeOH afforded 2-methyl-6-phenyl-3-nicotinic acid (**9**). The proton nuclear magnetic resonance spectrum (^{1}H-NMR) of **9** shows signals at δ 7.67 (1H, d, J=8.3 Hz) and δ 8.39 (1H, d, J=8.3 Hz).[8)] Therefore, the structures of **5**, **6**, **7**, and **10** are excluded as possible structures for the condensation product and the chemical



method A: AcONa, AcOH, 18-crown-6, toluene method B: KF, AcOH, dioxane

Chart 2

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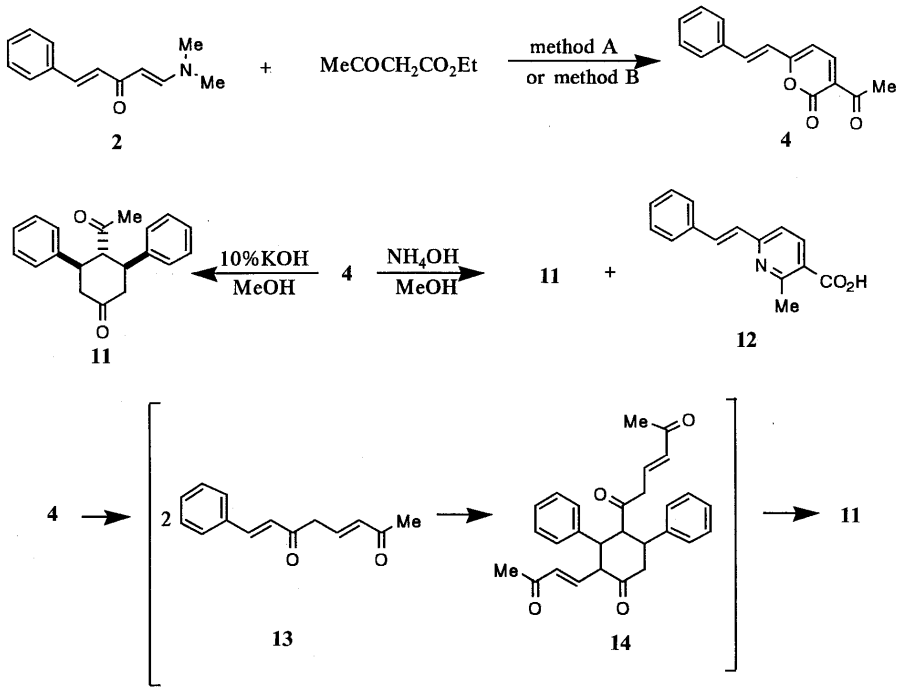

method A: AcONa, AcOH, 18-crown-6, toluene
method B: KF, AcOH, dioxane

Chart 3

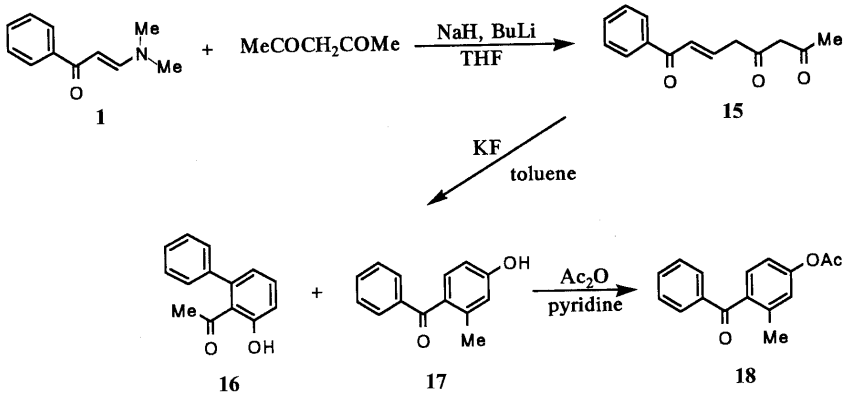

Chart 4

transformation product.

The structure of the condensation product **4** produced by the reaction of the enaminone **2** with ethyl acetoacetate was similarly established to be 3-acetyl-6-styryl-2-pyranone (**4**). Chemical transformations were performed as shown in Chart 3. Treatment of **4** with 10% KOH–MeOH (1 : 1) afforded 4-acetyl-3,5-diphenylcyclohexanone (**11**). An acetyl group and two phenyl groups of **11** may be equatorial in view of the ^{1}H-NMR signals at δ 3.43 (1H, t, J = 12.6 Hz) and δ 3.31 (2H, dt, J = 12.6 and 4.3 Hz). Compound **11** may be formed by the mechanism shown in Chart 3. That is, hydrolysis and decarboxylation of **4** may give **13**, which may dimerize to the intermediate **14**, and this in turn may be further hydrolyzed to yield **11**. Treatment of **4** with NH_4OH in MeOH afforded **11** and 2-methyl-6-styryl-3-nicotinic acid (**12**).

These results suggest that the reaction of enaminones with ethyl acetoacetate in the presence of Knoevenagel catalyst may proceed *via* pattern A shown in Chart 1.

Subsequently, the condensation reactions of the enaminones with ethyl acetoacetate through other procedures were investigated. The reaction of the enaminone **1** with the dianion prepared from the reaction of acetylacetone with NaH and butyl lithium in tetrahydrofuran (THF) (method C) was found in a preliminary experiment to give the condensation product **15**, which was transformed further to 2-acetyl-3-phenylphenol (**16**) and 4-hydroxy-2-methylbenzophenone (**17**) by treatment with KF in toluene. Acetylation of **17** with Ac_2O–pyridine afforded 4-acetoxy-2-methylbenzophenone (**18**).

Similarly, the reactions of the enaminones **1** and **2** with the dianion prepared from the reaction of ethyl acetoacetate with NaH and butyl lithium followed by treatment with KF afforded the condensation products **6** and **19** in yields of 14.8 and 24.0%, respectively (method C). The yields of condensation products **6** and **19** were raised to 33.1 and

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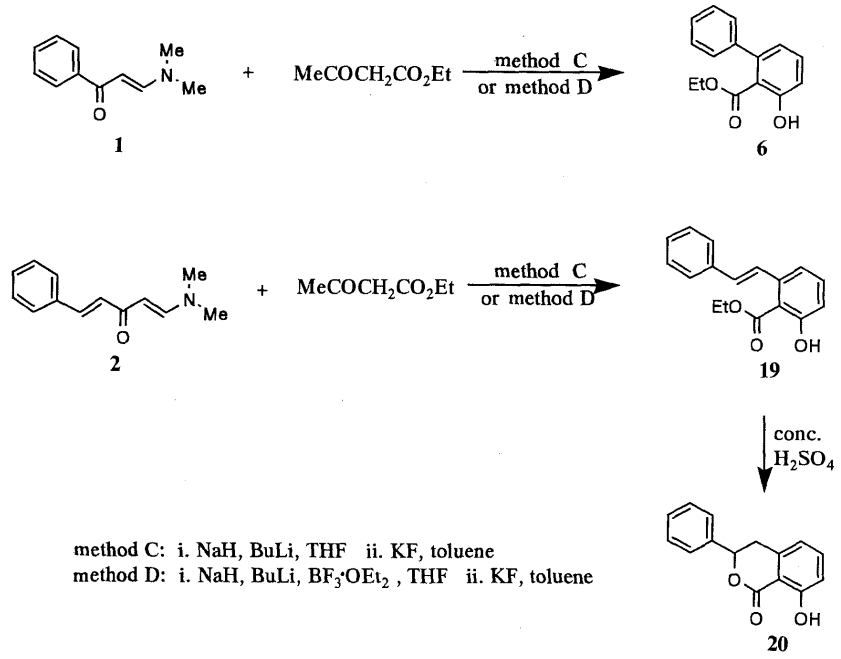

Chart 5

41.0%, respectively, by the addition of $BF_3 \cdot OEt_2$ to the above solution of the enaminones and the dianion of ethyl acetoacetate (method D).[9] The condensation product **19** was transformed subsequently to the dihydroisocoumarin **20** by treatment with concentrated H_2SO_4, in 69.9% yield.

The results obtained by the reactions of the enaminone **1** with the dianion of acetylacetone to give the products **16** and **17** and the enaminones **1** and **2** with the dianion of ethyl acetoacetate to give the products **6** and **19** show that these reactions proceed *via* pattern A shown in Chart 1, and may be applicable for the synthesis of natural dihydroisocoumarins, such as phyllodulcin,[4-6] hydrangenol,[4,10] *etc.*

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 260-10 spectrometer, NMR spectra with a JEOL JNM-FX 100 spectrometer with tetramethylsilane as an internal standard, and mass spectra (MS) with a JEOL JMS-D 300 spectrometer. Elemental analyses were done by Ms. M. Takeda, Kissei Pharmaceutical Company, Ltd., 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-Acetyl-6-phenyl-2-pyranone (3) Method A: Acetic acid (0.2 ml), dry sodium acetate (100 mg), and 18-crown-6 (200 mg) were added to a solution of the enaminone **1** (415 mg) and ethyl acetoacetate (470 mg) in dry toluene (20 ml), and the whole was refluxed for 6 h. The reaction mixture was concentrated under a vacuum, and the residue was acidified with 5% HCl and then extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and water, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 255 mg (50.3%) of **3** as yellow needles (ether–hexane), mp 151—153 °C. IR (Nujol) cm^{-1}: 1720, 1675, 1550. ^{1}H-NMR ($CDCl_3$) δ: 2.66 (3H, s, –COMe), 6.69 (1H, d, J=6.1 Hz, olefinic H), 7.23—7.47 (3H, m, aromatic H), 7.63—7.83 (2H, m, aromatic H), 8.10 (1H, d, J=6.1 Hz, olefinic H). MS *m/z*: 214 (M^+), 199, 186, 171, 115, 109, 105. High-resolution MS *m/z*: Calcd for $C_{13}H_{10}O_3$ (M^+): 214.0630. Found: 214.0641. *Anal.* Calcd for $C_{13}H_{10}O_3$: C, 72.89; H, 4.70. Found: C, 72.71; H, 4.63.

Method B: Acetic acid (0.5 ml) and potassium fluoride (230 mg) were added to a solution of the enaminone **1** (175 mg) and ethyl acetoacetate (236 mg) in dry dioxane (5 ml), and the whole was refluxed overnight. The reaction mixture was worked up as described under method A to give 68.7 mg (32.1%) of **3**.

3-Phenylphenol (8) A mixture of **3** (100 mg), 10% KOH (5 ml), and methanol (5 ml) was refluxed overnight. The reaction mixture was poured into ice-water, acidified with 10% HCl, and then extracted with ether. The ether layer was washed with water, and then dried and concentrated. The residue was subjected to silica gel chromatography. The benzene eluate gave 17.9 mg (22.5%) of **8** as colorless prisms (ether–hexane), mp 76—78 °C (lit.[7] mp 76—78 °C).

2-Methyl-6-phenyl-3-nicotinic Acid (9) Ammonia water (5 ml) was added to a solution of **3** (50 mg) in methanol (3 ml) and the whole was refluxed overnight. The reaction mixture was poured into ice-water, acidified with 10% HCl, and then extracted with ether. The ether layer was washed with water, and then dried and concentrated. The residue was recrystallized from ether–hexane to yield 22 mg (44.2%) of **9** as orange-yellow prisms, mp 179—181 °C. IR (Nujol) cm^{-1}: 1685, 1580. ^{1}H-NMR ($CDCl_3$) δ: 2.98 (3H, s, –Me), 4.00 (1H, br, $-CO_2H$), 7.43—7.52 (3H, m, aromatic H), 7.67 (1H, d, J=8.3 Hz, olefinic H), 7.93—8.13 (2H, m, aromatic H), 8.39 (1H, d, J=8.3 Hz, olefinic H). High-resolution MS *m/z*: Calcd for $C_{13}H_{11}NO_2$: 213.0790. Found: 213.0785. *Anal.* Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.12; H, 5.19; N, 6.67.

3-Acetyl-6-styryl-2-pyranone (4) Compound **4** was obtained as yellow flaky crystals (ether), mp 145—147 °C, from the enaminone **2** by methods A and B described above in yields of 28.4 and 14.4%, respectively. IR (Nujol) cm^{-1}: 1710, 1680, 1630, 1535. ^{1}H-NMR ($CDCl_3$) δ: 2.68 (3H, s, –Me), 6.34 (1H, d, J=7.6 Hz, olefinic H), 6.69 (1H, d, J=15.9 Hz, olefinic H), 7.30—7.52 (5H, m, aromatic H), 7.67 (1H, d, J=15.9 Hz, olefinic H), 8.21 (1H, d, J=7.6 Hz, olefinic H). MS *m/z*: 240 (M^+), 225, 212, 197, 187, 169, 141, 131, 115, 109. High-resolution MS *m/z*: Calcd for $C_{15}H_{12}O_3$ (M^+): 240.0786. Found: 240.0807. *Anal.* Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.95; H, 5.00.

4-Acetyl-3,5-diphenylcyclohexanone (11) A mixture of **4** (50 mg), 10% KOH (3 ml), and methanol (3 ml) was refluxed for 3 h. The reaction mixture was poured into ice-water, acidified with 10% HCl, and then extracted with chloroform. The organic layer was washed with saturated $NaHCO_3$ and water, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 25.5 mg (35.1%) of **11** as colorless prisms (ethyl acetate–chloroform), mp 207—209 °C. IR (Nujol) cm^{-1}: 1728, 1700, 1600, 1500. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, s, –Me), 2.67 (2H, dd, J=12.6, 4.3 Hz, methylene H), 2.80 (2H, t, J=12.6 Hz, methylene H), 3.31 (2H, dt, J=12.6, 4.3 Hz, methine H), 3.43 (1H, t, J=12.6 Hz, methine H), 7.20—7.36 (10H, m, aromatic H). High-resolution MS *m/z*: Calcd for $C_{20}H_{20}O_2$ (M^+): 292.1464. Found: 292.1470. *Anal.* Calcd for $C_{20}H_{20}O_2$: C, 82.15; H, 6.89. Found: C, 82.11; H, 6.94.

Reaction of 4 with Ammonia Water Ammonia water (5 ml) was added

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to a solution of **4** (150 mg) in methanol (3 ml) and the whole was refluxed for 1.5 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 73.6 mg (33.8%) of **11** as colorless prisms (ethyl acetate–chloroform), mp 207—209 °C. The water layer was acidified with concentrated HCl and then extracted with ethyl acetate. The organic layer was washed with water, then dried and concentrated. The residue was recrystallized from methanol–ethyl acetate to yield 22.4 mg (12.6%) of 2-methyl-6-styryl-3-nicotinic acid (**12**) as colorless powdery crystals, mp 182—184 °C. IR (Nujol) cm^{-1}: 1700, 1595, 1490. ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 3.16 (3H, s, –Me), 7.41—7.47 (2H, m, aromatic H), 7.69—7.79 (3H, m, aromatic H), 8.00 (2H, s, olefinic H), 8.18 (1H, d, J=8.8 Hz, aromatic H), 8.73 (1H, d, J=8.8 Hz, aromatic H). CI-MS m/z: 240 (M^++1). *Anal.* Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.28; H, 5.48; N, 5.89.

1-Phenyl-2-octene-1,5,7-trione (15) Sodium hydride (55%, 250 mg) was added to a solution of acetylacetone (330 mg) in dry THF (7.4 ml) with stirring at 0 °C for 10 min under a nitrogen atmosphere. A solution of 1.36 M butyl lithium in hexane (2.4 ml) was added and the mixture was stirred at 0 °C for 10 min under the same conditions. The enaminone **1** (500 mg) was then added, and the mixture was stirred at room temperature for 1 h under the same conditions. The reaction mixture was poured into ice-water, acidified with 10% HCl, and extracted with ether. The organic layer was washed with brine, then dried and concentrated. The residue was subjected to silica gel chromatography. The benzene eluate gave 373.2 mg (56.8%) of **15** as light yellow needles (ether–chloroform), mp 105—107 °C. IR (Nujol) cm^{-1}: 1678, 1645, 1592. High-resolution MS m/z: Calcd for $C_{14}H_{14}O_3$ (M^+): 230.0941. Found: 230.0940. *Anal.* Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.93; H, 6.11.

Reaction of 15 with Potassium Fluoride Potassium fluoride (75 mg) was added to a solution of **15** (100 mg) in dry toluene (5 ml), and the whole was refluxed overnight. The reaction mixture was concentrated under a vacuum, poured into ice-water, and then extracted with chloroform. The organic layer was washed with water, then dried and concentrated. The residue was subjected to silica gel chromatography. The first eluate with 30% hexane in chloroform gave 30.0 mg (32.5%) of 2-acetyl-3-phenylphenol (**16**) as a colorless oil. IR (neat) cm^{-1}: 1625, 1593, 1560, 1495. ^{1}H-NMR ($CDCl_3$) δ: 1.84 (3H, s, –COMe), 6.84 (1H, dd, J=7.3, 1.5 Hz, aromatic H), 6.99 (1H, dd, J=7.0, 1.5 Hz, aromatic H), 7.26—7.50 (6H, m, aromatic H), 11.6 (1H, s, –OH). High-resolution MS m/z: Calcd for $C_{14}H_{14}O_2$ (M^+): 212.0848. Found: 212.0859. The second eluate with 30% hexane in chloroform gave 39.9 mg (43.3%) of 4-hydroxy-2-methylbenzophenone (**17**) as a colorless oil. IR (neat) cm^{-1}: 3300, 1630, 1595, 1565, 1500. ^{1}H-NMR ($CDCl_3$) δ: 2.37 (3H, s, –Me), 6.12 (1H, br, –OH), 6.68 (1H, dd, J=8.4, 2.4 Hz, aromatic H), 6.75 (1H, d, J=2.4 Hz, aromatic H), 7.23—7.82 (6H, m, aromatic H). CI-MS m/z: 240 (M^++1).

4-Acetoxy-2-methylbenzophenone (18) Acetic anhydride (1.8 ml) was added to a solution of **17** (53 mg) in pyridine (0.6 ml) and the whole was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with saturated $NaHCO_3$, 10% HCl, and water, then dried and concentrated. The residue was subjected to silica gel chromatography. The eluate with 50% hexane in ethyl acetate gave 54 mg (85%) of **18** as a colorless oil. IR (neat) cm^{-1}: 1770, 1668, 1602, 1585, 1500. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s, –Me), 2.28 (3H, s, –Me), 6.92 (1H, dd, J=8.6, 2.2 Hz, aromatic H), 6.96 (1H, d, J=2.2 Hz, aromatic H), 7.19—7.54 (4H, m, aromatic H), 7.74 (2H, dd, J=7.8, 1.9 Hz, aromatic H). High-resolution MS m/z: Calcd for $C_{16}H_{14}O_3$ (M^+): 254.0943. Found: 254.0978.

Ethyl 6-Phenylsalicylate (6) Method C: Sodium hydride (55%, 52 mg) was added to a solution of ethyl acetoacetate (163 mg) in dry THF (3 ml) with stirring at 0 °C under a nitrogen atmosphere and the whole was stirred at 0 °C for 10 min. To the resulting mixture, a solution of 1.36 M butyl lithium in hexane (1.2 ml) was added, and the whole was stirred at 0 °C for 10 min under the same conditions. The enaminone **1** (200 mg) was then added, and the reaction mixture was stirred further at room temperature for 1 h under the same conditions, poured into ice-water, acidified with 10% HCl, and extracted with ether. The organic layer was washed with brine, dried and concentrated. The residue was dissolved in dry toluene (6.5 ml), potassium fluoride (104 mg) was added to the solution, and then the whole was refluxed overnight. The reaction mixture was concentrated under a vacuum, poured into ice-water, and extracted with chloroform. The organic layer was washed with water, then dried and concentrated. The residue was subjected to silica gel chromatography. The benzene eluate gave 41 mg (14.8%) of **6** as a colorless oil. IR (neat) cm^{-1}: 1658, 1598, 1566. ^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, t, J=7.3 Hz, –Me), 3.98 (2H, q, J=7.3 Hz, methylene H), 6.79 (1H, dd, J=7.3, 1.2 Hz, aromatic H), 6.99 (1H, dd, J=8.3, 1.2 Hz, aromatic H), 7.16—7.48 (6H, m, aromatic H), 10.79 (1H, s, –OH). High-resolution MS m/z: Calcd for $C_{15}H_{14}O_3$ (M^+): 242.0941. Found: 242.0928.

Method D: Sodium hydride (55%, 66 mg) was added to a solution of ethyl acetoacetate (325 mg) in dry THF (3 ml) with stirring at 0 °C under a nitrogen atmosphere and the whole was stirred similarly for an additional 10 min. A solution of 1.36 M butyl lithium in hexane (2.3 ml) was added to the mixture and the whole was stirred at 0 °C for 10 min under the same conditions. To the resultant solution, a solution of the enaminone **1** (52.5 mg) and $BF_3 \cdot OEt_2$ (0.4 ml) in dry THF (2 ml) was added, and the mixture was stirred at 0 °C for 1 h. The reaction mixture was worked up as described under method C to yield 24 mg (33.1%) of **6**.

Ethyl 6-Styrylsalicylate (19) Compound **19** was obtained as a colorless oil from the enaminone **2** by methods C and D described above in yields of 24.0 and 41.0%, respectively. IR (neat) cm^{-1}: 1678, 1622, 1598, 1520. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7.1 Hz, –Me), 4.45 (2H, q, J=7.1 Hz, methylene H), 6.80 (1H, d, J=16.3 Hz, olefinic H), 6.90—7.50 (8H, m, aromatic H), 7.76 (1H, d, J=16.3 Hz, olefinic H), 11.30 (1H, s, –OH). High-resolution MS m/z: Calcd for $C_{17}H_{16}O_3$ (M^+): 268.1098. Found: 268.1083.

3,4-Dihydro-8-hydroxy-3-phenylisocoumarin (20) A solution of **19** (16 mg) in concentrated H_2SO_4 (0.4 ml) was stirred at 0 °C for 2 h. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, then dried and concentrated. The residue was recrystallized from ether–hexane to yield 10 mg (69.9%) of **20** as colorless prisms, mp 108—109.5 °C (lit.[11] mp 108—109.5 °C).

References and Notes

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