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Reactivity of 2-Methylene-1,3-dicarbonyl Compounds. Syntheses of 2,2,3-Trisubstituted-3,4-dihydro-2*H*-pyrano[3,2-*c*][1]benzopyran-5-ones

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Michael condensation of 2-methylsulfinylmethyl-1,3-dicarbonyl compounds (**3**) or 2-methylene-1,3-dicarbonyl compounds (**4**) with 4-hydroxycoumarin (**5**) at ambient temperature gave 2-[(4-hydroxycoumarin-3-yl)methyl]-1,3-dicarbonyl compounds (**6**). Treatment of **6** with methanolic hydrogen chloride resulted in the regioselective formation of 2,2,3-trisubstituted-3,4-dihydro-2*H*-pyrano[3,2-*c*][1]benzopyran-5-ones.

Keywords——2-methylene-1,3-dicarbonyl compound; 2-methylsulfinylmethyl-1,3-dicarbonyl compound; 2,2,3-trisubstituted-3,4-dihydro-2*H*-pyrano[3,2-*c*][1]benzopyran-5-one; regioselective cyclization; Michael condensation

Recently we reported a method for the methylenation of 1,3-dicarbonyl compounds by using methylthiomethyl piperidine hydrochloride (Chart 1).[1] Although only a few reports have been published[2,3] on the preparation of 2-methylene-1,3-dicarbonyl compounds (**4**), they seem to be reactive synthetic intermediates as dienophiles[3] or heterodienes[4] in the Diels–Alder reaction and as electrophiles in various kind of carbon–carbon bond-forming reactions. We report herein that Michael condensation of **4** with 4-hydroxycoumarin (**5**)[5] followed by acid treatment gave 2,2,3-trisubstituted-3,4-dihydro-2*H*-pyrano[3,2-*c*] [1]-benzopyran-5-ones regioselectively but not stereoselectively.

2-Methylene-1,3-dicarbonyl compounds (**4**) were treated with 4-hydroxycoumarin (**5**) in pyridine to give polycarbonyl compounds (**6**) (Table I). The structure of **6** was clearly confirmed by the appearance of the pair of methine (triplet) and methylene (doublet) signals in the proton magnetic resonance (PMR) spectra. The poly carbonyl compounds (**6**) were also

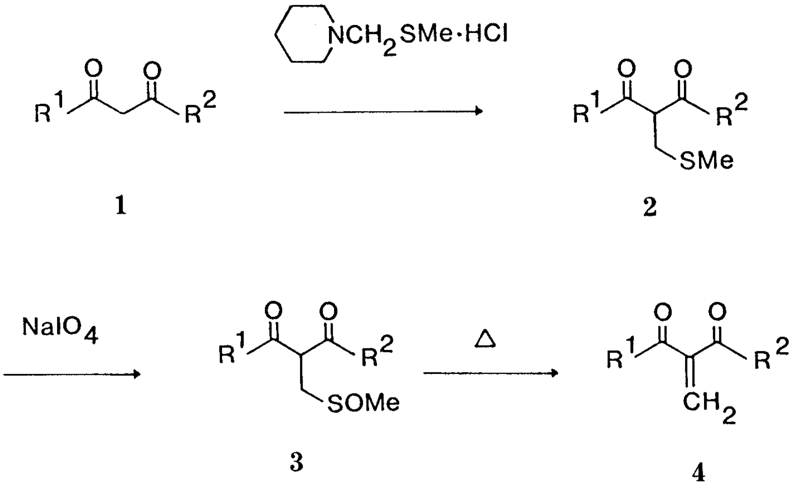
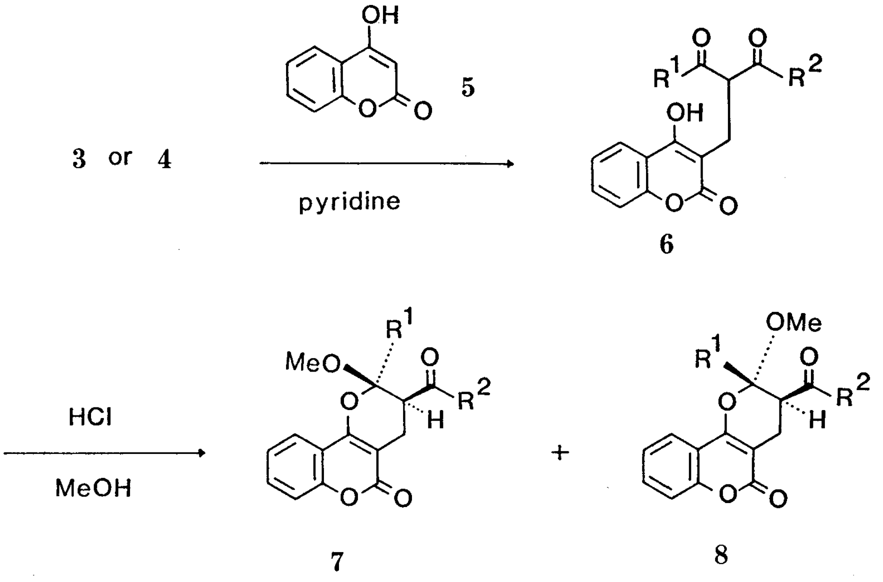


Chart 1

TABLE I. Yields, Analytical Data, and Physical Properties of **6**

Compd.	Yield (%)		mp (°C) Recrystn. solvent	Analysis (%) Calcd (Found)		IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}	PMR ($CDCl_3$) δ
	from **3**	from **4**		C	H		
6a	81	62	174—176 C_6H_6	71.41 (71.16	4.80 4.97)	1710, 1630, 1600	2.32 (3H, s, CH_3), 3.04 (2H, d, $J=7$ Hz, $=C-CH_2-$), 5.05 (1H, t, $J=7$ Hz, $-CH(CO)_2$), 7.20—8.43 (9H, m, aromatic H)
6b	82	76	192—193.5 C_6H_6/ *n*-hexane	75.36 (75.28	4.56 4.73)	1690, 1675, 1625, 1600	3.24 (2H, d, $J=7$ Hz, $=C-CH_2-$), 5.83 (1H, t, $J=7$ Hz, $-CH(CO)_2$), 7.22—8.42 (14H, m, aromatic H)
6c	74	—	91—92 C_6H_6/ *n*-hexane	65.87 (65.88	6.41 6.23)	1720, 1650	0.92 (6H, d, $J=6$ Hz, $-CH(C\underline{H}_3)_2$), 1.42—1.88 (3H, m, $-C\underline{H}_2C\underline{H}(CH_3)_2$), 2.42 (3H, s, $COCH_3$), 2.99 (2H, d, $J=7$ Hz, $=C-CH_2-$), 4.03 (1H, t, $J=7$ Hz, $-CH(CO)_2$), 4.22 (2H, t, $J=6$ Hz, $-OCH_2-$)
6d	72	70	111—113 C_6H_6/ *n*-hexane	68.84 (69.02	4.96 5.05)	1708, 1685, 1628, 1610	1.20 (3H, t, $J=8$ Hz, CH_3), 3.13 (2H, d, $J=7$ Hz, $=C-CH_2-$), 4.23 (2H, q, $J=8$ Hz, $-OCH_2-$), 4.87 (1H, t, $J=7$ Hz, $-CH(CO)_2$), 7.17—8.50 (9H, m, aromatic H), 9.65 (1H, s, enolic OH)



a: $R^1=Me$, $R^2=Ph$
b: $R^1=Ph$, $R^2=Ph$
c: $R^1=Me$, $R^2=O$-isoAm
d: $R^1=Ph$, $R^2=OEt$

Chart 2

TABLE II. Cyclization of 2-[(4-Hydroxycoumarin-3-yl)methyl]-1,3-dicarbonyl Compounds (**6**)

Substrate	Products	
	Yield[a]	(**7**:**8**)
6a	85	(68:32)[b]
6b	68	(49:51)[b]
6c	98	(45:55)[c]

a) Isolated yields.
b) Based on the isolated diastereomeric isomers.
c) Determined from the C-2 methoxyl signals in the PMR spectrum.

TABLE III. Analytical Data and Physical Properties of **7** and **8**

Compd.	mp (°C) Recrystn. solvent	Analysis (%) Calcd (Found)		IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}	PMR (CDCl$_3$) δ
		C	H		
7a	153—154 C_6H_6	72.00 (72.08	5.20 5.18)	1700, 1682, 1637, 1610, 1598	1.75 (3H, s, CH$_3$), 2.81 (1H, q, $J_{4a,4e}$= 17.1 Hz, $J_{4a,3}$=12.2 Hz, H-4a), 3.04 (1H, q, $J_{4e,4a}$=17.1 Hz, $J_{4e,3}$=5.4 Hz, H-4e), 3.46 (3H, s, OCH$_3$), 3.94 (1H, q, $J_{3,4a}$= 12.2 Hz, $J_{3,4e}$=5.4 Hz, H-3), 7.30—8.15 (9H, m, aromatic H)
7b	224—225.5 C_6H_6	75.71 (75.90	4.90 5.11)	1697, 1683, 1635, 1610, 1597	2.68 (1H, q, $J_{4a,4e}$=17.5 Hz, $J_{4a,3}$=11.3 Hz, H-4a), 3.33 (1H, q, $J_{4e,4a}$=17.5 Hz, $J_{4e,3}$=5.3 Hz, H-4e), 3.38 (3H, s, OCH$_3$), 4.11 (1H, q, $J_{3,4a}$=11.3 Hz, $J_{3,4e}$=5.3 Hz, H-3), 7.26—8.25 (14H, m, aromatic H)
8a	165.5—167.5 C_6H_6	72.00 (71.85	5.20 5.34)	1695, 1675, 1628, 1610, 1597	1.70 (3H, s, CH$_3$), 2.83 (1H, q, $J_{4a,4e}$= 17.8 Hz, $J_{4a,3}$=7.2 Hz, H-4a), 3.02 (1H, q, $J_{4e,4a}$=17.8 Hz, $J_{4e,3}$=5.2 Hz, H-4e), 3.50 (3H, s, OCH$_3$), 4.17 (1H, q, $J_{3,4a}$= 7.2 Hz, $J_{3,4e}$=5.2 Hz, H-3), 7.31—8.18 9H, m, aromatic H)
8b	222—225 C_6H_6	75.71 (75.74	4.90 5.05)	1720, 1685, 1642, 1615, 1595	2.82 (1H, q, $J_{4a,4e}$=17.7 Hz, $J_{4a,3}$=7.9 Hz, H-4a), 3.20 (1H, q, $J_{4e,4a}$=17.7 Hz, $J_{4e,3}$=1.1 Hz, H-4e), 3.21 (3H, s, OCH$_3$), 4.49 (1H, q, $J_{3,4a}$=7.9 Hz, $J_{3,4e}$=1.1 Hz, H-3), 7.23—8.25 (14H, m, aromatic H)
7c and **8c**		High resol. MS, Calcd for $C_{20}H_{24}O_6$ (M$^+$): 360.1571. Found: 360.1555.			

obtained by the reaction of 2-methylsulfinylmethyl-1,3-dicarbonyl compounds (**3**) with **5** in somewhat better yields (Table I). It is noteworthy that **6c** was only obtainable from **3c**, since pyrolysis of **3c** gave complex products from which **4c** was not isolated.

Treatment of the poly carbonyl compounds (**6**) with dry hydrogen chloride in absolute methanol at ambient temperature afforded a mixture of diastereomeric 2,2,3-trisubstituted-3,4-dihydro-2*H*-pyrano[3,2-*c*] [1]benzopyran-5-ones (**7** and **8**) (Table II). Compound (**6d**) was not converted to the corresponding pyranobenzopyran under the same reaction conditions as **6a**—**c**, and gave unidentified complex products at higher temperature. In the cases of **7a**, **8a** and **7b**, **8b**, the diastereomeric isomers were separated by means of preparative thin layer chromatography (TLC); **7c** and **8c** could not be separated by preparative TLC or preparative centrifugally accelerated chromatography (Chromatotron) or medium pressure column chromatography. The regioselective cyclization of **6a**, **c** was confirmed by the appearance of the methyl signals at *ca.* 1.7—1.9 ppm instead of the disappearance of the acetyl group in the PMR spectra of **7a**, **c** and **8a**, **c**. The relative stereochemistry at the two chiral centers of **7a** and **8a** was supported by the observance of about 15% nuclear Overhauser effect (NOE) between the C_2-methyl and C_3-proton in **7a** but not in **8a**. Furthermore, the signal of the C_3-proton in **8a** appeared at lower field than that in **7a** due to the anisotropy of the *cis*-oriented C_2-methoxyl group (Table III). The two diastereomeric isomers from cyclization of **6b**, having the structures **7b** and **8b**, are characterized by the appearance of the C_3-proton centered at δ 4.11 in **7b** and δ 4.49 in **8b**, identical in pattern with the C_3-protons in **7a** and **8a**.

Experimental[6)]

General Procedure for the Preparation of 2-[(4-Hydroxycoumarin-3-yl)methyl]-1,3-dicarbonyl Compounds (6)——a) From 2-Methylsulfinylmethyl-1,3-dicarbonyl Compounds (**3**): A solution of 4-hydroxycoumarin (4.0 mmol) in pyridine (12 ml) was added to a solution of 2-methylsulfinylmethyl-1,3-dicarbonyl compound (**3**; 2.0 mmol) in benzene (25 ml). Stirring was continued at ambient temperature for 18 h, then the reaction mixture was poured into cold 15% hydrochloric acid (60 ml) and extracted with ethyl acetate (3 × 30 ml). The ethyl acetate layer was washed with cold 15% hydrochloric acid (2 × 20 ml) and water (3 × 20 ml), then dried, and concentrated. The residue was subjected to column chromatography (Kieselgel 60, 70—230 mesh, Merck) using benzene as the eluent to afford the corresponding 2-[(4-hydroxycoumarin-3-yl)methyl]-1,3-dicarbonyl compound (**6**).

b) From 2-Methylene-1,3-dicarbonyl Compounds (**4**): A mixture of 2-methylene-1,3-dicarbonyl compound (**4**; 0.25 mmol) and 4-hydroxycoumarin (**5**; 0.29 mmol) in pyridine (5 ml) was stirred at ambient temperature for 24 h. The reaction mixture was poured into cold 5% hydrochloric acid (50 ml) and extracted with ethyl acetate (3 × 15 ml). The ethyl acetate layer was washed with cold 5% hydrochloric acid (2 × 10 ml) and water (3 × 10 ml), then dried, and concentrated. The resulting residue was subjected to column chromatography (Kieselgel 60, 70—230 mesh, Merck) using benzene as the eluent to afford the corresponding 2-[(4-hydroxycoumarin-3-yl)methyl]-1,3-dicarbonyl compound (**6**). The yeilds and the physical data are summarized in Table I.

General Procedure for the Preparation of 2,2,3-Trisubstituted-3,4-dihydro-2*H*-pyrano[3,2-*c*][1]benzopyran-5-ones (7 and 8)——A suspension of 2-[(4-hydroxycoumarin-3-yl)methyl-1,3-dicarbonyl compound (**6**; 1.0 mmol) in absolute methanol (50 ml) was treated with 8 ml of 32 w/w% hydrogen chloride in absolute methanol at 0 °C. Stirring was continued at the same temperature for 3 h (the precipitate disappeared within 30 min), then the reaction mixture was concentrated under reduced pressure. The residue was dissolved in C_6H_6/Et_2O (1:5) mixture (50 ml), washed with saturated $NaHCO_3$ solution (2 × 20 ml) and water (3 × 20 ml), and dried. Evaporation of the solvent gave a diastereomeric mixture of 3,4-dihydro-2*H*-pyrano[3,2-*c*] [1]benzopyran-5-ones (**7** and **8**). The diastereomers, **7a**, **8a** or **7b**, **8b**, were separated by preparative TLC (Kieselgel 60 PF_{254}, Merck) with *n*-hexane/CH_2Cl_2 (1:9). These results are summarized in Tables II and III.

References and Notes

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6) All melting points are uncorrected. The infrared (IR) spectra were recorded on a Hitachi 215 spectrometer, high resolution mass spectra with a JEOL JMS-01SG instrument. The PMR spectra were determined with a JEOL PS-100 spectrometer, with tetramethylsilane as an internal reference. Extracts were dried over anhyd. $MgSO_4$.