Convenient Synthesis of a Simple Coumarin from Salicylaldehyde and Wittig Reagent. II[1a]: Synthesis of Bromo- and Methoxycarbonylcoumarins

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Reaction of salicylaldehydes (1) with carbethoxymethylenetriphenylphosphorane in diethylaniline under reflux gave coumarins (3) in moderate to high yield except 3-methoxycarbonylsalicylaldehyde (1e) as summarized in Table I. The substituent effects are discussed. A substituent at C_6 on 1 usually facilitated the formation of the coumarin ring regardless of its electronic character.

Keywords salicylaldehyde; coumarin synthesis; Wittig reaction; substituent effect; bromocoumarin; methoxycarbonylcoumarin

Coumarins constitute an important class of naturally occurring compounds, some of which show various biological activities.[2] Many synthetic methods for coumarins (**3**) have been developed,[3] and we recently reported a convenient and effective synthetic method for simple (3,4-unsubstituted) coumarins by the Wittig reaction of salicylaldehydes (**1**) with carbethoxymethylenetriphenylphosphorane ($Ph_3P=CHCO_2Et$) in *N*,*N*-diethylaniline (Et_2NPh) under reflux,[1] as a modification of Mali's method.[4] The presence of C_4- and C_6-methoxy (hydroxy) groups on salicylaldehyde accelerated the formation of coumarin from *trans*-cinnamate and a plausible mechanism for the acceleration by the C_4-methoxy group is shown in Chart 1. According to this mechanism, an electron-withdrawing group at C_4 (and/or C_6) on salicylaldehyde (**1**) should retard the formation of the coumarin (**3**) from *trans*-cinnamate (**2**). Then, in order to examine the generality of our method and the effect of substituent groups on a coumarin ring formation, we planned to investigate the Wittig reaction of **1** having a bromo or methoxycarbonyl group with $Ph_3P=CHCO_2Et$. We have briefly described the results.[5] The details are the subject of this paper.

Results and Discussion

Reaction of bromo- and methoxycarbonylsalicylaldehydes (**1a—d** and **1e—h**) with $Ph_3P=CHCO_2Et$ in Et_2NPh under reflux (at 210—215 °C) was examined. The results are summarized in Table I, including those obtained with methoxysalicylaldehydes (**1i—l**)[4,5] for comparison. As can be seen from Table I, the present method usually produced a corresponding coumarin (**3**) from **1** in moderate to high yield regardless of the position and electronic character of the substituent group, except in the case of **1e**.

Bromosalicylaldehydes (**1a** and **1c**) yielded a debrominated product, the coumarin (**3m**), in 3% yield, whereas **1b** and **1d** yielded no debrominated product.[6] Interestingly, 3-methoxycarbonylsalicylaldehyde (methyl 3-formyl-2-hydroxybenzoate) (**1e**)[7] produced no coumarin, but gave the cinnamate (**2e**) and the unexpected diethyl ester (**4**) (run 5). It was assumed that the newly introduced ethyl group of **4** came from Et_2NPh , because reaction of **1e** with $Ph_3P=CHCO_2Me$ in Et_2NPh under reflux for 6 h produced an ester-exchanged product (**5**) in 46% yield along with a usual product (**6**)[8] in 19% yield. The structure of **5** was elucidated on the basis of ^1H–^{13}C long-range correlation spectroscopy (COSY) ($J=10$, 5 Hz) spectra, especially the observation of long-range coupling between the carbonyl group of CO_2Et (δ 170.2) and C_4-H (δ 7.89). Furthermore, reaction of **1e** with $Ph_3P=CHCO_2Et$ in the absence of solvent for 6 h at

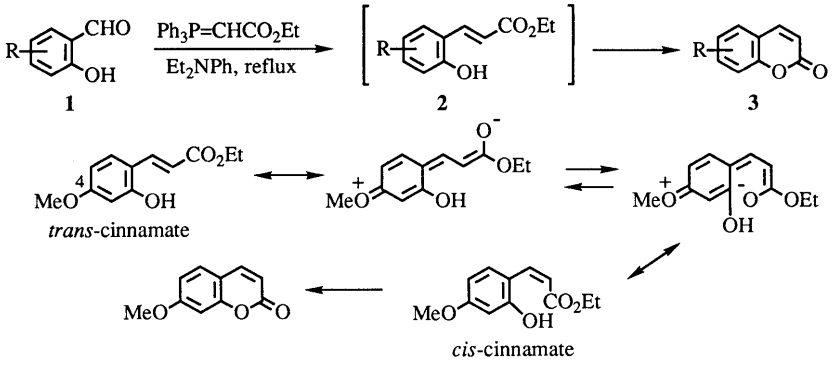
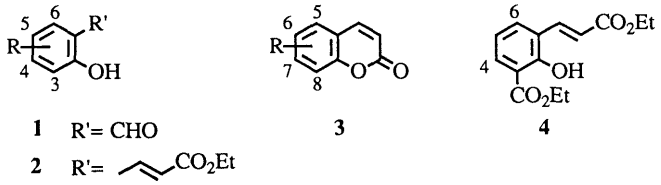


Chart 1

210—215 °C produced **2e** and **4** in 55% and 6% yields, respectively, proving that the origin of the ethyl group for ester exchange is mainly Et_2NPh used as the solvent (see Chart 3). Salicylaldehydes (**1f—h**) having a methoxycarbonyl group at a position other than C_3 produced the expected coumarins (**3f—h**) in high yield (see Table I) and no ester-exchanged product. Therefore, this ester exchange was characteristic of 3-methoxycarbonylsalicylaldehyde (**1e**), which has a methyl salicylate moiety.[9] However, the mechanism involved remains to be clarified.



1 R'= CHO
2 R'= $CH=CHCO_2Et$

3

4

a R = 3-Br	**a** R = 8-Br
b R = 4-Br	**b** R = 7-Br
c R = 5-Br	**c** R = 6-Br
d R = 6-Br	**d** R = 5-Br
e R = 3-CO_2Me	**e** R = 8-CO_2Me
f R = 4-CO_2Me	**f** R = 7-CO_2Me
g R = 5-CO_2Me	**g** R = 6-CO_2Me
h R = 6-CO_2Me	**h** R = 5-CO_2Me
i R = 3-OMe	**i** R = 8-OMe
j R = 4-OMe	**j** R = 7-OMe
k R = 5-OMe	**k** R = 6-OMe
l R = 6-OMe	**l** R = 5-OMe
	m R = H

Chart 2

TABLE I. The Results of Reaction of Salicylaldehydes (**1**) with Carbethoxymethylenetriphenylphosphorane in Et_2NPh under Reflux[a]

Run	Starting materials	Time	Products (%)	
			2/3	Other
1	3-Br (**1a**)	3 h	0/59	**3m** (3)
2	4-Br (**1b**)	3.5 h	0/75	
3	5-Br (**1c**)	3 h	0/65	**3m** (3)
4	6-Br (**1d**)	15 min	0/81	
5	3-CO_2Me (**1e**)	6 h	22/ 0	**4** (46)
6	4-CO_2Me (**1f**)	6 h	0/70	
7	5-CO_2Me (**1g**)	2.5 h	0/77	
8	6-CO_2Me (**1h**)	20 min	0/96	
9	3-OMe (**1i**)	6 h	11/81[b]	
10	4-OMe (**1j**)	15 min	0/95[b]	
11	4-OMe (**1k**)	2.5 h	0/93[b]	
12	6-OMe (**1l**)	20 min	0/90[b]	

a) Isolated yield. b) See reference 1.

In conclusion, the methoxycarbonyl group at C_3 on **1** disfavors the formation of a coumarin ring owing to steric hindrance. An electron-withdrawing group at C_4 such as a bromo or methoxycarbonyl group retards the formation of a coumarin ring, in contrast to an electron-donating group such as a methoxy group (runs 2, 6, and 10), supporting our mechanism shown in Chart 1. A substituent group at C_5 has little influence on the rate of coumarin ring formation (runs 3, 7, and 11). A substituent group at C_6 facilitates the formation of **3** irrespective of its electronic character (see runs 4, 8, and 12). A steric repulsion between the substituent group at C_6 and the propenoate side chain might favor the formation of a coumarin ring from *cis*-cinnamate and/or the formation of *cis*-cinnamate in the Wittig reaction of salicylaldehyde (**1**).[10]

Preparation of Salicylaldehydes (1) The silver salt of 3-formyl-2-hydroxybenzoic acid, prepared from 3-methyl-2-hydroxybenzoic acid by Eliels' method,[11] was methylated with methyl iodide to produce **1e**[7] in 60% yield.

The Duff reaction of methyl 3-hydroxybenzoate with hexamethylenetetramine in 75% polyphosphoric acid gave two products, methyl 2-formyl-3-hydroxybenzoate (**1h**)[12] and methyl 4-formyl-3-hydroxybenzoate (**1f**)[13] in 40% and 5% yields, respectively, differing from the reported result.[12]

Experimental

Melting points were measured on a micro melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded in Nujol on a JASCO A-102 spectrometer and ^{1}H-NMR spectra in deuteriochloroform on a Hitachi R-1500 (60 MHz), Varian VXR-200 (200 MHz), or JEOL GSX-500 (500 MHz) spectrometer, unless otherwise stated. The ^{1}H-NMR data are reported in parts per million down field from tetramethylsilane as an internal standard (δ 0.0) and coupling constants are given in hertz. Column chromatography was carried out on silica gel (Merck, Silica gel 60, No. 9385). All experiments were carried out in an argon atmosphere and the extract was washed with brine, dried over anhydrous $MgSO_4$, then filtered, and the filtrate was evaporated to dryness under reduced pressure, unless otherwise noted. The synthetic samples were identified by comparison of spectral (^{1}H-NMR and IR) data with those of commercial or synthetic authentic samples or by comparison with physical data in the cited references.

Materials Compounds **1a**,[14] **1b**,[15] **1d**,[15] and **1g**[16] were prepared according to the literature. 5-Bromosalicylaldehyde (**1c**) is commercially available.

General Procedure for the Wittig Reaction of Salicylaldehydes (1) with Carbethoxymethylenetriphenylphosphorane Reaction of salicylaldehyde (**1**) (1 mmol) with the Wittig reagent (1.2 mmol) in Et_2NPh (10 ml) under reflux was carried out for the reaction time indicated in Table I. The reaction mixture was diluted with 5% HCl solution and extracted with

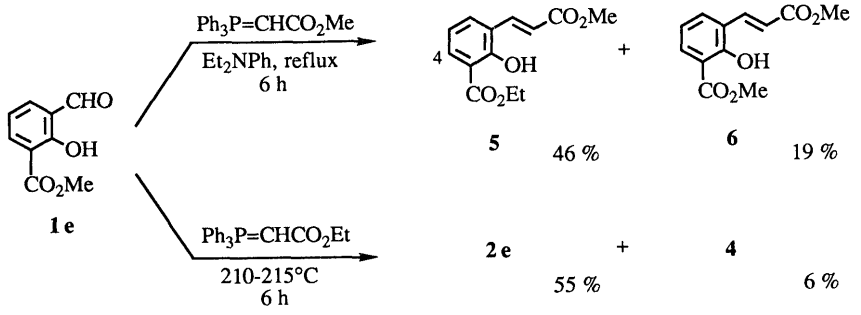


Chart 3

ether.

8-Bromocoumarin (3a) and Coumarin (3m) The residue in AcOEt was chromatographed on silica gel. Elution with hexane–AcOEt (7 : 1) gave **3a**, mp 136.5—137 °C (colorless needles from MeOH). *Anal.* Calcd for $C_9H_5BrO_2$: C, 48.04; H, 2.24. Found: C, 47.95; H, 2.10. IR cm^{-1}: 1735 (CO). ^{1}H-NMR (200 MHz) δ: 6.46 (1H, d, J=9.6 Hz, C_3-H), 7.17 (1H, t, J=7.6 Hz, C_6-H), 7.44 (1H, dd, J=7.8, 1.5 Hz, C_5-H), 7.71 (1H, d, J=9.6 Hz, C_4-H), 7.74 (1H, dd, J=7.8, 1.5 Hz, C_7-H). Further elution with the same solvent gave **3m**, mp 66—68 °C (lit.[17] mp 68—70 °C) (colorless prisms from CH_2Cl_2–hexane).

7-Bromocoumarin (3b) The residue in AcOEt was chromatographed on silica gel. Elution with hexane–AcOEt (8 : 1) gave **3b**, mp 122—124 °C (colorless needles from MeOH). *Anal.* Calcd for $C_9H_5BrO_2$: C, 48.04; H, 2.24. Found: C, 48.11; H, 2.24. IR cm^{-1}: 1725 (CO). ^{1}H-NMR (60 MHz) δ: 6.42 (1H, d, J=9.7 Hz, C_3-H), 7.38—7.47 (3H, m, aromatic protons), 7.68 (1H, d, J=9.7 Hz, C_4-H).

6-Bromocoumarin (3c) and Coumarin (3m) The residue in AcOEt was chromatographed on silica gel. Elution with hexane–AcOEt (5 : 1) gave **3c**, mp 165—167 °C (lit. mp 161—163 °C,[18a] 164 °C,[18b]) (colorless needles from MeOH). Further elution with the same solvent gave **3m**, mp 66—68 °C.

5-Bromocoumarin (3d) The residue in AcOEt was chromatographed on silica gel. Elution with hexane–AcOEt (8 : 1) gave **3d**, mp 94.5—96.5 °C (lit.[19] mp 97 °C) (colorless needles from MeOH).

Ethyl *trans*-3-Ethoxycarbonyl-2-hydroxycinnamate (4) and Ethyl *trans*-2-Hydroxy-3-methoxycarbonylcinnamate (2e) The residue in AcOEt was chromatographed on silica gel. Elution with hexane–AcOEt (50 : 1) gave **4**, mp 61—61.5 °C (colorless plates from EtOH). *Anal.* Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.76; H, 6.26. IR cm^{-1}: 3125 (OH), 1705 (CO), 1680 (CO). ^{1}H-NMR (60 MHz) δ: 1.34 (3H, d, J=7.0 Hz, $CO_2CH_2C\underline{H}_3$), 1.42 (3H, d, J=7.0 Hz, $CO_2CH_2C\underline{H}_3$), 4.31 (2H, d, J=7.0 Hz, $CO_2C\underline{H}_2CH_3$), 4.39 (2H, d, J=7.0 Hz, $CO_2C\underline{H}_2CH_3$), 6.61 (1H, d, J=16.4 Hz, $CH=C\underline{H}CO_2$), 6.89 (1H, t, J=7.6 Hz, C_5-H), 7.67 (1H, dd, J=7.6, 1.7 Hz, C_6-H), 7.89 (1H, dd, J=7.6, 1.7 Hz, C_4-H), 7.97 (1H, d, J=16.4 Hz, $C\underline{H}=CHCO_2$), 11.61 (1H, s, OH, exchangeable with D_2O). Further elution with the same solvent afforded **2e**, mp 73—74 °C (colorless needles from acetone). *Anal.* Calcd for $C_{13}H_{14}O_5$: C, 62.40; H, 5.64. Found: C, 62.36; H, 5.63. IR cm^{-1}: 3100 (OH), 1715 (CO), 1670 (CO). ^{1}H-NMR (60 MHz) δ: 1.34 (3H, d, J=7.0 Hz, $CO_2CH_2C\underline{H}_3$), 3.98 (3H, s, CO_2CH_3), 4.28 (2H, d, J=7.0 Hz, $CO_2C\underline{H}_2CH_3$), 6.62 (1H, d, J=16.4 Hz, $CH=C\underline{H}CO_2$), 6.90 (1H, t, J=7.6 Hz, C_5-H), 7.68 (1H, dd, J=7.6, 1.7 Hz, C_6-H), 7.88 (1H, dd, J=7.6, 1.7 Hz, C_4-H), 7.98 (1H, d, J=16.4 Hz, $C\underline{H}=CHCO_2$), 11.52 (1H, s, OH, exchangeable with D_2O).

7-Methoxycarbonylcoumarin (3f) The residue in CH_2Cl_2 was chromatographed on silica gel. Elution with hexane–CH_2Cl_2 (2 : 3) afforded **3f**, mp 182—183 °C (lit.[20] mp 173—175 °C) (pale yellow prisms from benzene).

6-Methoxycarbonylcoumarin (3g) The residue in CH_2Cl_2 was chromatographed on silica gel. Elution with hexane–AcOEt (3 : 1) afforded **3g**, mp 177.5—178 °C (lit.[21] mp 173—174 °C) (colorless needles from benzene).

5-Methoxycarbonylcoumarin (3h) The residue in CH_2Cl_2 was chromatographed on silica gel. Elution with hexane–CH_2Cl_2 (1 : 1) afforded **3h**, mp 143.5—144 °C (colorless needles from benzene). *Anal.* Calcd for $C_{11}H_8O_4$: C, 64.71; H, 3.95. Found: C, 64.78; H, 3.81. IR cm^{-1}: 1730 (CO). ^{1}H-NMR (60 MHz) δ: 3.98 (3H, s, CO_2CH_3), 6.51 (1H, d, J=10.0 Hz, C_3-H), 7.45—7.66 (2H, m, C_7-H and C_8-H), 7.95 (1H, dd, J=5.9, 2.9 Hz, C_6-H), 8.89 (1H, d, J=10.0 Hz, C_4-H).

Reaction of 1e with Carbomethoxymethylenetriphenylphosphorane in Et_2NPh A solution of **1e** (1.0 g, 5.55 mmol) and $Ph_3P=CHCO_2Me$ (2.23 g, 6.66 mmol) in Et_2NPh (55 ml) was heated at 215 °C for 6 h. The reaction mixture was diluted with water and extracted with ether. The extract was thoroughly washed with aqueous 5% HCl solution and then brine. The residue in CH_2Cl_2 was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (50 : 1) afforded methyl *trans*-3-ethoxycarbonyl-2-hydroxycinnamate (**5**) (636 mg, 46% yield), mp 82.5—83.5 °C (colorless prisms from acetone). *Anal.* Calcd for $C_{13}H_{14}O_5$: C, 62.40; H, 5.64. Found: C, 62.27; H, 5.61. IR cm^{-1}: 1705 (CO), 1680 (CO). ^{1}H-NMR (400 MHz) δ: 1.42 (3H, d, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$), 3.81 (3H, s, CO_2CH_3), 4.43 (2H, d, J=7.1 Hz, $CO_2C\underline{H}_2CH_3$), 6.64 (1H, d, J=16.2 Hz, $CH=C\underline{H}CO_2Me$), 6.90 (1H, t, J=7.8 Hz, C_5-H), 7.70 (1H, dd, J=7.8, 1.7 Hz, C_6-H), 7.89 (1H, dd, J=7.8, 1.7 Hz, C_4-H), 7.97 (1H, d, J=16.2 Hz, $C\underline{H}=CHCO_2$), 11.63 (1H, s, OH, exchangeable with D_2O). ^{13}C-NMR (100 MHz) δ: 14.1 ($CO_2CH_2\underline{C}H_3$), 51.6 ($CO_2\underline{C}H_3$), 61.8 ($CO_2\underline{C}H_2CH_3$), 113.2 (C_1), 118.9 (C_5), 119.4 ($CH=\underline{C}HCO_2$), 123.3 (C_3), 131.8 (C_4), 134.8 (C_6), 139.0 ($\underline{C}H=CHCO_2$), 160.7 (C_2), 167.7 ($\underline{C}O_2Me$), 170.2 ($\underline{C}O_2Et$). Further elution with the same solvent afforded methyl *trans*-2-hydroxy-3-methoxycarbonylcinnamate (**6**) (255 mg, 19% yield), mp 82—83 °C (lit.[8] mp 86—87 °C) (colorless needles from acetone–MeOH).

Reaction of 1e with Carbethoxymethylenetriphenylphosphorane without Solvent A solution of **1e** (1.0 g, 5.55 mmol) and $Ph_3P=CHCO_2Et$ (2.32 g, 6.66 mmol) was heated at 210—215 °C for 6 h. The reaction mixture in CH_2Cl_2 was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (50 : 1) gave **4** (94 mg, 6% yield), mp 61—62 °C. Further elution with the same solvent gave **2e** (761 mg, 55% yield), mp 73—74 °C.

Methyl 3-Formyl-2-hydroxybenzoate (1e) A solution of NaOH (0.24 g, 6 mmol) in distilled water (5.7 ml) was added to a stirred suspension of 3-formyl-2-hydroxybenzoic acid (1.0 g, 6 mmol) in distilled water (11.3 ml). A solution of $AgNO_3$ (1.1 g, 6.5 mmol) in distilled water (2.8 ml) was then added to the clear reaction mixture with stirring. The precipitate was collected by filtration and triturated twice successively with distilled water, absolute EtOH, and ether, and then dried in a desiccator under reduced pressure at 50 °C for 3 h. The silver salt suspended in dry ether (7 ml) was treated with methyl iodide (0.6 ml, 9.6 mmol) under reflux for 1.5 h. The precipitate was filtered off and the filtrate was concentrated to dryness *in vacuo*. The residue in AcOEt was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (8 : 1) gave **1e** (655 mg, 60% yield), mp 86 °C (lit.[7] mp 87 °C) (colorless needles from benzene).

The Duff Reaction of Methyl 3-Hydroxybenzoate Hexamethylenetetramine (7.0 g, 50 mmol) was added to a stirred solution of methyl 3-hydroxybenzoate (7.6 g, 50 mmol) in 75% polyphosphoric acid (40 ml) at 100 °C and the reaction mixture was stirred for 45 min. After cooling, the mixture was diluted with cold water and extracted with CH_2Cl_2. The residue in CH_2Cl_2 was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (9 : 1) provided **1h** (3.58 g, 40% yield), mp 56 °C (lit.[12] mp 53—54 °C) (pale yellow needles from MeOH). Further elution with the same solvent provided **1f** (0.44 g, 5% yield), mp 134—135 °C (lit.[13] 135—135.5 °C) (pale yellow needles from MeOH).

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