A CONVENIENT SYNTHESIS OF A SIMPLE COUMARIN FROM SALICYLALDEHYDE AND WITTIG REAGENT (I): A SYNTHESIS OF METHOXY- AND HYDROXYCOUMARINS§

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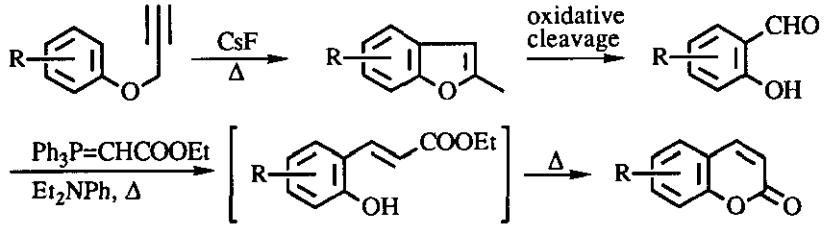
Abstract---Reaction of methoxy- and hydroxysalicylaldehydes (**1**) with phosphorane in diethylaniline under reflux gave only coumarins (**3**) in high yields except for 3-methoxysalicylaldehyde (**1b**). It was clarified that methoxy group(s) at C_4 and C_6 on **1** facilitated the formation of **3**.

Coumarins are widely distributed in nature[1] and have been reported to show various biologically interesting activities.[2] Although many synthetic methods to coumarins, especially to simple (3,4-unsubstituted) coumarins including the Perkin, Knoevenagel, and Pechmann reactions, are known,[3] much effort is still being devoted to developing new synthetic methods,[4] since they lack a generality and efficiency. Recently we reported new



Scheme 1

§ Dedicated to Dr. Arnold Brossi on the occasion of his 70th birthday.

synthetic methods of salicylaldehydes (**1**) *via* formation of benzofuran by CsF-mediated Claisen rearrangement of aryl propargyl ether followed by oxidative cleavage of furan ring,[5] being suitable for synthesizing aromatic compounds (salicylaldehydes) with successive substituents. Therefore, we planned to develop a general and convenient method for synthesis of simple coumarins by Wittig reaction of salicylaldehydes (**1**) with carbethoxymethylenetriphenylphosphorane (phosphorane). We have briefly described the results.[6] The details are the subject of this paper.

RESULTS AND DISCUSSION

Concerning with coumarin synthesis using Wittig reaction, Mali *et al.* reported a method by heating of **1** with phosphorane (the Wittig reagent) without solvent at 210-215°C.[7] Since reaction conditions of this method were severe and investigation of its generality was also insufficient, we planned to re-examine the Mali's method in order to improve the reaction conditions and investigate the effect(s) of substituent(s) on salicylaldehyde (**1**) to the formation of coumarin ring.

Since natural coumarins usually have a methoxy group at C_7 on coumarin ring, reaction of 4-methoxysalicylaldehyde (**1c**) with phosphorane at various temperatures was first examined. The results are summarized in Table I, showing that yield of coumarin (**3c**)[7c] rises as reaction temperature becomes high. Thus, reaction of **1c** with phosphorane in diethylaniline (Et_2NPh) under reflux (215°C), for only 15 min, afforded **3c** in 95% yield, whereas reaction of **1c** in pyridine under reflux (115°C) even for 4 h, afforded **3c** in 9% yield along with **2c**[8] in 89% yield (see runs 3 and 5 in Table I). Heating of **2c** in Et_2NPh at 140°C for 4 h gave **3c** in 42% yield with the recovery of **2c** in 36% yield, suggesting that basicity of solvent does not contribute to ease of coumarin ring formation in comparison with the result of run 4 in Table I. Next, in order to compare our method (in Et_2NPh at 215°C) with Mali's method (neat at 215°C), reaction of **1b** and **1j**[9] with phosphorane was performed. The results including **1c** are summarized in Table II. On using our method, coumarin (**3**) was obtained in a somewhat higher yield as can be seen from Table II and isolation of products was much easier. Natural coumarins commonly have alkoxy and/or hydroxy groups. In connection with synthetic studies on new coumarins, we successively investigated reaction of methoxy- and hydroxysalicylaldehydes (**1**) including salicylaldehyde (**1a**) itself with the Wittig reagent in Et_2NPh under reflux. The results are summarized in Table III. The Table shows that an electron-donating substituent such as methoxy or hydroxy group accelerates the formation of coumarin ring except for C_3-OMe group. The substituents at C_4 and C_6 on salicylaldehyde (**1**),

Table I. The Results of Reaction of 4-Methoxysalicylaldehyde (**1c**) with Carbethoxymethylenetriphenylphosphorane at Various Temperatures

Run	Solvent	Temperature	Time	Product (%)[a] **2c / 3c**
1	Benzene	room temperature	4 h	88 / 5
2	Benzene	Reflux (80°C)	4 h	91 / 7
3	Pyridine	Reflux (115°C)	4 h	89 / 9
4	Xylene	Reflux (140°C)	4 h	43 / 42
5	Diethylaniline	Reflux (215°C)	15 min	0 / 95

a) Isolated yield.

Table II. The Results of Reaction of Salicylaldehyde (**1**) with Phosphorane at 210—215℃

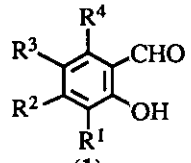
Run	Starting material	Reaction conditions Solvent	Time	Product (%)[a] **2 / 3**
1	**1b**	Diethylaniline	6 h	11 / 81
2	**1b**	- - -	6 h	5 / 70
3	**1c**	Diethylaniline	15 min	0 / 95
4	**1c**	- - -	5 h	0 / 71[b]
5	**1j**	Diethylaniline	30 min	0 / 90[c]
6	**1j**	- - -	10 min	0 / 75

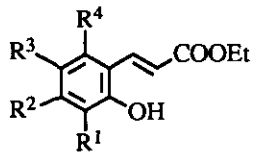
a) *Isolated yield.*
b) See ref. 7c.
c) See ref. 9.

Table III. The Results of Reaction of Salicylaldehyde (**1a-i**) with Phosphorane in Et_2NPh under Reflux.

Position of Substituent	H			OMe			OH		
		Time	Product (%)[a] **2 / 3**		Time	Product (%)[a] **2 / 3**		Time	Product (%)[a] **2 / 3**
3-				**1b**	6 h	11 / 81	**1f**	40 min	0 / 45
4-	**1a**	4h	0 / 89	**1c**	15 min	0 / 95	**1g**	15 min	0 / 70
5-				**1d**	2.5 h	0 / 93	**1h**	2 h	0 / 70
6-				**1e**	20 min	0 / 90	**1i**	20 min	0 / 81

a) Isolated yield.


(1)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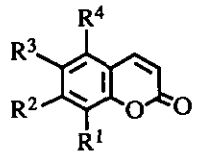
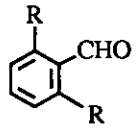

(3)

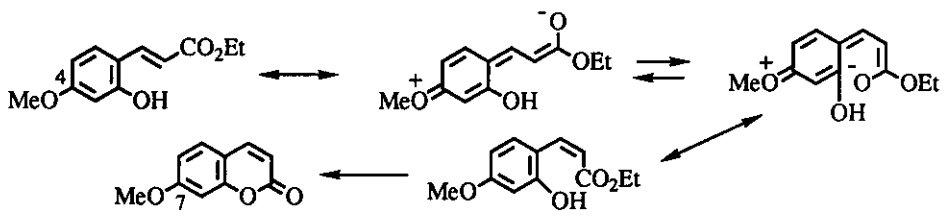
a: $R^1=R^2=R^3=R^4=H$
b: $R^1=OMe$, $R^2=R^3=R^4=H$
c: $R^2=OMe$, $R^1=R^3=R^4=H$
d: $R^3=OMe$, $R^1=R^2=R^4=H$
e: $R^4=OMe$, $R^1=R^2=R^3=H$

f: $R^1=OH$, $R^2=R^3=R^4=H$
g: $R^2=OH$, $R^1=R^3=R^4=H$
h: $R^3=OH$, $R^1=R^2=R^4=H$
i: $R^4=OH$, $R^1=R^2=R^3=H$

j: $R^1=R^2=OMe$, $R^3=H$, $R^4=Me$
k: $R^1=R^4=H$, $R^2=OMe$, $R^3=OPr^i$
l: $R^1=R^4=H$, $R^2=R^3=OMe$
m: $R^1=R^3=H$, $R^2=R^4=OMe$

Scheme 2


(**4**): R=OMe
(**5**): R=OCH_2OMe



Scheme 3

especially facilitates the ring closure in comparison with the substituent at other positions. This fact could be explained by supposing that C4- and C6-substituents favor the isomerization of *trans*-cinnamate to *cis*-cinnamate, which cyclized irreversibly to coumarin (**3**). Mechanism for C4-OMe as a representative example is illustrated in Scheme 3. This assumption is strongly supported by results summarized in Table IV. Thus, reaction of **1a** having no methoxy group at C4, with phosphorane in xylene under reflux (140°C) for 4 h gave **2a**[10] and **3a**[11] in 83% and 10% yields, respectively, whereas reaction of **1c** having methoxy group at C4 under the same reaction conditions gave **2c** and **3c** in 43% and 42% yields, respectively. On prolonging reaction time (22 h), **1c** gave **3c** in 75% yield along with 10% yield of **2c**. Furthermore, reaction of **1k**[9] and **1l**[12] having two alkoxy groups containing C4-OMe group provided only coumarins (**3k**[9] and **3l**[13]) in 87% and 83% yields, respectively, on refluxing in xylene (see runs 6 and 7 in Table IV). Surprisingly, reaction of **1m**[14] having methoxy groups at both C4 and C6 provided limmetin (**3m**[15]) in 92% yield on refluxing in xylene for only 1 h. Consequently, it is obvious that the methoxy group at C4 and C6 facilitates the formation of coumarin ring.

Table IV. The Results of Reaction of Salicylaldehyde (**1**) with Phosphorane in Xylene under Reflux.

Run	Starting material	Time	Product(%)[a] **2** / **3**
1	**1a**	4 h	83 / 10
2	**1b**	5 h	84 / 10
3	**1c**	4 h	43 / 42
4	**1c**	22 h	10 / 75
5	**1j**	11 h	36 / 51
6	**1k**	11 h	0 / 87
7	**1l**	4 h	0 / 83
8	**1m**	1 h	0 / 92

a) Isolated yield.

Natural coumarins were synthesized by using the present method,[9, 16] and synthetic studies on natural coumarins are now in progress.

Preparation of Salicylaldehydes

6-Methoxysalicylaldehyde (2-Hydroxy-6-methoxybenzaldehyde) (1e) Monodemethylation of 2,6-dimethoxybenzaldehyde (**4**)[17] with boron trichloride in methylene chloride at -78°C gave **1e**[18] in 84% yield. Interestingly, reaction of **4** with a combination reagent ($AlCl_3$-NaI-MeCN),[19] which cleaves preferencially aliphatic methyl ether to aromatic methyl ether, also gave **1e** in 96% yield.[20]

6-Hydroxysalicylaldehyde (2,6-Dihydroxybenzaldehyde) (1i) Reaction of 2,6-bis(methoxymethoxy)-benzaldehyde (**5**)[21] with concentrated HCl in methanol at 40°C afforded **1i**[22] in 47% yield.

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 Hitachi 215 spectrometer or JASCO A-102 and ^{1}H-nmr spectra in deuteriochloroform on JEOL FX-270 (270 MHz) or JEOL GSX-500 (500 MHz) spectrometers. 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 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, **1h**,[23] **1j**,[9] **1k**,[9] **1l**,[12] **4**,[17] and **5**[21] were prepared according to the literatures. Salicylaldehydes (**1a**, **1b**, **1c**, **1d**, **1f**, and **1g**) are commercially available.

General Procedure for Reaction of Salicylaldehydes (1) with Carbethoxymethylene-triphenylphosphorane Reaction of salicylaldehyde (**1**) (1 mmol) with the Wittig reagent (1.2 mmol) in solvent (10 ml) or without solvent was carried out under the reaction conditions indicated in Tables I, II, III, and IV. On using diethylaniline or pyridine as a solvent, the reaction mixture was diluted with 5% HCl solution and extracted with ether. On using benzene or xylene as a solvent, the solvent was removed under reduced pressure and the residue in ether was washed with water. For reaction of hydroxysalicylaldehydes (**1f**, **1g**, **1h**, and **1i**), the ethereal layer was extracted with 5% NaOH aqueous solution. The alkaline solution was acidified with 5% HCl solution and the acidic solution was extracted with ether.

Coumarin (3a) and Ethyl *trans*-2-hydroxycinnamate (2a) The residue in AcOEt-hexane (1 : 4) was chromatographed on silica gel. Elution with the same solvent gave **3a**, mp 66-67.5°C (lit.,[10] mp 68-70°C) (colorless prisms from CH_2Cl_2-hexane) and successive elution with the same solvent gave **2a**, mp 84-86°C (lit.,[9] mp 87°C)(colorless prisms from CH_2Cl_2-hexane).

Ethyl *trans*-2-hydroxy-3-methoxycinnamate (2b) and 8-Methoxycoumarin (3b) The residue in AcOEt-hexane (1 : 3) was chromatographed on silica gel. Elution with the same solvent gave **2b**, mp 65-66.5°C (lit.,[7a] mp 68-69°C)(colorless plates from ether-hexane) and successive elution with the same solvent gave **3b**, mp 88-90°C (lit.,[7a] mp 89°C)(colorless plates from CH_2Cl_2-hexane).

7-Methoxycoumarin (3c) and Ethyl *trans*-2-hydroxy-4-methoxycinnamate (2c) The residue in $CHCl_3$ was subjected to column chromatography on silica gel. Elution with the same solvent gave **3c**, mp 115-120°C (lit.,[7c] mp 118-119°C)(colorless prisms from CH_2Cl_2-hexane) and successive elution with the same solvent gave **2c**, mp 129.5-132°C (lit.,[8] mp 109°C) (colorless prisms from CH_2Cl_2-hexane). *Anal.* Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found : C, 64.80; H, 6.36. Ir (Nujol) cm^{-1} : 3340 (OH), 1672 (C=O). ^{1}H-Nmr (270MHz) δ : 1.35 (3H, t, *J*=7.1 Hz, $CH_2\underline{CH}_3$), 3.80 (3H, s, OCH_3), 4.28 (2H, q, *J*=7.1 Hz, $\underline{CH}_2CH_3$), 6.41 (1H, d, *J*=2.6 Hz, C_3-H), 6.49 (1H, dd, *J*=8.8 and 2.6 Hz, C_5-H), 6.54 (1H, d, *J*=16.2 Hz, CH=$\underline{CH}$-CO_2-), 6.96 (1H, br. s, OH), 7.39 (1H, d, *J*=8.8 Hz, C_6-H), 7.98 (1H, d, *J*=16.2 Hz, $\underline{CH}$=CH-CO_2-).

6-Methoxycoumarin (3d) The residue in $CHCl_3$ was subjected to column chromatography on silica gel. Elution with the same solvent gave **3d**, mp 104-105°C (lit.,[7a] mp 102-103°C)(colorless prisms from CH_2Cl_2-hexane).

5-Methoxycoumarin (3e) The residue in AcOEt was subjected to column chromatography on silica gel. Elution with AcOEt-hexane (1 : 3) gave **3c**, mp 82-82.5°C (lit.,[7c] mp 82°C)(pale yellow needles from ether-hexane).

8-Hydroxycoumarin (3f) The residue in AcOEt was subjected to column chromatography on silica gel. Elution with AcOEt-hexane (1 : 3) afforded **3f**, mp 152-156°C (lit.,[24] mp 156°C)(pale yellow needles from benzene).

7-Hydroxycoumarin (3g) The residue in AcOEt was chromatographed on silica gel. Elution with AcOEt-hexane (1 : 7) afforded **3g**, mp 230-232°C (lit.,[25] mp 230-232°C)(pale yellow needles from benzene).

6-Hydroxycoumarin (3h) The residue in AcOEt was chromatographed on silica gel. Elution with AcOEt-hexane (1 : 3) provided **3h**, mp 243-247°C (lit.,[26] mp 248-250°C)(pale yellow needles from benzene).

5-Hydroxycoumarin (3i) The residue in AcOEt-benzene (1 : 1) was chromatographed on silica gel. Elution with AcOEt-hexane (1 : 3) afforded **3i**, mp 232-234°C (lit.,[27] mp 228-229°C)(pale yellow needles from MeOH).

Heating of Ethyl *trans*-2-hydroxy-4-methoxycinnamate (2c) in Et_2NPh at 140°C A solution of **2c** (222 mg, 1 mmol) in Et_2NPh (10 ml) was heated at 140°C for 4 h. After cooling, the reaction mixture was diluted with ether and the ethereal solution was washed throughly with 5% HCl solution. The residue in $CHCl_3$ was subjected to column chromatography on silica gel. Elution with the same solvent gave **3c**, mp 117-120°C, (74 mg, 42% yield) and successive elution with the same solvent gave **2c**, mp 129-132°C, (80 mg, 36% yield).

***Ethyl trans*-2-hydroxy-3,4-dimethoxy-6-methylcinnamate (2j) and 7,8-Dimethoxy-5-methylcoumarin (3j)** The residue in AcOEt was chromatographed on silica gel. Elution with the same solvent afforded **2j**, mp 123-125°C (colorless prisms from CH_2Cl_2-hexane). *Anal.* Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found : C, 63.03; H, 6.85. Ir (Nujol) cm^{-1} : 3280 (OH), 1688 (C=O). ^{1}H-Nmr (500 MHz) δ : 1.33 (3H, t, *J*=7.0 Hz, $CH_2C\underline{H}_3$), 2.41 (3H, s, Ar-CH_3), 3.88 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.26 (2H, q, *J*=7.0 Hz, $C\underline{H}_2CH_3$), 6.35 (1H, s, C_6-H), 6.48 (1H, s, OH, exchangable with D_2O), 6.80 (1H, d, *J*=16.0 Hz, CH=C$\underline{H}$-CO_2-), 7.84 (1H, d, *J*=16.0 Hz, C$\underline{H}$=CH-CO_2-). Successive elution with the same solvent afforded **3j**, mp 117-118°C (lit.,[9] mp 117.5-119.5°C)(colorless needles from CH_2Cl_2-hexane).

6-Isopropoxy-7-methoxycoumarin (3k) The residue in ether-hexane (1 : 3) was chromatographed on silica gel. Elution with the same solvent gave **3k**, mp 126-128°C (lit.,[9] 126-128°C) (pale yellow prisms from CH_2Cl_2-hexane).

6,7-Dimethoxycoumarin (Aesculetin Dimethyl Ether) (3l) The residue in AcOEt was chromatographed on silica gel. Elution with AcOEt-hexane (1 : 5) provided **3l**, mp 147-148.5°C (lit.,[13a] 142-143°C, lit.,[13b] 148-149°C) (pale yellow prisms from ether).

5,7-Dimethoxycoumarin (Limettin) (3m) The residue in AcOEt was subjected to chromatography on silica gel. Elution with AcOEt : hexane (1 : 3) gave **3m**, mp 147-149°C (lit.,[15] 146-147.4°C) (pale yellow needles from MeOH).

2-Hydroxy-6-methoxybenzaldehyde (1e) a) By Boron Trichloride A solution of 2,6-dimethoxybenzaldehyde (**4**) (830 mg, 5 mmol) in dry CH_2Cl_2 (10 ml) was added to a solution of boron

trichloride (1.5 ml, 17.3 mmol) in dry CH_2Cl_2 (10 ml). The reaction mixture was stirred at -78°C for 2.5 h, diluted with water and then, extracted with CH_2Cl_2. The organic layer was extracted with 5% NaOH aqueous solution. The alkaline layer was acidified with 10% HCl solution and the acidic solution was extracted with ether. The residue was recrystallized from ether-hexane to gave **1e** (640 mg, 84% yield), mp 70-71°C (lit.,[18] mp 75°C). The starting material (**4**) was recovered in 11% yield (90 mg) from the CH_2Cl_2 layer mentioned above.

b) By Aluminum Chloride-Sodium Iodide-Acetonitrile System Aluminum chloride (20.0 g, 150 mmol) and sodium iodide (22.5 g, 150 mmol) were added to a solution of **4** (9.97 g, 60 mmol) in dry acetonitrile (600 ml) and dry CH_2Cl_2 (300 ml) at 0°C. The reaction mixture was stirred at room temperature for 45 min, poured into ice-water and then, extracted with CH_2Cl_2. The organic layer was washed with aqueous sodium thiosulfate. The residue was recrystallized from benzene-hexane to afford **1e** (8.76 g, 96% yield).

2,6-Dihydroxybenzaldehyde (1i) A solution of **5** (15.0 g, 66.3 mmol) in MeOH (150 ml) and concentrated HCl (7 ml) was refluxed for 2 h. After cooling, the reaction mixture was diluted with ice-water (500 ml) and extracted with AcOEt. The residue in benzene-AcOEt (1 : 2) was chromatographed on silica gel. Elution with hexane-AcOEt (4 : 1) gave **1i** (4.28 g, 47% yield), mp 154-158°C (decomp.) (lit.,[23] mp 154-155°C)(pale yellow needles from benzene)

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