

A CONVENIENT SYNTHESIS OF A SIMPLE COUMARIN

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Reaction of salicylaldehydes (**1**) with carbethoxymethylenephosphorane in diethylaniline under reflux gave coumarins (**3**) in excellent yields. Methoxy substituent at C4 on salicylaldehyde (**1**) facilitated the formation of coumarin from *trans*-cinnamate (**2**), which is first prepared by reaction of **1** with Wittig reagent.

KEYWORDS coumarin synthesis; Wittig reaction; salicylaldehyde; methoxy group effect; reaction temperature; mechanism

Coumarins are widely distributed in nature and have been reported to exhibit various biological and/or pharmaceutical activities.¹⁾ Although various synthetic routes to coumarins, especially to simple coumarins (**3**), are known,²⁾ much effort is still being devoted to exploring new synthetic methods³⁾ because of their lack of generality and/or efficiency.

Recently we developed a new synthesis method of salicylaldehydes (**1**) *via* formation of benzofuran by CsF-mediated Claisen rearrangement of aryl propargyl ether followed by oxidative cleavage of furan ring⁴⁾ (see Chart 1). Mali *et al.* reported a new coumarin synthesis by Wittig reaction of **1** with carbethoxymethylenephosphorane without solvent at 210–215°C.⁵⁾ We planned to re-examine the generality and efficiency of this method by Mali *et al.* in connection with synthetic studies on Reich's coumarin.⁶⁾ Herein we present an improved and practical synthetic method of synthesizing simple coumarins (**3**).

Since coumarins contained in *Rutaceae* plants⁷⁾ usually have a methoxy group at C7 ring, reaction of 4-methoxysalicylaldehyde (**1a**) with carbethoxymethylenephosphorane at various temperatures was first examined. The results are summarized in Table I, showing that yield of coumarin (**3a**) rises as reaction temperature becomes high. Thus, reaction of **1a** with phosphorane in diethylaniline under reflux, for only 15 min, gave **3a** in 95.2% yield, whereas reaction of **1a** in pyridine under reflux, even for 4h, gave **3a** in 9.0% yield (see runs 5 and 3 in Table I). Next, in order to compare our method (in diethylaniline at 215°C) with Mali's method (neat at 215°C), reaction of **1b** and **1f** with phosphorane was carried out. The results (see runs 3, 4, 8, and 9 in Table II, and also runs 1 and 2 in Table II) show that reaction by our method occurs readily to give a somewhat higher yield, and isolation of products was much easier. The additional results (see runs 5, 6, and 7 in Table II) indicate that our method is practically useful for the synthesis of simple coumarins (**3**). Furthermore, in connection with synthetic studies on Reich's coumarin,⁶⁾ reaction of 4-formyl-5-hydroxy-7-methoxy-2-methylbenzo[b]furan (**4**) under our reaction conditions for 30 min was carried out to give the corresponding coumarin (**5**) in 80.4% yield.⁸⁾ The methoxy substituent at C4 on salicylaldehyde (**1**), *i.e.* on cinnamate (**2**) which is first prepared by the Wittig reaction of **1** with phosphorane, facilitated the formation of coumarin ring in comparison with the methoxy group at other positions.

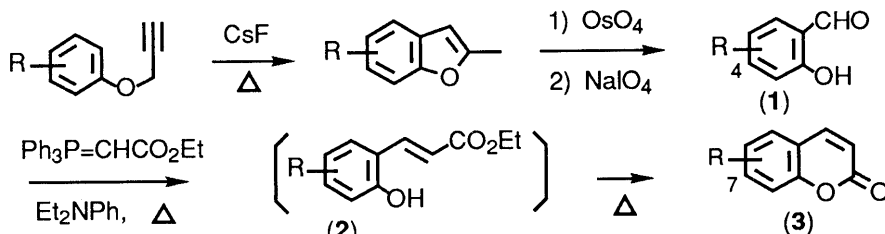


Chart 1

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

Run	Solvent	Temperature	Time	Product(%) ^{a)} 2a / 3a
1	Benzene	r.t.	4h	87.9 / 4.6
2	Benzene	Reflux(80°C)	4h	90.7 / 7.4
3	Byridine	Reflux(115°C)	4h	88.9 / 9.0
4	Xylene	Reflux(140°C) ^{b)}	4h	43.2 / 41.8
5	Diethylaniline	Reflux(215°C)	15min	0 / 95.2

a) Isolated yield.

b) Heating of **2a** in diethylaniline at 140°C for 4h gave **3a** in 41.5% yield with the recovery of **2a** in 36.2% yield.Table II. The Results of Reaction of Salicylaldehydes (**1**) with Carbethoxymethylenephosphorane at 210-215°C

Run	Starting material	Reaction conditions		Product (%) ^{a)} 2 / 3
		Solvent	Time	
1	1a	Diethylaniline	15min	0 / 95.2
2	1a	- - -	5h	0 / 71 ^{b)}
3	1b	Diethylaniline	30min	0 / 90
4	1b	- - -	10min	0 / 74.8
5	1c	Diethylaniline	40min	0 / 95.2
6	1d	Diethylaniline	2.5h	0 / 93.4
7	1e ^{c)}	Diethylaniline	4h	0 / 89.2
8	1f	Diethylaniline	6h	10.5 / 80.8
9	1f	- - -	6h	4.5 / 70.1

a) Isolated yield.

b) See ref. 5c).

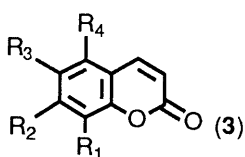
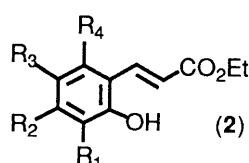
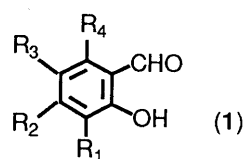
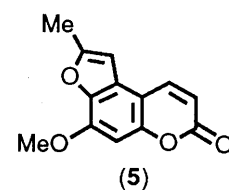
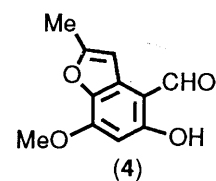
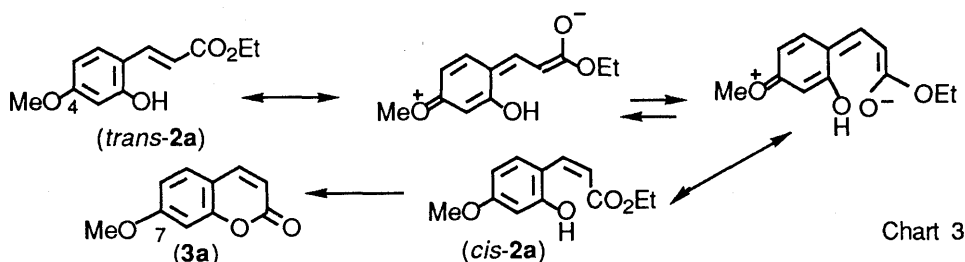
c) Perkin reaction of **1c** with Ac₂O-AcONa gave **3c** only in 43.3% yield.a: R₁=R₃=R₄=H, R₂=OMeb: R₁=R₂=OMe, R₃=H, R₄=Mec: R₁=R₄=H, R₂=OMe, R₃=OPrⁱd: R₁=R₂=R₄=H, R₃=OMee: R₁=R₂=R₃=R₄=Hf: R₁=OMe, R₂=R₃=R₄=H

Chart 2

This could be explained by supposing that C4-methoxy group favours the isomerization of *trans*-cinnamate (*trans*-2a) to *cis*-cinnamate (*cis*-2a), which cyclized irreversibly to coumarin (3) as shown in Chart 3.⁹⁾ Synthetic studies on natural coumarins using our method are now in progress.



A representative experimental procedure for preparing coumarin is as follows.

Reaction of 1a with Phosphorane A solution of salicylaldehyde (1a) (1 mmol) and carbethoxymethylenephosphorane (1.2 mmol) in diethylaniline (10 ml) was heated at 210–215°C for 15 min under an argon atmosphere. Reaction mixture was diluted with water and extracted with ether. The ether extract was thoroughly washed with 5% HCl and brine, dried over MgSO₄ and concentrated *in vacuo*. Chromatography on SiO₂ gave coumarin (3a) in 95.2% yield.

ACKNOWLEDGEMENT This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture (Japan).

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- 8) Compound (4) was synthesized from 5-formyl-7-methoxy-2-methylbenzo[b]furan⁴⁾ by a following sequence of reactions: a) 30% H₂O₂-HCO₂H, b) 5% NaOH, c) benzyl chloride-K₂CO₃ in dimethylformamide (DMF), d) DMF-POCl₃, e) H₂-5% Pd/C in AcOEt. Details will be reported elsewhere.
- 9) Reaction of 1e having no methoxy group at C₄, with phosphorane in xylene under reflux for 4h gave cinnamate (2e) and coumarin (3e) in 82.8% and 9.6% yields, respectively, whereas reaction of 1a having methoxy group at C₄ under the same conditions gave 2a and 3a in 43.2% and 41.8% yields, respectively. Interestingly, reaction of 1c having C₄-OMe group, with phosphorane in xylene, provided only coumarin (3c) in 86.7% yield on refluxing for 11h.

(Received October 15, 1991)