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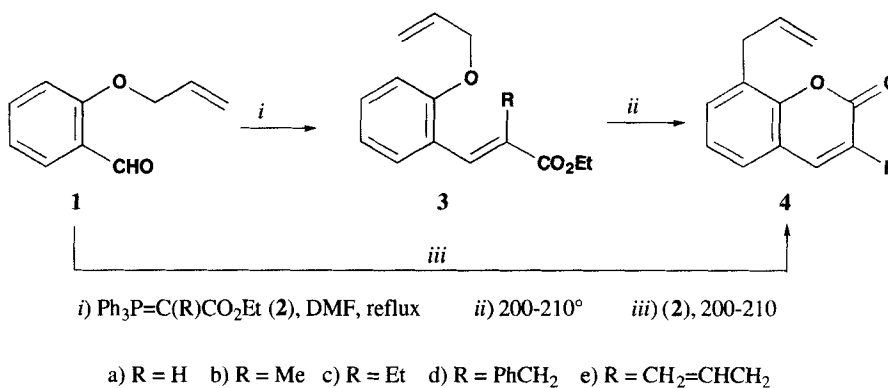
## SYNTHESIS OF 7-DESOXY-8-ALLYLCOUMARINS

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8-Allylcoumarins constitute an important class of naturally occurring coumarins.<sup>1</sup> Although various methods have been reported for their synthesis, most of them require preformed 7-hydroxycoumarins. Thus, 7-hydroxycoumarins on allylation followed by Claisen rearrangement provide 8-allyl-7-hydroxycoumarins either exclusively or along with some minor amounts of other products.<sup>1,3</sup> Because of this difficulty, the synthesis of 8-allylcoumarins unoxxygenated at C<sub>7</sub>-position has not been reported so far. We report herein a convenient synthesis of 8-allylcoumarin (**4a**) and 3-substituted 8-allylcoumarins (**4b-e**) which do not have oxygen function at C<sub>7</sub>-position.



The starting compound in our approach is 2-allyloxybenzaldehyde (**1**). Although **1** has been reported in the literature,<sup>4,7</sup> most of the known methods require high temperature and long reaction time. We have developed a simple procedure for its synthesis from salicylaldehyde. Thus, stirring a solution of salicylaldehyde and allyl bromide in N,N-dimethylformamide at room temperature for 2 hrs, in the presence of anhydrous potassium carbonate provided 2-allyloxybenzaldehyde (**1**) in 95% yield. When **1** was reacted with phosphorane (**2a**) at 205° for 3 hrs 8-allylcoumarin (**4a**) was obtained in 52% yield. Similarly reaction of **1** with phosphoranes (**2b-e**)<sup>8,10</sup> gave 3-substituted 8-allylcoumarins (**4b-e**). It is envisaged that conversion of **1** into **4a-e** involves initial Wittig reaction of **1** with **2a-e** to give **3a-e** which then underwent an *ortho* Claisen rearrangement followed by thermal isomerization and cyclization to provide **4a-e**. To check the feasibility of this process, 2-allyloxybenzaldehyde (**1**) was reacted with phosphorane (**2a**) in N,N-dimethylformamide at room temperature to afford the E-ester **3a** as a thick oil in 77% yield. Under similar conditions, reaction of **1** with **2b-e** did not give the desired products **3b-e** in good yields; however, at 165° for 3-6 hrs the E-esters **3b-e** could be obtained in 46-63% yield. The E-stereochemistry of esters (**3a-e**) was established on the basis of their <sup>1</sup>H NMR

spectral data. The olefinic  $\alpha$ - and  $\beta$ -protons in **3a** appeared as doublets ( $J = 16$  Hz) at 6.8 and 8.4  $\delta$ , respectively. The olefinic  $\beta$ -protons in compounds **3b-e** appeared as singlets at about 8.2  $\delta$ . The position of  $\beta$ -protons in **3a-e** are closer to the calculated<sup>11</sup> values of  $\beta$ -protons in the E-isomers of **3a-e**. This observation coupled with the magnitude of coupling constant ( $J = 16$  Hz) of the olefinic protons in **3a** thus indicate that the esters **3a-e** must be E-isomers. The esters **3a-e** on heating at 200-210° for 2-8 hrs, (monitored by TLC) were smoothly converted into 8-allylcoumarins (**3a-e**).

TABLE 1. Yield, mp, Spectral and Analytical Data of **3** and **4**

Cmpd	Yield (%)	mp. (°C)	IR (C=O) (cm <sup>-1</sup> )	<sup>1</sup> H NMR ( $\delta$ )	Elemental Analysis (Found)		Time (hrs)
					C	H	
<b>3a</b>	77		1720	1.34 (3H, t, $J = 7.5$ Hz, CH <sub>2</sub> CH <sub>3</sub> ), 4.4 (2H, q, $J = 7.5$ Hz, CH <sub>2</sub> CH <sub>3</sub> ), 4.80 (2H, brd, $J = 5$ Hz, OCH <sub>2</sub> ) 5.40-5.77 (2H m, CH=CH <sub>2</sub> ), 6.08-6.57 (1H, m, CH=CH <sub>2</sub> ), 7.08-7.90 (4H, m, ArH), 8.40 (1H, d, $J = 16$ Hz, CH=CH-COO).	72.39 (72.37)	6.94 (6.92)	14
<b>3b</b>	63		1703	1.34 (3H, t, $J = 7.5$ Hz, CH <sub>2</sub> CH <sub>3</sub> ), 2.08 (3H, bs, HC=C-CH <sub>3</sub> ), 4.40 (2H, q $J = 7.5$ Hz, CH <sub>2</sub> CH <sub>3</sub> ) 4.65-4.90 (2H, m, OCH <sub>2</sub> ) 5.37-5.77 (2H, m CH=CH <sub>2</sub> ), 6.05-6.51 (1H, m, CH=CH <sub>2</sub> ), 7.08-7.91 (4H, m, ArH), 8.20 (1H, bs, CH=C-).	73.14 (72.92)	7.37 (7.23)	6
<b>3c</b>	46		1706	1.14 (3H, t, $J = 7.5$ Hz, CH <sub>2</sub> CH <sub>3</sub> ), 1.34 (3H, t, $J = 7.5$ Hz, OCH <sub>2</sub> CH <sub>3</sub> ), 2.44 (2H, q, $J =$ 7.5 Hz, C-CH <sub>2</sub> CH <sub>3</sub> ), 4.42 (2H, q, $J = 7.5$ Hz, OCH <sub>2</sub> CH <sub>3</sub> ), 4.71 (2H, brd, $J = 5$ Hz, OCH <sub>2</sub> ), 5.37-5.74 (2H, m, CH=CH <sub>2</sub> ), 6.05-6.51 (1H, m, CH=CH <sub>2</sub> ), 7.08-7.68 (4H, m, ArH), 8.14 (1H, s, CH=C-).	73.82 (73.74)	7.74 (7.82)	4
<b>3d</b>	57		1707	1.22 (3H, t, $J = 7.5$ Hz, CH <sub>2</sub> CH <sub>3</sub> ), 4.0 (2H, s, CH <sub>2</sub> Ph), 4.34 (2H, q, $J = 7.5$ Hz, CH <sub>2</sub> CH <sub>3</sub> ), 4.71-4.91 (2H, m, OCH <sub>2</sub> ), 5.40-5.77 (2H, m, CH=CH <sub>2</sub> ), 6.05-6.54 (1H, m, CH=CH <sub>2</sub> ), 7.08-7.91 (9H, m, ArH), 8.42 (1H, s, CH=C-).	78.23 (78.42)	6.88 (7.05)	7.5

TABLE 1. Continued

Cmpd	Yield (%)	mp. (°C)	IR (C=O) (cm <sup>-1</sup> )	<sup>1</sup> H NMR (δ)	Elemental Analysis (Found)		Time (hrs)
					C	H	
<b>3e</b>	64		1720	1.37 (3H, t, J = 7.5 Hz, CH <sub>2</sub> CH <sub>3</sub> ), 3.30 (2H, brd, J = 5 Hz, C-CH <sub>2</sub> ), 4.42 (2H, q, J = 7.5 Hz, OCH <sub>2</sub> CH <sub>3</sub> ), 4.77-5.14 (2H, m, OCH <sub>2</sub> ), 5.14-5.77 (4H, m, 2xCH=CH <sub>2</sub> ), 6.00-6.51 (2H, m, 2xCH=CH <sub>2</sub> ), 7.22 (2H, t, J = 8 Hz, ArH), 7.48-7.71 (2H, m, ArH), 8.31 (1H, s, CH=C-).	74.97 (74.79)	7.40 (7.56)	6
<b>4a</b>	51	40-41	1709	3.74 (2H, brd, J = 5.5 Hz, Ar-CH <sub>2</sub> ), 5.11-5.48 (2H, m, CH=CH <sub>2</sub> ), 6.00-6.45 (1H, m, CH=CH <sub>2</sub> ), 6.65 (1H, d, J = 10 Hz, C <sub>3</sub> -H), 7.37-7.80 (3H, m, ArH), 8.00 (1H, d, J = 10 Hz, C <sub>4</sub> -H).	77.40 (77.60)	5.41 (5.33)	3
<b>4b</b>	61	69-71	1709	2.22 (3H, 3, CH <sub>3</sub> ), 3.71 (2H, brd, J = 6.0 Hz, Ar-CH <sub>2</sub> ), 5.20-5.45 (2H, m, CH=CH <sub>2</sub> ), 6.00-6.51 (1H, m, CH=CH <sub>2</sub> ), 7.42-7.68 (3H, m, ArH), 7.80 (1H, 3, C <sub>4</sub> -H).	77.98 (78.24)	6.04 (6.22)	6
<b>4c</b>	41	68-70	1712	1.25 (3H, t, J = 7.7 Hz, CH <sub>2</sub> CH <sub>3</sub> ), 2.68 (2H, q, J = 7.7 Hz, CH <sub>2</sub> CH <sub>3</sub> ), 3.74 (2H, brd, J = 6.0 Hz, Ar-CH <sub>2</sub> ), 5.17-5.45 (2H, m, CH=CH <sub>2</sub> ), 6.02- 6.51 (1H, m, CH=CH <sub>2</sub> ) 7.34-7.68 (3H, m, ArH), 7.71 (1H, s, C <sub>4</sub> -H).	78.48 (78.45)	6.62 (6.81)	4
<b>4d</b>	41	82-84	1708	3.71 (2H, brd, J = 6.0 Hz, Ar-CH <sub>2</sub> ), 4.02 (2H, s, CH <sub>2</sub> Ph), 5.17-5.42 (2H, m, CH=CH <sub>2</sub> ), 6.00-6.51 (1H, m, CH=CH <sub>2</sub> ) 7.42-7.71 (9H, m, ArH and C <sub>4</sub> -H).	82.58 (82.46)	5.84 (5.92)	8
<b>4e</b>	56	41-42	1733	3.42 (2H, brd, J = 6 Hz, C <sub>3</sub> -CH <sub>2</sub> ), 3.74 (2H, brd, J = 6.0 Hz, Ar-CH <sub>2</sub> ), 5.17-5.54 (4H, m, 2x CH=CH <sub>2</sub> ), 5.97-6.54 (2H, m, 2xCH=CH <sub>2</sub> ), 7.34-7.94 (4H, m, ArH and C <sub>4</sub> -H).	79.62 (79.53)	6.24 (6.34)	7

## EXPERIMENTAL SECTION

All melting points are uncorrected. The IR spectra were recorded on a Perkin-Elmer FTIR-1615 spectrophotometer and <sup>1</sup>H NMR in CDCl<sub>3</sub> solutions on Jeol FX 90 Q instrument. Chemical shifts are

expressed in  $\delta$  (ppm) downfield from TMS as an internal standard and coupling constants in Hertz. Analyses were obtained using Hosli's rapid carbon-hydrogen analyser.

**Preparation of 2-Allyloxybenzaldehyde (1).**- A mixture of salicylaldehyde (6.1g, 5.3 mmol), anhydrous potassium carbonate (13.8 g, 100 mmol) and allyl bromide (14.52 g, 12 mmol) in N, N-dimethylformamide (20 mL) was stirred at room temperature for 2 hrs. It was poured in ice cold water (100:1), and extracted with ethyl acetate. The organic layer was washed with 2N NaOH (2x15 mL) and then with water. It was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to give **1** as a pale yellow liquid (7.7g, 95%). IR(neat):  $1688\text{ cm}^{-1}$ ,  $^1\text{H NMR}$ :  $\delta$  4.85 (2H, brd,  $J = 5\text{ Hz}$ ,  $\text{OCH}_2$ ), 5.42-5.80 (2H, m,  $\text{CH}=\text{CH}_2$ ), 6.08-6.57 (1H, m,  $\text{CH}=\text{CH}_2$ ), 7.17-7.42 (2H, m, ArH), 7.85 (1H, dt,  $J = 8$  and  $2\text{ Hz}$ , ArH), 8.17 (1H, dd,  $J = 8$  and  $2\text{ Hz}$ , ArH), 10.81 (1H, s, CHO).

*Anal. Calcd.* for  $\text{C}_{10}\text{H}_{10}\text{O}_2$ : C, 74.05; H, 6.22. *Found*: C, 73.89; H, 6.38

**General Procedure for the Preparation of 8-Allylcoumarins (4a-e).**- A mixture of 2-allyloxybenzaldehyde (0.8g, 5 mmol) and the phosphorane (6 mmol) was heated at  $200\text{-}210^\circ$  for 3-8 hrs (see Table). The residue obtained was chromatographed on silica gel using hexane-benzene (1:1) as an eluent to give **4a-d** (in case of **4e** the eluent was hexane) as white solids which, on recrystallization from hexane provided **4a-d** as pure crystalline products (for analytical and spectral data see Table).

**General Procedure for the Preparation of (E)-Ethyl 2-Allyloxybenzylates (3a-e).**- A mixture of phosphorane (5.1 mmol) and 2-allyloxybenzaldehyde (5 mmol) in N,N-dimethylformamide (15 mL), was refluxed for 6-7.5 hrs (in case of **3a** stirred at room temperature for 14 hrs). The reaction mixture was cooled, poured in water, and extracted with chloroform (2x25 mL). The chloroform layer was washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to give an oily product, which was chromatographed over silica gel using hexane-benzene (1:1) as an eluent to give the pure esters **3a-e** as thick liquids (for analytical and spectral data see Table).

**General Procedure for the Conversion of (E)-Ethyl 2-Allyloxybenzylates (3a-e) into 8-Allylcoumarins (4a-e).**- Ethyl-2-allyloxybenzylate (**3a-e** 2.5 mmol) was heated at  $200\text{-}210^\circ$ , under nitrogen atmosphere for 2-8 hrs (monitored by TLC). The residue obtained was chromatographed over silica gel using hexane-benzene (1:1) as an eluent to give a solid which on recrystallization from hexane provided coumarins **4a-e** as pure crystalline products, which were identical (mp, TLC, IR and  $^1\text{H NMR}$ ) with authentic samples prepared above. **4a**: heated for 6 hrs (82% yield), **4b**: heated for 5.5 hrs (63%), **4c**: heated for 2 hrs (89%), **4d**: heated for 6 hrs (35%), **4e**: heated for 8 hrs (47%).

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## EXPEDIENT SYNTHESSES OF ESPINTANOL, *p*-METHOXYCARVACROL AND THYMOQUINOL DIMETHYL ETHER

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A substantial number of oxygenated *p*-cymene derivatives have been isolated from a variety of plant sources especially from trees. The title compounds, for example, were first isolated from the spruce tree *Oxandra espintata* (espintanol),<sup>1</sup> from the incense-cedar heartwood *Libocedrus decurrens* (*p*-methoxycarvacrol)<sup>2</sup> and from *Eupatorium triplinere* (thymoquinol dimethylether).<sup>3</sup> *p*-Cymene derivatives of this type were shown early on by Erdtman and Rennerfelt to exhibit varying degrees of toxicity toward wood-destroying fungi.<sup>4</sup> In addition, espintanol has been shown to have antiparasitic activity against a number of strains of *Trypanosoma cruzi* and *Leishmania*, the latter responsible for