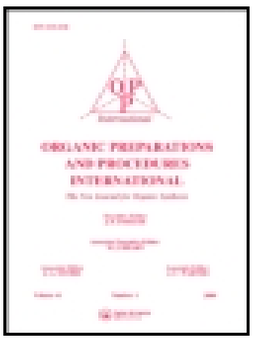

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SYNTHESIS OF 7-DESOXY-8-ALLYLCOUMARINS

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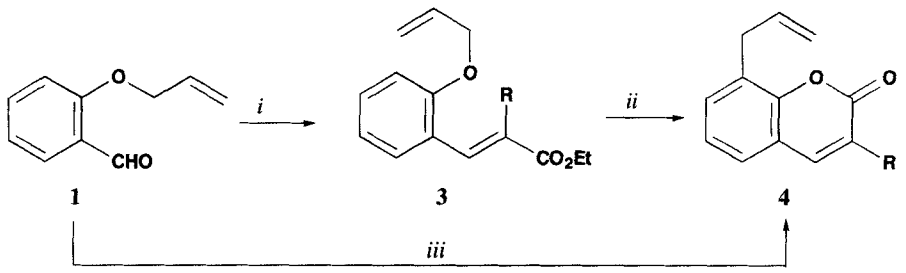
8-Allylcoumarins constitute an important class of naturally occurring coumarins.[1] Although various methods have been reported for their synthesis, most of them require preformed 7-hydroxycoumarins. Thus, 7-hydroxycoumarins on allylation followed by Claisen rearrangment provide 8-allyl-7-hydroxycoumarins either exclusively or along with some minor amounts of other products.[1,3] Because of this difficulty, the synthesis of 8-allylcoumarins unoxygenated at C_7-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_7-position.



i) $Ph_3P=C(R)CO_2Et$ (**2**), DMF, reflux *ii*) 200-210° *iii*) (**2**), 200-210

a) R = H b) R = Me c) R = Et d) R = $PhCH_2$ e) R = CH_2=$CHCH_2$

The starting compound in our approach is 2-allyloxybenzaldehyde (**1**). Although **1** has been reported in the literature,[4-7] 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**)[8,10] 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 ^1H NMR

spectral data. The olefinic α- and β-protons in **3a** appeared as doublets (J = 16 Hz) at 6.8 and 8.4 δ, respectively. The olefinic β-protons in compounds **3b-e** appeared as singlets at about 8.2 δ. The position of β-protons in **3a-e** are closer to the calculated[11] values of β-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^{-1})	^1H NMR (δ)	Elemental Analysis (Found) C	H	Time (hrs)
3a	77		1720	1.34 (3H, t, J = 7.5 Hz,CH_2CH_3), 4.4 (2H, q, J = 7.5 Hz, CH_2CH_3), 4.80 (2H, brd, J = 5 Hz, OCH_2) 5.40-5.77 (2H m, $CH=CH_2$), 6.08-6.57 (1H, m, $CH=CH_2$), 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
3b	63		1703	1.34 (3H, t, J = 7.5 Hz, CH_2CH_3), 2.08 (3H, bs, $HC=C-CH_3$), 4.40 (2H, q J = 7. 5 Hz, CH_2CH_3) 4.65-4.90 (2H, m, OCH_2) 5.37-5.77 (2H, m $CH=CH_2$), 6.05-6.51 (1H, m, $CH=CH_2$), 7.08-7. 91 (4H, m, ArH), 8.20 (1H, bs, CH=C-).	73.14 (72.92)	7.37 (7.23)	6
3c	46		1706	1.14 (3H, t, J = 7.5 Hz, CH_2CH_3), 1.34 (3H, t, J = 7. 5 Hz, OCH_2CH_3), 2.44 (2H, q, J = 7.5 Hz, C-CH_2CH_3), 4.42 (2H, q, J = 7. 5 Hz, OCH_2CH_3), 4.71 (2H, brd, J = 5 Hz, OCH_2), 5.37-5.74 (2H, m, $CH=CH_2$), 6.05-6.51 (1H, m, $CH=CH_2$), 7.08-7.68 (4H, m, ArH), 8.14 (1H, s, CH=C–).	73.82 (73.74)	7.74 (7.82)	4
3d	57		1707	1.22 (3H, t, J = 7.5 Hz, CH_2CH_3), 4.0 (2H, s, CH_2Ph), 4.34 (2H, q, J =7.5 Hz, CH_2CH_3), 4.71-4.91 (2H, m, OCH_2), 5.40-5.77 (2H, m, $CH=CH_2$), 6.05-6.54 (1H, m, $CH=CH_2$), 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^{-1})	^1H NMR (δ)	Elemental Analysis (Found) C	H	Time (hrs)
3e	64		1720	1.37 (3H, t, J = 7.5 Hz, CH_2CH_3), 3.30 (2H, brd, J = 5 Hz, C-CH_2), 4.42 (2H, q, J = 7.5 Hz, OCH_2CH_3), 4.77-5.14 (2H, m, OCH_2), 5.14-5.77 (4H, m, 2xCH=CH_2), 6.00-6.51 (2H, m, 2xCH=CH_2), 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
4a	51	40-41	1709	3.74 (2H, brd, J = 5.5 Hz, Ar-CH_2), 5.11-5.48 (2H, m, CH=CH_2), 6.00-6.45 (1H, m, CH=CH_2), 6.65 (1H, d, J = 10 Hz, C_3-H), 7.37-7.80 (3H, m, ArH), 8.00 (1H, d, J = 10 Hz, C_4-H).	77.40 (77.60)	5 41 (5.33)	3
4b	61	69-71	1709	2.22 (3H, 3, CH_3), 3.71 (2H, brd, J = 6.0 Hz, Ar-CH_2), 5.20-5.45 (2H, m, CH=CH_2), 6.00-6.51 (1H, m, CH=CH_2), 7.42-7. 68 (3H, m, ArH), 7.80 (1H, 3, C_4-H).	77.98 (78.24)	6.04 (6 22)	6
4c	41	68-70	1712	1.25 (3H, t, J = 7.7 Hz, CH_2CH_3), 2.68 (2H, q, J = 7. 7 Hz, CH_2CH_3), 3.74 (2H, brd, J = 6.0 Hz, Ar- CH_2), 5.17-5.45 (2H, m, CH=CH_2), 6.02-6.51 (1H, m, CH=CH_2) 7.34-7.68 (3H, m, ArH), 7.71 (1H, s, C_4-H).	78.48 (78.45)	6.62 (6.81)	4
4d	41	82-84	1708	3.71 (2H, brd, J = 6.0 Hz, Ar-CH_2), 4.02 (2H, s, CH_2Ph), 5.17-5.42 (2H, m, CH=CH_2), 6.00-6.51 (1H, m, CH=CH_2) 7.42-7.71 (9H, m, ArH and C_4-H).	82.58 (82.46	5.84 (5.92)	8
4e	56	41-42	1733	3.42 (2H, brd, J = 6 Hz, C_3-CH_2), 3.74 (2H, brd, J = 6. 0 Hz, Ar-CH_2), 5.17-5.54 (4H, m, 2x CH=CH_2), 5.97-6.54 (2H, m, 2xCH=CH_2), 7.34-7.94 (4H, m, ArH and C_4-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 ^1H NMR in $CDCl_3$ solutions on Jeol FX 90 Q instrument. Chemical shifts are

expressed in δ (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 (Na_2SO_4) and evaporated to give **1** as a pale yellow liquid (7.7g, 95%). IR(neat): 1688 cm^{-1}, ^1H NMR: δ 4.85 (2H, brd, J = 5 Hz, OCH_2), 5.42-5.80 (2H, m, $CH=CH_2$), 6.08-6.57 (1H, m, $CH=CH_2$), 7.17-7.42 (2H, m, ArH), 7.85 (1H, dt, J = 8 and 2 Hz, ArH), 8.17 (1H, dd, J = 8 and 2 Hz, ArH), 10.81 (1H, s, CHO).

Anal. Calcd. for $C_{10}H1_{10}O_2$: 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 200-210° 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-Allyloxycinnamates (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 (Na_2SO_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-Allyloxycinnamates (3a-e) into 8-Allylcoumarins (4a-e).- Ethyl-2-allyloxycinnamate (**3a-e** 2.5 mmol) was heated at 200-210°, 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 ^1H 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 SYNTHESES 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),[1] from the incense-cedar heartwood *Libocedrus decurrens* (p-methoxycarvacrol)[2] and from *Eupatorium triplinere* (thymoquinol dimethylether).[3] p-Cymene derivatives of this type were shown early on by Erdtman and Rennerfelt to exhibit varying degrees of toxicity toward wood-destroying fungi.[4] In addition, espintanol has been shown to have antiparasitic activity against a number of strains of *Trypanosoma cruzi* and *Leishmania*, the latter responsible for