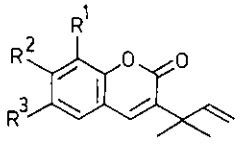
A CONVENIENT TWO-STEP SYNTHESIS OF 3-ALLYLCOUMARINS AND THEIR BENZODERIVATIVES

Raghao S. Mali*, Santosh G. Tilve, Suresh N. Yeola, and Anita R. Manekar
Department of Chemistry, University of Poona, Pune 411 007, India

Abstract - A convenient, high yield, two step synthesis of 3-allylcoumarins and their benzo derivatives is described from 2-hydroxybenzaldehydes. The benzaldehydes (2a-j) on reaction with phosphorane 3 provide E-ethyl-α- allylcinnamates (4a-j) in high yields. These esters (4a-j) on thermal or photochemical cyclisation give 3-allylcoumarins (6a-j).

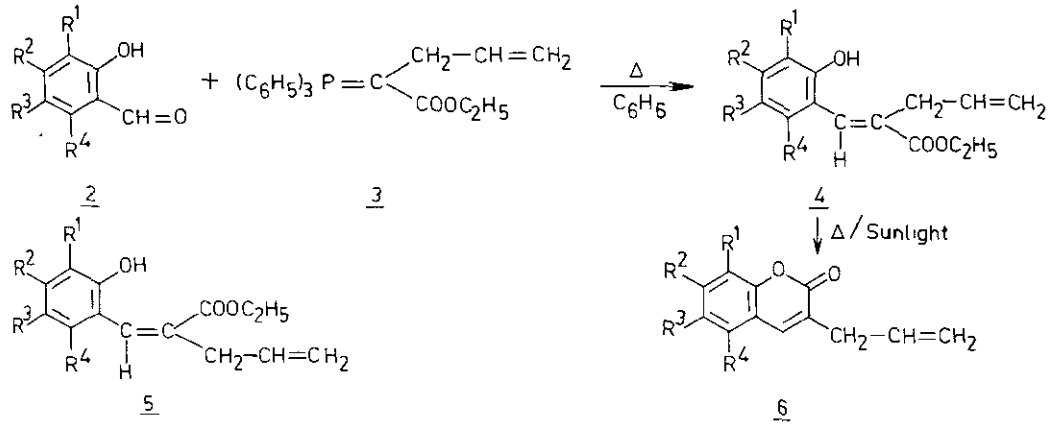
Several 3-alkenylcoumarins (1a-e) have been isolated from natural sources[1-3]. This ring system is also present in some pyranocoumarins.[4] Though a number of methods are available for preparation of 3-substituted coumarins[5,6] only two routes are reported for the synthesis of 3-alkenylcoumarins[7-9].



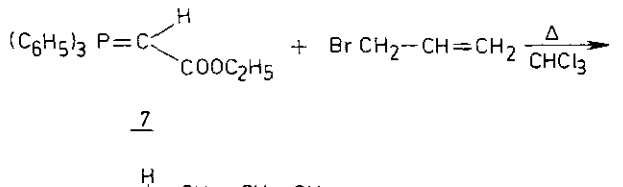
1

1	R^1	R^2	R^3
a	H	OCH_3	H
b	H	OCH_3	OCH_3
c	H	OH	OCH_3
d	OH	OCH_3	H
e	OCH_3	OCH_3	H

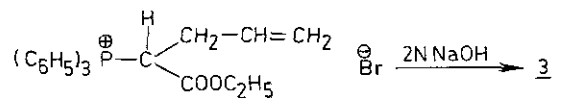
Both these routes utilize preformed coumarins as starting compounds and either involve several steps or provide 3-alkenylcoumarins in very low yields. Thus, the first method[8] requires 7-hydroxycoumarins, which on allylation followed by abnormal Claisen rearrangement gives 3-alkenyl-7-hydroxycoumarins in small amounts. The second method[7] employs 4-hydroxycoumarins, which on allylation followed by Claisen rearrangement provides 3-allyl-4-hydroxycoumarins. These are then converted to 3-allylcoumarins via tosylation of 4-OH group followed by reductive detosylation. We report herein a simple and general approach for the synthesis of 3-allylcoumarins which does not require preformed coumarins and provide 3-allylcoumarins in high



2 4 6	R^1	R^2	R^3	R^4
a	H	H	H	H
b	H	OCH_3	H	H
c	H	H	H	OCH_3
d	OCH_3	H	H	H
e	H	CH_3	H	H
f	H	OCH_3	CH_3	H
g	H	OCH_3	H	OCH_3
h	H	H	-(CH=CH)-$_2$	
i	-(CH=CH)-$_2$	H	H	
j	H	-(CH=CH)-$_2$	H	



7



8

SCHEME I

yields (Scheme I). In our method the ortho-hydroxybenzaldehydes (2a-j) were reacted with phosphorane (3) in dry benzene. A mixture of esters 4 and 5 was expected from this reaction, however, the hydroxy esters (4a-j) whose stereochemistry will be described later were formed exclusively. These esters were then cyclised either thermally or photochemically to give 3-allylcoumarins (6a-f) and their benzo derivatives (6h-j). The photochemical cyclisation was achieved by keeping their benzene solution under sunlight. Coumarin 6j was obtained from 4j, only by photochemical cyclisation while coumarins 6d, 6h and 6i were obtained only by thermal cyclisation from esters 4d, 4h and 4i respectively. In case of 2g, when it reacted with phosphorane 3 in refluxing benzene (for 3 h) the final product 6g was obtained directly in 80% yield.

Stereochemistry of E-Ethyl α-Allylcinnamates (4a-j) - It is well established that Wittig reaction of stable phosphorane with carbonyl compounds provide a mixture of E and Z isomers of the olefinic compounds, the E isomer being the major one. In our hands when hydroxyaldehydes

TABLE 1 : PREPARATION OF ESTERS 4[a]

Compd. No.	Reaction conditions time/temp	Yield %	m.p (°C)	IR ν(cm^{-1}) (Solvent)	^{1}H NMR ($CDCl_3$/TMS) δ(ppm)
4a	1 h/ r.t.	97	-	1700 (C=O) 3370 (OH) (Neat)	1.27 (t, 3H, J=7Hz, $CH_2\underline{CH}_3$); 3.14 (br.d., 2H, J=6Hz, $\underline{CH}_2$-CH=CH_2); 4.18 (q, 2H, J=7Hz, $\underline{CH}_2CH_3$); 4.8-5.1 (m, 2H, CH_2-CH=$\underline{CH}_2$); 5.6-6.1 (m, 1H, CH_2-$\underline{CH}$=CH_2); 6.5-7.2 (m, 5H, ArH_4 and OH, exch.); 7.78 (s, 1H, -$\underline{CH}$=C).
b	4 h/r.t.	93	87	1670(C=O) 3270(OH) (Nujol)	1.32 (t, 3H, J=7Hz, $CH_2\underline{CH}_3$); 3.25 (br.d., 2H, J=6Hz, $\underline{CH}_2$-CH=CH_2); 3.78(s,3H,OCH_3); 4.28 (q,2H,J=7Hz,$\underline{CH}_2CH_3$); 4.95-5.25(m, 2H, CH_2-CH=$\underline{CH}_2$); 5.75-6.18 (m, 1H, CH_2-$\underline{CH}$=CH_2); 6.22 (s, 1H, OH, exch.); 6.5(m,2H,ArH); 7.21(d, 1H, J=9Hz,ArH); 7.88 (s, 1H, -$\underline{CH}$=C).
c	4 h/r.t.	94	80	1700 (C=O) 3280(OH) (Nujol)	1.33(t,3H,J=7Hz,$CH_2\underline{CH}_3$); 3.01(br.d,2H,J=6Hz, $\underline{CH}_2$-CH=CH_2); 3.78 (s,3H,OCH_3); 4.27 (q,2H, J=7Hz, $\underline{CH}_2CH_3$); 4.85-5.12 (m,2H,CH_2-CH=$\underline{CH}_2$); 5.38 (s, 1H, OH, exch.); 5.6-6.05 (m, 1H, CH_2-$\underline{CH}$=CH_2); 6.43 (d, 1H, J=9Hz, ArH); 6.52 (d, 1H,J=9Hz, ArH); 7.12 (t,1H, J=9Hz, ArH); 7.44 (s, 1H, -$\underline{CH}$=C)[b].
d	4 h/r.t.	98	-	1710 (C=O) 3380 (OH) (Neat)	1.28(t,3H,J=7Hz, $CH_2\underline{CH}_3$); 3.15 (br.d, 2H, J=6Hz, $\underline{CH}_2$-CH=CH_2); 3.8 (s, 3H, OCH_3); 4.18 (q, 2H,J=7Hz, $\underline{CH}_2CH_3$); 4.85-5.15 (m, 2H,CH_2-CH=$\underline{CH}_2$); 5.65-6.1 (m, 2H, CH_2-$\underline{CH}$=CH_2 and OH, exch.); 6.6-6.92 (m, 3H, ArH); 7.76 (s, 1H, -$\underline{CH}$=C)[b].
e	1 h/reflux	99	-	1680 (C=O) 3350 (OH) (Neat)	1.29 (t,3H,J=7Hz, $CH_2\underline{CH}_3$); 2.22 (s, 3H, CH_3); 3.15 (br.d, 2H, $\underline{CH}_2$-CH=CH_2); 4.18 (q, 2H, J=7Hz $\underline{CH}_2CH_3$); 4.85-5.1 (m, 2H, -CH_2-CH=$\underline{CH}_2$); 5.65-6.1 (m, 1H, CH_2-$\underline{CH}$=CH_2); 6.45-6.8 (m, 3H, ArH_2 and OH, exch.); 7.04 (d, 1H, J=8Hz, ArH); 7.79 (s, 1H, $\underline{CH}$=C)
f	3 h/reflux	90	98	1675 (C=O) 3260 (OH) (Nujol)	1.32 (t, 3H,J=7Hz, $CH_2\underline{CH}_3$); 2.12 (s, 3H, CH_3); 3.26 (br.d, 2H, $\underline{CH}_2$-CH=CH_2); 3.8 (s,3H,OCH_3); 4.28 (q, J=7Hz, -$\underline{CH}_2CH_3$); 4.95-5.28 (m, 2H, -CH_2-CH=$\underline{CH}_2$); 5.78-6.26 (m,2H, -CH_2-$\underline{CH}$=CH_2 and OH, exch.); 6.41 (s, 1H, ArH); 7.09(s,1H,ArH); 7.88 (s,1H, -$\underline{CH}$=C).

Table 1 : Contd.

Compd. No.	Reaction conditions time/temp	Yield %	m.p (°C)	IR ν(cm⁻¹) (Solvent)	^{1}H NMR (CDCl$_3$/TMS) δ(ppm)
4h	6 h/r.t.	87	103	1685 (C=O) 3300 (OH) (Nujol)	1.38(t,3H,J=7Hz,$CH_2\underline{CH_3}$); 2.98 (br.d, 2H, J=6Hz, -$\underline{CH_2}$-CH=CH_2); 4.29 (q, 2H, J=7Hz, $\underline{CH_2}$ -CH_3); 4.7-4.98 (m,2H,-CH_2-CH=$\underline{CH_2}$); 5.42-5.93 (m,2H,-CH_2-$\underline{CH}$=CH_2 and OH, exch.); 7.02-7.7 (m, 7H, ArH_5 and -$\underline{CH}$=C).
i	7 h/r.t.	75	75	1680 (C=O) 3350 (OH) (Nujol)	1.34 (t,3H, J=7Hz, $CH_2\underline{CH_3}$); 3.2(br.d, 2H, J=6Hz, $\underline{CH_2}$-CH=CH_2); 4.3 (q, 2H, J=7Hz, $\underline{CH_2}CH_3$); 4.93-5.24 (m, 2H. -CH_2-CH=$\underline{CH_2}$); 5.74-6.24 (m, 2H, -CH_2-$\underline{CH}$=CH_2 and OH, exch.); 7.17-7.84 (m, 5H, ArH); 7.94 (s, 1H, -$\underline{CH}$=C); 8.24 (m, 1H, ArH).
j	1 h/r.t.	87	64	1680 (C=O) 3260 (OH) (Nujol)	1.32 (t, 3H, J=7Hz, -$CH_2\underline{CH_3}$); 3.32 (br.d, 2H, J=6Hz, -$\underline{CH_2}$-CH=CH_2); 4.3 (q, 2H, J=7Hz, $\underline{CH_2}CH_3$); 5.0-5.3 (m, 2H, CH_2 -CH=$\underline{CH_2}$); 5.81-6.3 (m, 2H, -$CH_2\underline{CH}$=CH_2 and OH, exch.); 7.17-8.1 (m, 7H, ArH_6 and -$\underline{CH}$=C).

[a] All products gave satisfactory elemental analyses.

[b] Measured in CCl_4/TMS

TABLE 2 : PREPARATION OF 3-ALLYLCOUMARINS 6[a]

Compd. No.	Reactions conditions Time/ temp.(°C) yield	Keeping in sunlight time/yield	m.p (°C)	IR (Nujol) ν(cm⁻¹)	^{1}H NMR (CDCl$_3$/TMS) δ(ppm)
6a	6h/180 80%	25 h/90%	43[12]	1725	3.34 (br.d.,2H, J=6Hz, $\underline{CH_2}$-CH=CH_2); 5.1-5.38 (m, 2H, CH_2-CH=$\underline{CH_2}$); 5.78-6.22 (m,1H,$CH_2\underline{CH}$=CH_2); 7.1-7.8 (m, 5H, ArH_4 and C_4-H)
b	3h/180 67%	23 h/74%	55[12]	1725	3.20 (br.d., 2H, J=6Hz, $\underline{CH_2}$-CH=CH_2); 3.8 (s, 3H, OCH_3); 5.0-5.30 (m, 2H, -CH_2-CH=$\underline{CH_2}$); 5.68-6.12 (m, 1H, -CH_2-$\underline{CH}$=CH_2); 6.65-6.78 (m, 2H, C_6-H and C_8-H); 7.21 (d, 1H, J=9Hz, C_5H); 7.31 (s, 1H, C_4-H).[b]

Table 2 : Contd.

Compd. No.	Reactions conditions Time/ temp.(°C) yield	Keeping in sunlight time/yield	m.p (°C)	IR (Nujol) ν (cm⁻¹)	^{1}H NMR ($CDCl_3$/TMS) δ (ppm)
6c	1h/170 64%	57 h/71%	80-81	1740	3.31 (br.d., 2H, J=6Hz, -C<u>H</u>$_2$-CH=CH$_2$); 3.9(s, 3H, OCH_3); 5.06-5.34 (m, 2H, CH$_2$-CH=C<u>H</u>$_2$); 5.76-6.22 (m, 1H, CH$_2$-C<u>H</u>=CH$_2$); 6.66 (d, 1H, J=9Hz, C_6-H); 6.86 (d, 1H, J=9Hz, C_8-H); 7.35 (t, 1H, J=9Hz, C_7-H); 7.84 (s, 1H, C_4-H).
d	2h/250 80%	-	77	1725	3.28 (br.d, 2H, J=6Hz, -C<u>H</u>$_2$-CH=CH$_2$); 3.95 (s, 3H, OCH_3); 5.0-5.54 (m, 2H, CH$_2$-CH=C<u>H</u>$_2$); 5.7-6.2 (m, 1H, CH$_2$-C<u>H</u>=CH$_2$); 6.8-7.25 (m,3H,ArH); 7.4 (s, 1H, C_4-H).
e	5h/180 65%	21 h/68%	123--124	1750	2.39 (s, 3H, CH_3); 3.2 (br.d, 2H, J=6Hz, C<u>H</u>$_2$-CH=CH$_2$); 5.0-5.28 (m, 2H, CH$_2$CH=C<u>H</u>$_2$); 5.65-6.15 (m, 1H, CH$_2$-C<u>H</u>=CH$_2$); 6.8-7.4 (m, 4H, ArH_3 and C_4-H).
f	2h/180 78%	18 h/80%	104--105	1725	2.15 (s, 3H, CH_3); 3.2 (br.d, 2H, J=6Hz, C<u>H</u>$_2$-CH=CH$_2$); 3.82 (s, 3H, OCH_3); 5.0-5.25 (m, 2H, -CH$_2$-CH=C<u>H</u>$_2$); 5.68-6.20 (m, 1H, CH$_2$-C<u>H</u>=CH$_2$); 6.72 (s, 1H, C_8-H), 7.02 (s, 1H, C_5-H); 7.25 (s, 1H, C_4-H).
g	-	-	131	1710	3.3 (br.d, 2H, J=6Hz, -C<u>H</u>$_2$ -CH=CH$_2$); 3.88 and 3.91 (s, 3H each 2 x OCH_3); 5.1-5.37 (m, 2H, -CH$_2$-CH=C<u>H</u>$_2$); 5.79-6.28 (m,1H,-CH$_2$-C<u>H</u>=CH$_2$); 6.3 (d, 1H, J=2Hz, C_6-H), 6.42 (d, 1H, J=2Hz, C_8-H); 7.79 (s, 1H, C_4-H).
h	1h/200 85%	-	90	1710	3.31 (br.d, 2H, J=6Hz, -C<u>H</u>$_2$-CH=CH$_2$); 4.9-5.38 (m,2H,-CH$_2$-CH=C<u>H</u>$_2$); 5.61-6.38 (m, 1H, CH$_2$-C<u>H</u>=CH$_2$); 7.12-8.15 (m, 7H, ArH_6 and C_4-H)
i	1h/200 69%	-	88	1710	3.36 (br.d, 2H, J=6Hz, -C<u>H</u>$_2$-CH=CH$_2$); 5.07-5.4 (m, 2H, -CH$_2$-CH=C<u>H</u>$_2$); 5.78-6.3 (m, 1H, -CH$_2$-C<u>H</u>=CH$_2$); 7.20-7.92 (m, 6H, ArH_5 and C_4-H), 8.51 (m, 1H, ArH).
j	-	28 h/86%	153	1715	3.26 (br.d, 2H, J=6Hz, -C<u>H</u>$_2$-CH=CH$_2$); 4.9-5.26 (m, 2H, -CH$_2$-CH=C<u>H</u>$_2$); 5.5-6.3 (m, 1H, -CH$_2$-C<u>H</u>=CH$_2$); 7.0-7.72 (m, 7H, ArH_6 and C_4-H)

[a] All products gave satisfactory elemental analyses.

[b] Measured in $CDCl_3$ + CCl_4 /TMS.

2a-j reacted with phosphorane 3 the E-isomer of ethyl α-allylcinnamates were formed exclusively in 87-99% yield (except in case of 4i, where the yield was 75%). The stereochemistry of these esters has been established on the basis of their ^{1}H-NMR properties. The olefinic proton in all these compounds appeared as a singlet at about δ 7.5. These values were closer to the calculated[10] value (δ 7.8) for E isomer(4). The calculated value for the olefinic proton in the Z-isomer (5) was found to be δ 6.23. The ^{1}H-NMR properties thus indicated that the esters formed were the E-isomers (4a-j).

The phosphorane 3 required for the synthesis of coumarins 6a-j was prepared from the easily available phosphorane 7[11]. Thus, the phosphorane 7 was reacted with allyl bromide in chloroform to give salt 8 which on reaction with 2 N sodium hydroxide furnished the stable phosphorane 3 in 75% overall yield.

The ready availability of the stable phosphorane having allyl group and superior overall yields makes the present method attractive.

EXPERIMENTAL

All melting points are uncorrected. ^{1}H-NMR spectra were recorded on a Perkin-Elmer R-32, 90 MHz instrument, Chemical Shifts are expressed in δ(ppm) downfield from TMS as an internal standard. IR spectra (ν_{max} in cm^{-1}) were recorded on a Beckman IR-20 infrared spectrophotometer.

Preparation of Phosphorane 3

A solution of allyl bromide (3.47 g, 2.87 mmol) in chloroform (5 ml) was added to a solution of triphenylethoxycarbonylmethylidenephosphorane[11] (7, 10 g, 2.87 mmol) in chloroform (20 ml). The reaction mixture was refluxed for 8 h and the solvent was removed under reduced pressure. Ether (20 ml) was added to the oily residue and cooled to 0°C. It was then scratched to get a white solid which was filtered and washed with benzene. It was recrystallized from chloroform-hexane to give the salt 8 (12.7 g, 94%), m p 150-151°C. Anal. Calcd. $C_{25}H_{26}O_2PBr$: C, 63.97; H, 5.58. Found : C, 63.94; H, 5.60%.

The above salt (8) dissolved in water (150 ml) and benzene (100 ml) was added to it. It was then made alkaline (at 25°C) with 2N NaOH. The benzene layer was separated and the aqueous layer was extracted with benzene (100 ml). The combined benzene layer was dried (Na_2SO_4) and the solvent removed under reduced pressure to get a crude product. It was recrystallised from benzene-hexane to furnish phosphorane 3 (8.20 g, 78%), m p 122°C. Anal. Calcd. $C_{25}H_{25}O_2P$: C, 77.30; H, 6.48. Found : C, 77.45; H, 6.53%.

General Procedure for the Preparation of Hydroxy Esters (4a-j)

A mixture of o-hydroxybenzaldehyde (2, 0.01 mol) and phosphorane (3, 0.01 mol) in benzene (20ml) was either stirred or refluxed according to the conditions mentioned in Table 1. The solvent was removed under reduced pressure and the residue obtained was chromatographed over silica gel using hexane-ehtyl acetate (90 : 10) as eluent, to furnish compound 4a-j. The solid products

(4b,c,f,h-j) were recrystallised from hexane-dichloromethane and the liquids (4a,d,e) were analysed as such (these compounds got cyclised during distillations).

General Procedure for 3-Allylcoumarins (6a-j)

The hydroxy esters (4) were either heated as such in nitrogen atmosphere or dissolved in benzene and kept in sunlight according to the conditions mentioned in Table 2. The residue obtained, either directly or after removal of the solvent was chromatographed over silica gel using hexane-ethyl acetate (95:5) as eluent, to get 3-allylcoumarins (6). The coumarin 6f was recrystallised from hexane while the other 3-allylcoumarins were recrystallised from hexane-chloroform.

ACKNOWLEDGEMENT

We thank Professor N. S. Narasimhan for helpful discussion and Dr. D. D. Dhavale, Smt. J. P. Chaudhari and Mr. A. P. Gadgil, for spectral and analytical data. One of us (SNY) thanks the CSIR, New Delhi for the award of a Senior Research Fellowship. Financial support from the CSIR, New Delhi is also gratefully acknowledged.

REFERENCES AND NOTES

1. R. D. H. Murray, J. Mendez and S. A. Brown, "The Natural Coumarins", John Wiley and Sons Ltd., Chichester, New York, 1982.
2. A. Shoeb, M. D. Manandhar, R. S. Kapil and S. P. Popli, Chem. Commun., 1978, 281.
3. G. S. R. Subba Rao, K. Raj and V. P. S. Kumar, Indian J. Chem., 1981, 20B, 88.
4. R. D. H. Murray, 'Progress in the Chemistry of Natural Products' ed. by W. Herz, H. Grisebach and G. Kirby, Wein-Springer-Verlag, New York, 1978, Vol. 35.
5. R. K. Singh and M. D. Rogers, J. Heterocyclic Chem., 1985, 22, 1713.
6a. R. S. Mali, S. N. Yeola and B. K. Kulkarni, Indian J. Chem., 1983, 22B, 352, and references cited therein.
6b. K. Sunitha, K. K. Balasubramanian and K. Rajgopalan, J. Org. Chem., 1985, 50, 1530.
7. V. K. Ahluwalia, C. Prakash and R. Gupta, Synthesis, 1980, 48.
8. R. B. Sharma, D. Swaroop and R. S. Kapil, Indian J. Chem., 1981, 20B, 153.
9. M. M. Ballantyne, P. H. McCabe and R. D. H. Murray, Tetrahedron, 1971, 27, 871.
10. E. Pretsch, T. Clerc, J. Seibl and W. Simon, Tabellen zur Strukturaufklarung Organischer Verbindungen mit Spektroskopischen Methoden, Springer, Berlin 1976.
11. D. B. Denney and S. T. Ross, J. Org. Chem., 1962, 27, 998.
12. The literature melting points (ref. 7) of coumarins 6a and 6b are 110-111°C and 124-125°C which are quite different from the observed mps. The elemental analysis, spectral data and the mode of formation suggested structures 6a and 6b for these coumarins. Except compounds 6a and 6b all the compounds reported in this paper are new.

Received, 11th August, 1986