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Vijayendra P. Kamat [a] , Ratnakar N. Asolkar [a] & Janardan K. Kirtany [a]
[a] Department of Chemistry , Goa University , Taleigao Plateau, Goa, 403206, India
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SYNTHESIS OF FLAVANS :ONE-POT SYNTHESIS OF FLAVANS FROM 4-METHYLCOUMARINS.

Vijayendra P. Kamat* , Ratnakar N. Asolkar and Janardan K. Kirtany

Department of Chemistry, Goa University,
Taleigao Plateau, Goa 403 206, India.

ABSTRACT : 4 -Methylcoumarins (2), obtained by condensation of suitable phenols (1) with ethyl acetoacetate in the presence of sulfuric acid, lead directly to flavans (3) when refluxed with sodium hydroxide and ethanediol.

In a recent communication, Yoshida,*et al.*[1] reported the isolation and structure elucidation of a thymol dimer, inulavosin (3a), from the root of *Inula nervosa* .This flavan was shown to be a piscicide, and since piscicides often exhibit other biological activities, as has been noted earlier[1], it was of interest to develop a general method for the synthesis of flavans having structure (3).

It has been reported by one of us[2] that flavan structure (3) could be obtained by dimerisation of appropriate *o*-isopropenylphenol. The latter, in principle, in turn, should be obtainable and has been obtained by Divakar and Rao[3] from the

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* To whom correspondence should be addressed.

appropriately substituted 4 -methylcoumarin by refluxing a mixture of the latter , ethanediol and sodium hydroxide.

It was anticipated by us therefore that *in situ* generation of *o*-isopropenylphenols from 4 - methylcoumarins(2), by treatment of the latter with ethanediol and sodium hydroxide, could lead directly to one-pot synthesis of flavans (3) (Scheme 1). This has indeed been realised in practice and the results are shown in Table 1. Thus, when 4,7-dimethylcoumarin (2a) was treated as described above, it furnished a product having structure (3a) in 68 % yield.The spectral data (^{1}H NMR, ^{13}C NMR) obtained on our synthetic (3a) agreed well with those reported[1] on natural inulavosin. A point of interest to note here is that our synthetic (3a) was a crystalline solid having m.p.76°C, in contrast to the natural product which is reported to be an oil. Similarly, the product (3b) obtained by Livant,*et al.*[4], by the reaction of resorcinol with acetone , was found to be identical with the product obtained by us from 7-hydroxy-4-methylcoumarin (2b) using the present method. Moreover, the above sequence when carried out on p-cresol furnished (3c), which has been shown to be identical with the corresponding product obtained by Dinge,*et al.*[2]. Further, the acetate (Ac_2O/Py) of our synthetic(3c) was proved to be identical with the corresponding acetate reported by the latter authors. Other phenols used in the present study are 2,3-dimethylphenol (1d) and 3,4 -dimethylphenol (1e). The corresponding 4 -methylcoumarins (2d & 2e) and the flavans (3d &3e) obtained by us have been satisfactorily characterised by spectral and analytical data (see Table 2).

SCHEME 1 :

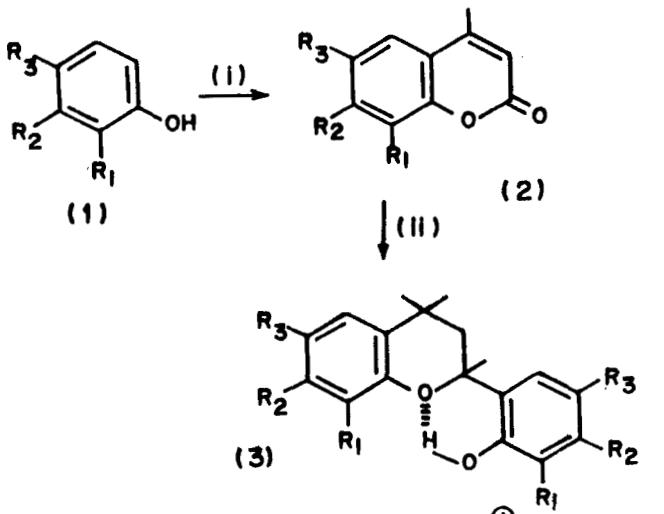

TABLE 1

Compound	R_1	R_2	R_3	Yield (%)
3a	H	CH_3	H	68
3b	H	OH	H	64
3c	H	H	CH_3	80
3d	CH_3	CH_3	H	61
3e	H	CH_3	CH_3	78

The method described herein is simple ,easy to perform,and is generally applicable to the synthesis of a large number of flavans having structure (3).

In summary , we have developed a general route to the synthesis of flavans having structure (3) starting from the appropriate phenols (1) via the corresponding 4 -methylcoumarins (2) as intermediates.

EXPERIMENTAL:

All melting points are uncorrected. Column chromatography was performed on silica gel 60 - 120 mesh size and tlc on silica gel G (13% $CaSO_4$ as binder). IR spectra were recorded on a Shimadzu FTIR -8001 (KBr pellet or neat sample), ^1H NMR spectra (TMS, $CDCl_3$) were recorded on a Bruker WM 400 MHz, and 200 MHz FT NMR spectrometer. Mass spectra were recorded on Jeol D -300 Mass spectrometer at 70 eV.

REPRESENTATIVE METHOD OF PREPARATION OF FLAVANS (3):

PREPARATION OF (3a)

A mixture of 4,7-methylcoumarin (2a) (3.0 g, 17.24 mmol), sodium hydroxide (3.5 g, 86.2 mmol) and ethanediol (20 mL) was refluxed at 210 °C under nitrogen for two and half hours, cooled, diluted with water and covered with diethyl ether (50 mL). Dilute HCl (aq) was added with stirring till pH was 2 . The organic layer was separated and aqueous layer extracted with ether (25 mL x 2). The combined diethyl ether extracts were washed with water and dried ($MgSO_4$). After removal of solvent, the residue was chromatographed on a silica gel column and eluted using

pet. ether (60^0C - 80^0C) : diethyl ether (97:3) as eluent,which furnished a crystalline solid (3a) (1.728 g , 68 %); m.p. 76 °C.

Table 2. Spectral data of Flavans (3a-e)

Compound (3a) : Solid , m.p. 76 °C (lit[1] Colourless oil) ; mol. formula $C_{20}H_{24}O_2$ (M^+ 296) ; ^{1}H NMR (400 MHz ,$CDCl_3$) : 1.18 (s, 3H), 1.43 (s,3H), 1.69 (s, 3H) , 1.69 (s, 3H) , 2.27 (s, 3H) , 2.30 (s, 3H) , 2.06 (d, 1H , J= 15 Hz), 2.54 (d, 1H , J= 15 Hz) , 6.65 (dd, 1H , J= 8 Hz , 2.5 Hz) , 6.81 (dd, 1H , J= 8 Hz , 2.5 Hz), 6.67 (d, 1H , J= 2.5 Hz) , 6.75 (d, 1H , J= 2.5 Hz), 7.04 (d , 1H , J= 8 Hz), 7.18 (d, 1H , J= 8 Hz) , 8.18 (s, 1H) ; ^{13}C NMR ($CDCl_3$,TMS) : 154.44 (quat) , 150.17 (quat) , 138.91 (quat), 137 (quat) , 129.00 (quat) , 126.95 (quat) , 126.58 (CH), 126.38 (CH) , 123.14 (CH), 120.47 (CH) , 118.35 (CH) , 118.12 (CH), 81.59 (quat) , 47.82 (CH_2) ,33.03 (CH_3), 32 (CH_3), 30.80 (quat), 29.68 (CH_3), 20.80 (CH_3) , 20.80 (CH_3).

Compound (3b) : Solid , m. p. 234 °C (lit[4] m.p. 231-232 ^{0}C) ; mol. formula $C_{18}H_{20}O_4$ (M^+300); ^{1}H NMR (200 MHz , $CD_3OD + D_2O$) : δ 0.72 (s, 3H), 1.17 (s, 3H), 1.6 (s, 3H), 1.79 (d, 1H, J= 13.8 Hz) , 3.0 (d, 1H, J= 13.8 Hz), 6.35 (d, 1H, J= 2.5 Hz), 6.21 (d, 1H, J=2.5 Hz), 6.30 (dd, 1H, J= 8.5 Hz, 2.5 Hz), 6.07 (dd, J= 8.5 Hz, 2.5 Hz), 6.92 (d, 1H, J= 8.5 Hz), 6.96 (d, J= 8.5 Hz); ^{13}C NMR (CD_3OD, 200 MHz) : 157.99 (quat), 157.17 (quat), 156.18 (quat), 154.82 (quat), 128.58 (CH), 128.40 (CH), 124.08 (quat , 2 C`s), 109.25

(CH), 106.84 (CH), 104.12 (CH), 104.05 (CH),79.10 (quat), 46.61 (CH_2), 33.59 (CH_3), 31.20 (quat), 30.23 (CH_3), 30.05 (CH_3).

Acetate of compound (3c) : Solid , m.p. 148 ^{0}C (lit[2] m.p. 147-148 ^{0}C) ; IR (KBr) 1745 cm^{-1} ; ^{1}H NMR (200 MHz,$CDCl_3$) : δ 0.83 (s ,3H), 1.31 (s ,3H), 1.62 (s ,3H), 2.22 (s , 3H), 2.27 (s , 3H), 2.34 (s, 3H), 2.07 (d, 1H , J= 15 Hz), 2.55 (d, 1H , J=15 Hz), 6.95 (m, 5H) , 7.31 (slightly bs, 1H).

Compound (3d) : Viscous oil ; ^{1}H NMR (200 MHz , $CDCl_3$) :δ 1.23 (s , 3H), 1.46(s , 3H), 1.69 (s , 3H), 2.05 (d , 1H , J=15 Hz) , 2.5 (d ,1H, J= 15 Hz), 2.18 (s, 3H) , 2.19 (s ,3H) 2.26 (s , 3H) , 2.27 (s , 3H) , 6.69 (d , 1H, J= 8 Hz), 6.84 (d , 1H, J= 8 Hz), 6.93 (d , 1H, J=8 Hz) 7.03 (d , 1H, J= 8 Hz) , 8.73 (s , 1H). Anal. Calcd. for $C_{22}H_{28}O_2$: C, 81.48 ; H , 8.64 . Found : C , 81.54 ; H , 8.47 .

Compound (3e) : Solid , m.p. 157 °C ; ^{1}H NMR (200 MHz , $CDCl_3$) : δ 1.21 (s , 3H) 1.43 (s , 3H), 1.67 (s , 3H), 2.05 (d , 1H , J=15 Hz) , 2.52 (d ,1H, J= 15 Hz), 2.18 (s, 6H) , 2.20 (s ,6H), 6.65 (s ,1H), 6.72 (s ,1H), 6.86 (s , 1H), 7.02 (s ,1H), 8.18 (s, 1H). Anal. Calcd. for $C_{22}H_{28}O_2$: C, 81.48 ; H , 8.64 . Found : C ,81.03 ; H , 8.74 .

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