SHORT PAPER

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Condensation of phenols with alkylcinnamates in the presence of $FeCl_3$[1†]

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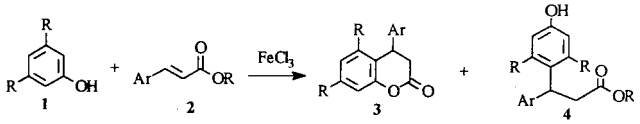
Ferric chloride catalyses the condensation of phenols with alkylcinnamates to produce 3,4-dihydro-4-arylcoumarins.

Coumarins constitute an important class of bioactive natural products.[2] They have been found to possess diverse biological properties including antimicrobial, insecticidal, estrogenic, anticoagulant and antithrombotic activities. Some coumarins have been identified as active nonpeptidic HIV protease inhibitors. In continuation of our recent work[3] on the synthesis of bioactive molecules we were interested in the preparation of 4-arylcoumarins and related compounds which will be utilized for evaluation of their biological properties.

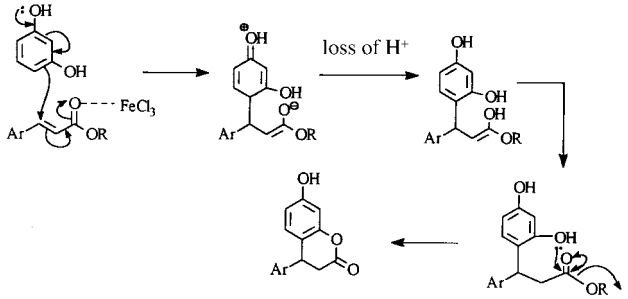
Several phenols (**1**) were condensed with alkylcinnamates (**2**) in the presence of $FeCl_3$ as catalyst to produce 3,4-dihydro-4-arylcoumarins (Scheme 1, Table 1). In some cases the uncyclised 3,3-diaryl alkylpropionates (**4**) were also obtained in low yields along with these coumarin. However, the condensation of catechol with 3-methoxy-4-hydroxyethylcinnamate (entry 9) produced no coumarin derivative and the uncyclised compound was formed as the sole product. The structures of all the products were established from their spectroscopic (^{1}H NMR and MS) properties. Some of the coumarin derivatives (entry 3,4,6 and 7) prepared by the present method were found to be the analogues of naturally occurring 4-aryl coumarins.[4] The prepared 3,4-dihydro-4-arylcoumarins could also be converted into the corresponding 4-aryl comarins by following the known oxidation method with DDQ.[5]



Scheme 1

The plausible mechanism of the $FeCl_3$ catalysed condensation of phenols with alkyl cinnamates is shown in Scheme 2. $FeCl_3$ possibly activated the carbonyl group of the ester function through co-ordination. The *para* position with respect to a phenolic hydroxyl group of a phenol in mainly involved in reaction with the C_3-portion of an alkylcinnamate.

This is the first report of the application of $FeCl_3$ as catalyst for condensation of phenols with alkylcinnamates. Previously the condensation was carried out with concentrated protogenic acids (H_2SO_4, HCl, H_2SO_4–HOAc, H_3PO_4, TFA) or with other Lewis acid in strong acidic media ($AlCl_3$–HCl, $ZnCl_2$–$POCl_3$) under reflux.[6] In the present case no other acid is added with $FeCl_3$ and the condensation generally proceeds within 2 h at room temperature. Uncatalysed condensation under reflux at high temperature is also reported[6] but usually it takes a longer reaction time.



Scheme 2

Experimental

Melting points were measured in a Buchi-510 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectometer using TMS as internal standard, IR spectra on Nicolet 740 FTIR spectrophotometer and mass spectra on VG Micromass 7070 H (70 eV).

Condensation of phenols with alkylcinnamate using $FeCl_3$

Phenol (1.2 eq.) and alkylcinnamate (1 eq.) were dissolved in $CHCl_3$ (10 ml). $FeCl_3$ (1.2 eq.) was added. The mixture was stirred for 2 h at room temperature under nitrogen atmosphere. For entry nos 5 and 6 the mixture was refluxed for 2 h. Water (10 ml) was added to the mixture and this was extracted with $CHCl_3$ (3 × 10 ml). The concentrated extract was subjected to column chromatography to produce 3,4-dihydro-4-arylcoumarins and 3,3-diaryl alkylpropionates.

The spectroscopic and analytical data of some selective compounds are given below.

3,4-Dihydro-4-(3-methoxy-4-hydroxy)-phenylcoumarin: White solid; m.p. 135–136°C (MeOH); ^{1}H NMR ($CDCl_3$): δ 7.35–6.56 (7H, m, Ar-H), 5.50 (1H, brs, -OH), 4.25 (1H, brt, *J* = 7.2 Hz, Ar–CH<), 3.85 (3H, s, -OMe), 3.12-2.90 (2H, m, -CH_2-); MS : *m/z* 270 ($M^{+\cdot}$), 252, 227; Anal. calcd. for $C_{16}H_{14}O_4$: C, 71.11; H, 5.18. Found: C, 71.18; H, 5.21.

3-(3-Methoxy-4-hydroxyphenyl)-3-(4-hydroxyphenyl)-ethylpropionate: White solid; m.p. 188–189°C (MeOH); ^{1}H NMR ($CDCl_3$) : δ 7.30 (2H, d, *J* = 10.0 Hz, Ar–H), 6.81-6.60 (5H, m, Ar–H), 5.42 (1H, brs, –OH), 5.30 (1H, brs, -OH), 4.38 (1H, t, *J* = 8.2 Hz, Ar–CH<), 4.02 (2H, q, *J* = 7.5 Hz,-O-CH_2-), 3.82 (3H, s, -OMe), 2.94 (2H, d, *J* = 8.2 Hz, -CH_2-COOEt), 1.16 (3H, t, *J* = 7.5 Hz, -Me); MS : *m/z* 316 (M+.), 229; Anal. calcd. for $C_{18}H_{20}O_5$: C, 68.35; H, 6.33. Found: C, 68.39; H, 6.28.

3,4-Diydro-4-(3-methoxy-4-hydroxyphenyl)-6-methylcoumarin: Viscous mass; ^{1}H NMR (CDCl3) : δ 6.95-6.80 (4H, m, Ar–H), 6.70–6.55 (2H, m, Ar–H), 5.48 (1H, brs, -OH), 4.20 (1H, brt, *J* = 7.5 Hz, Ar–CH<), 3.84 (3H, s, -OMe), 3.08–2.85 (2H, m, -CH_2-), 2.38 (3H, s, –Me); MS : *m/z* 284, 241, 211; Anal. calcd. for $C_{17}H_{16}O_4$: C, 71.83; H, 5.63. Found: C, 71.85; H, 5.66.

3-(2-Hydroxy-4-methylphenyl)-3-(3-methoxy-4-hydroxyphenyl)-ethylpropionate: Viscous mass; ^{1}H NMR (CDCl3): δ 7.40 (1H, d, *J* = 9.0 Hz, Ar-H), 6.73 (2H, d, *J* = 8.0 Hz, Ar–H), 6.65–6.50 (4H, m, Ar–H), 5.33 (1H, brs, –OH), 4.72 (1H, brs, –OH), 4.54 (1H, t, *J* = 8.4 Hz, Ar–CH<), 4.04 (2H, q, *J* = 7.5 Hz, -OCH_2-), 3.80 (3H, s, -OMe), 2.90 (2H, d, *J* = 8.4 Hz), 2.20 (3H, s, Ar-Me), 1.14 (3H, t, *J* = 7.5 Hz, -Me); MS: *m/z* 330 (M+.), 244; Anal. calcd. for $C_{19}H_{22}O_5$: C, 69.09; H, 6.66. Found: C, 69.14; H, 6.72.

3,4-Dihydro-4-phenyl-7-hydroxycoumarin: White solid; m.p. 161–162°C (MeOH); ^{1}H NMR ($CDCl_3$) : δ 7.25–6.95 (5H, m, Ar–H), 6.65 (1H, d, *J* = 9.0 Hz, Ar–H), 6.48–6.35 (2H, m, Ar-H), 4.13 (1H,

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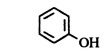
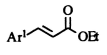
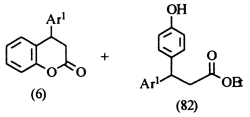
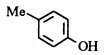
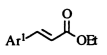
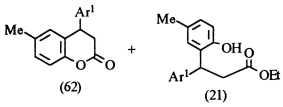
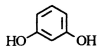
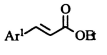
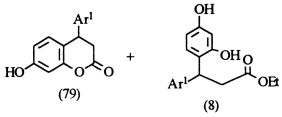
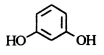
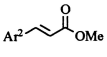
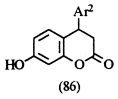
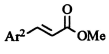
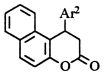
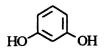
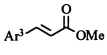
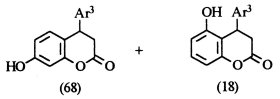
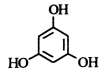
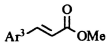
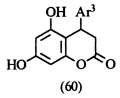
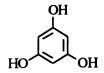
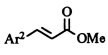
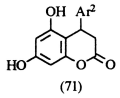
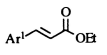
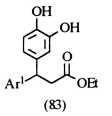
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Condensation of phenols with alkylcunnamates using $FeCl_3$

Entry	Phenol	Alkylcinnamate	Product(s) ([Isolated yield (%))
1			 (6) + (82)
2			 (62) + (21)
3			 (79) + (8)
4			 (86)
5			 (92)
6			 (68) + (18)
7			 (60)
8			 (71)
9			 (83)

Ar^1 = 3-Methoxy-4-hydroxyphenyl; Ar^2=3,4-Dimethoxyphenyl; Ar^3 = Phenyl

brt, *J* = 7.5 Hz, Ar–CH<), 2.99–2.78 (2H, m, -CH_2-); MS: *m/z* 240 ($M^{+\cdot}$), 197, 131; Anal. calcd. for $C_{15}H_{12}O_3$: C, 75.0; H, 5.0. Found: C, 75.23; H, 5.16.

3,4-Dihydro-4-phenyl-5-hydroxycoumarin: Viscous mass; ^{1}H NMR ($CDCl_3$): 7.32–7.08 (6H, m, Ar-H), 6.64 (2H, d, *J* = 9.0 Hz), 4.65 (1H, brt, *J* = 7.8 Hz, Ar–CH<), 3.12–2.95 (2H, m, –CH_2–); MS : *m/z* 240 (M+.), 212, 197; Anal. calcd. for $C_{15}H_{12}O_3$: C, 75.0; H, 5.0. Found : C, 74.94; H, 5.12.

3-(3,4-Dihydroxyphenyl)-3-(3-methoxy-4-hydroxyphenyl)-ethylpropionate: White solid; m.p. 152–154°C (MeOH); ^{1}H NMR ($CDCl_3$): δ 6.84–6.55 (6H, m, Ar–H), 5.55 (1H, brs, -OH), 5.40 (1H, brs, -OH), 4.32 (1H, t, *J* = 8.0 Hz, Ar–CH<), 4.04 (2H, q, *J* = 7.5 Hz, -OCH_2-), 3.81 (3H, s, -OMe), 2.92 (2H, d, J = 8.0 Hz, CH_2–COOEt), 1.15 (3H, t, *J* = 7.5 Hz, -Me); MS: *m/z* 332, 245; Anal. calcd. for $C_{18}H_{20}O_6$: C, 65.06; H, 6.02. Found: C, 65.12; H, 5.96.

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1 Part 9 in the series "*Studies on Novel Synthetic Methodologies*"; for part 8 see B. Das, N. Ravindranath, B. Venkataiah and P. Madhusudhan, *J. Chem. Res. (S)*, 2000 (submitted). IICT Communication No. 4588.

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