SYNTHESIS OF SUBSTITUTED 4-(METHOXYPHENYL)-3,4-DIHYDROCOUMARINS

Jacques Chenault*

Laboratoire de Chimie Organique - Chimie IV.

Jean-François E. Dupin

Laboratoire d'Etude des Composés Phénoliques.

U.E.R. de Sciences Fondamentales et Appliquées.

Université d'Orléans - 45046 Orléans Cédex - France

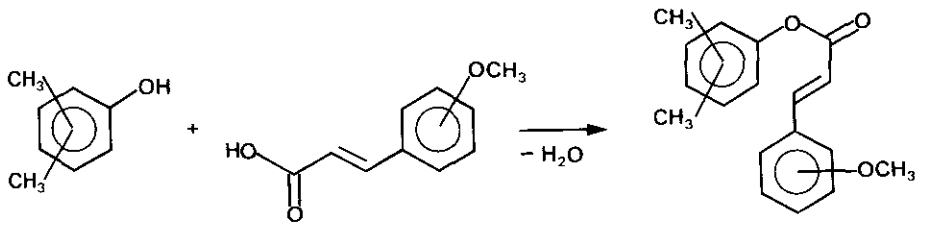
ABSTRACT - In polyphosphoric acid (PPA), 2- and 4-methoxycinnamic acids react with various dimethylphenols to give 4-phenyl-3,4-dihydrocoumarins by direct cycloaddition, whereas 3-methoxycinnamic acid, in the same conditions, also gives a flavanone formed by Fries rearrangement from a hydroxychalcone. These results are discussed in terms of electronic effects due to the methoxy substituents on the cinnamic acids.

Numerous 4-phenyl-3,4-dihydrocoumarins (*) have been synthesized by the reaction of phenols with cinnamic acids, cinnamates or corresponding nitriles with condensing reagents such as $AlCl_3$, $ZnCl_2$, $SbCl_3$, BF_3, H_2SO_4, HCl or polyphosphoric acid (PPA)[1-6]. In all these reports, reactions are performed between substituted phenols and cinnamic acids or derivatives without substituents on the phenol group. In this case, the course of the reaction is only affected by the substituents on the phenol moiety. It therefore seemed worthwhile to study the influence of a substituent on the phenyl moiety of cinnamic acids on the mechanism of the reaction. In order to test this we have condensed 2-, 3- and 4-methoxycinnamic acids on 3,4-, 3,5- and 2,4-dimethylphenols by means of polyphosphoric acid (a reagent often used in cyclodehydrations), at a temperature close to 50°C. The results show the importance of position of the methoxy group on the course of the reaction. 2-Methoxycinnamic acid condensed with the above dimethylphenols gives only dimethylated 4-(2'-methoxyphenyl)-3,4-dihydrocoumarins. In the same conditions, 3-methoxycinnamic acid leads to a mixture of 3,4-dihydrocoumarins, phenylcinnamate, hydroxychalcone and, occasionally, flavanone while 4-methoxycinnamic acid gives only 3,4-dihydrocoumarins at low temperature and, by increasing the temperature, coumarins by loss of the anisyl group.

(*) 2H-1,4-phenyl-3,4-dihydrobenzopyran-2-one.

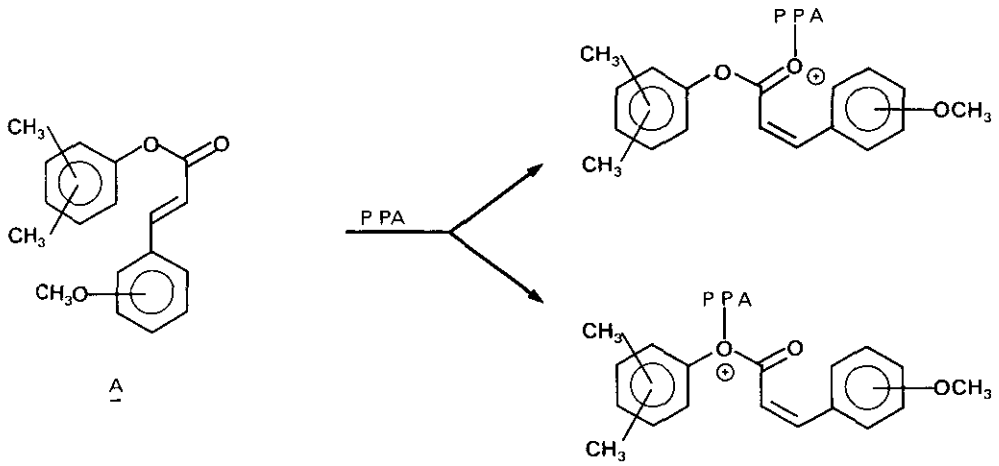
PPA is well known to catalyse cyclodehydration reactions[7,8]. It has been used in the synthesis of some 4-phenyl-3,4-dihydrocoumarins from phenols and cinnamic acid by Hasebe [5,6] and by Reichel and Proksch[9] in the condensation of o-coumaric acid with anisole. These authors don't propose an accurate mechanism to explain the influence of substituents.

Our results are summarized in Table I. The first step of the mechanism is the formation of a phenyl cinnamate by dehydration, as suggested by the formation of 6A by the reaction of 2,4-dimethylphenol with 3-methoxycinnamic acid.



A

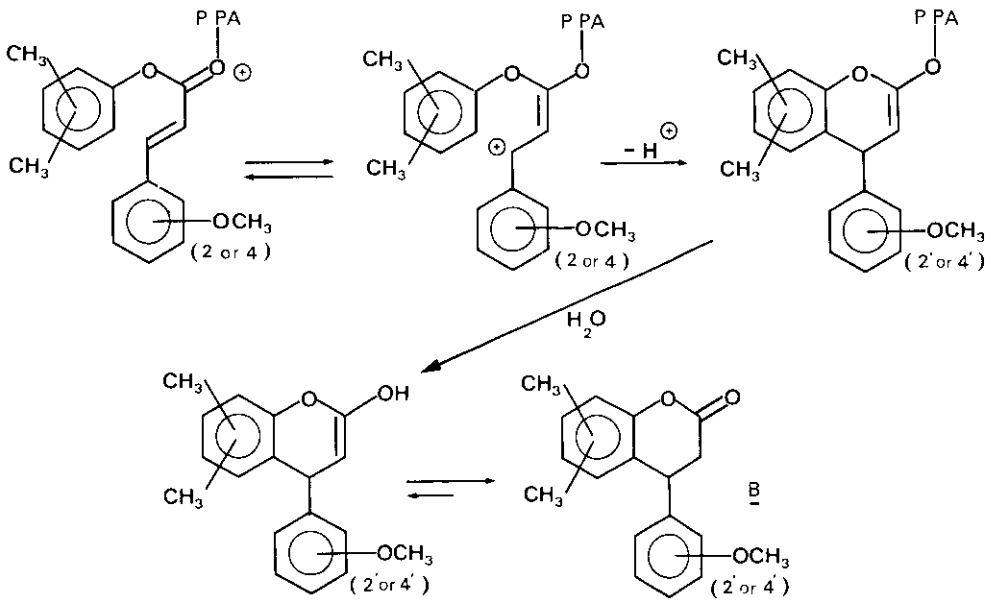
If we refer to the mechanisms reported by Conia and co-workers[10,11], Allen and co-workers[12], in relation to the cyclisation of α-alkenyl esters or alkenyl aryl ketones, solubilization of the ester seems to occur by the formation of a coordination complex between PPA and the more nucleophilic oxygen atom of the ester group.



Depending on the position of methoxy group on cinnamic acid, the second step of the mechanism could proceed via two schemes: in the case of 2-methoxy- and 4-methoxycinnamic acid, the +M (electron donating) effect of the methoxy groups could favor the formation of a coordination complex of

PPA with the carbonyl oxygen atom of the ester function ; the reaction would then continue by a Friedel-Crafts cyclisation and the hydrolysis would give a 4-methoxyphenyl-3,4-dihydrocoumarin (scheme 1). Reactions 1, 2, 3, 7, 8 and 9, summarized in Table I, agree with this assumption.

Scheme 1

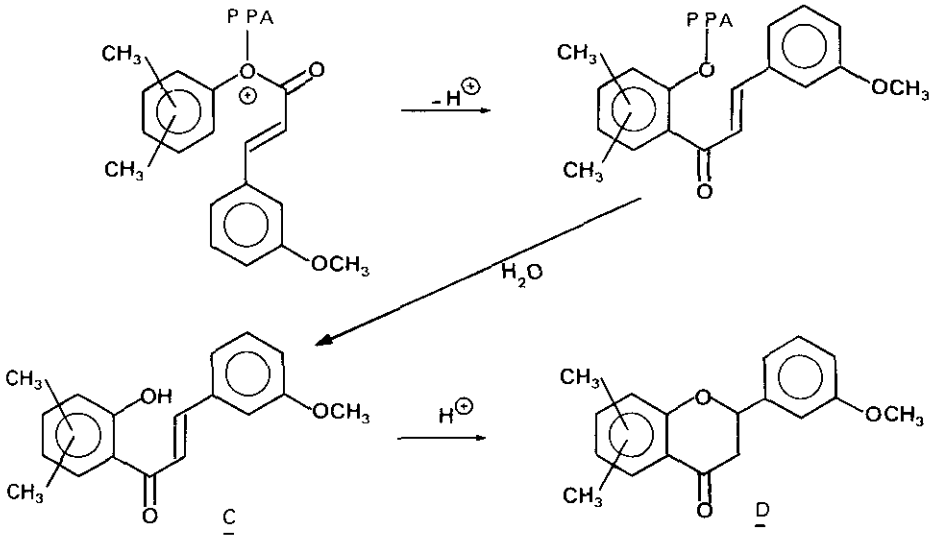


In the case of 3-methoxycinnamic acid, the -I(electron withdrawing) effect is weighty (this is supported by the acidic strength of 3-methoxycinnamic acid[16]). The coordination complex would be formed with PPA on the more nucleophilic phenoxy oxygen atom (scheme 2).

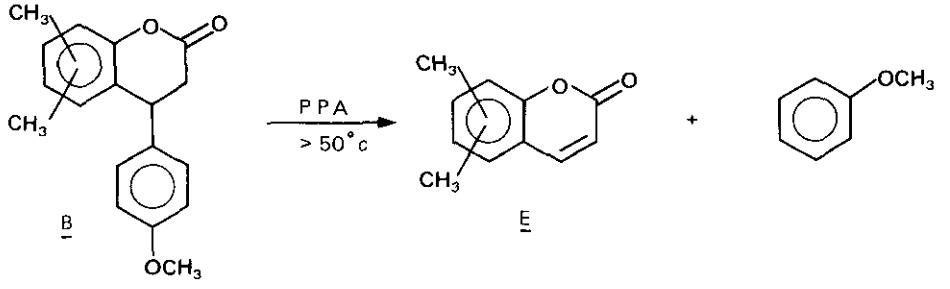
Heterolytic cleavage of the ester would then give an acylium ion which, by Fries rearrangement, would form a hydroxychalcone. The chalcone 4C obtained by reaction of 3-methoxycinnamic acid with 3,4-dimethylphenol supports this mechanism.

The coordination complex would give a flavanone by the cyclisation of the hydroxychalcone during hydrolysis. Thus, reaction of 3-methoxycinnamic acid with 3,5-dimethylphenol gives flavanone 5D. Scheme 2 is also supported by formation, in large proportion, of the cinnamate 6A. In this example hydroxychalcone characterised by TLC is only present as traces. This can be explained by the steric hindrance of the methyl group in the β position near the phenoxy oxygen atom which prevents the formation of the coordination complex. Cinnamate 6A heated in PPA at a temperature above 50°C only gives 4-(3'-methoxyphenyl)-3,4-dihydrocoumarin.

Scheme 2



We can compare this result with those of Starkov[13] who, by reaction of 3,5-dimethylphenol with cinnamic acid, obtained a mixture of 3,4-dihydrocoumarin and 5,7-dimethylflavanone. In the case of the reaction of formation of 4-(4'-methoxyphenyl)-3,4-dihydrocoumarin, we obtain a coumarin through an increase in temperature,by loss of the anisyl group. Manimaran[14,15] observes the same phenomenon by heating 4-phenyl-3,4-dihydrocoumarin at 120°C in the presence of $AlCl_3$. In our case, the formation of a coordination complex between PPA and the oxygen atom of anisyl group favors the mobility of the anisyl group, thus leading to products 7E and 8E.



Thus our results show that the position of methoxy groups in methoxycinnamic acids affects the course of the reaction leading to 4-methoxyphenyl-3,4-dihydrocoumarins in polyphosphoric acid according to the proposed mechanisms.

Table I

Reactions of dimethylphenols with methoxycinnamic acids in PPA during 24 h at 50°C

Phenols	2-methoxycinnamic acid yield (%)*	3-methoxycinnamic acid yield (%)*	4-methoxycinnamic acid yield (%)*
3,4-dimethyl-phenol	- 1B, 17 % - - -	- 4B, 4B', 21 %, 10 % 4C, 32 % - -	- 7B, 21 % - - 7E, traces
3,5-dimethyl-phenol	- 2B, 20 % - - -	- 5B, 25 % - 5D, 17 % -	- 8B, 24 % - - 8E, traces
2,4-dimethyl-phenol	- 3B, 56 % - - -	6A, 24 % 6B, 17 % 6C, traces - -	- 9B, 57 % - - -

*yields after twice recristallisations

EXPERIMENTAL

Satisfactory elemental analyses were obtained. Structures of all new compounds described were confirmed by ^1H nmr and infrared spectra. Infrared spectra were recorded on a Perkin-Elmer 297 spectrometer. ^1H nmr spectra were obtained on a R-24B Hitachi Perkin-Elmer spectrometer. Chemical shifts are reported in parts per million (δ)downfield from tetramethylsilane used as internal standard in carbon tetrachloride or deuteriochloroform solution. All melting points are uncorrected. All methoxycinnamic acids and dimethylphenols were purchased from Aldrich.

GENERAL PROCEDURE

To a mixture of 80 g of P_2O_5 and 96 ml of concentrated H_3PO_4 (85 %, d = 1.695) stirred at 50°C were added 4.03 g (0.033 mol) of dimethylphenol and 5.88 g (0.033 mol) of methoxycinnamic acid. After 24 hours, the mixture was poured on 500 g of crushed ice. The aqueous phase was extracted several times with chloroform and the combined organic phases were washed ($NaHCO_3$ 5 %, Na_2CO_3 5 %, NaOH 5 % and water), dried ($MgSO_4$) and evaporated under reduced pressure. When the residue was solid, it was collected and twice recrystallised from ethanol. When the residue was an oily liquid, it was column-chromatographied (silica, toluene).

Reaction of 3,4-dimethylphenol with 2-methoxycinnamic acid

Product 1B : *6,7-dimethyl-4-(2'-methoxyphenyl)-3,4-dihydrocoumarin.* mp 167-168°C. nmr($CDCl_3$) : 2.15 (3H, s, CH_3), 2.25 (3H, s, CH_3), 2.98 (2H, d, J = 6 Hz, CH_2), 3.82 (3H, s, OCH_3), 4.62 (1H, dd, J = 6 Hz, CH), 6.78-7.4 (6H, m, ArH). ir (KBr) : 1758 cm^{-1}, C=O.

Reaction of 3,4-dimethylphenol with 3-methoxycinnamic acid

Product 4C : *2'-hydroxy-4',5'-dimethyl-3-methoxychalcone.* mp 101-102°C. nmr (CCl_4) : 2.25 (6H, s, $2CH_3$), 3.83 (3H, s, OCH_3), 6.7-7.8 (8H, m, 2H + ArH). ir (KBr) : 1638 cm^{-1}, C=O.

Product 4B : *6,7-dimethyl-4-(3'-methoxyphenyl)-3,4-dihydrocoumarin.* mp 109°C. nmr($CDCl_3$) : 2.13 (3H, s, CH_3), 2.22 (3H, s, CH_3), 2.96 (2H, d, J = 6 Hz, CH_2), 3.75 (3H, s, OCH_3), 4.22 (1H, dd, J = 6 Hz, CH), 6.65-7.4 (6H, m, ArH). ir (KBr) : 1746 cm^{-1}, C=O.

Product 4B' : *5,6-dimethyl-4-(3'-methoxyphenyl)-3,4-dihydrocoumarin.* nmr($CDCl_3$) : 2.06 (3H, s, CH_3), 2.22 (3H, s, CH_3), 2.98 (2H, d, J = 6 Hz, CH_2), 3.7 (3H, s, OCH_3), 4.42 (1H, dd, J = 6 Hz, CH), 6.55-7.45 (6H, m, ArH). ir (KBr) : 1746 cm^{-1}, C=O.

Reaction of 3,4-dimethylphenol with 4-methoxycinnamic acid

Product 7B : *6,7-dimethyl-4-(4'-methoxyphenyl)-3,4-dihydrocoumarin.* mp 126-127°C. nmr ($CDCl_3$) : 2.1 (3H, s, CH_3), 2.2 (3H, s, CH_3), 2.8 (2H, d, J = 6 Hz, CH_2), 3.72 (3H, s, OCH_3), 4.15 (1H, dd, J = 6 Hz, CH), 6.55-7.20 (6H, m, ArH). ir (KBr) : 1755 cm^{-1}, C=O.

Product 7E : *6,7-dimethylcoumarin.* mp 149-151°C. nmr($CDCl_3$) : 2.28 (3H, s, CH_3), 2.33 (3H, s, CH_3), 6.9 (1H, d, J = 10 Hz, HC=),7.0(1H, d, J = 10 Hz, HC=), 7.08 (1H, s, ArH), 7.18 (1H, s, ArH). ir (KBr) : 1700 cm^{-1}, C=O.

Reaction of 3,5-dimethylphenol with 2-methoxycinnamic acid

Product 2B : *5,7-dimethyl-4-(2'-methoxyphenyl)-3,4-dihydrocoumarin.* mp 164°C. nmr(CCl_4) : 2.1 (3H, s, CH_3), 2.38 (3H, s, CH_3), 3.0 (2H, m, CH_2), 3.9 (3H, s, OCH_3), 4.8 (1H, dd, J = 6 Hz, CH), 6.7-7.5 (6H, m, ArH). ir (KBr) : 1760 cm^{-1}, C=O.

Reaction of 3,5-dimethylphenol with 3-methoxycinnamic acid

Product 5D : *5,7-dimethyl-5'-methoxyflavanone.* mp 60°C. nmr($CDCl_3$) : 2.22 (3H, s, CH_3), 2.56 (3H, s, CH_3), 2.9 (2H, m, CH_2), 3.7 (3H, s, OCH_3), 5.75 (1H, q, J_1 = 11 Hz, J_2 = 5 Hz, CH), 6.5-7.4 (6H, m, ArH). ir (KBr) : 1676 cm^{-1}, C=O.

Product 5B : *5,7-dimethyl-4-(3'-methoxyphenyl)-3,4-dihydrocoumarin.* mp 129-130°C. nmr ($CDCl_3$) : 2.1 (3H, s, CH_3), 2.3 (3H, s, CH_3), 2.85 (2H, d, J = 4 Hz, CH_2), 3.6 (3H, s, OCH_3), 4.18 (1H, dd, J = 4 Hz, CH), 6.3-7.2 (6H, m, ArH). ir (KBr) : 1752 cm^{-1}, C=O.

Reaction of 3,5-dimethylphenol with 4-methoxycinnamic acid

Product 8B : *5,7-dimethyl-4-(4'-methoxyphenyl)-3,4-dihydrocoumarin.* mp 166-168°C. nmr (CCl_4) : 2.18 (3H, s, CH_3), 2.33 (3H, s, CH_3), 3.0 (2H, d, J = 4 Hz, CH_2), 3.77 (3H, s, OCH_3), 4.33 (1H, dd, J = 4 Hz, CH), 6.7-7.2 (6H, m, ArH). ir (KBr) : 1760 cm^{-1}, C=O.

Product 8E : *5,7-dimethylcoumarin.* mp 133-135°C. nmr (CCl_4) : 2.43 (3H, s, CH_3), 2.5 (3H, s, CH_3), 7.15 (1H, d, J = 10 Hz, HC=), 7.33 (1H, d, J = 10 Hz, HC=), 7.0 (2H, m, ArH).ir(KBr) :1700 cm^{-1},C=O.

Reaction of 2,4-dimethylphenol with 2-methoxycinnamic acid

Product 3B : *6,8-dimethyl-4-(2'-methoxyphenyl)-3,4-dihydrocoumarin*. mp 106-108°C. nmr(CCl_4) : 3.2 (3H, s, CH_3), 2.33 (3H, s, CH_3), 3.0 (2H, d, J = 6 Hz, CH_2), 3.84 (3H, s, OCH_3), 4.62 (1H, dd, J = 6 Hz, CH), 6.6-7.5 (6H, m, ArH). ir (KBr) : 1760 cm^{-1}, C=O.

Reaction of 2,4-dimethylphenol with 3-methoxycinnamic acid

Product 6A : *3-(3'-methoxyphenyl)-2',4'-dimethylphenylpropenoate*. mp 77°C. nmr(CCl_4) : 2.14 (3H, s, CH_3), 2.28 (3H, s, CH_3), 3.74 (3H, s, OCH_3), 7.13 (1H, d, J = 16 Hz, HC=), 7.32 (1H, d, J = 16 Hz, HC=), 6.8-7.4 (7H, m, ArH). ir (KBr) : 1722 cm^{-1}, C=O.

Product 6B : *6,8-dimethyl-4-(3'-methoxyphenyl)-3,4-dihydrocoumarin*. mp 113-114°C. nmr($CDCl_3$) : 2.19 (3H, s, CH_3), 2.29 (3H, s, CH_3), 2.95 (2H, d, J = 6 Hz, CH_2), 3.73 (3H, s, OCH_3), 4.20 (1H, dd, J = 6 Hz, CH), 6.6-7.4 (6H, m, ArH). ir (KBr) : 1755 cm^{-1}, C=O.

Reaction of 2,4-dimethylphenol with 4-methoxycinnamic acid

Product 9B : *6,8-dimethyl-4-(4'-methoxyphenyl)-3,4-dihydrocoumarin*. mp 79-80°C. nmr($CDCl_3$) : 2.2 (3H, s, CH_3), 2.3 (3H, s, CH_3), 2.92 (2H, d, J = 6 Hz, CH_2), 3.7 (3H, s, OCH_3), 4.15 (1H, dd, J = 6 Hz, CH), 6.5-7.1 (6H, m, ArH). ir (KBr) : 1760 cm^{-1}, C=O.

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