An Improved Procedure for the Preparation of 2,2-Dimethyl-4-chromanones

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Our interest in 6- and 7-hydroxy- or -alkoxy-2,2-dimethyl-4-chromanones **3** as intermediates in the synthesis of biologically active compounds related to precocenes[1,2,3], has led us to a critical evaluation of the different methods available for their preparation. On the basis of the availability of starting materials, the above pattern of aromatic ring substitution restricts the synthetic routes to be considered to those involving cyclodehydration of a phenol **1** and 3-methyl-2-butenoic acid (**2**) or derivatives thereof. Described procedures include the use as condensing agents of metal halides, boron trifluoride, hydrofluoric acid, and polyphosphoric acid[4]; however, all of these reagents present serious drawbacks, either due to the relatively high temperatures (> 100 °C) required for the reactions to proceed or to the risks associated with their handling. Polyphosphoric acid has been so far the condensing agent of choice[1,4], despite its unpractical manipulation due to its high viscosity. However, this route is not applicable to some starting phenols for the synthesis of chromenes of biological interest[2,5]. In order to circumvent these problems, we examined methanesulphonic acid as an alternative condensing agent. This strong acid and efficient dehydrant allowed us to carry out the above reactions in a homogeneous medium at temperatures from 25 °C to 70 °C. The use of lower temperatures is especially important for phenols with acid-sensitive substituents.

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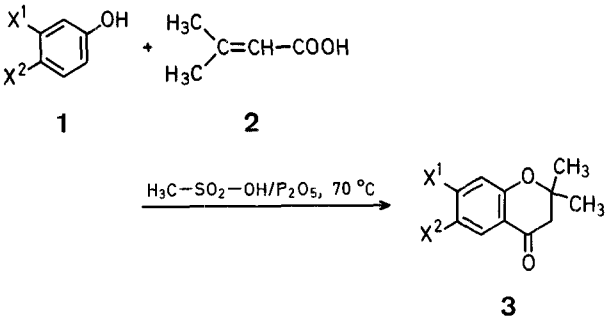
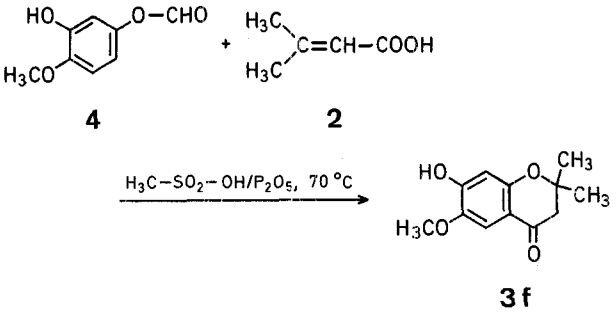


1 2 3

When equimolar amounts of a phenol **1** and the acid **2** were allowed to react in the presence of methanesulphonic acid saturated with phosphorus pentoxide[6], under mild conditions (30 min at 70 °C), 2,2-dimethyl-4-chromanones **3** were formed in good to excellent yields and the products were easily recovered from the crude reaction mixtures. Data for eight examples of this reaction are given in the Table. The requirement for anhydrous methanesulphonic acid is not absolute; in some instances (e.g. **3b**) the use of 97% methanesulphonic acid (prepared by drying the commercially available 70% acid solution in vacuo) afforded comparable yields.

The use of such mild reaction conditions reduces the competing *para*-acylation that can take place with substrates such as **1b** and **1c**. Side products from this reaction (less than 10% of total products) could be easily removed by dilute sodium hydroxide extraction. In the case of substrates with acid-labile substituents, such as sesamol (**1h**), modification of the above standard reaction conditions was required to avoid erratic results. When this condensation was carried out at room temperature, the corresponding chromanone **3h** was reproducibly obtained in good yields.

Since formates are usually synthetic intermediates for preparation of 3- and 4-hydroxy- or -alkoxyphenols through Baeyer-Villiger oxidation of benzaldehydes, a modification of the above procedure replacing phenols by phenol formates was considered advantageous. Accordingly, when 3-hydroxy-4-methoxyphenyl formate (derived from isovanillin) was allowed to react with **2** in methanesulphonic acid solution under standard reaction conditions, the corresponding chromanone **3f** was obtained in 84% yield (89% yield from free phenol).



4 2 3f

In summary, the procedure herein described constitutes a useful alternative for the direct preparation of 2,2-dimethyl-4-chromanones from phenols or formates and 3-methyl-2-butenoic acid. Reactions are clean, easy to perform and proceed under mild conditions, avoiding the difficulties in manipulation encountered using polyphosphoric acid. This reaction is generally applicable for syntheses

Table. 2,2-Dimethyl-4-chromanones **3a–h**

3	X^1	X^2	Reaction Conditions	Yield [%]	m.p. [°C] (Lit. m.p. [°C])	Molecular Formula[a]	I.R. ν [cm^{-1}]	^{1}H-N.M.R. δ [ppm]
a	OH	H	30 min, 70 °C	94	172–174° (169°)[7]	$C_{11}H_{12}O_3$ (192.2)	($CHCl_3$): 3520, 3250, 1675	(CD_3COCD_3): 1.44 (s, 6H); 2.65 (s, 2H); 3.1 (br, 1H); 6.36 (d, 1H, J=2 Hz); 6.50 (dd, 1H, J_o=9 Hz, J_m=2 Hz); 7.66 (d, 1H, J=9 Hz)
b	OCH_3	H	60 min, 70 °C[b]	80[c]	82–83° (81–82°)[8]	$C_{12}H_{14}O_3$ (206.2)	(CCl_4): 1685	(CCl_4): 1.40 (s, 6H); 2.54 (s, 2H); 3.78 (s, 3H); 6.28 (d, 1H, J=2 Hz); 6.43 (dd, 1H, J_o=9 Hz, J_m=2 Hz); 7.68 (d, 1H, J=9 Hz)
c	OC_2H_5	H	30 min, 70 °C	85[d]	79°	$C_{13}H_{16}O_3$ (220.3)	(CCl_4): 1675	(CCl_4): 1.44 (s, 6H and t, 3H, J=7 Hz); 2.56 (s, 2H); 4.03 (q, 2H, J=7 Hz); 6.23 (d, 1H, J=2 Hz); 6.42 (dd, 1H, J_o=9 Hz, J_m=2 Hz); 7.67 (d, 1H, J=9 Hz)
d	OH	OH	30 min, 70 °C[e]	42	207–209° (208°)[9]	$C_{11}H_{12}O_4$ (208.2)	(KBr): 3520, 1640	(CD_3COCD_3): 1.39 (s, 6H); 2.61 (s, 2H); 6.38 (s, 1H); 7.24 (s, 1H); 8.40 (br, 2H)
e	OCH_3	OH	30 min, 70 °C	91	98–100°	$C_{12}H_{14}O_4$ (222.2)	(neat): 3400, 1660	($CDCl_3$): 1.41 (s, 6H); 2.63 (s, 2H); 3.88 (s, 3H); 5.52 (br, 1H); 6.34 (s, 1H); 7.31 (s, 1H)
f	OH	OCH_3	30 min, 70 °C	89[f]	107° (81°)[9]	$C_{12}H_{14}O_4$ (222.2)	(KBr): 3520, 3450, 1660	($CDCl_3$): 1.43 (s, 6H); 2.64 (s, 2H); 3.88 (s, 3H); 6.44 (s, 1H); 6.45 (br, 1H); 7.27 (s, 1H)
g	OCH_3	OCH_3	45 min, 70 °C	85	104–105° (106°)[9]	$C_{13}H_{16}O_4$ (236.3)	(CCl_4): 1675	($CDCl_3$): 1.45 (s, 6H); 2.67 (s, 2H); 3.78 (s, 3H); 3.81 (s, 3H); 6.42 (s, 1H); 7.29 (s, 1H)
h	O—CH_2—O		15 h, 25 °C	75	59–60°	$C_{13}H_{14}O_3$ (218.3)	(CCl_4): 1680	(CCl_4): 1.39 (s, 6H); 2.51 (s, 2H); 5.90 (s, 2H); 6.24 (s, 1H); 7.09 (s, 1H)

[a] All products gave satisfactory microanalyses (C ±0.30%, H ±0.27%).

[b] An assay carried out using 97% CH_3SO_3H yielded **3b** (81%).

[c] The corresponding *para*-acylphenol was isolated (9%) and characterized by spectral data. I.R. (CCl_4): ν=3280 and 1650 cm^{-1}. ^{1}H-N.M.R. (CCl_4): δ=1.94 (s, 3H); 2.15 (s, 3H); 3.68 (s, 3H); 6.3–6.7 (m, 3H); 7.55 (d, 1H, J=9 Hz); 8.40 ppm (br, 1H).

[d] The corresponding *para*-acylphenol was isolated (5%) as a solid, m.p. 92–94 °C, and characterized by spectral data. I.R. (neat): ν=3300 and 1665 cm^{-1}. ^{1}H-N.M.R. ($CDCl_3$): δ=1.38 (t, 3H, J=7 Hz); 1.96 (s, 3H); 2.18 (s, 3H); 3.90 (q, 2H, J=7 Hz); 6.34 (d, 1H, J=2 Hz); 6.40 (d, 1H, J=9 Hz); 6.70 (br s, 1H); 7.52 (d, 1H, J=9 Hz); 8.60 ppm (br, 1H).

[e] 1,2,4-Triacetoxybenzene was used as starting material.

[f] An 84% yield of **3f** was obtained when 3-hydroxy-4-methoxyphenyl formate was used as starting material.

from phenols having activating *meta*-substituents, including those without *para*-alkoxy substituents that react poorly in the polyphosphoric acid system.

2,2-Dimethyl-7-hydroxy-4-chromanone (3a); Typical Procedure:
Resorcinol (**1a**; 2.75 g, 25 mmol) and 3-methyl-2-butenoic acid (**2**; 2.50 g, 25 mmol) are added simultaneously under nitrogen with vigorous stirring to a flask containing methanesulphonic acid (40 ml, 0.6 mol) saturated with phosphorus pentoxide (2.0 g, 14 mmol), at 70 °C. The reaction mixture is stirred for 30 min at 70 °C, cooled, poured into ice/water (300 g) and extracted with diethyl ether (3 × 150 ml). The combined organic fractions are washed with water, brine, and dried with magnesium sulphate. The residue obtained after solvent removal is distilled in a bulb to bulb apparatus (155–160 °C/0.3 torr) to afford **3a** which crystallizes on standing; yield: 4.65 g (94%); m.p. 172–174 °C (Ref.[5], m.p. 169 °C).

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