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CROWN ETHERS. APPLICATION IN THE SYNTHESIS OF CHALCONES

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It is known that isoflavones, pterocarpans, and rotenoids, which frequen ly contain a benzfuro moiety[1], are conveniently prepared from chalcone interm diates[2,3] as are flavonols[4] and dihydroflavonols[5]. However, the ultimate st in attempted synthesis of chalcones (1) and (3) by standard procedures was un successful where the 2-hydroxy group of the acetophenone (the equivalent of 2 in the chalcone) is unprotected prior to condensation. This difficulty is usually overcome by alkylation. From amongst the many protective methods, a kylation with monochlorodimethyl ether[6] seems attractive since excellent yiel are obtained[7,8], and the free phenolic chalcone can readily be regenerated by heating in acid medium.

Our efforts to protect the hydroxyl group in (5) by methoxymethylation according to procedures previously described[6,7,8] nevertheless failed and onl resinous tars and starting material were recovered. When (7) is methoxymeth lated with sodium ethoxide, absolute ethanol and chlorodimethylether by a method analogous to that described by Oyamada et al.[7], only (9) is obtained a pale yellow needles, mp. 190.1°C (from MeOH). This compound, identified as bis-(3-acetyl-4,6-dimethoxy-2-hydroxyphenyl)methane†, probably results from condensation of (7) with formaldehyde originating from action of alkali on chlorodimethylether. By using an alternative procedure (initial formation o sodium salt) described by Enebäck[8], methoxymethylation of (7) was achieved t

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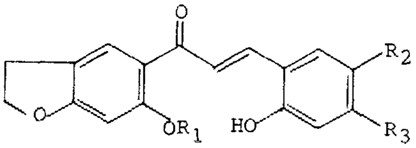
† Satisfactory ^{1}H n.m.r. and m.s. spectra were obtained.

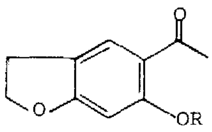


(1) R_1=H; R_2+R_3=OCH_2O

(2) R_1=CH_2OMe; R_2+R_3=OCH_2O

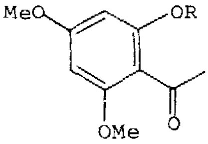
(3) R_1=H; R_2=R_3=OMe

(4) R_1=CH OMe; R_2=R_3=OMe



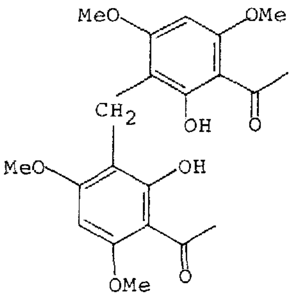
(5) R=H

(6) R=CH_2OMe

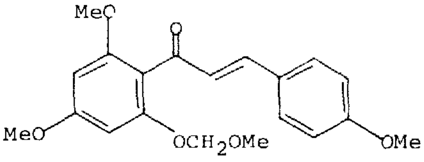


(7) R=H

(8) R=CH_2OMe



(9)



(10)

give (8) as a yellow oil in 57% yield.

We now report a general and convenient, high-yield conversion of phenols to their methoxymethyl ethers based on the ability of crown ethers to dissolve alkali metal salts[9] in non-polar solvents. The ether is formed by stirring a mixture of 18-Crown-6 (2mmol) and potassium salt of the phenol (18 mmol) in dry acetonitrile (50 ml) for 30 min at room temperature. Chlorodimethylether (25 mmol) is added and the resulting mixture stirred until reaction is com= plete (ca. 1 hr). After filtration the mixture is evaporated to dryness, taken up in ether, extracted once with water, and dried (Na_2SO_4). Evaporation gives the methoxymethyl derivative in high yield (Table). The chalcones are formed in almost quantitative yield from the ether compounds.

TABLE

PHENOL	METHOXYMETHYL ETHER	YIELD (%)	CHALCONE	YIELD (%)
5	6	79 (0)^{x}	2	93
5	6	82 (0)^{x}	4	95
7	8	84 (57)^{x}	10	97

^{x} Yield obtained with alternative method.

The principal advantages of this method are the avoidance of undesirable side reactions, increase yield of methoxymethyl derivatives, and application in the synthesis of otherwise inaccessible 2'-hydroxychalcones.

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