A Simple One-step Synthesis of Phenyl Ethers from Phenyl Acetates

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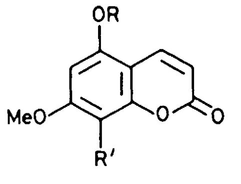
Phenyl acetates when refluxed with alkyl halides in acetone solution in the presence of a crown ether and anhydrous potassium carbonate undergo alkylation yielding phenyl ethers.

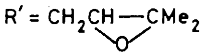
In the course of our work on the synthesis of coumarins we were faced with the problem of clean deacetylation of (**1**; R = Ac) or (**2**; R = Ac)[1] to the corresponding phenol for subsequent prenylation. Hydrolysis with aqueous-methanolic sodium carbonate followed by acidification gave a number of products from which the desired phenol could not be isolated. In an attempt to prenylate the acetate (**1**; R = Ac) in one step it was refluxed in acetone solution with anhydrous potassium carbonate and prenyl chloride for 4 h (*cf.* ref. 2) when no detectable prenylation took place. Alkylation of the acetate in 1,2-dimethoxyethane[3] was not tried in view of the long time of reflux (over 40 h). We now report an alternative but effective

Table 1. Phenyl ethers from phenyl acetates and alkyl halide–18-crown-6–K_2CO_3.

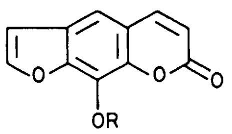
Starting phenyl acetate	Alkyl halide	Reflux time[a]/h	Phenyl ether (product)[b]	Yield, %
(**1**; R = Ac)	Prenyl chloride	0.5	(**1**; R = $CH_2CH{=}CMe_2$)	74
(**2**; R = Ac)	Prenyl chloride	0.5	(**2**; R = $CH_2CH{=}CMe_2$)	65
(**3**; R = Ac)	Methyl iodide	10	(**3**; R = Me)	67
(**3**; R = Ac)	Ethyl iodide	9	(**3**; R = Et)	69
(**3**; R = Ac)	n-Propyl iodide	7	(**3**; R = CH_2CH_2Me)	71
(**3**; R = Ac)	Allyl bromide	1.5	(**3**; R = $CH_2CH{=}CH_2$)	78
(**3**; R = Ac)	Prenyl chloride	0.5	(**3**; R = $CH_2CH{=}CMe_2$)	77
(**3**; R = Ac)	Benzyl bromide	1.5	(**3**; R = CH_2Ph)	73
(**4**; R = Ac)	Methyl iodide	10	(**4**; R = Me)	69
(**4**; R = Ac)	Ethyl iodide	9	(**4**; R = Et)	77
(**4**; R = Ac)	n-Propyl iodide	8	(**4**; R = CH_2CH_2Me)	79
(**4**; R = Ac)	Allyl bromide	1.5	(**4**; R = $CH_2CH{=}CH_2$)	81
(**4**; R = Ac)	Benzyl bromide	1.5	(**4**; R = CH_2Ph)	79
(**4**; R = Ac)	Prenyl chloride	0.5	(**4**; R = $CH_2CH{=}CMe_2$)	81
(**5**; R = Ac)	Methyl iodide	8	(**5**; R = Me)	55

[a] Reflux time refers to the time of reflux after the addition of the alkyl halide. Preliminary time of heating the phenyl acetates with K_2CO_3 and crown ether (18-crown-6) is not included in this time. [b] All the new compounds gave satisfactory elemental analysis data. Characterization of all the products is based on ^{1}H n.m.r. data and in the cases of known products by direct comparison with authentic samples. M.p.s of the phenyl ethers (products) are: (**1**), 107—109 °C; (**2**), 120—121 °C; (**3**; R = Me), 145—146 °C; (**3**; R = Et), 104—106 °C; (**3**; R = n-propyl), 81—82 °C; (**3**; R = allyl), 79—80 °C; (**3**; R = prenyl), 101—102 °C; (**3**; R = benzyl), 121—122 °C; (**4**; R = Me), 71—72 °C (picrate, m.p. 110—112 °C); (**4**; R = Et), oil (picrate, m.p. 100—101 °C); (**4**; R = n-propyl), oil (picrate, m.p. 72—74 °C); (**4**; R = allyl), oil (picrate, m.p. 100—102 °C); (**4**; R = benzyl), 97—99 °C; (**4**; R = prenyl), oil (picrate, m.p. 113—115 °C); (**5**), 90—91 °C.

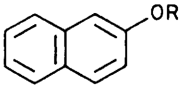


(1)

$R' = CH_2CH\text{—}CMe_2$ (epoxide, O)

(2) $R' = CH_2CH(OH)C(OH)Me_2$



(3)



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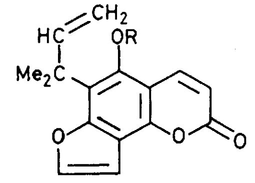

(5)

one-step method of preparing phenyl ethers from phenyl acetates.

The acetate (**1**; R = Ac) (1 mmol) in dry acetone (20 ml) was refluxed with anhydrous potassium carbonate (1 g) in the presence of 18-crown-6 (0.15 mmol). After 1 h prenyl chloride (1 ml) was added to this and the mixture refluxed for a further 30 min. The mixture was then cooled and the solid filtered off. The residue obtained on evaporation of the filtrate *in vacuo* and crystallization from acetone–hexane gave (**1**; R = $CH_2CH{=}CMe_2$) as needles (yield 74%), m.p. 107—109 °C. This method of prenylation[1] of phenyl acetate could be extended to prepare a number of phenyl ethers from the corresponding phenyl acetates. In all these one-pot alkylations of phenyl acetates, it is necessary to generate initially some phenoxide ions by refluxing the phenyl acetate in acetone solution for about 1 h in the presence of anhydrous potassium carbonate and a crown ether, the latter bringing the carbonate anion, a strong base in an aprotic solvent, into solution. However, the subsequent reflux time (see Table 1) depends on the ionisability of the alkylating agent, the alkyl halide. Alkylation is rapid with reactive halides such as allyl, prenyl, or benzyl halides. Methylation, however, requires heating for 8—10 h after the addition of methyl iodide (alkylating agent), added in 3—4 stages during the reflux. With the acetate of some intramolecularly hydrogen bonded phenol such as compound (**5**; R = Ac),[4] methylation is not complete even after heating for 16 h. Ethylation and n-propylation, using ethyl iodide and n-propyl iodide, respectively, require heating for 7—9 h. No significant alkylation was observed with isopropyl or t-butyl halides presumably owing to their undergoing base-catalysed elimination.

Whilst phenyl acetates are easily alkylated, other esters of phenols resist alkylation. Phenyl propionates are alkylated to only a small extent after prolonged heating (10 h). Benzoates however, do not appear to form any alkylated product even after 16 h. The alkylated products are isolated from the reaction mixture by filtering off the solid followed by evaporation of the filtrate. The residue is then crystallized or chromatographed (including p.l.c.) to obtain the ether.

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