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CONVENIENT ACID CATALYSED ETHERIFICATION OF HYDROXYIONONE

by

A. KHODABOCUS* and B. M. P. BEEBEEJAUN

Department of Chemistry, University of Mauritius, Réduit, Mauritius

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ABSTRACT

Ethers of Hydroxyionone can be conveniently prepared by a Methanesulfonic acid mediated reaction with the corresponding alcohol.

Keywords: *Ionone, acid catalysis, etherification.*

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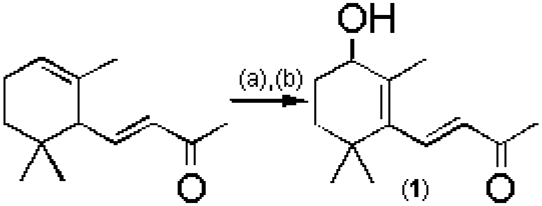
Our work on the synthesis of terpenoids required us to prepare the benzyl ether of hydroxyionone (**1**). The latter is readily obtained from commercially available a-ionone by a two-step protocol involving selective epoxidation of the free double bond using either m-chloroperbenzoic acid (m-CPBA) or magnesium monoperoxyperphthalate (MMPP) followed by a base catalysed isomerisation using potassium carbonate (Fig 1).



(a) m-chloroperbenzoic acid or magnesium monoperoxyperphthalate
(b) Potassium carbonate, MeOH, reflux; 65% overall

Fig 1. Preparation of Hydroxyionone from a-Ionone

Quite unexpectedly the benzylation was found to be non-trivial and under standard conditions e.g. NaH, $PhCH_2Br$ with or without Bu_4NI; Na_2CO_3, $PhCH_2Br$, DMF; KOH, $PhCH_2Br$, DMSO (Johnstone & Rose, 1979); $PhCH_2OH$, Diisopropyl Azodicarboxylate, Ph_3P (Mitsunobu, 1981); Benzyltrichloroamidate, Triflic acid (Iversen & Bundle, 1981) etc. none of the desired ether was obtained. It is noteworthy that the methyl ether was prepared in modest yield using silver(I) oxide and methyl iodide in refluxing benzene (Greene *et al.*1980).

However, it was observed that when hydroxyionone was treated with benzyl alcohol in the presence of trifluoroacetic acid, the corresponding trifluoroacetate was obtained in good yield. Thus it was reasoned that a stronger acid would probably furnish the desired ether. This expectation was realised as upon the treatment of hydroxyionone with benzyl alcohol in the presence of excess methanesulfonic acid the benzyl ether was obtained in 60% yield after purification by chromatography. The method was tested for a number of alcohols and the results are summarised in Table 1.

Table 1. Etherification of Hydroxyionone by different alcohols

Alcohol	Conditions	Yield (%)$^{\otimes}$
CH_3OH	0°C to RT	90
CH_3CH_2OH	,,	94
$(CH_3)_2CHOH$	,,	80
$PhCH_2OH$	,,	60
$HOCH_2CO_2Et$	-78°C	42
$(CH_3)_3COH$	,,	0
p-$MeOC_6H_4CH_2OH$	,,	0

All compounds gave satisfactory ^1H- NMR data.

It is found that the reaction works reasonably well for a number of alcohols. However, t-butanol and p-methoxybenzyl alcohol do not give any of the desired products possibly because these ethers are labile under the reaction conditions.

Typical procedure

Pure hydroxyionone (0.13g, 0.62 mmol) was dissolved in dichloromethane (3.0ml). The solution was cooled in ice and then methanol (0.5ml, xs) was added followed by methane sulfonic acid solution (70%, 0.5ml). The mixture was stirred and was monitored by TLC (1:1 Ether / Petroleum Ether 40-60). When the reaction was completed, the mixture was diluted with dichloromethane (25ml) and was successively washed with water (1 x 20ml), sodium bicarbonate solution (1 x 20ml) and brine (1 x 20ml). The organics were dried ($MgSO_4$) and then the volatiles were evaporated on the rotorvap. The crude product was chromatographed (SiO_2, 2:1 Light Petroleum ether / Ether) to give the desired product as a pale yellow oil (0.13g, 94 %).
d ($CDCl_3$; 300 MHz) 7.15 (1H, d, J= 16 Hz); 6.15 (1H, d, J= 16 Hz); 3.5 (1H, t); 3.4 (3H, s); 2.3 (3H, s); 1.8 (3H, s); 1.7-1.3 (4H, m); 1.05 (6H, s).

Etherification using ethanol
d ($CDCl_3$; 300 MHz) 7.15 (1H, d, J= 16 Hz); 6.1 (1H, d, J= 16 Hz); 3.7-3.3 (2H, dm); 3.6 (1H, bs); 2.26 (3H, s); 1.75-1.25 (4H, m); 1.2 (3H, t, J= 7 Hz); 1.0 (6H, s).

Etherification using isopropanol
d ($CDCl_3$; 300 MHz) 7.15 (1H, d, J=16 Hz); 6.1 (1H, d, J=16 Hz); 3.68 (1H, m); 3.65 (1H,

bs); 2.25 (3 H, s); 1.8 (3H, bs); 1.75-1.25 (4H, m); 1.15 (6H, d, J=6 Hz); 1.0 (6H, s).

Etherification using benzyl alcohol

d ($CDCl_3$; 300 MHz) 7.3 (5H, m); 7.15 (1H, d, J=16 Hz); 6.1 (1H, d, J= 16 Hz); 4.55 (2H, dd, J= 10 Hz); 3.73 (1H, bs); 2.2 (3H, s); 1.75 (3H, bs); 1.5-1.11 (4H, m); 1.05 (6H, s).

Etherification using ethyl glycolate

(CDCl3; 300 MHz) 7.1 (1H, d, J= 17 Hz); 6.1 (1H, d, J= 17 Hz); 4.2 (2H, q, J= 6 Hz); 4.1 (2H,s); 2.3 (3H, s); 1.8 (3H, s); 1.6-1.1 (4H, m); 1.25 (3H, t, J= 6 Hz); 1.0 (6H, s).

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