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ISOMERISATION OF ω-ALKENYL SUBSTITUTED CYCLOHEXANE-1,3-DIONE ENOL DERIVATIVES USING RHODIUM CATALYSIS. A PRACTICAL SYNTHESIS OF SUBSTITUTED RESORCINOLS

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Summary: Treatment of the ω-alkenyl substituted cyclohexane-1,3-dione enol derivatives (1),(11), and (13) with rhodium trichloride trihydrate leads to the corresponding resorcinol derivatives (2),(12), and (15) respectively. By contrast, the $RhCl_3.3H_2O$ catalysed isomerisations of the related enol ethers (5) and (9) instead produce the dienones (6) and (10) respectively.

Substituted resorcinols are used widely in synthesis, and a number of methods are available for their preparation[1,2]. In connection with investigations of the synthesis of aromatic compounds from aliphatic and alicyclic precursors we have examined the rhodium catalysed isomerisation of some ω-alkenyl substituted cyclohexane-1,3-dione enol derivatives[3]. In this Letter we summarise the outcome of this study, and show how rhodium trichloride trihydrate catalysed isomerisation of the 6- and 5-alkenyl substituted derivatives (1) and (13) provides a practical route to the corresponding 4- and 5- alkyl substituted resorcinols (2) and (15) respectively[4].

In a typical procedure, a solution of 3-methoxy-6-(prop-2-enyl)cyclohex-2-enone(1)[5] (2.7 mmol) in methanol (10 ml) was heated under reflux in a nitrogen atmosphere for 24 h, in the presence of $RhCl_3.3H_2O$ (20% ; 0.54 mmol). The cooled mixture was then filtered through a short column of alumina to give an approximate 1:1 mixture of the mono-(2) and di-methyl ethers (3a) of 4-n-propyl resorcinol in a combined yield of 81%; the phenol (2) was easily separated by extraction with aqueous sodium hydroxide solution, and showed spectral data identical to those of an authentic sample[6]. Both the yield and proportion of (2) and (3a) produced from the isomerisation of (1) were found to be sensitive to changes in reaction conditions (i.e. temp., time, solvent, mole ratio of catalyst)[7]. Thus, under the aforementioned conditions in ethanol as solvent, only the resorcinol diethyl ether (3b); 67%) was produced. In addition, treatment of the enol ether (1) with 5% $RhCl_3.3H_2O$ in refluxing 1:1

chloroform-ethanol led to none of the corresponding resorcinol. Instead, a 4:1 mixture of Z-E-isomers of the isomeric conjugated dienone (4) was isolated (65%). The structure of the dienone followed from spectral data: λ_{max}(EtOH) 278 nm, ν_{max}($CHCl_3$) 1655, 1620, 1585 cm^{-1}; δ 6.41, 6.2 (t, J 6, :C$\underline{H}$CH_2-, two isomers), 5.25, 5.2 (:C$\underline{H}$), 3.9 (q, J 7, OC$\underline{H}_2CH_3$), 2.1 - 2.8 (m, 6H), 1.2 - 1.4 (overlapping t, J ∿ 7, :CHCH_2C$\underline{H}_3$), 1.1 (t, J 7, OCH_2C$\underline{H}_3$): δ_{carbon} (major isomer) 199.1, 169.7, 134.2 (d), 128.1, 102.4 (d), 64.2 (t), 36.5 (t), 23.7 (t), 21.4 (t), 14.1 (q), 13.7 (q) p.p.m. In an analogous manner, the $RhCl_3 \cdot 3H_2O$ catalysed (20%) isomerisation of the enol ether (5)[5] containing a longer ω-alkenyl side chain, in methanol, led to a similar mixture of Z- and E-isomers of the dienone (6) (58%).[8] We assume that the differing results obtained with (1) and (5) under the various reaction conditions are associated with rapid acid-catalysed enol ether equilibration i.e. (7)⇌(8), [producing the isomers (8)] compared to slow double bond migration in the starting enol ethers (1) and (5); this is particularly likely in the case of (5) where four successive double bond migrations are implicated in the formation of (6). Some support for the above proposal came with the observation that both of the enol ether isomers (9a) and (9b)[5] corresponding to (1) and (5), also gave (∿ 50%) the isomeric dienones (10a) and (10b) (≡6) respectively on treatment with $RhCl_3.3H_2O$ in methanol; we were unable to obtain evidence for the co-formation of resorcinol derivatives from this study.

The problem of enol ether equilibration in (5), promoting the formation of (6), was overcome when the corresponding enol acetate (11)[5] was treated with $RhCl_3.3H_2O$ (20%) in methanol. This isomerisation instead led to the resorcinol derivative (12) (56%)[8], whose formation was accompanied by only a small amount of (6) (< 5%). Presumably in this instance, the ester hydrolysis and enol ether formation processes, leading to the stable dienone (6) are slow compared to the rhodium catalysed migration of the ω-double bond in (11) into the 6-ring exo-position.

Treatment of 5-(but-3-enyl)-3-methoxycyclohex-2-enone (13)[5] with $RhCl_3.3H_2O$ (20%) in methanol led to its smooth isomerisation to a 1:1 mixture of mono-(15a) and di-methyl ethers (15b) (70%) of 5-n-butylresorcinol. The efficiency with which the isomerisation is accomplished probably reflects the facility with which (14) aromatises in comparison with (6).

Not unexpectedly, the 2-(prop-2-enyl) substituted enol ether (16) failed to produce any aromatised product on treatment with $RhCl_3.3H_2O$ (9%). Instead, a range of other products was produced, only one of which was fully characterised. This was the product (18)[8] expected from addition of methanol to the alkene (17) resulting from simple double bond migration in (16).

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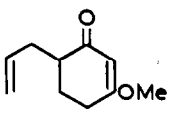
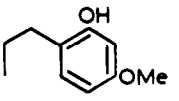


(1)



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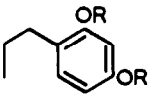

(3)

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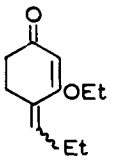
b R = Et



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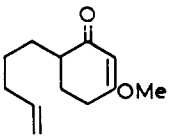

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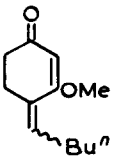

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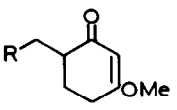
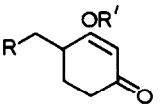


(7)

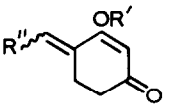
R = CH:CH$_2$ or (CH$_2$)$_2$CH:CH$_2$

RhCl$_3$·3H$_2$O ⇌ R'OH

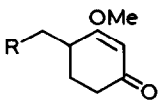


(8)

R' = Me or Et

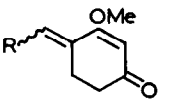


R' = Me or Et
R'' = Et or *n*-Bu



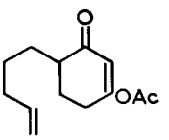
(9)

a R = CH:CH$_2$
b R = (CH$_2$)$_2$CH:CH$_2$



(10)

a R = Et
b R = *n*-Bu



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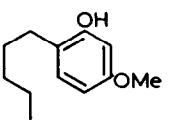

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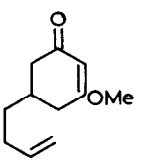

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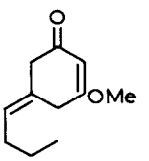

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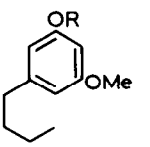
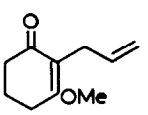


(15)

a R = H
b R = Me



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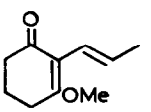

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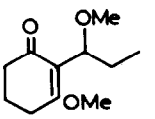

(18)

References

1. see: R. Mechoulam, 'Marijuana', Academic Press, London and New York, 1973; R.K. Razdan 'The Total Synthesis of Cannabinoids' in the Total Synthesis of Natural Products, Vol.4, Edt. J. ApSimon, John Wiley and Sons, Inc. 1981.

2. see: A.A. Jaxa-Chamiec, P.G. Sammes and P.D. Kennewell, J. Chem. Soc., Perkin Trans I, 1980, 170; A.G.M. Barrett, T.M. Morris and D.H.R. Barton, ibid., 1980, 2272 and refs. cited therein.

3. For illustrations of the use of cyclohexane-1,3-dione intermediates in resorcinol syntheses see ref.2.

4. For related investigations, leading to phenols see: P.A. Grieco and N. Marinovic, Tetrahedron Letter, 1978, 2545.

5. Enol ethers (1) and (5) were prepared by the general procedure of G. Stork and R.L. Danheiser, J. Org. Chem., 1973, 38, 1775, whereas the enol ether (13) was obtained by a modified procedure reported by T. Szychowski and D.B. MacLean, Canad. J. Chem., 1979, 57, 1631. The isomeric enol derivatives (9a) and (9b) were separated from mixtures by chromatography.

6. Kindly provided by Fisons plc Pharmaceuticals Division, Loughborough.

7. We were unable to effect any of the double bond migrations described in this paper using $RhCl(PPh_3)_3$. cf. J.P. Genet and J. Ficini, Tetrahedron Letter, 1979, 1499 and refs. cited therein.

8. All new compounds described showed satisfactory spectral data (n.m.r., u.v., m.s), and analytical or high resolution m.s. data.

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