



Lewis acid-catalysed reaction of (cyclo)alkenes with oxiranes

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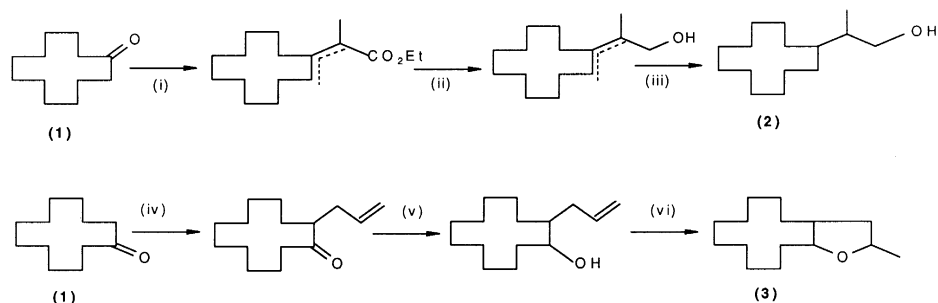
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Abstract

The Lewis acid-catalysed reaction of (cyclo)alkenes with oxiranes can give homologous aldehydes, unsaturated alcohols, and fused furans. Many of these materials are of interest to the fragrance industry. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: alcohol; aldehyde; alkene; flavour and fragrance; furan; oxirane.

Woody-amber odour is greatly appreciated in the fragrance industry, but is frequently associated with molecules which are relatively expensive to produce. Two such materials are Hydroxyambran® (2) and Lignoxan® (3). The literature syntheses of these molecules^{1,2} utilise cyclododecanone (1) as starting material (Scheme 1).

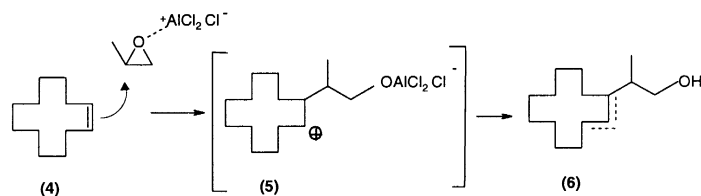


Scheme 1. Reagents: (i) BrCH(CH₃)CO₂Et, Zn; (ii) LiAlH₄; (iii) Raney Ni, H₂, EtOH; (iv) allyl bromide, NaOH (aq.), phase transfer; (v) Al(OPrⁱ)₃; (vi) H⁺, toluene, reflux

In principle, it appeared that (2) could be obtained via a Friedel–Crafts type reaction of cyclododecene (4) with propylene oxide. The desired overall process is indicated in Scheme 2, where the intermediate carbonium ion collapses to give a mixture of isomeric 2-(cyclododecenyl)propan-1-ols (6). Catalytic hydrogenation would then give Hydroxyambran® (2).

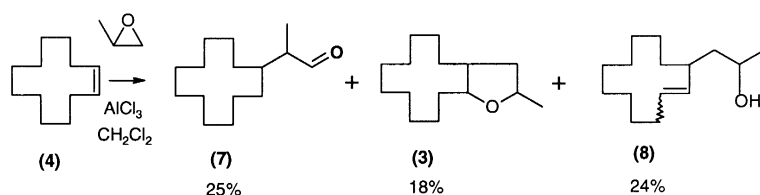
However, unlike the well-known Friedel–Crafts reaction of aromatic systems, the use of alkenes as substrates is known to have problems as a reliable synthetic method.³ No relevant prior art was found in the Lewis acid-catalysed reaction of (cyclo)alkenes with oxiranes.

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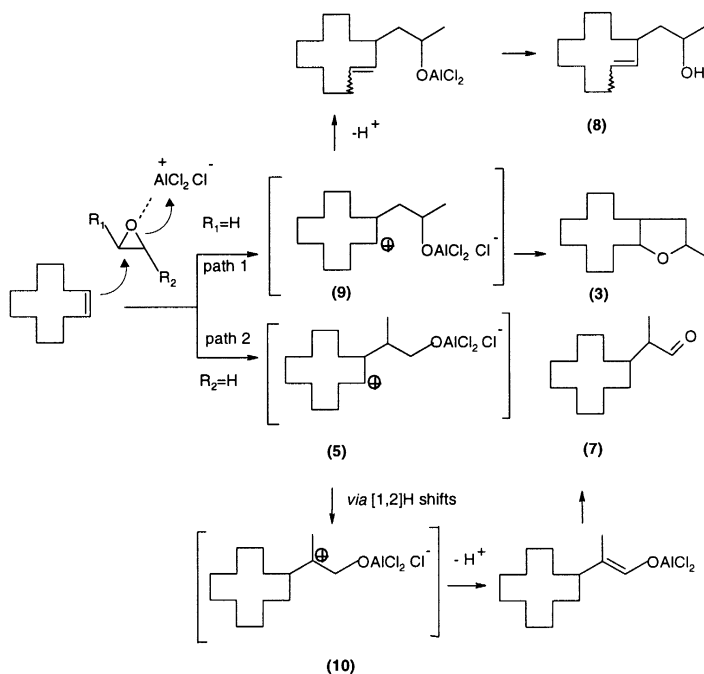
Scheme 2.

The AlCl_3 -catalysed reaction of cyclododecene (4) with propylene oxide in dichloromethane at -30°C was found to give three major products (Scheme 3). These were the aldehyde (7) obtained in 25% yield, the furan (3) (as an unresolved mixture of diastereomers) isolated in 18% yield, and the isomeric unsaturated alcohols, containing mainly 1-(2-cyclododeceny)propan-1-ol (8), which was isolated as a mixture of *E:Z*-isomers, (ratio 82:11.5).



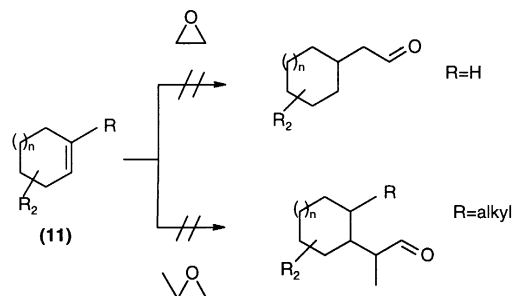
Scheme 3.

The aldehyde (7) was readily reduced to give the target molecule (2). This procedure, therefore, allowed access to both desirable woody-amber materials (2) and (3), together with (8), a useful material for related areas of investigation. In this reaction, it appears that two isomeric carbonium ion intermediates (5) and (9) are initially formed (Scheme 4). Intermediate (9) can ring close to give the tetrahydrofuran (2), or can lose a proton to give the unsaturated alcohol (8). Intermediate (5) undergoes rearrangement by hydrogen shift to give the aldehyde (7).



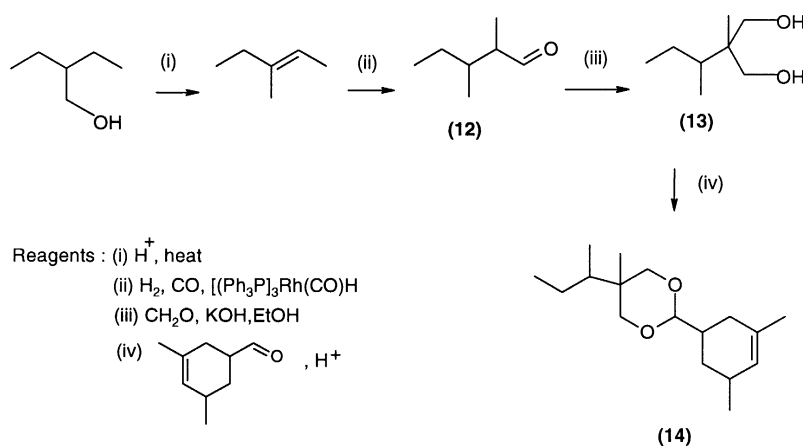
Scheme 4.

A substituted oxirane is necessary in order to obtain an aldehyde as the final product of reaction path 2. The use of ethylene oxide offers no stabilisation of the intermediate corresponding to (10). Also, if 1-alkylcycloalkenes (**11**: R=alkyl) are used, the carbonium ion will not migrate out of the ring (Scheme 5).



Scheme 5.

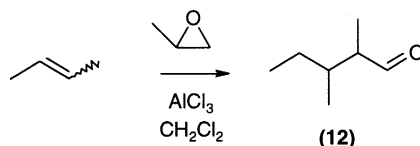
These considerations apart, the reaction has been shown to be general for (optionally substituted) cycloalkenes (**11**: R=H, $n=1, 3, 7$), and alkyl-substituted oxiranes. Introduction of further unsaturation into the cycloalkene substrates gave products derived from domino-type reactions, and will be reported separately.⁴ The utilisation of open-chain alkenes in this reaction also gives valuable products. For example, 5-(*sec*-butyl)-2-(3,5-dimethyl-3-cyclohexenyl)-5-methyl-1,3-dioxane (**14**) is an intense amber material with woody, floral overtones. It is produced⁵ by Quest International under the trade name Karanal[®]. The intermediate diol (**13**) has been obtained by hydroformylation of 3-methylpent-2-ene to give 2,3-dimethylpentan-1-al (**12**) (as an unresolved mixture of diastereomers), followed by the Tollens reaction (Scheme 6).



Scheme 6.

The dehydration–rearrangement [step (i)] and the hydroformylation [step (ii)] both require dedicated facilities, a problem which can be circumvented by the present methodology. When 2-butene and propylene oxide are reacted at -30°C using AlCl_3 as catalyst, 2,3-dimethylpentan-1-al (**12**) is obtained in 33% isolated yield (Scheme 7).

Further applications of this reaction⁶ to materials of fragrance interest have been carried out. While this work was in progress, a further synthesis of molecule (2) was reported,⁷ via radical-initiated addition of propionic acid derivatives to cyclododecene (**4**), followed by high pressure hydrogenation.



Scheme 7.

1. Experimental

AlCl_3 -Catalysed reaction of cyclododecene with propylene oxide: AlCl_3 (180 g:1.35 mol) was suspended in CH_2Cl_2 (1 litre), and cooled to -30°C . A mixture of cyclododecene (200 g:1.2 mol) and propylene oxide (100 g:1.72 mol) was added dropwise with stirring under N_2 , maintaining this temperature with external cooling. After complete addition (1 h), the reaction mixture was immediately quenched by addition to a stirred mixture of ice (2 litres) and Et_2O (2 litres). The organic layer was separated, washed, and dried over MgSO_4 . The solvent was removed in vacuo, and the residue chromatographed (silica:hexane) to give recovered cyclododecene (19.6 g). Further elution, using (hexane 90%: Et_2O 10%) as eluent gave a colourless oil (61.3 g:25.2%), identified as 2-cyclododecylpropan-1-al (**7**), which could be reduced by various procedures (NaBH_4 or H_2 , 5% Pd/C) to give material (**2**), spectroscopic properties identical to an authentic sample. Continued elution gave a colourless oil (44.6 g:18.3%), identified as 2-methyltetradecahydrocyclododeca[*b*]furan (**3**), whose spectroscopic characteristics were identical to a commercial sample of (**3**) (Lignoxan[®], ex Wacker).

The solvent polarity was increased (hexane 50%: Et_2O 50%). Following elution of two poorly-defined multicomponent mixtures [(2.3 g)+(8.7 g)], a further discrete major product was isolated as a colourless oil (64.8 g:26.6%). This material was identified as 1-(2-cyclododecenyl)propan-2-ol (**8**). ^{13}C NMR (CDCl_3): δ 135.7 (CH=CH), 132.2 (CH=CH), 67.7 (CH(CH₃)OH), 46.0 (CH₂CH(CH₃)OH), 41.9 (CHCH₂CH(CH₃)OH), 34.0 (CH₂), 32.4 (CH₂), 26.5 (CH₂), 26.1 (CH₂), 26.1 (CH₂), 25.7(CH₂), 24.7 (CH₂), 23.6 (CH₂), 23.4 (CH₂), 22.8 (CH₃).

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