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One-Pot Synthesis of Hexahydro-4*H*-chromens via Rhodium-Catalysed Tandem Hydroformylation starting from 1,5-Dienes

Rafael Roggenbuck, Peter Eilbracht *

Organische Chemie 1 (FB 3), Universität Dortmund, Otto-Hahn-Str. 6, D-44221 Dortmund Germany

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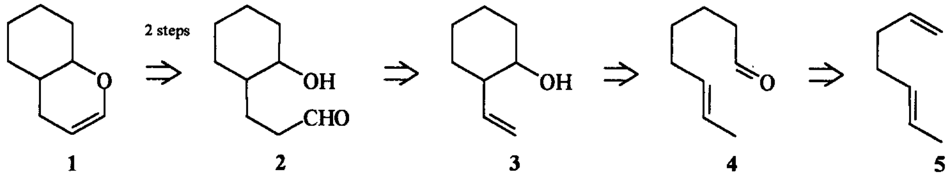
Abstract: A convenient one-pot preparation of substituted hexahydro-4*H*-chromens via rhodium catalysed tandem hydroformylation starting from 1,5-dienes is described. The multi-step procedure starts with a hydroformylation of one double bond followed by carbonyl ene reaction, a second hydroformylation and enol ether forming cyclisation.

Keywords: 1,5-Dienes, Terpenes, Rhodium catalysis, Hydroformylation, Acetalisation, Heterocycles

Unsaturated terpenoid hydrocarbons provide a valuable and renewable feedstock for the synthesis of synthetic building blocks. Thus, transformation of acyclic and cyclic terpenes via transition metal catalysed hydroformylation offers a convenient access to new carbon chain and ring skeletons.[1] Following our interest in tandem hydroformylation reactions,[2] we envisaged a one-pot preparation of 4*H*-chromens of type **1** in a five step reaction sequence starting from 1,5-dienes of type **5** as shown in the retrosynthetic Scheme 1. This procedure requires monohydroformylation of the diene **5** to form an unsaturated aldehyde **4**, followed by cyclisation via intramolecular carbonyl-ene reaction to form the carbocyclic ring **3**. A second hydroformylation is followed by a hemi acetal and enol ether forming heterocyclisation of aldehyde **2**.



Scheme 1

Since all individual steps of this sequence are known to proceed with transition metal catalysts, the combination to a one-pot procedure might be expected under optimised conditions. The first hydroformylation step, if using geraniolene (**9a**), and cobalt or rhodium catalysts occurs at the more reactive terminal double bond to give citronellal[1a,3]. Carbonyl-ene reaction can be induced by various means.[4] Thus, Sakai et al.[4a] reported that intramolecular carbonyl-ene reaction, if using citronellal, forms isopulegol (**6a**) not only thermally at elevated temperatures (180°C) or with Lewis acid catalysts, but also in the presence of equimolar amounts of Wilkinsons' catalyst. Finally, regarding the last step, homoallylic alcohols of type **3** are known to give lactols and dihydropyrans under hydroformylation conditions.[1d,2f]

If starting from isopulegol **6a** under hydroformylation conditions with $Rh(CO)(PPh_3)_3/PPh_3$ as the catalyst precursor, Chalk[1d] obtained the lactol **7a**, whereas with a dinuclear thiolato-bridged rhodium catalyst precursor Kalck [1b, 1e] obtained the lactol **7a** and small amounts of the dehydrated enolic ether **8a**. Based on these results, we investigated the direct synthesis of the 4*H*-chromen skeleton, starting from 1,5-dienes. In our first efforts to optimise the hydroformylation – dihydropyran forming steps, we found that the yield of the enolic ether **8a** can be enhanced by using $Rh(CO)_2(acac)$ / triphenylphosphite as catalyst precursor. Higher temperatures further support the dehydration of lactol **7a**. With $[RhCl(cod)]_2$ or Wilkinson's catalyst at a temperature of 120°C under an atmosphere of 100 bar CO/H_2 (1:1) the yield of **8a** is increased up to 59 %.[5]

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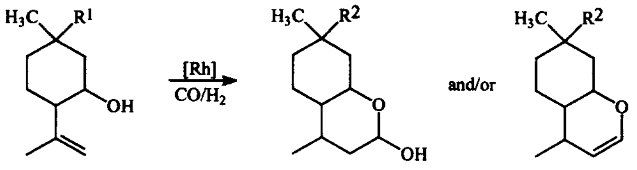
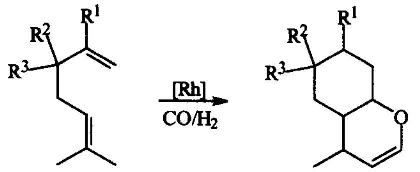


6a R^1 = H   **7a** R^2 = H   **8a** R^2 = H

6b R^1 = vinyl   **8b** R^2 = $(CH_2)_3OH$

Similarly, vinyl isopulegol **6b** under these conditions gives the dihydropyran system **8b** in 80 % yield with an additional hydroformylation/reduction at the vinyl group. Furthermore, if using these conditions for the complete reaction sequence starting from the dienes **9a** or **9b**, the direct synthesis of chromens **10a** and **10b** is achieved in 21 rsp. 40 % yield [5,6].



9a,b   **10a,b**

a R^1= CH_3, R^2= R^3= H 21 % (**9** → **10**)
b R^1= H, R^2= R^3= CH_3 40 % (**9** → **10**)

Thus, we have shown for two selected examples that preparation of 4*H*-chromens can be performed in a one-pot procedure involving a transition metal catalysed five step reaction sequence starting from 1,5-dienes. Further investigations towards synthetic applications and effective stereo control of this transformation are underway.

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5. **Typical procedure for 10a,b**: The reaction is carried out in an autoclave. A solution of the substrate (5 mmol), $RhCl(PPh_3)_3$ (1.0 mol%) and PPh_3 (3 mol%) in 10 ml anhydrous dioxane or toluene was heated for 70 h to 120 °C under an atmosphere of 50 bar carbon monoxide and 50 bar hydrogen. The crude product was filtered through basic alumina (eluated with MTBE). After evaporation of the solvent further purification by coloumn chromatography on silica gel with mixtures of PE/MTBE as solvent followed.
6. **^{13}C-NMR** ($CDCl_3$, 100 MHz) **10a** (mixture of diastereomers): δ [ppm] = 17.7/23.5 (CH_3), 22.3/22.2 (CH_3), 27.1/27.1 (CH_2), 28.1/26.6 (CH), 31.1/31.5 (CH), 34.5/34.6 (CH_2), 40.7/40.7 (CH), 41.0/39.6 (CH_2), 72.1/69.4 (CH), 107.4/104.9 (CH), 142.1/141.9 (CH).

   10b (mixture of diastereomers): δ [ppm] = 23.6/17.5 (CH_3), 24.4/24.3 (CH_3), 27.4/28.3 (CH_2), 30.4/30.8 (Cq), 31.5/28.2 (CH), 32.9/37.1 (CH_2), 33.0/32.8 (CH_3), 36.6/36.2 (CH), 40.0/40.5 (CH_2), 68.4/72.9 (CH), 104.1/107.5 (CH), 142.1/142.0 (CH).