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Sequential Hydroformylation/Aldol Addition Reactions of β,γ-Unsaturated Ketones and their Derivatives

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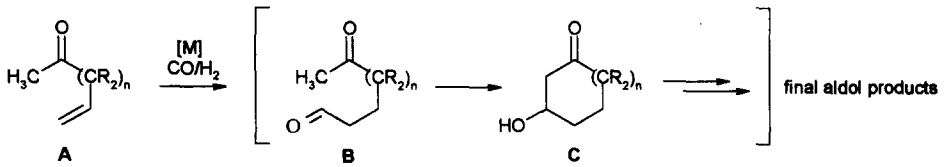
Abstract: Novel rhodium(I) complex catalysed tandem hydroformylation/aldol reactions of a β,γ-unsaturated ketone **1** or its silyl enol ethers **4** in a one-pot procedure are presented to give varying cyclisation products depending on the reaction conditions.

Keywords: aldol reactions; amines; hydroformylation; rhodium catalysis

Aldol products are usually observed as side products in olefin conversions under hydroformylation conditions.[1] However, there are only few examples reported where this sequential reaction is performed with synthetically useful selectivities.[2] Continuing our investigations on tandem hydroformylation reactions[3], we found that the hydroformylation of unsaturated ketones leads to a variety of functionalised aldol cyclisation products via multistep one-pot procedures. As outlined in scheme 1 unsaturated ketones of type **A** can undergo hydroformylation at the olefinic double bond followed by a mixed aldol type cyclisation. According to earlier investigations[4] in intramolecular aldol reactions of keto aldehydes **B** the ketone moiety usually reacts as the enolate equivalent and undergoes nucleophilic addition to the aldehyde function.



Scheme 1.

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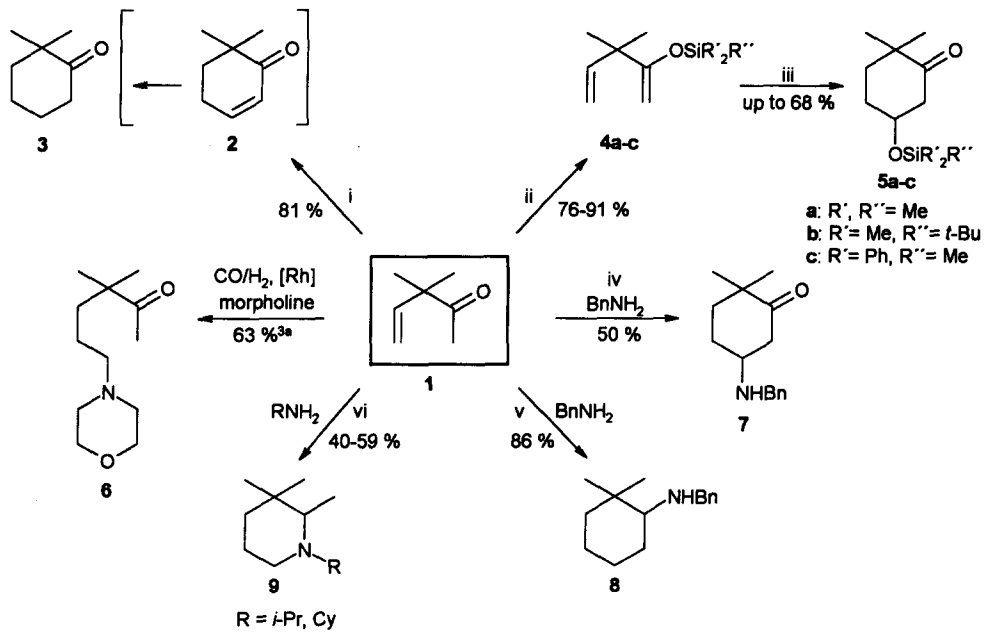
For a detailed study of a combination of both steps in a tandem procedure the β,γ-unsaturated ketone 3,3-dimethyl-4-penten-2-one[5] (**1**) was chosen as the substrate. Rhodium(I) catalysed hydroformylation of the double bond gives the corresponding *n*-aldehyde in high selectivity due to steric effects of the adjacent geminal dimethyl group. If adding catalytical amounts of acid as cocatalyst (e.g. *p*-toluenesulphonic acid) immediate aldol condensation of the intermediate δ-keto aldehyde takes place under the hydroformylation conditions. After dehydration the α,β-unsaturated ketone **2** thus generated undergoes complete hydrogenation to the substituted cyclohexanone **3**[6] (scheme 2, path i).



Scheme 2[7]. i: CO/H_2 (1:1), 80 bar, 100 °C, 3 d, CH_2Cl_2, $[Rh(cod)Cl]_2$, *p*-TsOH·H_2O (10 mol %); ii: a)[8] LDA, THF, -78 °C b) R'$_2$R''SiCl, -78 °C to 20 °C; iii: CO/H_2 (1:1), 80 bar, 90 °C, 3 d, CH_2Cl_2, $[Rh(cod)Cl]_2$; iv: CO/H_2 (1:2), 30 bar, 60 °C, 3 d, benzylamine, dioxane, $Rh(CO)_2(acac)$, BIPHEPHOS[9]; v and vi: CO/H_2 (1:2), 90 bar, 120 °C, 3 d, benzylamine or RNH_2 (R = *i*-Pr, Cy), dioxane, $[Rh(cod)Cl]_2$, $P(OPh)_3$.

Under acid catalysis and the conditions applied the initial aldol adduct could not be obtained. This unfavourable loss of functionality can successfully be suppressed if silyl enol ethers are used as enolate equivalents for this type of tandem aldol addition. Silyl enol ethers on one hand are reported to be stable against hydroformylation.[10] On the other hand, directed aldol addition can be catalysed by a large number of transition metal complexes.[11] Rhodium(I) catalysed aldol type reactions of enol silanes and aldehydes are reported by Matsuda[12], Reetz[13] and Heathcock[14]. According to the results of Matsuda[12], who described rhodium(I) carbonyl complex catalysed

Mukaiyama aldol addition[11b], it can be expected, that rhodium hydrido carbonyl species as formed under hydroformylation conditions can equally catalyse the aldol reaction of the hydroformylation product.

Thus trialkylsilyl enol ethers **4a-c** of the unsaturated ketone **1** undergo *n*-hydroformylation at the olefinic double bond followed by an intramolecular Mukaiyama type aldol addition in order to form silylated aldol adducts **5a-c** in good yields (scheme 2, path iii). This one-pot conversion was carried out using different silyl moieties, e.g. trimethyl silyl, *tert*-butyl dimethyl silyl and the diphenyl methyl silyl group. Best results were achieved using the trimethyl silyl group and CH_2Cl_2 as solvent.

Different reaction products are obtained if the hydroformylation of the unsatured ketone **1** is carried out in the presence of amines. With secondary amines a straightforward hydroaminomethylation of the olefinic double bond is observed, leaving the ketone carbonyl group unaffected.[3a] In contrast, with primary amines, e.g. benzylamine, under mild hydroformylation conditions in the presence of BIPHEPHOS[9] the β-amino substituted cyclic ketone **7** is obtained as the final product (scheme 2, path iv). This sequence might either proceed via hydroformylation, imine condensation of the newly generated aldehyde and subsequent aldol reaction with the ketone enolate or via the unsaturated ketone **2** and conjugate addition of the amine to the activated double bond. Under more severe hydroformylation conditions the conversion of **1** and benzylamine proceeds in a different fashion. Here the secondary cyclic amine **8** is isolated as the sole product of a multistep sequence (scheme 2, path v). The product suggests a mechanism similar to those above including reductive amination of the ketone moiety. Although the individual reaction steps can follow each other in different orders, obviously, due to the higher temperature, the condensation of the ketone and benzylamine takes place before the more reactive aldehyde functionality is generated via hydroformylation.

If using bulkier primary amines, e.g. isopropyl or cyclohexyl amine, no aldol type reaction is observed. Instead N-heterocycles of type **9** are generated via double amine condensation and reductive amination of both carbonyl functions. Similar reaction products of unsaturated ketones were isolated according to earlier observations in our group.[3b]

In conclusion we have shown that unsaturated carbonyl compounds can be converted in selective tandem hydroformylation/aldol additions to form various products depending on the reaction conditions. According to preliminary results tandem reactions of this type can be achieved with various other unsaturated ketones.[15] In rare cases dienes can be converted to intramolecular aldol condensation products after hydroformylation of both double bonds.[16] Therefore further investigations towards an extension of the synthetic potential of these reactions are in current progress.

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7. a) **General procedure:** *Hydroformylation/aldol reaction of functionalised olefins:*
   The reactions were carried out in an autoclave. A solution of the functionalised olefin (10.0 mmol), the additive and the Rh complex (1 mol %) in 10 ml anhydrous solvent was magnetically stirred and heated under carbon monoxide and hydrogen pressure. The remaining solution was filtered through alumina using diethyl ether as eluent. The solvent was removed by rotary evaporation and the products were separated by column chromatography on silica gel using mixtures of petrol ether (30/60) and methyl *t*-butyl ether as eluent. - b) Spectral data of 2,2-dimethyl-5-trimethylsilanyloxy-cyclohexanone (**5a**): ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C) δ = 0.06 (s, 9 H), 1.03 (s, 3 H), 1.08 (s, 3 H), 1.40 (m, 1 H), 1.75 (m, 2 H), 1.85 (m, 1 H), 2.45 (dd, ^{2}J = 14.0 Hz, ^{3}J = 8.0 Hz, 1 H), 2.52 (ddd, ^{2}J = 14.0 Hz, ^{3}J = 4.7 Hz, J = 1.4 Hz, 1 H), 3.95 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C) δ = 0.0 (CH_3), 24.7 (CH_3), 24.9 (CH_3), 30.5 (CH_2), 34.9 (CH_2), 44.2 (Cq), 47.6 (CH_2), 70.6 (CH), 213.7 (Cq). IR (NaCl, neat) ν = 2963 (vs), 2874 (m), 1714 (vs), 1456 (m), 1252 (s), 1101 (s), 1055 (m), 1010 (m), 841 (vs) cm^{-1}. GC-MS (EI, 70 eV) m/z (%) = 287 (M^+ + $Si(CH_3)_3$, 95), 197 (100), 169 (16), 141 (58), 125 (50), 107 (81), 95 (62), 73 (64). $C_{11}H_{22}O_2Si$ (214.38): Calcd. C, 61.63; H, 10.34; Found C, 61.5; H, 10.2.
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