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Note

Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds. Selective Inhibition of Benzyl Ether Hydrogenolysis by NH_4OH/MeOH

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Uma série de alquil e aril cetonas, ésteres e N-metóxi-N-metil amidas (Amidas de Weinreb) α,β-insaturadas contendo um grupo protetor O-benzyl sofrem redução conjugada por H_2/Pd/C na presença de solução 2N de NH_4OH/MeOH a temperatura ambiente e pressão normal deixando o grupo benzil intacto.

A series of α,β-unsaturated alkyl and aryl ketones, esters and N-methoxy-N-methyl-amides (Weinreb amides) containing an O-benzyl protecting group undergo conjugate reduction by H_2/Pd/C in the presence of 2N NH_4OH/MeOH at room temperature and ordinary pressure leaving the benzyl group intact.

Keywords: *conjugate reduction, inhibition of benzyl ether hydrogenolysis, chemoselective reduction of α,β-unsaturated compounds, selective catalytic hydrogenation*

A number of synthetic methods have been developed which effect the conjugate reduction of α,β-unsaturated carbonyl compounds[1-6]. However, chemoselective reduction of α,β-unsaturated carbonyl functionality in more complex molecules containing benzyl and 4-methoxybenzyl (MPM) protecting groups in the substrate is more complicated, although Evans and Fu obtained good yields of conjugate reduction with a fairly complex molecule[7]. Catalyst poisoning or hydrogenolysis may complicate double bond reduction under conditions of catalytic hydrogenation[1].

The presence of amine functions inhibiting O-debenzylation has been reported by a number of groups[8,9]. The addition of ammonia, ammonium acetate (0.5 equiv.) and pyridine to the Pd/C catalyst has been recently reported to inhibit hydrogenolysis of aliphatic benzyl ethers during reduction of conjugated olefins, benzyl ester, and azide functional groups in methanol[10]. More recently, the selective catalytic hydrogenolysis (in MeOH-dioxan or DMF on Pd/C catalyst in the presence of pyridine) of phenolic O-benzyl ethers, Cbz, benzyl esters, and selective reduction of nitro groups and conjugated olefins in phenols protected with the 4-methoxybenzyl (MPM) group was described[11].

We decided to explore the synthetically attractive possibility that NH_4OH might be used to retain an O-benzyl group while hydrogenation took place at the α,β-unsaturated double bond. For this purpose we synthesized a series of α,β-unsaturated carbonyl compounds containing an O-benzyl protecting group (Table 1, substrates **1-8**). We wish to report here that α,β-unsaturated carbonyl compounds containing a benzyl protecting group undergo selective hydrogenation of the unsaturated double bond in the presence of 2N NH_4OH/MeOH leaving the O-benzyl group intact.

Control experiments indicated that, in the absence of NH_4OH complete removal of the benzyl protecting group in compounds **1-8** was observed. However, addition of 2N NH_4OH/MeOH results in conjugate reduction of these α,β-unsaturated carbonyl compounds under very mild conditions (25 °C, 1 atm, 30 min). When compounds **1-8** were

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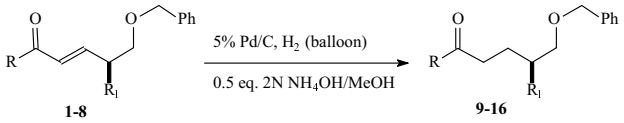
submitted to these conditions, a smooth reduction to compounds **9-16** was observed without any indication of benzyl ether hydrogenolysis (Table 1). The selectively hydrogenated products **9-16** were obtained in excellent isolated yields[12].

This mild method for conjugate reduction is compatible with a variety of carbonyl functional groups and is amenable to large scale preparations. The products **10** and **14** (esters), **12** and **16** (Weinreb amides) can be easily converted to the corresponding primary alcohols and aldehydes, respectively, increasing the scope of this reaction.

Representative experimental procedure: After two vacuum/H_2 cycles to remove air from the reaction flask, the stirred mixture of **1-8** (1.0 mmol), 5% Pd/C (25 mg) and freshly prepared 2N NH_4OH/MeOH solution (0.3 mL) in MeOH (5 mL) was hydrogenated at 1 atm and room temperature for 45 min. The reaction mixture was filtered (Celite), and the filtrate was concentrated and purified directly by flash chromatography to afford the pure products **9-16** as shown in Table 1 (filtration of the reaction solution through Celite and evaporation gave almost pure products)[13].

In conclusion, the reaction described herein comprises a mild, high yielding and convenient method for effecting the selective the conjugate reduction of α,β-unsaturated carbonyl compounds having an O-benzyl protecting group. These results are apparently attributable to the effect of NH_4OH. Further studies defining the scope and limitations of this reaction as well as its application in the total synthesis of natural products are in progress[14].

Table 1. Inhibition of hydrogenolysis in the conjugate reduction of α,β-unsaturated carbonyl compounds.



1-8 **9-16**

Substrates **1-8** [a]		Products **9-16**
R	R_1	Yield (%) [b,c]
1, Ph	H	**9** (94%)
2, OEt	H	**10** (91%)
3, Me	H	**11** (99%)
4, N(OMe)Me	H	**12** (99%)
5, Ph	Me	**13** (80%)
6, OEt	Me	**14** (99%)
7, Me	Me	**15** (96%)
8, N(OMe)Me	Me	**16** (94%)

[a] The α,β-unsaturated compounds **1-8** were prepared in good yields (70-90%) by the Horner-Emmons reaction between aldehydes and the corresponding activated phosphoranes.
[b] Reactions were complete within 45 min and all the products were identified by ^{1}H-NMR, ^{13}C-NMR and Infrared spectra. Satisfatory analytical data were obtained for all compounds.
[c] Isolated yields after chromatographic separation.

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13. Selected Data for compounds **6** and **14**. α,β-unsaturated ester **6**: ^{1}H-NMR (300 MHz, $CDCl_3$): 1,09 (d, 3H, J = 6,96 Hz); 1,29 (t, 3H, J = 7,14 Hz); 2,67 (m, 1H); 3,38 (dd, 1H, J = 9,15 and 6,23 Hz); 3,43 (dd, 1H, J = 9,15 and 6,96 Hz); 4,52 (s, 2H); 4,19 (q, 2H, J = 6,96 Hz); 5,87 (dd, 1H, J = 15,80 and 1,46 Hz); 6,96 (dd, 1H, J = 15,80 and 7,14 Hz); 7,26-7,39 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$): 13.99; 15.81; 36.60; 60.14; 73.04; 73.85; 121.13; 127.76; 127.79; 128.56; 138.40; 151.38; 167.04 ppm; IR (film): 3030, 2978,

2858, 1716, 1653, 1455, 1367, 1270, 1097, 1037, 737 cm^{-1}. Saturated ester **14**: ^{1}H-NMR (300 MHz, $CDCl_3$): 0,89 (d, 3H, J = 6,59 Hz); 1,24 (t, 3H, J = 7,14 Hz); 1,46 (m. 1H); 1,78 (m, 2H); 2,32 (m, 2H); 4,11 (q, 2H, J = 7,14 Hz); 4,49 (s, 2H); 7,25-7,37 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$): 13.95; 16.56; 28.61; 31.83; 32.86; 60.13; 72.93; 75.36; 127.63; 127.67; 128.49; 138.82; 174.24 ppm; IR (film): 3030, 2958, 2922, 2868, 1734, 1454, 1373, 1254, 1179, 1098, 1028, 737 cm^{-1}.

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