Chemoselective Reduction of Aldehydes in the Presence of Ketones Utilizing Raney Nickel

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Abstract: Raney nickel is an effective reagent to achieve the chemoselective reduction of aldehydes in the presence of ketones, which takes place in high yield. Only highly hindered aldehydes do not undergo reduction.

Key words: chemoselectivity, reduction, aldehydes, ketones

In a previous paper[1] the effectiveness of Raney nickel to accomplish the chemoselective reduction of conjugated olefins in α,β-unsaturated carbonyl compounds, that also contain isolated carbon-carbon double bond, was reported. Our recent research has revealed that this reagent may also be very effective for carrying out the selective reduction of aldehydes in the presence of ketones.

The selective reduction of aldehydes in the presence of ketones constitutes an important challenge in organic synthesis, due to the similar reactivity of these functions; in most cases it is necessary to use expensive reagents and/or work at low temperatures. This can be accomplished by using aminoborane or *tert*-butylaminoborane.[2] High selectivity is also achieved with tributylstannane,[3] especially in the presence of low-valency titanium.[4] The use of bulky hydrides has also demonstrated to be effective. Thus, tetrabutylammonium triacetoxyborohydride affords high yields of primary alcohols.[5] Potassium triphenylborohydride is effective when used at -78 °C.[6] Lithium trialkoxyaluminium hydrides also convert ketoaldehydes into the corresponding ketoalcohols at a low temperature:[7] for example, lithium tris(triethylmethoxy)aluminium hydride shows high selectivity against the system hexanal-cyclohexanone at temperatures below 0 °C.

Although heterogeneous catalytic hydrogenation is a classical method of hydrogenation in preparative organic chemistry, it has not been very widely used for reducing carbonyl groups; however some studies into the catalytic hydrogenation of aldehydes and ketones have been reported. The use of Raney nickel and other modified nickel catalysts for this purpose has been described.[8-10] Saturated aliphatic aldehydes are converted to the corresponding alcohols quantitatively using Raney nickel. Unsaturated aliphatic aldehydes undergo complete reduction, including both the aldehyde and carbon-carbon double bond; thus, cinnamaldehyde was converted into hydrocinnamyl alcohol by treating with Raney nickel.[8] This reagent also allows the hydrogenation of benzaldehyde into benzyl alcohol practically without any hydrogenolysis.[8] Some examples of the reduction of ketones with Raney nickel have been reported: acetone, benzophenone and acetophenone were transformed into the corresponding secondary alcohols after hydrogenation at 1-3 atm.

During our research into the use of Raney nickel as chemoselective reductor we have found that the low reactivity of this agent makes possible to achieve the selective reduction of the aldehyde group in the presence of the ketone function under mild conditions. Some representative examples are summarized in the Table. The treatment of a solution of an equimolecular mixture of acetophenone (**1a**) and benzaldehyde (**2a**) in tetrahydrofuran with Raney nickel at room temperature for 10 min afforded benzyl alcohol in a quantitative yield, with acetophenone being recovered unaltered. The behaviour of ketoaldehydes **3a-13a**, having different structural features, against Raney nickel is shown in the Table. In most cases the corresponding primary ketoalcohol was obtained in a high yield. Aldehydes bearing formyl group on a quaternary carbon were also reduced. Only the very highly hindered aldehydes were unreactive; for example, compounds **10a** and **13a**, in which the aldehyde group has a 1,3-diaxial interaction with the angular methyl, remained unaltered after prolongued exposure to the reducing agent.

In summary, Raney nickel is an effective reagent for achieving the chemoselective reduction of aldehydes in the presence of ketones. Only highly hindered aldehydes do not undergo reduction.

Acknowledgement

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References and Notes

(1) Barrero, A.F.; Manzaneda, E.A.; Chahboun, R.; Meneses, R. *Synlett* **1999** 1663.
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(5) Nutaitis, C.F.; Gribble, G.W. *Tetrahedron Letters* **1983**, *24* 4287.
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(7) Krishnamurthy, S. *J. Org. Chem.* **1981**, *46*, 4628.
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Table Chemoselective Reduction of Aldehydes in the Presence of Ketones with Raney Nickel

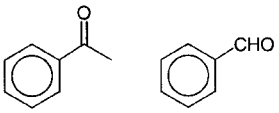
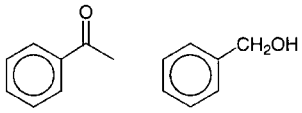
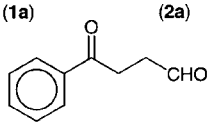
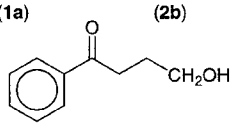
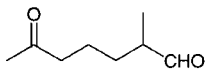
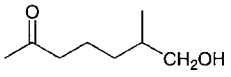
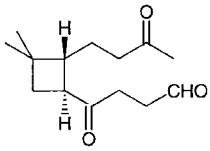
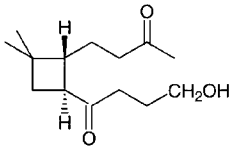
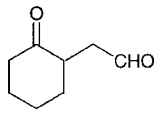
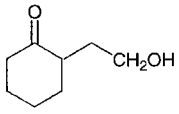
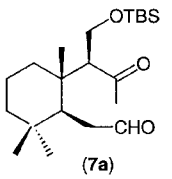
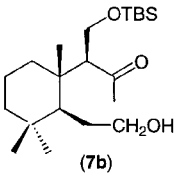
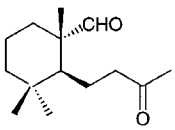
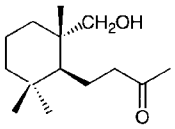
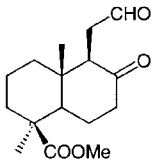
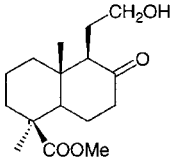
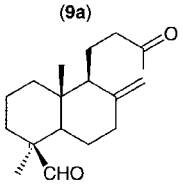
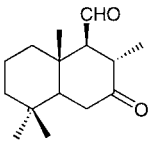
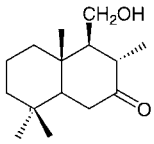
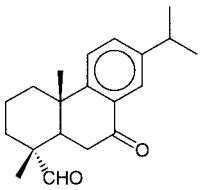
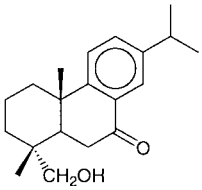
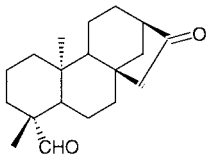
Substrate	Product	Reaction Time	Yield
 (1a) (2a)	 (1a) (2b)	10 min.	100%
 (3a)	 (3b)	40 min.	89%
 (4a)	 (4b)	1 h.	92%
 (5a)	 (5b)	1 h.	96 %
 (6a)	 (6b)	30 min.	98%
 (7a)	 (7b)	50 min.	95 %
 (8a)	 (8b)	30 min.	93 %
 (9a)	 (9b)	1 h.	91 %
 (10a)	No Reaction	6 h.	----

Table (continued)

Substrate	Product	Reaction Time	Yield
 (**11a**)	 (**11b**)	30 min.	75 %
 (**12a**)	 (**12b**)	45 min.	97 %
 (**13a**)	No Reaction	4 h.	----

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(14) All new compounds were fully characterized spectroscopically and had satisfactory high resolution mass spectroscopy data. For preparation of compounds **8a**, **9a** and **12a** see references 12, 11 and 13, respectively. Compounds **10a** and **11a** are intermediates of our synthetic research and are a part of unpublished results. Compounds **5a** and **7a** were prepared by ozonolysis of caryophyllene and of the *O*-silylderivative of drimenol, respectively. **13a** was obtained by ozonolysis of *ent*-kaur-16-en-18-ol and further oxidation with PCC.
Selected data:
5a ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.03 (s, 3H), 1.05 (s, 3H), 1.61 (m, 2H), 1.73 (t, *J* = 10.3 Hz, 2H), 1.87 (t, *J* = 9.2 Hz, 2H), 2.10 (s, 3H), 2.34 (dd, *J* = 6.7 and 2.8 Hz, 1H), 2.36 (dd, *J* = 7.5 and 2.8 Hz), 1H), 2.65 (m, 2H), 2.73 (m, 2H), 2.79 (d, *J* = 9.4 Hz, 1H), 2.84 (d, *J* = 9.4 Hz, 1H), 9.79 (s, 1H).
5b ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.04 (s, 3H, 1.06 (s, 3H), 1.63 (m, 2H), 1.84 (m, 4H), 2.10 (s, 3H), 2.39 (m, 4H), 2.50 (dt, *J* = 6.7 and 1.6 Hz, 2H), 2.78 (d, *J* = 9.5 Hz, 1H), 2.85 (d, *J* = 9.5 Hz, 1H), 3.63 (t, *J* = 6.1 Hz, 2H).
7a ^{1}H NMR (300 MHz, $CDCl_3$) δ: -0.05 (s, 3H), -0.02 (s, 3H), 0.80 (s, 9H), 0.84 (s, 3H), 0.85 (s, 3H), 0.87 (s, 3H), 1.60 (m, 2H), 1.72 (dq, *J* = 13.4 and 2.8 Hz, 1H), 2.15 (s, 3H), 2.96 (dd, *J* = 9.8 and 3.5 Hz, 1H), 3.95 (m, 2H), 3.64 (dd, *J* = 9.4 and 3.5 Hz, 1H), 3.87 (t, *J* = 9.4 Hz, 1H).
7b ^{1}H NMR (300 MHz, $CDCl_3$) δ: -0.06 (s, 3H), -0.04 (s, 3H), 0.73 (s, 3H), 0.78 (s, 9H), 0.85 (s, 6H), 1.40 (m, 3H), 1.71 (dq, *J* = 13.2 and 2.8 Hz, 1H), 1.96 (t, *J* = 4.7 Hz, 1H), 2.11 (s, 3H), 2.44 (d, *J* = 4.2 Hz, 1H), 2.61 (dd, *J* = 10.3 and 4.1 Hz, 1H), 3.75 (dd, *J* = 9.2 and 4.1 Hz, 1H), 3.85 (dd, *J* = 10.3 and 9.2 Hz, 1 H), 9.77 (t, *J* = 1.3 Hz, 1H).
8a ^{1}H NMR (400 MHz, $CDCl_3$) δ:0.91 (s, 3H), 0.95 (s, 3H), 1.18 (s, 3H), 1.20-1.78 (m, 9H), 2.09 (s, 3H), 2.29 (ddd, *J* = 17.1, 10.6 and 5.5 Hz, 1H), 2.39 (ddd, *J* = 17.1, 10.8 and 5.6 Hz, 1H), 9.28 (s, 1H).
8b ^{1}H NMR (300 MHz, $CDCl_3$) δ:0.71 (s, 3H), 0.82 (s, 3H), 0.84 (s, 3H), 2.08 (s, 3H), 2.46 (ddd, *J* = 16.5, 9.7 and 6.9 Hz, 1H), 2.60 (ddd, *J* = 16.5, 9.7 and 6.9 Hz, 1H), 2.96 (d, *J* = 11.1 Hz, 1H), 3.36 (d, *J* = 11.1 Hz, 1H).
9a ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.56 (s, 3H), 1.28 (s, 3H), 2.05-2.50 (m, 2H), 2.25 (dd, *J* = 17.2 and 2.6 Hz, 1H), 2.90 (m, 2H), 3.62 (s, 3H), 9.79 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.5 (C-20), 19.5 (C-2), 24.9 (C-6), 28.6 (C-18), 37.1 (C-11), 37.8 (C-3), 39.5 (C-1), 41.8 (C-7), 41.9 (C-10), 44.2 (C-4), 51.3 (MeO), 54.4 (C-5), 56.9 (C-9), 176.9 (C-19), 201.0 (C-12), 209.7 (C-8).
9b ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 0.50 (s, 3H), 1.25 (s, 3H, 2.1-2.4 (m, 3H), 3.60 (m, 2H), 3.61 (s, 3H). ^{13}C NMR (75 MHz, CD_3COCD_3) δ:13.5 (C-20), 20.5 (C-2), 26.1 (C-6), 26.2 (C-11), 28.9 (C-18), 38.6 (C-3), 39.9 (C-1), 43.3 (C-7), 43.5 (C-10), 44.9 (C-4), 51.5 (MeO), 55.2 (C-5), 59.4 (C-9), 61.7 (C-12), 177.4 (C-19), 211.9 (C-8).
11a ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88 (s, 3H), 0.90 (s, 3H), 0.97 (d, *J* = 6.5 Hz, 3H), 1.24 (s, 3H), 1.39 (dd, *J* = 13.7 and 3.6 Hz, 1H), 1.64 (dt, *J* = 13.4 and 3.4 Hz, 1H), 1.75 (br d, *J* = 12.5 Hz), 2.12 (dd, *J* = 12.1 and 3.5 HZ, 1H), 2.36 (t, *J* = 14.6 Hz, 1H), 2.48 (dd, *J* = 14.6 and 3.6 Hz), 1H), 2.87 (dq, *J* = 12.2 and 6.4 Hz, 1H), 9.78 (d, *J* = 3.5 Hz, 1H).

11b ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.82 (s, 3H), 0.87 (s, 3H), 1.11 (d, *J* = 6.7 Hz, 3H), 1.15 (s, 3H), 1.23 (dd, *J* = 13.7 and 3.7 Hz), 1.65 (dt, *J* = 13.5 and 3.5 Hz), 1.95 (bd, *J* = 12.5 Hz, 1H), 2.32 (t, 14.5 Hz, 1H), 2.43 (dd, *J* = 14.5 and 3.5 Hz, 1H), 2.56 (dq, *J* = 12.2 and 6.5 Hz, 1H), 3.78 (dd, *J* = 11.1 and 3.9 Hz, 1H), 3.84 (dd, *J* = 11.1 and 2.5 Hz, 1H).
12b ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (s, 3H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.25 (s, 3H), 2.24 (dd, *J* = 11.1 and 6.6 Hz, 1H), 2.31 (br d, *J* = 12.9 Hz, 1H), 2.63 (dd, *J* = 17.8 and 6.6 Hz, 1H), 2.64 (dd, *J* = 17.8 and 11.1 Hz, 1H), 2.89 (h, *J* = 6.9 Hz, 1H), 3.14 (d, *J* = 10.9 Hz, 1H), 3.43 (d, *J* = 10.9 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.37 (dd, *J* = 8.1 and 1.5 Hz, 1H), 7.82 (d, *J* = 1.5 Hz, 1H).

13a ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88 (s, 3H), 0.96 (s, 3H), 2.10 (br d, *J* = 13.4 Hz, 1H), 2.22 (dd, *J* = 11.9 and 2.5 Hz, 1H), 2.34 (br s, 1H), 9.70 (d, *J* = 1.2 Hz, 1H).

(15) Typical experimental procedure:
0.8 g of an aqueous suspension of Raney nickel (Fluka, cat. no. 83440) was added to a stirred solution of compound (1.0 mmol) in tetrahydrofuran (10 ml) and the mixture was further stirred at room temperature for the specified time (Table). The mixture was diluted with ether and filtered through celite, and the solvent was evaporated to yield the reduced compound.

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