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LETTERS

A green and selective reduction of aldehydes

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Abstract

Aldehydes are reduced to alcohols with sodium formate in subcritical water at temperatures and pressures below those required to reduce cyclic ketones. Acyclic ketones afford only minor amounts of alcohol with sodium formate even under more forcing conditions. © 2000 Elsevier Science Ltd. All rights reserved.

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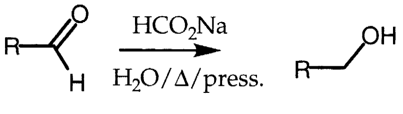
Developments in highly specialized (chemo-, regio- and stereoselective) reagents can be at odds with the goals of green chemistry.[1] For example, tetrabutylammonium cyanoborohydride in acidic HMPA or NaBH(S^{t}Bu)$_3$ elegantly provides selectively for the reduction of aldehydes in the presence of ketones,[2] but reaction conditions and by-products are not environmentally benign.[3] Here we describe a selective reduction of aldehydes that is profoundly green[4] and achievable with very simple equipment.[5] We needed an aqueous reducing agent that had some thermal and aqueous stability. Sodium formate has an extensive history[6] and was chosen based on its green by-products. Other possible hydrogen sources were judged to be either environmentally unfriendly or were achieved by a complicated work-up. For example, reductions with cyclohexene or cyclohexadiene[7] would form benzene or reductions with alcohol[8] in water would change the critical point properties of water and yield a product(s) in alcohol interfering with a green work-up and separation.

Indeed, aqueous HCO_2Na in water at 250–350°C (~1300 psi)[9] without a co-solvent or added catalyst will reduce aldehydes and a number of ketones. These conditions are below the critical point of water but were at temperatures and pressures selected such that the organic substrate was believed to have reasonable solubility.[10] Yields of alcohol have not been optimized and are obtained generally by distillation of the organic phase that has been separated from the water layer.[11]



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Experiments comparing the amount of sodium formate to the efficiency of the carbonyl reduction have leveled at 3 equivalents of sodium formate being generally favored. Even using 3 equivalents there is a noticeable positive pressure when opening the cooled pressure reactor due to formed CO_2. Running at different temperatures reveals selectivity for aldehyde reduction. Aldehyde reduction is observed at 250 to 300°C and ~1200 psi with reaction times up to 3 h; at 300°C or greater cyclic ketones show substantial reduction, and acyclic ketones afford only poor conversion to alcohols at 340°C even with extended reaction times. If selectivity is not an issue, higher temperatures (Table 1) and/or longer reaction times generally improve yields. To verify the tunability of this reduction, a mixture of **1** and **2** (1:1, 310°C) are treated with 3 equivalents of sodium formate effecting reduction of only benzaldehyde (to **3**) (Table 2). Higher temperatures generally increase yields of primary alcohols but other processes (presumably aldol, Cannizzaro reaction, and dehydration) become significant making separations difficult. Similarly, reduction (350°C) of a 1 to 1 mixture of heptanal (**5**) and 2-heptanone (**2**) yields a mixture of ketone **2** and 1-heptanol (60% based on heptanal) with no **4**.

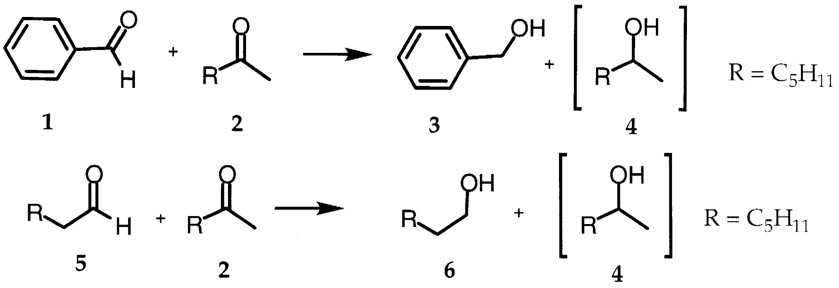


Table 1
Aldehyde reduction with 3 equivalents of HCO_2Na

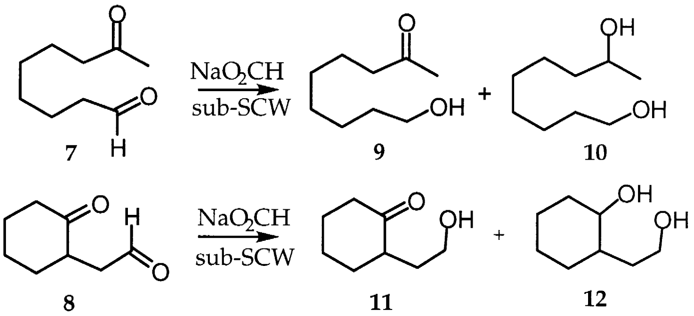
RCHO	yield[a]	temperature
R = C_5H_{11}	58%[a]	340-350°C
R = C_6H_5	74%	300-315°C
R = $C_{11}H_{23}$	48%	340-350°C
R = CH_2CH_2Ph	40%	300-315°C
R = CH_2Ph	15%[12]	340-350°C

[a] Distilled yield

Table 2
Representative ketones

ketone	**temperature °C**	**% yield**
cyclopentanone	310 / 340	23 / 51
cyclohexanone	310 / 340	34 / 53
estrone	340	~1
α-tetralone	340	~10

This selectivity was further tested with 8-oxononal (**7**) and 2-(2-oxocyclohexyl)ethanal (**8**). Sodium formate and **7** (290°C, 0.5 h) afforded a 7 to 1 mix of ketone **9** and diol **10** in 56%, while **8** (240°C, 0.5 h) formed 2-(2-hydroxyethyl)cyclohexanone (**11**), 78%, with less than 2% of diol **12** formed.[13]



Typically, a 10 cc pressure reactor equipped with a thermocouple[5] is charged with a 4 ml mixture of degassed water, carbonyl compound (0.05 to 0.4 g, 1 equiv.) and sodium formate (3 equiv.) and flushed with nitrogen. The reactor is placed in a preheated muffle oven, brought to and maintained at the targeted temperature (250/310/340°C) for 0.5 h (or 3 h) and quickly cooled. The reactor is cautiously opened, the organics separated by heavily salting the aqueous phase and the product distilled.[14]

Aldehydes and some ketones can be reduced with sodium formate under pressure and at elevated temperatures in water without co-solvents or additional catalysts or reagents.[15] Aspects of this process and other green transformations are currently under study.

Acknowledgements

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4. By-products are CO_2 and H_2O or NaOH.
5. Equipment: Two types of reactors have been employed: A Parr pressure reactor heated in a sand bath or oven and a capped 316 stainless steel tube heated in a muffle oven. The latter can be equipped with a thermocouple and fiber optic probe.
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11. GC analysis of products indicates yields are much better than reported above.
12. Based on data from GC–mass spectra of the products, it appears aldol/dehydration (2,4-diphenylbut-2-enal) and subsequent reduction (2,4-diphenylbut-2-en-1-ol) are the major reactions with this highly enolizable aldehyde.

13. Product analysis shows 60% of **11** plus a mixture of enol ethers (18%) presumably formed from dehydration of the hemiacetal on heating (GC or distillation). These same products formed on hydrolysis of the ketal of **11**. Amounts of **12** were based on GC comparison to an authentic, epimeric sample.
14. Products were characterized by IR, ^{13}C and ^{1}H NMR, mass spectroscopy and chromatographic comparison to authentic compounds. Some work-up procedures required pH adjustment and chromatography.
15. Preliminary results indicate that ethyl formate affords a similar selectivity for aldehyde reduction. The primary difference observed, so far, between sodium formate (basic) and ethyl formate is that the latter tends to promote dehydration of certain alcohol reduction products.