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Uncatalysed hydrogen-transfer reductions of aldehydes and ketones

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Aldehydes and ketones are reduced to the corresponding alcohols by transfer hydrogenation at high temperature with EtOH, Pr^{n}OH or Pr^{i}OH as hydrogen donors in the absence of catalysts and base.

Hydrogen-transfer occurs when covalently bonded hydrogen changes its site of attachment, either inter- or intra-molecularly.[1] The reduction of aldehydes and ketones usually involves unlike donors and acceptors.[2–4] It has been long considered that catalysts are required,[3] that alcohols are preferred hydrogen donors[5] and that base promotion is beneficial.[4,6] For example, Meerwein–Ponndorf–Verley (MPV) reductions are typically conducted using a stoichiometric amount of $Al(OPr^i)_3$ and excess Pr^{i}OH.[4,7] However, such conditions can give substantial amounts of side-products[4] and generate environmentally undesirable salts during work-up.[8]

Our work toward the development of cleaner processes for preparative organic chemistry has produced new thermolytic methods.[9] Now we report hydrogen-transfer reactions that employ elevated temperatures without added metallic catalysts, acids or bases.

The starting aldehydes and ketones were heated with low-boiling alcohols in stainless steel autoclaves, with or without glass liners, at 220–230 °C. After cooling, the products were isolated by rotary evaporation and/or distillation. Solvent extraction was avoided and recycling of the unreacted volatile alcohols was facilitated.

Initially, EtOH, Pr^{n}OH or Pr^{i}OH were evaluated as the sources of hydrogen, with PhCHO as the reductant. BzOH was formed at comparable rates in these alcohols, including in all-glass systems. After treating PhCHO for 24 h in Pr^{i}OH at 225 °C (entry 1 in Table 1), the product mixture comprised BzOH (92% isolated yield), starting material (4%) and (*E*)-4-phenylbut-3-en-2-one (the aldol by-product from the reaction of the starting PhCHO with Me_2CO formed by oxidation of the Pr^{i}OH; 2%). $PhCO_2H$ and $PhCO_2Bz$ (possible by-products from Cannizzarro and Tishchenko reactions, respectively) were either present in trace amounts or not detected. Thus, the reaction proceeded slowly but selectively and competing processes were retarded in the absence of added base.

A similar result was obtained for the reduction of cinnamaldehyde (entry 2).[10] The major product was (*E*)-cinnamyl alcohol. 3-Phenylpropanol (up to 7%) was formed by reduction of the double bond followed by that of the aldehydic function. The stability of cinnamyl alcohol under similar conditions (entry 7) confirmed this reduction sequence.

High-boiling hydrocarbons have been used by others as hydrogen donors for the reduction of carbonyl compounds, at temperatures around 400 °C.[11,12] However, in contrast with the present work (which employed considerably lower temperatures), α,β-unsaturated carbonyl compounds were selectively hydrogenated at the carbon–carbon double bond, while the carbonyl group remained intact.[11]

Herein, cyclohexanone and acetophenone afforded cyclohexanol and 1-phenylethanol, respectively (entries 5 and 6). The rate of reduction of ketones was slower than that for aldehydes. Dehydration of the products was not observed.

To the best of our knowledge, this is the first report of synthetic hydrogen-transfer reductions by low-boiling alcohols such as Pr^{i}OH, Pr^{n}OH or EtOH, alone. Significantly, in all cases so far examined, the products were the same as those reported for corresponding MPV reactions.[13] A co-ordinating metal was not added to our experiments, so despite the similarities of the products, an alternative mechanism is obligatory to that proposed for MPV reactions by Jackman and Mills[14] and widely accepted.[4,6,15]

In summary, this environmentally benign method of selective transfer-hydrogenation employs inexpensive, renewable reagents and affords minimal waste, with no inorganic salts introduced or formed. It offers considerable promise for cleaner processing and for biomimetic applications. Investigation of the converse approach, *i.e.* the use of low-boiling aldeydes and ketones for Oppenauer-type oxidations[16] of alcohols, is underway.

Table 1 Example reactions and conditions[a]

Entry	Starting material	*T*/°C	*t*/h	Major product	Yield[b] (%)
1	PhCHO	225[c]	24	BzOH	92[d]
2	(*E*)-PhCH=CHCHO	227[c]	27	(*E*)-$PhCH{=}CHCH_2OH$	83
3	*p*-Anisaldehyde	225[c]	29	*p*-methoxybenzyl alcohol	81
4	*n*-Dodecanal	225[c]	29	*n*-dodecanol	68
5	Cyclohexanone	226[c]	22	cyclohexanol	50
6	Acetophenone	225[c]	24	1-phenylethanol	24
7	(*E*)-$PhCH{=}CHCH_2OH$	225[c]	29	no reaction	0
8	4-Chlorobenzaldehyde	225[c]	29	4-chlorobenzyl alcohol	91
9	3-Bromo-4-methoxybenzaldehyde	226[c]	29	3-bromo-4-methoxybenzyl alcohol	74

[a] All reactions were performed in Pr^{i}OH. [b] When yields were low to moderate, the residue was mainly starting material. [c] At 220 and 232 °C, the vapour pressure of Pr^{i}OH is 4 and 5 MPa, respectively. [d] In a typical experiment, a solution of PhCHO (2.2 g) and Pr^{i}OH (150 ml) was heated in a sealed autoclave at 225 °C for 29 h. The product was concentrated by fractional distillation and then purified by distillation under reduced pressure.

Notes and references

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