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A CONVENIENT ONE-POT PROCEDURE FOR THE SELECTIVE REDUCTION OF KETONES IN THE PRESENCE OF ALDEHYDES

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Abstract: The title process has been accomplished by a three-step sequence involving protection of aldehyde as the imine, in situ reduction of ketone with lithium tri-*tert*-butoxyaluminohydride, and regeneration of aldehyde on hydrolytic work-up.

The preferential *in situ* ketalization or hydration of aldehydes relative to ketones using a lanthanoid ion as the catalyst have been recently exploited in the first two one-pot methods for the selective reduction of a keto group in the presence of an aldehyde.[1]

Inspired by the reduction outcome observed in the case of some steroidal ketoaldehydes on treatment with poly(N-isopropyliminoalane),[2] we have devised another approach for the simplification of this important synthetic problem.

Our procedure consists in the selective reaction of the aldehyde with *tert*-butylamine, followed by the *in situ* reduction of the ketone with lithium tri-*tert*-butoxyaluminohydride, and final cleavage of the aldimine to the parent aldehyde with aqueous HCl.

This essentially simple sequence does not seem to have been assembled before in a general one-pot method, although the use of a related masking group has been repeatedly reported in the selective reduction of steroidal dicarbonyl compounds.[3]

The standard procedure is as follows. To a stirred mixture of the two carbonyl compounds (2 mmol each), 4Å molecular sieves (2 g),[4] and *n*-dodecane or *n*-tetradecane (internal standards for GLC analysis, ~0.15 g) in dry THF (5 ml) under nitrogen was added dry *tert*-butylamine (0.42 ml, 4 mmol). After the appropriate period, lithium tri-tert-butoxyaluminohydride (1.12 g, 4.4 mmol) in dry THF (5 ml) was added, and stirring was continued for 0.5 h. Excess hydride was destroyed at 0 °C with cold water (0.3 ml), and the mixture was acidified by addition of cold 2N HCl (10 ml). After a further 10 min period at room temperature, the suspension was extracted with ether, the organic phase was washed with small portions of brine, dried (Na_2SO_4), and analysed by GLC. In the experiment with geranial (Table I, entry 7), an elution through a column of silica gel (30 g, ether as eluant) replaced advantageously the treatment with HCl.[5]

The results of the competitive reduction experiments summarized on Table I show that the selectivity which can be achieved is quite remarkable, even better than that exhibited by the two previous one-pot methods.[1]

Moreover, the scope of our procedure can be extended to conjugated and aromatic aldehydes, where the process based on the selective hydration of aldehydes fails.[1b] An additional advantage is represented by the use of a more stereoselective reducing agent.

The different reaction rates for the formation of the imino derivatives are also of interest for they allow a moderate discrimination in the reduction of aldehydes of different nature. Thus, for example, a mixture of octanal and benzaldehyde (2 mmol each), when reacted as above (tert-butylamine, 2.5 mmol; time of protection step, 0.5 h) gave benzyl alcohol in 71 % yield and 90 % recovery of octanal.

However, it must be pointed out that our method does not appear much suitable for conjugated ketones owing to the competitive conjugate reduction observed.[6] In fact, (E)-2-octen-4-one afforded in a control experiment a mixture of 4-octanone, (E)-2-octen-4-ol, and 4-octanol, with the first product predominant.

Notwithstanding this limitation, the process described in this paper promises to be of value in synthetic work in virtue of its large applicability, mild conditions employed, and high yields.

Eventually, it provides a definite support to the assumptions made to explain the unexpected reduction pathway observed in the treatment of some steroidal ketoaldehydes with poly(N-isopropyliminoalane).[2]

Further improvement and extensions to difunctional compounds are in progress.

Table I. Reduction of Ketones in the Presence of Aldehydes.

Entry	Initial Mixture	Time(h) Protection Step[a]	Recovered Starting Material, %[b]	Reduction Product, %[b]
1	Octanal	0.5	98	1
	2-Heptanone		0	100
2	Octanal	0.5	97	2
	Cyclohexanone		0	100
3	Cyclohexane-carboxaldehyde	1	96	1
	2-Heptanone		0	100
4	Cyclohexane-carboxaldehyde	1	99	<1
	Cyclohexanone		<1	99
5	Benzaldehyde	6	97	<1
	2-Heptanone		0	100
6	Benzaldehyde	6	94	2
	Acetophenone		0	100
7	Geranial	5	83 (95)[c]	<1
	Acetophenone		0	99

[a] Time required for the complete conversion of the aldehyde to imine, as determined by NMR analysis in preliminary experiments. Under these conditions the relative ketone was practically unchanged.

[b] Yields calculated by GLC (Carlo Erba Fractovap 2350, 5 m x 2 mm i.d. column packed with 3% Carbowax 20 M on Chromosorb G) from the response ratios determined for authentic samples.

[c] Isomeric purity. The original geranial was 97% pure; thus, only a negligible isomerization to neral has taken place.

References and Notes

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5. The conventional procedure resulted in fact in a very poor yield of aldehyde. The corresponding imine proved to be resistant to hydrolysis and was recovered in high yield by alkalization of the aqueous phase.
6. For a recent discussion on this subject, see S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **42**, 1197 (1977), and references therein.

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