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B. R. Rao [a] & M. E. N. Nambudiry [a]
[a] Hindustan Lever Research Centre , Chakala, Andheri (East), Bombay, 400 099, India
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A ONE-POT REDUCTIVE ACETYLATION OF ALDEHYDES AND KETONES

B.R. Rao and M.E.N. Nambudiry*
Hindustan Lever Research Centre,
Chakala, Andheri (East),
Bombay 400 099, India.

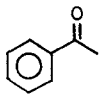
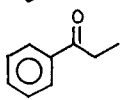
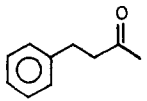
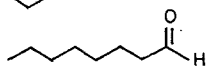
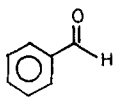
Abstract: Sodium borohydride reduction of saturated aliphatic and aromatic aldehydes and ketones in ethyl acetate at reflux is a facile route for one-pot preparation of acetates from such carbonyl precursors.

Generally, aldehydes and ketones are converted to acetates via reduction followed by acetylation. Very few methods[1-5] of direct reductive acetylations of such compounds are reported; these involve use of zinc-acetic anhydride[1], zinc-acetic anhydride-pyridine[2], zinc-acetic anhydride-sodium acetate[3,4] and acetyl chloride-tri-n-butyltin hydride[5].

During the course of a study on asymmetric reduction of acetophenone using Sodium borohydride ($NaBH_4$) in the presence of chiral auxiliaries, we had occasions to evaluate its reduction in different solvents. When acetophenone was refluxed in ethyl acetate with $NaBH_4$, its reduction was accompanied by concomitant

* To whom correspondence should be addressed.

Table : Reductive Acetylation of Aldehydes and Ketones

Substrate	Time (hrs)[a]	Yield (%)[b,c] Acetate	Carbinol	^{1}HNMR ($CDCl_3$) of the Acetates[d] δ(ppm)
	7	80.0	18.4	1.53 (d,3H,CH3); 2.07 (d,3H,CH_3-C=O); 5.83 (q,1H,CH) and 7.31 (m,5H,Ar-H).
	15	85.7	14.0	0.87 (t,3H,CH_3); 1.87 (m,2H,CH_2); 2.07 (s,3H,CH_3-C=O); 5.66 (t,1H,CH) and 7.31 (m,5H,Ar-H).
	10	89.2	7.7	1.24 (d,3H,CH_3); 1.89 (m,2H,Ar-CH_2-CH_2); 2.02 (s,3H,CH_3-C=O); 2.64 (m,2H,Ar-CH_2-CH_2); 4.93 (m,1H,CH) and 7.26 (m,5H,Ar-H).
	7	86.3	12.3	1.39 (m,6H,3xCH_2); 1.81 (m,4H,2xCH_2); 2.03 (s,3H,CH_3-C=O) and 4.73(m,1H,CH).
	7	78.5	21.0	0.88 (t,3H,CH_3); 1.29(m,10H,5xCH_2); 1.61 (m,2H,CH_2-CH_2-O); 2.05 (s,3H,CH_3-C=O) and 4.0 (t,2H,CH_2-O).
	7	67.5	31.0	2.11 (s,3H,CH_3-C=O); 5.11 (s,2H,Ar-CH_2) and 7.33 (m,5H,Ar-H).

(a) Time of reflux for complete dissapearance of the substrate by gc analysis. All the reactions were done using the general procedure given in the experimental, (b) Isolated yield by column chromatography as percentage of theoretical yield; both the esters and the carbinols were pure by gc analysis, (c) ν_{max} in IR (neat) were as expected, (d) All these acetates and carbinols are reported in literature; see 'Beilsteins Handbuch Der Organishen Chemie'.

alcoholysis of ethyl acetate and the major product was α-phenylethyl acetate. We have optimised the procedure and evaluated its generality and the results are given in the Table. This method offers a facile one-pot conversion of saturated aliphatic and aromatic aldehydes and ketones to the acetates of the respective reduction products - carbinols - in good yields. Its extension to other reductive acylations was unsuccessful. For example, when acetophenone was heated at ~80°C with $NaBH_4$ in benzyl propionate, traces of α-phenylethyl alcohol was the sole product; addition of a phase transfer catalyst - tetra-n-butylammonium bisulfate - did not facilitate reduction or reductive acetylation.

Similar alcoholysis of ethyl acetate (Et OAc) was noticed earlier[6] when it was used for destroying unreacted lithium aluminium hydride ($LiAlH_4$) after carboxylic acids were reduced with excess of this hydride; similarly N-ethylation presumably via N-acetylation was noticed when ethyl acetate was used for quenching an N-aryl amide - $LiAlH_4$ reaction mixture[7]. However, attempted reductive acetylation of 5-nonanone using the $LiAlH_4$-EtOAc route was unsuccessful[6]. When esters are reduced with $NaBH_4$ in methanol, in cases where reductions are not facile, methanolysis of the esters are reported to progress well[8]; alcoholysis of the lactone group during $NaBH_4$ reduction of an isoxazolone in alcohols[9] was reported recently. Examination of

the reduction products of cinnamic aldehyde under the experimental conditions reported herein showed the presence of cinnamyl alcohol, 3-phenylpropyl alcohol, cinnamyl acetate and 3-phenylpropyl acetate in the ratio 1:31:8:63 respectively (by gc analysis) indicating no 1,2-selectivity comparable with that of the $NaBH_4$-HOAc combination reported by others[10]. We have yet to ascertain whether $NaBH_4$-EtOAc would behave similar to $LiBH_4$-EtOAc in the hydroborations of alkenes and alkynes studied earlier[11].

Mechanistically, the present reaction seems to involve formation of the expected boron complex by the interaction of the substrate and $NaBH_4$ which in turn exchange the alkoxy group with ethyl acetate generating the desired acetates at elevated temperatures in a reversible step. At ambient temperature ($\sim 25^{\circ}C$), the acetophenone reaction gave about 35% α-phenylethyl alcohol in 2 hrs and only around 1% of the acetate was formed. Addition of the phase transfer catalyst given above, though enhanced the rate of formation of the alcohol - 65% in 2 hrs at $\sim 25^{\circ}C$ - no detectable reductive acetylation was evident. No selectivity was noticeable when equimolar quantities of a carbinol and a ketone were subjected to the present reaction.

Experimental:

All the substrates and $NaBH_4$ used were commercial samples of >98% purity. Ethylacetate was distilled over $NaBH_4$ and was devoid of

any HOAc contamination. GC analyses were done using a Chemito-3800 model Toshnival instrument using a 10% 10 ft DEGA column under isothermal conditions at temperatures chosen in the 90-170°C region depending on the retention times and efficiency of separations of the components. IR spectra were recorded for neat samples on a Nicolet 20 FXB FTIR and ^{1}HNMR using a Varian-VXR 300 MH_z instrument using $CDCl_3$ solvent.

Reductive Acetylation : General Procedure

To a solution of the substrate (acetophenone, 9.6 g, 80 m mol) in ethyl acetate (48 g, 5 times the weight of the substrate), sodium borohydride (3.04 g, 80 m mol) was added and heated on an oil bath at reflux under anhydrous conditions (pot temperature 83°C) till gc analysis indicated complete disappearance of the substrate (7 hrs in the case of acetophenone; gc analysis on 10% DEGA column of 10 ft length at 150°C). The reaction mixture was washed with brine solution (3 x 50 ml) and the separated organic phase was dried (anhydrous Na_2SO_4) and solvent stripped (14 g crude product for the acetophenone case). This material was mixed with silica gel (14 g) and quantitatively transferred onto a silica gel column (50 g; 20 x 3 cm) prepared using petroleum-ether (40-60°C). Initial elution using petroleum ether (3.2 litres for acetophenone case) gave the pure ester [α-phenylethyl acetate (10.5 g), single peak in gc, satisfactory IR and ^{1}HNMR]. Subsequent elution with petroleum ether-diethyl ether (1:1) gave

after a brief mixed fraction, the pure carbinol [750 ml eluate for acetophenone case; α-phenylethyl alcohol (1.8 g), single peak in gc, satisfactory IR and ^{1}HNMR].

Except for the duration of reflux and variations in the volume of solvents for elution during the chromatography (fraction monitoring by gc) the above procedure remained essentially the same for all the substrates given in the Table. Both the acetates and the carbinols had identical gc retention times as those of the respective authentic samples.

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