Tetrahedron Letters Vol. 22, pp 675 - 678
0040-4039/81/0208-0675$02.00/0

SELECTIVITY IN THE ACID CATALYSED REDUCTION OF CARBONYL COMPOUNDS TO ALCOHOLS BY BIS(TRIPHENYLPHOSPHINE)COPPER(I) TETRAHYDROBORATE: REDUCTION OF ALDEHYDES IN THE PRESENCE OF KETONES

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Summary: Bis(triphenylphosphine)copper(I) tetrahydroborate reduces carbonyl compounds to alcohols in the presence of acid catalysts in excellent yields with high stereoselectivity; α,β-unsaturated aldehydes are reduced regioselectively. In a mixture of an aldehyde and a ketone, an aldehyde may be reduced preferentially.

There is continuing interest in functional group[1] and stereo-[2-4] selectivity in the reduction of carbonyl compounds by complex hydrides. The size of complex transition metal borohydrides, together with their solubility in non-hydroxylic organic solvents, make them ideal candidates for studies of selective reduction. Accounts of the stoichiometric reduction of carbonyl groups by μ-bis(cyanotrihydroborato)tetrakis-(triphenylphosphine) dicopper(I) under acid conditions[5] and bis(cyclopentadienyl)chlorotetrahydroboratozirconium(IV) under neutral conditions[6] have prompted us to report our work on the acid catalysed reactions of bis(triphenylphosphine)copper(I) tetrahydroborate; this reagent under neutral conditions has been shown to be effective in the reduction of acid chlorides to aldehydes,[7-9] tosylhydrazones to alkanes[10] and aromatic azides to phenylamines.[11]

Under neutral conditions, no substantial reduction of any aldehyde by bis(triphenylphosphine) copper(I) tetrahydroborate in acetone at room temperature was observed; in contrast, although most aldehydes are not affected by the reagent in chloroform or dichloromethane, aromatic aldehydes with o- or p- electron withdrawing groups give the corresponding alcohols in high yields. 4-Nitrobenzaldehyde is quantitatively reduced by two molar equivalents of the modified copper borohydride to 4-nitrobenzyl alcohol in chloroform solution; under similar conditions, 2-nitro- and 4-cyano-benzaldehyde are reduced to 2-nitro- and 4-cyano-benzyl alcohol respectively.

Several aldehydes and ketones form complexes reversibly with bis(triphenylphosphine) copper(I) tetrahydroborate in dichloromethane and chloroform. Thus 50% of cinnamaldehyde in chloroform disappears when the reagent is added (shown by quantitative g.l.c.); subsequent addition of methanol destroys the complex and causes the quantitative regeneration of both cinnamaldehyde and bis(triphenylphosphine)copper(I) tetrahydroborate. If the complex is treated with acetic acid, the copper borohydride is decomposed whereas cinnamaldehyde is regenerated; in contrast, addition of HCl or a Lewis acid leads to quantitative reduction of cinnamaldehyde to cinnamyl alcohol. We have found that aldehydes

TABLE

Carbonyl compound	Acid Catalyst	Molar ratio of $(Ph_3P)_2CuBH_4$	Product	% Yield[a]	
4-*tert*-butylcyclohexanone	HCl[b]	1	4-*tert*-butylcyclohexanol	91	94% trans
	1/3 $AlCl_3$	1		92[c]	92% trans
	$ZnCl_2$	1		71[b]	92% trans
	BF_3-Et_2O	1		82[c]	80% trans
3,3,5-trimethylcyclohexanone	HCl	1	3,3,5-trimethylcyclohexanol	(d)	84% trans
	$AlCl_3$	1.5		86	72% trans
	[e]$AlCl_3$	1.5		(d)	82% trans
norbornanone	HCl	1	norbornanol	98	92% endo
camphor	2$AlCl_3$	2	isoborneol	73	98% exo
	HCl	1		0	
nonanal	HCl	1	nonan-1-ol	94	
4-nitrobenzaldehyde	-	2	4-nitrobenzylalcohol	98[f]	
benzophenone	HCl	1	benzhydrol	(d)	
	$AlCl_3$	1.5		92	
cinnamaldehyde	HCl	1	cinnamyl alcohol	99	
	1/3 $AlCl_3$	1		67[f]	
	$ZnCl_2$	1		74[f]	
	BF_3-Et_2O	1		(g)	
citral	HCl	1	geraniol	82	
cyclohexenone	HCl	1		(g)	
benzylideneacetone	HCl	1		(g)	

a) Yield for products isolated by flash chromatography[12] unless otherwise stated and shown to be pure by comparison (m.p., n.m.r., g.l.c., i.r.) with authentic material; ratio of diastereomers determined by g.l.c.

b) HCl gas bubbled into reaction mixture.

c) isolated by 40-60 petrol extraction of crude product.

d) incomplete reduction.

e) reaction at -78°.

f) purification by aqueous extraction.

g) complex mixture of products.

and ketones may be reduced in excellent yields to the corresponding alcohols by bis(triphenylphosphine)copper(I) tetrahydroborate in the presence of acid catalysts. (Table).

Complete reduction of aldehydes and ketones by one molar equivalent of bis(triphenylphosphine)copper(I) tetrahydroborate in dichloromethane to the corresponding alcohols is obtained if gaseous hydrogen chloride is passed through the solution for 10 min; the yields of the alcohols were generally quantitative and the products may be readily isolated by evaporation of the solvent, followed by ether extraction and flash chromatography.[12] This is generally the most convenient procedure, although Lewis acids such as aluminium chloride, zinc chloride or boron trifluoride etherate may be used as alternatives to hydrogen chloride. Addition of aqueous HCl to provide a two phase system showed that a 1.5 to 2 molar excess of the reducingagent was necessary to effect complete reduction since under these conditions destruction of the complex borohydride competes with carbonyl reduction; a similar result wasobtained when a solution of dry hydrogen chloride in dichloromethane was used. These observations may explain the relatively low yields and large molar ratios of reagent required in the reduction of carbonyl compounds by μ-bis(cyanotrihydroborato)tetrakis(triphenylphosphine)dicopper(I) in aqueous acidic tetrahydrofuran.[5] Weak acids, such as acetic acid, were found to decompose preferentially the complex rather than promote acid catalysis of attack on the carbonyl groups, and so are unsuitable as catalysts for this reaction.

The reaction is sensitive to steric hindrance. Redcutions of 3,3,5-trimethylcyclohexanone, camphor and benzophenone using hydrogen chloride as the acid catalyst lead to low overall yields of the alcohols (in the case of camphor no reduction was observed at all). However, use of a strong Lewis acid ($AlCl_3$) together with an excess of bis(triphenylphosphine)copper(I) tetrahydroborate gives high yields of the corresponding alcohols. Seric hindrance has also been observed in the reduction of toluenesulphonyl hydrazones by the reagent.[10]

The reaction is highly stereoselective; the predominance of the trans alcohols from 4-tert-butylcyclohexanone and 3,3,5-trimethylcyclohexanone, of the endo alcohol from norbornanone and the exo alcohol from camphor are among the highest observed for metal hydride reagents,[4] even though all the reactions were performed at room temperature. Unsurprisingly, the milder the conditions employed, the greater the selectivity of the reagent. In the reduction of 3,3,5-trimethylcyclohexanone, catalysed by hydrogen chloride, the reaction is incomplete although the alcohol formed is 84% trans; at room temperature with aluminium chloride as catalyst the proportion of trans alcohol is only 72%, although the same procedure at -78^{o} leads to 82% trans product.

Although α,β-unsaturated aldehydes (cinnamaldehyde, citral) are regioselectively reduced to allylic alcohols in excellent yields,α,β-unsaturated ketones form complex mixtures of products. Secondary allylic alcohols do not survive the conditions of the reaction, presumably due to the ease of acid catalysed formation of secondary allylic carbonium ions.

The reaction conditions are functional group selective for the reduction of aldehydes in the presence of ketones. Treatment of a 1:1 mixture of nonanal and nonan-5-one with one equivalent of bis(triphenylphosphine)copper(I) tetrahydroborate and hydrogen chloride gas causes 90% reduction of the aldehyde with no reduction of the ketone; a similar result is observed with a mixture of benzaldehyde and acetophenone with complete preferential reduction of benzaldehyde. No selectivity was observed in the attempted competitive reduction of a mixture of nonanal and benzaldehyde.

In summary bis(triphenylphosphine)copper(I) tetrahydroborate in dichloromethane is an excellent reagent for the acid catalysed reduction of carbonyl groups to alcohols in good yield with high stereoselectivity. There is considerable scope for modifying the reagent either with a chiral phosphine ligand with the prospect of asymmetric induction or with different ligands to affect the functional group selectivity of the reagent. The procedure for the reduction of cinnamaldehyde is illustrative.

Reduction of cinnamaldehyde. Bis(triphenylphosphine)copper(I) tetrahydroborate (2.66 g, 4.41 mmole) was added to a stirred solution of cinnamaldehyde (0.58 g, 4.39 mmole) in dichloromethane (25 ml). Dry hydrogen chloride gas was bubbled through this solution for 10 min; at the end of this period all cinnamaldehyde was shown by g.l.c. to be eliminated. The solvent was removed and the residue extracted with ether. The insoluble white precipitate was removed by filtration. The filtrate was concentrated and the product purified by flash chromatography,[12] using 60% ether - 40% 40-60 petrol as eluant, to give analytically pure cinnamyl alcohol (0.58 g, 99%) identical with authentic material.

Acknowledgements. We wish to thank Drs. R.A. Bowie and K.B. Mallion for helpful discussions, and are pleased to acknowledge a CASE award (to PJCH) with ICI Pharmaceutical Division, Hurdsfield Industrial Estate, Macclesfield. We are also grateful to Dr. R.T. Aplin for help with g.c.-m.s.

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(Received in UK 14 November 1980)