Tetrahedron Letters, Vol.22, No.37, pp 3663 - 3666, 1981
Printed in Great Britain

0040-4039/81/373663-04$02.00/0

ALKYL METAL ASYMMETRIC REDUCTION. 11. THE REACTION OF α,β-UNSATURATED KETONES WITH β-BRANCHED TRIALKYLALUMINIUM COMPOUNDS.

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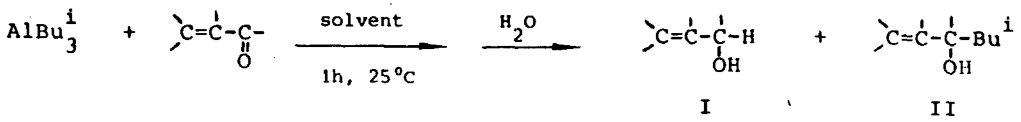
Summary: The reduction of a series of α,β-unsaturated ketones has been studied under various experimental conditions, by using β-branched trialkylalanes. Asymmetric induction phenomena are observed when optically active trialkylalanes are used.

Despite an increased interest in methods for achieving regioselective addition to α,β-unsaturated systems,[1] surprisingly little is presently known about alkyl metal reductions of enones.[2] During recent years, we have carried out some investigations on the asymmetric reductions of dialkyl ketones by optically active aluminium trialkyls.[3] In this context, it appeared interesting to investigate the reaction of α,β-unsaturated ketones with β-branched aluminium trialkyls, such as $AlBu^i_3$ and tris/(S)-2-methylbutyl/aluminium,[4] with a twofold purpose in mind: to examine the possibility of effecting regioselective 1,2- or 1,4-reductions of enones under various experimental conditions[5] and to further support the stereochemical picture previously proposed for the asymmetric reductions of alkyl phenyl ketones.[3,4]

We report here some preliminary results on the reductions of selected enones: the experiments were carried out at room temperature, in anhydrous pentane or diethyl ether as solvents, by treating the organoaluminium compound with the stoichiometric amount of the ketone. The hydrolysis was accomplished with water or a saturated NH_4Cl solution. The data obtained with $AlBu^i_3$ are collected in Table 1.

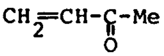
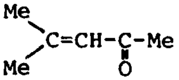
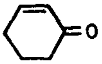
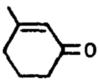
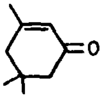
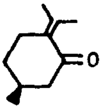
In all the cases investigated, no significant conjugate reduction or conjugate addition to the α,β-unsaturated system occur, the corresponding saturated ketones being present only in traces in the reaction mixtures. However,contrary to what was observed with saturated ketones,[6,7] significant amounts of the 1,2-addition products (II) can be detected depending on the nature of the enone and the solvent employed. Thus, whereas in diethyl ether only the secondary allyl carbinol (I) is recovered, in pentane the 1,2-addition of the isobutyl group bound to the aluminium atom is generally competitive with the reduction, except when isophorone and pulegone are used. Moreover, in the cases investigated, an appreciable

TABLE 1



$$AlBu^i_3 + \,>C{=}C{-}\underset{\|}{\overset{|}{C}}{-} \xrightarrow[\text{1h, 25°C}]{\text{solvent}} \xrightarrow{H_2O} \,>C{=}C{-}\underset{OH}{C}{-}H + \,>C{=}C{-}\underset{OH}{C}{-}Bu^i$$

I II

Substrate	Solvent	Conversion %	Products, yield % (by g.l.c.) I	II
 $CH_2{=}CH{-}\underset{O}{\underset{\|}{C}}{-}Me$	Pentane[a]	100	86	14
	Ether[a]	100	99	-
	Pentane	100	64	36
	Ether	97	96	-
	Pentane	100	63	37
	Ether	96	96	1
	Pentane	96	98	2
	Ether	78	99	-
	Pentane[b]	37	100	-
	Ether[c]	13	100	-
	Pentane	97	86[d] (100% *cis*)	-
	Ether	56	70[d] (88% *cis*)	-

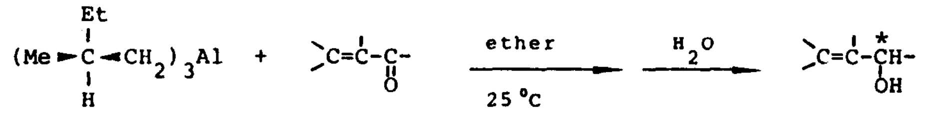
[a] The reaction is complete within 10 minutes. [b] Conversion is complete after 15 h. [c] After 15 h, the conversion is 83%. [d] The other products are isomers of pulegol, mainly 3-p-menthen-3-ol.

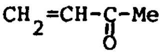
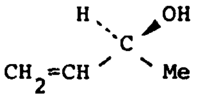
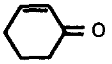
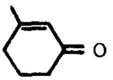
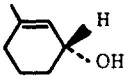
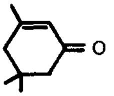
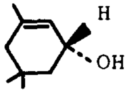
rate retardation is noted when the reactions are carried out in diethyl ether. Such a rate retardation is expected because of the relatively low Lewis acid character of the organoaluminium diethyl etherate with respect to that of the uncomplexed $AlBu^i_3$.[4] Even the nature of the enone influences markedly the rate of the reaction: in particular, in the case of isophorone, the reaction requires more than 15 h for completion. However, based on the overall results, we can suggest that the greater the steric bulk of the enone the slower the reaction but the greater the selectivity towards the 1,2-reduction (Table 1).

In the case of pulegone the reaction proceeds rather rapidly and, in addition to the expected pulegol, significant amounts of its allylomer, 3-p-menthen-8-ol, are detected, in particular using diethyl ether as solvent. Moreover (-) *cis*-pulegol is formed prevalently, in agreement with a previous report,[2] suggesting that the hydride transfer to the carbonyl carbon atom occurs preferentially from the equatorial side leading to an axial -OH.

Analogous to what was observed for saturated ketones,[4] the reduction of prochiral α,β-unsaturated ketones by tris/(S)-2-methylbutyl/aluminium diethyl etherate affords optically active carbinols. As shown in Table 2, whereas the reduction of methyl vinyl ketone gives the corresponding (S) allyl carbinol with a 7% enantioselectivity, the reduction of selected cyclohexenones yields optically active cyclohexenols of absolute (R) configuration, the extent of enantioselectivity increasing from cyclohexenone to isophorone. Following our previous considerations,[3,4] even the reduction of the enones by chiral organoaluminium compounds is assumed to proceed via diastereomeric cyclic transition states of different free energies. On this picture, the carbinols from asymmetric reduction of the α,β-unsaturated ketones we employed must have the absolute (S) configuration. However, this stereochemical approach[3,4] does not fit all the results obtained,

TABLE 2



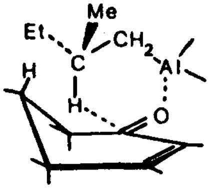
Substrate	Recovered Carbinol[a]	$[\alpha]_D^t$ (°C, solvent)	e.e.%[b]
 $CH_2{=}CH{-}\underset{\displaystyle O}{\overset{}{C}}{-}Me$		+ 2.23 (30, neat)	7[c]
		+10.35 (25, $CHCl_3$)	7[d]
		+10.15 (20, $CHCl_3$)	11[e]
		+ 2.04 (25, C_6H_{14})	14.5[f]

[a] *All the reactions were brought to completion.* [b] *Corrected for the minimum optical purity of the organoaluminium used.* [c] K.L.Olivier and W.G.Young, *J.Am.Chem.Soc.*, 81,5811(1959). [d] R.K.Hill and J.W.Morgan, *J.Org.Chem.*, 33,927(1968). [e] K.Mori, S.Tamada, M.Uchida, N.Mizumachi,Y.Tachibana, and M.Matsui, *Tetrahedron*, 34,1901(1978). [f] K.Takeya and H.Itokawa, *Chem.Pharm.Bull.*, 25,1947(1977).

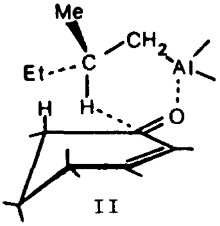
as the cyclohexenols recovered have the absolute configuration opposite to the predicted one.

We think that this reversal of stereochemistry is not due to a change of the reaction mechanism[3,4] but depends mainly on steric compressions of the alkyl groups of the complexed organoaluminium compound in the six-center transition state against the hydrogens or the substituents in the 5- or 6-position of the cyclohexenone ring.

It is conceivable that cyclohexenones complexed to aluminium alkyls exist in half-chair conformations.[8] Close scrutiny of molecular models shows that top-side hydride transfer, leading to the (S) carbinol, would be hindered owing to the steric compressions between the ethyl group of the organoaluminium compound and the flagpole C-5 hydrogen (or methyl group in the other cases) in conformation I and the axial C-6 hydrogen in conformation II. On the other hand, bottom-side attack would be somewhat favoured because of the minor interactions that involve only the methyl group bound to the chiral carbon atom of the organoaluminium compound. Bottom-side hydride transfer would, of course, produce the (R) carbinol. On this assumption, the extent of enantioselectivity might rise with increasing bulkiness of the cyclohexenone ring.



I



II

REFERENCES

1. E.C.Ashby and S.A.Noding, *J. Org. Chem.*, 44, 4792 (1979).
2. E.H.Eschinasi, *J.Org.Chem.*, 35, 2010 (1970).
3. G.Giacomelli, R.Menicagli, A.M.Caporusso, and L.Lardicci, *J.Org.Chem.*, 43, 1790 (1978) *and references therein.*
4. G.Giacomelli, R.Menicagli, and L.Lardicci, *J.Org.Chem.*, 38, 2370 (1973).
5. A.M.Caporusso, G.Giacomelli, and L.Lardicci, *communication to* ESOC II, *Stresa (Italy), June 1-5 1981.*
6. E.C.Ashby and Simon H.Yu, *J.Org.Chem.*, 35, 1034 (1970) *and references cited.*
7. G.E.Heinsohn and E.C.Ashby, *J. Org.Chem.*, 38, 4232 (1973).
8. P.Chamberlain and G.H.Whithman, *J.Chem.Soc., Perkin Trans.2,* 130 (1972); J.J.Barieux, J.Gore, and J.C.Richer, *Bull.Soc.Chim.France*, 1020 (1974); C.Paris, G.Torri, L.Elegant,and M.Azzaro, *ibid.*, 1449 (1974).

(Received in UK 1 June 1981)