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Highly diastereoselective reduction of (-) menthylphenylglyoxalate and (-) menthylpyruvate using new hindered lithiumtrialkoxyaluminohydrides

Boireau G.and Deberly A.
Institut de Chimie Moléculaire d'Orsay
Laboratoire de Chimie Organométallique, Université de Paris-Sud, Centre d'Orsay 91405 ORSAY cedex - France

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Abstract :
Reduction of the keto group of (-)menthylphenylglyoxalate and (-)menthyl pyruvate can be achieved with high diastereoisomeric excess (80-90%) using newly synthesized hindered lithium trialkoxyaluminium hydrides in THF at -78°C. Hindered borohydrides such as lithium trisiamylborohydride reduce those ketoesters with a lower diastereoselectivity.

In the course of our previous studies on the nucleophilic addition of alkoxytrialkylaluminates to (-) menthylphenylglyoxalate, we have shown that the stereochemical outcome of the reaction was dependent on the steric bulkiness of the reagent (1). More recently, we reported that the diastereoselectivity of the addition of various organozinc compounds to the aforementioned ketoester was again sensitive to the size of the organometallic species and this could be rationalized by consideration of a mechanistic pathway involving a chelated transition state (2).

In the light of the above results, it appeared likely that reduction of (-) menthyl α ketoesters could be rendered highly stereoselective by the use of hindered reagents.

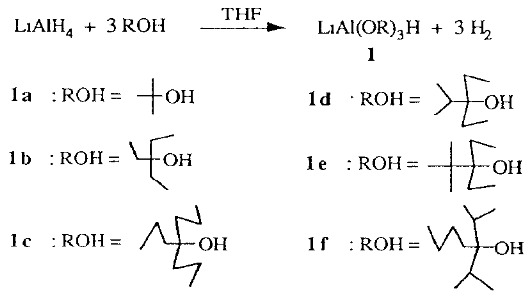
Results and discussion

Early works (3,4) have shown that the reduction of (-) menthylphenylglyoxalate by an excess of $LiAlH_4$ affords the R(-) phenylethanediol expected accordingly to Prelog's rule (5) only with 10% ee. The same ketoester could be reduced to R(-) menthyl mandelate with a degree of diastereoselectivity up to 49% when a chiral lithium trialkoxyaluminohydride was used (6). More recently, Whitesell and al. (7) could achieve the reduction of (-) 8-phenylmenthylglyoxalate and pyruvate by potassium triisopropoxyborohydride with d.e. of respectively 50% and 90%.

In the present study, we undertook to test our tentative hypothesis on the influence of steric factors in the chiral outcome of the reduction of (-) menthylphenylglyoxalate and (-) menthyl pyruvate by a variety of trialkoxyaluminohydrides and borohydrides, which are known to be unreactive towards the ester functional group.

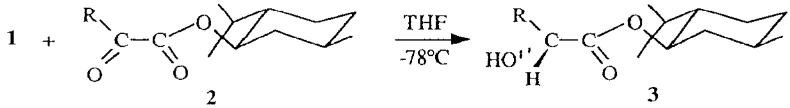
1) *Lithium trialkoxyaluminohydrides*

Scheme I



1a and **1b** : solutions 1M and 0.5M in THF are commercialy available (ALDRICH) ; **1c-f** : have been prepared from 1M solutions of $LiAlH_4$ in THF, using a 10% excess of ROH and refluxing for 2h to obtain complete reaction of the third mole of ROH (8).

Scheme II



2a : R = C_6H_5
2b : R = CH_3
3a : R = C_6H_5
3b : R = CH_3

The results are summarized in Table I. As expected, a sharp improvement of the diastereoselectivity could be observed when the reduction of 2a and **2b** was performed with the more hindered reagents **1d**, **1e** and **1f**. Total conversion to the corresponding alcohols 3 was achieved after 2 hours at -78°C as proved by quenching the reaction mixtures with methanol. GLC and ^1H nmr analysis after the usual work-up showed that the diastereoisomeric alcohols **3** were the only products formed, the major diastereoisomer being in all cases the one predicted by Prelog's rule.

The stereoselectivity may be rationalized in the same way as for the reduction of and nucleophilic addition to ketoesters of (-) 8-phenylmenthol (9) or as for the nucleophilic addition of organozinc compounds to (-) menthylphenylglyoxalate (2) that is, by consideration of a transition state in which the chelation of the two carbonyl groups by Li and the steric requirement of the isopropyl substituent at the 2-position of the menthyl group direct the face selectivity

Scheme III

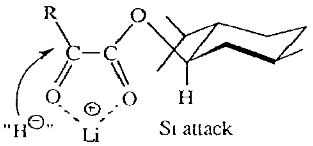


Table I

Run	Ketoester	LiAl(OR)3H	Yield (%) 3 [a]	d.e.(%) [b]	conf.abs. [c]
1	**2a**	**1a**	92	51	R
2	**2a**	**1b**	90	71	R
3	**2a**	**1c**	90	73	R
4	**2a**	**1d**	91	83	R
5	**2a**	**1e**	92	81	R
6	**2a**	**1f**	94	86	R
7	**2b**	**1a**	90	31	R
8	**2b**	**1b**	92	65	R
9	**2b**	**1c**	90	67	R
10	**2b**	**1d**	94	72	R
11	**2b**	**1e**	93	90	R
12	**2b**	**1f**	93	88	R

All the reactions were carried out in THF at -78°C for 3h starting from solutions of $LiAl(OR)_3H$ 1M (runs 1,7), 0.5M (runs 2,8), 0.4M (runs 3,4,5,6,9,10,11,12) and 0.26M solutions of ketoester. $LiAl(OR)_3H$/ketoester ratio 1/0.8.

a) Isolated yields after evaporation under reduced pressure (25-30°C, 10^{-6}bar) of the hindered alcohols.

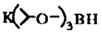
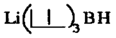
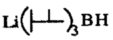
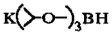
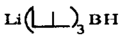
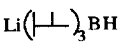
b) d.e. were determined : 1) by capillary GLC analysis : runs 1-6 : OV1 25m, 150°C and Carbowax 20M, 25m, 180°C ; runs 7-12 : OV1 100°C and Carbowax 120°C. 2) from 250MHz ^1H nmr ($CDCl_3$) analysis of the signals corresponding to the benzylic protons δ ppm = 5.1 (major diastereoisomer), 5.15 (minor diastereoisomer) (runs 1-6)

c) 1) runs 1-6 : the absolute configurations were assigned as R by measurement of the optical rotations of 1-phenyl 1,2-ethanediol obtained by $LiAlH_4$ reduction of **3a** (run 2) and purified by silica gel chromatography (eluant benzene/acetone 4/1). $[\alpha]_D^{25}$= -27.4 (c=4.1,95% EtOH). Lit R(-) 1-phenyl 1,2-ethanediol $[\alpha]_D^{20}$= -39.7 (c=4.33,95% EtOH) (4). 2) Runs 7-12 : the R configuration was assigned byidentification (GLC) of the minor diastereoisomer with an authentic sample of (S)(-) menthyl lactate.

2) *Borohydrides*

The data presented in Table II clearly indicate that, again, an increase of the steric bulkiness of the reagent parallels an increase of the diastereoselectivity, as examplified with lithium trisiamylborohydride (entries 3,6). However, examination of the results summarized in tables I and II shows that the borohydrides appear to be of less potential value in the stereoselective reduction of ketoesters **2a** and **2b** in comparision to the trialkoxyaluminohydrides.

Table II

Run	Ketoester	Borohydride	Yield (%) 3	d.e. (%)	Conf.abs.
1	**2a**		90	52	R
2	**2a**		75[a]	63	R
3	**2a**		73[a]	67	R
4	**2b**		88	38	R
5	**2b**		76[a]	44	R
6	**2b**		74[a]	74	R

The reactions were carried out in THF at -78°C for 3h and then at room temperature for 30m., starting from solutions of borohydrides 1M and of ketoesters 0.6M. Borohydride/ketoester ratio 1/0.8.

a) Isolated yields in **3** after the usual alkaline H_2O_2 work-up of the trialkylbores (10).

b) d.e. were determined by capillary GLC and from ^1H nmr (see Table I). GLC analysis prior to and after the alkaline H_2O_2 work-up of the trialkylbores showed that no racemization occured during the oxidation.

Conclusion

New lithium trialkoxyaluminohydrides were synthesized, with increased steric bulkiness compared to those previously described. These reagents permit the quantitative reduction of the carbonyl group of (-) menthyl α ketoesters with 80-90% asymmetric induction. Thus, a secondary asymmetric carbon of known absolute configuration may be created from ketoesters readily synthesized from a ketoacid and menthol,a very common and unexpensive source of chirality

References

1. Deberly,A. ; Boireau,G. ; Abenhaim,D. *Tetrahedron Lett.*, **1984**, 655-658.
2. Boireau,G. ; Deberly,A. ; Abenhaim,D. *Tetrahedron* , **1989**, *45*, 5837-5844.
3. Prelog,V. ; Wilhelm,M. ; Bruce Bright,D. *Helv.Chim.Acta*, **1954**, *37*, 221-224.
4. Dale,J.A. ; Mosher,H.S. *J.Org.Chem.*, **1970**, *35*, 4002-4003
5. Morisson,J.D. ; Mosher,H.S., *Asymmetric Organic Reactions"*, Printice Hall Inc, **1971**, Sec 2, 50-83.
6. Horeau,A. ; Kagan,H.B. ; Vigneron,J.P. *Bull.Soc.Chim.Fr.*, **1968**, [N°9], 3795-3797.
7. Whitesell,J.K. ; Deyo,D. ; Bhattacharya,A. *J.Chem.Soc.,Chem.Commun*, **1983**, 802-
8. Krishnamurthy,S. *J.Org.Chem.*, **1981**, *46*, 4628-4629.
9. Whitesell,J.K. *Acc.Chem.Res.*, **1985**, *18*, 280-284.
10. Krishnamurthy,S. ; Brown,H.C. *J.Am.Chem.Soc.*, **1976**, 3383-3384.