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Preliminary communication

ASYMMETRIC SYNTHESIS OF OPTICALLY ACTIVE HALOHYDRINS AND OXIRANES BY ENANTIOSELECTIVE REDUCTION OF PROCHIRAL α-HALOKETONES WITH CHIRALLY MODIFIED LITHIUM BOROHYDRIDE

KENSO SOAI*, TAKASHI YAMANOI and HITOSHI HIKIMA

Department of Applied Chemistry, Faculty of Science, University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162 (Japan)

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Summary

Prochiral α-haloketones are reduced enantioselectively with the asymmetric reducing system lithium borohydride *N,N'*-dibenzoylcystine /t-butyl alcohol to give the corresponding halohydrins with up to 86% enantiomeric excess, some of which are converted to optically active oxiranes.

Optically active halohydrins (I) [1] and oxiranes (II) [2] are important synthetic intermediates [3]. Preparation of I by reduction of α-haloketones (III) with chiral alkylborane [1a] requires a long reaction time in the order of several days, and cannot be applied to sterically hindered III.

We report that optically active halohydrins (I) were obtained in good to high enantiomeric excesses (e.e.) by reduction of the corresponding III with lithium borohydride ($LiBH_4$) which had been modified with *N,N'*-dibenzoyl-

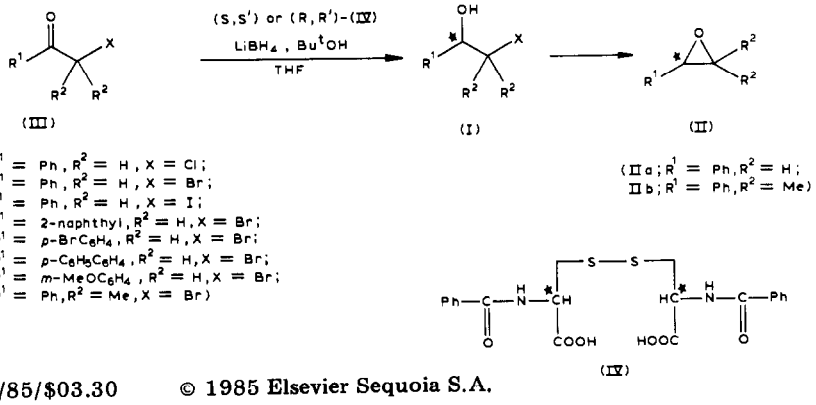

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TABLE 1

ASYMMETRIC REDUCTION OF III TO I

Entry [a]	III	I			
		Yield (%)	$[\alpha]_D^{20}$ (c, solvent)	Enantiomeric excess (% e.e.)	Configuration
1	IIIa	76	+37.0° (2.81, cyclohexane)	72 [b]	S [c]
2	IIIb	72	+38.7° (7.71, $CHCl_3$)	80 [b]	S [d]
3 [e]	IIIb	80	−40.1° (8.12, $CHCl_3$)	82 [b] (78 [f])	R [f]
4	IIIc	49	+36.3° (5.29, $CHCl_3$)	86 [b]	S [f]
5	IIId	74	+33.9° (5.17, $CHCl_3$)	63 [b]	S [g]
6	IIIe	78	+22.8° (6.23, $CHCl_3$)	57 [b]	
7	IIIf	81	+27.0° (4.04, $CHCl_3$)	64 [b]	
8	IIIg	74	+31.6° (4.88, $CHCl_3$)	82 [h]	
9	IIIh	60	+16.1° (4.55, $CHCl_3$)	67 [i]	

[a] Reaction of $LiBH_4$, IV, and Bu^tOH; THF reflux, 30 min. Reduction of III; −78° C, 2—3 h. Molar ratio of III/$LiBH_4$/IV/Bu^tOH = 1.0/3.6/1.2/1.6. Unless otherwise noted, (R,R')-IV was used. [b] Ia—If were reduced (dehalogenated), respectively, to alcohols such as 1-phenylethanol with lithium triethylborohydride, and determined by ^1H NMR or GLC analyses of the corresponding (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters. J.A. Dale, D.L. Dull and H.S. Mosher, J. Org. Chem., 34 (1969) 2543. [c] J.W. Hartgerink, L.C.J. Van der Laan, J.B.F.N. Engberts, and T.J. de Boen, Tetrahedron, 27 (1971) 4323. [d] See ref. 1b. [e] (S,S')-IV was used. [f] (R)-(+)-2-Phenyloxirane (IIa). $[\alpha]_D^{20}$ +36.7° (c 1.07, benzene), based on lit. value of (R)-(+)-IIa of 95% e.e. $[\alpha]_D^{18}$ +44.5° (c 1.05, benzene); G. Berti, F. Bottari, P.L. Ferrarini and B. Macchia, J. Org. Chem., 30 (1965) 4091. [g] Based on the lit. assignment of (R)-(+)-1-(2-naphthyl)ethanol; S.R. Landor, B.J. Miller and A.R. Tatchell, J. Chem. Soc. C, (1967) 197. [h] Determined by ^1H NMR analysis of Ig using $Pr(hfc)_3$ as chiral shift reagent. [i] Determined by ^1H NMR analysis of (−)-MTPA ester of Ih, cf. Footnote b.

cystine (IV) [4] and Bu^tOH. Reduction of α-bromoacetophenone (IIIb) in the presence of (R,R')-IV during 3 h led to the corresponding halohydrin (S)-(+)-Ib of 80% e.e. (Table 1, entry 2), but with (S,S')-IV (R)-(−)-Ib was obtained of 82% e.e. (entry 3). Thus, either enantiomer of Ib was synthesized exclusively using the corresponding of IV, which is unusual in microbial reductions [1b]. The effect of halogen atoms of IIIa,b,c on asymmetric induction increased with the atomic number Cl<Br<I (entries 1, 2, and 4). Reduction of IIIc afforded Ic of 86% e.e. Even the sterically hindered IIIh was reduced by the present procedure to afford Ih (entry 9).

Compounds I were transformed to the corresponding oxiranes II by alkaline treatment. For example, (R)-(−)-Ib (82% e.e.) and (+)-Ih afforded (R)-(+)-2-phenyloxirane (IIa) (78% e.e., entry 3) and (+)-2,2-dimethyl-3-phenyloxirane (IIb, $[\alpha]_{365}^{20}$ +34.2° (c 1.99, $CHCl_3$)), respectively.

A typical experimental procedure for the reduction of α-haloketones is the following (entry 2): a mixture of (R,R')-N,N'-dibenzoylcystine (IV) (1.2 mmol), $LiBH_4$ (3.6 mmol) and Bu^tOH (1.6 mmol) in tetrahydrofuran (THF, 13 ml) was refluxed for 30 min. The resulting solution was cooled to −78°C and α-bromoacetophenone (IIIb, 1.0 mmol) in THF (2 ml) was added. The reaction mixture was stirred for 3 h, and quenched with 1 M HCl (3 ml). Water was added, and the mixture was extracted with dichloromethane. The organic extract was dried over anhydrous sodium sulfate, and then evaporated under reduced pressure. The resulting precipitate was filtered off and washed with carbon tetrachloride. After the washings were combined and concentrated,

(S)-(+)-2-bromo-1-phenylethanol (Ib) was purified by TLC with silica gel (CH_2Cl_2/MeOH 60/1, as developing solvent), and was further purified by distillation with a Kugelrohr apparatus (bath temperature 113°C/7 Torr, 72% yield, 80% e.e.).

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