

PREPARATION OF SECONDARY ALCOHOLS OF HIGH OPTICAL PURITY*

Otakar ČERVINKA, Anna FÁBRYOVÁ and Irina SABLUKOVA**

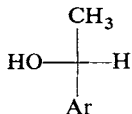
*Department of Organic Chemistry,
Prague Institute of Chemical Technology, 166 28 Prague 6*

Received January 4th, 1985

Partially resolved enantiomers of optically active alcohols *I–V*, obtained by enantioselective reduction of the corresponding ketones with lithium aluminium hydride in the presence of (–)-quinine, were converted into crystalline 3,5-dinitrobenzoates or phenylcarbamates. The esters of the nearly optically pure enantiomers were separated by crystallization from the generally more soluble esters of the racemates. Optical purity of the hydrolytically liberated alcohols was determined by ¹H NMR spectroscopy in the presence of chiral shifting agents.

Optically active secondary alcohols are usually obtained by cleavage of racemic half-esters of dicarboxylic acids, followed by preparation of crystalline diastereoisomeric salts with optically active amines¹. A much better route is an enantioselective reaction affording a mixture of alcohols, with one enantiomer prevailing over the other². As is known from the literature³, a racemic mixture of enantiomers can be resolved by repeated crystallization, until it is enriched in one enantiomer, or possibly even an optically pure enantiomer can be obtained. By contrast, in recrystallization of enriched racemic compounds the result depends on the course of the phase diagram and is usually far from satisfactory³.

The possibility of resolving a racemic mixture by crystallization has been made use of by us to increase optical purity of the alcohols *I–V*, obtained by enantioselective reduction of the corresponding ketones with an agent prepared from lithium aluminium hydride and (–)-quinine⁴. The optical yields of the reduction of alkyl aryl ketones exceeded 50%.



Ar = phenyl (*I*), 2-tolyl (*II*), 2,4,6-trimethylphenyl (*III*), *p*-bromophenyl (*IV*) and 4-tolyl (*V*).

* Part LXI in the series Asymmetric Reactions; Part LX: This Journal 48, 3565 (1983).

** Present address: Riga Polytechnical Institute, Riga, U.S.S.R.

The secondary alcohols *I–IV* thus prepared were converted into their 3,5-dinitrobenzoates. The esters were repeatedly crystallized from suitable solvents, and the melting points and optical rotation were determined both with the crystals separated and with the portions obtained by removing the solvents from the mother liquors. The portions exhibiting the highest values of optical rotation were subjected to alkaline hydrolysis to release the alcohols. As another form of suitable crystalline derivatives of the secondary alcohols we prepared their phenylcarbamates, but these proved more difficult to resolve than the 3,5-dinitrobenzoates. With phenylcarbamates of the alcohols *I* and *V*, recrystallized from a mixture ethanol–light petroleum, the resolution was satisfactory (Table I). With 3,5-dinitrobenzoates of the alcohols *I* and *IV*, forming racemic mixtures, the solubility of the racemic esters was higher than that of the enantiomers, which crystallized. The opposite was true of the alcohols *II* and *III*; in recrystallization of their 3,5-dinitrobenzoates the separated portion had a smaller optical rotation and the enantiomers got enriched in the mother liquors, like with phenylcarbamates of the alcohols *I* and *V*. Naturally, for the purpose of isolation the former case is better than the latter.

Enantiomeric purity of the obtained secondary alcohols was determined by ^1H NMR spectroscopy with the aid of tris (7,7-dimethyl-3-oxo-2-perfluorobutyryl-bicyclo[2,2,1]heptano) europium or the praseodymium analogue. The rotatory powers of the alcohols *I* and *III* were reported^{4,5}.

TABLE I
Preparation of alcohols

Compound	Starting alcohol		Ester		Released alcohol [α] _D (solid substance)	Enantiomeric purity, %
	(α) _D (solid substance)	B.p. °C/kPa	M.p., °C (cyclohexane)	(α) _D (c 2, CHCl ₃)		
3,5-dinitrobenzoate						
<i>I</i>	−14	86–89/2	116–118 ^a	−49.6	+42.5	98
<i>II</i>	+19	103–104/2	—	−54.2	+33.8	90
<i>III</i>	+20 ^b	63–66 ^c	108–110	−58	+51.3	93
<i>IV</i>	+36	127–130/1.6	116–122	−34	+78	90
phenylcarbamate						
<i>I</i>	+12.6	87–89/2	78–80	+46	+30	69
<i>V</i>	+22.2	93–95/1.8	—	+68.3	+36	62

^a Ethanol; ^b c 2, methanol; ^c m.p. °C.

As has been shown, conversion of partially resolved enantiomers of secondary alcohols into well crystallizing suitable derivatives and recrystallization of a disproportionate mixture of the enantiomers may afford products close to optical purity. Since the traditional way of resolving alcohols *via* diastereoisomeric salts is rather tedious, we believe that the method described in the present paper might prove useful.

EXPERIMENTAL

Asymmetric reduction of aryl methyl ketones: To a stirred suspension of 110 mmol of lithium aluminium hydride in 160 ml of ether was added, in small portions during 1 h, a total of 110 mmol of (–)-quinine. The stirring was continued for 45 min, then 100 mmol of a ketone in 350 ml of ether was added dropwise in the course of 40 min. The mixture was boiled 4 h under a reflux condenser, decomposed with 150 ml of water and 150 ml of 20% sulphuric acid. The ethereal layer was shaken with five 100 ml portions of 20% sulphuric acid and five 100 ml portions of water, then dried with magnesium sulphate. After evaporation of ether the alcohol was distilled.

Preparation of 3,5-dinitrobenzoates: To a solution of 80 mmol of an alcohol in 50 ml of benzene and 60 ml of pyridine, stirred and cooled to 0–5°C, 350 ml of 10% 3,5-dinitrobenzoyl chloride in benzene was added. The mixture was briefly agitated and left standing for 2 h at room temperature. Pyridine hydrochloride was filtered off and the filtrate was successively shaken with 50% potassium hydroxide (2 . 100 ml), 2M-HCl (2 . 100 ml) and water (3 . 100 ml), then it was dried with sodium sulphate. The benzene was distilled off and the ester was recrystallized from a suitable solvent.

Hydrolysis of 3,5-dinitrobenzoates: To a mixture of 12.5 mmol of a 3,5-dinitrobenzoate and 50 ml of 10% sodium hydroxide 30 ml of ethanol was added. The monophasic mixture was boiled 2 h under a reflux condenser, then shaken with ether. The ethereal extract was dried with magnesium sulphate, the ether was removed and the product was distilled.

Preparation of phenylcarbamates: These were obtained by boiling equimolar amounts of an alcohol and phenylisocyanate in benzene for 6 h. From the phenylcarbamates the alcohols were released by re-esterification with ethanol in the presence of sodium ethoxide.

REFERENCES

1. Wilen H. S. in the book: *Topics in Stereochemistry* (N. L. Allinger and E. L. Eliel, Eds) Vol 6, p. 114. Wiley-Interscience, New York 1971.
2. Fiaud J. C. in the book: *Stereochemistry* (H. B. Kagan, Ed.) Vol 3, p. 95. Thieme, Stuttgart 1977.
3. Wilen S. H., Collet A., Jacques J.: *Tetrahedron* 33, 2725 (1977).
4. Červinka O.: *This Journal* 30, 1684 (1965).
5. Prelog V., Philbin E., Watanabe E., Wilhelm M.: *Helv. Chim. Acta* 39, 1086 (1956).

Translated by J. Salák.