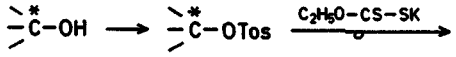
A Mild Synthesis of Optically Active Thiols

Elvezio BERETTA, Mauro CINQUINI, Stefano COLONNA, and Roberto FORNASIER.

Centro C.N.R. e Istituto di Chimica Industriale dell'Università, Via C. Golgi 19, Milano 20133, Italy.

The synthesis of optically active thiols is limited to a few methods, namely the conversion of halides or tosylates *into thiols by reaction with hydrosulphide ions*[1], *or more* usually, via the corresponding thiouronium salts[2]; Reaction of tosylates with thiocyanide ions, followed by conversion into disulphides, and reduction to thiols constitutes *an alternative pathway*[1]. *The synthesis of (R) and (S)-1-*phenylethanethiol by decomposition of the diastereomeric [*O*-(–)-menthyl]-*S*-1-phenylethanedithiocarbonates, prepared by action of 1-phenylethyl bromide on (–)-menthyl sodium *xanthogenate, has recently been reported*[3]. Methods involving halides as intermediates suffer from the difficulty of obtaining such compounds optically pure in high yield[4]. Furthermore most of the methods imply at some stage quite drastic conditions, so that a partial recemization may occur, and yields are low.

We report a mild synthesis of optically active thiols in a two-step sequence involving reaction of optically active tosylates (*1*) with potassium ethylxanthogenate and decomposition[5] of the xanthogenic ester (2) with ethylenediamine.



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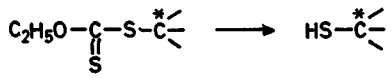

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Yields for the overall conversion alcohols to thiols are reported in table together with optical rotations of the products.

The low yield met with in the case of menthol is likely due to the relevant steric hindrance at the reaction centre. Attempts to extend the method to derivatives having an aryl group α to the chiral centre, such as phenyltrifluoromethyl or α-naphtylmethyl carbinol, failed since the tosylates did not react in the usual conditions, and decomposition occured at higher temperatures. Although the optical purity of the thiols is unknown[6], the high degree of stereospecificity of the reaction, which proceeds with overall inversion at the chiral carbon atom, is indicated by the values of optical rotation of the compounds in comparison with the highest values reported in the literature.

Another proof, albeit indirect, is given by the conversion of *trans-4-t-butylcyclohexanol* (*3*) *into the cis-thiol* (*4*) which is at least 95% diastereomerically pure, as proved by the chromatographic analysis of the parent methyl sulphone (*6*). Formations of the *cis*-thiol (*4*) is kinetically controlled, since it has been shown[8] that the *trans*-diequatorial isomer is thermodynamically more stable, and indicates the reaction to proceed with overall inversion. Two of the steps, i.e. formation of tosylates and conversion of xanthates in thiols, do not affect the chiral centre, so that inversion occurs in the reaction of tosylates with potassium ethylxanthogenate, likely through S_N2 attack at carbon.

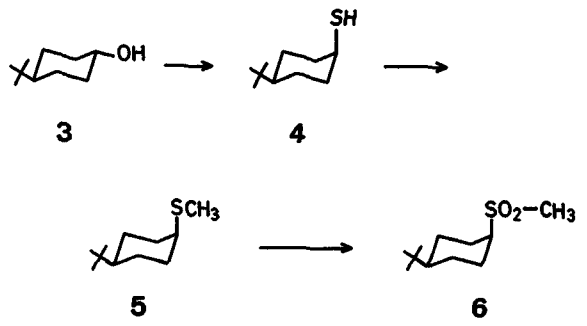

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Table. Conversion of Alcohols into the Corresponding thiols

Alcohol	Thiol	$[\alpha]_D^{25}$	Yield (%)
(–) *n*-C_6H_{13}–CH(CH$_3$)–OH	(+) *n*-C_6H_{13}–CH(CH$_3$)–SH	+29.3[a]	70
(+) *n*-C_6H_{13}–CH(CH$_3$)–OH	(–) *n*-C_6H_{13}–CH(CH$_3$)–SH	–28.0[b]	65
(+) C_6H_5–CH_2–CH(CH$_3$)–OH	(–) C_6H_5–CH_2–CH(CH$_3$)–SH	–18.5[c]	45
(–) menthol	(+) neomenthylthiol	+39.0[d]	14
 3	 4		50

[a] Neat; $[\alpha]_{546}^{25}$ +36.6°; Ref.[9] $[\alpha]_{546}^{26}$ +37.3°, (neat); $[\alpha]_{546}^{26}$ +37.6°, (C_2H_5OH).
[b] Neat; $[\alpha]_{546}^{26}$ –35.0°; Ref.[9] $[\alpha]_{546}^{28}$ –36.9°, (C_2H_5OH).
[c] In $CHCl_3$; $[\alpha]_D^{25}$ –14.9°, (C_2H_5OH); Ref.[1] $[\alpha]_D$ –15.1°, (C_2H_5OH).
[d] In $CHCl_3$.

Optically Active Alcohols:
Racemic alcohols were resolved by fractional crystallization of the brucine salts of the respective phthalic monoesters, prepared by conventional methods[10]. *(+)-Octan-2-ol* and *(–)-octan-2-ol* were prepared by the method of Kenyon[11]; $[\alpha]_D^{25}$ +9.9° and –9.9° (l 1 neat), respectively; b.p. 86°/20 torr (Ref.[11], $[\alpha]_D^{17}$ ±9.9°, neat; b.p. 86°/20 torr).
(+)-1-Phenylpropan-2-ol had $[\alpha]_D^{25}$ +26° (l 1, neat), b.p. 100°/10 torr (lit.[2] $[\alpha]_D^{19}$ +27,2°, neat; b.p. 104°/15 torr).
(–)-Menthol, a commercial product, had m.p. 42–43°, $[\alpha]_D^{20}$ –50° (c 5, ethanol).

***trans*-4-*t*-Butylcyclohexanol:**
trans-4-*t*-Butylcyclohexanone was reduced to the *trans*-alcohol according to Eliel's procedure[12]. It had m.p. 82–83° (Ref.[13] m.p. 82.5–83°).

Tosylates:
The alcohols were reacted at 0° with 1 molar excess of tosyl chloride in pyridine[14]. Yields were in the range 80–95%. *(+)* and *(–)-2-Octyl p-toluenesulphonates*, used as crude products, had $[\alpha]_D^{25}$ ±4° (c 5, acetone, n_D^{25} 1.5050 (Ref. [15] $[\alpha]_D^{26.5}$ +7.3°, neat, and $[\alpha]_D^{19}$ –6.78°, neat, respectively); *(+)-α-methylphenethyl p-toluenesulphonate* had $[\alpha]_D^{25}$ +28° (c 2, $CHCl_3$), m.p. 72–74° (lit.[2] $[\alpha]_D^{20}$ +25.2°, $CHCl_3$; m.p. 67.5–68°); *(–)-menthyl p-toluenesulphonate* had $[\alpha]_D^{25}$ –67° (c 1, $CHCl_3$), m.p. 94° (from hexane) (Ref.[16] $[\alpha]_D^{24}$, –68.2°, $CHCl_3$, m.p. 94–95°); *trans-4-t-butylcyclohexyl p-toluenesulphonate* had m.p. 89–90° (Ref.[17] m.p. 89–90°).

Thiols:
The tosylate (0.1 mol) was added to a solution of potassium ethylxanthogenate (0.15 mol) in acetone (300 ml) and the mixture

was refluxed for 3 days (in the case of (+) and (−)-2-octyl derivatives the reaction time was 8 h). The precipitated potassium salt was filtered and the solvent evaporated at reduced pressure at room temperature. Chloroform was added to the residue, the organic solution was washed with water, dried and evaporated at reduced pressure. The crude xanthogenic ester (0.1 mol) was decomposed at room temperature in a nitrogen current to the corresponding thiol by stirring for 5 h in the presence of ethylenediamine (30 ml), according to Mori and Nakamura's procedure[5]. Optical rotations and yields are reported in Table.

(−) and (+)-2-Octylthiol had b.p. 44–47°/2 torr, n_D^{25} 1.4580 (lit.[2] b.p. 80–82°/25 torr, n_D^{20} 1.4520); (−)-1-phenylpropane-2-thiol had b.p. 84–85°/5 torr, n_D^{20} 1.5350 (lit.[1] b.p. 105–110°/16 torr, n_D^{20} 1.5312); (+)-neomenthylthiol had b.p. 90–82°/10 torr, n_D^{20} 1.4738.

$C_{10}H_{20}S$	calc.	C 69.70	H 11.70
(172.3)	found	69.60	11.68

Crude *cis*-4-*t*-butylcyclohexyl thiol was converted according to Eliel[8] into the corresponding methyl sulphone, m.p. 175–176° (lit.[8] m.p. 176.5–177.5°). Its diastereomeric purity (≥ 95%) was proved by N.M.R. analysis and by column chromatographic separation (silica, eluent ethyl ether).

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