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NEW SYNTHETIC REACTIONS BASED ON 1-METHYL-2-FLUOROPYRIDINIUM SALTS. STEREOSPECIFIC PREPARATION OF THIOALCOHOLS FROM ALCOHOLS

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Treatment of various alcohols with 1-methyl-2-fluoropyridinium salt and sodium N,N-dimethyldithiocarbamate afforded alkyl N,N-dimethyldithiocarbamates of inverted configuration. The latter compounds were converted to thioalcohols with retention.

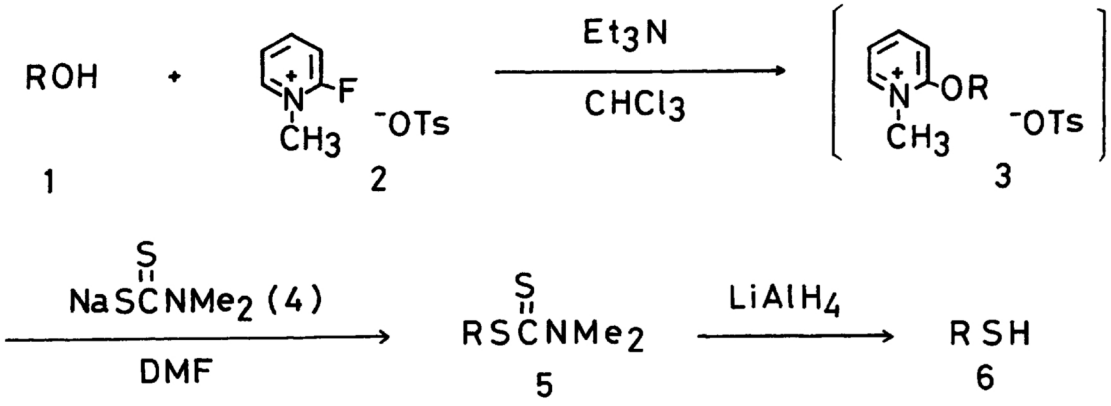
Thioalcohols have been widely used as versatile synthetic intermediates and a number of their preparative methods have been reported.[1] Most of these methods consist of three steps starting from alcohols, namely, i) conversion of alcohols to halides or tosylates, ii) bimolecular substitution with sulfur-containing nucleophiles, and iii) subsequent conversion to thioalcohols.[2] Although the Walden inversion was implied in most of the methods, stereochemical ambiguities involved in some stages remained to be resolved.[3,4] Recently we demonstrated that 2-alkyloxypyridinium salts, formed 'in situ' with retention from alcohols and 2-fluoropyridinium salt, reacted with potassium ethanethioate to give corresponding thiolesters (with inversion) in fairly good yields and with high stereospecificity.[1]

In order to develop efficient methods for the stereospecific conversion of alcohols to thioalcohols based on the onium salts of azaaromatics, it is necessary to find out suitable combinations of sulfur-containing nucleophiles and the onium salts.

After screening possible combinations, it was found that the combination of 1-methyl-2-fluoropyridinium tosylate and sodium N,N-dimethyldithiocarbamate shown in the full equation was effective for this purpose. Thus various alcohols including steroids and carbohydrate were successfully converted to the corresponding thioalcohols in high yields with high stereospecificity.

The procedure consists of i) the reaction of alcohols with 1-methyl-2-fluoropyridinium tosylate to give 2-alkyloxypyridinium salts, ii) S_N2 type reaction of the 2-alkyloxy salts with sodium N,N-dimethyldithiocarbamate to give alkyl dithiocarbamates, and iii) reductive cleavage to thioalcohols.

When optically active alcohol, such as (S)-(+)-2-octanol, $[\alpha]_D^{20}$+9.9°(neat), was treated with 2-fluoropyridinium salt and dithiocarbamate, and then reduced with $LiAlH_4$, (R)-(-)-2-octanethiol, $[\alpha]_D^{23}$-32.7°(c 1.74, ab. EtOH), was obtained in good yields with complete inversion of configuration.[5]

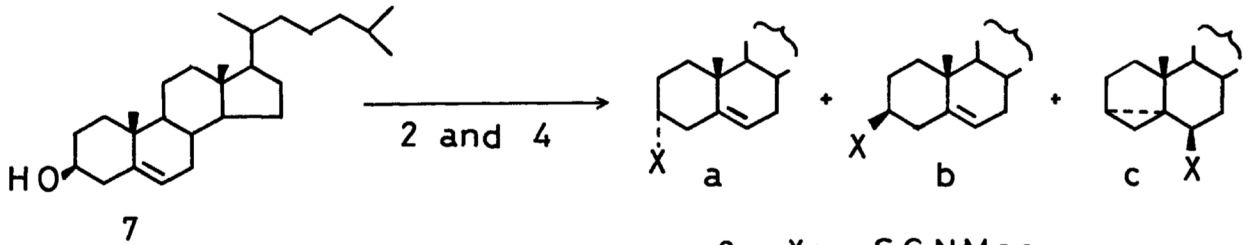


A clean inversion of configuration also occurred in the case of alicyclic alcohols. For instance, 3 β-cholestanol was converted to 3 α-cholestanethiol in overall 97% yield according to the above-mentioned method.

Typical experimental procedures are described below; to a stirred suspension of 2-fluoropyridinium tosylate (185mg, 0.654mmol) in dry $CHCl_3$ (4ml) was added anhydrous 3 β-cholestanol (192mg, 0.494mmol) and triethylamine (73mg, 0.721mmol) in $CHCl_3$ (4ml). A pale yellow homogeneous solution was stirred at room temperature for one hour under an argon atmosphere. Chloroform was evaporated in vacuo, and to the residual white solid were added dry DMF (9ml) and anhydrous sodium N,N-dimethyldithiocarbamate (152mg, 1.06mmol).[6] The solution was heated with stirring at 90°C for 4 hours. The usual work-up followed by column chromatography (silica gel/benzene-hexane) afforded 3 α-cholestanyl N,N-dimethyldithiocarbamate (239mg, 98%): mp 158.5-159°C; NMR($CDCl_3$) δ=4.4(m, 1, CHS), 3.5(broad s, 6, NMe_2)[7]; $[\alpha]_D^{19}$+39.7° (c 1.6, $CHCl_3$). The lithium aluminum hydride reduction of the carbamate (216mg, 0.439mmol) gave 3 α-cholestanethiol (176mg, 99%): mp 79-80°C (lit. mp 80°C)[8]; NMR($CDCl_3$) δ=3.5(m, 1, CHS); $[\alpha]_D^{21}$+26.1°(c 1.8, $CHCl_3$). Acetyl derivatives: mp 122-123°C (lit. mp 120-121°C)[8]; NMR($CDCl_3$) δ=4.05(m, 1, CHS), 2.35(s, 3, acetyl); IR(KBr) 1680cm^{-1}; $[\alpha]_D^{21}$+39.8° (c 1.0, $CHCl_3$).

Various alkyl dithiocarbamates prepared according to the present method are listed in the table.

Similar treatment of 3 β-cholesterol (7) afforded a 5:1 mixture of isomeric dithiocarbamates (8, 76%), where a major component was α isomer (8a, inversion), and a minor component was β (8b, retention), both of which were converted to corresponding thiols (9) and their acetyl derivatives (10), and identified.[9]



8 X: $-S-\overset{\overset{S}{\|}}{C}-NMe_2$

9 : $-SH$

10 : $-S-\overset{\overset{O}{\|}}{C}-CH_3$

Table. Preparation of alkyl dithiocarbamates from alcohols.[a]

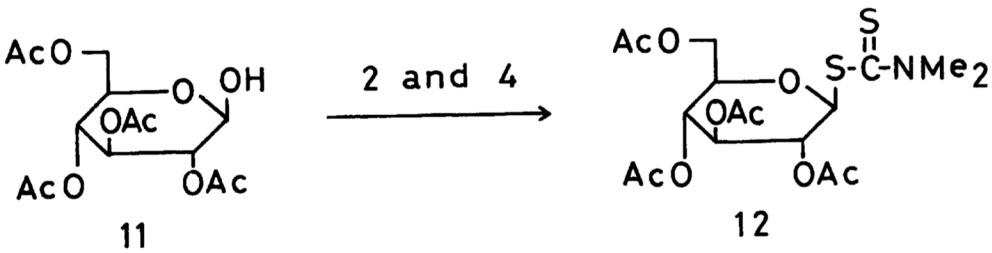
Entry No.	ROH	Temp. (°C)	Time[b] (hr.)	$RSCSNMe_2$ Isolated yield (%)	
1	$CH_3(CH_2)_{10}CH_2OH$	80	1	97	
2	$C_6H_5CH_2OH$	r.t.	0.5	98	
3	$C_6H_5CH{=}CHCH_2OH$	r.t.	0.5	98[c]	
4	dl-$C_6H_{13}CH(CH_3)OH$	90	1	94	
5	(S)-(+)-$C_6H_{13}CH(CH_3)OH$	90	1	90	$[\alpha]_D^{18}$+11.5° (c 2.6, benzene)
6	1-menthol	90	3	66	mp 91.5-92.5°C
7	3β-cholestanol	90	4	98	mp 158-159°C
8	3β-cholesterol	90	2	76[d]	mp 162-163°C
9	2,3,4,6-tetra-O-acetyl-β-D-glucopranose	85	1	93	mp 111-113°C $[\alpha]_D$+29.2° (c 2.5, $CHCl_3$)

a) All the compounds exhibited NMR and IR spectra in agreement with the structures.
b) Unless otherwise indicated, the first step was carried out in dry $CHCl_3$ at room temperature over a period of 30 min. to 1 hour, and the second step in dry DMF at temperature and a period of time specified in the table.
c) First step was performed in acetone-benzene (1:1). In the second step, 4 in DMF was added to the reaction mixture of the same solvent system (acetone-benzene).
d) 3,5-Cholestadiene (10%) was isolated as a by-product.

Since it is generally known that preparative methods for cholestenethiol using 3β-cholesteryl chloride and potassium thiocyanate,[10] or 3β-cholesteryl tosylate and thiourea,[11] give only β isomer (9b), the formation of β isomer with inversion according to the present method seems of particular synthetic importance.[12]

In allylic system (entry 3 of the table), substitution took place exclusively at a carbon atom attached to an oxygen in the starting alcohol, and no isomeric dithiocarbamate (S_N2') was detected.

Treatment of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranose (11) with 2 and 4 produced a single dithiocarbamate, β-isomer (12),[13] formed with retention of configuration. The result can be explained by considering a participation of neighboring acetoxy group trans to the leaving group.[14]



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It is noted that various alcohols including steroids and carbohydrate are directly converted to the corresponding dithiocarbamate derivatives in excellent yields with high stereospecificity by the use of 2-fluoropyridinium salt (2). Therefore the present method provides an important tool for the preparation of thioalcohols including optically active ones.

Further investigations are in progress.

References and Notes

1) Preceding paper in this series: K. Hojo, H. Yoshino, and T. Mukaiyama, Chem. Lett., 133 (1977).

2) Review article: J. L. Wardwell, in S. Patai Ed., "The chemistry of the thiol group", P. 519, John Wiley & Sons, 1974.

3) a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", p. 517, Cornell University Press, Ithaca, 1969.
b) H. M. R. Hoffmann and E. D. Hughes, J. Chem. Soc., 1252 (1964).

4) E. Beretta, M. Cinquini, S. Colonna, and R. Fornasier, Synthesis, 425 (1974), and references cited therein.

5) Reported rotation values for (R)-(-)-2-octanethiol is $[\alpha]_D^{23}$ -32.8° (c 1.48, ab. EtOH).[1] Inversion of configuration was also observed in similar reactions using onium salts: a) K. Hojo and T. Mukaiyama, Chem. Lett., 619 (1976).
b) T. Mukaiyama and K. Hojo, ibid., 893 (1976).

6) M. Kulka, Can. J. Chem., 34, 1093 (1956).

7) All the NMR data reported in this paper are those measured in $CDCl_3$. The methyl signal of N,N-dimethyldithicarbamoyl group showed temperature dependent NMR spectra.

8) D. A. Swann and J. H. Turnbull, Tetrahedron, 20, 1265 (1964).

9) A trace amount of 8c was also isolated from the reaction mixture. Physical data for acetyl derivatives:
10a: mp 123-124°C; NMR($CDCl_3$) δ =4.05(m, 1, CHS), 2.30(s, 3, acetyl); IR(KBr) 1690cm^{-1}.
10b: mp 110-111°C; NMR($CDCl_3$) δ =3.47(m, 1, CHS), 2.34(s, 3, acetyl); IR(KBr) 1690cm^{-1}.
10c: NMR($CDCl_3$) δ =4.02(broad d, 1, J=12Hz, CHS), 2.30(s, 3, acetyl), 0.15-0.65 (m, 3, cyclopropyl); IR(CH_2Cl_2)1682cm^{-1}.

10) G. L. O'Connor and H. R. Nace, J. Am. Chem. Soc., 75, 2118 (1953).

11) L. C. King, R. M. Dodson, and L. A. Subluskey, ibid., 70, 1176 (1968), and ref. 8.

12) In a separate experiment, we found that the reaction of 3β-cholesteryl tosylate with 4 under the similar reaction conditions employed in the present method produced a mixture (69%) of 8a, 8b, and 8c in the ratio of 5:2:1 together with 24% of 3,5-cholestadiene.

13) S. Tejima and S. Ishiguro, Chem. Pharm. Bull., 15, 255 (1967).

14) Such a phenomenon is well documented in substitution reaction in carbohydrate Chemistry:
a) R. U. Lemieux, Adv. Carbohydrate Chem., 9, 1 (1954).
b) L. Goodman, ibid., 22, 109 (1967).

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