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NEW SYNTHETIC REACTIONS BASED ON 1-METHYL-2-FLUOROPYRIDINIUM SALTS. FACILE CONVERSION OF ALCOHOLS TO THIOALCOHOLS

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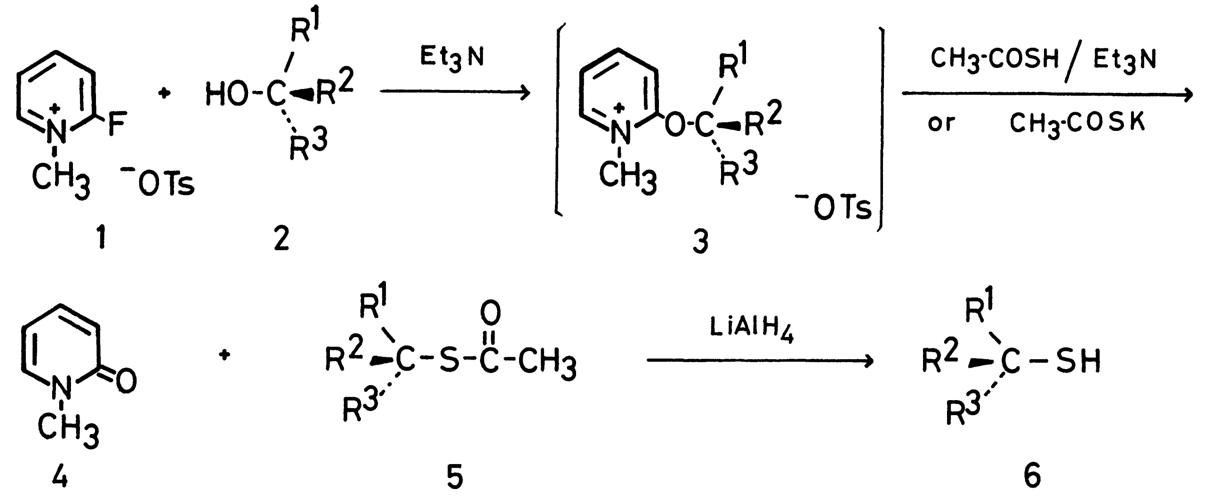
Facile conversion of alcohols to thioalcohols via thiolesters is described. The synthetic scheme involves (i) preparation of thiolesters(5) by the reaction of ethanethioate anion with 2-alkyloxypyridinium salts(3), formed from 1-methyl-2-fluoropyridinium salt(1) and alcohols, and (ii) subsequent reduction of 5 to thioalcohols. A clean inversion of configuration is noted.

A number of synthetic methods for the preparation of thioalcohols have been reported in recent years, which include reactions of alkyl halides or tosylates with thiourea or alkyl dithiocarbonate ion, thiocarboxylate ion, thiocyanate ion, thiosulfate ion, dithiocarbamate ion, and trithiocarbonate ion.1) In most cases, conversion to thioalcohols are carried out by a base- or acid-catalyzed hydrolysis. These methods, however, found only limited use in synthetic works because of difficulties in introducing a thiol group to complex molecules having labile functional groups. Further, extensive isomerization (or racemization) usually accompanies in the final stage of hydrolysis.

We now wish to report a convenient method for the conversion of alcohols into thioalcohols by two steps under mild conditions.

The present procedure consists of (i) preparation of thiolesters(5) by treatment of 2-alkyloxypyridinium salts(3)2) formed from 2-fluoropyridinium salt(1) and alcohols(2) with potassium ethanethioate or a mixture of ethanethioic S-acid and triethylamine,3) and (ii) facile conversion of 5 to corresponding thioalcohols(6) by a mild reductive cleavage.4)



A typical procedure is described for the preparation of 1-dodecanethiol: To a stirred suspension of 2-fluoro salt 1 (6.23g, 22mmol) in a 1:1 mixture (50ml) of dry benzene and dry acetone, was added 1-dodecanol (3.98g, 21mmol) and triethylamine (2.22g, 22mmol) at room temperature, and the reaction mixture was stirred for one hour under an argon atmosphere. A mixture of ethanethioic S-acid (1.67g, 22mmol) and triethylamine (2.22g, 22mmol) in acetone-benzene (10ml)[5] was further added to the solution. The reaction mixture was refluxed for two hours, and then concentrated. The residual liquid was dissolved in benzene, washed with water to remove 1-methyl-2-pyridone (4), and dried. Removal of the solvent gave S-dodecyl ethanethioate (4.87g, 93%), bp 133°C/3mmHg. Reduction of this thiolester by lithium aluminum hydride in ether at room temperature gave 1-dodecanethiol (95%). In a similar manner, several thiolesters were prepared as listed in Table 1.

As expected from our previous studies,[6] the reaction of ethanethioate anion with 2-alkyloxy salt(3) proceeded with a clean inversion of configuration at an asymmetric carbon attached to oxygen atom. For example, (S)-(+)- and (R)-(-)-2-octanol was converted according to the present method to (R)-(-)- and (S)-(+)-2-octanethiol, respectively, in good yields. High optical purity as reflected in high optical rotations is noteworthy (Table 2).

An inversion of configuration was also observed in cyclic systems. For instance, 3β-cholestanol was transformed to S-3α-cholestanyl ethanethioate (72%) which was in turn converted into 3α-cholestanethiol (98%), mp. 80.0-81.5°C (rep. 80-81°C),[7] by lithium aluminum hydride reduction.

Table 1. Preparation of Thiolesters

Alcohol	Temp.	Time (hr)	Thiolester	Isolated Yield (%)
1. $CH_3(CH_2)_{10}CH_2OH$	refl.	2	$CH_3(CH_2)_{10}CH_2SCOCH_3$	93
2. $C_6H_5CH_2CH_2CH_2OH$	refl.	2	$C_6H_5CH_2CH_2CH_2SCOCH_3$	86
3. $C_6H_5CH_2OH$	r.t.	2	$C_6H_5CH_2SCOCH_3$	89
4. dl-$C_6H_5CH(CH_3)OH$	refl.	3	dl-$C_6H_5CH(CH_3)SCOCH_3$	87
5. (S)-(+)-$C_6H_5CH(CO_2Et)OH$	r.t.	1	(R)-(-)-$C_6H_5CH(CO_2Et)SCOCH_3$	89
6. (R)-(-)-$C_6H_{13}CH(CH_3)OH$	refl.	2	(S)-(-)-$C_6H_{13}CH(CH_3)SCOCH_3$ $[\alpha]_D^{25}$-6.4°(c 2.5, benzene)	79
7. (S)-(+)-$C_6H_{13}CH(CH_3)OH$	refl.	2	(R)-(+)-$C_6H_{13}CH(CH_3)SCOCH_3$ $[\alpha]_D^{23}$+6.9°(c 2.5, benzene)	80
8. 3β-cholestanol	80°C[a]	2	S-3α-cholestanyl ethanethioate mp 120-121.5°C (rep. 120-121°C)[7]	72

a) Reaction was carried out in DMF.

Table 2. Preparation of Optically Active Thioalcohols[a]

Alcohol	$[\alpha]_D^{20}$(neat)	Thioalcohol	$[\alpha]_D^{23}$(ab. EtOH)
(S)-(+)-2-octanol	+9.9°	R-(-)-2-octanethiol	-32.8° (c 1.48) -28.0° (neat)[b]
(R)-(-)-2-octanol	-9.7°	(S)-(+)-2-octanethiol	+32.7° (c 1.50)

a) Optical rotation measurements were performed in a 1 dm cell by the automatic polarimeter.

b) E. Beretta, M. Cinquini, S. Colonna, and R. Fornasier, Synthesis, 425 (1974).

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References and Notes

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

2) a) T. Mukaiyama, S. Ikeda, and S. Kobayashi, Chem. Lett., 1159 (1975),
b) S. Kobayashi, M. Tsutsui, and T. Mukaiyama, ibid., 373 (1976).

3) A similar transformation is possible using 2-fluorobenzothiazolium salt although in lower yield.

4) For mild methods for conversion of thiolesters to thioalcohols see: T. Endo, K. Oda, and T. Mukaiyama, Chem. Lett., 443 (1974).

5) Alternatively, potassium ethanethioate dissolved in DMF can be used.

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