Tetrahedron Letters, Vol.22, No.33, pp 3119 - 3122, 1981
Printed in Great Britain

0040-4039/81/333119-04$02.00/0

A NEW, HIGHLY EFFICIENT METHOD FOR THE CONVERSION OF ALCOHOLS TO THIOLESTERS AND THIOLS

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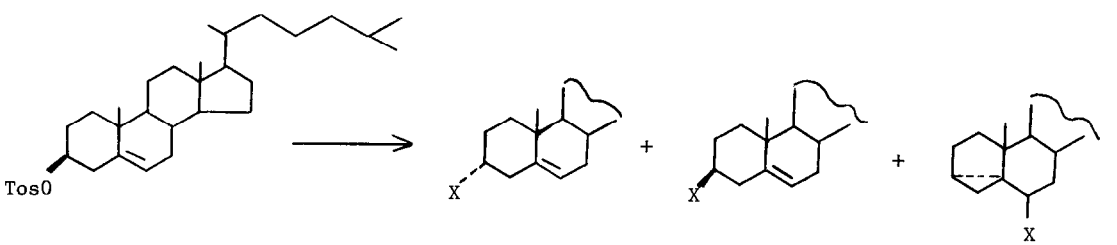
Summary: Various alcohols were converted to their corresponding thiolacetates by treatment with triphenylphosphine and diisopropyl azodicarboxylate in the presence of thiolacetic acid. The overall conversion was both highly efficient (89-99% yields) and stereoselective (99.5% inversion).

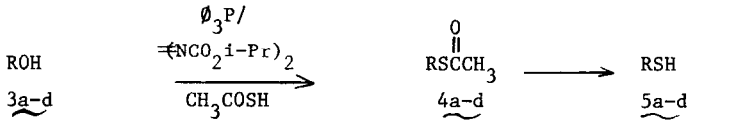
Several methods for the conversion of alcohols to thiolesters (and thiols) have been reported[1]. However, these methods generally require a series of transformations; i) initial activation of the hydroxyl function by conversion to a halide or tosylate, ii) displacement with a suitable sulfur containing nucleophile, and iii) saponification or reduction to the desired thiol. Inversion of configuration is implied in most of the above methods; however, mixtures of products and low yields are often observed due to the harshness of the conditions typically employed. For example, in the conversion of 3β-cholesteryl tosylate 1 to the 3α-cholesteryl N,N-dimethyldithiocarbamate 2a, both the 3β (2b) and the cyclopropylcarbinyl (2c) N,N-dimethyldithiocarbamates were produced as by-products[1a].



1 2a 2b 2c

X= S
‖
SCN(CH$_3$)$_2$

We now wish to report a mild, highly stereoselective method for the one-step conversion of alcohols to thiolesters. We have prepared thiolesters 4 directly from alcohols 3 using a modification of the triphenylphosphine-dialkyl azodicarboxylate inversion procedure of Mitsunobu[2]. The method consists of treating the preformed adduct of triphenylphosphine and diisopropyl azodicarboxylate[3], in tetrahydrofuran at 0°C, with a mixture of the alcohol and an appropriate thiolacid. The mixture is stirred for 1 hour at 0°C and an additional hour at 22-25°C after which the inverted thiolesters can be isolated in high yield. The free thiols can then be obtained by standard saponification or reduction methods[4].

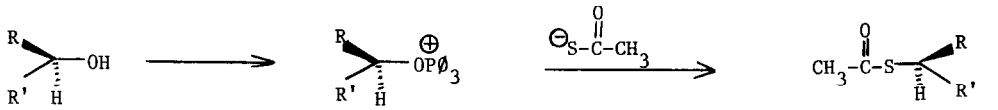


	ROH 3	RSCOCH$_3$ 4 (% yield)	RSH 5 (% yield)
a	R-(-)-2-octanol[f]	98	90[a,g]
b	ØCH=CHCH$_2$OH	89	99[b,c]
c	3β-cholesterol	94[d]	81
d	ØCH$_2$OH	96	97[e]

a. bp 65-70°C (15 torr), lit.[5] bp 80-82°C (25 torr); b. bp 140-145°C (25 torr), lit.[7] bp 124-125°C (13 torr); c. Thiol 5b was also characterized by conversion to dicinnamyl disulfide by oxidation with iodine (disulfide mp 88-92°C, lit.[7] mp 90.5°C); d. mp 121-124°C, lit.[1a] mp 123-124°C; e. bp 78-80°C (20 torr), lit.[6] bp 194-196°C; f. $[\alpha]_D^{20} = -8.0°$ (neat), lit.[9] $[\alpha]_D = -9.33°$ (neat); g. $[\alpha]_D^{22} = 28.72°$ (c 1.56, abs. EtOH), lit.[9] $[\alpha]_D = 35.7°$ (c 5.1, abs. EtOH).

The high stereochemical integrity of this inversion reaction is indicated by the results shown in the table. Optically active R(-)-2-octanol (80.8% optical purity) was converted to its corresponding thiolacetate 4a and then reduced to S(+)-2-octanethiol 5a (80.4% optical purity, 99.5% inversion[9]) with complete inversion of configuration. Similarly 3β-cholesterol 3c was converted to 3α-cholesteryl thiol 5c in high yield with no 3β or cyclopropylcarbinyl thiol detected by nmr measurements. It is also noted that allylic alcohol 3b gave only the

product of S_N2 attack with no S_N2' product detected. These results indicate that the activated alkoxy-phosphonium salt intermediate 6 undergoes displacement by thiolacetate anion in a highly stereospecific and regioselective manner to produce the inverted thiol-esters 4. A typical experiment is described below.



3 6 4

S(+)-2-octanethiol

Diisopropyl azodicarboxylate (8.33 g, 40 mmol) was added to an efficiently stirred solution of triphenylphosphine (10.50 g, 40 mmol) in 100 mL of tetrahydrofuran at 0°C. The mixture was stirred at 0°C for 30 min. A white precipitate resulted. R-(-)-2-Octanol (2.60 g, 20 mmol) and thiolacetic acid (3.04 g, 40 mmol) in 50 mL of tetrahydrofuran was added dropwise over 10 min and the mixture was stirred for 1 h at 0°C and at 22-25°C for 1 h. A clear yellow solution resulted. The solution was concentrated and then purified by column chromatography over silica gel (elution with hexanes-methylene chloride, 1:1) to give 3.70 g (98%) of the desired octane thiolacetate. The thiolacetate (3.00 g, 15.95 mmol) was dissolved in 25 mL of anhydrous ether and added dropwise to a suspension of lithium aluminum hydride (0.61 g, 4.0 equiv) in 15 mL of anhydrous ether under a nitrogen atmosphere. The reaction mixture was stirred at 22-25°C for 30 min and the excess lithium aluminum hydride was destroyed by the careful addition of 10 mL of 1N hydrochloric acid solution. The ether layer was separated and dried over sodium sulfate to give 2.37 g (100%) of S-(+)-2-octanethiol as a clear oil which was homogeneous by nmr. A purified sample was prepared by distillation (2.05 g, 88.6%, bp 65-70°C, (15 torr), lit.[5] bp 80-82°C (25 torr)).

References and Notes

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3. Preformation of the triphenylphosphine-diisopropyl azodicarboxylate adduct is essenti: for the success of this reaction. The standard sequence of reagent additions results in preliminary deactivation of the azodicarboxylate reagent by reaction with the thiolacid.

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9. % inversion = $\frac{10^4\ ([\alpha]\ \text{product})}{(\%\ \text{optical purity ROH})\ (\text{max}\ [\alpha]\ \text{product})}$

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(Received in USA 29 April 1981)