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A MILD AND EFFICIENT SYNTHESIS OF THIOLESTERS FROM ALCOHOLS

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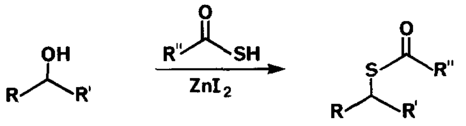
Summary: Numerous functionally diverse thiolesters are prepared in high yield in a mild "one-pot" synthesis from activated alcohols and thiolacids under Lewis acid catalysis.

Among the large number of methods available for the synthesis of thiols those which make use of alkenes and alkyl halides as starting materials have been the most extensively studied.[2] In principle, many are simple processes but the further reaction of the initially formed thiols to give sulfides or disulfides often serves to severely limit their utility as synthetic methods. Other routes, such as by the direct reaction between alcohols and hydrogen sulfide or phosphorus pentasulfide have also been reported.[3] They however require the presence of a basic catalyst, high temperatures and pressures, conditions which may be incompatible with many common functionalities present on an organic molecule. Since the thiolester is a versatile and relatively stable functional group which can produce thiols by mild saponification or reduction[4], the development of a procedure for converting alcohols to thiolesters is very attractive. Some have already been described, but they require the initial activation of the hydroxyl function by conversion to a halide[5] or tosylate[6] and their displacement with a suitable sulfur containing nucleophile. Recently a highly efficient and stereoselective conversion of alcohols to thiolesters by a modification of the triphenylphosphine dialkylazodicarboxylate inversion procedure of Mitsonubu was reported.[7]

Following our interest in the C-S bond formation for the synthesis of leukotrienes and related analogs we have described new C-S bond forming reactions based on the sulfenyllactonization reaction[8], the reaction of thiosilane reagents with epoxides[9] and the direct synthesis of thioethers from thiols and alcohols under zinc iodide catalysis[10].

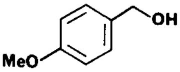
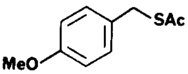
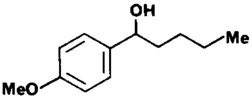
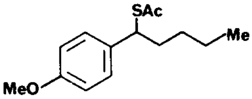
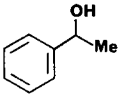
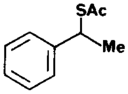
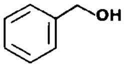
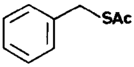
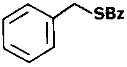
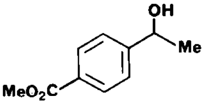
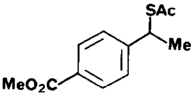
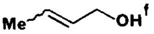
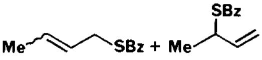
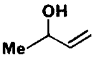
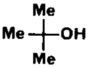
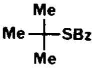
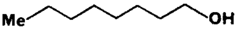
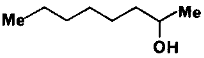
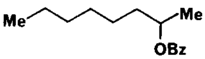
We now wish to report a simple, efficient and high yielding "one-pot" synthesis of a wide range of thiolesters (and therefore of thiols) which proceeds through the displacement of alcohols by thiolacids under Lewis acid catalysis. It is based on the observation that benzylic, allylic and tertiary alcohols can be activated with Lewis acids, and in particular zinc iodide, to generate carbocationic species which are efficiently trapped by thiolacids. The thiolesters were prepared by the sequential addition of thiolacetic acid (or thiobenzoic acid when a chromophore was desired) (1.2 equiv.) and zinc iodide (0.5 equiv.) to a solution of the alcohol in dichloroethane (2 cc/mmole). Reaction times vary from a few minutes to a few hours whereas warming of the mixture will effect a clean conversion of less activated alcohols in a shorter period of time. The reaction mixtures were treated with water, organic materials extracted into dichloromethane and products purified by chromatography.[10] The results are presented in the table.



R=aryl, alkenyl, alkyl; R'=H, alkyl; R''=Me, Ph.

Although a more detailed investigation of the mechanism is still underway, it is suggested by the relative rate of the reaction, the complete lack of sterospecificity, and the observed regioselectivity in the case of allylic alcohols, that the transformation proceeds through an S_N1 type mechanism. Furthermore, the conversion proceeds normally when performed in the absence of light. We have noted, at least in the case of benzyl alcohol (entries 7-10), that benzyl iodide is formed at an early stage of the reaction and could be isolated when the reaction was stopped before the usual required reaction time to achieve complete conversion to the product was reached. In comparison with benzyl alcohol, the reaction of benzyl iodide was considerably slower. Thus, while iodides may be intermediates in some of these reactions, we suspect that in the majority of cases the alcohols proceed directly to the thiolesters. As can be seen from the table, in the case of benzylic alcohols the rate of displacement of the hydroxyl group increases with the presence of electron-donating substituents on the ring and with the level of substitution at the benzylic position. The reaction is not affected by the steric hindrance (entry 14). Finally, the sequential treatment of (S)-α-phenethyl alcohol under the reaction conditions, hydrolysis of the thiolacetate (NaOMe, THF, 0°C) and etherification (NaH, MeI, THF, 0°C) gave methyl α-phenethyl sulfide[11] which was completely racemized.

In contrast to the results obtained by Guindon et al.[10] who observed only external products for allylic alcohols, both 2-buten-1-ol and 3-buten-2-ol give a 1:2.6 mixture of the internal and external product (entries 12,13). This suggests that the process here is more completely S_N1 and the observed product mixture is a reflection of the reduced nucleophilicity of thiolacids as compared to thiols. Only the (E)-isomer of 2-buten-1-thiobenzoate could be detected from careful high field NMR analysis of the reaction mixture. It is pointed out that the product obtained in these cases is the immediate precursor to 2-butene-1-thiol, a rather interesting natural product. 2-butene-1-thiol is a constituent of the malodorous, volatile portion of the scent of the striped skunk (M. mephitis) and has been used to mask human odor. Alternate preparations of this compound are limited[12,13]. Thiols esters were not obtained from primary and secondary aliphatic alcohols under the reaction conditions; instead, a clean conversion to their O-acetates or O-benzoates was observed. This unexpected result might give rise to a new method for

ENTRY	SUBSTRATE	CONDITIONS[a]	TIME[b]	PRODUCT[c]	YIELD, %[d]
1		A	30min		85
2		A	30min		89
3		A	18h		85
4	"	B	24h	"	79
5	"	C	24h	"	50
6	"	D	2.5h[e]	"	35
7		A	45min[e]		32
8	"	E	45min[e]	"	75
9	"	F	45min[e]		71
10	"	F	48h	"	42
11		A	45min[e]		79
12	 [f]	F	48h	 2.6 : 1	68
13		F	48h	" 2.6 : 1	66
14		F	30min[e]		71
15		F	2h[e]		92
16		F	2h[e]		86

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[a] Reagents, catalysts and solvents used were dry and the reaction was performed under N_2.
Conditions: **A.** AcSH(1.2 equiv.), ZnI_2(0.5 equiv.); **B.** AcSH(1.2 equiv.), ZnI_2(0.2 equiv.); **C.** AcSH(1.2 equiv.), $ZnCl_2$(0.5 equiv.); **D.** AcSH(1.2 equiv.), CF_3CO_2H(0.5 equiv.); **E.** AcSH(2.4 equiv.), ZnI_2(0.5 equiv.); **F.** BzSH(1.2 equiv.), ZnI_2(0.5 equiv.).

[b] Time required for the disappearance of starting material.

[c] The products were characterized by NMR, I.R., mass spectra and chemical analysis.

[d] Yield based on isolated material.

[e] The reaction was performed in refluxing dichloroethane.

[f] Mixture of isomers.

preparing acetates and benzoates under very mild conditions and is now under investigation. From the results obtained in this study and from our experience with related systems, we believed that zinc iodide is the Lewis acid of choice although others also achieved the transformation, but usually in lower yields (entries 5-6). As well, it is commercially available and easy to handle. Dichloroethane and dichloromethane are the preferred solvents since they contain no sites of coordination for Lewis acids. Thiobenzoic acid may be preferred to thiolacetic acid for substrates which do not have a chromophor, in order to facilitate subsequent purification.

In conclusion, the mild conditions employed, simplicity, effectiveness and the generality shown make this method very attractive and should even make it the procedure of choice over the "classical" approaches for the preparation of a wide range of thiols from activated alcohols.

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