Communications to the Editor

A Highly Efficient Reaction for the Synthesis of Esters and for the Inversion of Secondary Alcohols

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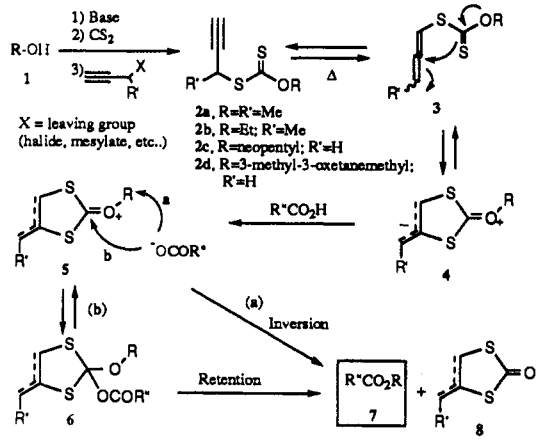
Esters occupy a central position in organic synthesis because of their ubiquity and their widespread use as protecting groups or even as key intermediates in the construction of complex organic molecules. It is not surprising, therefore, that a very large number of methods have been developed over the years to introduce such a functionality, ranging from the classical acid-catalyzed esterification procedures to those involving sophisticated tailor-made reagents for specific problems.[1] Nevertheless, convenient general approaches are still in need. We now describe a novel yet experimentally simple and highly efficient reaction for making esters which also allows the inversion of secondary alcohols. It consists of heating a carboxylic acid with an *S*-propargyl dithiocarbonate (xanthate) **2**[2] derived from the appropriate primary or secondary alcohol **1**, typically in refluxing toluene or chlorobenzene.

Mechanistically, the process may be viewed as occurring through the sequence outlined in Scheme 1. On heating, the propargylic xanthate undergoes a sigmatropic rearrangement to the corresponding allene **3**, which exists in equilibrium with the novel betaine structure **4**. The carboxylic acid is too weak an acid to protonate either the starting *S*-propargyl or the intermediate *S*-allenyl xanthates but strong enough to react with the more basic betaine.[2c] This key step leads to an ion pair **5**, where the initially poorly leaving xanthate group attached to R is now converted, *under very mild conditions,* into a powerful nucleofuge, with the required nucleophile, i.e., the carboxylate, being in close proximity as the counterion. The system is thus ideally set for a substitution reaction leading to the desired ester. The following examples will serve to illustrate the scope of this methodology,

Scheme 1



which can in fact be used for the synthesis of not only esters but also other derivatives that can arise through a similar mechanistic pathway.

Methyl esters are simply made by heating for several hours a carboxylic acid with a xanthate such as **2a** derived from methanol.[3] A number of complex and even sensitive and/or hindered primary, secondary, and tertiary carboxylic acids (**9a–17a**) belonging to various families of natural products reacted smoothly to give the corresponding methyl esters (**9b–17b**) in generally high yield, as indicated in the drawings of Chart 1. In many of the examples, the desired methyl ester crystallized out on cooling. The dithiolanone coproduct (**8**, R′ = Me) consisted of a mixture of endo and exo isomers in variable proportions, depending on the carboxylic acid used, and was easily removed. Xanthate **2a** thus represents a convenient and safe substitute for diazomethane for the direct preparation of methyl esters from carboxylic acids. In fact, like diazomethane and other diazoalkanes, betaine **4** becomes an alkylating agent only after protonation.[4]

Replacing *O*-methyl xanthate **2a** by *O*-ethyl xanthate **2b** provides the ethyl ester, as shown by the obtention of **9c** in 87% yield from acid **9a**. Even neopentyl esters can be efficiently made by using *O*-neopentyl xanthate **1c** (**16a** into **16c**, 93%). Esters of 3-methyl-3-hydroxymethyloxetane, also of the neopentylic type, are accessible in the same manner starting from xanthate **1d**, as illustrated by the conversion of *N*-acetyltryptophan (**15a**) into the neopentyl ester **15c** in 79% yield. Such derivatives are precursors of Corey's highly useful 4-methyl-2,6,7-trioxabicyclo-[2,2,2]octane (OBO) orthoester protecting group for carboxylic acids.[5] Conventional coupling procedures (e.g., with DCC) sometimes require a vast excess (up to 20-fold) of 3-methyl-3-(hydroxymethyl)oxetane.[6]

Esters derived from secondary alcohols are also cleanly produced, as shown by the transformation of xanthate **20** into benzoate **21** or galacturonate **22** in 91% and 86% yield on heating with benzoic acid and protected galacturonic acid **16**, respectively. That the reaction occurs with inversion[7] at the secondary alcohol center was demonstrated by examining the behavior of *O*-

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(1) (a) Mulzer, J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon Press: Oxford, 1991; Vol. 6, pp 323–380. (b) Ogliaruso, M. A.; Wolfe, J. F. In *The Chemistry of Functional Groups*; Patai, S., Ed; Wiley: Chichester, 1979; Supplement B, Part 1, pp 411–441. (c) Pielartzik, H.; Imrich-Pielartzik, B.; Eicher, T. *Methoden der Organischen Chemie (Houben-Weyl)*; Regitz, M., Ed; Georg Thieme Verlag: Stuttgart, 1985; Vol. 5E, Part 1, pp 656–772.

(2) For our earlier work on *S*-propargyl xanthates, see: (a) Boivin, J.; Tailhan, C.; Zard, S. Z. *J. Am. Chem. Soc.* **1991**, *113*, 5874–5876. (b) Boivin, J.; Tailhan, C.; Zard, S. Z. *Tetrahedron Lett.* **1992**, *33*, 7853–7856. (c) Boivin, J.; Henriet, E. B.; Tailhan, C.; Zard, S. Z. *Tetrahedron Lett.* **1993**, *34*, 2763–2766.

(3) Reagents **2a** and **2b** made from 3-butyn-2-ol (via the mesylate) were used as they were available from another study. The simpler and cheaper xanthates derived from propargyl chloride (or bromide), i.e., **2** (R = Me or Et and R′ = H), are in fact as effective. Gibberellic acid (**10a**) and *N*-acetyltryptophan (**15a**), for example, were converted into their respective methyl esters **10b** (81%) and **15b** (87%) on heating with xanthate **2** (R = Me; R′ = H) in toluene. A typical experimental procedure is as follows. A solution of the carboxylic acid (0.4 mmol) and the appropriate propargylic xanthate (0.6 mmol) in toluene or chlorobenzene (4 mL) is heated to reflux until disappearance of the starting acid (usually a few hours). The solution is allowed to cool, and the ester is purified either by chromatography after removal of the solvent or by filtration and recrystallization when the corresponding ester crystallizes from the reaction mixture. In cases where the xanthate is the expensive reagent (e.g., **23**), the carboxylic acid is used in slight excess (1.1–1.5 equiv).

(4) Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press, Inc.: Orlando, FL, 1986; Chapter 3.

(5) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571–5574.

(6) Blaskovich, M. A.; Lajoie, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 5021–5030; *Tetrahedron Lett.* **1993**, *34*, 3837–3840.

(7) It is reasonable to envisage that instead of an S_N2-type substitution, the reversibly formed tetrahedral adduct **6** could also collapse into an ester with retention of configuration. Such a mechanism cannot be excluded *a priori* for each and every case and could possibly operate under special circumstances.

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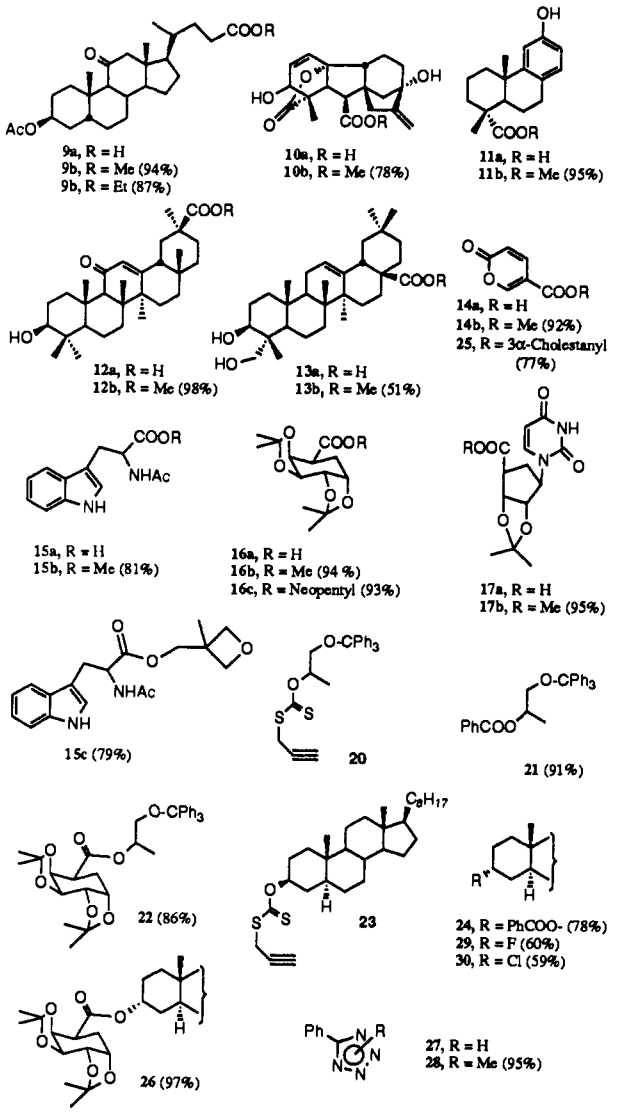
Chart 1



cholestanyl xanthate **23**, which indeed yielded the 3α-benzoate **24** in 78% yield on heating with benzoic acid in toluene or the more complex 3α-esters **25** (77%) and **26** (97%) on reaction with coumalic acid **14** and galacturonic acid **16**, respectively. Thus, unlike the widely used Mitsunobu reaction,[8] our process does not appear to be too sensitive to the nature of the carboxylic acid used. In addition, the cheapness and less hazardous nature of the reagents involved, as well as a much simpler purification of the product, are further nonnegligible advantages of the present method, especially for large-scale preparations.

Although this preliminary work has concentrated on the formation of esters, the process can be extended to the syntheses of a variety of other substances. Tetrazoles, for example, have a pK_a close to that of carboxylic acids[9] and can thus be alkylated in the same way, as illustrated by the methylation of 5-phenyltetrazole (**27**) with xanthate **2a** to give a 1:7 mixture of 1-methyl- and 2-methyl-5-phenyltetrazole (**28**) (95%). Another perhaps even more important application concerns the synthesis of halides (especially fluorides) from alcohols, with inversion in the case of secondary alcohols. This can be accomplished by heating the requisite propargylic xanthate of the alcohol with an ammonium or pyridinium halide (the free acid is too acidic), as shown by the transformation of cholestanyl xanthate **23** into 3α-fluorocholestane **29** or 3α-chlorocholestane **30** in 60% and 59% yield by heating with triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$), further neutralized with 2 equiv of triethylamine, and *p*-chloropyridinium hydrochloride, respectively.[10] Some 2-cholestene was also produced as a side product.

In summary, we have uncovered a powerful and useful general method for making esters and related derivatives. None of the yields reported have been optimized, and further improvements can be envisaged. The rate-limiting step appears to be the thermal sigmatropic rearrangement, which could in principle be tuned by modifying the structure of the propargylic subunit. Studies along these lines, as well as further variations and extensions, are currently being pursued.

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(8) (a) Mitsunobu, O. *Synthesis* **1981**, 1–28. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335–656. For a recent study on the effect of the acid in the Mitsunobu reaction, see: Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234–236.

(9) Butler, R. N. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds; Pergamon Press: Oxford, 1984; Vol. 5, pp 816–817.

(10) Halides can also be made by the Mitsunobu process: Manna, S.; Falck, J. R.; Mioskowski, C. *Synth. Commun.* **1985**, *15*, 663–668. See also ref 8.