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A Xanthate Transfer Radical Process for the Introduction of the Trifluoromethyl Group

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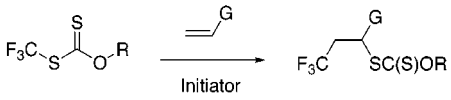
ABSTRACT



S-Trifluoromethyl xanthates efficiently add to unactivated alkenes by a radical mechanism to give adducts with a trifluoromethyl group at the least hindered terminus of the olefin.

The trifluoromethyl group appears in a large number of biologically active structures of interest to the pharmaceutical and agrochemical industry.[1] The presence of the fluorinated motif increases the lipophilicity as well as the metabolic stability, often resulting in an improved activity profile in comparison with the nonfluorinated analogues. As a consequence, a large number of methods have been devised to introduce the trifluoromethyl group and research in this area is still intense.[2] In the case of aliphatic derivatives, various reagents equivalent to the trifluoromethyl anion and cation have been described but the trifluoromethyl radical remains perhaps the most useful species for the practical, large scale preparation of trifluoromethylated synthons. Trifluoromethyl halides, especially bromo- and iodotrifluoromethane, have proved to be the most practical reagents in this respect, but their industrial production is being phased out because of their presumed deleterious effect on the ozone layer. Other routes involving trifluoromethanesulfonyl halides or trifluorothioacetates[3] and the decarboxylation of trifluoroacetic acid via its Barton ester have been described.[4] As part of our ongoing study of the radical and nonradical chemistry of xanthates and related dithiocarbonyl derivatives,[5] we have found that trifluoroacetonyl radicals can be generated and

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(2) (a) Hudlicky, M. *Chemistry of Organic Fluorine Compounds;* Ellis Horwood Ltd: Chichester, 1992. (b) Hudlicky, M.; Pavlath, A. E. *Chemistry of Organic Fluorine Compounds II*; ACS Symposium Series: American Chemical Society: Washington, DC, 1995. (c) Rozen, S.; Filler, R. *Tetrahedron* **1985**, *41*, 1111−1153. (d) Bégué, J. P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, *47*, 3207−3258. (e) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555−6666. (f) Lin, P.; Jiang, J. *Tetrahedron* **2000**, *56*, 3635−3671.

(3) (a) Huang, W.-Y.; Chen, J.-L.; Hu, L.-Q. *Bull Soc. Chim. Fr.* **1986**, 881−884. (b) Kamigata, N.; Fukushima, T.; Terakawa, Y.; Yoshida, M.; Sawada, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 627−633. (c) Lan-Hargest, H.-Y.; Elliott, J. D.; Eggleston, D. S.; Metcalf, B. W. *Tetrahedron Lett.* **1987**, *28*, 6557−6560. (d) Billard, T.; Roques, N.; Langlois, B. R. *Tetrahedron Lett.* **2000**, *41*, 3069−3072.

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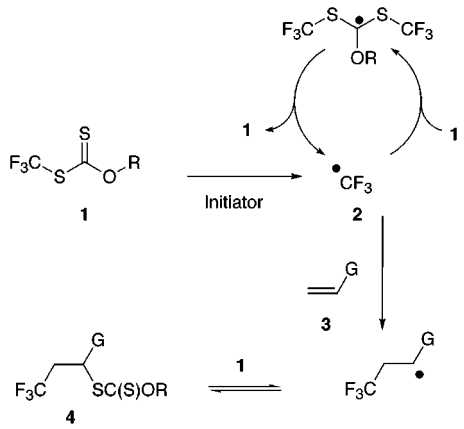
captured in a useful manner to give a variety of densely functionalized trifluoromethyl ketones.[6] In the present study, we describe the extension of this approach to the production of trifluoromethyl radicals.

The mechanistic picture underlying our work is outlined in Scheme 1. Rupture of the sulfide bond in xanthate **1** following the initiation step leads to the desired trifluoromethyl radical, which then adds to the olefinic trap **3**. The chain process is finally propagated by the reversible transfer of the xanthate group to give **4**. The reaction of the trifluoromethyl radical with its xanthate precursor **1**, although fast, is degenerate and does not therefore interfere with the desired pathway.

Scheme 1



Unlike most xanthates we have examined so far and which were simply prepared by substitution of a halide or sulfonate with a xanthate salt, the synthesis of an *S*-trifluoromethyl xanthate of structure **1** was far from trivial. Direct substitution of a trifluoromethyl halide is not only difficult but also defeats the purpose of this work since the industrial production of trifluoromethyl halides will cease in the future. After some experimentation, we found the decarbonylation of an *S*-trifluoroacetyl xanthate, as depicted in Scheme 2, to be the most convenient route. This ingenious process, applied to non-fluorinated carboxylic acids, was first reported by Barton and co-workers in 1962.[7] We later showed that the mechanism is in fact a radical chain rather than a radical recombination, as initially proposed.[8]

We elected to prepare the *O*-phenethyl xanthate **1a** rather than the simpler *O*-ethyl analogue **1** (R = Et) in order to avoid having to handle a potentially volatile and perhaps malodorous substance.[9] The intermediate acyl xanthate **6** was not isolated but simply heated in the presence of lauroyl peroxide to trigger the radical chain reaction leading to the desired xanthate **1a** via loss of carbon monoxide.[10] In this way, compound **1a** was isolated in a non-optimized yield of nearly 40%. It is important to use the xanthate salt **5** as the limiting reagent and to add it to the trifluoroacetic anhydride. The reason is that the desired *S*-acyl xanthate **6** can be completely decomposed by a small amount of the xanthate salt **5** through an *ionic chain reaction* leading ultimately to xanthic anhydride **7** and trifluorothioacetic anhydride **9**. Thus, as outlined in Scheme 2, nucleophilic addition of **5** to the *thiocarbonyl* group of **6** leads to anhydride **7** and sodium thiofluoroacetate **8** (addition of **5** to the *carbonyl* group of **6** results in a degenerate reaction). In a second step, addition of thiofluoroacetate **8** to the *carbonyl* group of **6** gives anhydride **9** and the initial xanthate salt **5** to propagate the chain (similarly, addition of **8** to the *thiocarbonyl* group of **6** also results in a degenerate reaction).

With a ready supply of xanthate **1a**, we examined its potential as a trifluoromethyl transfer agent. Indeed, a smooth reaction took place upon heating **1a** with various functionalized, unhindered terminal alkenes in refluxing 1,2-dichloroethane in the presence of lauroyl peroxide as initiator.[10] Our results are compiled in Table 1. A variety of useful functional groups are tolerated, and the unoptimized yields are quite acceptable, except for phenyl vinyl sulfone **3i** (for entries f and i, the yield in parentheses is based on unconsumed starting material). The cause of the low yield is not clear in this case but may be due to the reluctance of the electrophilic trifluoromethyl radical to react with an electrophilic olefin.

One important aspect of the xanthate transfer technology is the possibility of starting another radical sequence from the product, since it is itself a xanthate. This is illustrated by the transformation in Scheme 3. Addition of the elements of xanthate **1a** to protected *N*-allyl *p*-fluoroaniline **3j** gives adduct **4j** in 64% yield. Exposure of the latter to stoichio-

Scheme 2

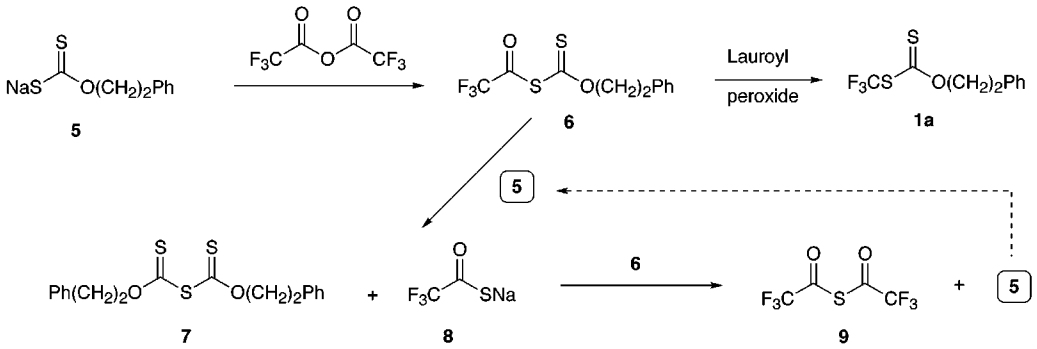
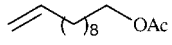
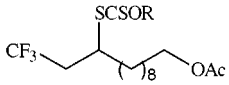
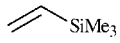
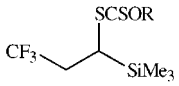
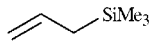
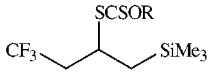
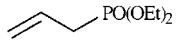
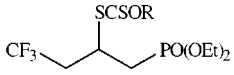
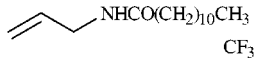
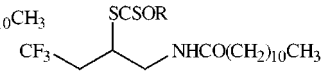
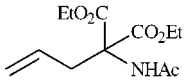
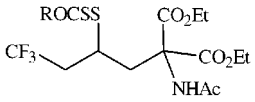
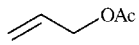
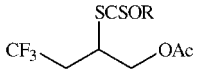
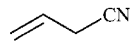
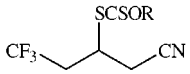
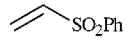
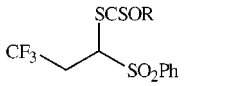


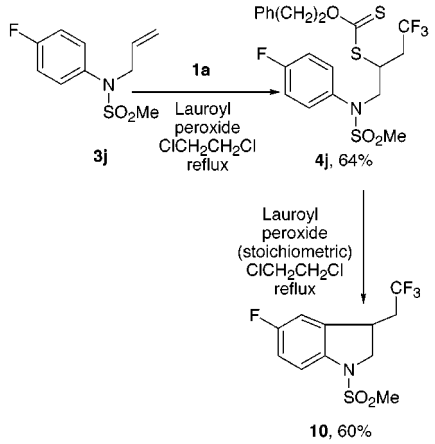
Table 1. Radical Reaction of Xanthate **1a** with Olefins **3a**−**3i** (R = CH_2CH_2Ph)

Olefin	Radical Adduct
 **3a**	 **4a** 84%
 **3b**	 **4b** 44%
 **3c**	 **4c** 61%
 **3d**	 **4d** 60%
 **3e**	 **4e** 67%
 **3f**	 **4f** 60% (80%)
 **3g**	 **4g** 55%
 **3h**	 **4h** 64%
 **3i**	 **4i** 12% (17%)

metric amounts of lauroyl peroxide leads ultimately to indoline **10** in 60% yield.[11]

In summary, the present approach to trifluoromethylated derivatives is efficient, flexible, and experimentally quite simple. The conditions are neutral and the method is compatible with a wide variety of functional groups of interest to medicinal chemists. Finally, no heavy metals are involved and the process is in principle applicable to the generation and capture of higher perfluoroalkyl radicals.

Scheme 3



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Supporting Information Available: Full analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Denieul, M.-P.; Quiclet-Sire, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1996**, 2511−2512

(7) Barton, D. H. R.; George, M. V.; Tomoeda, M. *J. Chem. Soc.* **1962**, 1967−1974.

(8) Delduc, P.; Tailhan, C.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1988**, 308−310.

(9) The synthesis of *O*-ethyl-*S*-trifluoromethyl xanthate using the photochemical decomposition of the corresponding *S*-trifluoroacetyl xanthate as well as one example of UV mediated addition to 1-decene have been claimed in a patent: Langlois, B.; Roques, N.; Wakselman, C.; Tordeux, M.; Forat, G. (Rhône-poulenc Agrochimie) WO 9626185.

(10) **Typical experimental procedure: (a) Synthesis of 1a.** To an ice-cooled solution of trifluoroacetic anhydride (13.3 mL; 90.1 mmol) in anhydrous acetonitrile (40 mL) was added dropwise a solution of sodium *O*-phenethyl xanthate (10 g; 45.0 mmol) in anhydrous acetonitrile under an inert atmosphere. Once the addition was complete, the mixture was heated to reflux for 15 min; then three portions of lauroyl peroxide (907 mg; 4.5 mmol) were added at intervals of 1.5 h. The solvent was then evaporated under reduced pressure and the residue taken up in dichloromethane. The organic layer was washed with saturated sodium bicarbonate, dried, and evaporated. Chromatography of the residue on silica (heptane) did not give a totally pure material, so further purification was accomplished by distillation in a Kugelruhr apparatus (80 °C/0.1 Torr) to give the desired xanthate in 38% yield as a pale yellow oil. (b) **General procedure for the radical additions to olefin:** A solution of the xanthate (1 mmol) and olefin (2−5 mmol) in 1,2-dichloroethane (ca. 1 mL) was heated to reflux for 15 min; then lauroyl peroxide (2.5 mol %) was added every 1.5 h until almost complete consumption of the xanthate. The solvent was then removed under reduced pressure and the residue purified by chromatography on silica.

(11) Ly, T.-M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533−2536.