Trifluoroacetonyl radicals: a versatile approach to trifluoromethyl ketones

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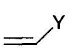
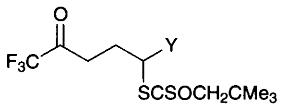
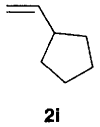
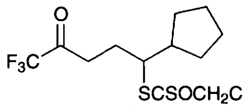
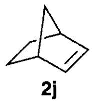
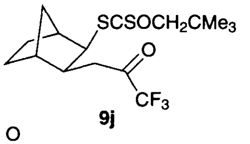
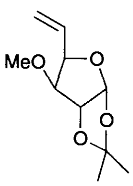
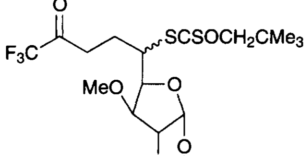
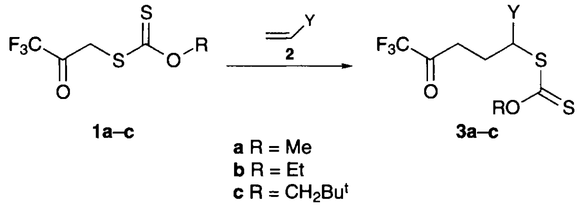
Radical addition of *S*-trifluoroacetonyl *O*-neopentyl dithiocarbonate 1c across an alkene occurs smoothly in the presence of a small amount of dilauroyl peroxide as initiator to give variously functionalised trifluoromethyl ketones in good yields.

The presence of fluorine atoms in organic molecules often causes a profound modification of their physical and chemical properties as well as of their biological activity profile.[1] Within this family, trifluoromethyl ketones are of special importance,[2] either as intermediates for the synthesis of other fluorinated derivatives or as targets, since many such compounds exhibit a marked inhibitory effect on hydrolytic enzymes such as esterases and proteases.[2,3] The trifluoromethyl ketone analogue of arachidonic acid for example was found to be a slow, tight-binding inhibitor of human cytosolic phospholipase A_2.[4] It is believed that the hydrated form of the trifluoromethyl ketone acts as a tetrahedral transition state mimic for the hydrolysis reaction.[2,3] We now report a mild, versatile approach to this class of compounds involving trifluoroacetonyl radicals which complements existing, mostly ionic, methods.[2]

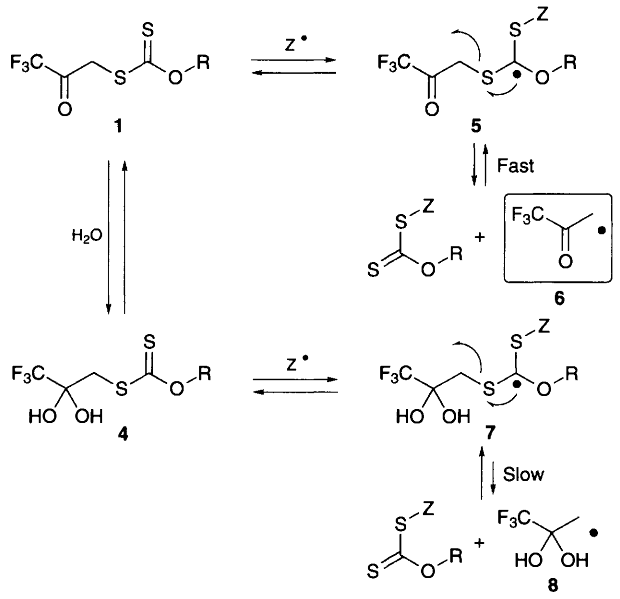
A trifluoromethyl group next to the carbonyl function increases dramatically its electrophilicity as well as the acidity of the remaining enolisable hydrogens.[5] But, even though the trifluoroacetonyl anion is easily made, it is rather unreactive and does not undergo readily many of the alkylation reactions typical of enolates.[2] Even aldol reactions are complicated by self-condensation.[6] In constrast, very little is known of the reactivity of trifluoroacetonyl radicals. Rare studies in the gas phase indicate them, not unexpectedly, to be considerably more electrophilic than the parent acetonyl radicals, the estimated difference in electron affinity between the two being a staggering 19 kcal mol^{-1} (1 cal = 4.184 J).[7] As for their chemistry in solution, no examples of a synthetic application have been recorded in the literature as far as we are aware, presumably because of a lack of a useful method for generating such radicals. The highly electrophilic carbonyl group hinders the application of stannane methodology to potential precursors like 1-bromo- or 1-iodo-3,3,3-trifluoroacetone.[8] In fact the latter, which could have perhaps been employed in an iodine

Table 1 Radical reaction of dithiocarbonate 1c with alkenes 2a–j

Alkene	Radical adduct	Yield (%)
 2	 9	
a	$Y = -CH_2OAc$	65
b	$Y = -CH_2SiMe_3$	78
c	$Y = -CH_2PO(OMe)_2$	58
d	$Y = -PO(OEt)_2$	42
e	$Y = -(CH_2)_8COOH$	84
f	$Y = -(CH_2)_8CH_2OAc$	95
g	$Y = CH_2NPhth$	85
h	$Y = CH_2C(CO_2Et)_2NHAc$	62
 2i	 9i	78
 2j	 9j	70
 2k	 9k 2:3 mixture of epimers	80



Scheme 1



Scheme 2 Z· is a radical from the initiator or from the last propagation step

transfer reaction,[9] has not yet been described and is probably too labile to handle, acting almost certainly as a source of positive iodine.

We have now found that the difficulties mentioned above can be circumvented by using *S*-trifluoroacetonyl dithiocarbonates (xanthates).[10] The radical addition summarized in Scheme 1 could thus be accomplished, providing an unusual route to a variety of functionalized trifluoromethyl ketones that are inaccessible by other means. The required dithiocarbonates **1** are easily prepared by treating commercially available 3-bromo-1,1,1-trifluoroacetone with the appropriate dithiocarbonate salt. We were however dismayed when preliminary experiments to test the radical addition gave erratic and mostly negative results. The cause of this difficulty was eventually traced to the propensity of the dithiocarbonate reagent to form a hydrate **4**, like trifluoromethyl ketones in general.[2] As depicted in Scheme 2, the corresponding hydrated intermediate **7**, as a consequence, fragments much less readily than **5** since the resulting radical **8** cannot be stabilised by resonance in the same way as in the trifluoroacetonyl radical **6**. Although water does not normally interfere with radical reactions, it had in this case an indirect deleterious effect. To circumvent this difficulty, we selected the neopentyl derivative **1c** instead of the simpler but more hydrophilic methyl or ethyl analogues **1a** or **1b**, although even **1c** still gives a nicely crystalline hydrate on standing in an open flask. Traces of humidity were further azeotropically removed by distillation of part of the solvent (usually cyclohexane) before addition of the initiator.

Once these precautions had been taken, reliable and generally useful yields (shown next to the structures) of adducts **9a–k** were obtained from a variety of alkenes (**2a–k**). The reactions were conducted by simply heating dithiocarbonate **1c** with excess alkene (2–8 equiv., depending on volatility) in cyclohexane (2 ml mmol^{-1} dithiocarbonate) in the presence of a small amount (*ca.* 5–10 mol%) of dilauroyl peroxide as initiator. The fact that the reactions can be carried out in such a concentrated medium may be contrasted with intermolecular radical additions involving tributylstannane where high dilution or syringe pump additions are usually necessary.[9] Unhindered terminal alkenes are the best substrates, even though certain disubstituted alkenes such as norbornylene (example **9j**) can also be used. In many cases simple distillation under vacuum of the solvent and excess alkene left behind essentially pure adduct in almost quantitative yield. Chromatographic purification was often complicated by the ready formation of the hydrate on silica causing in some instances a serious loss of material.

The method represents to the best of our knowledge the first synthetic utilisation of trifluoroacetonyl radicals and, in addition to its simplicity, does not involve the use of heavy metals and appears to be tolerant of many functional groups (**9h** and **9k** are especially revealing in this respect). Moreover, the dithiocarbonate function in the products provides a handle for further elaboration through the rich chemistry of sulfur, or eventually through the chemistry of the substituent already present in the alkene. The synthesis of a variety of trifluoromethylated sulfur or nitrogen containing heterocyclic systems can thus be easily conceived. The reaction with diethyl vinylphosphonate **2d** is noteworthy since the addition of the highly electrophilic trifluoroacetonyl radical to an electrophilic alkene is not normally a favourable combination. Yet, despite its high electrophilicity, the trifluoroacetonyl radical is still able to distinguish between two alkenes with different groups in the allylic position. Thus in a competition experiment involving 1 equiv. of dithiocarbonate **1c** and 2 equiv. each of allyl acetate **2a** and allyl trimethylsilane **2b**, a large selectivity for the latter was observed (greater than 6 : 1 by ^{13}C NMR, confirmed by GC–MS). It seems therefore that, in contrast to the anion whose nucleophilicity is subdued by the attracting trifluoromethyl group, the reactivity of the corresponding radical remains synthetically useful.

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