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# A Convergent Radical Based Route to Trifluoromethyl Ketones and to α,β-Unsaturated Trifluoromethyl Ketones

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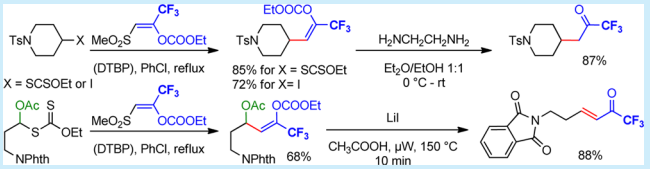
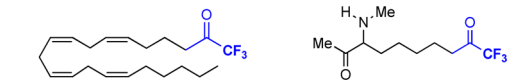
Supporting Information

**ABSTRACT:** A convergent synthesis of trifluoromethyl ketones and α,β-unsaturated trifluoromethyl ketones is described, starting with aliphatic iodides and dithiocarbonates (xanthates) and exploiting both the α- and β-fragmentations of a sulfonyl radical. The transformation initially furnishes the ketones in a masked enol carbonate form, from which they can be easily regenerated.




Incorporating fluorine atoms into small molecules can drastically change their physicochemical properties, metabolic stability, and binding affinities.[1,2] As a subclass, trifluoromethyl ketones[3] and α,β-unsaturated trifluoromethyl ketones[4] have proven particularly useful as enzyme inhibitors[5] and as probes in the study of hydrolytic enzymes.[6] The hydrate form of the ketone is stabilized by the strongly electron-withdrawing $CF_3$− group and acts as a mimic for the tetrahedral intermediates involved in the hydrolysis of esters and amides. For instance, trifluoromethyl ketone analog **1** of arachidonic acid (or **ATK** for **A**rachidonyl **T**rifluoromethyl **K**etone) is a powerful reversible inhibitor of certain human phospholipases,[7] and trifluoromethyl ketone **2** is a potent histone deacetylase inhibitor (Figure 1).[8] Trifluoromethyl ketones are also valuable precursors for the synthesis of $CF_3$-substituted heterocycles,[9] olefins,[10] medicinal substances,[11] or fluorinated analogs of natural products.[12]




Arachidonyl Trifluoromethyl Ketone (ATK) **1** **2**

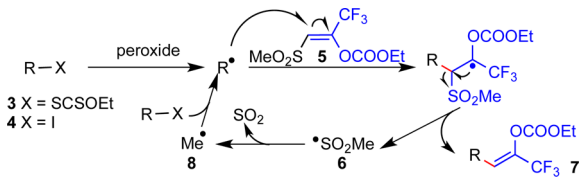
**Figure 1.** Biologically active trifluoromethyl ketones.

Traditionally, the preparation of trifluoromethyl ketones has relied on the Friedel−Crafts type addition of trifluoroacetic anhydride (TFAA) onto electron-rich alkenes and (hetero)-aromatic nuclei, the monoaddition of organometallic reagents to ethyl trifluoroacetate, or the oxidation of the corresponding trifluoromethyl alcohol.[13] The synthesis of aliphatic trifluoromethyl ketones remains however a challenge. Thus, although the synthesis of the trifluoromethyl carbinol precurors is well covered by the addition of $CF_3$TMS (the Ruppert−Prakash reagent) to aldehydes,[14] the oxidation step is slow and requires either an excess of oxidizing agent[15] or strong oxidants with limited functional group compatibility.[16] Qu and co-workers recently reported the synthesis of trifluoromethyl ketones by an alkylation−decarboxylation process, but their approach requires a strong base and presents limitations in the substrate scope.[17]

Some time ago, we devised a simple procedure for converting a primary or secondary aliphatic carboxylic into the corresponding trifluoromethyl ketone through reaction with TFAA and pyridine.[18] This method was used to prepare the two compounds in Figure 1. We also reported an approach hinging on the intermolecular addition of a trifluoroacetonyl radical to an alkene.[19] This latter route exploits the properties of the degenerative xanthate transfer, which has emerged as a powerful enabling tool for C−C bond formation.[20] We now describe yet another strategy allowing access to both trifluoromethyl ketones and α,β-unsaturated trifluoromethyl ketones.

We previously took advantage of both the α- and β-fragmentations of aliphatic sulfonyl radicals to design a tin-free allylation and vinylation of dithiocarbonates (xanthates) **3** and iodides **4**, an approach we have now been able to extend to the formation of enol carbonates of trifluoromethyl ketones (Scheme 1).[21] This convergent route to protected trifluoromethyl ketones builds on earlier observations by Fuchs[22] and on a successful preliminary example in our group.[23] Thus, addition of a radical generated from dithiocarbonate **3** or iodide **4** on vinyl alkyl sulfones **3** is followed by β-fragmentation to give the desired protected trifluoromethyl ketone **7** with concomitant expulsion of sulfonyl radical **6**. The latter evolves

**Scheme 1. Radical Addition to Enol Sulfone 5**

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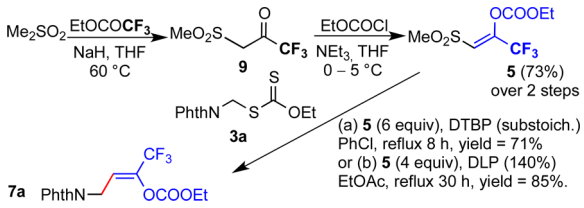
by $\alpha$-scission into one molecule of sulfur dioxide and a methyl radical **8**, which is able to propagate the radical chain (Scheme 1).

Access to vinyl sulfone **5** requires first the synthesis of trifluoromethyl ketone **9** by treatment of dimethylsulfone with ethyl trifluoroacetate under basic conditions (Scheme 2). After

**Scheme 2. Synthesis of Vinyl Sulfone 5**




screening different bases such as *n*-butyllithium or potassium *tert*-butoxide, NaH as a 60% dispersion in oil proved best for gram-scale synthesis. Intermediate **9** could not be purified on silica, as only the hydrate form was recovered after column chromatography. The ketone was therefore directly protected as its enol carbonate and purified by filtration over silica previously deactivated by acetone, followed by recrystallization from $Et_2O$/pentane at −20 °C. These conditions were optimized to afford 10 g of **5** in 73% overall yield. The purification by recrystallization is particularly valuable since the product seems to slowly decompose on silica.

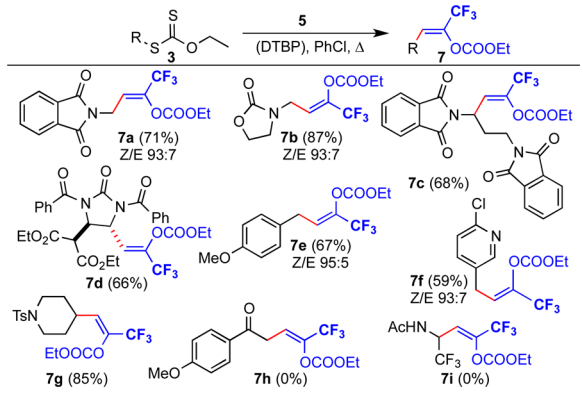
Interestingly, vinyl carbonate **5** was obtained as a single geometrical isomer. The coupling constant of 4 Hz between the $CF_3$ carbon and the vinylic hydrogen, measured in the undecoupled $^{13}C$ NMR, is characteristic of a *Z* configuration (the one drawn in Scheme 2).[24] If the reaction temperature is allowed to rise above 5 °C, the second geometrical isomer starts forming and can be detected in the crude reaction mixture.

In a preliminary example, the radical vinylation proceeded in good yield, both in refluxing chlorobenzene and ethyl acetate (Scheme 2). The reaction was much slower in the latter solvent and required stoichiometric amounts of a radical initiator. In refluxing ethyl acetate, the $\alpha$-scission of sulfonyl radical **6** leading to the unstabilized methyl radical is sluggish and the chain can thus no longer propagate normally. Also, the use of di-*tert*-butyl peroxide (DTBP) over dilauroyl peroxide (DLP) is more convenient since all its decomposition products are volatile.

Chlorobenzene was therefore used as the solvent, although the reaction could also be run at a lower temperature with more fragile substrates. Olefin **5** is somewhat volatile, and its continuous addition in excess was sometimes necessary for complete conversion. By circulating ice-cold water in the refluxing condenser, only 3 equiv of olefin **5** were needed and the excess reagent could be easily recovered.

As our olefin is electron-poor, we anticipated that electron-rich radicals would react better because of polarity matching. Indeed, xanthates leading radicals with nucleophilic character reacted efficiently (Scheme 3). Radicals substituted by an amide-type nitrogen atom are a moderately electron-rich species and provide access to latent amino trifluoromethyl ketones **7a**–**d**. The masked 1,3- and 1,2-diamines **7c** and **7d** are particularly interesting. In contrast, a trifluoromethyl group on the radical center negated the electron-donating effect of the nitrogen and blocked the desired transformation leading to compound **7i**. An electron-withdrawing ketone also had a

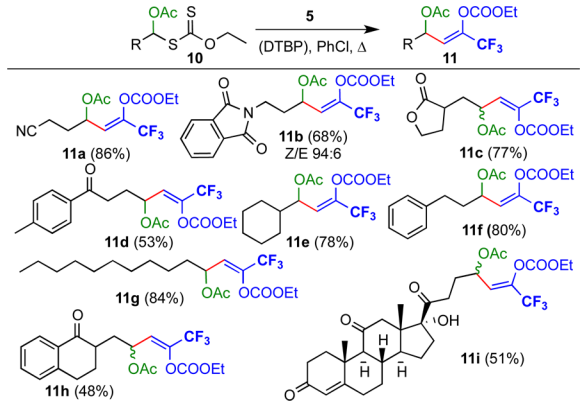
**Scheme 3. Synthesis of Enol Carbonates 7**




deleterious effect and prevented the formation of enol carbonate **7h**. Gratifyingly, xanthates leading to the rather unreactive benzylic radicals nevertheless reacted with reasonable efficiency, as illustrated by examples **7e** and **7f**. In all cases, the reactions gave rise to the enol carbonates as the *Z*-isomers with high or complete stereoselectivity, as determined by NMR spectroscopy.[24a,c]

The mildly nucleophilic $\alpha$-acetoxy substituted radicals also reacted well with the electrophilic vinylating reagent **5**. The requisite precursor xanthates **10** are readily obtained either directly, by reaction of $\alpha$-acetoxy chlorides [RCHCl(OAc)] by potassium *O*-ethyl xanthate, or indirectly (and more interestingly), by radical addition of a xanthate onto vinyl acetate.[25] The underlying idea was to introduce a leaving group in the $\beta$-position in order to later access $\alpha,\beta$-unsaturated trifluoromethyl ketones (see Scheme 7). The radical reaction was in most cases indeed faster and more efficient than with the first set of xanthates **3** (Scheme 4). Variously substituted enol carbonates

**Scheme 4. Synthesis of Enol Carbonates 11**




**11** were thus readily obtained, again as the *Z*-isomer, even with complex substrates such as corticosteroid **11i** (DLP/refluxing EtOAc was used in this case).

Iodides **4g** and **4j** reacted in comparably good yields under the same conditions (Scheme 5), but the reactions were slightly slower and less efficient than with dithiocarbonates **3** and, unexpectedly, the reaction mixtures turned dark in color. Nevertheless, iodides are interesting substrates since some iodides are more readily accessible than the corresponding xanthates. For example, precursor **4j** is trivially obtained by a classical iodolactonization from the unsaturated carboxylic acid.



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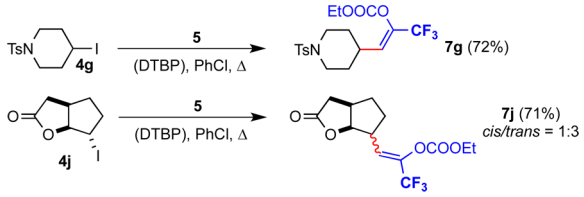
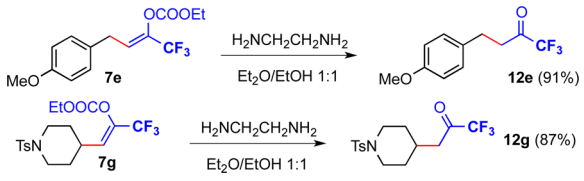
**Scheme 5. Enol Carbonates 7 from Iodides**



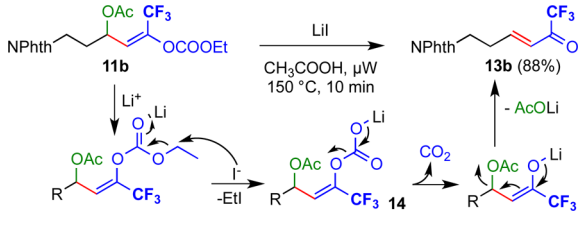

With a convenient access to enol carbonates **7**, our next task was the regeneration of the free trifluoromethyl ketone under conditions that do not require extensive purification on silica so as to minimize losses though formation of the hydrate. We first examined methods previously applied to ordinary enol carbonates.[26] However, enol carbonates **7** proved unusually resistant to acidic treatment owing to the presence of the strongly electron-withdrawing trifluoromethyl group. They were thus not affected by neat formic or trifluoroacetic acid, or even by aqueous sulfuric acid. Such harsh acidic conditions would normally destroy ordinary enol carbonates almost instantly. In contrast, exposure to ethylenediamine at rt cleaved the enol carbonate and furnished the desired trifluoromethyl ketones **12** cleanly and without chromatographic purification (Scheme 6).

**Scheme 6. Deprotection of Enol Carbonates 7**




Enol carbonates **11** containing an allylic acetoxy group were less robust and degraded under strong acidic conditions. Furthermore, deprotection of these adducts leads to reactive α,β-unsaturated trifluoromethyl ketones (see Scheme 7) that

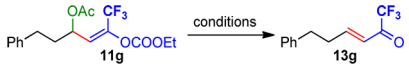
**Scheme 7. Synthesis of α,β-Unsaturated Ketones 11**




are incompatible with the presence of ethylenediamine. We therefore had to devise an alternative to the aminolysis better suited for this particular class. We first attempted a Krapcho-type dealkylcarboxylation by heating compound **11g** in DMSO in the presence of NaCl.[27] Unfortunately, to start detecting product **13g** we had to raise the temperature to above 130 °C for over 4 h, which caused extensive decomposition.

This setback led us to examine conditions we previously used in the synthesis of thiophenes.[28] Unfortunately, heating compound **11g** for 1 h at 110 °C with potassium iodide in acetic acid under microwave irradiation did not induce any transformation and only the starting material was recovered (Table 1, entry a). By increasing the temperature to 150 °C, the desired product was obtained, albeit quite slowly and in modest

**Table 1. Optimization of the Formation of α,β-Unsaturated Trifluoromethyl Ketones**




| entry | conditions | time | yield |
|---|---|---|---|
| a | KI, AcOH, 0.2 M, 110 °C | 1 h | –[a] |
| b | KI, AcOH, 0.2 M, 150 °C | 1 h | 23%[b] |
| c | LiI, AcOH, 0.2 M, 150 °C | 10 min | –[c] |
| d | LiI, $HCO_2H$, 0.25 M, 150 °C | 10 min | 35%[c] |
| e | LiI, TFA, 0.2 M, 110 °C | 5 min | –[a] |
| f | LiI, TFA, 0.2 M, 150 °C | 10 min | –[b] |
| g | LiI, AcOH, 0.5 M, 150 °C | 10 min | 94% |

[a]Starting material only. [b]Degradation. [c]Presence of the product and of a side product.

yield (Table 1, entry b). In the hope of accelerating the reaction by taking advantage of the greater oxophilicity of lithium cations, we replaced potassium iodide with lithium iodide. The desired enone **13g** was indeed formed, accompanied by another more polar side product (Table 1, entry c). Other acid solvents, such as TFA or formic acid, were also tried in parallel with no improvement (Table 1, entries d–f). Surmising that the side product was arising from the addition of adventitious water to the reactive enone, we concentrated the reaction medium and indeed found that enone **13g** was produced cleanly in high yield and without chromatographic purification (Table 1, entry g).

These conditions were applied successfully to enol carbonate **11b**, which afforded enone **13b** in equally high yield (Scheme 7). Complexation by the lithium cation polarizes the carbonyl group and encourages attack of the ethyl group by an iodide anion to generate volatile ethyl iodide and the lithium enol carbonate **14**. Loss of carbon dioxide and lithium acetate finally furnishes the desired enone (Scheme 7).

In summary, we have established a modular route to trifluoromethyl enol carbonates starting with either xanthates or iodides with high functional group tolerance. Depending on the substrates, the products can then be converted into aliphatic trifluoromethyl ketones or α,β-unsaturated trifluoromethyl ketones. In the case of xanthates, the ability to perform first an intermolecular addition to an alkene allows access to complex structures quite tedious to attain otherwise. The present synthesis complements useful previous approaches, especially in the case of α,β-unsaturated trifluoromethyl ketones where the number of synthetic routes is more limited.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, full spectroscopic data, and copies of $^1H$ and $^{13}C$ NMR for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01344.

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### Notes

The authors declare no competing financial interest.



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## ■ DEDICATION

This paper is dedicated with respect to the memory of Professor Marcel Fétizon (Ecole Polytechnique).

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