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A Practical Source of Chlorodifluoromethyl Radicals. Convergent Routes to *gem*-Difluoroalkenes and -dienes and (2,2-Difluoroethyl)-indoles, -azaindoles, and -naphthols

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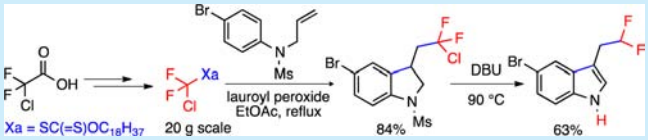
Supporting Information

ABSTRACT: The preparation of *O*-octadecyl-*S*-chlorodifluoromethyl xanthate from chlorodifluoroacetic acid and its use as a convenient source of chlordifluoromethyl radicals is described. This reagent may be used to access *gem*-difluoroalkenes and -dienes, as well as (2,2-difluoroethyl)-indolines, -indoles, and -naphthols.



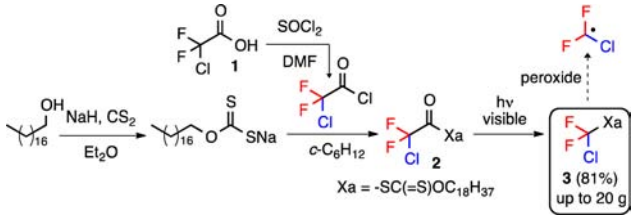
The incorporation of fluorine atoms into organic scaffolds has been the subject of intense investigations over the past decades.[1] The ability of fluorine to deeply modify the chemical and physicochemical properties of organic molecules has proven to be of much importance to the pharmaceutical, agrochemical, and materials industries. In medicinal chemistry, the use of fluorinated bioisosteres to impact electronic and conformational properties or to modify lipophilicity and metabolic stability has become a widespread tactic in the "hit to lead" approach.[2] Of the numerous reactions used in the synthesis of organofluorine derivatives, radicals offer unique possibilities. Indeed, radical-based methods have enjoyed increased importance in recent years.[3]

The reversible addition-transfer process based on xanthates and related thiocarbonyl derivatives[4] has been exploited to introduce various fluorinated motifs into highly functionalized molecules.[5] However, with respect to the chlorodifluoromethyl radicals, the only precursor so far described is bromochlorodifluoromethane, and its use remains very limited.[6] We therefore envisioned preparing xanthate **3** as a convenient source of these radicals, allowing perhaps a facile incorporation of the chlorodifluoromethyl motif into complex substrates.

By analogy with our earlier work,[7] we considered using commercially available and cheap acid **1** as a precursor for xanthate **3**, since a more classical approach involving direct substitution does not proceed well in the fluorinated series. Thus, treatment of chlorodifluoroacetic acid with thionyl chloride produced chlorodifluoroacetic chloride as a gas, which was condensed into a stirred solution of sodium *O*-octadecyl xanthate in cyclohexane, resulting in the formation of the corresponding *S*-acyl xanthate **2**. For practical reasons related to the extreme sensitivity to hydrolysis of *S*-acyl xanthates and possible volatility of the product, the commonly used potassium *O*-ethyl xanthate salt was replaced by the more hydrophobic and bulkier sodium *O*-octadecyl xanthate.

Without isolation, *S*-acyl xanthate **2** was directly irradiated with a 250 W tungsten halogen lamp, which induced a radical chain decarbonylation[8] and furnished the desired chlorodifluoromethyl xanthate **3** in 81% yield (Scheme 1). This expedient preparation of xanthate **3** was reproducibly performed on up to 20 g scale. With the desired reagent in hand, we first explored the simple radical addition to various alkenes. The results are displayed in Scheme 2. To simplify characterization, the xanthate group in the adducts **4a**−**i** was reductively removed using $(Me_3Si)_3SiH$ to give products **5a**−**i** (Scheme 2).[9] Olefins derived from pyrazole, D-glucose, several substituted aromatic rings, and natural products such as sclareol and an androstanol derivative were successfully transformed. Functions such as carbamates, acetals, or free alcohols were well tolerated under these mild conditions, and the overall yield for the two steps was generally good (up to 90% over two steps; see Scheme 2). Moreover, the reduction proved totally selective for the xanthate group, and absolutely no reduction of the chlorine atom was observed. Reductive dechlorination of 1-chloro-1,1-difluoro derivatives has been reported to proceed readily with Bu_3SnH.[10]

Scheme 1. Synthesis of *O*-Octadecyl-*S*-chlorodifluoromethyl Xanthate



In comparison with bromochlorodifluoromethane, xanthate **3** appears to be a superior precursor of chlorodifluoromethane radicals, as far as yields and functional group tolerance are concerned.[6] In cases where the xanthate must be used in slight excess (typically 1.5 equiv), the unreacted reagent is easily

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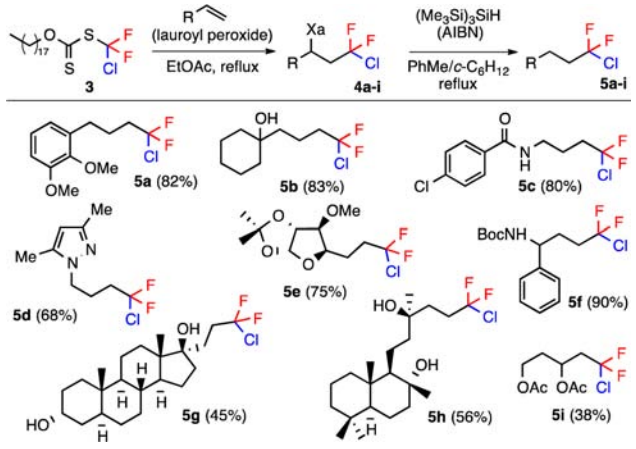
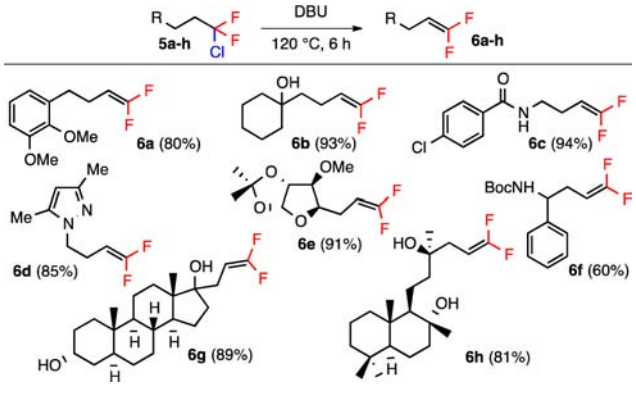
Scheme 2. Formation of 1-Chloro-1,1-difluoro-Substituted Derivatives



recovered at the end of the reaction. Product **5i** is the result of a double radical addition to vinyl acetate, accomplished by having 2 equiv of vinyl acetate present in the medium. Terminal, unhindered monosubstituted alkenes are the best substrates, but previous work on xanthates has shown that 1,1-disubstituted alkenes and strained olefins, such norbornenes and cyclobutenes, are also suitable.[4]

A known synthetic modification of the -ClF_2 motif is dehydrochlorination by treatment with an organic[11] or inorganic[12] base, leading to a terminal *gem*-difluoroalkene. In the present case, heating products **5a–h** with large excess of DBU at 120 °C provided the desired difluoro-olefins **6a–h** in very good yield (Scheme 3).

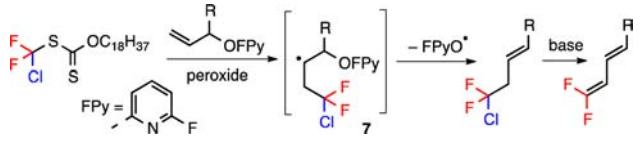
Scheme 3. Synthesis of *gem*-Difluorovinyl Compounds



The difluorovinyl group is useful as an isostere of a carbonyl,[1,2] and while some of the compounds described above could have been made using more traditional sources of chlorodifluoromethyl radicals, those obtained in the following section are much less accessible by previous routes. Difluorodienes, for example, are relatively rare, and the few approaches reported in the literature rely on either a Wittig reaction on enones or on organometallic coupling of halogen-substituted *gem*-difluoro-olefins.[13] By using 2-fluoropyridyl derivatives[14] of allylic alcohols as radical allylating agents, access to functionalized difluorodienes becomes particularly easy.

We had shown recently that homolysis of the otherwise strong C–O bond in alcohols becomes possible by converting the alcohol into its 2-fluoropyridyl derivative (Scheme 4). Even though the homolysis is relatively slow, the degenerate nature

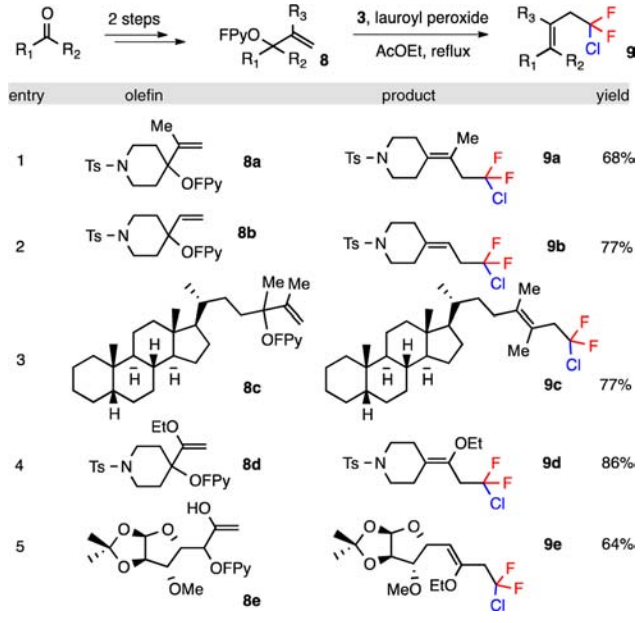
Scheme 4. Synthesis of 1,1-Difluorodienes



of the xanthate exchange provides the intermediate carbon radical **7** with sufficient lifetime to overcome this kinetic barrier.

Furthermore, the base-induced elimination of HCl from allylated derivatives **9a–e** should be significantly easier because of the increased acidity of the allylic proton and the formation of a conjugated difluorodiene. Since the starting allylic alcohol is often prepared from a ketone or an aldehyde by addition of a vinyl metal reagent, the process would correspond to an overall difluoro-olefination of a carbonyl substrate. In the event, exposure of fluoropyridine derivative **8a** to xanthate **3** in the presence of a stoichiometric amount of lauroyl peroxide (DLP) gave the desired adduct **9a** in a good 68% yield (Scheme 5 entry 1).

Scheme 5. Radical Addition–Fragmentation on Activated Allylic Alcohols



Other examples are collected in Scheme 5. A particularly important feature is the possibility of generating difluoroenol ethers such as **9d** and **9e** by this approach (Scheme 5, entries 4 and 5). Such chlorodifluoroenol ethers are extremely scarce in the literature, and their chemistry has remained largely unexplored. We found, for example, that they were completely resistant to acid hydrolysis under conditions where the starting enol ether is totally cleaved. This is obviously a manifestation of the electron-withdrawing effect of the chlorodifluoro motif.

The dehydrochlorination indeed occurred more easily, as was expected. The reaction took place at 50 °C using an excess of DBU as the base and was complete within 2 h. The *gem*-difluorodienes **10a–d** were obtained in generally good yields (Scheme 6). Unfortunately, in the case of **9e** the reaction gave a

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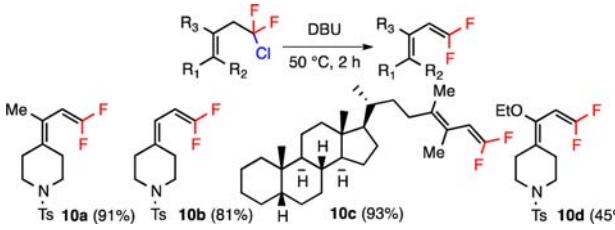
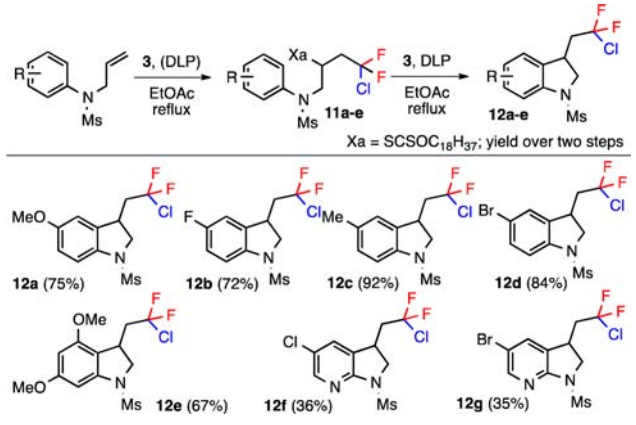
Scheme 6. Synthesis of 1,1-Difluorodienes and 1,1-Difluorodienol Ethers



complex mixture, even at room temperature. The glucose-derived structure does not tolerate neat DBU and decomposes rapidly, possibly through base-induced β-elimination of alkoxides and ultimate opening of the tetrahydrofuran ring. Traces of the desired product were nevertheless observed and isolated, proving that the elimination occurred anyway. Attempts with milder conditions, such as replacing DBU with TEA or pyridine at different temperatures, were unsuccessful, and no clean elimination could be accomplished.

Another unique feature of the present approach is the ability of using the xanthate group in the adduct to accomplish a ring closure on a nearby aromatic ring, thus opening access to valuable fluorinated polycyclic aromatic and heteroaromatic derivatives of importance to the pharmaceutical and agrochemical industries.[4] The reaction of xanthate **3** with *N*-allyl-*N*-mesyl anilines initiated by a small amount of DLP gave the corresponding adducts **11a–e**, which when exposed to stoichiometric amounts of peroxide proceeded to the corresponding indolines **12a–e** in good to excellent yield, with the exception of the pyridine derivatives **11f,g** where the cyclization step proved disappointingly poor for reasons that are not yet clear (Scheme 7).

Scheme 7. Synthesis of Indolines with Fluorinated Side Chains

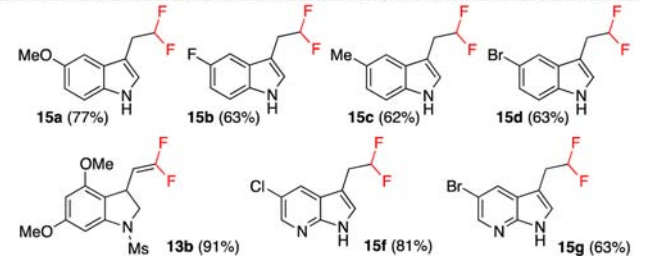


Other heteroaromatic rings could in principle act as viable substrates. We have previously shown, for example, that addition–cyclization sequences involving xanthates can be performed efficiently on pyrimidines.[4e] Furthermore, the use of a mesyl instead of an acyl group in the present case was motivated by the desire to avoid unnecessary complications due to amide rotamers.

We were surprised to find that the reaction of indoline **12a** with excess DBU occurred already at 40 °C instead of the usual 120 °C required in the purely aliphatic series. Furthermore, in addition to the expected difluoroalkene **13a**, another product appeared, which turned out to be indole **14a**. This compound became almost the exclusive product when the temperature was raised to 55 °C and the reaction time was extended to 14 h (Scheme 8).

Scheme 8. From Indolines to Indoles, an Unexpected Double Bond Migration

entry	t °C	time (h)	13a (%)	14a (%)	15a (%)	12a (%)
1	35	8	92 (80)	8	-	-
2	40	2.5	90	10	-	-
3	40	1	50	-	-	50
4	45	14	30	70	-	-
5	55	14	-	100	-	-
6	70	5	18	72 (29)	10	-
7	90	1	15	70	15	-
8	90	2.5	-	80	20	-
9	90	14	-	-	100 (77)	-



An unexpectedly facile double bond migration of the olefinic bond appears to be taking place to give ultimately the thermodynamically more stable indole structure. A further increase in the temperature to 90 °C for 14 h resulted in the formation of another new compound, which proved to be the demesylated indole **15a**, isolated in a good 77% yield. By an appropriate choice of conditions, it is therefore possible to access either **13a**, **14a**, or **15a** as summarized in Scheme 8 (the yields in parentheses are for isolated products; the others were determined by NMR spectroscopy).

The other indolines behaved in the same manner (Scheme 8), except for compound **12e**, where no migration was observed, and **13b** could be isolated as the only elimination product. The presence of the two electron-donating groups presumably deactivates the difluorovinyl indoline toward base-induced migration of the alkene. In contradistinction, the formation of azaindoles **15f,g** occurred particularly readily, within 2 h, because of the electron-withdrawing nature of the pyridine ring.

Access to such difluoroethyl indolines is not generally easy but sometimes highly desirable. Thus, in the case of BACE1 inhibitor **16** (Figure 1), the presence of a difluoroethyl side chain on the indole portion has a dramatic effect on the potency, since a 4-fold increase in activity was observed in comparison with the nonfluorinated analogue.[15]

This strategy appears to be applicable to the synthesis of 4-(2,2-difluoroehtyl)-1-naphthols. Indeed, the addition of reagent **3** to 1-(4-methoxyphenyl)-4-buten-1-one followed by peroxide-mediated ring closure onto the aromatic ring furnished difluoroethyltetralone **17** in 50% yield (Scheme 9). Exposure

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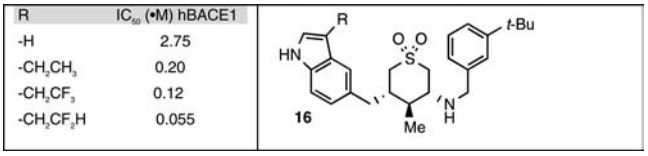
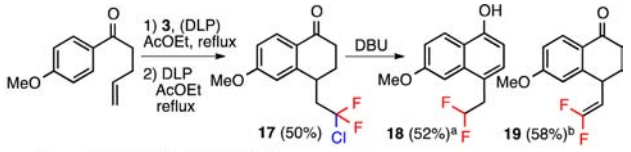


Figure 1. Example of a 3-(2,2-difluoroethyl)indole derivative possessing biological activity.

Scheme 9. Synthesis of 4-(2,2-Difluoroethyl)naphthol



to DBU at 90 °C gave directly naphthol **18** in 52% yield, while under milder conditions the intermediate difluorovinyltetralone **19** could be isolated in 58% yield. The synthesis of naphthalenes with a specific substitution pattern is seldom trivial, and the present route nicely complements existing procedures.[16]

In conclusion, we have developed an efficient, flexible synthesis of a new, convenient precursor of chlorodifluoromethyl radicals. It allows the synthesis of *gem*-difluoroalkenes and -dienes with a high tolerance for functional groups. Moreover, an unusually facile double bond migration provides a route to an interesting class of difluoro-substituted indoles, azaindoles, and naphthols.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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