Deoxygenative trifluoromethylthiolation of carboxylic acids†

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Here we describe a deoxygenative trifluoromethylthiolation method that yields trifluoromethyl thioesters from readily available carboxylic acids. The method is built upon an “umpolung” strategy where triphenylphosphine is used to first activate an electrophilic trifluoromethylthiolating reagent and then serves as an oxygen acceptor for the deoxygenation. The method is mild, efficient, broad-scope, and tolerant. It can be applied for the late-stage functionalization of numerous natural products and drug molecules containing a carboxylic acid group. The trifluoromethyl thioesters can be converted into trifluoromethyl thioethers by Pd-catalyzed decarbonylation.

Organofluorine compounds have widespread applications in medicinal and materials sciences.1–4 Among fluorine-containing moieties, the trifluoromethylthio group (–SCF₃) is of considerable interest because of its high lipophilic and electron-withdrawing nature. Significant progress has been made in direct trifluoromethylthiolation of C–H and C–X moieties.4–19 However, there are still few efficient methods for the synthesis of trifluoromethyl thioesters. Trifluoromethyl thioesters could be prepared by reactions of acid chlorides with Hg(SCF₃)₂, NMe₄SCF₃ or (bpy)CuSCF₃ (Fig. 1A).17,20,21 These reactions were limited by the use of reactive or toxic reagents, or the generation of a stoichiometric amount of metallic byproducts. The groups of Glorius*18 and Shen19 reported elegant methods of accessing trifluoromethyl thioesters from aldehydes via a hydrogen atom transfer (HAT) process (Fig. 1A). Nevertheless, among organic carbonyl compounds aldehydes are relatively instable and less available. Carboxylic acids, on the other hand, are abundant, stable, and non-toxic. The deoxygenative trifluoromethylthiolation of carboxylic acids would represent an efficient and highly desirable approach to the synthesis of trifluoromethyl thioesters.

Despite its conceptual simplicity, the deoxygenative trifluoromethylthiolation of carboxylic acids is challenging to achieve. It was reported that in the presence of a carboxylic acid, a CF₃S⁻ anion would lose an F⁻ to form carbonothioic difluoride, which further reacted with carboxylic acids to give eventually an acyl fluoride.16,22 Inspired by the rich chemistry of phosphorus reagents and (acyl)oxyphosphonium ions I (Fig. 1B) in peptide couplings,23 Mitsunobu,24,25 and Appel26 reactions, we...
hypothesized that such intermediates could be possibly transformed into trifluoromethyl thioesters from carboxylic acids under suitable conditions. Here we describe an “umpolung” strategy that allows the use of electrophilic trifluoromethylthiolating reagents and avoids the decomposition of CF₃S⁻/CO₂⁻ anion by carboxylic acids (Fig. 1C). The “umpolung” is achieved with triphenylphosphine (PPh₃), which first captures a CF₃⁺ cation to form a SCF₃-phosphonium salt (II), followed by a metathesis reaction with a carboxylate to give an oxyphosphonium intermediate (III), which is prone to deoxygenative trifluoromethylthiolation to give a trifluoromethyl thioester while eliminating triphenylphosphine oxide (PPh₃O) (Fig. 1C). This strategy is applicable for the rapid synthesis of a diverse set of trifluoromethyl thioesters from readily available aromatic and aliphatic carboxylic acids, including many natural products and drugs.

We began our investigation by optimizing the reaction of 4-phenylbenzoic acid (1a) with N-(trifluoromethylthio)phthalimide (2a) to give the corresponding trifluoromethyl thioester (3a). To our delight, the reaction proceeded in the presence of 1.1 equiv. of P₃H in tetrahydrofuran (THF, 0.2 M) with a yield
of 40% (Table 1, entry 1). The reaction was then optimized by varying reaction parameters (Table ESI, S1–S5†). A summary of key observations is shown in Table 1. THF was the best solvent (Table S2†). A small amount of Lewis acid could enhance the reactivity of 2a (Table 1, entries 2–6; Table S3†). The binding of a Lewis acid by the phthalimide group might polarize N-(trifluoromethylthio)phthalimide, facilitating the nucleophilic attack of PPh3 to N-(trifluoromethylthio)phthalimide and subsequent generation of the key intermediate SCF3-phosphonium salt (Fig. 1C, II). Anhydrous FeCl3 (5 mol%) was the best Lewis acid, giving a yield of 95% (Table 1, entry 2). Among various trifluoromethylthiolating agents,27 2a proved to be superior than other electrophilic trifluoromethylthiolating reagent 2b–2d (Table 1, entries 7–9). When the nucleophilic NMe3SCF3 (2e) was used, no product was formed (Table 1, entry 10). Addition of an external base slightly lowered the yields (Table 1, entries 11 and 12; Table S4†). Further optimization indicated Ph3P was the best mediator (Table 1, entries 2 and 13; Table S5†). It was worthy to note that the reaction completed within 30 minutes at room temperature.

With the optimized conditions in hand (entry 2, Table 1), we probed the generality of this transformation (Table 2). A myriad of aryl carboxylic acids containing electron-donating (3b–3f) and electron-withdrawing (3g–3o) substituents were coupled to give the corresponding trifluoromethyl thioesters in moderate to excellent yields. Notable, aryl halides (3g–3m), including relatively reactive aryl iodides (3j, 3m), were tolerated in the reaction. Functional groups such as trifluoromethyl (3n), ester (3o), (tert-butoxycarbonyl)amino (3p), thiomethyl (3q), boronic ester (3r), alkene (3t), 1,3-benzodioxole (3u) and naphthalene (3v) were all compatible. The reactions also proceeded smoothly with various heteroaryl carboxylic acids, giving the desired products (3w–3x) in satisfying yields. Importantly, the reactions worked with aliphatic carboxylic acids as well. Primary, secondary, tertiary carboxylic acids were all suitable substrates, affording the corresponding trifluoromethyl thioesters (4a–4e) in good yields. The trifluoromethylthiolation was also successful for various cinnamic acids containing electron-neutral (5a), electron-withdrawing (5b–5e, 5h), and electron-donating (5f–

| Table 3 Late-stage trifluoromethylthiolation of natural products and drugs containing a carboxylic group a |

| ![Chemical Structures](https://example.com/chemical_images) |

6a (91%) from adapalene  
6b (46%) from probenecid  
6c (88%) from lanosterol  
6d (86%) from L-menthol derivative  
6e (71%) from piperic acid  
6f (89%) from caffeic acid isomer  
6g (66%) from zaltoprofen  
6h (66%) from ibuprofen  
6i (82%) from ketoprofen  
6j (75%) from naproxen  
6k (59%) from gemfibrozil  
6l (42%) from abietic acid

a Carboxylic acid (1.0 equiv.), triphenylphosphine (Ph3P, 1.1 equiv.), N-(trifluoromethylthio)phthalimide (1.3 equiv.), FeCl3 (5 mol%) in THF (0.2 M), room temperature, 30 min, isolated yield.
Fig. 3 A tentative reaction pathway.

Thus, our method enables the synthesis of trifluoromethyl thioethers from readily available carboxylic acids.

Based on results from the control experiments (Table 1 and S1–S5†), 31P NMR study (Fig. S51†), and previous reports, we propose a tentative mechanism for the deoxygenative trifluoromethylthiolation (Fig. 3). N-(Trifluoromethylthio)phthalimide (2a) coordinates to FeCl₃ via the phthalimide group. This coordination increases the electrophilicity of the SCF₃ group, promoting the nucleophilic attack of PPh₃. The latter generates a trifluoromethylthiophosphonium ion II, which reacts with a carboxylic acid to generate an acyloxyphosphonium CF₃S⁺ intermediate III. Intramolecular attack of the CF₃S⁺ anion on the acyl carbon of III then gives the thioester product as well as the Ph₃PO byproduct.

Conclusions

In summary, by using PPh₃ as a mediator to “umpolung” the electrophilic trifluoromethylthiolating agent 2a, we have achieved, for the first time, deoxygenative trifluoromethylthiolation of carboxylic acids. The reactions are rapid and occur at room temperature. They allow the access of a wide range of trifluoromethyl thioethers from readily available carboxylic acids. The method can be applied for the late-stage functionalization of many natural products and drug molecules. The trifluoromethyl thioethers can be converted into trifluoromethyl thiocarbonyl compounds in one step by Pd-catalyzed decarbonylation.

Conflicts of interest

The authors declare no conflict of interest.

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Lewis acids could enhance the yields of the reactions but they were not indispensable (Table 1, entries 1–6, Table S3†). However, PR₃ and electrophilic SCF₃ reagent were absolutely needed (Tables S1 and S5†).