

C–H Functionalization

Simple Sulfinate Synthesis Enables C–H Trifluoromethylcyclopropanation**

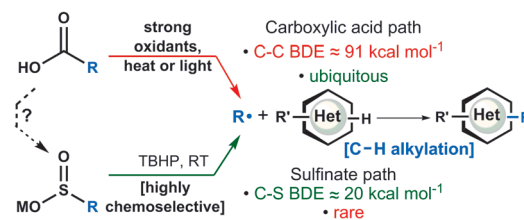
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In memory of Carlos F. Barbas, III

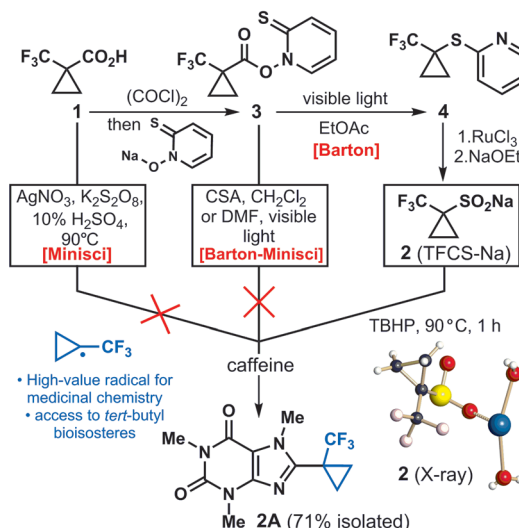
Abstract: A simple method to convert readily available carboxylic acids into sulfinate salts by employing an interrupted Barton decarboxylation reaction is reported. A medicinally oriented panel of ten new sulfinate reagents was created using this method, including a key trifluoromethylcyclopropanation reagent, TFCS-Na. The reactivity of six of these salts towards C–H functionalization was field-tested using several different classes of heterocycles.

The decoration of C–H bonds on heteroarenes by using radicals generated from sulfinate salts has emerged as a predictable and chemoselective method for both the early and late stages of a synthesis,^[1] for the prediction and prevention of drug metabolism,^[2] and for the native chemical tagging of complex molecules.^[3] In a recent report, a sulfinate salt was used to append a trifluoromethyl group onto (–)-agelastatin A, which led to the synthesis of the most potent derivative of this natural product.^[4] The surging commercial demand for sulfinate reagents pointed to a clear drawback in that only a limited set are currently available. In contrast to their more widely available relatives, carboxylic acids, sulfonates have a significantly weaker energy barrier for homolysis leading to alkyl radicals (as judged by bond dissociation energies (BDEs), Scheme 1 A). The relatively weak C–S bond in sulfonates makes them ideal radical precursors as compared to carboxylic acids, which often require strong oxidants, heat, light, specialized transition-metal catalysts, or further functionalization.^[5] Herein, we report a simple procedure for the conversion of a variety of carboxylic acids into

A. Challenge: Conversion of acids into sulfonates



B. Case study: The trifluoromethylcyclopropyl radical



Scheme 1. A) Logic behind the conversion of carboxylic acids into sulfonates; ubiquitous but less reactive carboxylic acids could be used as precursors to rare but useful sulfonates. B) The “interrupted” Barton reaction allows for the development of a high-value reagent for the introduction of isosteric units for medicinal chemistry. CSA = camphor-sulfonic acid.

sulfonate salts, thus enabling the direct synthesis of a variety of important bioisosteres and setting the stage for significant expansion of the commercially available sulfonate toolkit.

The invention of a route to sulfonate salts from carboxylic acids was actually prompted by a recent report from a research group at Novartis, where the trifluoromethylcyclopropyl group was found to function as a metabolically stable replacement for a *tert*-butyl moiety.^[6] The introduction of this group was problematic, and the reported method requires a multistep synthesis (using diazomethane), thus making it an excellent candidate for a C–H functionalization strategy using sulfonates. The commercial availability of acid 1 conveniently allowed us to determine if it was even necessary to invent such a reagent bearing this motif (2). As shown in

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Scheme 1B, classic Minisci conditions were screened using a variety of acids and temperatures with caffeine as the test substrate, and no product (**2A**) was detected by LC/MS. These findings are consistent with our previous studies, where Minisci conditions generally fail when using fluorinated acids.^[1] We then turned to Barton's classic work on visible light mediated photolytic radical formation from *O*-esters of thiohydroxamic acids.^[7] Acid **1** was converted into ester **3**, which was subjected to Barton's conditions for the generation of alkyl radicals and a Minisci-type addition in the presence of a Brønsted acid.^[8] Although we were able to reproduce the reported addition of an adamantyl radical to caffeine, the identical conditions using **3** as the radical donor in either DMF or CH₂Cl₂ led to less than 1 % conversion by LC/MS. Further analysis by LC-MS showed that the attempted homolysis of **3** led to small quantities of thiopyridyl substrate **4**, an intermediate that represented a possible pathway to sulfinate **2**. After extensive solvent screening, ethyl acetate was found to be the optimal medium to obtain synthetically useful yields of **4**. This empirical finding is useful given the reported inefficiency of the "interrupted" Barton decarboxylation on small-sized ring systems.^[7o-q] Subsequent oxidation using RuCl₃ was facile and cleavage of pyridine with NaOEt led to the coveted trifluoromethylcyclopropyl sulfinate salt in 75 % yield (TFCS-Na, **2**, structure verified by X-ray crystallography, CCDC 1010780). To our delight, when caffeine was exposed to sulfinate salt **2** (3.0 equiv) and TBHP (5.0 equiv)

at 60 °C, significant amounts of **2A** were observed by LC/MS. After screening various solvents and temperatures, a mixture of diethyl carbonate and water (3:2) at 90 °C led to a 71 % yield of **2A** after only one hour. The elevated temperature relative to other sulfinate additions^[1] is presumably required to generate the radical and forge the quaternary carbon center.

As illustrated in Table 1, this procedure for the net conversion of carboxylic acids into sulfinate salts is simple and general. The sequence involves only one isolated intermediate (sulfone), with the intermediate Barton ester carried on crude after aqueous workup, and the rearranged sulfide submitted directly to the RuCl₃-catalyzed oxidation. Ten different sulfinate reagents were prepared using this route and ranged in structural complexity, fluorine content, and heteroatom presence.^[9]

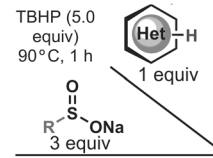
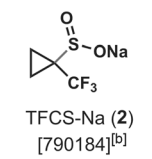
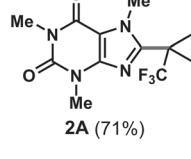
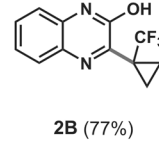
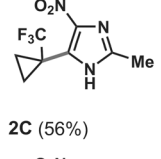
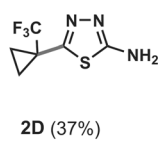
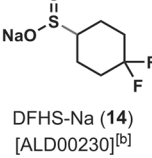
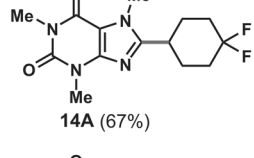
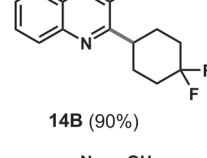
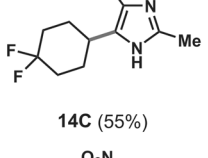
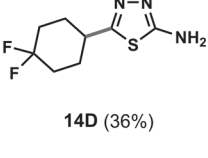
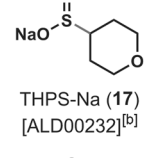
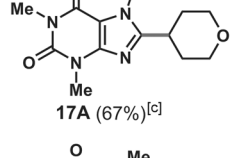
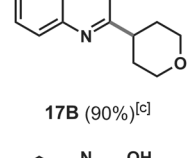
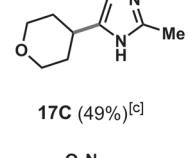
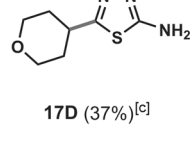
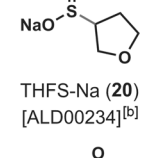
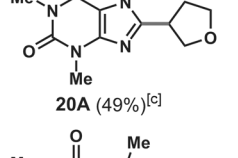
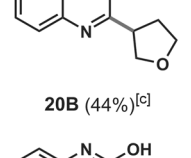
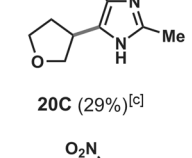
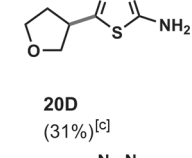
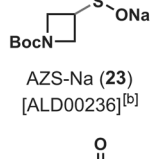
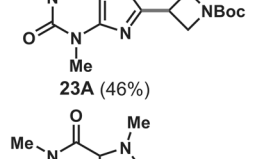
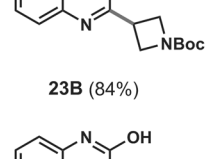
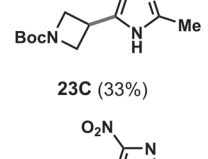
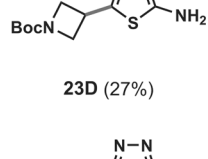
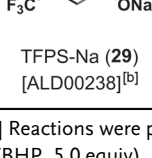
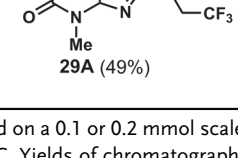
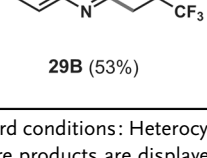
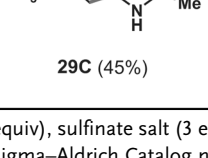
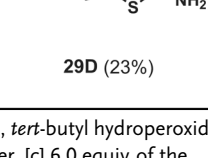
In addition to TFCS-Na **2**, several other salts may find use in medicinal chemistry programs (Table 2). It is important to note that difluorinated congeners of common cyclic ethers were synthesized as isosteric replacements of oxygen (e.g., **14**). Azetidine **23** could be used to increase the solubility of medicinally relevant compounds, and removal of the Boc group could lead to further derivatization. Other sulfonates such as **17**, **20**, and **29** contain motifs popular in medicinal chemistry^[10] and they were selected for commercialization. As such, their synthesis was conducted on multigram scales.

Table 1: Conversion of readily available carboxylic acids into sulfinate reagents.^[a]

Carboxylic acid	Sulfone	Sulfinate salt	Carboxylic acid	Sulfone	Sulfinate salt
1	5 (50%)	2 (75%) [X-ray]	18	19 (71%)	20 (34%)
6	7 (30%)	8 (35%)	21	22 (42%)	23 (63%)
9	10 (47%)	11 (30%)	24	25 (71%)	26 (50%)
12	13 (78%)	14 (73%)	27	28 (92%)	29 (88%)
15	16 (56%)	17 (98%)	30	31 (42%)	32 (95%)

[a] Conditions: carboxylic acid (1 equiv), (COCl)₂ (1.5 equiv), DMF (0.1 equiv), 0 to 23 °C; 250 W or 600 W tungsten lamp, EtOAc; RuCl₃ (5 mol %), NaO₄ (6 equiv), EtOAc/H₂O; NaOEt (1.1 equiv), DMA, 0 to 30 °C or NaSEt, THF, 0 to 23 °C. Boc = *tert*-butoxycarbonyl, DMA = *N,N*-dimethylacetamide.

Table 2: Reactions of newly designed sodium alkanesulfinate salts and heteroarenes.^[a]

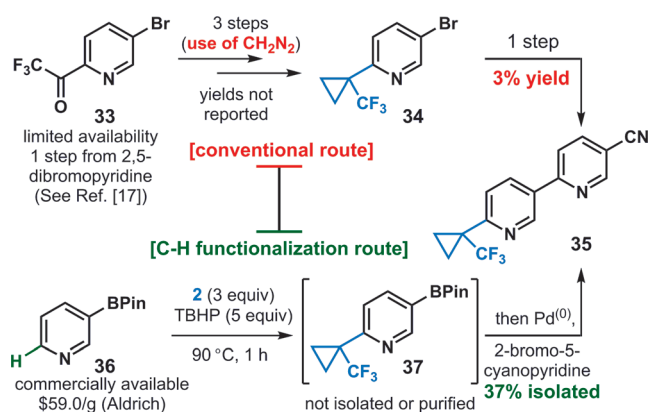
	A	B	C	D
 TFCS-Na (2) [790184] ^[b]	 2A (71%)	 2B (77%)	 2C (56%)	 2D (37%)
 DFHS-Na (14) [ALD00230] ^[b]	 14A (67%)	 14B (90%)	 14C (55%)	 14D (36%)
 THPS-Na (17) [ALD00232] ^[b]	 17A (67%) ^[c]	 17B (90%) ^[c]	 17C (49%) ^[c]	 17D (37%) ^[c]
 THFS-Na (20) [ALD00234] ^[b]	 20A (49%) ^[c]	 20B (44%) ^[c]	 20C (29%) ^[c]	 20D (31%) ^[c]
 AZS-Na (23) [ALD00236] ^[b]	 23A (46%)	 23B (84%)	 23C (33%)	 23D (27%)
 TFPS-Na (29) [ALD00238] ^[b]	 29A (49%)	 29B (53%)	 29C (45%)	 29D (23%)

[a] Reactions were performed on a 0.1 or 0.2 mmol scale. Standard conditions: Heterocycle (1 equiv), sulfinate salt (3 equiv), *tert*-butyl hydroperoxide (TBHP, 5.0 equiv), 0 to 90 °C. Yields of chromatographically pure products are displayed. [b] Sigma–Aldrich Catalog number. [c] 6.0 equiv of the sulfinate salt and 10 equiv of TBHP were used.

The C–H functionalization of four different classes of heterocycles **A–D** was explored with these six newly commercialized sulfinate salts (Table 2). All of these sulfonates gave products in good to moderate yields. As can be expected with sulfinate chemistry,^[1] these reactions are conducted under air, in the presence of water, and without using transition metals, which makes them very practical and operationally simple. Similarly to **1** (Scheme 1 B), standard Minisci reaction conditions were screened with caffeine (RCO₂H, AgNO₃, (NH₄)₂S₂O₈, and H₂SO₄ in H₂O at 90 °C) using **12**, **15**, **18**, **21**, and **27**, but zero or slight conversion (less than 5%) was observed.^[11] Although we only tested the potential of some of these new salts for C–H functionalization, sulfinate salts have shown reactivity in cross-coupling^[12]

and can be converted into other functional groups such as sulfonamides.^[13]

This method compares well with other state-of-the-art routes to introduce medicinally important functional groups onto heteroarenes. For example, sulfinate salt **14** allows for the facile attachment of a difluorinated isostere of a tetrahydropyran ring onto a heterocycle, which would otherwise require four steps to install starting from the corresponding carboxylic acid.^[14] Another method to directly append tetrahydropyran, tetrahydrofuran, azetidine, and cyclobutane rings onto heteroarenes has been developed by Molander and co-workers.^[15] Also, a trifluoropropyl group can be incorporated into a heteroarene through a condensation reaction with 4,4,4-trifluorobutanal, 2-oxopropanal, and ammonium hydroxide.^[16] However, the only method to directly append



Scheme 2. Comparison of conventional and C–H functionalization routes to **35**. Reagents and conditions: **36** (1 equiv), **2** (3.0 equiv), *tert*-butylhydroperoxide (TBHP, 5.0 equiv), 0 to 90 °C; then 2-bromo-5-cyanopyridine (1.1 equiv), [Pd(PPh₃)₄], DME/H₂O (3:1), reflux. Reaction performed on a 0.05 mmol scale. BPin = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, DME = dimethoxyethane.

a trifluoromethylcyclopropyl group onto a heteroarene is achieved using sulfinate radical chemistry.

Lastly, our attention was turned to one of the highlighted substrates in the Novartis report: bispyridine **35** (Scheme 2).^[6] The reported synthesis started from **33**, a compound with limited availability but easily prepared from 2,5-dibromopyridine. Three steps are required to convert **33** into the trifluoromethylcyclopropylpyridine **34**. A final (presumably unoptimized) Suzuki coupling proceeded in 3% yield to furnish **35**. In stark contrast, commercially available pyridine **36** bearing a C-3 boron functionality could be trifluoromethylcyclopropanated using **2** to chemoselectively furnish **37**. This intermediate was used directly without isolation or purification in a Suzuki coupling to afford **35** in a 37% yield of the isolated product over the two-step, one-pot operation.

In summary, a simple sequence to convert widely available carboxylic acids into sulfinate salts has been devised using classic Barton chemistry. Several of these salts were commercialized and used to functionalize a panel of heterocycles. The simplicity of this C–H functionalization (a cheap industrial oxidant, simple solvent, and no metals) is a clear advantage over other radical donors. Judging from the demonstrated utility of these and other sulfinate salts at Pfizer, we anticipate their rapid adoption for use in drug discovery.

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