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Silver-mediated radical aryltrifluoromethylthiolation of activated alkenes by *S*-trifluoromethyl 4-methylbenzenesulfonothioate

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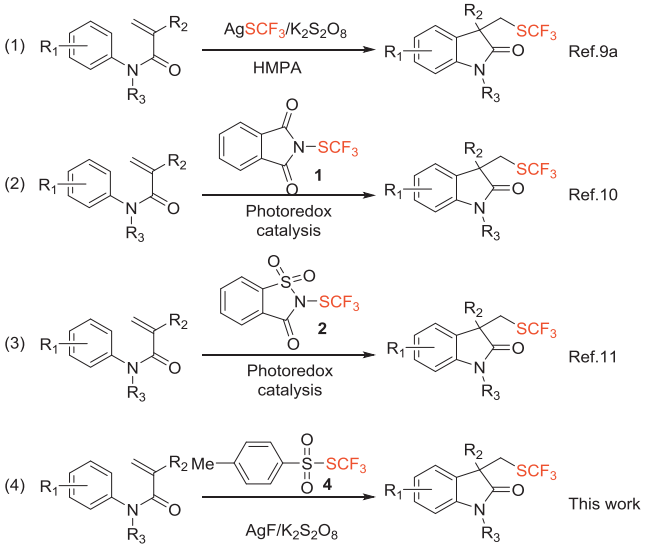
ABSTRACT

Herein, we describe the preparation of trifluoromethylthiol-substituted oxindoles by silver-mediated aryltrifluoromethylthiolation of activated alkenes, using *S*-trifluoromethyl 4-methylbenzenesulfonothioate as a F_3CS radical source and showing that the reagent availability, mild conditions, and broad functional group compatibility of this transformation make it a viable alternative strategy of constructing C_{sp3}—SCF_3 bonds.

Introduction

Trifluoromethylthiolation has recently emerged as a hot organic/medicinal chemistry research field.[1] Since the trifluoromethylthiol (CF_3S) group is highly lipophilic (Hansch parameter $\pi_R = 1.44$)[2] and electron-withdrawing, its incorporation into bioactive molecules can improve their cell membrane permeation ability[3] and metabolic stability,[4] which makes the development of mild and efficient trifluoromethylthiolation methods a task of high significance.

In addition to nucleophilic trifluoromethylthiolation employing $AgSCF_3$,[5] $CuSCF_3$,[6] or Me_4NSCF_3[7] as SCF_3^- sources, great progress has been made in the field of electrophilic trifluoromethylthiolation, with a series of easy-to-handle and shelf-stable trifluoromethylthiolation reagents currently being available.[8] However, although a number of aromatic molecules have been trifluoromethylthiolated by the above nucleophilic/electrophilic reagents, the radical trifluoromethylthiolation of alkenes remains underexplored, mainly due to the limited number of reliable methods of generating the F_3CS radical. The most common F_3CS radical source, used in many impressive transformations, is $AgSCF_3$, which, however, is expensive and requires *in situ* oxidation by a strong oxidant to generate the SCF_3 radical (Scheme 1, Eq. 1).[9] In 2016, Hopkinson et al. reported visible-light-promoted radical trifluoromethylthiolation of styrenes by 2-((trifluoromethyl)thio)isoindoline-1,3-dione (**1**) (Scheme 1, Eq. 2).[10] Recently, Dagousset and Magnier reported visible-light-driven radical trifluoromethylthiolation of alkenes



Scheme 1. Radical aryltrifluoromethylthiolation of activated alkenes.

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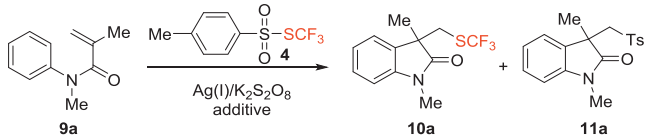
by *N*-trifluoromethylthiosaccharin (**2**) (Shen's reagent) (Scheme 1, Eq. 3).[11] However, the preparation of compounds **1** and **2** requires the use of expensive $AgSCF_3$ or $CuSCF_3$. In 2016, Shen et al. reported an elegant radical-mediated phenylsulfonyl-difluoromethylthio-1,2-difunctionalisation of alkenes by *S*-difluoromethyl benzenesulfonothioate (**3**).[12] Recently, Xu et al. reported a gold and visible-light mediated phenylsulfonyl-trifluoromethylthio-1,2-difunctionalisation of alkenes by *S*-trifluoromethyl 4-methylbenzenesulfonothioate (**4**).[13] Due to being interested in the development of efficient C—S bond construction methods,[14] we herein utilised compound **4**, easily prepared from trimethyl(trifluoromethyl)silane (**5**), *N*,*N*-diethyl-1,1,1-trifluoro-l4-sulfanamine (**6**), aniline (**7**), and sodium 4-methylbenzenesulfinate (**8**) in two steps,[8a,15] as an alternative F_3CS radical source, successfully achieving silver-mediated oxidative aryltrifluoromethylthiolation of activated alkenes to produce trifluoromethylthiol-substituted oxindoles (Scheme 1, Eq. 4).

Results and discussion

Treatment of *N*-methyl-*N*-phenylmethacrylamide (**9a**) with **4** in the presence of $AgNO_3$, $K_2S_2O_8$, and hexamethylphosphoramide (HMPA) in dimethyl sulfoxide (DMSO) at 40 °C afforded the desired aryltrifluoromethylthiolation product **10a** (24% yield, Table 1, entry 1) and the non-desired arylsulfoxidation product **11a** (40% yield). When the reaction was carried out without HMPA, the yield of **10a** increased to 38%, with only trace amount of **11a** detected (Table 1, entry 2). To optimise the reaction conditions, various oxidants ($Na_2S_2O_8$, $(NH_4)_2S_2O_8$, *t*-BuOOH, and $(t\text{-BuO})_2$ (Table 1, entries 3–6)) were investigated, but none of them was superior to $K_2S_2O_8$, with subsequent screening of silver salts ($AgSbF_6$, AgOTf, and AgF) showing that AgF afforded the best yield (Table 1, entries 7–9). Finally, the loading of **4** and AgF, reaction temperature, reactant concentration, and solvent were examined. When the loadings of **4** and AgF were increased from 1.2 to 1.8 equivalents, the yield of **10a** increased from 42 to 58% (Table 1, entries 10 and 11). However, a further loading increase to 2.0 equivalents was counterproductive (Table 1, entry 12). Decreasing the reaction temperature to 20 °C improved the yield to 71% (Table 1, entry 13), whereas increasing the concentration of **9a** from 0.083 to 0.125 M or decreasing it from 0.083 to 0.063 M diminished the yield (Table 1, entries 14 and 15). When other solvents such as acetonitrile (CH_3CN), toluene, and 1-methylpyrrolidin-2-one (NMP) were used, no desired product was obtained, except for DMF, in which case **10a** was isolated in 34% yield (Table 1, entries 16–19). Thus, the optimised reaction conditions for the aryltrifluoromethylthiolation of **9a** were as follows: **9a** (0.25 mmol), **4** (0.45 mmol), AgF (0.45 mmol), $K_2S_2O_8$ (0.9 mmol), and DMSO (3 mL) at 20 °C.

With the optimised reaction conditions in hand, the scope of activated alkenes was investigated, with the results presented in Scheme 2. *N*-Methyl-*N*-phenylmethacryl amides **9** with both electron-donating and electron-withdrawing substituents in *ortho*-, *meta*-, and *para*-positions of the aniline ring (**9b**–**9l**) were smoothly converted into the corresponding oxindoles. Notably, when *N*-methyl-*N*-(pyridin-2-yl)methacrylamide (**9m**) and *N*-methyl-*N*-(-naphthalen-1-yl)methacrylamide (**9n**) were employed as substrates, the desired products **10m** and **10n** were obtained in relatively low yields. Then, other *N*-substitutes-*N*-phenylmethacryl amides (**9o**–**9s**) were tested, affording the desired aryltrifluoromethylthiolation products in moderate yields except for **9r**, which was transformed into **10r** in 34% yield. Finally, α-substituted acrylamides (**9t**–**9w**) were examined, and it was found that ethyl, benzyl, and methoxymethyl substituents were tolerated, and the desired products (**10t**–**10w**) were obtained in moderate to good yields.[16]

Table 1
Optimisation of aryltrifluoromethylthiolation of **9a** by **4** in the presence of diverse silver salts and oxidants.[a]



Entry	**4**/equiv.	Ag(I)/equiv.	Oxidant/equiv.	Temperature (°C)	Solvent	Yield of **10a** (%)[b]
1	1.2	$AgNO_3$/1.2	$K_2S_2O_8$/3.6	40	DMSO	24[c]
2	1.2	$AgNO_3$/1.2	$K_2S_2O_8$/3.6	40	DMSO	38
3	1.2	$AgNO_3$/1.2	$Na_2S_2O_8$/3.6	40	DMSO	Trace
4	1.2	$AgNO_3$/1.2	$(NH_4)_2S_2O_8$/3.6	40	DMSO	29
5	1.2	$AgNO_3$/1.2	*t*-BuOOH/3.6	40	DMSO	0
6	1.2	$AgNO_3$/1.2	$(t\text{-BuO})_2$/3.6	40	DMSO	0
7	1.2	$AgSbF_6$/1.2	$K_2S_2O_8$/3.6	40	DMSO	40
8	1.2	AgOTf/1.2	$K_2S_2O_8$/3.6	40	DMSO	40
9	1.2	AgF/1.2	$K_2S_2O_8$/3.6	40	DMSO	42
10	1.5	AgF/1.5	$K_2S_2O_8$/3.6	40	DMSO	55
11	1.8	AgF/1.8	$K_2S_2O_8$/3.6	40	DMSO	58
12	2.0	AgF/2.0	$K_2S_2O_8$/3.6	40	DMSO	52
13	1.8	AgF/1.8	$K_2S_2O_8$/3.6	20	DMSO	71
14	1.8	AgF/1.8	$K_2S_2O_8$/3.6	20	DMSO	58[d]
15	1.8	AgF/1.8	$K_2S_2O_8$/3.6	20	DMSO	65[e]
16	1.8	AgF/1.8	$K_2S_2O_8$/3.6	20	CH_3CN	0
17	1.8	AgF/1.8	$K_2S_2O_8$/3.6	20	Toluene	0
18	1.8	AgF/1.8	$K_2S_2O_8$/3.6	20	NMP	0
19	1.8	AgF/1.8	$K_2S_2O_8$/3.6	20	DMF	34

[a] Reaction conditions: **9a** (0.25 mmol), **4** (0.3–0.5 mmol), Ag(I) salt (0.3–0.5 mmol), and oxidant (0.9 mmol) in solvent (3 mL) for 5 h at the indicated temperature.
[b] Yield of isolated product after silica gel chromatography.
[c] HMPA (0.125 mmol) was used as an additive.
[d] DMSO (2 mL) was used.
[e] DMSO (4 mL) was used.