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Triphosgene/Sodium Organosulfinate System: A General and Efficient Electrophilic Thiolation of Silylenol Ethers and Electron-Rich Heteroaromatics

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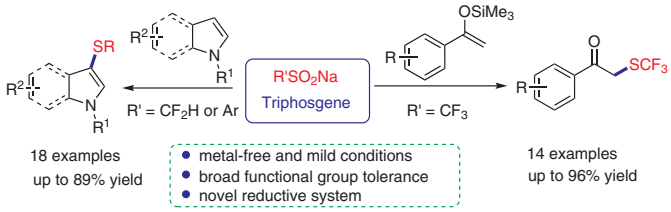

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Abstract An efficient and practical approach to electrophilic thiolation was developed by using commercially available triphosgene as a reductant and the appropriate alkyl- or arylsulfinates, which were transformed in situ into electrophilic RSCl intermediates in the presence of triphosgene. This procedure represents a general and powerful approach for the synthesis of α-(trifluoromethyl)thio-substituted ketones and thiolated electron-rich heteroaromatic compounds.

Key words drifluoromethylthiolation, difluoromethylthiolation, triphosgene, silylenol ethers, indoles

Organosulfur and organofluorine compounds have recently attracted considerable attention because of their interesting applications in medicine, agrochemicals, and materials science.[1] The incorporation of (trifluoromethyl)thio and (difluoromethyl)thio groups into potential drug molecules has been recognized as a useful improvement strategy owing to various characteristics of these groups, such as their strong electron-withdrawing effect, high lipophilicity, and ideal bioavailability.[2] Furthermore, compounds containing a F_3CS- or F_2CHS- group are easily oxidized to form sulfoxides, thereby altering their biological activity, which is beneficial in the design of potential prodrugs.

In the last decade, there have been considerable efforts to develop efficient and general approaches for selective installation of the F_3CS– group onto the α-position of ketones. Early protocols for the synthesis of α-SCF_3-substituted ketones normally involved the reactions of α-bromo ketones with various nucleophilic reagents.[3] Recently, an electrophilic strategy has attracted significant attention, and many new electrophilic trifluoromethylthiolation reagents such as Munavalli's *N*-[(trifluoromethyl)thio]phthalimide,[4] Billard's (trifluoromethane)sulfanyl amides,[5] and Shen's *N*-[(trifluoromethyl)thio]saccharin[6] have been developed. However, many of these strategies involve multiple steps and require expensive substrates for the preparation of the trifluoromethylthiolation reagents.

It is widely known that silyl enol ethers are advantageous in terms of their electrophilic addition to electrophilic reagents. In 2014, Shibata discovered a bistrifluoromethylthiolation reaction of silyl enol ethers by using TsN(Me)SCF_3 as an electrophilic trifluoromethylthiolation reagent that gave the corresponding products in moderate to good yields.[6b] Shortly afterwards, the same group found that a catalytic amount of CuF_2 promoted the trifluoromethylthiolation of silyl enol ethers when a trifluoromethanesulfonyl hypervalent iodonium ylide was used as an electrophilic reagent, giving the corresponding α-CF_3S-substituted ketones in good yields (Scheme 1a).[7] In 2018, Saravanan and Anbarasan developed an efficient and creative approach to electrophilic trifluoromethylthiolation, in which a combination of (diethylamino)sulfur trifluoride (DAST) and (trifluoromethyl)trimethylsilane (F_3CTMS) were used as the source of CF_3S groups to give α-trifluoromethylthiolated carbonyl compounds (Scheme 1b).[8] However those methods are limited by the nature of the CF_3S source, which are difficult to prepare, and by the high cost of the substrates. Thus, the use of more readily available or more easily handled sources of the CF_3S group to promote the trifluoromethylthiolation of silyl enol ethers is highly desirable. We recently discovered a general trifluoromethylthiolation method involving the treatment of F_3CSO_2Na with triphosgene,[9] Interestingly, by using triphosgene as a reductant, sulfinates could be used as electrophilic reagents. In continuation of our interest in the potential uses of the sulfinate/triphosgene system, we have expanded the range of uses of sulfinates to include the thiolation of silyl enol ethers or electron-rich aromatics under mild conditions (Scheme 1c).

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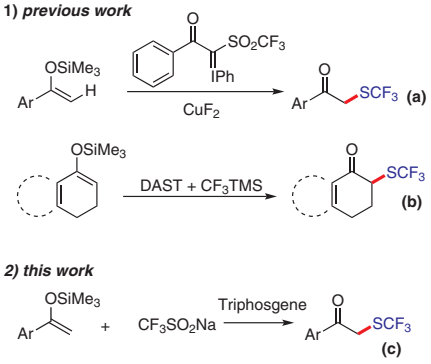
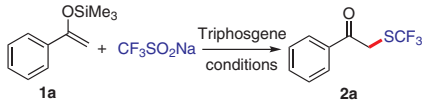


Scheme 1 Synthesis of α-CF_3S-substituted ketones from silyl enol ethers

We began our studies by exploring the reaction of 1-phenyl-1-(trimethylsiloxy)ethene (**1a**) with the F_3CSO_2Na/triphosgene system as a model to optimize the reaction conditions (Table 1). First, we examined the use of F_3CSO_2Na and triphosgene in various ratios. To our delight, at room temperature in MeCN, without other additives, the α-trifluoromethylthiolated product **2a** was obtained in 56% isolated yield (Table 1, entry 1) when the **1a**/F_3CSO_2Na/triphosgene mole ratio was 1:1:1. Experiments with various amounts of F_3CSO_2Na and triphosgene revealed that the optimal mole ratio of **1a** to F_3CSO_2Na was 1:2 and the optimal mole ratio of F_3CSO_2Na to triphosgene was 1:1 (Table 1, entries 1–6). The reaction was next shown to be sensitive to temperature, and the optimal performance was achieved at –78 °C, giving 93% of the α-CF_3S-substituted ketone **2a** (entries 5–9). Finally, replacement of MeCN by other solvents (CH_2Cl_2, EtOAc, or THF) gave the trifluoromethylthiolated product **2a** in good yields, whereas none of the target product was obtained in DMSO.

Having established the optimal reaction conditions (Table 1, entry 9), we then subjected silyl enol ethers with various substituents on the benzene ring to these conditions (Table 2). Electron-neutral, electron-withdrawing, and electron-donating groups in the *ortho*-, *meta*- and *para*-positions were all tolerated, and the corresponding α-trifluoromethylthiolated ketones were obtained in moderate to good yields. With electron-donating methyl, methoxy, alkylthio, or phenyl groups in the *para*-position of the aryl ring, the corresponding products **2b–e** were obtained in yields of 88–96%. In comparison, substrates with electron-withdrawing groups at the *para*-position on the aryl ring were less reactive, giving the target products **2f–i** in moderate to good yields; for example, trimethyl({1-[4-(trifluoromethyl)phenyl]vinyl}oxy)silane, with a strongly electron-withdrawing trifluoromethyl group on the benzene ring, gave the corresponding α-trifluoromethylthiolated ketone **2i** in 82% yield. Products with halogen substituents on the benzene ring **2f–n** were obtained in yields of 81–85%, irrespective of the halogen and its position on the aromatic ring. Reactants with methyl or bromo *ortho*-substituents on the aromatic ring were also converted effectively into the corresponding trifluoromethylthio-substituted ketones **2m** and **2n** in yields of 83 and 81%, respectively. The above results hint that steric hindrance by substituents on the aromatic rings has a limited influence on this transformation.

Table 1 Optimization of the Reaction Conditions[a]



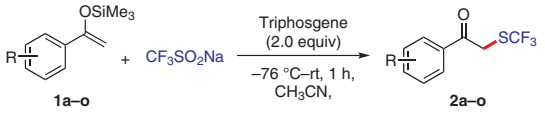
Entry	**1a**/F_3CSO_2Na/triphosgene	Solvent	Temp (°C)	Yield[b] (%)
1	1:1:1	MeCN	25	56
2	1:1.5:1.5	MeCN	25	65
3	1:2:1.5	MeCN	25	75
4	1:2:2	MeCN	25	78
5	1:2:4	MeCN	25	70
6	1:2:2	MeCN	0	82
7	1:2:2	MeCN	–20	85
8	1:2:2	MeCN	–60	91
9	1:2:2	MeCN	–78	**93**
10	1:2:2	CH_2Cl_2	–60	85
11	1:2:2	EtOAc	–60	88
12	1:2:2	THF	–60	86
13	1:2:2	DMSO	–60	0

[a] Reaction conditions: **1** (0.2 mmol), triphosgene, F_3CSO_2Na, solvent (3 mL), under N_2, 1 h.
[b] Isolated yield.

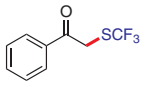
We next examined the use of the F_2CHSO_2Na/triphosgene system with electron-rich indoles to check the applicability and generality of this approach (Table 3). Treatment of indoles **3** with the F_2CHSO_2Na/triphosgene system in MeCN at –78 °C gave the corresponding products **4a–n** in moderate to good yields. A wide range of N-protected or N-unsubstituted indoles with electron-donating or electron-withdrawing substituents were compatible with the reaction conditions, and underwent direct C–H difluoromethylthiolation to give the corresponding 3-difluoromethylthiolated indoles **4a–g** in moderate to good yields. Notably, substitution at both the C2 and C4 atoms was also well tolerated (**4b–d**, **4g**), and even the substrate with a bulky 2-phenyl group provided the expected product **4b** in 65% yield.

Indole and its derivatives can be directly functionalized by various electrophiles due to the electron-rich nature of the indole ring. Similarly, the $ArSO_2Na$/triphosgene reagent combination is also suitable for preparing 3-(arylsulfanyl)indoles through an electrophilic substitution process

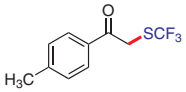
Table 2 Scope of the Silyl Enol Ether[a]



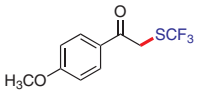
1a–o 2a–o



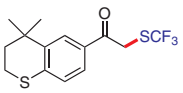
2a (93%)[b]



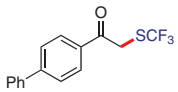
2b (92%)



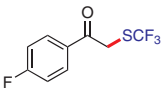
2c (96%)



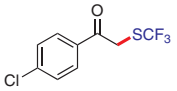
2d (88%)



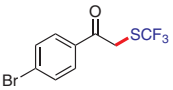
2e (89%)



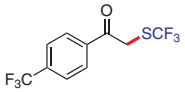
2f (81%)



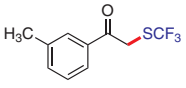
2g (82%)



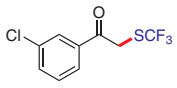
2h (83%)



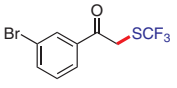
2i (82%)



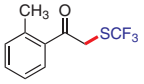
2j (88%)



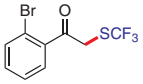
2k (81%)



2l (85%)



2m (83%)



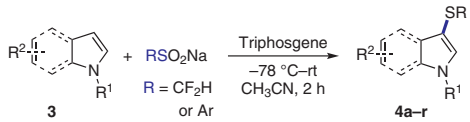
2n (81%)

[a] Reaction condition: **1** (0.2 mmol), F_3CSO_2Na (0.4 mmol, 2 equiv), triphosgene (0.6 mmol, 3 equiv), MeCN (3 mL), –78 °C, N_2, 1 h.
[b] Isolated yields are reported throughout.

initiated by an ArS^+ intermediate. Arylsulfinic acid sodium salts containing alkyl or halogen substituents reacted smoothly with indole under the optimized reaction conditions to give the corresponding 3-(arylsulfanyl)indoles **4h–n** in moderate yields. However, we observed that electronic effects of the substituents on the aryl ring exerted an obvious effect on the reaction reactivity, and sulfinates with strongly electron-withdrawing groups, such as NO_2 or CF_3, failed to give the corresponding C3-arylthioindole products.

Lastly, we turned our attention to the scope of another N-heteroarene, *N*-methylpyrrole (**4o–r**). Several sulfinates with methyl, bromo, or nitro substituents reacted with *N*-methylpyrrole to give the corresponding 2-sulfonyl pyrroles **4o–q** in yields of up to 68%. Sodium (2-methylbenzene)sulfinate gave product **4r** in a low 37% yield, mainly because of steric hindrance. Note that pyrrole without an N-protecting group did not afford the expected product, owing to its decomposition in the presence of triphosgene.

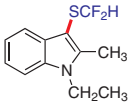
Table 3 Thiolation of Indoles and *N*-Methylpyrrole with RSO_2Na in the Presence of Triphosgene[a]



3 4a–r

4a (89%)

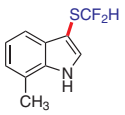
4b (65%)



4c (84%)

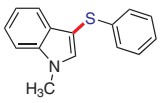
4d (81%)

4e (85%)

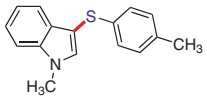


4f (78%)

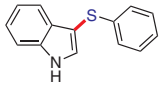
4g (47%)



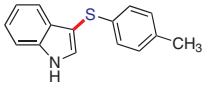
4h (73%)



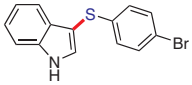
4i (68%)



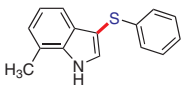
4g (54%)



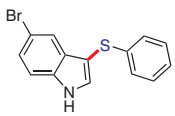
4k (51%)



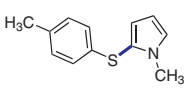
4l (66%)



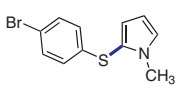
4m (68%)



4n (65%)

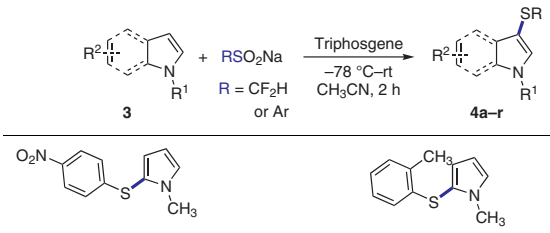


4o (45%)



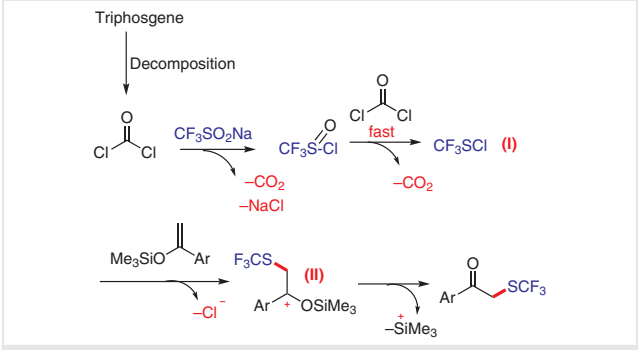
4p (57%)

Table 3 (continued)



[a] Reaction conditions: Indole or *N*-methylpyrrole **3** (0.2 mmol), RSO_2Na (2.0 equiv), triphosgene (2.0 equiv), MeCN (2.0 mL), under N_2, –78 °C to rt, 2 h.

Although the exact reaction mechanism is still unclear, on the basis of the above-mentioned results and reports in the literature,[5a,b,6a,10] we hypothesized that the generation of highly reactive electrophilic CF_3S^+, CF_2HS^+, and ArS^+ species through deoxygenative reduction of RSO_2Na with triphosgene is the key step (Scheme 2). Initially, F_3CSO_2Na is reduced by phosgene (formed in situ by decomposition of triphosgene) to give the highly reactive electrophilic intermediate F_3CSCl (**I**), together with CO_2, NaCl, and HClO, among other products. The silyl enol ether then reacts with the key intermediate F_3CSCl (**I**) through electrophilic addition to give intermediate **II**. Finally, rapid elimination of the Me_3Si^+ cation from intermediate **II** results in the generation of the corresponding product.



Scheme 2 Plausible reaction mechanism

In summary, an efficient and practical approach has been developed for the electrophilic trifluoromethylthiolation of silyl enol ethers and for the difluoromethylthiolation of indoles with various organosulfinates.[11] This conversion employs the appropriate sulfinate RSO_2Na as a trifluoromethylthiolating, difluoromethylthiolating, or arylthiolating reagent, with the assistance of triphosgene as a reducing agent and activator to generate the key electrophilic RS^+ intermediate in situ. Indeed, the use of F_3CSO_2Na, F_2CHSO_2Na, and $ArSO_2Na$ as sulfonyl precursors is well known, but this combination of a sodium organosulfinate with triphosgene has general applicability owing to its strong electrophilicity. It can therefore serve as an alternative and practical strategy for introducing sulfur-containing functionalities into organic molecules. Studies on the mechanism, scope expansion, and limitations of this RSO_2Na/triphosgene system are in progress and will be reported shortly.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707299.

References and Notes

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(11) **Electrophilic Trifluoromethylthiolation of Silyl Enol Ethers; General Procedure**

A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with F_3CSO_2Na (0.4 mmol), the appropriate silyl enol ether (0.2 mmol), and MeCN (1 mL), and the mixture was stirred at –78 °C for the initial time. A solution of triphosgene (0.4 mmol) in MeCN (1 mL) was then added slowly from a syringe. After 1 h at –78 °C, the mixture was warmed to rt over 1 h, then diluted with CH_2Cl_2 (20 mL). The mixture was washed 5% aq $NaHCO_3$ (10 mL), and the combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel).

1-Phenyl-2-[(trifluoromethyl)sulfanyl]ethanone (2a)

Yellow oil; yield: 40.9 mg (93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 6.8 Hz, 2 H), 7.65 (t, *J* = 6.8 Hz, 1 H), 7.54 (t, *J* = 6.8 Hz, 2 H), 4.53 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.1 (s), 134.7 (s), 134.3 (d, *J* = 1.5 Hz), 130.7 (q, *J* = 306.4 Hz), 129.0 (s), 128.5 (s), 38.5 (q, *J* = 1.8 Hz). HRMS (EI-TOF): *m/z* [M]+ calcd for $C_9H_7F_3OS$: 220.0170; found: 220.0162.

Electrophilic Thiolation of Indoles or *N*-Methylpyrrole; General Procedure

A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with RSO_2Na (0.4 mmol) and the appropriate indole or *N*-methylpyrrole (0.2 mmol). The tube was then evacuated and backfilled with dry N_2 (this operation was repeated three times), and the mixture was stirred at –78 °C for the initial time. A solution of triphosgene (0.4 mmol) in MeCN (1 mL) was added slowly from a syringe, and the mixture was stirred at –78 °C for 1 h. When the reaction was complete, the mixture was warmed to rt and diluted with CH_2Cl_2 (20 mL). The mixture was then washed with 5% aq $NaHCO_3$ (10 mL), and the combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel).

3-[(Difluoromethyl)sulfanyl]-1-methyl-1*H*-indole (4a)

Yellow oil; yield: 37.9 mg (89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.8 Hz, 1 H), 7.42–7.20 (m, 4 H), 6.67 (t, *J* = 57.7 Hz, 1 H), 3.83 (s, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 137.31, 136.14, 130.50, 122.82, 121.15 (t, *J* = 275 Hz), 120.98, 119.47, 109.82, 94.28, 33.23. MS (EI): *m/z* = 213.1 $[M]^+$. HRMS (EI-TOF): *m/z* $[M]^+$ calcd for $C_{10}H_9F_2NS$: 213.0424; found: 213.042.