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Alkoxide- and Hydroxide-Induced Nucleophilic Trifluoromethylation Using Trifluoromethyl Sulfone or Sulfoxide

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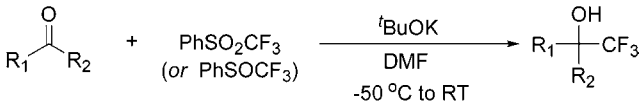
ABSTRACT



The first alkoxide- and hydroxide-induced nucleophilic trifluoromethylation of carbonyl compounds, disulfides, and other electrophiles, using phenyl trifluoromethyl sulfone 1a (sulfoxide 1b) is reported. The trifluoromethyl sulfone 1a or sulfoxide 1b acts as a "CF_3^-" synthon. Both sulfone 1a and sulfoxide 1b are commercially available and can also be conveniently prepared from trifluoromethane. The new methodology provides a convenient route for efficient trifluoromethylation.

In the past two decades, organofluorine compounds have attracted much attention due to their unique properties and unusual reactivities.[1] Among them, trifluoromethyl group (CF_3)-containing compounds are of particular importance for different applications in the fields of materials, pharmaceuticals, and agrochemistry. Although many trifluoromethylation methods have appeared in the literature, including organometallic,[2] nucleophilic,[3] electrophilic,[4] and radical trifluoromethylations,[5] fluoride-induced nucleophilic trifluoromethylation with (trifluoromethyl)trimethylsilane (TMS−CF_3) developed by us previously is considered to be a straightforward, convenient, and versatile method.[3] TMS−CF_3 was commonly prepared from ozone-depleting trifluoromethyl halides, but recently, we reported its non-Freon-based preparation.[6]

Since the 1990s, there has been increasing research interest in trifluoromethylation using trifluoromethane (CF_3H) as a trifluoromethylating precursor. CF_3H has low toxicity and is not ozone-depleting. It is a side-product of the multistep industrial synthesis of Teflon.[7a] The efficient production of CF_3H has been disclosed via fluorination of methane with hydrogen fluoride and chlorine.[7b] Shono and co-workers[8] used electrochemically reduced 2-pyrrolidone base to deprotonate CF_3H to generate the trifluoromethyl anion equivalent that reacts with aldehydes and ketones. Troupel et al.[9] also reported that cathodic reduction of iodobenzene generates a strong base, which deprotonates CF_3H, inducing its addition to aldehydes. Thereafter, two research groups carried out extensive studies on the nucleophilic trifluoromethylation

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(8) Shono, T.; Ishifume, M.; Okada, T.; Kashimura, S. *J. Org. Chem.* **1991**, *56*, 2.

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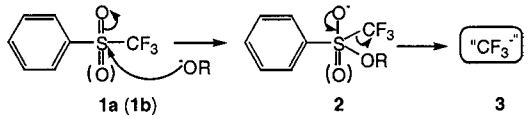
using CF_3H as a precursor. Normant and co-workers[7a,10] have demonstrated the trifluoromethylation of aldehydes by CF_3H/potassium dimsylate in DMF. They suggested that the CF_3^-/DMF adduct was the key intermediate in the trifluoromethyl transfer process. Roques, Langlois, and co-workers[11] reported the nucleophilic trifluoromethylation of carbonyl compounds and disulfides with CF_3H and different bases in DMF. CF_3^-/*N*-formylmorpholine adduct was also developed as a stable reagent for the trifluoromethylation of nonenolizable carbonyl compounds.[12] Under similar consideration, piperazino hemiaminal of trifluoroacetaldehyde was also used as a trifluoromethylating agent.[13a,b] However, trifluoromethane-derived methods have their drawbacks: first of all, trifluoromethane is a low-boiling gas (bp −84 °C) and thus its handling as a reagent in the laboratory is not convenient; second, the quoted trifluoromethylations do not work well with enolizable carbonyl compounds.

Trifluoromethyl iodide (CF_3I) has also been successfully used as a nucleophilic trifluoromethylating agent under the activation of electron-donating tetrakis-(dimethylamino)ethylene (TDAE).[14a] Motherwell and Storey[14b] reported the nucleophilic trifluoromethylation using trifluoromethylacetophenone-*N*,*N*-dimethyl-trimethylsilylamine adduct. Langlois and co-workers also have reported nucleophilic trifluoromethylations of nonenolizable carbonyl compounds using trifluoroacetic acid derivatives,[13c,d] trifluoromethanesulfinic acid derivatives,[13e] and trifluoroacetophenone.[13f] More recently, a nucleophilic trifluoromethylation method using trifluoroactetamides from amino alcohols was reported.[13g]

We previously reported a reductive trifluoromethylation using trifluoromethyl sulfides, sulfoxides and sulfones as trifluoromethyl (CF_3) group precursors.[6] However, under the reductive condition, where magnesium metal was used, the reaction only worked with chlorosilanes as electrophiles, while attempts to react with carbonyl compounds failed. We anticipated that by using a nucleophilic base such as alkoxides, the carbon−sulfur bond of trifluoromethyl phenyl sulfone **1a** or sulfoxide **1b** can be cleaved to give a trifluoromethyl anion (CF_3^-) synthon that can undergo addition to carbonyl compounds (Scheme 1). The driving force of this substitution is the formation of a strong S−O bond (348∼551 kJ/mol)[15] and the high polarity of the C−S bond of sulfone **1a** or sulfoxide **1b**. The generation of pseudohalide CF_3^- species is somewhat similar to the reaction between benzenesulfonyl halides with alkoxides.

Scheme 1. Mechanistic Consideration



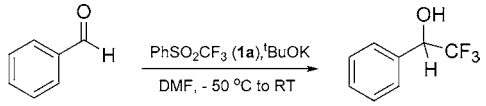
1a (1b) 2 3

Nucleophilic displacement of the trifluoromethyl group has been reported for trifluoromethyl aryl sulfones with sodium methoxide.[16] Similar reaction between trifluoromethyl aryl sulfone and Grignard reagents has been reported for the preparation of sulfones.[17] More recently, Cheburkov et al. reported that perfluoroalkyl sulfones react with metal hydroxides in water or alcohol solution and with ammonia to form fluorinated sulfonic acid derivatives.[18] However, alkoxide- and hydroxide-induced nucleophilic trifluoromethylation using trifluoromethyl sulfones or sulfoxides has not been previously reported.

Herein, we wish to report the first alkoxide- and hydroxide-induced nucleophilic trifluoromethylation of carbonyl compounds, disulfides, and other electrophiles, using trifluoromethyl phenyl sulfone **1a** (sulfoxide **1b)**. The trifluoromethyl sulfone **1a** or sulfoxide **1b** can be used as a "CF_3^-" synthon. Both phenyl trifluoromethyl sulfone **1a** and sulfoxide **1b** are commercially available (bp 203 °C/760 mmHg for **1a**, bp 85∼87 °C/10 mmHg for **1b**) and can also be conveniently prepared from trifluoromethane in high yields.[19] Thus, the new methodology provides a convenient route for efficient nucleophilic trifluoromethylation.

Potassium *tert*-butoxide (^{t}BuOK) was first used as a nucleophile to attack the sulfur center of phenyl trifluoromethyl sulfone **1a** generating trifluoromethyl anion (Scheme 1). Into an equimolar mixture of sulfone **1a** and benzaldehyde **4** in DMF at −50 °C was slowly added a DMF solution of ^{t}BuOK (2 molar equiv). The reaction mixture was stirred at −50 °C for 1 h and then warmed to room temperature over a period of 2 h. 1-Phenyl-2-trifluoromethylethanol **5** was produced in 71% yield (Scheme 2).

Scheme 2. Trifluoromethylation of PhCHO with **1a**



4 5

Shono and co-workers[8] found that when they used CF_3H/^{t}BuOK/DMF to react with benzaldehyde at −50 °C, benzyl

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Table 1. Trifluoromethylation of Benzaldehyde by $PhSO_2CF_3$ Induced by Alkoxide or Hydroxide

	benzaldehyde	sulfone **1a**	alkoxide	solvent	temperature	time	yield (**5**,%)
a	1 equiv	1 equiv	t-BuOK (2 equiv)	DMF	−50 °C	1 h	71
b	3 equiv	1 equiv	t-BuOK (2 equiv)	DMF	−30 °C to rt	30 min	91
c	1 equiv	2 equiv	t-BuOK (2 equiv)	DMF	−50 °C to rt	3 h	84
d	3 equiv	1 equiv	MeONa (3 equiv)	DMF	−30 °C to rt	3 h	30
e	3 equiv	1 equiv	KOH (8 equiv)	DMF	rt	20 h	45
f	3 equiv	1 equiv	t-BuOK (2 equiv)	DMSO	rt	1 h	76

[a] Yields were determined by ^{19}F NMR on the basis of the amount of **1a** used.

alcohol and benzoic acid were formed by the competing Cannizzaro reaction. Russell and Roques[11a] repeated the reaction using excess CF_3H (9.5 equiv) and ^{t}BuOK (2.2 equiv) at − 50 °C, and 67% yield of trifluoromethylated product **5** was formed and no benzyl alcohol was detected. They mentioned that the high reaction temperature with excess base could lead to Cannizzaro reaction and jeopardize the nucleophilic trifluoromethylation. In our reaction, as shown in Scheme 2, only traces of benzoic acid and benzyl alcohol were detected by NMR. This implies that in our reaction at low temperature, the Cannizzaro reaction rate is much slower than the *tert*-butoxide-induced trifluoromethylation process. The reaction conditions have been optimized (Table 1). When excess benzaldehyde was introduced, the yield of product **5** could be improved in terms of the amount of sulfone **1a** used (Table 1, entry b).

Besides ^{t}BuOK, sodium methoxide (CH_3ONa) and potassium hydroxide (KOH) were tried as nucleophiles (Table 1, entries d and e). Both of them worked but gave lower yields. There are several possible reasons. First of all, both sodium methoxide and KOH cannot readily dissolve in DMF, which affects the reaction rate. Second, unlike potassium *tert*-butoxide, sodium methoxide may react with benzaldehyde via a Meerwein−Pondorff−Verley-type reduction pathway.[20] Third, KOH has lower nucleophilicity than ^{t}BuOK, so the reaction rate can be slow. Here, Cannizzaro reaction may still happen as a competing side-reaction, but it should not be a dominating factor to affect the yield since excess benzaldehyde is present.[21]

It is worth noting that DMF is not the only convenient solvent for the reaction. Dimethyl sulfoxide (DMSO) was also used, and the reaction worked well (Table 1, entry f). This indicates that the CF_3^-/DMF adduct[7a,10,11a] is not a necessary intermediate for this new type of nucleophilic trifluoromethylation. From a mechanistic point of view, however, it can be reasonably postulated that the intermediate species **2** (in Scheme 1) is formed and could act as a real trifluoromethylating agent.

We also attempted to carry out the reaction by using a catalytic amount of ^{t}BuOK. However, when a small amount of ^{t}BuOK was introduced, only a low yield of product **5** was obtained (after hydrolysis), which can be monitored by ^{19}F NMR. Introduction of additional ^{t}BuOK increased the product yield, and an excellent yield of **5** was achieved when excess ^{t}BuOK was used.

An excess of ^{t}BuOK (2 equiv) was found to be helpful to achieve high yields in the trifluoromethylation reactions. There are several reasons and advantages. ^{t}BuOK reacts with water readily and may be partially hydrolyzed during storage and handling. Furthermore, excess ^{t}BuOK also removes the moisture from the solvent and reagents. More importantly, excess ^{t}BuOK in the reaction mixture eliminates the possibility of hydrolysis of CF_3^- to form CF_3H. It is known that CF_3H can be deprotonated by ^{t}BuOK and undergo trifluoromethylation of carbonyl compounds,[9−11] Thus, the present methodology allows the preparation of trifluoromethylated products in high yields in the case of nonenolizable aldehydes (Table 2, entries 1−5). Similarly, nonenolizable ketones can also be easily trifluoromethylated using this methodology (Table 2, entries 7−12). Since there is no Cannizarro reaction between ketones and ^{t}BuOK, these reactions can be carried out even at higher temperatures (such as 25 °C). Due to the lower reactivity of ketones compared with aldehydes, the ketone reactions need a slightly longer time (2−3 h) to go to completion. However, with enolizable aldehydes and ketones, only low yield (10−30%) of trifluoromethylated products were observed, because of the competing and facile aldol reactions.

It is noteworthy that phenyl trifluoromethyl sulfoxide **1b** worked equally well as **1a**, and similar trifluoromethylations were observed with aldehyde and ketone (Table 2, entries 6 and 13).

Another advantage of the reaction is the simple workup procedure. Since the byproduct of the reaction is *tert*-butyl benzenesulfonate, it can be readily hydrolyzed into *tert*-butyl alcohol and benzenesulfonic acid derivatives. Aqueous washing thus can remove most of the byproducts and simplifies the purification process.

The novel trifluoromethylating method was also found to work with disulfides. As shown in Scheme 3, $PhSO_2CF_3$ (1 equiv) and ^{t}BuOK (2 equiv) reacted with diphenyl disulfide (**6**, 1.2 equiv) at temperatures between −30 °C and room temperature in 30 min to give quantitative conversion (87% isolated) of trifluoromethyl phenyl sulfide **7**

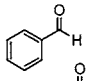
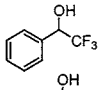
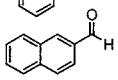
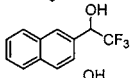
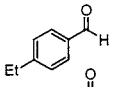
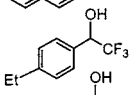
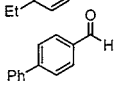
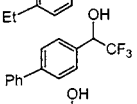
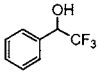
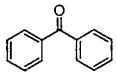
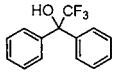
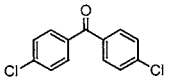
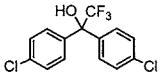
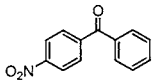
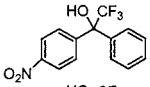
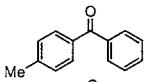
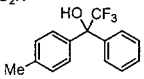
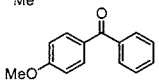
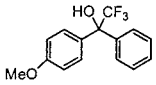
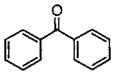
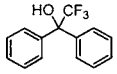
(18) Barrera, M. D.; Cheburkov, Y.; Lamanna, W. M. *J. Fluorine Chem.* **2002**, *117*, 13.

(19) Trifluoromethyl phenyl sulfide, sulfoxide, and sulfone are all commercially available. A number of reports on their preparation have appeared in the literature. See: (a) ref 11 (a). (b) Gerard, F.; Jean-Mannel, M.; Laurent, S.-J. *Eur. Pat. Appl.* **1996**, EP 733614. (c) Chen, Q.-Y.; Duan, J.-X. *Chem. Commun.* **1993**, 918. (d) Yang, J.-J.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1998**, *63*, 2656.

(20) Hassner A., Stumer, C., Eds. *Organic Syntheses Based on Name Reactions and Unnamed Reactions*; Pergamon: New York, 1994; p 251.

(21) Stahly, G. P. *J. Fluorine Chem.* **1989**, *43*, 53.

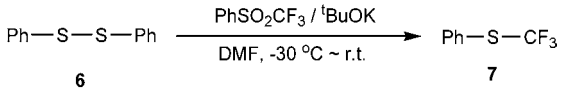
Table 2. Reaction of Trifluoromethyl Phenyl Sulfone (**1a**) or Sulfoxide (**1b**) (2 equiv) with Nonenolizable Carbonyl Compounds (1 equiv) and ^{t}BuOK (2.5 equiv) in DMF between −50 °C and Room Temperature

entry	carbonyl compound	trifluoromethylating agent	product	yield[a] (%)	^{19}F NMR (ppm)[b]
1		**1a**		77	-78.5 (d)
2		**1a**		62	-78.4 (d)
3		**1a**		83	-78.9 (d)
4		**1a**		76	-78.7 (d)
5		**1a**		79[c]	-72.3 (d)
6		**1b**		68	-78.5 (d)
7		**1a**		86	-74.5
8		**1a**		74	-75.1
9		**1a**		83	-74.7
10		**1a**		85	-74.4
11		**1a**		73	-75.0
12		**1a**		82	-76.1
13		**1b**		83	-74.5

[a] Isolated yields. [b] $CFCl_3$ was used as an internal reference. [c] Determined by ^{19}F NMR using $PhOCF_3$ as an internal standard.

(^{19}F NMR: − 43.3 ppm). This reaction was even more facile than that of carbonyl compounds.

Scheme 3. Trifluoromethylation of PhSSPh with **1a**



The **1a**/^{t}BuOK trifluoromethylation method was also applied to other systems. For instance, methyl benzoate can be trifluoromethylated to generate 2,2,2-trifluoroacetophenone in 30% yield at temperatures between −50 and −20 °C. CF_3Cu can be generated in situ with **1a**/^{t}BuOK and copper iodide (CuI) and then further react with iodobenzene at 80 °C for 20 h to give α,α,α-trifluorotoluene in 26% yield.

We also attempted the use of other types of sulfones such as methyl trifluoromethyl sulfone (**1c**) as the trifluoromethylating agent. When diphenyl disulfide was used as the model substrate, however, the reaction only gave a minimal yield of product **7** (∼ 2%). This is probably due to the facile deprotonation of the methyl group by ^{t}BuOK, leading to other products.

In summary, potasium *tert*-butoxide-induced trifluoromethylation using phenyl trifluoromethyl sulfone ($PhSO_2CF_3$, **1a**) or sulfoxide ($PhSOCF_3$, **1b**) enables us to transfer CF_3 group into nonenolizable carbonyl compounds and disulfides in high yields. Since both compounds **1a** and **1b** are stable high-boiling liquids that can be readily produced from nonozone-depleting trifluoromethane, the reported new trifluoromethylating method offers an inexpensive and convenient synthetic methodology. Investigations to extend the scope of this novel type of fluoroalkylation methodology to reactions such as difluoroalkylation using difluoromethyl sulfones or sulfoxides are underway.

Acknowledgment. Support of our work in part by Loker Hydrocarbon Research Institute is gratefully acknowledged.

Supporting Information Available: General experimental paragraph; experimental procedures for trifluoromethylation with **1a** (**1b**)/*tert*-BuOK, and ^{1}H, ^{19}F, and ^{13}C NMR and Mass characterization data of the isolated products. This material is available free of charge via the Internet at http://pubs.acs.org.

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