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Trifluoromethyl-Substituted Sulfonium Ylide: Rh-Catalyzed Carbenoid Addition to Trifluoromethylthioether

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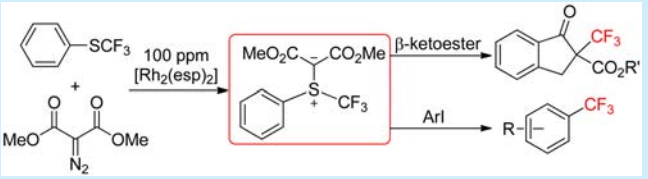
Supporting Information

ABSTRACT: A highly efficient Rh-catalyzed carbenoid addition to trifluoromethylthioether for the formation of trifluoromethyl-substituted sulfonium ylide is described. The trifluoromethyl-substituted sulfonium ylide can act as an electrophilic trifluoromethylation reagent, as demonstrated by trifluoromethylation of β-ketoesters and aryl iodides.



As the most sought-after fluoroalkyl group, the trifluoromethyl group has been frequently utilized by medicinal chemists to manipulate the biological properties of drug molecules[1] due to its unique size, electronic properties, and excellent metabolic stability,[2] as evidenced by a large number of trifluoromethylated pharmaceuticals and drug candidates, such as cholesteryl ester transfer protein (CETP) inhibitors Evacetrapid and Anacetrapid that are undergoing clinical trials,[3] antidepressant Prozac,[4] fungicide Trifloxystrobin,[5] and the herbicide Fusilade.[6] Consequently, development of new efficient methods for the introduction of the trifluoromethyl group into small molecules has become a subject of intense recent study. Tremendous progress has been achieved in the past several years for transition-metal-catalyzed or radical mediated trifluoromethylation of aryl, alkenyl, or alkynyl substrates under mild conditions.[7]

Among the rapidly increasing and powerful trifluoromethylating methods, nucleophilic trifluoromethylation arguably represents the most versatile and actively studied methods, mainly indebted to the availability of the cheap nucleophilic reagent trifluoromethyl-trimethylsilane ($TMSCF_3$).[7l,m] Direct trifluoromethylation of a nucleophile with an electrophilic trifluoromethylating reagent in the presence or absence of a transitional metal catalyst has generally been considered as an alternative straightforward strategy for the preparation of trifluoromethylated compounds.[8] In this respect, the development of several classes of electrophilic trifluoromethylating reagents (Figure 1) by the groups of Yagupolskii,[9] Umemoto,[8a,10] Togni,[8f,11] Shibata,[8c,12] Shreeve,[13] Magnier,[8d,14] Xiao,[15] and Adachi and Ishihara,[16] among others, has provided a strong driving force for the discovery of the new trifluoromethylation methodologies. These reagents now allow the effective trifluoromethylation of a wide range of nucleophiles.

Even though some of these reagents have been commercialized, further broad applications of these electrophilic trifluoromethylating reagents were largely hampered by their relatively complicated synthetic procedures. With a few exceptions,[14,15] most of them required a multistep synthetic

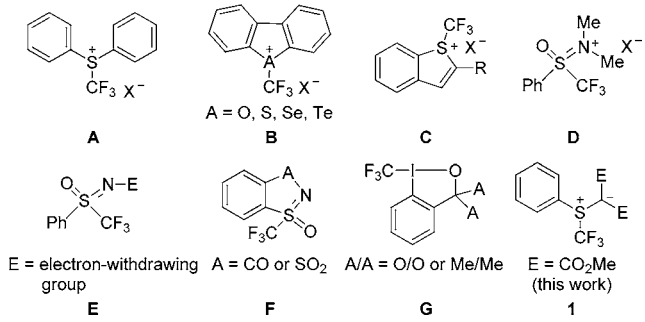


Figure 1. Electrophilic trifluoromethylating reagents.

sequence that significantly lowers the overall efficiency of the preparation process, which makes the reagents rather expensive. Thus, development of new reactive electrophilic trifluoromethylating reagents that could be synthesized highly efficiently remains a considerable unmet need.

Trifluoromethylthioethers can now be easily synthesized and some of them are commercially available, as a result of the recent emergence of new trifluoromethylthiolating reagents and methods.[17] We envisaged that if a carbenoid could add to a trifluoromethylthioether to form a trifluoromethyl-substituted sulfonium ylide,[18] a new class of electrophilic trifluoromethylating reagents might be developed. Herein, we disclose the invention of such a trifluoromethylating reagent **1i** that was generated highly efficiently by a Rh-catalyzed carbenoid addition to trifluoromethylthioether with a catalyst loading as low as 100 ppm. The electrophilicity of the new shelf-stable reagent was then further demonstrated by trifluoromethylation of β-ketoesters under basic conditions or aryl iodides via a copper-mediated single-electron transfer mechanism. Sulfonium ylides have previously been introduced as versatile reagents for functional group transformations such as epoxidation, cyclopropanation, aziridination, the Stevens

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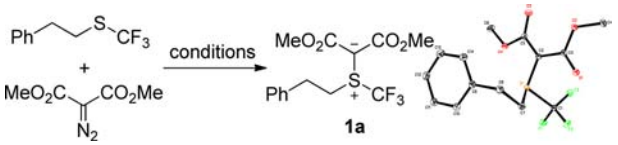
rearrangement, and [2,3]-sigmatropic shifts,[18] our discovery adding an unprecedented yet synthetic valuable new entry to sulfonium ylide's application scaffold.

Reaction of dimethyl diazomalonate with phenylethyl(trifluoromethyl)thioether was chosen at the start of our investigation as a model reaction to identify conditions for the ylide formation. Initial trials using several transition metal catalysts such as $[Cu(OTf)]_2$·benzene, $Cu(CH_3CN)_4PF_6$, $AgNO_3$, $(Ph_3P)AuCl$, or $Fe(acac)_3$ (acac = acetylacetonato) were unsuccessful, and the yields for the desired trifluoromethyl-substituted sulfonium ylide **1a** were less than 30%, as determined by ^{19}F NMR spectroscopy. To our delight, the yield was significantly increased to 87% when 0.1 mol % of $Rh_2(OAc)_4$[18b,19] was used as the catalyst and the reaction was conducted in dichloromethane at 40 °C for 4 h (Table 1, entry 1). The structure of compound **1a** was initially assigned as a trifluoromethyl-substituted sulfonium ylide based on ^1H, ^{19}F, and ^{13}C NMR spectroscopies and elemental analysis. The structure was further confirmed by X-ray diffraction of its single crystals. Since compound **1a** might serve as a new electrophilic trifluoromethylating reagent, we optimize the conditions by studying the effect of different rhodium catalysts and solvents. Switching the catalyst to more soluble $Rh_2(OPiv)_4$ (OPiv = pivalate) or $Rh_2(esp)_2$ (esp = tetramethyl *m*-benzenedipropionate)[20] resulted in an improvement of the yield to 93% and 96%, respectively (Table 1, entries 2–3). In general, reactions in noncoordinating solvents such as dichloromethane, 1,2-dichloroethane, or toluene formed the desired ylide **1a** in excellent yields, while the same reaction in polar coordinating solvents such as THF, dioxane, diglyme, acetone, acetonitrile, or DMF occurred in less than 23% yield (Table 1, entries 4–11). Further studies indicated that the catalyst loading can be decreased to 50–100 ppm and the yields of the reaction were not significantly affected if the reaction time was elongated to 24–48 h (Table 1, entries 12–16). For example, the desired sulfonium ylide **1a** was formed in 78% yield after 48 h at 40 °C when 50 ppm of $Rh_2(esp)_2$ was used, which corresponds to a turnover number (TON) of 7800 (Table 1, entry 16). The only side product observed in the reaction was the dimer from decomposition of dimethyl diazomalonate. The side product was minimized when 0.8 equiv of dimethyl diazomalonate was used (Table 1, entry 15). In the absence of the rodium catalyst, no formation of the sulfonium ylide was observed (Table 1, entry 17).

Table 1. Optimization of the Rh-Catalyzed Reaction of Dimethyl Diazomalonate with Phenylethyl(trifluoromethyl)thioether[a]

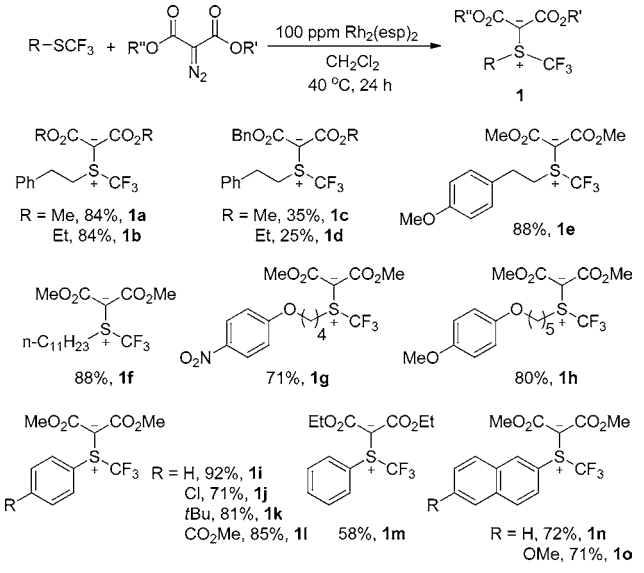


entry	catalyst	loading (mol %)	solvent	time (h)	yield (%)[b]
1	$Rh_2(OAc)_4$	0.1	CH_2Cl_2	4	87
2	$Rh_2(OPiv)_4$	0.1	CH_2Cl_2	4	93
3	$Rh_2(esp)_2$	0.1	CH_2Cl_2	4	96
4	$Rh_2(esp)_2$	0.1	1,2-dichloro ethane	4	92
5	$Rh_2(esp)_2$	0.1	toluene	4	89
6	$Rh_2(esp)_2$	0.1	THF	4	<5
7	$Rh_2(esp)_2$	0.1	dioxane	4	12
8	$Rh_2(esp)_2$	0.1	diglyme	4	6
9	$Rh_2(esp)_2$	0.1	acetone	4	13
10	$Rh_2(esp)_2$	0.1	CH_3CN	4	23
11	$Rh_2(esp)_2$	0.1	DMF	4	<5
12	$Rh_2(esp)_2$	0.05	CH_2Cl_2	24	85
13	$Rh_2(esp)_2$	0.025	CH_2Cl_2	24	86
14	$Rh_2(esp)_2$	0.01	CH_2Cl_2	24	89
15[c]	$Rh_2(esp)_2$	0.01	CH_2Cl_2	24	90 (84%[d])
16	$Rh_2(esp)_2$	0.005	CH_2Cl_2	48	78
17	–	–	CH_2Cl_2	48	–

[a]Reaction conditions: dimethyl diazomalonate (0.10 mmol), phenylethyl(trifluoromethyl)thioether (0.11 mmol), rhodium catalyst (0.01–0.2 mol %) in solvent at 40 °C for 4–48 h. [b]Yields were determined by ^{19}F NMR analysis of the crude reaction mixture with an internal standard. [c]0.8 equiv of dimethyl diazomalonate was used. [d]Isolated yield.

With an efficient method for the formation of trifluoromethyl-substituted sulfonium ylide in hand, we then tried to apply the method to other substituted trifluoromethylthioethers and substituted diazomalonates. In general, reactions of both alkyl- and aryl-substituted trifluoromethylthioethers with dimethyl or diethyl diazomalonate occurred in excellent yields when 100 ppm of $Rh_2(esp)_2$ was used as the catalyst, as summarized in Scheme 1. The reaction was sensitive to the steric hindrance of the substituent of the diazomalonates. Reactions of methyl benzyl diazomalonate or ethyl benzyl diazomalonate occurred in 35% and 25% yields, respectively (Scheme 1, **1c–d**). The yields of the sulfonium ylides were not significantly affected by the substituted groups on the *para*-position of aryl trifluoromethylthioethers. Reactions of both electron-donating or -withdrawing groups substituted aryltrifluoromethylthioethers occurred to give the corresponding CF_3-substituted sulfonium ylides in good to excellent yields (Scheme 1, **1i–l**). Sulfonium ylides **1a–1o** are not air and

Scheme 1. Scope of Rh-Catalyzed Formation of Trifluoromethyl-Substituted Sulfonium Ylides[a,b]



[a]Reaction conditions: dimethyl diazomalonate (0.4 mmol), trifluoromethylthioether (0.5 mmol), $Rh_2(esp)_2$ (100 ppm) in 1.5 mL of CH_2Cl_2 at 40 °C for 24 h. [b]Isolated yields.

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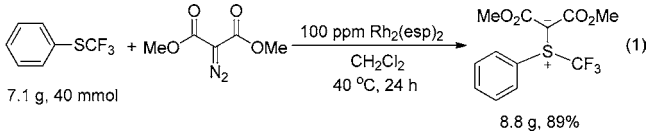
moisture sensitive. No decompositions were observed when they were stored in a vial on a bench for three months.

The reaction can be easily scaled up. Reactions of 7.1 g of trifluoromethylthiolated benzene with 5.0 g of dimethyl diazomalonate in the presence of 3.0 mg of $Rh_2(esp)_2$ afforded 8.8 g of sulfonium ylide **1i** in 89% yield (eq 1).



To probe if trifluoromethyl-substituted sulfonium ylides can serve as the electrophilic trifluoromethylating reagents, we studied the nucleophilic trifluoromethylation of cyclic β-ketoester with different trifluoromethyl-substituted sulfonium ylides.[12b,21] As shown in Figure 2, reaction of alkyl substituted

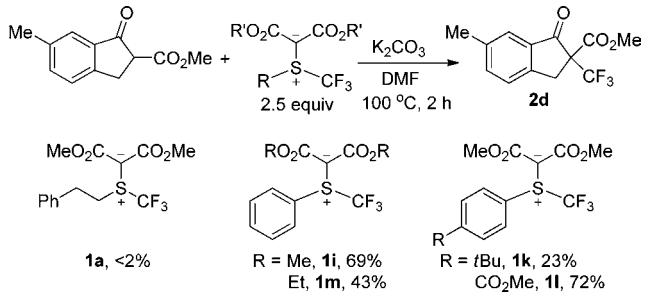
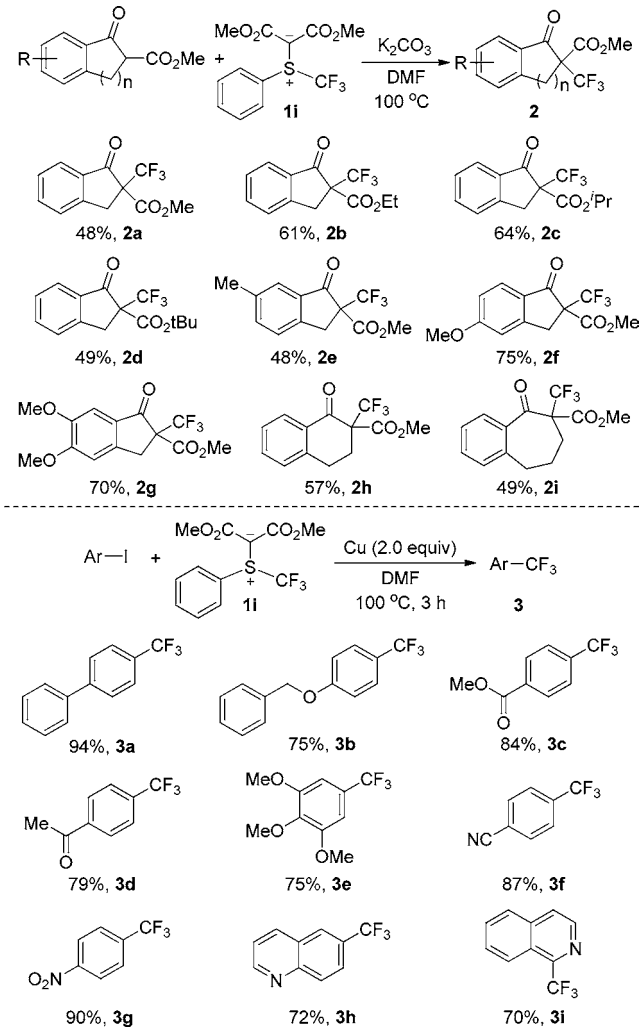


Figure 2. Nucleophilic trifluoromethylation of β-ketoester with different trifluoromethyl-substituted sulfonium ylides. Yields were determined by ^{19}F NMR analysis of the reaction mixture with an internal standard.

sulfonium ylide **1a** occurred in less than 2% yield, while reactions of aryl substituted sulfonium ylides generated the corresponding trifluoromethylated β-ketoesters in 23−72% yields. More specifically, sulfonium ylide **1i** derived from dimethyl diazomalonate gave the product in a much higher yield than its ethyl derivative **1m**, which indicates that the electrophilicity of the sulfonium ylide is greatly affected by the steric hindrance of the sulfonium ylide. Furthermore, it was found that the *para-tert*-butyl substituted phenyl sulfonium ylide **1k** gave the corresponding trifluoromethylated product in much lower yields than sulfonium ylide **1i** and **1l**. These results suggest that the electron-poor or -neutral aryl substituted sulfonium ylides are more reactive than electron-rich derivatives.

Considering the easy availability of the starting material and the cost,[22] we chose sulfonium ylide **1i** as the electrophilic trifluoromethylating reagent for further investigation. As summarized in Scheme 2, a variety of cyclic β-ketoesters afforded the corresponding trifluoromethylated compounds bearing a quaternary carbon center in moderate to good yields in the presence of K_2CO_3 as the base. Likewise, reactions of a variety of aryl and heteroaryl iodides with sulfonium ylide **1i** occurred in good to excellent yields in the presence of 2.0 equiv of copper powder, a trifluoromethylation protocol initially reported by Xiao and co-workers using trifluoromethylated sulfonium salt as the trifluoromethyl source.[23] Notably, various functional groups such as ester, enolizable ketone, nitro, and cyano were compatible with the reaction conditions (Scheme 2).

Scheme 2. Trifluoromethylation of β-Ketoesters and Aryl Iodides with Trifluoromethyl-Substituted Sulfonium Ylides[a,b]



[a]Reaction conditions: β-ketoester (0.5 mmol), compound **1i** (1.25 mmol), K_2CO_3 (0.6 mmol) in 3.0 mL of DMF at 100 °C for 2 h; isolated yields. [b]Reaction conditions: ArI (0.5 mmol), compound **1i** (1.75 mmol), Cu (1.0 mmol) in 5.0 mL of DMF at 100 °C for 3 h; isolated yields.

In summary, we have developed a new electrophilic trifluoromethylation reagent which can be synthesized by a highly efficient Rh-catalyzed carbenoid addition to trifluoromethylthioether with a catalyst loading of 100 ppm. The electrophilic trifluoromethylating ability of the reagent was demonstrated by trifluoromethylation of β-ketoesters and aryl iodides. The advantage of this new reagent includes easy synthesis and scale-up, moisture and air stability, low cost, and structural flexibility. Further modification of the reagent to improve its reactivity and investigation of its synthetic applications are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

All experimental procedures and spectroscopic data of compounds **1a−o**, **2a−i**, and **3a−i**; X-ray crystallography data of **1a**. The Supporting Information is available free of charge on

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Notes

The authors declare no competing financial interest.

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