JOC*Note*

Mild Electrophilic Trifluoromethylation of β-Ketoesters and Silyl Enol Ethers with 5-Trifluoro Methyldibenzothiophenium Tetrafluoroborate

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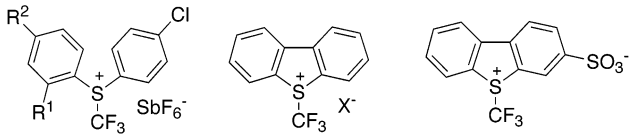
Abstract: Cyclic and acyclic β-ketoesters were efficiently trifluoromethylated with 5-trifluoromethyldibenzothiophenium tetrafluoroborate in the presence of a phase-transfer catalyst to afford the corresponding α-substituted α-trifluoromethyl β-ketoesters in good to excellent yields. In a second approach, 5-trifluoromethyldibenzothiophenium tetrafluoroborate and tetrabutylammonium difluorotriphenylstannate were used for efficient electrophilic trifluoromethylation of various silyl enol ethers leading to the corresponding α-trifluoromethyl ketones in good to high yields.

Organofluorine compounds have received considerable attention and become the focus of intense research efforts due to their fascinating potential applications to the life science fields, agrochemistry, and material science.[1−3] Among fluoroorganic compounds, trifluoromethyl-substituted molecules have gained growing interest during the past decade.[4] The introduction of a trifluoromethyl group with powerful electron-withdrawing ability can lead to significant changes in the physical, chemical, and biological properties of trifluoromethylated compounds when compared with their nonfluorinated analogues.[5] Methods for the incorporation of the trifluoromethyl group into organic molecules may be considered as either nucleophilic, electrophilic, radical, or carbene processes. Recently, nucleophilic, free radical, or carbene trifluoromethylations have been extensively studied and utilized for preparation of trifluoromethylated compounds.[6,7] Electrophilic trifluoromethylation, however, has been developed relatively slowly. Yagupol'skii reported in 1984 the first electrophilic trifluoromethylating agents **1** (Figure 1), which showed low reactivity.[8] The research work of Umemoto in the early 1990s led to the development of highly reactive trifluoromethyl dibenzoheterocyclic salts such as **2a**,**b** and **3** (Figure 1).[9] However, until recently, there were few reports of reactions where a trifluoromethyl group is introduced by electrophilic reagents into an organic molecule.[10] The introduction of the trifluoromethyl group is still a nontrivial exercise, and new methods for direct electrophilic trifluoromethylation are eagerly sought.



1 **2a**, X = OTf **2b**, X = BF_4 **3**

FIGURE 1. Electrophilic trifluoromethylating agents.

α-Substituted α-trifluoromethyl β-ketoesters are attractive compounds because they are regarded as nonenolizable β-ketoesters. In addition, since ketones are easily converted into other functional groups, α-trifluoromethyl ketones and β-ketoesters would be versatile synthetic precursors of various α-trifluoromethyl carbonyl derivatives. Although Umemoto et al. have reported a

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(5) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123−3197.

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(7) Recent articles on nucleophilic process: (a) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757−786. (b) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613−7632. (c) Billard, T.; Bruns, S.; Langlois, B. R. *Org. Lett.* **2000**, *2*, 2101−2103. (d) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Synlett* **2001**, 77−78. (e) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589−590. (f) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Org. Lett.* **2001**, *3*, 2847−2850. (g) Singh, R. P.; Leitch, J. M.; Twamley, B.; Shreeve, J. M. *J. Org. Chem.* **2001**, *66*, 1436−1440. (h) Prakash, G. K. S.; Mandal, M. *J. Am. Chem. Soc.* **2002**, *124*, 6538−6539. (i) Motherwell, W. B.; Storey, L. J. *Synlett* **2002**, 646−648. (j) Langlois, B. R.; Billard, T. *Synthesis* **2003**, *2*, 185−194.

(8) Yagupol'skii, L. M.; Kondratenko, N. V.; Timofeeva, G. N. *J. Org. Chem. USSR* **1984**, *20*, 103−106.

(9) (a) Umemoto, T.; Ishihara, S. *Tetrahedron Lett.* **1990**, *31*, 3579−3582. (b) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156−2164. (c) Umemoto, T.; Adachi, K. *J. Org. Chem.* **1994**, *59*, 5692−5699. (d) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757−1777. (e) Umemoto, T.; Ishihara, S. *J. Fluorine Chem.* **1998**, *92*, 181−187.

(10) (a) Tamiaki, H.; Nagata, Y.; Tsudzuki, S. *Eur. J. Org. Chem.* **1999**, 2471−2473. (b) Blazejewski, J.-C.; Wilmshurst, M. P. Popkin, M. D.; Wakselman, C.; Laurent, G.; Nonclercq, D.; Cleeren, A.; Ma, Y.; Seo, H.-S.; Leclercq, G. *Bioorg. Med. Chem.* **2003**, *11*, 335−345.

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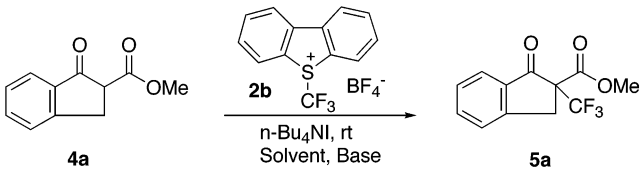
TABLE 1. Phase-Transfer-Catalyzed Electrophilic Trifluoromethylation of 4a with 2b



4a 5a

entry	solvent	*n*-Bu_4NI (mol %)	base	time (h)	yield (%)[a]
1	toluene	10	K_2CO_3	48	0[b]
2	THF	10	K_2CO_3	12	70
3	CH_2Cl_2	10	K_2CO_3	24	72
4	CH_3CN	10	K_2CO_3	24	68
5	DMF	10	K_2CO_3	1	92
6	CH_3OH	10	K_2CO_3	28	0[c]
7	DMF	5	K_2CO_3	3	99
8	DMF	5	K_2CO_3	1	88
9	DMF	1	K_2CO_3	1	80
10	DMF	5	Na_2CO_3	3	82
11	DMF	5	Cs_2CO_3	3	86
12	DMF	5	NaOH	3	65
13	DMF	5	KOH	3	58
14	DMF	5	$CsOH·H_2O$	6	92

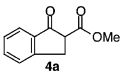
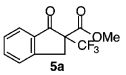
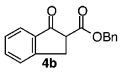
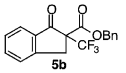
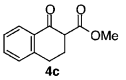
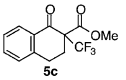
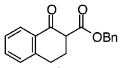
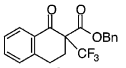
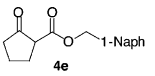
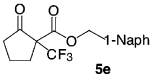
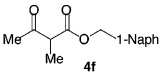
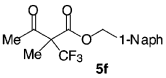
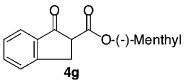
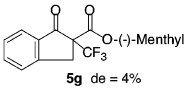
[a] Isolated yield. [b] Substrate **4a** was recovered quantitatively. [c] Trifluoromethylating agent **2b** decomposed (detected by TLC and ^{19}F NMR).

method for trifluoromethylation of β-ketoesters and enolate anions, the reaction conditions remained harsh and provided limited examples. To further develop the electrophilic trifluoromethylation into an efficient protocol, we embarked on the development of convenient reaction conditions. As part of our research program toward the development of organofluorine compounds,[11] we report herein electrophilic trifluoromethylation reactions under mild conditions of various β-ketoesters and silyl enol ethers with commercially available 5-trifluoromethyldibenzothiophenium salt **2b**.

Electrophilic Trifluoromethylation of β-Ketoesters. To determine suitable reaction conditions for electrophilic trifluoromethylation of β-ketoesters, we initially employed 1-oxo-indan-2-carboxylic acid methyl ester **4a** as a model compound and 5-trifluoromethyldibenzothiophenium tetrafluoroborate **2b** as the electrophilic trifluoromethylating agent in the presence of 10 mol % tetrabutylammonium iodide (*n*-Bu_4NI) as a phase-transfer catalyst at room temperature.[12] Results of the phase-transfer-catalyzed electrophilic trifluoromethylation in various solvents and optimization of the reaction conditions are listed in Table 1.

Among the solvents evaluated, polar ones proved to be effective for the reaction; DMF[13] provided the best result, while no reaction occurred in toluene most likely because 5-trifluoromethyl dibenzothiophenium tetrafluoroborate **2b** is insoluble in this solvent (Table 1, entry 1). It is noteworthy that the reaction did not proceed in methanol in which trifluoromethylating agent **2b** quickly decomposed. The amount of phase-transfer catalyst was reduced to 1 mol %, and slightly lower yield was obtained (Table 1, entry 9). K_2CO_3, Na_2CO_3, Cs_2CO_3, and $CsOH·H_2O$ were effective bases in this reaction. As we expected, the reaction proceeded, but slowly and not completely without a phase-transfer catalyst.

TABLE 2. Catalytic Electrophilic Trifluoromethylation of Various β-Ketoesters

Entry	Substrate	Product	Yield (%)[a]	δ (^{19}F) (ppm)[b]
1	 4a	 5a	99	- 69.82
2	 4b	 5b	94	- 69.62
3	 4c	 5c	52 (34)	- 69.31
4	 4d	 5d	60 (28)	- 69.22
5	 4e	 5e	36 (60)	- 69.27
6	 4f	 5f	28 (52)	- 68.93
7[c]	 4g	 5g de = 4%	97	- 69.49/ - 69.50

[a] Isolated yields. Values in brackets are for the recovery of substrates. [b] Measured in $CDCl_3$, relative to $CFCl_3$. [c] Diastereomeric excess was measured by ^{19}F NMR before isolation.

Optimal conditions were established for DMF as a solvent at room temperature in the presence of 5 mol % phase-transfer catalyst, and various substrates were trifluoromethylated. As can be seen by the results summarized in Table 2, α-trifluoromethyl β-ketoesters were obtained in good to excellent yields (Table 2, entries 1−4). The reaction of cyclic and acyclic substrates **4e** and **4f** afforded trifluoromethylated products with relatively low yields (36 and 28%, respectively). Preliminary attempts to extend this reaction to stereoselective trifluoromethylation of β-ketoesters **4g** led to poor selectivity (4% de, Table 2, entry 7), probably due to trifluoromethylation being remote from the chiral centers.

In contrast to the effect of solvent on C- vs O-alkylation of ethyl acetoacetate with alkyl halides,[14] Matsuyama reported that C-alkylation of enolate ions of β-ketoesters with (*p*-chlorophenyl)ethylmethylsulfonium salt increased and O-alkylation decreased in higher polarity solvents.[15] However, it should be noted that in all our experiments, the reaction gave only C-trifluoromethylated products, and O-trifluoromethylated compounds were not detected

(11) (a) Cahard, D.; Audouard, C.; Plaquevent, J.-C.; Roques, N. *Org. Lett.* **2000**, *2*, 3699−3671. (b) Cahard, D.; Audouard, C.; Plaquevent, J.-C.; Roques, N. *Tetrahedron Lett.* **2001**, *42*, 1867−1869. (c) Mohar, B.; Baudoux, J.; Plaquevent, J.-C.; Cahard, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4214−4216. (d) Baudequin, C.; Plaquevent, J.-C.; Audouard, C.; Cahard, D. *Green Chem.* **2002**, *4*, 584−586.

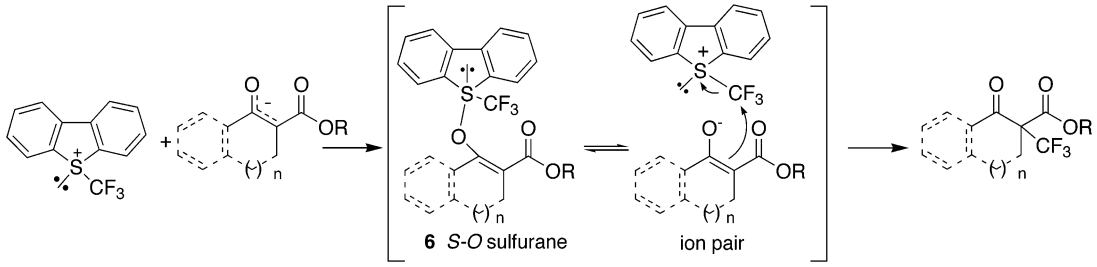
(12) For analogous electrophilic fluorination: Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545−547.

(13) Anhydrous and standard DMF give equal yields of trifluoromethylation.

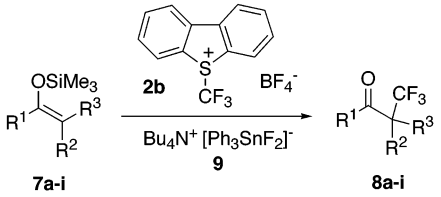
(14) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; The Organic Chemistry Monograph Series; W. A. Benjamin: Menlo Park, CA, 1972; pp 492−628.

(15) Umemura, K.; Matsuyama, H.; Watanabe, N.; Kobayashi, M.; Kamigata, N. *J. Org. Chem.* **1989**, *54*, 2374−2383.

SCHEME 1. Proposed Mechanism for the Reaction of β-Ketoesters with the Trifluoromethylating Agent 2b



SCHEME 2. Fluoride-Mediated Electrophilic Trifluoromethylation of Silyl Enol Ethers

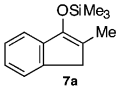
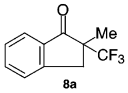
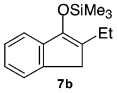
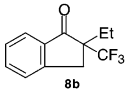
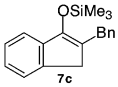
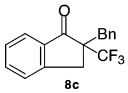
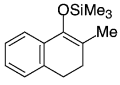
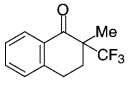
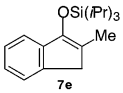
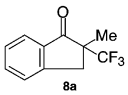
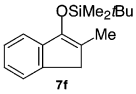
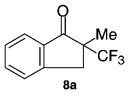
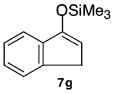
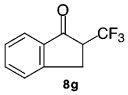
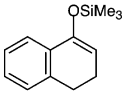
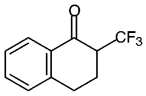
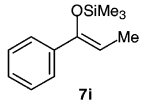
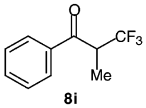


(^{19}F NMR and IR). Concerning the reaction mechanism, the reaction may proceed via sulfurane intermediate **6** (Scheme 1). First, the enolate ion attacks the cationic sulfur atom of the 5-trifluoromethyldibenzothiophenium salt to form *S*-*O*-sulfurane intermediate **6**. Cleavage of the S−O bond forms a tight ion pair, and the enolate attacks the trifluoromethyl group to yield the C-trifluoromethylated product.

Fluoride-Mediated Electrophilic Trifluoromethylation of Silyl Enol Ethers. In the first series of results on electrophilic trifluoromethylation of ketone enolates reported by Umemoto et al.,[9a,b] it was found that electrophilic trifluoromethylation of highly reactive alkali enolates was unsuccessful with only one exception.[16] Therefore, the reactivity of the enolate was moderated by means of various boron Lewis acids to produce a more suitable match between the substrate and the reagent.[9c] Silyl enol ethers of ketones were then considered as moderate reactive substrates for electrophilic trifluoromethylation. However, the reaction conditions were quite harsh (DMF at 80−100 °C in the presence of 1 equiv of pyridine) to provide the trifluoromethylated products in at best 65% yield.[9a] We herein report a new mild and convenient method for the synthesis of α-trifluoromethyl ketones from ketone silyl enol ethers, based on the electrophilic trifluoromethylation by means of 5-trifluoromethyldibenzothiophenium tetrafluoroborate **2b** mediated by tetrabutylammonium difluorotriphenylstannate **9** (Scheme 2).

When silyl enol ethers of ketones were used as substrates, the reaction proceeded smoothly in the presence of cesium fluoride to give the trifluoromethylated products in 59−88% yields. During these investigations we encountered a problem: hydrogen-substituted silyl enol ethers failed to react with the electrophilic trifluoromethylating agent because of the basic nature of CsF. Use of low temperatures and an excess of trifluoromethylating agents was not helpful. Gingras reported that tetrabutylammonium difluorotriphenylstannate, a soluble and non-hygroscopic fluoride source, is very effective in the alkylation of silyl enol ethers.[17] We found that this salt is also effective in our electrophilic trifluoromethylation reaction. Most interestingly, we demonstrated that the order of addition of the reagents was crucial for the trifluoromethylation reaction to occur. Little or no reaction was observed when treatment of silyl enol ethers with Gingras' salt was followed by the addition of the

TABLE 3. Electrophilic Trifluoromethylation of Silyl Enol Ethers

Entry	Silyl enol ether	Product	Yield (%)[a]	δ (^{19}F) (ppm)[b]
1	 7a	 8a	72 (59)	- 74.25 (s)
2	 7b	 8b	80 (80)	- 72.33 (s)
3	 7c	 8c	61 (77)	- 72.60 (s)
4	 7d	 8d	53 (88)	- 73.56 (s)
5	 7e	 8a	65	- 74.25 (s)
6	 7f	 8a	56	- 74.25 (s)
7	 7g	 8g	61 (0)	- 68.20 (d, *J* = 8.2 Hz)
8	 7h	 8h	53 (0)	- 68.04 (d, *J* = 8.7 Hz)
9	 7i	 8i	56 (0)	- 68.77 (d, *J* = 7.9 Hz)

[a] Isolated yields. In brackets are values obtained with CsF as a fluoride source. [b] Measured in $CDCl_3$, relative to $CFCl_3$.

(16) Lithium enolate of 2-methyl-1-indanone treated with **2a** gave 2-methyl-2-trifluoromethyl-1-indanone in 51% yield.

(17) (a) Gingras, M. *Tetrahedron Lett.* **1991**, *32*, 7381−7384. (b) Beckmann, J.; Dakternieks, D.; Duthie, A.; Tiekink, E. R. T. *J. Organomet. Chem.* **2002**, *648*, 204−208.

electrophilic trifluoromethylating agent. This result indicated that the reactivity of enolate anions derived in situ from silyl enol ethers with a fluorine source may have been too great, leading to decomposition prior to reaction with the trifluoromethylating agent. We attempted a different addition order. Indeed, when tetrabutylammonium difluorotriphenylstannate **9** was slowly added to a mixture of silyl enol ether and trifluoromethylating agent, or when this mixture was added to a solution of **9**, the desired products were obtained. Thus, the reaction of silyl enol ethers **7a**−**i** of various ketones with 5-trifluoromethyldibenzothiophenium tetrafluoroborate **2b** in the presence of Gingras' salt **9** afforded α-trifluoromethyl ketones **8a**−**i** in good to high isolated yields (see Table 3).

Trifluoromethylation of silyl enol ethers **7a**−**f** producing α-quaternary trifluoromethylated ketones proceeded smoothly to give the desired products in moderate to high yields (Table 3, entries 1−6). Silyl enol ethers having a bulky trialkylsilyl substituent underwent similar trifluoromethylation (Table 3, entries 5−6). Even hydrogen-substituted silyl enol ethers **7g**−**i**, which lead to enolizable α-trifluoromethylated ketones, reacted smoothly to afford the trifluoromethylated products in good to moderate yields (Table 3, entries 7−9).

In summary, we have developed a very efficient and practical method presenting a remarkable rate acceleration for the preparation of α-substituted α-trifluoromethyl *β*-ketoesters and α-trifluoromethyl ketones using 5-trifluoromethyldibenzothiophenium tetrafluoroborate. The work reported herein enlarges the scope and defines the limitations of the electrophilic trifluoromethylation of carbonyl compounds. We have demonstrated that these reactions can be carried out under milder conditions. Various *β*-ketoesters and silyl enol ethers were trifluoromethylated in good to excellent yields. Extensions of this convenient trifluoromethylation process to other enolizable substrates and to the corresponding asymmetric reaction are in progress.

Experimental Section

Representative Procedure of Trifluoromethylation of *β*-Ketoesters 4a. To a stirred solution of **4a** (19.0 mg, 0.1 mmol), K_2CO_3 (43.0 mg, 0.3 mmol), and tetrabutylammonium iodide (2.0 mg, 0.005 mmol) in DMF (1 mL) was added 5-trifluoromethyldibenzothiophenium tetrafluoroborate (51.0 mg, 0.15 mmol) at room temperature. The mixture was stirred for 3 h and then diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography to afford 1-oxo-2-trifluoromethyl-indan-2-carboxylic acid methyl ester **5a** (25.5 mg, 99%).

Representative Procedure of Trifluoromethylation of Silyl Enol Ethers 7a. To a solution of silyl enol ether **7a** (43.7 mg, 0.2 mmol) and 5-trifluoromethyldibenzothiophenium tetrafluoroborate (102.0 mg, 0.3 mmol) in DMF (1 mL) was slowly added tetrabutylammonium difluorotriphenylstannate (139.0 mg, 0.22 mmol) in DMF (1 mL) at 0 °C using a syringe pump over a period of 1 h. After stirring overnight at room temperature, the resulting mixture was passed through a short column of silica gel and eluted with ether. Concentration of this eluate followed by column chromatography afforded 2-methyl-2-trifluoromethyl-indan-1-one **8a** (30.9 mg, 72%).

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Supporting Information Available: Spectroscopic characterization data for fluorinated new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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