Chemoselective Trifluoromethylation of Methyl Esters Using an $Et_3GeNa/C_6H_5SCF_3$ Combination: Efficient Synthesis of Trifluoromethyl Ketones

Yasuo Yokoyama and Kunio Mochida

Department of Chemistry, Faculty of Science, Gakushuin University, 1-5-1 Mejiro, Toshima-ku, Tokyo 171, Japan

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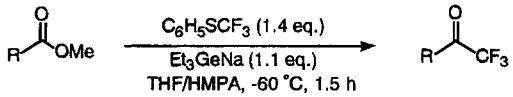
Abstract: Various trifluoromethyl ketones were synthesized from the corresponding methyl esters by effective nucleophilic trifluoromethylation using an $Et_3GeNa/C_6H_5SCF_3$ combination. This trifluoromethylation proceeded chemoselectively. When, cyclohexyl, *i*-propyl and *t*-butyl esters coexisted in the reaction system, only the methyl ester was easily transformed to the desired compounds in excellent yield. Furthermore, some protective groups were remained under this reaction condition.

Trifluoromethyl ketones have been of great interest to synthetic, physical, and medicinal chemists due to their unique biological, chemical, and physical properties.[1] For example, it was suggested that these compounds were isosteric analogues of tetrahedral intermediates formed in the hydrolysis of esters and amides.[2] Various serine esterases could be inhibited by these compounds.[3] Moreover, trifluoromethyl ketones were significant as starting materials of α-trifluoromethyl carbinols which are contained in the basic skeleton of ferroelectric liquid crystals.[4] Many synthetic reactions of the foregoing compounds have so far been reported,[5] among which nucleophilic trifluoromethylation of carboxylic esters is the most effective and straightforward method. However, because of the lability of the trifluoromethylmetallic reagent, there were until recently few reports of successful synthetic methodology.[6] Trifluoromethylzinc reacted with activated esters to give the corresponding compounds.[7] Di-*t*-butyl oxalate was transformed to the trifluoropyruvic acid in its hydrated form by use of a Ruppert reagent (CF_3-TMS).[8] While, these reactions gave the target products, the yields were low and activated substrates must be used. Thus, the development of more powerful nucleophilic trifluoromethylation in which a wide range of esters could be usable as substrates is strongly required. Herein we report a new and convenient method for the synthesis of trifluoromethyl ketones, based on the nucleophilic trifluoromethylation of methyl esters by use of an $Et_3GeNa/C_6H_5SCF_3$ combination which was useful for the syntheses of trifluoromethyl- carbinols[9] and amines[10] (Scheme).

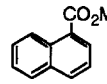
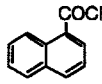
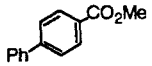
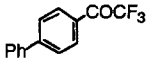
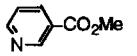
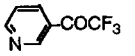
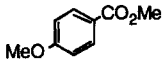
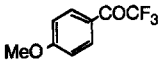
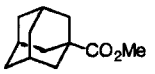
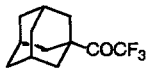
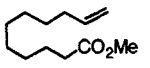
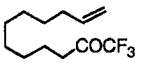
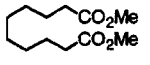
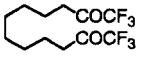


Scheme. Trifluoromethylation of Methyl Esters

This reaction proceeded smoothly and only the methyl esters could be transformed to the desired trifluoromethyl ketone selectively while other type substituents were ineffective.

In the first place, we investigated transformation of various methyl esters to trifluoromethyl ketones. When methyl 1-naphthalenecarboxylate was treated with $C_6H_5SCF_3$ and Et_3GeNa at -60 °C for 1.5 h, the corresponding trifluoromethyl ketone was obtained in 95% yield (Entry 1). Other aryl carboxylates, such as 4-phenylbenzoate, nicotinate and 4-methoxybenzoate, were easily transformed to the desired products quantitatively (Entries 2-4). Furthermore, less reactive alkyl esters could be used as substrates in this trifluoromethylation. Decanoate, undecanoate, dodecanoate and 3-phenylpropionate reacted with an active intermediate (CF_3 anion) to give trifluoromethyl ketones in 95, 98, 96, and 95% yields, respectively (Entries 5-8). Methyl esters having a bulky substituent or an olefin-contained compound were also employed as starting materials in this reaction (Entries 9 and 10). If a substrate which has more than one methyl ester units was utilized for this reaction, multiple trifluoromethylation proceeded. 1,1,1,12,12,12,-Hexafluorododeca-2,11-dione was synthesized from dimethyl sebacinate effectively (Entry 11). Interestingly, ω-pivaloyloxy- and ω-benzoyloxyesters could be transformed to the corresponding trifluoromethyl ketones perfectly without decomposition of their structures (Entries 12 and 13). In all cases, the corresponding bistrifluoromethyl carbinols were not detected at all. These facts prompted us to investigate the chemoselectivity of this method.

Table 1. Trifluoromethylation of Various Methyl Esters

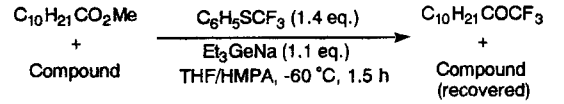
Entry	Substrate	Product[a]	Yield[b] /%
1			95
2			96
3			93
4			94
5	$C_9H_{19}CO_2Me$	$C_9H_{19}COCF_3$	95
6	$C_{10}H_{21}CO_2Me$	$C_{10}H_{21}COCF_3$	98
7	$C_{11}H_{23}CO_2Me$	$C_{11}H_{23}COCF_3$	96
8	$Ph(CH_2)_2CO_2Me$	$Ph(CH_2)_2COCF_3$	95
9			96
10			96
11[c]			97
12	$PivO(CH_2)_7CO_2Me$	$PivO(CH_2)_7COCF_3$	96
13	$BzO(CH_2)_7CO_2Me$	$BzO(CH_2)_7COCF_3$	94

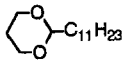
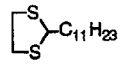
a) All compounds were identified by ^1H-, ^{13}C-, and ^{19}F-NMR. b) Isolated yield. c) 2.8 equivalent amount of $C_6H_5SCF_3$ and 2.2 equivalent amount of Et_3GeNa were used.

The trifluoromethylation of methyl undecanoate was then carried out under this reaction condition with several compounds having a variety of substituents (Table 2). As expected, when sterically hindered esters, such as cyclohexyl-, *i*-propyl, and *t*-butylesters, coexisted in this reaction system, only methyl undecanoate reacted with the active species to give 1,1,1-trifluorododecan-2-one quantitatively, and the foregoing esters were recovered perfectly (Entries 1-3). This reaction also proceeded under coexistence of compounds which had various protective groups. Methoxymethyl (MOM), methoxyethoxymethyl (MEM), and *t*-butyldimethylsilyl (TBDMS) substituents which are known as protective groups of the hydroxyl function did not decompose in this reaction at all (Entries 4-6). Furthermore, a compound having a 6-membered cyclic acetal substituent was perfectly recovered from the

reaction mixture (Entry 7). The desired trifluoromethyl ketone was obtained in 96-97% yields in all cases (Entries 4-7). On the other hand, thioacetal derivative decomposed slightly to form dodecanal in 13% yield (Entry 8). Moreover, when reaction of methyl undecanoate was carried out in the presence of styrene oxide, the desired trifluoromethyl ketone was formed quantitatively and the epoxide was recovered perfectly (Entry 9). These facts suggested that this method was usable as a chemoselective preparation of the trifluoromethyl ketone in organic synthesis.

Table 2. Chemoselective Reactions of Methyl Undecanoate



Entry	Compound	Recovery[a] /%	Yield[b] /%
1	$C_{10}H_{21}CO_2c$-Hex	99	97
2	$C_{10}H_{21}CO_2i$-Pr	99	96
3	$C_{10}H_{21}CO_2t$-Bu	97	96
4	$MOMOC_{11}H_{23}$	99	97
5	$MEMOC_{11}H_{23}$	98	97
6	$TBDMSOC_{11}H_{23}$	97	96
7		99	96
8		87	85
9		98	96

a) Recovered yield (isolated). b) Isolated yield.

A typical procedure is as follows. To a THF (5 mL) solution of $C_6H_5SCF_3$ (386 mg, 2.17 mmol) and methyl 1-naphthalenecarboxylate (289 mg, 1.55 mmol) was added Et_3GeNa in 4 mL of HMPA solution[11] (0.428 mol/dm^3, 1.71 mmol) slowly at -60 °C. After stirring for 1.5 h at -60 °C, the resulting mixture was passed through a short column of slica gel and eluted with ether. Concentration of this eluate followed by column chromatographic purification afforded 330 mg (95%) of the corresponding trifluoromethyl ketone (Table 1, Entry 1).

In summary, we have developed a novel and efficient synthesis of trifluoromethyl ketones. This reaction could be used for efficient transformation of methyl esters to the desired compound, because other type substituents were not affected at all, except for the thioacetal. This is the first and most significant example of chemoselective trifluoromethylation of the methyl ester in the field of organic synthesis. Further investigation is now in progress.

References and Notes

(1) Liebman, J. K.; Greenberg, A; Dolbier, Jr., W. R. *Fluorine-containing Molecules, Structure, Reactivity, Synthesis*; VCH: New York, 1988. Welch, J. T.; Eshwarakrishman, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991.

(2) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1913. Allen, K. N.; Abeles, R. H. *Biochemistry* **1989**, *28*, 8466. Brady, K.; Liang, T.-C.; Abeles, R. H. *Biochemistry* **1989**, *28*, 9066. Parisi, M. F.; Abeles, R. H. *Biochemistry* **1992**, *31*, 9429.

(3) Hammock, B. D.; Wing, K. D.; McLaughlin, J.; Lovell, V. M.; Sparks, T. C. *Pestic. Biochem. Physiol.* **1982**, *17*, 76. Hammock, B. D.; Abdel-Aal, Y. A. I.; Mullin, C. A.; Hanzlik, T. A.; Roe, R. M. *Pestic. Biochem. Physiol.* **1984**, *22*, 209. Ashour, M-B.; Hammock, B. D. *Biochem. Pharmacol.* **1987**, *36*, 1869.

(4) For example, Nohira, H. *J. Synth. Org. Chem. Jpn.* **1991**, *49*, 467 and references cited therein.

(5) Benayoud, F.; Bégué, J. P.; Bonnet-Delpon, D.; Fischer-Durand, N.; Sdassi, H. *Synthesis* **1993**, 1083. Bégué, J. P.; Bonnet-Delpon, D.; Kornilov, A. *Synthesis* **1996**, 529. For a review, see: Bégué, J. P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, *47*, 3207.

(6) Nucleophilic trifluoromethylation of carboxylic esters using trifluoromethylmetallic reagent is difficult, but perfluoroalkylation by use of perfluoroalkylmetallic reagent is applicable for the effective formation of perfluoroalkyl ketones. See: McBee, E. T.; Roberts, C. W.; Curtis, S. G. *J. Am. Chem. Soc.* **1955**, *77*, 6387. Chen, L. S.; Chen, G. J.; Tamborski, C. *J. Fluorine Chem.* **1984**, *26*, 341. Uno, H.; Shiraishi, Y.; Simokawa, K.; Suzuki, H. *Chem. Lett.* **1987**, 1153. Uno, H.; Shiraishi, Y.; Suzuki, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2636. Uno, H.; Matsushima, Y.; Tasaka, T.; Suzuki, H. *Bull Chem. Soc. Jpn.* **1990**, *63*, 293.

(7) Francése, C.; Tordeux, M.; Wakselman, C. *Tetrahedron Lett.* **1988**, *29*, 1029. Tordeux, M.; Francése, C.; Wakselman, C. *J. Chem. Soc. Perkin I* **1990**, 1951 and references cited therein.

(8) Broicher, V.; Geffken, D. *Tetrahedron Lett.* **1989**, *30*, 5243. Broicher, V.; Geffken, D. *Naturforsch, B: Chem. Ser.* **1990**, *45*, 401.

(9) Yokoyama, Y.; Mochida, K. *Synlett* **1996**, 1991.

(10) Yokoyama, Y.; Mochida, K. *Tetrahedron Lett.* in press.

(11) Bulten, E. J.; Noltes, J. G. *Tetrahedron Lett.* **1966**, 4389. Bulten, E. J.; Noltes, J. G. *Tetrahedron Lett.* **1967**, 1443.