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Mg-promoted C-trifluoroacetylation of benzophenone

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ABSTRACT

Mg-promoted reduction of benzophenones in the presence of ethyl trifluoroacetate and trimethylchlorosilane in *N*-methyl-2-pyrrolidinone afforded the corresponding cross-coupling products, which were easily transformed into C-trifluoroacetylated compounds of benzophenones through desilylation by tetrabutylammonium fluoride.

Partially fluorinated compounds sometimes show interesting behaviors based on the characteristics of a fluorine atom and are used as agrochemicals, pharmaceutical compounds, and the other organic functional materials. Synthesis of such fluorine-containing compounds has been focused in recent years and is also attractive in view of fluorous chemistry. Numerous processes have been developed as direct fluorinating methods[1–3] and trifluoromethylation by a trifluoromethyl anion[4–7] is often applied as direct introduction of three fluorine atoms as well. However, trifluoroacetylation[8] is limited except for Friedel–Crafts-type acylation,[9,10] palladium-catalyzed trifluoroacetylation,[11] and coupling between an organometallic compound and a trifluoroacetic acid derivative.[12–16]

On the other hand, we have already reported the electrochemical and Mg-promoted acylation of carbonyl compounds[17] and α,β-unsaturated system[18] using acid anhydride or acid chloride although acylation of carbonyl carbon atoms requires acyl anion equivalents, whose generation and deprotection may frequently require severe reaction conditions and/or use of hazard reagents.[19] In our series of acylation, trifluoroacetylation has never been achieved with trifluoroacetic anhydride under the similar reaction conditions.

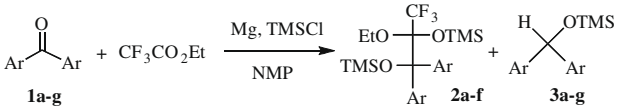
Mg-promoted reductive elimination of a fluoride anion from trifluoromethylcarbonyl compound and its application are reported by Uneyama and coworkers to give defluorinated compound.[20,21]

In this study, Mg-promoted reduction of benzophenone (Ar = Ph) **1a** in the presence of ethyl trifluoroacetate and trimethylchlorosilane in *N*-methyl-2-pyrrolidinone (NMP) gave a C-trifluoroacetylated coupling compound **2a** as a main product (Scheme 1).[22]

Aprotic polar solvents such as NMP, DMF, and *N,N*-dimethylacetamide are applicable as the solvent of this coupling reaction, and NMP gave the best result among them. THF and acetonitrile, which are frequently used in organic synthesis, gave no coupling products.[23]

C-Trifluoroacetylation of benzophenone under various reaction conditions is summarized in Table 1. Excess amount of trimethylchlorosilane led to decrease of the coupling compound **2a** accompanying simply reduced alcohol trimethylsilyl ether **3a** (entries 2–5) and the best result was obtained in the case of use of 4 equiv trimethylchlorosilane. Addition of more than 8 equiv of ethyl trifluoroacetate gave good yield of **2a** (entries 3, 6–9), while addition of less than 7 equiv of ethyl trifluoroacetate in the reaction mixture failed and gave low yield of **2a**. The best result was obtained by accompanying minimum formation of by-products under the conditions of entry 9, and excess amount of magnesium decreased the yield of the product **2a** probably because of electron transfer to trimethylchlorosilane.

Ethyl trifluoroacetate is also more favorable and available reagent rather than trifluoroacetic anhydride, trifluoroacetylimidazole, and phenyl trifluoroacetate, which are more reactive, and surprisingly, all the trifluoroacetylating reagents except ethyl trifluoroacetate gave neither corresponding coupling product **2a**



Scheme 1.

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Table 1
C-Trifluoroacetylation of benzophenone

Entry	TMSCl (equiv mol)	CF_3CO_2Et (equiv mol)	Mg	Yield (%)	
				2a	**3a**
1	5	9	1	29	12
2	3	9	2	14	57
3	4	9	2	63	26
4	5	9	2	52	30
5	6	9	2	44	27
6	4	7	2	45	28
7	4	8	2	54	33
8	4	10	2	58	20
9	4	11	2	63	10
10	5	9	3	53	38
11	5	9	5	36	49

Substrate (5 mmol), NMP (30 ml), rt, N_2 atmosphere.

nor hydrolyzed trifluoromethyl ketone under similar reaction conditions.

The ethoxy group of **2a** did not eliminate in spite of carbanion's attack of benzophenone to the carbonyl carbon of ester group in trifluoroacetate, while similar reactivity and tendency of ethyl trifluoroacetate were reported in previous works.[8,13] The structure of **2a** was confirmed by X-ray crystalline analysis shown in Figure 1.[24]

The coupling reactions of benzophenone derivatives are shown in Table 2. Reduction of *para*- and *meta*-substituted benzophenones afforded the coupling compounds in moderate to excellent yields. However *ortho* isomer was transformed into the simply reduced compound as a main product probably because of the steric hinderance.

Application of perfluoroalkyl carboxylic acid ester instead of ethyl trifluoroacetate to this coupling gave a perfluoroacetylated mixture of acetal **4** and ketone **5** accompanying **3a** (Scheme 2). However, the simply reduced product, **3a** was also obtained quantitatively in the case of ethyl difluoroacetate as a coupling compound, probably because the electrophilicity of ethyl difluoroacetate would not be enough to attack to the anionic species derived from benzophenone (Scheme 3).

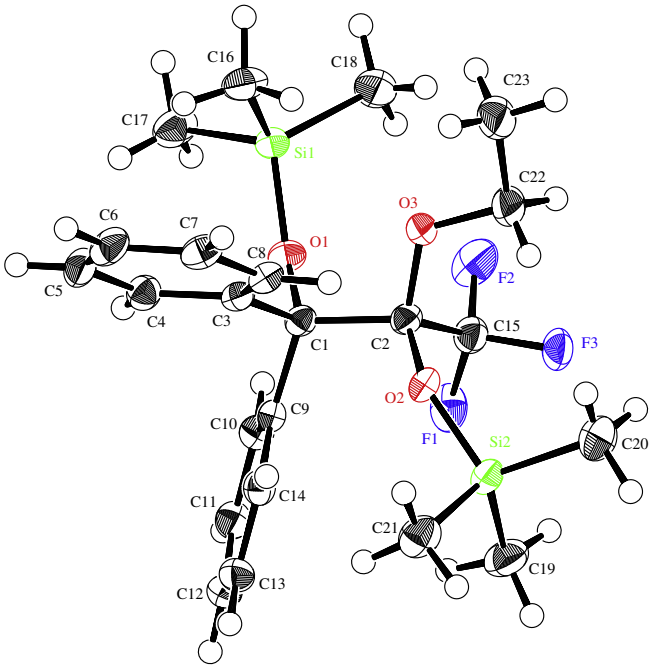
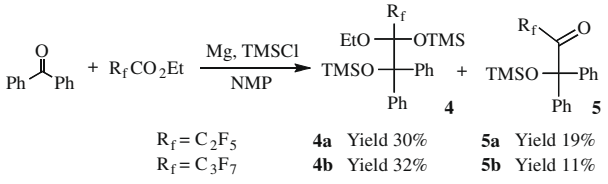


Figure 1. Chemical structure of **2a** by X-ray crystalline analysis.

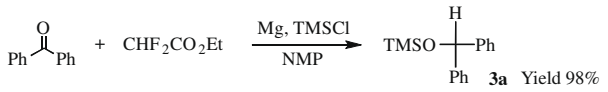
Table 2
C-Trifluoroacetylation of various benzophenones

Entry	Ar		Yield (%)			
			2		**3**	
1	$4\text{-}CH_3C_6H_4$	**1b**	67	**2b**	13	**3b**
2	$4\text{-}CH_3OC_6H_4$	**1c**	74	**2c**	12	**3c**
3	$4\text{-}ClC_6H_4$	**1d**	63	**2d**	20	**3d**
4	$4\text{-}FC_6H_4$	**1e**	90	**2e**	4	**3e**
5	$3\text{-}CH_3C_6H_4$	**1f**	47	**2f**	34	**3f**
6	$2\text{-}CH_3C_6H_4$	**1g**	–		50	**3g**

Ethyl trifluoroacetate (11 equiv mol), Mg (2 equiv mol), TMSCl (4 equiv mol), NMP (30 ml), rt, N_2 atmosphere.



Scheme 2.



Scheme 3.

A benzophenone imine, containing a double bond between carbon and nitrogen, obtained from benzophenone and butylamine, an analogue of benzophenone gave no trifluoroacetylated compound under the similar reaction conditions because of decomposition of the Schiff base.

The compounds **2** and **4** resisted against hydrolysis in typical acidic conditions and cannot be hydrolyzed even under strongly acidic conditions as shown in Table 3.

Tetrabutylammonium fluoride, typical desilylating reagent, is necessary for the removal of trimethylsilyl group to give the corresponding trifluoroacetylated compound **6a** that is a trifluoroacetylation product at the carbonyl carbon of benzophenone as shown in Scheme 4.[25] Catalytic amount of tetrabutylammonium fluoride (0.15 equiv mol) works effectively for this transformation of acetal to ketone (Table 3).

The coupling products of benzophenone derivatives were easily desilylated under similar reaction conditions to give the corresponding fluorinated ketones **6** in good to excellent yield (Table 4).

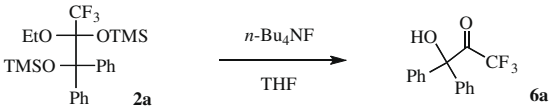
Desilylation of the pentafluorinated coupling compound **4a** by tetrabutylammonium fluoride was also successful to give the pentafluoropropionylated product **7a** in 80% yield (Scheme 5).

Reduction potential of ketone **1a**, acetal **2a**, desilylated compound **6a**, and trifluoroacetylating reagents was measured by cyclic voltammetry and the results are summarized in Table 5.

Table 3
Synthesis of fluorinated ketone **6a** by desilylation of acetal **2a**

Entry	Desilylating reagent	Equiv mol		Yield (%)
1	AcOH	14		No reaction
2	H_2SO_4	15		No reaction
3	$n\text{-}Bu_4NF$	3	**6a**	51
4	$n\text{-}Bu_4NF$	0.5	**6a**	79
5	$n\text{-}Bu_4NF$	0.15	**6a**	86
6	$n\text{-}Bu_4NF$	0.1	**6a**	69

Reaction conditions: **2** (2.5 mmol), −10 to 5 °C, N_2 atmosphere.

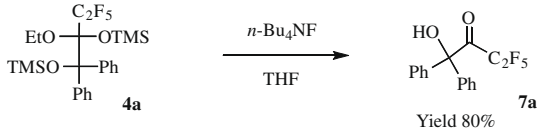


Scheme 4.

Table 4
Desilylation of acetal

Entry	Ar	2		Yield (%) 6
1	4-$CH_3C_6H_4$	**2b**	**6b**	57
2	4-$CH_3OC_6H_4$	**2c**	**6c**	80
3	4-ClC_6H_4	**2d**	**6d**	57
4	4-FC_6H_4	**2e**	**6e**	92
5	3-$CH_3C_6H_4$	**2f**	**6f**	88

Reaction conditions: 2 (2.5 mmol), *n*-Bu_4NF (0.15–0.5 equiv mol), THF (20 ml), −10 to 5 °C, N_2 atmosphere.



Scheme 5.

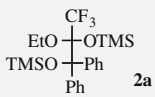
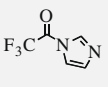
Benzophenone showed more positive reduction potential than ethyl trifluoroacetate[26], while any significant reduction peak cannot be detected for trifluoroacetic anhydride, trifluoroacetylimidazole, and acetal **2a**. Since the trifluoroacetylated compound **6a** showed the same reduction potential at −1.74 V versus Ag/AgCl as the starting benzophenone **1a**, **6a** could be obtained in two steps through the formation of the acetal **2a** without easily reduced carbonyl group.

This reaction is initiated by one electron transfer from Mg to benzophenone followed by the attack of trimethylchlorosilane and ethyl trifluoroacetate to give the product **2** as shown in Scheme 6.

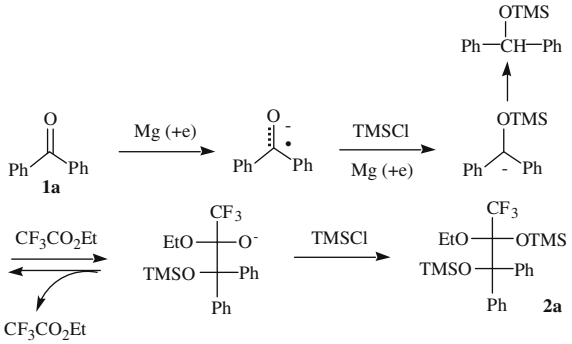
Trifluoroacetic acid derivatives with a good leaving group, such as phenyl trifluoroacetate, trifluoroacetic anhydride, and trifluoroacetylimidazole did not give the coupling compounds, and the result implies that this reaction depends on the nature of leaving group of trifluoroacetic acid derivatives.[27] Acetal **2a** cannot be easily reduced owing to its more negative reduction potential under the reaction conditions, therefore, ethyl trifluoroacetate might be an excellent trifluoroacetylating reagent.

As a summary, Mg-promoted reduction of benzophenones in the presence of ethyl trifluoroacetate gave acetals of trifluoroacetylated

Table 5
Reduction potential of reagents

 **1a**	−1.74 V	CF_3CO_2Et	−2.47
 **6a**	−1.74 V	$(CF_3CO)_2O$	–
 **2a**	–		–

Working electrode: Pt, counter electrode: Pt, reference electrode: Ag/AgCl, substrate (7 mmol/l), solvent: NMP (15 ml), supporting electrolyte: 1% *n*-Bu_4NClO_4, scan rate: 200 mV/s.



Scheme 6.

compounds at the carbonyl carbon atom of benzophenone in high yield and the acetals can be easily converted into the corresponding ketones. This trifluoroacetylation is a novel method for the introduction of trifluoroacetyl group through electron transfer.

Acknowledgment

Authors thank Dr. Motoo Shiro, Rigaku Cooperation for X-ray crystalline analysis of our product **2a**.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.110.

References and notes

1. Hudlicky, M. *Org. React.* **1988**, *35*, 513.
2. Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431. and references cited therein.
3. Kitazume, T.; Yamazaki, T. *Experimental Methods in Organic Fluorine Chemistry*; Kodansha: Tokyo, 1998.
4. Wiedemann, J.; Heiner, T.; Molston, G.; Prakash, G. K. S.; Olah, G. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 820.
5. Singh, R. P.; Cao, G.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1999**, *64*, 2873.
6. Gassman, P. G.; O'Reilly, N. J. *J. Org. Chem.* **1987**, *52*, 2481.
7. Chang, Y.; Cai, C. *J. Fluorine Chem.* **2005**, *126*, 937.
8. Bégué, J. P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, *47*, 3207. and references cited therein.
9. Keumi, T.; Shimada, M.; Takahashi, M.; Kitajima, H. *Chem. Lett.* **1990**, 783.
10. Moriguchi, T.; Endo, T.; Takata, T. *J. Org. Chem.* **1995**, *60*, 3523.
11. Kakino, R.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 371.
12. Chen, L. S.; Chen, G. J.; Tamborski, C. *J. Fluorine Chem.* **1981**, *18*, 117.
13. Creary, X. *J. Org. Chem.* **1987**, *52*, 5026.
14. Villuendas, I.; Parrilla, A.; Guerrero, A. *Tetrahedron* **1994**, *50*, 12673.
15. Kerdesky, F. A. J.; Bahsa, A. *Tetrahedron Lett.* **1991**, *32*, 2003.
16. Guiles, J. W. *Synlett* **1995**, 165.
17. Nishiguchi, I.; Sakai, M.; Maekawa, H.; Ohno, T.; Yamamoto, Y.; Ishino, Y. *Tetrahedron Lett.* **2002**, *43*, 635.
18. Ohno, T.; Sakai, M.; Ishino, Y.; Shibata, T.; Maekawa, H.; Nishiguchi, I. *Org. Lett.* **2001**, *3*, 3439.
19. Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.
20. Nakamura, Y.; Uneyama, K. *J. Org. Chem.* **2007**, *72*, 5894.
21. Hosokawa, T.; Matsumura, A.; Katagiri, T.; Uneyama, K. *J. Org. Chem.* **2008**, *73*, 1468.
22. *General procedure for coupling reaction of benzophenone and ethyl trifluoroacetate:* A typical procedure is as follows. A solution containing TMSCl (20 mmol), ethyl trifluoroacetate (55 mmol) in dry NMP (10 ml) is added to Mg turnings (10 mmol) for Grignard reagent with no pre-treatment in a four-necked flask and after 30 min, a solution of benzophenone (5 mmol) in NMP (20 ml) was added dropwise at room temperature. The reaction mixture was stirred until benzophenone disappeared by TLC monitoring. Then the reaction mixture was poured into 300 ml of a saturated sodium hydrogen carbonate solution and was extracted with ethyl acetate. Usual work-up, subsequent silica gel column chromatography and recrystallization with methanol gave 2-ethoxy-1,1,1-trifluoro-2,3-bis (trimethylsiloxy)-3,3-diphenylpropane **2a** in good yield.*2-Ethoxy-1,1,1-trifluoro-2,3-bis(trimethylsiloxy)-3,3-diphenylpropane* (**2a**): ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): −0.12 (9H, s), 0.16 (9H, s), 1.28 (3H, t, J = 7.1 Hz), 3.87–4.00 (2H, m), 7.23–7.25 (6H, m), 7.48–7.54 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 1.74, 1.89, 15.48, 60.31 (m), 86.03, 100.70 (q, $^2J_{CF}$ = 26.6 Hz), 121.72 (q, $^1J_{CF}$ = 298.1 Hz),

126.54, 126.77, 126.90, 126.94, 129.52, 130.40, 144.55, 144.65. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): −69.07. IR (KBr): 3059, 2959, 1208, 760, 701 (cm^{-1}). MS (APCI): m/z 471 [M^+]. Anal. Calcd for $C_{23}H_{33}F_3O_3Si_2$: C, 58.69; H, 7.07. Found: C, 58.68; H, 6.90. Mp 57.0–57.9 °C.

23. The yields of **2a** and **3a** in NMP, DMF, and *N,N*-dimethyl-acetamide under the same conditions are shown below.NMP (**2a**: 53%, **3a**: 38%), DMF (**2a**: 34%, **3a**: 20%), *N,N*-dimethylacetamide (**2a**: 11%, **3a**: 8%).
24. Crystallographic data for the structural analyses of **2a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 749289). Copy of this information can be obtained free of charge via www.ccdc.cam.ac.uk.
25. *General procedure for desilylation of acetal* **2a**: A typical procedure is as follows. To a solution of **2a** (2.5 mmol) in dry THF (20 ml) is added dropwise 1 M tetrabutylammonium fluoride (0.38 ml) at −10 °C and the reaction mixture was stirred until **2a** disappeared by TLC monitoring. Then 50 ml of water was added at 5 °C and stirring was continued for 30 min. The reaction mixture was extracted with ethyl acetate. Usual work-up and subsequent silica gel column chromatography gave 1,1,1-trifluoro-3-hydroxy-3,3-diphenylpropanone **6a** in a good to excellent yield.

1,1,1-Trifluoro-3-hydroxy-3,3-diphenylacetone (**6a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.22 (1H, s), 7.31–7.39 (10H, m). ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ (ppm): 84.83, 116.23 (q, $^1J_{CF}$ = 294.0 Hz), 127.29, 128.66, 129.00, 139.76, 191.25 (q, $^2J_{CF}$ = 32.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): −71.50. IR (Neat): 3558, 3064, 2929, 1758, 727, 701 (cm^{-1}). MS (APCI): m/z 280 [M^+]. Anal. Calcd for $C_{15}H_{11}F_3O_2$: C, 64.29; H, 3.96. Found: C, 63.84; H, 4.14.

26. Electroreductive C-alkylation and C-silylation of ethyl trifluoroacetate were reported in the following papers Stepanov, A. A.; Minyaeya, T. V.; Martinov, B. I. *Tetrahedron Lett.* **1999**, *40*, 2203; Bordeau, M.; Clavel, P.; Barba, A.; Berlande, M.; Biran, C.; Roques, N. *Tetrahedron Lett.* **2003**, *44*, 3741; Uneyama, K. *J. Fluorine Chem.* **2008**, *129*, 550.
27. Elimination of good leaving group may predominantly proceed in the case of phenyl trifluoroacetate, trifluoroacetic anhydride, and trifluoroacetylimidazole, which would cause further complex reactions. It is also plausible that reduction of such active trifluoroacetylating reagents by Mg metal results into decomposition.