2-Chloro-2,2-difluoroacetophenone: A Non-ODS-Based Difluorocarbene Precursor and Its Use in the Difluoromethylation of Phenol Derivatives

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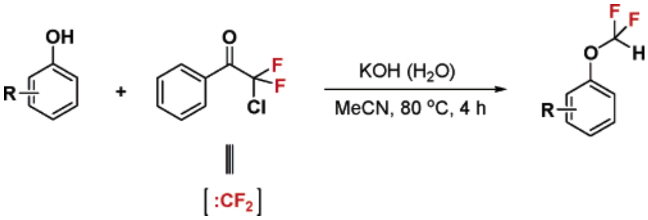

A novel and non-ODS-based (ODS = ozone-depleting substance) preparation of 2-chloro-2,2-difluoroacetophenone (**1**) was achieved in high yield by using 2,2,2-trifluoroacetophenone as the starting material. Compound **1** was found to act as a good difluorocarbene reagent, which readily reacts with a variety of structurally diverse phenol derivatives **4** in the presence of potassium hydroxide or potassium carbonate to produce aryl difluoromethyl ethers **5** in good yields. This new and easy-to-handle synthetic methodology offers an environmentally friendly alternative to other Freon- or Halon-based difluoromethylating approaches.

Difluoromethoxy (OCF_2H) functionality plays an important role in many bioactive organic molecules and in liquid crystal materials for display applications.[1] Although aliphatic difluoromethoxy-containing compounds have important applications such as anesthetics, recently, more attention has been paid to the compounds bearing an aromatic difluoromethoxy group, i.e., aryl difluoromethyl ethers.[1−9] Many aryl difluoromethyl ethers have found applications such as enzyme inhibitors,[2] anti-HIV agents,[3] antimicrobial agents,[4] potassium channel activators,[5] fungicides,[6] pestcides,[7] herbcides,[8] and smectic phase liquid crystals.[9]

Despite the fact that numerous structurally diverse aryl difluoromethyl ethers were synthesized during the past half century, efficient synthetic methods are few.[1] The most commonly used method is the reaction between chlorodifluoromethane ($CHClF_2$, Freon-22) and phenols in the presence of a base.[10] Chlorodifluoroacetates ($ClCF_2COONa$ or $ClCF_2$-COOMe) are also useful reagents for the preparation of aryl difluoromethyl ethers from phenols.[11] Other reported methods, such as using CF_2Br_2,[12] CF_3COONa,[13] FSO_2CF_2COOH,[14] CF_3-ZnBr,[15] CHF_2I,[16] CHF_2Br,[17] and XeF_2,[18] are scarcely used due to the low product yields of aryl difluoromethyl ethers and/or the difficulty in preparing the reagents themselves. On the other hand, chlorodifluoromethane (Freon-22) itself is a ozone-depleting substance (ODS), and chlorodifluoroacetic acid derivatives are commonly prepared directly or indirectly from ozone-depleting precursors.[19] The Montreal protocol has regulated the use of ODS (such as CFCs, HCFCs, and other halogenated ozone-depleting substances); thus, the development of alternative non-ODS-based reagents and synthetic methods for the synthesis of aryl difluoromethyl ethers is highly desired. We have been interested in developing efficient and environmentally benign difluoromethylation methods to synthesize aryl difluoromethyl ethers, with the expectation that *the new difluoromethylating agents and the intermediates in their preparation should not be Freon- or Halon-based*. Herein, we wish to

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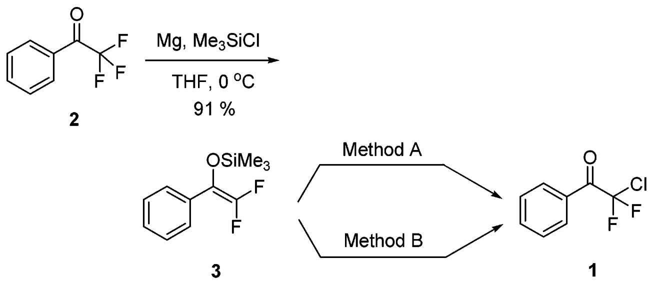
SCHEME 1



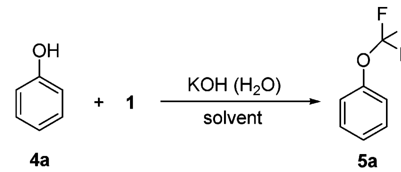
Method A: NCS, TBAF, CH_2Cl_2-THF, rt, 4h; 68% yield;
Method B: Cl_2, CH_2Cl_2, -78 °C, 30 min; 87% yield.

disclose the non-ODS-based preparation of 2-chloro-2,2-difluoroacetophenone **1** ($PhCOCF_2Cl$) and the use of **1** as a novel and convenient difluoromethylating agent for phenol derivatives.

2-Chloro-2,2-difluoroacetophenone **1** is a commercially available compound, and it has been used to synthesize 2,2-difluoro enol silyl ethers,[20] 2,2-difluoro enol phosphates,[21] and other chlorodifluoromethyl-containing compounds.[22−24] However, compound **1** has never been used as a difluorocarbene reagent to prepare difluoromethyl ethers. Currently, the preparation of **1** is mainly based on the reaction between phenyl Grignard reagents (PhMgX) and chlorodifluoroacetic acid.[25] In order to avoid the use of chlorodifluoroacetic acid, we decided to develop a Freon- and Halon-free new synthetic method for the preparation of **1**. Since the commercially available 2,2,2-trifluoroacetophenone **2** is derived from trifluoroacetic acid, a compound commercially produced by the electrochemical fluorination of acetyl fluoride by HF−KHF_2,[26,27] we chose compound **2** as the Freon- and Halon-free precursor to prepare **1** via 2,2-difluoro enol silyl ether intermediates **3** (see Scheme 1). By using Uneyama's magnesium metal-mediated reductive defluorination procedure,[28] trifluoroacetophenone **2** was readily transformed to 2,2-difluoro enol silyl ether **3** in excellent yield (91%). The initial chlorination of **3** with *N*-chlorosuccinimide (NCS) in the presence of tetrabutylammonium fluoride (TBAF) at room temperature was successful, but with only moderate yield (68% isolated) of 2-chloro-2,2-difluoroacetophenone **1** (Scheme 1, method A). When we used the elemental chlorine (Cl_2) as the chlorinating agent to react with **3** in CH_2Cl_2 at −78 °C, the yield of **3** was remarkably improved (87% isolated; Scheme 1, method B). This simple and facile preparation of chlorodifluoroacetophenone **1** from trifluorocetophenone **2** (via both method A and B) was previously never reported, and we found that the reactions with method B are easy to scale up with reproducible chemical yields.

With the chlorodifluoroacetophenone **1** in hand, we carried out the difluoromethylation of phenol derivatives using **1** as a difluorocarbene source. First of all, phenol **4a** was chosen as a model compound to optimize the reaction conditions. As shown in Table 1, increasing the reaction temperature (80 °C) is helpful for the reaction, and acetonitrile-water solvent mixture gave the best yield (entry 6) when 5 equiv of **1** was applied as the difluorocarbene reagent. Although 1,4-dioxane, diglyme, and dimethoxyethane (DME) can be also used as cosolvent for the reaction, the yields were somewhat lower (entries 7−12).

TABLE 1. Survey of Reaction Conditions



entry[a]	reactant ratio[b] (**4a**/**1**/KOH)	solvent[c]	*T* (°C)	yield[d] (%)
1	1:2:21	MeCN−H_2O	0	28
2	1:2:21	MeCN−H_2O	rt	30
3	1:2:21	MeCN−H_2O	80	34
4	1:3:21	MeCN−H_2O	80	45
5	1:4:21	MeCN−H_2O	80	56
6	1:5:21	MeCN−H_2O	80	63
7	1:2:21	dioxane−H_2O	80	25
8	1:2:21	diglyme−H_2O	80	40
9	1:2:21	DME−H_2O	80	32
10	1:3:21	diglyme−H_2O	80	45
11	1:4:21	diglyme−H_2O	80	49
12	1:5:21	diglyme−H_2O	80	53

[a] Reaction conditions: **4a** (1 mmol), KOH (30 wt % in H_2O, 4 mL, ca. 21 mmol) and **1** were mixed in a pressure tube at −78 °C, and the tube was sealed. The reaction mixture was heated to desired temperature for 4 h. [b] Molar ratio. [c] Organic solvent/water (v/v) = 1:1. [d] Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard.

By using the optimized reaction condition, we studied the scope of this new type of difluoromethylation chemistry with reagent **1**. The results are summarized in Table 2. A variety of structurally diverse phenol derivatives **4a**−**k** were difluoromethylated by **1** in the presence of KOH in acetonitrile−water solvent mixture to give the corresponding products **5a**−**k** in moderate to good yields. The reaction was compatible with bromo- and iodo-substituted phenols (entries 7−11) to give products **5g**−**k**, which are possible for further elaboration through transition metal-catalyzed cross-coupling reaction.

We also applied the present non-ODS-based difluoromethylation methodology in the synthesis of key intermediate **9** for the antimicrobial agent garenoxacin mesylate **10**.[29] As shown in Scheme 2, the precursor compound **8** was prepared from 2,6-difluorophenol (**6**) by using the known procedures.[29] Difluoromethylation of **8** by using $PhCOCF_2Cl$ (**1**) in the presence of potassium carbonate (*not* KOH) in CH_3CN−H_2O solvents at 80 °C was proved to be successful, and the desired product **9** was obtained in 60% isolated yield. Intermediate **9** can be further transformed to the target drug garenoxacin mesylate **10** through known procedures.[29]

The plausible reaction mechanism was proposed as shown in Scheme 3. Chlorodifluoroacetophenone **1** reacts with hydroxide (OH^-) to give chlorodifluoromethyl anion species **11** that readily undergoes α-elimination of a chloride ion to afford difluorocarbene intermediate (:CF_2). The phenoxide (ArO^-)

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TABLE 2. Difluoromethylation of Phenyl Derivatives 4 with Reagent 1

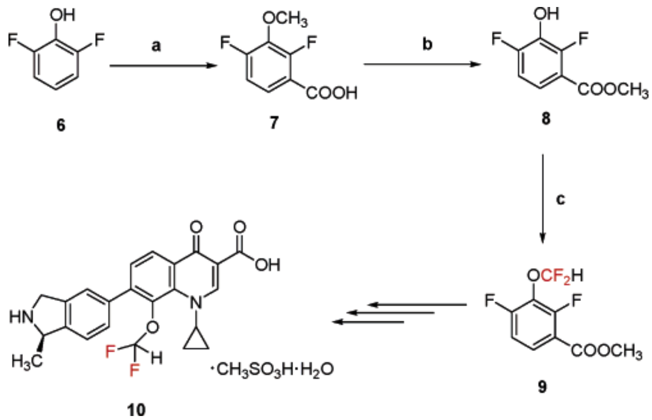
Entry	Substrate **4**	Product **5**	Yield (%)[a]
1	PhOH (**4a**)	$PhOCF_2H$ (**5a**)	63
2	2-naphthol (**4b**)	(**5b**)	77 (76)
3	1-naphthol (**4c**)	(**5c**)	79 (75)
4	4-F-phenol (**4d**)	(**5d**)	70
5	4-Cl-phenol (**4e**)	(**5e**)	69 (60)
6	2,4-Cl_2-phenol (**4f**)	(**5f**)	69 (62)
7	4-Br-phenol (**4g**)	(**5g**)	71 (66)
8	4-I-phenol (**4h**)	(**5h**)	61 (58)
9	2-Br-phenol (**4i**)	(**5i**)	55 (54)
10	2-I-phenol (**4j**)	(**5j**)	71 (65)
11	2,4,6-Br_3-phenol (**4k**)	(**5k**)	51 (50)
12	4-phenylphenol (**4l**)	(**5l**)	(66)
13	4-styrylphenol (**4m**)	(**5m**)	74 (72)

[a] Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard, and the data in parentheses are isolated yields. The isolated yields for entries 1 and 4 are not listed due to the high volatility of the products **5a** and **5d**.

reacts with difluorocarbene species to give the product **5** via anionic species $ArOCF_2^-$. It is also possible that the ArO^- anion attacks **1** to give chlorodifluoromethyl anion **11** and ester **13**. Species **11** decomposes into difluorocarbene and chloride ion, while the ester **13** can be transformed back to ArO^- by the nucleophilic attack of hydroxide ion (Scheme 3).

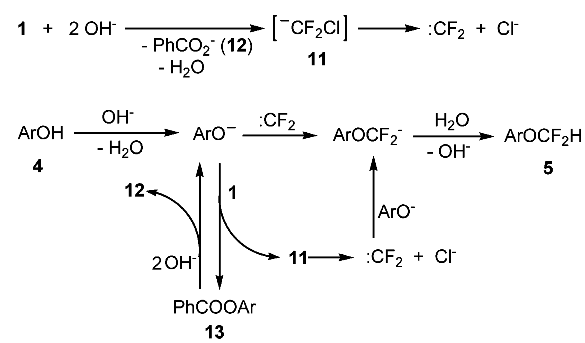
In summary, a novel and non-ODS-based preparation of 2-chloro-2,2-difluoroacetophenone **1** was achieved in high yield using 2,2,2-trifluoroacetophenone as a starting material. Compound **1** was found to act as a good difluorocarbene reagent, which readily reacts with a variety of structurally diverse phenol derivatives **4** in the presence of hydroxide to produce aryl difluoromethyl ethers **5** in good yields. Since reagent **1** derives from non-ozone-depleting precursors, this new and easy-to-handle synthetic methodology offers an environmentally friendly alternative to other Freon- or Halon-based difluoromethylating approaches. The present difluorocarbene chemistry promises to find many applications in the fields of pharmaceutical, agrochemical chemistry, and materials science.

SCHEME 2[a]



[a] Conditions: (a) (1) CH_3I, K_2CO_3, 50 °C, DMF, (2) *n*-BuLi, THF, −78 °C, then add CO_2, 51% yield; (b) (1) CH_3I, KOH, K_2CO_3, DMSO, rt, (2) BBr_3, CH_2Cl_2, −30−0 °C, 57% yield; (c) compound **1**, K_2CO_3, CH_3CN-H_2O, 80 °C, 4 h, 60% yield.

SCHEME 3



Experimental Section

Preparation of Chlorodifluoroacetophenone (1). Method A. Into a mixture of 2,2-difluoro-1-phenyl-1-trimethylsiloxyethene **3** (5.70 g, 25 mmol), CH_2Cl_2 (60 mL), and *N*-chlorosuccinimide (3.99 g, 30 mmol) was added TBAF (2.0 mL, 1 M in THF). Then the mixture was stirred for 4 h at rt. The completion of the reaction was monitored by ^{19}F NMR. After the removal of solvent under vacuum, the crude product was further purified by silica gel column chromatography to give product **1** as a colorless liquid: yield 68% (3.22 g).

Method B. Compound **3** (22.8 g, 100 mmol) was dissolved in CH_2Cl_2 (150 mL) at −78 °C. Then Cl_2 was passed through the mixture for 30 min. The completion of the reaction was monitored by ^{19}F NMR. After the removal of solvent under vacuum, the crude product was further purified by silica gel column chromatography to give product **1** as a colorless liquid: yield 87% (16.53 g). The characterization data of **1** was consistent with the previous report.[25]

Typical Procedure for Difluoromethylation of Phenols Using Compound 1. Into a mixture of 1-naphthol (0.144 g, 1 mmol), aqueous KOH (30 wt %, 4 mL), and CH_3CN (4 mL) at −78 °C was added chlorodifluoroacetophenone (**1**). The reaction tube was sealed, and the mixture was heated to 80 °C and stirred for 4 h. Then the mixture was extracted with Et_2O (25 mL × 3), and the combined organic phase was dried over $MgSO_4$. After the removal of solvents under vacuum, the crude product was further purified by silica gel column chromatography to give product **5c** as a colorless liquid. Yield: 75% (146 mg). ^{1}H NMR: δ 8.18 (t, J = 5.0 Hz, 1H), 7.85 (t, J = 4.4 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.54 (t, J = 4.3 Hz, 2H), 7.40 (t, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 6.65 (t, J = 73.9 Hz, 1H). ^{19}F NMR: δ −79.8 (d, J = 72.5 Hz, 2F). ^{13}C NMR: δ 147.5, 134.7, 127.8, 126.9, 126.6, 126.5, 125.4, 125.3, 121.6, 116.6 (t, J = 257.3 Hz), 113.7. MS (EI, *m/z*): 194 (M^+, 79.16), 144 (100.00). IR (film): 3060, 1600, 1582, 1510, 1467, 1375, 1263, 773 cm^{-1}. Anal. Calcd for $C_{11}H_8F_2O$: C, 68.04; H, 4.15; Found: C, 68.18; H, 4.14.

Preparation of Compound 9. Into a mixture of compound **8** (188 mg, 1.0 mmol), K_2CO_3 (4.968 g, 36.0 mmol), CH_3CN (4 mL), and H_2O (4 mL) at rt was added chlorodifluoroacetophenone (950 mg, 5.0 mmol). The reaction tube was sealed, and the mixture was heated to 80 °C and stirred for 4 h. Then the mixture was extracted with Et_2O (25 mL × 3), and the combined organic phase was dried over $MgSO_4$. After the removal of solvents under vacuum, the crude product was further purified by silica gel column chromatography to give product **9** as a white solid. Yield: 60% (143 mg). ^{1}H NMR: δ 7.89 (m, 1H), 7.06 (t, J = 8.8 Hz, 1H), 6.61 (t, J = 73 Hz, 1H), 3.95 (s, 3H). ^{19}F NMR: δ −82.6 (dt, J = 73.5 Hz, 7 Hz, 2F), −116.7 (m, 1F), −120.2 (m, 1F). The characterization data was consistent with the previous report.[4,29]

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Supporting Information Available: General experimental information and characterization data of the isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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