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Reactions of 1,1-difluoroalkylzinc halides with chlorinating reagents*

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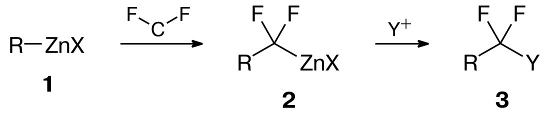
Compounds bearing chlorodifluoromethyl group can be assembled from organozinc chlorides, (chlorodifluoromethyl)trimethylsilane (Me_3SiCF_2Cl), and sulfuryl chloride as a chlorine source. Reactions of 1,1-difluoro-substituted organozinc bromides (RCF_2ZnBr) with different chlorinating reagents lead to predominant or partial formation of the products bearing bromodifluoromethyl group.

Key words: organozinc reagents, chlorination, chlorodifluoromethyl group.

A wide range of practical applications of organofluorine compounds has stimulated the development of efficient and versatile procedures for the introduction of fluorinated moieties. Despite the great progress in this research area,[1] synthetic methods to afford several fluorine-containing functional groups are limited. For instance, compounds bearing the CF_2Cl group are hardly accessible and conventional methods for their synthesis involve free radical reactions,[2] chlorine—fluorine exchange in the trichloromethyl group[3] (required treatment with anhydrous HF), and the use of CF_2Cl-containing building blocks.[4]

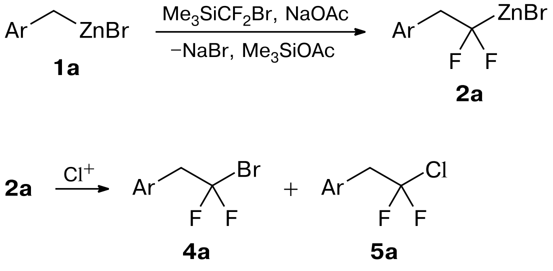
Recently, we have described a novel approach to access compounds bearing the CF_2 group *via* reactions of organozinc compound **1** with difluorocarbene followed by the reaction of 1,1-difluoro-substitited derivatives **2** with electrophiles[5—7] (Scheme 1). Compounds bearing the CF_2Br and CF_2I groups can be readily synthesized using bromine and iodine.[5,6] In the present communication, we extended this approach to the synthesis of compounds with the CF_2Cl group (see Scheme 1, Y = Cl).

Scheme 1



1,1-Difluoro-substituted organozinc reagent **2a** was synthesized following the known procedure[5] from [4-(methoxycarbonyl)benzyl]zinc bromide **1a** and silane Me_3SiCF_2Br as a difluorocarbene source using MeCN as a solvent (Scheme 2). On the next step, reagent **2a** was treated with different chlorinating reagents (Table 1). It was found that **2a** reacts with all sources of electrophilic chlorine atom to give compound **4a** as by-product or even

Scheme 2



Ar = 4-$MeO_2CC_6H_4$

Table 1. Chlorination of organozinc reagent **2a**

Reagent	*T*/°C	Ratio of **4a** : **5a***
Cl_2	−78 → 20	45 : 55
N-Chlorosuccinimide	−25 → 20	>99 : 1
Trichloroisocyanurate	−25 → 20	>99 : 1
$PhICl_2$	−25 → 20	>99 : 1
SO_2Cl_2	20	93 : 7
$CuCl_2$	20	56 : 44
$CuCl_2$ + 4 $BnNEt_3Cl$	20	45 : 55

* ^{19}F NMR data.

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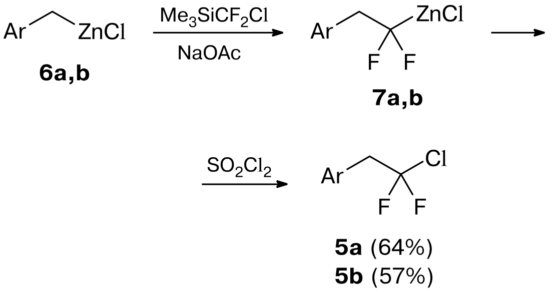
dominant product. Apparently, chlorinating reagents oxidize the bromide ions both present in the reagent **2a** and formed from Me_3SiCF_2Br. However, addition of silver acetate capable of acting as a bromide ion scavenger results in decomposition of reagent **2a**. It should be noted that separation of a mixture of compounds **4a** and **5a** is very complicated due to the similarity of their physicochemical properties.

To exclude the possibility of bromination, we employed the corresponding organozinc chlorides **6a**,**b** together with (chlorodifluoromethyl)thrimethylsilane as a source of the CF_2 species in the presence of sodium acetate as an activator. Chlorination of intermediate reagents **7a**,**b** was achieved with sulfuryl chloride (Scheme 3). This procedure allows us to obtain compounds **5a**,**b** bearing the chlorodifluoromethyl group in 57—64% yields.

Scheme 3



5—7: Ar = 4-$MeO_2CC_6H_4$ (**a**), 1-naphthyl (**b**)

In summary, we demonstrated that compounds bearing the chlorodifluoromethyl group are readily available *via* reactions involving organozinc reagents. It should be emphasized that this method can be accomplished only with organozinc chlorides since organozinc bromides lead to undesired bromodifluoro-substituted products due to oxidation of the bromide ions with the chlorinating reagents.

Experimental

^1H, ^{13}C, and ^{19}F NMR spectra were run on a Bruker AM-300 instrument in $CDCl_3$. Acetonitrile was distilled over CaH_2. (1-Naphthylmethyl)zinc chloride[5] and (chlorodifluoromethyl)trimethylsilane[8] were synthesized by the known procedure.

Methyl 4-(chloromethyl)benzoate. A mixture of methyl 4-(bromomethyl)benzoate (5.13 g, 22.4 mmol) and LiCl (1.90 g, 44.8 mmol) in diglyme (20 mL) was stirred at 0 °C for 18 h. Then, ice water (10 mL) and hexane (10 mL) were added. The organic layer was separated, filtered through Na_2SO_4, and concentrated *in vacuo*. To the residue, diglyme (10 mL) and LiCl (0.95 g, 22.4 mmol) were added and the mixture was stirred at 0 °C for 5 h. The stirred reaction mixture was diluted with water (30 mL), the precipitate formed was collected, dried *in vacuo*, and recrystallized form methanol. Methyl 4-(chloromethyl)benzoate was obtained in the yield of 2.89 g (70%).[9]

[4-(Methoxycarbonyl)benzyl]zinc chloride (6a). To a suspension of zinc dust (1.21 g, 18.5 mmol) in THF (8 mL), two drops of Me_3SiCl were added and the mixture was heated to reflux. After cooling the mixture using ice-water, methyl 4-(chloromethyl)benzoate (1.66 g, 9.0 mmol) was added. The mixture was stirred at 0 °C for 2 h and then at room temperature for 16 h. The 0.94 *M* solution (iodometry data) was obtained.

Methyl 4-(2-chloro-2,2-difluoroethyl)benzoate (5a). A solution of [4-(methoxycarbonyl)benzyl]zinc chloride **6a** (0.47 mmol, 0.50 mL, 0.94 *M* solution in THF) was diluted with diglyme (0.5 mL) and anhydrous NaOAc (50.7 mg, 0.62 mmol) was added. The mixture was cooled to –25 °C and Me_3SiCF_2Cl (98 mg, 0.62 mmol) was added with stirring. The reaction mixture was stirred at –25 °C for 45 h and at 0 °C for 1 h. Then, SO_2Cl_2 (80.4 mg, 0.60 mmol) was added and stirring was continued at 0 °C for 30 min. The volatiles were removed *in vacuo* (~15 Torr), and the residue was diluted with hexane (5 mL) and 1 *M* H_2SO_4 (5 mL). Aqueous layer was extracted with hexane (2×3 mL). Combined organics were washed with 1 *M* H_2SO_4 (3 mL), dried with Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography (gradient elution with EtOAc—hexane, 1 : 40 → 1 : 20) afforded compound **5a** in the yield of 71 mg (64%), colorless oil, R_f 0.29 (EtOAc—hexane, 1 : 8). ^1H NMR (300 MHz), δ: 8.04 (d, 2 H, CH_{Ar}, J = 8.1 Hz); 7.39 (d, 2 H, CH_{Ar}, J = 8.1 Hz); 3.92 (s, 3 H, OMe); 3.62 (t, 2 H, CH_2, J = 13.0 Hz). ^{13}C NMR (75 MHz), δ: 166.7; 136.0 (t, J = 2.9 Hz); 130.7, 130.2, 129.9; 128.2 (t, J = 292.5 Hz); 52.3; 47.8 (t, J = 25.3 Hz). ^{19}F NMR (282 MHz), δ: –51.8 (t, J = 13.0 Hz). Found (%): C, 51.08; H, 4.01. $C_{10}H_9ClF_2O_2$. Calculated (%): C, 51.19; H, 3.87.

1-(2-Chloro-2,2-difluoroethyl)naphthalene (5b). A solution of (1-naphthyl)zinc chloride (1.25 mmol, 1.0 mL, 1.25 *M* solution in THF) was diluted with *N*-methylpyrrolidone (1.0 mL), and anhydrous NaOAc (130 mg, 1.59 mmol) was added. After cooling the mixture to –25 °C, Me_3SiCF_2Cl (239 mg, 1.51 mmol) was added with stirring and stirring was continued for 24 h at the same temperature. Then, SO_2Cl_2 (201 mg, 1.49 mmol) was added and stirring was continued for 20 min. The cooling was removed, the stirred reaction mixture was treated with hexane (3 mL) and saturated aqueous $NaHCO_3$ (5 mL). After warming up to room temperature, the organic layer was separated and the aqueous layer was extracted with hexane (2×5 mL). The combined organics was dried with Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography (elution with hexane) afforded compound **5b** in the yield of 162 mg (57%), colorless oil, crystallized on standing. R_f 0.28 (hexane), m.p. 38—41 °C. ^1H NMR (300 MHz), δ: 8.06 (d, 1 H, CH_{Ar}, J = 8.2 Hz); 7.94—7.85 (m, 2 H, CH_{Ar}); 7.63—7.44 (m, 4 H, CH_{Ar}); 4.10 (t, 2 H, CH_2, J = 13.3 Hz). ^{13}C NMR (75 MHz), δ: 134.1, 132.6, 130.1, 129.3; 129.1 (t, J = 293.4 Hz); 129.0; 127.4 (t, J = 2.3 Hz); 126.7; 126.0; 125.3; 123.9 (t, J = 1.7 Hz); 44.5 (t, J = 25.1 Hz). ^{19}F NMR (282 MHz), δ: –50.5 (t, J = 13.3 Hz). Found (%): C, 63.71; H, 4.09. $C_{12}H_9ClF_2$. Calculated (%): C, 63.59; H, 4.00.

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