Preparation and reaction of 2-chloro-3,3-difluorocyclopropenylzinc reagent

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2-Chloro-3,3-difluorocyclopropenylzinc reagent 1, readily prepared by the direct reaction of 1-chloro-3,3-difluoro-2-iodocyclopropene with zinc powder in dimethylformamide–hexamethylphosphoric triamide co-solvent, exhibits excellent stability at room temperature in the absence of oxygen and/or moisture. The reaction of this zinc reagent with a variety of acyl and alkyl halides is found to be catalysed by copper(I) bromide and represents a convenient route to the synthesis of previously inaccessible substituted 3,3-difluorocyclopropenes.

Introduction

Although much effort has been devoted in recent years to the development of new synthetic methodologies in organofluorine chemistry, there are still many synthetic limitations to the preparation of fluoroorganic compounds some of which may possess interesting biological properties.[1] Vinylic substituted 3,3-difluorocyclopropene derivatives are such compounds, which are expected to be useful synthetic intermediates[2] in fluorine chemistry, but have been little explored because of their relative inaccessibility.

Small ring compounds such as antimycotic azoles[3] and antibacterial quinolinecarboxylic acids[4] are also of interest in medicinal chemistry. The 1,2-addition of difluorocarbene generated from $(CF_3)_3PF_2$ or $(CH_3)_3SnCF_3$ by pyrolytic decomposition to acetylene would be a plausible way of preparing the unknown 3,3-difluorocyclopropene derivatives, although, for practical reasons, this direct approach is hard to realize.[5] Further, nucleophilic substitution of polyhalogenated derivatives of 3,3-difluorocyclopropene which require both extremely low temperatures and are limited to a few nucleophiles, are often unsuccessful.[6]

As far as we know, there are no earlier reports that deal with fluorocyclopropenylmetal reagents as intermediates for the synthesis of fluorocyclopropene derivatives, compounds which are of interest in connection with our continuing studies of organometallic reagents derived from polyfluorocycloalkenes.[7]

In this paper, we report the facile synthesis of the stable 2-chloro-3,3-difluorocyclopropenylzinc reagent **1** from the reaction of 1-chloro-3,3-difluoro-2-iodocyclopropene with zinc metal and the utilization of this reagent for the synthesis of vinylic substituted 3,3-difluorocyclopropene derivatives.

Results and discussion

The starting material, 1-chloro-3,3-difluoro-2-iodocyclopropene was prepared by a literature method,[8] although a significant improvement was achieved by using flash distillation rather than steam distillation in the work-up procedure.

The reaction of 1-chloro-3,3-difluoro-2-iodocyclopropene with activated zinc powder at room temperature in a variety of solvents [dimethylformamide (DMF), tetrahydrofuran (THF), acetonitrile, glymes, DMF–hexamethylphosphoric triamide (HMPA), THF–HMPA] gave, after 2 h, the zinc reagents as a mono/bis mixture.[9] They were identified by ^{19}F NMR spectroscopy (Fig. 1); the ratio of products was affected by the reaction temperature.

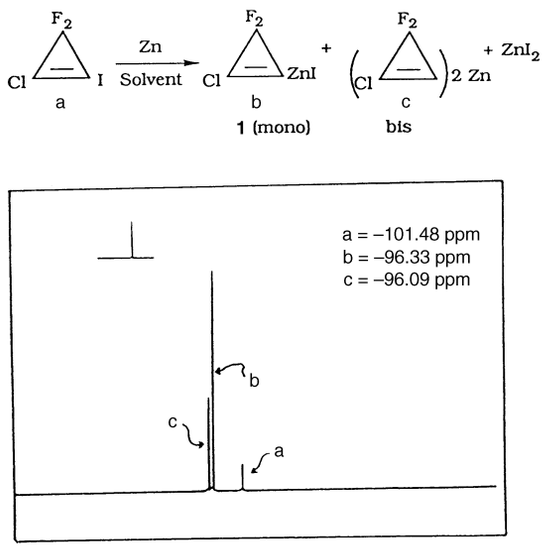

Fig. 1 ^{19}F NMR spectrum of starting iodide and mono, bis zinc reagents

Optimization of reaction conditions in terms of solvent and temperature showed that a co-solvent system such as DMF–HMPA at 5~15 °C gave the best yield of the zinc reagent **1**. At higher temperatures, the ratio of bis-zinc reagent was increased.

Therefore, 1-chloro-3,3-difluoro-2-iodocyclopropene was allowed to react with activated zinc powder at 10 °C in DMF–HMPA (7:1, v/v). After a short induction period, the reaction mixture became warm and its colour changed from grey to light brown; the reaction was completed in *ca.* 2 h. The yield of zinc reagent **1**, determined by ^{19}F NMR analysis, was 85%. The ^{19}F NMR signal of the allylic fluorines in the zinc reagent **1** is shifted downfield by 5.15 ppm (−101.48 to −96.33) from that of the allylic fluorines in the starting material, 1-chloro-3,3-difluoro-2-iodocyclopropene. This zinc reagent is found to be quite stable at room temperature in the absence of oxygen and/or moisture; *e.g.* there was a 20% loss of activity after 3 days at room temperature under a nitrogen atmosphere. However, this

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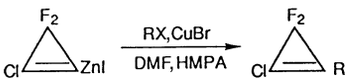
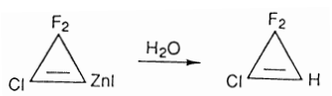
Table 1 Reaction of 2-chloro-3,3-difluorocyclopropenylzinc iodide with alkyl and acid halides at −70 °C



Entry	RX	Time (h)	Product (R)	Yield(%)[a]
1	$PhCH_2Br$	3	CH_2Ph	88 (**2**)
2	CH_2=$CHCH_2Br$	3	CH_2CH=CH_2	75 (**3**)
3	CH_3CH=$CHCH_2Br$	3	CH_2CH=$CHCH_3$	78 (**4**)
4	HC≡CCH_2Br	3	CH_2C≡CH	70 (**5**)
5	MeI	6	—	—
6	PrBr	6	—	—
7	PhCOCl	1	COPh	90 (**6**)
8	MeCOCl	1	$COCH_3$	50 (**7**)
9	EtCOCl	1	$COCH_2CH_3$	70 (**8**)
10	2-Thienyl-COCl	1	2-Thienyl-CO	80 (**9**)
11	2-Furyl-COCl	1	2-Furyl-CO	75 (**10**)

[a] Isolated yields. Yields are based on alkyl and acid halides used.

reagent is moisture sensitive and readily hydrolysed to the reduced olefin (Scheme 1).

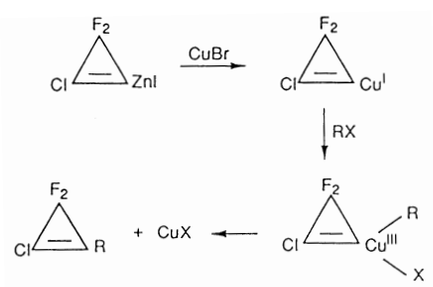


Scheme 1

To demonstrate the synthetic utility for the synthesis of 3,3-difluorocyclopropene derivatives, we have investigated the reactivity of zinc reagent **1** with a variety of alkyl and acid halides. Although this zinc reagent by itself fails to react with these electrophiles at room temperature, with reactive alkyl halides and acid halides in the presence of a catalytic amount of copper(I) bromide[10,11] it readily gives the corresponding vinylic substituted compounds. It fails, however, to react with methyl iodide and propyl bromide.

Although the 2-chloro-3,3-difluorocyclopropenylcopper reagent prepared from metathesis of the zinc reagent **1** with copper(I) bromide was not observed in the ^{19}F NMR spectrum, the change in reactivity suggests the formation of an intermediate copper reagent which is responsible for the reactivity in these reactions. These reactions were, therefore, carried out at low temperature (−70 °C) to minimize the decomposition of copper reagent. Without HMPA as co-solvent, these reactions gave only low conversions into corresponding products. The reaction results are summarized in Table 1.

Copper(III) complexes have been postulated as reaction intermediates[12] and a mechanism involving oxidative addition and reductive elimination explains the reactivity of the organocopper reagents. Thus, oxidative addition of an alkyl halide to the copper(I) reagent would yield a planar copper(III) intermediate, as illustrated in Scheme 2. Reductive elimination of



Scheme 2

two organic ligands from the copper(III) intermediate would lead to a coupled product and copper(I) species.

Experimental

General

^{1}H NMR spectra were recorded on a Varian T-60A or Varian FT-80A NMR spectrometer, and chemical shifts are reported relative to tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded on a Bruker AM-300 NMR spectrometer, and *J* values are given in Hz. ^{19}F NMR spectra were recorded on a Varian FT-80A NMR spectrometer with trifluoroacetic acid (TFA) as external standard. Chemical shifts are reported relative to $CFCl_3$ (δ_F of 77). ^{19}F NMR yield was determined by comparison of peak integrations using $PhCF_3$ as the internal standard. IR spectra were recorded on a Perkin-Elmer Model 267 grating spectrometer with thin films. Mass spectra were recorded on a Hewlett-Packard 5985A GC/MS system using the electron impact (EI) method. Bps determined during distillation are uncorrected. All reactions were performed under nitrogen.

Materials

All solvents were stored under nitrogen in brown bottles capped with a rubber septum. DMF was distilled from P_2O_5 under reduced pressure and stored over 4 Å molecular sieves under nitrogen. HMPA was distilled from CaH_2. Unless otherwise indicated, all other reagents were purified prior to use in the usual manner. Copper(I) bromide was purchased from the Aldrich Chemical Co. and was purified by a method similar to that of Osterlof.[13] Zinc powder was activated by washing successively with dilute hydrochloric acid and then distilled water and dried *in vacuo* overnight at 120 °C.

2-Chloro-3,3-difluorocyclopropenylzinc iodide 1

A 50-cm^3, two-neck round-bottom flask fitted with a thermometer and septum port was charged with acid-washed zinc powder (2.5 g, 38.2 mmol) and dry DMF–HMPA (7:1 v/v; 20 cm^3). The apparatus was maintained under a nitrogen atmosphere and cooled using an ice–water bath. 1-Chloro-3,3-difluoro-2-iodocyclopropene (7.9 g, 33.4 mmol) was added dropwise to the reaction mixture which was then stirred until the mild exotherm had subsided. The excess of zinc was then removed by filtration through a medium fritted glass filter (Schlenk funnel). ^{19}F NMR analysis of the resultant solution indicated an 80% yield of product **1**; $\delta_F(CDCl_3)$ −96.33 (2 F, s).

1-Benzyl-2-chloro-3,3-difluorocyclopropene 2

To a pre-cooled (−70 °C) solution of the reagent **1** prepared from 1-chloro-3,3-difluoro-2-iodocyclopropene (7.9 g, 33.4 mmol) and zinc (2.5 g, 38.2 mmol) in DMF–HMPA (7:1, v/v; 20 cm^3) was added dropwise a catalytic amount of CuBr (about 10 mol%) and benzyl bromide (4.8 g, 28.1 mmol). The mixture was stirred for 3 h at −70 °C, and then slowly warmed to room temperature. The reaction mixture was flash distilled and the distillate was diluted with water (25 cm^3) and extracted with methylene dichloride (20 cm^3). The extract was washed with water (15 cm^3), dried ($MgSO_4$) and evaporated. The residue was distilled to give compound **2** (5.0 g, 88%), bp 53–55 °C (5 mmHg) (Found: C, 59.78; H, 3.49; Cl, 17.75; F, 18.88. $C_{10}H_7ClF_2$ requires C, 59.87; H, 3.51; Cl, 17.67; F, 18.94%); $\delta_F(CDCl_3)$ −100.22 (2 F, s); $\delta_H(CDCl_3)$ 4.6 (2 H, s) and 7.2–7.6 (5 H, m); *m*/*z* 127 (81.2%) and 91 ($PhCH_2$, 100).

1-Allyl-2-chloro-3,3-difluorocyclopropene 3

Bp 42–45 °C (42 mmHg) (Found: C, 47.81; H, 3.36; Cl, 23.63; F, 25.19. $C_6H_5ClF_2$ requires C, 47.86; H, 3.35; Cl, 23.55; F, 25.24%); $\delta_F(CDCl_3)$ −103.94 (2 F, s); $\delta_H(CDCl_3)$ 3.4 (2 H, d), 5.2–5.6 (2 H, m) and 5.7–6.2 (1 H, m); $\delta_C(CDCl_3)$ 30.5, 96.8 (t, J_{CF} 280), 98.5, 107.2, 118.6 and 135.4; *m*/*z* 151 (M^+ + 2, 2.3%), 149 (M, 5.8), 115 (76.9) and 95 (100).

1-(But-2-enyl)-2-chloro-3,3-difluorocyclopropene 4
Bp 54–55 °C (45 mmHg) (Found: C, 48.39; H, 2.01; Cl, 23.95; F, 25.71. $C_6H_3ClF_2$ requires C, 48.51; H, 2.04; Cl, 23.87; F, 25.58%); $\delta_F(CDCl_3)$ −101.53 (2 F, s); $\delta_H(CDCl_3)$ 1.6 (3 H, d), 3.2 (2 H, d), 5.3 (1 H, m) and 5.5 (1 H, m).

1-Chloro-3,3-difluoro-2-(prop-2-ynyl)cyclopropene 5
Bp 38–40 °C (35 mmHg) (Found: C, 51.01; H, 4.22; Cl, 21.48; F, 23.15. $C_7H_7ClF_2$ requires C, 51.08; H, 4.29; Cl, 21.54; F, 23.09%); $\delta_F(CDCl_3)$ −104.49 (2 F, s); $\delta_H(CDCl_3)$ 2.3 (1 H, m) and 3.6 (2 H, m); *m*/*z* 150 ($M^+ + 2$, 3.6%), 148 (M, 12.8) and 113 (M − Cl, 100).

1-Benzoyl-2-chloro-3,3-difluorocyclopropene 6
To a pre-cooled (−70 °C) solution of the zinc reagent **1** prepared by the above procedure was added a catalytic amount of CuBr and benzoyl chloride (3.9 g, 27.7 mmol). The reaction mixture was stirred for 1 h at −70 °C, and then slowly warmed to room temperature. The reaction mixture was flash distilled and the distillate was diluted with 0.1 M aqueous NaOH and extracted with methylene dichloride. The extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was distilled to give compound **6** (5.3 g, 90%), bp 67–69 °C (5 mmHg) (Found: C, 56.13; H, 2.32; Cl, 16.60; F, 17.68. $C_{10}H_5ClF_2O$ requires C, 55.97; H, 2.35; Cl, 16.52; F, 17.71%); $\delta_F(CDCl_3)$ −99.02 (2 F, s); $\delta_H(CDCl_3)$ 7.5–8.0 (5 H, m); ν_{max}(neat)/cm^{-1} 1810 and 1680; *m*/*z* 105 (PhCO, 100%) and 77 (Ph, 45).

1-Acetyl-2-chloro-3,3-difluorocyclopropene 7
Bp 58–60 °C (40 mmHg) (Found: C, 39.19; H, 1.92; Cl, 23.31; F, 25.05. $C_5H_3ClF_2O$ requires C, 39.37; H, 1.98, Cl, 23.24; F, 24.91%); $\delta_F(CDCl_3)$ −99.49 (2 F, s); $\delta_H(CDCl_3)$ 2.2 (3 H, s); $\delta_C(CDCl_3)$ 32.6, 98.2 (t, J_{CF} 286), 100.6, 112.3 and 191.5; ν_{max}(neat)/cm^{-1} 1820 and 1670.

1-Chloro-3,3-difluoro-2-propionylcyclopropene 8
Bp 67–69 °C (25 mmHg) (Found: C, 43.26; H, 3.93; Cl, 21.25; F, 22.88. $C_6H_5ClF_2O$ requires C, 43.27; H, 3.03; Cl, 21.29; F, 22.82%); $\delta_F(CDCl_3)$ −99.26 (2 F, s); $\delta_H(CDCl_3)$ 1.3 (3 H, t) and 2.5 (2 H, q); ν_{max}(neat)/cm^{-1} 1820 and 1680; *m*/*z* 57 (CH_3CH_2CO, 100%).

1-Chloro-3,3-difluoro-2-(2-thenoyl)cyclopropene 9
Bp 48–49 °C (20 mmHg) (Found: C, 43.41; H, 1.38; Cl, 16.12; F, 17.19. $C_8H_3ClF_2OS$ requires C, 43.55; H, 1.37; Cl, 16.07; F, 17.22%); $\delta_F(CDCl_3)$ −98.78 (2 F, s); $\delta_H(CDCl_3)$ 7.2 (1 H, m), 7.7 (1 H, m) and 7.9 (1 H, m); ν_{max}(neat)/cm^{-1} 1800 and 1680; *m*/*z* 111 (C_5H_3SO, 100%).

1-Chloro-3,3-difluoro-2-(2-furoyl)cyclopropene 10
Bp 38–41 °C (35 mmHg) (Found: C, 46.91; H, 1.43; Cl, 17.51; F, 18.53. $C_8H_3ClF_2O_2$ requires C, 46.97; H, 1.48; Cl, 17.33; F, 18.58%); $\delta_F(CDCl_3)$ −98.53 (2 F, s); $\delta_H(CDCl_3)$ 6.7 (1 H, m), 7.3 (1 H, m) and 7.7 (1 H, m).

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