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Short communication

Reaction of Halothane with *sec*-butyllithium in the presence of zinc halides—one-pot preparation of chlorodifluorovinylzinc reagent and its derivatization to α-chloro-β,β-difluorostyrene

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Abstract

Halothane, 2-bromo-2-chloro-1,1,1-trifluoroethane, reacts with *sec*-butyllithium in the presence of zinc halides to afford a chlorodifluorovinylzinc reagent. This zinc reagent reacts with aryl halides in the presence of a palladium catalyst to give chlorodifluorostyrene derivatives in moderate to good yields.

Keywords: Halothane; *sec*-Butyllithium; Aryl iodide; Chlorodifluorostyrene; Cross-coupling reaction

1. Introduction

1-Chloro-2,2-difluorovinylzinc chloride (**3**) has been used for the cross-coupling reaction with aryl iodides in the presence of palladium catalyst to give α-chloro-β,β-difluorostyrenes. Normant and co-workers [1] reported preparation of the vinylzinc reagent from 1-chloro-2,2-difluoroethene (**1**) through hydrogen abstraction and metallation. On the other hand, Percy and co-workers [2] reported that **2** was formed from 1-chloro-2,2,2-trifluoroethane (**4**) by the reaction with BuLi, in situ. In these reactions, 1-chloro-2,2-difluorovinyllithium (**2**), a common intermediate, is very unstable even at a low temperature. We have reported the modification of synthesis of a fluorovinylzinc reagent. Thus, lithiation of **1** was carried out in the presence of zinc chloride so as to make **2** react promptly with zinc chloride. By this modification, a new vinylzinc reagent was obtained invariably as a colorless clear solution. This vinylzinc reagent was quite stable and showed a different ^{19}F NMR from that of **3**. We temporarily assigned its structure as bis(1-chloro-2,2-difluoroethenyl)zinc (**5**) [3]. Using a similar method, Burton and co-workers reported recently that treatment of **4** by lithium diisopropylamide (LDA) in the presence of zinc chloride gave **3** [4]. While **1** and **4** are gas at room temperature and difficult to do with, Halothane (2-bromo-2-chloro-1,1,1-trifluoroethane, **6**) is a liquid at room temperature and much easier to work with. We would like to describe herein a simple preparation of **5** by the reaction of **6** with *sec*-BuLi in the presence of zinc chloride and its application for the synthesis of α-chloro-β,β-difluorostyrenes (Scheme 1).

2. Results and discussion

We have reported the reaction of Halothane (**6**) with carbonyl compounds that gave abnormal products (**13**) that was not expected from the normal Grignard reaction [5]. Our previous study was focused on elucidating the mechanism of this abnormal Grignard reaction. Halothane (**6**) has an acidic hydrogen atom on the same carbon that has bromine and chlorine atoms. So, deprotonation of **6** with LDA gave 1-bromo-1-chloro-2,2,2-trifluoroethyllithium (**14**), which reacted with a carbonyl compound to afford **13** (Scheme 2) [6].

If **14** loses lithium fluoride, it may provide the ethene (**7**). If another mole of *sec*-BuLi is present in addition to zinc chloride, **7** will be lithiated and then converted to a zinc

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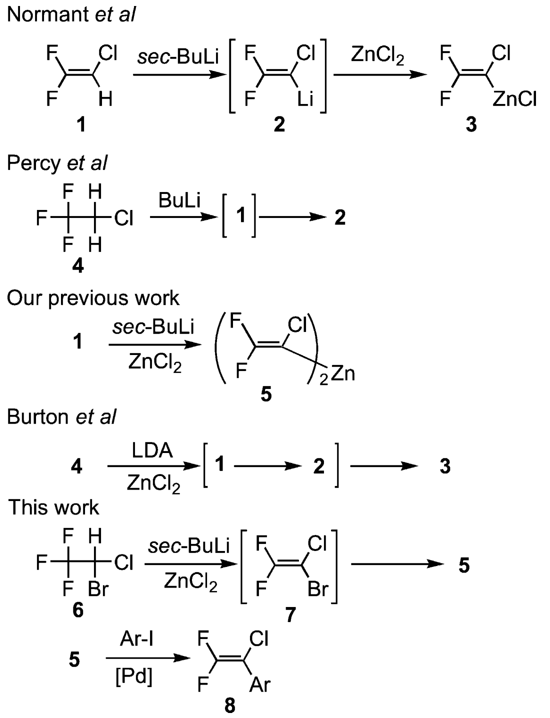
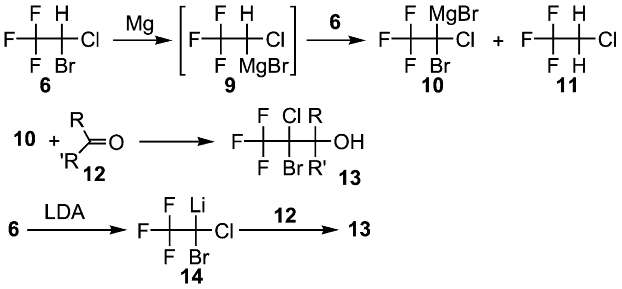


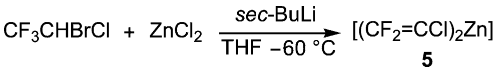
Scheme 1.



Scheme 2.

reagent. Therefore, we tried the reaction of Halothane with *sec*-BuLi in the presence of zinc halides.

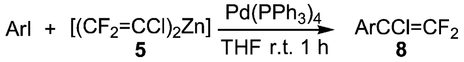
When a solution of *sec*-BuLi (9.1 mmol) was added to a mixture of Halothane (4.4 mmol) and zinc chloride (4.0 mmol) in THF (10 ml) at −60 °C for 1 h, a clear and colorless solution of a zinc reagent was obtained, which showed the same ^{19}F NMR spectrum as that of **5** (Scheme 3).[2] This solution is stable enough to be kept in a freezer for several months. When zinc bromide was used in THF, the reaction mixture colored dark brown. Thus, we usually used zinc chloride. By using Et_2O as a solvent for the reaction of zinc bromide, a clear solution could be obtained.



$$CF_3CHBrCl + ZnCl_2 \xrightarrow[\text{THF } -60\ ^{\circ}C]{sec\text{-BuLi}} [(CF_2{=}CCl)_2Zn]$$

5

Scheme 3.



$$ArI + [(CF_2{=}CCl)_2Zn] \xrightarrow[\text{THF r.t. 1 h}]{Pd(PPh_3)_4} ArCCl{=}CF_2$$

5 **8**

Scheme 4.

Table 1
Reaction of bis(1-chloro-2,2-difluorovinyl)zinc with aryl iodides

Entry	Ar–I	Yields[a]	MS (M^+)
1	C_6H_5–	57	$C_8H_5ClF_2$: 174.005
2	4-$CH_3C_6H_4$–	61	$C_9H_7ClF_2$: 188.020
3	2-$NO_2C_6H_4$–	13	–
4	4-$NO_2C_6H_4$–	66	$C_8H_4ClF_2NO_2$: 218.990
5	4-$C_2H_5O_2CC_6H_4$–	83	$C_{11}H_9ClF_2O_2$: 246.026
6	4-$CH_3OC_6H_4$–	66	$C_9H_7ClF_2O$: 204.015
7	4-ClC_6H_4–	96	$C_8H_4Cl_2F_2$: 207.966

[a] Yields were estimated by ^{19}F NMR.

Next, the cross-coupling reaction of our vinylzinc reagent with aryl iodides in the presence of palladium catalyst is described. A solution of the vinylzinc reagent (0.8 mmol) was added to a mixture of 4-iodoanisole (0.2 mmol) and tetrakis(triphenylphosphine)palladium (0.012 mmol) in THF (3 ml) at room temperature, and the mixture was stirred at the same temperature for 1 h.[3] By a usual workup, 4-(1-chloro-2,2-difluorovinyl)anisole was obtained at 66% yield. The yield was estimated by ^{19}F NMR (entry 6 in Table 1). The structure of the product was determined by spectral data of a sample purified by a column chromatography. This reaction proceeded with most of aryl iodides at room temperature in a short reaction time in moderate to good yields. The results are shown in Scheme 4 and Table 1.

2-Nitroiodobenzene was less reactive and gave the product at 13% yield (entry 3). In this case, the cross-coupling reaction might be disturbed with the bulky *o*-nitro group.

Burton suggested that our zinc reagent was same one as theirs and that our ^{19}F NMR spectrum must be that of 2-chloro-1,1-difluoroethene (**1**). In our experiment, any peaks of Burton's 1-chloro-2,2-difluorovinylzinc chloride (**3**) were not observed. The zinc reagent, which we temporarily assigned as bis(1-chloro-2,2-difluorovinyl)zinc (**5**), can be stored

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[2] Typical procedure for the preparation of chlorodifluorovinylzinc (**5**) reagent is as follows. To a solution of Halothane (0.423 ml, 4.4 mmol) and zinc chloride (0.547 g, 4.0 mmol) in THF (10 ml), *sec*-BuLi (0.978 M in hexane/cyclohexane, 9.3 ml/9.1 mmol) was added at −60 °C for 1 h. This shows the same ^{19}F NMR spectrum as that obtained from 2-chloro-1,1-difluoroethene [3]. The solution was transferred to a sealed bottle and stored in a freezer under Ar atomosphere.

[3] Typical procedure of the cross-coupling reaction is as follows. To a mixture of 4-iodoanisole (47 mg, 0.2 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.012 mmol) in THF (3 ml), the zinc reagent (4 ml, 0.8 mmol) was added at room temperature, and the mixture was stirred for 1 h at same temperature. The reaction mixture was poured into ice and 10% HCl. The whole mixture was extracted with Et_2O. The Et_2O layer was washed with saturated NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the yield was determined by ^{19}F NMR. Purification of the residue gave a colorless oil (**8**, Ar = 4-$CH_3OC_6H_5$–). MS *m/z*: 204 (M^+). HRMS calculated for $C_9H_7ClF_2O$ (M^+): 204.015. Found: 204.015. ^1H NMR ($CDCl_3$) δ: 7.44 (2H, d, $J = 9$ Hz), 6.92 (2H, d, $J = 9$ Hz), 3.83 (3H, s). ^{19}F NMR ($CDCl_3$) δ: −21.09 (1F, d, $J = 38.1$ Hz), −26.03 (1F, d, $J = 38.1$ Hz). All the other products showed reasonable spectral data.

for several months and reactive enough for the cross-coupling reaction. We believe that the zinc reagent by our method is formed through a different mechanism from that of Burton's. In our method, equimolar amount of *sec*-BuLi was used for the deprotonation of Halothane, and then another mole of *sec*-BuLi was used for halogen–lithium exchange reaction. Burton's group used LDA as a base at a much higher temperature. So, the structure and reactivity of zinc reagent obtained by our method are different from Burton's reagent.

3. Conclusion

Treatment of Halothane with *sec*-BuLi in the presence of zinc chloride gave a zinc reagent that we had temporarily assigned as bis(1-chloro-2,2-difluorovinyl)zinc (**5**). Reaction of **5** with aryl iodides in the presence of tetrakis(triphenylphosphine)palladium gave moderate to good yields of (1-chloro-2,2-difluorovinyl)arenes.

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