Germyl anion species-promoted formation of cyanofluoromethylene compounds: first and efficient synthesis of fluorinated homoallylic and homoprop-2-ynylic cyanides

Yasuo Yokoyama*† and Kunio Mochida‡

Department of Chemistry, Faculty of Science, Gakushuin University, 1-5-1 Mejiro, Toshima-ku, Tokyo 171-8588, Japan

Various fluorinated homoallylic and homoprop-2-ynylic cyanides could be synthesized from 2-fluoro-2-phenylthio-2-phenylacetonitrile and some allylic or prop-2-ynylic chlorides in excellent yields by use of a germyl anion species.

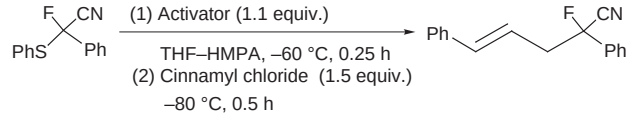
Recently, fluorine-contained organic compounds have attracted wide attention among scientists in the fields of agrochemicals, pharmaceuticals and material sciences. Various antiviral, antitumor and antifungal agents and advanced materials have been synthesized in which fluorine substitution plays a significant role in their biological activities and physical properties.[1] Thus, the formation of an organofluorine compound is a most important reaction in organic synthesis. Particularly, synthetic methodology for a monofluorinated compound ($R^1R^2R^3CF$)[2] is a very attractive target of study, because it is difficult due to the chemical lability of the foregoing compound in some cases. Concerning this problem, we focused on the synthesis of the cyanofluoromethylene compound [$R^1R^2C(CN)F$] as an easy and effective formation of a monofluorinated product. This compound has cyano and fluoro substituents on the same carbon, and could be employed as a useful fluorine-containing building block, because the cyano group is easily transformed to other substituents.[3] Moreover, this molecule is important from the viewpoint of the multifunctional carbon structure.[4] There are two strategies which give the foregoing molecule. One is a stepwise introduction of cyano and fluoro groups,[5] and the other is introduction of a cyanofluoromethylene unit to a substrate. In particular, the latter method is suitable for the synthesis of cyanofluoromethylene compounds because the target molecule can be formed more straightforwardly. However, only a few synthetic examples have been reported at the present time.[6] In this regard, we have developed the germyl anion species-promoted synthesis of a cyanofluoromethylene compound by use of 2-fluoro-2-phenylthio-2-phenylacetonitrile as the cyanofluoromethylene source. Herein we report the first and efficient syntheses of fluorinated homoallylic and homoprop-2-ynylic cyanides.

Some selected data of reactions of 2-fluoro-2-phenylthio-2-phenylacetonitrile with (*E*)-3-chloro-1-phenylprop-1-ene (cinnamyl chloride) in the presence of various activators are summarized in Table 1.

As expected, some germyl anion species were found to give fluorinated homoallylic cyanides (entries 1–3). The yield of the desired compound was affected by the nature of the counter cation. When germyl anions having Li^+ and K^+ were used, the yield of the target product was low. Many unidentified by-products were obtained, whereas the starting cyanide was consumed completely (entries 1 and 3). On the other hand, 2-fluoro-2-phenylthio-2-phenylacetonitrile could be activated effectively by Et_3GeNa to give the active intermediate. This species reacted with cinnamyl chloride to give the corresponding compound quantitatively (entry 2). Other group 14 element-containing anions, such as Me_3SiNa,[7] Et_3SnNa§ and Bu^nLi were not useful for this type of reaction (entries 4–6). In addition, the starting cyanide was transformed to the desired homoallylic cyanide in low yield when lithium naphthalenide (LN), which is well known as a strong one-electron reducing agent,[9] was applied (entry 7). These facts suggested that only Et_3GeNa was suitable for the synthesis of the fluorinated homoallylic cyanide. The reason why Et_3GeNa was favorable for the activation and the cleavage of a sulfur–carbon bond¶ is unclear, but this phenomenon is probably due to the thiophilicity of the germanium atom and the stability of the active intermediate.

Various allylic and prop-2-ynylic chlorides could be also used as substrates instead of cinnamyl chloride under the same reaction conditions (Table 1, entry 2). In Table 2, the results of application of this reaction for some substrates are presented. When 3-chloroprop-1-ene was used as an electrophile, the desired simple homoallylic cyanide was obtained in excellent yield (entry 1). When 1-chlorobut-2-ene (*E*:*Z* = 73:27) was employed, the *E*-isomer of the target compound was obtained predominantly (entry 2, *E*:*Z* = 73:27). Some *E*-allylic chlorides, such as (*E*)-1-chlorohex-2-ene, (*E*)-1-chlorooct-2-ene, (*E*)-1-chlorononon-2-ene and (*E*)-1-chloro-3,5-dimethylocta-2,6-diene could be transformed to the desired products having *E*-configuration in excellent yields (entries 3–6). These results suggested that no isomerization of the olefin occurred under these reaction conditions. Other primary allylic chlorides were also employed as electrophiles (entries 7 and 8). On the other hand, when secondary allylic chloride (3-chlorobut-1-ene) was used, the desired compound was obtained in moderate yield (76%, *syn*:*anti* = 64:36, entry 9). An *E*-isomer of entry 2 was obtained which was formed by the attack of a nucleophile at the γ-carbon as a by-product (24%), because the intermediate was sterically hindered. Furthermore, 1-chlorohexa-2,4-diene and some prop-2-ynylic chlorides could react with the active intermediate to give the corresponding fluorinated cyanides in excellent yields without decomposition of the starting chlorides (entries 10–12). In these cases, products formed by attack of the nucleophile to the γ-position (or ε-position) of chlorides could not be detected at all, except in the case of entry 9. These results revealed that the presented method was applicable to the

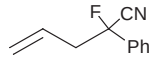
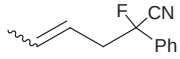
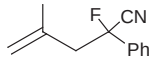
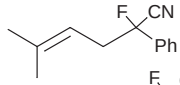
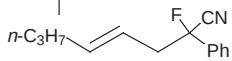
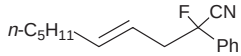
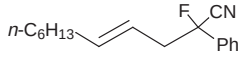
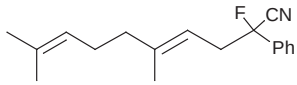
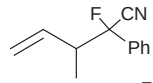
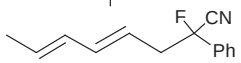
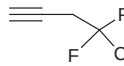
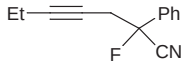
Table 1 Synthesis of fluorinated cyanides by use of various activators



Entry	Activator	Yield[a] (%)
1	Et_3GeLi	35
2	Et_3GeNa	98
3	Et_3GeK	5.6
4	Me_3SiNa	NR[b]
5	Et_3SnNa	2.8
6	Bu^nLi	36
7	LN[c]	36

[a] Isolated yield. Identified by ^1H, ^{19}F and ^{13}C NMR analysis. [b] Starting cyanide was recovered (98%). [c] Lithium naphthalenide.

Table 2 Synthesis of various fluorinated homoallylic and homoprop-2-ynylic cyanides

Entry	Product[a]	Yield[b] (%)
1		96
2		99
3		95
4		97
5		96
6		96
7		96
8		95
9[c]		76
10		96
11		97
12		95

[a] All compounds were identified by ^{1}H, ^{19}F and ^{13}C NMR analysis. [b] Isolated yield. [c] The second operation was carried out for 3 h.

synthesis of many types of fluorinated homoallylic and homoprop-2-ynylic cyanides.

A typical procedure is as follows. To a THF solution (20 ml) of 2-fluoro-2-phenylthio-2-phenylacetonitrile (377 mg, 1.55 mmol) was added an HMPA solution of Et_3GeNa[11] (4 ml, 0.42 M) slowly at −60 °C. After stirring for 0.25 h at −60 °C, the temperature was lowered to −80 °C, and cinnamyl chloride (355 mg, 2.32 mmol) was added. The mixture was stirred for 0.5 h at −80 °C and then was passed through a short column of silica gel and eluted with Et_2O. Concentration of this eluate followed by column chromatographic purification afforded 380 mg (98%) of the corresponding compound (Table 1, entry 2).

In conclusion, we have developed the first syntheses of fluorinated homoallylic and homoprop-2-ynylic cyanides. This reaction proceeded smoothly to give the corresponding product in excellent yield under mild reaction conditions. The efficient synthesis presented here can presumably be employed in fluorine chemistry as a useful method for monofluorinated compounds. Further investigation of applications of this reaction and a mechanistic study are now in progress.

Notes and references

† E-mail: 940429@gakushuin.ac.jp
‡ E-mail: kunio.mochida@gakushuin.ac.jp
§ A stannyl anion (Bu_3SnLi)-promoted reductive lithiation of a phenyl sulfide and an ethyl sulfide was reported by T. Takeda and co-workers (ref. 8).
¶ Effective activation of a carbon–sulfur bond using germyl anion species has already been presented in our previous work (ref. 10).

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