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α-Fluorohydrazones as useful precursors in nucleophilic substitutions

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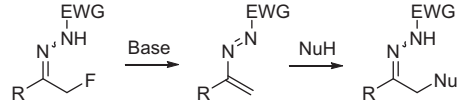
ABSTRACT

C–F bonds on α-fluorohydrazones can be substituted with a wide range of nucleophiles with the aid of mild bases. The present reaction shows that α-fluorohydrazones can be useful building blocks in synthetic chemistry.

Introducing fluorine atoms to organic molecules often causes dramatic changes in the physical and biological properties, and the benefit is maximally utilized in medicinal chemistry.[1] Strong C–F bonds (BDE: 109.9 kcal mol^{-1} for CH_3F) contribute to the stability of fluorine organic compounds, implying, on the other hand, that decomposition of fluorine compounds is difficult.[2] Traditionally, C–F bonds have been recognized to be useless for chemical transformation due to their extremely high bond energy, except for a few examples such as aromatic nucleophilic substitution reactions (S_NAr reactions).[3] Recently, however, development of methods for activation of unreactive C–F bonds is a hot topic in organic chemistry.[4,5] Although these reactions often require transition metal catalysts, Lewis acids, or harsh conditions, compounds bearing C–F bonds can now work as sufficiently useful synthetic precursors.

α-Haloketones (halogen: chloro, bromo, and iodo) are important building blocks to install ketone moieties in organic molecules in synthetic chemistry because they are highly reactive electrophiles in the S_N2 substitution reaction.[6] On the other hand, α-fluoroketones are seldom used for this purpose owing to the poor reactivity of C–F bonds, though α,α,α-trifluorocarbonyl compounds can be activated by electroreduction.[4c] They are usually useful precursors for the synthesis of fluorine compounds.[7]

In this Letter, we report that C–F bonds on α-fluorohydrazones, which are derivatives of α-fluoroketones, are readily substituted with various nucleophiles under mild basic conditions. In this reaction, C–F bond cleavage is likely to be triggered by electron-pushing from a nitrogen atom of the hydrazone moiety to form the corresponding azoalkene intermediate. Since this intermediate works as an excellent Michael acceptor, substituted products are formally provided by addition reactions of nucleophiles (Scheme 1). Such a formal nucleophilic substitution of α-halohydrazones is a synthetically useful method as with the usual S_N2 reaction of α-halocarbonyl compounds, though these two reactions cannot be bracketed together due to the difference in the mechanism (elimination-addition process versus stereospecific substitution) and reaction conditions. For instance, efficient C–C bond formation reactions of α-chloro- or bromo hydrazones using this methodology are known.[8] In addition, C–F cleavage reactions of α,α-difluoro- and α,α,α-trifluorohydrazones based on the similar mechanism have been reported.[9] However, there are not many practical applications of this concept involving the C–F cleavage to general synthetic methods. We herein demonstrate synthetic usefulness of α-fluorohydrazones by showing results of reactions with a variety of nucleophiles.



Scheme 1. Elimination of a fluorine atom followed by the addition of nucleophiles.

α-Fluorohydrazone **1** (mixture of two isomers; ca. 85:15), which was easily prepared by condensation of the corresponding α-fluoroketone[10] with methyl hydrazinecarboxylate, was designed

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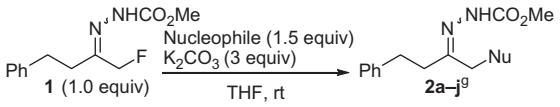
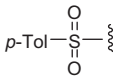
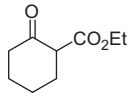
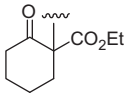
Table 1
Scope of nucleophiles



Entry	Nucleophile	Nu		Time	Yield (%)
1[a]	MeOH[b]	MeO	**2a**	15 min	68
2[a]	CF_3CH_2OH[b]	CF_3CH_2O	**2b**	3 h	91
3[c]	AcONa	AcO	**2c**	4 h	49
4[d]	$Me_2NH{\cdot}HCl$[e]	Me_2N	**2d**	2 h	81
5			**2e**	7 h	95
6[f]	$TMSN_3$	N_3	**2f**	5 min	89
7	PhSH	PhS	**2g**	3 h	95
8	*p*-$TolSO_2Na$		**2h**	2.5 h	69
9	$(CO_2Me)_2CH_2$	$(CO_2Me)_2CH$-	**2i**	24 h	82
10[d]			**2j**	4 h	64

[g]Isomer ratios (approximately estimated by ^{1}H NMR): **2a** (65:35), **2b** (78:22), **2c** (>95:5), **2d** (>95:5), **2e** (76:24), **2f** (80:20), **2g** (58:42), **2h** (55:45), **2i** (75:25), **2j** (>95:5).
[a] 1.5 equiv of K_2CO_3 was used.
[b] Used as a solvent instead of THF.
[c] DMF was used as a solvent instead of THF.
[d] 65 °C.
[e] 3 equiv.
[f] DBU was used instead of K_2CO_3.

as a model substrate to test nucleophiles. Results of reactions of **1** with a variety of nucleophiles are summarized in Table 1. Treatment of **1** with potassium carbonate (1.5 equiv) in methanol (0.2 M) at room temperature caused methanolysis to afford α-methoxyhydrazone **2a** in 68% yield (entry 1).[11] The reaction with 2,2,2-trifluoroethanol gave the corresponding substituted product **2b** in excellent yield under similar conditions (entry 2). Acetoxylation of **1** with sodium acetate proceeded in *N*,*N*-dimethylformamide (DMF) to give compound **2c** in moderate yield (entry 3). Reactions of **1** with amines such as dimethylamine and morpholine were fast and afforded the corresponding amine compounds **2d** and **2c** in 81% and 95% yields (entries 4 and 5).[12] When sodium azide was used for azidation of **1**, azide compound **2f** was obtained, but the yield was moderate (46%, not shown in Table 1). We soon found that a combination of trimethylsilylazide ($TMSN_3$) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave **2f** in improved yield (89%) (entry 6). Sulfur nucleophiles such as benzenethiol and sodium *p*-toluenesufinate readily reacted with **1** to provide the corresponding sulfide **2g** and sulfone **2h** in good yields (entries 7 and 8). When dimethylmalonate and ethyl 2-oxocyclohexanecarboxylate were employed as nucleophiles, C–C bond formation on the C–F bond of **1** occurred to give compounds **2i** and **2j** (entries 9 and 10).

Examples of reactions between various α-fluorohydrazones and nucleophiles are shown in Figure 1. α-Fluorohydrazones bearing *tert*-butoxycarbonyl or *p*-toluenesulfonyl groups gave the corresponding substituted products **3**–**5** in good yields, whereas product **6** was obtained in only 32% yield from an acetylated hydrazone material. This might be due to the difference in the electronic properties of carbamates and amides. Substitution reactions of hydrazones possessing other side chains, such as phenyl, benzyl, benzyloxybutyl, heptenyl, and isopropyl, smoothly produced various substituted derivatives **7**–**13** in good yields. Secondary and tertiary fluoro derivatives also caused substitution reactions with oxygen and nitrogen nucleophiles and afforded products **14**–**17**.

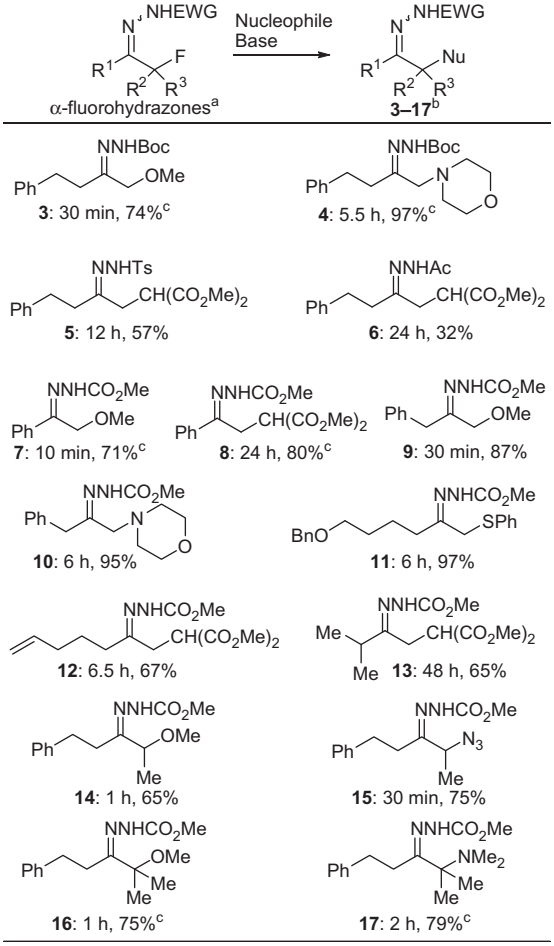
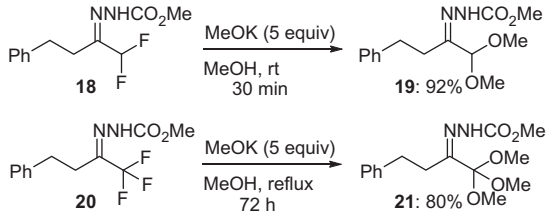


Figure 1. Scope of substrates. Same conditions are used for each nucleophile. [a]Starting materials were used as mixtures of two isomers (ca. 80:20–95:5) unless otherwise noted. [b]Isomer ratios (approximately estimated by ^{1}H NMR): **3** (>95:5), **4** (>95:5), **5** (91:9), **6** (>95:5), **7** (>95:5), **8** (>95:5), **9** (82:18), **10** (94:6), **11** (70:30), **12** (83:17), **13** (75:25), **14** (>95:5), **15** (91:9), **16** (>95:5), **17** (95:5). [c]Single isomers of starting materials were used.



Scheme 2. Reactions of di- and trifluorohydrazone derivatives.

α,α-Difluorohydrazone **18** (single isomer) reacted with methoxide anions to give dimethylacetal **19** (single isomer) (Scheme 2).[9] In this reaction, replacement of potassium carbonate by potassium methoxide (5 equiv) gave a better result. Interestingly, α,α,α-trifluorohydrazone **20** (single isomer) also underwent a substitution reaction of all fluorine atoms to give α,α,α-trimethoxyhydrazone **21** (single isomer) in high yield, though a high temperature (reflux in methanol) and long reaction time (72 h) were required (Scheme 2).[9,13]

Exposure of α-fluoroketone **22** to the methanolysis conditions complicated the result, and no substituted product was isolated from the reaction mixture. In addition, α,α,α-trifluoroketone **23** did not react with potassium methoxide at all (Scheme 3). Com-