Tetrahedron Letters 54 (2013) 4102–4105

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

α-Fluorohydrazones as useful precursors in nucleophilic substitutions

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ARTICLE INFO

Article history:
Received 17 April 2013
Revised 21 May 2013
Accepted 24 May 2013
Available online 4 June 2013

Keywords:
Alkyl halides
Cleavage
Fluorine
Hydrazones
Nucleophiles

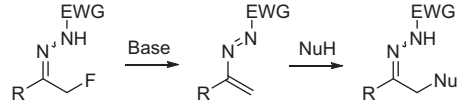
ABSTRACT

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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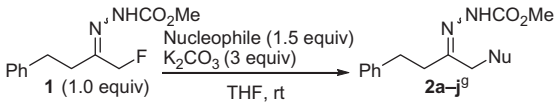
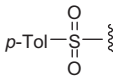
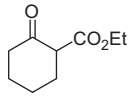
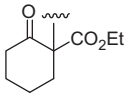
http://dx.doi.org/10.1016/j.tetlet.2013.05.110

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**.

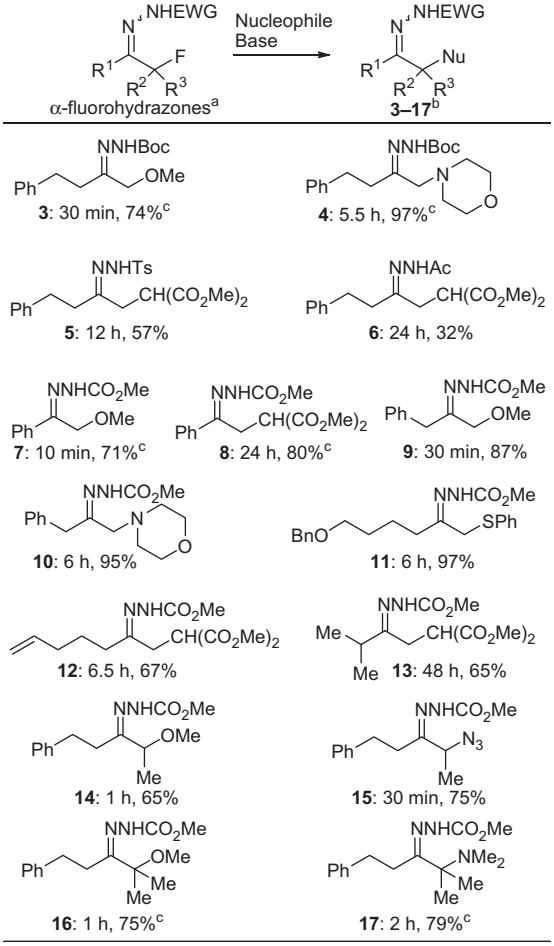
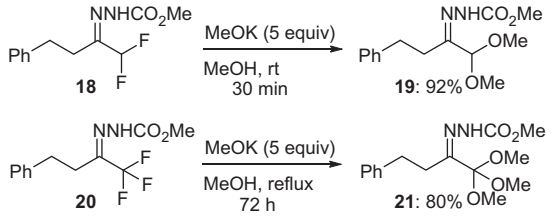


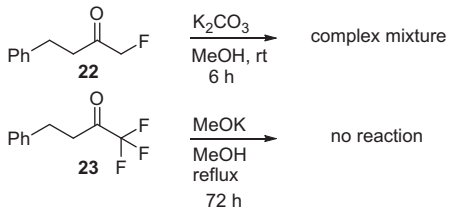
Figure 1. Scope of substrates. Same conditions are used for each nucleophile. [a]Starting materials were used as mixtures of two isomers (ca. 80:20–95:5) unless otherwise noted. [b]Isomer ratios (approximately estimated by ^{1}H NMR): **3** (>95:5), **4** (>95:5), **5** (91:9), **6** (>95:5), **7** (>95:5), **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.



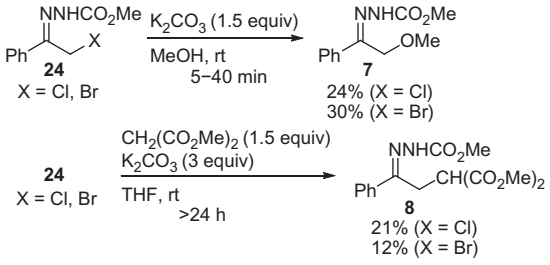
Scheme 2. Reactions of di- and trifluorohydrazone derivatives.

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-



Scheme 3. Exposure of fluoroketones to the methanolysis conditions.



Scheme 4. Reactions of α-chloro- and bromohydrazones.

bined with the production of **16** and **17**, these results support the mechanism shown in Scheme 1.

Interestingly, reactivity of α-chloro- and bromohydrazones was clearly different from that of α-fluorohydrazones (Scheme 4). When chloro- and bromohydrazones **24** (mixture of two isomers: ca. 55:45 and 85:15) were subjected to the methanolysis conditions, product **7** was obtained in only low yield along with multiple unidentified products. Likewise, reactions with dimethylmalonate gave product **8** in low yield. Although we did not test other reaction conditions such as a low temperature, it seems to be difficult to control substitution reactions of α-chloro- and bromohydrazones by the simple procedure used in the reactions of α-fluorohydrazones because of their high reactivity.[14] These contrasting results proved that α-fluorohydrazones were excellent precursors in substitution reactions.

In conclusion, we revealed that α-fluorohydrazone derivatives were good precursors in nucleophilic substitution reactions, which could be conducted under mild basic conditions to give various substituted products. No expensive and toxic reagent is required, and the experimental procedure is very simple. Since hydrazones can be used as masked ketones or amine precursors, α-fluorohydrazones are promising as useful building blocks. Furthermore, the original stability of α-fluorohydrazones would be advantageous when they are used as building blocks. This work has illustrated a good example of the positive use of C–F bonds in synthetic chemistry. Further studies such as studies on C–C bond formation reactions with organometallic reagents are currently underway.

Acknowledgments

This work was supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT).

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11. *General procedure for methanolysis of α-fluorohydrazones:* to a solution of α-fluorohydrazone (0.2 mmol) in MeOH (1 mL, 0.2 M) was added K_2CO_3 (41.5 mg, 0.3 mmol), and the mixture was stirred at room temperature. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine and dried with Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (*n*-hexane/EtOAc) to give the corresponding α-methoxyhydrazones. Spectroscopic data of the representative product are shown as below.
Methyl 2-(1-methoxy-4-phenylbutan-2-ylidene)hydrazinecarboxylate (***2a***): colorless oil. Mixture of two isomers (65:35). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.35–7.20 (5H and 5H, m, for major and minor), 4.09 (2H, s, for minor), 4.00 (2H, s, for major), 3.81 and 3.77 (3H and 3H, both br, for major and minor), 3.38 (3H, s, for minor), 3.33 (3H, s, for major), 2.89–2.84 (2H and 2H, m, for major and minor), 2.59–2,54 (2H and 2H, m, for major and minor) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 128.9, 128.5, 128.4, 128.1, 126.8, 126.2, 77.2, 74.9, 58.9, 58.3, 38.0, 33.2, 31.1 ppm; IR ($CDCl_3$): 2360, 1743, 1508, 1456, 1236 cm^{-1}; HRMS (DART): calcd for $C_{13}H_{19}N_2O_3$ [M+H$^+$]: 251.1396; found: 251.1397.
12. *General procedure for reactions of α-fluorohydrazones with nucleophiles:* to a solution of α-fluorohydrazone (0.2 mmol) in THF (1 mL, 0.2 M) were added nucleophile (0.3 mmol) and K_2CO_2 (82.9 mg, 0.6 mmol), and the mixture was stirred at room temperature. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine and dried with Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (*n*-hexane/EtOAc) to give the corresponding α-substituted hydrazones. Spectroscopic data of representative products are shown as below.
Methyl 2-(1-morpholino-3-phenylpropan-2-ylidene)hydrazinecarboxylate (***10***): Colorless oil. Mixture of two isomers (94:6). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.64 (1H, s, for major, a minor peak is ambiguous), 7.34–7.25 (3H and 3H, m, for major and minor), 7.18 (2H and 2H, d, *J* = 7.6 Hz, for major and minor), 3.78–3.57 (11H and 11H, m, for major and minor), 3.16 (2H, s, for major), 3.12 (2H, s, for minor), 2.45 (2H, br s, for major), 2.19 (2H, br, for minor) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 134.2, 129.2, 129.1, 128.6, 128.3, 127.1, 66.9, 66.6, 63.9, 53.5, 52.4, 33.1 ppm; IR ($CDCl_3$): 2358, 1736, 1508, 1455, 1238 cm^{-1}; HRMS (DART): calcd for $C_{15}H_{22}N_3O_3$ [M+H$^+$]: 292.1661; found: 292.1668.
Dimethyl 2-(2-(2-(methoxycarbonyl)hydrazono)hept-6-en-1-yl)malonate (***12***): colorless oil. Mixture of two isomers (83:17). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.80 (1H, br, for minor), 7.83 (1H, br, for major), 5.81–5.75 (1H and 1H, m,

for major and minor), 5.08–5.04 (2H, m, for major), 5.01 (1H, dq, J = 17.0. 1.7 Hz, for minor), 4.98–4.95 (1H, m, for minor), 3.97 (1H, br, for major), 3.70 and 3.76 (total 9H and 9H, both s, for major and minor), 3.62 (1H, t, J = 7.0 Hz, for minor), 2.89 (2H, d, J = 7.6 Hz, for major), 2.78 (2H, d, J = 7.8 Hz, for minor), 2.27 (2H, t-like, J = 7.9 Hz, for minor), 2.18 (2H, t-like, J = 7.9 Hz, for major), 2.12–2.07 (2H, m, for major and minor), 1.69–1.61 (2H, m, for major and minor) ppm ; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.7, 137.9, 137.1, 116.2, 115.1, 53.3, 52.6, 48.1, 48.0, 35.7, 34.9, 33.23, 33.17, 28.5, 25.9, 24.0 ppm; IR ($CDCl_3$): 1749, 1731, 1504, 1460, 1230 cm^{-1}; HRMS (DART): calcd for $C_{14}H_{23}N_2O_6$ [M+H$^+$]: 315.1556; found: 315.1539.

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14. Although we did not identify all byproducts, a dimerization-like compound produced by a self-reaction was tentatively identified as a main byproduct. This would be because α-chloro- and bromohydrazones can be usual electrophiles like α-chloro- and bromoketones.