Heterocycle Formation

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Substitution of Two Fluorine Atoms in a Trifluoromethyl Group: Regioselective Synthesis of 3-Fluoropyrazoles**

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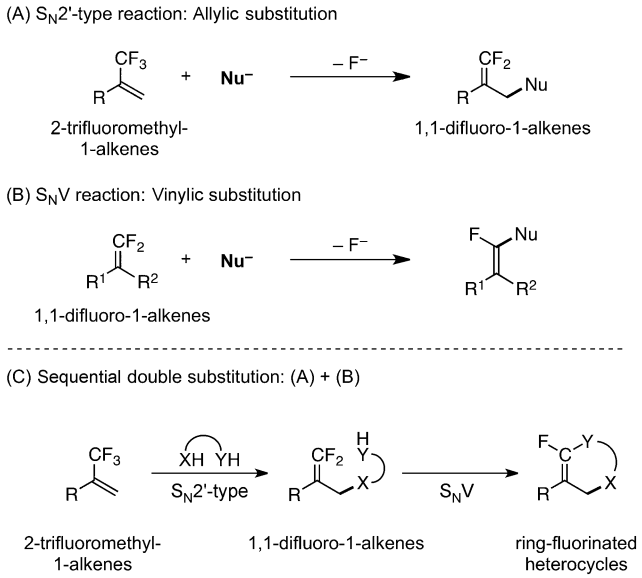
Fluorine atoms in vinylic and allylic positions are highly versatile substituents.[1] Among the compounds bearing these fluorine atoms, 2-trifluoromethyl-1-alkenes and 1,1-difluoro-1-alkenes are attractive as building blocks for organic syntheses.[2] Because these fluoroalkenes are electron-deficient, they inherently react with nucleophiles instead of electrophiles. 2-Trifluoromethyl-1-alkenes are subjected to nucleophilic attack at the carbon atom in the position γ with respect to the fluorine substituents (Scheme 1 A).[2] Successive elimination of fluoride ions proceeds, which is caused by migration of the double bond, resulting in the formation of 1,1-difluoro-1-alkenes (S_N2'-type reaction).[3] On the other hand, nucleophilic substitution occurs in the 1,1-difluoro-1-alkenes at the vinylic CF_2 carbon atom (Scheme 1 B).[2] This substitution provides monofluorinated and non-fluorinated alkenes through an addition–elimination process (S_NV reaction).[4] Both substitutions have been useful in organic syntheses.[5–9]



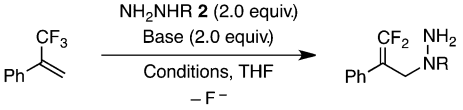
Scheme 1. Background and concept of our ring construction.

On the basis of the concept of combining these two substitutions, we adopted a simple method of constructing fluorinated ring systems using bifunctional nucleophiles (XH-YH, Scheme 1 C). In the proposed ring constructions, S_N2'-type reactions of 2-trifluoromethyl-1-alkenes would proceed with one of the nucleophilic centers (XH-) to give the corresponding 1,1-difluoro-1-alkenes, and the 1,1-difluoro-1-alkenes formed would then be subjected to intramolecular S_NV reactions with the other nucleophilic moiety (-YH), to give ring-fluorinated cyclic compounds. In this sequence, the substitution of two fluorine atoms in a trifluoromethyl group could be used to construct two bonds, which would promote an unprecedented ring formation.

Herein, we report a simple method for the synthesis of 3-fluoropyrazoles using hydrazines as bifunctional nucleophiles. Pyrazoles bearing fluoroalkyl groups have been synthesized for their use in agrochemicals and pharmaceuticals.[10] In contrast, methods for the synthesis of ring-fluorinated pyrazoles have not been extensively studied and have not been well developed to date.[11–13]

S_N2'-type reactions of trifluoromethylstyrene **1a** with substituted hydrazines were examined (Table 1). When meth-

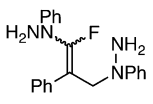
Table 1: S_N2'-type reactions of trifluoromethylstyrene **1a**.[a]



1a **3**

Entry	R	Base	Conditions	Yield [%]
1	Me	*n*BuLi	−78 °C, 2 h	66 (55:45)[b]
2	Ac	NaH	reflux, 4.5 h	11[c]
3	Bz	NaH	55 °C, 24 h	–
4	Ts	*n*BuLi	−78 to 0 °C, 3 h	–
5	Boc, **2a**[d]	NaH	0 °C, 1 h	92, **3a**
6	Ph, **2b**	*n*BuLi	−60 °C, 2 h	75,[c] **3e**; 6,[c] **4e**

[a] THF = tetrahydrofuran. [b] The regioisomeric ratio was determined by ^{19}F NMR spectroscopy. The regiochemistry was not assigned. [c] Yield as determined by ^{19}F NMR spectroscopy. [d] **2a** (1.8 equiv.) and NaH (1.8 equiv.).



4e

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ylhydrazine was used, the corresponding substitution products **3** were obtained as a roughly 1:1 mixture of regioisomers in terms of the hydrazine nitrogen atoms (66% yield, entry 1). S_N2'-type reactions with acetyl (Ac), benzoyl (Bz), and *p*-toluenesulfonyl (Ts, tosyl) hydrazines were tested without success (entries 2–4). However, *tert*-butoxycarbonyl (Boc) hydrazine **2a** regioselectively gave 1,1-difluoro-1-alkene **3a**, which is the desired S_N2'-type product with a Boc group on the inner nitrogen, in 92% yield (entry 5). Phenylhydrazine **2b** was also subjected to the regioselective S_N2'-type reaction using treatment with butyllithium at −60 °C to give **3e** in 75% yield (entry 6) with a small amount of the overreaction product **4e** (6%).[14]

Similarly, several 2-trifluoromethyl-1-alkenes **1** were subjected to S_N2'-type reactions with Boc- and arylhydrazines **2** to form difluorostyrenes **3**, the tosylation of which gave the corresponding tosylhydrazides **5** (Figure 1 and Table 2). The

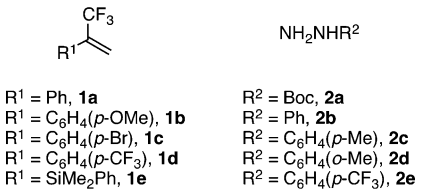
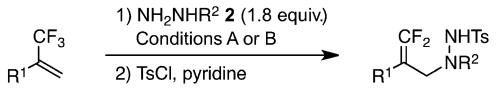


Figure 1. List of substrates.

rates of the S_N2'-type reactions were significantly affected by the substituent: the electron-donating methoxy group on **1b** decreased the rate of the S_N2'-type reaction (7 hours, 95% yield, entry 2) and the electron-withdrawing bromo- and trifluoromethyl groups on **1c** and **1d** increased the rate of the reaction (0.5 hours each, 72% and 79% yields, entries 3 and 4, respectively). Tolylhydrazines **2c** and **2d**, each bearing an electron-donating methyl group, gave the corresponding S_N2'-type products **3f** and **3g** in 80% and 88% yields, respectively (entries 6 and 7), while **2e** bearing an electron-withdrawing trifluoromethyl group gave **3h** in 32% yield (entry 8).

Table 2: Regioselective S_N2'-type reaction and tosylation.



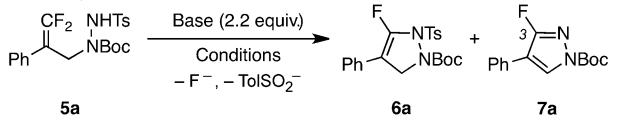
	1			5	
Entry	**1**	**2**	Conditions[a]	**3** [%][b]	**5** [%][c]
1	**1a**	**2a**	A, 1 h	97, **3a**	96 [89], **5a**
2	**1b**	**2a**	A, 7 h	95, **3b**	99 [88], **5b**
3	**1c**	**2a**	A, 0.5 h	72, **3c**	98 [72], **5c**
4	**1d**	**2a**	A, 0.5 h	79, **3d**	quant. [69], **5d**
5	**1a**	**2b**	B, 2 h	76, **3e**	92 [63], **5e**
6	**1a**	**2c**	B, 2 h	80, **3f**	96 [57], **5f**
7	**1a**	**2d**	B, 2 h	88, **3g**	83 [73], **5g**
8	**1a**	**2e**	B, 2 h	32,[d] **3h**	94 [30], **5h**

[a] Condition A: **2a**, NaH (1.8 equiv.), THF, 0 °C. Condition B: **2b–e**, *n*BuLi (1.8 equiv.), THF, −78 to −55 °C. [b] Yield as determined by ^{19}F NMR spectroscopy. [c] Yield as determined by ^{19}F NMR spectroscopy for tosylation step. Yield of the isolated product over two steps is shown in square brackets. [d] −98 °C.

The difluoroalkenes **3** formed were tosylated without purification on their terminal nitrogen atom to give tosylhydrazides **5a–h** in excellent yield. Hydrazides **5** were expected to afford aromatized 3-fluoropyrazoles directly through intramolecular S_NV reactions and elimination of *p*-toluenesulfinic acid.

When tosylhydrazide **5a** was treated with NaH (2.2 equiv.) in refluxing THF, ring closure proceeded to give the cyclized product, dihydropyrazole **6a** in 10% yield and the desired aromatized 3-fluoropyrazole **7a** in 11% yield (Table 3, entry 1). The yield of the desired **7a** was remarkably

Table 3: Cyclization and elimination reactions of **5a**.



5a **6a** **7a**

Entry	Base	Solvent[a]	Conditions	**6a** [%][b]	**7a** [%][b]
1	NaH	THF	reflux, 9 h	10	11
2	NaH	HMPA	RT, 12 h	4	32
3	NaH	DMA	RT, 12 h	13	68
4	NaH	DMF	RT, 5 h	12[c]	86[c]
5	LHMDS	DMF	RT, 20 h	6	47
6	KH	DMF	RT, 6.5 h	8[c]	56[c]

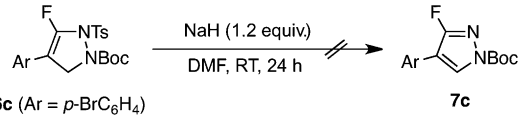
[a] HMPA = hexamethylphosphoramide; DMA = *N*,*N*-dimethylacetamide; DMF = dimethylformamide. [b] Yield as determined by ^{19}F NMR spectroscopy. [c] Yield of the isolated product.

improved to 86% by conducting the reaction in DMF as opposed to other solvents (entries 2–4). Lithium hexamethyldisilazide (LHMDS) and KH were found to be less effective as bases for the reaction than NaH (entries 5 and 6).[15]

Ring closure and elimination reactions completed our sequential synthesis of 3-fluoropyrazoles (Table 4). Boc-hydrazides **5a–d** were treated with NaH in DMF to give the corresponding 3-fluorinated *N*-Boc-pyrazoles **7a–d** in 55–86% yields (entries 1–4). Arylhydrazides **5e–h** also afforded the corresponding 3-fluorinated *N*-arylpyrazoles **7e–h** in 96–98% yields (entries 5–8). These products **7** and **6** were obtained as single regioisomers.[16]

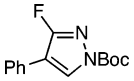
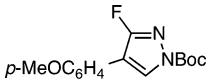
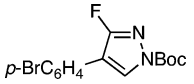
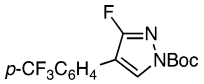
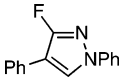
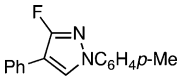
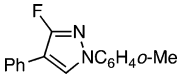
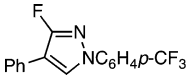
Synthesis of 4-unsubstituted 3-fluoropyrazoles was also accomplished by using 2-silylated trifluoromethylalkenes (Scheme 2). Although the parent, 2-unsubstituted 3,3,3-trifluoropropene was not a suitable substrate for the S_N2'-type reaction with hydrazines,[17] 2-silylated trifluoropropene **1e** was readily subjected to S_N2'-type reactions with Boc- and phenylhydrazines, **2a** and **2b**.[3a] Desilylation occurred during cyclization to give 3-fluoropyrazoles **7i** and **7j** in high yields.

To elucidate the cyclization mechanism, we performed several experiments. When the isolated dihydropyrazole **6c** was treated with NaH, **7c** was not obtained [Eq. (1)]. This suggests that the formation of fluoropyrazoles **7** proceeds

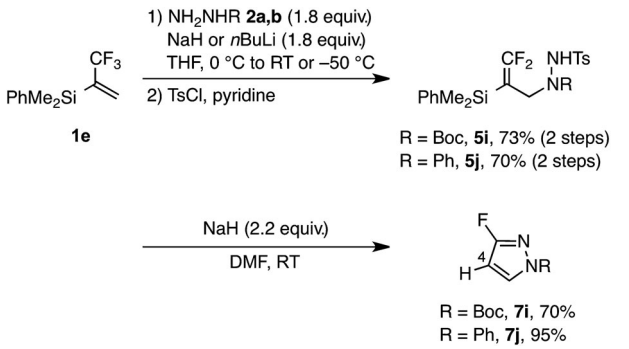


6c (Ar = *p*-BrC$_6$H$_4$) **7c** (1)

Table 4: Synthesis of 3-fluoropyrazoles.[a]

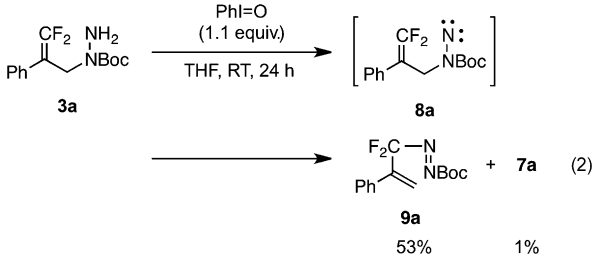
Entry	5	t [h]		7 [%]	6 [%]
1	**5a**	5		86, **7a**	12, **6a**
2	**5b**	72		85, **7b**	–
3	**5c**	14		55, **7c**	20, **6c**
4	**5d**	14		56, **7d**	23, **6d**
5	**5e**	6		98, **7e**	–
6	**5f**	6		98, **7f**	–
7	**5g**	6		96, **7g**	–
8	**5h**	6		97, **7h**	–

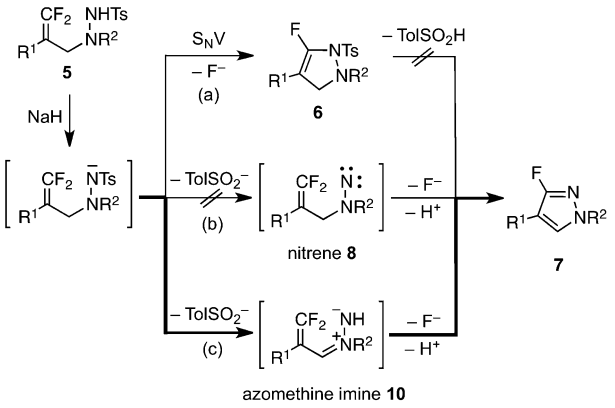
[a] Conditions: **5**, NaH (2.2 equiv.), DMF, RT.



Scheme 2. Synthesis of 4-unsubstituted 3-fluoropyrazoles.

through a pathway other than the originally assumed S_NV process of **5** (Scheme 3a).[18] One possible alternative is the pathway involving nitrene intermediates **8** (Scheme 3b). However, this is not true because the separately-formed nitrene **8a** generated by treating **3a** with iodosylbenzene[19] gave the [2,3]-rearrangement product **9a** along with only a trace amount of **7a** [Eq. (2)]. Therefore, we propose that the cyclization proceeds through azomethine imine intermediates





Scheme 3. Plausible mechanism for pyrazole formation.

10 (Scheme 3c).[20] Azomethine imines are normally prepared from hydrazine derivatives and aldehydes and have been used mainly in 1,3-dipolar cycloadditions to prepare pyrazolidines and dihydropyrazoles.[21] The pyrazole ring formation achieved in this study provides a novel use for azomethine imines in organic synthesis.

Thus, we have achieved substitution of two fluorine atoms in a trifluoromethyl group by combining two substitutions of allylic and vinylic fluorine atoms, which allows the regioselective synthesis of 3-fluoropyrazoles: 1) the S_N2'-type reaction of 2-trifluoromethyl-1-alkenes with lithio- or sodiohydrazines gave 1,1-difluoro-1-alkenes and 2) the cyclization of tosylated 1,1-difluoro-1-alkenes afforded 3-fluoropyrazoles in good to excellent yield. We hypothesize that the cyclization process proceeds via azomethine imine intermediates, which will potentially promote the use of azomethine imines in organic synthesis.

Experimental Section

Synthesis of tosylhydrazide **5a** (Condition A): Sodium hydride (43 mg, 1.8 mmol) was added to a THF (2.0 mL) solution of α-trifluoromethylstyrene (**1a**, 172 mg, 1.00 mmol) and Boc-hydrazine (**2a**, 239 mg, 1.80 mmol) at 0 °C. After the mixture was stirred for 1 h at 0 °C, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was transferred to a reaction flask with ethyl acetate for the following tosylation step. Ethyl acetate was removed under vacuum and the residue was azeotropically dehydrated with pyridine under reduced pressure three times to give crude **3a**.

Tosyl chloride (515 mg, 2.70 mmol) was added to a pyridine (2.0 mL) solution of the crude **3a** at room temperature. After the mixture was stirred for 2.5 h at room temperature, phosphate buffer (pH 7) was added to quench the reaction. The mixture was filtered, and organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/AcOEt 4:1) on silica gel. After removal of the solvent under reduced pressure, hexane was added to the viscous liquid. The obtained solid was washed with hexane three times, and tosylhydrazide **5a** was obtained as a white powder (390 mg, 89%, two steps).

Synthesis of 3-fluoropyrazole **7a**: Sodium hydride (24 mg, 1.0 mmol) was added to a DMF (0.9 mL) solution of tosylhydrazide

5a (200 mg, 0.456 mmol) at room temperature. After the mixture was stirred for 5 h at room temperature, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/AcOEt 10:1) on silica gel to give fluoropyrazole **7a** (104 mg, 86%) and dihydrofluoropyrazole **6a** (23 mg, 12%) as colorless liquids.

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[15] Non-tosylated hydrazine **3a** gave only 15% yield of cyclized product upon treatment with NaH (DMF, RT).

[16] X-ray crystal structure analysis of **7c** confirmed that **7c** has a fluorine substituent at the C3 position. Comparison of ^{1}H and ^{19}F NMR spectra of other fluoropyrazoles suggests that all of the products listed in Table 4 have the same C3-fluorinated skeletons. CCDC 889343 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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