PP-68

Sequential Substitutions of 2-Trifluoromethyl-1-alkenes: Regioselective Synthesis of 3-Fluoropyrazoles

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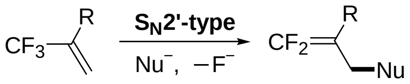
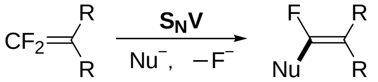
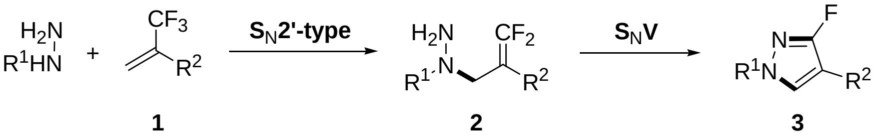
2-Trifluoromethyl-1-alkenes and 1,1-difluoro-1-alkenes exhibit electrophilic character because of the electronegative fluorine atoms. 2-Trifluoromethyl-1-alkenes readily undergo nucleophilic substitution at the carbon γ to the fluorines to produce the corresponding 1,1-difluoro-1-alkenes (eq 1, S_N2'-type reaction).[1] 1,1-Difluoro-1-alkenes undergo nucleophilic substitution at the vinylic carbon (CF_2) to afford substituted monofluoroalkenes (eq 2, S_NV reaction).[2] With these facts in mind, we focused on the synthesis of fluoropyrazoles by the combination of the S_N2'-type reaction and the S_NV reaction (eq 3): The S_N2'-type reaction of 2-trifluorometyl-1-alkene **1** with hydrazines would provide 1,1-difluoro-1-alkenes **2**. Intramolecular S_NV reaction of **2** could afford the targeted fluoropyrazoles **3** after aromatization. Despite the importance of fluorinated pyrazoles as pharmaceuticals and agrochemicals, their synthetic methods have been still quite limited.[3]



(1)



(2)



(3)

The S_N2'-type reaction of 2-trifluoromethyl-1-alkenes were well performed with Boc-hydrazines or phenylhydrazines by using NaH (method A, eq 4) or *n*-BuLi (method B) as a base, respectively (Table 1). Treatment of **1** with in-situ generated lithiohydrazines or sodiohydrazines gave the corresponding difluoroalkenes **2** in 72–97% yield.

Although the expected S_NV reaction of **2** did not proceed on treatment with bases (not shown), the cyclization was accomplished by introducing a tosyl group onto **2**. Treatment of sulfonohydrazide **4** (71%–quant) with NaH (2.2 equiv) gave the desired fluoropyrazoles **3** in 55–98% yield. It is worth noting that accompanying desulfination achieved aromatization to afford **3** in a one-pot operation.

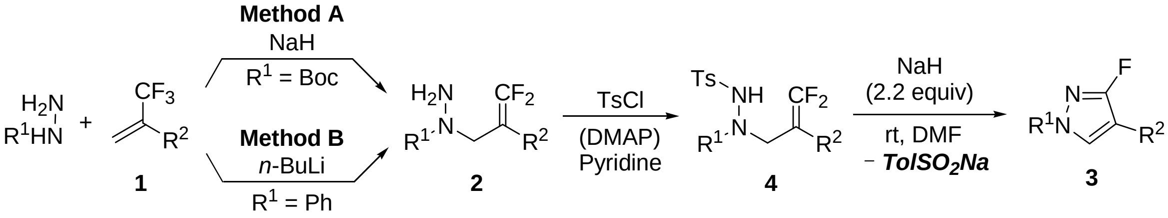
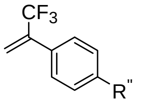
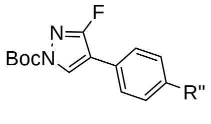
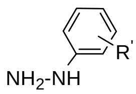
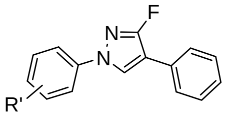
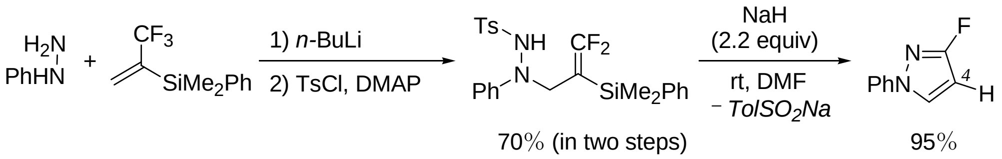

(4)

Table 1

Entry	Hydrazine		Trifluoropropene **1**		Pyrazole	Yield / %		
						2^a	4^a	3
1	NH_2-NHBoc			R'' = H		97	99	86
2	NH_2-NHBoc			R'' = OMe		95	96	85
3	NH_2-NHBoc			R'' = Br		72	98	55
4	NH_2-NHBoc			R'' = CF_3		79	quant	56
5		R' = H		R'' = H		76	92	98
6		R' = *p*-Me		R'' = H		80	87	98
7		R' = *o*-Me		R'' = H		88	71	96

Method A: NaH (1.8 equiv), THF, 0 °C. **Method B**: *n*-BuLi (1.8 equiv), THF, −50 to −60 °C. a: ^{19}F NMR yield.

4-Unsubstituted fluoropyrazole was also synthesized starting from silyltrifluoropropene (eq 5). Desilylation took place during the cyclization step.


(5)

In summary, we have developed a novel method for the synthesis of fluoropyrazoles. Sequential substitutions of 2-trifluoromethyl-1-alkenes with hydrazine derivatives successfully provide 3-fluoropyrazoles.

[1] Begue, J.; Delpon, D.; Rock, M., *Tetrahedron Lett.* **1995**, *36*, 5003. See also: Ichikawa, J.; Ishibashi, Y.; Fukui, H., *Tetrahedron Lett.* **2003**, *44*, 707.

[2] See for example: Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T., *Chem. Commun*. **1997**, 1537; Ichikawa, J.; Lapointe, G.; Iwai, Y., *Chem. Commun*. **2007**, 2698; Ichikawa, J.; Wada, Y.; Kuroki, H.; Mihara, J.; Nadano, R., *Org. Biomol. Chem.* **2007**, *5*, 3956; Okuhara, K., *J. Org. Chem*. **1976**, *41*, 1487.

[3] Clark, D.; Lahm, G.; Smith, B.; Barry, J.; Clagg, D., *Bioorg. Med. Chem.* **2008**, *16,* 3163; Volle, J.; Schlosser, M., *Eur. J. Org. Chem.* **2000**, 823; Ichikawa, J.; Kobayashi, M.; Noda, Y.; Yokota, N.; Amano, K.; Minami, T., *J. Org. Chem*. **1996**, *61*, 2763; Fabra, F.; Vilarrasa, J., *J. Heterocycl. Chem*. **1978**, *15*, 1447; Makino, K.; Yoshioka, H., *J. Fluorine Chem*. **1988**, *39*, 435.