Synthesis of 3-Fluoropyrazoles from 2-Trifluoromethyl-1-alkenes

**Significance:** Reported is a three-step protocol for the de novo synthesis of substituted 3-fluoropyrazoles through annulation of 2-trifluoromethyl-1-alkenes with monosubstituted hydrazines. The first step in this unconventional approach is an SN2′ addition of an N-deprotonated hydrazine to the trifluoromethyl-substituted alkene to give a 3,3-difluoro allylic hydrazide, which is subsequently tosylated (1→2). While N-alklylation proceeds in a highly regioselective manner when aryl- and Boc-substituted hydrazines are employed, methyl-hydrazine affords a 55:45 mixture of N-regioisomers (66% combined yield, not shown above). Treatment of 2 with NaH in DMF affords the substituted 3-fluoropyrazole 3; control experiments established the need to employ toslyhydrazides in this reaction. 4-Unsubstituted 3-fluoropyrazoles 5 were accessible from the corresponding 2-silyl allylic hydrazide 4.

**Comment:** Pyrazoles are among the most metabolically stable unsaturated five-membered heterocycles (see Review below) and are frequently incorporated into drug candidates. A successful example is the COX-2 inhibitor celebrex®. The present method provides efficient access to synthetically challenging substituted 3-fluoropyrazoles through a non-obvious and generally high-yielding annulation sequence that utilizes readily accessible starting materials. On the down side, no mention was made of attempts to achieve the synthesis of C5-substituted pyrazoles; alkyl substitution at C4 was also not explored. Control experiments suggest that base-mediated ring closure (2→3) proceeds through neither direct nucleophilic vinylic substitution (SN2V) nor an intermediate nitrene. Instead, an unusual pathway is suggested that features an azomethine imine intermediate.


**CF3**

\[ \text{CF}_3 \text{R}_1 \]

\[ \text{TsCl, py} \]

\[ \text{H}_2\text{NNHR}_2 \text{ (1.8 equiv)} \]

\[ \text{conditions} \]

\[ \text{F} \]

\[ \text{F} \]

\[ \text{R}_1 \]

\[ \text{N} \]

\[ \text{NHTs} \]

\[ \text{R}_2 \]

\[ \text{NaH} \text{ (2.2 equiv)} \]

\[ \text{DMF, r.t.} \]

\[ \text{F} \]

\[ \text{F} \]

\[ \text{R}_1 \text{N} \text{NHTs} \text{R}_2 \]

\[ \text{NaH} \text{ (2.2 equiv)} \]

\[ \text{DMF, r.t.} \]

\[ \text{F} \]

\[ \text{F} \]

\[ \text{R}_2 \]

\[ \text{NaH} \text{ (2.2 equiv)} \]

\[ \text{DMF, r.t.} \]

\[ \text{F} \]

\[ \text{Boc} \]

\[ \text{N} \]

\[ \text{N} \]

\[ \text{F} \]

\[ \text{Boc} \]

\[ \text{MeO} \]

\[ \text{Me}_3\text{PhSi} \text{N} \text{NHTs} \text{R}_2 \]

\[ \text{NaH} \text{ (2.2 equiv)} \]

\[ \text{DMF, r.t.} \]

\[ \text{F} \]

\[ \text{Boc} \]

\[ \text{N} \]

\[ \text{N} \]

\[ \text{F} \]

\[ \text{Boc} \]

\[ \text{88% yield of 2} \]

\[ \text{85% yield of 3} \]

\[ \text{89% yield of 2} \]

\[ \text{86% yield of 3} \]

\[ \text{73% yield of 2} \]

\[ \text{90% yield of 3} \]

\[ \text{30% yield of 2} \]

\[ \text{97% yield of 3} \]