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

**Significance:** Reported is a three-step protocol for 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 SN$_2'$ addition of an N-deprotonated hydrazine to the trifluoromethyl-substituted alkene to give a 3,3-difluoro allylic hydrazide, which is subsequently tosylated ($1 \rightarrow 2$). While N-alkylation proceeds in a highly regioselective manner when aryl- and Boc-substituted hydrazines are employed, methylhydrazine 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 tosylhydrazides 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 ($2 \rightarrow 3$) proceeds through neither direct nucleophilic vinylic substitution (SN$_1$V) nor an intermediate nitrene. Instead, an unusual pathway is suggested that features an azomethine imine intermediate.

**Representative examples:**

- For $R^2 = \text{Boc}$; conditions = NaH, THF, 0 °C
  - 88% yield of $2$
  - 85% yield of $3$

- For $R^2 = \text{Ar}$; conditions = n-BuLi, THF, –60 °C
  - 89% yield of $2$
  - 86% yield of $3$

- For $R^2 = \text{Boc}$: 70% yield
  - 89% yield of $2$
  - 95% yield of $3$

- For $R^2 = \text{Ph}$: 95% yield
  - 90% yield of $3$

- 88% yield of $2$
  - 86% yield of $3$

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