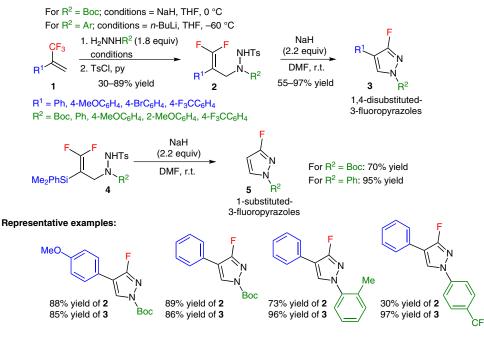
K. FUCHIBE, M. TAKAHASHI, J. ICHIKAWA* (UNIVERSITY OF TSUKUBA, JAPAN) Substitution of Two Fluorine Atoms in a Trifluoromethyl Group: Regioselective Synthesis of 3-Fluoropyrazoles *Angew. Chem. Int. Ed.* **2012**, *51*, 12059–12062.

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



Category

Synthesis of Heterocycles

Key words

3-fluoropyrazoles

hydrazines

trifluoromethylstyrenes

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 highyielding 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 (S_NV) nor an intermediate nitrene. Instead, an unusual pathway is suggested that features an azomethine imine

Review: D. K. Dalvie et al. *Chem. Res. Toxicol.* **2002**, *15*, 269–299.

intermediate.

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 S_N2' 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 Bocsubstituted 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.

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