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Substitution of Two Fluorine Atoms in a Trifluoromethyl Group: Regioselective Synthesis of 3-Fluoropyrazoles
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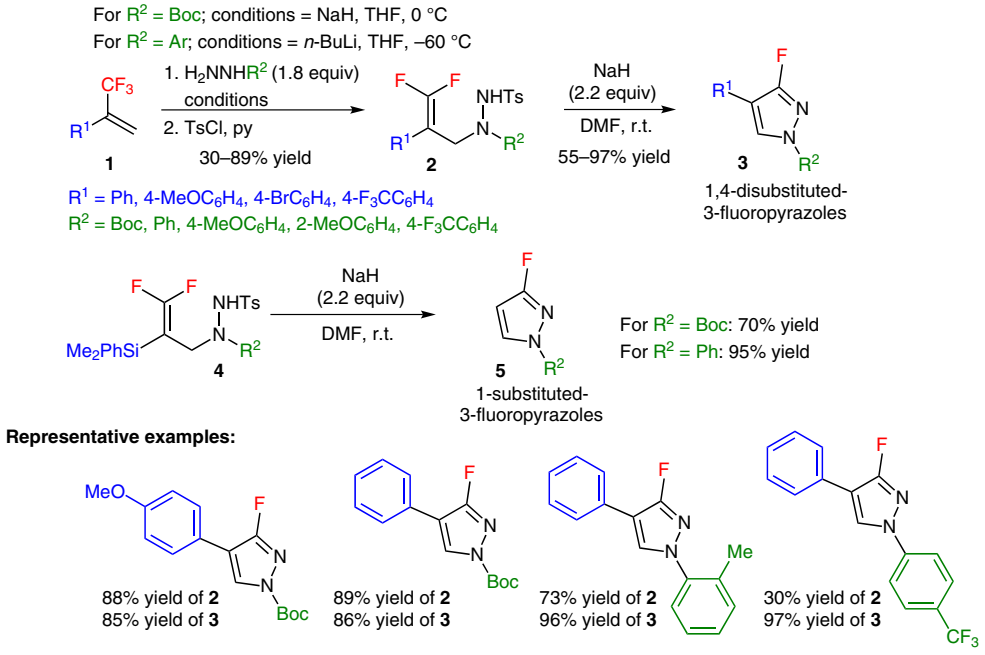
Synthesis of 3-Fluoropyrazoles from 2-Trifluoromethyl-1-alkenes



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 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**→**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**→**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 intermediate.

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

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Category

Synthesis of Heterocycles

Key words

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hydrazines

trifluoromethyl-styrenes