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Substitution of Two Fluorine Atoms in a Trifluoromethyl Group: Regioselective Synthesis of 3-Fluoropyrazoles


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-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-Substituted 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 (SnV) nor an intermediate nitrene. Instead, an unusual pathway is suggested that features an azomethine imine intermediate.

Representative examples:

For R2 = Boc; conditions = NaH, THF, 0 °C
For R2 = Ar; conditions = n-BuLi, THF, –60 °C

1. H2NNH2 (1.8 equiv) conditions
2. TsCl, py

R1 = Ph, 4-MeOC6H4, 4-BrC6H4, 4-FC6H4
R2 = Boc, Ph, 4-MeOC6H4, 2-MeOC6H4, 4-FC6H4

N
N
F
NHTs
R1
R2

For R2 = Boc: 70% yield
For R2 = Ph: 95% yield

N
N
F
Boc

88% yield of 2
85% yield of 3

N
N
F
Boc

89% yield of 2
86% yield of 3

N
N
F
Boc

73% yield of 2
96% yield of 3

N
N
F
Boc

30% yield of 2
97% yield of 3