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Practical Synthetic Method for Functionalized 1-Methyl-3/5-(trifluoromethyl)-1H-pyrazoles
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Regioselective Scalable Approaches to Trifluoromethylated Pyrazoles

Significance: The regioselective scalable synthesis of 3/5-trifluoromethyl pyrazole derivatives represents an important challenge, given the prominence of these motifs in both agrochemicals and pharmaceuticals. The current report details a kilogram synthesis and efficient distillation-based separation of 1-methyl-(3-trifluoromethyl)-1H-pyrazole (4) and 1-methyl-(5-trifluoromethyl)-1H-pyrazole (3), and their subsequent regioselective elaboration in either batch or flow mode through a series of strategies based on lithiation/electrophilic trapping chemistries (M. Schlosser et al. *Eur. J. Org. Chem.* **2002**, 2913).

Comment: Several approaches for the synthesis of the parent pyrazoles were evaluated, and the reaction of 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (1) with methyl hydrazine hydrochloride (2) was scaled to provide access to the desired compounds. Functionalization of the 5-position was achieved by lithiation in flow followed by trapping in batch with a series of electrophiles (for example, 5). Judicious control of the concentration in flow proved important in avoiding precipitation. Bromination with NBS cleanly afforded the 4-bromopyrazoles 6, which could be subsequently elaborated either through halogen-metal exchange followed by functionalization (see 7) or by direct *ortho*-lithiation, functionalization, and debromination (for example, 9), although in the latter sequence control of temperature proved critical to avoid the formation of isomers through a ‘halogen-dance’ reaction (see Review below).

Review: M. Schnürch, M. Spina, A. F. Khan, M. D. Mihovilovic, P. Stanetty *Chem. Soc. Rev.* **2007**, *36*, 1046–1057.

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