Synthesis and reactivity of N-difluoro-cyclopropyl-substituted pyrazoles

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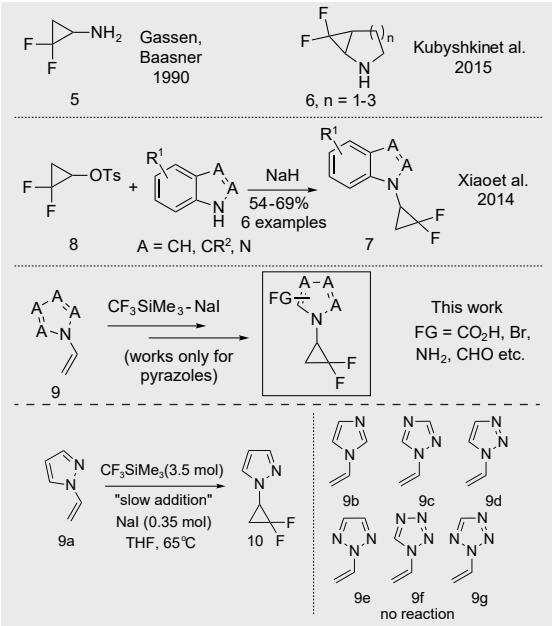
Introduction and Aim

Fluorinated cyclopropanes have become extraordinary structural motifs which attracted much attention in organic synthesis, drug discovery and agrochemistry over the last years.

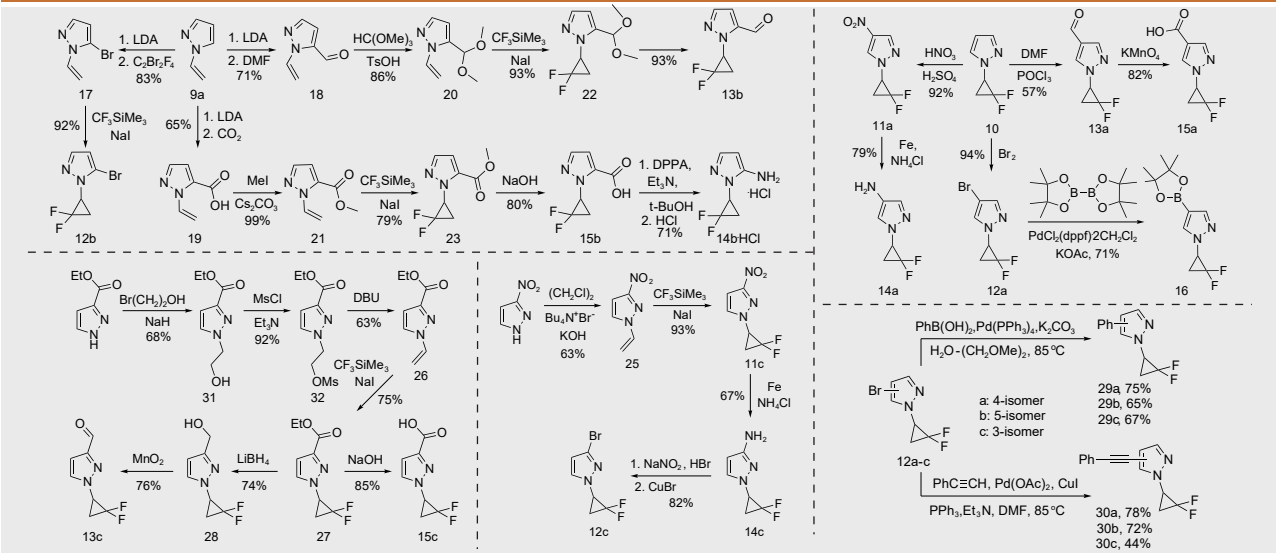
While a number of papers describe synthetic approaches to the compounds having a *gem*-difluorocyclopropyl group attached to the carbon atom, as well as their chemical transformations, the corresponding N-substituted analogues are much less known.

Difluorocyclopropanation of N-vinylazoles with the CF_3SiMe_3–NaI system was studied. It was found that N-vinylpyrazolescould be transformed into the corresponding N-difluorocyclopropyl-substituted derivatives. The method was efficient on a 100 g scale and could be applied for the preparation of various functionalized regioisomeric pyrazole derivatives bearing a gem-difluorocyclopropane moiety, such as amines, carboxylic acids, aldehydes, bromides, and boronic esters. It was found that N-difluorocyclopropylpyrazole moiety tolerated many common reagents including nitrating mixture, bromine, aqueous acids and alkali, $KMnO_4$, $LiBH_4$, and Pd^0 complexes; it was unstable towards $AlCl_3$, catalytic hydrogenation and lithiation conditions. The products obtained are advanced building blocks which of potential importance to medicinal and agrochemistry.

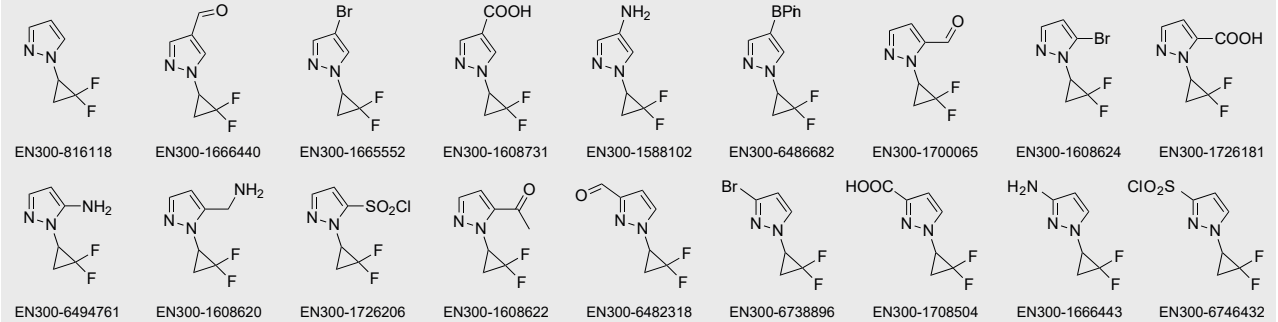
Therefore, building blocks described herein can be considered as readily available to scientific community and are promising reagents for drug discovery and agrochemistry, which are fully compatible with even the strictest compound selection criteria.



Additional Functionalization



Results



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ref. Nosik et. al Eur. J. Org. Chem. 2019, 4311–4319.