NOVEL PYRAZOLE SYNTHESIS VIA [2+3]-DIPOLAR CYCLOADDITION OF ALKYNE SURROGATES

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Abstract: Heterocycles are popularly known for displaying a wide range of biological properties. The recent success of pyrazole based COX-II inhibitors and their application in medicinal chemistry have amplified the importance of pyrazoles to even a greater extent. Several pharmaceutical drugs including celecoxib and rimonabant utilize the pyrazole as their core molecular entity, and a regioselective synthetic method for the synthesis of similarly substituted pyrazoles is still in demand. One of the most frequently used protocol used to synthesize pyrazoles is 1,3-dipolar cycloaddition, and the usual dipolarophiles for this purpose are alkynes and the alkyne surrogates. The use of alkyne synthons can serve to alleviate many of the alkyne preparatory and cycloaddition regioselectivity issues. These alkyne surrogates are usually alkenes that have a functional group that can be eliminated in situ during cycloaddition. Recently, we reported a facile application of geminally disubstituted alkenes with a bromine atom as one of the substituents as effective alkyne surrogates towards the regioselective synthesis of isoxazoles. However, this protocol can be applied toward the regioselective construction of several heterocyclic templates of pharmaceutical interest. Herein we report the syntheses of an important class of hitherto unreported novel pyrazoles. The regioselective synthesis of 1,3,4,5-tetrasubstituted pyrazoles was achieved by the Huisgen cyclization of nitrile imines with -bromocinnamaldehyde. The substituted bromoalkene functions as an alkyne synthon which was used to construct bromopyrazoline intermediates that undergo aromatization to the analogous pyrazoles through the loss of HBr, as evidenced by single X-ray crystal data.

Keywords: Cycloaddition, Heterocycles, Pyrazoles, Bromoalkenes, Regioselectivity, Alkyne synthons

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