The title

Copper-Catalyzed Regioselective 2-Arylation of 5-Substituted Tetrazoles under Mild Conditions

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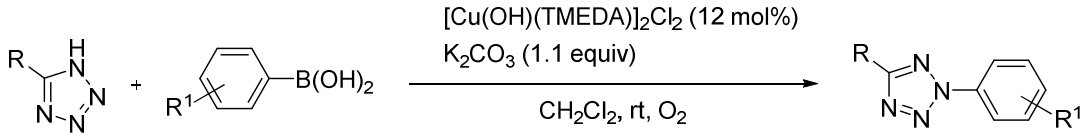
Tetrazoles are versatile, N-containing heterocyclic compounds used in pharmaceuticals, agrochemicals, and materials science. Moreover, 1-aryl-5-substituted tetrazoles are particularly useful as synthetic intermediates in biological research and medicinal chemistry. An efficient synthetic method of 1-aryl-5-substituted tetrazoles, therefore, has been developed.

Historically, 2-aryl-5-substituted tetrazoles have been regarded as less important than 1-aryl-5-substituted tetrazoles. However, the former have recently exhibited remarkable biological properties such as modulators of metabotropic glutamate receptors and G-protein-coupled receptor agonism. Despite these findings, however, reported methods for synthesizing 2-aryl-5-substituted tetrazoles are few. Several transition-metal-catalyzed direct 2-arylation of 5-substituted tetrazoles have been reported. Although 2-aryl-5-substituted tetrazoles were selectively obtained, these reported methods have been required a high reaction temperature and troublesome preparation of starting materials. It is known that tetrazoles are potentially explosive, and avoiding high reaction temperature is necessary. In addition, only 5-aryltetrazoles were used as substrates.

In this presentation, we report a novel method for the regioselective synthesis of 2-aryl-5-substituted tetrazoles by direct coupling of 5-substituted tetrazoles with arylboronic acids in the presence of a catalytic amount of $[Cu(OH)(TMEDA)]_2Cl_2$ in an O_2 atmosphere. The reaction can be conducted at room temperature and is applicable to both 5-aryltetrazoles and 5-alkyltetrazoles.



Applicable to Various Tetrazoles
(R = Alkyl, Thioalkyl, Halogen, Carbonyl, Aryl)