Synthesis of Substituted 1,2,4-Triazoles from Formamidrazones and Isocyanides

**Significance:** Reported is the synthesis of 3-aryl/vinyl-4-alkyl-1,2,4-triazoles \(3\) by the cyclization of formamidrazones \(2\). These intermediates were prepared by the reaction of thiosemicarbazones \(1\) with isocyanides in the presence of chlorotrimethylsilane, a reaction which was previously described by the same authors. The reaction could be performed using unpurified formamidrazones, but better yields and easier purification was achieved when using formamidrazones purified by silica gel column chromatography to greater than 80% purity as established using LC–MS. Formamidrazones \(2\) exist as a mixture of tautomers in the free-base form as shown by \(^1\)H NMR spectroscopy. The proposed mechanism of this reaction to give triazoles \(3\) is simply an aromatization of the tautomeric cyclized dihydrotriazole, although the authors state that they have not observed this tautomer. Although the reactions were run using a sealed tube, there is no mention if this was necessary and if the reactions work in an open vessel. In addition, due to the use of an ‘equal amount w/w’ of palladium on carbon, the catalyst loadings of the reactions vary considerably which is less than optimal when trying to reduce costs on large-scale reactions.

**Comment:** As described in the introduction to the current work, 1,2,4-triazoles are an important class of heterocycles which have found increased and effective use in the synthesis of pharmaceutically active compounds. The presented method complements existing methods for the synthesis of 1,2,4-triazoles (see Review and Book below) and has the advantage of modest to good yield, mild conditions, ready availability and ease of synthesis of the starting materials. The substrate scope was moderately studied and it was found that the reaction failed when \(R_1 = \text{alkyl}\), or when \(R_2 = \text{aryl}\). The reaction appears not to have been optimized with respect to palladium-catalyst loading.


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