Optimized Syntheses of Novel, Medicinally Applicable 1,2,3-Triazole Derivatives

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Due to its ability to serve as a linkage within larger molecules, 1,2,3-triazole derivatives are widely used in pharmaceuticals as means to facilitate stability, utility, and permeability. This study reports the first documented synthesis and optimization of the 4,5- (bis)trimethylsilyl-5-ethynyl-1,2,3-triazole; the 5-ethynyl-1,2,3-triazole; and the 4-trimethylsilyl- 5-ethynyl-1,2,3-triazole, using environmentally friendly and cost-effective synthesis protocols. Synthesis of the 4,5-(bis)trimethylsilyl-5-ethynyl-1,2,3-triazole involved a 1,3-dipolar cycloaddition reaction between benzyl azide and 1,4(bistrimethylsilyl)-1,3-butadiyne (BTMSBD). Optimization of this reaction, which involved testing varying quantities of BTMSBD, gave a maximized yield of 82%. This synthesis was followed by a silver tetrafluoraborate-, copper(II) sulfate-, and sodium L-ascorbate(+)-catalyzed desilylation of the 4,5-(bis)trimethylsilyl-5-ethynyl-1,2,3-triaozle to synthesize the 5-ethynyl-1,2,3-triazole. Optimization of the 5-ethynyl-1,2,3-triazole involved varying time, temperature, and reagent quantities, and gave a maximized yield of 73%. During optimization of the 5-ethynyl-1,2,3-triazole, a less expensive silver ion catalyst, silver nitrate, was tested, which resulted in the unexpected synthesis of 4-trimethylsilyl-5-ethynyl-1,2,3-triazole. The 4-trimethylsilyl-5-ethynyl-1,2,3-triazole was optimized in terms of reagent quantities, time, and temperature to give a maximized yield of 92%. The optimized protocols developed for the three 5-substituted-1,2,3-triazoles reported in this paper will be published and then added to a chemical library to enable syntheses of additional 1,2,3-triazole derivatives for use in pharmaceutical drug discovery.

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