



Thermal, non-catalyzed Huisgen cycloaddition for the preparation of 4,5-bis(trimethylsilyl)-1H-1,2,3-triazoles

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ABSTRACT

The 1,2,3-triazole scaffold is an important pharmacophore and a versatile, increasingly leveraged, substructure in biochemical, materials, polymer, and metal-coordinating applications. Continuing advances in 1,2,3-triazole construction, by either non-catalyzed or metal-catalyzed azide/alkyne cycloaddition, foster further creative use. The work reported here establishes a general protocol for the synthesis of 4,5-bis(trimethylsilyl)-1H-1,2,3-triazoles via thermal Huisgen cycloaddition between azides and bis(trimethylsilyl)acetylene.

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Introduction

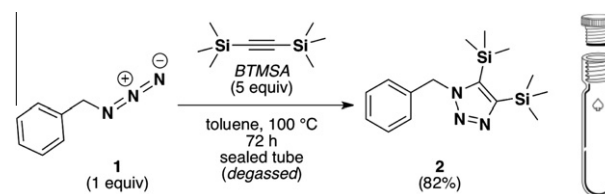
The 1,2,3-triazole scaffold, which is chemically robust, can act as a hydrogen bond acceptor, and imparts a significant local dipolarity ($\mu = 5.2\text{--}5.6\text{ D}$),¹ has been known in the literature for about 120 years,² and these heterocyclic aromatic systems have remained valuable as pharmacophores in biologically active molecules.³ Huisgen pioneered synthetic access to 1,2,3-triazoles by demonstrating the effectiveness of thermal [3+2] dipolar cycloaddition between azides and alkynes.⁴ In general, Huisgen cycloaddition is limited by the lack of regiocontrol obtained for reactions between azides and unsymmetrically substituted alkynes. The development of Cu-catalyzed Huisgen cycloaddition (the essentially de facto example of a *click* reaction)⁵ and the complementary Ru-catalyzed approach⁶ have furnished regiocontrol and facilitated a renaissance extending 1,2,3-triazole synthesis and creative application to biochemical ligating and tagging,⁷ polymers,⁸ metal coordination complexes,⁹ and enhancement of photo-physical properties (e.g., *click-activated* fluorescence).¹⁰ Such increased attention in 1,2,3-triazole synthesis and application has also motivated further, recent investigations of thermal Huisgen cycloaddition, with the so-called *strained promoted* reactions having gained particular notoriety.¹¹

Among our interests regarding applications of Huisgen cycloaddition, we have recently begun preparing novel, *click-activated*

fluorophores.^{10,12} We envisioned incorporation of 4,5-bis(trimethylsilyl)-1,2,3-triazole moieties into our targeted *click-activated* fluorophores because of likely influence on solubility imparted by trialkylsilyl substituents and because fluorophore derivatization via metal-catalyzed cross coupling becomes possible upon replacement of trialkylsilyl substituents by a halogen atom.^{13,14} We intended to construct 4,5-bis(trimethylsilyl)-1,2,3-triazole moieties via Huisgen cycloaddition between azide precursors and commercially available bis(trimethylsilyl)acetylene (BTMSA), and our search of the literature in this regard found only seven such scaffolds previously reported and no established general procedure.^{13a,15,16} Thus, we decided to optimize a protocol for Huisgen cycloaddition between azides and BTMSA and explore its scope and limitations.

Results and discussion

Our preliminary optimization experiments were performed with 2 equiv of BTMSA and 1 equiv of benzyl azide **1**. We quickly



Scheme 1.

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Table 1

Entry	Azide ^a	4,5-Bis(TMS) product ^b (%yld)	Entry	Azide ^a	4,5-Bis(TMS) product ^b (%yld)
1			11		
2			12 ^c		
3			13		
4			14		
5			15		

(continued on next page)

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