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Synthesis of Unsymmetrical 1,1′-Disubstituted Bis(1,2,3-triazole)s Using Monosilylbutadiynes

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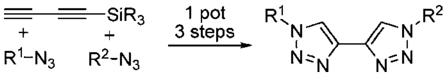
ABSTRACT



Bis(1,2,3-triazole)s have attracted recent interest as coordinating ligands for transition metals. Here we report a rapid, modular method for the synthesis of 1,1′-disubstituted-4,4′-linked unsymmetrical bis(1,2,3-triazole)s. The method employs sequential copper catalyzed azide−alkyne cycloaddition and deprotection steps on a monosilylbutadiyne. TMS (trimethylsilyl) and TIPS (triisopropylsilyl) were both investigated with TIPS being the preferred protecting group due to increased stability. The reactions were amenable to one-pot synthesis, and an optimized one-pot, three-step procedure was developed.

The copper(I)−catalyzed azide−alkyne cycloaddition (CuAAC) was reported in 2002 independently by both the Meldal and Sharpless groups and has come to be the quintessential click reaction.[1] It is generally high yielding and can be conducted under mild conditions leading to its widespread application in chemistry. The resulting triazole moiety has attracted attention for its coordinating properties,[2] including those of the symmetrical bis(1,2,3-triazole)s.[3] Metal-coordinated triazoles have been shown to be efficient catalysts and to form supramolecular structures, and varying substituents plays an important role in tuning these properties.[4] Despite this interest, a flexible and efficient synthesis of unsymmetrical 4,4′-linked bis(1,2,3-triazole)s has had little attention until very recently.

Fiandanese et al.[5a] first reported the synthesis of a number of simple unsymmetrical bistriazoles using mono TMS-butadiyne (TMS, trimethylsilyl). Initial CuAAC with an azide followed by deprotection with TBAF (tetrabutylammonium fluoride) and subsequent CuAAC gave the desired unsymmetrical bis(1,2,3-triazole)s. More recently Aizpurua et al. reported a synthesis which employed a CuAAC with propargyl alcohol, followed by conversion to the ethynyltriazole (Swern oxidation, then Ohira−Bestmann homologation) and then subsequent CuAAC to the unsymmetrical bis(1,2,3-triazole)s.[5b] Recognizing the limitations associated with this method, Aizpurua et al. also employed the TMS-butadiyne method to produce a number of unsymmetrical bis(1,2,3-triazole)s.

At the same time, our laboratory was investigating a TMS-butadiyne based approach; however as we describe below, we encountered limitations that drove us to develop a more widely applicable approach to unsymmetrical 1,1′-disubstituted-4,4′-linked bis(1,2,3-triazole)s, which we report here.

Initially, we utilized the monodeprotection of bis-TMS-butadiyne to give TMS butadiyne (**1**),[6] and reaction with benzyl azide under standard CuAAC conditions produced the silyl protected ethynyltriazole **2**,[5] along with small amounts of deprotected ethynyltriazole **3** and symmetrical

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(1) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (c) Meldal, M.; Tornoe, C. W. *Chem. Rev.* **2008**, *108*, 2952.

(2) (a) Struthers, H.; Mindt, T. L.; Schibli, R. *Dalton Trans.* **2010**, *39*, 675. (b) Yano, M.; Tong, C. C.; Light, M. E.; Schmidtchen, F. P.; Gale, P. A. *Org. Biomol. Chem.* **2010**, *8*, 4356. (c) Crowley, J. D.; Bandeen, P. H.; Hanton, L. R. *Polyhedron* **2010**, *29*, 70. (d) Urankar, D.; Pinter, B.; Pevec, A.; De Proft, F.; Turel, I.; Kosšmrlj, J. *Inorg. Chem.* **2010**, *49*, 4820.

(3) (a) Monkowius, U.; Ritter, S.; Konig, B.; Zabel, M.; Yersin, H. *Eur. J. Inorg. Chem.* **2007**, *29*, 4597. (b) Fletcher, J. T.; Bumgarner, B. J.; Engels, N. D.; Skoglund, D. A. *Organometallics* **2008**, *27*, 5430. (c) Crowley, J. D.; Bandeen, P. H. *Dalton Trans.* **2010**, *39*, 612.

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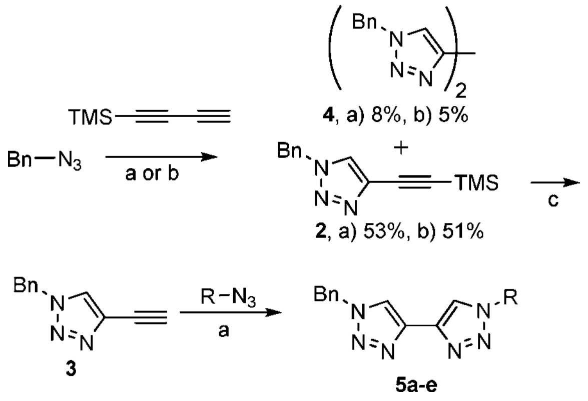
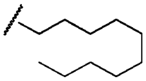
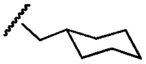
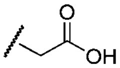
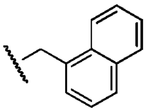
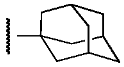
bistriazole **4**. Aizpurua et al. also noted isolation of symmetrical bistriazoles from some azides in this manner and reported overcoming this by changing conditions to CuI, EtN(i-Pr)$_2$ in acetonitrile; in our hands these conditions also gave similar amounts of symmetrical bistriazole. Deprotection with KF gave ethynyl triazole **3** in quantitative yield, and subsequent CuAAC with a variety of azides then gave a number of unsymmetrical bistriazoles **5a**−**e** in moderate to low yields (Table 1).

Table 1. Initial Synthesis of Unsymmetrical Bistriazole with TMS Protection[a]

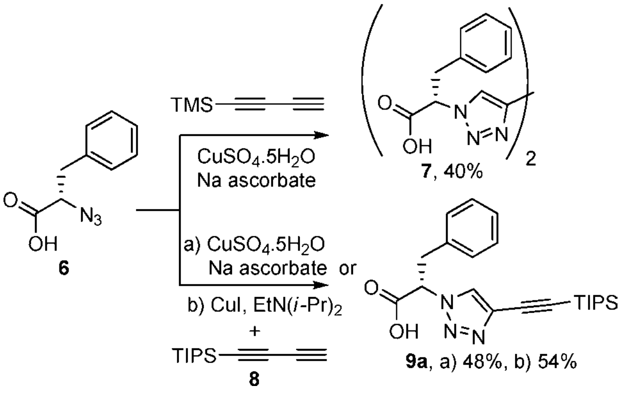


product	R =	yield (%)[b]
5a		65
5b		52
5c		40
5d		34
5e		19

[a] Conditions: (a) CuSO$_4$•5H$_2$O, Na ascorbate, 2:1 t-BuOH/H$_2$O; (b) CuI, EtN(i-Pr)$_2$, MeCN; (c) KF, MeOH. [b] Yield of isolated purified product.

In seeking to investigate a broader range of substitutents in this reaction, we trialled the CuAAC with (S)-azidobenzylacetic acid (**6**) under standard conditions but found the symmetrical bistriazole **7** as the major product in 40% yield (Scheme 1). The increased yield of bistriazole was attributed to the acidic nature of azide **6** leading to cleavage of the TMS group. Noting the reported instability of the TMS group to copper,[7] we sought to utilize the more stable TIPS-protected butadiyne (TIPS, triisopropylsilyl), in order to retain the selective and modular nature of the synthesis but with greater functional group tolerance.

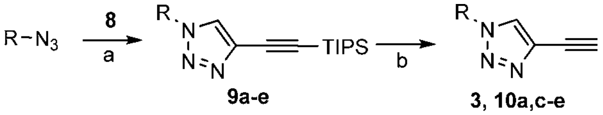
Scheme 1. Synthesis of Symmetrical Bistriazole **7**, and 4-(TIPSethynyl)triazole **9a**

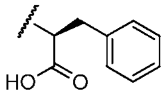
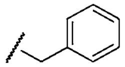
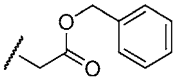
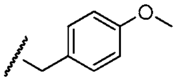
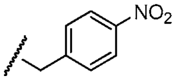


TIPS-protected butadiyne **8** was prepared according to the reported procedure in 70% yield over three steps.[8]

Subsequent CuAAC with azide **6** then gave silyl protected ethynyl triazole **9a** in 54 and 48% yield with copper iodide and copper sulfate/sodium ascorbate procedures respectively; no symmetrical bistriazole was observed. Given the moderate yield of silyl protected ethynyl triazole **9a**, optimization by excluding oxygen and the addition of catalytic amounts of tris-(benzyltriazolylmethyl)amine (TBTA) was undertaken, improving the yield of **9a** to 65% (Table 2).[9] Both TBAF and CsF were used to deprotect TIPS ethynyl triazole **9b** in

Table 2. Synthesis of 4-Ethynyltriazoles with TIPS Protection[a]



R	product	step a yield (%)[b]	product	step b yield (%)[b]
	**9a**	65	**10a**	26[c]
	**9b**	70	**3**	97 (80)[d]
	**9c**	81	**10c**	67
	**9d**	57	**10d**	67
	**9e**	78	**10e**	66

[a] Conditions: (a) CuI, EtN(i-Pr)$_2$, TBTA, under N$_2$; (b) TBAF. [b] Yield of isolated purified product. [c] Decomposed during purification. [d] CsF procedure.

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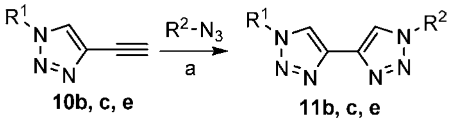
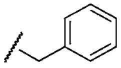
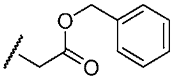
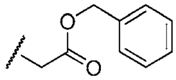
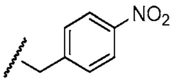
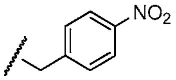
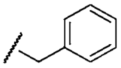
(5) (a) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A.; Capuzzolo, F. *Tetrahedron* **2009**, *65*, 10573. (b) Aizpurua, J. M.; Azcune, I.; Fratila, R. M.; Balentova, E.; Sargartzazu-Azipurua, M.; Miranda, J. I. *Org. Lett.* **2010**, *12*, 1584.

(6) Holmes, A. B.; Jennings-White, C. L. D.; Schulthess, A. H. *Chem. Commun.* **1979**, 840.

97 and 80% yield respectively, demonstrating TBAF to be the preferred fluoride source. A number of TIPS ethynyl triazoles **9b**−**e** were then synthesized by this method (Table 2), and some converted to bistriazoles (Table 3).

Table 3. Synthesis of Bis(1,2,3-triazole)s[a]



product	R^1	R^2	yield **11** (%)[b]
11b			63
11c			50
11e			68

[a] Conditions: CuI, EtN(i-Pr)$_2$, TBTA, under N$_2$. [b] Isolated purified yield.

Scheme 2. One-Pot Two-Step Procedures

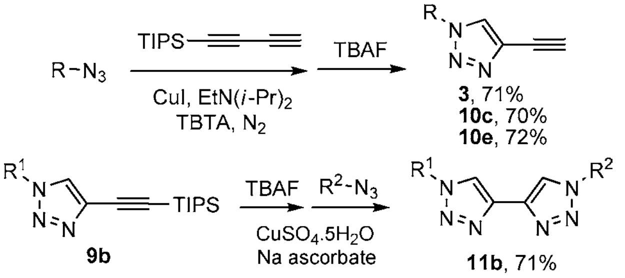
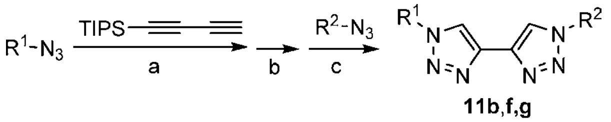
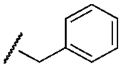
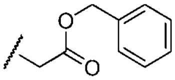
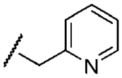
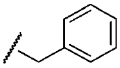
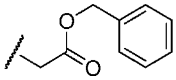
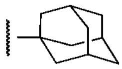


Table 4. One-Pot Three-Step Synthesis of Bistriazoles[a]



product	R^1	R^2	yield **11** (%)[b]
11b			49
11f			42
11g			34

[a] Conditions: (a) CuI, EtN(i-Pr)$_2$, TBTA, MeCN, under N$_2$, 20 h; (b) TBAF, 20 min then AcOH; (c) 16 h. [b] Isolated purified yield.

After TBAF deprotections, the ^{1}H NMR spectrum of the crude product showed that both the CuAAC and silyl deprotection generally proceeded with high conversion and gave only inoffensive byproducts. This suggested a one-pot multistep procedure may also give the desired bistriazoles while reducing time and the number of isolation and purification steps required.

Initially, one-pot two-step procedures for the initial CuAAC/TBAF deprotection and alternately the TBAF deprotection/final CuAAC were conducted with good results; in either case, the overall yield for the three steps was 45% for bistriazole **11b** (Scheme 2), compared to 43% overall for the three separate reactions. Two additional one-pot click and deprotection reactions (Scheme 2) gave similar results.

We next investigated a one-pot three-step procedure. The one-pot three-step synthesis of bistriazole **11b** gave a yield of 49% for a slight improvement over the multipot approaches (Table 4, entry b). Two additional novel bistriazoles were then synthesized via the one-pot procedure (Table 4), demonstrating a viable synthetic approach involving a single purification step.

In summary, an efficient and selective modular synthesis of 1,1′-unsymmetrical-4,4′-linked bis(1,2,3-triazole)s from silylbutadiynes was developed. This method is amenable to a simple, one-pot three-step procedure.

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Supporting Information Available: Experimental procedures and spectroscopic data for all novel compounds and key literature compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Jiang, M. X.-W.; Rawat, M.; Wulff, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 5970.

(9) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853.