ORGANIC LETTERS

2010
Vol. 12, No. 7
1584−1587

"Click" Synthesis of Nonsymmetrical Bis(1,2,3-triazoles)

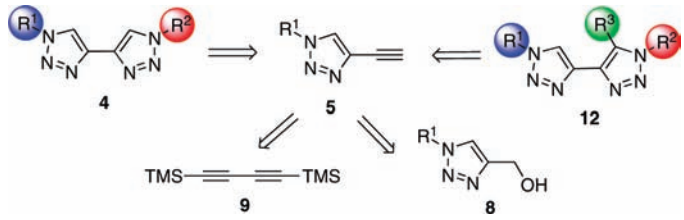
Jesus M. Aizpurua,*,† Itxaso Azcune,† Raluca M. Fratila,*,‡ Eva Balentova,† Maialen Sagartzazu-Aizpurua,† and Jose I. Miranda

Departamento de Química Orgánica-I, Universidad del País Vasco, Joxe Mari Korta R&D Center, Avda Tolosa-72, 20018 San Sebastián, Spain, and Faculty of Science and Technology, SupraMolecular Chemistry & Technology (SMCT), University of Twente, 7500 AE Enschede, The Netherlands

jesusmaria.aizpurua@ehu.es; r.m.fratila@tnw.utwente.nl

Received February 5, 2010

ABSTRACT



Unsymmetrically 1,1′-disubstituted 4,4′-bis-1*H*-1,2,3-triazoles 4 have been prepared from 4-ethynyl-1,2,3-triazoles 5 and azides. Following a "double-click" strategy, two complementary approaches were implemented for the preparation of the key 4-ethynyltriazole intermediates 5: (a) the stepwise Swern oxidation/Ohira−Bestman alkynylation of readily available 4-hydroxymethyl-1,2,3-triazoles 8 and (b) the stepwise cycloaddition of TMS-1,4-butadiyne 9. The method is highlighted by its compatibility with orthogonally protected and functionalized saccharide−peptide hybrids and its ability to be extended to the trisubstituted counterparts 12.

Since the discovery and recent development of the Cu(I)-catalyzed alkyne−azide "click" cycloaddition reaction,[1] the 1,2,3-triazole heterocyclic motif has rapidly become one of the most popular structures in conjugate chemistry finding applications in the preparation of hybrid compounds, surface modification of materials and biomaterials, and molecular scaffolding.[2,3]

In contrast to this breakthrough in monocyclic triazole chemistry, the bis(1,2,3-triazole) counterparts **1** and **2** (Figure 1) have received little attention, despite their evident

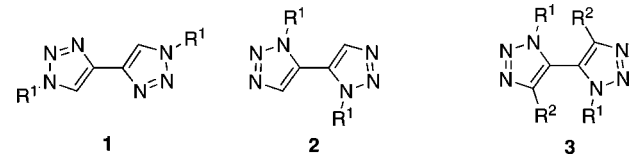


Figure 1. Symmetrically substituted bis(1,2,3-triazoles).

similarities with biaryl compounds.[4] In addition, 4,4′,5,5′-tetrasubstituted bis(1,2,3-triazoles) **3** may display axial

† Universidad del País Vasco.
‡ University of Twente.

(1) (a) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2598.

(2) For reviews, see: (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021. (b) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128–1137. (c) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018–1025. (d) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249–1262. (e) Lutz, J.-F.; Zarafshani, Z. *Adv. Drug Delivery Rev.* **2008**, *60*, 958–970. (f) Moorhouse, A. D.; Moses, J. E. *ChemMedChem* **2008**, *3*, 715–723. (g) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008**, *28*, 278–308.

(3) *QSAR Comb. Sci.* **2007**, *26*(11)is a special issue on click chemistry and its applications.

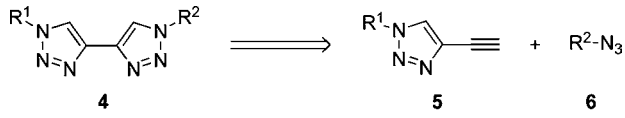
(4) (a) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447–2464. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.

10.1021/ol1003127
Published on Web 03/02/2010

chirality, as demonstrated by Burgess.[5] To the best of our knowledge, however, only symmetrically substituted bis(1,2,3-triazoles) **1**−**3** have been prepared to date,[6] and no practical method for the synthesis of the unsymmetrically substituted counterparts is known.[7]

Herein we report an approach to unsymmetrically disubstituted bis-1,2,3-triazoles (Scheme 1) involving a "click"

Scheme 1. Retrosynthesis of 4,4′-Disubstituted Bis(1,2,3-triazoles) **4** from 4-Ethynylmonotriazoles **5** and Azides **6**

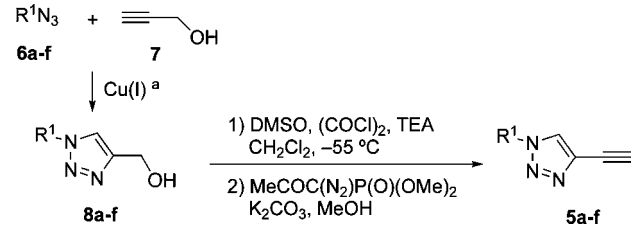


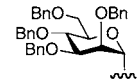
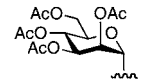
disconnection into 4-ethynyl-1,2,3-triazoles **5** and azides **6**.

The synthesis of 4-alkynyl-1,2,3-triazoles **5** was itself challenging. Not surprisingly, the thermal cycloaddition of terminal diacetylenes with 1 equiv of benzyl azide resulted in mixtures of 1,4- and 1,5-regioisomers of bis-triazoles together with small amounts of the desired 4-ethynyl-1,2,3-triazole.[8] Tykwinski et al. have reported the regioselective trapping of terminal di-, tri-, and tetraynes with benzyl azide to afford alkynyl-, butadiynyl-, and hexatriynyltriazoles in moderate to good yields.[9] 4-Ethynyl-1,2,3-triazoles or their trimethylsilyl-protected counterparts were also prepared as antibacterial agents[10] or tachykinin receptor antagonists.[11] On the other hand, Hawker et al. have employed the azide/acetylene coupling of 1-trimethylsilyl-2-vinylacetylene[12] or propargyl alcohol[13] with azides to prepare vinyl-1,2,3-triazolyl monomers.

We reasoned that the desired 4-ethynyltriazoles **5** could be obtained from the readily available 4-hydroxymethyl derivatives **8** through a two-step procedure involving the Swern oxidation followed by the Ohira−Bestmann alkynylation.[14] As disclosed in Table 1, the Cu(I)-catalyzed click

Table 1. Stepwise Preparation of 4-Ethynyl-1,2,3-triazoles **5**



entry	azide	R^1–	product	yield (%)[b]	product	yield (%)[b]
1	**6a**	Ph CH_2–	**8a**	96	**5a**	75
2	**6b**	4-NCC_6H_4–	**8b**	95	**5b**	80
3	**6c**		**8c**	99[c]	**5c**	50
4	**6d**		**8d**	72[c]	**5d**	–
5	**6e**	BnO_2CCH_2–	**8e**	85	**5e**	–
6	**6f**		**8f**	85[c]	**5f**[d]	15[e]

[a] $CuSO_4$, Na ascorbate, *t*-BuOH/H_2O: 1/1. [b] Yields of pure isolated products. [c] TBTA (1 mol %) was used as an additive. [d] Spontaneous debenzylation of **8f** was observed during the alkynylation step to give the corresponding triazolyl carboxylic acid instead of the expected benzyl ester. The acid was then submitted to methylation to **5i** with trimethylsilyldiazomethane. [e] Yield of the methyl ester **5i** (see Table 3).

reactions of propargyl alcohol **7** with different azides (**6a**−**f**) proceeded in 72−99% yields, but catalytic amounts (1−5%) of TBTA[15] were required when sterically hindered azides were used (entries 3, 4, and 6, Table 1). Alkynyltriazoles **5a**−**c** were prepared in good overall yields; however, when benzyl ester and *O*-acetyl protective groups were present, the final alkynylation step was problematic, leading to complicated reaction crudes and low yields of the expected products (entries 4−6).

Obviously, the conditions of the Swern oxidation step also limited the method to azide residues (R^1) bearing no oxidation-sensitive groups (e.g., hydroxyl groups). To overcome these important limitations, we implemented a different synthetic approach starting from commercial 1,4-bis(trimethylsilyl)butadiyne **9**. Accordingly, chemoselective desily-

(5) Angell, Y.; Burgess, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3649–3651.

(6) (a) Monkowius, U.; Ritter, S.; König, B.; Zabel, M.; Yersin, H. *Eur. J. Inorg. Chem.* **2007**, *459*, 7–4606. (b) Fletcher, J. T.; Bumgarner, B.; Engels, N. D.; Skoglund, D. A. *Organometallics* **2008**, *27*, 5430–5433.

(7) A stepwise double-click strategy has been applied successfully to the preparation of α,ω-bis(1,2,3-triazolyl)peptides; see: (a) Aucagne, V.; Leigh, D. A. *Org. Lett.* **2006**, *8*, 4505–4507. For an iterative synthesis of triazolamers containing amino acids side chains, see: (b) Angelo, N. G; Arora, P. S. *J. Am. Chem. Soc.* **2005**, *127*, 17134−17135and *J. Org. Chem.* **2007**, *72*, 7963−7967. Oligomeric peptidomimetic compounds were synthesized from orthogonally protected 1,4-disubstituted-1,2,3-triazoles, see: (c) Montagnat, O. D.; Lessene, G.; Hughes, A. B. *Tetrahedron Lett.* **2006**, *47*, 6971–6974.

(8) Tikhonova, L. G.; Serebryakova, E. S.; Proidakov, A. G.; Sokolova, I. E.; Vereshchagin, L. I. *J. Org. Chem. USSR* **1981**, *17*, 645–648.

(9) Luu, T.; McDonald, R.; Tykwinski, R. R. *Org. Lett.* **2006**, *8*, 6035–6038.

(10) (a) Reck, F.; Zhou, F.; Girardot, M.; Kern, G.; Eyermann, C. J.; Hales, N. J.; Ramsay, R. R.; Gravestock, M. B. *J. Med. Chem.* **2005**, *48*, 499–506. (b) Josyula, V. P. V. N.; Boyer, F. E., Jr.; Kim, J.-Y. PCT Int. Appl. WO 2007/000644 A1.

(11) Amegadzie, A. K.; Gardinier, K. M.; Hembre, E. J.; Hong, J. E.; Jungheim, L. N.; Muehl, B. S.; Remick, D. M.; Robertson, M. A.; Savin, K. A. PCT Int. Appl. WO 03/091227 A1.

(12) Thibault, R. J.; Takizawa, K.; Lowenheilm, P.; Helms, B.; Mynar, J.; Fréchet, J. M. J.; Hawker, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 12084–12085.

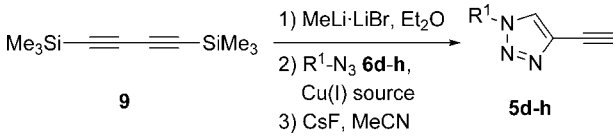
(13) Takizawa, K.; Nulwala, H.; Thibault, R. J.; Lowenheilm, P.; Yoshinaga, K.; Wooley, K. L.; Hawker, C. J. *J. Polym. Sci., Part A* **2008**, 2897–2912.

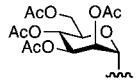
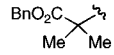
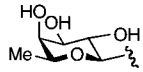
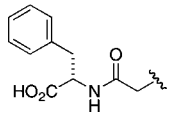
(14) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521–522.

(15) Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA): Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853–2855.

lation with MeLi·LiBr complex afforded 1-trimethylsilylbutadiyne **10**[16] which was further submitted to click reaction with azides **6d**−**h** (Table 2). The use of the standard

Table 2. Synthesis of Triazoles **5d**−**f**



entry	azide	R^1–	product	yield (%)[a] $CuSO_4$ Na ascorbate THF/H_2O	yield (%)[a] CuI DIPEA MeCN
1	**6d**		**5d**	60	80
2	**6e**	BnO_2CCH_2–	**5e**	63[b]	70
3	**6f**		**5f**	45[c]	45
4	**6g**		**5g**	37	50
5	**6h**		**5h**	–	80

[a] Overall yields of pure isolated products. [b] Symmetrical bis-triazole was obtained in an additional 14% yield. [c] Symmetrical bis-triazole was obtained in an additional 37% yield.

Sharpless conditions ($CuSO_4$/Na ascorbate/THF/H_2O) proved unexpectedly troublesome, causing partial desilylation of the intermediate 4-(trimethylsilylethynyl)-1,2,3-triazoles[17] and subsequent formation of mixtures containing up to 37% of the symmetrical bis-triazoles (entries 2 and 3). Finally, when the CuI/DIPEA system was used as catalyst the silylated triazole was obtained as the single reaction product. Complete desilylation was achieved upon in situ treatment with CsF affording the expected 4-ethynyltriazoles **5** as pure products in good overall yields. Following this methodology, peracetylated mannose **5d** and amino acid benzyl esters **5e**−**f** were introduced in the core, albeit the sterically hindered azide **6f** showed low reactivity and extended reaction time was necessary. This method could also be applied successfully to the preparation of cycloadducts from unprotected saccharides like fucose **5g** or from free carboxylic acid peptides like **5h**.

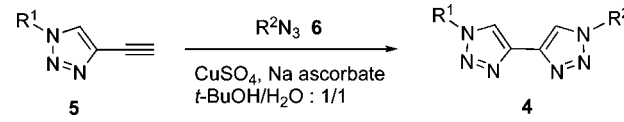
(16) (a) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron Lett.* **2003**, *44*, 9087–9090. (b) Holmes, A. B.; Jennings-White, C. L. D.; Schulthess, A. H.; Akinde, B.; Walton, D. R. M. *J. Chem. Soc., Chem. Commun.* **1979**, 840–842. (c) Holmes, A. B.; Jones, G. E. *Tetrahedron Lett.* **1980**, *21*, 3111–3112.

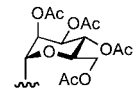
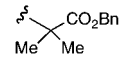
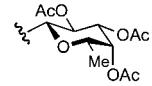
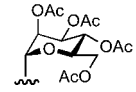
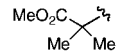
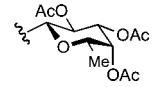
(17) A test reaction pointed out that 1,4-bis(trimethylsilyl)butadiyne **9** remained unchanged after several days upon treatment with $CuSO_4$/Na ascorbate in THF/H_2O.

Alternatively, we explored the possibility to conduct an one-pot cascade fluoride-induced desilylation−double click reaction between 1,4-bis(trimethylsilyl)butadiyne **9** and two different azides in order to obtain the corresponding nonsymmetrical bis-triazoles in a single operation, but this approach turned less convenient than the sequential double click.[18]

Monotriazoles **5** were subsequently submitted to a second click cycloaddition with different azides to give the expected nonsymmetrical bis-triazoles **4** (Table 3). Both electron-donor

Table 3. Nonsymmetrical 1,1′-Disubsituted 4,4′-Bis-1*H*-1,2,3-triazoles **4a**−**h** from 4-Ethynyltriazoles **5**



entry	R^1-	azide	R^2	product	yield (%)[a]
1	$PhCH_2$–	**6i**	–$CH_2C_6H_4$(4-NO_2)	**4a**	85[b]
2	$PhCH_2$–	**6j**	–$CH_2C_6H_4$(4-*t*-Bu)	**4b**	99
3	$PhCH_2$–	**6k**	–CH_2CH_2OH	**4c**	99
4	$PhCH_2$–	**6e**	–CH_2CO_2Bn	**4d**	85
5	$PhCH_2$–	**6d**		**4e**	95[c]
6	$PhCH_2$–	**6l**	–C_6H_4Me	–	–[c]
7	4-NCC_6H_4–	**6e**	–CH_2CO_2Bn	**4f**	70[c]
8	4-NCC_6H_4–	**6f**		**4g**	79[c]
9	BnO_2CCH_2–	**6m**		**4h**	90[c]
10	BnO_2CCH_2–	**6d**		**4i**	79[c]
11		**6m**		**4j**	80[c]

[a] Yield of pure isolated products. [b] Reaction conducted in the presence of CuI and DIPEA. [c] TBTA (1 mol %) was used as an additive.

and electron-withdrawing groups were tolerated and densely functionalized substituents could be appended to the central bis(1,2,3-triazole) core. Only the reaction with aromatic azide *p*-azidotoluene **6l** failed (entry 6). In this case, tiny product signals were detected by NMR analysis of the reaction crude, but the reaction did not proceed further, despite the several combinations of conditions tested: copper source ($CuSO_4$/Na ascorbate; CuI), solvent (*t*-BuOH/H_2O, MeCN, DMF), and warming to 70−100 °C.

The scope and synthetic potential of the double-click approach was apparent from the examples quoted in entries 9−11 of Table 3 and in Figure 2. Fragments scaffolded

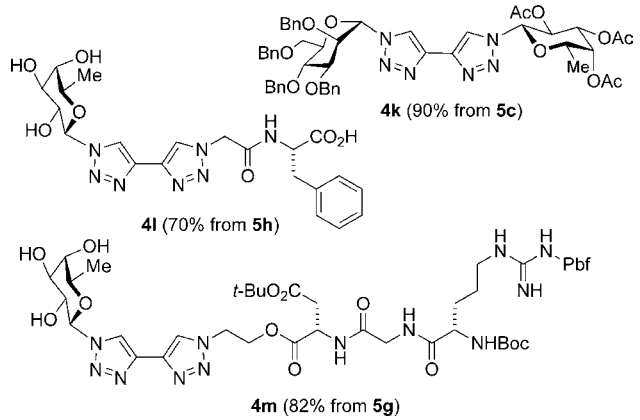
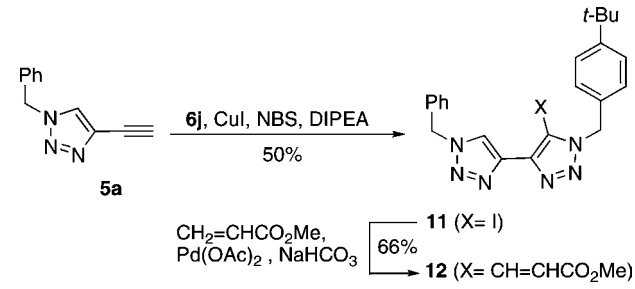


Figure 2. Nonsymmetrically substituted bis(1,2,3-triazoles). Pbf: 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonyl.

around the bis-triazole moiety included (a) orthogonally protected amino esters and carbohydrates (**4h**−**j**), (b) an α-L-mannose/β-D-fucose disaccharide mimetic (**4k**); (c) a fully deprotected Gly-Phe peptide−saccharide hybrid (**4l**), and (d) the β-D-fucose/RGD hybrid (**4m**) obtained by clicking the alkynyl triazole **5g** and the tripeptide azide Boc-Arg(Pbf)-Gly-Asp(O^{t}Bu)-$OCH_2CH_2N_3$.

Finally, the potential of the method was explored to prepare polysubstituted bis(1,2,3-triazoles), and as a proof of principle, we prepared the trisubstituted derivative **12**. Accordingly, the 4-ethynyltriazole **5a** was first submitted to an iodinative "click" cycloaddition[19] with 4-*tert*-butylbenzyl azide **6j**, *N*-bromosuccinimide, and a stoichiometric amount of CuI to afford the halogenated bis-triazole **11** in 50% isolated yield (Scheme 2). Then, the palladium acetate-

Scheme 2. Trisubstituted Bis(1,2,3-triazoles) from 4-Ethynyltriazole **5a**



catalyzed Heck reaction of **11** with methyl acrylate provided the trisubstituted bis-triazole **12** in 66% isolated yield.

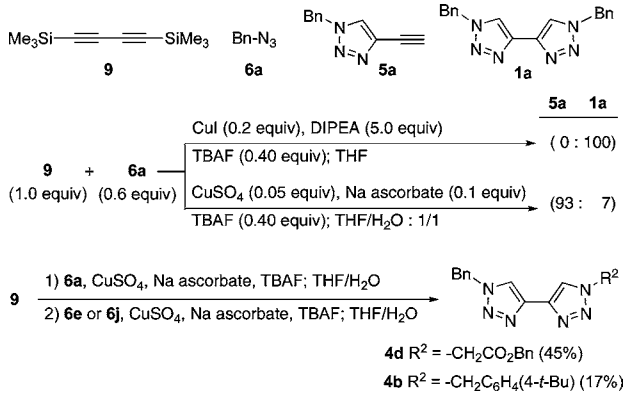
In conclusion, the combination of two methods to synthesize 4-ethynyl-1,2,3-triazoles, followed by click attachment of a second azide, allows for the efficient preparation of 1,1′-disubsituted 4,4′-bis-1*H*-1,2,3-triazoles in good to excellent yields. The procedure is simple, applicable to a large variety of azides, and can be used for the preparation of mixed structures, as demonstrated by the synthesis of several amino acid (peptide)−sugar and sugar−sugar hybrids.

Acknowledgment. We thank the Ministerio de Educación y Ciencia (MEC, Spain) (Project No. CTQ2006-13891/BQU), UPV/EHU, and Gobierno Vasco (ETORTEK-inanoGUNE IE-08/225) for financial support and SGIker UPV/EHU for NMR facilities. Predoctoral grants from Gobierno Vasco to I.A. and M.S.-A. are acknowledged.

Supporting Information Available: Preparation procedures, physical and spectroscopic data for compounds **4a**−**m**, **5a**−**h**, **6h**,**n**, **8a**−**f**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1003127

(18) We found that desilylation of **9** with 0.4 equiv of TBAF (1 M, THF) in the presence of benzyl azide **6a** and CuI/DIPEA led to the exclusive formation of symmetric bis-triazole **1a**, whereas replacement of the copper(I) catalyst by the Sharpless system in aqueous−organic medium resulted in the formation of 5-ethynyltriazole **5a** as the major reaction product. Importantly, the one-pot sequential "click" cycloaddition of **9** with azide **6a**, followed by the addition of **6e** or **6j**, provided reaction mixtures containing, respectively, the unsymmetrically substituted bis-triazoles **4d** and **4b** as major products. Unfortunately, the chromatographic isolation of the products from symmetrical byproducts was laborious and afforded the desired compounds in modest yields.



(19) Li, L.; Zhang, G.; Zhu, A.; Zhang, L. *J. Org. Chem.* **2008**, *73*, 3630–3633.