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Regioselective Trapping of Terminal Di-, Tri-, and Tetraynes with Benzyl Azide

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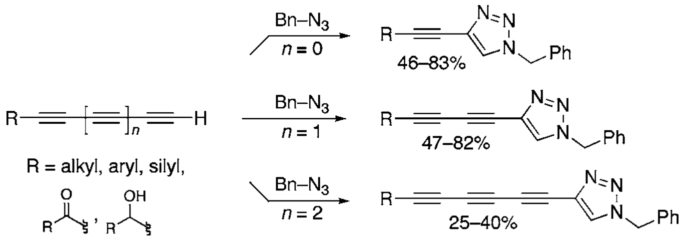
ABSTRACT



The reaction of benzyl azide with terminal di-, tri-, and tetraynes appended with a range of functional groups has been explored. Standard reaction conditions for BnN$_3$ catalyzed by CuSO$_4$·5H$_2$O gave alkynyl, butadiynyl, and hexatriynyl triazoles in moderate to good yields. The reaction proceeds regioselectively as determined by the X-ray crystallographic analysis of three derivatives (1c, 1d, and 3c), and no evidence of multiple azide addition to the polyyne framework is observed.

A small but interesting subset of naturally occurring organic molecules contains a conjugated polyyne skeleton composed of a di-, tri-, tetra-, or pentayne structure.[1] Many of these compounds have been isolated in quantities sufficient to probe their biological activities, and these studies have shown that polyynes display an array of interesting properties, including antibacterial, antimicrobial, antifungal, antitumor, and pesticidal activities. As a result of their unsaturated framework, polyynes are typically heat and light sensitive when neat or in concentrated solution, a fact that can hamper both isolation and characterization.[2] This is particularly true for polyynes that lack functionality at one terminus (terminal polyynes). Even so, a surprising number of terminal di- and triynes, and even a tetra- and pentayne, have been identified from natural sources, such as the C9 triynes isolated from the Basidiomycete *Coprinus quadrifidus*,[3] the tetrayne caryoynencin from plant pathogen *Pseudomonas caryophylli*,[4] and a pentayne isolated from several Peruvian plants of the species *Leuceri* (Figure 1).[5]

We became intrigued by the possibility that additional terminal polyynes might occur naturally, but their kinetic instability could preclude identification under normal isolation procedures. One potential solution to this problem would be to trap the terminal polyyne in solution as a stable substrate that could then be more easily characterized. The recent development of procedures for triazole formation through the reaction of terminal alkynes with azides under Cu(I) catalysis and mild conditions seemed ideal for such an application.[6] Several questions, however, presented themselves with respect to the outcome of these reactions, including: (a) Would conditions be sufficiently mild to trap di-, tri-, and tetraynes with an azide for triazole formation?[7] (b) Would the regiochemistry remain consistent with that

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(1) (a) Shi Shun, A. L. K.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1034−1057. (b) Bohlmann, F.; Burkhardt, H.; Zdero, C. *Naturally Occurring Acetylenes*; Academic Press: New York, 1973. (c) *Chemistry Biology of Naturally Occurring Acetylenes and Related Compounds (NOARC)*; Lam, J., Breteler, H., Arnason, T., Hansen, L., Eds.; Elsevier: New York, 1988. (d) Jones, E. R.; Thaller, V. *The Chemistry of the Carbon−Carbon Triple Bond*; Patai, S., Ed.; John Wiley & Sons: New York, 1978; Vol. Part 2, Chapter 14.

(2) Some terminal diynes are, however, surprisingly stable. For examples, see: West, K.; Wang, C.; Batsanov, A. S.; Bryce, M. R. *J. Org. Chem.* **2006**, *71*, 8541−8544.

(3) Jones, E. R. H.; Stephenson, J. S. *J. Chem. Soc.* **1959**, 2197−2203.

(4) Kusumi, T.; Ohtani, I.; Nishiyama, K.; Kakisawa, H. *Tetrahedron Lett.* **1987**, *28*, 3981−3984.

(5) Bittner, M.; Jakupovic, J.; Bohlmann, F.; Silva, M. *Phytochemistry* **1989**, *28*, 271−273.

(6) For a recent review, see: Bock, V. D.; Hiemstra, H.; van Marseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51−68.

10.1021/ol062522a CCC: $33.50

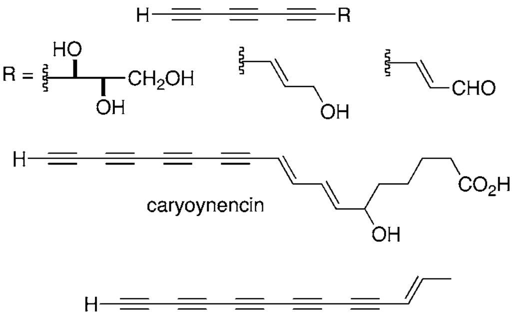
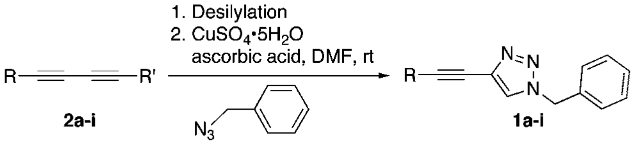
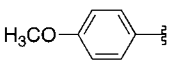
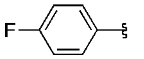
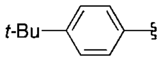
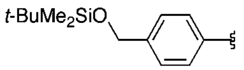
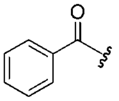
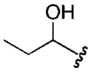


Figure 1. Examples of naturally occurring terminal polyynes.

Table 1. Synthesis of Triazoles **1a−i** from Diynes **2a−i**



	R	R'	desilylation conditions	yield (%)[a]
a	*t*-BuMe$_2$Si	Me$_3$Si	K$_2$CO$_3$/MeOH[b]	75
b	*i*-Pr$_3$Si	Me$_3$Si	K$_2$CO$_3$/MeOH	67
c	Ph	Me$_3$Si	K$_2$CO$_3$/MeOH	73
d	 H$_3$CO	Me$_3$Si	K$_2$CO$_3$/MeOH	83
e	 F	*i*-Pr$_3$Si	TBAF/THF	72
f	 *t*-Bu	Me$_3$Si	K$_2$CO$_3$/MeOH	74
g	 *t*-BuMe$_2$SiO	Me$_3$Si	K$_2$CO$_3$/MeOH[b]	71
h	 O	Me$_3$Si	K$_2$CO$_3$/MeOH	68
i	 OH	*i*-Pr$_3$Si	TBAF/THF	46

[a] Isolated yield based on benzyl azide. [b] The *t*-BuMe$_2$Si group is not affected.

reported for the reaction of azides with terminal alkynes?[8,9] (c) Would multiple additions occur due to the more activated nature of the di-, tri-, or tetrayne substrates?[10] We report herein our preliminary investigations into the trapping of di-, tri-, and tetraynes with benzyl azide under mild conditions, which provide initial answers to the questions above.

Terminal diynes were tested first toward formation of ethynyl triazoles **1a−i** (Table 1). Silylated diynes **2a−i** were available via known procedures, and the trimethyl- or triisopropylsilyl protecting group could be readily removed through the reaction with methanolic K_2CO_3 or tetrabutylammonium fluoride (TBAF) in THF, respectively. Once desilylation was complete, the reaction was subjected to an aqueous workup, and ca. 2 mL of DMF was added to the organic phase. The solution was then concentrated to ca. 1−2 mL, taking care not to let the sample go to dryness, which typically resulted in partial or complete decomposition of the terminal diyne product. The resulting solution was then diluted with DMF (10 mL) and water (2 mL), and the reaction with benzyl azide in the presence of $CuSO_4$•$5H_2O$ and ascorbic acid produced the desired triazoles **1a−i**. The ethynyl triazoles could be purified by either column chromatography or in the case of less soluble products **1c**, **1d**, and **1f** recrystallization from hexanes.[11]

The reaction of benzyl azide with diynes provides reasonable to good yields of the 1,4-triazole adducts, regardless of the terminal substituent. The last two examples in Table 1 represent reactions with known diyne natural products. The terminal diyne derived from **2h** has been isolated from the crown daisy (*Chrysanthemum coronarium*) by Bohlmann and co-workers,[12] whereas (*S*)-hepta-4,6-diyn-3-ol (from desilylation of **2i**) is a natural product isolated from *Gymnopilus spectabilis* by Jones and co-workers.[13] In no case was any evidence of a multiple addition product found, which would result from reaction of the resulting ethynyl triazole with a second equivalent of benzyl azide.

With the successful formation of triazoles from diynes established, the trapping of terminal triynes was explored. Overall, the general procedure used for the reaction of **2a−i**

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(7) To our knowledge, the reaction of terminal tri- or tetraynes with azides under Cu(I) catalysis has not been explored, whereas one example exists for the reaction with a terminal diyne. See: 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. For a recent report that may involve the reaction of an internal diyne with azides under similar conditions to give ethynyl triazoles, see: Gerard, B.; Ryan, J.; Beeler, A. B.; Porco, J. A., Jr. *Tetrahedron* **2006**, *62*, 6405−6411.

(8) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.

(9) (a) Lee, L. V.; Mitchell, M. L.; Huang, S.-J.; Folkin, V. V.; Sharpless, K. B.; Wong, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 9588−9589. (b) Aucagne, V.; Leigh, D. A. *Org. Lett.* **2006**, *8*, 4505−4507. (c) Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2006**, *8*, 4145−4148. (d) Lee, J. W.; Kim, B.-K. *Bull. Korean Chem. Soc.* **2005**, *26*, 658−660.

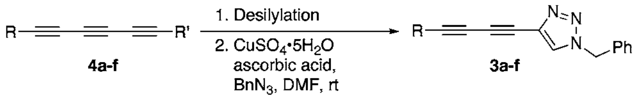
(10) The thermal reaction of terminal diynes with benzyl azide affords some bisadduct. See: Tikhonova, L. G.; Serebryakova, E. S.; Proidakov, A. G.; Sokolova, I. E.; Vereshchagin, L. I. *J. Org. Chem. USSR* **1981**, *17*, 645−648.

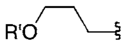
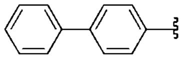
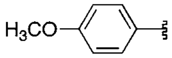
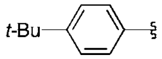
(11) **General procedure for the reaction of di-, tri-, and tetraynes with benzyl azide.** A mixture of the appropriate trimethylsilyl- or triisopropylsilyl-protected polyyne and K_2CO_3 (0.05 g) or TBAF (2.0 equiv) in wet THF/MeOH (1:1 5 mL) or THF (10 mL), respectively, was added and stirred at room temperature until TLC analysis showed the formation of the terminal alkyne. Et_2O and saturated aqueous NH_4Cl were added, and the organic phase was separated, washed with saturated NH_4Cl (2 × 10 mL) and saturated aqueous NaCl (10 mL), and then dried over $MgSO_4$. DMF (1−2 mL) was then added, and the solution was concentrated to ca. 1−2 mL via rotary evaporation. To the resulting solution of the terminal polyyne was added DMF (10 mL), followed by benzyl azide (0.66−1.0 equiv based on the starting silylated polyyne), $CuSO_4$•$5H_2O$ (0.1 g), ascorbic acid (0.1 g), and H_2O (2 mL). This mixture was then stirred at room temperature until TLC analysis no longer showed the presence of benzyl azide. Aqueous workup, solvent removal, and purification via column chromatography (silica gel) or recrystallization from hexanes gave the desired triazole. For diyne precursors, ca. 0.8−0.9 equiv of BnN_3 was used, whereas for triynes, slightly less was used (ca. 0.7−0.8 equiv) due to increasing material losses observed during the desilylation process. See Supporting Information for details.

(12) Bohlmann, F.; Arnt, C.; Bornowski, H.; Kleine, K.-M.; Herbst, P. *Chem. Ber.* **1964**, *97*, 1179−1192.

(13) Hearn, M. T. W.; Jones, E. R. H.; Pellatt, M. G.; Thaller, V.; Turner, J. L. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2785−2788.

Table 2. Synthesis of Triazoles from Triynes **4a−f**



	R	R'	desilylation conditions	yield (%)[a]
a	Bu	*i*-Pr_3Si	TBAF/THF	71
b	 **4b** R' = *t*-$BuMe_2Si$ **3b** R' = H	*i*-Pr_3Si	TBAF/THF[b]	47
c	Ph	Me_3Si	K_2CO_3/MeOH	68
d		*i*-Pr_3Si	TBAF/THF	63
e		*i*-Pr_3Si	TBAF/THF	82
f		Me_3Si	K_2CO_3/MeOH	73

[a] Isolated yield based on benzyl azide. [b] The *t*-$BuMe_2Si$ group was also removed.

was equally effective with triynes **4a−f** (Table 2), although care must be taken to ensure that the solution containing the terminal triyne after desilylation is neither heated nor concentrated to less than ca. 1−2 mL.[14] The formation of butadiynyl triazoles **3a−f** showed a reasonable level of functional group tolerance for the precursor polyyne, which included alkyl (**3a**,**b**) and aryl (**3c−f**) moieties. The triyne alcohol resulting from exhaustive desilylation of **4b** has been predicted to be a product of hydrolysis of the allenediyne fungal natural product marasin, from *Aleurodiscus roseus*,[15] and this compound was successfully trapped with BnN_3 to give triazole **3b**.

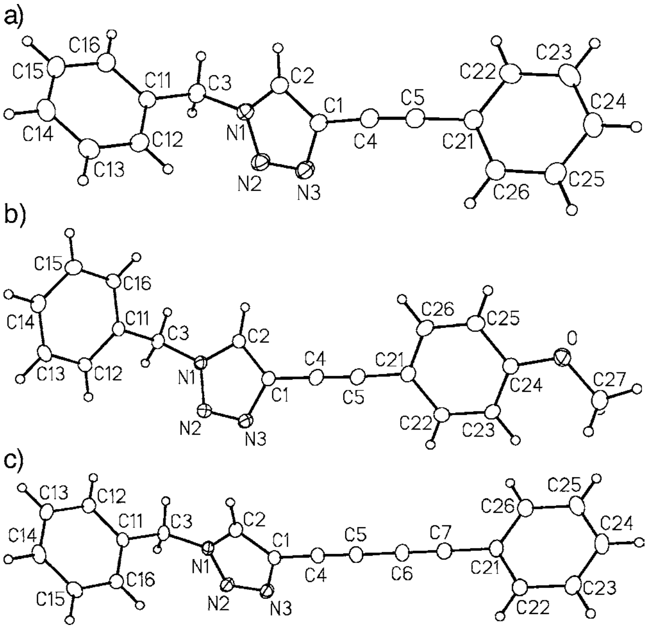
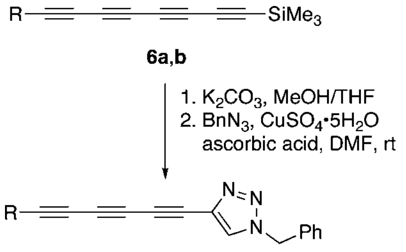


Figure 2. ORTEP drawings (20% probability level) and selected bond lengths (Å) and angles (deg) for (a) compound **1c**, C1−C4 1.4301(18), C4−C5 1.1948(18), C5−C21 1.4378(18); C1−C4−C5 174.45(14), C4−C5−C21 176.95(14); (b) compound **1d**, C1−C4 1.4284(19), C4−C5 1.200(2), C5−C21 1.4395(19), C1−C4−C5 179.25(17), C4−C5−C21 177.01(16); (c) compound **3c**, C1−C4 1.426(2), C4−C5 1.196(2), C5−C6 1.372(2), C6−C7 1.200(2), C7−C21 1.435(2), C1−C4−C5 176.85(18), C4−C5−C6 178.12(18), C5−C6−C7 177.64(19), C6−C7−C21 178.33(18).

The butadiynyl triazoles **3b−f** were isolated as stable solids (**3a** was oil) by column chromatography or crystallization from hexanes. Also, no evidence of multiple addition of benzyl azide to the diyne core of the products **3a−f** was observed.

The trapping of highly unstable terminal tetraynes was then explored toward producing triynyl triazoles **5a**,**b** (Scheme 1). Desilylation of **6a**,**b** with methanolic K_2CO_3 in THF followed by trapping with BnN_3 under the conditions developed for di- and triynes resulted in reasonable yield of the triazoles **5a**,**b**. Great care must be taken when handling the terminal tetraynes to ensure that they remain in solution

Scheme 1



5a R = *i*-Pr_3Si 40%
5b R = Ph 25%

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(14) **Caution!** Phenylhexatriyne has been reported to explode upon attempted isolation. See: Armitage, J. B.; Entwistle, N.; Jones, E. R. H.; Whiting, M. C. *J. Chem. Soc.* **1954**, 147−154. Although we have never had any problems with explosive decomposition of terminal di-, tri-, or tetraynes under the reaction conditions described, care should nonetheless be taken.

(15) Cambie, R. C.; Hirschberg, A.; Jones, E. R. H.; Lowe, G. *J. Chem. Soc.* **1963**, 4120−4130.

(16) Bettison, R. M.; Hitchcock, P. B.; Walton, D. R. M. *J. Organomet. Chem.* **1988**, *341*, 247−254.

(17) Crystals suitable for X-ray crystallography were obtained by vapor diffusion of hexanes into a solution of **1c**, **1d**, or **3c** in CH_2Cl_2 at room temperature. Crystal data for **1c**: $C_{17}H_{13}N_3$; $M = 259.30$; monoclinic space group $P2_1/c$ (an alternate setting of $P2_1/c$ [No. 14]); $\rho_c = 1.262$ g cm^{-3}; $a = 5.7277(8)$, $b = 14.2042(18)$, $c = 16.811(2)$ Å; $\beta = 93.6141(18)°$; $V = 1365.0(3)$ Å^3; $Z = 4$; $\mu = 0.077$ mm^{-1}. Final $R(F) = 0.0409$ (2030 observations $[F_o^2 \geq 2\sigma(F_o^2)]$); $wR_2(F^2) = 0.1147$ for 181 variables and 2800 data with $F_o^2 \geq -3\sigma(F_o^2)$; CCDC 623595. Crystal data for **1d**: $C_{18}H_{15}N_3O$; $M = 289.33$; monoclinic space group $P2_1$ (No. 4); $\rho_c = 1.296$ g cm^{-3}; $a = 9.1938(9)$, $b = 5.6198(6)$, $c = 14.7114(14)$ Å; $\beta = 102.6687(14)°$; $V = 741.59(13)$ Å^3; $Z = 2$; $\mu = 0.083$ mm^{-1}. Final $R(F) = 0.0303$ (2779 observations $[F_o^2 \geq 2\sigma(F_o^2)]$); $wR_2(F^2) = 0.0792$ for 199 variables and 3025 data with $F_o^2 \geq -3\sigma(F_o^2)$; CCDC 623596. Crystal data for **3c**: $C_{19}H_{13}N_3$, $M = 283.32$; triclinic space group $P\bar{1}$ (No. 2); $\rho_c = 1.260$ g cm^{-3}; $a = 6.3632(8)$, $b = 7.9519(9)$, $c = 15.1874(18)$ Å; $\alpha = 102.3564(18)°$, $\beta = 95.3363(18)°$, $\gamma = 91.0645(18)°$; $V = 746.84(15)$ Å^3; $Z = 2$; $\mu = 0.076$ mm^{-1}. Final $R(F) = 0.0436$ (2130 observations $[F_o^2 \geq 2\sigma(F_o^2)]$); $wR_2(F^2) = 0.1274$ for 199 variables and 3013 data with $F_o^2 \geq -3\sigma(F_o^2)$; CCDC 623597. X-ray data have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033.

to prevent decomposition of the substrate prior to reaction with BnN_3. In an attempt to circumvent the isolation/concentration step following desilylation, a one-pot reaction with **6b** was explored in which desilylation was followed directly by in situ reaction with BnN_3. Although successful, the yield was slightly lower (21%).

Reaction of azides with terminal alkynes under thermal conditions typically affords a mixture of 1,4- and 1,5-triazole products, whereas reactions with alkynes under Cu catalysis give selectively 1,4-triazoles.[8,9] Under thermal conditions, terminal diynes also give a mixture of products,[10] whereas the reaction of bis(trimethylsilyl)butadiyne and -hexatriyne with azides is regioselective.[16] The regiochemistry for triazole products **1**, **3**, and **5** could be inferred from their ^1H NMR spectra, which showed resonances for the triazole ring proton in the expected range of δ 7.47−7.65.[10] The only exception to this trend is the ynone-substituted **1h**, where this signal is shifted downfield to δ 7.81, presumably due to conjugation with the ketone.

In addition to ^1H NMR spectroscopic data, X-ray crystallographic analysis was used to confirm the constitution of the 4-ethynyl and 4-butadiynyl triazoles **1c**, **1d**, and **3c** formed under Cu catalysis (Figure 2).[17,18] The bond angles and bond lengths for the three structures are for the most part unremarkable. Interesting, however, is the fact that in each case there is a significant dihedral angle between a plane generated by the triazole ring and that of the terminal phenyl or anisyl groups of **1c**, **1d**, and **3c** (**1c**, 39.30(4)°; **1d**, 20.43(8)°; and **3c**, 62.92(5)°). This fact will significantly disrupt electronic communication along the π-conjugated framework of these molecules in the solid state.

In conclusion, we have demonstrated the trapping of terminal di-, tri-, and tetraynes with benzyl azide under Cu catalysis to give 4-ethynyl, 4-butadiynyl, and 4-hexatriynyl triazoles in moderate to good yields. Reaction occurs exclusively at the terminal alkyne unit, and no evidence of multiple addition to the polyyne framework has been observed. X-ray crystallography has been used to confirm that only one regioisomeric product has been formed.

Acknowledgment. This work has been supported by the University of Alberta and the Natural Sciences and Engineering Research Council of Canada (NSERC) through the Discovery grant program. T.L. thanks the University of Alberta for a Dissertation Fellowship and Edward Ha for help with some of the trapping experiments.

Supporting Information Available: Experimental procedures, spectroscopic data for new compounds, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062522A

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(18) Only three structures of ethynyltriazole derivatives were found in the CCDC (GIRMUP, GIRNAW, TUGVEW), and none were derived from terminal polyynes. See ref 16 and: Adamson, G. A.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1535−1543.