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Alkynylation of Benzotriazole with Silylethynyliodonium Triflates. Regioselective Synthesis of 2-Ethynyl-2*H*-benzotriazole Derivatives

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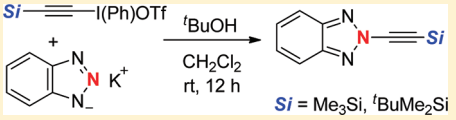
Supporting Information

ABSTRACT: Phenyl(trimethylsilylethynyl)iodonium and *tert*-butyldimethylsilylethynyl(phenyl)iodonium triflates were applied to alkynylation of benzotriazole. Treatment of the silylethynyliodonium triflates with the potassium salt of benzotriazole ion in ^{t}BuOH and CH_2Cl_2 gave 2-(trimethylsilylethynyl)-2*H*-1,2,3-benzotriazole and 2-(*tert*-butyldimethylsilylethynyl)-2*H*-1,2,3-benzotriazole in 74% and 76% yields, respectively. The regioisomers, 1-silylethynyl-1*H*-1,2,3-benzotriazole derivatives, were minor. In both cases of the silyl-substituted ethynyliodonium salts, novel regioselective alkynylation of benzotriazole at the 2 position was observed.



Benzotriazoles belong to one of the important compounds in nitrogen-containing heterocycles, and they have been widely used for organic synthesis as a synthetic auxiliary.[1] In addition, benzotriazoles are useful for functional materials,[2] pharmaceuticals, and agricultural chemicals.[3] The parent 1,2,3-benzotriazole exists predominantly as the 1*H* isomer over the 2*H* isomer because of its stability.[4] Therefore, most benzotriazoles studied so far include 1*H*-1,2,3-benzotriazole derivatives.

On the other hand, *N*-ethynyl compounds, as represented by ynamines, are synthetically valuable, and their significance has been raised by Katritzky and co-workers.[5] Since alkynyliodonium salts undergo a successive Michael addition/rearrangement reaction generating alkyne derivatives,[6] they can serve as an alkynylation reagent. Previously, we have found that 1-arylethynyl-1*H*-1,2,3-benzotriazoles are obtained selectively by the reaction of arylethynyl(phenyl)iodonium tosylates using benzotriazole ion as a nucleophile.[7] Although this reaction provides a direct method introducing an alkynyl group into the 1 position of benzotriazoles, there is the serious restriction that this can apply only to arylethynyl derivatives. Aliphatic alkynyliodinium salts did not afford the corresponding 1-alkynyl-1*H*-1,2,3-benzotriazoles.[7b] This result suggests that the substituent on the ethynyl group is required to have a high migratory aptitude. To explore the scope of this alkynylation reaction, thus we examined phenyl(trimethylsilylethynyl)iodonium triflate (**1a**) as an alkynylating agent.[8]

Benzotriazole anion formed by removal of a proton from 1*H*-1,2,3-benzotriazole has two resonance forms, as shown in Scheme 1. Functionalization at the N-1 position gives 1*H*-benzotriazole derivatives, whereas functionalization at the N-2 position leads to the formation of 2*H*-benzotriazole derivatives.[9] In the reaction of arylethynyliodonium salts, 1-arylethynyl-1*H*-benzotriazoles were obtained exclusively.[7] Unexpectedly, the reaction of trimethylsilylethynyliodonium triflate **1a** gave 2-trimethylsilylethynyl-2*H*-benzotriazole as a major product. Although 2*H*-1,2,3-benzotriazole is a minor tautomer, 2-aryl-2*H*-1,2,3-benzotriazoles are known as stable compounds and have been applied to UV absorbents.[2] To the best of our knowledge, there are no reports on direct and regioselective functionalization of benzotriazole at the 2 position. In this paper, we want to report this novel N-2 alkynylation of benzotriazole as a new method for synthesis of 2-alkynyl-2*H*-1,2,3-benzotriazoles.

First, silylethynyliodonium salts, phenyl(trimethylsilylethynyl)-iodonium triflate (**1a**) and *tert*-butyldimethylsilylethynyl(phenyl)-iodonium triflate (**1b**), were synthesized by the reactions of the corresponding 1,2-bis(silyl)acetylenes with $PhI(OAc)_2$/TfOH in CH_2Cl_2, according a literature procedure.[10] The outline of synthesis and reaction of silylethynyliodonium triflates **1** is shown in Scheme 2. Then, when silylethynyliodonium triflate **1a** was treated with potassium salt of benzotriazole ion in ^{t}BuOH and CH_2Cl_2 at room temperature for 12 h, 2-(trimethylsilylethynyl)-2*H*-1,2,3-benzotriazole (**2a**) was obtained in 74% yield. The regioisomer, 1-(trimethylsilylethynyl)-1*H*-1,2,3-triazole (**3a**), was obtained in 17% yield. The regioisomers **2a** and **3a** were easily distinguishable from ^{1}H and ^{13}C NMR (see Supporting Information). In the ^{1}H NMR of **2a**, two sets of aromatic protons appeared symmetrically, but the ^{1}H NMR of **3a** showed three sets of aromatic protons. In the ^{13}C NMR, **2a** gave only 3 peaks of aromatic carbons, whereas **3a** showed the presence of 6 peaks. The reaction of more bulky *tert*-butyldimethylsilylethynyliodonium triflate **1b** gave 2-(*tert*-butyldimethylsilylethynyl)-2*H*-1,2,3-benzotriazole (**2b**) and 1-(*tert*-butyldimethylsilylethynyl)-1*H*-1,2,3-benzotriazole (**3b**) in 76% and 8% yields, respectively. In both cases, the reaction of silyl-substituted ethynyliodonium salts gave 2-ethynyl-substituted benzotriazole derivatives selectively.

To understand the effect of the silyl group, we studied ethynylaton of benzotriazole ion with parent ethynyl(phenyl)iodonium triflate (**1c**). Ethynyliodonium triflate **1c** was prepared according

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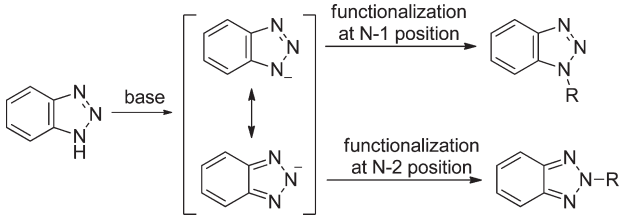
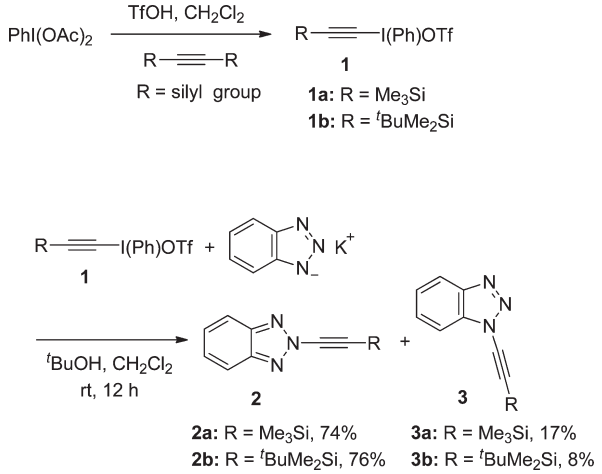
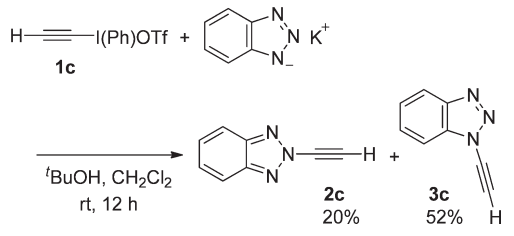
Scheme 1. Ambident Character of Benzotriazole Anion for Functionalization



Scheme 2. Synthesis and Reaction of Silylethynyliodonium Triflates 1



Scheme 3. Reaction of Ethynyl(phenyl)iodonium Triflate 1c

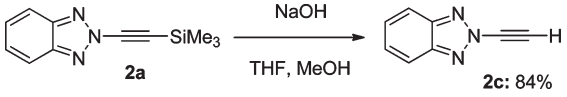


to Ochiai's procedure.[11] Treatment of ethynyliodonium triflate **1c** with potassium salt of benzotriazole ion under the same conditions above afforded 2-ethynyl-2*H*-1,2,3-benzotrizaole (**2c**) and 1-ethynyl-1*H*-1,2,3-benzotriazole (**3c**) in 20% and 52% yields, respectively (Scheme 3). Although 1-ethynylbenzotriazole **3c** generates predominately, this result suggests that there is no selectivity because of its almost statistical ratio. It is thought that the high regioselectivity at the 2 position of benzotriazole ion is attributable to the effect by a silyl group.

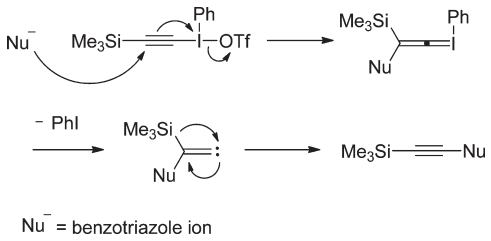
In addition, 2-ethynylbenzotriazole **2c** could be obtained from 2-trimethylsilylbenzotriazole **2a**. Treatment of **2a** with NaOH in THF/MeOH efficiently afforded **2c** in 84% yield (Scheme 4). Although **2c** was unstable under ambient conditions, it was reasonably characterized by ^{1}H and ^{13}C NMR.

The effect of the silyl group on the preferential formation of 2-alkynylation of benzotriazole is not clear. However, since the

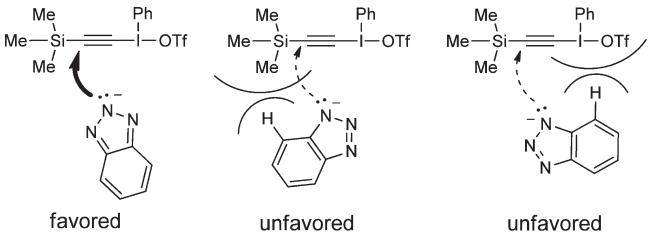
Scheme 4. Desilylation of 2a



Scheme 5. Possible Mechanism



Scheme 6. Proposal for Preference of N2 Attack



reaction of alkynyliodonium salts with nucleophiles has been investigated so far,[6] the same mechanism is considered to operate in this reaction. A possible mechanism is illustrated in Scheme 5. In this way, it is considered that benzotriazole ion attacks on the β carbon of the alkynyl group to generate an alkenylideneiodonium ylide intermediate, where elimination of phenyliodonio group occurs to give an alkenylidencarbene. Finally, the alkynylidenecarbene undergoes rearrangement to form an alkynylbenzotriazole. In the formation of alkynylbenzotriazoles, it is considered that the migration of silyl groups and a hydrogen atom takes place rather than a benzotriazolyl group because of their higher migratory aptitude. In the previous reaction of alkyl-substituted ethynyliodonium salts,[7b] rearranged products, i.e., alkynylbenzotriazoles, were not obtained at all. This indicates that the benzotriazolyl group has low migratory ability. However, the nucleophilic addition of benzotriazole ion gives 1-alkynyl- and 2-alkynylbenzotriazoles because benzotriazole ion is an ambident anion. Although a high regioselectivity of 2-alkynylation by the silyl group is not clear in the present study, it may be attributable to a bulkiness of the silyl group. The nucleophilic addition by the N1 atom of the benzotriazole ion may cause a steric hindrance higher than that by the N2 atom, as shown in Scheme 6.

In summary, we have demonstrated that silylethynyliodonium triflates undergo regioselective alkynylation at the 2 position of benzotriazole to give 2-silylethynyl-2*H*-1,2,3-benzotriazoles as a major product. Desilylation of 2-(trimethylsilylethynyl)benzotriazole **2a** generates a parent 2-ethynylbenzotrizole **2c** in a high yield.

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EXPERIMENTAL SECTION

General. All solvents and starting materials were used as received without further purification. Melting points were measured with a micro melting apparatus and are uncorrected. Column chromatographic separations were carried out using silica gel as the stationary phase. Precoated plates (silica gel 60 F_{254}) were used for TLC examination. 1,2-Bis(*tert*-butyldimethylsilyl)acetylene[12] and phenyl(trimethylsilylethynyl)-iodonium triflate (**1a**)[10] were prepared according to the literature.

Synthesis of *tert*-Butyldimethylsilylethynyl(phenyl)iodonium Triflate (1b). Trifluoromethanesulfonic acid (1.59 mL, 18 mmol) was added dropwise to a solution of (diacetoxy)iodobenzene (3.22 g, 10 mmol) in CH_2Cl_2 (40 mL) at 0 °C. After 30 min of stirring, bis(*tert*-butyldimethylsilyl)acetylene (2.55 g, 10 mmol) was added, and the mixture was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was washed by decantation with hexane and then dissolved in CH_2Cl_2. The solution of CH_2Cl_2 was washed with water and dried over anhydrous Na_2SO_4. Evaporation of CH_2Cl_2 gave 3.15 g (64%) of **1b** as colorless crystals, mp 131−132.5 °C (hexane/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, Me, 6H), 0.91 (s, Me, 9H), 7.52 (t, J = 7.5 Hz, ArH, 2H), 7.65 (t, J = 7.5 Hz, ArH, 1H), 8.07 (d, J = 7.5 Hz, ArH, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3, 16.7, 25.7, 44.2, 77.2, 117.0, 132.3, 132.5, 133.9. Anal. Calcd for $C_{15}H_{20}F_3IO_3SSi$: C, 36.59; H, 4.09. Found: C, 36.32; H, 4.02.

Synthesis of Ethynyl(phenyl)iodonium Triflate (1c)[13]. A solution of trimethylsilylethynyliodonium triflate **1a** (0.9006 g, 2 mmol) in CH_2Cl_2 (4 mL) was prepared in a Teflon tube. Aqueous HF (56%, 0.14 mL) was added, and the mixture was stirred at room temperature for 2 h. To the reaction mixture was added anhydrous Na_2SO_4, and the mixture was filtrated. Concentration of the solution gave 0.578 g (76%) of **1c** as colorless crystals, mp 111.5−113 °C (hexane/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.24 (s, ≡CH, 1H), 7.53−7.58 (m, ArH, 2H), 7.67−7.72 (m, ArH, 1H), 8.08−8.11 (m, ArH, 2H); ^{13}C NMR (75 MHz, CD_3CN) δ 29.7, 97.9, 117.4, 121.3, 133.2, 133.8, 136.0.

Reaction of Silylethynyliodonium Triflates 1a and 1b with Benzotriazole Ion. To a solution of ^{t}BuOK (0.168 g, 1.5 mmol) in ^{t}BuOH (10 mL) was added dropwise a solution of benzotriazole (0.179 g, 1.5 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 1 h and diluted with CH_2Cl_2 (10 mL). The solution of the potassium salt of the benzotriazole ion thus prepared was added dropwise to a solution of silylethynyliodonium triflate **1** (1.0 mmol) in CH_2Cl_2 (10 mL), and the mixture was stirred at room temperature for 12 h. The reaction mixture was poured into water, and the product was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water and brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the product was separated by column chromatography with hexane/CH_2Cl_2 as eluent. The product was further purified by recrystallization from CH_2Cl_2/hexane.

2-Trimethylsilylethynyl-2*H*-1,2,3-benzotriazole (2a). The product was obtained in 74% yield as colorless crystals, mp 76.5−77.5 °C (hexane/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.35 (s, $SiMe_3$, 9H), 7.42−7.47 (m, ArH, 2H), 7.80−7.86 (m, ArH, 2H); ^{13}C NMR(75 MHz, acetone-d_6) δ −0.6, 77.2, 93.7, 118.7, 129.8, 145.2. Anal. Calcd for $C_{11}H_{13}N_3Si$: C, 61.36; H, 6.09; N, 19.51. Found: C, 61.50; H, 6.12; N, 19.35.

1-Trimethylsilylethynyl-1*H*-1,2,3-benzotriazole (3a). The product was obtained in 17% yield as brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, $SiMe_3$, 9H), 7.32−7.37 (m, ArH, 1H), 7.49−7.62 (m, ArH, 2H), 7.99 (d, J = 8.4 Hz, ArH, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.3, 83.7, 87.4, 110.1, 120.4, 125.2, 129.3, 134.1, 143.6. Anal. Calcd for $C_{11}H_{13}N_3Si$: C, 61.36; H, 6.09; N, 19.51. Found: C, 61.63; H, 6.00; N, 19.51.

2-(*tert*-Butyldimethylsilylethynyl)-2*H*-1,2,3-benzotriazole (2b). The product was obtained in 76% yield as colorless crystals, mp 67.5−69 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, $SiMe_2$, 6H), 1.06 (s, Me, 9H), 7.43−7.47 (m, ArH, 2H), 7.82−7.85 (m, ArH, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.0, 16.7, 26.0, 76.0, 93.3, 118.1, 128.7, 144.5. HRMS (EI) calcd for $C_{14}H_{19}N_3Si$ 257.1348, found 257.1346.

1-(*tert*-Butyldimethylsilylethynyl)-1*H*-1,2,3-benzotriazole (3b). The product was obtained in 8% yield as light yellow crystals, mp 48−49 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, $SiMe_2$, 6H), 1.06 (s, Me, 9H), 7.43−7.49 (m, ArH, 1H), 7.63−7.65 (m, ArH, 2H), 8.11 (d, J = 8.1 Hz, ArH, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.7, 16.6, 26.1, 82.2, 88.0, 110.1, 120.5, 125.3, 129.4, 134.3, 143.7. HRMS (EI) calcd for $C_{14}H_{19}N_3Si$ 257.1348, found 257.1351.

2-Ethynyl-2*H*-1,2,3-benzotriazole (2c). The product was obtained in 20% yield as colorless crystals, mp 63−63.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.48 (s, ≡CH, 1H), 7.42−7.48 (m, ArH, 2H), 7.81−7.87 (m, ArH, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.8, 74.6, 118.2, 128.9, 144.6. HRMS (EI) calcd for $C_8H_5N_3$ 143.0483, found 143.0481.

1-Ethynyl-1*H*-1,2,3-benzotriazole (3c)[14]. The product was obtained in 52% yield as colorless crystals, mp 81−81.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, ≡CH, 1H), 7.45−7.50 (m, ArH, 1H), 7.61−7.70 (m, ArH, 2H), 8.12 (d, J = 8.4 Hz, ArH, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.5, 69.5, 109.9, 120.6, 125.4, 129.6, 134.3, 143.7.

Preparation of 2-Ethynyl-2*H*-1,2,3-benzotriazole (2c) by Desilylation of 2a. To a solution of **2a** (0.108 g, 0.5 mmol) in THF (1 mL) and MeOH (1 mL) was added 1 M NaOH solution (1 mol/L, 0.5 mL) dropwise, and the mixture was stirred for 5 min. The product was extracted with CH_2Cl_2 and separated by column chromatography on silica gel. Elution with CH_2Cl_2/hexane gave **2c** as colorless crystals in 84% yield.

ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra of alkynylbenzotriazoles **2a**−**2c** and **3a**−**3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) For reviews:(a) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409–548. (b) Katritzky, A. R.; Manju, K.; Singh, S. K.; Meher, N. K. *Tetrahedron* **2005**, *61*, 2555–2581.

(2) (a) Heller, H. J.; Blattmann, H. R. *Pure Appl. Chem.* **1973**, *36*, 141–161. (b) Keck, J.; Stüber, G. J.; Kramer, H. E. A. *Angew. Makromol. Chem.* **1997**, *252*, 119–138.

(3) Kale, R. R.; Prasad, V.; Mohapatra, P. P.; Tiwari, V. K. *Monatsh. Chem.* **2010**, *141*, 1159–1182.

(4) Fan, W.-Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 4, Storr, R. C., Vol. Ed.; pp 1−126.

(5) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455–1475.

(6) For reviews, see:(a) Ochiai, M.; Nagao, Y. *Yuki Gosei Kagaku Kyokaishi* **1986**, *44*, 660−673; CAN 106:84682. (b) Ochiai, M. *Rev. Heteroatom. Chem.* **1989**, *2*, 92–111. (c) Stang, P. J *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274–285. (d) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997–3008. (e) Brand, J. P.; González, D. F.; Nicolai, S.; Waser, J. *Chem. Commun.* **2011**, *47*, 102–115.

(7) (a) Kitamura, T.; Tashi, N.; Tsuda, K.; Fujiwara, Y. *Tetrahedron Lett.* **1998**, *39*, 3787–3790. (b) Kitamura, T.; Tashi, N.; Tsuda, K.; Chen, H.; Fujiwara, Y. *Heterocycles* **2000**, *52*, 303–312.

(8) Bachi, M. D.; Bar-Ner, N.; Crittell, C. M.; Stang, P. J.; Williamson, B. L. *J. Org. Chem.* **1991**, *56*, 3912–3915.
(9) (a) Katritzky, A. R.; Yannakopoulou, K.; Kuzmierkiewicz, W.; Aurrecoechea, J. M.; Palenik, G. J.; Koziol, A. E.; Szczesniak, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2673–2679. (b) Lee, H.-G.; Won, J.-E.; Jun, K.-J.; Kim, B. R.; Lee, S.-G.; Yoon, Y.-J. *J. Org. Chem.* **2009**, *74*, 5675–5678.
(10) Kitamura, T.; Kotani, M.; Fujiwara, Y. *Synthesis* **1998**, 1416–1418.
(11) Ochiai, M.; Ito, T.; Takaoka, Y.; Masaki, Y.; Kunishima, M.; Tani, S.; Nagao, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 118–119.
(12) West, R.; Quass, L. C. *J. Organomet. Chem.* **1969**, *18*, 55–67.
(13) Stang, P. J.; Arif, A. M.; Crittel, C. M. *Angew. Chem., Int. Ed.* **1990**, *29*, 287–288.
(14) Katritzky, A. R.; Singh, S. K.; Jiang, R. *Tetrahedron* **2006**, *62*, 3794–3797.