Organic LETTERS

Letter

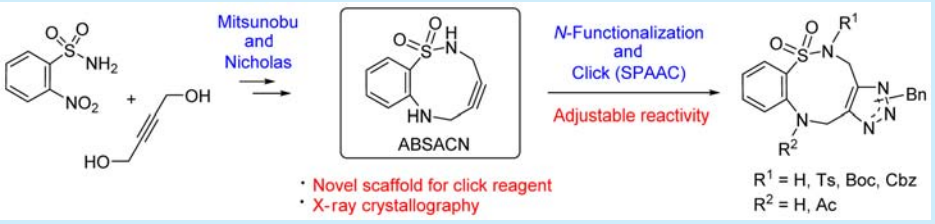
pubs.acs.org/OrgLett

2-Aminobenzenesulfonamide-Containing Cyclononyne as Adjustable Click Reagent for Strain-Promoted Azide–Alkyne Cycloaddition

Kyosuke Kaneda,* Risa Naruse, and Syota Yamamoto

Hokkaido Pharmaceutical University School of Pharmacy, 7-15-4-1 Maeda Teine Sapporo, Hokkaido 006-8590, Japan

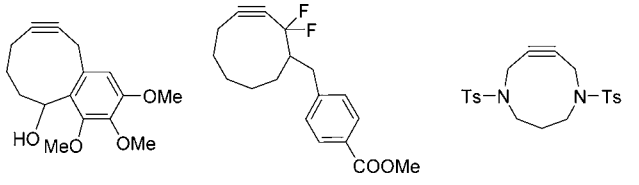
Supporting Information



ABSTRACT: The synthesis of 2-aminobenzenesulfonamide-containing cyclononyne (ABSACN), starting from 2-nitrobenzenesulfonamide and but-2-yne-1,4-diol via Mitsunobu and Nicholas reactions, is described for the development of an adjustable alkyne reagent in click reactions. In a strain-promoted azide–alkyne cycloaddition (SPAAC) reaction, the reactivity of the alkyne is controlled by introducing various *N*-functionalities. The structure–reactivity relationship is found to be influenced by a transannular hydrogen bond between amino and sulfonyl groups.

A medium-sized ring-containing alkyne is an important reagent for use of a bioorthogonal reaction in biological studies.[1] A bent alkyne spontaneously and chemoselectively reacts with an azide to form a triazole product in a living cellular environment, as a representative reaction of click chemistry,[2] namely copper-free click reaction[3] and/or strain-promoted azide–alkyne cycloaddition (SPAAC) reaction.[4] The designed syntheses of various cycloalkyne analogues have been developed over the past decade.[5] Among them, although the cyclooctyne analogue is primarily used as a highly activated reagent, the cyclononyne analogue has been studied as an alternative ring framework due to its good balance of chemical reactivity and physical stability.[5f] To date, three types of cyclononyne analogues have been reported to the best of our knowledge (Figure 1).

In 2012, a trimethoxybenzo-fused cyclononyne (**1** TMBN) was reported by the Dudley group.[5f] In 2014, a difluorinated cyclononyne (**2** DIFN) was reported by the Bertozzi group.[5g] In 2015, a 1.4-diazacyclononyne (**3** DACN) was reported by the Tomooka group.[5i] In designing a medium-sized cyclo-

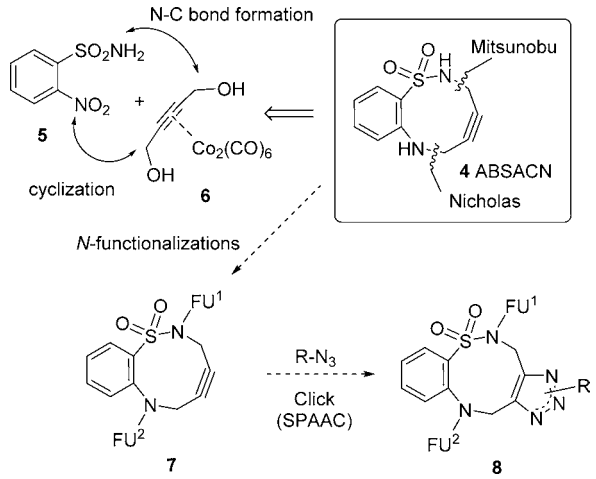


1, TMBN (Dudley) 2012[5f] **2**, DIFN (Bertozzi) 2014[5g] **3**, DACN (Tomooka) 2015[5i]

Figure 1. Representative cyclononyne analogues.

alkyne, the construction of the bent alkyne moiety is difficult in an organic synthesis.[6] Additionally, the unfavorable conformation states of a medium-sized ring would interrupt the synthesis through a ring formation process.[7] Recent development of our synthetic method for a medium-sized heterocyclic system[8] encouraged us to produce a 2-aminobenzenesulfonamide-containing cyclononyne (**4** ABSACN in Scheme 1), which conformed to the advantageous heterocyclic alkyne design criteria postulated previously by the Alabugin group.[9] More-

Scheme 1. Synthetic Plan of 4 and Its Functionalization



Received: January 13, 2017
Published: February 14, 2017

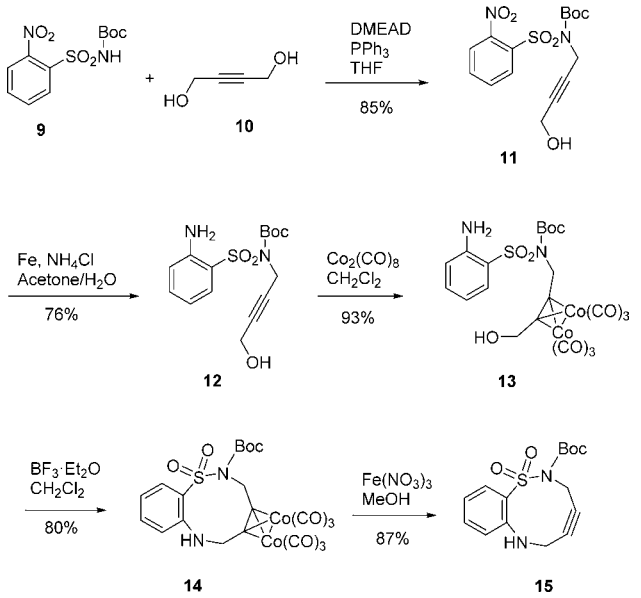
DOI: 10.1021/acs.orglett.7b00123
Org. Lett. 2017, 19, 1096–1099

over, the aminobenzenesulfonamide has two different nitrogen atoms, so that, from **4**, several derivatives **7** can be obtained with different chemical and physical properties. In this letter, we introduce the synthesis and reactivity of **4** as an adjustable click reagent for SPAAC.

Our research plan including the retrosynthesis of **4** is summarized in Scheme 1. First, as a concept of the molecular design, a compound containing a sulfonamide moiety within a cyclononyne framework is featured. Sulfonamide is an interesting functional group in both the synthetic and pharmaceutical fields.[10] The relatively acidic proton can be used by the C−N bond formation with an alcohol via the Mitsunobu reaction.[11] Also, to construct the nine-membered ring, we selected the Nicholas reaction, which is a useful cyclization method for medium-sized heterocycles via a cobalt−alkyne complex.[12] Therefore, the synthesis of **4** would be started from both 2-nitrobenzenesulfonamide **5** and but-2-yne-1,4-diol coordinated with dicobalt−hexacarbonyl complex **6**. After preparation of **4**, various *N*-functionalization reactions would be attempted to reveal the reactivity of the two nitrogen atoms. Finally, to demonstrate SPAAC, **7** would react with an azide reagent to form the corresponding triazole **8**.

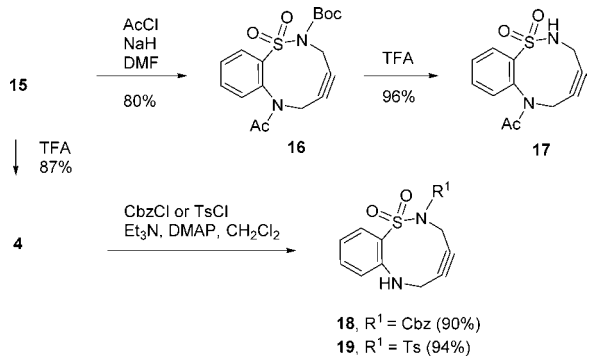
A synthetic route toward *N*-Boc ABSACN **15** is shown in Scheme 2. The starting material, *N*-Boc 2-nitrobenzenesulfonamide **9**, was prepared from 2-nitrobenzenesulfonyl chloride in two steps according to the Fukuyama protocol.[13] The Mitsunobu reaction of **9** with but-2-yne-1,4-diol **10** by employing dimethoxyethyl azodicarboxylate (DMEAD), which was developed by the Sugimura group as a water-soluble azodicarboxylate reagent,[14] provided the propargyl sulfonamide **11** in 85% yield. Reduction of the nitro group on the aromatic ring was then performed using the Fe/NH_4Cl/acetone/H_2O system[15] to afford the aniline derivative **12** in 76% yield. Three sequential operations were needed to construct the alkyne-containing nine-membered ring via the Nicholas protocol: (i) the cobalt−alkyne complex **13** was prepared in 93% yield, (ii) ring closure was carried out using boron trifluoride in dilute CH_2Cl_2 to give **14** in 80% yield, and (iii) oxidative liberation of the cobalt complex was carried out using ferric nitrate [$Fe(NO_3)_3$] in methanol to give **15** in 87% yield.[16]

Scheme 2. Synthetic Route toward *N*-Boc ABSACN 15



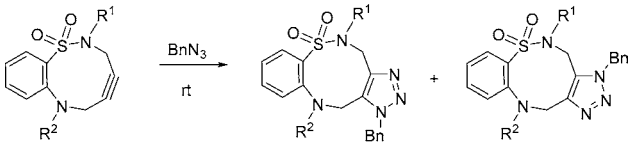
N-Functionalization reactions for adding various groups to the ABSACN scaffold are described in Scheme 3. The acetylation reaction at the anilic nitrogen atom in **15** was carried out by using the combination of AcCl and NaH in DMF, giving **16** in 80% yield. The Boc group was removed from **16** by adding TFA, which provided **17** in 96% yield. Under the same conditions, the Boc group was removed from **15** to give **4** in 87% yield. *N*-Benzyloxycarbonylation of **4** was carried out by applying CbzCl in the presence of Et_3N with a catalytic amount of DMAP to give **18** in 90% yield. *N*-Tosylation of **4** was performed by applying TsCl in the presence of Et_3N with a catalytic amount of DMAP to give **19** in 94% yield.

Scheme 3. *N*-Functionalization Reactions



With the derivatives in hand, we then attempted the SPAAC reaction using a representative azide reagent, benzyl azide. The yields and regioisomer ratios of SPAAC are summarized in Table 1. All reactions (entries a−f) were conducted in a 0.05 M solution of CH_2Cl_2 or CH_3CN, and the reaction mixtures were stirred at room temperature for 4−24 h to give the mixed product in 88%−99% yield. Due to the unsymmetrical structure of the cyclononyne ring, regioisomers **20a−f** and **20′a−f** were generated with various ratios, which were determined by ^1H NMR measurement. **20** and **20′** could be separated by silica gel column chromatography except for entry a.

Table 1. Result of SPAAC



entry	4, 15−19	20+20′ yield (%)	20/20′[a]
a	**4**, R^1 = H, R^2 = H	97	5:2[b]
b	**15**, R^1 = Boc, R^2 = H	99	5:3
c	**16**, R^1 = Boc, R^2 = Ac	99	4:3
d	**17**, R^1 = H, R^2 = Ac	88	3:2
e	**18**, R^1 = Cbz, R^2 = H	92	3:2
f	**19**, R^1 = Ts, R^2 = H	99	2:1

[a]Ratio was determined by ^1H NMR measurement. [b]Isomers were inseparable using silica gel chromatography.

The structures of **20** and **20′** were determined by observation of NOESY correlation between the methylene

DOI: 10.1021/acs.orglett.7b00123
Org. Lett. 2017, 19, 1096−1099

group within the nine-membered ring and the benzyl group. Interestingly, the major products were **20** in all entries except for entry a. Additionally, **20′b** could be recrystallized using EtOH and its structure was confirmed by a single-crystal X-ray crystallographic measurement (Figure 2).

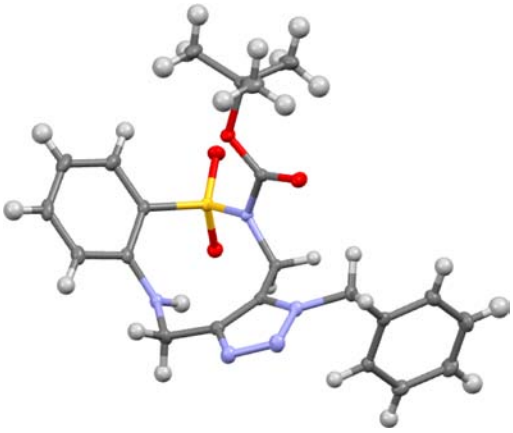
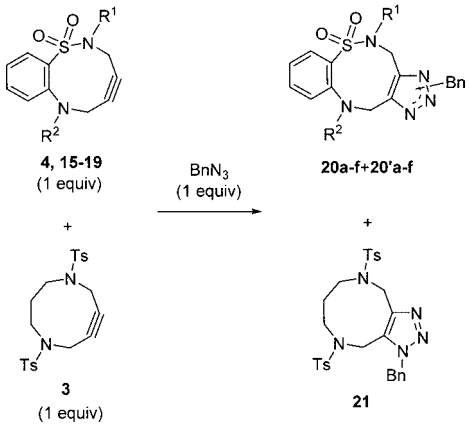


Figure 2. Structure of **20′b** by X-ray crystallography.

Next, to evaluate the reactivity of the alkyne in ABSACN derivatives, we conducted a competing reaction in which DACN (**3**, purchased by Kanto Chemical Company) was selected as a competitor due to its structure similarity (Scheme 4). A 1 equiv amount of each of the analogues (**4** or **15**−**19**)

Scheme 4. Competing Reaction



and **3** were dissolved in a solvent, and then 1 equiv of benzyl azide was added to the stirred mixture. After benzyl azide was consumed according to TLC monitoring, the reaction mixture was directly measured by ^{1}H NMR. The ^{1}H NMR spectrum showed the corresponding peaks of **20**, **20′**, and **21**, and we calculated the ratios by recording each constant of integration.

Based on the results of the competing reaction, the order of reactivity of the derivatives is shown in Figure 3. The values in parentheses below the structure refer to the relative reactivity compared with an internal standard **3** (1.0). While **17** (0.27) exhibited lower reactivity than **4** (0.43), **15** (1.5) exhibited higher reactivity than **4** (0.43). This shows that the Ac group on the anilic nitrogen atom inhibits SPAAC, whereas the Boc group on the sulfonamidic nitrogen atom promotes it. The order **19** < **15** < **18** demonstrates that the Cbz group is far superior to Ts and Boc for promotion of SPAAC. ABSACN

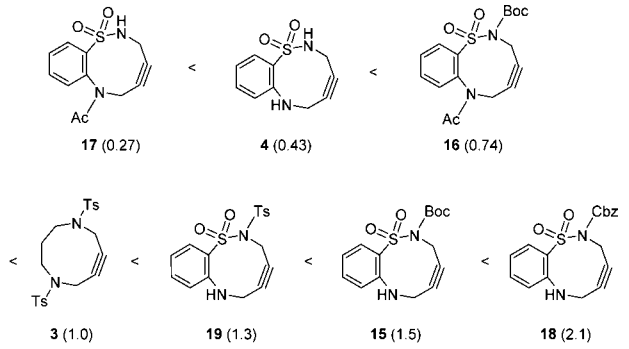


Figure 3. Order of reactivity (values in parentheses refer to relative reactivity).

exhibited a useful level of reactivity that could be tuned by addition of suitable functional groups (Ac, Boc, Cbz, and Ts) to each nitrogen atom.

4 could be recrystallized using EtOH, and its structural conformation was revealed by X-ray crystallographic analysis (Figure 4). The bond angles between the alkyne and the

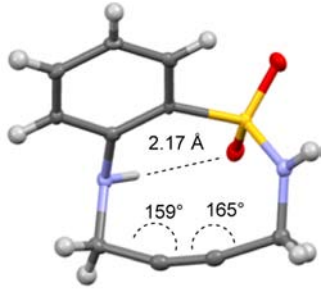


Figure 4. Structure of **4** by X-ray crystallography.

propargylic carbons were bent at 159° and 165°, which is similar to the case in **3**.[5i] In addition, the intramolecular hydrogen bond between the anilic amine and the sulfonyl group was observed with the H···O distance at 2.17 Å. This observation supports the result that the intramolecular hydrogen bond accelerates the click reactivity of ABSACN.

In summary, we have established a synthetic route to 2-aminobenzenesulfonamide-containing cyclononynes (**4** ABSACN) by employing the Mitsunobu and Nicholas methods. The reactivity of **4** in SPAAC was compared with that of **3**, and it was found that the reactivity was adjustable by introducing *N*-functionalities, with the relative reactivity ranging from 0.27 to 2.1. Moreover, X-ray crystallography indicated that an intramolecular hydrogen bond influenced the structure−reactivity relationship. Further study of related reactions of ABSACN analogues is currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00123.

Detailed procedures and characterization of the newly synthesized compounds (PDF)
X-ray crystallography of **4** (CIF)
X-ray crystallography of **20′b** (CIF)

DOI: 10.1021/acs.orglett.7b00123
Org. Lett. 2017, 19, 1096−1099

AUTHOR INFORMATION

Corresponding Author

*E-mail: kaneda@hokuyakudai.ac.jp.

ORCID

Kyosuke Kaneda: 0000-0003-2415-2685

Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by a grant from Hokkaido Pharmaceutical University. We acknowledge Prof. Tsubuki and Dr. Kasai (Hoshi University, Japan) for performing mass spectrometry measurement and Dr. Hiroto (Nagoya University, Japan) for performing X-ray crystallography measurement. This work was partly supported by Nanotechnology Platform Program (Molecule and Material Synthesis) of Ministry of Education, Culture, Sports, Science, and Technology (MEXT), Japan.

REFERENCES

(1) (a) Jewett, J. C.; Bertozzi, C. R. *Chem. Soc. Rev.* **2010**, *39*, 1272−1279. (b) Ostrovskis, P.; Volla, C. M. R.; Turks, M.; Markovic, D. *Curr. Org. Chem.* **2013**, *17*, 610−640. (c) King, M.; Wagner, A. *Bioconjugate Chem.* **2014**, *25*, 825−839.

(2) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565−598. (b) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021.

(3) Baskin, J. M.; Prescher, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 16793−16797.

(4) (a) Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2004**, *126*, 15046−15047. (b) Dommerholt, J.; Rutjes, F. P. J. T.; van Delft, F. L. *Top. Curr. Chem.* **2016**, *374* (374), 16.

(5) For selective synthetic examples of cycloalkynes: (a) Sletten, E. M.; Bertozzi, C. R. *Org. Lett.* **2008**, *10*, 3097−3099. (b) Debets, M. F.; van Berkel, S. S.; Schoffelen, S.; Rutjes, F. P. J. T.; van Hest, J. C. M.; van Delft, F. L. *Chem. Commun.* **2010**, *46*, 97−99. (c) Dommerholt, J.; Schmidt, S.; Temming, R.; Hendriks, L. J. A.; Rutjes, F. P. J. T.; van Hest, J. C. M.; Lefeber, D. J.; Friedl, P.; van Delft, F. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9422−9425. (d) Jewett, J. C.; Sletten, E. M.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 3688−3690. (e) Gordon, C. G.; Mackey, J. L.; Jewett, J. C.; Sletten, E. M.; Houk, K. N.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2012**, *134*, 9199−9208. (f) Tummatorn, J.; Batsomboon, P.; Clark, R. J.; Alabugin, I. V.; Dudley, G. B. *J. Org. Chem.* **2012**, *77*, 2093−2097. (g) Sletten, E. M.; de Almeida, G.; Bertozzi, C. R. *Org. Lett.* **2014**, *16*, 1634−1637. (h) Debets, M. F.; Prins, J. S.; Merkx, D.; van Berkel, S. S.; van Delft, F. L. *Org. Biomol. Chem.* **2014**, *12*, 5031−5037. (i) Ni, R.; Mitsuda, N.; Kashiwagi, T.; Igawa, K.; Tomooka, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 1190−1194.

(6) Krebs, A.; Wilke, J. *Top. Curr. Chem.* **1983**, *109*, 189−233.

(7) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102.

(8) (a) Asamizu, T.; Naruse, R.; Yongxue, G.; Kaneda, K. *Tetrahedron Lett.* **2015**, *56*, 4674−4677. (b) Kaneda, K.; Fujita, M.; Naruse, R. *Heterocycles* **2016**, *92*, 291−304. (c) Akimura, N.; Fujii, A.; Kamada, F.; Nogiwa, R.; Yamamoto, S.; Sato, T.; Ishikawa, S.; Okazaki, T.; Kaneda, K. *Synthesis* **2016**, *48*, 3931−3940.

(9) Gold, B.; Dudley, G. B.; Alabugin, I. V. *J. Am. Chem. Soc.* **2013**, *135*, 1558−1569.

(10) (a) Majumdar, K. C.; Mondal, S. *Chem. Rev.* **2011**, *111*, 7749−7773. (b) Chen, Y. *Synthesis* **2016**, *48*, 2483−2522.

(11) (a) Mitsunobu, O. *Synthesis* **1981**, *1981*, 1−28. (b) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709−5712.

(12) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207−214.

(13) Fukuyama, T.; Cheung, M.; Kan, T. *Synlett* **1999**, *1999*, 1301−1303.

(14) Sugimura, T.; Hagiya, K. *Chem. Lett.* **2007**, *36*, 566−567.

(15) Xiao, Z. P.; Wang, Y. C.; Du, G. Y.; Wu, J.; Luo, T.; Yi, S. F. *Synth. Commun.* **2010**, *40*, 661−665.

(16) Hagendorn, T.; Brase, S. *RSC Adv.* **2014**, *4*, 15493−15495.

DOI: 10.1021/acs.orglett.7b00123
Org. Lett. 2017, 19, 1096−1099