Organic LETTERS

Letter

pubs.acs.org/OrgLett

Heterocyclization of Enediynes Promoted by Sodium Azide: A Case of Ambiguity of X-ray Data and Structure Revision

Anna V. Gulevskaya,* Alexander S. Tyaglivy, Alexander F. Pozharskii, Julia I. Nelina-Nemtseva, and Dmitry V. Steglenko

Department of Organic Chemistry, Southern Federal University, Zorge 7, Rostov-on-Don 344090, Russian Federation

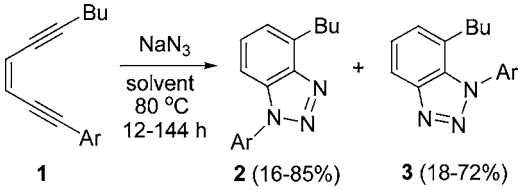
Supporting Information

ABSTRACT: It has been shown that contrary to the literature data the tandem cyclization of (*Z*)-1-aryl-3-hexen-1,5-diynes promoted by sodium azide results in the formation of the corresponding [1,2,3]triazolo[1,5-*a*]pyridines, not 1*H*-benzotriazole derivatives. Apparently, incorrect structure elucidation made by previous investigators originates from misinterpretation of X-ray data. A number of new transformations of this type as well as X-ray and NMR experiments are discussed.

Enediynes and structurally related compounds have attracted much attention since the discovery of naturally occurring antibiotics having a (*Z*)-hexa-3-en-1,5-diyne fragment in their structures.[1] It is supposed that the antitumor and antibacterial activity of enediyne antibiotics is based on the Bergman cyclization[2] which generates benzene-1,4-diradicals, capable of cleaving DNA and rupturing the protein structure. The challenging chemical structures of enediyne antibiotics and fascinating mode of their biochemical action have attracted considerable attention.[1f] Most of the work on enediyne chemistry is focused on the synthesis of designed enediynes, their thermal reactivity modulation, and anticancer activity evaluation. Besides a thermal[1g] and photochemical[1h] Bergman reaction, cyclizations of enediynes can be induced by various reagents: radicals,[3] nucleophiles,[4] electrophiles,[5] transition metal complexes,[6] a frustrated Lewis pair,[7] and so on. In addition, substituents at the alkyne termini can also be involved in the cyclization process leading to polycyclic products.[8]

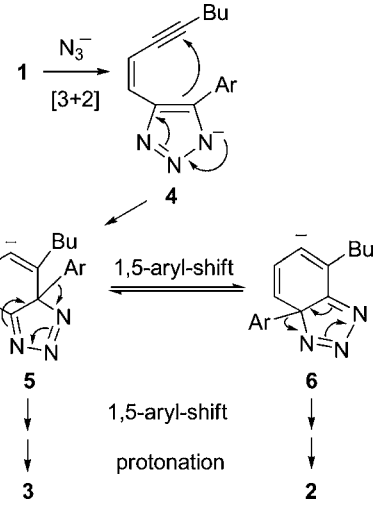
In this strategy, some time ago Taiwanese chemists claimed that treatment of (*Z*)-1-aryl-3-hexen-1,5-diynes **1a**–**h** with sodium azide in DMF or DMSO resulted in the formation of a mixture of 1-aryl-4-butyl- and 1-aryl-7-butyl-1*H*-benzotriazoles **2** and **3** (Scheme 1).[9] The proposed reaction mechanism

Scheme 1. Reaction of (*Z*)-1-Aryl-3-hexen-1,5-diynes with Sodium Azide Reported by Taiwanese Chemists



Ar = Ph (**a**), *p*-$NO_2C_6H_4$ (**b**), *o*-$NO_2C_6H_4$ (**c**), *p*-$MeOC_6H_4$ (**d**), *o*-$MeOC_6H_4$ (**e**), *o*-$CF_3C_6H_4$ (**f**), pyridinyl (**g**), *p*-$CF_3C_6H_4$ (**h**)

Scheme 2. Original Mechanism Proposed for the Reaction of (*Z*)-1-Aryl-3-hexen-1,5-diynes with NaN_3



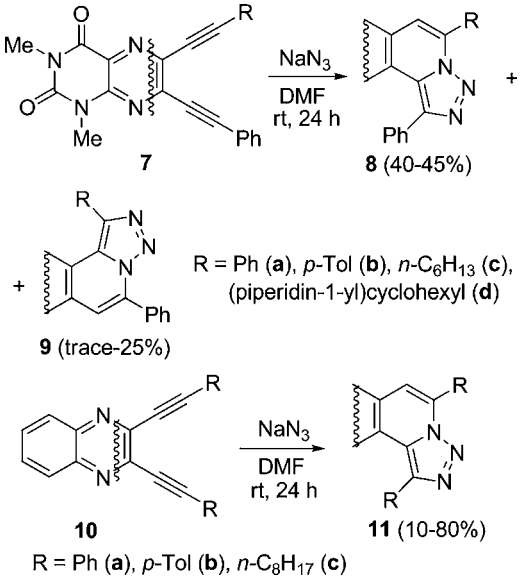
(Scheme 2), with the exception of the primary [3 + 2] cycloaddition step, appeared rather unlikely. It was improbable that the nucleophilic center during cyclization **4**→**5** could be located on the triazole carbon atom rather than on the much more electronegative N-1 or N-3 atom.

Justifying these doubts, somewhat later[10] we found that the reaction of 6,7-dialkynyl-1,3-dimethyllumazines **7** and 2,3-dialkynylquinoxalines **10** with NaN_3 actually produced not the corresponding benzotriazole derivatives but isomeric bridge-head [1,2,3]triazolo[1,5-*a*]pyridines **8**, **9**, and **11** (Scheme 3). The proposed reaction pathway is shown in Scheme 4. It involves formation of the triazole anion **12** and subsequent attack of its nitrogen atom on the neighboring triple

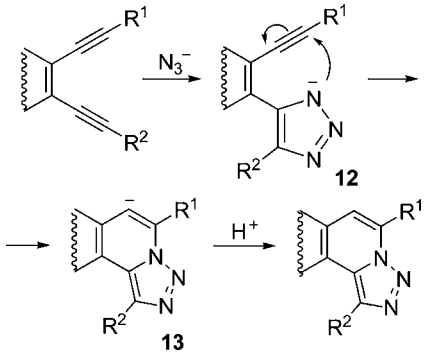
Received: January 14, 2014
Published: March 5, 2014

dx.doi.org/10.1021/ol500125j | *Org. Lett.* 2014, 16, 1582–1585

Scheme 3. Reactions of 6,7-Dialkynyl-1,3-dimethyllumazines and 2,3-Dialkynylquinoxalines with NaN_3



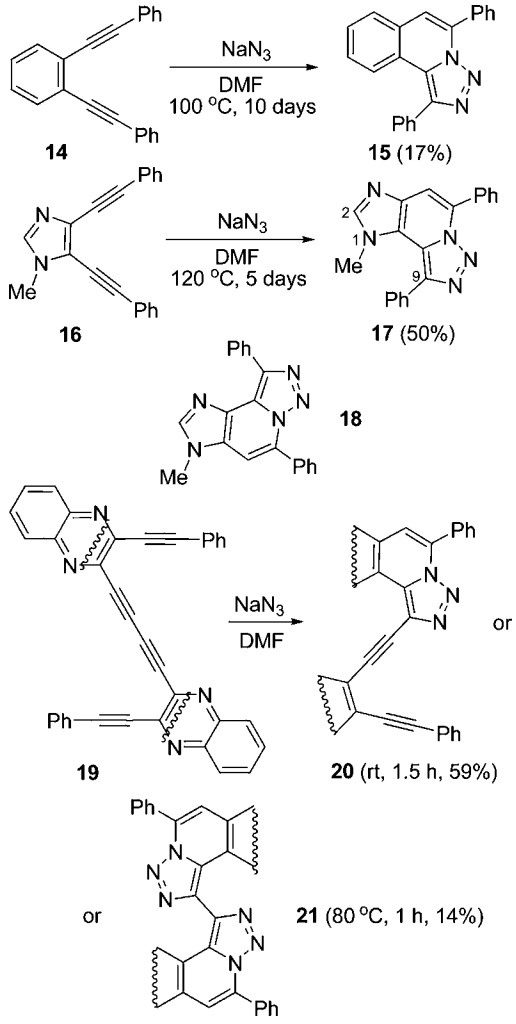
Scheme 4. Mechanism Proposed for Heterocyclization of *ortho*-Dialkynyl (Het)arenes into Triazolopyridines



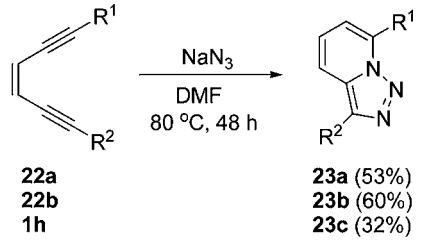
bond yielding, after proton quenching of intermediate carbanion **13**, a [1,2,3]triazolo[1,5-*a*]pyridine derivative.

We now report on some new examples of this reaction and speculate on the reasons causing the mistake of the previous investigators. The transformations performed by us of 1,2-diphenylethynylbenzene **14** into 1,5-diphenyl[1,2,3]triazolo-[5,1-*a*]isoquinoline **15**, 1-methyl-4,5-di(phenylethynyl)-imidazole **16** into compound **17**, and 1,4-bis(3-(phenyl-ethynyl)quinoxalin-2-yl)buta-1,3-diyne **19** into products of mono- and dicyclization **20**, **21** are presented in Scheme 5.[11] Structures of compounds **15**, **17**, **20**, and **21** were proven by mass, IR, and ^1H and ^{13}C spectra (Supporting Information (SI), Figures S5–S13). Besides, for **15** (SI, Figure S24) and **20** (SI, Figure S22) the single crystal X-ray measurements were also performed. Since cyclization of imidazole **16** is ambiguous and allows the formation of isomeric product **18**, we applied the COSY and NOESY $^1H-^1H$ methods for structure elucidation (SI, Figures S9, S10). The correctness of structure **17** was confirmed by the presence in its NOESY $^1H-^1H$ spectrum of the correlation peaks which correspond to the through-space spin–spin coupling of the N-Me group protons with the *ortho* protons of the 9-phenyl ring, thus demonstrating their close proximity to be impossible in structure **18** (see also ref 12).

Scheme 5. New Examples of Heterocyclization of *ortho*-Dialkynyl (Het)arenes into Triazolopyridines



Scheme 6. Cyclization of (*Z*)-3-Hexen-1,5-diynes into [1,2,3]Triazolo[1,5-*a*]pyridines



Probably, the 1,3-dipolar cycloaddition of an azide ion to the C≡C bond is the rate-determining step of the process. This follows, for example, from the higher reactivity of the 7-alkynyl group in **7** as compared with the 6-alkynyl group. By analogy, more electron-deficient 2,3-dialkynylquinoxalines **10** are cyclized with NaN_3 much easier than 1,2-dialkynylbenzene **14** and 1-methyl-4,5-di(phenylethynyl)imidazole **16**.

It can be assumed that the difference in reactivity of acyclic enediynes **1** and *ortho*-dialkynyl (het)arenes **7**, **10**, **14**, **16**, and **19** toward sodium azide originates from the difference in their

dx.doi.org/10.1021/ol500125j | *Org. Lett.* 2014, 16, 1582–1585

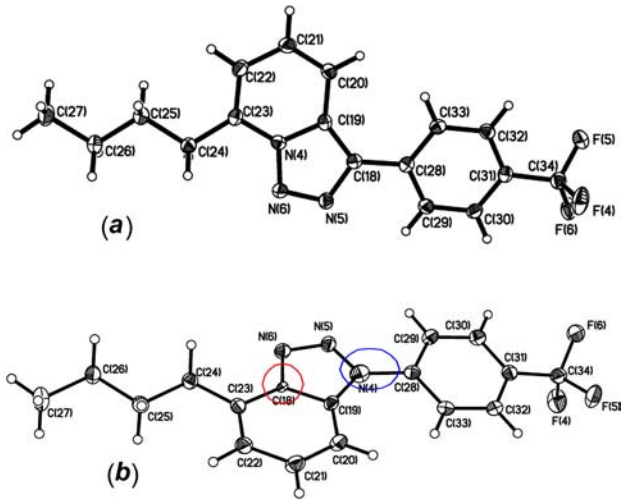


Figure 1. ORTEP plots for X-ray crystal structure of **23c** (a) and refined for structure **2h** (b). Incorrectly refined C and N atoms are circled (red and blue, respectively).

nature. However, we now proved that the reaction of enediynes **22a,b** with NaN_3 gave [1,2,3]triazolo[1,5-*a*]pyridines **23a,b** (Scheme 6). Their structures were confirmed by mass and ^1H, ^{13}C spectra (SI, Figures S14−S17). Structure **23b** was also verified by X-ray analysis (SI, Figure S25).

As the main evidence for the formation of benzotriazoles **2** and **3**, the researchers[9] presented only an X-ray experiment for compound **2h**. Surprisingly, this structure together with the corresponding refinement details has not been so far deposited in the Cambridge Crystallographic Data Centre (CCDC). Moreover, no synthetic protocols and physical constants including melting points were given for compounds **2h** and **3h**, neither in the Letter nor in the SI. Under these circumstances we were forced to reinvestigate the synthesis and some properties of **2h**. On treatment of enediyne **1h** with a small excess of NaN_3 in DMF (80 °C, 48 h) we were unable to reproduce the original[9] yields of **2h** (54%) and **3h** (20%). In our hands, a single product was isolated only in 32% yield (Scheme 6). The X-ray experiment demonstrated that it had [1,2,3]triazolo[1,5-*a*]pyridine structure **23c** instead of **2h** (Figure 1). Thus, we established that the cyclization pathway of enediynes upon their treatment with sodium azide does not depend on their nature and is described by Scheme 4.

Next, we tried to understand the cause of the error. There is the possibility that this may be a rare case of misleading X-ray diffraction studies without deeper investigation into the fine details. Yet, as it is seen from the above-mentioned findings, we have confirmed our results by the X-ray data for most of the compounds obtained. Moreover, we consciously misinformed the X-ray operator (when sample **23c** was delivered for analysis) that the compound likely had the structure **2h**, and the very experienced operator confirmed it! However, when we disclosed our trick and the diffraction pattern was carefully reconsidered, it turned out that the *R* factor for the alternative bridge-head structure **23c** was actually better (4.90 against 6.03) and thus the latter structure became obviously preferable. Table S1 (SI) summarizes the refinement indices and residual electron density for both the correct and incorrect structures for all X-ray experiments performed to date and clearly demonstrates the absolute superiority of the [1,2,3]triazolo[1,5-*a*]pyridine structures. Another feature supporting this conclusion is the manifestation of key thermal ellipsoids. While for all correct structures the sizes of N and C atom ellipsoids in the triazole ring are quite close to each other, for the wrong structures the ellipsoids of erroneously assigned carbon and nitrogen atoms (red and blue circled, respectively, in Figures 1 and S23−S25 (SI)) fall out of the overall picture by their abnormally small or big size.

To gain independent evidence for the correctness of structure **23c** we have conducted the NMR HMQC $^1H-^{13}C$ and HMBC $^1H-^{13}C$ experiments (for details, see SI, Figures

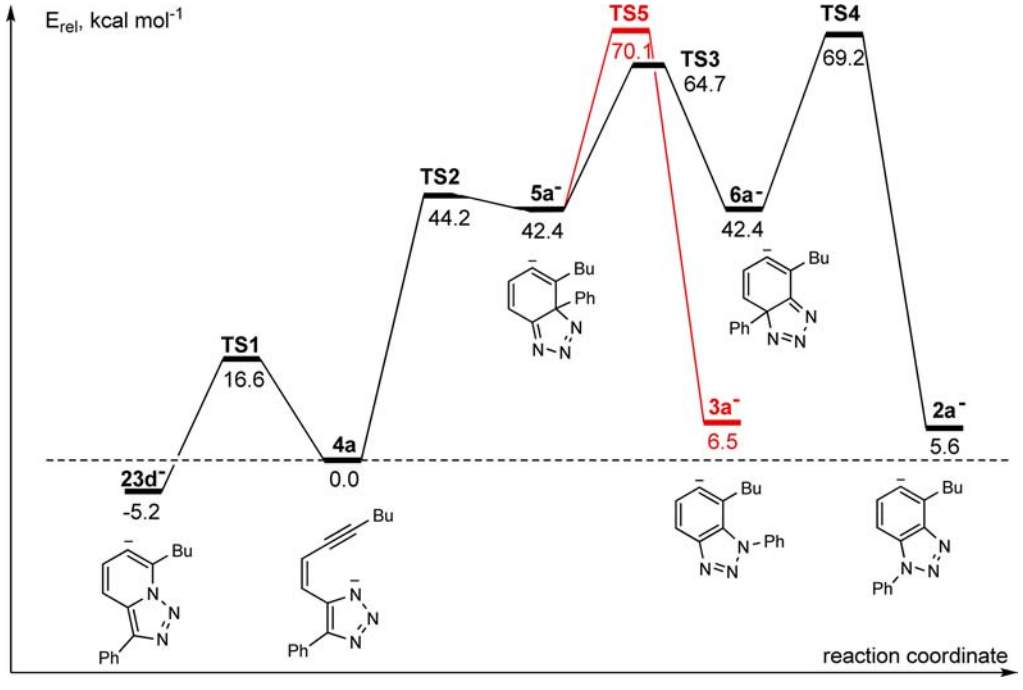


Figure 2. Energy profile for cyclizations of intermediate **4a** in the gas phase as derived from M05-2X/6-31+G** calculations.

dx.doi.org/10.1021/ol500125j | *Org. Lett.* 2014, 16, 1582−1585

S20 and S21). The key correlation between H-2′(6′) protons of the R^2 substituent (δ_H 8.09) and C-1 nucleus (δ_C 136.9), which makes it possible to distinguish structures **23c** and **2h**, has been found in the HMBC spectrum.

Additionally, a large preference for the formation of the [1,2,3]triazolo[1,5-*a*]pyridine system over the benzotriazole one in the reactions discussed was confirmed by quantum-chemical calculations. Thus, M05-2X/6-31+G** calculations of the potential energy surface for the cyclization of the reference anion **4a** (Figure 2 and Table S2 (SI)) showed that its conversion into [1,2,3]triazolo[1,5-*a*]pyridine structure **23d**$^-$ occurs through transition state **TS1** with a moderate activation energy (16.6 kcal mol^{-1}) and is accompanied by minimal energy output (−5.2 kcal mol^{-1}). In contrast, the transformation of **4a** into benzotriazole structure **5a**$^-$ with participation of the negatively charged ring carbon atom as a nucleophile, as well as the following processes of phenyl group migration, demands much higher energies (*cf.* transition states **TS2**−**TS5**). Theoretically, for N-centered nucleophiles such as anion **4a**, along with 6-*endo-dig* cyclization, 5-*exo-dig* cyclization is also possible.[13] However, our calculations have shown that the 6-*endo-dig* closure of **4a** is preferred both kinetically and thermodynamically (SI, Figures S33−S35, Table S3).

We believe that two main conclusions can be deduced from this work. First, it was found that a relatively simple tandem reaction of enediynes with sodium azide represents a new approach to a wide range of otherwise difficult to obtain [1,2,3]triazolo[1,5-*a*]pyridines.[14] Second, it was shown that even the use of an arsenal of modern physical methods, including X-ray diffraction analysis, does not relieve us of the need to delve into the finest details of data.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data for all new compounds, and X-ray diffraction as well as quantum-chemical studies. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: agulevskaya@sfedu.ru.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the Russian Foundation for Basic Research for financial support (Project No. 11-03-00079) and Professor V. A. Ozeryanskii (Southern Federal University) for valuable discussions.

■ DEDICATION

This paper is dedicated to the memory of Dr. Zoya A. Starikova (expert in the X-ray analysis, N. D. Zelinsky Institute of Organic Chemistry Russian Academy of Sciences) who recently passed away.

■ REFERENCES

(1) For review, see: (a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (b) Basak, A.; Mandal, S.; Beg, S. S. *Chem. Rev.* **2003**, *103*, 4077. (c) Rawat, D. S.; Zaleski, J. M. *Synlett* **2004**, 0393. (d) Maretina, I. A.; Trofimov, B. A. *Russ. Chem. Rev.* **2006**, *75*, 825. (e) Kar, M.; Basak, A. *Chem. Rev.* **2007**, *107*, 2861. (f) Joshi, M. C.; Rawat, D. S. *Chem. Biodiversity* **2012**, *9*, 459. (g) Breiner, B.; Kaya, K.; Roy, S.; Yang, W.-Y.; Alabugin, I. V. *Org. Biomol. Chem.* **2012**, *10*, 3974. (h) Mohamed, R. K.; Peterson, P. W.; Alabugin, I. V. *Chem. Rev.* **2013**, *113*, 7089.

(2) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660.

(3) (a) Kovalenko, S. V.; Peabody, S.; Manoharan, M.; Clark, R. J.; Alabugin, I. V. *Org. Lett.* **2004**, *6*, 2457. (b) König, B.; Pitsch, W.; Klein, M.; Vasold, R.; Prall, M.; Schreiner, P. R. *J. Org. Chem.* **2001**, *66*, 1742. (c) Scott, J. L.; Parkin, S. R.; Anthony, J. E. *Synlett* **2004**, 0161. (d) Peabody, S. W.; Breiner, B.; Kovalenko, S. V.; Patil, S.; Alabugin, I. V. *Org. Biomol. Chem.* **2005**, *3*, 218.

(4) (a) Wu, M.-J.; Lin, C.- F.; Lu, W.-D. *J. Org. Chem.* **2002**, *67*, 5907. (b) Whitlock, H. W.; Sandvick, P. E.; Overman, L. E.; Reichardt, P. B. *J. Org. Chem.* **1969**, *34*, 879. (c) Sugiyama, H.; Yamashita, K.; Nishi, M.; Saito, I. *Tetrahedron Lett.* **1992**, *33*, 515. (d) Magnus, P.; Eisenbeis, S. A. *J. Am. Chem. Soc.* **1993**, *115*, 12627. (e) Wu, M.-J.; Lin, C.-F.; Chen, S.-H. *Org. Lett.* **1999**, *1*, 767. (f) Gulevskaya, A. V.; Nguyen, H. T. L.; Tyaglivy, A. S.; Pozharskii, A. F. *Tetrahedron* **2012**, *68*, 488. (g) For a review, see: Gulevskaya, A. V.; Tyaglivy, A. S. *Chem. Heterocycl. Comp. (Engl. Transl.)* **2012**, *48*, 82.

(5) (a) Whitlock, H. W.; Sandvick, P. E. *J. Am. Chem. Soc.* **1966**, *88*, 4525. (b) Whitlock, B. J.; Whitlock, H. W. *J. Org. Chem.* **1972**, *37*, 3559. (c) Zhou, Q.; Carroll, P. J.; Swager, T. M. *J. Org. Chem.* **1994**, *59*, 1294. (d) Schreiner, P. R.; Prall, M.; Lutz, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5757. (e) Werner, C.; Hopf, H.; Grunenberg, J.; Jones, P. G. *Eur. J. Org. Chem.* **2010**, 4027. (f) Chase, D. T.; Rose, B. D.; McClintock, S. P.; Zakharov, L. N.; Haley, M. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1127. (g) Gulevskaya, A. V.; Lazarevich, R. Yu.; Pozharskii, A. F. *Tetrahedron* **2013**, *69*, 910. (h) For a review, see: Gulevskaya, A. V.; Lazarevich, R. Yu. *Chem. Heterocycl. Comp. (Engl. Transl.)* **2013**, *49*, 116.

(6) (a) Lee, C.-Y.; Wu, M.-Y. *Eur. J. Org. Chem.* **2007**, 3463. (b) Müller, E.; Munk, K.; Fritz, H.-G.; Sauerbier, M. *Liebigs Ann. Chem.* **1969**, *723*, 76. (c) Iyoda, M.; Fuchigami, K.; Kusaka, A.; Yoshida, T.; Yoshida, M.; Matsuyama, H.; Kuwatani, Y. *Chem. Lett.* **2000**, 860.

(7) Liedtke, R.; Fröhlich, R.; Kehr, G.; Erker, G. *Organometallics* **2011**, *30*, 5222.

(8) (a) Li, H.; Zang, H.-R.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2001**, *66*, 6662. (b) Li, Z.; Hong, J.; Weng, L.; Zhou, X. *Tetrahedron* **2012**, *68*, 1552. (c) Byers, P. M.; Alabugin, I. V. *J. Am. Chem. Soc.* **2012**, *134*, 9609.

(9) Chen, Z.-Y.; Wu, M.-J. *Org. Lett.* **2005**, *7*, 475.

(10) Gulevskaya, A. V.; Dang, V. S.; Tyaglivy, A. S.; Pozharskii, A. F.; Kazheva, O. N.; Chekhlov, A. N.; Dyachenko, O. A. *Tetrahedron* **2010**, *66*, 146.

(11) Previously, we have reported[10] that reactions of **16** and **14** with NaN_3 in DMF did not proceed under conditions described for acyclic enediynes (80 °C, 24 h).[9] Later we have found that higher temperatures (100−120 °C) and much more prolonged heating (5−10 days) provided desired [1,2,3]triazolo[1,5-*a*]pyridine derivatives **15** and **17**.

(12) To obtain an independent argument for the higher reactivity of the 5-alkynyl group in **16** towards N_3^- we have performed calculations for the NBO charges and frontier orbital parameters responsible for the cycloaddition reaction (SI, Figures S31, S32).

(13) (a) Vasilevsky, S. F.; Mikhailovskaya, T. F.; Mamatyuk, V. I.; Salnikov, G. E.; Bogdanchikov, G. A.; Manoharan, M.; Alabugin, I. V. *J. Org. Chem.* **2009**, *74*, 8106. (b) Vasilevsky, S. F.; Gold, B.; Mikhailovskaya, T. F.; Alabugin, I. V. *J. Phys. Org. Chem.* **2012**, *25*, 998. (c) Alabugin, I. V.; Gilmore, K. *Chem. Rev.* **2011**, *111*, 6513.

(14) (a) Sliskovic, D.R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier, 1996; Vol. *8*, Chapter 8.13, p 383. (b) Bischoff, L. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier, 2008; Vol. *11*, Chapter 11.13, pp 609−611.