Organic LETTERS

Letter

pubs.acs.org/OrgLett

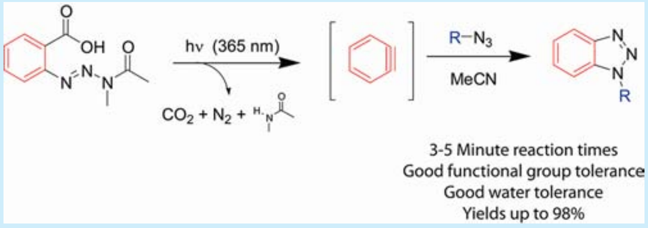
A Photoinduced, Benzyne Click Reaction

Adam W. Gann, Jon W. Amoroso, Vincent J. Einck, Walter P. Rice, James J. Chambers, and Nathan A. Schnarr*

Department of Chemistry, University of Massachusetts, 710 North Pleasant Street, Amherst, Massachusetts 01003, United States

Supporting Information

ABSTRACT: The [3 + 2] cycloaddition of azides and alkynes has proven invaluable across numerous scientific disciplines for imaging, cross-linking, and site-specific labeling among many other applications. We have developed a photoinitiated, benzyne-based [3 + 2] cycloaddition that is tolerant of a variety of functional groups as well as polar, protic solvents. The reaction is complete on the minute time scale using a single equivalent of partner azide, and the benzyne photoprecursor is stable for months under ambient light at room tempurature. Herein we report the optimization and scope of the photoinitiated reaction as well as characterization of the cycloaddition products.



Development of reliable click chemistry techniques is without question one of the most important endeavors of the past decade and remains an exciting and evolving area of modern synthetic methodology.[1−6] As the applications of this chemistry become increasingly complex, so do the demands for improved kinetics, specificity, and functional group tolerance. The [3 + 2] cycloaddition of alkynes and azides remains the gold standard in the area of conjugation chemistry, and more recently developed approaches using strained alkynes to eliminate the need for a copper catalyst have greatly expanded the scope of target applications in both aqueous and organic environments.[7−10] However, these techniques are not without their drawbacks. The direct correlation between lipophilicity and reactivity coupled with often difficult syntheses of the alkyne component may prove prohibitive as faster kinetics in aqueous environments and readily available material become increasingly desirable.[11−14] With this in mind, we were tempted to explore copper-free click chemistry from a different angle.

We were initially inspired by impressive work from Larock and co-workers where benzyne served as the reactive alkyne species for click chemistry via treatment of appropriately functionalized benzene with a fluoride ion (Figure 1).[15] Despite generally good yields and a broad substrate scope, several hours to days were required for completion, presumably due to sluggish benzyne formation. Addition of crown ethers led to faster reaction times, but most of these reactions still required at least 1 h for completion.[16] To improve kinetics, we envisioned fast photochemical generation of benzyne in the presence of an azide click partner to achieve the desired coupling. The use of light as an initiator also offers the potential for spatiotemporal control of the reaction, a highly desired feature for examining dynamic systems. Several photochemical click approaches have been developed including a light-induced Diels−Alder reaction,[17] azirine to alkene cycloaddition,[18] and nitrile ylide to alkene cycloaddition.[19] Additionally, a similar approach to our proposed benzyne click reaction has been developed where photochemical uncaging of cyclooctynes in the presence of azide partners results in the desired conjugation.[20,21] However, the overall reaction remains dependent on the relatively slow cycloaddition step. We therefore hypothesized that our click reaction would take full advantage of the benefits of each strategy, specifically, fast photolysis and a very reactive benzyne intermediate.

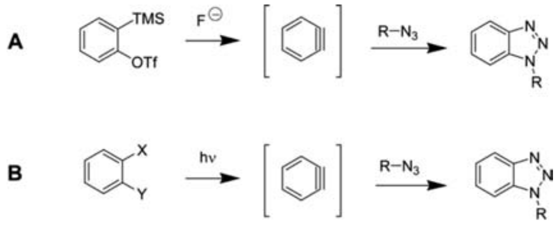


Figure 1. Comparison of fluoride-induced benzyne click reaction (A) with a photochemical approach (B). Fast benzyne formation via photolysis of appropriately substituted benzenes will vastly improve click reaction kinetics.

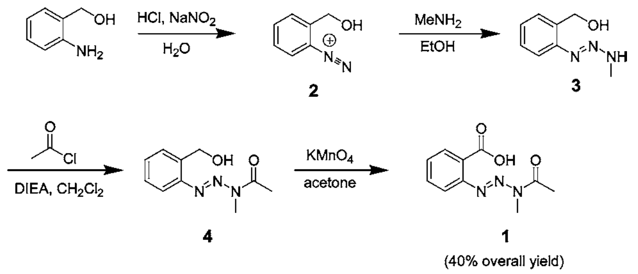
Our goals for development of this reaction were (1) reaction times on the minute scale, (2) reliable and synthetically straightforward preparation of the benzyne photoprecursor, and (3) yields consistent with those observed for the previously reported chemical methods.[15] Herein, we describe our initial efforts toward establishing a photoinduced, benzyne-based click reaction.

Following a substantial search for an appropriate benzyne photoprecursor, 2-(3-acetyl-3-methyltriaz-1-en-1-yl)benzoic acid (**1**) was deemed the best candidate for further exploration and development.[22,23] To our satisfaction, this compound was

Received: February 6, 2014
Published: March 13, 2014

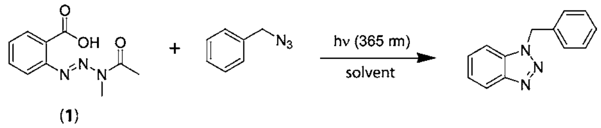
prepared in four straightforward steps from *o*-aminobenzyl alcohol without the need for chromatographic purification of any synthetic intermediates (Scheme 1). With the target compound in hand, we began to explore optimal parameters for the photoclick reaction using benzyl azide as a coupling partner for **1** (Table 1). To our delight, the reaction nears completion after only 3 min of irradiation and good yields can be achieved using a mere 1 equiv of azide. Yields can be improved by using higher azide equivalents when necessary. In addition, a variety of solvents are tolerated although acetonitrile appears the most suitable of those examined.

Scheme 1. Synthesis of 2-(3-Acetyl-3-methyltriaz-1-en-1-yl)benzoic Acid[a]



[a]The target compound **1** is available in four straightforward synthetic steps from commercially available *o*-aminobenzyl alcohol in 40% overall yield. See Supporting Information for experimental details.

Table 1. Reaction Optimization



entry	solvent	irraditation time (min)	azide equivalents	yield (%)[a]
1	tetrahydrofuran	3	1	3
2	tetrahydrofuran	3	2	3
3	tetrahydrofuran	3	5	13
4	tetrahydrofuran	3	10	23
5	chloroform	3	1	47
6	chloroform	3	2	56
7	chloroform	3	5	65
8	chloroform	3	10	61
9	dioxane	3	1	25
10	dioxane	3	2	28
11	dioxane	3	5	39
12	dioxane	3	10	46
13	acetonitrile	0.1	1	2
14	acetonitrile	1	1	56
15	acetonitrile	3	1	82
16	acetonitrile	5	1	83
17	acetonitrile	3	2	90
18	acetonitrile	3	5	97
19	acetonitrile	3	10	98

[a]All yields were calculated from fitting HPLC peak area to a standard curve for the click product (see Supporting Information for details).

Satisfied with the optimized reaction conditions, we set out to explore the reaction scope. Yields were generally good (68–88%) with the notable exception of the phenyl azide series with *p*-nitrophenyl azide managing only a 3% yield of the expected product (**9**) (Figure 2). These lower yields are potentially due to formation of nitrenes upon photolysis of the azides.[24−26]

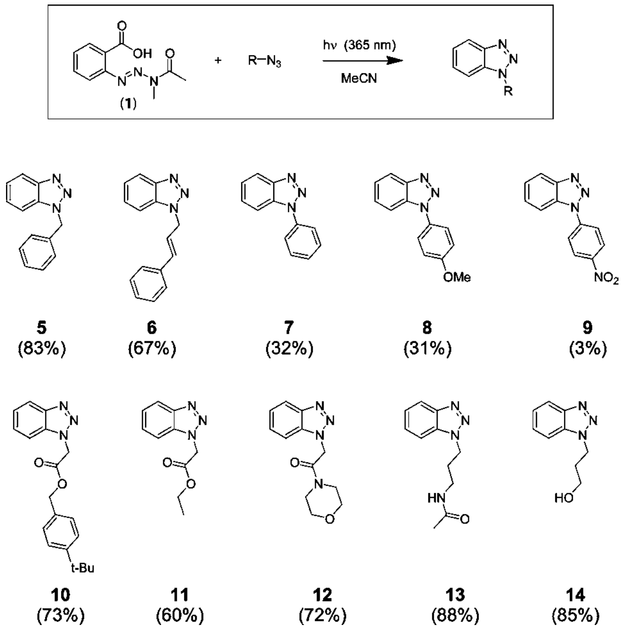


Figure 2. Scope of our photoinduced, benzyne click reaction. All reactions were executed on 15 mM (0.75 μM compound **1**) scale at room temperature using an LED light source (3 min irradiation) and 1 equiv of azide. Yields were obtained from fitting spectroscopic data to standard curves for each compound. Each yield is an average of three reactions (see Supporting Information).

Overall, the reaction appears to be quite tolerant of common functional groups including alcohols, amides, esters, alkenes, and ethers, and in all cases both LC retention times and mass profiles matched perfectly with authentic standards prepared via the Larock method.[15]

With an eye for potential downstream applications, we were motivated to examine the water tolerance of this chemistry (Figure 3). In our hands, the fluoride induced benzyne click reaction was effectively stalled when even small amounts (~5%) of water were introduced presumably due to fluoride sequestration (data not shown). Therefore, we were pleasantly surprised to find detectable product formation in acetonitrile solution with up to 70% water content, the limit of solubility for compound **1**. As above, these results were obtained using only 1 equiv of azide, which bodes well for future development of this chemistry aimed at applications in aqueous environments.

In summary, we have developed a photoinitiated, benzyne click reaction. The reaction is complete on the minute time scale in acetonitrile using a simple LED light source and a single equivalent of azide although higher azide equivalents do lead to increased efficiency. A wide variety of functional groups are tolerated, and yields are generally good with the exception of phenyl azides as coupling partners. In addition, the benzyne photoprecursor is very stable at room temperature under ambient light (see Supporting Information) and is available in four synthetic steps from commercially available starting materials without the need for chromatographic purification of any synthetic intermediates. Finally, unlike chemically induced benzyne click reactions, the photochemical process is quite tolerant of water with observable product yields generated

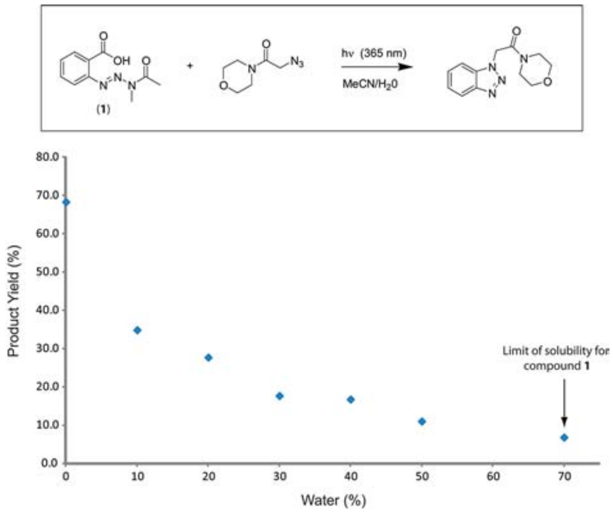


Figure 3. Water tolerance of our photoinduced, benzyne click reaction. Benzotriazole yields were obtained as above in acetonitrile solution with increasing water percentage. Above 70% water, the starting materials were insoluble. All reactions were executed on 15 mM (0.75 μM compound **1**) scale at room temperature using an LED light source (3 min irradiation) and 1 equiv of azide.

out to the limit of solubility of compound **1** in an acetonitrile/water solution.

We expect this transformation to be a valuable addition to the click chemistry toolbox for those interested in the spatiotemporal control that light-induced reactions offer. Although further optimization is required, we are confident that this chemistry will ultimately prove useful for applications in both organic and aqueous environments. The straightforward synthesis of compound **1** offers considerable potential for incorporation of tethers, targeting agents, and fluorophores onto the aromatic core. Lastly, development of alternative azides that lead to fluorescent benzotriazoles upon photoclick conjugation will further expand the possible applications of this chemistry. Efforts aimed at all of these improvements are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization of compounds, raw data for yield calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: schnarr@chem.umass.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by start-up funding from the University of Massachusetts, Amherst (to N.A.S. and J.J.C.). The authors would like to thank Mr. Thomas Sullivan (Berkshire Community College) for assistance in assembly and use of the LED light source.

■ REFERENCES

(1) Huisgen, R.; Szeimies, G.; Mobius, L. *Chem. Ber.-Recl.* **1967**, *100*, 2494.

(2) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 2004.

(3) Sletten, E. M.; Bertozzi, C. R. *Acc. Chem. Res.* **2011**, *44*, 666.

(4) Jewett, J. C.; Bertozzi, C. R. *Chem. Soc. Rev.* **2010**, *39*, 1272.

(5) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249.

(6) Nwe, K.; Brechbiel, M. W. *Cancer Biother. Radiopharm.* **2009**, *24*, 289.

(7) Yao, J. Z.; Uttamapinant, C.; Poloukhtine, A.; Baskin, J. M.; Codelli, J. A.; Sletten, E. M.; Bertozzi, C. R.; Popik, V. V.; Ting, A. Y. *J. Am. Chem. Soc.* **2012**, *134*, 3720.

(8) 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.

(9) Beatty, K. E.; Szychowski, J.; Fisk, J. D.; Tirrell, D. A. *ChemBioChem* **2011**, *12*, 2137.

(10) Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2004**, *126*, 15046.

(11) Debets, M. F.; van Berkel, S. S.; Dommerholt, J.; Dirks, A. T.; Rutjes, F. P.; van Delft, F. L. *Acc. Chem. Res.* **2011**, *44*, 805.

(12) Debets, M. F.; van Berkel, S. S.; Schoffelen, S.; Rutjes, F. P.; van Hest, J. C.; van Delft, F. L. *Chem. Commun.* **2010**, *46*, 97.

(13) Jewett, J. C.; Sletten, E. M.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 3688.

(14) Sletten, E. M.; Bertozzi, C. R. *Org. Lett.* **2008**, *10*, 3097.

(15) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409.

(16) Campbell-Verduyn, L.; Elsinga, P. H.; Mirfeizi, L.; Dierckx, R. A.; Feringa, B. L. *Org. Biomol. Chem.* **2008**, *6*, 3461.

(17) Arumugam, S.; Popik, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 5573.

(18) Lim, R. K.; Lin, Q. *Chem. Commun.* **2010**, *46*, 7993.

(19) Lim, R. K.; Lin, Q. *Acc. Chem. Res.* **2011**, *44*, 828.

(20) Starke, F.; Walther, M.; Pietzsch, H.-J. *ARKIVOC* **2010**, 350.

(21) Poloukhtine, A. A.; Mbua, N. E.; Wolfert, M. A.; Boons, G. J.; Popik, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 15769.

(22) Maki, Y.; Furuta, T.; Suzuki, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 553.

(23) Maki, Y.; Furuta, T.; Kuzuya, M.; Suzuki, M. *J. Chem. Soc., Chem. Commun.* **1975**, 616.

(24) Schnapp, K. A.; Platz, M. S. *Bioconjugate Chem.* **1993**, *4*, 178.

(25) Liu, L. H.; Yan, M. *Acc. Chem. Res.* **2010**, *43*, 1434.

(26) Nakanishi, K.; Zhang, H.; Lerro, K. A.; Takekuma, S.; Yamamoto, T.; Lien, T. H.; Sastry, L.; Baek, D. J.; Moquin-Pattey, C.; Boehm, M. F.; Derguini, F.; Gawinowicz, M. A. *Biophys. Chem.* **1995**, *56*, 13.