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PII: S0040-4039(13)01438-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.08.065
Reference: TETL 43428

To appear in: *Tetrahedron Letters*

Received Date: 22 July 2013
Revised Date: 15 August 2013
Accepted Date: 19 August 2013

Please cite this article as: Ellison, A., Boyer, R., Hoogestraat, P., Bell, M., Microwave Assisted Synthesis of Triazolobenzoxazepine and Triazolobenzoxazocine Heterocycles, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.08.065

Microwave Assisted Synthesis of Triazolobenzoxazepine and Triazolobenzoxazocine Heterocycles

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Abstract - Intramolecular click chemistry was utilized to effect synthesis of the benzofused, triazole ring systems. The trimethylsilyl group was found to impede the reaction progress, and therefore, conditions employing in situ removal of the TMS group coupled with microwave irradiation gives the penultimate targets with good conversion.

The synthesis of 1,2,3-triazole ring systems represents an interesting study in structural diversity.[1] The widespread application of a 1,3 dipolar cycloaddition with readily prepared substituted azides and alkynes offers a broad spectrum of triazole species containing unique structural elements.[2] The relatively straightforward chemistries applied to synthesize these analogs cement the triazole motif as a key heterocycle in the medicinal chemists' aresenal. Although general in nature, the subtleties of this complex annulation are significant and often require fine tuning synthetic conditions in order to achieve the desired regiochemical control. To this end, a number of authors have published papers describing the highly refined nature of a given set of conditions applied to ensure the most desirable outcome. The directed synthesis of 1,5-triazoles can be achieved through the use of silicon as a directing group,[5] or inclusion of ruthenium complexes.[11] The corresponding 1,4-isomer can usually be obtained with the addition of copper (I) iodide.[7] In many cases, nearly absolute regiochemical control can be obtained. The 1,2,3-triazole ring has established biologically relevant activity in a number of areas. Of recent interest include cardiovascular diseases,[1f] anti-HIV,[1e] and anti-bacterial agents,[1a,d] to name only a few. Given the ease of intermediate synthesis, the high degree of structural flexibility, and the biological importance of these molecules, investigative studies into the mechanistic understanding of different synthetic approaches offers a field worthy of exploration.

Over the course of the last decade, a number of benzofused heterocyclic systems have been targeted.[3,6] Interestingly, very few have broached the issue of a 1,3 dipolar cycloaddition to afford seven and eight membered fused triazole systems. Of note is the work by Alajarin et al in the synthesis of triazolobenzodiazepines,[6] where utilization of a novel triphenylphosphorane affords a number of N-phenyl triazole systems. Of particular interest to our group was the work of Chowdhury et al, in which a one pot synthesis of isoindolotriazoles is described,[3] and sufficient utility is demonstrated. However, the specific targeting of the triazolobenzoxazepine and triazolobenzoxazocine systems have yet to be described. Herein, we report the successful synthesis and characterization of both fused, tricyclic ring systems **1** and **2**, shown in Figure 1.

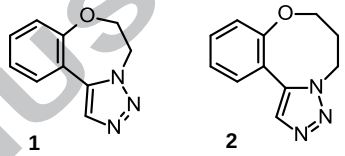
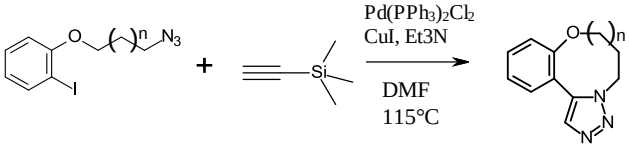


Figure 1. Triazolobenzoxazepine **1** and triazolobenzoxazocine **2**.

Initial scanning of the literature revealed the previously mentioned Chowdhury paper, and their convenient one pot synthesis of isoindolotriazoles. A number of structural analogs were prepared highlighting the utility of the reaction, noting minimal impact of substituting the alkyne on the overall yield. Further analysis of the proposed mechanism suggested that application to larger ring synthesis, while favourable according to Baldwin's rules, may not be quite as straightforward. In our hands, application of this route according to Scheme 1 provided **1** and **2,** in very low yield (12% and 10% yields, respectively). In this particular set of conditions, several aspects were hypothesized to conspire against a successful reaction. First, inherent entropic cost in preparing seven and eight membered rings cannot be discounted. Second, silicon containing alkynes, although directing to the 1,5 regioisomer, may decrease reaction rates not observed in the isoindolotriazole system. It is quite plausible that the activation energies required for the 1,3-dipolarcycloaddition with the silyl group intact, were sufficiently high as to impede the reaction. And third, the presence of even residual amounts of copper (I) iodide should actually retard the overall rate, as the reaction strives to deliver the preferred 1,4 regioisomer under those conditions.



n = 0, 12% yield
n = 1, 10% yield

Scheme 1. Penultimate step of the literature inspired synthesis of **1** and **2.**

Keywords: click chemistry, 1,3-dipolar cycloaddition, microwave, triazole.

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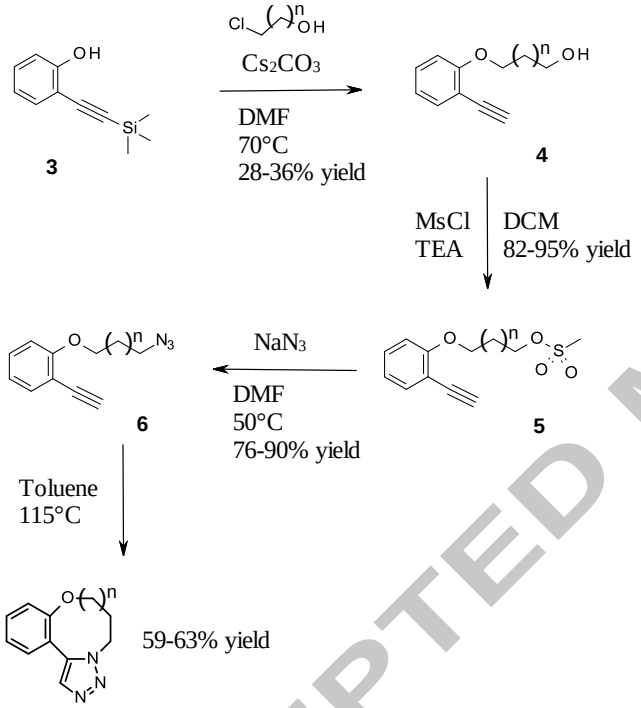
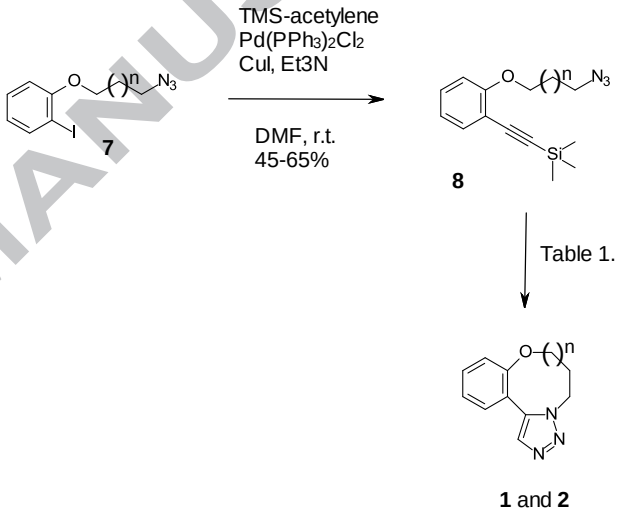
Contrary to synthesis of the isoindolotriazoles, in which CuI was required for appreciable yields, our lab sought to investigate dipolar click chemistry in order to obtain the targets in the absence of any additives. To this end, both benzofused triazole structures **1** and **2** above were prepared in good overall yield as shown in Scheme 2. From the commercially available 2-iodophenol, the trimethylsilylacetylene phenol **3** can be prepared according to literature methods.[9] The subsequent alkylation with either the chloroethanol or chloropropanol is accompanied with desilylation to give **4**. With the alcohol **4** in hand, the mesylate **5** is formed, followed by azide displacement in very good yield over both steps, to afford the key intermediate **6**.[8] Finally, subjecting the respective azido-alkynes to thermal click conditions provides the penultimate targets, **1** and **2** in good overall yields.



Scheme 2. Complete synthesis of the triazolobenzoxazepine and triazolobenzoxazocine systems.

The question remains as to why application of the one pot synthesis described by the Chowdhury group was not successful when applied to the triazolobenzoxazepine and triazolobenzoxazocine systems. Based on the yield of the dipolar cycloadditions to deliver **1** and **2**, simple entropic cost arguments can be discounted. Both reactions occurred in greater than 60% yields. This places the emphasis on either the silicon group or one or more reagents needed for the Sonagoshira coupling. In order to more fully assess this, the silicon containing azido alkynes **8** were prepared and a number of test reactions ensued as shown in Scheme 3. The advanced intermediate **7** was prepared in an analogous manner to **6**, simply starting with the 2-iodophenol in place of compound **3**, in excellent overall yield. Therefore according to Table 1, the data firmly points to the silicon group as the culprit. Whereas the cycloaddition works well in the absence of the TMS protecting group, inclusion of this motif retards the reaction to less than 20% conversion, demonstrating a significant reduction from 59-63% yield as shown in Scheme 2. Neither addition of CuI, nor the ruthenium catalyst improved the conversion compared to solvent alone. It is important to note, that in every case, there was a mixture of starting material, product, and then predominantly baseline material, possibly polymerization due to intermolecular reactions. Even after exhaustive analysis of crude mixtures, no other side products or minor components could be identified. Finally, additions of cesium fluoride and DMF (to aid solubility) showed rapid removal of the TMS group within four hours. Because conversion from the desilylated alkyne **6** to each product was already demonstrated, we set out to combine all of these learnings into one optimized set of conditions. Therefore, from the advanced intermediate **8**, cesium fluoride was used to effect an in situ desilylation. DMF was choosen to enhance solubility of cesium fluoride, but also is a suitable solvent for the extreme temperatures of microwave chemistry. Microwave irradiation was desirable to achieve high temperatures in a very short timeframe. Gratifyingly, all of these when taken together in a two-step, one pot reaction, provided excellent conversion to the respective products in thirty minutes.



Scheme 3. Optimized synthesis of the triazolobenzoxazepine and triazolobenzoxazocine systems.

Recognizing that the increased flexibility of the seven and eight membered rings gives rise to the potential for 1,5- and 1,4-regioisomers, we sought to confirm the desired isomer through NMR experiments (Figure 2). First, looking at the triazolobenzoxazocine systems, ^{13}C, ^{1}H NMR, and heteronuclear single quantum coherence (HSQC) experiments allowed for a reasonable identification of the key signals at C2 and H10. Next, heteronuclear multiple bond correlation (gHMBC) studies showed a long range correlation between C2 and H10 which further supported the 1,5-isomer **9**. This data was consistent for both ring systems, providing the necessary support for the given assignment.

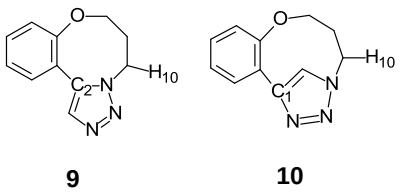


Figure 2. NMR experiments to confirm the 1,5-regioisomer.

In conclusion, we have successfully applied standard Huisgen 1,3-dipolar cycloaddition conditions to the synthesis of the triazolobenzoxazepine and triazolobenzoxazocine ring systems. Attempts to utilize the chemistry developed for the synthesis of the isoindolotriazole rings gave low yields and therefore a re-evaluation of the standard was employed to good success. Investigation into the reaction conditions revealed the trimethylsilyl group to be a rate limiting culprit. Interestingly, although the use of silicon as a directing group normally favors the desired 1,5 regioisomer, in the case of these two analogs, the reaction simply failed to progress in a reasonable timeframe. Further investigation into the reaction conditions demonstrated that in situ deprotection and subsequent cyclization could be achieved with cesium fluoride in DMF, and microwave heating, all within thirty minutes. NMR characterization confirmed formation of the assigned 1,5-isomers completing the first published synthesis of the triazolobenzoxazepine and triazolobenzoxazocine systems.

Table 1. Various reaction conditions optimizing **8** to **1** and **2**.

Ring System (n)	Solvent	Additive	Temp (^{o}C)	LCMS[d] % Conversion
0	Toluene	---	115	23%
1	Toluene	---	115	19%
0	Toluene	CuI	100	20%
0	Toluene	Ru[a]	100	30%
1	Toluene	CuI	115	21%
1	Toluene	Ru[a]	115	17%
0	Toluene	CsF	100	0%
0	Toluene/DMF	CsF	100	100%[b]
0	DMF	CsF	180 [c]	61%
1	DMF	CsF	180 [c]	87%

[a] Chloro(cyclopentadienyl)bis(triphenylphosphine)ruthenium (II) [b] Complete conversion to desilylated intermediate with less 10% product after 4 hours. [c] microwave irradiation, 30 minutes. [d] Liquid chromatography – mass spectroscopy.

[1] a) M. J. Genin, D. A. Allwine, D. J. Anderson, M. R. Barbachyn, D. E. Emmert, S. A. Garmon, D. R. Graber, K. C. Grega, J. B. Hester, D. K. Hutchinson, J. Morris, R. J. Reischer, C. W. Ford, G. E. Zurenko, J. C. Hamel, R. D. Schaadt, D. Stapert, and B. H. Yagi *J. Med. Chem.* ,**2000** *, 43*, 953; b) A. K. Mandadapu, S. K. Sharma, S. Gupta, D. G. V. Krishna, and B. Kundu. *Org. Lett*. **2011**, *13* (12), 3162–3165; c) F. Suzuki, T. Kuroda, T. Kawakita, H. Manabe, S. Kitamura, K. Ohmori, M. Ichimura, H. Kase, S. Ichikawa *J. Med. Chem*. **1992**, *35* (26), 4866–4874; d) M. Yamada, S. Hamamoto, K. Hayashi, K. Takaoka, H. Matsukura, M. Yotsuji, K. Yonezawa, K. Ojima, T. Takamatsu, K. Taya, H. Yamamoto, T. Kiyoto, H. Kotsubo, PCT Int. Appl., WO 9921849, **1999**; e) R. Alvarez, S. Velazquez, F. San, S. Aquaro, C. De-Clercq, C. Perno, A. Karlsson, J. Balzarini, M. J. Camarasa, *J. Med. Chem.* **1994**, *37*, 4185–4194; f) M. G. Bell, R. A. Doti, M. S. Dowling, M. J. Genin, P. A. Lander, T. Ma, N. B. Mantlo, J. M. Ochoada, L. S. Stelzer, R. E. Stites, A. M. Warshawsky, US 8106077, **2012**.

[2] a) R. Huisgen, Pure Appl. Chem., **1989**, 61, 613; b) R. Huisgen, In 1,3-Dipolar Cycloaddition chemistry, A. Padwa, Ed., Wiley, New York, NY, **1984**, pp. 1-176.

[3] C. Chowdhury, S. Mandal, B. Achari, *Tetrahedron Lett*., **2005**, *46*, 8531-8534.

[4] Yamakoshi et al, *ACS Med. Chem. Lett.,* **2010** *, 1*, 273-276.

[5] S. Coats, J. Link, D. Gauthier, and D. Hlasta, *Organic Letters*, **2005**, *7*, 1469-1472.

[6] M. Alajarin, J. Cabrera, A. Pastor, J. M. Villalgordo, *Tetrahedron. Lett*., **2007**, 3495-3499.

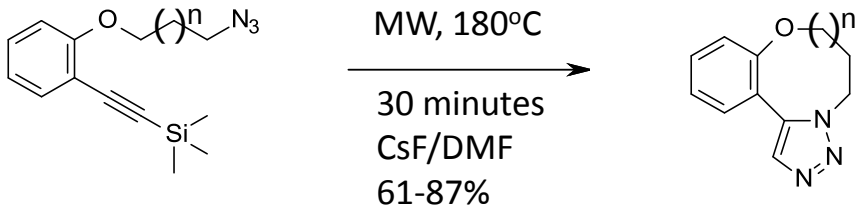
[7] V. Rostovtsev, L. Green, V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, p. 2596-2599.

[8] H. Yamakoshi, N. Kanoh, C. Kudo, A. Sato, K. Ueda, M. Muroi, S. Kon, M. Satake, H. Ohori, C. Ishioka, Y. Oshima, H. Osada, N. Chiba, H. Shibata, and Y. Iwabuchi, *ACS Med. Chem. Lett.,* **2010**, *1*, 273-276.

[9] M. Khan, M. Alam, M. Rashid, R. Chowdhury, *Bioorg. Med. Chem.* **2005**, *13*, 4796-4805.

[10] B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin*, J. Am. Chem. Soc*., **2008**, *130*, 8923-8930.

[11] B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, *J. Am. Chem. Soc*., **2008**, *130*, 8923-893.



1: Triazolobenzoxazepine, n = 0

2: Triazolobenzoxazocine, n = 1