

A Microwave-Assisted Click Chemistry Synthesis of 1,4-Disubstituted 1,2,3-Triazoles via a Copper(I)-Catalyzed Three-Component Reaction

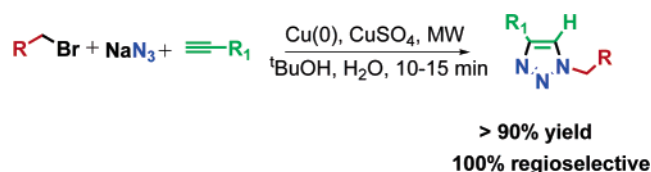
Prasad Appukkuttan,[†] Wim Dehaen,[†] Valery V. Fokin,^{*,‡} and Erik Van der Eycken^{*,†}

Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium, and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

erik.vandereycken@chem.kuleuven.ac.be; fokin@scripps.edu

Received August 20, 2004

ABSTRACT



A microwave-assisted three-component reaction was used to prepare a series of 1,4-disubstituted-1,2,3-triazoles from corresponding alkyl halides, sodium azide, and alkynes. This procedure eliminates the need to handle organic azides, as they are generated in situ, making this already powerful click process even more user-friendly and safe.

The ever increasing demand for novel medicinally active compounds and the laborious process of lead discovery and optimization have resulted in the continuous search for simple and efficient methods for generation of libraries for biological screening. “Click chemistry” has emerged as a fast and efficient approach to synthesis of novel compounds with desired function making use of selected “near perfect” reactions.¹ The Huisgen 1,3-dipolar cycloaddition² of azides and alkynes resulting in 1,2,3-triazoles is one of the most powerful click reactions. Several members of the 1,2,3-triazole family have indeed shown interesting biological properties, such as anti-allergic,³ anti-bacterial,⁴ and anti-HIV activity.⁵ Additionally, 1,2,3-triazoles are found in herbicides, fungicides, and dyes.⁶ The recently discovered copper(I) catalysis of this transformation,⁷ which accelerates

the reaction up to 10⁷ times, has placed it in a class of its own and has enabled many novel applications.⁸ To further improve the utility and user-friendliness of this process, we developed its practical multicomponent variant described herein. The azides are generated in situ from corresponding halides,⁹ whereupon they are captured by copper(I) acetyl-

(3) (a) Buckle, D. R.; Rockell, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 627–630. (b) Buckle, D. R.; Outred, D. J.; Rockell, C. J. M.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1983**, 26, 251–254. (c) Buckle, D. R.; Rockell, C. J. M.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1986**, 29, 2269–2267.

(4) Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, 43, 953–970.

(5) Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; Perno, C.-F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, 37, 4185–4194.

(6) Wamhoff, H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 5, pp 669–732.

(7) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, 41, 2596–2599. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, 67, 3057–3064. (c) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. R.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. chem. Soc.* **2004**, in press.

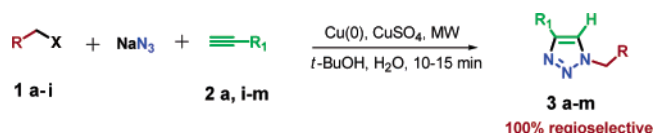
[†] University of Leuven.

[‡] The Scripps Research Institute.

(1) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, 40, 2004–2021. (b) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, 8, 1128–1137.

(2) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984.

Scheme 1. Microwave-Assisted Three-Component Synthesis of 1,4-Disubstituted 1,2,3-Triazoles **3a–m**



ides, forming the corresponding 1,4-disubstituted-1,2,3-triazoles (Scheme 1). Performing both steps of this process under microwave irradiation¹⁰ significantly reduces the time of the reaction. Products are easily isolated by simple filtration. As the starting point of our exploration, we chose the reaction between benzyl bromide **1a** and phenylacetylene **2a**. The alkyne, alkyl halide, and sodium azide were suspended in a 1:1 mixture of *t*-BuOH and water, together with the catalyst, in a 10-mL sealed glass vial. The Cu(I) catalyst was prepared in situ by the comproportionation of Cu(0) and Cu(II). After 10 min of irradiation and subsequent cooling to room temperature, the triazole product crystallized from the reaction mixture and was isolated by simple filtration. Comparison with an authentic sample established that the triazole was formed in a completely regioselective manner, with no contamination by the 1,5-regioisomer. The best conditions were found to be 100 W irradiation power

(8) (a) Punna, S.; Diaz, D. D.; Li, C.; Sharpless, K. B.; Fokin, V. V.; Finn, M. G. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **2004**, 45, 778–779. (b) Lee, L. V.; Mitchell, M. L.; Huang, S.-J.; Fokin, V. V.; Sharpless, K. B.; Wong, C.-H. *J. Am. Chem. Soc.* **2003**, 125, 9588–9589. (c) Seo, T. S.; Li, Z.; Ruparel, H.; Ju, J. *J. Org. Chem.* **2003**, 68, 609–612. (d) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, 125, 3192–3193. (e) Löber, S.; Rodríguez, P.-L.; Gmeiner, P. *Org. Lett.* **2003**, 5, 1753–1755; Perez, F.-B.; Ortega, M.-M.; Morales, J.-S.; Hernández, F.-M.; Calvo, F. G. –F.; Calvo, J. A.-A.; Isac, J.-G.; Santoyo, F.-G. *Org. Lett.* **2003**, 5, 1951–1954.

(9) To the best of our knowledge, there is only one report describing an in situ formation of 1,2,3-triazoles from alkyl halides, alkynes, and sodium azide. The methodology reported therein requires heating at high temperatures for an extended period of time (up to 18 h), results in low yields of the products, and produces both 1,4- and 1,5-regioisomers. See: Maksikova, A. V.; Serebryakova, E. S.; Tikhonova, L. G.; Vereshagin, L. I. *Chem. Heterocycl. Compd.* **1980**, 1284–1285.

(10) (a) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, 57, 9225–9283. (b) Lidström, P.; Westman, J.; Lewis, A. *Comb. Chem. High Throughput Screening* **2002**, 6, 441–458. (c) Kappe, C. O. *Curr. Opin. Chem. Biol.* **2002**, 6, 314–320. (d) Larhed, M.; Möberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, 35, 717–727. (e) Loupy, A. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002 and references therein. (f) Perez-Balderas, F.; Ortega-Munoz, M.; Morales-Sanfrutos, J.; Hernandez-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asin, J. A.; Isac-Garcia, J.; Santoyo-Gonzalez, F. *Org. Lett.* **2003**, 5, 1951–1954. (g) Sing, P. N. D.; Muthukrishnan, S.; Murthy, R. S.; Kilma, R. F.; Mandel, S. M.; Hawk, M.; Yarbrough, N.; Gudmundsdóttir, A. D. *Tetrahedron Lett.* **2003**, 44, 9169–9171.

(11) **Typical Experimental Procedure.** (ATTENTION: copper azides are shock-sensitive when dry. Care should be taken to remove traces of these compounds from the products by washing with basic ammonium citrate or dilute HCl). Benzyl bromide (0.170 g, 1.0 mmol), phenylacetylene (0.107 g, 1.05 mmol), and sodium azide (0.068 g, 1.05 mmol) were suspended in a 1:1 mixture of water and *t*-BuOH (1.5 mL each) in a 10-mL glass vial equipped with a small magnetic stirring bar. To this was added copper turnings (50 mg) and copper sulfate solution (1 M, 200 μL), and the vial was tightly sealed with an aluminum/Teflon crimp top. The mixture was then irradiated for 10 min at 125 °C, using an irradiation power of 100 W. After completion of the reaction, the vial was cooled to 50 °C by air jet cooling before it was opened. It was then diluted with water (20 mL), and precipitated product was collected by filtration and washed with cold water (20 mL), followed by 0.25 M HCl (10 mL), and finally with petroleum ether (50 mL) to furnish **3a** as a white solid (0.219 g, 93%).

Table 1. One-Pot Synthesis of 1,2,3-Triazoles from Alkyl Halides, Sodium Azide, and Phenylacetylene^a

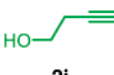
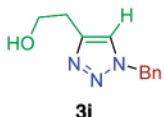
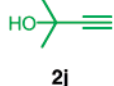

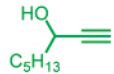
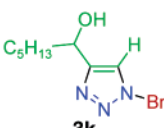
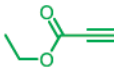

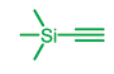

no.	halide	product	time (min)	yield (%)
1			10	93
2			10	91
3			10	86
4			10	84
5			15	87
6			15	91
7			10	90
8			10	88
9			10	89

^a All reactions were carried out on a 1 mmol scale at 125 °C, using 100 W irradiation power; 1.05 equiv each of sodium azide and alkyne were used with 1.0 equiv of halide in 3 mL of a 1:1 water/*t*-BuOH mixture, with 50 mg of Cu turnings and 200 μL of 1 M CuSO₄ solution.

and 125 °C. The product, 1-benzyl-4-phenyl-1*H*-1,2,3-triazole¹¹ (**3a**), has been isolated in 93% yield (Table 1, entry 1). This prompted us to extend our studies toward the incorporation of different alkyl halides (Table 1, entries 2–9).

As exemplified in Table 1, the reactions proceeded smoothly to completion, and the products were isolated in excellent yields and high purity. The *o*-nitro- and trimethoxybenzyl derivatives **1d** and **1e** were found to be less reactive than other halides. However, the reactions were finished (as analyzed by TLC and CI-MS) in 15 min, and products **3d** and **3e** were isolated in 87% and 91% yields, respectively.

Table 2. One-Pot Synthesis of 1,2,3-Triazoles from Benzyl Bromide, NaN₃, and Alkynes^a

no.	alkyne	product	temp (°C)	time (min)	yield (%)
1	 2i	 3i	125	10	81
2	 2j	 3j	125	10	84
3	 2k	 3k	125	10	89
4	 2l	 3l	75	15	83
5	 2m	 3m	75	15	88

^a All reactions were carried out on 1 mmol scale; 1.05 equiv each of azide and alkyne were used with 1.0 equiv of halide in 1.5 mL each of water and *t*BuOH, 50 mg of Cu turnings, and 200 μ L of 1 M CuSO₄ solution.

When methyl iodide **1h** was used as the halide, the reaction proceeded smoothly in 10 min, and the product **3h** was isolated in 89% yield (entry 9). This example clearly demonstrates the power of the new strategy, as the synthesis of **3h** is otherwise difficult owing to the hazardous nature of methyl azide.

The scope of the reaction regarding the alkyne component was then examined and was found to be excellent. Benzyl azide was formed in situ from benzyl bromide **1a** and sodium azide. Alkynes containing various functionalities participated in the three-component process, as Table 2 shows. The yields remained good to excellent, and regioselectivity was exclusive: only 1,4-regioisomeric products were formed.

Most reactions easily tolerated the 125 °C temperature and the 100 W power that was applied (Table 2, entries 1–4). However, in case of ethyl propiolate **2l** (Table 2, entry 5) and trimethylsilyl acetylene **2m** (Table 2, entry 6), the high temperature resulted in diminished yields. Reducing the temperature to 75 °C circumvented this problem, and products **3l** and **3m** were isolated in good yields (83% and 88%, respectively).

In conclusion, a microwave-enhanced, fast, and efficient three-component reaction for generation of 1,4-disubstituted-1,2,3-triazoles in a completely regioselective manner has been developed. The method avoids isolation and handling of potentially unstable small organic azides and provides triazole products in pure form. Microwave irradiation dramatically decreases reaction time from hours to minutes. 1,2,3-Triazole products often crystallize from the reaction mixture and do not require any purification, rendering the process an ideal multicomponent click reaction.

Acknowledgment. We are grateful to Prof. K. Barry Sharpless for his advice. We thank the F.W.O. (Fund for Scientific Research-Flanders (Belgium)) and the Research Fund of the University of Leuven for financial support to the laboratory. P.A. is grateful to the University of Leuven for obtaining a scholarship. V.V.F. thanks Biotage AB for providing a Microwave Synthesizer under the Scientific Partnership Program. We also wish to thank Mr. K. Duerinckx for his valuable help with NMR experiments.

Supporting Information Available: Characterization data (¹H, ¹³C, and DEPT NMR, EI-MS) of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL048341V