ORGANIC LETTERS

2004
Vol. 6, No. 22
3897−3899

One-Pot Synthesis of 1,4-Disubstituted 1,2,3-Triazoles from In Situ Generated Azides

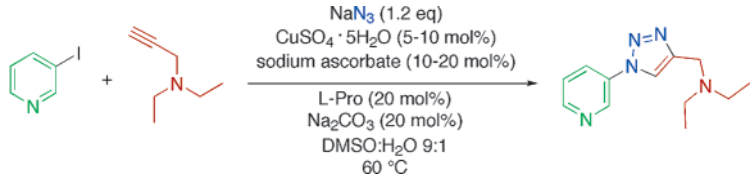
Alina K. Feldman, Benoît Colasson, and Valery V. Fokin*

Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

fokin@scripps.edu

Received June 16, 2004

ABSTRACT



1,4-Disubstituted 1,2,3-triazoles are obtained in excellent yields by a convenient one-pot procedure from a variety of readily available aromatic and aliphatic halides without isolation of potentially unstable organic azide intermediates.

Cu(I)-catalyzed ligation of organic azides and terminal alkynes has enjoyed much use since its discovery. Exclusive regioselectivity, wide substrate scope, mild reaction conditions, and very high yields[1] have made it the method of choice for making permanent connections by means of 1,4-disubstituted 1,2,3-triazoles. The methodology has found applications in drug discovery, bioconjugations, and materials science.[2]

Although organic azides are generally safe compounds, those of low molecular weight can be unstable and, therefore, difficult to handle.[3] This is especially true for small molecules with several azide functionalities that would be of much interest for the generation of polyvalent structures. Thus, a methodology that avoids isolation of organic azides is desirable.

Aliphatic azides can be readily prepared from the corresponding halides by nucleophilic displacement or, in cases of aryl and vinyl azides, by a Cu(I)-catalyzed reaction (vide infra) with sodium azide. The substitution is especially facile when activated halides, such as allylic, propargylic, and benzylic, are used. Herein, we report an efficient and safe one-pot, two-step procedure for trapping thus generated azides by alkynes to obtain the corresponding triazole products (Table 1).[4]

The reagents were simply mixed in a vial (0.5 M) and stirred overnight. In most cases, the pure products were isolated by filtration. Furthermore, the efficiency of each step is retained in this one-pot procedure (the formation of tris-triazolyl derivative **3d**, entry 4, requires six reactions).

When the nucleophilic substitution of the halide is less efficient, the competing formation of an N−H triazole is observed. Inorganic azide adds to the alkyne, producing N−H triazole byproducts. Further studies to eliminate this undesired pathway are currently underway.

(1) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornœ, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

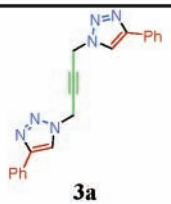
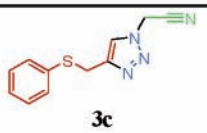
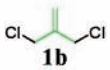
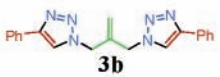
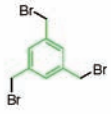
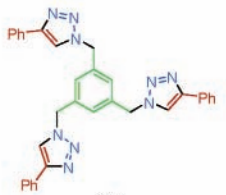
(2) For recent examples of the azide−acetylene ligation reaction, please see: (a) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192. (b) Speers, A. E.; Adam, G. C.; Cravatt, B. F. *J. Am. Chem. Soc.* **2003**, *125*, 4686. (c) Anderson, J. C.; Schultz, P. G. *J. Am. Chem. Soc.* **2003**, *125*, 11782. (d) Link, A. J.; Tirrell, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 11164. (e) Collman, J. P.; Devaraj, N. K.; Chidsey, C. E. D. *Langmuir* **2004**, *20*, 1051. (f) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2004**, *43*, 3928−3932.

(3) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *2*, 351.

(4) 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. This method requires heating the reagents at high temperatures for extended periods of time, resulting in a mixture of both regioisomers, and gives low yields. Maksikova, A. V.; Serebryakova, E. S.; Tikhonova, L. G.; Vereshagin, L. I. *Chem. Heterocycl. Comp.* **1980**, 1284.

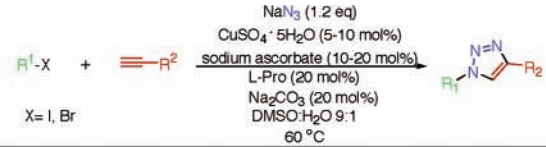
10.1021/ol048859z CCC: $27.50
Published on Web 09/25/2004

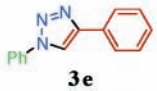
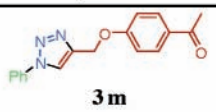
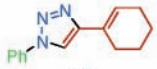
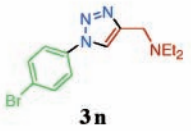
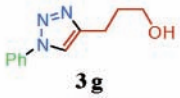
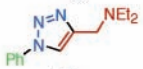
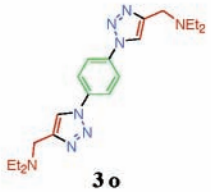
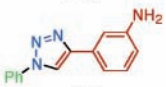
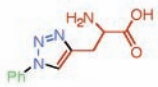
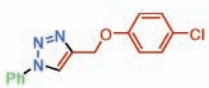
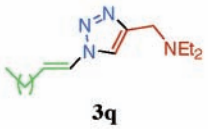
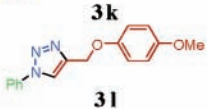
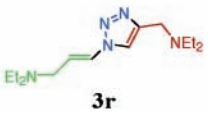
Table 1. One-Pot Synthesis of 1,2,3-Triazoles from Alkyl Halides, NaN_3, and Alkynes

entry	halide	product	yield (%)[b]	entry	halide	product	yield (%)[b]
1	 **1a**	 **3a**	84	3	 **1c**	 **3c**	72
2	 **1b**	 **3b**	83	4	 **1d**	 **3d**	93

[a] Performed with 1.2 equiv of NaN_3, 5 mol % $CuSO_4 \cdot 5H_2O$, and 10 mol % sodium ascorbate per halide functionality; all reactions were performed at ambient temperature, except for reaction 4 (65 °C). [b] Isolated yield.

Table 2. One-Pot Synthesis of 1,2,3-Triazoles from Aryl and Vinyl Halides, NaN_3, and Alkynes



entry	halide	product	yield(%)[a]	entry	halide	product	yield(%)[a]
1	 **1e**	 **3e**	84	9		 **3m**	87
2		 **3f**	74	10	 **1f**	 **3n**	78
3		 **3g**	98				
4		 **3h**	90	11	 **1g**	 **3o**	66
5		 **3i**	74				
6		 **3j**	52[b]	12	 **1h**	 **3p**	94
7		 **3k**	83	13	 **1i**	 **3q**	73
8		 **3l**	76	14	 **1j**	 **3r**	73

[a] Isolated yield. [b] Due to high water solubility, some product was lost during isolation.

The methods for generation of aryl and vinyl azides that would be compatible with the copper catalysis have not been available until now. We were, therefore, pleased to find that a recently published report describing preparation of aryl and vinyl azides from the corresponding halides via a Cu(I)-catalyzed proline-promoted reaction[5] provided a convenient route to the azide intermediates used in a one-pot method.

The results are summarized in Table 2. After screening a variety of copper sources, ligands, and solvent combinations, we arrived at the experimentally simple and safe general procedure for this one-pot two-step process.[6] Under the optimized conditions, the triazole products are obtained in good yields, and formation of the undesired N−H triazole byproducts is suppressed. The regioselectivity of the reaction is maintained even at the elevated temperatures.

As is the case with the parent reaction,[1a] the one-pot process exhibits excellent scope with regards to both the halide and the alkyne components.

Since aryl iodides are generally more reactive than the corresponding bromides, the *p*-bromo iodobenzene **1f** was successfully converted to the mono-triazole product **3n** without affecting the aryl bromide functionality, thus making it available for further transformations. Heteroaryl halides such as 3-iodopyridine **1h** also readily participate in this process.

Even though reactivity of alkenes with azides is generally higher than of alkynes, we successfully converted vinyl iodides to the corresponding allylic triazole derivatives (entries 13 and 14).

In conclusion, a safe and efficient method for the synthesis of 1,4-disubstituted 1,2,3-triazoles directly from a variety of alkyl and aryl halides, sodium azide, and terminal alkynes has been developed. The procedure does not require isolation of the azide intermediates and should prove to be especially useful when unstable low-molecular weight and polyvalent azides are needed.

Acknowledgment. We thank Prof. K. Barry Sharpless for his scientific advice. We thank the National Institute of General Medical Sciences, the National Institutes of Health (GM-28384), and Pfizer, Inc., for financial support. B.C. thanks the French Ministère des Affaires Etrangères for the Lavoisier fellowship. A.K.F. thanks the Skaggs Foundation for a graduate fellowship.

Supporting Information Available: Spectral characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048859Z

(5) Zhu, W.; Ma, D. *Chem. Commun.* **2004**, *7*, 888.

(6) **Typical Experimental Procedure A.** Products precipitate from the reaction mixture. Iodobenzene **1e** (102 mg, 0.5 mmol, 1 equiv) was mixed with 1-chloro-4-prop-2-ynyloxy-benzene **2g** (84 mg, 0.5 mmol, 1 equiv) in a 20 mL scintillation vial. To the mixture were added L-proline (12 mg, 0.1 mmol, 0.2 equiv), Na_2CO_3 (12 mg, 0.1 mmol, 0.2 equiv), NaN_3 (39 mg, 0.6 mmol, 1.2 equiv), sodium ascorbate (20 mg, 0.05 mmol, 0.1 equiv), 9:1 DMSO/H_2O (1 mL), and $CuSO_4 \cdot 5H_2O$ (13 mg, 0.025 mmol, 0.05 equiv). The mixture was stirred overnight at 65 °C. Upon completion (monitored by TLC or LC-MS), the crude mixture was poured into 30 mL of ice-cold water. The off-white precipitate was isolated by filtration and washed with dilute NH_4OH (ATTENTION: this step is important, as copper azides are explosive when dry, and their traces should be removed before the product is dried) to yield **3k** as an off-white solid (211 mg, 83%). **Typical Experimental Procedure B.** Products do not precipitate from the reaction mixture. 3-Iodopyridine **1h** (103 mg, 0.5 mmol, 1 equiv) is mixed with 3-diethylamino-1-propyne (56 mg, 0.5 mmol, 1 equiv) in a 20 mL scintillation vial. To the mixture were added L-proline (12 mg, 0.1 mmol, 0.2 equiv), Na_2CO_3 (12 mg, 0.1 mmol, 0.2 equiv), NaN_3 (39 mg, 0.6 mmol, 1.2 equiv), sodium ascorbate (20 mg, 0.05 mmol, 0.1 equiv), 9:1 DMSO/H_2O (1 mL), and $CuSO_4 \cdot 5H_2O$ (13 mg, 0.025 mmol, 0.05 equiv). The mixture was heated overnight at 65 °C. Upon completion (monitored by TLC or LC-MS), the crude mixture was poured into dilute NH_4OH (30 mL; ATTENTION: this step is important, as copper azides are explosive when dry, and their traces should be removed before the product is dried) and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with brine (2 × 20 mL), dried over $MgSO_4$, and evaporated to yield **3p** as a pale yellow oil (112 mg, 94%).