ORGANIC LETTERS

2008
Vol. 10, No. 6
1267−1269

Copper-Catalyzed Multicomponent Reaction: Facile Access to Novel Phosphorus Amidines

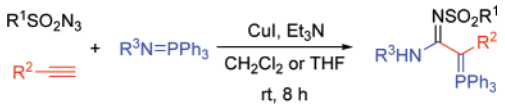
Sun-Liang Cui, Jing Wang, and Yan-Guang Wang*

Department of Chemistry, Zhejiang University, Hangzhou 310027, P.R. China

orgwyg@zju.edu.cn

Received January 22, 2008

ABSTRACT



The synthesis of a novel class of phosphorus amidines via a copper-catalyzed multicomponent reaction of sulfonyl azides, alkynes and iminophosphoranes is described. The protocol is efficient and general.

The amidine functional group is found in many biological molecules[1] and is widely used in heterocyclic synthesis.[2] The benzamidine variant is often employed as an excellent guanidine surrogate in medicinal chemistry.[3] Consequently, a number of synthetic methods have been developed for the preparation of amidines. Most of these methods rely on the nucleophilic addition of amines or ammonia equivalents to nitriles under forcing conditions or to suitably activated carboxylate equivalents, such as imidoyl chlorides, imidoylbenzotriazoles, imidates, and thioimidates,[4] while transition metal-catalyzed strategies have also been investigated for the synthesis of amidines.[5] We herein report a copper-catalyzed three-component domino approach to a novel class of phosphorus amidines.

Iminophosphoranes have attracted much attention due to their wide application in organic synthesis since they were first prepared in 1919 by Staudinger and Meyer.[6] As isoelectronic compounds of the Wittig reagent, iminophosphoranes were proved to have versatile properties and to undergo a series of interesting chemical reactions.[7] Previously, we developed three-component reactions of sulfonyl azides, alkynes and salicaldehydes, 2-acylanilines or aziridines, which furnished iminocoumarins, 2-imino-1,2-dihydroquinolines and 5-arylidene-2-imino-3-pyrrolines, respectively.[8] The domino process involves a *N*-sulfonyl keteneimine intermediate *in situ* generated from the copper-catalyzed cycloaddition of sulfonyl azide and terminal alkyne.[5a,9] We anticipated that this kind of keteneimine intermediates would

(1) Patai, S.; Rappoport, Z. *The Chemistry of Amidines and Imidates*; Wiley: New York, 1991; Vol. 27.

(2) (a) Nötzel, M. W.; Rauch, K.; Labahn, T.; de Meijere, A. *Org. Lett.* **2002**, *4*, 839−841. (b) Szczepankiewicz, B. G.; Rohde, J. J.; Kurukulasuriya, R. *Org. Lett.* **2005**, *7*, 1833−1835.

(3) (a) Zablocki, J. A.; Miyano, M.; Garland, R.; Pireh, D.; Schretzman, L.; Rao, S. N.; Lindmark, R. J.; Panzer-Knodle, S. G.; Nicholson, N. S.; Taite, B. B.; Salyers, A. K.; King, L. W.; Campion, J. G.; Feigen, L. P. *J. Med. Chem.* **1993**, *36*, 1811−1819. (b) Greenhill, J. V.; Lue, P. In *Amidines and Guanidines in Medicinal Chemistry, Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier: New York, 1993; Vol. 30, Chapter 5, pp 203−326.

(4) (a) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347−1350. (b) Katritzky, A. R.; Cai, C. M.; Singh, S. K. *J. Org. Chem.* **2006**, *71*, 3375−3380 and the cited references.

(5) (a) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038−2039. (b) Chang, S.; Lee, M.; Jung, D. Y.; Yoo, E. J.; Cho, S. H.; Han, S. K. *J. Am. Chem. Soc.* **2006**, *128*, 12366−12367. (c) Kissounko, D. A.; Hoerter, J. M.; Guzei, I. A.; Cui, Q.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 1776−1783. (d) Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. *Org. Lett.* **2002**, *4*, 983−985.

(6) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635−646.

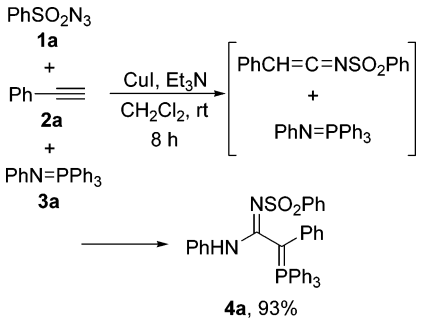
(7) (a) Eric, F. V. S.; Kenneth, T. *Chem. Rev.* **1988**, *88*, 297−368. (b) Johnson, A. W. *Ylides and Imines of Phosphorus*; John Wiley & Sons: New York, 1993. (c) Monina, P.; Alajarín, M.; López-Leondardo, C.; Claramunt, R. M.; Foces-Foces, M. C.; Cano, F. H.; Catalán, J.; de la Paz, J. L. G.; Elguero, J. *J. Am. Chem. Soc.* **1989**, *111*, 355−363. (d) Molina, P.; Alajarín, M.; Vidal, A. *J. Org. Chem.* **1992**, *57*, 6703−6711. (e) Alajarín, M.; Ortín, M. M.; Sanchez-Andrada, P.; Vidal, A.; Bautista, D. *Org. Lett.* **2005**, *7*, 5281−5284. (f) Alajarín, M.; Ortín, M. M.; Sanchez-Andrada, P.; Vidal, A. *J. Org. Chem.* **2006**, *71*, 8126−8139. (g) Alajarín, M.; Bonillo, B.; Sanchez-Andrada, P.; Vidal, A.; Bautista, D. *J. Org. Chem.* **2007**, *72*, 5863−5866.

(8) (a) Cui, S. L.; Lin, X. F.; Wang, Y. G. *Org. Lett.* **2006**, *8*, 4517−4520. (b) Cui, S. L.; Wang, J.; Wang, Y. G. *Tetrahedron* **2008**, *64*, 487−492. (c) Cui, S. L.; Wang, J.; Wang, Y. G. *Org. Lett.* **2007**, *9*, 5023−5025.

10.1021/ol800160q CCC: $40.75
Published on Web 02/20/2008

react with iminophosphoranes through a [2+2] cycloaddition to yield 1,2,4-phosphadiazetidines[7c,7d] or 1,2-phosphazetidines as intermediates,[10] which undergo subsequent domino reactions to give some interesting products. In this regard, we investigated the three-component reaction of sulfonyl azide (**1a**, 0.6 mmol), phenylacetylene (**2a**, 0.6 mmol) and iminophosphorane (**3a**, 0.5 mmol) in the presence of CuI (0.1 mmol) and Et_3N (1 mmol) (Scheme 1). We found that the

Scheme 1



reaction afforded a phosphorus-containing amidine **4a** in 93% yield.

The structure of **4a** was unambiguously confirmed by X-ray analysis (Figure 1), which is in accordance with ^1H NMR, ^{13}C NMR, ^{31}P NMR, and HRMS spectra.

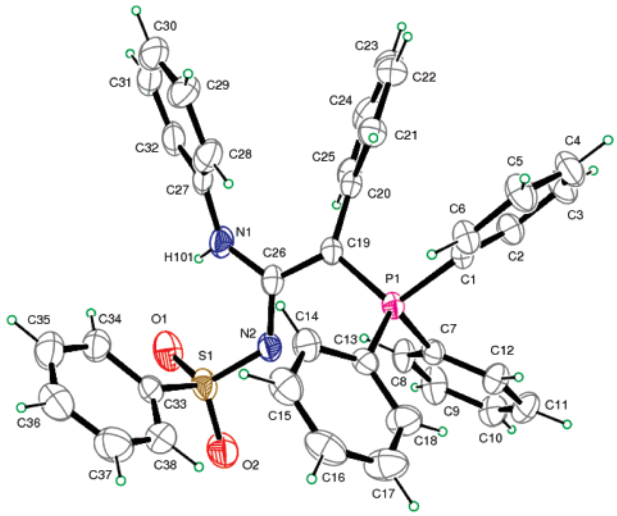
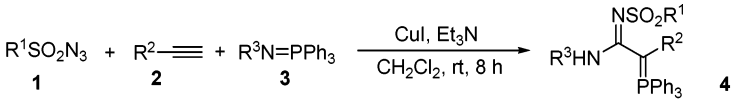
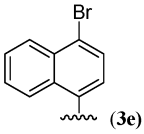
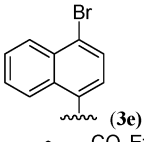
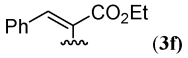


Figure 1. X-ray analysis of **4a**.

With the results in hand, we next explored the protocol with a variety of sulfonyl azides **1**, alkynes **2** and iminophosphoranes **3**.[6,11] As shown in Table 1, the one-pot three-component reaction afforded the amidine-stabilized phosphorus ylides in moderate to excellent yields (65%-95%). The aromatic iminophosphoranes (Table 1, entries 1−11 and 13) gave higher yields than the olefinic substances (Table

Table 1. Three-Component Reaction of Sulfonyl Azides (**1**), Alkynes (**2**), and Iminophosphoranes (**3**)[a]

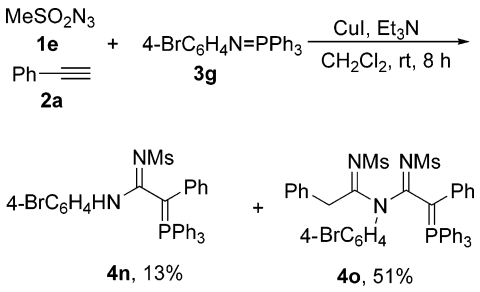


entry	R^1	R^2	R^3	product	yield (%)[b]
1	C_6H_5 (**1a**)	C_6H_5 (**2a**)	C_6H_5 (**3a**)	**4a**	93
2	C_6H_5 (**1a**)	C_6H_5 (**2a**)	3,4-$(MeO)_2C_6H_3$ (**3b**)	**4b**	92
3	C_6H_5 (**1a**)	4-$MeOC_6H_4$ (**2b**)	4-MeC_6H_4 (**3c**)	**4c**	93
4	C_6H_5 (**1a**)	4-$MeOC_6H_4$ (**2b**)	$C_6H_5CH_2$ (**3d**)	**4d**	90
5	C_6H_5 (**1a**)	CO_2Et (**2c**)	C_6H_5 (**3a**)	**4e**	91
6	4-MeC_6H_4 (**1b**)	C_6H_5 (**2a**)	4-MeC_6H_4 (**3c**)	**4f**	91
7	4-MeC_6H_4 (**1b**)	CO_2Et (**2c**)	4-MeC_6H_4 (**3c**)	**4g**	88
8	4-ClC_6H_4 (**1c**)	4-$MeOC_6H_4$ (**2b**)	 (**3e**)	**4h**	69
9	4-ClC_6H_4 (**1c**)	 (**2d**)	4-MeC_6H_4 (**3c**)	**4i**	87
10	4-$NO_2C_6H_4$ (**1d**)	C_6H_5 (**2a**)	4-MeC_6H_4 (**3c**)	**4j**	78
11	Me (**1e**)	C_6H_5 (**2a**)	 (**3e**)	**4k**	92
12	$C_6H_5CH_2$ (**1f**)	C_6H_5 (**2a**)	 (**3f**)	**4l**	65
13	$C_6H_5CH_2$ (**1f**)	4-MeC_6H_4 (**2e**)	4-MeC_6H_4 (**3c**)	**4m**	95

[a] Reaction conditions: sulfonyl azide (0.6 mmol), alkyne (0.6 mmol), iminophosphorane (0.5 mmol), CuI (0.1 mmol), CH_2Cl_2 (4 mL), Et_3N (1 mmol), N_2, 8 h. [b] Yields refer to iminophosphoranes.

1, 12). The reaction of sulfonyl azide **1e** (1.2 equiv), alkyne **2a** (1.2 equiv), and iminophosphorane **3g** (1 equiv) afforded amidine **4n** as a minor product and bisamidine **4o** as a major product (Scheme 2). Probably, the keteneimine intermediate generated from methylsulfonyl azide (**1e**) is more reactive than the keteneimine from aryl sulfonyl azides, which leads to the nucleophilic addition of the resulting product **4n** to the keteneimine intermediate and the formation of bisamidine **4o**.

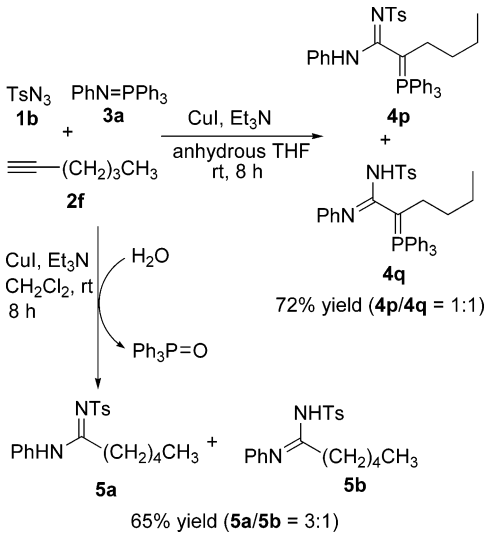
Scheme 2



The structure of **4o** was firmly established by X-ray analysis (see Supporting Information).

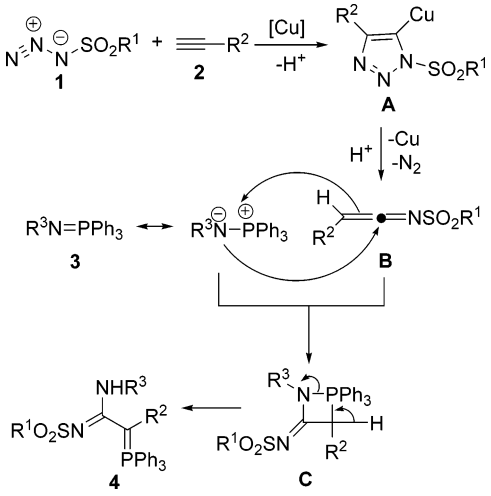
We also examined aliphatic alkynes such as 1-hexyne (**2f**) and found that the resulting phosphorus ylide was completely hydrolyzed to aliphatic amidine **5a** and its tautomer **5b** (3:1) under the reaction conditions (Scheme 3). We then used anhydrous THF as the solvent to perform the reaction and isolated the desired phosphorus amidine **4p** and its tautomer **4q** (1:1) in 72% yield (Scheme 3). For prodcuts **4a**−**m** as presented in Table 1, their R^2 groups are aryl, which could conjugate with the C═P bond in ylides. In this case, however, **4p** bears an alkyl group at the carbon atom of its C═P bond, so it is unstable as compared with **4a**−**m**. We believe that the hydrolysis and the tautomerization of product **4p** are due to its unstability.

Scheme 3



On the basis of these results, we depicted our working hypothesis in Scheme 4. The formation of phosphorus amidines can be rationalized as being initiated by the Cu-catalyzed cycloaddition reaction of azides and alkynes. The resulting triazolyl Cu-species **A** releases N_2 to result in a key intermediate keteneimine **B**.[5a,9] Iminophosphorane **3** then nucleophilically attacks the central carbon atom of keteneimine **B** to form 1,2-phosphazetidine intermediate **C**. Finally, the ring-opening of **C** affords amidine **4**.

Scheme 4



In conclusion, we have explored a copper-catalyzed three-component reaction, which furnished a novel class of functionalized amidines from readily available sulfonyl azides, alkynes and iminophosphoranes. The procedure is efficient and general. Moreover, it is possible that the ylide group of the products can be further transformed through Wittig reaction. Our method will find its applications in the synthesis of heterocyclic compounds.

Acknowledgment. We thank the National Natural Science Foundation of China (No. 20672093) and the Natural Science Foundation of Zhejiang Province (R404109).

Supporting Information Available: Detailed experimental procedures, characterizaton data, copies of ^1H, ^{13}C, and ^{31}P NMR spectra for all products, and crystallographic information files for compounds **4a** and **4o**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800160Q

(9) (a) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046−116047. (b) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154−3157. (c) Whiting, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3157−3161.

(10) The cycloaddition reactions of *N*-sulfonyl substituted keteneimines with the C═N bond-containing compounds such as carbodiimides have been reported; see: Lábbé, G.; Sorgeloos, D.; Toppet, S. *Tetrahedron Lett.* **1982**, *23*, 2909−2912.

(11) Iminophosphoranes **3** were easily prepared via Staudinger reaction of azides with triphenylphosphine; see: Alajarín, M.; Vidal, A.; Ortín, M. M.; Bautista, D. *New J. Chem.* **2004**, *28*, 570−577.