ORGANIC LETTERS

2007
Vol. 9, No. 24
5023−5025

Copper-Catalyzed Multicomponent Reaction: Facile Access to Functionalized 5-Arylidene-2-imino-3-pyrrolines

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

Department of Chemistry, Zhejiang University, Hangzhou 310027, China

orgwyg@zju.edu.cn

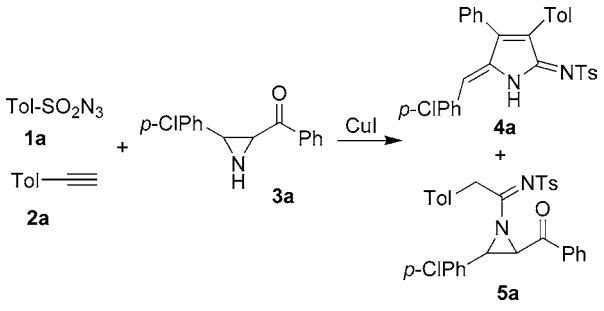
Received September 12, 2007

ABSTRACT

The synthesis of a novel class of 2-imino-5-arylidene-3-pyrrolines via a copper-catalyzed multicomponent reaction of sulfonyl azides with alkynes and aziridines is described. The protocol is efficient and general.

3-Pyrrolines are a synthetically useful and biologically interesting class of *N*-containing compounds.[1,2] They serve as inhibitors of monoamine oxidase (MAO), which plays an important role in psychopharmacology.[3] The transition metal-catalyzed cyclization/cycloisomerization of amino allenes,[4] the regioselective Rh-catalyzed allylic amination/ring-closing metathesis,[5] and the intramolecular cyclization strategy have been developed for the preparation of 3-pyrrolines.[6] 3-Pyrrolin-2-ones constitute an important class of pyrroline derivatives. They display interesting biological activities, e.g., antibiotic, antiviral, or cytotoxic activities.[7] These five-member-ring lactams have successfully been used in routes to various alkaloids and are suitable precursors for unusual

Scheme 1



γ-amino acids such as statine and its analogues.[8] These versatile building blocks have been synthesized via regiose-

(1) For use of pyrrolines in aza sugar synthesis, see: Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1995**, *36*, 1621−1624.

(2) (a) Sahlberg, C.; Ross, S. B.; Fagervall, I.; Ask, A.-L.; Claesson, A. *J. Med. Chem.* **1983**, *26*, 1036−1042. (b) Smith, R. A.; White, R. L.; Krantz, A. *J. Med. Chem.* **1988**, *31*, 1558−1566 and references cited therein.

(3) For pyrrolines as monoamine oxidase inhibitors, see: (a) Lee, Y.; Ling, K.-Q.; Lu, X.; Silverman, R. B.; Shepard, E. M.; Dooly, D. M.; Sayre, L. M. *J. Am. Chem. Soc.* **2002**, *124*, 12135−12143. (b) Williams, C. H.; Lawson, J. *Neurobiology* **1999**, *7*, 225−233. (c) Williams, C. H.; Lawson, J. *Biochem. J.* **1998**, *336*, 63−67. (d) Lee, Y.; Huang, H.; Sayre, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 7241−7242.

(4) (a) Dieter, R. K.; Chen, N. Y.; Gore, V. K. *J. Org. Chem.* **2006**, *71*, 8755−8760. (b) Dieter, R. K.; Yu, H. Y. *Org. Lett.* **2001**, *3*, 3855−3858. (c) Dieter, R. K.; Chen, N. Y.; Yu, H. Y.; Nice, L. E.; Gore, V. K. *J. Org. Chem.* **2005**, *70*, 2109−2119. (d) Krause, N.; Morita, N. *Org. Lett.* **2004**, *6*, 4121−4123.

(5) Evans, P. A.; Robinson, J. E. *Org. Lett.* **1999**, *1*, 1929−1931.

(6) (a) Kinder, F. R.; Jarosinski, M. A., Jr.; Anderson, W. K. *J. Org. Chem.* **1991**, *56*, 6475−6477. (b) Warmus, J. S.; Dilley, G. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 270−271. (c) Green, M. P.; Prodger, J. C.; Sherlock, A. E.; Hayes, C. J. *Org. Lett.* **2001**, *3*, 3377−3379.

(7) Petti, G. R.; Kamano, Y.; Dufresne, C.; Cerny, R. L.; Herald, C. L.; Schmidt, J. M. *J. Org. Chem.* **1989**, *54*, 6005−6006.

(8) (a) Jouin, P.; Castro, B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1177−1121. (b) Ma, D.; Ma, J.; Ding, W.; Dai, L. *Tetrahedron: Asymmetry* **1996**, *7*, 2365−2370.

10.1021/ol702241e CCC: $37.00
Published on Web 11/03/2007

Table 1. Screening of the Reaction Conditions[a]

entry	solvent	reaction temp	yield (%)[b] 4a	5a
1	CH_2Cl_2	rt	trace	93[c]
2	CH_2Cl_2	reflux	trace	91
3	CH_3CN	rt	trace	95
4	CH_3CN	50 °C	35	47
5	CH_3CN	reflux	73	trace
6	THF	reflux	41	35
7	$ClCH_2CH_2Cl$	reflux	65	trace
8	DMF	reflux	47	trace

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.6 mmol), **3a** (0.5 mmol), CuI (0.1 mmol), and TEA (1.0 mmol), 8 h. [b] Yields refer to aziridine **3a**. [c] Reaction time: 12 h.

lective oxidation of pyrrole-2-carboxaldehydes[9] and 4-*O*-alkylation of pyrrolidine-2,4-diones.[10] The Ugi four-component reaction could also lead to the construction of 3-pyrrolin-2-ones.[11] We herein report a copper-catalyzed three-component domino approach to the construction of 2-imino-5-arylidene-3-pyrrolines, a new class of 3-pyrrolin-2-one derivatives.

Previously, we developed an efficient synthesis of iminocoumarins via a domino reaction of sulfonyl azides, alkynes, and salicaldehydes, which involves a ketenimine intermediate in situ generated from copper-catalyzed cycloaddition of azides and alkynes.[12] We anticipated that this kind of ketenimine intermediates would react with a carboxy group-containing aziridine synthon to furnish diverse azaheterocycles. In this regard, 2-acyl aziridines were selected as one of the reaction components. As a preliminary study, we examined the three-component reaction of tolylsulfonyl azide (**1a**) with 4-methylphenylacetylene (**2a**) and aziridine **3a** in the presence of CuI and triethylamine (TEA) in CH_2Cl_2 at room temperature (Scheme 1). However, the resulting mixture only delivers the uncyclized amidine product **5a**.

We then examined several conditions to establish the protocol (Table 1). When the process was performed at low temperature, **5a** was formed as the only product and traceless **4a** was detected (Table 1, entries 1−3). Increasing the temperature affects the reaction outcome greatly (Table 1, entries 4−8). When the reaction was performed in CH_3CN under reflux for 8 h, the best yield and the highest selectivity were obtained (Table 1, entry 5).

With the suitable reaction conditions in hand, we next explored the protocol with a variety of sulfonyl azides **1**, alkynes **2**, and aziridines **3**, which are easily prepared from the corresponding chalcone.[13] As shown in Table 2, the one-pot multicomponent reaction afforded the corresponding

Scheme 2

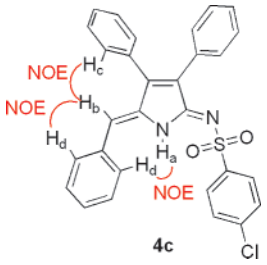
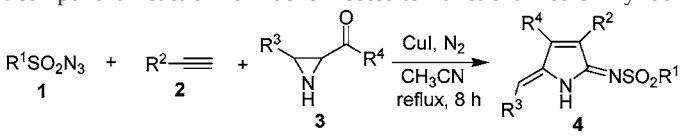
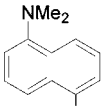


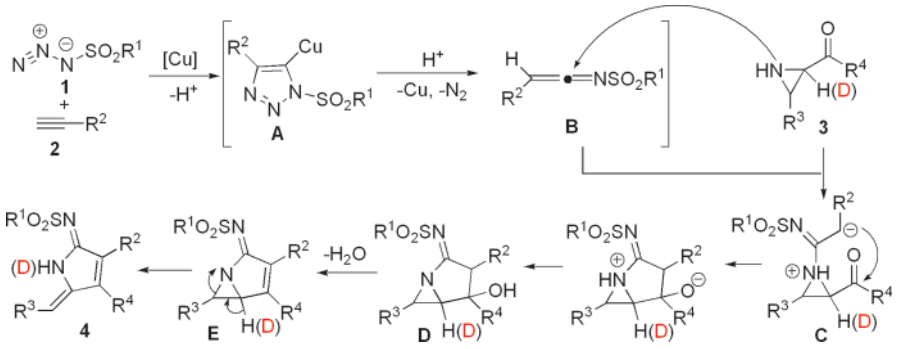
Table 2. Copper-Catalyzed Multicomponent Reaction for Facile Access to Functionalized 5-Arylidene-2-imino-3-pyrrolines[a]



entry	R^1	R^2	R^3/R^4	product	yield[b] (%)
1	4-MeC_6H_4 (**1a**)	4-MeC_6H_4 (**2a**)	4-ClC_6H_4/Ph (**3a**)	**4a**	73
2	Ph (**1b**)	Ph (**2b**)	Ph/Ph (**3b**)	**4b**	71
3	4-ClC_6H_4 (**1c**)	Ph (**2b**)	**3b**	**4c**	65
4	**1a**	2-pyridyl (**2c**)	3,4-$Me_2C_6H_3$/Ph (**3c**)	**4d**	78
5	**1b**	**2a**	**3c**	**4e**	71
6	4-$O_2NC_6H_4$ (**1d**)	**2b**	**3c**	**4f**	62
7	**1a**	**2b**	2-furyl/Ph (**3d**)	**4g**	67
8	**1b**	4-FC_6H_4 (**2d**)	**3d**	**4h**	81
9	**1d**	**2b**	2-naphthyl/2-ClC_6H_4 (**3e**)	**4i**	65
10	**1a**	**2b**	**3e**	**4j**	70
11	**1a**	4-$MeOC_6H_4$ (**2e**)	3,4-$(OCH_2O)C_6H_3$/2-ClC_6H_4 (**3f**)	**4k**	68
12	**1a**	**2b**	4-PhC_6H_4/2-MeC_6H_4 (**3g**)	**4l**	65
13	**1c**	**2b**	 /2-MeC_6H_4 (**3h**)	**4m**	73
14	 (**1e**)	**2a**	Ph/3-$O_2NC_6H_4$ (**3i**)	**4n**	58
15	Me (**1f**)	**2b**	**3b**	**4o**	53

[a] Reaction conditions: sulfonyl azide (0.6 mmol), alkyne (0.6 mmol), aziridine (0.5 mmol), CuI (0.1 mmol), CH_3CN (4 mL), TEA (1 mmol), N_2, reflux, 8 h. [b] Yields refer to aziridines.

Scheme 3



5-arylidene-2-imino-3-pyrrolines **4** in moderate to good yields (53−81%). The aromatic sulfonyl azides **1b** and **1c** (Table 2, entries 2 and 3) gave higher yields than the aliphatic sulfonyl azides **1f** (Table 2, entry 15).

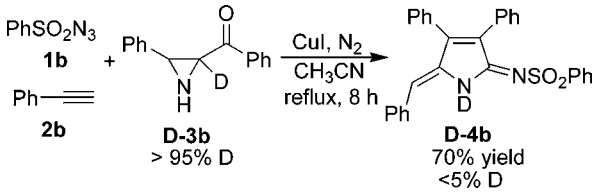
Alkyl alkyne such as hex-1-yne was also examined, but we found that the process proceeded only to deliver the amidine as product either at room temperature or under reflux rather than the cyclized five-membered scaffold presumably because of the relative poor ketenimine intermediate.

The stereochemistry of the product was established by the NOESY analysis of **4c**. As shown in Scheme 2, the ^{1}H−^{1}H interactions between H_a and H_d, H_b and H_c, as well as H_b and H_d were observed. These results suggest a *Z* configuration of the C═C bond in compound **4c**.

Herein we depicted our working hypothesis in Scheme 3. The formation of the strained heterocycles 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 ketenimine **B**.[14] Then amine **3** attacks the central carbon atom of the ketenimine to form **C**, which cyclizes to 1-aza-bicyclo[3.1.0]-hexane **D**. Finally, the dehydration of **D** and the subsequent ring-opening affords pyrroline **4**.

Further insight into the reaction mechanism was gained by conducting a deuterium-labeling experiment, i.e., the deuterated aziridine **D-3b** (>95% D) was employed following the general procedure (Scheme 4). We found that the

Scheme 4



amino hydrogen of product exhibited less than 5% deuterium due to a H−D exchange of the deuterium at the nitrogen atom of **4** with the resulting H_2O. This result supports the suggested mechanism in Scheme 3, which allows the deuterium atom to shift from the α-carbon atom of ketone **3** to the nitrogen atom of pyrroline **4**.

In conclusion, we have explored a copper-catalyzed multicomponent reaction of sulfonyl azides, alkynes, and 2-acylaziridines for the preparation of functionalized 5-arylidene-2-imino-3-pyrrolines, a new class of pyrroline derivatives. The procedure is efficient and general. Further application of the methodology to synthesize heterocyclic compound libraries is in progress in our laboratory.

Acknowledgment. We thank the National Natural Science Foundation of China (No. 20672093), the Natural Science Foundation of Zhejiang Province (R404109), as well as the Specialized Research Fund for Doctoral Program of Higher Education (20050335101).

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

OL702241E

(9) Coffin, A. R.; Roussel, M. A.; Tserlin, E.; Pelkey, E. T. *J. Org. Chem.* **2006**, *71*, 6678−6681.
(10) Hosseini, M.; Kringelum, H.; Murray, A.; Tønder, J. E. *Org. Lett.* **2006**, *8*, 2103−2106.
(11) Beck, B.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett*. **2004**, *6*, 39−42.
(12) Cui, S. L.; Lin, X. F.; Wang, Y. G. *Org. Lett*. **2006**, *8*, 4517−4520.
(13) (a) Shen, Y. M.; Zhao, M. X.; Xu, J. X.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8005−8008. (b) Armstrong, A.; Baxter, C. A.; Lamont, S. G.; Pape, A. R.; Wincewicz, R. *Org. Lett.* **2007**, *9*, 351−353.
(14) (a) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038−2039. (b) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046−16047. (c) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154−3157. (d) Whiting, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3157−3161.