ORGANIC LETTERS

2007
Vol. 9, No. 8
1585−1587

Copper-Catalyzed Highly Efficient Multicomponent Reactions: Synthesis of 2-(Sulfonylimino)-4-(alkylimino)azetidine Derivatives

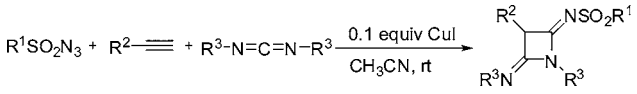
Xiaoliang Xu,*,† Dongping Cheng,‡ Jinghua Li,‡ Hongyun Guo,† and Jie Yan†

College of Chemical Engineering and Materials Science and College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou 310014, People's Republic of China

xuxiaoliang@zjut.edu.cn

Received February 26, 2007

ABSTRACT



18 examples in 65-96%

Under very mild conditions, functionalized 2-(sulfonylimino)-4-(alkylimino)azetidine derivatives were prepared in good to excellent yields via a copper-catalyzed multicomponent reaction of readily available terminal alkynes, sulfonyl azides, and carbodiimides without the assistance of a base. The mechanism may be through a [2 + 2] cycloaddition.

Four-membered nitrogen heterocycles are of considerable interest. Besides possessing a wide range of biological activities and being used as antibiotic and antibacterial agents, they have found increasing applications as important intermediates in the synthesis of pharmaceuticals.[1] Among them, the four-membered azetidine series, especially azetidin-2-ones, has gained enormous attention.[2] However, reports concerning the synthesis of the 2,4-diiminoazetidine ring system are rare,[3] for which two reasons may be responsible. First, the Dunitz−Schomaker strain exists which is significant in four-membered rings.[4] Second, the 2,4-diiminoazetidine ring system is highly functionalized. L'abbé and Chen described two routes for the construction of such a ring; however, the method was too tedious and suffered from major shortcomings such as limited substituents, very low yields in most examples, and troublesome chemical managing processes.[3] Therefore, the development of convenient, general, and synthetically useful methodologies for the synthesis of 2,4-diiminoazetidines is highly desirable.

The MCR (multicomponent reaction), offering an efficient route to generate complex molecular frameworks from simple and readily available substrates, is a powerful tool in modern organic synthesis as well as in the field of combinatorial

† College of Chemical Engineering and Materials Science.
‡ College of Pharmaceutical Science.

(1) (a) Alcaide, B.; Almendros, P. In *Progress Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier: Oxford, 2005; Vol. 17, pp 64−83. (b) Roth, H. J. *Deutsche Apotheker Zeitung* **2005**, *145*, 56−62. (c) Parrick, J.; Mehta, L. K. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Eds.; Elsevier: Oxford, 1996; pp 659−720. (d) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 491−504.

(2) For reviews, see: (a) Alcaide, B.; Almendros, P. *Org. Prep. Proced. Int.* **2001**, *33*, 317−334. (b) De Kimpe, N. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Eds.; Elsevier: Oxford, 1996; pp 507−589. (c) Cromwell, N. H.; Philips, B. *Chem. Rev.* **1979**, *79*, 331−358.

(3) For the synthesis of 2,4-diimino azetidine: (a) Chen, C. T.; Chan, Y. S.; Tzeng, Y. R.; Chen, M. T. *Dalton Trans.* **2004**, 2691−2696. (b) L'abbé, G.; Sorgeloos, D.; Toppet, S. *Tetrahedron Lett.* **1982**, *23*, 2909−2912. For the synthesis of 2,3-diimino azetidine: (a) Schaffer, P.; Morel, P.; Britten, J. F.; Valliant, J. F. *Inorg. Chem.* **2002**, *41*, 6493−6499. (b) Marchand, E.; Morel, G.; Sinbandhit, S. *Eur. J. Org. Chem.* **1999**, 1729−1738. (c) Aumann, R.; Heinen, H. *Chem. Ber.* **1986**, *119*, 2289−2307. (d) Deyrup, J. A.; Vestling, M. M.; Hagan, W. V.; Yun, H. Y. *Tetrahedron* **1969**, *25*, 1467−1478.

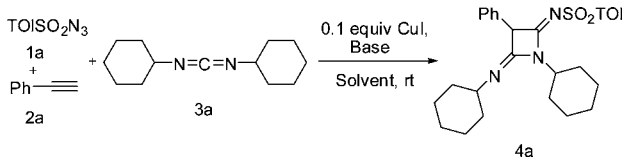
(4) Cremer, D.; Gauss, J. *J. Am. Chem. Soc.* **1986**, *108*, 7467−7477.

10.1021/ol070485x CCC: $37.00
Published on Web 03/24/2007

chemistry and drug discovery.[5] Although little attention was paid to the novel MCRs in the second half of the last century, they have naturally become a rapidly evolving research area and have attracted the attention of both academic and industrial scientists in the past few years. Among them, the transition-metal-catalyzed MCRs are of high importance because they have excellent catalytic efficiency in most cases.[6] Recently, CuI-catalyzed[7] MCRs concerning sulfonyl azides and alkynes have drawn special interest.[8] Chang et al. reported the MCR reaction between sulfonyl azides, alkynes, and amines in the presence of CuI, which afforded a useful method for the preparation of *N*-sulfonylamidines.[8f] The reaction starting from sulfonyl azides, alkynes, and water or alcohol produced hydrative amides and *N*-sulfonylimidates in good yields, respectively,[8b,c,e] and with imines or salicylaldehydes as the third component, the three-component reactions generated *N*-sulfonylazetidin-2-imines and iminocoumarins, respectively.[8a,d] Herein, we report a novel CuI-catalyzed three-component reaction between terminal alkynes, sulfonyl azides, and carbodiimides to give functionalized 2-(sulfonylimino)-4-(alkylimino)azetidine derivatives in good to excellent yields.

At first, *p*-toluenesulfonyl azide **1a**, phenylacetylene **2a**, and *N*,*N*′-dicyclohexylcarbodiimide **3a** were selected as the model substrates (Table 1). Catalyzed by CuI, several bases and solvents were examined to set up standard reaction conditions. When the reaction was performed in THF in the presence of 2 equiv of triethylamine at rt for 16 h, it was found that the desired product **4a** was indeed obtained albeit in only 28% yield (Table 1, entry 1). Prolonging the reaction time (24 h) or use of 2 equiv of pyridine or K_2CO_3 instead of triethylamine as the base could not improve the result (Table 1, entries 2−4). Besides THF, a number of other solvents such as ether, CH_3CN, CH_2Cl_2, and toluene were further surveyed under basic conditions; however, no obvious improvement was observed (Table 1, entries 5−9). Finally, we were pleased to find that when the reaction was carried out in the absence of a base the expected product **4a** was isolated in 62% yield with toluene as a solvent (Table 1, entry 10). A better result came from the use of CH_3CN as a solvent in the absence of a base, and **4a** was obtained in 94% yield (Table 1, entry 11). It clearly showed that this reaction system differentiated itself from the other similar reactions in that it did not require a base as a promoter.[8] Although the detailed mechanism was not yet fully understood, DCC acted both as a reactant and, probably, as a weak base to forward this reaction.

Table 1. CuI-Catalyzed Synthesis of **4a** via a Three-Component Reaction



entry	base	solvent	time (h)	yield (%)[a,b]
1	TEA[c]	THF	16	28
2	TEA	THF	24	19
3	K_2CO_3	THF	16	17
4	pyridine	THF	16	33
5	TEA	CH_3CN	16	34
6	TEA	CH_2Cl_2	16	38
7	TEA	ether[d]	16	15
8	TEA	toluene	16	39
9	pyridine	toluene	16	41
10	none	toluene	16	62
11	none	CH_3CN	16	94

[a] *p*-Toluenesulfonyl azide (1 mmol), phenylacetylene (1 mmol), DCC (1.2 mmol), base (2 mmol), and CuI (0.1 mmol) in solvent (3 mL) under rt. [b] Isolated yields based on alkyne. [c] Triethylamine. [d] Diethyl ether.

The structure of **4a** was confirmed unambiguously by X-ray diffraction analysis,[9] which was in accordance with ^{1}H NMR, ^{13}C NMR, HMQC, and HRMS spectra (Figure 1).

It can be summarized from Table 1 that the combination of CuI and CH_3CN was a more efficient catalytic system to catalyze the MCR of *p*-toluenesulfonyl azide with phenyl-

(5) For reviews, see: (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17−89. (b) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Ed.; Wiley-VCH: Weinheim, 2005. (c) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602−1634. (d) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekenth, A. R.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899−907. (e) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471−1499. (f) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101−4111. (g) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (h) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.−Eur. J.* **2000**, 3321−3329. (i) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366−374.

(6) For reviews, see: (a) Chen, L.; Li, C. J. *Adv. Synth. Catal.* **2006**, *348*, 1459−1484. (b) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *30*, 3890−3908. (c) Ikeda, S. *Kagaku to Kogyo* (*Tokyo*) **2000**, *53*, 146−149. (d) Itoh, K.; Matsuda, I.; Yamamoto, Y. *Yuki Gosei Kagaku Kyokaishi* **1999**, *57*, 912−923. (e) Marshall, J. A.; McNulty, L. M. *Chemtracts* **1997**, *10*, 50−52.

(7) For the selected papers of Cu-catalyzed MCRs recently, please see: (a) Zhang, L.; Malinakova, H. C. *J. Org. Chem.* **2007**, *72*, 1484−1487. (b) Colombo, F.; Benaglia, M.; Orlandi, S.; Usuelli, F. *J. Mol. Catal. A: Chem.* **2006**, *260*, 128−134. (c) Huang, B. S.; Yao, X. Q.; Li, C. J. *Adv. Synth. Catal.* **2006**, *348*, 1528−1532. (d) Gheorghe, A.; Matsuno, A.; Reiser, O. *Adv. Synth. Catal.* **2006**, *348*, 1016−1020. (e) Zhao, L.; Li, C. J. *Chem. Asian J.* **2006**, *1*, 203−209. (f) Pirali, T.; Tron, G. C.; Zhu, J. P. *Org. Lett.* **2006**, *8*, 4145−4148. (g) Margathe, J.; Shipman, M.; Smith, S. C. *Org. Lett.* **2005**, *7*, 4987−4990. (h) Black, D. A.; Arndtsen, B. A. *J. Org. Chem.* **2005**, *70*, 5133−5138. (i) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223−4225. (j) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107−1110. (k) Cuny, G.; Bois-choussy, M.; Zhu, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 14475−14484. (l) Kozuka, M.; Inoue, A.; Tsuchida, T.; Mitani, M. *Synlett* **2004**, 2756−2760. (m) Shi, L.; Tu, Y. Q.; Wang, M.; Zhang, F. M.; Fan, C. A. *Org. Lett.* **2004**, *6*, 1001−1003. (n) Kamijo, S.; Jin, T.; Huo, Z. B.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 2386−2393. (o) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763−5766.

(8) (a) Whiting, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3157−3161. (b) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154−3157. (c) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347−1350. (d) Cui, S. L.; Lin, X. F.; Wang, Y. G. *Org. Lett.* **2006**, *8*, 4517−4520. (e) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046−16047. (f) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038−2039.

(9) Crystal data: $C_{28}H_{35}N_3O_2S$, M_r = 477.65 g mol^{-1}, orthorhombic, *Pbcn*, a = 17.220(3), b = 11.154(2), c = 27.154(5) Å, V = 5215.4(18) Å^3, Z = 8, T = 293(2) K, crystal size = 0.37 × 0.34 × 0.20 mm^3, ρ_{calcd} = 1.217 g cm^{-3}, μ(Mo Kα) = 0.153 mm^{-1}, θ_{max} = 27.41, measured/independent reflections = 46 044/5941 (R_{int} = 0.0339), S = 1.064, final R_1 = 0.0411 (for 4456 data $I > 2\sigma(I)$), R_w = 0.1090 (all data). CCDC-635462 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

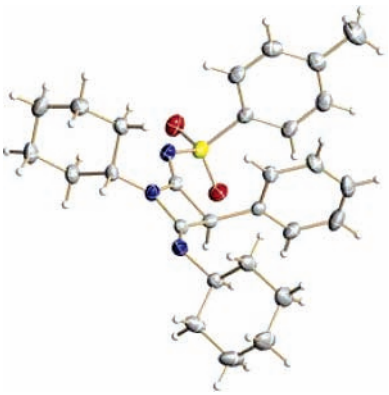
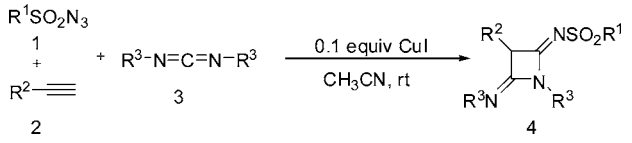


Figure 1. X-ray crystal structure of compound **4a**.

acetylene and *N*,*N*′-dicyclohexylcarbodiimide. To explore the scope of this catalytic system, more substrates were applied, and the results are shown in Table 2.

Aromatic sulfonyl azides gave the corresponding 2-(sulfonylimino)-4-(alkylimino)azetidines in good to excellent yields. Methylsulfonyl azide, an aliphatic one, was also an appropriate substrate. As far as the alkynes were concerned, both aromatic and alkyl alkynes afforded satisfactory results.

Table 2. CuI-Catalyzed Synthesis of 2-(Sulfonylimino)-4-(alkylimino)azetidine Derivatives



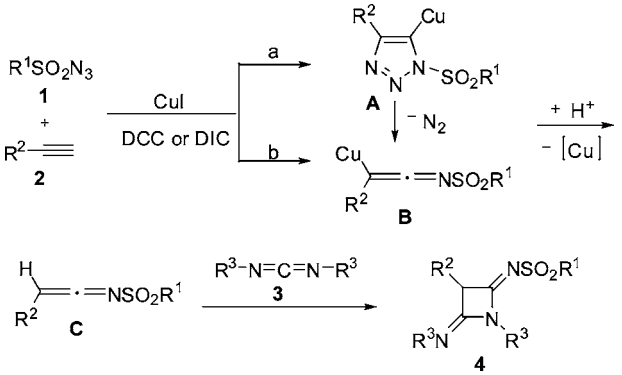
entry	R^1	R^2	R^3	yield (%)[a,b]
1	4-MeC_6H_4 (**1a**)	Ph (**2a**)	*c*-C_6H_{11} (**3a**)	94 (**4a**)
2	**1a**	$CH_3(CH_2)_3$ (**2b**)	**3a**	65 (**4b**)
3	**1a**	CO_2Et (**2c**)	**3a**	93 (**4c**)
4	**1a**	4-MeC_6H_4 (**2d**)	**3a**	87 (**4d**)
5	**1a**	$CH_3(CH_2)_4$ (**2e**)	**3a**	71 (**4e**)
6	**1a**	**2a**	*i*-Pr (**3b**)	88 (**4f**)
7	**1a**	**2c**	**3b**	95 (**4g**)
8	C_6H_5 (**1b**)	**2c**	**3b**	95 (**4h**)
9	**1b**	**2a**	**3a**	91 (**4i**)
10	**1b**	4-$MeOC_6H_4$ (**2f**)	**3b**	88 (**4j**)
11	**1b**	4-EtC_6H_4 (**2g**)	**3b**	79 (**4k**)
12	**1b**	4-PrC_6H_4 (**2h**)	**3b**	81 (**4l**)
13	**1b**	4-BuC_6H_4 (**2i**)	**3b**	83 (**4m**)
14	Me (**1c**)	**2a**	**3a**	76 (**4n**)
15	**1c**	**2d**	**3a**	77 (**4o**)
16	4-ClC_6H_4 (**1d**)	**2a**	**3b**	84 (**4p**)
17	**1d**	**2a**	**3a**	86 (**4q**)
18	**1a**	**2j**	**3a**	76 (**4r**)[c]
19	**1a**	**2a**	Ph	0[d]

[a] Sulfonyl azide (1 mmol), alkyne (1 mmol), DCC (1.2 mmol), base (2 mmol), and CuI (0.1 mmol) for 16 h in CH_3CN (3 mL) at rt. [b] Isolated yields based on the alkynes. [c] Yield of the desilylated azetidine product. [d] No reaction.

Aromatic alkynes substituted at the phenyl ring with Me, Et, Pr, Bu, and MeO were all converted into the corresponding products efficiently. 1-Hexyne and 1-heptyne also worked well. It is noteworthy that ethyl propiolate, a conjugated alkyne, afforded the desired product in excellent yields. Two kinds of carbodiimides, DCC and DIC, can be used successfully for this reaction. When *p*-toluenesulfonyl azide **1a** with trimethylsilylacetylene **2j** and *N*,*N*′-dicyclohexylcarbodiimide **3a** were used as the substrates, unexpectedly, the desilylated azetidine compound **4r** was obtained (Table 2, entry 18). This observation showed that trimethylsilylacetylene can serve as a two-carbon source for the formation of **4r** under this reaction system, which was in accordance with the result of Chang.[8c] Nevertheless, no desired product was obtained using *N*,*N*′-diphenylcarbodiimide as the substrate under this reaction condition (Table 2, entry 19).

A possible mechanism for this CuI-catalyzed MCR is shown in Scheme 1. In the presence of DCC or DIC and

Scheme 1. Proposed Mechanism for the CuI-Catalyzed MCR of the Terminal Alkynes, Sulfonyl Azides, and Carbodiimides



CuI, alkyne **2** reacts with sulfonyl azide **1** through two possible pathways to form the ketenimine species **B** according to Chang and Fokin's proposal,[8] in which DCC or DIC maybe acts as a weak base. Protonation of **B** gives rise to the highly reactive ketenimine **C** and regenerates the copper catalyst. Then, **C** reacts with carbodiimide **3** through a [2 + 2] cycloaddition to afford the desired product **4**.

In conclusion, an efficient CuI-catalyzed MCR of sulfonyl azides, terminal alkynes, and carbodiimides is successfully established, notably without the assistance of a base. The reaction described here is mild, general, and efficient, thus providing an extremely preferable path for the synthesis of a variety of 2-(sulfonylimino)-4-(alkylimino)azetidine derivatives. Further synthetic applications of this reaction system are now under investigation.

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

OL070485X