ORGANIC LETTERS

2012
Vol. 14, No. 24
6266–6269

Three-Component Reaction of Propargyl Amines, Sulfonyl Azides, and Alkynes: One-Pot Synthesis of Tetrasubstituted Imidazoles

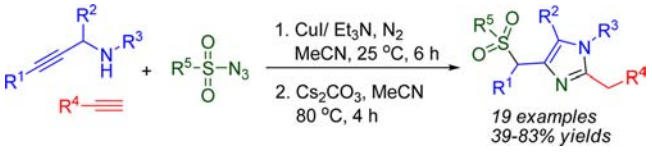
Zheng Jiang, Ping Lu,* and Yanguang Wang*

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

pinglu@zju.edu.cn; orgwyg@zju.edu.cn

Received November 3, 2012

ABSTRACT



An efficient and straightforward strategy for the synthesis of tetrasubstituted imidazoles from propargyl amines, sulfonyl azides, and terminal alkynes is described. *N*-Sulfonyl ketenimine and aminoallene are believed to be the key intermediates for this two-step one-pot transformation.

Imidazole and its derivatives are an important class of heterocyclic compounds, which are widely used in biology as inhibitors,[1] and are also used in medicinal chemistry[2] and as functionalized materials.[3] Classic methods for the synthesis of imidazoles include Debus–Radziszewski imidazole synthesis,[4] Weidenhagen imidazole synthesis,[5] and Van Leusen imidazole synthesis.[6] Recently, a number of multicomponent syntheses of imidazoles have also been developed.[7] Nonetheless, the development of more efficient and versatile approaches to functionalized imidazoles remains very important.

Since Staudinger and Hauser prepared the first ketenimine in 1921,[8] this class of reactive intermediates has been

(1) (a) Chabin, R. M.; McCauley, E.; Calaycay, J. R.; Kelly, T. M.; MacNaul, K. L.; Wolfe, G. C.; Hutchinson, N. I.; Madhusudanaraju, S.; Schmidt, J. A.; Kozarich, J. W.; Wong, K. K. *Biochemistry* **1996**, *35*, 9567. (b) Jensen, N. P.; Schmitt, S. M.; Windholz, T. B.; Shen, T. Y. *J. Med. Chem.* **1972**, *15*, 341. (c) Swett, L. R.; Yellin, T. O. *J. Med. Chem.* **1970**, *13*, 968. (d) Herrador, M. M.; Buruaga, J. S.; Suarez, M. D. *J. Med. Chem.* **1985**, *28*, 146. (e) Gising, J.; Nilsson, M. T.; Odell, L. R.; Yahiaoui, S.; Lindh, M.; Iyer, H.; Sinha, A. M.; Srinivasa, B. R.; Larhed, M.; Mowbray, S. L.; Karlén, A. *J. Med. Chem.* **2012**, *55*, 2894. (f) Lombardino, J. G.; Wiseman, E. H. *J. Med. Chem.* **1974**, *17*, 1182. (g) Zarić, S. D.; Popović, D. M.; Knapp, E. W. *Biochemistry*. **2001**, *40*, 7914.

(2) (a) Bhatnagar, A.; Sharma, P. K.; Kumar, N. *Int. J. PharmTech. Res.* **2011**, *3*, 268. (b) De Luca, L. *Curr. Med. Chem.* **2006**, *13*, 1. (c) Boiani, M.; Gonzalez, M. *Mini-Rev. Med. Chem.* **2005**, *5*, 68.

(3) Bromberg, L.; Chen, L.; Chang, E. P.; Wang, S.; Hatton, T. A. *Chem. Mater*. **2010**, *22*, 5383.

(4) (a) Debus, H. *Ann*. **1858**, *107*, 204. (b) Radziszewski, B. *Ber* **1882**, *15*, 2706.

(5) Huebner, C. F. *J. Am. Chem. Soc*. **1951**, *73*, 4667.

(6) (a) Gracias, V.; Gasiecki, A. F.; Djuric, S. W. *Tetrahedron Lett*. **2005**, *46*, 9049. (b) Gracias, V.; Darczak, D.; Gasiecki, A. F.; Djuric, S. W. *Tetrahedron Lett*. **2005**, *46*, 9053. (c) Gracias, V.; Gasiecki, A. F.; Pagano, T. G.; Djuric, S. W. *Tetrahedron Lett*. **2006**, *47*, 8873. (d) Beebe, X.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett*. **2006**, *47*, 3225. (e) Wang, L.; Woods, K. W.; Li, Q.; Barr, K. J.; McCroskey, R. W.; Hannick, S. M.; Gherke, L.; Credo, R. B.; Hui, Y. H.; Marsh, K.; Warner, R.; Lee, J. Y.; Zielinski-Mozng, N.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *J. Med. Chem*. **2002**, *45*, 1697.

(7) (a) De Moliner, F.; Hulme, C. *Org. Lett*. **2012**, *14*, 1354. (b) Li, S.; Li, Z. K.; Yuan, Y. F.; Peng, D. J.; Li, Y. J.; Zhang, L. S.; Wu, Y. M. *Org. Lett*. **2012**, *14*, 1130. (c) Xiao, Y. J.; Zhang, L. M. *Org. Lett*. **2012**, *14*, 4662. (d) Guchhait, S. K.; Chandgude, A. L.; Priyadarshani, G. *J. Org. Chem*. **2012**, *77*, 4438. (e) Hu, B.; Wang, Z.; Ai, N.; Zheng, J.; Liu, X. H.; Shan, S.; Wang, Z. W. *Org. Lett*. **2011**, *13*, 6362. (f) Petit, S.; Fruit, C.; Bischoff, L. *Org. Lett*. **2010**, *12*, 4928. (g) Jiang, B.; Wang, X.; Shi, F.; Tu, S. J.; Ai, T.; Ballew, A.; Li, G. G. *J. Org. Chem*. **2009**, *74*, 9486.

(8) Staudinger, H.; Hauser, E. *Helv. Chim. Acta* **1921**, *4*, 887.

(9) For recent reviews, see: (a) Lu, P.; Wang, Y. G. *Chem. Soc. Rev*. **2012**, *41*, 5687. (b) Kim, S. H.; Park, S. M.; Choi, J. H.; Chang, S. *Chem.—Asian. J*. **2011**, *6*, 2618. (c) Lu, P.; Wang, Y. G. *Synlett* **2010**, 165. (d) Yoo, E. J.; Chang, S. *Curr. Org. Chem*. **2009**, *13*, 1766.

(10) (a) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc*. **2005**, *127*, 2038. (b) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc*. **2005**, *127*, 16046.

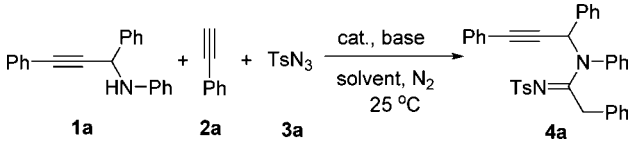
(11) (c) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett*. **2006**, *8*, 1347. (d) Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed*. **2007**, *46*, 1897. (e) Yoo, E. J.; Chang, S. *Org. Lett*. **2008**, *10*, 1163. (f) Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed*. **2008**, *47*, 2836. (g) Yoo, E. J.; Ahlquist, M.; Bae, I.; Sharpless, K. B.; Fokin, V. V.; Chang, S. *J. Org. Chem*. **2008**, *73*, 5520. (h) Kim, J.; Lee, Y.; Lee, J.; Do, Y.; Chang, S. *J. Org. Chem*. **2008**, *73*, 9454. (i) Yoo, E. J.; Park, S. H.; Lee, S. H.; Chang, S. *Org. Lett*. **2009**, *11*, 1155.

10.1021/ol303023y
Published on Web 11/30/2012

explored and applied in the construction of various heterocycles.[9] The most attractive and sustainable method for generating ketenimines is the copper catalyzed azide–alkyne cycloaddition (CuAAC).[10] Chang,[10,11] our group,[12] and others[13] developed a number of three-component reactions by trapping ketenimines generated in situ from sulfonyl azides and terminal alkynes via this CuAAC process. Amines, alcohols, and water could all be the nucleophiles. The skeletons of diverse heterocycles, such as coumarins,[12a,h] quinolines,[12c] pyrrolines,[12b] pyrimidines,[12e] azetidines,[13c] and oxetanes,[13d] were successfully constructed by this strategy. Encouraged by these results, we used substituted propynyl amines, which could be easily prepared from aldehydes, amines, and alkynes via a Mannich-type reaction[14] to trap the in situ generated ketenimines for the synthesis of cyclization products in a cascade process. Herein, we would like to report the result of this effort.

Primarily, when the mixture of *N*-(1,3-diphenylprop-2-yn-1-yl)aniline (**1a**), ethynylbenzene (**2a**), 4-methylbenzenesulfonyl azide (**3a**), CuI, and Et_3N was stirred at 25 °C for 6 h, we obtained a three-component product **4a** in good yield. Optimization of reaction conditions for the formation of **4a** was then conducted (Table 1). Several solvents, such as acetonitrile, toluene, dichloroethane (DCE), dichloromethane (DCM), and tetrahydrofuran (THF), were screened for this transformation, and acetonitrile was found to be the best one (Table 1, entries 1–5). Triethylamine was the best base in comparison with pyridine and potassium carbonate (Table 1, entries 4, 6 and 7). Altering the copper source to CuBr, the yield actually decreased (Table 1, entry 8). Thus, the best reaction conditions for the formation of **4a** were established (Table 1, entry 4).

Table 1. Screening for the Reaction Conditions[a]

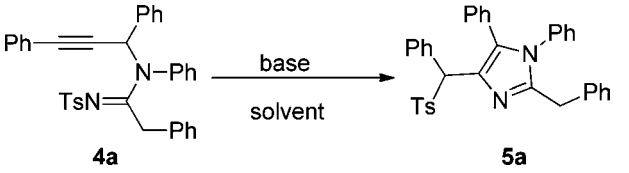


entry	catalyst	base	solvent	time (h)	yield[b] (%)
1	CuI	Et_3N	DCM	6	70
2	CuI	Et_3N	DCE	6	71
3	CuI	Et_3N	toluene	6	83
4	CuI	Et_3N	MeCN	6	89
5	CuI	Et_3N	THF	6	75
6	CuI	Py	MeCN	6	45
7	CuI	K_2CO_3	MeCN	6	76
8	CuBr	Et_3N	MeCN	6	62

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.1 mmol), **3a** (1.2 mmol), base (1.2 mmol), catalyst (0.1 mmol), solvent (10 mL). [b] Isolated yield referred to **1a**.

We envisioned that the cyclization of **4a** could lead to the formation of a heterocyclic compound using a Lewis acid or a base as catalyst. First, we examined several silver and palladium salts that could activate the triple bond,[15] but no reaction occurred in these cases. I_2 and NIS[16] were also tried, and complex mixtures were yielded. As the next step, we focused our attention on the base-promoted cyclization of **4a**. In this case, fortunately, we obtained tetrasubstituted imidazole **5a** (Table 2). Then we studied the reaction conditions for cyclization of **4a** in the presence of base (Table 2). Various bases, such as K_2CO_3, Cs_2CO_3, KOH, *t*-BuONa, Et_3N, and DBU were examined in MeCN at 80 °C, and Cs_2CO_3 gave the best yield (Table 2, entries 1–6). Other solvents, such as DCE, toluene, THF, and DMF, were also screened, but they gave lower yields as compared with MeCN (Table 2, entries 7–10). Decreasing the reaction temperature led to a lower yield (Table 2, entries 11 and 12). Cs_2CO_3 could be reduced to 0.2 equiv, while the reaction time could be reduced to 2 h (Table 2, entries 13–17).

Table 2. Screening for the Reaction Conditions[a]



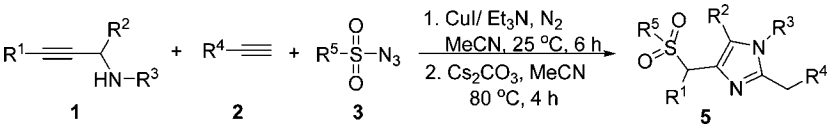
entry	base/equiv	solvent	temp (°C)	time (h)	yield[b] (%)
1	K_2CO_3/2	MeCN	80	4	nd[c]
2	Cs_2CO_3/2	MeCN	80	0.5	80
3	KOH/2	MeCN	80	4	trace
4	*t*-BuONa/2	MeCN	80	0.5	28
5	Et_3N/2	MeCN	80	4	trace
6	DBU/2	MeCN	80	1.5	69
7	Cs_2CO_3/2	toluene	80	1.5	78
8	Cs_2CO_3/2	DCE	80	4	trace
9	Cs_2CO_3/2	THF	80	1	72
10	Cs_2CO_3/2	DMF	80	0.5	34
11	Cs_2CO_3/2	MeCN	50	2	74
12	Cs_2CO_3/2	MeCN	25	4	38
13	Cs_2CO_3/1.5	MeCN	80	0.5	81
14	Cs_2CO_3/1	MeCN	80	0.5	80
15	Cs_2CO_3/0.5	MeCN	80	0.5	79
16	Cs_2CO_3/0.2	MeCN	80	2	80
17	Cs_2CO_3/0.1	MeCN	80	4	55

[a] Reaction conditions: **4a** (1 mmol), solvent (10 mL), equivalent molar to **4a**. [b] Isolated yield referred to **4a**. [c] nd = not detected.

(12) (a) Cui, S. L.; Lin, X. F.; Wang, Y. G. *Org. Lett.* **2006**, *8*, 4517. (b) Cui, S. L.; Wang, J.; Wang, Y. G. *Org. Lett.* **2007**, *9*, 5023. (c) Cui, S. L.; Wang, J.; Wang, Y. G. *Tetrahetron.* **2008**, *64*, 487. (d) She, J.; Jiang, Z.; Wang, Y. G. *Synlett.* **2009**, 2023. (e) Lu, W.; Song, W. Z.; Hong, D.; Lu, P.; Wang, Y. G. *Adv. Synth. Catal.* **2009**, *351*, 1768. (f) Song, W. Z.; Lu, W.; Wang, J.; Lu, P.; Wang, Y. G. *J. Org. Chem.* **2010**, *75*, 3481. (g) Li, Y.; Hong, D.; Zhu, Y. X.; Lu, P.; Wang, Y. G. *Tetrahetron* **2011**, *67*, 8086. (h) Shen, Y.; Cui, S. L.; Wang, J.; Chen, X. P.; Lu, P.; Wang, Y. G. *Adv. Synth. Catal.* **2010**, *352*, 1139.

(13) (a) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154. (b) Whiting, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3157. (c) Xu, X.; Cheng, D.; Li, J.; Guo, H.; Yan, J. *Org. Lett.* **2007**, *9*, 1585. (d) Yao, W. J.; Pan, L. J.; Zhang, Y. P.; Wang, G.; Wang, X. Q.; Ma, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 9210.

Table 3. One-Pot Synthesis of **5**[a]



entry	**1** ($R^1/R^2/R^3$)	**2** (R^4)	**3** (R^5)[b]	**5**/ yield (%)[c]
1	**1a** (Ph/Ph/Ph)	**2a** (Ph)	**3a** (4-MeC_6H_4)	**5a**/69
2	**1a**	**2a**	**3b** (Ph)	**5b**/62
3	**1b** (Ph/Ph/$PhCH_2$)	**2a**	**3c** (CH_3)	**5c**/60
4	**1a**	**2a**	**3d** (4-ClC_6H_4)	**5d**/52
5	**1b**	**2a**	**3e** (2-naphthyl)	**5e**/59
6	**1a**	**2b** (2-BrC_6H_4)	**3a**	**5f**/52
7	**1a**	**2c** (3-BrC_6H_4)	**3a**	**5g**/58
8	**1a**	**2d** (4-MeC_6H_4)	**3a**	**5h**/65
9	**1a**	**2e** (*n*-C_4H_9)	**3a**	**5i**/66
10	**1b**	**2f** (4-$MeOC_6H_4$)	**3a**	**5j**/39
11	**1b**	**2a**	**3a**	**5k**/78
12	**1c** (Ph/Ph/4-MeC_6H_4)	**2a**	**3a**	**5l**/71
13	**1d** (Ph/Ph/*n*-C_8H_{17})	**2a**	**3a**	**5m**/83
14	**1e** (Ph/4-BrC_6H_4/Ph)	**2a**	**3a**	**5n**/49
15	**1f** (Ph/4-MeC_6H_4/Ph)	**2a**	**3a**	**5o**/50
16	**1g** (Ph/2-furanyl/$PhCH_2$)	**2a**	**3a**	**5p**/59
17	**1h** (Ph/3-$OMeC_6H_4$/ Ph)	**2a**	**3a**	**5q**/64
18	**1i** (4-$OMeC_6H_4$/Ph/Ph)	**2a**	**3a**	**5r**/57
19	**1j** (2-BrC_6H_4/ Ph/$PhCH_2$)	**2a**	**3a**	**5s**/56
20	**1b**	**2a**	**3a**	**5k**/75[d]

[a] Reaction conditions: **1** (1 mmol), **2** (1.1 mmol), **3** (1.2 mmol), Et_3N (1.2 mmol), CuI (0.1 mmol), Cs_2CO_3 (0.5 mmol), MeCN (10 mL). [b] Although the mixture of sulfonyl azides is the safest of a group of diazo compounds, one should keep in mind the inherent instability, shock sensitivity, and explosive power of azides. All users should exercise appropriate caution. [c] Isolated yield referred to **1**. [d] The reaction was performed on 3 mmol scale, 0.2 M.

We then tried to combine the formation and cyclization of **4a** in one pot by adding Cs_2CO_3 after the three-component reaction of **1a**, **2a**, and **3a**. Thus, the two-step one-pot reaction was accomplished successfully. In this case, the total yield for the two-step reaction was 69% when 0.5 equiv of Cs_2CO_3 was used and the reaction was carried out at 80 °C for 4 h.

With the optimized reaction conditions in hand, we investigated the substrate scope for this transformation (Table 3). Several substituted sulfonyl azides **3a**−**e** were examined, and the yields ranged from 52% to 69% (Table 3, entries 1−5). The substituent effect on the alkynes **2a**−**f** was also explored (Table 3, entry 1 and entries 6−10). The strong electron-donating group substituted ethynylbenzene (Table 3, entry 10) gave a much lower yield (39%) than ethynylbenzene (Table 3, entry 5). An aliphatic alkyne, hex-1-yne (**2e**), could also work with a 66% yield (Table 3, entry 9). For substituted propynyl amines, it was found that benzyl amine **1b** (Table 3, entry 11) and aliphatic amine **1d** (Table 3, entry 13) gave higher yields than the aromatic amines **1a**, **1c**, and **1e**−**1j** (Table 3, entries 1, 12, and 14−19) due to the stronger nucleophilicity of **1b** and **1d**.

The gram scale reaction was performed using 3 mmol of **1b**, 3.3 mmol of **2a**, and 3.6 mmol of **3a**. In this case, we obtained 1.28 g of **5k** in 75% yield (Table 3, entry 20). The structure of **5k** was established by X-ray crystal analysis (Figure 1).

To gain good insight into the cyclization mechanism, especially the sulfonyl group shift, we investigated the possibility of a cross reaction between **4b** and **4c** (Scheme 1). Only two products **5o** and **5t** were detected in the reaction mixture. This result suggested that the migration of the sulfonyl group should undergo an intramolecular process.

According to these results, a possible mechanism for this cascade reaction is proposed in Scheme 2. In the first step, ketenimine **A** is generated in situ from **2a** and **3a** via a CuAAC process. Then, the nitrogen of **1a** nucleophilically

(14) (a) Wu, Y. Y.; Zhang, Y. H.; Jiang, Y. W.; Ma, D. W. *Tetrahedron. Lett.* **2009**, *50*, 3683. (b) Yoo, W. J.; Li, C. J. *Adv. Synth. Catal.* **2008**, *350*, 1503. (c) Dube, H.; Gommermann, N.; Knochel, P. *Synthesis.* **2004**, 2015.

(15) For selected examples for the activation of a triple bond using transitional metal salts as Lewis acids, see: (a) Peshkov, V. A.; Pereshivko, O. P.; Sharma, S.; Meganathan, T.; Parmar, V. S.; Ermolat'ev, D. S.; Eycken, E. V. V. D. *J. Org. Chem.* **2011**, *76*, 5867. (b) Giles, R. L.; Sullivan, J. D.; Steiner, A. M.; Looper, R. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 3116. (c) Arcadi, A.; Cacchi, S.; Cascia, L.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2001**, *3*, 2501. (d) Aschwanden, P.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 2331. (e) Barber, D. M.; Sanganee, H.; Dixon, D. J. *Chem. Commun.* **2011**, *47*, 4379. (f) Fei, N.; Yin, H.; Wang, S. Z.; Wang, H. Q.; Yao, Z. J. *Org. Lett.* **2011**, *13*, 4208.

(16) For selected examples for the activation of a triple bond using I_2 or NIS as a Lewis acid, see: (a) Okitsu, T.; Sato, K.; Wada, A. *Org. Lett.* **2010**, *12*, 3506. (b) Zhang, X. X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 12230. (c) Zhang, X. X.; Campo, M. A.; Yao, T. L.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763.

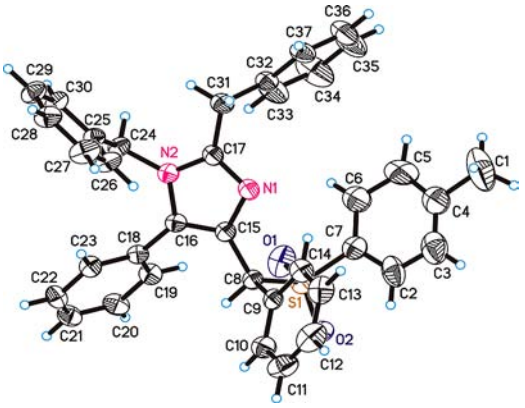
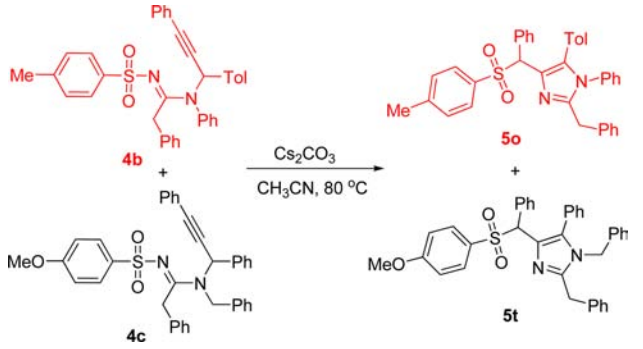


Figure 1. X-ray analysis of **5k**.

Scheme 1. Reaction Design To Validate the Migration of Sulfonyl Group

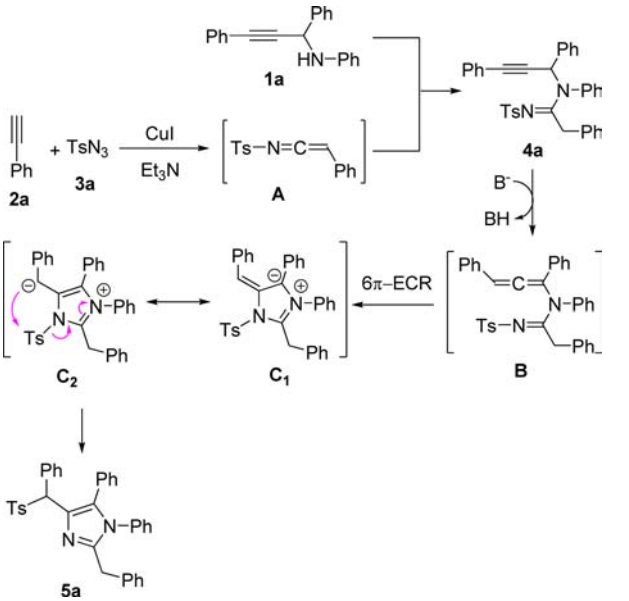


attacks the central carbon of ketenimine **A** to generate **4a**. In the second step, in the presence of base, the propargyl moiety of **4a** may transform into allene **B**,[17] which undergoes a 6π-ECR[18] to form **C** with two resonance structures

(17) (a) Xin, X. Y.; Wang, D. P.; Li, X. C.; Wan, B. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 1693. (b) Saito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2010**, *12*, 372.

(18) For recent examples, see: (a) Hayashi, R.; Walton, M. C.; Hsung, R. P.; Schwab, J. H.; Yu, X. L. *Org. Lett.* **2010**, *12*, 5768. (b) Tang, X. Y.; Wei, Y.; Shi, M. *Org. Lett.* **2010**, *12*, 5120. (c) Hayashi, R.; Feltenberger, J. B.; Hsung, R. P. *Org. Lett.* **2010**, *12*, 1152. (d) Hayashi, R.; Hsung, R. P.; Feltenberger, J. B.; Lohse, A. G. *Org. Lett.* **2009**, *11*, 2125.

Scheme 2. Proposed Mechanism for the Transformation



C_1 and C_2. Finally, the outcome of imidazole **5a** occurs via a sulfonyl 1,3-shift.[19]

In summary, we have developed an efficient approach to tetrasubstituted imidazoles via a two-step one-pot reaction of propargyl amines, *N*-sulfonyl azides, and alkynes. A possible mechanism for this reaction was proposed, which involves the formation of a *N*-sulfonyl ketenimine intermediate and an aminoallene intermediate, a 6π-ECR, and a sulfonyl 1,3-shift. Further investigations on the synthetic applications of this chemistry are ongoing in our laboratory.

Acknowledgment. We thank the National Nature Science Foundation of China (20972137, 21032005).

Supporting Information Available. Experimental procedures, characterization data, and ^{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.

(19) Prasad, B.; Adepu, R.; Sandra, S.; Rambabu, D.; Krishna, G. R.; Reddy, C. M.; Deora, G. S.; Misra, P.; Pal, M. *Chem. Commun.* **2012**, *48*, 10434.

The authors declare no competing financial interest.