

Novel and Efficient Synthesis of Iminocoumarins via Copper-Catalyzed Multicomponent Reaction

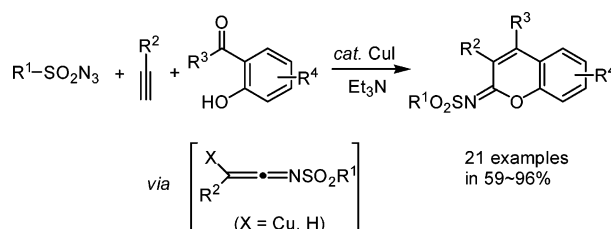
Sun-Liang Cui, Xu-Feng Lin, and Yan-Guang Wang*

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

orgwyg@zju.edu.cn

Received July 9, 2006

ABSTRACT



A variety of substituted iminocoumarins are prepared in good to excellent yields via a copper-catalyzed multicomponent reaction of sulfonamides, terminal alkynes, and salicylaldehydes or *o*-hydroxyacetophenones. The method is general, mild, versatile, and efficient. A plausible mechanism for the domino process is proposed.

Coumarins are an important class of compounds that exist widely in nature and have numerous applications in medicine¹ and perfumery,² as dyes in laser technology,³ and as fluorescent indicators.⁴ A number of coumarins possess interesting biological activity, including anticancer, antifungal, and anti-HIV activities.⁵ Coumarin derivatives, iminocoumarins have been reported to be a type of protein tyrosine kinase (PTK) inhibitors that are most valuable for the treatment of diseases involving excess cell proliferation as well as the antitumor process.⁶ Classic methods for the

synthesis of iminocoumarins, such as Knoevenagel reaction and derivation from coumarins, suffer from major shortcomings such as limited substituents and troublesome chemical managing processes.⁷ Thus general and efficient approaches to iminocoumarin are attractive and challenging.

Multicomponent reactions (MCRs) involving a domino process with at least three different simple substrates have emerged as a powerful strategy.⁸ This methodology allows molecular complexity and diversity to be created by the facile formation of several new covalent bonds in a one-pot transformation quite closely approaching the concept of an ideal synthesis and is particularly well-adapted for combinatorial synthesis.⁹

(1) (a) *Coumarins: Biology, Applications, and Mode of Action*; O'Kennedy, R., Thomas, R. D., Eds.; Wiley: Chichester, UK, 1997. (b) Yu, D.; Suzuki, M.; Xie, L.; Morris-Natschke, S. L.; Lee, K.-H. *Med. Res. Rev.* **2003**, *23*, 322–345. (c) Murray, R. D. H.; Mendez, J.; Brown, S. A. *The Natural Coumarins*; Wiley: Chichester, U.K., 1982.

(2) Clark, G. S. *Perfum. Flavor.* **1995**, *20*, 23–34.

(3) Sekar, N. *Colourage* **2003**, *50*, 55–56.

(4) Brun, M.-P.; Bischoff, L.; Garbay, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3432–3436.

(5) (a) Hariprasad, V.; Talele, T. T.; Kulkarni, V. M. *Pharm. Pharmacol. Commun.* **1998**, *4*, 365–372. (b) Sardari, S.; Nishibe, S.; Daneshmandi, M. *Stud. Nat. Prod. Chem.* **2000**, *23*, 335–393. (c) Lacy, A.; O'Kennedy, R. *Curr. Pharm. Des.* **2004**, *10*, 3797–3811.

(6) (a) Burke, T. R.; Lim, B.; Marquez, V. E.; Li, Z.-H.; Bolen, J. B.; Stefanova, I.; Horak, I. D. *J. Med. Chem.* **1993**, *36*, 425–432. (b) O'Callaghan, C. N.; Conalty, M. L. *Proc. R. Ir. Acad., Sect. B* **1979**, *6*, 87–98.

(7) (a) Volmajer, J.; Toplak, R.; Bittner, S.; Leban, I.; Le Marechal, A. M. *Tetrahedron Lett.* **2003**, *44*, 2363–2366. (b) El-Emary, T. I.; Khalil, A.; El-Hag Ali, G. A. M.; El-Adasy, A. A. M. *Phosphorus, Sulfur Silicon the Relat. Elem.* **2005**, *180*, 19–30.

(8) (a) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223–4225. (b) Liéby-Muller, F.; Constantieux, T.; Rodriguez, J. J. *Am. Chem. Soc.* **2005**, *127*, 17176–17177. (c) Byk, G.; Kabahn, E. *J. Comb. Chem.* **2004**, *6*, 596–603. (d) Marcaccini, S.; Miguel, D.; Torroba, T.; Garcia-Valverde, M. *J. Org. Chem.* **2003**, *68*, 3315–3318. For some recent reviews of MCRs, see: (e) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634. (f) Bienaymé, H.; Hulme, C.; Odon, G.; Schmitt, P. *Chem.-Eur. J.* **2000**, *6*, 3321–3329. (g) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (h) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144.

More recently, Chang et al. reported several CuI-catalyzed multicomponent reactions of sulfonyl azides with alkynes as well as amines, water, or imines, which furnished the synthesis of *N*-sulfonylamidines, hydrative amides, *N*-sulfonylazetid-2-imines.¹⁰ As a part of our research program aiming at new approaches to diverse aromatic ring systems,¹¹ we developed a novel synthesis of substituted iminocoumarins via a CuI-catalyzed multicomponent reaction of sulfonyl azides with alkynes and salicylaldehydes.

We began our investigations by looking into the CuI-catalyzed reaction of *p*-toluenesulfonyl azide (**1a**) with phenyl acetylene (**2a**) and salicylaldehyde (**3a**) in the presence of triethylamine (TEA). When the reaction was performed in CH₂Cl₂ at room temperature for 12 h, we obtained iminocoumarin **4a** (in 82% yield) along with benzopyranone **5** (in 8% yield).¹² We then tried to optimize the reaction conditions for the selective formation of iminocoumarin **4a**. As shown in Table 1, the desired product

Table 1. CuI-Catalyzed Reaction of *p*-Tolylsulfonyl Azide with Phenylacetylene and Salicylaldehyde under Various Conditions

entry	base ^a	solvent	temp (°C)	time (h)	yield (%) ^b	
					4a	5
1	TEA	CH ₂ Cl ₂	rt	12	82	8
2	TEA	CH ₃ CN	rt	12	57	12
3	TEA	THF	rt	12	91	trace
4	Pyridine	THF	rt	12	68	trace
5	K ₂ CO ₃	CH ₂ Cl ₂	rt	12	41	trace
6	TEA	THF	50	12	87	5
7	TEA	THF	rt	6	78	trace

^a 2 equiv of base was used. ^b Yields refer to phenyl acetylene.

could be obtained in 57–82% yield using CH₃CN or CH₂-Cl₂ as a solvent (Table 1, entry 1 and 2). THF afforded high yield and selectivity (Table 1, entry 3). Other bases, such as

(9) de Meijere, A.; Nüske, H.; Es-Sayed, M.; Labahn, T.; Schroen, M.; Bräse, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3669–3672.

(10) (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*, 16046–116047. (c) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347–1350. (d) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154–3157. (e) Whiting, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3157–3161.

(11) (a) Wang, Y. G.; Cui, S. L.; Lin, X. F. *Org. Lett.* **2006**, *8*, 1241–1244. (b) Cui, S. L.; Lin, X. F.; Wang, Y. G. *J. Org. Chem.* **2005**, *70*, 2866–2869.

(12) Benzopyranone **5** was previously synthesized from phenyl acetylene and salicylaldehyde, see: Lin, C. F.; Lu, W. D.; Wang, I. W.; Wu, M. J. *Synlett* **2003**, 2057–2061.

pyridine and K₂CO₃, gave low yields (Table 1, entries 4 and 5). Increasing the temperature to 50 °C (Table 1, entry 6) or shortening the reaction time to 6 h (Table 1, entry 7) led to a significant decrease of yield.

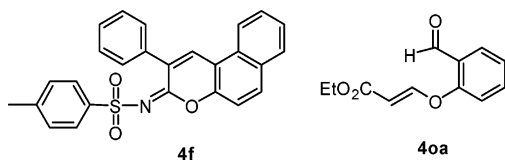
As a next step, we investigated the scope of the reaction with various sulfonyl azides, terminal alkynes, and salicylaldehydes or 2-hydroxyl-1-naphthaldehyde under the optimized reaction conditions (Table 2). It was found that all

Table 2. CuI-Catalyzed Multicomponent Reaction of Sulfonyl Azides, Alkynes, Salicylaldehyde, or 2-Hydroxyl-1-naphthaldehyde for the Synthesis of Iminocoumarins^a

entry	R ¹	R ²	R ³	product	yield (%) ^b
1	4-MeC ₆ H ₄ (1a)	Ph (2a)	H (3a)	4a	91
2	C ₆ H ₅ (1b)	2a	4-Br (3b)	4b	93
3	4-ClC ₆ H ₄ (1c)	2a	5-CH ₃ O (3c)	4c	90
4	Me (1d)	2a	3a	4d	91
5	1d	2a	3b	4e	89
6	1a	2a	2-hydroxyl-1-naphthaldehyde (3d)	4f	89
7	1a	4-EtC ₆ H ₄ (2b)	3b	4g	91
8	1b	4-FC ₆ H ₄ (2c)	3a	4h	88
9	1a	4-MeOC ₆ H ₄ (2d)	3a	4i	93
10	1d	pyridine-2-yl (2e)	3a	4j	64
11	1c	<i>n</i> -Bu (2f)	3c	4k	95
12	1c	<i>t</i> -Bu (2g)	3b	4l	96
13	1a	THPOCH ₂ (2h)	3a	4m	95
14	1a	TMS (2i)	3d	4n	71
15	1a	CO ₂ Et (2j)	3a	4o	59

^a Sulfonyl azide (1 mmol), alkyne (1 mmol), salicylaldehyde (1.1 mol), TEA (2 mmol), and CuI (0.1 mmol) in THF (3 mL). ^b Isolated yields refer to alkyne.

phenyl and methylsulfonyl azides worked well to give the corresponding iminocoumarins in moderate to excellent yields. 2-Hydroxyl-1-naphthaldehyde (**3d**) (Table 2, entry 6) gave benzocoumarin **4f** in comparable yield with salicylaldehyde (**3a**) (Table 2, entry 5). The conjugated alkyne ethyl propiolate (**2j**) afforded the desired product **4o** in low yield (Table 2, entry 15) with byproduct **4oa**, which is believed to be the product of Michael addition of **2j** and **3a**.



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

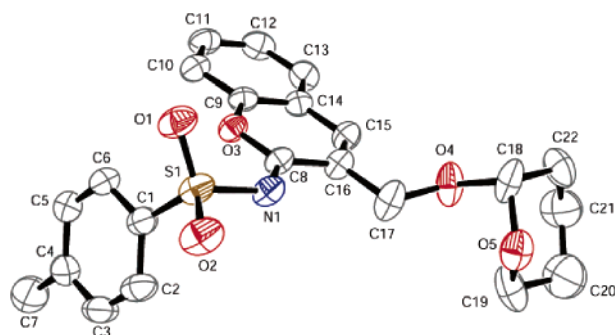


Figure 1. X-ray crystal structure of compound **4m**.

Encouraged by these results obtained with salicylaldehydes and 2-hydroxyl-1-naphthaldehyde, we extended our reaction to *o*-hydroxyacetophenone (**6**) (Table 3). It was found that

Table 3. CuI-Catalyzed Multicomponent Reaction of Sulfonyl Azides, Alkynes, and *o*-Hydroxyacetophenone^a

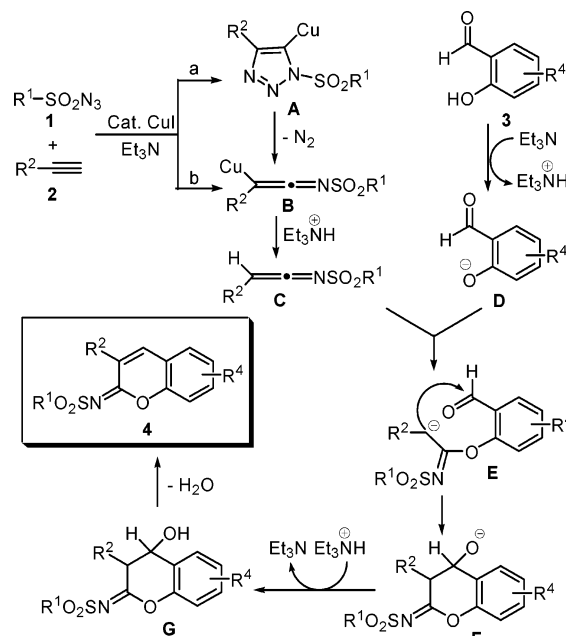
$\begin{array}{c} \text{R}^1\text{-SO}_2\text{N}_3 \\ \mathbf{1} \\ \text{R}^2\text{-}\equiv \\ \mathbf{2} \end{array} + \begin{array}{c} \text{O} \\ \parallel \\ \text{HO-C}_6\text{H}_4 \\ \mathbf{6} \end{array} \xrightarrow[\text{THF, 12 h}]{\begin{array}{c} 0.1 \text{ equiv CuI} \\ 2 \text{ equiv TEA} \end{array}} \begin{array}{c} \text{R}^2\text{-CH}_3 \\ \text{R}^1\text{O}_2\text{SN} \\ \text{O} \\ \parallel \\ \text{C}_6\text{H}_4 \\ \mathbf{7} \end{array}$				
entry	R ¹	R ²	product	yield (%) ^b
1	1a	2a	7a	77
2	1b	2a	7b	80
3	1d	2a	7c	75
4	1c	2b	7d	81
5	1a	2f	7e	65
6	1b	2h	7f	68

^a Sulfonyl azide (1 mmol), alkyne (1 mmol), *o*-hydroxyacetophenone (1.1 mmol), TEA (2 mmol), and CuI (0.1 mmol) in THF (3 mL). ^b Isolated yields refer to alkyne.

o-hydroxyacetophenone followed the same rules as salicylaldehyde, giving the corresponding iminocoumarins (**7a–f**) in 65–81% yields (Table 3, entries 1–6).

We propose a plausible mechanism for this three-component domino process as shown in Scheme 1. In the presence of TEA and CuI, sulfonyl azide **1** reacts with alkyne to form the ketenimine species **B** through two possible pathways (Scheme 1, pathways a and b) according to

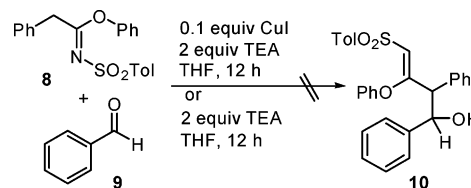
Scheme 1. Postulated Mechanism for Formation of Iminocoumarins



Chang's proposal.¹⁰ Protonation of **B** gives rise to the highly reactive ketenimine **C**, which is quickly attacked by nucleophile **D** to generate the anionic intermediate **E**. The subsequent intramolecular nucleophilic addition of **E** followed by protonation and dehydration generates iminocoumarin **4**.

The intramolecular nucleophilic addition of the anionic intermediate **E** is one of critical steps for the domino process, which is supported by the fact that the intermolecular reaction between imide **8** and benzaldehyde (**9**) did not take place whether in the presence or in the absence of CuI (Scheme 2).

Scheme 2. Intermolecular Reaction between Imide **8** and Benzaldehyde



In summary, we have developed a general, mild, efficient, and versatile synthesis of substituted iminocoumarin derivatives via a multicomponent reaction of sulfonyl azides, terminal alkynes, and salicylaldehydes. The starting materials are commercially available or readily prepared. The synthetic applications of this method are under investigation.

Acknowledgment. We thank the Specialized Research Fund for Doctoral Program of Higher Education (20050335101), the Natural Science Foundation of Zhejiang

Province (R404109), as well as the Teaching and Research Award Program for Outstanding Young Teachers in Higher Education Institutions of MOE, P.R.C.

Supporting Information Available: Detailed experimental procedures, characterization data, copies of ^1H and

^{13}C NMR spectra for all products and crystallographic information files in CIF format for compound **4l**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL061685W