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

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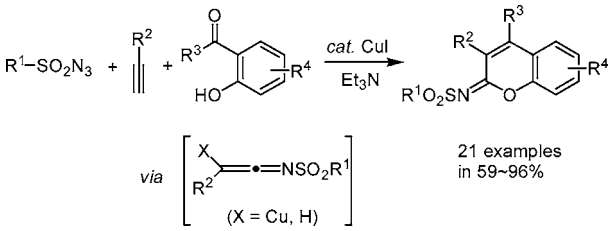
ABSTRACT



A variety of substituted iminocoumarins are prepared in good to excellent yields via a copper-catalyzed multicomponenet reaction of sulfonyl azides, terminal alkynes, and salicylaldehydes or *o*-hydroxylacetophenones. 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 medicine[1] 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]

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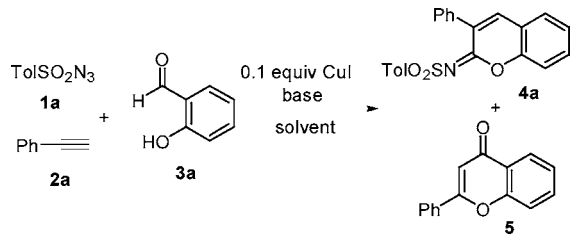
More recently, Chang et al. reported several CuI-catalyzed muticomponent reactions of sulfonyl azides with alkynes as well as amines, water, or imines, which furnished the synthesis of *N*-sulfonylamidines, hydratuve amides, *N*-sulfonylazetidin-2-imines.[10] As a part of our research program aiming 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 CH_2Cl_2 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



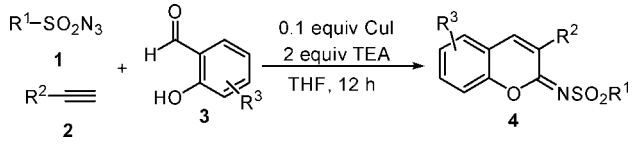
entry	base[a]	solvent	temp (°C)	time (h)	yield (%)[b] 4a	5
1	TEA	CH_2Cl_2	rt	12	82	8
2	TEA	CH_3CN	rt	12	57	12
3	TEA	THF	rt	12	91	trace
4	Pyridine	THF	rt	12	68	trace
5	K_2CO_3	CH_2Cl_2	rt	12	41	trace
6	TEA	THF	50	12	87	5
7	TEA	THF	rt	6	78	trace

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

could be obtained in 57−82% yield using CH_3CN or CH_2Cl_2 as a solvent (Table 1, entry 1 and 2). THF afforded high yield and selectivity (Table 1, entry 3). Other bases, such as pyridine and K_2CO_3, 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_6H_4 (**1a**)	Ph (**2a**)	H (**3a**)	**4a**	91
2	C_6H_5 (**1b**)	**2a**	4-Br (**3b**)	**4b**	93
3	4-ClC_6H_4 (**1c**)	**2a**	5-CH_3O (**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_6H_4 (**2b**)	**3b**	**4g**	91
8	**1b**	4-FC_6H_4 (**2c**)	**3a**	**4h**	88
9	**1a**	4-$MeOC_6H_4$ (**2d**)	**3a**	**4i**	93
10	**1d**	pyridine-2-yl (**2e**)	**3a**	**4j**	64
11	**1c**	n-Bu (**2f**)	**3c**	**4k**	95
12	**1c**	*t*-Bu (**2g**)	**3b**	**4l**	96
13	**1a**	$THPOCH_2$ (**2h**)	**3a**	**4m**	95
14	**1a**	TMS (**2i**)	**3d**	**4n**	71
15	**1a**	CO_2Et (**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**.

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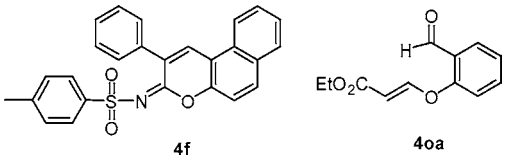


The structure of iminocoumarin **4m** was unambiguously confirmed by X-ray diffration analysis, which was in accordance with ^{1}H NMR, ^{13}C NMR, and HRMS spectra (Figure 1).

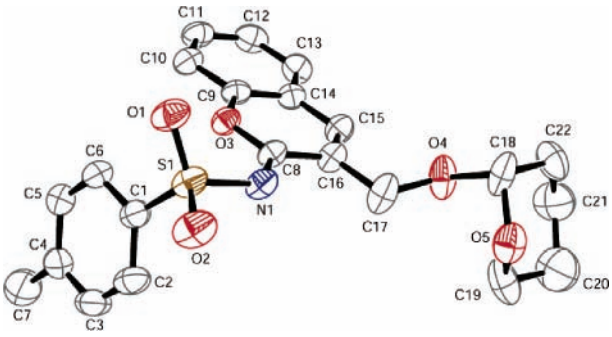
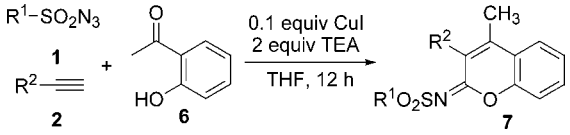


Figure 1. X-ray crystal structure of compound **4m**.

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

Table 3. CuI-Catalyzed Multicomponent Reaction of Sulfonyl Azides, Alkynes, and *o*-Hydroxylacetophenone[a]



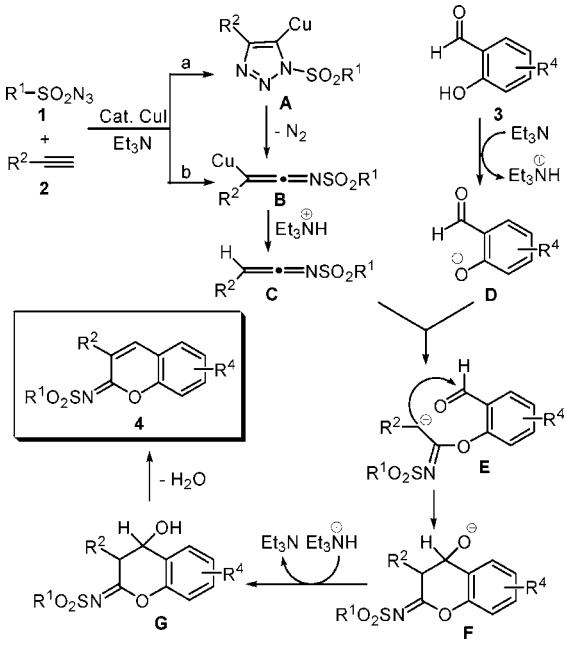
entry	R^1	R^2	product	yield (%)[b]
1	**1a**	**2a**	**7a**	77
2	**1b**	**2a**	**7b**	80
3	**1d**	**2a**	**7c**	75
4	**1c**	**2b**	**7d**	81
5	**1a**	**2f**	**7e**	65
6	**1b**	**2h**	**7f**	68

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

o-hydroxylacetophenone 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

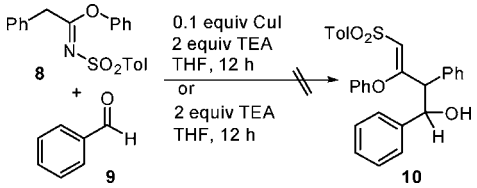
Scheme 1. Postulated Mechanism for Formation of Iminocoumarins



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 imidate **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 Imidate **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.

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Supporting Information Available: Detailed experimental procedures, characterizaton data, copies of ^{1}H 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.

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