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Novel Copper-Catalyzed Multicomponent Cascade Synthesis of Iminocoumarin Aryl Methyl Ethers

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ABSTRACT

A copper(I)-catalyzed one-pot synthesis of iminocoumarin aryl methyl ethers has been developed from ynal, phenol, and sulfonyl azide at ambient conditions *via* a cascade [3 + 2]-cycloaddition, 1,3-pseudopericyclic ketenimine rearrangement, 1,4-conjugate addition, and aldol-type condensation. This protocol provides a potential route for the construction of a library of iminocoumarin aryl methyl ethers in good yields.

The transformation of simple substrates into a library of complex molecules with structural diversity constitutes a great challenge in organic synthesis. The use of a one-pot multicomponent reaction (MCR) with cascade processes offers an extremely powerful tool for this strategy.[1−6] Iminocoumarins are privileged structural frameworks exhibiting widespread biological, medicinal, and material applications. For example, iminocoumarins exhibit antitumor,[7a] anticancer,[7b] and antimicrobial properties.[7c] In addition, they serve as inhibitors of protein-tyrosine kinase p56lck,[7d] dynamins I and II GTPase,[7e] and HIV-1 integrase.[7f] Furthermore, iminocoumarins are widely used as dyes[8a] and fluorescent sensors for the estimation of metal ions in micromolar concentrations.[8b] Whereas the common methods for the synthesis of iminocoumarins take advantage of the Knoevenagel reaction,[9] some difficulties are often encountered such as the limited substrate scope and harsh reaction conditions. Development of effective methods for the synthesis of iminocoumarin

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derivatives is thus attractive and challenging. Recently, Wang and co-workers reported the copper(I)-catalyzed synthesis of iminocoumarins from an alkyne and sulfonyl azide with either salicylaldehyde[5t] or 2-ethynylphenol[5u] (Scheme 1). In continuation of our studies on heterocycle syntheses,[10] we report herein the synthesis of iminocoumarin aryl methyl ethers **4** from the coupling of ynals **1**, phenols **2**, and sulfonyl azides **3** using copper(I) catalysis *via* a cascade [3 + 2]-cycloaddition, ketenimine rearrangement,[11] 1,4-conjugate addition, and aldol condensation. This protocol provides a potential route for the synthesis of the target products using the rearrangement of the ketenimine as a key step.

First, our investigation started with ynal **1a**, phenol **2a**, and *p*-toluenesulfonyl azide (TsN_3) **3a** as the model substrates for the scrutinization of the reaction conditions, which was carried out using different Cu(I) sources, bases, additives, and solvents at room temperature under air (Table 1). Gratifyingly, the reaction proceeded to afford the iminocoumarin aryl methyl ether **4a** in 30% yield when the substrates **1a**, **2a**, and **3a** were reacted with 10 mol % CuI and 2.2 equiv of K_2CO_3 in CH_2Cl_2 under ambient conditions (entry 2). Surprisingly, the use of tetrabutylammonium iodide (TBAI) as an additive led to an increase in the yield to 83%, whereas tetrabutylammonium bromide (TBAB) and tetrabutylammonium chloride (TBAC) afforded a 76% and 71% yield, respectively.[12] In a set of bases screened, K_2CO_3 furnished the best results, while Na_2CO_3 resulted in a moderate yield. In contrast, Cs_2CO_3, K_3PO_4, and Et_3N showed no effect for the target reaction. CuI provided a superior yield compared to the other copper(I) salts such as CuBr, CuCl, and Cu_2O that were tested. Consequently, CH_2Cl_2 was found to be the solvent of choice. Other solvents such as toluene, THF, CH_3CN, and 1,2-dichloroethane has no appreciable effect on **4a**, as it resulted in a sluggish conversion. A control experiment confirmed that, without the Cu source, the target reaction was not observed.

With the optimal conditions in hand, the scope of the procedure was next explored for the reactions of a series of substituted phenols **2a**–**n** with ynal **1a** and azide **3a** as standard substrates (Table 2). The reactions occurred readily to afford the target heterocycles in good yields. For example, the reactions of the substituted phenols **2a**–**e** with phenyl, 2-iodo, 3-bromo, and 2-methyl groups furnished the iminocoumarin aryl methyl ethers **4a**–**e** in 55–79% yields, while the phenols **2f**–**h** with 4-fluoro,

Scheme 1. Multicomponent Syntheses of Iminocoumarins

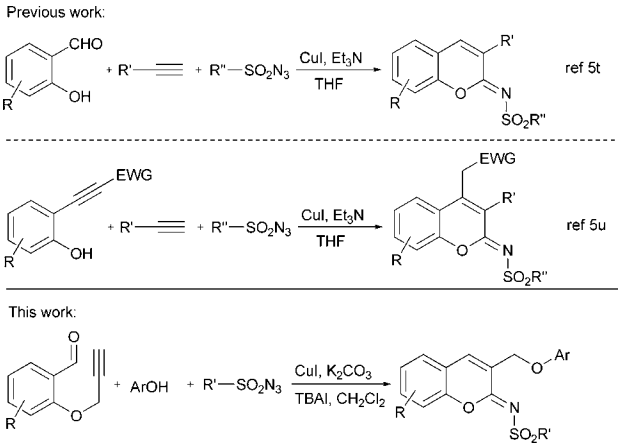
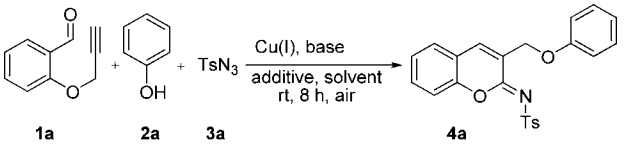


Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3a** **4a**

entry	catalyst	base	additive	solvent	yield (%)[b]
1	CuI	Et_3N	–	CH_2Cl_2	n.d.
2	CuI	K_2CO_3	–	CH_2Cl_2	30
3	CuI	K_2CO_3	TBAB	CH_2Cl_2	76
4	CuI	K_2CO_3	TBAC	CH_2Cl_2	71
5	**CuI**	**K_2CO_3**	**TBAI**	**CH_2Cl_2**	**83**
6	CuI	K_2CO_3	TBAI	CH_3CN	42
7	CuI	K_2CO_3	TBAI	$(CH_2Cl)_2$	74
8	CuI	K_2CO_3	TBAI	THF	28
9	CuI	K_2CO_3	TBAI	toluene	60
10	CuI	Na_2CO_3	TBAI	CH_2Cl_2	35
11	CuI	Cs_2CO_3	TBAI	CH_2Cl_2	n.d.
12	CuI	K_3PO_4	TBAI	CH_2Cl_2	n.d.
13	CuBr	K_2CO_3	TBAI	CH_2Cl_2	67
14	CuCl	K_2CO_3	TBAI	CH_2Cl_2	71
15	Cu_2O	K_2CO_3	TBAI	CH_2Cl_2	41
16	–	K_2CO_3	TBAI	CH_2Cl_2	n.d.

[a] Ynal **1a** (0.5 mmol), phenol **2a** (0.6 mmol), azide **3a** (0.6 mmol), catalyst (10 mol %), base (1.1 mmol), additive (10 mol %), solvent (3.0 mL), 8 h, air. [b] Determined by 400 MHz ^{1}H NMR. n.d. = not detected.

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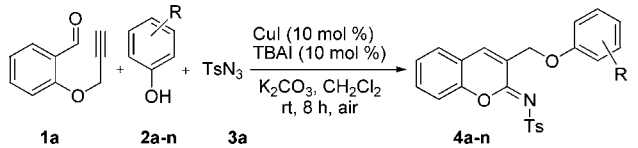
4-bromo, and 4-chloro groups reacted to give the target products **4f**–**h** in 60–63% yields. Similar results were observed with the phenols **2i**–**k** containing 4-CHO, 4-methoxy, and 4-methyl substituents affording **4i**–**k** in 49–66% yields, whereas the disubstituted phenols **2l**–**n** with dimethyl groups gave the iminocoumarin aryl methyl ethers **4l**–**n** in 72–77% yields. Phenols containing electron-donating groups exhibited greater reactivity in comparison to bearing-electron withdrawing groups. The crystallization of **4j** in a 1:1 mixture of CH_2Cl_2 and MeOH gave crystals whose structure was confirmed by a single crystal X-ray analysis (Figure 1).

Table 2. Reaction of Ynal **1a**, *p*-Toluene Sulfonyl Azide **3a** with Different Substituted Phenols[a]



entry	2	R	4	yield (%)[b]
1	**2a**	H	**4a**	79
2	**2b**	2-I	**4b**	60
3	**2c**	2-Me	**4c**	78
4	**2d**	3-Br	**4d**	55
5	**2e**	3-Me	**4e**	64
6	**2f**	4-Br	**4f**	61
7	**2g**	4-Cl	**4g**	60
8	**2h**	4-F	**4h**	63
9	**2i**	4-CHO	**4i**	49
10	**2j**	4-MeO	**4j**	66
11	**2k**	4-Me	**4k**	65
12	**2l**	2,3-Me_2	**4l**	72
13	**2m**	3,4-Me_2	**4m**	77
14	**2n**	3,5-Me_2	**4n**	74

[a] Ynal **1a** (0.5 mmol), phenol **2** (0.6 mmol), azide **3a** (0.6 mmol), CuI (10 mol %), K_2CO_3 (1.1 mmol), TBAI (10 mol %), CH_2Cl_2 (3.0 mL), 8 h, air. [b] Isolated yield.

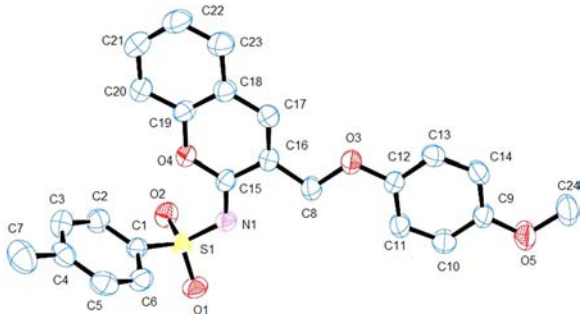
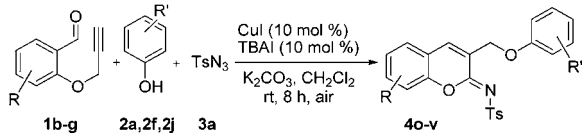


Figure 1. ORTEP diagram of (*Z*)-*N*-(3-((4-methoxyphenoxy)-methyl)-2*H*-chromen-2-ylidene)-4-methylbenzenesulfonamide **4j**. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity.

The reaction of the substituted ynals **1b**–**g** was further studied with phenols **2a**, **2f**, and **2j** and *p*-toluenesulfonyl azide **3a** (Table 3). As above, the reactions took place to provide the iminocoumarin aryl methyl ethers in good yields. The ynals **1b**–**c** bearing a methoxy group underwent reactions with phenol **2a** to give the target products **4o**–**p** in 70% and 62% yield, respectively. Likewise, the ynal **1d** with the 5-bromo substituent proceeded to react with phenols **2a** and **2j** to furnish the desired heterocycles **4q**–**r** in 57% and 65% yield, respectively, while the ynal **1e** having a 5-methoxy group reacted with **2a** and **2f** to provide **4s**–**t** in 65%–71% yield. Similarly, the ynals **1f**–**g** with 5-methyl and di-*tert*-butlyl groups proceeded to react with **2a** to give the iminocoumarin aryl methyl ethers **4u**–**v** in 63%–77% yield.

Finally, the reaction of sulfonyl azides **3b**–**d** was examined with ynal **1a** and phenol **2a** (Table 4). These substrates proceeded to react in moderate to good yields. For example, the reactions of methanesulfonyl azide **3b**

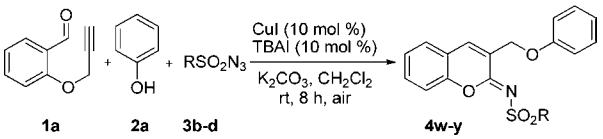
Table 3. Reaction of *p*-Toluene Sulfonyl Azide with Different Substituted Ynals and Phenols[a]



entry	1	R	2	R′	4	yield (%)[b]
1	**1b**	3-MeO	**2a**	H	**4o**	70
2	**1c**	4-MeO	**2a**	H	**4p**	62
3	**1d**	5-Br	**2a**	H	**4q**	57
4	**1d**	5-Br	**2j**	4-MeO	**4r**	65
5	**1e**	5-MeO	**2a**	H	**4s**	65
6	**1e**	5-MeO	**2f**	4-Br	**4t**	71
7	**1f**	5-Me	**2a**	H	**4u**	77
8	**1g**	3,5-*t*-Bu_2	**2a**	H	**4v**	63

[a] Ynal **1** (0.5 mmol), phenol **2** (0.6 mmol), azide **3a** (0.6 mmol), CuI (10 mol %), K_2CO_3 (1.1 mmol), TBAI (10 mol %), CH_2Cl_2 (3.0 mL), 8 h, air. [b] Isolated yield.

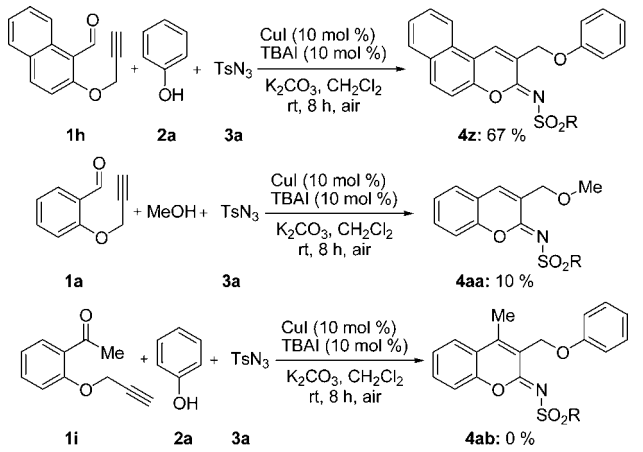
Table 4. Reaction of Ynal **1a**, Phenol **2a** with Different Sulfonyl Azides[a]



entry	3	R	4	yield (%)[b]
1	**3b**	Me	**4w**	70
2	**3c**	Ph	**4x**	67
3	**3d**	4-$NO_2C_6H_4$	**4y**	39

[a] Ynal **1a** (0.5 mmol), phenol **2a** (0.6 mmol), azide **3** (0.6 mmol), CuI (10 mol %), K_2CO_3 (1.1 mmol), TBAI (10 mol %), CH_2Cl_2 (3.0 mL), 8 h, air. [b] Isolated yield.

Scheme 2

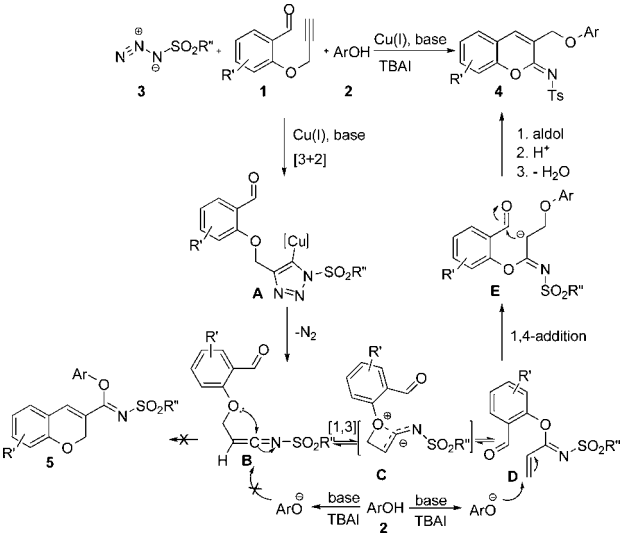


and phenylsulfonyl azide **3c** could be accomplished in 70% and 67% yield, respectively, while the azide **3d** with a nitro group exhibited moderate reactivity affording the iminocoumarin aryl methyl ether **4y** in 39% yield. This study revealed that the reaction is not limited to only tosyl azide, but other types of sulfonyl azide such as methane sulfonyl azide, benzenesulfonyl azide, and *p*-nitrobenzenesulfonyl azide can also be utilized. The substrates with an electron-donating group exhibited greater reactivity compared to those having electron-withdrawing groups.

The protocol was further examined for the reaction of ynal **1h** with phenol **2a** and sulfonyl azide **3a** (Scheme 2). The reaction occurred to give the iminocoumarin aryl methyl ether **4z** in 67% yield. Under these conditions, the use of methanol in place of phenol **2a** was less effective affording the iminocoumarin methyl methyl ether **4aa** in 10% yield. Futhermore, the reaction of ketone **1i** was studied with phenol **2a** and sulfonyl azide **3a**. However, the substrate **1i** underwent decomposition and the target product **4ab** was not obtained.

The proposed catalytic cycle is shown in Scheme 3. The Cu(I)-catalyzed azide−alkyne cycloaddition (CuAAC) of alkyne **1** with azide **2** may generate ketenimine[5] **B** via intermediate **A**, which may undergo the pseudopericyclic [1,3]-migration[11] of 2-formylaryloate through the four-membered cyclic zwitterionic transition state **C** to give the intermediate **D**. The 1,4-conjugate addition of the phenoxide ion with **D** may lead to the formation of the intermediate **E**. The aldol-type condensation followed by dehydration of **E** could yield the target product **4**. The absence of the formation of **5** suggests that this protocol involves the rearrangement of the ketenimine **B** to afford **D** compared to the direct intermolecular reaction of the ketenimine **B** with the phenoxide ion that could lead to **5**.

Scheme 3. Proposed Catalytic Cycle



In summary, we have developed a copper-catalyzed three-component synthesis of iminocoumarin aryl methyl ethers from ynal **1**, phenols **2**, and sulfonyl azide **3** at room temperature under air. The reaction takes place *via* a cascade [3 + 2]-cycloaddition, ketenimine rearrangement, 1,4-conjugate addition, and aldol-type condensation. This protocol allows us to rapidly generate a series of functionalized iminocoumarin aryl methyl ethers that are of tremendous importance in medicinal and material sciences. Further studies on the precise mechanism and application to other reactions are currently underway.

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Supporting Information Available. Experimental procedure, characterization data, and NMR spectra (^{1}H and ^{13}C) of the products **4a**−**4aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.