Synthetic Methods

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Copper-Catalyzed Coupling of Oxime Acetates with Sodium Sulfinates: An Efficient Synthesis of Sulfone Derivatives**

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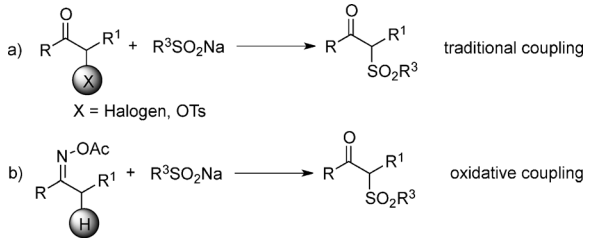
Abstract: *Sulfone derivatives are important synthetic intermediates. However, the general method for their preparation is through traditional coupling reaction: the alkylation of sodium sulfinates with phenacyl halides. Based on our previous work on sodium sulfinates and oxime acetates, we herein report a novel method for sulfone derivatives by oxidative coupling with sodium sulfinates and oxime acetates using copper as catalyst. The sulfonylvinylamine products could be formed in excellent yields. Upon hydrolysis by silica gel in CH_2Cl_2, β-ketosulfones could also be efficiently constructed. Various sulfonylvinylamines and β-ketosulfones were obtained in good to excellent yields under the optimized reaction conditions. Mechanistic studies indicated that this transformation involved copper-catalyzed N–O bond cleavage, activation of a vinyl sp^2 C–H bond, and C–S bond formation. The oxime acetates act as both a substrate and an oxidant, thus the reaction needs no additional oxidants or additives.*

Oxidative coupling has emerged as an attractive and challenging method to construct carbon–carbon and carbon–heteroatom bonds, an eco-friendly and green method.[1] This strategy has been realized by many kinds of catalysts, such as enzymes, organocatalysts, transition metals,[2] among others. Transition-metal-catalyzed oxidative coupling reactions, generally with the use of oxidants, have successfully been developed and applied in laboratory and industrial chemical syntheses;[3] these have many advantages, such as simplifying reaction steps, reducing waste, and maximizing resource efficiency. However, it also faces some challenges: the late transition metal catalysts are expensive and toxic, and stoichiometric amounts of oxidants, such as $PhI(OAc)_2$, H_2O_2, and copper salts, are needed. Therefore, the first-row transition metals, especially copper[4] and iron,[5] have received more and more attention recently, owing to their availability, low cost, low toxicity, and ease of use. To solve the oxidant problem, green oxidants such as O_2[6] or an internal oxidant[7] are used. Reactions that use an internal oxidant are redox neutral, and do not need stoichiometric external oxidants; oxime is one such internal oxidant.[8] Traditionally, oximes are used for constructing amides and nitriles, and for the development of metal catalysis, oxime derivatives have been applied to Pd-,[9a,b] Rh-,[9c–e] Fe-,[9f,g] and Cu-catalyzed[9h-j] reactions. Among which, copper not only shows good catalytic activity, but also is one of the most readily available metals.

β-Ketosulfones important synthetic intermediates, which have been widely used in the construction of natural products, such as lycopodine alkaloid,[10] polyfunctionalized 4H-pyrans,[11] quinolines,[12] vinyl sulfones, among others. They can be easily transformed into the corresponding alkynes,[13] epoxy sulfones, and β-hydoxysulfones. They are also used in antifungal and antibacterial drugs, and are potent nonnucleoside inhibitors. owing to their good reactivity and synthetic utility, numerous methods have been reported for their preparation.[14] The general method is a traditional coupling: the alkylation of sodium sulfinates with phenacyl halide (Scheme 1a). However, they often have drawbacks, such as prolonged reaction times, the use of expensive reagents, multistep syntheses, and the limitations of phenacyl halide. The biggest problem is the limitations of the reaction substrates. Therefore, it is meaningful and challenging to develop new methods that use new reagents and go through a new mechanism to obtain β-ketosulfones. Based on our previous work with sodium sulfinates (Scheme 2a),[15a] oxime acetates (Scheme 2b),[15b] and copper-catalyzed carbon–heteroatom bond and carbon–carbon bond construction,[15c–f] we wondered whether we could construct β-ketosulfones through oxidative coupling using copper as a catalyst and green oxidants such as O_2 or an internal oxidant (Scheme 1b). Herein, we report a copper-catalyzed synthesis of sulfone derivatives from oxime acetates and sodium sulfinates (Scheme 2c). The oxime acetates are used as an internal oxidant; external oxidants are not necessary. To the best of our knowledge, it is the first example of the construction of β-



Scheme 1. Traditional coupling and oxidative coupling reactions. OTs = *para*-toluenesulfonate.

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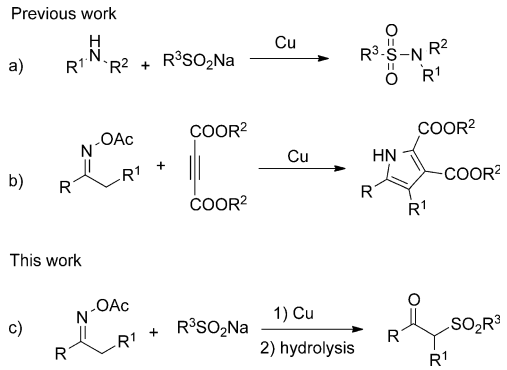
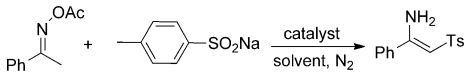


Scheme 2. Copper catalyzed coupling reactions.

ketosulfones and β-sulfonylvinylamines by transition-metal-catalyzed direct C–S bond formation through oxidative coupling with vinyl sp^2 C–H bonds using internal oxidant.

Our initial investigations of this copper-catalyzed coupling of oxime acetates with sodium sulfinates focused on acetophenone oxime acetate (**1a**) with sodium *p*-toluenesulfinate (**2a**) in the presence of CuI in toluene at 100 °C under N_2. We were excited that the desired product **3aa** could be detected in 77 % yield (Table 1, entry 1). The screening of

Table 1: Impact of reaction parameters on the coupling of oxime acetate with sodium sulfinate.[a]



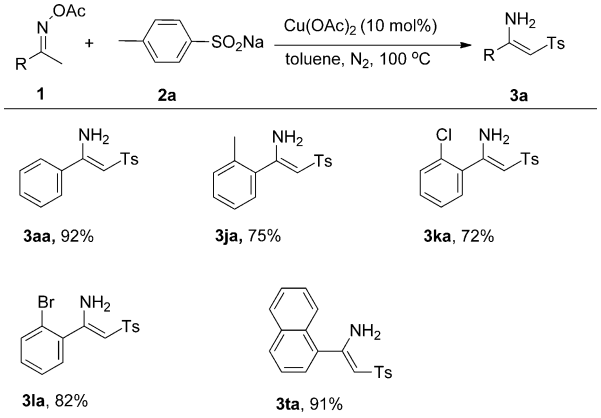
1a **2a** **3aa**

Entry	Catalyst	Solvent	Yield [%][b]
1	CuI	toluene	77
2	CuBr	toluene	82
3	CuCl	toluene	85
4	$Cu(OTf)_2$	toluene	80
5	$CuBr_2$	toluene	82
6	$CuCl_2$	toluene	84
7	**$Cu(OAc)_2$**	**toluene**	**95 (92)**
8	none	toluene	0
9	$Cu(OAc)_2$	DCE	62
10	$Cu(OAc)_2$	1,4-dioxane	81
11	$Cu(OAc)_2$	DMF	76
12	$Cu(OAc)_2$	DMSO	87

[a] Unless otherwise noted, all reactions were performed with **1a** (0.5 mmol), **2a** (0.5 mmol), and catalyst (10 mol %), in 2 mL solvent at 100 °C for 6 h. [b] Yields determined by GC analysis; value in parenthesis is the yield of the isolated product. Ac = acetyl, Tf = trifluoromethanesulfonyl.

different copper salts, such as CuBr, CuCl, $Cu(OTf)_2$, $CuBr_2$, $CuCl_2$, and $Cu(OAc)_2$, revealed that **3aa** could be formed in good yields (entries 2–7). $Cu(OAc)_2$ was found to be the best and the yield could reach 95 %. Other metal species such as AgCl, $NiCl_2$, $MnCl_3$, $PdCl_2$, and $CoCl_2$ did not show any catalytic activity, and no product was formed without metal catalysts (entry 8). Different solvents were also examined (entries 9–12). When 1,2-dichloroethane (DCE), 1,4-dioxane, *N*,*N*-dimethylformamide (DMF), and DMSO were used as solvents, the yields of **3aa** were 62 %, 81 %, 76 %, and 87 %, respectively, with toluene giving the best result for this reaction. Thus, the optimized catalytic system for this copper-catalyzed coupling reaction was: **1a** (0.5 mmol), **2a** (0.5 mmol), $Cu(OAc)_2$ (10 mol %), in toluene at 100 °C under N_2 for 6 h.

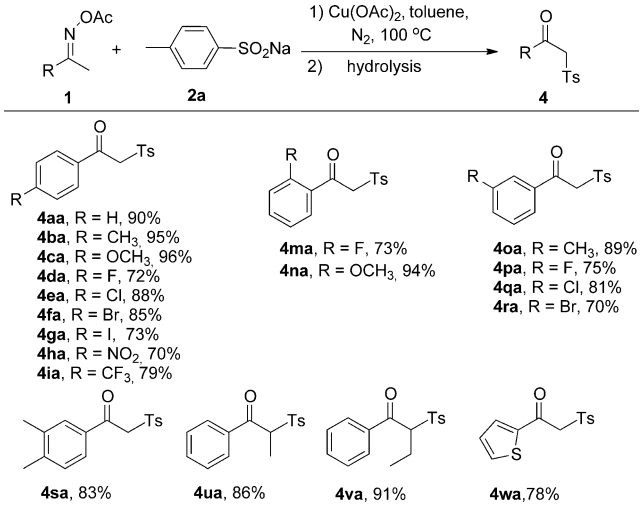
With the optimized reaction conditions in hand, we then explored the scope of the substrates (Scheme 3). The products **3aa**, **3ja**, **3ka**, **3la**, and **3ta** were isolated in good to excellent yields (72–92 %). A single crystal of product **3ta** was obtained



Scheme 3. Preliminary substrate screen. All reactions were performed with **1** (0.5 mmol), **2a** (0.5 mmol), $Cu(OAc)_2$ (10 mol %), in toluene (2 mL) at 100 °C under N_2 for 6 h. Yields shown are of isolated products.

by slow crystallization from a mixture of petroleum ether and ethyl acetate, and its structure was confirmed by single-crystal X-ray analysis.[16] Owing to the intramolecular hydrogen bonding between the sulfone groups and amine, the enamine has a *Z* alkene geometry. To the best of our knowledge, very few methods have been developed to construct β-sulfonylvinylamines.[17,18]

As β-ketosulfones are important synthons, we decided to take β-ketosulfones as our final product (catalytic reaction followed by hydrolysis), to explore this transformation (Scheme 4). Various oxime acetates could couple with sodium *p*-tolylsulfinate to form sulfonylvinylamine, which was transformed into β-ketosulfones after hydrolysis. Different *para*-substituted acetophenone oxime acetates could be converted into the corresponding β-ketosulfones in good to excellent yields (**4aa**–**4ia**), and electron-withdrawing groups did not show a positive effect on our reaction. When using the *ortho*-substituted acetophenone oxime acetates (F and OMe) as the substrates, the corresponding products were formed in 73 % and 94 % yields, respectively (**4ma**–**4na**). When the *meta* position is substituted with CH_3, F, Cl, or Br, the products were obtained in 89 %, 75 %, 81 %, and 70 % yields, respectively (**4oa**–**4ra**). The substrates 3′,4′-dimethylacetophenone, propiophenone, and *n*-butyrophenone oxime acetates also gave good yields of β-ketosulfones **4sa**–**4va**. Heteroaromatic substrtates such as thiophene oxime acetate could give **4wa** in 78 % yield. Unfortunately, alkyl oxime acetates were not suitable for our reaction. **3ja**, **3ka**, **3la**, and **3ta** could also not undergo the hydrolysis process to afford

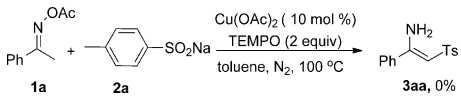


Scheme 4. Substrate scope of various oxime acetates. All reactions were performed with **1** (0.5 mmol), **2a** (0.5 mmol), $Cu(OAc)_2$ (10 mol%), in toluene (2 mL) at 100°C under N_2 for 6 h, followed by stirring in CH_2Cl_2 with silica gel at room temperature overnight. Yields shown are of isolated products.

the corresponding β-ketosulfones under the same conditions. When stronger acids such as hydrochloric acid and acetic acid were used, the corresponding ketones were formed.

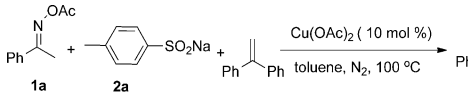
Based on the optimization study, the scope of the sodium sulfinates was also studied; the results are summarized in Scheme 5. The nature of the sulfinic acid sodium salts did not have a great effect on the results. However, the electron-donating groups were advantageous to the reaction. When sodium benzenesulfinate was used as substrate, the corresponding product **4ab** was formed in 93% yield. Various *para*-substituted sodium benzenesulfinates such as those bearing F, Cl, Br, CF_3, or OMe groups afforded the products **4ac**–**4ag** in good yields. Sodium 2-chlorobenzenesulfinate and 2-naphthalenesulfinate could also transform into the corresponding products in 81% and 76% yields (**4ah**–**4ai**). We are excited that aliphatic sulfinic acid sodium salts were also good starting materials, and the desired products were formed in good yields (**4aj**–**4al**).

To investigate the reaction mechanism, several experiments were performed. When the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added to our reaction, no product was detected, which indicated that a radical pathway might be involved [Eq. (1)]. However,

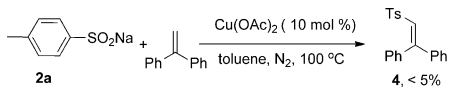


(1)

when we tried to use 1,1-diphenylethylene to trap the radical in the presence or absence of oxime acetates, the yields of the radical coupling products were very low [Eqs. (2) and (3)].

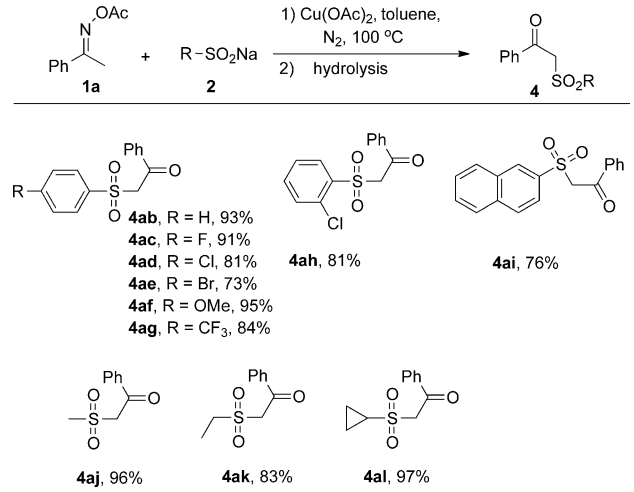


(2)

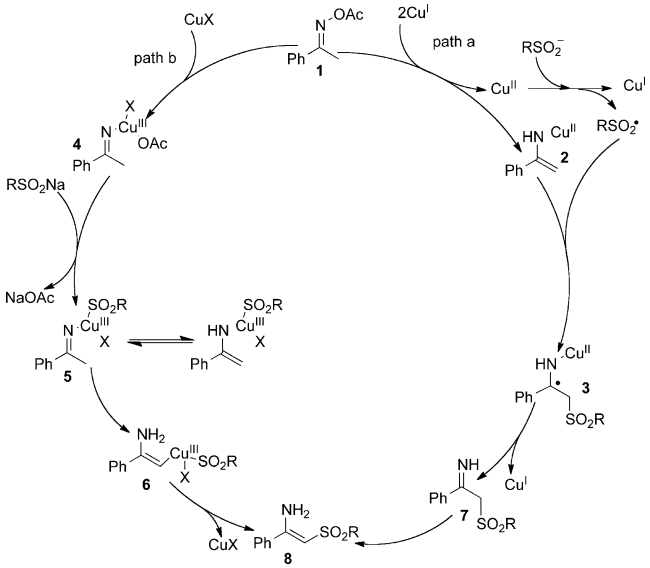


(3)

Therefore, we could not overlook an organometallic pathway in this transformation. The plausible mechanisms that rationalize the observed results are shown in Scheme 6. One proposed mechanism is that acetophenone oxime acetate **1** was easily converted into copper enamide intermediate **2** by the copper catalyst and another Cu^{II} was obtained in this



Scheme 5. Substrate scope of various sodium sulfinates. All reactions were performed with **1a** (0.5 mmol), **2** (0.5 mmol), $Cu(OAc)_2$ (10 mol%), in toluene (2 mL) at 100°C under N_2 for 6 h, followed by stirring in CH_2Cl_2 with silica gel at room temperature overnight. Yields shown are of isolated products.



Scheme 6. Studies on the reaction mechanism for the copper-catalyzed coupling of oxime acetates with sodium sulfinates

process.[19] The Cu^{II} species made sodium sulfinate form the sulfonyl free radical and itself became Cu^{I}.[15a] Then, the sulfonyl free radical combined with copper enamide intermediate **2**, giving free radical intermediate **3**. Intermediate **7** was obtained through a single-electron-transfer (SET) process and released Cu^{I}. The final product **8** is the tautomeric form of intermediate **7** (path a). Another possible mechanism might involve organo-copper(III) intermediates. First, intermediate **4** was formed by oxidative addition of the N–O bond of **1** to Cu^{I}.[9i,j] Coordination of sodium sulfinates to **4** formed intermediate **5** and simultaneously released NaOAc. Then, intermediate **6** was obtained after tautomerization and the Cu^{III} species activated the vinyl C–H. Finally, the desired product **8** was generated from reductive elimination of intermediate **6** (path b).[20]

In conclusion, we have developed a novel method for the synthesis of sulfone derivatives through the copper-catalyzed coupling of oxime acetates with sodium sulfinates. This process involves copper-catalyzed N–O bond cleavage, activation of a vinyl sp^2 C–H bond, and C–S bond formation. The present method employs simple oxime acetates and sodium sulfinates to synthesize sulfonylvinylamine products. Upon hydrolysis, useful β-ketosulfones are also obtained. Oxime acetates act not only as a substrate, but also as an oxidant, thus the reaction needs no additional oxidants or additives.

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[16] CCDC 965756 (**3ta**) 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. A single crystal of product **3ta** is in Supporting Information.

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