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Copper-Mediated Decarboxylative Sulfonylation of Arylacetic Acids with Sodium Sulfinates

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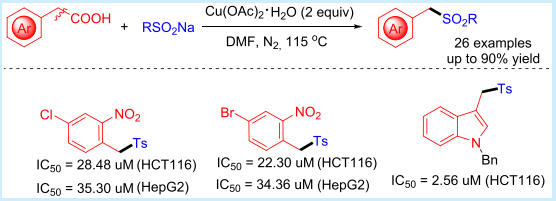
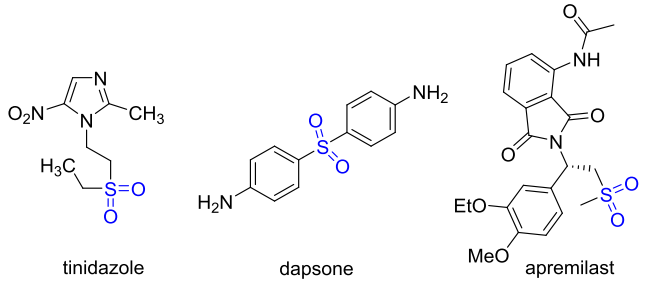
ABSTRACT: Herein, we present a copper-mediated decarboxylative sulfonylation of arylacetic acids with sodium sulfinates that provides viable access to sulfone compounds. This protocol features readily available feedstocks, simple operations, high regioselectivities, and moderate to good yields. The newly obtained products could be converted to other useful compounds. Importantly, the products and their derivatives exhibited potent antitumor activities in vitro, which were tested by MTT assay.



Sulfones are ubiquitous in nature. They are privileged functional groups in pharmaceuticals,[1] such as tinidazole (antiparasitic drug), dapsone (treatment of leprosy and skin diseases), and apremilast (anti-inflammatory) (see Scheme 1).

Scheme 1. Structures of Representative Sulfone-Based Drugs



At the same time, they also serve as versatile synthons in organic transformations involving alkynylation,[2] alkenylation,[3] Michael addition,[4] and cycloaddition.[5] Because of their importance, a large of valuable protocols have been developed for the synthesis of sulfones.[6] Although some progresses have been made toward heteroatom–SO_2 and $C(sp^2)$–SO_2 bond formations in recent years,[7] $C(sp^3)$–SO_2 bond formations remained underdeveloped.[8] The traditional method for constructing $C(sp^3)$–SO_2 bond was via nucleophilic substitution of organic halides with sodium sulfinates.[9] However, the preparation and use of the organic halides inevitably cause environmental pollution. On the other side, some substrates cannot be transformed into their corresponding halides, because of the harsh conditions of halogenation. Therefore, it is very desirable to develop new methods for constructing the $C(sp^3)$–SO_2 bond, which widely exists in drugs and natural products.

Carboxylic acids are attractive raw materials, because they are readily available, highly stable, and inexpensive, and they have long been utilized as a handle to construct chemical bonds.[10] In recent years, the transition-metal-catalyzed decarboxylative couplings of carboxylic acids have achieved great success, and gradually became alternative approaches for carbon–carbon and carbon–heteroatom bond formations.[11] For example, Gooßen and other groups utilized benzoic acids to build $C(sp^2)$–C, $C(sp^2)$–N, $C(sp^2)$–O, and $C(sp^2)$–S bonds via metal-catalyzed oxidative decarboxylative coupling (ODC) reactions.[12] Li, Xu, Lee, Guo and others widely reported alkynyl and alkenyl carboxylic acids that were used as alkynyl and alkenyl sources via decarboxylative cross-couplings.[13] Furthermore, some pioneering works of decarboxylative functionalization of aliphatic carboxylic acids have been reported by Li and other groups.[14]

We have also been working on the transformations of sodium sulfinates.[15] Previously, we developed a copper-catalyzed oxidative coupling of oxime esters with sodium sulfinates for β-ketosulfones, where the N–O bond was used as an internal oxidant (Scheme 2a).[15a] We also reported a one-pot synthesis of β-ketosulfones from ketones and sodium sulfinates with DMSO as an oxidant (Scheme 2b).[15b] Herein, we present a copper-mediated decarboxylative sulfonylation of arylacetic acids with sodium sulfinates (Scheme 2c). To the best of our knowledge, it is the first example of the construction of the $C(sp^3)$–SO_2 bond via decarboxylative coupling with unactivated alkyl carboxylic acids.

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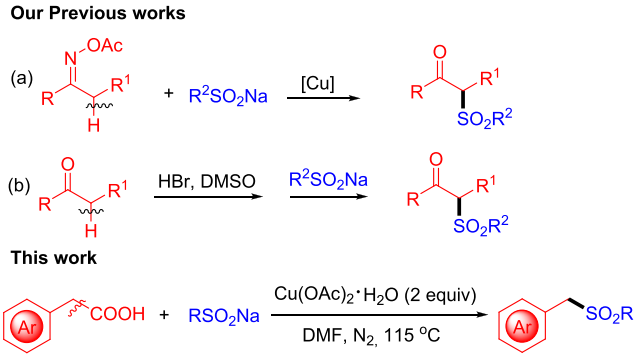
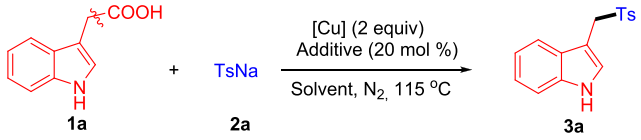
Scheme 2. Our Works Regarding C(sp^3)−SO_2 Bond Formation



Our investigation of the copper-mediated decarboxylative sulfonylation began with 2-(1*H*-indol-3-yl)acetic acid (**1a**) and sodium 4-methylbenzenesulfinate (**2a**) as coupling partners (see Table 1). To our delight, when we treated **1a** with 2.0 equiv of **2a** in the presence of 2.0 equiv $Cu(OAc)_2{\cdot}H_2O$, with dioxane as a solvent under N_2 at 115 °C for 6 h, the desired product **3a** was isolated in 54% yield (Table 1, entry 1). Next, different solvents were screened (Table 1, entries 2−5), and we found the reaction proceeded better in polar, aprotic solvents, such as dimethylsulfoxide (DMSO) and dimethylformamide (DMF). Switching the copper salts to CuO, $Cu(OTf)_2$, $Cu(OTFA)_2$, $CuBr_2$ or CuI, the reaction almost could not occur (Table 1, entries 6−10). The 20 mol % additives, including $NaHCO_3$, K_2CO_3, NEt_3, DBU, and imidazole, all resulted in reduced reaction performance (Table 1, entries 11−15). Control experiments showed that O_2 was bad for the reaction (Table 1, entries 16 and 17). Conducting the reaction at a lower temperature or decreasing the amount of **2a** led to lower product yields (Table 1, entries 18 and 19). Furthermore, we tried to perform the reaction with catalytic amounts of copper salts and suitable oxidants, but the yields of the product **3a** were sharply decreased (Table 1, entries 20−24). Hence, the optimal conditions are as shown in entry 4 by performing the reaction of **1a** (0.5 mmol), **2a** (1.0 mmol), $Cu(OAc)_2{\cdot}H_2O$ (1.0 mmol) in DMF (3 mL) at 115 °C for 6 h under N_2.

With the optimal reaction conditions in hand, we next evaluated the scope of arylacetic acids with sodium 4-methylbenzenesulfinate **2a** as the sulfone reagent (Scheme 3). At first, a variety of indoleacetic acids in combination with **2a** were tested. Indoleacetic acids bearing different substituents (2-Me, 4-Cl, 5-Me, 5-OMe, 6-OMe, and 2-Me-5-OMe) gave corresponding products **3b**−**3g** in good to excellent yields (63%−81%).[16] Other arylacetic acids then were also tested. To our delight, a range of 2-and 4-nitrophenylacetic acids worked well under standard conditions. 2-(4-nitrophenyl)acetic acid and 2-(2-nitrophenyl)acetic acid could be transformed to the corresponding products **3h** and **3i** in 69% and 59% yields, respectively. The halogens (Cl, Br) on the benzene ring of 2-nitrophenylacetic acids were compatible in the reaction (**3j**, **3k**), illustrating the further modifications of the products were feasible. In addition, the reaction of 2-(4-nitrophenyl)-propanoic acid with **2a** also produced the desired product **3l** in 63% yield. Unfortunately, no NO_2-substituted phenylacetic acids such as 2-(4-cyanophenyl)acetic acid, 2-(2-cyanophenyl)acetic acid, 2-(4-(methylsulfonyl)phenyl)acetic acid, 2-(4-chlorophenyl)acetic acid, and 2-(*p*-tolyl)acetic acid did not react under the current reaction conditions.

Table 1. Optimization of the Reaction Conditions[a]



entry	[Cu]	solvent	additive	yield[b] (%)
1	$Cu(OAc)_2{\cdot}H_2O$	dioxane	–	54
2	$Cu(OAc)_2{\cdot}H_2O$	toluene	–	24
3	$Cu(OAc)_2{\cdot}H_2O$	DCE	–	50
4	$Cu(OAc)_2{\cdot}H_2O$	DMF	–	90
5	$Cu(OAc)_2{\cdot}H_2O$	DMSO	–	88
6	CuO	DMF	–	trace
7	$Cu(OTf)_2$	DMF	–	trace
8	$Cu(OTFA)_2$	DMF	–	trace
9	$CuBr_2$	DMF	–	trace
10	CuI	DMF	–	12
11	$Cu(OAc)_2{\cdot}H_2O$	DMF	$NaHCO_3$	60
12	$Cu(OAc)_2{\cdot}H_2O$	DMF	K_2CO_3	67
13	$Cu(OAc)_2{\cdot}H_2O$	DMF	NEt_3	65
14	$Cu(OAc)_2{\cdot}H_2O$	DMF	DBU	50
15	$Cu(OAc)_2{\cdot}H_2O$	DMF	imidazole	66
16[c]	$Cu(OAc)_2{\cdot}H_2O$	DMF	–	80
17[d]	$Cu(OAc)_2{\cdot}H_2O$	DMF	–	24
18[e]	$Cu(OAc)_2{\cdot}H_2O$	DMF	–	59
19[f]	$Cu(OAc)_2{\cdot}H_2O$	DMF	–	63
20[g]	$Cu(OAc)_2{\cdot}H_2O$	DMF	–	28
21[h]	$Cu(OAc)_2{\cdot}H_2O$	DMF	–	50
22[i]	$Cu(OAc)_2{\cdot}H_2O$	DMF	–	41
23[j]	$Cu(OAc)_2{\cdot}H_2O$	DMF	–	38
24[k]	$Cu(OAc)_2{\cdot}H_2O$	DMF	–	32

[a]Unless otherwise stated, the reaction was performed with **1a** (0.5 mmol), **2a** (1 mmol), [Cu] (1 mmol), additive (20 mol %), in solvent (3 mL) at 115 °C for 6 h under N_2. Abbreviations used: DCE, dichloroethane; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; NEt_3, trietylamine; and DBU, 1,8-diazabicycloundec-7-ene. [b]Isolated yield. [c]The reaction was under air. [d]The reaction was under O_2. [e]Yield was with respect to the temperature at 100 °C. [f]0.75 mmol TsNa was used. [g]Using 20 mol % $Cu(OAc)_2{\cdot}H_2O$ and O_2 as an oxidant. [h]Using 20 mol % $Cu(OAc)_2{\cdot}H_2O$ and Ag_2CO_3 (2 equiv) as an oxidant. [i]Using 20 mol % $Cu(OAc)_2{\cdot}H_2O$ and DDQ (2 equiv) as an oxidant. [j]Using 20 mol % $Cu(OAc)_2{\cdot}H_2O$ and $K_2S_2O_8$ (2 equiv) as an oxidant. [k]Using 20 mol % $Cu(OAc)_2{\cdot}H_2O$ and $PhI(OAc)_2$ (2 equiv) as an oxidant.

Subsequently, the scope of the reaction, with respect to variation of sodium sulfinates, was examined (Scheme 4). Various alkyl- and halogen-substituted sodium benzenesulfinate smoothly gave products **3m**−**3p** with the 2-(1*H*-indol-3-yl)acetic acid. Unfortunately, sodium benzenesulfinate bearing strong electron-withdrawing substituents such as NO_2 and CF_3 cannot give the desired products. Notably, sodium alkylsulfinates were readily transformed to the target products in good yields (**3r**, **3s**, **3t**). Furthermore, we also utilized 2-(4-nitrophenyl)acetic acid as a coupling partner to react with different sodium sulfinates. A series of substituted sodium benzenesulfinates and sodium alkylsulfinates were proven to be compatible in the reaction with 2-(4-nitrophenyl)acetic acid, and the corresponding products were obtained in moderate to good yields (**3u**−**3z**).

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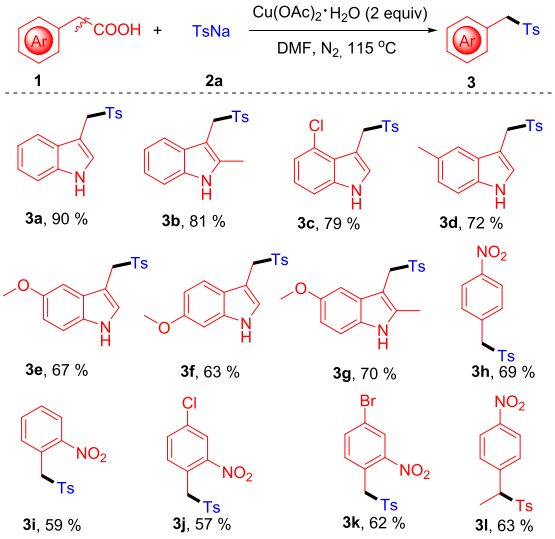
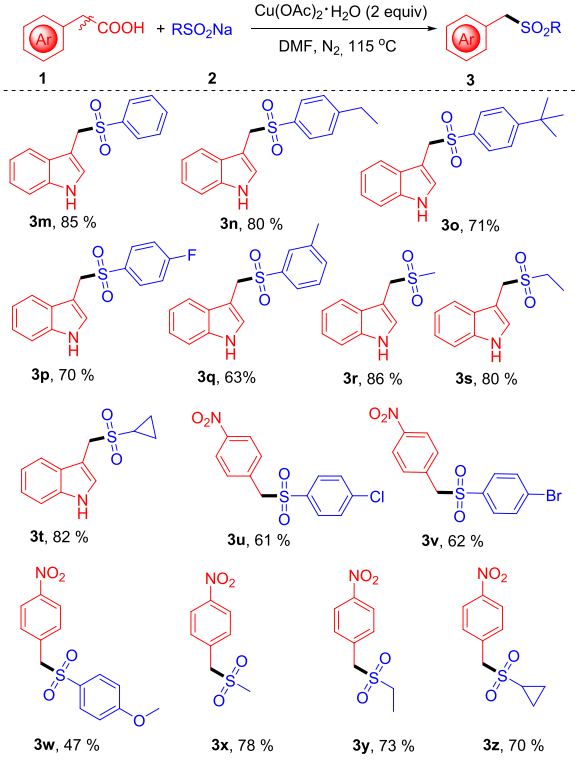
Scheme 3. Exploration of the Scope of the Reaction Employing Various Arylacetic Acids[a]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (1 mmol), $Cu(OAc)_2.H_2O$ (1 mmol), in DMF (3 mL) at 115 °C for 6 h under N_2. Isolated yield.

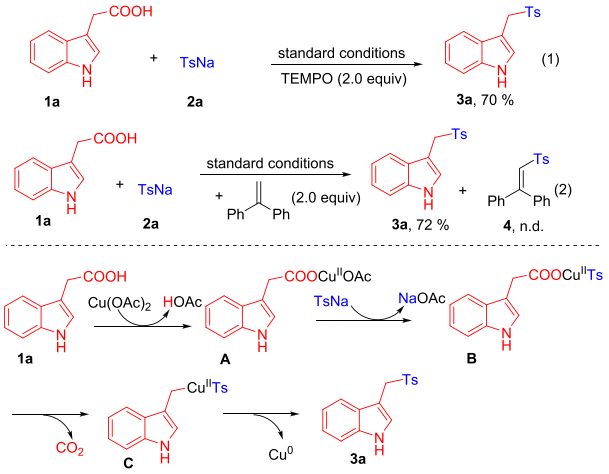
Scheme 4. Exploration of the Scope of the Reaction Employing Various Sodium Sulfinates[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), $Cu(OAc)_2.H_2O$ (1 mmol), in DMF (3 mL) at 115 °C for 6 h under N_2. Isolated yield.

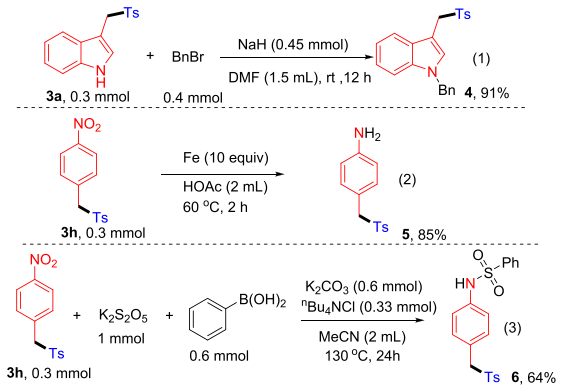
To probe the mechanism of the reaction, we conducted several control experiments. Initially, we added 2.0 equiv of radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine) in the reaction under standard conditions; product **3a** was delivered in 70% yield (Scheme 5, eq 1). Whereafter, we researched whether sulfonyl radical produced in the reaction by adding 2.0 equiv 1,1-diphenylethylene and vinyl sulfone **4** was not detected (Scheme 5, eq 2). The above observations demonstrated that the reaction possibly did not undergo a radical pathway. Based on the above findings, a plausible reaction mechanism was illustrated in Scheme 5. A Cu(II) carboxylate intermediate **A** is formed via the reaction of **1a** with $Cu(OAc)_2{\cdot}H_2O$.[14b] Coordination of sodium sulfinate **2a** to **A** produces intermediate **B** with the release of NaOAc.[15a] Intermediate **B** is decarboxylated to give an active copper specie **C**. Finally, reductive elimination of intermediate **C** generates the desired decarboxylative sulfonylation product **3a**.[14b,c]

Scheme 5. Control Experiments and Plausible Reaction Pathway



To illustrate the synthetic utility of the newly developed decarboxylative sulfonylation method, some transformations of the products were performed (Scheme 6). Benzylation of the **3a** with BnBr and NaH was performed to give product **4** in 91% yield (Scheme 6, eq 1). The nitro group of **3h** was easily reduced to amino group by iron powder (Scheme 6, eq 2). Meanwhile, **3h** can be transformed to sulfonamides, using the method developed by Wu and coworkers (Scheme 6, eq 3).[17]

Scheme 6. Derivatization of Products



Besides the derivatization of products, the biological application of the products and their derivatives was also investigated (see Table 2). The compounds were evaluated for their in vitro cytotoxicity against the human cancer cell lines HCT116, A549, and HepG2 by MTT assay, with 5-fluorouracil (5-Fu) as a reference drug. To our delight, some compounds exhibited potent inhibitory activities against the

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Table 2. Biological Applications

	$IC_{50}(\mu M)$		
compound	HCT116	HepG2	A549
3j	28.48 ± 2.10	35.30 ± 2.50	99.54 ± 12.56
3k	22.30 ± 1.70	34.36 ± 3.90	86.77 ± 3.80
3v	33.18 ± 2.70	74.42 ± 4.65	72.94 ± 3.14
3w	>100	35.21 ± 3.78	>100
4	2.56 ± 0.60	>100	>100
5	30.86 ± 1.40	>100	84.69 ± 14.57
6	6.72 ± 0.50	93.37 ± 5.94	59.75 ± 1.20
5-Fu	33.59 ± 9.53	56.78 ± 8.34	>100

human cancer cell lines. Among them, **4** displayed the highest cytotoxicity against HCT116 cell (IC_{50} = 2.56 μM).

In conclusion, we have developed a copper-mediated decarboxylative sulfonylation of arylacetic acids and sodium sulfinates for the sythesis of sulfone compounds with moderate to good yields. This work provides a simple strategy for decarboxylative couplings with unactivated alkyl carboxylic acids. The transformation has several notable features, including available and stable reagents, simple operations, and good regioselectivities. Above all, we found the products and their derivatives possessing potent antitumor activities in vitro via MTT assay. Further efforts to expand unactivated alkyl carboxylic acids as decarboxylative coupling partners are now underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02516.

General information; experimental section for products **3**; procedure for copper-mediated decarboxylative sulfonylation of arylacetic acids with sodium sulfinates in 1 mmol scale; cell culture and evaluation of the antiproliferative activity; characterization data for all of the products; associate references; NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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