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Synthesis of Vinyl Sulfides by Copper-Catalyzed Decarboxylative C−S Cross-Coupling

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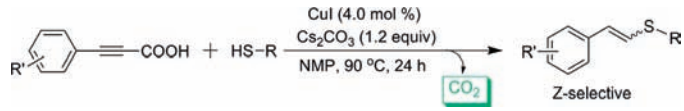
ABSTRACT



A novel method for the synthesis of vinyl sulfides by the decarboxylative cross-coupling of arylpropiolic acids with thiols using copper(I) salts as catalysts has been developed. In the presence of CuI and Cs_2CO_3, a variety of thiols reacted with arylpropiolic acids to afford the corresponding vinyl sulfides in good to excellent yields with high stereoselectivity for *Z*-isomers.

The utility of vinyl sulfides has increased enormously over the past several years. Vinyl sulfides can be used as complementary building blocks to carbonyl compounds[1] and Michael acceptors[2] for synthesis of many polymeric materials,[3] natural products,[4] and synthetic reagents.[5] Conventional approaches to the synthesis of vinyl sulfides include the addition of thiols to alkynes under free-radical[6] or metal-catalyzed conditions,[7] Wittig olefination,[8] and direct nucleophilic substitution through use of vinyl halides.[9] Despite their usefulness, these approaches either require harsh reaction

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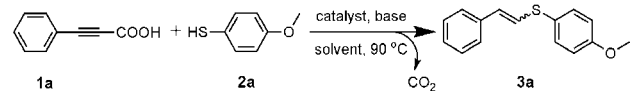
conditions, costly starting materials, and solvents or lack stereocontrol at the double bond geometry.

Numerous methods have been developed for the stereoselective synthesis of (*E*)-vinyl sulfides.[10] In contrast, it has been challenging to prepare *Z*-isomers.[11] In 2005, Kondoh et al.[12] reported the synthesis of (*Z*)-1-alkenyl sufides via a cesium-catalyzed hydrothiolation of alkynes in the presence of 2,2,6,6-tetramethylpiperidine-*N*-oxyl as a radical inhibitor. However, this synthetic strategy is only applicable to alkylthiols. More recently, Wang et al.[13] have reported the synthesis of (*Z*)-1-alkenyl sufides via a copper-catalyzed hydrothiolation of alkynes with diaryl disulfides, but the reaction requires large amounts of rongalite (4 equiv) as the radical initiator.

Recently, coupling reactions initiated by the decarboxylation of carboxylic acids have shown great promise in the field of synthetic chemistry.[14] In particular, we have shown that a broad range of aryl sulfides can be prepared through decarboxylative C−S cross-coupling.[15] Herein, we demonstrate a novel copper-catalyzed decarboxylative thiolation of arylpropiolic acids, resulting in stereoselective formation of (*Z*)-vinyl sulfides under mild reaction conditions.

Phenylpropiolic acid (**1a**) and 4-methoxybenzenethiol (**2a**) were used as the substrates to screen and optimize reaction conditions. Copper(I) complexes generally gave significantly higher yields of the product than copper(II) source (Table 1).

Table 1. Decarboxylative C−S Cross-Coupling under Different Conditions[a]



1a 2a 3a

entry	catalyst (mol %)	base	solvent	yield of **3a**[b] (%)
1		KF	NMP	<5
2	CuI (20)	K_2CO_3	DMSO	57
3	CuI (4)	K_2CO_3	DMSO	74
4	CuI (4)	K_2CO_3	NMP	88
5	CuI (4)	K_2CO_3	PEG	77
6	CuI (4)	K_2CO_3	DMF	35
7	CuI (4)	K_2CO_3	toluene	0
8	CuI (4)	K_2CO_3	dioxane	5
9	CuI (4)	$KHCO_3$	NMP	77
10	CuI (20)	KF	NMP	10
11	CuI (4)	piperidine	NMP	30
12	CuI (4)	TEA	NMP	5
13	**CuI (4)**	**Cs_2CO_3**	**NMP**	**99(96)**
14	CuCN (4)	Cs_2CO_3	NMP	85
15	CuCI (4)	Cs_2CO_3	NMP	80
16	CuBr (4)	Cs_2CO_3	NMP	82
17	$CuCl_2$ (4)	Cs_2CO_3	NMP	35
18	$CuCO_3{\cdot}Cu(OH)_2$ (4)	Cs_2CO_3	NMP	5
19	$Cu(OTf)_2$ (4)	Cs_2CO_3	NMP	40

[a] All of the reactions were carried out with phenylpropiolic acid **1a** (0.5 mmol) and 4-methoxybenzenethiol **2a** (0.75 mmol) in the presence of a metal catalyst, NMP (3 mL), and base (1.2 equiv) at 90 °C for 24 h under air atmosphere. [b] GC yield. Isolated yield is in parentheses.

The amount of CuI can be decreased down to 4.0 mol %. Different bases were screened, and the combination of cesium carbonate with CuI afforded the best conversion efficiency (Table 1, entry 13). In contrast to our previously reported synthesis of aryl sulfides,[15] we observe that palladium(II) is not needed and milder reaction conditions are possible.

Under the optimal reaction conditions, a wide range of thiols including aromatic, benzylic, and aliphatic thiols were examined to react with phenylpropiolic acid via decarboxylative cross-coupling reactions. The results are summarized in Table 2. We observed that in the presence of the phenylpropiolic acid all thiols afforded *anti*-Markovnikov coupling products in good to excellent yields with high stereoselectivity for *Z*-isomers. The arylthiols with electron-rich and electron-deficient aromatic moieties were effectively converted to the corresponding vinyl sulfides. Importantly, the decarboxylative coupling reactions are tolerant of a broad range of functional groups including ethers, amines, alcohols, halides, and nitrogen-containing heterocycles. The functional group tolerance should enable further derivatization of the as-synthesized vinyl sulfides (**3k**,**o**−**s**) through cross-coupling reactions such as Suzuki−Miyaura, Sonogashira, and Heck reactions.

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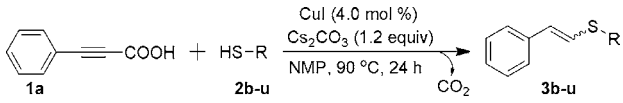
Table 2. Decarboxylative Cross-Coupling of Phenylpropiolic Acid with Thiols[a]

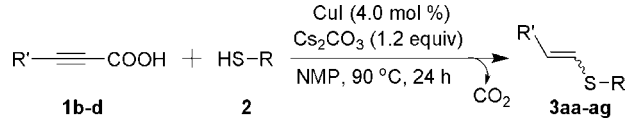


entry	thiols **2**	product **3**	yield[%][b]; [*Z*:*E*][c]
1	$H_3C(H_2C)_{11}-SH$ **2b**	**3b**	78 [83:17]
2	$H_3C(H_2C)_7-SH$ **2c**	**3c**	95 [88:12]
3	$H_3C(H_2C)_3-SH$ **2d**	**3d**	93 [88:12]
4	**2e**	**3e**	90 [79:21]
5	**2f**	**3f**	80 [90:10]
6	**2g**	**3g**	89 [90:10]
7	**2h**	**3h**	90 [90:10]
8	**2i**	**3i**	95 [90:10]
9	**2j**	**3j**	95 [80:20]
10	**2k**	**3k**	75 [85:15]
11	**2l**	**3l**	87 [84:16]
12	**2m**	**3m**	90 [90:10]
13	**2n**	**3n**	95 [90:10]
14	**2o**	**3o**	82 [93:07]
15	**2p**	**3p**	88 [100:0]
16	**2q**	**3q**	81 [92:08]
17	**2r**	**3r**	94 [94:06]
18	**2s**	**3s**	80 [85:15]
19	**2t**	**3t**	92 [90:10]
20	**2u**	**3u**	81 [94:06]

[a] All of the reactions were carried out with phenylpropiolic acids (0.5 mmol) and thiols (0.75 mmol) in the presence of CuI (4.0 mol %) and Cs_2CO_3 (1.2 equiv) in 3 mL of NMP at 90 °C under air atmosphere. [b] Yields of isolated products are the average of at least two experiments. [c] The *Z*/*E* ratio was based on the analysis of ^{1}H NMR spectra.

To expand the scope of the general reaction conditions further, we carried out decarboxylative C−S cross-coupling via different aryl-substituted alkynyl carboxylic acids (Table 3). All alkynyl carboxylic acids were converted into the corresponding alkenyl sulfides in excellent yields. However, alkynyl carboxylic acids with electron-withdrawing substituents in the *para* position led to low stereoselectivity (entries 1, 2, and 4−7). In stark contrast, introduction of an electron-donating group in the *ortho*-position resulted in the quantitative formation of the corresponding *Z*-isomer (entry 3).

Table 3. Decarboxylative Cross-Coupling of Substituted Phenylpropiolic Acids with Thiols[a]



entry	R'	product **3**	yield[%][b]; [*Z*:*E*][c]
1	*p*-Br−C_6H_4 **1b**	**3aa**	90 [30:70]
2	*p*-Cl−C_6H_4 **1c**	**3ab**	93 [44:56]
3	*o*-H_3C−C_6H_4 **1d**	**3ac**	95 [100:0]
4	**1b**	**3ad**	94 [68:32]
5	**1c**	**3ae**	95 [51:49]
6	**1b**	**3af**	89 [70:30]
7	**1c**	**3ag**	94 [58:42]

[a] All of the reactions were carried out with acids (0.5 mmol) and thiols (0.75 mmol) in the presence of CuI (4.0 mol %) and Cs_2CO_3 (1.2 equiv) in 3 mL of NMP at 90 °C under air atmosphere. [b] Yields of isolated products are the average of at least two experiments. [c] The *Z*/*E* ratio was based on the analysis of ^{1}H NMR spectra.

In summary, we have disclosed a copper-based decarboxylative cross-coupling method for the synthesis of vinyl sulfides with high stereoselectivity for *Z*-isomers. This method is important not only for expanding our understanding of the decarboxylative reaction but also for providing a convenient synthetic pathway for facile synthesis of biologically or pharmaceutically relevant vinyl sulfide compounds. Further investigations of the substrate scope of this transformation and the reaction mechanism are currently in progress in our laboratory.

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Supporting Information Available: Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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