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Iron-Catalyzed Regio- and Stereoselective Chlorosulfonylation of Terminal Alkynes with Aromatic Sulfonyl Chlorides

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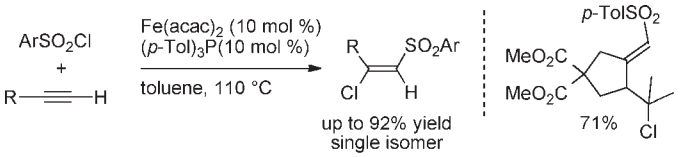
ABSTRACT



Cl, Br, I, NO_2, ketone, aldehyde tolerated

Terminal alkynes react with aromatic sulfonyl chlorides in the presence of an iron(II) catalyst and a phosphine ligand to give (*E*)-β-chlorovinylsulfones with 100% regio- and stereoselectivity. Various functional groups, such as chloride, bromide, iodide, nitro, ketone, and aldehyde, are tolerated under the reaction conditions. Addition of tosyl chloride to a 1,6-enyne followed by radical 5-*exo-trig* cyclization gave an exocyclic alkenylsulfone.

Regio- and stereoselective synthesis of polysubstituted olefins has been a challenging task for synthetic chemists.[1] Addition of an organic sulfonyl chloride across an acetylene derivative is one attractive methodology because of the ready availability of the starting materials and the rich functionality in the product. Copper-catalyzed chlorosulfonylation of alkynes with sulfonyl chlorides has met with various degrees of success in controlling the selectivity,[2] and thermal or photochemical radical initiation has also been used with organic sulfonyl bromides and iodides.[3] We report here a highly regio- and stereoselective synthesis of (*E*)-β-chlorovinylsulfones by iron-catalyzed[4] addition of aromatic sulfonyl chlorides to terminal alkynes. The tolerance for chloride, bromide, iodide, nitro, ketone, and aldehyde groups is a synthetically attractive feature of this new reaction. The reaction can be extended to cyclization of 1,6-enynes into a five-membered ring.

Our recent discovery of copper-catalyzed desulfitative activation of organic sulfonyl chlorides,[5] as well as our interest in selective synthesis of olefins,[6] prompted the present study on iron catalysis, in which we have been interested for some time.[7,8] After extensive experimentation, we found that tosyl chloride (**1**) reacts with phenylacetylene (**2**, 1.2 equiv) in the presence of $Fe(acac)_2$ (10 mol %) and

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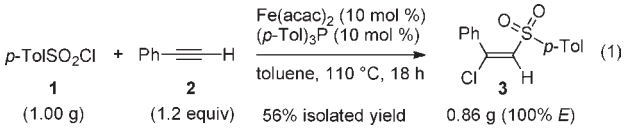
(p-Tol)$_3$P (10 mol %) in toluene at 110 °C for 8 h to give (E)-(2-chlorostyryl)-4-tolylsulfone (**3**) in 56% yield on a 1 g scale and 66% yield on a 0.5 mmol scale, together with the recovery of **1** in 8% yield. Notably, **3** was obtained with 100% selectivity, and we could not observe any other stereo- or regioisomers by GC, GC−MS, or NMR. The stereochemistry of **3** was determined by comparison with the literature data[2c] and stereospecific reduction[9] to the corresponding (Z)-styrylsulfone. The stereochemistry of the product determined at 2%, 4%, and 70% conversion was uniformly 100% E, indicating that the selectivity is kinetically determined.



In the absence of the iron catalyst, the reaction did not proceed at all, and **1** was completely recovered (Table 1, entry 1). Fe(acac)$_3$ gave similar results, but $FeCl_2$, $FeCl_3$, and Fe(OTf)$_2$ performed poorly (entries 4−8). CuCl[2] resulted in complete recovery of the starting material (entry 2). A palladium catalyst was inefficient under these conditions (entry 3). The phosphine ligand improved the yield (entries 10 and 11), but its presence was not mandatory (entry 4). A small excess of phenylacetylene (**2**) improved the yield (cf. entry 12), presumably because of the formation of a small amount of uncharacterized polymeric compounds. The reaction proceeded much more slowly at lower temperature (entry 13).

Table 1. Investigation of the Reaction Conditions for the Chlorosulfonylation of Phenylacetylene (**2**) with Tosyl Chloride (**1**)[a]

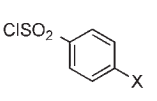
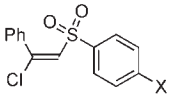
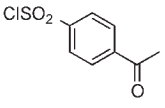
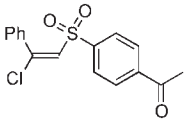
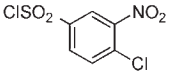
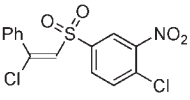
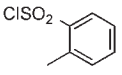
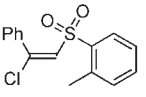
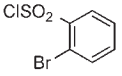
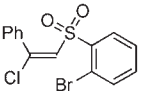
entry	catalyst	ligand	**3** (%)[b]	**1** (%)[b]
1	none	none	0	98
2	CuCl	none	0	93
3	$PdCl_2(PPh_3)_2$	none	0	80
4	Fe(acac)$_2$	none	46	21
5	Fe(OTf)$_2$	none	6	25
6	$FeCl_2$	none	12	22
7	Fe(acac)$_3$	none	37	34
8	$FeCl_3$	none	13	34
9	Fe(acac)$_2$	dtbpy[c]	28	41
10	Fe(acac)$_2$	Ph_3P	63	8
11	Fe(acac)$_2$	(p-Tol)$_3$P	72 (66)	8
12[d]	Fe(acac)$_2$	(p-Tol)$_3$P	40	39
13[e]	Fe(acac)$_2$	(p-Tol)$_3$P	44	65

[a] Reaction conditions: tosyl chloride (**1**, 0.50 mmol), phenylacetylene (**2**, 1.2 equiv), catalyst (10 mol %), ligand (10 mol %) in toluene (0.50 mL) at 110 °C for 8 h, unless mentioned otherwise. See the Supporting Information for details. [b] NMR yield. Isolated yield in parentheses. [c] 4,4′-Di-*tert*-butyl-2,2′-dipyridyl. [d] Reaction performed with 1.0 equiv of **2**. [e] Reaction performed at 90 °C for 12 h.

With the optimized conditions in hand, we investigated the scope of the aromatic sulfonyl chloride in the reaction with phenylacetylene (Table 2). The reaction of an electron-deficient aromatic sulfonyl chloride (entry 2) was higher yielding than that of an electron-rich reagent (entry 1), suggesting more facile generation of a sulfonyl radical.[2] Substitution at the ortho position did not affect the reaction (entries 7 and 8). Aromatic sulfonyl chlorides possessing sensitive functional groups, such as chloride (entries 3 and 6), bromide (entry 8), iodide (entry 4), ketone (entry 5), and nitro (entry 6), gave the desired (E)-β-chlorovinylsulfones in good yield with complete selectivity. Alkylsulfonyl chlorides did not give the desired product under the same reaction conditions.

The scope of the terminal alkyne is shown in Table 3. The reaction of phenylacetylene gave the desired product in 56%−66% yield on a scale of 100 mg to 1 g (eq 1 and entry 1). Both electron-deficient (entries 2, 3, and 5) and electron-rich (entry 4) alkynes reacted smoothly, and the reaction tolerates even an aldehyde group (entry 5). An alkyne possessing a thienyl group (entry 6) or an alkyl group (1-hexyne, entry 7) reacted well. In all of the cases, the product was obtained as a single isomer. An internal alkyne, such as diphenylacetylene, was unreactive, and only a trace amount of compounds produced by desulfitative addition[5] could be observed.

Table 2. Iron-Catalyzed Chlorosulfonylation of Phenylacetylene with Various Aromatic Sulfonyl Chlorides[a]

entry	$ArSO_2Cl$	product	yield (%)[b]
1			55 (X = OMe)
2			92 (Ar = CF_3)
3			67 (X = Cl)
4			63 (X = I)
5			83
6			58
7			62
8			49

[a] Reaction conditions: aromatic sulfonyl chloride (0.50 mmol), phenylacetylene (**2**, 1.2 equiv), Fe(acac)$_2$ (10 mol %), (p-Tol)$_3$P (10 mol %) in toluene (0.50 mL) at 110 °C for 8 h. See the Supporting Information for details. [b] Isolated yield.

Considering that the reaction involves a radical species, we examined the application of this iron-catalyzed reaction

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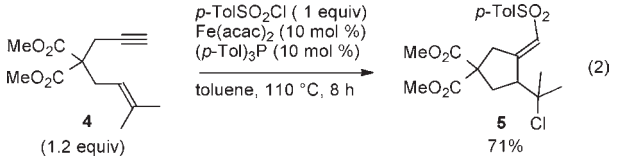
Table 3. Iron-Catalyzed Chlorosulfonylation of Various Terminal Alkynes with Tosyl Chloride[a]

entry	alkyne	product	yield (%)[b]
1	Ph—≡	Ph, SO_2-*p*-Tol, Cl	66 (56)[c]
2	R—C≡C—	R, SO_2-*p*-Tol, Cl	63 (R = F)
3			48 (R = CF_3)
4			52 (R = OMe)
5			45 (R = CHO)
6	S, ≡	S, SO_2-*p*-Tol, Cl	46
7	*n*-Bu—≡	*n*-Bu, SO_2-*p*-Tol, Cl	67

[a] Reaction conditions: tosyl chloride (**1**, 0.50 mmol), terminal alkyne (1.2 equiv), $Fe(acac)_2$ (10 mol %), $(p\text{-Tol})_3P$ (10 mol %) in toluene (0.50 mL) at 110 °C for 8 h. See the Supporting Information for details. [b] Isolated yield. [c] Reaction performed with 1 g of **1**.

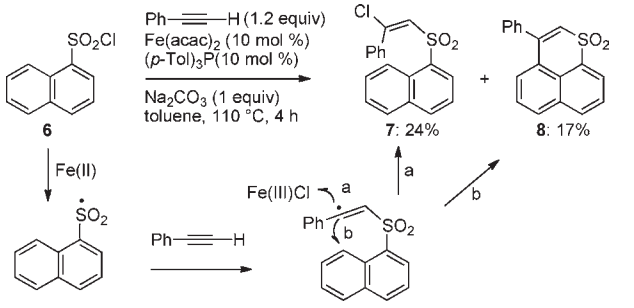
to the cyclization of the 1,6-enyne **4**, a compound known to undergo radical cyclization.[10] Our standard reaction conditions smoothly induced the expected addition/cyclization sequence to give the functionalized exocyclic alkenyl sulfone **5** in good yield. The stereochemistry of this compound was determined to be as shown in eq 2 by NOE experiments (Supporting Information).



Given the observed cyclization and the suggested radical mechanism of the copper-catalyzed chlorosulfonylation reaction,[2] we consider that the present reaction involves an initial electron transfer from the iron catalyst to the aromatic sulfonyl chloride, followed by a radical addition of the resulting sulfonyl radical to the alkyne, and trapping of the vinyl radical by iron(III) chloride. This stands in contrast to the recently reported iron-catalyzed desulfitative cross-coupling of sulfonyl chlorides with Grignard reagents,[11] which assumes involvement of low-valent iron species.

Additional support for the radical mechanism comes from the reaction of naphthalenesulfonyl chloride (**6**) with phenylacetylene to give a mixture of the chlorosulfonylation product **7** and a cyclic sulfone **8** (Scheme 1). Apparently, competitive inter- and intramolecular reactions took place. The intermolecular reaction giving 100% *E* chlorosulfonylation product **7** suggests that the iron(III) chloride species acts as a bulky chlorine donor. The intramolecular reaction necessarily takes the opposite stereochemical course to give **8**.

Scheme 1. Competitive Pathways for the Reaction of Naphthalenesulfonyl Chloride with Phenylacetylene



In summary, an iron catalyst was effective in the radical addition of an aromatic sulfonyl chloride to a terminal alkyne, producing (*E*)-β-chlorovinylsulfones with 100% stereoselectivity. The reaction adds to the repertoire of catalysis utilizing environmentally benign reagents that are increasingly attracting the attention of chemists.[12]

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

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The authors declare no competing financial interest.