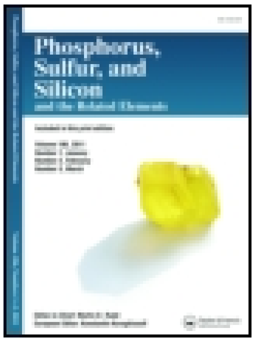

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Zn-catalyzed dihydrosulfenylation of alkynes using thiols

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ABSTRACT
Zinc-catalyzed hydrosulfenylation of alkenes afforded regioselectively the corresponding sulfides in good yields. Furthermore, the method can promote dihydrosulfenylation of alkynes. The procedure could produce anti-Markovnikov type dithioacetals in excellent yields.

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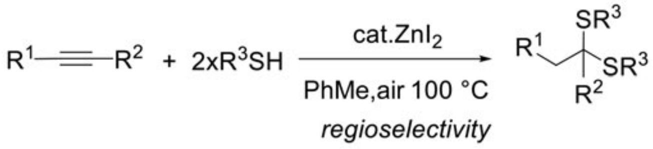
Hydrosulenylation; alkene; alkyne; thiol; zinc catalyst

GRAPHICAL ABSTRACT



Introduction

Dithioacetals are important compounds in organic synthesis.[1] These are usually prepared from carbonyl compounds with thiols, and are widely used as convenient intermediates.[2]

Although the method has been well established, a synthesis by alkyne dihydrosulfenylation has been hardly researched. However, several reports have been published to date (Scheme 1).[3,4] These procedures employ alkynes having electron-withdrawing groups or a specialized calcium catalyst under microwave irradiation.

As a general rule, it is known that the reaction of alkynes with thiols affords the corresponding vinyl sufides via radical process (Figure 1).[5] The reaction proceeds via *anti*-Markovnikov addition. However, the dihydrosulfenylation hardly proceeds.

Therefore, we challenged to synthesize regioselectively *anti*-Markovnikov type dithioacetals.

To solve this problem, the choice of metal catalysts is very important. Initially, the activity of numerous metal catalysts for alkene hydrosulfenylations was investigated.

Results and discussion

To establish suitable conditions, the hydosulfenylation of alkenes was surveyed. As shown in Table 1, when a mixture of 4-toluenethiol with styrene was conducted in CH_2Cl_2, the disulfide was obtained in 71% yield (Entry 1). The addition of a $CeCl_3$ catalyst in DMF gave no product (Entry 2). However, the reaction in CH_2Cl_2 produced the expected sulfide **2a** in 75% yield (Entry 3). Similar results were obtained when the reaction was performed with $LaCl_3$ or $ZnCl_2$ (Entries 4–5). Moreover, the zinc-catalyzed reaction gave good regioselective results in various solvents, and the formation of disulfides was suppressed (Entries 6–8). On the other hand, a reaction using $PdCl_2$ and CuF_2 afforded unsatisfactory results (Entries 9–10). Thus, the $ZnCl_2$ catalyst efficiently promoted the hydrosulfenylation of styrene.

On the basis of the obtained results, we then focused our attention on the addition of thiols to alkynes. Initially, to find suitable conditions, a reaction of 1-phenylacetylene with toluenethiol was investigated. When the reaction was treated by zinc catalyst in toluene, the corresponding dithioacetal **6a** was obtained in 76–79% yield (Entries 1–2 in Table 2). However, as shown in entry 3, the reaction with 4-bromobenzenethiol afforded vinyl sulfide **7a** in 90% yield, while dihydrosulfenylation hardly proceeded. To promote this procedure, several zinc salts were examined. When the $ZiBr_2$ catalyst was employed, the expected dithioacetal **6a** was obtained in 60% yield, and **7a** was produced at 33% yield (Entry 4). Fortunately, the ZnI_2 catalyzed reaction was increased the yield to 71%, and the formation of vinyl sulfide was suppressed (Entry 5). Other zinc catalysts were inferior to ZnI_2 (Entries 6–7).

Sequentially, various dihydrosulfenylations of alkynes were evaluated (Table 3). When a mixture of terminal aryl alkynes with thiols was treated by ZnI_2, the corresponding dithioacetals **6** were obtained in excellent yields. The procedure with arenethiols afforded excellent results whereas using alkyl thiols slightly decreased the reactivity.

Furthermore, internal alkynes as well as terminal alkynes gave good results (Entries 15–16).

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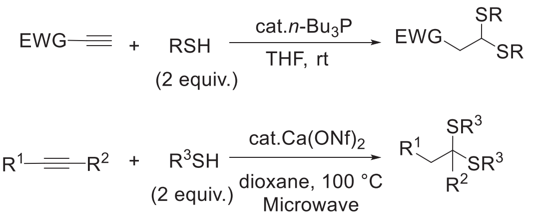


Scheme 1. Previous dihydrosulfenylation of alkyne.

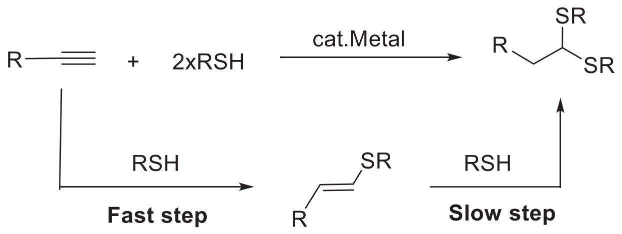
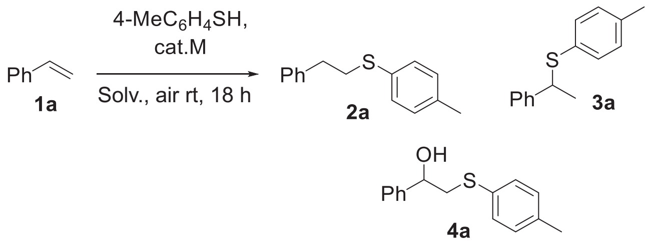


Figure 1. General process of dihydrosulfenylation.

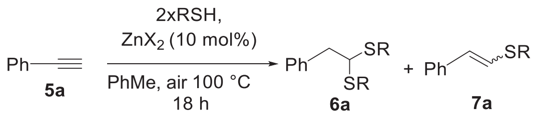
Table 1. Investigation of reactivity of styrene with thiol by metal catalysts[a].



Entry	M (mol%)	Solv.	**2a** (%)[b]	**3a** (%)[b]	**4a** (%)[b]	$(ArS)_2$ (%)[b]
1	none	CH_2Cl_2	0	0	trace	71
2	$CeCl_3$(10)	DMF	trace	0	trace	trace
3	$CeCl_3$(10)	CH_2Cl_2	75	0	trace	trace
4	$LaCl_3$(10)	CH_2Cl_2	76	0	trace	trace
5	$ZnCl_2$(10)	CH_2Cl_2	72	0	trace	trace
6	$ZnCl_2$(10)	DMF	70	0	trace	trace
7	$ZnCl_2$(10)	PhMe	70	0	trace	trace
8	$ZnCl_2$(10)	dioxane	72	0	trace	trace
9	$PdCl_2$(10)	CH_2Cl_2	41	0	trace	42
10	CuF_2(5)	DMF	0	0	0	91

[a]Reaction conditions: A mixture of **1a** (0.3 mmol), 4-MeC_6H_4SH (0.33 mmol) and metal catalysts in solvent (0.3 mL) was treated at rt in air. [b]Isolated yield after silica gel chromatography.

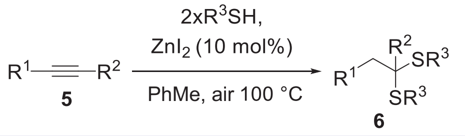
Table 2. Investigation of suitable condition[a].



Entry	RSH	ZnX_2	**6a**(%)[b]	**7a**(%) (E/Z)[c]
1	4-MeC_6H_4SH	$ZnCl_2$	76	trace
2	4-MeC_6H_4SH	ZnI_2	79	trace
3	4-BrC_6H_4SH	$ZnCl_2$	trace	90(91/9)
4	4-BrC_6H_4SH	$ZnBr_2$	60	33(88/12)
5	4-BrC_6H_4SH	ZnI_2	71	trace
6	4-BrC_6H_4SH	$Zn(OAc)_2$	0	91(87/13)
7	4-BrC_6H_4SH	$ZnSO_4$	trace	90(95/5)

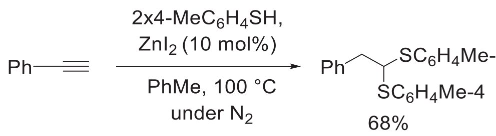
[a]Reaction conditions: A mixture of **5a** (0.3 mmol), thiol (0.63 mmol) and ZnX_2 (10 mol%) in PhMe (0.3 mL) at 100 °C in air.
[b]Isolated yield after silica gel chromatography.
[c]The ratio was determined by ^1H NMR.

Table 3. Zn-catalyzed dihydrosulfenylation[a].

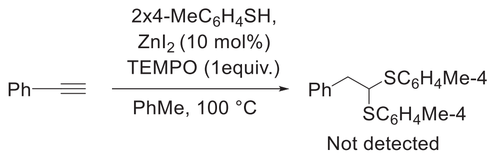


Entry	**6**	h	**6** (%)[b]
1	$PhCH_2CH(SPh)_2$	18	77
2	$PhCH_2CH(SC_6H_4Me\text{-}4)_2$	18	79
3	$PhCH_2CH(SC_6H_4OMe\text{-}4)_2$	18	82
4	$PhCH_2CH(SC_6H_4Br\text{-}4)_2$	18	71
5	$PhCH_2CH(SC_6H_4Cl\text{-}4)_2$	18	78
6	$PhCH_2CH(SC_6H_4Me\text{-}2)_2$	24	80
7[c]	$PhCH_2CH(SC_6H_4Br\text{-}2)_2$	36	50
8	$PhCH_2CH(S\textit{n}Bu)_2$	42	43
9	4-$MeC_6H_4CH_2CH(SC_6H_4Me\text{-}4)_2$	18	87
10	4-$MeOC_6H_4CH_2CH(SC_6H_4Me\text{-}4)_2$	18	74
11	4-$PhC_6H_4CH_2CH(SC_6H_4Me\text{-}4)_2$	18	67
12	4-$FC_6H_4CH_2CH(SC_6H_4Me\text{-}4)_2$	18	82
13[c]	*n*$HexCH_2CH(SC_6H_4Me\text{-}4)_2$	64	78
14	$EtO_2CCH_2CH(SC_6H_4Me\text{-}4)_2$	18	81
15	$PhCH_2C(Me)(SC_6H_4Me\text{-}4)_2$	18	72
16	$PhCH_2C(Et)(SC_6H_4Me\text{-}4)_2$	18	68

[a]Reaction conditions: A mixture of **5** (0.3 mmol), thiol (0.63 mmol) and ZnI_2 (10 mol%) in PhMe (0.3 mL) was treated at 100 °C in air.
Isolated yield after silica gel chromatography. [c]$ZnCl_2$ (20 mol%).



Scheme 2. A reaction under nitrogen atmosphere.



Scheme 3. A reaction in the presence of TEMPO.

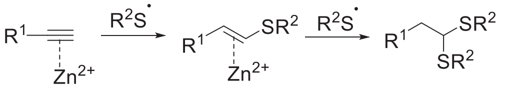


Figure 2. A plausible mechanism.

To clear the reaction mechanism, some experiments were then performed. When a reaction was examined in the absence of oxygen, the corresponding dithioacetal was obtained in 68% yield, and this procedure was slightly inhibited (Scheme 2).

On the other hand, a reaction in the presence of TEMPO as a radical scavenger was also investigated (Scheme 3). The procedure was completely inhibited.

From these results, it is considered that the dihydrosulfenylation proceeds via radical processes (Figure 2).[6] Finally, the procedure is promoted by a zinc catalyst as a Lewis acid.[7] Further investigation into the exact details of the conditions and the mechanism are now in progress.

Conclusions

In conclusion, we achieved the zinc-catalyzed dihydrosulfenylation of alkynes with thiols. The procedure could regioselectively afford numerous desired dithioacetals in excellent yields.

Acknowledgment

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