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# Sulfur-Participated Nazarov-Type Cyclization: A Simple and Efficient Synthesis for 3-Thio-1*H*-indenes

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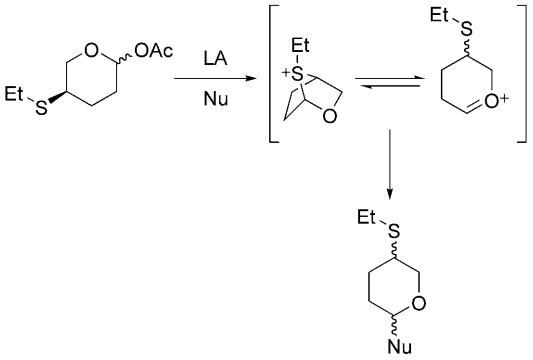
**Abstract:** An intramoluclar addition of sulfur-participated Nazarov-type cyclization affording 3-thio-1*H*-indenes was reported. As a result of the ready availability of the starting materials and the simple and convenient operation, the type of reaction presented here has potential utility in organic synthesis.

**Keywords:** carbocations; intramolecular addition; Nazarov cyclization; sulfur-participation; 3-thio-1*H*-indenes



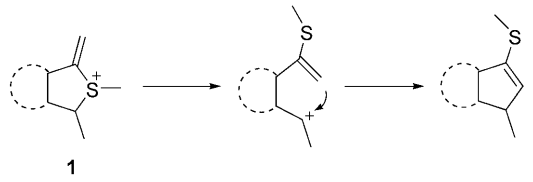

**Scheme 1.**

The indene moiety is present in a class of drug candidates possessing interesting biological activities[1] and metallocene complexes utilized in the catalysis of olefin polymerizations.[2] Therefore, a number of classical methods for the construction of indene ring systems[3] including transition metal-catalyzed carboannulations of alkynes,[4] has been developed. However, the synthesis of thioindenes is not well-documented.[5].

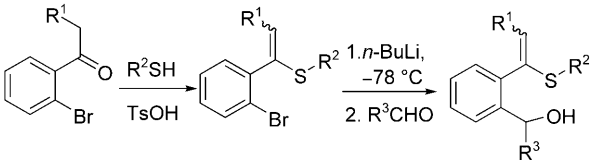
The use of sulfur participation has proven to be an effective strategy for a large number of transformations.[6] Generally, a nucleophilic sulfur atom attacks the leaving group to form a cyclic thionium intermediate,[7,8] which could proceed further through migration, substitution or elimination.

Recently, an excellent report by Woerpel gave spectroscopic evidence for the formation of an intermediate sulfonium ion in a 4-thio-substituted tetrahydropyran acetal system.[9] Interestingly, the subsequent nucleophilic substitution reactions are formed from oxocarbenium ion intermediates released by the bridged sulfonium ion instead of the sulfonium ion itself (Scheme 1).

Enlightened by this knowledge, we proposed a cyclic thionium **1**, which could release a carbocation




**Scheme 2.** Proposed cyclic thionium species.



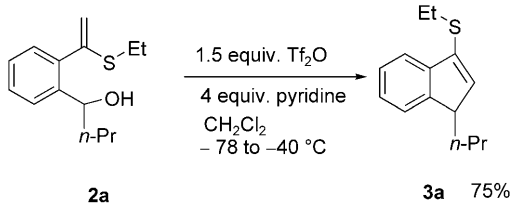

**Scheme 3.** Preparation of starting materials.

to attack the neighboring carbon-carbon double bond to form a five-membered ring (Scheme 2).

This proposal stimulated us to investigate the possibility of the cyclization of [2-(1-thiovinyl)phenyl] acohol (**2**), which could be easily prepared by the reaction of [2-(1-thiovinyl)phenyl]lithium with aldehyde (Scheme 3).

Using 1-{2-[1-(ethylthio)vinyl]phenyl}butan-1-ol (**2a**) as the starting material, we examined the cyclization reaction of **2a** in the presence of trifluoromethanesulfonic anhydride and pyridine in dichloromethane at −20 °C. Luckily, we isolated 3-ethylthio-1-propyl-1*H*-indene (**3a**) from a mixture containing at least 10 compounds in a yield of 28%. Considering the reactivity of the carbocation, we reduced the reaction temperature to −78 °C and obtained **3a** as the major product in 75% yield (Scheme 4).




**Scheme 4.** The first attempt for the proposal.

Encouraged by this result, a series of [2-(1-thiovinyl)phenyl]acohols was synthesized as substrates, and 3-thio-1*H*-indenes (**3**) were obtained in moderate to good yields (Table 1).

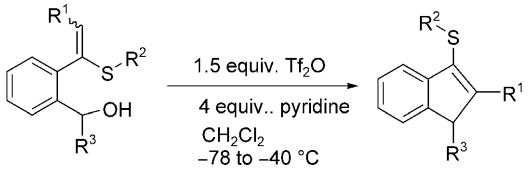
We proposed a plausible pathway as shown in Scheme 5. At first the sulfur atom attacks the trifluoromethanesulfonate to afford cyclic thionium **1**[10] *via* an $S_N2$ process. Intermediate **1** releases carbon cation **A**,[9] which gives intermediate **B** *via* a Nazarov-type cyclization. The intermediate **B** affords the product in the presence of pyridine (Scheme 5).

The point of the pathway is whether the intermediate **A** originates from the cyclic thionium **1** (*pathway 2*, $S_N2$ process) or from the solvolysis of benzyl triflate (*pathway 1*, $S_N1$ process). Thus, we firstly prepared 1-[2-(1-ethoxyvinyl)phenyl]propan-1-ol (**4a**) and 1-[2-(1-methoxyvinyl)phenyl]-propan-1-ol (**4b**) for replacing the sulfur by oxygen and conducted the reaction under the same conditions. Only an unidentified mixture was observed, illustrating that the sulfur atom might play a role in this reaction (Scheme 6).

Then we synthesized 1-phenyl-1-{2-[1-(phenylthio)-vinyl]phenyl}ethanol (**2t**) as the substrate to examine the reaction, in which the secondary alcohols (**2a–2s**) were changed to a tertiary alcohol for blocking the $S_N2$-type attack of the sulfur atom. If the reaction proceeded through the $S_N1$-type pathway 1, the tertiary alcohol **2t** should not prevent the generation of a tertiary carbocation. Interestingly, we obtained an unexpected product **5** (Scheme 7). This totally different result demonstrates that the $S_N2$-type pathway is more reasonable.

The product **5** might originate from the cyclization of phenyl{1-[2-(1-phenylvinyl)phenyl]vinyl}sulfane, which could be produced *via* the elimination of the

**Table 1.** Synthesis of 3-thio-1*H*-indenes.[a]




2 3

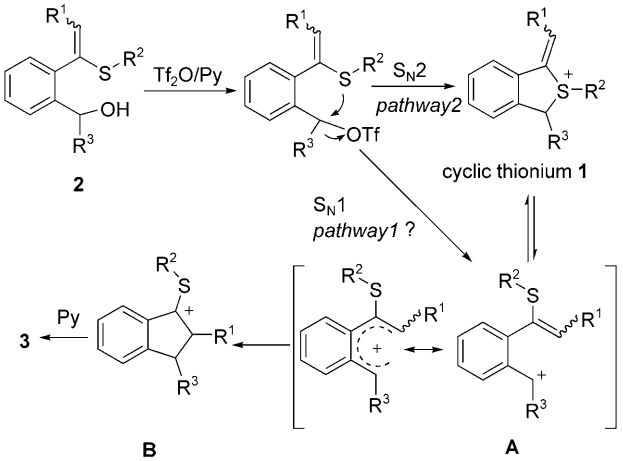
| Entry | $R^1$ | $R^2$ | $R^3$ | Yield [%] |
|---|---|---|---|---|
| 1 | H | Et | *n*-Pr | 75 (**3a**) |
| 2 | Me | Et | *n*-Pr | 68 (**3b**) |
| 3 | Me | Et | Et | 72 (**3c**) |
| 4 | H | Et | Et | 78 (**3d**) |
| 5 | *n*-Pr | Et | *t*-Bu | 76 (**3e**) |
| 6 | *n*-Pr | Et | *n*-Pr | 63 (**3f**) |
| 7 | *n*-Pr | Et | Et | 70 (**3g**) |
| 8 | H | Et | *i*-Pr | 77 (**3h**) |
| 9 | H | Et | Bn | 58 (**3i**) |
| 10 | H | Et | *t*-Bu | 79 (**3j**) |
| 11 | Me | Et | *i*-Pr | 80 (**3k**) |
| 12 | H | Ph | Et | 72 (**3l**) |
| 13 | Ph | Me | *n*-Pr | 75 (**3m**) |
| 14 | Ph | Me | *t*-Bu | 77 (**3n**) |
| 15 | Ph | Me | 2-prop-1-enyl | 69 (**3o**) |
| 16 | Me | Et | 2-prop-1-enyl | 61 (**3p**) |
| 17 | H | Ph | *n*-Pr | 60 (**3q**) |
| 18 | Me | Et | vinyl | 46 (**3r**)[c] |
| 19 | Me | Et | Ph | 50 (**3s**)[d] |

[a] All reactions were run under the following conditions, unless otherwise specified: 0.5 mmol of **2**, 0.75 mmol of $Tf_2O$ and 2 mmol of pyridine in 3 mL of $CH_2Cl_2$ at −78 °C followed by warming to −40 °C under an $N_2$ atmosphere for 2 h.

[b] Isolated yields.

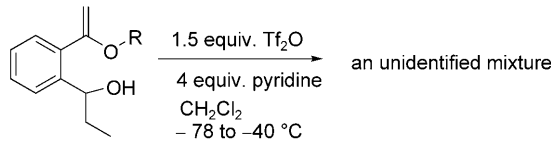
[c] 22% of *E*-1-ethylidene-3-ethylthio-2-methyl-1*H*-indene was observed.

[d] 10% of 1-ethylthio-2-methyl-3-phenyl-1*H*-indene was observed.




**Scheme 5.** The proposed mechanism.

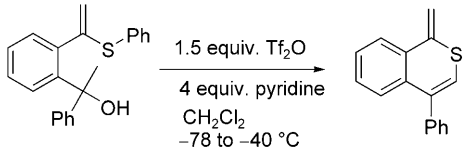
  




**4**

**4a**, R = Et, O-analogue of **3d**
**4b**, R = Me, less bulky on oxygen

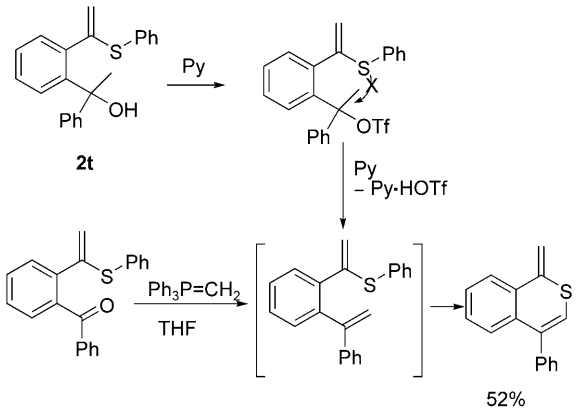
**Scheme 6.** The O-analogue.




**2t** **5**

**Scheme 7.** Reaction of a tertiary alcohol.

triflate of **2t** in the presence of pyridine. We tried to prepare phenyl{1-[2-(1-phenylvinyl)phenyl]vinyl}sulfane *via* a Wittig reaction using phenyl{2-[1-(phenylthio)vinyl]phenyl}methanone as the material. However, after work-up, we just isolated **5** in 52% yield, showing that phenyl{1-[2-(1-phenylvinyl)phenyl]-vinyl}sulfane is very reactive even under mild conditions, which gave indirectly further proof for the pathway proposed in Scheme 5 (Scheme 8).




**2t**

**Scheme 8.**

In summary, we have developed a facile and efficient method for the synthesis of 3-thio-1*H*-indenes. As a result of the ready availability of the starting materials and the simple and convenient operation, the type of reaction presented here has potential utility in organic synthesis. Studies on the application and expansion of the sulfur-activated carbocations are currently in progress.

# Experimental Section

### General Procedure for Synthesis of 3-Thio-1*H*-indenes (3)

To a solution of [2-(1-thiovinyl)phenyl]acohol (**2**) (0.5 mmol) and 2 mmol of pyridine in 3 mL of anhydrous $CH_2Cl_2$ was added 0.75 mmol of $Tf_2O$ under an $N_2$ atmosphere at −78 °C, followed by a warming to −40 °C for 2 h. The reaction mixture was quenched with water, extracted with $CH_2Cl_2$, and dried over anhydrous $Na_2SO_4$. After evaporation, chromatography on silica gel (eluent: petroleum ether) of the crude product afforded the desired product **3** in yields 58–80%.

**Compound 3a:** Yield: 82 mg (75%); oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.44$–$7.38$ (m, 2H), 7.34–7.30 (m, 1H), 7.28–7.24 (m, 1H), 6.23 (d, $J = 1.8$ Hz, 1H), 3.57–3.54 (t, $J = 5.4$ Hz, 1H), 3.03–2.98 (q, $J = 7.2$ Hz, 2H), 1.93–1.88 (m, 1H), 1.54–1.46 (m, 3H), 1.44–1.41 (t, $J = 7.4$ Hz, 3H), 1.00–0.96 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta = 147.7$, 143.3, 136.6, 131.0, 126.4, 125.4, 122.7, 119.2, 49.8, 34.2, 25.8, 20.9, 14.4, 14.1; MS: $m/z = 218$ (M, 18), 217 (M−1, 90); IR (neat): $\nu = 1713.3$, 1604.9, 1462.4, 748.1 cm$^{-1}$; HR-MS: $m/z = 218.1122$, calcd. for $C_{14}H_{18}S$: 218.1129.

# Acknowledgements

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