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Thionium ion promoted Michael acceptor: a sequence of Pummerer/Michael reactions for the stereoselective synthesis of 5-(1-(arylthio)vinyl)-oxazolines

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ABSTRACT

The synthesis of polysubstituted oxazolines is of great interest due to the synthetic and pharmaceutical importance. We developed a sequence of Pummerer/Michael reactions for the stereoselective synthesis of 5-(1-(arylthio)vinyl)-oxazolines.

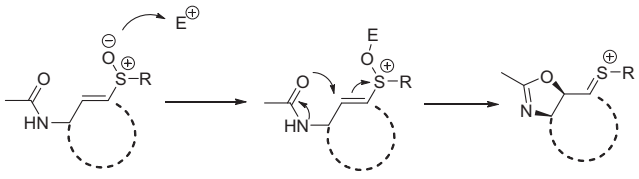
The oxazolines are arguably one of the most ubiquitous heterocyclic compounds used in asymmetric catalysis as chiral ligands.[1] Besides, oxazoline derivatives are also usually encountered as biologically active compounds in pharmaceutical fields.[2]

Generally, oxazolines could be prepared by the reaction of carboxylic acids (or derivatives) with amino alcohols.[3] However, in some cases, the highly substituted amino alcohols are not so available and therefore the synthesis of polysubstituted oxazolines is still meaningful for organic community.

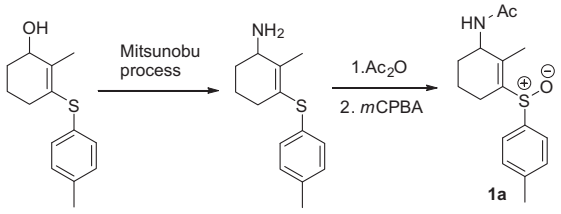
During our research on organosulfur chemistry,[4] we developed a Pummerer-type cyclization to prepare 1,3-oxazoles.[4a] Herein we wish to report a stereoselective cyclization of vinyl sulfoxide under the Pummerer conditions, to afford polysubstituted oxazolines (Scheme 1).

As a first attempt, we chose *N*-(2-methyl-3-(*p*-tolylsulfinyl)cyclohex-2-enyl) acetamide (**1a**) as the starting material, which could be easily prepared via a Mitsunobu process, acylation and oxidation of 2-methyl-3-(*p*-tolylthio)cyclohex-2-enol (Scheme 2).

Based on the previous investigation, we initiated our study by treatment of **1a** with acetic anhydride and trifluoroacetic anhydride (TFAA) in dichloromethane at room temperature and obtained 2,7*a*-dimethyl-7-(*p*-tolylthio)-3*a*,4,5,7*a*-tetrahydrobenzo[*d*]oxazole (**2a**) in 15% and 48% yield, respectively (Scheme 3).



Scheme 1.



Scheme 2.

The stereochemistry of the product **2a** was established by NOESY experiment which clearly showed an NOE effect between the H1 and the methyl proton (Fig. 1).

We believed that the treatment of **1a** with TFAA offers an active vinyl thionium ion A, which could be thought of as a Michael acceptor. The oxygen of amide attacks A intramolecularly, afford-

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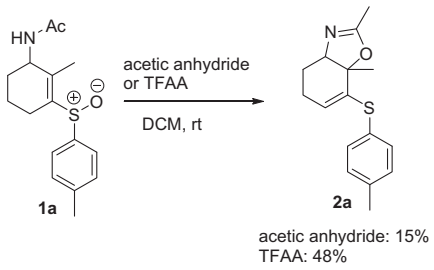


Scheme 3.

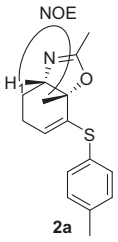
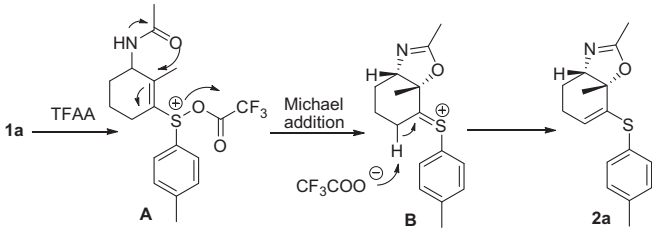


Figure 1. NOESY experiment of **2a**.



Scheme 4.

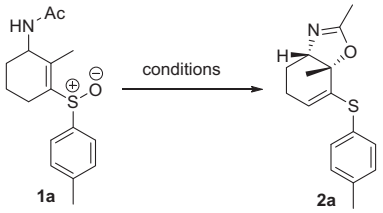
ing the sulfonium B; the sulfonium B gives product **2a** via a proton elimination (Scheme 4).

Next, we optimized the reaction by testing the electrophiles and examining the temperature effect. Acetyl chloride and trifluoromethanesulfonic anhydride offered unidentified mixture (Table 1, entries 1 and 2) and the reaction favored lower temperature (Table 1, entries 5–8); we tested the addition of triethylamine or pyridine for improving the reaction but only got sluggish results (Table 1, entries 9 and 10). Therefore, the reaction in the presence of TFAA in DCM at −20 °C was established as the standard condition to explore the reaction scope (Table 1, entry 6).

With this result in hand, we examined the scope of the reaction and obtained 5-(1-(arylthio)vinyl)-oxazolines in moderate to good yields. The results summarized in Table 2 showed that aryl amide gave slightly higher yield than the similar alkyl amide (entries 1 and 2); the urea type of amide offered lower yield (entry 7); and unexpectedly, the 5-position substituted substrates did not block the proton elimination of the sulfonium (entries 5 and 6).[5]

5-(1-(Arylthio)vinyl)-oxazolines, containing a vinyl sulfane moiety, could be used in the transformations such as hydrolysis to ketones,[4a] [3+2] cycloaddition to cyclopentanones,[6] glyoxylate-ene reaction to α-hydroxy esters,[7] and cross coupling reaction to olefins,[8] besides as the oxazoline derivative. Thus, it may be reasonably envisioned that the 5-(1-(arylthio)vinyl)-oxazolines might also be useful building blocks in organic synthesis.

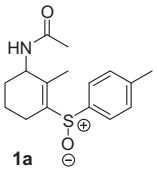
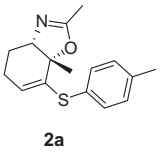
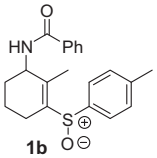
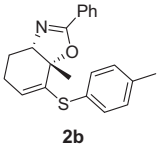
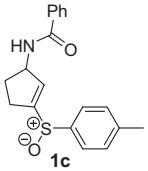
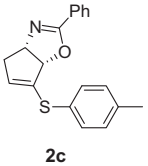
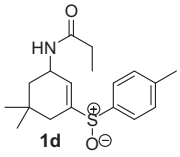
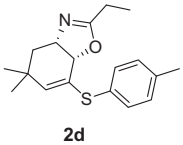
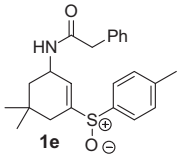
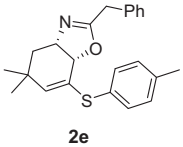
Table 1
Optimization of the reaction[a,b]



Entry	Electrophile	Temp (°C)	Base	Yield (%)
1	MeCOCl	rt	—	0
2	Tf_2O	rt	—	0
3	Ac_2O	rt	—	18
4	TFAA	rt	—	48
5	TFAA	0	—	62
6	**TFAA**	**−20**	**—**	**75**
7	TFAA	−40	—	70
8	TFAA	−60	—	72
9	TFAA	−20	Et_3N	22
10	TFAA	−20	Pyridine	28

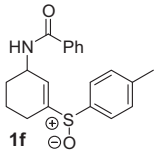
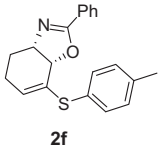
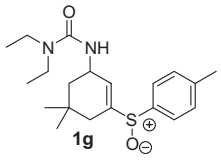
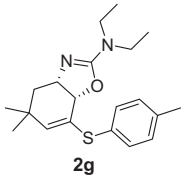
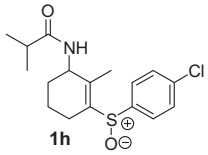
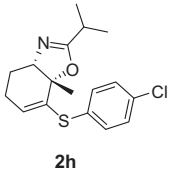
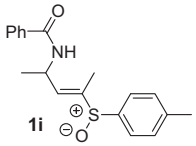
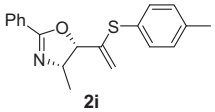
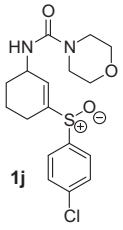
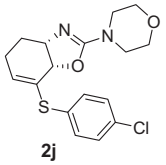
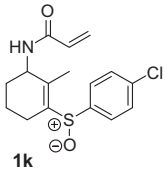
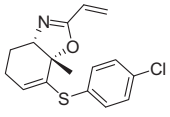
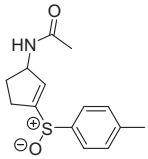
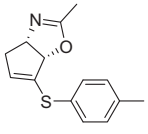
[a] All reactions were conducted on a 0.5 mmol scale and monitored by TLC.
[b] Isolated yields.

Table 2
Synthesis of 5-(1-(arylthio)vinyl)-oxazolines[a,b]

Entry	Substrate	Product	Yield (%)
1	 **1a**	 **2a**	75
2	 **1b**	 **2b**	85
3	 **1c**	 **2c**	54
4	 **1d**	 **2d**	55
5	 **1e**	 **2e**	58

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Product	Yield (%)
6	 **1f**	 **2f**	57
7	 **1g**	 **2g**	48
8	 **1h**	 **2h**	85
9	 **1i**	 **2i**	60
10	 **1j**	 **2j**	50
11	 **1k**	 **2k**	65
12	 **1l**	 **2l**	52

[a] All reactions were conducted on a 0.5 mmol scale and monitored by TLC.
[b] Isolated yields.

In summary, we have developed a mild procedure for the synthesis of 5-(1-(arylthio)vinyl)-oxazolines. Studies on the application and expansion of Pummerer/Michael sequence are currently in progress.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.112.

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5. *General procedure for the synthesis of* ***2a****:* To a solution of *N*-(2-methyl-3-(*p*-tolylsulfinyl)cyclohex-2-enyl)acetamide (**1a**, 0.5 mmol) in DCM (3 mL) under N_2 atmosphere at −20 °C was added TFAA (158 mg, 0.75 mmol). After stirred for 30 min, the reaction mixture was diluted with 20 mL of water and extracted with DCM (2 × 20 mL). The extract was washed with water (2 × 20 mL) and dried with anhydrous Na_2SO_4. After evaporation, chromatography on silica gel (hexane/ethyl acetate: 4:1) of the reaction mixture afforded **2a** (103 mg, 75% yield).
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