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Improved Synthetic Method for 5-[(Phenylthio)methyl]oxazoline Derivatives: Electrophilic Cyclization of Allylic Amide Using a Brønsted Acid and Tetrabutylammonium Chloride under Mild Conditions

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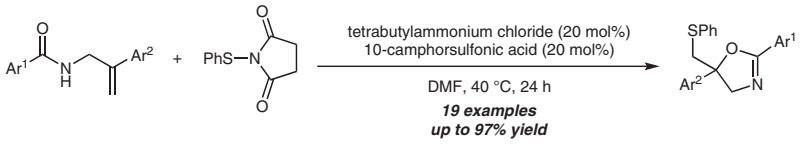

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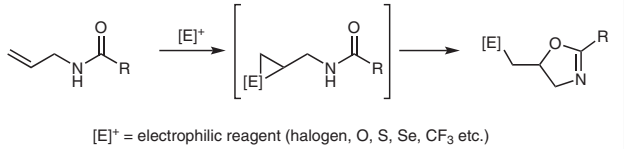
Abstract The synthesis of oxazolines using electrophilic cyclization of allylic amide is a simple and powerful method. However, cyclization involving arylsulfenylation requires harsh reaction conditions. We found that the reaction proceeds under mild heating conditions with the combination of a Brønsted acid and tetrabutylammonium chloride. This method enabled the synthesis of 5-[(arylsulfenyl)methyl]oxazoline derivatives under mild conditions and demonstrated high tolerance for various functional groups.

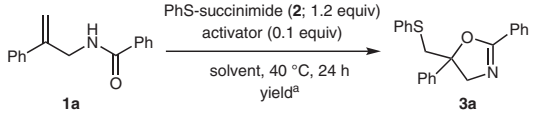
Key words oxazoline, oxazine, thioether, sulfide, electrophilic cyclization

Oxazolines are important compounds frequently found in natural products[1] and biologically active molecules;[2] some of their derivatives are often used as ligands[3] or directing groups.[4] Since the development of a facile synthetic method, oxazoline derivatives have been recognized as an important research field and various strategies have been reported.[5] An electrophilic cyclization reaction using allylic amide and a cationic reagent is currently one of the most reliable approaches; this reaction is also a convenient method for introducing a heteroatom into the carbon–carbon double bond under mild reaction conditions (Scheme 1).



Scheme 1 Electrophilic cyclization of allylic amide

Table 1 Conditions Screenings



Entry	Activator	Solvent	Yield (%)[a]
1[b]	$MgCl_2$	CH_2Cl_2	N.R.
2[b]	$FeCl_3$	CH_2Cl_2	N.R.
3[b]	$Ce(OTf)_3$	CH_2Cl_2	N.R.
4[b]	$B(C_6F_5)_3$	CH_2Cl_2	N.R.
5[b]	$AlCl_3$	CH_2Cl_2	23
6	HCl aq.	MeCN	20
7	TsOH	MeCN	N.R.
8	TsOH, TBAC	MeCN	56
9	TBAC	MeCN	N.R.
10	CSA, TBAC	MeCN	59
11	PPTS, TBAC	MeCN	25
12	BzOH, TBAC	MeCN	9
13	TsOH, TBAB	MeCN	57
14	TsOH, TBAI	MeCN	2
15	CSA, TBAC	THF	33
16	CSA, TBAC	AcOEt	51
17	CSA, TBAC	CH_2Cl_2	52
18	CSA, TBAC	DMF	88
19[c]	CSA, TBAC	DMF	>99

[a] Yields were determined by ^1H NMR spectroscopy.
[b] 1.0 equiv of activator was used.
[c] 0.2 equiv of activator were used.

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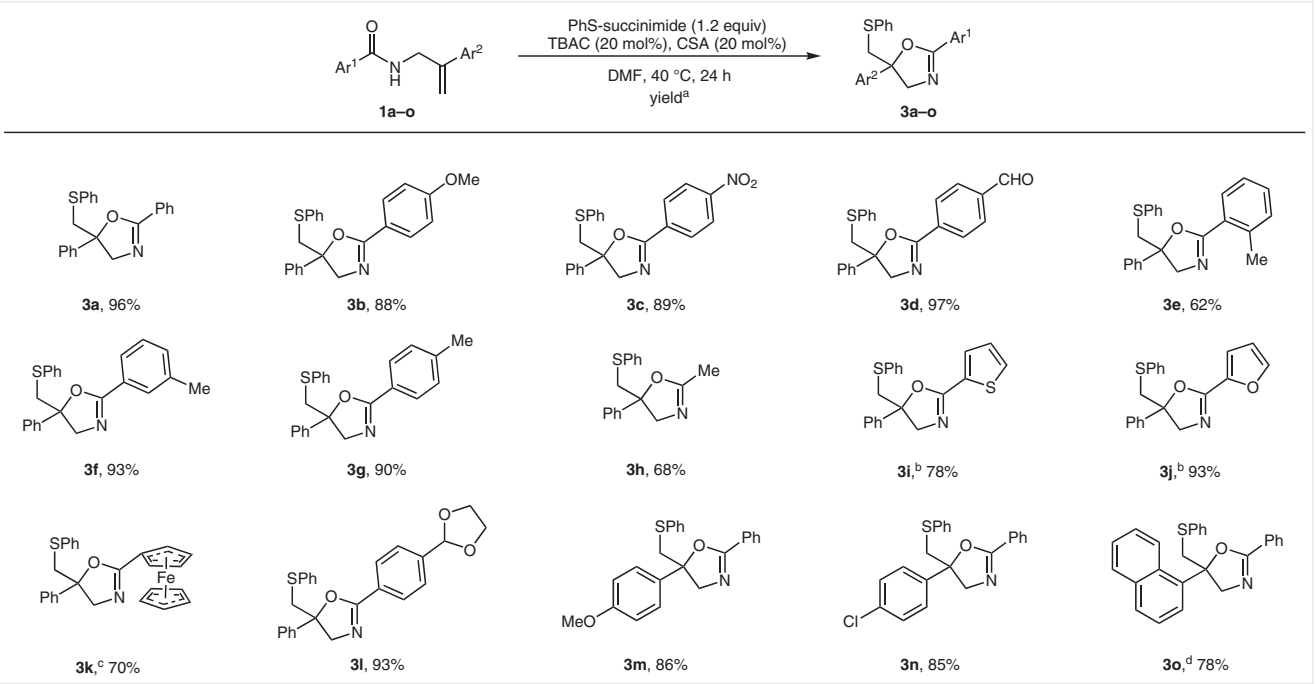
However, most previous research has focused on an halocyclization reaction with cationic halogen species,[6a–h] while there are only a few reports on the use of other electrophiles (e.g., selenium,[6i,j] sulfur,[7] oxygen,[6k,l] CF_3 cation,[6m] and hypervalent iodine compounds.[6n,o] In particular, there are insufficient studies on electrophilic cyclization reactions involving carbon–sulfur bond formation.

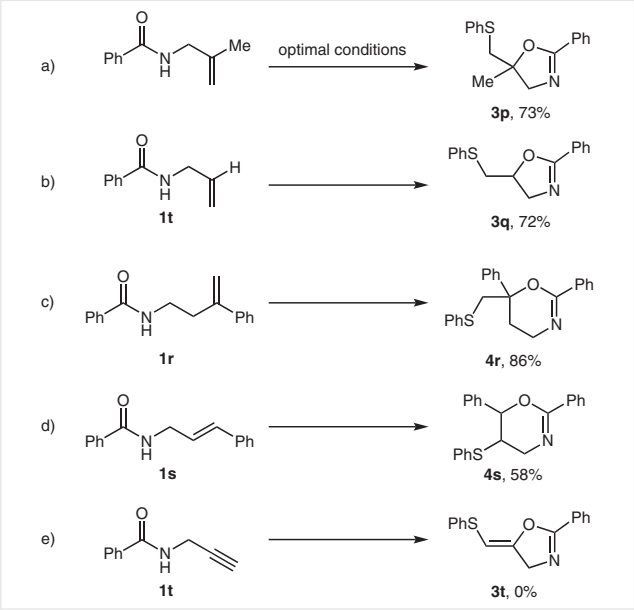
Recently, Fu et al.[7d] reported a synthetic method for 5-[(arylsulfenyl)methyl]oxazoline derivatives using activated (phenylsulfenyl)succinimide with BF_3·OEt_2. Although their method was successful, it required temperatures greater than 100 °C. Therefore, improving their method under milder reaction conditions is essential for the synthesis of oxazolines that have sensitive functional groups. Herein, we report that a catalytic amount of a Brønsted acid and tetrabutylammonium salt as an activator are the most suitable conditions for this reaction.

We investigated the initial conditions for the electrophilic cyclization reaction of *N*-2-phenylallyl)benzamide (**1a**) with *N*-(phenylsulfenyl)succinimide (**2**) in the presence of activators (Table 1). We used various metal reagents (entries 1–5). The desired oxazoline **3a** was obtained in low yield only when using a stoichiometric amount of aluminum chloride(III) after 24 h. Referring to Hostier et al.,[8] we tried using a Brønsted acid as an activator. When a catalytic amount of diluted hydrochloric acid was added, the reaction underwent moderate conversion, but **3a** was obtained in low yield due to the acid-catalyzed hydrolysis of **3a** (entry 6). Using *p*-toluenesulfonic acid instead of hydrochloric acid, the reaction was carried out under anhydrous conditions to avoid hydrolysis, but it did not proceed (entry 7). Considering that hydrochloric acid releases chloride anions as well as protons, we added chloride ions to this reaction. The desired product was obtained in moderate yield through the addition of 10 mol% of tetrabutylammonium chloride (TBAC; entry 8), while no reaction occurred in the absence of a Brønsted acid (entry 9). These entries suggested that a combination of protons and halide anions plays an important role in this reaction. In addition, while camphorsulfonic acid could have been used instead of *p*-toluenesulfonic acid, other acids tended to decrease the yield according to acidity (entries 10–12). Tetrabutylammonium bromide (TBAB) produced the desired product in the same yield as TBAC,[10] but tetrabutylammonium iodide (TBAI) was not applicable (entries 13 and 14). Finally, examining solvent effects, we confirmed that DMF is a suitable solvent (entries 15–18). Increasing the amount of catalyst from 10 mol% to 20 mol% gave quantitative yields (entry 19). Therefore, we decided that entry 19 had the optimal conditions for this reaction.

Next, we investigated the substrate scopes (Scheme 2). The aromatic ring in the benzamide moiety gave the corresponding oxazolines in good yield regardless of electron density and substituent position (**3a–h**). Although heteroaryl amide required an extension of the reaction time, the reaction proceeded smoothly (**3i,j**). A ferrocene derivative, which is an easily oxidizable moiety, gave a moderate yield by improving the reaction conditions and shortening



Scheme 2 Substrate scope for allylic amides. [a] Isolated yield. [b] Reaction time was 48 h. [c] 100 mol% of TBAC and CSA were used, reaction time was 1 h. [d] Reaction time was 72 h.

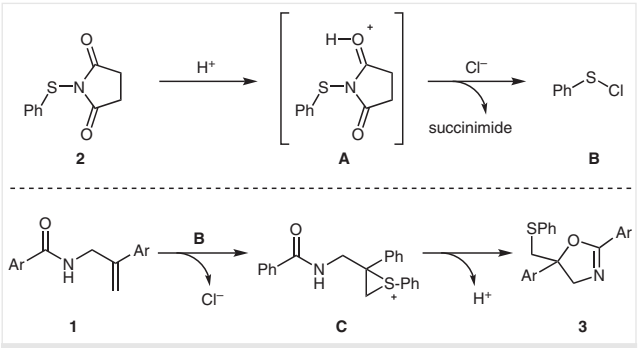


Scheme 3 Substrate scope for miscellaneous unsaturated benzamides

the reaction time (**3k**). A substrate with cyclic acetal moiety proceeded smoothly without the loss of acetal (**3l**). Substituent studies of the olefin part, which could be applied to both electron-rich and electron-poor olefins, also proceed well with a bulky structure, such as 1-naphthyl moiety (**3m–o**).

This reaction can be applied to not only the *N*-(2-aromatic)allylic amide but also methallylic amide (Ar^2 = Me) or unsubstituted allylic amide (Ar^2 = H, Scheme 3, eq. a and b). The 1,3-oxazine derivative **4r** was obtained as a result of 6-*exo* cyclization when using homoallylamide **1r** (Scheme 3, eq. c). In *trans*-cinnamic amide, which is a 1,2-disubstituted olefin, 6-*endo* cyclization was preferred to 5-*exo* cyclization to obtain oxazine **4s** (Scheme 3, eq. d). However, these reaction conditions could not be applied to the alkynyl amide **1t** (Scheme 3, eq. e).

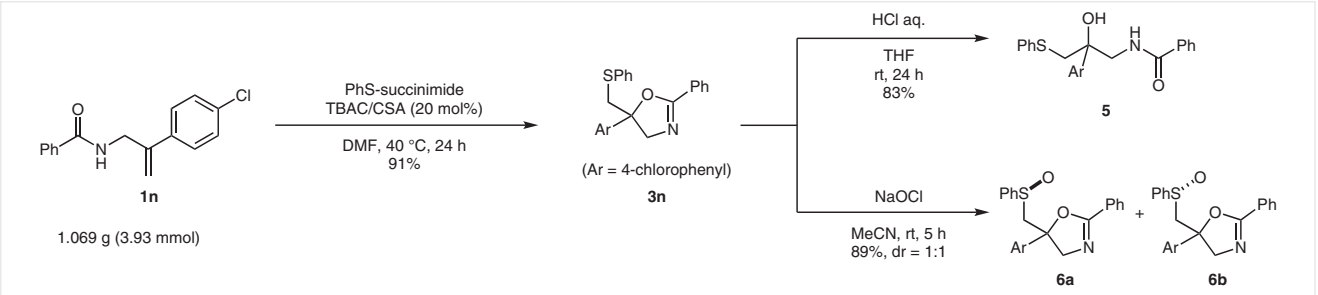
We deduced a plausible mechanism for this reaction from the results of our examination and previous literature (Scheme 4).[11,12] The sulfenylating reagent **2** became **A** through protonation and generated phenylsulfenyl chloride **B** from nucleophilic attack of the chloride ion. The olefin of **1** interacted with **B** to form a thiiranium ion **C**, and the corresponding oxazoline **3** was obtained by subsequent intramolecular cyclization. Although phenylsulfenyl chloride **B** is known to be a highly reactive sulfenylating reagent, it has been reported to spontaneously explode during storage, even in a refrigerator.[13] Thus, **B** presents problems for large-scale preparation and storage. In this reaction, **B** could be prepared catalytically; therefore, the reaction was safer than the conventional method.



Scheme 4 Plausible reaction mechanism

Finally, the transformations of the oxazoline are presented in Scheme 5. This reaction proceeded with good yield even with 1.0 g of **1n**. Oxazoline **3n** was easily opened by an acid-catalyzed hydrolysis reaction and converted into 1,2-aminoalcohol derivative **5** with good yield. The oxidation of **3n** using an aqueous sodium hypochlorite solution could be converted into sulfoxides **6a** and **6b** without the loss of the oxazoline moiety. Moreover, sulfoxides are also important chemical compound groups.[14]

We found that the combination of a Brønsted acid and TBAC proceeded at 40 °C in an electrophilic cyclization reaction involving sulfide formation. The substrate scope of this reaction was wide, and the desired oxazolines were obtained in good yields.[15–17] In addition, this reaction gave the desired product without loss of yield even on the gram scale, and the product could be easily converted into 1,2-aminoalcohol or sulfoxide, which is important for synthetic compounds, which can be useful building blocks.



Scheme 5 Transformation of oxazoline derivative

Acknowledgment

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690836.

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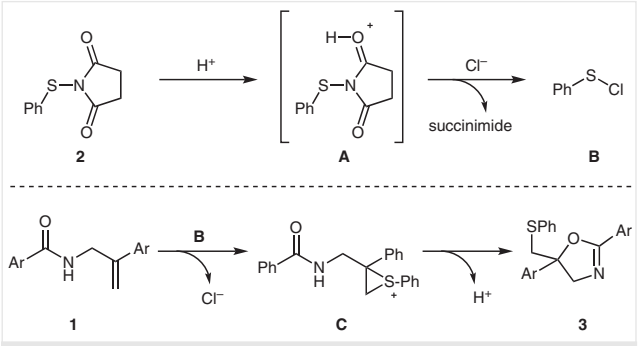
(9) When TBAB was used, small amount of the 5-(bromomethyl)oxazoline derivative was produced as a byproduct (Scheme 6).



Scheme 6

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(14) **Experimental Procedure for Substrate Scopes (Scheme 2)**
A 15 mL test tube equipped with a three-way cock was charged with a magnetic stirrer, *N*-(2-phenylprop-2-en-1-yl)benzamide (**1a**, 47.5 mg, 0.20 mmol), *N*-(phenylthio)pyrrolidine-2,5-dione (**2**, 49.7 mg, 0.24 mmol, 1.2 equiv), and tetrabutylammonium chloride (11.1 mg, 0.04 mmol, 20 mol%). The test tube was evacuated and refilled with dry argon gas three times. Dry DMF (2.0 mL) was added to give a clear solution. (+)-10-Camphorsulfonic acid (9.2 mg, 0.40 mmol, 20 mol%) was added under a slow stream of argon gas. The reaction mixture was heated to 40 °C for 24 h. After being cooled to room temperature, the reaction mixture was quenched by adding of saturated aqueous $Na_2S_2O_3$ (1.0 mL) and saturated aqueous $NaHCO_3$ (1.0 mL). The separated aqueous layer was extracted with EtOAc three times, and the combined organic layers were washed with brine, dried over

anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc, 7:3) as eluent to give to **3a** (66.4 mg, 0.192 mmol, 96%) as a colorless oil.^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.0 Hz, 2 H), 7.48 (t, *J* = 7.4 Hz, 1 H), 7.39 (t, *J* = 7.7 Hz, 2 H), 7.33 (s, 4 H), 7.31–7.27 (m, 2 H), 7.20–7.11 (m, 3 H), 4.45 (d, *J* = 14.6 Hz, 1 H), 4.17 (d, *J* = 14.6 Hz, 1 H), 3.57 (d, *J* = 14.0 Hz, 1 H), 3.49 (d, *J* = 14.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.8, 141.8, 135.9, 133.7, 131.4, 130.4, 128.8, 128.7, 128.3, 128.2, 127.3, 126.5, 126.3, 88.2, 66.5, 45.9.

(15) **Experimental Procedure for the Synthesis of Compound 5**

To a solution of 5-(4-chlorophenyl)-2-phenyl-5-[(phenylthio)-methyl]-4,5-dihydrooxazole (**3n**, 51.3 mg, 0.135 mmol) in THF (1.3 mL), dilute hydrochloric acid (1.0 mol/L, 1.3 mL) was added. The reaction mixture stirred at room temperature. After being stirred for 24 h, the reaction mixture was quenched by saturated aqueous $NaHCO_3$. The organic phase was separated, and the aqueous phase was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc, 6:4) as eluent to give to **5** (44.8 mg, 0.113 mmol, 83%) as a white solid.^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 7.4 Hz, 2 H), 7.48 (t, *J* = 7.4 Hz, 1 H), 7.43–7.36 (m, 4 H), 7.29–7.23 (m, 4 H), 7.22–7.14 (m, 3 H), 6.48 (br s, 1 H), 4.02 (dd, *J* = 13.9, 6.3 Hz, 1 H), 4.03 (br s, 1 H), 3.68 (dd, *J* = 13.9, 6.3 Hz, 1 H), 3.58 (d, *J* = 13.5 Hz, 1 H), 3.39 (d, *J* = 13.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.4, 141.1, 135.5, 133.8, 133.5, 131.8, 130.5, 129.0, 128.6, 128.5, 127.0, 126.9, 126.8, 76.4, 49.0, 45.9.

(16) **Experimental Procedure for the Synthesis of Compound 6**

To a solution of 5-(4-chlorophenyl)-2-phenyl-5-[(phenylthio)methyl]-4,5-dihydrooxazole (**3n**, 50.4 mg, 0.127 mmol) in MeCN (2.7 mL), sodium hypochloride solution (10.5%, 0.21 mL, 1.1 equiv) was added. The reaction mixture stirred at room temperature. After completion of the reaction, the reaction mixture was quenched by saturated aqueous $Na_2S_2O_3$. The organic phase was separated, and the aqueous phase was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc 4:6) as eluent to give an inseparable mixture of diastereoisomers **6a** and **6b** (46.7 mg, 0.113 mmol, 89%) as a colorless oil.^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.0 Hz, 2 H, diastereomer A), δ = 7.92 (d, *J* = 8.0 Hz, 2 H, diastereomer B), 7.68–7.40 (m, 8 H, A), 7.68–7.40 (m, 12 H, B), 7.38–7.30 (m, 4 H, A), 4.80 (d, *J* = 14.9 Hz, 1 H, A), 4.55 (d, *J* = 14.9 Hz, 1 H, B), 4.28 (d, *J* = 14.9 Hz, 1 H, B), 4.22 (d, *J* = 14.9 Hz, 1 H, A), 3.60 (d, *J* = 13.7 Hz, 1 H, B), 3.51 (d, *J* = 14.3 Hz, 1 H, A), 3.40 (d, *J* = 14.3 Hz, 1 H, A), 3.33 (d, *J* = 13.7 Hz, 1 H, B). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.8, 162.6, 144.5, 144.3, 141.6, 140.1, 134.4, 134.1, 131.8, 131.8, 131.3, 131.2, 129.4, 129.4, 129.2, 129.1, 128.5, 128.5, 128.4, 128.2, 127.0, 127.0, 126.5, 125.9, 124.1, 123.9, 86.1, 85.9, 70.1, 69.1, 67.6, 66.8.