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Triple Role of Phenylselenonyl Group Enabled a One-pot Synthesis of 1,3-Oxazinan-2-ones From α-Isocyanoacetates, Phenyl Vinyl Selenones and Water**

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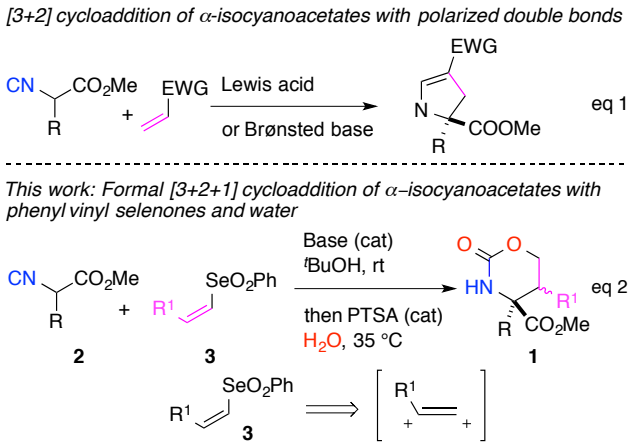
ABSTRACT: Reaction of α-substituted α-isocyanoacetates with phenyl vinyl selenones in the presence of a catalytic amount of base (DBU or Et_3N, 0.05-0.1 equiv) followed by addition of *p*-toluenesulfonic acid (PTSA, 0.1-0.2 equiv) afforded 4,4,5-trisubstituted 1,3-oxazinan-2-ones in good to excellent yields. Enantiomerically enriched heterocycles can also be prepared using *Cinchona* alkaloid-derived bifunctional organocatalyst for the Michael addition step. Phenylselenonyl group served as an activator for the Michael addition, a leaving group and a latent oxidant in this integrated reaction sequence.

INTRODUCTION

Isocyanoacetates, by virtue of their multifunctionalities and easily modulable reactivities, have attracted attentions of synthetic chemists for several decades and many useful transformations have been developed.[1] Among them, the propensity of these chemical entities to undergo [2+3] cycloaddition with dipolarphiles, taking advantage of the nucleophilicity of the α-carbon and the carbene-like reactivity of the divalent carbon of isocyano group has been extensively exploited. Indeed, a number of Lewis acid- and small organomolecule-catalyzed [2+3] cycloaddition of α-isocyanoacetates with aldehydes,[2] imines,[3] azodicarboxylates[4] and polarized carbon-carbon double bonds such as nitroalkenes,[5] α,β-unsaturated ketones,[6] maleimides,[7] carbodiimides,[8] triple bonds[9] etc[10] have been elegantly developed for the access to biologically relevant 5-membered heterocycles (eq 1, Scheme 1). Mechanistically, these reactions are initiated by enantioselective aldol, Mannich or Michael reactions followed by intramolecular nucleophilic addition of resulting anion to the pendant isocyano group. It has been established that any Lewis-acid-catalyzed nucleophilic addition of α-isocyanoacetates to polarized double bond provided inevitably the [2+3] cycloadduct, the same trend holds for organocatalytic processes.[11] We report herein a completely different reaction involving α-isocyanoacetates, phenyl vinyl selenone[12] and water that leads to the formation of 4,4,5-trisubstituted 1,3-oxazinan-2-ones **1** (eq 2, Scheme 1). In this operationally simple transformation, four chemical bonds were created by a formal [3+2+1] process. Key to the success is the ability of phenylselenonyl group to act as an activator for Michael addition, as a leaving group and as a latent oxidant. To the best of our knowledge, such a triple roles of phenylselenonyl group has never been exploited previously in a one-pot transformation. We document also an enantioselective synthesis of **1** (R = aryl, R[1] = H) using chiral *Cinchona* alkaloid-derived bifunctional organocatalyst for the initial Michael addition step.

Scheme 1. Integrated one-pot synthesis of 1,3-oxazinan-2-ones **1**



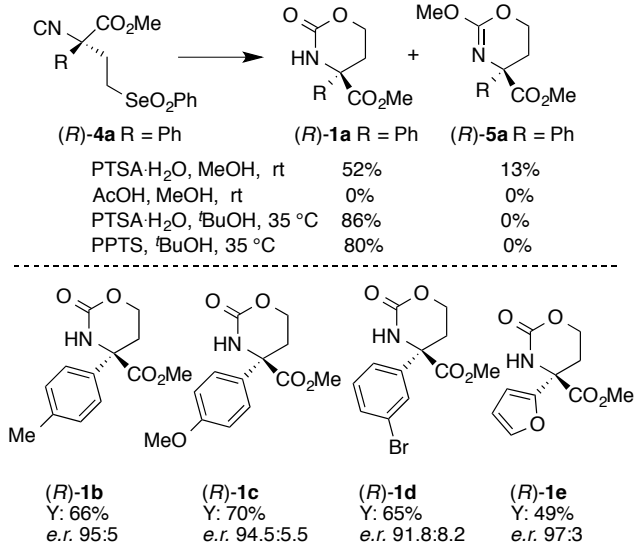
1,3-Oxazinan-2-one **1** is a core structure found in many bioactive compounds displaying antibacterial,[13] anti-inflammatory,[14] antidiabetes[15] and anti-HIV activities.[16] It is also a structural unit found in a number of natural products such as maytansinoids that are potent antitumor agents.[17] In addition, these 6-membered cyclic carbamates have also been used as key intermediates in the synthesis

of drugs (Prozac®),[18] bioactive natural products such as (+)-nagamycin[19] and L-ristosamine,[20] a carbohydrate constituent of ristomycin belonging to vancomycin family glycopeptides.[21] Among many existing methodologies, halonium-mediated[22] or metal-catalyzed[23] 6-*exo*-trig-cyclization, intramolecular 6-*exo*-Michael addition[24] of properly functionalized homoallylamines/homoallylic alcohols, allylic C-H amination[25] and tethered aminohydroxylation of olefins[26] are the most popular ones. Inherent to the activation and cyclization modes, these methods were difficultly applicable to the synthesis of 6-unsubstituted 1,3-oxazinan-2-ones. The conceptually different but operationally simple one-pot synthesis of 4,4,5-trisubstituted 1,3-oxazinan-2-ones **1** from α-substituted α-isocyanoacetates, phenyl vinyl selenones and water represents therefore an interesting alternative to the existing synthetic methods.

RESULTS AND DISCUSSION

We have recently reported an enantioselective synthesis of α,α-disubstituted α-isocyanoacetates **4**.[27] In an attempt to convert the isocyano group to the *N*-formamide under mild acidic conditions, we observed the formation of 1,3-oxazinan-2-one **1a** and 2-methoxy-5,6-dihydro-4*H*-1,3-oxazine **5a** in a 4 to 1 ratio (Scheme 2). Intrigued by this unprecedented transformation involving formally an oxidative cyclization sequence, conditions were optimized towards the formation of 1,3-oxazinan-2-one **1a** by varying the solvents (MeOH, toluene, ^{t}BuOH, ^{t}BuOH-THF, DMF), the catalysts (PTSA·H_2O, PPTS, AcOH, $PhSeO_2H$, $Zn(OTf)_2$, Pd/C, $PdCl_2$), and the temperature (rt, 35 °C, 60 °C). The best conditions found consisted of performing the reaction in ^{t}BuOH in the presence of PTSA·H_2O (0.1 equiv) at 35 °C. Under these conditions, **4a** (***e.r.*** 98.1:1.9) was converted to **1a** (***e.r.*** 96.8:3.2) in 86% yield with very little erosion of enantiomeric purity.

Scheme 2. Oxidative cyclization of **4a** to 1,3-oxazinan-2-one **1a**.[a]



[a] abbreviations: PTSA = *p*-toluenesulfonic acid; PPTS = pyridinium *p*-toluenesulfonate.

The transformation turned out to be general and the structure of enantiomerically enriched 1,3-oxazinan-2-ones synthesized by this protocol is enlisted in Scheme 2. As it is evident, the reaction was not sensitive to the electronic effect of the aromatic ring and heteroarene (furan) is well tolerated. The structure as well as the absolute configuration of compound **1d** was confirmed by single crystal X-ray structural analysis (Figure 1).[28]

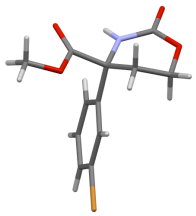
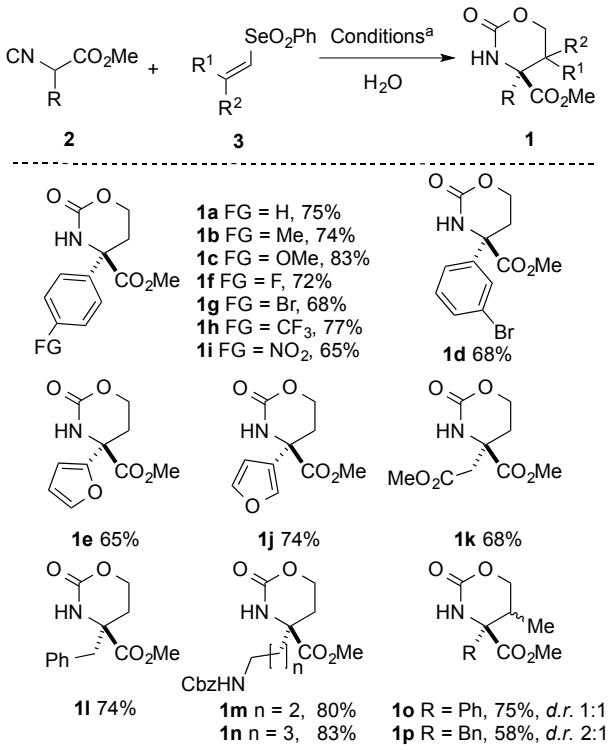


Figure 1. X-ray structure of (*R*)-**1d**

Scheme 3. Integrated one-pot synthesis of 1,3-oxazinan-2-ones **1**.



[a]Conditions A for R = Aryl: Et_3N (0.1 equiv), ^{t}BuOH (*c* 0.25 M), rt then PTSA·H_2O (0.2 equiv) in ^{t}BuOH (final *c* 0.05 M), 35 °C; Conditions B for R = Alkyl: DBU (0.05 equiv), ^{t}BuOH (*c* 0.25 M), rt then PTSA·H_2O (0.1 equiv) in ^{t}BuOH (final *c* 0.05 M), 35 °C.

The enantio-enriched quaternary α-isocyanoacetates **4** were synthesized by a chiral *Cinchona* alkaloid-catalyzed Michael addition of α-substituted-α-isocyanoacetates **2** to phenyl vinyl selenone (**3a**).[27] The fact that PPTS (pyridinium *p*-toluenesulfonate, Scheme 2) can catalyze the domino oxidative cyclization of Michael adduct **4** to **1** as effi-

ciently as PTSA (*p*-toluenesulfonic acid) prompted us to investigate the direct synthesis of **1** from **2** and **3** by an integrated Brønsted base-catalyzed Michael addition and Brønsted acid-catalyzed oxidative cyclization of the resulting Michael adducts.[29,30] Indeed, PTSA is a strong acid (pK_a = 4.8 in H_2O) capable of protonating most of the Brønsted bases leading to the corresponding ammonium *p*-toluenesulfonate similar to PPTS.

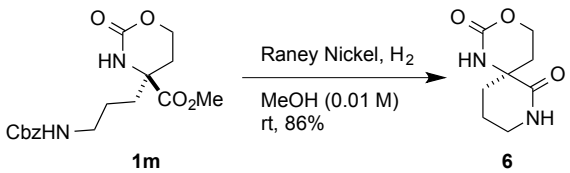
We started with the racemic version using methyl α-phenyl-α-isocyanoacetate **2a** (R = Ph) and **3a** ($R^1 = R^2 = H$) as test substrates (Scheme 3). The optimum conditions found are as follows: Et_3N (0.1 equiv), ^{t}BuOH (*c* 0.25 M), room temperature then PTSA·H_2O (0.2 equiv) in ^{t}BuOH (final *c* 0.05 M), 35 °C. Under these conditions, reaction of **2a** with **3a** afforded directly (±)-**1a** in 75% yield. It is interesting to note that dihydropyrrole resulting from the [3+2] cycloaddition (*cf* eq 1, Scheme 1) was not observed. As it is shown in Scheme 3, the scope of the reaction was quite general. α-Isocyanoacetates bearing arenes/heteroarenes with different electronic properties (electron-rich and -poor) all participated in the reaction to give the corresponding 4,4-disubstituted 1,3-oxazinan-2-ones (**1a**-**1j**). The yields (> 65%) are excellent considering that four chemical bonds are created in this one-pot process. The average yield of per chemical bond formation is therefore higher than 90%.

With α-alkyl substituted α-isocyanoacetates, a stronger base (DBU) is needed to catalyze the Michael reaction due to the reduced aciditity of the α-CH of compound **2**. Under optimized conditions [DBU (0.05 equiv), ^{t}BuOH (*c* 0.25 M), room temperature then PTSA·H_2O (0.1 equiv) in ^{t}BuOH (final *c* 0.05 M), 35 °C], the one-pot procedure worked well to produce the 4-alkyl-4-methoxycarbonyl-1,3-oxazinan-2-ones (**1k**-**1n**) in good to excellent yields (Scheme 3).

To further explore the scope of this transformation, *E*-(prop-1-en-1-ylselenonyl)benzene (*E*-**3b**, R^1 = H, R^2 = Me) and it's *Z*-isomer (*Z*-**3b**, R^1 = Me, R^2 = H) were prepared. Interestingly, while *E*-**3b** was inactive, reaction of **2a** with *Z*-**3b** under standard conditions afforded 4,4′,5-trisubstituted oxazinanone **10** in 75% yield as a mixture of two diastereomers (*d.r.* 1:1). Likewise, methyl α-benzyl-α-isocyanoacetate reacted with *Z*-**3b** to furnish **1p** in 58% yield (*d.r.* 2:1).

To illustrate the synthetic potential of this cyclic carbamate, compound **1m** was converted to spiropiperidinone **6**, a core structure of a series of NK1 antagonists (Scheme 4).[31]

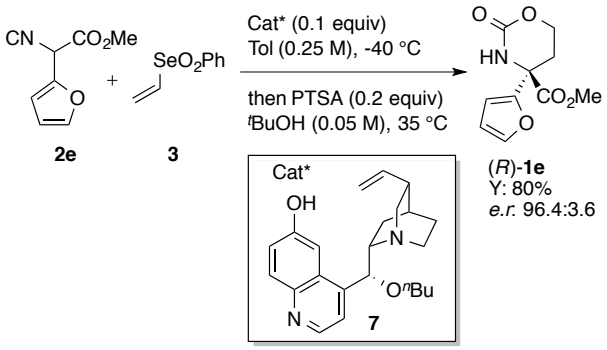
Scheme 4. Synthesis of spiropiperidinone.



1m **6**

Integrated one-pot enantioselective synthesis of **1** is also possible. As shown in Scheme 5, enantioselective Michael addition between **2e** and **3** in toluene in the presence of a bifunctional organocatalyst **7**[32] followed by adding a solution of PTSA in ^{t}BuOH afforded **1e** in 80% yield with an *e.r.* of 96.4 to 3.6. However, **7** failed to catalyze the enantioselective Michael addition of α-alkyl-α-isocyanoacetates to phenyl vinyl selenone, hence the corresponding alkyl substituted oxazinanone **1**.

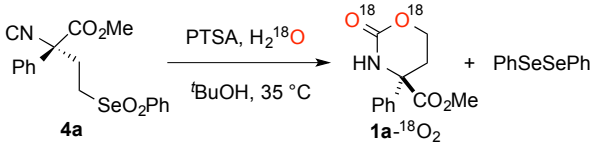
Scheme 5. Integrated one-pot enantioselective synthesis of 1,3-oxazinan-2-one.



2e **3** **7**

To gain mechanistic insights on the conversion of **4** to **1**, a set of control experiments were conducted using **4a** as a reference compound. The oxidative cyclization of **4a** worked equally well under strictly inert atmosphere (glove box) indicating that isocyanate resulting from the adventitious air oxidation of isocyano group might not be the intermediate. No reaction took place when the same reaction was carried out in anhydrous ^{t}BuOH in the presence of anhydrous PTSA. On the other hand, by adding $H_2{}^{18}O$ (^{18}O content 97.7%) into the above reaction mixture, we observed the formation of the same product with double and mono ^{18}O incorporation in a ratio of 89 to 7 (Scheme 6). The up-field shift of ^{13}C NMR signals of carbamate carbonyl (C2) and C6 in **1a**-$^{18}O_2$ relative to **1a** [$\Delta\delta_{(C=O)}{}^{18}O - {}^{16}O$ = -3.5 Hz, $\Delta\delta_{(C6)}{}^{18}O - {}^{16}O$ = -3.3 Hz] is observed, which is in agreement with literature precedents.[33] This labelling experiment clearly indicated that two molecules of water were involved in the conversion of oxidative cyclization of **4** to **1**.

Scheme 6. ^{18}O labeling experiment

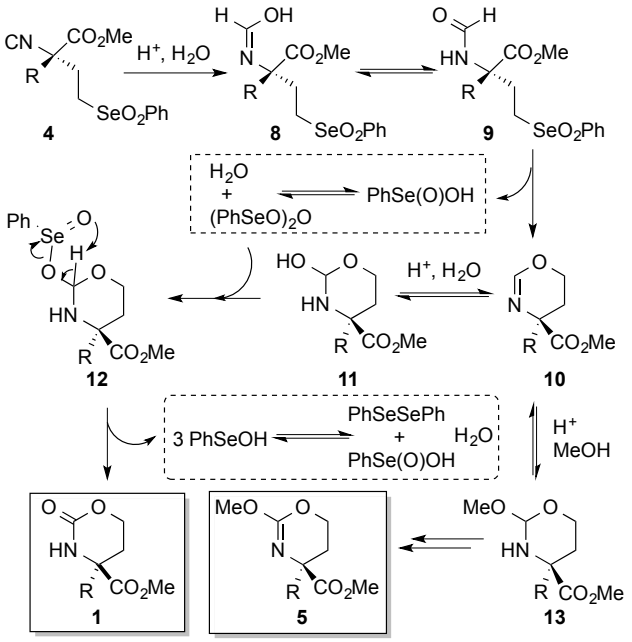


4a **1a**-$^{18}O_2$

Based on the results of aforementioned control experiments, a possible reaction pathway accounting for the formation of **1** from **4** is depicted in Scheme 7. Acid-catalyzed hydration of isocyano group led to *N*-alkylformimidic acid **8**. The initial stereochemistry of the

C=N bond is of no consequence as it is readily isomerized *via* the *N*-formamide form **9**. Intramolecular nucleophilic displacement of phenylselenonyl group by amide oxygen[34] would afford 5,6-dihydro-4*H*-1,3-oxazine **10** with concurrent release of benzeneseleninic acid, which would be in equilibrium with its benzeneseleninic anhydride (BSA). Alternatively, intermolecular displacement of phenylselenonyl group by water followed by intramolecular insertion of isocyano group to OH bond could also account for the formation of **10**. Trapping of **10** by a molecule of water under acidic conditions would produce **11** that could be oxidized by BSA to **1** via intermediate **12**.[35] Alternatively, phenylseleninylation of **12** at the nitrogen atom followed by selenoxide elimination and tautomerization of the resulting iminoalcohol to amide could also be operating.[36] This reaction pathway could also account for the formation of imidate **5** observed in our initial experiment when methanol was used as solvent. In this case, methanol could compete with water to trap **10** leading to **13**. Oxidation of secondary amine to imine by benzeneseleninic anhydride would provide 2-methoxy-5,6-dihydro-4*H*-1,3-oxazine (**5**).[36] We were able to isolate diphenyldiselenide, a reduced form of benzeneseleninic acid,[37] from the reaction mixture. Overall, the integrated reaction system involving **2**, **3** and two molecules of water is an oxidative multicomponent reaction (ABC_2)[38] with an internal redox process.[39] A tiny percentage of **4** or **9** may undergo the retro-Michael/Michael addition reaction before the cyclization, accounting therefore for the slight decreases of enantiomeric excess of products relative to the starting materials.

Scheme 7. One-pot synthesis of 1,3-oxazinan-2-one (**1**): Possible reaction pathway.



Theoretically, two equivalents of water were required to convert **4** to oxazinone **1** according to above mechanistic consideration. To check the optimum amount of water needed for this transformation, the reaction of **4a** in anhydrous ^{t}BuOH and PTSA was performed in the presence of various equivalents of water. While no reaction took place in the absence of water, adding 2 equivalents of H_2O is enough to drive the reaction to completion.[40]

Conclusion

In summary, we developed a novel and efficient one-pot synthesis of 1,3-oxazinan-2-ones from simple starting materials. The integrated reaction system comprised of a Brønsted base-catalyzed Michael addition of α-isocyanoacetates to phenyl vinyl selenone followed by an unprecedented Brønsted acid-catalyzed domino oxidative cyclization sequence that converted the isocyano group to the carbamate function. Four chemical bonds were created in this operationally simple transformation. Key to the success is the ability of phenylselenonyl group to act as an activator for Michael addition, as a leaving group and as a latent oxidant. To the best of our knowledge, such a triple roles of phenylselenonyl group has never been exploited previously in a one-pot transformation.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectroscopic and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

All authors have given approval to the final version of the manuscript.

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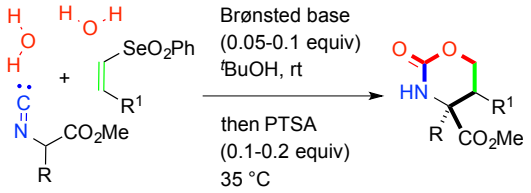
TOC Graphic


Brønsted base
(0.05-0.1 equiv)
tBuOH, rt
then PTSA
(0.1-0.2 equiv)
35 °C
SeO2Ph
R1
CO2Me
R
HN
O
H
N
C