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Access to the 2*H*-Tetrahydro-4,6-dioxo-1,2-oxazine Ring System from Nitrone via a Tandem Nucleophilic Addition and Transesterification Reaction

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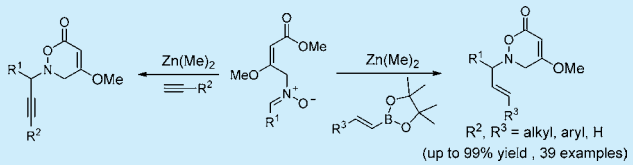
Supporting Information

ABSTRACT: A general and efficient synthesis of the 2*H*-tetrahydro-4,6-dioxo-1,2-oxazine ring system through a tandem nucleophilic addition and transesterification reaction is described. The reaction is highly functional-group-tolerant and proceeds under mild conditions, affording the corresponding products in good to excellent yields. This method represents the first general synthetic route to access this heterocyclic scaffold, which exists in the complex natural products alchivemycin A and B with significant antibiotic activities.



Because of their significant biological activities, heterocyclic compounds have attracted broad attention from both academia and the pharmaceutical industry worldwide. They not only constitute some of the most interesting and biologically meaningful natural products[1] but also exist in many clinically used drugs[2] as central building blocks. Accordingly, synthetic chemists have devoted a great deal of effort to the development of optimal synthetic approaches to access a variety of heterocyclic compounds. An unprecedented heterocyclic ring system, 2*H*-tetrahydro-4,6-dioxo-1,2-oxazine (TDOR), has been identified in the complex natural products alchivemycin A and B, which show significant antibiotic and antitumor activities (Figure 1).[3] TDOR has never been described in any synthetic substrates before. The closely related 1,2-oxazine scaffolds bearing an *N*-carbonyl group exist in a number of pharmaceuticals such as 1*H*-2,3-benzoxazine-1,4(3*H*)-diones **1** and 2*H*-1,2-oxazine-3,6-diones **2** (Figure 1), which display fungicidal and anti-β-lactamase inhibitory activities.[4] 3,5-Isoxazolidinediones **3**[4] are potent inhibitors of the type-2 isoform of inosine-5′-monophosphate dehydrogenase (IMPDH) as well as aldose reductase. Interestingly, the C-3 hydroxamate-substituted cephalosporin derivatives **4**[5] have recently been developed as a new generation of β-lactam antibacterial and medium-dependent antituberculosis agents.[6] In addition, TDOR would be a good synthetic precursor to generate 4,5-epoxy-1,2-oxazin-6-ones **5**,[7] which can be utilized to access unnatural γ-amino acids. Despite the broad and significant applications of TDOR or related structures, a general and efficient approach to access them is still elusive. In particular, no total synthesis or synthetic studies toward alchivemycin A and B have been reported in the literature to date. Herein we report the first synthetic method enabled by a tandem nucleophilic addition and transesterification reaction to generate TDORs with excellent yields and substrate scope.

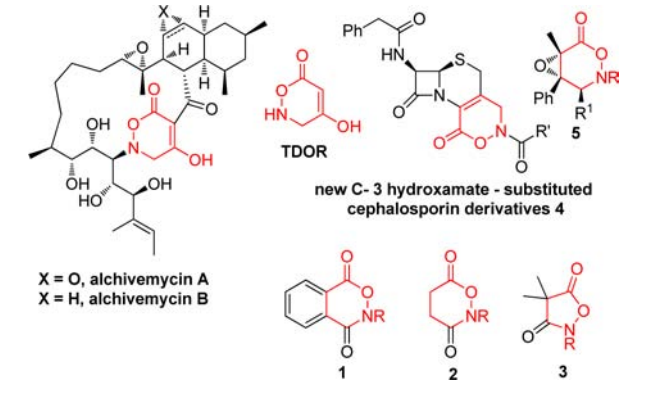


Figure 1. Representative bioactive molecules containing TDOR-type moieties.

Initially, we attempted to synthesize TDOR **7** according to the biomimetic hypothesis[3a] through Dieckmann condensation of the biosynthetic precursor *N*-hydroxyglycine **6** (Scheme 1). A number of conditions were examined to elicit this process, but all of these attempts failed. We also extensively evaluated a number of other methods reported in the literature, for example, the ring-closing metathesis (RCM) approach (**8** to **7**) catalyzed by Grubbs' catalyst,[8] the [4 + 2] hetero-Diels–Alder reaction between nitroso **9** and Brassard's diene **10**,[9] the [3 + 3] cycloaddition of nitrone **11** and **12**,[10] and the tandem

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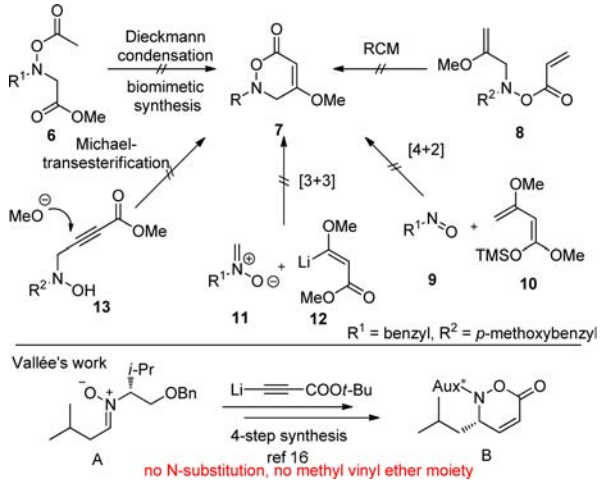
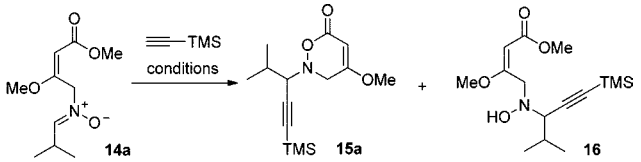
Scheme 1. Attempted Strategies for the Synthesis of the 4,6-Dioxo-1,2-oxazine Ring System



Michael addition and transesterification of **13**, but all of the listed starting matierals decomposed. All of these attempts proved that it was challenging to construct the TDOR efficiently, especially because of the labile carboxylic ester and methyl enol ether moieties as well as the basicity of the nitrogen atom and its susceptibility to oxidation.[11] Finally, we decided to focus on the nitrone as an appropriate precursor candidate because of its electrophilicity toward organometallic compounds.[12] Several groups have examined the synthesis of propargylic alcohols,[13] propargylic amines,[14] and propargyl-*N*-hydroxylamines[15] via the addition of a metalated acetylide to a C═O or C═N double bond. Inspired by these elegant examples, we designed and investigated a tandem nucleophilic addition and transesterification reaction in the presence of a variety of metals such as Al and Zn under mild reaction conditions. We envisioned that Lewis acid-activated nitrones may be attacked by metalloalkynes or -alkenes, triggering the corresponding cyclization to afford the TDOR. In addition, this tandem process may not require the use of strong bases, which would provide a mild reaction system to generate the desired TDOR. In fact, Vallée and co-workers previously reported a nucleophilic addition strategy using lithiopropiolate and nitrone to generate a simplified TDOR structure in four steps.[16] However, this method was not able to afford our desired substrate **7** that contains a nitrogen substitution as well as a labile methyl vinyl ether moiety. Therefore, a new synthetic method was required for the synthesis of compound **7**.

A screen of the reaction conditions was pursued using trimethylsilylacetylene and nitrone **14a** (see the Supporting Information) as model substrates (Table 1). Initially, *n*-BuLi was used, and the desired product **15a** was obtained in 26% yield along with free hydroxylamine **16** (39%) (entry 1). When $Zn(OTf)_2$/DIPEA[15a] and $AlMe_3$[15c] were used, the expected product **15a** could not be obtained (entries 2 and 3). Instead, TDOR **15a** was determined to be the major product when $ZnEt_2$[17] or $ZnMe_2$[18] was utilized. Conveniently, under the zinc-mediated conditions, the free hydroxylamine **16** showed good reactivity to further undergo the transesterification in a one-pot manner to form the desired TDOR. In addition, other solvents such as THF, CH_2Cl_2, and Et_2O were also evaluated. As a result, **15a** was obtained in 66−78% yield (entries 5−7). After further optimization of the reaction conditions, we found the optimal conditions to be the use of 1 equiv of $ZnMe_2$ and 1.2 equiv of trimethylsilylacetylene in toluene at room temperature for 8 h, which furnished the desired product **15a** in 88% isolated yield (entry 8).

Table 1. Initial Reaction Optimization of the Tandem Nucleophilic Addition and Transesterification Reaction[a]



entry	additive	solvent	temp (°C)	product	yield (%)[b]
1[c]	*n*-BuLi	THF	−78	**15a**:**16** = 2:3	65
2[d]	$Zn(OTf)_2$/DIPEA	DCM	rt	NR[e]	–
3[d]	$AlMe_3$	DCM	rt	NR[e]	–
4[f]	$Zn(Et)_2$	toluene	rt	**15a**	65
5	$Zn(Me)_2$	DCM	rt	**15a**	67
6	$Zn(Me)_2$	THF	rt	**15a**	78
7	$Zn(Me)_2$	Et_2O	rt	**15a**	66
8[g]	$Zn(Me)_2$	toluene	rt	**15a**	88
9	$Zn(Me)_2$	toluene	rt	**15a**	45
10	$Zn(Me)_2$	toluene	rt	**15a**	53

[a]See the Supporting Information for the detailed procedure; the reaction time was 8−24 h. TMS = trimethylsilyl, THF = tetrahydrofuran, Tf = trifluoromethanesulfonyl, DIPEA = *N*,*N*-diisopropylethylamine. [b]Isolated yields after column chromatography. [c]Determined by ^{1}H NMR and LC−MS analyses. [d]Previously described method. [e]No reaction. [f]Using 1 equiv of $ZnMe_2$, 3 equiv of trimethylsilylacetylene, and a reaction time of 4 h. [g]Using 1 equiv of $ZnMe_2$, 1.2 equiv of trimethylsilylacetylene, and a reaction time of 8 h.

After the optimal reaction conditions were established, the substrate scope of this tandem transformation was further investigated (Scheme 2). First, we used trimethylsilylacetylene to react with different nitrones. A variety of aliphatic nitrones with diverse functional groups served as substrates. As a result, the nucleophilic addition and transesterification reaction smoothly generated the corresponding TDOR derivatives. The sterically hindered nitrones (*i*-Pr, *t*-Bu, cyclopropyl, cyclohexyl) furnished TDORs **15a−d** in high yields. The structure of **15b** was further unambiguously confirmed by X-ray crystallographic analysis (see the Supporting Information). In contrast, for aliphatic nitrones without steric hindrance (*n*-Bu, homoallylic, azidooctyl, protected hydroxyethyl group, phenyl ring, acetal, and trimethylsilylacetylene), the desired products **15e−k** were obtained in moderate yields. When trimethylsilylacetylene was changed to methyl propiolate, all of the isolated yields for TDORs **15l−s** were significantly improved.

We next examined the substrate scope of alkynes (Scheme 3). Butyn-4-ol was tolerated well to give **17a** in 82% yield. *N*-Boc-propargylamine also provided the desired product **17b** in 79% yield. We were also pleased to find that alkynes possessing a Cl, Br, or CN group were all compatible under these conditions, furnishing **17c−e** in high yields. In addition, aliphatic alkynes were smoothly converted into the target products **17f−h** in 79−85% yields. Notably, a number of benzene or heterocycle-substituted alkynes such as pyridine and thiazole were also tolerated well under these conditions to afford **17i−n** in excellent yields. Moreover, aryl alkynes substituted with an electron-donating group (*p*-OMe) or an electron-withdrawing group (*p*-Br, *p*-COOMe) all smoothly

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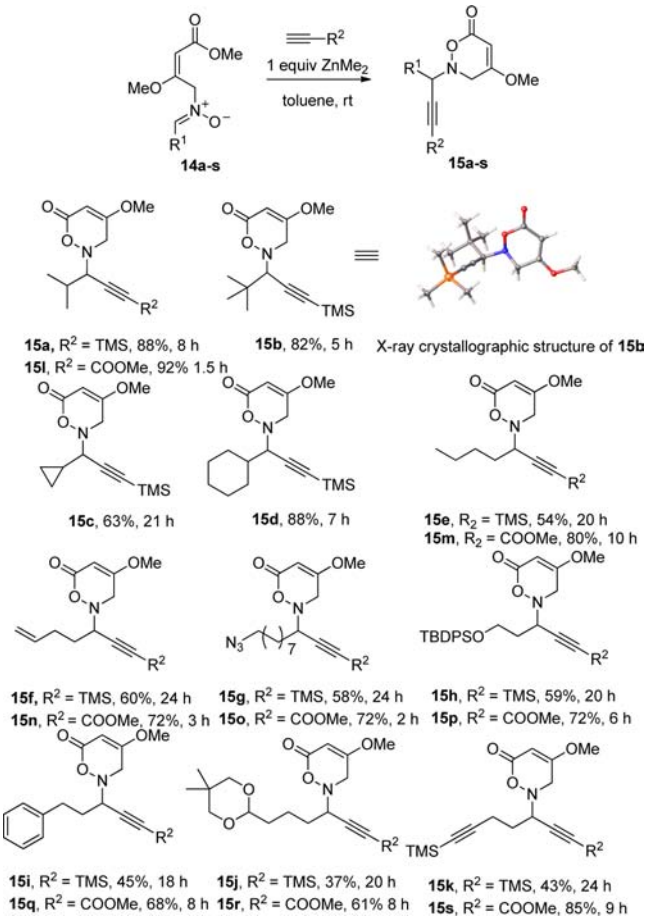
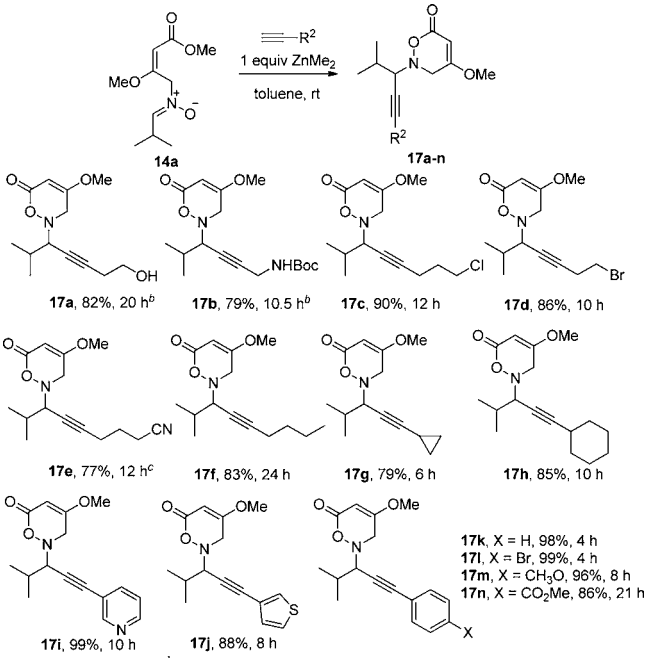
Scheme 2. Substrate Scope of Nitrones[a]



[a]Isolated yields are shown.

Scheme 3. Substrate Scope of Alkynes[a]

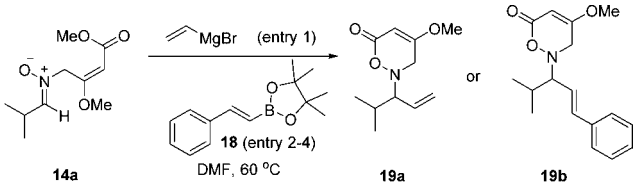


[a]Isolated yields are shown. [b]2.2 equiv of $ZnMe_2$. [c]1.5 equiv of $ZnMe_2$.

provided the desired TDOR derivatives **17k–n** in 86–99% yields.

To further illustrate the scope of this new tandem reaction toward other nucleophiles such as alkenes, we first evaluated the reaction using vinylmagnesium bromide.[19] Unfortunately, the desired product was obtained in only 31% yield (Table 2, entry 1). Then we decided to examine the alternative vinylboronic esters[20] under these conditions. After a series of reaction optimizations, we ultimately found the optimal conditions to be the use of 3 equiv of dimethylzinc in DMF at 60 °C (Table 2, entry 4), which signicantly facilitated this tandem transformation to afford the desired product in 85% yield. We also further investigated the substrate scope of alkenes (Scheme 4). With the optimized protocol in hand, we evaluated various vinylboronic esters, including both electron-donating and electron-withdrawing substitutions (*p*-Br, *p*-OMe, *p*-COOMe) as well as chloride- and ester-containing reagents.

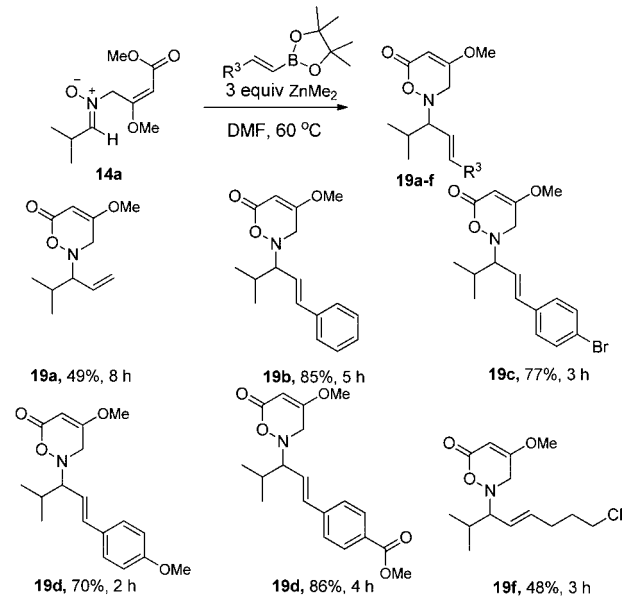
Table 2. Optimization of the Tandem Nucleophilic Addition and Transesterification Reaction Using Vinylboronic Ester[a]



entry	additive (equiv)	solvent	temp (°C)	yield (%)[b]
1[c]	vinyl-MgBr (2)	Et_2O	0	**19a**: 31
2	$Zn(Me)_2$ (2.5)	toluene	rt	**19b**: 40
3	$Zn(Me)_2$ (3)	DMF	rt	**19b**: 46[d]
4	$Zn(Me)_2$ (3)	DMF	60	**19b**: 85

[a]See the Supporting Information for the detailed optimization procedure; 1.5 equiv of **18** and a reaction time of 2–8 h were used. DMF = *N*,*N*-dimethylformamide. [b]Isolated yields. [c]In the absence of **18** with a reaction time of 50 min. [d]83% yield of recovered starting material.

Scheme 4. Substrate Scope of Alkenes[a]



[a]Isolated yields are shown.

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All of the tested substrates showed moderate to good yields. Collectively, these results indicated that this tandem nucleophilic addition and transesterification reaction is robust and has a wide substrate scope and high functional group tolerance.

In conclusion, we have developed a novel approach to efficiently access the 2*H*-tetrahydro-4,6-dioxo-1,2-oxazine ring system (TDOR). The synthesis relies on a tandem nucleophilic addition and transesterification reaction of various nitrones and organozinc regents. The reaction is highly functional-group-tolerant and proceeds under mild conditions, affording the corresponding products in good to excellent yields with a broad substrate scope. Further exploration of this transformation and the syntheses of TDOR-containing natural products as well as other related bioactive molecules are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03374.

Experimental procedures and characterization data for all new compounds (PDF)

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Author Contributions

§S.Y. and D.L. contributed equally.

Notes

The authors declare no competing financial interest.

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