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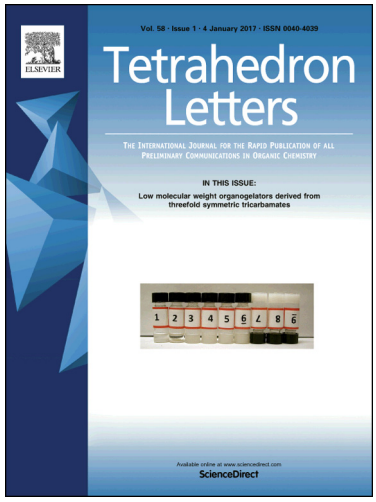

A convenient synthesis of *N*-vinyl enamides via the lithiation and ring-opening reaction of 2-phenyl-2-oxazolines

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Graphical Abstract

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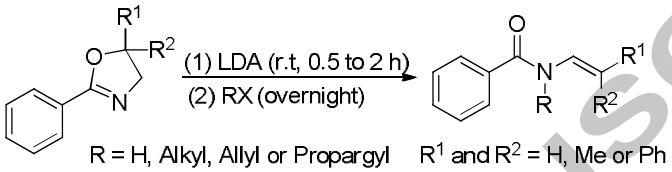

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A convenient synthesis of *N*-vinyl enamides via the lithiation and ring-opening reaction of 2-phenyl-2-oxazolines

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ABSTRACT

A simple and efficient synthesis of *N*-vinyl enamides via the lithiation and ring-opening reaction of 2-phenyl-2-oxazolines with lithium diisopropylamide at room temperature has been developed. This method is especially suitable for the synthesis of multifunctional enamides. Good yields have been obtained when the reactions were amplified to gram scale.

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Introduction

The stable enamide structure, as an intriguing motif in the studies on natural products, has been found to present in numerous bioactive molecules (Figure 1).[1] Enamides have been extensively used as versatile building blocks in various organic transformations,[2] covering the areas from asymmetric synthesis,[3] total synthesis[4] to many other stereoselective C–C and C–N bond-forming reactions.[5] Such a wide range of applications benefited from their variable reactivity modes, which originated from the structural features of enamines including one double bond,[6] the nucleophilic nitrogen and β carbon atoms,[7] and the electrophilic α carbon atom.[8] In view of crucial applications of enamide derivatives, their synthetic methodologies have been widely investigated. A variety of methods for the synthesis of enamides have been developed in literatures,[9] ranging from traditional condensations of carbonyl compounds with amine derivatives[10] to metal-catalyzed cross-coupling and *N*-alkenylation reactions,[11] hydroamidation of alkynes,[9,12] transformation of ynamides,[13] isomerization of *N*-allylamide,[14] and so on. The lithiation of 4-aryl-2-oxazolidinones and subsequent ring-opening reactions have been developed for the synthesis of styrenyl enamides.[15] In spite of all these achievements for the synthesis of enamides, many processes are usually not general, being limited to only certain classes of substrates. Consequently, the development of new synthetic methods for enamide derivatives from simple and readily available starting materials is highly desirable. Herein, we report a mild and efficient synthesis of *N*-vinyl tertiary enamides via ring-opening reaction of 2-phenyl-2-oxazolines with lithium diisopropylamide (LDA) at room temperature.

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Results and discussion

The ortho lithiation of 2-phenyl-2-oxazolines with *n*-BuLi is highly effective,[16] and the yielding o-oxazolinylphenyllithium can react with electrophiles to afford various functionalized oxazoline derivatives.[17] On the other hand, the rate of ortho lithiation of 2-phenyl-2-oxazolines with LDA at 0 °C is very slow even in the presence of LiCl.[18] However, we found that treatment of 2-phenyl-2-oxazoline with LDA at room temperature for half an hour, which was then quenched with water, afforded *N*-vinylbenzamide in excellent yield (Table 1, compound **1**). Furthermore, when benzoyl chloride and methyl iodide were used as the electrophiles instead of water, compounds **2** and **3** were also obtained in excellent yields. For other electrophiles with relatively low activity, the addition of DMF was beneficial to the formation of *N*-vinyl tertiary enamides after completion of

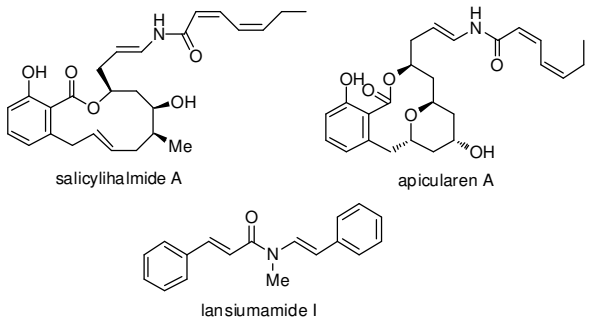

Fig. 1. Some natural products and bioactive molecules with enamide moiety.

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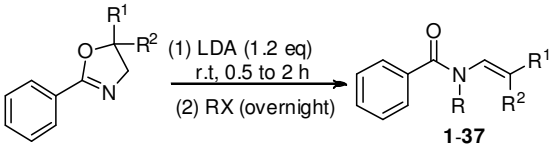
the lithiation (Table 1, compounds **4**–**11**), which may be the result of the enhanced nucleophilicity of the anions through their dissociation from the cations in strong polar aprotic solvents.[19] Propargyl bromide also acted as a good electrophile in this reaction (Table 1, compound **10**) though it has a relatively acidic terminal hydrogen.

Based on the results above in the model reaction, we moved on to investigate the influence of substituents at oxazoline ring on the formation of *N*-vinylbenzamides, and found that 5-methyl-2-phenyl-2-oxazoline (Table 1, compounds **12**–**22**), 5,5-dimethyl-2-phenyl-2-oxazoline (Table 1, compounds **23**–**32**) and 2,5-diphenyl-2-oxazoline (Table 1, compounds **33**–**37**) could give the corresponding *N*-vinyl enamides in moderate to high yields. However, the lithiation reaction time was significantly prolonged, and the yields of *N*-vinyl tertiary enamides decreased with the increase of the number and size of substituents (see compounds **10**, **21**, **31** and **37** in Table 1). Being contrary to the tolerance of alkyl or aryl group on the 5-position of oxazoline ring, adding substituents at the 4-position could fatally impede the occurring of the reaction. For example, similar reaction of 4-methyl-2-phenyl-2-oxazoline or 4,4-dimethyl-2-phenyl-2-oxazoline with LDA was unsuccessful.

Table 1

Synthesis of *N*-vinylbenzamides



1-37

Comp.	R	R^1	R^2	RX	t (h)	Yield (%)[d]
1	H	H	H	H_2O[c]	0.5	95
2	PhCO	H	H	PhCOCl[c]	0.5	95
3	CH_3	H	H	CH_3I[c]	0.5	92
4	CH_3CH_2	H	H	CH_3CH_2I	0.5	73
5	*n*-Bu	H	H	*n*-BuBr	0.5	45
6	$PhCH_2$	H	H	$PhCH_2Br$	0.5	88
7	*o*-$BrC_6H_4CH_2$	H	H	*o*-$BrC_6H_4CH_2Br$	0.5	63
8	CH_2=$CHCH_2$	H	H	CH_2=$CHCH_2Br$	0.5	88
9	PhCH=$CHCH_2$	H	H	PhCH=$CHCH_2Br$	0.5	88
10	HC≡CCH_2	H	H	HC≡CCH_2Br	0.5	81
11	PhC≡CCH_2	H	H	PhC≡CCH_2Br	0.5	84
12	H	CH_3	H	H_2O[c]	1.0	96
13	PhCO	CH_3	H	PhCOCl[c]	1.0	90
14	CH_3	CH_3	H	CH_3I	1.0	86
15	CH_3CH_2	CH_3	H	CH_3CH_2I	1.0	77
16	*n*-Bu	CH_3	H	*n*-BuBr	1.0	46
17	$PhCH_2$	CH_3	H	$PhCH_2Br$	1.0	81
18	*o*-$BrC_6H_4CH_2$	CH_3	H	*o*-$BrC_6H_4CH_2Br$	1.0	73
19	CH_2=$CHCH_2$	CH_3	H	CH_2=$CHCH_2Br$	1.0	85
20	PhCH=$CHCH_2$	CH_3	H	PhCH=$CHCH_2Br$	1.0	87
21	HC≡CCH_2	CH_3	H	HC≡CCH_2Br	1.0	71
22	PhC≡CCH_2	CH_3	H	PhC≡CCH_2Br	1.0	74
23[a]	H	CH_3	CH_3	H_2O[c]	1.5	90
24[a]	PhCO	CH_3	CH_3	PhCOCl[c]	1.5	88
25[a]	CH_3	CH_3	CH_3	CH_3I	1.5	70
26[a]	CH_3CH_2	CH_3	CH_3	CH_3CH_2I	1.5	67
27[a]	$PhCH_2$	CH_3	CH_3	$PhCH_2Br$	1.5	62
28[a]	*o*-$BrC_6H_4CH_2$	CH_3	CH_3	*o*-$BrC_6H_4CH_2Br$	1.5	58
29[a]	CH_2=$CHCH_2$	CH_3	CH_3	CH_2=$CHCH_2Br$	1.5	63
30[a]	PhCH=$CHCH_2$	CH_3	CH_3	PhCH=$CHCH_2Br$	1.5	62
31[a]	HC≡CCH_2	CH_3	CH_3	HC≡CCH_2Br	1.5	61
32[a]	PhC≡CCH_2	CH_3	CH_3	PhC≡CCH_2Br	1.5	64
33[b]	H	Ph	H	H_2O[c]	2.0	67
34[b]	PhCO	Ph	H	PhCOCl	2.0	60
35[b]	$PhCH_2$	Ph	H	$PhCH_2Br$	2.0	43
36[b]	CH_2=$CHCH_2$	Ph	H	CH_2=$CHCH_2Br$	2.0	51
37[b]	HC≡CCH_2	Ph	H	HC≡CCH_2Br	2.0	52

[a] The quantity of LDA and RX is 1.5 eq, respectively.
[b] The quantity of LDA and RX is 2.0 eq, respectively.
[c] Without addition of DMF.
[d] Isolated yield.

To gain further understanding of the deprotonation process in the reaction of 2-phenyl-2-oxazoline with LDA, we reexamined this lithiation reaction at different temperatures. No deprotonation reactions at the phenyl group or the oxazoline ring were observed at -78 °C. The ortho lithiation of phenyl group was very slow at 0 °C reported in literature,[18] but in fact we found that the ^{1}H NMR spectrum of the reaction mixture showed that about 60% of the starting materials were converted into compound **1** during 15 min when the reaction temperature rose to 0 °C, and the conversion was completed in *ca.* 2 h (see supporting information). Moreover, no deuterated 2-phenyl-2-oxazoline at the ortho position of phenyl group or the 4-position of oxazoline ring was observed in recovered starting materials, as shown by deuterated experiments at 0 °C (see supporting information). The above-mentioned results demonstrate that the lithiation of 2-phenyl-2-oxazoline with LDA is different from the corresponding lithiation process with *n*-BuLi.[16,17] The lithiation reaction only proceeded at the 4-position of oxazoline ring in the present work. Once the anion at the 4-position of oxazoline ring was formed, it underwent a very fast ring-opening reaction to generate *N*-vinylbenzamidato anion,[20] thus it was not trapped as an intermediate.

Although the formation of *N*-vinyl enamides through the ring-opening reaction of 5-substituted-2-oxazolines has been reported, the reaction conditions are relatively drastic, such as high reaction temperature, large excess of strong bases and long reaction time.[20] What is more, the ring-opening reaction of 5-unsubstituted-2-oxazolines does not afford similar *N*-vinyl enamides. These disadvantageous factors have been avoided in our present work. This work is especially suitable for the synthesis of multifunctional enamides, which have been used as the starting materials for intramolecular cyclization reactions to form various nitrogen hetercycles.[21] To prove the practical application value of this method, the amplification experiments were done when 2-phenyl-2-oxazoline and ally bromide or propargyl bromide were used as substrates. Good yields (83% for **8** and 75% for **10**, respectively) have been obtained when the reactions were amplified to gram scale. Another obvious advantage of the present work is the relatively high E/Z ratio for *N*-propenylbenzamide derivatives.[14,20] For example, the ^{1}H NMR spectrum of the crude reaction mixture for 5-methyl-2-phenyl-2-oxazoline (for **12**) showed an E:Z ratio of 96:4. Furthermore, the E-isomers were easily purified by column chromatography (Table 1, compounds **12**–**22** and **33**–**37**).

All synthesized compounds have been characterized by ^{1}H and ^{13}C NMR spectra, among which the new compounds have been also characterized by HRMS. These spectroscopic data are in good agreement with their structures. It should be pointed out that ^{1}H NMR spectra of some *N*-vinylbenzamide derivatives (such as compounds **14**–**16**) showed these compounds to be the mixtures of two rotamers of the amides in solution at room temperature. A similar phenomenon has been observed in other related *N*-vinylbenzamides.[22]

In summary, a simple and convenient synthesis of *N*-vinyl enamides via the lithiation and ring-opening reaction of 2-phenyl-2-oxazolines under the mild reaction conditions has been developed, which provides a good complementary method for the diverse synthesis of multifunctional enamides from readily available starting materials.

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Experimental

Typical procedure for the synthesis of N-vinylbenzamides

A THF solution of LDA (2 M, 1.2 mL, 2.4 mmol) was added to the stirred solution of 2-phenyl-2-oxazolines (2 mmol) in THF (10 mL) at room temperature under an argon atmosphere. After the resulting mixture was stirred for a given period of time, RX (2 mmol) and DMF (5 mL) were added. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica using ethyl acetate/petroleum ether (v/v=1:8) as the eluent to give the corresponding *N*-vinylbenzamides.

Gram scale synthesis

A THF solution of LDA (2 M, 4.8 mL, 9.6 mmol) was added to the stirred solution of 2-phenyl-2-oxazoline (1.18 g, 8 mmol) in THF (40 mL) at room temperature under an argon atmosphere. After the resulting mixture was stirred for 0.5 h, allyl bromide (0.59 mL, 8 mmol) or propargyl bromide (0.60 mL, 8 mmol) and DMF (15 mL) were added, respectively. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica using ethyl acetate/petroleum ether (v/v=1:8) as the eluent to give **8** or **10**. Yield: 1.25 g (83%) for **8** and 1.12 g (75%) for **10**, respectively.

Acknowledgments

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Supplementary material

Experiment details, spectroscopic data, ^{1}H and ^{13}C NMR spectra of compounds **1**-**37** as well as ^{1}H NMR spectra for the reaction of 2-phenyl-2-oxazoline with LDA at $0^{o}C$ under different reaction times are provided.

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Highlights

The lithiation of 2-phenyl-2-oxazoline with lithium diisopropylamide

Ring-opening reaction of 2-phenyl-2-oxazoline at room temperature

Synthesis of multifunctional *N*-vinyl tertiary enamides

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