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An efficient synthesis of styrenyl enamides from 4-aryl-2-oxazolidinones in the presence of strong base

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ABSTRACT

Efficient synthesis of styrenyl enamides can be achieved from the corresponding 4-aryl-2-oxazolidinones, 2-thioxooxazolidines, and 2-thioxothiazolidines in the presence of the strong base lithium diisopropylamine. The reaction proceeded efficiently to achieve the enamides in good to excellent yields (up to 92%). This reaction provides an easy, rapid, and good-yielding method for the synthesis of styrenyl enamides.

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Enamides are present as an important scaffold in various drugs, natural products, and key intermediates in organic synthesis.[1] Among them, the styrenyl enamides can act as a nucleophile to perform addition to aldehydes/ketones, imines, and Michael acceptors in the presence of a suitable Lewis acid catalyst.[1a,b] With metal catalyst, the α- and β-carbon of styrenyl enamides can be regioselective functionalized.[1f] The products so generated can be easily transformed to other nitrogen-containing compounds or other functional groups. On the other hand, styrenyl enamides are remarkable substrates in a range of asymmetric reactions.[1c] Especially, they were frequently utilized in asymmetric hydrogenation for the synthesis of various chiral amines and amides building blocks with chiral catalyst including metal complexes and organic molecules.[2] In recent years, more and more such compounds are used for stereoselective C–C and C–N bond forming reactions.[3] In spite of the extensive applications of styrenyl enamides, the development of their preparation remains challenging and synthetically useful.

Because of widespread applications of styrenyl enamides, many efforts have been made toward to general, efficient, and stereoselective methods access to this class of compounds. Different methods could be applied to synthesize these enamides (Scheme 1), including traditional approaches such as direct condensations of amides to ketones with catalysts,[4] the addition of organomagnesium or organolithium reagents to nitriles as intermediates and then constructing enamides with different substances,[5] the metal-catalyzed cross coupling of alkenyl compounds with amides,[6] and the Heck reaction of *N*-vinyl amide with aryl triflates or halide compounds.[7] In the recent decades, great progress has been achieved in the preparation of enamides. According to the references, reducing agents have been developed in this catalyzed reductive acylation reaction.[8–15]

Aiming at the development of a more direct and friendly process, herein we report a direct, very rapid, relatively mild, and efficient procedure that promoted by the strong base LDA for the synthesis of enamides. This process could provide a broad scope of styrenyl enamides in high yields.

When we tried to run the α-arylation of 4-phenyl-3-propionyl-oxazolidin-2-one (**1a**) with diaryliodonium salts and base, we failed to obtain the α-arylation product (Scheme 2). It is very interesting that the starting material was transformed into enamide after careful purification and characterization with NMR, which was further confirmed by single-crystal X-ray crystallography. Owing to the interesting transformation and the significance of styrenyl enamides, we decided to investigate the reaction in details.

We initially studied the reaction of 4-phenyl-3-propionyloxazolidin-2-one (**1a**) with various additives in THF at −78 °C. As shown in Table 1, no reaction occurred with potassium *tert*-butoxide,

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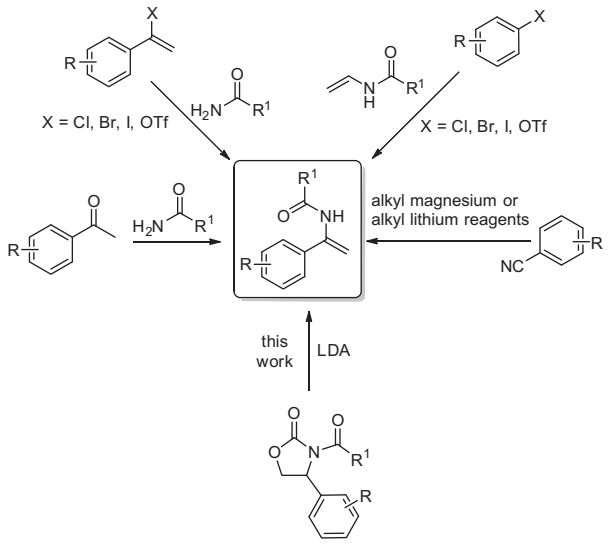
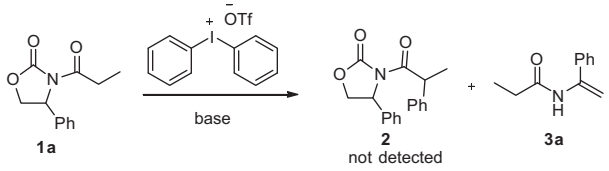


Scheme 1. The synthetic methods of styrenyl enamides.



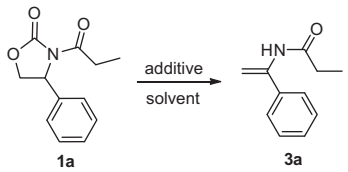
Scheme 2. α-Arylation with diaryliodonium salt.

sodium hydroxide, sodium hydride, cesium carbonate, and potassium carbonate as bases (entries 1–5). In order to find the suitable reaction conditions, we attempted to use the stronger base such as *n*-butyl lithium, lithium diisopropylamide (LDA), and lithium bis (trimethylsilyl)amide (LiHMDS). It was pleased to find that the reaction proceeded with these three bases. The product **3a** was obtained in 70%, 85%, and 78% yield correspondingly (entries 6–8). As we known, Kinoshita and co-workers reported a procedure to prepare (*E*)-α,β-didehydroamino acid derivatives by reaction of *cis*-4,5-oxazolidinone and LiHMDS, which shared a similar chemistry with this work, and they obtained the desired products in good yield and high *E* selectivity.[16] Next the effect of different solvents was subsequently surveyed (entries 9–11). The results indicated that the reaction performed well in both ether and alkane solvents, while all the solvents gave the desired product in moderate yield. Further increasing the reaction time did not provide a better result (entry 12). Thus, the best optimized conditions for this reaction have been established, LDA as the strong base in THF at −78 °C for 30 min.

With the optimal reaction conditions in hand, the substrate scope of the reaction was then investigated. A variety of differently substituted oxazolidinones **1** were subjected to the above reaction conditions. The results are shown in Table 2. It is satisfactory that all the reactions completed in short reaction time, and provided the desired products in good to excellent yields, exhibiting good functional group and extensive *N*-acyl group tolerance. The reactions of oxazolidone substrates with alkyl acetyl groups gave excellent yields (**3a**–**f**). Among these results, oxazolidinones with bulky acetyl groups gave slightly high yield (**3e** and **3f**), probably due to the inherent steric effect of substitutes. Especially, 3-pivaloyloxazolidin-2-one **1e** gave the product **3e** in 92% yield.

In addition, when oxazolidinones substituted with unsaturated acetyl groups were used, the desired compounds **3g** and **3h** were obtained in good yields, and the sequent intramolecular Michael addition was not observed. Furthermore, in spite of different electron-donating or electron-withdrawing groups in the phenyl ring, the yields were good to excellent as well (**3i**–**n**). Fortunately, when the oxazolidinones were substituted with protected amino acid, the reaction could give the corresponding products with amino amide motifs in good yields (**3o** and **3p**). Oxazolidinones with long unsaturated carbon and saturated carbon chains were good substrates for this reaction. The reactions proceeded well under −78 °C for 40 min, and the corresponding products were obtained (**3q** and **3r**). Subsequently, further exploration of the scope of the reaction was conducted with 2-thioxooxazolidine, 2-thioxothiazolidine, and the reactions also gave the desired products in good

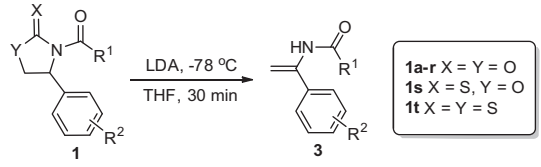
Table 1
Optimization of the reaction conditions [a]



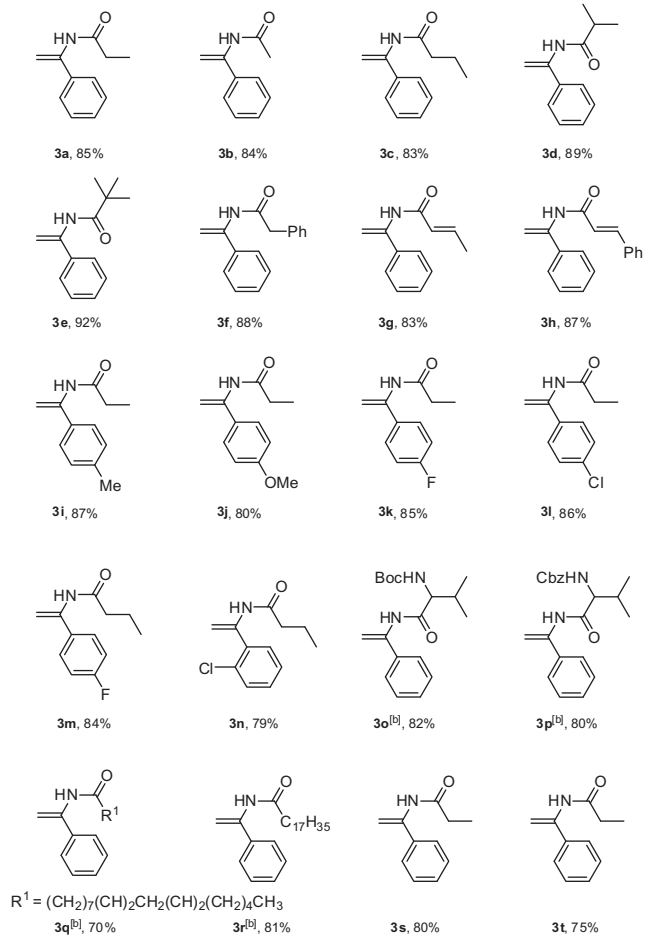
Entry	Additive	Solvent	Temp (°C)	Yield[b] (%)
1[c]	*t*-BuOK	THF	−78→rt	0
2[c]	NaOH	THF	−78→rt	0
3[c]	NaH	THF	−78→rt	0
4[c]	Cs_2CO_3	THF	−78→rt	0
5[c]	K_2CO_3	THF	−78→rt	0
6	*n*-BuLi	THF	−78	70
7	LDA	THF	−78	85
8	LiHMDS	THF	−78	78
9	LDA	Dioxane	−78	65
10	LDA	*n*-Hexane	−78	63
11	LDA	Et_2O	−78	76
12[d]	LDA	THF	−78	84

[a] Unless otherwise noted, all the reactions were carried out by using 1.0 mmol of **1a**, 2.0 equiv of additive, 2.0 mL of solvent, under a nitrogen atmosphere for 30 min.
[b] Isolated yield of **3a** after column chromatography.
[c] The reaction was performed at −78 °C for 3 h and then at room temperature for 5 h.
[d] The reaction was performed at −78 °C for 1 h.

Table 2
Scope of synthesizing enamides from oxazolidinones [a]



1 3



[a] Unless otherwise noted, all the reactions were carried out by using 1.0 mmol of substrate **1**, 2.0 equiv of LDA, 2.0 mL of THF, under a nitrogen atmosphere at −78 °C for 30 min, isolated yields of product **3** after column chromatography.
[b] The reaction was performed at −78 °C for 40 min.

yields (**3s** and **3t**). Unfortunately when 5,5-dimethyl-4-phenyl-3-propionyloxazolidin-2-one, the analog of **1a** with two methyl groups at 5-position was used as substrate, the corresponding enamide with four substituents was not detected.

The structure of product **3a** was unambiguously determined by a single crystal X-ray analysis and the corresponding structure is shown in Figure 1.

According to the experimental results and the related reports,[16,17] a probable mechanism was proposed and is shown in Scheme 3. The enamide formed by deprotonation with a base such as LDA, subsequently ring opening of oxazolidinone, decarboxylation, and protonation.

In summary, we have developed a rapid and convenient method for the synthesis of *N*-acyl styrenyl enamides from 4-aryl-2-oxazolidinones, 2-thioxooxazolidine, and 2-thioxothiazolidine in the presence of the strong base LDA. This process indicated good functional group tolerance, and could be applied in various substrates providing good to excellent yields.

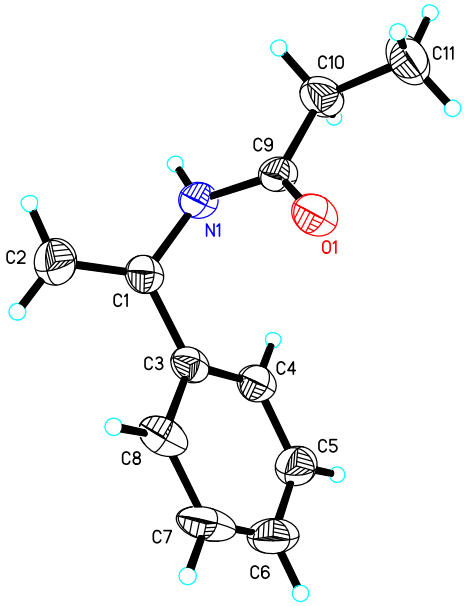
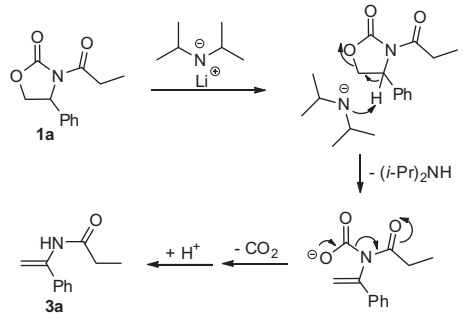


Figure 1. X-ray structure of the product **3a**.



Scheme 3. Proposed reaction mechanism.

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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.2015.08.026.

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