Tetrahedron Letters 66 (2021) 152821

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Organotin-catalyzed synthesis of hydroxyalkylamides from lactones via a ring-opening process

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ARTICLE INFO

*Article history:*
Received 21 November 2020
Revised 21 December 2020
Accepted 3 January 2021
Available online 16 January 2021

*Keywords:*
Hydroxyalkylamide
Ring-opening
Lactone
Amine
Dibutyltin acetate

ABSTRACT

A new strategy for the facile synthesis of hydroxyalkylamides through the ring-opening reaction of lactone with amine promoted by dibutyltin acetate was developed. A series of hydroxyalkylamide compounds were obtained and the method was successfully applied to the synthesis of pharmaceutically active molecules tyrosinase inhibitor V and HDAC inhibitor VI via a three-step synthetic pathway. The broad substrate scope, mild reaction conditions and practical application proved the effectiveness, compatibility and practicality of this method.



## Introduction

Amide structure exists widely and plays an important role in many natural products, pharmaceuticals, ligands, and functional materials [1–4]. The hydroxyl amides obtained from the ring opening reaction of lactones and amines are utilized in novel surfactants, carrier-prodrugs and drug intermediates [5–11]. However, the reaction is usually restricted by the activity of lactones and the nucleophilicity of amines, thus defining the optimal condition for ring-opening is to be addressed and currently under intensive exploration. Matsumoto and co-workers provided the primary example of ammonolysis of lactones with amines at room temperature and under a high pressure in 1989 [12]. Then, Lesimple et al. reported that a series of hydroxyalkamides were obtained in good yields by ring opening reaction in the presence of $AlCl_3$ [13] Later on, the ring opening reaction catalyzed by $AlMe_3$, which is sensitive and flammable, was reported [14,15]. In 2001, Huang et al. successfully used DIBAL-H-$H_2NR$ and DIBAL-H-$HNR^1R^2$·HCl complexes as amidating reagents for the aminolysis of γ- butyrolactone [31]. In 2017, Barreto et al. prepared hydroxyl amides from a variety of amines and lactones by microwave irradiation under the conditions without solvent and catalysis [16]. Compared with all the works described so far, the microwave-mediated reaction is milder and with the ability to shorten the reaction time more efficiently. However, the restrict requirements for equipment and high reaction temperature limited the application scope of this method. Guo et al. revealed the ammonolysis of lactones for the synthesis of *N*-aryl amide through organocatalysis of aniline and various lactones in 2017, which proceeded under milder and more favorable reaction conditions [17]. As mentioned above, some limitations might jeopardize these synthesis schemes reported, for instance, the harsh reaction conditions, and the relatively long reaction times. Therefore, a practical and efficient synthesis strategy for these valuable hydroxyalkamide compounds is on the call. Organotin catalysts, a new kind of neutral multifunctional homogeneous catalysts developed in recent years, are different from other metal compounds in terms of structural stability due to its insensitivity to air and water [18,19], which have been utilized in the ring-opening polymerization of lactones and alcohols [20–23]. The coordination of tin and carbonyl oxygen increases the electrophilicity of carbonyl carbon and facilitates the attack of nucleophile to form polyester compound [24–26]. Multiple polyester products are commonly obtained under the initiation of strong nucleophiles, due to the fact that the traditional tin salts have poor control over the polymerization process. Different from polyesters, we hypothesized whether the lactone ammonolysis reaction can run smoothly when using organotin as catalyst and amine as a nucleophilic reagent, which is capable to obtain corresponding hydroxyalkanamide compounds (Scheme 1).

Thereafter, our group reported that the amines could react with lactones efficiently and produce hydroxyalkylamides in good yields under a mild condition without using inert gas and dry solvent through the dibutyltin acetate catalysis. The method is

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https://doi.org/10.1016/j.tetlet.2021.152821
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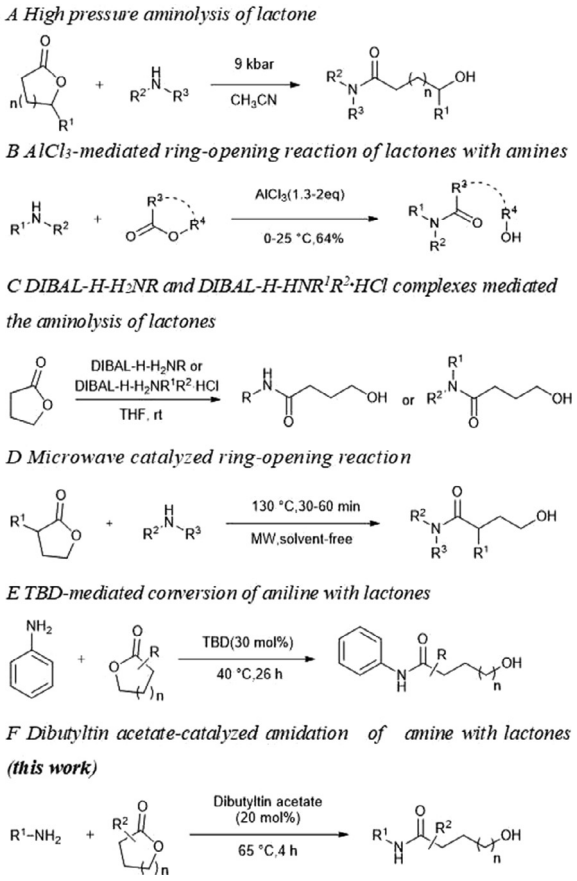



**Scheme 1.** The strategies to the synthesis of hydroxyalkylamides.

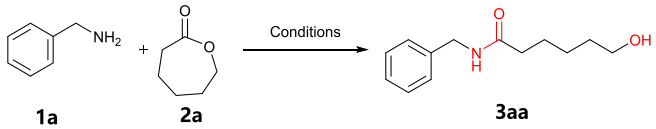
generally applicable to various types of amines and lactones with different ring sizes, and moreover, the reaction conditions required are milder, and the reaction time is shorter, when compared to other existing methods (Table 1).

## Results and discussion

Initially, we explored the direct ring-opening amidation of ε-caprolactone (**2a**) with benzylamine (**1a**) in the presence of 10 mol% of various organotin catalysts in THF. The reaction ran smoothly at 65 °C with the dibutyltin acetate catalyst and gave Benzyl-6-hydroxyhexanamide **3aa** in 76% yield within 12 h. No reaction happened in the absence of the catalyst (entry 8). The results of catalyst screening showed that the disubstituted organotin catalysts had a relatively intensive catalytic activity (entry 2, 5, 6), and the steric effect of the catalysts had a great impact on the reaction progression. The reactions with bis(tributyltin) oxide, dioctyltin oxide and dibutyltin dilaurate displayed (entry7, 4, 6), the larger the steric effect of organotin catalysts, the lower the conversion rate. Meanwhile, we also investigated the effects of the reaction temperature (entries 23–24), and found that the yield could reach 80% after 16 h of reaction under 40℃. Lower reaction temperature effectively increased the yield, but accompanying the reaction time prolonged. Through the extensive screening of catalyst loading (entries 8–12), stoichiometric ratio (entries 11,13–17), and solvent (entries18-22), it was found that reaction of ε-caprolactone, benzylamine (2 equivalents), and 20 mol% dibutyltin acetate in THF at 65 °C for 4 h afforded the optimal isolated yield of 77% of **3aa** (entry 11).

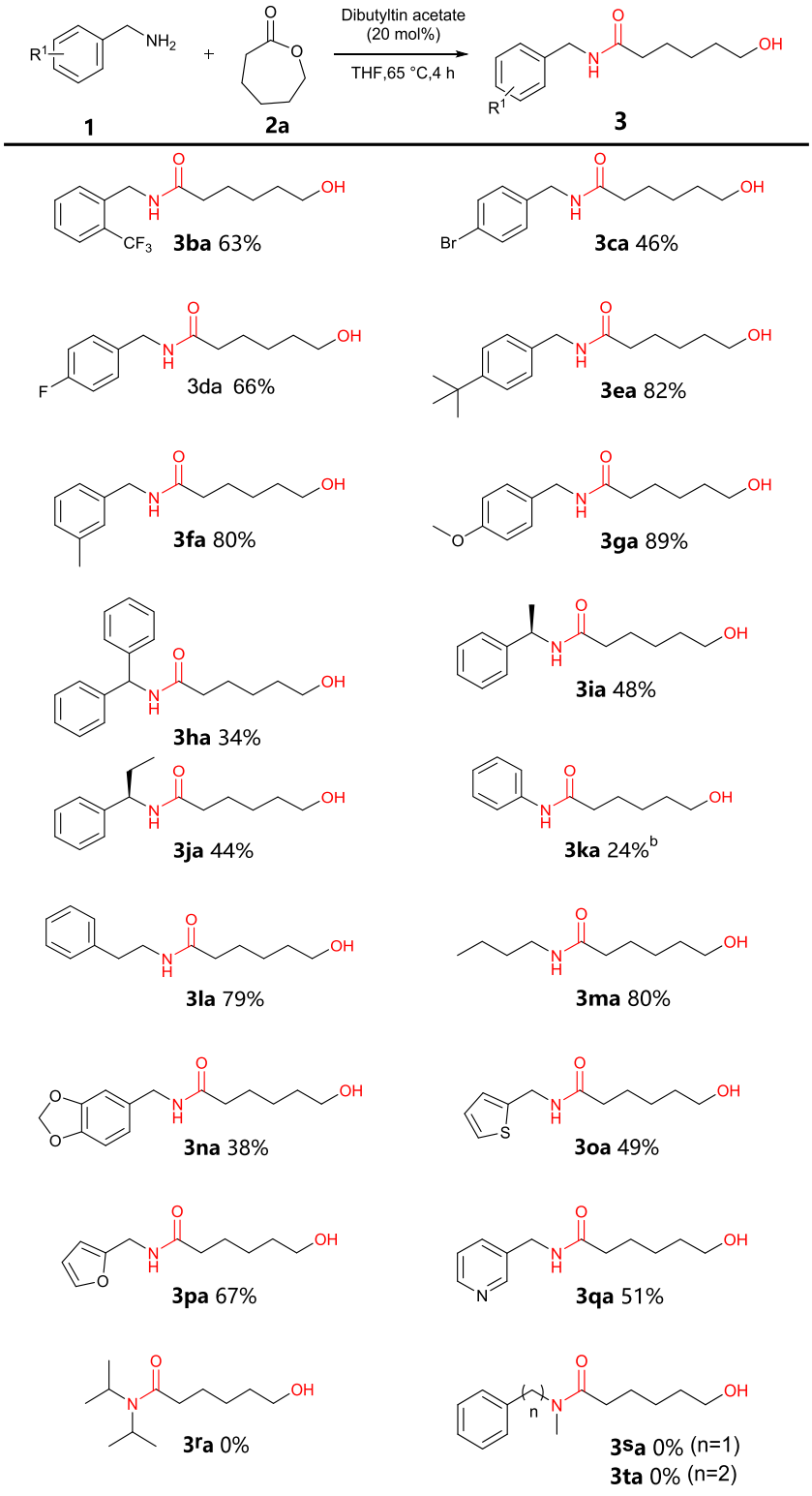
A series of *N*-benzyl hydroxyalkylamides were synthesized under the optimal reaction conditions found above. As shown in Scheme 2, we examined the substrate scope by varying the substituents of benzylamines. When a set of electron-withdrawing

**Table 1**
Optimization of the Reaction Conditions.[a]



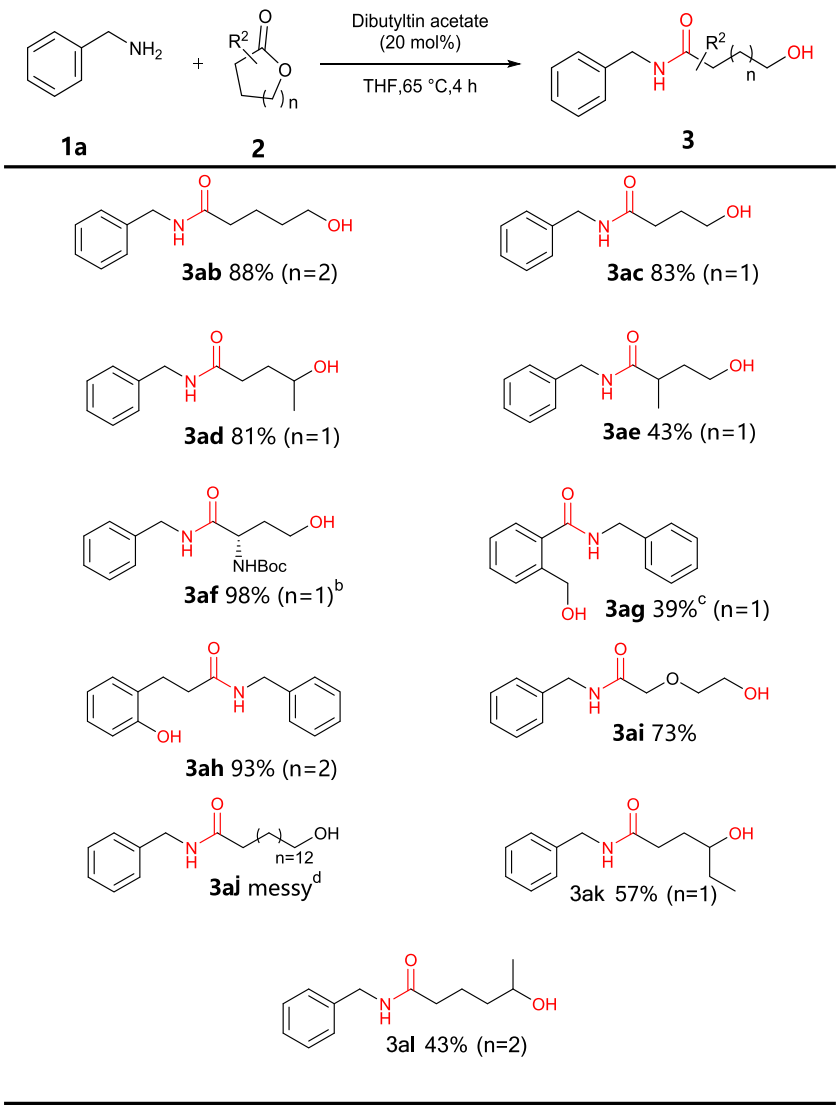

| Entry | Catalyst (mol%) | Solvent | Ratio (**1a:2a**) | Time (h) | Yield (**3aa**, %)[b] |
|---|---|---|---|---|---|
| 1 | Butyltin oxide (10) | THF | 2:1 | 12 | 51 |
| 2 | Dibutyltin oxide (10) | THF | 2:1 | 12 | 57 |
| 3 | Bis(tributyltin) oxide (10) | THF | 2:1 | 12 | 18 |
| 4 | Dioctyltin Oxide (10) | THF | 2:1 | 12 | 41 |
| 5 | Dibutyltin acetate (10) | THF | 2:1 | 12 | 76 |
| 6 | Dibutyltin dilaurate (10) | THF | 2:1 | 12 | 63 |
| 7 | Bis(lauroyloxy)dioctyltin (10) | THF | 2:1 | 12 | 50 |
| 8 | Dibutyltin acetate (0) | THF | 2:1 | 12 | 0 |
| 9 | Dibutyltin acetate (5) | THF | 2:1 | 10 | 57 |
| 10 | Dibutyltin acetate (10) | THF | 2:1 | 6 | 74 |
| 11 | Dibutyltin acetate (20) | THF | 2:1 | 4 | 77 |
| 12 | Dibutyltin acetate (30) | THF | 2:1 | 4 | 76 |
| 13 | Dibutyltin acetate (20) | THF | 1:1 | 4 | 67 |
| 14 | Dibutyltin acetate (20) | THF | 1.2:1 | 4 | 69 |
| 15 | Dibutyltin acetate (20) | THF | 1.5:1 | 4 | 72 |
| 16 | Dibutyltin acetate (20) | THF | 1.8:1 | 4 | 75 |
| 17 | Dibutyltin acetate (20) | THF | 2.5:1 | 4 | 77 |
| 18 | Dibutyltin acetate (20) | DCE | 2:1 | 4 | 54 |
| 19 | Dibutyltin acetate (20) | Toluene | 2:1 | 4 | 67 |
| 20 | Dibutyltin acetate (20) | MeCN | 2:1 | 4 | 42 |
| 21 | Dibutyltin acetate (20) | 1,4-Dioxane | 2:1 | 4 | 72 |
| 22 | Dibutyltin acetate (20) | DMSO | 2:1 | 4 | 37 |
| 23[b] | Dibutyltin acetate (20) | THF | 2:1 | 16 | 80 |
| 24[c] | Dibutyltin acetate (20) | THF | 2:1 | 30 | 21 |

[a] Reaction conditions: Benzylamine (1a, 4.38 mmol), ε-caprolactone (2a, 2.19 mmol), Organotin catalyst (20 mol%), THF (5 mL) were added in a flask (20 mL) and reacted at 65 °C for 12 h.
[b] Reacting at 40 °C for 16 h.
[c] Reacting at rt for 30 h.




**Scheme 2.** Substrate Scope of benzylamine and the expansion of amines. [a]Conditions: substituted benzylamine (1, 4.38 mmol), ε-caprolactone (2a) (2.19 mmol), Dibutyltin acetate (20 mol%), THF (5 mL), reaction for 4 h at 65 °C, isolated yields are based on the amount of (2a). [b]Using 1,4-dioxane as solvent and reacting for 12 h at 100 °C.

(**3ba-3da**) groups located on the benzene rings, such as halogen and trifluoromethyl, the reaction yields decreased significantly, and either prolonging reaction time or increasing catalyst loading had no effect on it. Nevertheless, the opposite result was observed for substrates with electron-donating groups (**3ea-3ga**) because the electron-donating effect on the benzene ring improves the nucleophilic ability of amino group. Generally, moderate to excellent yields were obtained, and the highest conversion was achieved for the product **3ga** with a 89% yield. We also selected some benzylamines with steric hindrance as substrate, and the hydroxyalkylamide products bearing a tertiary alkyl group (**3ha-3ja**) were isolated in moderate to low yields. Beside benzylamines, some

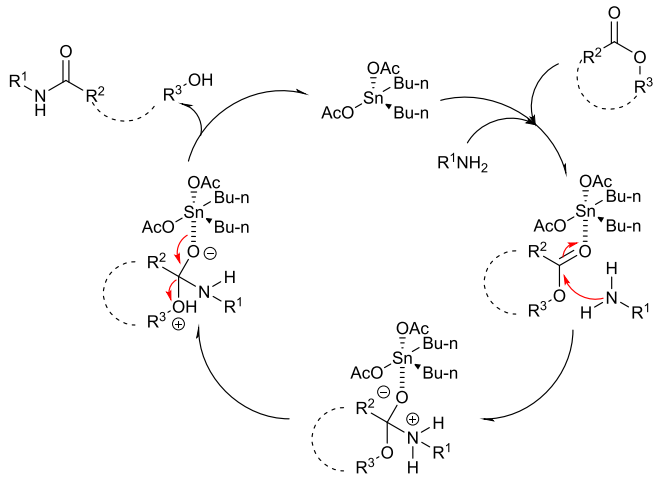



**Scheme 3.** Substrate Scope of lactones with different ring sizes and substituent groups. [a]Conditions: (1a, 4.38 mmol), lactone (2) (2.19 mmol), Dibutyltin acetate (20 mol%), THF (5 mL), reaction for 4 h at 65 °C, isolated yields are based on the amount of (2). [b]The enantioselectivity up to 97%. [c]Using 1,4-dioxane as solvent and increasing the catalyst loading to 30 mol%, reaction for 12 h at 100 °C. [d]Using 1,4-dioxane as solvent and reacting for 20 h at 100 °C.

different heteroatoms (**1oa–1qa**) with **2a**. Aromatic amines and fatty amines including aniline, phenethylamine and *n*-butylamine were also tested, which reacted with ε-caprolactone smoothly to give yield up to 80%. However, because of aniline compounds with lower nucleophilicity (**3ka**), we need to heat the system to 100 °C in 1, 4-dioxane and extend the reaction time to 12 h to complete the reaction. In order to further expand the product diversity, we conducted the reactions of heterocyclic amines bearing various heteroaton (**3oa–3qa**). All the corresponding products were accessed in moderate yields, showing good compatibility of the reaction conditions to the different amines. We carried this reaction further with secondary amines (such as *N*-methylaniline, *N*-methylbenzylamine and diisopropylamine), and the favourable results were not obtained. The experimental results showed that the reaction state remained in the ε-caprolactone ring-opening and the amine hadn't attack furthermore. We also carried this reaction further with the nucleophilic cyclic amines (morpholine and pyrrolidine), but the result was also not ideal. The results of these investigations are summarized in Scheme 2.

Next, we explored the range of lactones with different ring sizes and substituents as substrates. The reaction results demonstrated that both 5-membered lactones (**3ac-3af**) and 6-membered lactones (**3ab**) reacted smoothly and there were few by-products formed. The results also showed this approach could be compatible with giving secondary alcohols (**3ad**, **3ak-3al**). Unfortunately, treatment of pentadecanolide (**2j**) with benzylamine and dibutyltin acetate under the standard conditions did not incur any reaction. In addition, reactions with higher reaction temperatures and longer reaction time led to a relatively complicated mixture, and no expected product (**3aj**) was successfully isolated. We also selected the 6-membered lactones with oxygen aza-atom as substrate (**3ai)** and found clearly the presence of heteroatoms doesn't affect the reaction efficiency. The ring-opening of benzolactone (**3ag**) showed the conjugation of benzene ring with carbonyl group reduced the positivity of the carbonyl carbon, leading to a challenge for amino attacked furthermore. For lactones with chiral structure (**3af**), racemization was not observed in the ring-opening process, and the enantioselectivity (up to 96%) remained excellent when reacting on standard conditions or increasing the reaction temperature. The results of these investigations are summarized in Scheme 3.

Based on the above results, we propose the following possible mechanism for the tin-catalyzed ring-opening reaction. The tin



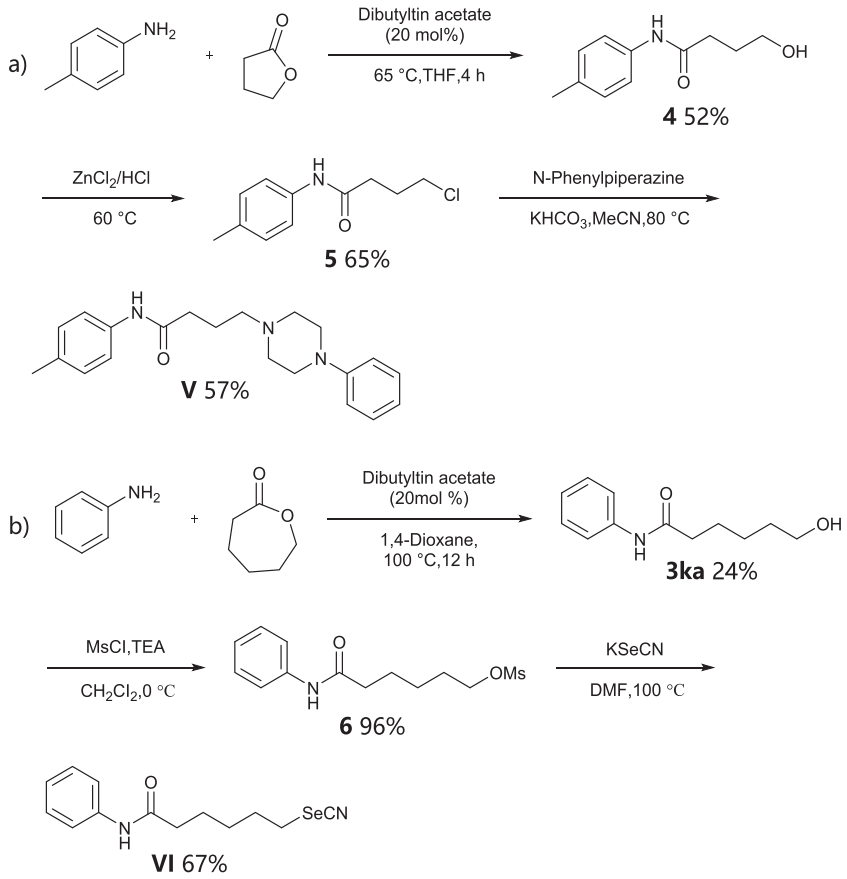
**Scheme 4.** Proposed mechanism.

atom with the empty d orbitals in outer shell can accept lone pair electrons from p orbitals of oxygen atom to form coordination bond and increase the electrophilicity of carbonyl carbon during chemical reactions. Subsequently, amine as nucleophilic reagent to attack the carbonyl carbon of lactone, causes the ring-opening to form the hydroxyalkylamide compound. Nevertheless, the exact reaction mechanism is still unclear (Scheme 4).

To examine the practicality and robustness of this method, we performed the gram scale synthesis of **3aa**. Under the standard conditions, 1.68 g (7.6 mmol) of **3aa** was successfully produced from 1.14 g (10 mmol) of starting material **2a** and 2.15 g (20 mmol) of **1a**, and the yield reached to 76%. To further examine the feasibility of this method on constructing small molecule pharmaceuticals, the tyrosinase inhibitor V [27] and HDAC inhibitor VI [28,29] were synthesized through a three-step pathway based on this ring-opening reaction (Scheme 5). The first step in the synthesis of tyrosinase inhibitor V began with the ring-opening reaction of butylactone with p-toluidine and the compound 4-hydroxy-*N*-(4-methylphenyl)-butanamide reacted with the Lucas reagent to provide the chlorinated product **5** in 65% yield. Then, **5** was treated with *N*-phenylpiperazine at 80 °C overnight and successfully formed the tyrosinase inhibitor (V) [30]. Furthermore, the ring-opening products of aniline and caprolactone could be converted into HDAC inhibitors (VI) by similar method. Comparing with traditional methods of obtaining these two compounds, this method provides an alternative synthetic route.

## Conclusion

In summary, we have developed an effective strategy for the synthesis of hydroxyalkanamide compounds by ring-opening reaction of lactones and amines mediated by dibutyltin acetate. There is a high compatibility in the substrate scope that various substituted hydroxyalkanamide compounds are synthesized[1] and easily scaled up to the gram level. Moreover, hydroxyalkylamides with a single enantiomer can be prepared by this method under mild conditions. Furthermore, the utility of this new method has been demonstrated by the three-step synthesis of the bioactive molecules V and VI. This effective strategy provides a direct pathway




**Scheme 5.** The synthetic routes to compound V and VI.

to obtain hydroxyalkanamide compounds, which is possible to apply in medicinal chemistry.

## Experimental section

*General information*

All reagents and solvents were purchased from commercial sources and used without further purification. All reactions were carried out under an air atmosphere. Unless otherwise specified, NMR spectra are recorded in $CDCl_3$ or $CD_3OD$ on a 500 or 400 MHz (for $^1H$), or 126 MHz (for $^{13}C$) spectrometer. All chemical shifts are reported in ppm relative to TMS ($^1H$ NMR, 0 ppm) as an internal standard. Melting points of the products were measured and uncorrected. MS experiments were performed on a TOF-Q ESI instrument.

*General procedure for ring-opening processes*

An oven-dried reaction flask (20 mL) was charged with amine (1, 4.38 mmol), lactone (2, 2.19 mmol, 1.0 equiv), dibutyltin acetate (20 mol%) and THF (5 mL). The resulting mixture was stirred at 65 °C for 4 h. The crude products were purified by flash column chromatography on silica gel to give the desired product.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgement

The synthetic and analytical facilities were supported by Wuhan University of technology.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152821.

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