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A practical one-pot synthesis of dehydroalanine esters†

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A practical one-pot synthesis of various dehydroalanine esters was realized *via* a Cs_2CO_3-mediated simultaneous esterification/elimination process, starting from commercially available N-protected serines and various haloalkanes. This protocol provided easy access to structurally diverse dehydroalanine-based building blocks, which were successfully applied to construct more complex dehydroalanine derived molecules.

Introduction

Dehydroalanine is an important structural motif that broadly occurs in many complex natural products,[1] multifunctional probes,[2] modified peptides and proteins.[3] Especially, as a highly active α, β-unsaturated amino acid residue, it always appears in some natural polycyclic peptide toxins, such as microcystins[1b] and thiostrepton.[1c] Due to their good stability and reactivity under physiological conditions, dehydroalanine and its derivatives are highly efficient Michael acceptors, which have strong chemical utilities for the synthesis of modified peptides and proteins.[3] For example, the dehydroalanine unit incorporated in proteins, acting as a "chemical tag", can undergo conjugate addition reactions with versatile nucleophiles, which mimics posttranslational modification of proteins through a variety of β,γ-bond formation (C–S, C–N, C–Se, *et al.*).[3a] This dehydroalanine-modification strategy has also been applied to design novel dehydroalanine-based activity probes for biological research and drug development.[2] In addition, dehydroalanine derivatives are the key building blocks that are widely utilized to synthesize various β-substituted α-amino acids *via* metal-catalyzed cross-coupling processes,[4] Michael-type additions,[5] catalytic tandem transformations,[6] *etc.*

In view of their wide applications in molecular biology and organic synthesis, much effort has been devoted to develop simple and efficient synthetic methods for dehydroalanine derivatives.[7,8] Generally, serine and cysteine are the controllable dehydroalanine precursors,[7] which first transformed into leaving groups, followed by elimination to yield dehydroalanine (Fig. 1). Unlike this typical method, Rivera and coworkers reported a two-step approach for the synthesis of dehydroalanine derivatives *via* a consecutive Ugi-4CR/elimination reaction.[8] Herein, we described an efficient one-pot synthesis of dehydroalanine esters, starting from commercially available N-protected serines and various haloalkanes by a Cs_2CO_3-mediated simultaneous esterification/elimination process (Fig. 1). This protocol provided easy access to structurally diverse dehydroalanine esters, that has been successfully utilized to synthesize more complex dehydroalanine derived molecules.

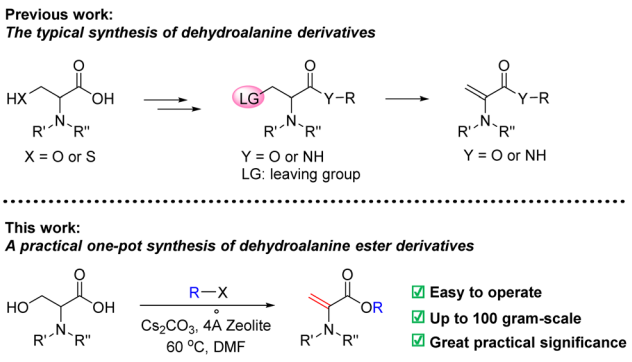

Fig. 1 Synthetic routes to dehydroalanine derivatives.

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Results and discussion

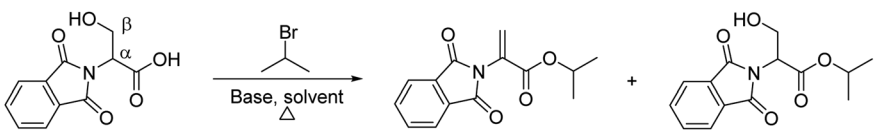
Under alkaline conditions, the elimination of β-hydroxyl groups to form α,β-unsaturated carbonyl compounds[9] and the esterification of carboxylic acid with a haloalkane[10] are general reactions in organic synthesis. Based on these two conventional reactions, commercially available *N*-phthaloylserine (**1a**) and 2-bromopropane were employed as model substrates to explore one-pot synthesis of dehydroalanine ester **2a**. The results are presented in Table 1. The efficiency of various inorganic carbonates was first investigated for this reaction. Li_2CO_3, Na_2CO_3 and K_2CO_3 were inefficient for the generation of **2a**, only affording *N*-phthaloylserine isopropyl ester **3a** in moderate yields (52–79%) with DMF as solvent at 60 °C (entries 1–3). Due to an increase in the alkalinity, Rb_2CO_3 and Cs_2CO_3 utilized as base provided the desired *N*-phthaloyldehydroalanine isopropyl ester (**2a**) in 18% and 58% yields, respectively (entries 4 and 5). However, very large amounts of **3a** were inevitably produced.

Next, we found that the reaction temperature had an important effect on the formation of **2a**. The low reaction temperature was not conducive to the elimination of β-hydroxyl group of **1a** (entry 6), and the high reaction temperature might lead to further ester hydrolysis of **2a** (entry 7). It was sufficient for this reaction to proceed smoothly at 60 °C. Surprisingly, owing to its good water absorption characteristics, 4 Å zeolite was beneficial to improve the yield of **2a** (68–70%), and 12 h was the appropriate reaction time (entries 8 and 9). In addition, increasing the amount of 2-bromopropane didn't improve the yield of **2a** (entry 8).

Subsequently, increasing/reducing the amount of Cs_2CO_3 had no benefits for this reaction (entries 10 and 11), and provided **2a** in low yields (22–35%). In addition, different solvents were evaluated aiming at increasing the yield of **2a** (entries 12–15), but only *N*-methyl-2-pyrrolidone (NMP) and *N*,*N*-dimethylacetamide (DMAC) gave **2a** in moderate yields (62–63%). Finally, the optimized reaction conditions were determined that **1a** (1.0 equiv.) and 2-bromopropane (1.5 equiv.) were smoothly converted into dehydroalanine ester **2a** in 70% yield with Cs_2CO_3 (1.5 equiv.) as base and DMF as solvent at 60 °C (entry 8).

With the optimal reaction conditions in hand, we further investigated the generality of Cs_2CO_3-mediated simultaneous esterification/elimination of various N-protected serine **1** with 2-bromopropane, to prepare N-substituted dehydroalanine isopropyl ester **2**. As shown in Table 2, **1b–1e** containing alkoxycarbonyl protecting group (R^1 = Ethoxycarbonyl, Alloc, Boc and Teoc) provided the desired dehydroalanine esters **2b–2e** in moderate to good yields (51–69%), with N-protected serine isopropyl esters **3b–3e** in 19–35% yields. By contrast, N-Cbz serine **1f** gave the desired dehydroalanine ester **2f** in lower yield (25%), mainly affording the corresponding product **3f**. When *N*-acetylserine **1h** used as substrate, the corresponding dehydroalanine ester **2h** was obtained in 52% yield. However, due to its instability under alkaline conditions, N-Fmoc serine **1g** didn't yield the desired product under the standard

Table 1 Optimization of the reaction conditions[a]

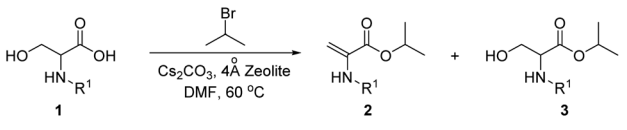


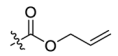
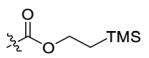
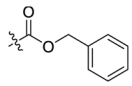
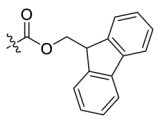
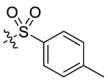
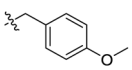
1a **2a** **3a**

Entry	Base	Solvent	4 Å zeolite	T (°C)	Time (h)	Yield of **2a** (%)[b]	Yield of **3a** (%)[b]
1	Li_2CO_3	DMF	☒	60	12	0	52
2	Na_2CO_3	DMF	☒	60	12	0	60
3	K_2CO_3	DMF	☒	60	12	0	79
4	Rb_2CO_3	DMF	☒	60	12	18	65
5	Cs_2CO_3	DMF	☒	60	12	58	38
6	Cs_2CO_3	DMF	☒	40	12	25	40
7	Cs_2CO_3	DMF	☒	80	12	46	40
8	Cs_2CO_3	DMF	☑	60	12	70, 65[c]	24, 30[c]
9	Cs_2CO_3	DMF	☑	60	24	68	20
10	Cs_2CO_3[d]	DMF	☑	60	12	22	70
11	Cs_2CO_3[e]	DMF	☑	60	12	35	9
12	Cs_2CO_3	THF	☑	60	24	0	10
13	Cs_2CO_3	DMSO	☑	60	12	10	20
14	Cs_2CO_3	NMP	☑	60	12	62	29
15	Cs_2CO_3	DMAC	☑	60	12	63	30

[a] Reaction conditions: **1a** (1.0 mmol), 2-bromopropane (1.5 mmol), base (1.5 mmol), 4 Å zeolite (90 mg), solvent (5 mL). [b] Isolated yield. [c] 2-bromopropane: 2.0 mmol. [d] Cs_2CO_3: 1.0 mmol. [e] Cs_2CO_3: 2.0 mmol.

Table 2 Synthesis of various N-substituted dehydroalanine isopropyl ester **2** and N-substituted serine isopropyl ester **3** [a]



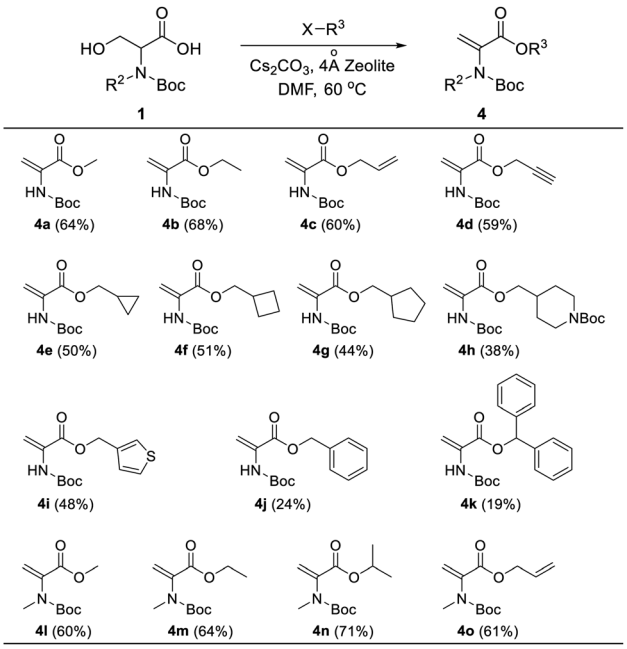
Entry	Substrate	R^1	Yield of 2 (%)[b]	Yield of 3 (%)[b]
1	**1b**		59	30
2	**1c**		61	27
3	**1d**		69	19
4	**1e**		51	35
5	**1f**		25	50
6	**1g**		0	0
7	**1h**		52	33
8	**1i**		0	15
9	**1j**		0	41
10	**1k**		0	45

[a] Reaction conditions: **1** (1.0 mmol), 2-bromopropane (1.5 mmol), Cs_2CO_3 (1.5 mmol) and 4 Å zeolite (90 mg) in DMF (5 mL) at 60 °C for 12 h. [b] Isolated yield.

conditions. In addition, some other types of N-protected serines **1i–1k** (R^1 = Tos, Bn and PMB) mainly produced N-protected serine isopropyl esters **3i–3k** in 15–45% yields, without the generation of dehydroalanine esters. These results indicate that the carbonyl group on nitrogen is the key factor for Cs_2CO_3-mediated simultaneous esterification/elimination of **1** with haloalkanes.

To further expand the structural diversity of dehydroalanine esters, N-Boc serine **1d** and N-Boc-*N*-methyl serine **1l** were selected to react with various haloalkanes. As depicted in Table 3, N-Boc serine **1d** reacted with a series of primary haloalkanes under the standard conditions, to give the corresponding dehydroalanine esters **4a–4j** in 24–68% yields.

Table 3 Synthesis of various N-Boc dehydroalanine ester **4** [a]



[a] Reaction conditions: **1** (1.0 mmol), haloalkane (1.5 mmol), Cs_2CO_3 (1.5 mmol) and 4 Å zeolite (90 mg) in DMF (5 mL) at 60 °C for 12 h.

Unsatisfactorily, the greater steric hindrance of some haloalkanes containing cycloalkane and aromatic rings resulted in a significant decrease in the yields of target compounds. Similarly, the secondary haloalkane diphenylbromomethane as the substrate afforded dehydroalanine ester **4k** in lower yield (19%). Interestingly, N-Boc-*N*-methyl serine **1l** reacted well with less sterically hindered primary haloalkanes, to provide the corresponding dehydroalanine esters **4l–4o** in good yields (60–71%). This result gives us more opportunities to construct more complex dehydroalanine derivatives.

In view of dehydroalanine derivatives having great potential for application in molecular biology and organic synthesis, we performed 100 gram-scale preparation of N-Boc dehydroalanine isopropyl ester **2d** (63% yield), which was further employed as a key building block for the synthesis of highly functionalized molecules **5–8** in 46–83% yields (Fig. 2). **5a** and **5b** are the key medicine intermediates for the preparation of calcitonin gene-related peptide receptor antagonists.[11] **6a** and **6b** can serve as the precursors to synthesize a variety of unnatural amino acids.[12] **7a** and **7b** have the potential for application in molecular imaging[13] and target identification.[14] In addition, **8a–8d** as the building blocks derived from **2d** can be successfully prepared using conventional chemical methods such as Michael-type addition, halogenation and reduction reactions.

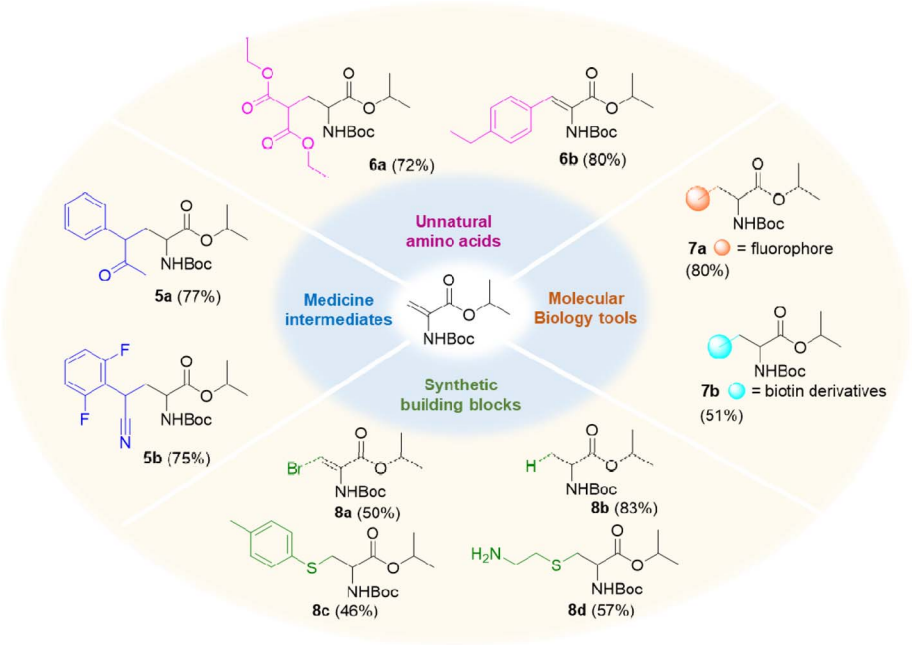


Fig. 2 Synthetic application of N-Boc-dehydroalanine isopropyl ester **2d**.

Conclusions

In summary, we establish a practical one-pot synthesis of structurally diverse dehydroalanine esters *via* a Cs_2CO_3-mediated simultaneous esterification/elimination process, starting from commercially available N-protected serines and various haloalkanes. Compared to traditional synthesis methods, this approach has many advantages, including simplified operation, reagent economy, large-scale preparation and wide application scenarios. Additionally, the newly synthesized dehydroalanine esters can serve as the key building blocks to prepare a series of highly functionalized molecules. Further applications of these dehydroalanine derived functionalized molecules are ongoing in our laboratory.

Data availability

The authors confirm that the data supporting the findings of this study are all available within the article.

Author contributions

D. C., H. H. and F. L. conceived the idea and designed the research. Q. S., M. Z., Z. L. and X. D. performed the research. M. Z., L. Y. and P. S. analyzed the data. D. C. and Q. S. wrote the original manuscript. C. X. and X. Z. reviewed the manuscript and suggested improvements. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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