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Dehydrogenative Cyclization of *N*-Acyl Dipeptide Esters for the Synthesis of Imidazolidin-4-ones

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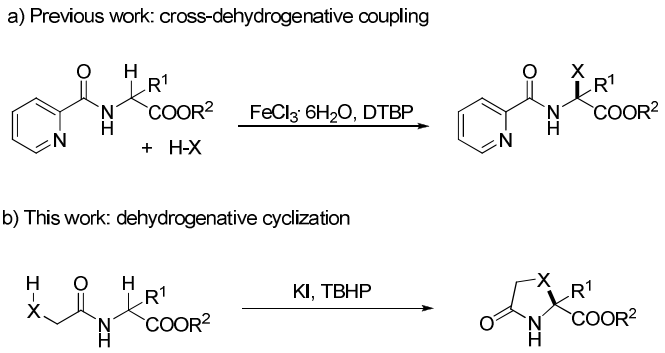
A dehydrogenative cyclization reaction for the synthesis of imidazolidin-4-ones was developed under mild conditions. Using *tert*-butyl hydroperoxide as oxidant and potassium iodide as catalyst, *N*-acyl dipeptide esters were converted to imidazolidin-4-ones in an atom-economical intramolecular C-N bond formation process in good yields.

In recent years, the direct α-functionalization of α-amino acid derivatives has gained increasing consideration as a powerful tool for the synthesis of non-natural α-amino acids required to assemble artificial peptides with novel properties[1]. This method could also be used for the direct modification of existing peptides in the pursuit of enhanced stability and bioactivity[2]. Among the developed methods for the α-functionalization of α-amino acids ester, the cross-dehydronative coupling (CDC) of C-H bonds has attracted much attention because of their atom-economical and environmentally friendly properties[3]. *N*-Aryl and *N*-acyl glycine derivatives were popular substrates for the investigation of such reactions[4]. Under transition metals catalyzed conditions, glycine derivatives were oxidized to generate aldimine intermediates, which were attacked subsequently by nucleophiles such as indoles, alkynes, and ketones to form new C-C bonds, and α-tertiary amino acid derivatives were obtained as the products. However, reports on the oxidative preparation of α-quaternary amino acid derivatives are rare for the difficult formation of ketimine intermediates. You and co-workers introduced a 2-pyridinecarbonyl group onto α-tertiary amino acid derivatives as an auxiliary group to promote the formation of ketimine intermediate and then an α-quaternary carbon centre was established by subsequent nucleophilic attack[5] (Scheme 1a). Herein, we described a dehydrogenative cyclization process of dipeptide esters[6], which allows for simple access to *N*-heterocyclic compound containing α-quaternary carbon centre under transition metal-free conditions [7] (Scheme 1b).



Scheme 1. Dehydrogenative coupling reaction for the formation of α-quaternary amino acid derivatives

Imidazolidin-4-ones are important *N*-heterocyclic compounds necessary in organic and pharmaceutical chemistry, and these compounds are used widely as herbicides and bactericides such as Imazapyr, Imazapic, and Fenamidone[8]. Traditional methods towards the synthesis of imidazolidin-4-one generally required multiple steps and harsh conditions[9]. Steckman and co-workers explored a convenient way to synthesis imidazolidin-4-ones by the cyclization of dipeptide esters，but the electrolysis condition using Pt as the anode must be determined[10]. As a continuation of our efforts on the oxidative functionalization of C-H bonds adjacent to an amide N atom[11], we wish to present our work on the synthesis of imidazolidin-4-ones by an intramolecular functionalization of α-peptido C-H bond in an efficient manner.

Initially, *N*-acyl protected dipeptide ethyl ester *N*-Bz-Gly-α-PhGlyOEt **1a** was chosen as the model substrate to optimize the reaction conditions of this dehydrogenative coupling cyclization. As

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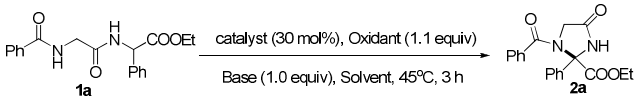
shown in table 1, the reaction of **1a** with 1.1 equiv TBHP (5M solution in decane) was firstly examined in CH_3CN with TBAI (30 mol %) as the catalyst at 45℃. 3 hours later, all the start material disappeared monitored by TLC and the desired product imidazolidin-4-one **2a** was isolated in 70% yield (Table 1, entry 1). When other iodide source such as I_2, NIS and NH_4I was used as the catalyst, the desired product **2a** was obtained in low yield (Table 1, entries 2-4). CuI was also tested and no product could be found (Table 1, entry 5). When alkali metal iodides were used as the catalyst, **2a** could be obtained in excellent yield and KI gave better result than NaI and CsI (Table 1, entries 6-8). Increasing the reaction temperature to 60℃ or decreasing the reaction temperature to room temperature led to lower yield of **2a** (Table 1, entries 9–10). Other commercial oxidants such as TBHP (70% solution in water) and CHP were also tested to give lower yields of **2a**, and in case of DTBP, no product was found (Table 1, entries 11–13). Different bases were screened and K_2CO_3 remained as the best one (Table 1, entries 14–16). Changing the solvent to EtOAc, Tolune or CH_2Cl_2 resulted in the formation of **2a** in only 0-25% yields (Table 1, entries 17–19). Finally, it was found that 92% yield of **2a** could be isolated when the amount of K_2CO_3 was reduced to 10 mol%. On the basis of these results, entry 20 represents the best conditions.

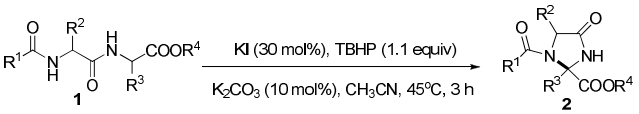
Table 1. Screening conditions[a]



Entry	Catalyst (0.3 equiv)	Oxidative (1.1 equiv)	Solvent (2 mL)	Base (1.0 equiv)	Yield (%)[b]
1	TBAI	TBHP	CH_3CN	K_2CO_3	70
2	I_2	TBHP	CH_3CN	K_2CO_3	20
3	NIS	TBHP	CH_3CN	K_2CO_3	40
4	NH_4I	TBHP	CH_3CN	K_2CO_3	NR
5	CuI	TBHP	CH_3CN	K_2CO_3	NR
6	NaI	TBHP	CH_3CN	K_2CO_3	60
7	KI	TBHP	CH_3CN	K_2CO_3	90
8	CsI	TBHP	CH_3CN	K_2CO_3	62
9	KI	TBHP	CH_3CN	K_2CO_3	45[c]
10	KI	TBHP	CH_3CN	K_2CO_3	61[d]
11	KI	TBHP aq	CH_3CN	K_2CO_3	83
12	KI	CHP	CH_3CN	K_2CO_3	75
13	KI	DTBP	CH_3CN	K_2CO_3	NR
14	KI	TBHP	CH_3CN	Cs_2CO_3	73
15	KI	TBHP	CH_3CN	DBU	80
16	KI	TBHP	CH_3CN	Et_3N	NR
17	KI	TBHP	EtOAc	K_2CO_3	25
18	KI	TBHP	Toluene	K_2CO_3	15
19	KI	TBHP	CH_2Cl_2	K_2CO_3	NR
20	KI	TBHP	CH_3CN	K_2CO_3	92[e]

[a]Reaction condition: 0.5 mmol **1a**, 0.55 mmol TBHP (5M in decane), in 2.0 mL CH_3CN at 45℃ for 3h. [b]Isolated yield. [c] Reaction carried out at 60℃. [d] Reaction carried out at room temperature. [e] 10 mol % K_2CO_3 was used. DTBP = Di-tert-butyl peroxide. CHP = Cumene hydroperoxide

Table 2. Scope of substrates



Entry	Substrate	Product	Yield(%)[a]
1	R^1 = 4-MePh, **1b**		**2b,** 84%
2	R^1 = 4-ClPh, **1c**		**2c,** 67%
3	R^1 = 2-Naphthyl, **1d**		**2d,** 50%
4	R^1 = 2-Furyl, **1e**		**2e,**50%
5	R^1 = 2-thienyl, **1f**		**2f,** 70%
6	R^1 = isopropenyl, **1g**		**2g,** 85%
7	R^1 = Methyl, **1h**		**2h,** 0%
8	R^1 = *t*-BuO, **1i**		**2i,** 0%
9	R^3 = 4-ClPh, **1j**		**2j,** 81%
10	R^3 = H/Me **1k**		**2k,** 0%
11	**1l**		**2l,** 78%
12	R^1 = Ph, R^2 = Me, R^4 = Me, **1m** (1:1)		**2m,** 73% (3:1)
13	R^1 = 4-MePh, R^2 = Me, R^4 = Me, **1n** (4:1)		**2n,** 79% (4.5:1)
14	R^1 = 4-BrPh, R^2 = Me, R^4 = Me, **1o** (5:1)		**2o,** 74% (2.5:1)
15	R^1 = Ph, R^2 = Me, R^4 = Et, **1p** (1.2:1)		**2p,** 83% (2:1)
16	R^1 = Ph, R^2 = *i*-Pr, R^4 = Et, **1q** (4:1)		**2q,** 80% (5:1)

[a] Isolated yield.

Under the optimized reaction conditions, the scope of substrate was investigated with results summarized in Table 2. Firstly, the *N*-terminal protective group of the substrate was examined. Regardless of the electron-donating or electron-withdrawing group on the benzene ring, substituted benzoyl protected dipeptide ethyl esters **1b** and **1c** gave the corresponding imidazolidin-4-ones in good yields (Table 2, entries 1-2). 2-Naphthoyl protected dipeptide ethyl ester **1d** also afforded the desired product in 86% yield under the optimized reaction (Table 2, entry 3). Substrates containing heterocyclic protective group such as 2-furoyl and 2-thenoyl reacted smoothly to furnish the product in moderate yields (Table 2, entries 4-5). Aliphatic acyl such as methylacryloyl protected dipeptide ethyl ester **1g** could also be converted into the corresponding products in good yields, but acetyl protected dipeptide ethyl ester **1h** remained

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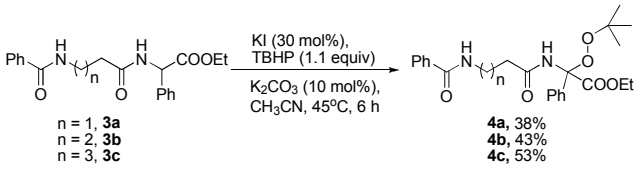
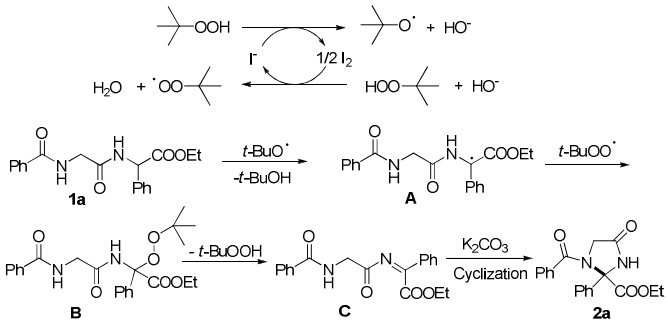
untouched (Table 2, entries 6-7). *N*-Boc protected dipeptide ethyl ester **1i** decomposed under the optimized reaction and no product could be found (Table 2, entry 8). Next, the effect of the α-substitutent group adjacent to ester was studied. The reaction proceeded smoothly to afford the corresponding product in good yield when R^3 was changed to 4-ClPh group, but failed with H and Me (Table 2, entries 9-10). Dipeptide methyl ester *N*-Bz-Gly-α-PhGlyOMe **1l** also gave good yield under the reaction conditions (Table 2, entry 11). Moreover, the diastereoselectivity of this cyclization process was also investigated. *N*-Bz-L-Ala-α-PhGlyOMe **1m** (1:1 mixture of two diastereomers) gave the corresponding product **2m** in moderate yield and diastereoselectivity (73% yield, 3:1 d.r.), and *cis*-**2m** was identified as the major stereoisomer in accordance with the literature[10]. The same result was obtained if each of the pure diastereomer of **1m** was employed to the reaction independently (Table 2, entry 12). Changing the *N*-terminal protective group to 4-Methyl and 4-Bromo-benzoyl group, the corresponding products **2n** (79% yield, 4.5:1 d.r.) and **2o** (74% yield, 2.5:1 d.r.) were obtained as anticipated (Table 2, entries 13-14). When dipeptide ethyl esters *N*-Bz-L-Ala-α-PhGlyOEt **1p** and *N*-Bz-L-Val-α-PhGlyOEt **1q** were utilized in this transformation, the desired products were isolated in 83% (2:1 d.r.) and 80% yield (5:1 d.r.) respectively (Table 2, entries 15-16).

Furthermore, substrates with extended carbon chain **3a-c** were also employed aiming at medium member ring products. However, when **3a, 3b** and **3c** were subjected to the optimized reaction conditions , no desired cyclic products could be found and only peroxides **4a-c** were isolated as the major products in 38%, 43% and 53% yield respectively.



Scheme 2. Synthesis of the peroxide products



Scheme 3. Possible mechanism

To gain insight into the reaction mechanism, 1.0 equiv of TEMPO was added to the reaction, and the yield of **2a** decreased remarkably to 35%, which suggests the possibility of a radical pathway. Based on the results in hand and the mechanism we reported before[11], a radical reaction process is proposed as shown in Scheme 3. The *tert*-butoxyl and *tert*-butylperoxy radicals were generated from the KI-TBHP system[12]. Then the benzylic α-H atom on the C-terminal amino acid of dipeptide ester **1a** was abstracted by the *tert*-butoxyl radical to afford radical **A**, which was trapped by the *tert*-butylperoxy radical to give the peroxide **B**. Finally, *N*-acylimino ester **C** was formed through the elimination of TBHP from **B**[13], which underwent cyclization reaction to give imidazolidin-4-one **2a** in the presence of K_2CO_3[10]. The mechanism detail requires further investigation.

Conclusions

In conclusion, we have demonstrated a simple, facile and transition-metal free approach to imidazolidin-4-ones through dehydrogenative cyclization of *N*-acyl dipeptide esters with moderate to good yields under mild conditions. Peroxide is believed to be the key intermediate for this cyclization process and further investigation into the mechanism is currently underway in our laboratory.

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