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One-pot dehydrogenation of carboxylic acid derivatives to α,β-unsaturated carbonyl compounds under mild conditions

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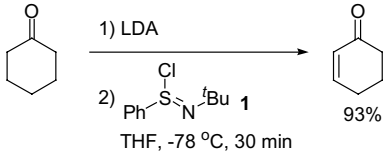
Abstract—Carboxylic acid derivatives such as *N*-acyl-2-oxazolidones, δ-lactones, and δ-lactams were smoothly dehydrogenated to the corresponding α,β-unsaturated carbonyl compounds in one-pot manner at −78 °C just by treating their lithium enolates with *N*-*tert*-butylbenzenesulfinimidoyl chloride.

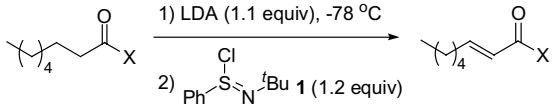
Dehydrogenation of carboxylic acid derivatives to the corresponding α,β-unsaturated compounds is an important organic transformation in living organisms as well as in organic synthesis: living organisms utilize fatty acids to produce acetyl CoA via direct dehydrogenation (β-oxidation) of acyl-CoA, a fatty acid derivative, to enoyl-CoA, which is catalyzed by acyl-CoA dehydrogenase.[1] However, such direct dehydrogenation of carboxylic acid derivatives by nonenzymatic (chemical) methods has not yet been studied, though several two-step procedures are known for this transformation. That is, dehydrogenation is usually carried out by three methods: (i) α-halogenation and subsequent elimination in the presence of a base, (ii) preparation of α-phenylsulfide[2] or α-phenylselenide[3] followed by elimination of the corresponding oxides, and (iii) preparation of silyl ketene acetals followed by treatment with palladium acetate.[4] We have recently reported a new method for dehydrogenation of ketones to the corresponding α,β-unsaturated ketones by using *N*-*tert*-butylbenzenesulfinimidoyl chloride (**1**),[5] and the dehydrogenation was unique in that it proceeded in a one-pot manner under very mild conditions (−78 °C, within 30 min) (Eq. 1). Its synthetic utility has been demonstrated in its successful application to the total synthesis of several natural products.[6] In order to broaden the synthetic utility of **1**, dehydrogenation of carboxylic acid derivatives such as carboxylic esters, thioesters, amides, lactones, and lactams were then investigated, and we would like to report here results on one-pot and mild dehydrogenation of these carboxylic acid derivatives with **1**.



(1)

First, one-pot dehydrogenation of ethyl octanoate was tried by generating the corresponding lithium enolate with LDA in THF at −78 °C, followed by treatment with **1** at the same temperature (Table 1, entry 1). It

Table 1. One-pot dehydrogenation of octanoic acid derivatives to the corresponding α,β-unsaturated carbonyl compounds by using **1**



Entry	X	Yield[a] (%)
1	OEt	60
2	OPh	71
3	SPh	75
4		90
5[b]	N(Bn)SO_2Ph	41

[a] Determined by ^{1}H NMR analysis using an internal standard.
[b] *N*-Benzenesulfonyl-*N*-benzylbutyramide was employed.

Keywords: Dehydrogenation; Amide; Ester; Lactone; Lactam.
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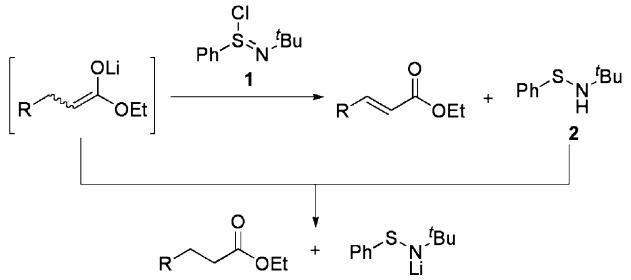
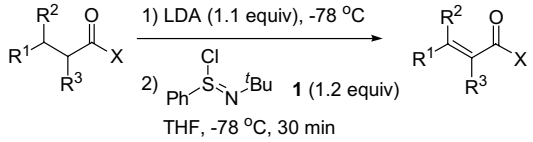
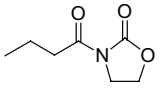
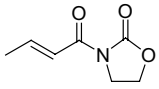
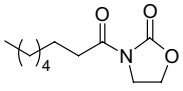
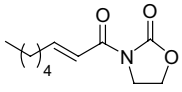
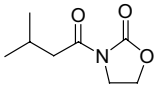
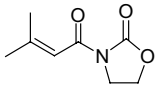
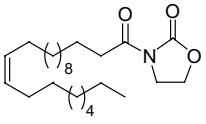
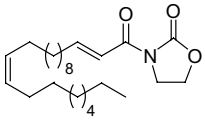
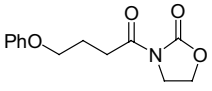
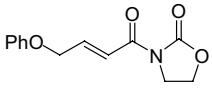
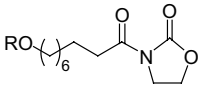
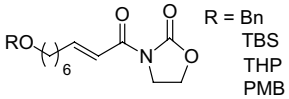
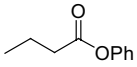
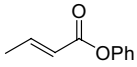
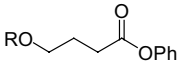
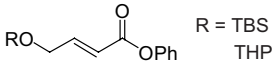


Scheme 1. Possible mechanism for incomplete dehydrogenation of carboxylic ester with **1**.

was disappointingly found that the dehydrogenation proceeded incompletely and the desired product was obtained in 60% yield, though reaction conditions such as reaction temperature, reaction time, and equivalents of **1**, and substituent groups on the phenyl ring of **1** were screened. Considering the successful dehydrogenation of ketones with **1**,[5] it was assumed that the efficiency of the present dehydrogenation was influenced by the acidity of carbonyl α-proton: that is, in the case of ethyl octanoate, the reaction of **1** and lithium enolate of ethyl octanoate was competitively inhibited by protonation of the lithium enolate with *N*-*tert*-butylbenzenesulfenamide (**2**), which was formed from **1** (Scheme 1). Therefore, the same dehydrogenation of several octanoic acid derivatives having more acidic α-protons was examined, and it was expectedly found that the yield of the dehydrogenation was improved to 71% and 75% when phenyl octanoate and *S*-phenyl octanethioate were employed, respectively (Table 1, entries 2 and 3). 2-Oxazolidone derivative was dehydrogenated to the corresponding α,β-unsaturated compound exceptionally in high yield (90%, entry 4), while *N*-acyl-*N*-benzylbenzenesulfon-

Table 2. One-pot dehydrogenation of *N*-acyl-2-oxazolidones and carboxylic acid phenyl esters to the corresponding α,β-unsaturated compounds by using **1**



Entry	Substrate	Product	Yield[a] (%)
1			78
2			90
3			67
4			83
5			87
6 7 8 9		 R = Bn TBS THP PMB	88 92 91 91
10			75
11 12		 R = TBS THP	63 72

[a] Determined by ^{1}H NMR analysis using an internal standard.

amide gave the desired product in low yield (entry 5). It was then revealed that *N*-acyl-2-oxazolidone was a suitable carboxylic acid derivative for dehydrogenation with **1**.

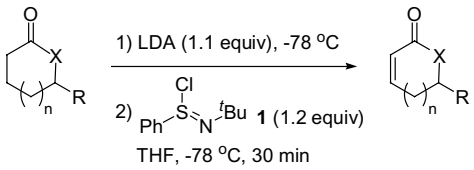
Next, the scope and limitations of the present dehydrogenation of *N*-acyl-2-oxazolidones and carboxylic acid phenyl esters were investigated (Table 2). The dehydrogenation of *N*-acyl-2-oxazolidones proceeded more efficiently than that of carboxylic acid phenyl esters (entries 1–9 vs entries 10–12), and linear *N*-acyl-2-oxazolidones were smoothly dehydrogenated at −78 °C within 30 min to afford the corresponding α,β-unsaturated compounds in high yields. Only (*E*)-isomers were stereoselectively formed by this reaction. The dehydrogenation of a β-branched *N*-acyl-2-oxazolidone gave the desired product in moderate yield (entry 3), probably because the reaction between sterically hindered lithium enolate and **1** took place slowly. It should be noted that protecting groups such as benzyl, TBS, THP, and PMB, and an isolated double bond were not damaged nor oxidized at all under the present dehydrogenation conditions. Even a long carboxylic acid derivative was smoothly dehydrogenated by the present method (entry 4).

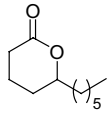
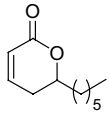
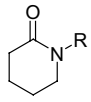
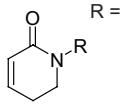
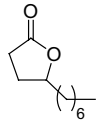
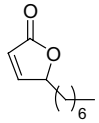
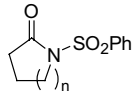
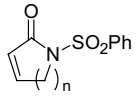
The one-pot dehydrogenation of lactones and lactams was also investigated by the same procedure (Table 3). Dehydrogenation of δ-lactone gave the corresponding α,β-unsaturated δ-lactone in good yield (entry 1), and δ-lactams were also dehydrogenated effectively when lactam-nitrogen was protected by appropriate electron-withdrawing groups such as benzenesufonyl and Boc groups (entries 2–4). On the other hand, the dehydrogenation of *N*-benzyl-2-piperidone and *N*-BOM-2-piperidone gave the dehydrogenated compounds in 45% and 44% yields, respectively (entries 5 and 6) presumably due to competitive protonation of their lithium enolates with **2**, which was described before. Contrary to the dehydrogenation of six-membered lactone and lactams, five-membered cyclic compounds and a seven-membered lactam were dehydrogenated in low yields.

A typical experimental procedure is as follows (Table 2, entry 2): a solution of *n*-butyllithium (1.51 N in hexane, 0.23 mL, 0.35 mmol) was added to a solution of diisopropylamine (38 mg, 0.38 mmol) in THF (1.7 mL) at −78 °C. A solution of *N*-octyryl-2-oxazolidone (67.5 mg, 0.32 mmol) in THF (1 mL) was then added to the reaction mixture, followed by adding a solution of **1**[†] (82.6 mg, 0.38 mmol) in THF (0.5 mL). After the reaction mixture was stirred at −78 °C for 30 min, the reaction was quenched with saturated $NaHCO_3$. The mixture was extracted with AcOEt, and extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The yield of dehydrogenated compound (90%) was determined by ^1H NMR analysis using triphenylmethane as an internal standard.

Thus, one-pot dehydrogenation of *N*-acyl-2-oxazolidones, δ-lactone, and δ-lactams by treating their lithium enolates with **1** at −78 °C afforded the corresponding α,β-unsaturated carbonyl compounds in high yields. The formed α,β-unsaturated *N*-acyl-2-oxazolidones are useful synthetic intermediates in organic synthesis, especially for stereoselective Michael addition reactions[7] and Diels–Alder reactions,[8] and the method for removing the 2-oxazolidone moiety has already been established.[9] This method has the possibility of being applied not only to the synthesis of molecular building blocks but also to introduction of α,β-unsaturation to natural products for derivatizing them to more interesting compounds because of its mild reaction conditions.

Table 3. One-pot dehydrogenation of lactones and lactams with **1**



Entry	Substrate	Product	Yield[a] (%)
1			72
2		 R = Bz	70
3			SO_2Ph 80
4			Boc 79
5			Bn 45
6			BOM 44
7			Tf 57
8			44
9		 n = 1	53
10			n = 2 15

[a] Determined by ^1H NMR analysis using an internal standard.

Acknowledgements

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[†] Commercially available from Tokyo Kasei Kogyo Co., Ltd. (TCI).

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