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One-pot oxidative Mannich-type reaction of lactams with alkyl malonates

Jun-ichi Matsuo,* Yumi Tanaki and Hiroyuki Ishibashi*

Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

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Abstract—One-pot substitution of a C–H bond at the position next to the nitrogen atom of lactams with alkyl malonates proceeded effectively by dehydrogenation of lactams with *N*-*tert*-butylbenzenesulfinimidoyl chloride, followed by Mannich-type addition of alkyl malonates.

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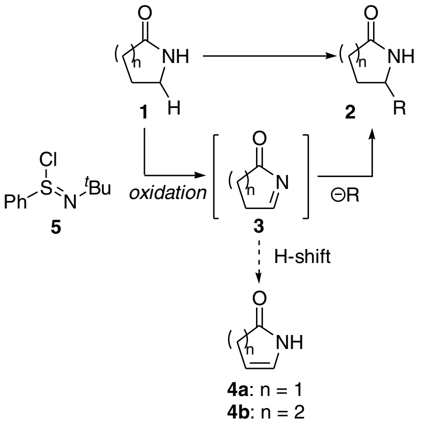
A highly substituted lactam moiety is often found in biologically active compounds such as β-lactam antibiotics,[1] salinosporamide A,[2] and lactasystin.[3] Formation of a new carbon–carbon bond onto a lactam ring is a promising and convenient method for preparing a variety of lactam derivatives. Direct carbon–carbon bond formation at the α-position of the carbonyl group of lactams has been conducted by enolate chemistry. On the other hand, direct carbon–carbon bond formation at the α-position of the nitrogen atom of lactams (**1** to **2**) has remained a challenging subject in organic synthesis since it is difficult to activate the C–H bond of that position under mild conditions. Oxidation of lactam **1** to cyclic *N*-acylimine **3** might be considered as one of the activating methods of the C–H bond. However, it is known that **3** easily isomerizes to the corresponding enamides **4**,[4,5] and some methods for preparation of the isomerized product **4** such as pyrrolin-2-ones (**4a**, $n = 1$) and dihydro-2-pyridones (**4b**, $n = 2$) have been reported.[6] Although cyclic *N*-acylimines **3** have been generated at a low temperature from lactams having a leaving group at the α-position of the nitrogen atom (e.g., 4-acetoxy-2-azetidinone, 5-acetoxy-2-pyrrolidinone and 6-acetoxy-2-piperidinone[7]) by Lewis acid-catalysis, preparation of **3** from lactams **1** has not been reported to date. We have recently developed a mild and convenient method for oxidation of *N*-alkyl carbamates to *N*-Cbz imines or ketimines using *N*-*tert*-butylbenzenesulfinimidoyl chloride (**5**).[8,9] We expected that oxidation of lactam **1** with **5** at a low temperature would give **3** with minimal isomerization to enamide **4** and that the thus formed **3** would react with appropriate carbon nucleophiles to form a new carbon–carbon bond in a one-pot fashion (Scheme 1). We would like to report here the one-pot carbon–carbon bond formation at the α-position of the nitrogen atom of various lactams using **5** and alkyl malonates.



Scheme 1. Carbon–carbon bond formation of **1** to **2** via cyclic *N*-acylimine **3**.

Appropriate reaction conditions for oxidative Mannich-type reaction of lactam were investigated by employing

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Keywords: Lactam; Oxidation; Mannich-type reaction.

* Corresponding authors. Tel./fax: +81 76 234 4439 (J.M.); e-mail: jimatsuo@p.kanazawa-u.ac.jp

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valerolactam (**6**) and diethyl malonate (Table 1). Lithiated lactam formed by the reaction of **6** and *n*-BuLi in THF was treated with **5** at −78 °C followed by the addition of diethyl malonate and allowing the reaction temperature to rise to room temperature. When diethyl malonate was reacted for 0.5 h at room temperature, Mannich product **7** was isolated in 47% yield (entry 1). Minor improvement in the yield of **7** was observed after a prolonged reaction time (entry 2), and further improvement was achieved by employing four equivalents of HMPA as an additive (entry 4).[10] An effect of HMPA was not observed after a short reaction time (entries 1 and 3) but was clearly observed after 6 h (entries 2 and 4). It was assumed that lithiated **6** smoothly reacted with **5** at −78 °C, and HMPA would accelerate the addition of diethyl malonate to **3**, which was formed during the rise in reaction temperature from −78 °C to room temperature. Employment of other bases such as NaH, NaHMDS, and KHMDS and other additives such as AcOH and LiCl did not improve the yield of **7**.

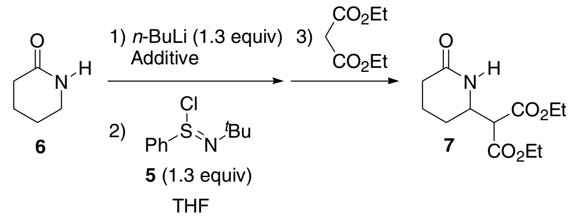


Table 1. Effect of HMPA on oxidative Mannich-type reaction of **6** to **7**

Entry	Additive (equiv)	Reaction time (h)	Yield[a] (%)
1	None	0.5	47
2	None	6	57
3	HMPA (4)	0.5	44
4	HMPA (4)	6	71

[a] Isolated yield.

The scope and limitations of the one-pot oxidative Mannich-type reaction of various lactams were next investigated (Table 2). Cyclic *N*-acylimines generated from

Table 2. One-pot oxidative Mannich reaction of various lactams (**6**, **8a–e**) with malonic acid esters to **9a–j**[a]

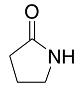
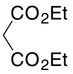
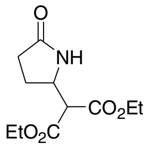
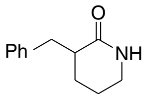
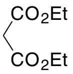
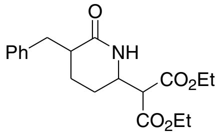
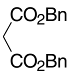
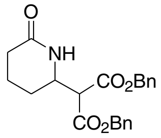
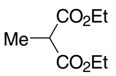
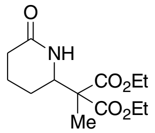
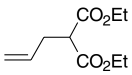
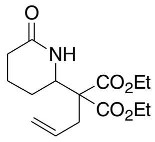
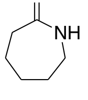
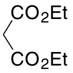
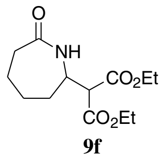
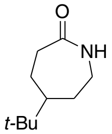
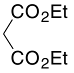
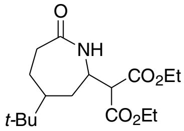
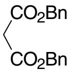
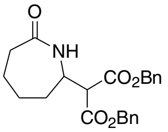
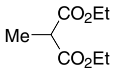
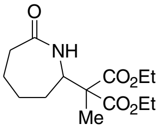
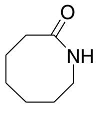
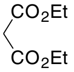
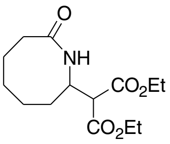
Entry	Lactam	Alkyl malonate	Product	Yield[b] (%)
1	 **8a**		 **9a**	48[c]
2	 **8b**		 **9b**	70 (1:1.5)
3	**6**		 **9c**	71
4	**6**		 **9d**	58
5	**6**		 **9e**	65
6	 **8c**		 **9f**	72

Table 2 (*continued*)

Entry	Lactam	Alkyl malonate	Product	Yield[b] (%)
7	 **8d**		 **9g**	80 (1:1)
8	**8c**		 **9h**	80
9	**8c**		 **9i**	55
10	 **8e**		 **9j**	32

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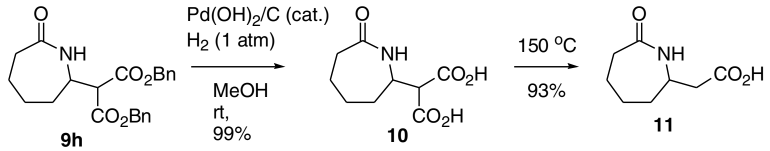
[a] For reaction conditions, see a typical experimental procedure in the text.

[b] Isolated yield unless otherwise noted. Ratios in parentheses are diastereomeric ratios of the products.

[c] Determined by ^{1}H NMR analysis.



Scheme 2. Deprotection of Mannich product **9h**.

six- and seven-membered lactams reacted with diethyl malonate to give the corresponding Mannich adducts in good to high yields (entries 2, 6, and 7), while five- and eight-membered lactams gave adducts in lower yields (entries 1 and 10). A substituent on a lactam ring did not affect the efficiency of the present oxidative Mannich-type reaction (entries 2 and 7). In addition to diethyl malonate, the desired carbon–carbon bond was formed by using dibenzyl malonate, diethyl methylmalonate, and diethyl allylmalonate (entries 3, 4, 5, 8, and 9). Deprotection of the benzyl group of Mannich adduct **9h** gave diacid **10**, and decarboxylation of **10** gave **11** in 93% yield (Scheme 2).

A typical experimental procedure (Table 2, entry 8) is as follows: To a mixture of **8c** (100 mg, 0.89 mmol) and HMPA (0.62 mL, 3.56 mmol) in THF (3 mL) was added a solution of *n*-BuLi (1.58 N in hexane, 0.73 mL, 1.15 mmol) at −78 °C and the resulting solution was stirred for 15 min. A solution of **5** (247 mg, 1.15 mmol) in THF (1 mL) was added at −78 °C, and the mixture was stirred for 30 min. Then dibenzyl malonate (0.29 mL, 1.16 mmol) was added at −78 °C, and the mixture was stirred at room temperature for 6 h. Usual workup and purification by column chromatography on silica gel afforded **9h** (281 mg, 0.71 mmol, 80%).

In summary, alkyl malonates reacted with labile cyclic *N*-acylimines, which were generated by oxidation of five- to eight-membered lactams (**6** and **8**) with **5** under mild conditions, to afford the corresponding Mannich adducts in a one-pot manner. This unique oxidative Mannich-type reaction enables regioselective introduction of a variety of carbon–carbon bonds after the construction of a lactam ring and will contribute to the development of a strategy for synthesizing various nitrogen-containing compounds.

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Supplementary data

Supplementary data including spectral data of the products (**7**, **9a**–**j**, and **11**) and experimental procedures can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.025.

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10. Addition of ten equiv of HMPA gave the same result as that obtained by using 4 equiv of HMPA.