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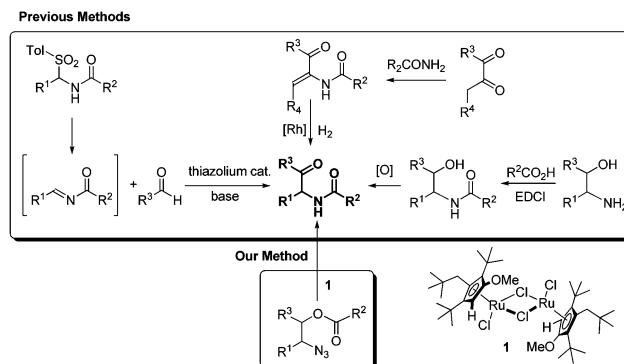
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The esters of 1,2-azido alcohols were transformed into α -amido ketones without external oxidants through the Ru-catalyzed formation of N–H imines with the liberation of N_2 followed by intramolecular migration of the acyl moiety. A wide range of α -amido ketones were obtained, and one-pot transformation into the corresponding oxazoles (or a thiazole) was demonstrated.

α -Amido ketones are biologically relevant molecules and useful building blocks for valuable compounds in organic synthesis.¹ In addition, they are useful substrates in various organic transformations such as the Robinson–Gabriel reaction to oxazoles² and thiazoles,^{2e} the Norrish–Yang photocyclization to 2-amino-cyclobutanols,³ the epoxy-annulation reaction to epoxide-fused heterocycles⁴ and the reaction with ammonium acetate (or primary amines) to imidazoles.⁵

For the versatile transformations, α -amido ketones have been synthesized by various methods, including Pd-catalyzed coupling reaction of methylene aziridines with carboxylic acids,⁶ Rh-catalyzed denitrogenative hydration of *N*-sulfonyl-1,2,3-triazoles,⁷ the Dakin–West reaction of α -amino acids with acid anhydrides,⁸ the Neber rearrangement of ketoxime sulfonates⁹ and a radical cascade reaction of alkynes with *N*-fluoroaryl sulfonimides and alcohols.¹⁰ However these methods suffer from the difficulty in preparing substrates, harsh reaction conditions, and/or limitations of the substrate scope.

Additional and noticeable methods are compared with our new finding in Scheme 1. The aza-benzoin condensation reaction of aldehydes with *N*-acyl imines is an interesting method using thiazolium organocatalysts.^{5c,11} However, the synthesis of tosylamides from tosylsulfinic acid, amides, and aldehydes is required to generate the intermediate *N*-acyl imines, and is not effective for enolizable aldehydes.¹² The asymmetric hydrogenation of α -dehydroamido ketones can provide optically active α -amido ketones,¹³ but the scope is limited by the intrinsic

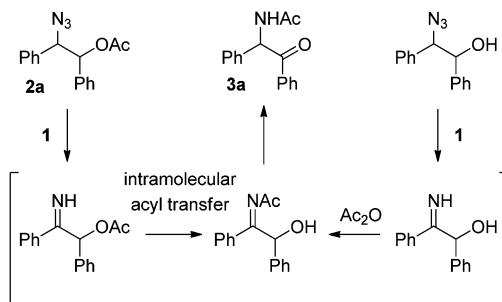


Scheme 1 Synthetic methods for α -amido ketones.

regioselectivity problem in the condensation reaction of 1,2-diketones and primary amides. An old method employing 1,2-amino alcohols as the starting substrates looks simple but suffers practically from inefficiency in the *N*-acylation and the subsequent oxidation.^{5c,14} A carboxyl-activating agent and an oxidant are required in a stoichiometric amount in the acylation and the oxidation, respectively. Meanwhile, 1,2-amino alcohols are frequently prepared from 1,2-azido alcohols by the Staudinger reaction using triphenylphosphine as a reductant. Herein we wish to report an efficient synthesis of α -amido ketones from 1,2-azido alcohols without oxidation and reduction steps through a novel one-step catalytic transformation of 1,2-azido esters under neutral and mild conditions.

Recently we found an interesting Ru-catalyzed transformation of alkyl azides to N–H imines.¹⁵ As an application of the catalytic transformation, we have developed an efficient method for the synthesis of enamides from alkyl azides and acyl donors utilizing the *N*-acylation of intermediate N–H imines.¹⁶ In a related study on the *N*-acylation of N–H imines containing a hydroxyl group, we observed the unexpected formation of α -amido ketones in the catalytic reactions of 1,2-azido alcohols. For example, *N*-(2-oxo-1,2-diphenylethyl)acetamide (**3a**) was obtained in 55% yield by the reaction of 2-azido-1,2-diphenylethanol with acetic anhydride in the presence of the ruthenium catalyst **1** (Scheme 2). Then we envisioned

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Scheme 2 Formation of α -amido ketone **3a** from 1,2-azido acetate **2a** or from the corresponding 1,2-azido alcohol.

that its intramolecular version would improve the efficiency of the transformation. We examined the transformation of 2-azido-1,2-diphenylethyl acetate (**2a**) under various conditions (Table 1). The transformation was more efficient in polar solvents than in non-polar ones such as THF and toluene (entries 1 and 2). In dimethylformamide (DMF), **3a** was formed in 89% yield (entry 3). Noticeably, the transformation was effective in ionic liquids,¹⁷ which have some advantages such as being experimentally safe and recycled. In particular **3a** was formed in almost quantitative yield in 1-butyl-3-methylimidazolium chloride ([bmim]Cl) (entry 4). A gram-scale reaction was also effective to give **3a** in 91% isolated yield (entry 5), and recycling of [bmim]Cl was possible simply by removing water from the aqueous phase by heating after the workup procedure (entry 6).¹⁸ Decreasing the reaction temperature to 50 °C significantly lowered the yield of **3a** (entry 7), while increasing it to 100 °C was not beneficial (entry 8). As in the synthesis of enamides involving *N*-acylation of N-H imines,¹⁶ a catalytic amount of triethylamine was helpful for the formation of **3a** (entry 9).¹⁷

The transformation to α -amido ketones was applicable for a broad range of acetates of 1,2-azido alcohols (Table 2). The electronic effect of the substituents of aromatic rings was not so

Table 1 Transformation of **2a** to **3a** under various conditions^a

Entry	Solvent	Additive	Temp. (°C)	Yield ^b (%)	Reaction conditions	
					1 (0.1 mol%)	solvent (2.0 mol%)
1	THF	Et ₃ N	70	15		
2	Toluene	Et ₃ N	70	28		
3	DMF	Et ₃ N	70	89		
4	[bmim]Cl	Et ₃ N	70	96 (94) ^c		
5	[bmim]Cl	Et ₃ N	70	91 ^{c,d}		
6	[bmim]Cl	Et ₃ N	70	90 ^e		
7	[bmim]Cl	Et ₃ N	50	15		
8	[bmim]Cl	Et ₃ N	100	91		
9	[bmim]Cl	None	70	85		

^a Typical reaction conditions: a solution of an azide (0.25 mmol), **1** (1.0 mol%) and Et₃N (2.0 mol%) in a solvent (1.0 mL) was stirred for 12 h. ^b Estimated by ¹H NMR using nitromethane as an internal standard. ^c Isolated yield. ^d A large scale reaction employing 1.06 g (3.6 mmol) of **2a** and 15 mg (0.5 mol%) of **1** in 6.0 mL of [bmim]Cl at 70 °C for 36 h. ^e The yield of the reaction using [bmim]Cl recovered from the 5th recycling reaction.

significant (**3a**–**3c** and **3g**–**3h**). The yields of α -amido ketones were high in the transformation of the derivatives having alkyl groups (**3d**–**3j**). The low yield of **3i** was due to the formation of unidentified side-products, and the use of DMF as a solvent gave **3i** in 62% yield. The transformation of esters of primary β -hydroxy azides to α -amido ketones (**3k**–**3r**) was also successful despite the fact that the intermediates are unstable N-H aldimines. The transformation was effective for various derivatives containing functional groups on aromatic rings such as methyl, methoxy, halides and nitrile substituents. The yield of the α -amido ketone (**3s**), which has a benzyl moiety, was moderate with the formation of unidentified side products. The transformation of cyclic substrates (**3t**–**3w**) was less efficient than that of linear ones, probably due to the rigidity of ring structures. A six-membered cyclic α -amido ketone (**3u**) was obtained in moderate yield, while a five-membered one (**3t**) was not formed. However, interestingly, a seven-membered cyclic one (**3w**) was obtained in high yield, and a benzofused six-membered bicyclic one (**3v**) was formed in a much higher yield than the monocyclic one (**3u**).

Then, the scope of α -amido ketones was explored for the derivatives having various *N*-acyl groups (Table 3). R³ in the α -amido ketones **5** could be varied not only to an ethyl (**5a**), isopropyl (**5b**), or a *tert*-butyl (**5c**) group but also to a conjugated alkenyl (**5d**), chloromethyl (**5e**), or an ester (**5f**) group. The derivatives containing phenyl (**5g**), furyl (**5h**), and thiofuryl (**5i**)

Table 2 Synthesis of α -amido ketones from 1,2-azido acetates^a

^a Standard reaction conditions: a solution of an azide (0.25 mmol), **1** (1.0 mol%) and Et₃N (2.0 mol%) in [bmim]Cl (1.0 mL) was stirred for 12 h. ^b Reaction was carried out in DMF. ^c Not detected. ^d Reaction was carried out for 24 h. ^e Reaction was carried out for 36 h.

Table 3 Synthesis of α -amido ketones from various esters of 1,2-azido alcohols^a

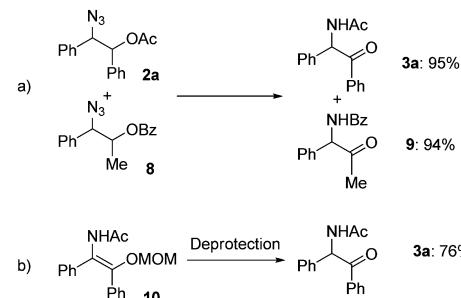
	1 (1.0 mol%) Et ₃ N (2.0 mol%) [bmim]Cl (1.0 mL) 70 °C, 12 h	

^a Standard reaction conditions: a solution of an azide **4** (0.25 mmol), **1** (1.0 mol%) and Et₃N (2.0 mol%) in [bmim]Cl (1.0 mL) was stirred for 12 h. ^b Reaction was carried out in DMF for 36 h at 100 °C.

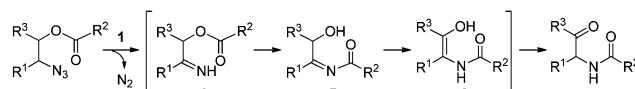
groups were also obtained in high yields. The migration of the butyloxycarbonyl (Boc) group was possible, although heating at a higher temperature for a longer reaction time was required to give an *N*-Boc protected derivative (**5j**) in good yield.

To demonstrate the utility of our synthesis of α -amido ketones, we carried out one-pot transformations to oxazoles (**6a–c**) and a thiazole (**7**) (Scheme 3). Treatment of **3a** *in situ* generated from **2a** with sulfuric acid afforded oxazole **6a** in 94% yield. The corresponding thiazole (**7**) was obtained by the treatment with Lawesson's reagent in 87% yield. Noticeably, oxaprozin (**6b**), which is a well-known non-steroidal anti-inflammatory drug,¹⁹ was obtained directly from **4f** in 89% yield. The stereochemistry of **4k** at the α -position was practically maintained during the one-pot transformation to **6c**,²⁰ although the intermediate α -amido ketone was formed as a 1:1 diastereomeric mixture.

To obtain mechanistic insights into the transformation of 1,2-azido esters to α -amido ketones, a crossover experiment and the generation of an enol amide were examined: only non-crossover



Scheme 4 Mechanistic investigation.



Scheme 5 Plausible pathway for the formation of α -amido ketones.

products (**3a** and **9**) were formed in high yields in the transformation of a mixture of the 1,2-azido acetate **2a** and another azide (**8**) containing a benzoyl group (Scheme 4a), and the α -amido ketone **3a** was obtained in 76% yield in the deprotection reaction of a MOM-protected enol amide (**10**) (Scheme 4b).²¹

Now we can propose a plausible pathway for the transformation of the esters of 1,2-azido alcohols into α -amido ketones (Scheme 5). On the basis of our previous reports on the formation of enamides from *N*-acyl imines,¹⁶ the results of the crossover experiment support intramolecular migration of the acyl group in the intermediate N-H imine **A** to give the α -hydroxyl *N*-acylimine **B**. And the result of the deprotection reaction of **10** is indicative of the intermediacy of the enol amide **C**, which is tautomerized to the final α -amido ketone product.

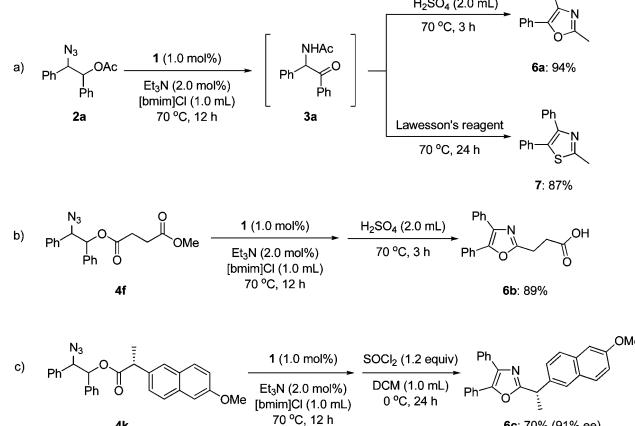
In summary, we developed a new and simple method for the synthesis of α -amido ketones from the esters of 1,2-azido alcohols just by the liberation of molecular nitrogen under mild conditions. Our method is effective for the synthesis of a wide range of multi-substituted α -amido ketones, and efficient for gram scale synthesis in recyclable ionic liquids. In addition, we demonstrated the one-pot synthesis of oxazoles and a thiazole using α -amido ketones as intermediates.

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17 For screening of ionic liquids and additives, see the ESI†.

18 For more detailed results for the recycling of [bmim]Cl, see the ESI†.

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