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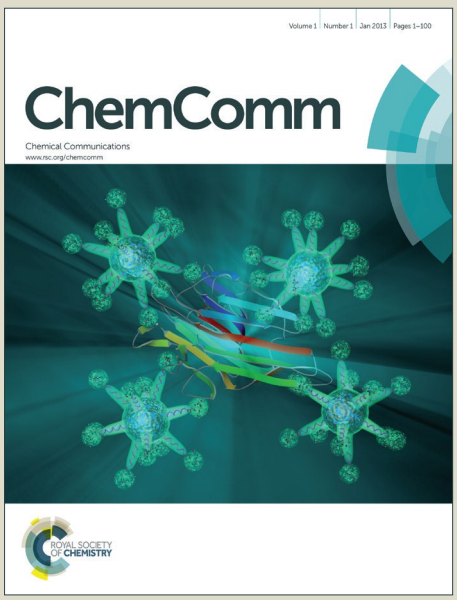




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# Catalytic transformation of esters of 1,2-azido alcohols into α-amido ketones

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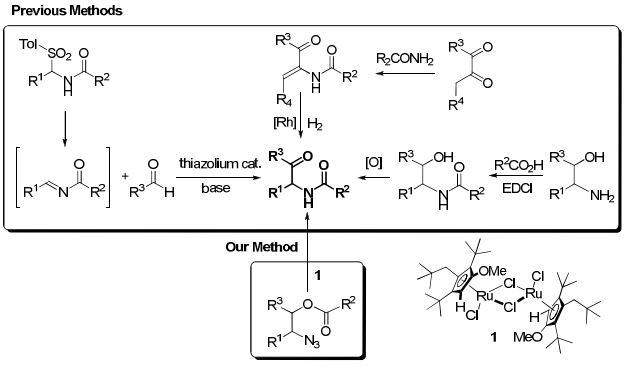
**The esters of 1,2-azido alcohols were transformed into α-amido ketones without external oxidants through the Ru-catalyzed formation of N-H imines with liberation of $N_2$ followed by intramolecular migration of the acyl moiety. A wide range of α-amido ketones were obtained, and one-pot transformation 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 oxazoles[2] and thiazoles,[2e] the Norrish-Yang photocyclization to 2-aminocyclobutanols,[3] the epoxy-annulation reaction to epoxide-fused heterocycles[4] 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 sulfonates[9] and a radical cascade reaction of alkynes with *N*-fluoroarylsulfonimides and alcohols.[10] However these methods suffer from difficulty in preparing substrates, harsh reaction conditions, and/or limitation of 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 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 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.




**Scheme 1.** Synthetic methods for α-amido ketones.

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 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 from the reaction of 2-azido-1,2-diphenylethanol with acetic anhydride in the presence of the ruthenium catalyst **1** (Scheme 2). Then we envisioned that its intramolecular version would improve efficiency of the transformation. We examined the transformation of 2-azido-

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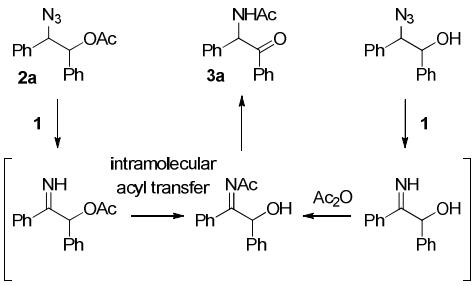
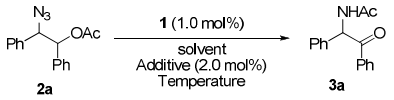
1,2-diphenylethyl acetate (**2a**) under various conditions (Table 1). The transformation was more efficient in polar solvents than in non-polar ones such as THF and toluene (entries 1 and 2). In dimethylformamide (DMF), **3a** was formed in 89% yield (entry 3). Noticeably, the transformation was effective in ionic liquids,[17] which have some advantages in experimental safety and in recycling. 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] catalytic amount of triethylamine was helpful for the formation of **3a** (entry 9).[17]




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

**Table 1.** Transformation of **2a** to **3a** under various conditions.[a]

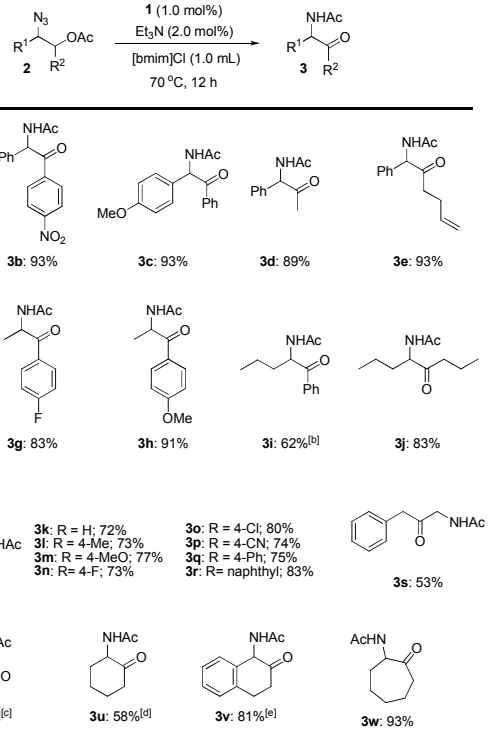



| Entry | Solvent | Additive | Temp. (°C) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | THF | $Et_3N$ | 70 | 15 |
| 2 | Toluene | $Et_3N$ | 70 | 28 |
| 3 | DMF | $Et_3N$ | 70 | 89 |
| 4 | [bmim]Cl | $Et_3N$ | 70 | 96 (94)[c] |
| 5 | [bmim]Cl | $Et_3N$ | 70 | 91[c,d] |
| 6 | [bmim]Cl | $Et_3N$ | 70 | 90[e] |
| 7 | [bmim]Cl | $Et_3N$ | 50 | 15 |
| 8 | [bmim]Cl | $Et_3N$ | 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 $Et_3N$ (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.

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 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 effect for various derivatives containing functional groups on aromatic rings such as methyl, methoxy, halides and nitrile substituent. The yield of the α-amido ketone (**3s**), which has benzyl moiety, was moderate with forming 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, seven-membered cyclic one (**3w**) was obtained in high yield, and benzofuzed six-membered bicyclic one (**3v**) was formed in much higher yield than the monocyclic one (**3u**).

**Table 2.** Synthesis of α-amido ketones from 1,2-azido acetates.[a]




[a] Standard reaction conditions: a solution of an azide **2** (0.25 mmol), **1** (1.0 mol%) and $Et_3N$ (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.

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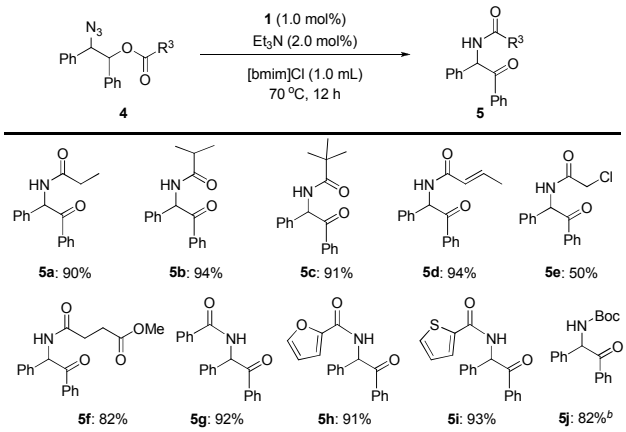
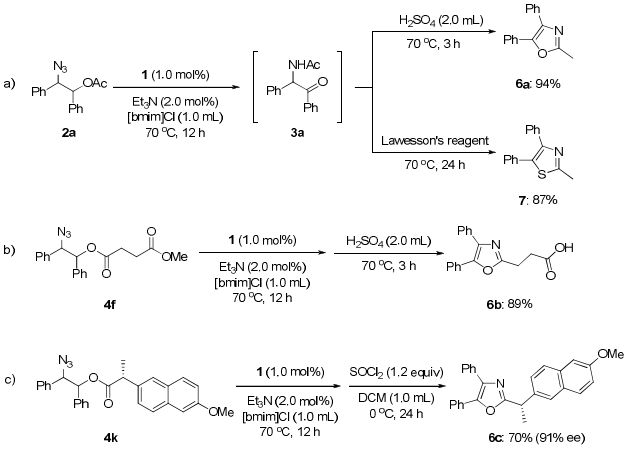
Then, the scope of α-amido ketones were explored for the derivatives having various *N*-acyl groups (Table 3). The $R^3$ in the α-amido ketones **5** could be varied not only to ethyl (**5a**), isopropyl (**5b**), or *tert*-butyl group (**5c**) but also to a conjugated alkenyl (**5d**), chloromethyl (**5e**), or an ester group (**5f**). The derivatives containing phenyl (**5g**), furyl (**5h**), and thiofuryl group (**5i**) were also obtained in high yields. The migration of butyloxycarbonyl (Boc) group was possible, although heating at a higher temperature for a longer reaction time was required to give *N*-Boc protected derivative (**5j**) in good yield.

**Table 3.** Synthesis of α-amido ketones from various esters of 1,2-azido alcohols. [a]



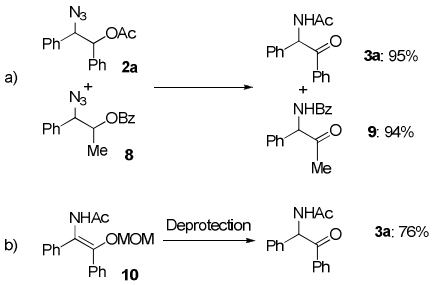

[a] Standard reaction conditions: a solution of an azide **4** (0.25 mmol), **1** (1.0 mol%) and $Et_3N$ (2.0 mol%) [bmim]Cl (1.0 mL) was stirred for 12 h. [b] Reaction was carried out in DMF for 36 h at 100 °C.

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.



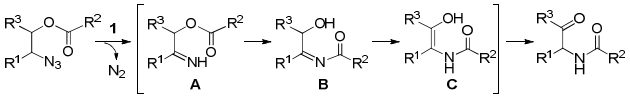

**Scheme 3.** One-pot transformations to oxazoles and a thiazole.

To obtain mechanistic insight on 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 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 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]




**Scheme 4**. Mechanistic investigation.

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 about 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.




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

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 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 liquid. 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 Supporting Information

18 For more detailed results for the recycling of [bmim]Cl, see the Supporting Information

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