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

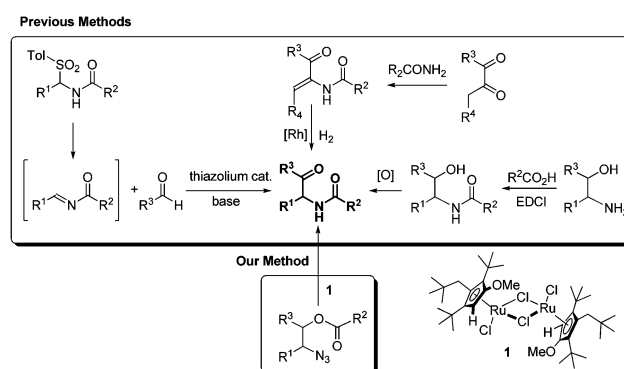
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The esters of 1,2-azido alcohols were transformed into α -amido ketones without external oxidants through the Ru-catalyzed formation of N–H imines with the liberation of N₂ followed by intramolecular migration of the acyl moiety. A wide range of α -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*-fluoroarylsulfonimides 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 tosylsulfonic 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

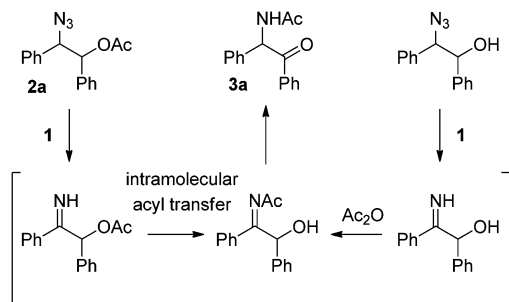
Scheme 1 Synthetic methods for α -amido ketones.

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

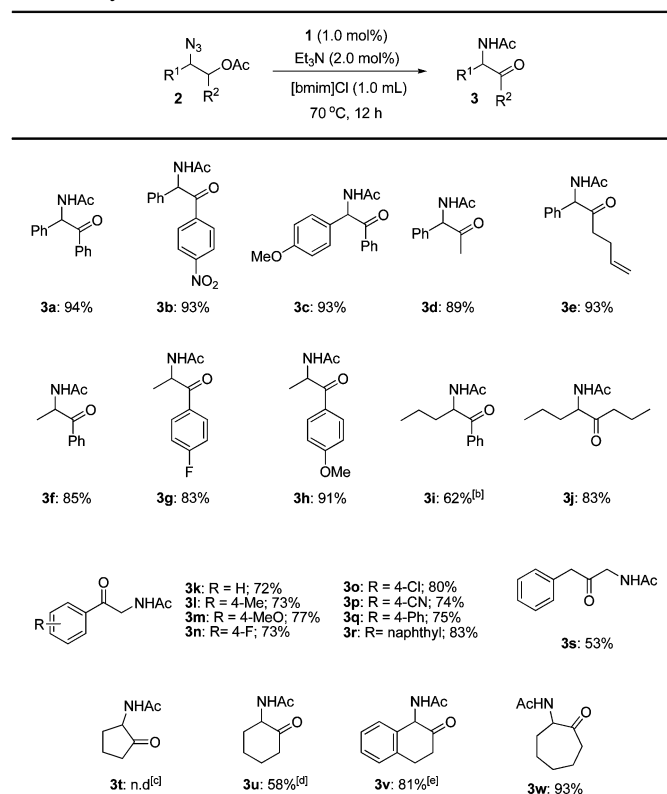
Entry	Solvent	Additive	Temp. (°C)	Yield ^b (%)
1	THF	Et ₃ N	70	15
2	Toluene	Et ₃ N	70	28
3	DMF	Et ₃ N	70	89
4	[bmim]Cl	Et ₃ N	70	96 (94) ^c
5	[bmim]Cl	Et ₃ N	70	91 ^{c,d}
6	[bmim]Cl	Et ₃ N	70	90 ^e
7	[bmim]Cl	Et ₃ N	50	15
8	[bmim]Cl	Et ₃ N	100	91
9	[bmim]Cl	None	70	85

^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.

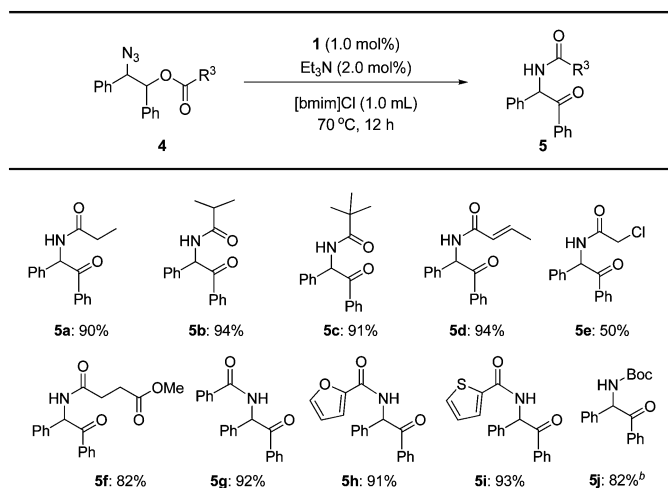
significant (**3a–3c** and **3g–3h**). The yields of α -amido ketones were high in the transformation of the derivatives having alkyl groups (**3d–3j**). The low yield of **3i** was due to the formation of unidentified side-products, and the use of DMF as a solvent gave **3i** in 62% yield. The transformation 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 **2** (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.

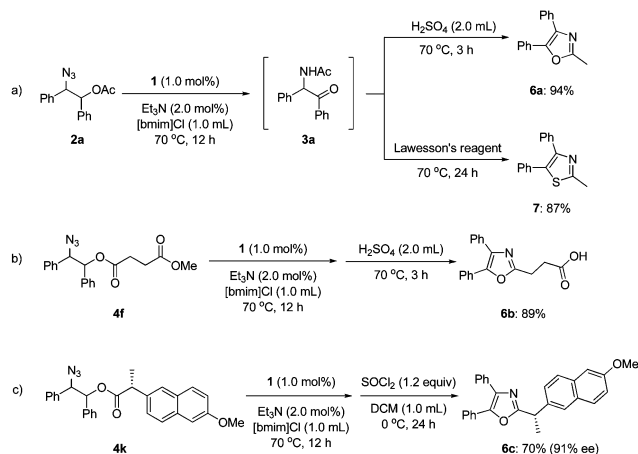
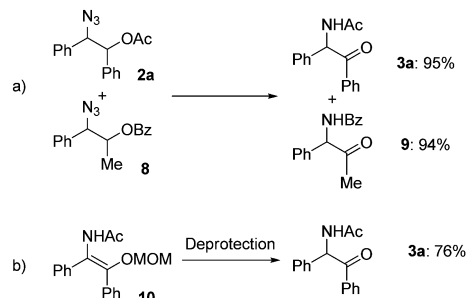
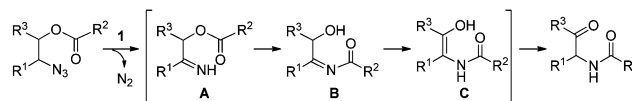
Table 3 Synthesis of α -amido ketones from various esters of 1,2-azido alcohols^a

^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 3** One-pot transformations to oxazoles and a thiazole.**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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Notes and references

- (a) A. Lee, L. Huang and J. A. Ellman, *J. Am. Chem. Soc.*, 1999, **121**, 9907; (b) C. Béguin, S. V. Andurkar, A. Y. Jin, J. P. Stables, D. F. Weaver and H. Kohn, *Bioorg. Med. Chem.*, 2003, **11**, 4275; (c) A. Białas, J. Grembecka, D. Krowarsch, J. Otlewski, J. Potempa and A. Mucha, *J. Med. Chem.*, 2006, **49**, 1744; (d) H. Azuma, S. Ijichi, M. Kataoka, A. Masuda, T. Izumi, T. Yoshimoto and T. Tachibana, *Bioorg. Med. Chem.*, 2007, **15**, 2860; (e) A. El-Dahshan, S. I. Al-Gharabli, S. Radetzki, T. H. Al-Tel, P. Kumar and J. Rademann, *Bioorg. Med. Chem.*, 2014, **22**, 5506.
- (a) P. Wipf and C. P. Miller, *J. Org. Chem.*, 1993, **58**, 3604; (b) T. Morwick, M. Hrapchak, M. DeTuri and S. Campbell, *Org. Lett.*, 2002, **4**, 2665; (c) K. C. Nicolaou, J. Hao, M. V. Reddy, P. B. Rao,

- G. Rassias, S. A. Snyder, X. Huang, D. Y. K. Chen, W. E. Brenzovich, N. Giuseppone, P. Giannakakou and A. O'Brate, *J. Am. Chem. Soc.*, 2004, **126**, 12897; (d) M. Keni and J. J. Tepe, *J. Org. Chem.*, 2005, **70**, 4211; (e) E. Biron, J. Chatterjee and H. Kessler, *Org. Lett.*, 2006, **8**, 2417; (f) J. Zhang and M. A. Ciufolini, *Org. Lett.*, 2011, **13**, 390.
- 3 (a) A. G. Griesbeck, H. Heckroth and J. Lex, *Chem. Commun.*, 1999, 1109; (b) A. G. Griesbeck and H. Heckroth, *J. Am. Chem. Soc.*, 2002, **124**, 396.
- 4 (a) M. G. Unthank, N. Hussain and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2006, **45**, 7066; (b) M. G. Unthank, B. Tavassoli and V. K. Aggarwal, *Org. Lett.*, 2008, **10**, 1501.
- 5 (a) T. N. Sorrell and W. E. Allen, *J. Org. Chem.*, 1994, **59**, 1589; (b) H. B. Lee and S. Balasubramanian, *Org. Lett.*, 2000, **2**, 323; (c) D. E. Frantz, L. Morency, A. Soheili, J. A. Murry, E. J. J. Grabowski and R. D. Tillyer, *Org. Lett.*, 2004, **6**, 843.
- 6 B. H. Oh, I. Nakamura and Y. Yamamoto, *J. Org. Chem.*, 2004, **69**, 2856.
- 7 T. Miura, T. Biyajima, T. Fujii and M. Murakami, *J. Am. Chem. Soc.*, 2012, **134**, 194.
- 8 (a) N. L. Allinger, G. L. Wang and B. B. Dewhurst, *J. Org. Chem.*, 1974, **39**, 1730; (b) G. L. Buchanan, *Chem. Soc. Rev.*, 1988, **17**, 91; (c) A. G. Godfrey, D. A. Brooks, L. A. Hay, M. Peters, J. R. McCarthy and D. Mitchell, *J. Org. Chem.*, 2003, **68**, 2623; (d) R. C. Wende, A. Seitz, D. Niedek, S. M. M. Schuler, C. Hofmann, J. Becker and P. R. Schreiner, *Angew. Chem., Int. Ed.*, 2016, **55**, 2719.
- 9 (a) C. O'Brien, *Chem. Rev.*, 1964, **64**, 81; (b) T. Ooi, M. Takahashi, K. Doda and K. Maruoka, *J. Am. Chem. Soc.*, 2002, **124**, 7640.
- 10 G. Zheng, Y. Li, J. Han, T. Xiong and Q. Zhang, *Nat. Commun.*, 2015, **6**, 7011.
- 11 (a) J. A. Murry, D. E. Frantz, A. Soheili, R. Tillyer, E. J. J. Grabowski and P. J. Reider, *J. Am. Chem. Soc.*, 2001, **123**, 9696; (b) A. E. Mattson and K. A. Scheidt, *Org. Lett.*, 2004, **6**, 4363; (c) S. M. Mennen, J. D. Gipson, Y. R. Kim and S. J. Miller, *J. Am. Chem. Soc.*, 2005, **127**, 1654; (d) D. A. DiRocco and T. Rovis, *Angew. Chem., Int. Ed.*, 2012, **51**, 5904; (e) M. M. D. Wilde and M. Gravel, *Org. Lett.*, 2014, **16**, 5308.
- 12 T. Mecozzi and M. Petrini, *J. Org. Chem.*, 1999, **64**, 8970.
- 13 T. Sun, G. Hou, M. Ma and X. Zhang, *Adv. Synth. Catal.*, 2011, **353**, 253.
- 14 K. H. Bleicher, F. Gerber, Y. Wüthrich, A. Alanine and A. Capretta, *Tetrahedron Lett.*, 2002, **43**, 7687.
- 15 J. H. Lee, S. Gupta, W. Jeong, Y. H. Rhee and J. Park, *Angew. Chem., Int. Ed.*, 2012, **51**, 10851.
- 16 (a) J. Han, M. Jeon, H. K. Pak, Y. H. Rhee and J. Park, *Adv. Synth. Catal.*, 2014, **356**, 2769; (b) H. K. Pak, J. Han, M. Jeon, Y. Kim, Y. Kwon, J. Y. Park, Y. H. Rhee and J. Park, *ChemCatChem*, 2015, **7**, 4030.
- 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†.
- 19 D. J. Greenblatt, R. Matlis, J. M. Scavone, G. T. Blyden, J. S. Harmatz and R. I. Shader, *Br. J. Clin. Pharmacol.*, 1985, **19**, 373–378.
- 20 A. K. Ghosh, N. Kumaragurubaran, L. Hong, H. Lei, K. A. Hussain, C.-F. Liu, T. Devasamudram, V. Weerasena, R. Turner, G. Koelsch, G. Bilcer and J. Tang, *J. Am. Chem. Soc.*, 2006, **128**, 5310–5311.
- 21 H. Han, Y. E. Kwon, J.-H. Sohn and D. H. Ryu, *Tetrahedron*, 2010, **66**, 1673.