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

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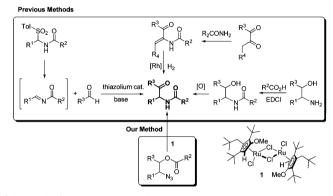
The esters of 1,2-azido alcohols were transformed into α -amido ketones without external oxidants through the Ru-catalyzed formation of N-H imines with the liberation of N2 followed by intramolecular migration of the acyl moiety. A wide range of α -amido ketones were obtained, and one-pot transformation 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-aminocyclobutanols,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 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

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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 vield 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

	Ph OAc	solvent Additive (2.0 mol%) Temperature 3a		
Entry	Solvent	Additive	Temp. (°C)	Yield ^b (%)
1	THF	Et ₃ N	70	15
2	Toluene	Et ₃ N	70	28

1 (1.0 mol%)

NHAc

Entry	Solvent	Additive	Temp. (°C)	Yield ^b (%)
1	THF	Et ₃ N	70	15
2	Toluene	Et_3N	70	28
3	DMF	Et_3N	70	89
4	[bmim]Cl	Et_3N	70	96 $(94)^c$ 91 c,d
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 $\rm Et_3N$ (2.0 mol%) in a solvent (1.0 mL) was stirred for 12 h. b Estimated by 1 H 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-3i). 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 (3**u**) 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)

> 1 (1.0 mol%) Et₃N (2.0 mol%)

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

3v: 81%[e]

3u: 58%^[d]

^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.

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Table 3 Synthesis of α -amido ketones from various esters of 1.2-azido alcohols^a

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 (5i) 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 $6c_1^{20}$ 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.

Mechanistic investigation Scheme 4

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

- 1 (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,

^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.

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- 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.
- (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.