COMMUNICATION

Indium-mediated facile synthesis of 3-unsubstituted β-lactams

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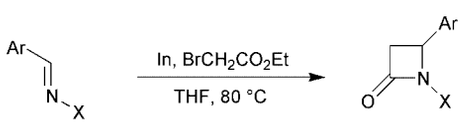
A simple synthesis of 3-unsubstituted β-lactams was achieved through indium-mediated reaction of imines with ethyl bromoacetate.

Synthesis of β-lactams and their biological application is an increasingly active area. Because of the recent developments in using β-lactams as synthons for the synthesis of several natural and non-natural products, research on this topic has gained tremendous attention in spite of the clinical resistance of some organisms to the β-lactam antibiotics.[1] Monocyclic β-lactams with diverse substituents have been of considerable interest to the synthetic community in the past few decades. The use of 3-unsubstituted β-lactams in synthetic chemistry is widespread[2] and consequently a few methods have been reported for the synthesis of this type of β-lactams.

In continuation of our studies[3] on metal-induced oxidation–reduction reactions, we became interested in indium-mediated reduction[4] and addition reactions to imines. Our study on indium-mediated reaction of imines with bromoesters culminated in a facile synthesis of 3-unsubstituted β-lactams and the results are reported below.

The synthetic application of indium metal is growing.[5–8] This metal has been used for the allylation of imines[7] in the presence of allyl bromide and for the addition to a keto group in some β-lactams.[8] These reports indicated that under appropriate conditions, indium can be used in conjunction with allyl bromide and that 4-membered cyclic amides are stable under indium treatment. We have combined these two approaches for the facile synthesis of 3-unsubstituted β-lactams by indium-mediated addition of a bromoester to imines.

Reaction of various imines **1** with ethyl bromoacetate in the presence of indium metal using anhydrous tetrahydrofuran as the solvent produced the β-lactams **2** (Scheme 1). It was

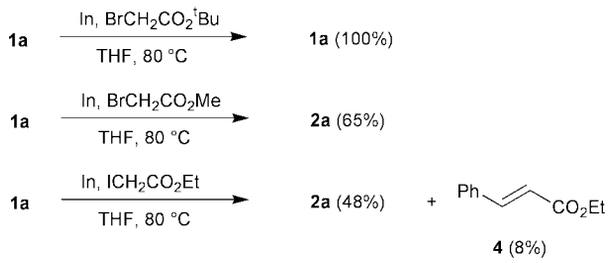


1 **2**

Scheme 1

found that the imines **1a**–**1f** derived from arylalkylamines, allylamine and *p*-anisidine produced only the β-lactams **2a**–**2f** (Table 1). Alternatively, imines derived from aniline (**1g** and **1h**) produced the β-lactams (**2g** and **2h**) along with the β-amino esters (**3a** and **3b**) (Table 1, entries 7 and 8). This indicated that the basicity of the β-amino ester[9] is an important factor in the cyclization reaction.

In order to establish the effects of using other haloesters, a few reactions with *tert*-butyl bromoacetate, methyl bromoacetate and ethyl iodoacetate were investigated with imine **1a** (Scheme 2). No reaction was observed with *tert*-butyl bromoacetate and the imine **1a** was recovered unchanged from this reaction. Methyl bromoacetate and ethyl iodoacetate gave **2a** in 65 and 48% yields respectively. However, a small amount of unsaturated ester **4** (8%) was also formed from the reaction of **1a** and ethyl iodoacetate. The formation of the unsaturated



Scheme 2

ester could be explained by the decomposition of the imine **1a** in the presence of the iodoester, Reformatsky-type addition to the resulting benzaldehyde and a subsequent elimination reaction. These results indicated that the nature of the haloesters is important in this indium-mediated reaction. The iodoester was moderately effective, while the bulkier *tert*-butyl ester was not effective at all. However, methyl and ethyl bromoesters were equally effective and the yields were comparable.

In conclusion, we have demonstrated a simple and rapid synthesis[10,11] of several 3-unsubstituted β-lactams by indium-mediated reaction with ethyl bromoacetate or methyl bromoacetate. An ultrasound-promoted synthesis of 3-unsubstituted β-lactam using ethyl bromoacetate, zinc and imines has been reported[12] (*e.g.* **2e**, 82%). However, prior activation of zinc was necessary and imines containing only aryl groups were found to produce β-lactams. In our case, β-lactams having a wide range of substituents at nitrogen, such as arylalkyl, aryl and allyl groups, could be prepared. In general, imines obtained from arylalkylamines produced the β-lactams in higher yield than those obtained from aryl- or allylamines. Other advantages of this procedure are its use of commercially available indium[13] powder without any pre-treatment and that no extra equipment, like ultrasound, is needed.

Acknowledgements

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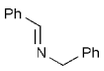
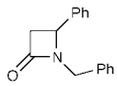
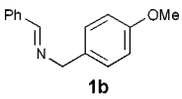
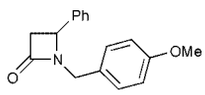
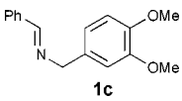
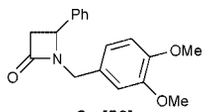
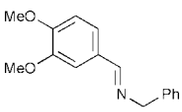
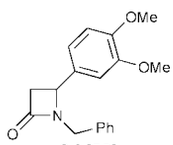
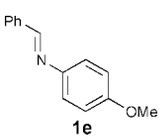
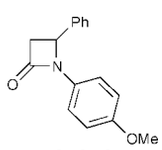
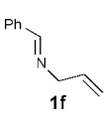
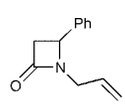
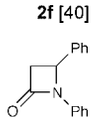
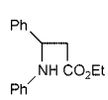
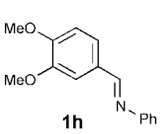
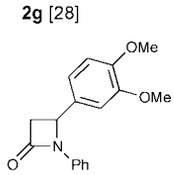
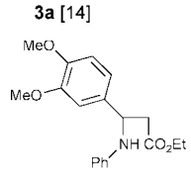
Notes and references

1 For some recent examples, see: (*a*) A. K. Bose, B. K. Banik, C. Mathur, D. R. Wagle and M. S. Manhas, *Tetrahedron*, *Symposium in Print*, 2000, 0000; (*b*) M. S. Manhas, B. K. Banik, A. Mathur, J. E. Vincent and A. K. Bose, *Tetrahedron*, *Symposium in Print*, 2000, 0000; (*c*) A. K. Bose, M. S. Manhas, B. K. Banik and V. Srirajan, in *The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry, and Material Science*, eds. A. Greenberg, C. M. Breneman and J. F. Liebman, Wiley-Interscience, New York, 2000, p. 157.

2 The usefulness of 3-unsubstituted β-lactams has been documented, see: A. K. Bose, M. S. Manhas, A. Mathur and D. R. Wagle, in

Table 1 Indium-mediated synthesis of 3-unsubstituted β-lactams[a]

Entry	Imine	β-Lactam [Yield (%)[b]]	β-amino ester [Yield (%)[–]]
1	 **1a**	 **2a** [60]	—
2	 **1b**	 **2b** [60]	—
3	 **1c**	 **2c** [58]	—
4	 **1d**	 **2d** [59]	—
5	 **1e**	 **2e** [45]	—
6	 **1f**	 **2f** [40]	—
7	 **1g**	 **2g** [28]	 **3a** [14]
8	 **1h**	 **2h** [30]	 **3b** [23]

[a] Reaction time for each entry is 12 h. [b] Isolated yield.

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4 B. K. Banik, M. Suhendra, I. Banik and F. F. Becker, *Synth. Commun.*, 2000, 0000.

5 Chan and Li have carried out significant work on indium-mediated reactions, for example, see: (*a*) Y. Yang and T. H. Chan, *J. Am. Chem. Soc.*, 2000, **122**, 402; (*b*) T. H. Chan and Y. Yang, *J. Am. Chem. Soc.*, 1999, **121**, 3228; (*c*) C. J. Li and T. H. Chan, *Tetrahedron*, 1999, **55**, 11149; (*d*) C. J. Li and T. H. Chan, *Organic Reactions in Aqueous Media*, J. Wiley & Sons, New York, 1997; (*e*) C. J. Li, *Tetrahedron*, 1996, **52**, 5643; (*f*) C. J. Li, *Chem. Rev.*, 1993, **93**, 2023; (*g*) C. J. Li and T. H. Chan, *Tetrahedron Lett.*, 1991, **32**, 7017.

6 For various indium-mediated reactions, see: (*a*) P. K. Choudhury, F. Foubelo and M. Yus, *J. Org. Chem.*, 1999, **64**, 3376; (*b*) P. K. Choudhury, F. Foubelo and M. Yus, *Tetrahedron Lett.*, 1998, **39**, 3581; (*c*) B. C. Ranu, P. Dutta and A. Sarkar, *Tetrahedron Lett.*, 1998, **39**, 9557; (*d*) B. C. Ranu, S. K. Guchhait and A. Sarkar, *Chem. Commun.*, 1998, 2113; (*e*) C. J. Moody and M. R. Pitts, *Synlett* 1998, 1028; (*f*) C. J. Moody and M. R. Pitts, *Synlett*, 1998, 1029; (*g*) B. C. Ranu and A. Majee, *Chem. Commun.*, 1997, 1225.

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8 (*a*) L. A. Paquette, R. R. Rothhaar, M. Isaac, L. M. Rogers and R. D. Rogers, *J. Org. Chem.*, 1998, **63**, 5463; (*b*) M. B. Isaac and L. A. Paquette, *J. Org. Chem.*, 1997, **62**, 5333; (*c*) M. Jayaraman, M. S. Manhas and A. K. Bose, *Tetrahedron Lett.*, 1997, **38**, 709.

9 Grignard-mediated cyclizations of β-amino esters has been reported by several groups. For some examples, see: (*a*) E. W. Colvin, D. McGarry and M. J. Nugent, *Tetrahedron*, 1988, **44**, 4157; (*b*) E. J. Thomas and A. C. Williams, *J. Chem. Soc., Chem. Commun.*, 1987, 992.

10 All new compounds described here gave satisfactory spectral data.
11 General experimental procedure: a mixture of imine **1** (2 mmol), indium powder (4.4 mmol) and ethyl bromoacetate (4 mmol) in anhydrous THF (12 mL) was heated at 80 °C with vigorous stirring under argon for 12 hours. The reaction mixture was cooled, saturated NH_4Cl solution (0.5 mL) added and diluted with CH_2Cl_2. It was filtered through a pad of Celite, dried (Na_2SO_4) and concentrated. Column chromatography over silica gel afforded the β-lactam **2.**
12 A. K. Bose, K. Gupta and M. S. Manhas, *J. Chem. Soc.*, *Chem. Commun.*, 1984, 86.
13 According to MSDS (Material Safety Data Sheets) obtained from Acros Organics, the toxicological properties of indium have not been fully investigated, but it may be harmful if swallowed.