COMMUNICATION

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

Bimal K. Banik,* Anjan Ghatak and Frederick F. Becker

The University of Texas, M. D. Anderson Cancer Center, Department of Molecular Pathology, Box-089, 1515 Holcombe Blvd., Houston, TX 77030, USA

Received (in Cambridge, UK) 10th April 2000, Accepted 14th June 2000
Published on the Web 30th June 2000

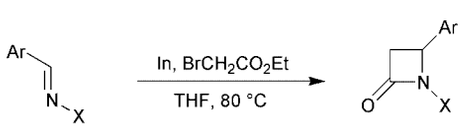
A simple synthesis of 3-unsubstituted β-lactams was achieved through indium-mediated reaction of imines with ethyl bromoacetate.

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

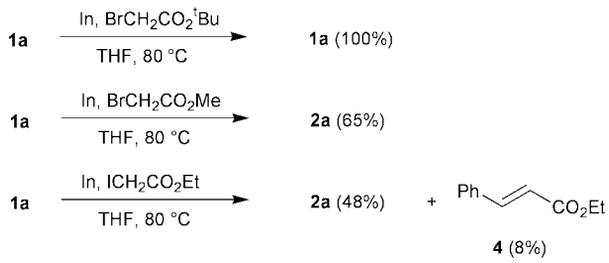


1 **2**

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

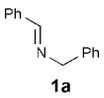
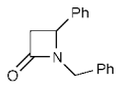
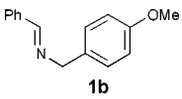
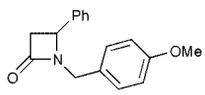
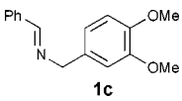
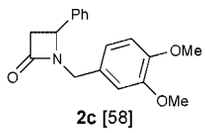
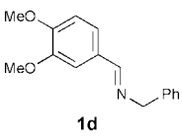
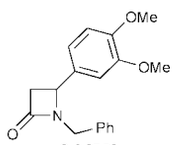
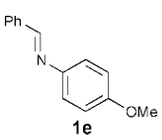
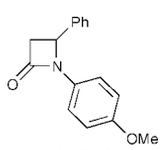
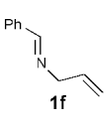
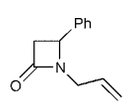
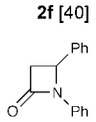
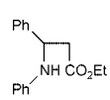
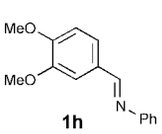
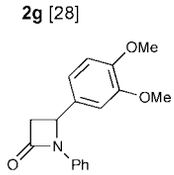
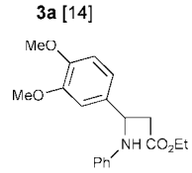
We gratefully acknowledge the funding support received for this research project from The Golden Family Fund for Cancer Research and NIH Cancer Center Support Grant, 5-P30-CA16672-25, and in particular the shared resources of the Pharmacology and Analytical Center Facility and Centralized Histopathology Laboratory.

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 (%)[b]]
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.

Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products, ed. G. Lukacs, Springer-Verlag, New York, 1993, vol. 2, p. 551.

3 For oxidation reactions: (*a*) B. K. Banik, A. Ghatak, M. S. Venkatraman and F. F. Becker, *Synth. Commun.*, 2000, **30**, 2701; (*b*) B. K. Banik, A. Ghatak, C. Mukhopadhyay and F. F. Becker, *J. Chem. Res. (S)*, 2000, 108; (*c*) B. K. Banik, M. S. Venkatraman, C. Mukhopadhyay and F. F. Becker, *Tetrahedron Lett.*, 1998, **39**, 7247. For reduction reactions: (*d*) A. Ghatak, F. F. Becker and B. K. Banik, *Tetrahedron Lett.*, 2000, **41**, 3493; (*e*) B. K. Banik, O. Zegrocka, I. Banik, L. Hackfeld and F. F. Becker, *Tetrahedron Lett.*, 1999, **40**, 6731; (*f*) B. K. Banik, C. Mukhopadhyay, M. S. Venkatraman and F. F. Becker, *Tetrahedron Lett.*, 1998, **39**, 7243.

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.

7 For indium-mediated allylation of imines, see: (*a*) H. A. Hoppe, C. G. Lloyd-Jones, M. Murray, T. M. Peakman and K. E. Walsh, *Angew. Chem., Int. Ed.*, 1998, **37**, 1545; (*b*) S. M. Capps, C. G. Lloyd-Jones, M. Murray, T. M. Peakman and K. E. Walsh, *Tetrahedron Lett.*, 1998, **39**, 2853; (*c*) C. G. Lloyd-Jones and T. Russell, *Synlett*, 1998, 903; (*d*) M. Carda, E. Castillo, S. Rodriguez, J. Murga and J. A. Marco, *Tetrahedron: Asymmetry*, 1998, **9**, 1117.

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.