TRIETHYLBORANE-MEDIATED ATOM TRANSFER CYCLIZATION OF *N*-ALLYLIC α-IODOACETAMIDES: A CONVENIENT SYNTHESIS OF β-IODOMETHYL-γ-LACTAMS

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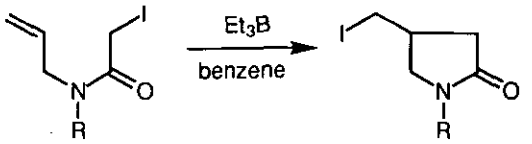
Abstract — In the presence of triethylborane, *N*-allylic α-iodoacetamides underwent atom transfer cyclization to give β-iodomethyl-γ-lactams in high yields.

Since the pioneering works by Oshima and Utimoto[1, 2] on the use of triethylborane (Et_3B) as an initiator[3] in radical reactions, great interest has developed in recent years in Et_3B-mediated radical addition and cyclization reactions.[4] This is probably because that the reaction with Et_3B has several advantages over those with azobis(isobutyronitrile) (AIBN) as a radical initiator, which requires relatively drastic conditions.

The ω-haloalkenes, when treated with Et_3B, may give different types of cyclization products either in the presence or in the absence of tributyltin hydride (Bu_3SnH). In the presence of Bu_3SnH, the cyclized intermediacy of radical, generated by Et_3B-initiated ring-closure of ω-haloalkene, attacks on Bu_3SnH to give the *reductive cyclization product*.[2c,4d,4f,4g,4i] On the other hand, in the absence of Bu_3SnH, the cyclized radical attacks on the halogen atom of another ω-haloalkene to lead to the formation of the *atom transfer cyclization product*. Since the atom transfer reactions can introduce a versatile halogen atom to the products, the method is highly useful in organic synthesis. However, there are only a few reports[2d,2i,4c] on the use of Et_3B alone in the atom transfer cyclizations.[5] The present paper describes an efficient synthesis of β-iodomethyl-γ-lactams (*e. g.*, **2**) by means of Et_3B-mediated atom transfer cyclization of *N*-allylic α-iodoacetamides (*e. g.*, **1**).

We initiated our investigation by examining the cyclization of *N*,*N*-diallyl-α-iodoacetamide (**1a**).[6] When a solution of 0.2 molar equivalents of Et_3B in hexane was added at once to a benzene solution of **1a** at room temperature, the starting material (**1a**) was rapidly consumed. After a 10-minute period of stirring, the solvent was evaporated off and the residue was chromatographed on silica gel to give the expected iodine

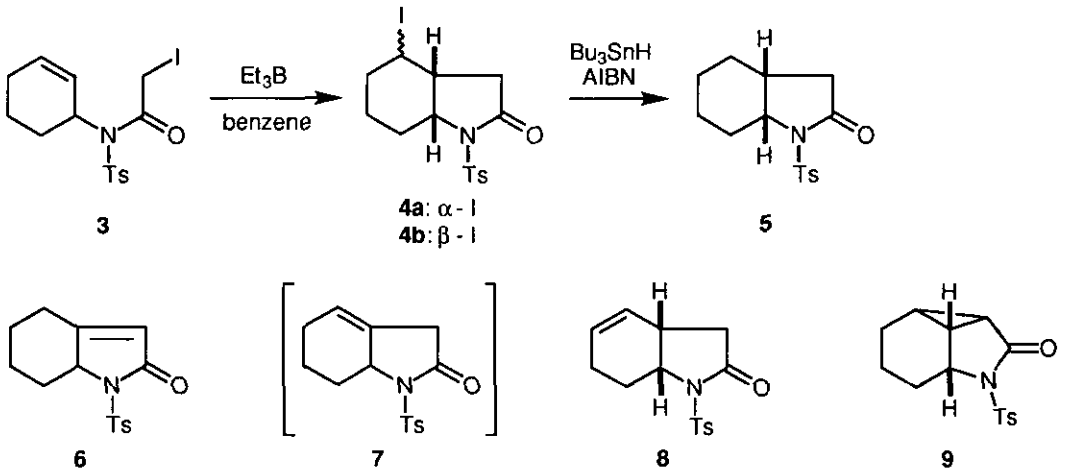


1a-d **2a-d**

a: R = Allyl, **b**: Me, **c**: R = Ph, **d**: R = Ts

atom transfer cyclization product (**2a**)[7] in 81% yield. When the same reaction was carried out in boiling benzene, the yield of **2b** was improved to 89%.[8] Similar reactions of a range of α-iodoacetamides (**1b-d**) in boiling benzene in the presence of Et_3B (0.4-0.6 equiv.) gave the corresponding β-iodomethyl-γ-lactams (**2b**),[7] (**2c**), and (**2d**)[9] in 71, 77, and 92% yields, respectively.

Taking into account the result observed for the *N*-tosyl derivative (**1d**) which gave **2d** in high yield, our attention was next turned to the *N*-tosyl-α-iodoacetamides (**3**) and (**10**). When a mixture of **3** and Et_3B (0.5 equiv.) was heated in boiling benzene for 10 min, the *cis*-octahydro-4-iodoindol-2-ones (**4a**: mp 174-175.5 °C) and (**4b**: mp 130-131.5 °C) were obtained in 48 and 24% yields, respectively. The *cis*-stereochemistry of the ring-junction of **4a,b** was confirmed by reducing them with Bu_3SnH/AIBN to the known compound (**5**)[10] (mp 146.5-147 °C). Upon treatment with DBU, the major isomer (**4a**) gave the unsaturated lactam (**6**) in 93% yield, probably through the dehydroiodination product (**7**), while the minor isomer (**4b**) gave the 2,3,3a,6,7,7a-hexahydroindol-2-one (**8**) and the tricyclic compound (**9**) in 43 and 55% yields, respectively. These observations clearly indicate that the iodine atoms of the cyclization products (**4a**) and (**4b**) should occupy the α- and β-positions, respectively, based on the stereoelectronic effect in the elimination of the iodine atom.

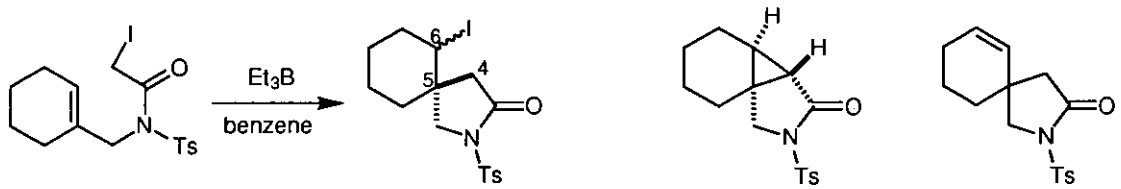


3 **4a**: α - I, **4b**: β - I **5**

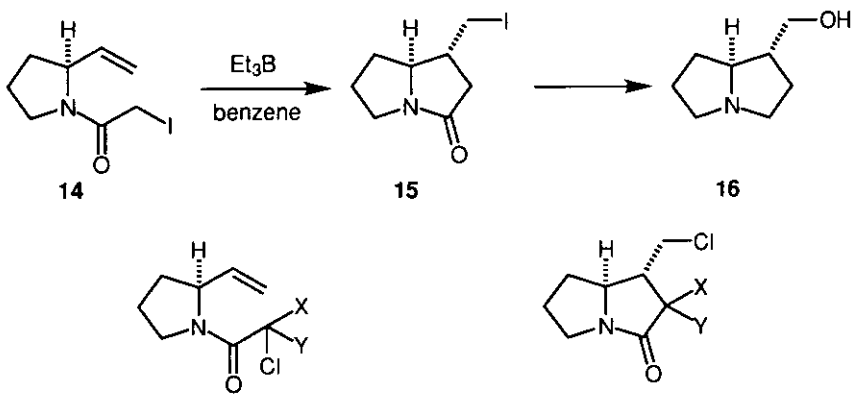
6 **7** **8** **9**

The iodoacetamide (**10**), when heated with Et_3B (0.7 equiv.) in boiling benzene, afforded the spiro compounds (**11a**: mp 158-159 °C) and (**11b**: mp 147.5-148.5 °C) in 40 and 31% yields, respectively. Upon treatment with DBU, the major stereoisomer (**11a**) gave the tricyclic compound (**12**) in 73% yield,

while the minor isomer (**11b**) gave the unsaturated compound(**12**), thereby indicating the stereochemical relationships between C_4-C_5 and C_6-I bonds of **11a** and **11b** to be *anti* and *syn*, respectively.



The reaction of the iodoacetamide (**14**), prepared from L-prolinol, also proceeded smoothly within 10 min in boiling benzene in the presence of Et_3B (0.4 equiv.) to give, in 68% yield, (1*R*,8*S*)-1-(iodomethyl)pyrrolizidin-3-one (**15**), which contained a trace amount of the corresponding (1*S*,8*S*)-isomer (<5% by ^1H NMR spectroscopy). Recrystallization of the mixture from hexane gave the pure (1*R*,8*S*)-isomer (**15**) [mp 46°C; lit.,[11b] mp 48-49°C, $[\alpha]_D^{21}$ -22.9° (*c* 2.10, EtOH); lit.,[11b] $[\alpha]_D^{25}$ -23.9° (*c* 1.13, EtOH)]. Since the compound (**15**) can readily be converted into a pyrrolizidine alkaloid (–)-trachelanthamidine (**16**), several reports have appeared in the literature on the synthesis of this compound and its analogues using the atom transfer methods: i) $Pd(PPh_3)_4$-catalyzed cyclization of **14** [MeCN, 65°C, 28% yield of **15**],[11a] ii) $(Bu_3Sn)_2$-mediated cyclization of **14** [room temp., benzene-EtI, hv, 58% yield of **15**],[11b] iii) CuCl-catalyzed cyclization of the trichloroacetamide (**17a**) [MeCN, 150°C, 93% yield of **18a**],[11c] and iv) $RuCl_2(PPh_3)_3$-catalyzed cyclization of the chlorosulfide (**17b**) [benzene, 150°C, 67% yield of **18b**].[11d] The present method is far superior in simplicity and yield to any thus far reported.



In summary, clearly the described atom transfer methodology involving Et_3B has several advantages in terms of mildness, efficiency, and convenience. Further work will be continued on the refinement of the feasibility of using Et_3B in other atom transfer systems.

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REFERENCES AND NOTES

1. For a review, see: K. Oshima and K. Utimoto, *J. Synth. Org. Chem., Jpn.*, 1989, **47**, 42.
2. (a) K. Nozaki, K. Oshima, and K. Utimoto, *J. Am. Chem. Soc.*, 1987, **109**, 2547. (b) K. Nozaki, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, 1988, **29**, 1041. (c) K. Nozaki, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, 1988, **29**, 6127. (d) Y. Ichinose, S. Matsunage, K. Fugami, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, 1989, **30**, 3155. (e) Y. Takeyama, Y. Ichinose, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, 1989, **30**, 3159. (f) K. Miura, Y. Ichinose, K. Nozaki, K. Fugami, K. Oshima, and K. Utimoto, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 143. (g) J. Sugimoto, K. Miura, K. Oshima, and K. Utimoto, *Chem. Lett.*, 1991, 1319. (h) K. Miura, Y. Takeyama, K. Oshima, and K. Utimoto, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 1542. (i) K. Matsumoto, K. Miura, K. Oshima, and K. Utimoto, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 625.
3. It is believed that upon exposure to a molecular oxygen dissolved in a solvent, Et_3B generates an ethyl radical. See: H.C. Brown and M.M. Midland, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 692.
4. For selected examples, see: (a) D.P. Curran and L. Balas, *Synlett*, 1995, 119. (b) Y. Guindon, B. Guérin, C. Chabot, N. Mackintosh, and W.W. Ogilvie, *Synlett*, 1995, 449. (c) T.J. Woltering and H.M.R. Hoffmann, *Tetrahedron*, 1995, **51**, 7389. (d) M. Nishida, H. Hayashi, A. Nishida, and N. Kawahara, *Chem. Commun.*, 1996, 579. (e) J. Marco-Contelles, *Chem. Commun.*, 1996, 2629. (f) P.A. Evans and J.D. Roseman, *J. Org. Chem.*, 1996, **61**, 2252. (g) S. Czernecki, E. Ayadi, and J. Xie, *Tetrahedron Lett.*, 1996, **37**, 9193. (h) M.P. Sibi and J. Ji, *J. Am. Chem. Soc.*, 1996, **118**, 9200. (i) K. Goodall and A.F. Parsons, *Tetrahedron Lett.*, 1997, **38**, 491.
5. For intermolecular atom transfer reactions with Et_3B, see: refs. 2d, 2e and 2h.
6. All α-iodoacetamides herein described were prepared from the corresponding bromo congeners by treating with NaI in MeCN.
7. D.P. Curran and J. Tamine, *J. Org. Chem.*, 1991, **56**, 2746.
8. A similar reaction of the bromo congener of **1a** gave no atom transfer cyclization product, but afforded only the starting material.
9. S. Ozaki, H. Matsushita, M. Emoto, and H. Ohmori, *Chem. Pharm. Bull.*, 1995, **43**, 32.
10. G. Stork and R. Mah, *Heterocycles,* 1989, **28**, 723.
11. (a) M. Mori, N. Kanda, I. Oda, and Y. Ban, *Tetrahedron*, 1985, **41**, 5465. (b) R.S. Jolly and T. Livinghouse, *J. Am. Chem. Soc.*, 1988, **110**, 7536. (c) J.A. Seijas, M.P. Vázquez-Tato, L. Castedo, R.J. Estévez, M.G. Ónega, and M. Ruíz, *Tetrahedron,* 1992, **48**, 1637. (d) H. Ishibashi, N. Uemura, H. Nakatani, M. Okazaki, T. Sato, N. Nakamura, and M. Ikeda, *J. Org. Chem.*, 1993, **58**, 2360.

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