

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

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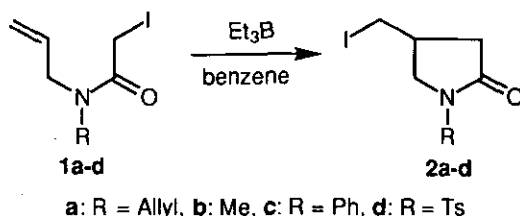
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Abstract — In the presence of triethylborane, *N*-allylic α -iodoacetamides underwent atom transfer cyclization to give β -iodomethyl- γ -lactams in high yields.

Since the pioneering works by Oshima and Utimoto^{1,2} on the use of triethylborane (Et₃B) as an initiator³ in radical reactions, great interest has developed in recent years in Et₃B-mediated radical addition and cyclization reactions.⁴ This is probably because that the reaction with Et₃B has several advantages over those with azobis(isobutyronitrile) (AIBN) as a radical initiator, which requires relatively drastic conditions.

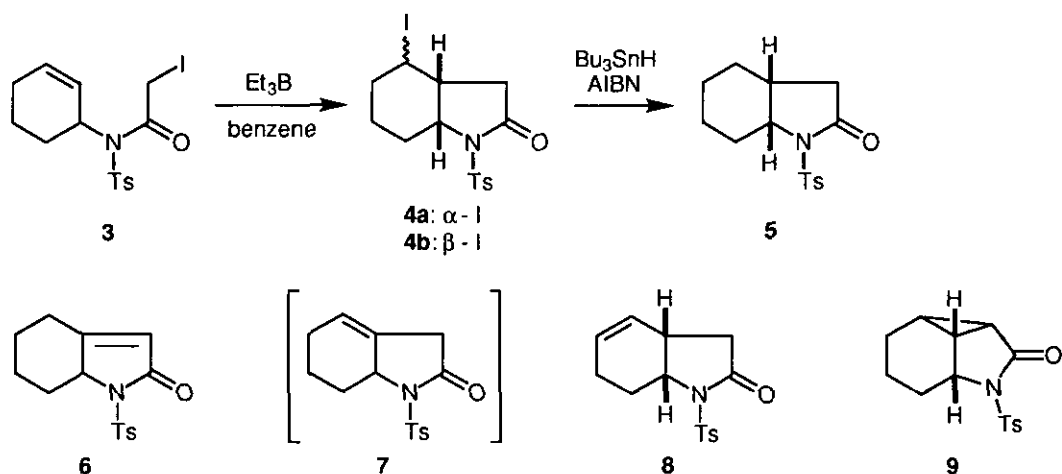
The ω -haloalkenes, when treated with Et₃B, may give different types of cyclization products either in the presence or in the absence of tributyltin hydride (Bu₃SnH). In the presence of Bu₃SnH, the cyclized intermediacy of radical, generated by Et₃B-initiated ring-closure of ω -haloalkene, attacks on Bu₃SnH to give the *reductive cyclization product*.^{2c,4d,4f,4g,4i} On the other hand, in the absence of Bu₃SnH, 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 Et₃B 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 Et₃B-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 Et₃B 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



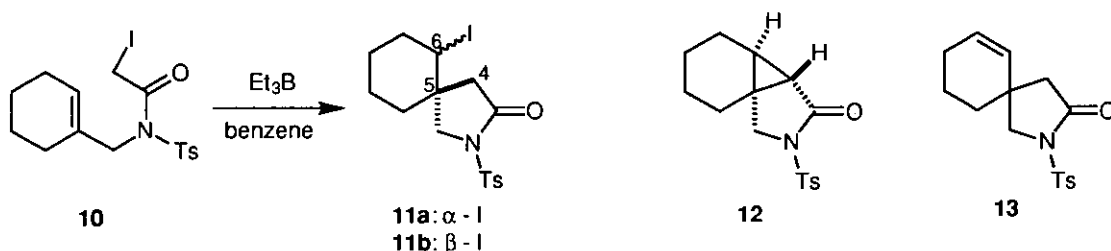
atom transfer cyclization product (**2a**)⁷ in 81% yield. When the same reaction was carried out in boiling benzene, the yield of **2b** was improved to 89%.⁸ Similar reactions of a range of α -iodoacetamides (**1b-d**) in boiling benzene in the presence of Et₃B (0.4-0.6 equiv.) gave the corresponding 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 Et₃B (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 Bu₃SnH/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.

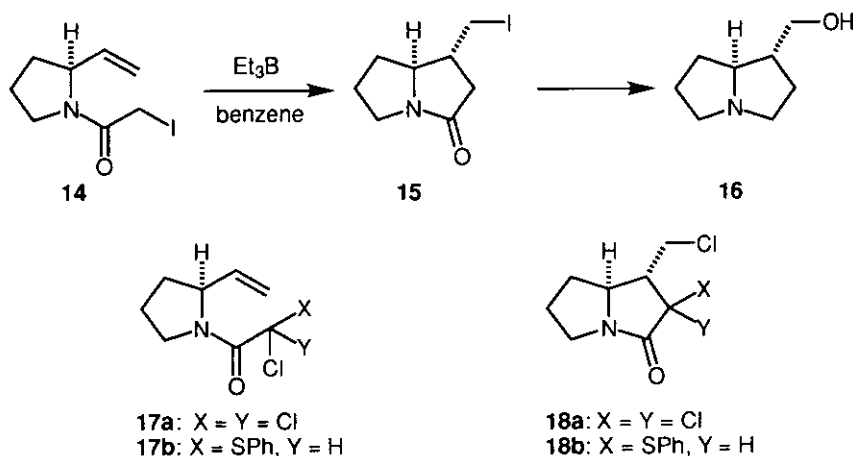


The iodoacetamide (**10**), when heated with Et₃B (0.7 equiv.) in boiling benzene, afforded the spiro compounds (**11a**: mp 158-159 °C) and (**11b**: mp 147.5-148.5 °C) in 40 and 31% yields, respectively. Upon treatment with DBU, the major stereoisomer (**11a**) gave the tricyclic compound (**12**) in 73% yield,

while the minor isomer (**11b**) gave the unsaturated compound (**12**), thereby indicating the stereochemical relationships between C₄-C₅ and C₆-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, $[\alpha]_{\text{D}}^{21}$ -22.9° (*c* 2.10, EtOH); lit.,^{11b} $[\alpha]_{\text{D}}^{25}$ -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) $\text{Pd}(\text{PPh}_3)_4$ -catalyzed cyclization of **14** [MeCN, 65°C, 28% yield of **15**],^{11a} ii) $(\text{Bu}_3\text{Sn})_2$ -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) $\text{RuCl}_2(\text{PPh}_3)_3$ -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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