TRIETHYLBORANE-MEDIATED ATOM TRANSFER CYCLIZATION OF N-ALLYLIC \( \alpha \)-IODOACETAMIDES: A CONVENIENT SYNTHESIS OF \( \beta \)-iodomethyl-\( \gamma \)-LACTAMS

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Abstract — In the presence of triethylborane, N-allylic \( \alpha \)-iodoacetamides underwent atom transfer cyclization to give \( \beta \)-iodomethyl-\( \gamma \)-lactams in high yields.

Since the pioneering works by Oshima and Utimoto\(^1,2\) on the use of triethylborane (Et\(_3\)B) as an initiator\(^3\) in radical reactions, great interest has developed in recent years in Et\(_3\)B-mediated radical addition and cyclization reactions.\(^4\) This is probably because that the reaction with Et\(_3\)B has several advantages over those with azobis(isobutyronitrile) (AIBN) as a radical initiator, which requires relatively drastic conditions.

The \( \omega \)-haloalkenes, when treated with Et\(_3\)B, may give different types of cyclization products either in the presence or in the absence of tributyltin hydride (Bu\(_3\)SnH). In the presence of Bu\(_3\)SnH, the cyclized intermediacy of radical, generated by Et\(_3\)B-initiated ring-closure of \( \omega \)-haloalkene, attacks on Bu\(_3\)SnH to give the reductive cyclization product.\(^2c,4d,4f,4g,4i\) On the other hand, in the absence of Bu\(_3\)SnH, the cyclized radical attacks on the halogen atom of another \( \omega \)-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\(^2d,2l,4c\) on the use of Et\(_3\)B alone in the atom transfer cyclizations.\(^5\) The present paper describes an efficient synthesis of \( \beta \)-iodomethyl-\( \gamma \)-lactams (e. g., 2) by means of Et\(_3\)B-mediated atom transfer cyclization of N-allylic \( \alpha \)-iodoacetamides (e. g., 1).

We initiated our investigation by examining the cyclization of \( N,N \)-diallyl-\( \alpha \)-iodoacetamide (1a).\(^6\) When a solution of 0.2 molar equivalents of Et\(_3\)B 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 \(\alpha\)-idoacetamides (1b-d) in boiling benzene in the presence of Et\(_3\)B (0.4-0.6 equiv.) gave the corresponding \(\beta\)-iodomethyl-\(\gamma\)-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-\(\alpha\)-idoacetamides (3) and (10). When a mixture of 3 and Et\(_3\)B (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\(_3\)SnH/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 \(\alpha\)- and \(\beta\)-positions, respectively, based on the stereoelectronic effect in the elimination of the iodine atom.

The iodoacetamide (10), when heated with Et\(_3\)B (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 Et3B (0.4 equiv.) to give, in 68% yield, (1R,8S)-1-(iodomethyl)pyrrolizidin-3-one (15), which contained a trace amount of the corresponding (1S,8S)-isomer (<5% by 1H NMR spectroscopy). Recrystallization of the mixture from hexane gave the pure (1R,8S)-isomer (15) [mp 46°C; lit.,11b mp 48-49°C, [a]D 21 -22.9° (c 2.10, EtOH); lit.,11b [a]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(PPh3)4-catalyzed cyclization of 14 [MeCN, 65°C, 28% yield of 15],11a ii) (Bu3Sn)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) RuCl2(PPh3)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 Et3B has several advantages in terms of mildness, efficiency, and convenience. Further work will be continued on the refinement of the feasibility of using Et3B in other atom transfer systems.
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REFERENCES AND NOTES


5. For intramolecular atom transfer reactions with Et₃B, 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.


8. A similar reaction of the bromo congener of Ia gave no atom transfer cyclization product, but afforded only the starting material.


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