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RADICAL BASED ANNULATIONS OF IODO LACTAMS

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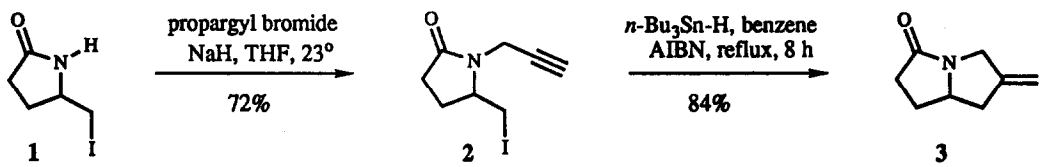
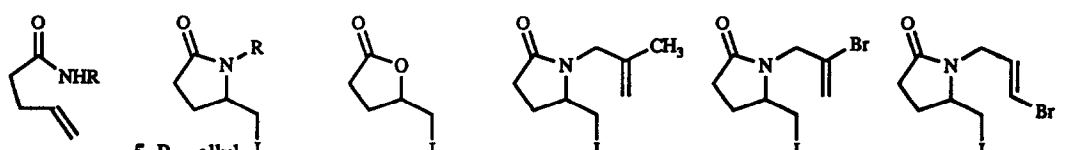
Summary: *N-Alkylation of iodo lactams with reactive alkyl halides, or of the derived selenide lactams with less reactive alkyl halides, leads to substrates for free radical initiated cyclization to pyrrolizidinones and indolizidinones, e. g. 2 → 3 . The first examples of iodide / vinyl bromide, selenide / aldehyde, and selenide / vinyl chloride radical cyclizations are described.*

"Iodolactamization"[1] of unsaturated amides provides access to iodo lactams, such as **1**, whose reactions[2] demonstrate some interesting synergy between the two functional groups. The corresponding *N*-alkylated iodo lactams (e. g. **2**) also deserve attention, since these could potentially serve as substrates for free radical, cationic, or anionic cyclization reactions involving the *N*-alkyl substituent. We report here the preparation of a series of *N*-alkyl iodo lactams, and some equally useful *N*-alkyl selenide lactams, and their conversion to pyrrolizidine and indolizidine derivatives by free radical initiated cyclization.[3]



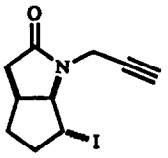
1 **2** **3**

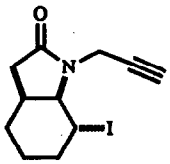
Efforts to convert *N*-alkyl unsaturated amides **4** directly to *N*-alkyl iodo lactams by iodocyclization of the derived *O*-(trimethylsilyl)imidate met with limited success. For example *N*-propargyl, *N*-allyl, and *N*-butyl-4-pentenamide gave the corresponding iodo lactams **2**, **5**, and **6** in 22, 11, and 40% yields, respectively, accompanied by large amounts of the iodo lactone **7**. We infer that silylation is occurring on nitrogen to a significant extent, which limits the desired *N*-cyclization path.[4,5] However, **2** was prepared by *N*-alkylation of **1** using 4 equiv of propargyl bromide in tetrahydrofuran solution, with sodium hydride as the base. Similarly, allyl iodide, methallyl iodide, 2-bromo-3-iodopropene, and 1-bromo-3-iodopropene gave the alkylated products **5**, **8**, **9**, and **10** in 80, 88, 40, and 50% yields, respectively. 1-Iodobutane did not intercept the sodium salt of **1** before it decomposed. Yields in these iodo lactam alkylation reactions therefore roughly parallel the reactivity of the alkylating agent. Several other *N*-alkylated iodo lactams (**11** - **14**) were similarly prepared in the yields shown by alkylation of the corresponding lactam nitrogen.

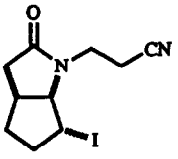


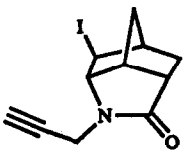
4 5, R = allyl **5** 6, R = 1-butyl **6** **7** **8** **9** **10**

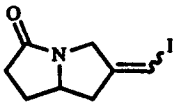
Reductive 5-*exo*-dig cyclization of **2** occurred upon treatment with tributyltin hydride under conditions described by Curran,[6] and the pyrrolizidinone **3** was isolated in good yield. Shorter reaction times led to mixtures of **3** and iodide **15** (equal mixture of E/Z isomers), the product of an atom transfer process.[7] Resubjection of **15** to the cyclization conditions gave **3**, indicating that **15** serves as an intermediate.


11 (88%)

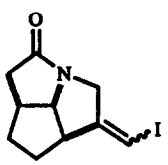

12 (90%)


13 (70%)


14 (70%)


15

Reductive cyclization of **11** similarly gave a mixture of tricyclic alkenes **16** and **17** (72% yield, 6:1), and as before, the iodides **16** could be completely converted to **17** by further tributyltin hydride treatment. The homologous iodo lactam **12** was cyclized to **18** in 62% yield. Iodo nitrile **13**, which might have been expected to cyclize to a ketone,[8] instead gave (after acid hydrolysis) a complex mixture of products lacking a ketone carbonyl stretch in the IR spectrum. Fraser-Reid has recently reported a very low yield for this type of cyclization.[9] Attempted cyclization of **14** gave only deiodinated lactam **19**, probably because the sp^2 lactam nitrogen resists formation of the strained tetracyclic product.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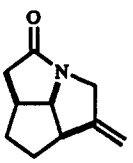
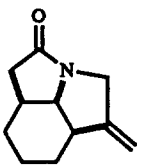

17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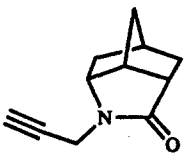
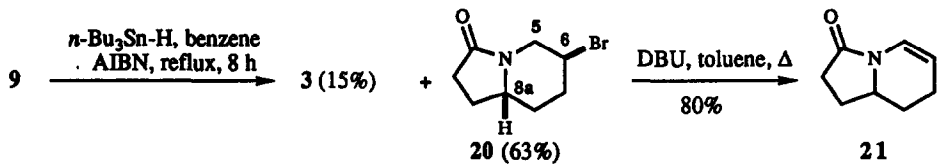
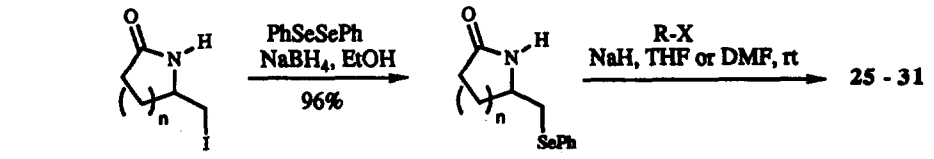

19

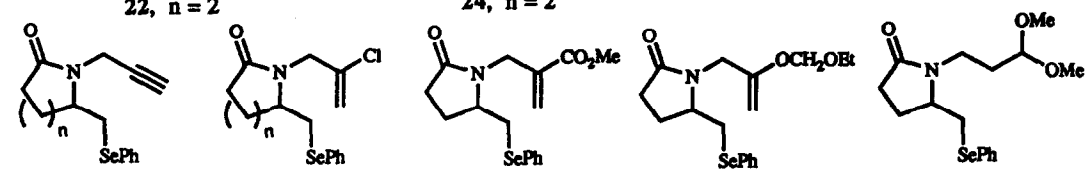
Cyclization of the vinyl bromide **9** presents an interesting case where a primary iodide must be selectively reduced in the presence of the secondary bromide of the expected product and the vinyl bromide of **9**. To our knowledge, no comparable cyclization has been reported in the literature. Treatment of **9** with tributyltin hydride as before gave a 1:4 mixture of two products: the familiar alkene **3**, and a single bromolactam to which we assign structure **20**.[10] Dehydrobromination of **20** gave the *N*-acyl-enamine **21**. Thus **9** has cyclized with good site selectivity and excellent stereoselectivity. The preference for formation of the indolizidinone product may be attributed to the steric bulk and radical stabilizing properties of the bromine atom,[11] and to the greater strain in the alternative pyrrolizidinone ring system. The *exo* stereochemistry of the bromo substituent in **20** results from pseudo-axial hydrogen atom transfer to the intermediate α-bromo radical. Bromide **20** has the skeleton and functionality suggestive of the indolizidine slaframine.[12]



20 (63%) 21

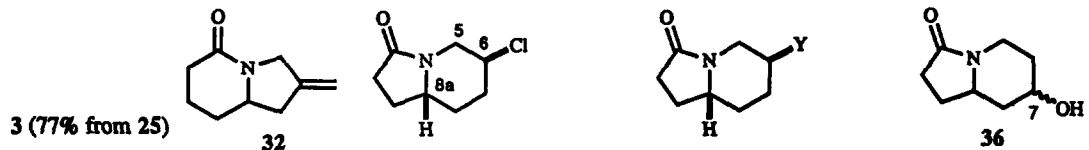
The instability of iodo lactams toward the alkylation conditions can be circumvented in certain cases by use of the corresponding phenylselenides. Although we have not yet been able to achieve a high yielding "selenolactamization"[13] of unsaturated *N,O-bis*(trimethylsilyl)imidates, selenide lactams **23** and **24** are nevertheless available in high yield from iodo lactam **1** and its piperidone analogue **22** by S_N2 displacement of iodide. Alkylation of **23** and **24** through their respective sodium salts occurred without significant decomposition of the anions, and a variety of alkyl halides gave the *N*-alkyl selenide lactam products (**25** - **31**) in the yields shown. 4-Butynyl iodide and triflate gave no alkylated product, presumably because of competing E2 reaction.





Free radical initiated cyclization of the selenide lactam substrates was carried out under the previously defined conditions, except that 12 h of reflux was typically required for disappearance of starting material (TLC analysis). The *N*-propargyl substrates **25** and **26** gave the alkenes **3** and **32**, respectively, in the yields shown, without evidence of a competing atom transfer process. The *N*-chlorallyl lactam **27** gave the chloroindolizidinone **33** as a single isomer whose structure[14] was assigned by analogy to **20**; very little pyrrolizidinone **3** was formed. In apparent contradiction to the guideline[15] offered by Jorgensen, *abstraction of the divalent selenium atom is clearly preferred over abstraction of the monovalent chloride* in either starting material or product. Curiously, the homologous substrate **28** gave only the alkene **32**, whose formation could be attributed to the greater rate of radical cyclization to the five membered ring in this case where forming the strained pyrrolizidinone ring system is not an option.

Cyclization of **29** and **30** afforded the *exo* indolizidine ester **34** and ether **35**, respectively.[16] The aldehyde derived[17] from **31** (aq TFA, $CHCl_3$, rt, 90%) was cyclized to a mixture of indolizidinone alcohols **35**, which were characterized as the corresponding acetates. ^1H NMR analysis[18] indicated a 2:3 *exo:endo* ratio of isomers, an unsurprising result for kinetically controlled cyclization to an aldehyde carbon.[19]



In summary, iodo lactams provide one- to three-step access to substrates, some of them unusual, for free radical initiated cyclization. The resulting pyrrolizidinones and indolizidinones possess useful functionality for further transformations and application to alkaloid total synthesis.

Acknowledgments: We are grateful to the Charles and Johanna Busch Memorial Fund for financial support of this work, and NSF grant CHEM-8300444 and NIH grant 1510RRO1486 for support of instrumentation.

References and Notes

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2. For example, treatment of iodo lactams with sodium hydride in DMF results in the formation of an *N*-acylaziridine, which in certain cases can be isolated or intercepted with nucleophiles. (a) Knapp, S.; Levorse, A. T. *Tetrahedron Lett.* **1987**, *28*, 3213. (b) Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006.
3. Recent reviews: (a) Critch, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413. (b) Curran, D. P. *Synthesis* **1988**, 417 and 489. (c) Giese, B. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 969.
4. Although we have seen efficient bromocyclization on nitrogen of a silylated *N*-(1-phenethyl)-amide, the bulkiness of the phenethyl substituent in this case may have been responsible for apparent silylation on the oxygen atom. See Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4773.
5. Several experiments involving modifying the silylating reagent failed to improve the apparent extent of *O*-silylation (and thus *N*-cyclization) for **4**. For example, use of the bulky silylating agent triisopropylsilyl triflate, or the "harder" electrophile dimethoxy(methyl)silyl triflate, did not significantly improve the product ratio of iodo lactam to iodo lactone.
6. Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943. See also Keusenkothen, P. F.; Smith, M. B. *Tetrahedron Lett.* **1989**, *30*, 3369, and references therein.
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9. Yeung, B.-W. A.; Contelles, J. L. M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1989**, 1160.
10. Compound **20**: CI-MS 218 ($M^+ + 1$); IR (film) 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 4.49 (ddd, 1 H, J = 12.9, 5.1, 2.0, H_{5endo}), 3.80 (tt, 1 H, J = 11, 4, H_6), 3.44-3.53 (m, 1 H, H_{8a}), 2.87 (t, 1 H, J = 12.1, H_{5exo}).
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12. Elbein, A. D.; Molyneux, R. J. *Alkaloids: Chemical and Biochemical Perspectives, Vol. 5*, Pelletier, S. W., Ed.; John Wiley and Sons: New York, 1987, pp 1-49.
13. Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321. See pp 3385-3387 in particular.
14. Compound **33**: CI-MS 174 ($M^+ + 1$); ^1H NMR (400 MHz, $CDCl_3$) 4.43 (ddd, 1 H, J = 12.9, 5.1, 2.0, H_{5endo}), 3.71 (tt, 1 H, J = 11.4, 4.3, H_6), 3.42-3.49 (m, 1 H, H_{8a}), 2.71 (t, 1 H, J = 12.0, H_{5exo}).
15. Laird, E. R.; Jorgensen, W. L. *J. Org. Chem.* **1990**, *55*, 9.
16. Compound **34**: IR (film) 1732, 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 4.35 (ddd, 1 H, J = 12.9, 4.3, 1.6, H_{5endo}), 3.71 (s, 3 H, CO_2Me), 3.32-3.47 (m, 1 H, H_{8a}), 2.71 (dd, 1 H, J = 12.2, 12.9, H_{5exo}). A related *endo*-indolizidinone-6-carboxylate showed H_{5endo} as a *doublet* (J = 13.8): Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 7065 (compound **13** therein). Compound **35**: IR (film) 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 4.71 (app t, 2 H, J = 6.8, OCH_2O), 4.32 (ddd, 1 H, J = 12.6, 5.3, 1.8, H_{5endo}), 3.58 (app qd, 2 H, J = 7.1, 2.5, OCH_2CH_3), 2.46 (t, 1 H, J = 11.5, H_{5exo}).
17. Ellison, R. A.; Lukenbach, E. R.; Chiu, C.-W. *Tetrahedron Lett.* **1975**, 499.
18. Acetates of **35** (as mixture): CI-MS 198 ($M^+ + 1$); IR (film) 1732, 1682 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 5.16 (br s, 1 H, H_{7exo}, major isomer), 4.82 (td, 1 H, J = 12, 5, H_{7endo}, minor isomer), 4.16 (app dt, 1 H, J = 14, 2, H_{5exo}, minor isomer), 3.99 (dd, 1 H, J = 13, 5.5, H_{5exo}, major isomer), 2.06 (s, 3 H, $COCH_3$, major isomer), 2.02 (s, 3 H, $COCH_3$, minor isomer).
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