

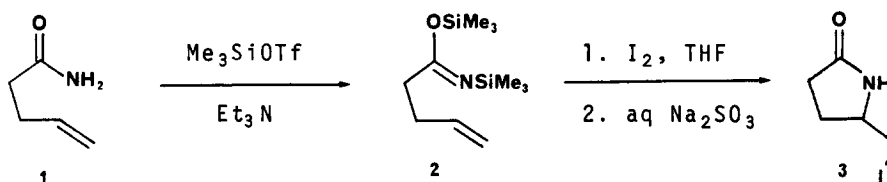
A PROCEDURE FOR "IODOLACTAMIZATION"

Spencer Knapp*, Karen E. Rodriques,
Anthony T. Levorse, and Raphael M. Ornaf

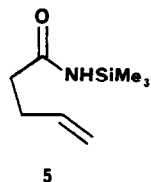
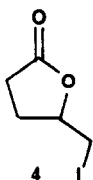
Department of Chemistry
Rutgers, The State University of New Jersey
New Brunswick, New Jersey 08903 USA

Summary: Treatment of an unsaturated amide with TMS-OTf, then iodine in THF gives the iodolactam.

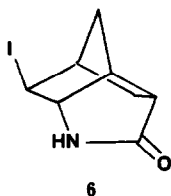
We have developed a method for iodocyclization of an amide nitrogen onto a carbon-carbon double bond.^{1,2} As an example, conversion of 4-pentenamide (1) to its N,O-bis(trimethylsilyl) derivative 2,³ followed by treatment of 2 with a THF solution of iodine and aqueous sodium sulfite quench gave the iodolactam 3 in 64% overall yield.



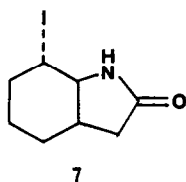
Prior conversion of 1 to the imidate derivative 2 is necessary for N-cyclization, since direct iodocyclization of 1 gave only the iodolactone 4. The monosilylated derivative 5 also gave 4 upon iodocyclization, whereas 4 was not produced from 2. No products from Hofmann rearrangement were observed, and n-octanamide was recovered uncontaminated after bis-silylation, iodine treatment, and sulfite quench.



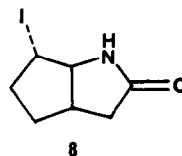
Using this procedure several other unsaturated amides were converted to the corresponding iodolactams 6-10 in 52-68% yield (shown below). All the γ -lactams show the characteristic carbonyl absorption at about 1680 cm^{-1} . Stereochemistry is assigned by analogy to the corresponding iodolactonization⁴ reactions. In the cases



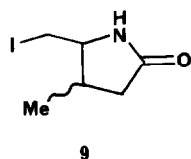
63%, mp 120° (subl)



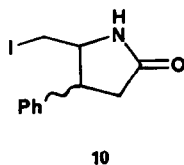
68%, mp $115-116^\circ$



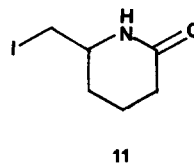
63%, mp $138.5-139^\circ$



58%, t:c = 11:1

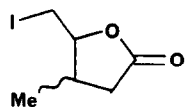


52%, t:c = 22:1



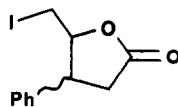
35%, mp $157.5-158^\circ$

of 9 and 10, the trans:cis ratios (based on isolated yields) closely match those of the related lactones 12 and 13, obtained by Bartlett using "thermodynamic" conditions (iodine in acetonitrile).⁵ Thus the trans:cis ratios observed for 9 and 10 probably also reflect the relative stabilities of the respective stereoisomers.



12

t:c = 10:1

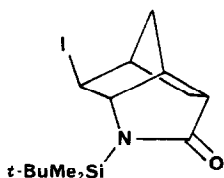


13

t:c = 20:1

3-Butenamide could not be cyclized to 4-iodomethyl-azetidino-2-one by this sequence. Instead, crotonamide was isolated in 55% yield. Although 5-hexenamamide was cyclized successfully to 11, the yield was reduced by partial reversion of 11 to starting material during chromatography. Once purified, however, all the iodolactams could be stored at 25° and did not decompose or revert to the unsaturated amide.

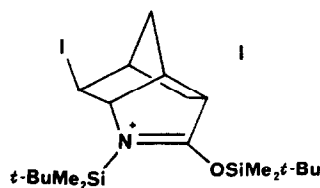
In addition to the iodolactam, 4-iodobutanol was also isolated from the product mixtures, suggesting that tetrahydrofuran becomes silylated during the course of the iodocyclization reaction. To test this idea, 5-norbornene-2-carboxamide was bis-silylated using $t\text{-BuMe}_2\text{Si-OTf}$,⁶ and the reaction with iodine was carried out in the usual way. After aqueous sodium bisulfite quench, the products isolated by chromatography were the N-silylated iodolactam 14 (62%) and O-silylated iodobutanol 15 (97%). We therefore propose that the iodocyclization reaction proceeds through an iminium species, in this case 16, which transfers trialkylsilyl from oxygen to the oxygen of THF prior to the quench. Analogous iminium salt intermediates have been isolated from other halocyclizations.^{1,7} Also pertinent is the observation that iodocyclization of 2 to 3 is less successful when pentane, dichloromethane, toluene, or acetonitrile is used as the solvent.



14



15



16

General Procedure for Iodolactamization. For a 1-2 mmol scale, a solution of 1 equiv of the unsaturated amide and 2.2 equiv of triethylamine in dichloromethane was treated under an argon atmosphere with 2.0 equiv of trimethylsilyl triflate and one crystal of 4-(dimethylamino)-pyridine. After 15 min the infrared spectrum of an aliquot showed no N-H bands in the region 3200-3600 cm^{-1} . The dichloromethane was carefully removed at aspirator pressure, and the yellow residue was washed three times with pentane under argon. The pentane extracts, which contain the N,O-bis-silylated amide, were transferred to another flask, and the pentane was removed at aspirator pressure. A solution of 2.0 equiv of iodine in THF was added under argon, and the resulting solution was stirred for 10 min. The reaction was quenched with aqueous sodium sulfite and extracted with dichloromethane. The organic solution was dried with sodium sulfate, concentrated, and chromatographed on silica without delay to afford the pure iodolactam.

Acknowledgments. We are grateful to the Public Health Service (grant number AI-18703) for financial support of this work.

References and Notes

- For recent related olefin cyclization reactions see ref. 2 and the following: (a) Knapp, S.; Patel, D.V. J. Amer. Chem. Soc. 1983, 105, 6985. (b) Knapp, S.; Patel, D.V. J. Org. Chem. 1984, 49, 5072.
- (a) Biloski, A.J.; Wood, R.D.; Ganem, B. J. Amer. Chem. Soc. 1982, 104, 3233. (b) Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. Tetrahedron Lett. 1984, 25, 1063. (c) Webb, R.R.; Danishefsky, S. ibid. 1983, 23, 1357. (d) Aida, T.; Legault, R.; Dugat, D.; Durst, T. ibid. 1979, 20, 4993. (e) Harding, K.E.; Burks, S.R. J. Org. Chem. 1984, 49, 40. (f) Barluenga, J.; Jimenez, C.; Najera, C.; Yus, M. J. Chem. Soc., Chem. Commun. 1981, 1178. (g) Clive, D.L.J.; Wong, C.K.; Kiel, W.A.; Menchen, S.M. ibid. 1978, 379. (h) Toshimitsu, A.; Terao, K.; Uemura, S. Tetrahedron Lett. 1984, 25, 5917.
- Yoder, C.H.; Copenhafer, W.C.; DuBeshter, B. J. Amer. Chem. Soc. 1974, 96, 4283.
- For leading references on iodolactonization see Chamberlin, A.R.; Dezube, M.; Dussault, P.; McMills, M.C. ibid. 1983, 105, 5819.
- Bartlett, P.A. Tetrahedron 1980, 36, 2.
- Corey, E.J.; Cho, H.; Rucker, C.; Hua, D.H. Tetrahedron Lett. 1981, 22, 3455.
- Winstein, S.; Goodman, L.; Boschan, R. J. Amer. Chem. Soc. 1950, 72, 2311.

(Received in USA 28 December 1984)