

Highly Selective Iodine-Induced Lactam Formation from γ,δ -Unsaturated Thioimidates. New Entry to Functionalized γ -Lactams

Hiroki Takahata,*^a Tamotsu Takamatsu,^a Mayumi Mozumi,^a Yin-Shan Chen,^a Takao Yamazaki,*^a and Keiichi Aoe^b

^a Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan.

^b Analytical Center, Tanabe Seiyaku Co. Ltd., Toda, Saitama 335, Japan

Iodine-induced lactam formation from γ,δ -unsaturated thioimidates proceeds regio- and stereo-selectively, providing highly functionalized γ -lactams.

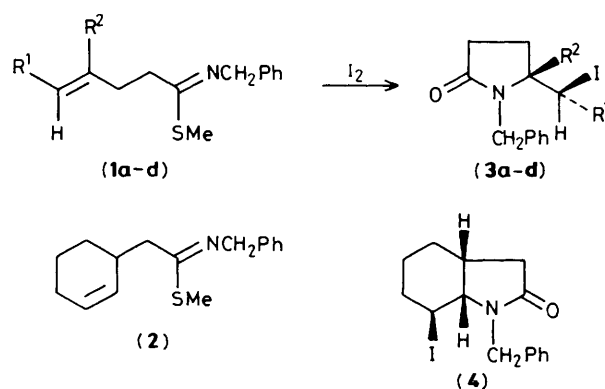
Electrophilic alkene cyclization processes that form carbon-heteroatom bonds are of growing importance, particularly in the regio- and stereo-selective synthesis of heterocycles leading to biologically active natural products.¹ Here we describe attractive examples of 1,2-*cis*- and 1,3-*trans* asymmetric induction using iodine-induced lactamization in β -hydroxy or α -alkyl substituted γ,δ -unsaturated thioimide systems.

Although halogenolactonization is a well established important synthetic tool, the analogous lactamization has been less studied.² We found that γ,δ -unsaturated thioimidates underwent regioselective iodine-induced cyclization to afford γ -lactams. The present iodolactamization of (1a-d) and (2) can be performed by using I₂ in tetrahydrofuran (THF) at ambient temperature (see Table 1).[†] The reaction proceeded diastereoselectively to give a single isomer (entries 2, 3, and 5).[‡] In each reaction, no trace of six-membered rings such as piperidone derivatives were detected. Consequently this cyclization proceeded regioselectively (5-*exo-trig* process).³

Having obtained these results, we were interested in the iodolactamization of β -hydroxy or α -alkyl substituted γ,δ -unsaturated thioimidates. First the iodolactamization of β -hydroxy- γ,δ -unsaturated thioimidates (5)–(7) was carried

out (Table 2).[†] It was predicted that the configuration of the major diastereoisomer (8a) would be 4,5-*cis* owing to the 1,2-*cis* directing ability of the iodonium ion and the hydroxy

Table 1. Iodolactamization of γ,δ -unsaturated thioimidates (1a-d) and (2).^a

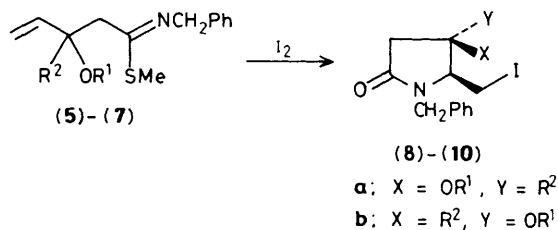


Entry	Thioimide	R ¹ R ²		Product ^b	Yield ^c (%)
		R ¹	R ²		
1	(1a)	H	H	(3a)	72
2	(1b)	Ph	H	(3b)	32
3	(1c)	Me	H	(3c)	51
4	(1d)	H	Me	(3d)	56
5	(2)			(4)	63

[†] All new compounds described herein gave satisfactory combustion or high resolution mass spectral and spectral data consistent with their structures.

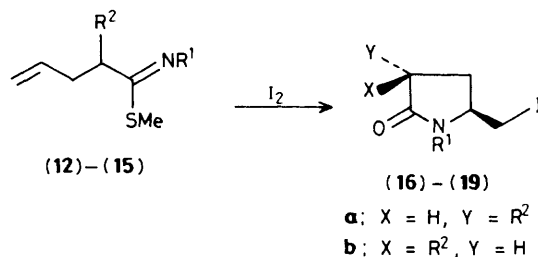
[‡] A wealth of examples in cyclic systems have demonstrated that the addition of electrophile and nucleophile to the double bond is *anti*.¹ Based on these examples, the stereochemistries of (3b), (3c), and (4) were determined. Selected spectral data of (3b): ν_{\max} (neat) 1680 cm^{-1} (C=O); δ_{H} (270 MHz) 1.84–3.00 (m, 4H), 3.25 (m, 1H, C-5-H), 3.68 and 5.17 (ABq, each 1H, *J* 15.2 Hz, CH₂Ph), 5.40 (d, 1H *J* 4.6 Hz, ICHPh), 7.38 (m, 10H); *m/z* 391 (*M*⁺).

^a Reaction conditions; I₂ (1.5 equiv.), solvent (0.1 mole), ambient temperature for 1 day, and aq. Na₂SO₃ as quenching reagent. ^b In the i.r. spectra carbonyl absorptions appeared at 1680 cm^{-1} which indicated the five-membered ring lactam structure. ^c Isolated yields.

Table 2. Iodolactamization of β -hydroxy- γ,δ -unsaturated thioimidates (5)–(7).^a

Entry	Thioimide	R ¹	R ²	Product	Yield ^b (%)	Ratio (a:b) ^c
1	(5)	H	H	(8a,b)	61	12:1
2	(6)	Bu ^t Me ₂ Si	H	(9a,b) ^d	56	7:1
3	(7)	H	Me	(10a,b) ^e	40	10:1

^a Reaction conditions; I₂ (1.5 equiv.), tetrahydrofuran (0.02 mole), at ambient temperature for 1 day. ^b Yield for the two steps from the γ,δ -unsaturated secondary thioamide. ^c Product ratios were determined by ¹H n.m.r. spectroscopy (270 MHz). ^d Spectral data of (9a) were consistent with those of the sample prepared by *t*-butyldimethylsilylation of (8a). ^e Stereochemistry tentative.

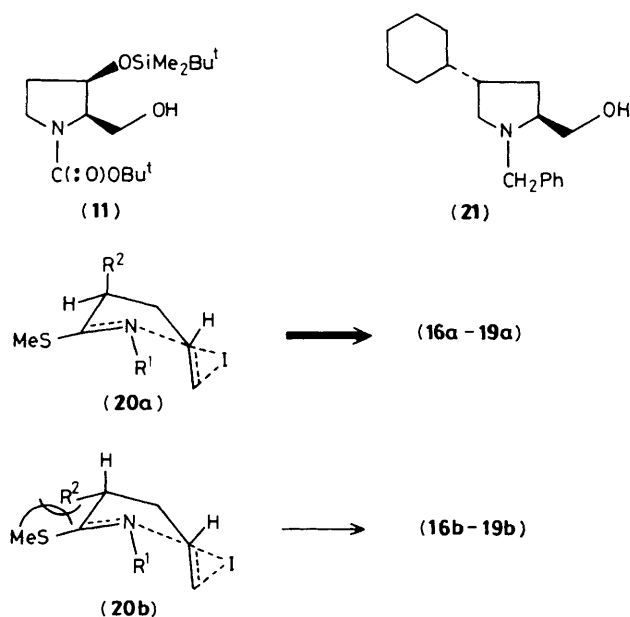
Table 3. Iodolactamization of α -alkyl- γ,δ -unsaturated thioimidates (12)–(15).^a

Entry	Thioimide	R ¹	R ²	Product	Yield (%)	Ratio (a:b)
1	(12)	Ph	Me	(16a,b)	69	6:1 ^b
2	(13)	CH ₂ Ph	Me	(17a,b)	48	12:1 ^c
3	(14)	CH ₂ Ph	Cyclohexyl	(18a,b)	42	13:1 ^c
4	(15)	CH ₂ Ph	Ph	(19a,b)	48	14:1 ^c

^a Reactions were carried out under conditions described in Table 2. ^b Ratio of isolated products. ^c Ratio determined by ¹H n.m.r. spectroscopy (270 MHz).

group in the transition state of this cyclization.⁴ Its stereochemistry was determined by a stereocontrolled transformation[§] of (8a) into the key intermediate (11) of (–)-detoxinine.^{5,6} Spectral data (¹H n.m.r. and i.r.) of (11) thus obtained were identical with those of an authentic sample.⁶

In view of the conformational flexibility of the five-membered ring transition state, the stereocontrol due to the homoallylic substituent is not expected to be high in contrast to the control shown by the allylic substituent as shown above. Fortunately, a high 1,3-*trans* selectivity in the iodolactamization of α -alkyl- γ,δ -unsaturated thioimidates (12)–(15) was observed (Table 3).[†] This interesting *trans*-stereoselectivity may be rationalized as follows. Among possible cyclic transition states, the most likely one, the 1,3-di-*quasi*-equatorial transition state (20b), may be discounted owing to A(1,2) strain⁷ between R² and the methylthio group. This strain forces the substituent R² to take a *quasi*-axial orientation and hence the iodomethyl group a *quasi*-equatorial orientation as in transition state (20a). The structure of (16a) was confirmed by X-ray crystallographic analysis.[§] Furthermore, compound



[§] Details will be described in a full paper.

(18a) was converted into the racemic intermediate (21)§¶ of *trans*-4-cyclohexyl-L-proline,⁸ which is a constituent of fosenopril (angiotensin converting enzyme inhibitor).⁹

In summary, this iodolactamization of γ,δ -unsaturated thioimidates exhibited good 1,2- and 1,3-asymmetric induction in the formation of γ -lactams. The present method provides a new and promising access to highly functionalized pyrrolidines, which should be convertible into related biologically active compounds such as alkaloids.

We thank Professor M. M. Joullie (University of Pennsylvania) for spectra of (11) and the Ministry of Education, Science and Culture for partial financial support.

Received, 2nd June 1987; Com. 756

¶ The ¹³C n.m.r. spectrum of (21) was consistent with that of the reported sample.⁸

References

- 1 P. A. Bartlett, 'Asymmetric Synthesis', ed. J. D. Morrison, Academic Press, Orland, 1984, Vol 3, Part B, p. 411; H. Takahata, K. Moriyama, M. Maruyama, and T. Yamazaki, *J. Chem. Soc., Chem. Commun.*, 1986, 1671.
- 2 J. J. Biloski, R. D. Wood, and B. Ganem, *J. Am. Chem. Soc.*, 1982, **104**, 3233; G. Rajendara and M. J. Miller, *Tetrahedron Lett.*, 1985, **26**, 5385; S. Knapp, K. E. Roliques, A. T. Levorse, and M. Ornaf, *ibid.*, 1985, **26**, 1803; S. Kano, T. Yokomatsu, H. Iwasawa, and S. Shibuya, *Heterocycles*, 1987 **26**, 359.
- 3 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.
- 4 A. R. Chamberlin, R. L. Mulholland, S. D. Kahn, and W. J. Hehre, *J. Am. Chem. Soc.*, 1987, **109**, 672.
- 5 Y. Ohfuné and H. Nishio, *Tetrahedron Lett.*, 1984, **25**, 4133.
- 6 W. R. Ewing, B. D. Harris, K. L. Bhat, and M. M. Joullie, *Tetrahedron*, 1986, **42**, 2421.
- 7 F. Johnson, *Chem. Rev.*, 1968, **68**, 375.
- 8 J. K. Thottathil, J. L. Moniot, R. H. Mueller, M. K. Y. Wong, and T. P. Kissick, *J. Org. Chem.*, 1986, **51**, 3140.
- 9 M. J. Wyvratt and A. A. Patchett, *Med. Res. Rev.*, 1985, **5**, 483.