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

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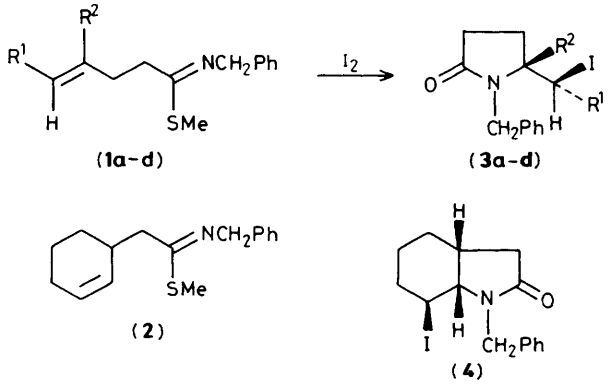
Iodine-induced lactam formation from γ,δ-unsaturated thioimidates proceeds regio- and stereo-selectively, providing highly functionalized γ-lactams.

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 thioimidate 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 I_2 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]



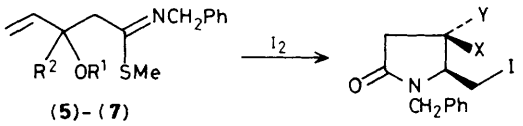
Entry	Thioimidate	R^1	R^2	Product[b]	Yield[c] (%)
1	(**1a**)	H	H	(**3a**)	72
2	(**1b**)	Ph	H	(**3b**)	32
3	(**1c**)	Me	H	(**3c**)	51
4	(**1d**)	H	Me	(**3d**)	56
5	(**2**)			(**4**)	63

[a] Reaction conditions; I_2 (1.5 equiv.), solvent (0.1 mole), ambient temperature for 1 day, and aq. Na_2SO_3 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.

† 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, CH_2Ph), 5.40 (d, 1H *J* 4.6 Hz, IC*H*Ph), 7.38 (m, 10H); *m/z* 391 (M^+).

Table 2. Iodolactamization of β-hydroxy-γ,δ-unsaturated thioimidates (**5**)—(**7**).[a]



(**5**)–(**7**) (**8**)–(**10**)

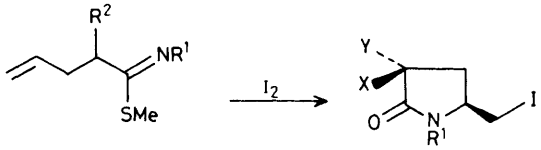
a; X = OR^1, Y = R^2

b; X = R^2, Y = OR^1

Entry		Thioimidate R^1	R^2	Product	Yield[b] (%)	Ratio (**a**:**b**)[c]
1	(**5**)	H	H	(**8a,b**)	61	12:1
2	(**6**)	Bu^tMe_2Si	H	(**9a,b**)[d]	56	7:1
3	(**7**)	H	Me	(**10a,b**)[e]	40	10:1

[a] Reaction conditions; I_2 (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 ^{1}H 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]



(**12**)–(**15**) (**16**)–(**19**)

a; X = H, Y = R^2

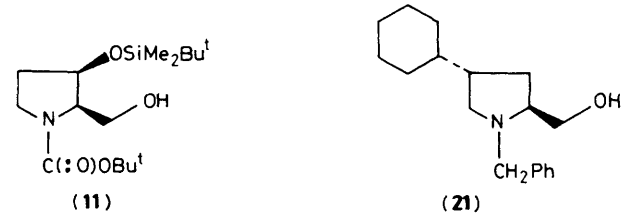
b; X = R^2, Y = H

Entry		Thioimidate R^1	R^2	Product	Yield (%)	Ratio (**a**:**b**)
1	(**12**)	Ph	Me	(**16a,b**)	69	6:1[b]
2	(**13**)	CH_2Ph	Me	(**17a,b**)	48	12:1[c]
3	(**14**)	CH_2Ph	Cyclohexyl	(**18a,b**)	42	13:1[c]
4	(**15**)	CH_2Ph	Ph	(**19a,b**)	48	14:1[c]

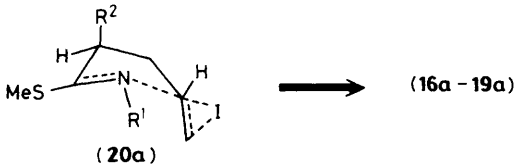
[a] Reactions were carried out under conditions described in Table 2. [b] Ratio of isolated products. [c] Ratio determined by ^{1}H n.m.r. spectroscopy (270 MHz).

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 (^{1}H n.m.r. and i.r.) of (**11**) thus obtained were identical with those of an authentic sample.[6]

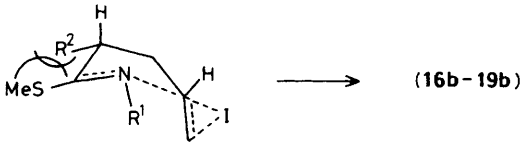
In view of the conformational flexibility of the five-membered ring transition state, the stereocontrol due to the homoallylic substituent is not expected to be high in contrast to the control shown by the allylic substituent as shown above. Fortunately, a high 1,3-*trans* selectivity in the iodolactamization 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) strain[7] between R^2 and the methylthio group. This strain forces the substituent R^2 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



(**11**) (**21**)



(**20a**) (**16a**–**19a**)



(**20b**) (**16b**–**19b**)

§ 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.

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¶ The ^{13}C n.m.r. spectrum of (**21**) was consistent with that of the reported sample.[8]

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