ELECTROPHILIC OLEFIN HETEROCYCLIZATION IN ORGANIC SYNTHESIS. FORMATION OF δ-LACTAMS BY IODINE-INDUCED LACTAMIZATION OF δ,ε-UNSATURATED THIOIMIDATES

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Abstact-The diastereoselective iodine-induced lactamization of δ,ε-unsaturated thioimidates (**1**) accessible from allylation of a dianion of *N*-benzyl-3-phenylsulfonylpropionamide (**3**) followed by elaboration gave the substituted δ-lactams (**2**).

Activation of a double bond, by interaction with an electrophile , followed by cyclization of either an oxygen or nitrogen nucleophile (electrophilic olefin heterocyclization) provides a flexible entry into a range of substituted oxygen- or nitrogen-containing heterocycles.[1] In particular, considerable attention is focussed on the stereoselective synthesis of highly functionalized heterocycles leading to biologically active natural products.[2] In connection with our research objectives directed to development of the electrophile-mediated diastereoselective intramolecular aminocyclization, we have reported the highly stereoselective synthesis of γ-lactams *via* iodolactamization of γ,δ-unsaturated thioimidates.[3] In contrast to the formation of γ-lactams, the cyclization to δ-lactams has been less investigated.[4] Our interest has been therefore turned to the formation of δ-lactams by iodolactamization of δ,ε-unsaturated thioimidates. In this communication, we disclose the stereoselective iodine-induced lactamization of δ,ε-unsaturated thioimidates (**1**) available from allylation of a dianion of *N*-benzyl-3-phenylsulfonylpropionamide (**3**) followed by manipulation, providing the substituted δ-lactams (**2**).

Our synthesis of *N*-benzyl-5-hexenethioamides (**4**), precursors to **1**, began with allylation of the dianion generated from the amide (**3**) as a homoenolate anion.[5] Treatment of the dianion,[6] generated from **3** by action of 2.2 equiv. of n-butyllithium (n-BuLi), with allyl bromides (**5**) in THF at -40 °C for 15 h afforded the allylated products (**6a-e**). The substituted compounds (**6f,g**) were prepared by treatment of *N*-benzyl-3-(phenylsulphonyl)-5-hexenamide (**6a**) with 2.2 equiv. of n-BuLi followed by alkylation. Desulfonylation of **6** was carried out with the Trost's condition[7] (sodium amalgam in the presence of disodium hydrogen phosphate) to afford the amides (**7**), which without purification were converted to the thioamides (**4**) by thionation with the Lawesson reagent.[8] The results are summarized in Table 1.[9,10]

Scheme 1

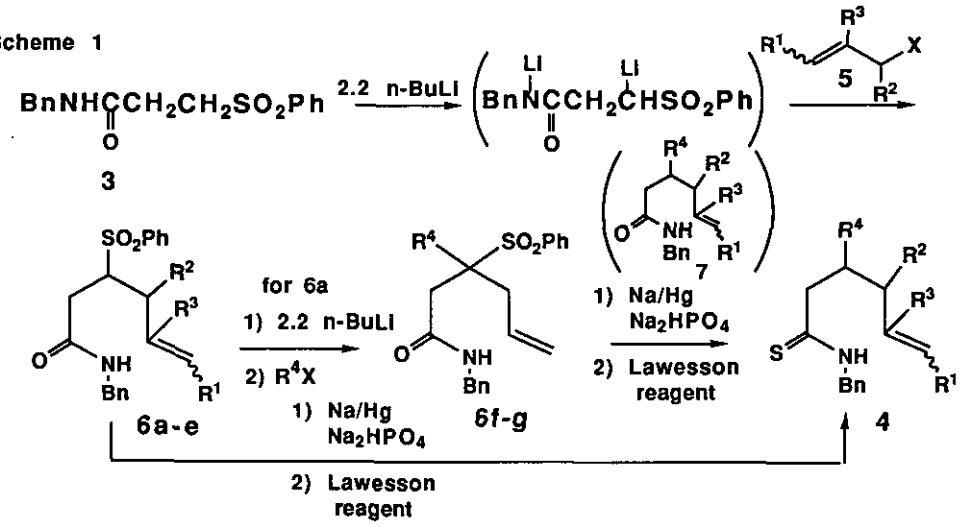


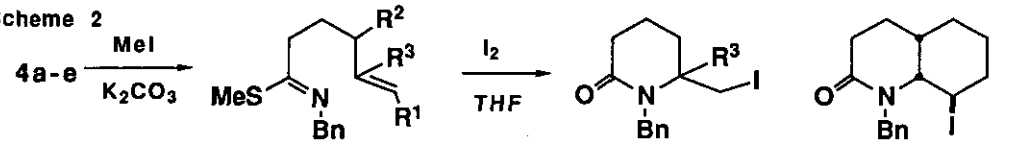
Table 1 Preparation of **6** and **4**

No	R^1	R^2	R^3	R^4	**6** (Yield %)	**4** (Yield %)[a]
a	H	H	H	H	83	88
b	H	H	Me	H	85	58
c	-$(CH_2)_4$-		H	H	35	67
d	Me	H	H	H	61	77
e	Ph	H	H	H	65	62
f	H	H	H	Me	68[b]	86
g	H	H	H	Bn	84[b]	52
h	H	H	H	SO_2Ph	--	89[c]

a Overall yields from **6** . b Yield from **6a** .
c Yield for thionation of **6a**.

The iodolactanmization of the δ,ε-unsaturated *N*-benzylthioimidate (**1a**), prepared from the secondary thioamide (**4a**) by methylation with methyl iodide in the presence of potassium carbonate, can be performed by using iodine in THF at 5 °C for 5 days to give the δ-lactam (**2a**)[10] regioselectively (6-exo-trigonal)[11] in 72% overall yield from **4a**. Similarly, the thioimidates (**1b,c**) underwent the iodolactamization to afford the δ-lactams(**2b,c**).[10] However, the iodolactamization of **1d,e**, the imidates having substituents at the olefinic terminal, was unsuccessful.[12]

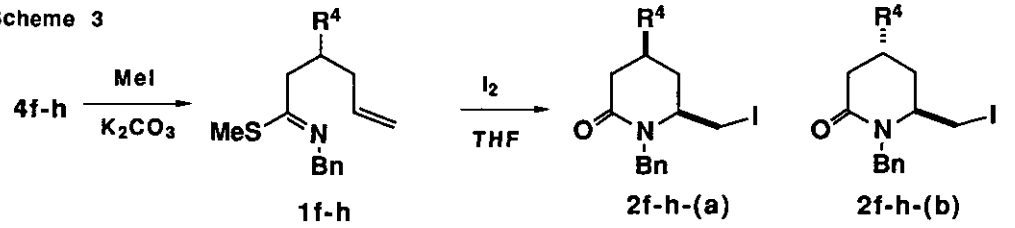
Scheme 2



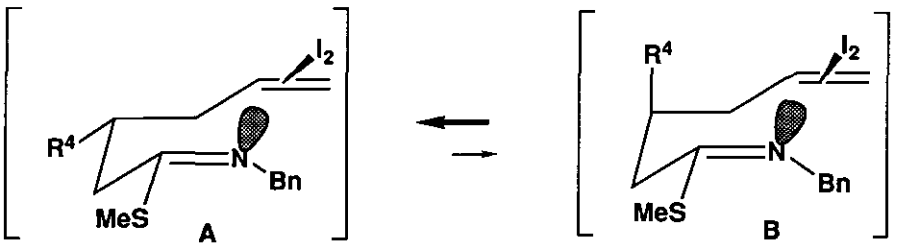
1a-e **2a** (72%) **2b** (61%) **2c** (32%)

Next, the iodolactamization of the β-substituted δ,ε-unsaturated thioimidates (**1f-h**) provided diasteromeric mixtures of δ-lactams [**2f-(a,b)-2h-(a,b)**],respectively, with relative 1,3-asymmetric induction as shown in Table 2 (Scheme 3).[10] Assuming that conformer A with minimum nonbonded interaction is more favored than conformer B with the trans relationship between β-substituents (R^4) and I_2-alkene complex in transition states, it is expected that the configuration of the major diastereomer would be of 4,6-cis. In fact, the trans assignment for the minor product [**2f-(b)**] was confirmed by X-ray crystallographic analysis.[13,14]

Scheme 3



1f-h **2f-h-(a)** **2f-h-(b)**



(a) cis **(b) trans**

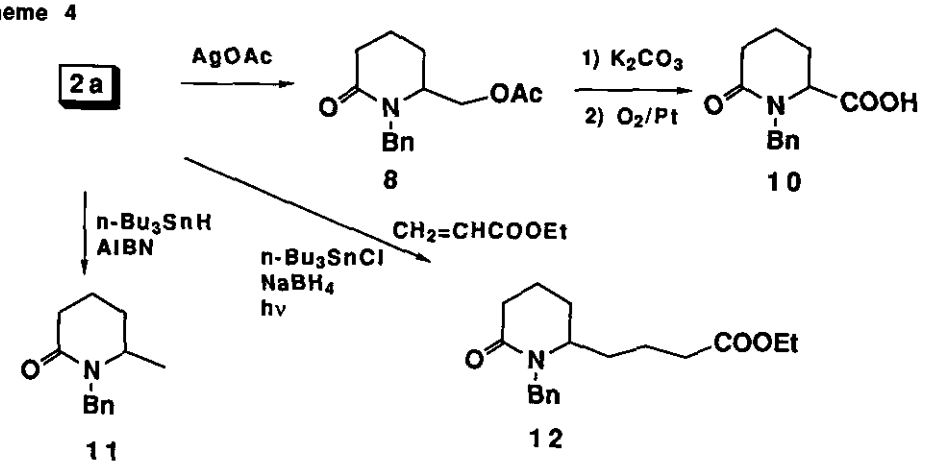
Table 2. Iodolactamization of **1f-h**

Product	(a) Yield (%)[a]	(b) Yield (%)[a]	ratio (a:b)
2f	56	4.1	14:1
2g	63	5.3	12:1
2h	24	6.0	4:1

a Overall yields from **4** are shown.

We turned our attention to the chemical behavior of the iodo lactam (**2a**) as shown in Scheme 4. At the begining, the displacement of the iodine in **2a** by an oxygen nucleophile using silver acetate in DMF was carried out to afford the acetate (**8**),[3,15] which was transformed into the lactam acid (**10**)[10] by alkaline hydrolysis followed by oxidation[16] with oxygen in the presence of platinum in 45% overall yield from **2a**. The radical reduction[17] of **2a** with n-Bu3SnH in the presence of AIBN gave the lactam(**11**)[10] in 67% yield. The radical propagation of **2a** with ethyl acrylate by Giese's procedure[18] (Bu_3SnCl, $NaBH_4$, hv) was performed to provide the ester lactam (**12**)[10] in 56% yield.

Scheme 4



In summary, this work has demonstrated an expedient preparation of δ,ε-unsaturated thioamides and the formation of substituted δ-lactams by diastereoselective iodolactamization of δ,ε-unsaturated thioimidates. The present procedure provides a new access to functionalized piperidones, which should be convertible into piperidine alkaloids[19] such as coniine and solenopsin. Further investigation is currently ongoing.

ACKNOWLEDGMENT

We acknowledge partial financial support from the Ministry of Education, Sciences an Culture, the Japanese Goverment.

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9. The thioamides (**4a,b**) have been prepared by another procedure: H. Takahata, E. Ohkura, K. Ikuro, and T. Yamazaki, *Synth. Commun.*, **1990**, *20*, 285.
10. All new compounds described herein gave satisfactory combustion or high resolution mass (HRms) spectral data consistent with their structures.

    Some selected data: **2a**: an oil; ir (neat) 1640 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.80 (m, 4 H), 2.14 (m, 2 H), 3.29 (m, 2H), 3.43 (m, 1 H), 4.03, 5.42 (ABq, *J*=15.0 Hz, each 1 H), 7.38 (m, 5 H); HRms calcd $C_{13}H_{16}NOI$ 329.0278, found 329.0263.

    2f-(a), an oil ir (neat) 1640 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.02 (d, *J*=6.1 Hz, 3 H), 1.41 (m, 1 H), 1.94 (m, 2 H), 2.10 (m, 1 H), 2.56 (m, 1 H), 3.12 (m, 2 H), 3.40 (m, 1 H), 3.84, 5.59 (ABq, *J*=15.6 Hz, each 1 H), 7.27 (m, 5H); HRms calcd $C_{14}H_{18}NOI$ 343.0434, found 343.0434.

    2f-(b), mp 94-97 °C; ir (nujol) 1640 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.02 (d, *J*=6.1 Hz, 3 H), 1.52 (m, 1 H), 2.02-2.26 (m, 2 H), 2.60 (m, 1 H), 3.16 (m, 1 H), 3.35 (m, 1 H), 3.52 (m, 1 H), 3.98, 5.34 (ABq, *J*=15.1 Hz, each 1 H); Anal. Calcd for $C_{14}H_{18}NOI$ C, 48.99; H, 5.29; N, 4.08. Found, C, 49.22; H, 5.36; N, 3.92.

10, mp 189-194 °C; ir (nujol) 1705, 1640 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.81-2.67 (m, 5 H), 3.69, 5.60 (ABq, *J*=15.1 Hz, each 1 H), 4.03 (m, 1 H), 7.28 (m, 5 H); Anal. Calcd for $C_{13}H_{15}NO_3$ C, 66.94; H, 6.48; N, 6.00. Found, C, 66.61; H, 6.45; N, 6.02.

12; an oil; ir (neat) 1735, 1640 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.24 (t, *J*=9 Hz, 3 H), 1.32-2.54 (m, 12 H), 3.92, 5.42 (ABq, *J*=15.0 Hz, each 1 H), 4.26 (q, *J*=7.6 Hz, 2 H), 7.31 (m, 5 H); HRms calcd $C_{18}H_{25}NO_3$ 303.1833, found 303.1833.

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12. After work up, the amides (**7d, e**) were recovered.
13. Details will be described in a full paper.
14. The stereochemistry of **2g** and **2h** is estimated in the light of both the mechanism and chemical shift data for the methylene protons of *N*-benzyl groups in the ^1H nmr spectra. The value (3.84, 5.59, ABq) of the signal for methylene of 4,6-*cis* -**2f-(a)** rsembles to those [(3.78, 5.60, ABq) for **2g-(a)** and (3.83, 5.50, ABq) for **2h-(a)**] of the major isomers. Similarly, its value (3.98, 5.34, ABq) of 4,6-*trans*-**2f-(b)** is nearly consistent with those [(3.98, 5.35, ABq) for **2g-(b)** and (3.99, 5.28, ABq) for **2h-(b)**] of the minor isomers.
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Received, 2nd December, 1991