

**ELECTROPHILIC OLEFIN HETEROCYCLIZATION IN ORGANIC SYNTHESIS.  
FORMATION OF  $\delta$ -LACTAMS BY IODINE-INDUCED LACTAMIZATION OF  $\delta,\epsilon$ -  
UNSATURATED THIOIMIDATES**

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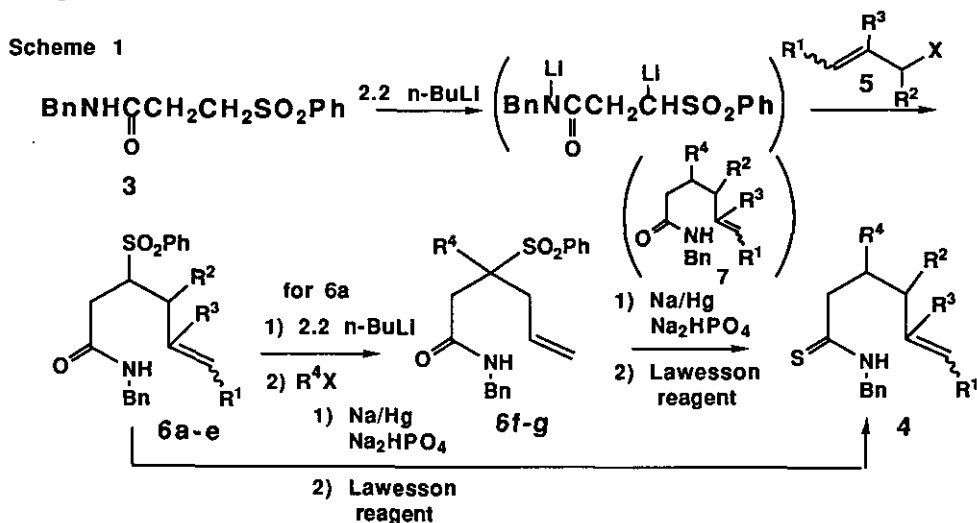
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**Abstract**-The diastereoselective iodine-induced lactamization of  $\delta,\epsilon$ -unsaturated thioimidates (**1**) accessible from allylation of a dianion of *N*-benzyl-3-phenylsulfonylpropionamide (**3**) followed by elaboration gave the substituted  $\delta$ -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.<sup>1</sup> In particular, considerable attention is focussed on the stereoselective synthesis of highly functionalized heterocycles leading to biologically active natural products.<sup>2</sup> In connection with our research objectives directed to development of the electrophile-mediated diastereoselective intramolecular aminocyclization, we have reported the highly stereoselective synthesis of  $\gamma$ -lactams *via* iodolactamization of  $\gamma,\delta$ -unsaturated thioimidates.<sup>3</sup> In contrast to the formation of  $\gamma$ -lactams, the cyclization to  $\delta$ -lactams has been less investigated.<sup>4</sup> Our interest has been therefore turned to the formation of  $\delta$ -lactams by iodolactamization of  $\delta,\epsilon$ -unsaturated thioimidates. In this communication, we disclose the stereoselective iodine-induced lactamization of  $\delta,\epsilon$ -unsaturated thioimidates (**1**) available from allylation of a dianion of *N*-benzyl-3-phenylsulfonylpropionamide (**3**) followed by manipulation, providing the substituted  $\delta$ -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.<sup>5</sup> Treatment of the dianion,<sup>6</sup> 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<sup>7</sup> (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.<sup>8</sup> The results are summarized in Table 1.<sup>9,10</sup>



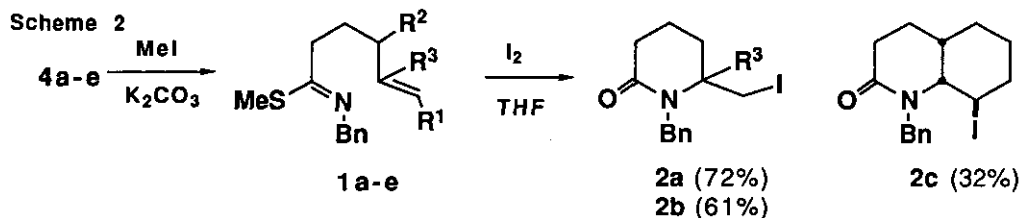
**Table 1** Preparation of **6** and **4**

No	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	<b>6</b> (Yield %)	<b>4</b> (Yield %) <sup>a</sup>
a	H	H	H	H	83	88
b	H	H	Me	H	85	58
c	-(CH <sub>2</sub> ) <sub>4</sub> -	H	H	H	35	67
d	Me	H	H	H	61	77
e	Ph	H	H	H	65	62
f	H	H	H	Me	68 <sup>b</sup>	86
g	H	H	H	Bn	84 <sup>b</sup>	52
h	H	H	H	SO <sub>2</sub> Ph	--	89 <sup>c</sup>

a Overall yields from **6**. b Yield from **6a**.

c Yield for thionation of **6a**.

The iodolactamization of the  $\delta,\epsilon$ -unsaturated *N*-benzylthioimide (**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  $\delta$ -lactam (**2a**)<sup>10</sup> regioselectively (6-exo-trigonal)<sup>11</sup> in 72% overall yield from **4a**. Similarly, the thioimides (**1b,c**) underwent the iodolactamization to afford the  $\delta$ -lactams (**2b,c**)<sup>10</sup>. However, the iodolactamization of **1d,e**, the imidates having substituents at the olefinic terminal, was unsuccessful.<sup>12</sup>



Next, the iodolactamization of the  $\beta$ -substituted  $\delta,\epsilon$ -unsaturated thioimides (**1f-h**) provided diastereomeric mixtures of  $\delta$ -lactams [**2f-(a,b)**-**2h-(a,b)**], respectively, with relative 1,3-asymmetric induction as shown in Table 2 (Scheme 3).<sup>10</sup> Assuming that conformer A with minimum nonbonded interaction is more favored than conformer B with the trans relationship between  $\beta$ -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.<sup>13,14</sup>

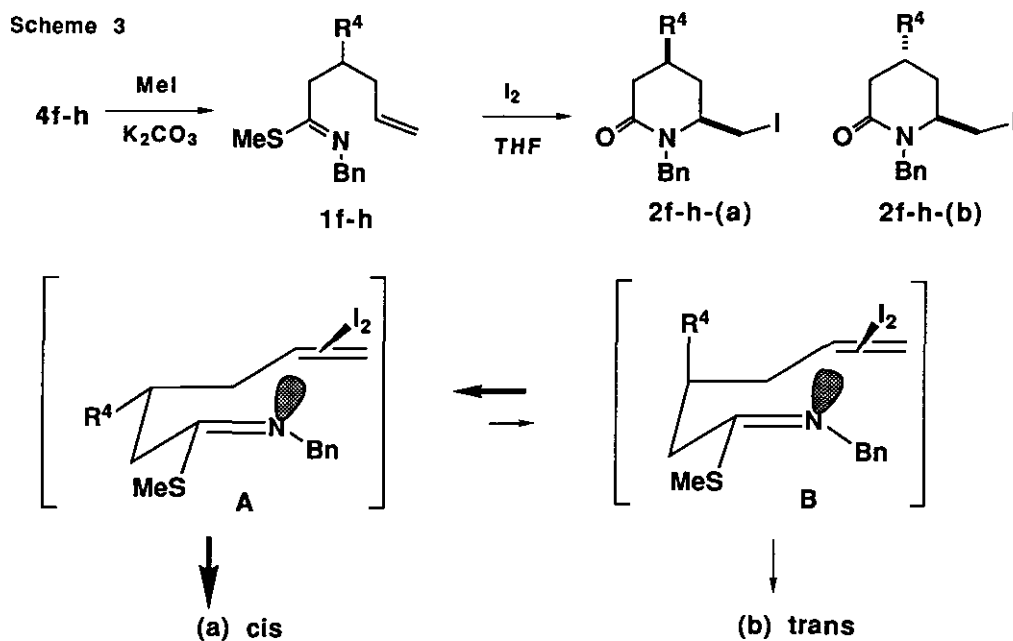


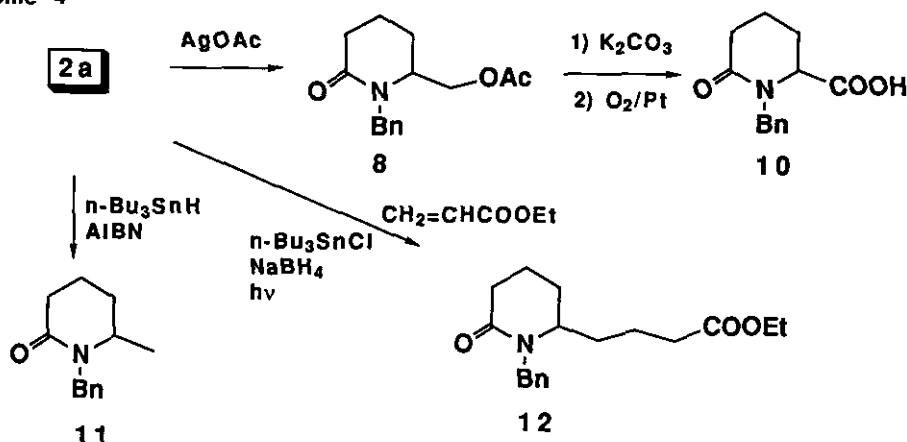
Table 2. Iodolactamization of 1f-h

Product	(a) Yield (%) <sup>a</sup>	(b) Yield (%) <sup>a</sup>	ratio (a:b)
2f	56	4.1	14:1
2g	63	5.3	12:1
2h	24	6.0	4:1

<sup>a</sup> 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 beginning, the displacement of the iodine in 2a by an oxygen nucleophile using silver acetate in DMF was carried out to afford the acetate (8),<sup>3,15</sup> which was transformed into the lactam acid (10)<sup>10</sup> by alkaline hydrolysis followed by oxidation<sup>16</sup> with oxygen in the presence of platinum in 45% overall yield from 2a. The radical reduction<sup>17</sup> of 2a with *n*-Bu<sub>3</sub>SnH in the presence of AIBN gave the lactam (11)<sup>10</sup> in 67% yield. The radical propagation of 2a with ethyl acrylate by Giese's procedure<sup>18</sup> (Bu<sub>3</sub>SnCl, NaBH<sub>4</sub>, hv) was performed to provide the ester lactam (12)<sup>10</sup> in 56% yield.

Scheme 4



In summary, this work has demonstrated an expedient preparation of  $\delta,\epsilon$ -unsaturated thioamides and the formation of substituted  $\delta$ -lactams by diastereoselective iodolactamization of  $\delta,\epsilon$ -unsaturated thioimides. The present procedure provides a new access to functionalized piperidones, which should be convertible into piperidine alkaloids<sup>19</sup> such as coniine and solenopsin. Further investigation is currently ongoing.

## ACKNOWLEDGMENT

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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  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{13}\text{H}_{16}\text{NOI}$  329.0278, found 329.0263.  
**2f-(a)**, an oil ir (neat) 1640  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{14}\text{H}_{18}\text{NOI}$  343.0434, found 343.0434.  
**2f-(b)**, mp 94-97  $^\circ\text{C}$ ; ir (nujol) 1640  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{14}\text{H}_{18}\text{NOI}$  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  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{13}\text{H}_{15}\text{NO}_3$  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  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{18}\text{H}_{25}\text{NO}_3$  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  $^1\text{H}$  nmr spectra. The value (3.84, 5.59, ABq) of the signal for methylene of 4,6-*cis*-**2f**-(a) resembles 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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