

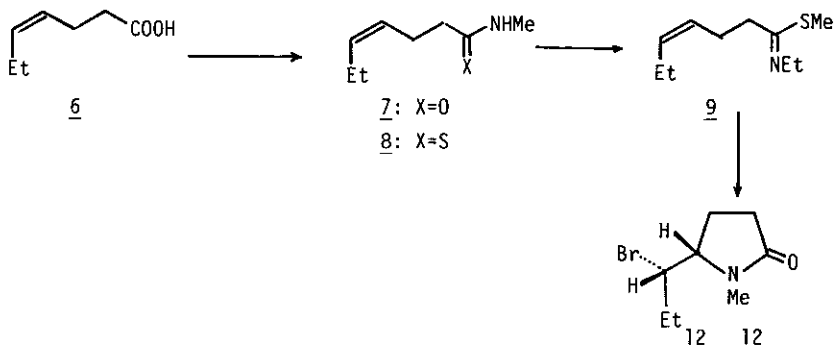
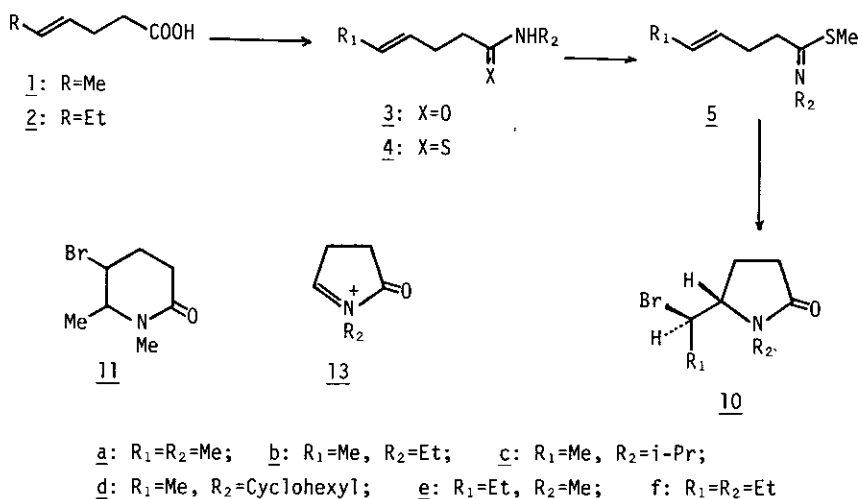
A REGIO AND DIASTEREOSELECTIVE BROMOLACTAMIZATION OF  $\delta,\gamma$ -UNSATURATED THIOIMIDATES

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**Abstract** — Cyclization of *N*-substituted *E*- $\delta,\gamma$ -unsaturated thioimides (5a-f) with bis(collidine)bromonium perchlorate, followed by treatment with aqueous sodium carbonate afforded the corresponding *N*-substituted *threo*-2-(2'-bromoalkyl)pyrrolidin-5-ones (10a-f), respectively, with high diastereoselectivity. Cyclization of *Z*-unsaturated thioimide (9) gave the *erythro*-isomer (12).

Although halolactonization and related oxidative cyclization reaction of alkenoic acid are well known,<sup>1</sup> early attempts to prepare lactams from olefinic amides by similar procedures afforded the lactones.<sup>2</sup> Recently, however, several efficient oxidative cyclizations of olefinic amides to lactams and related compounds have been reported.<sup>3</sup> In connection with the study on an effective approach to functionalized *N*-heterocycles, we investigated a new halolactamization of  $\delta,\gamma$ -unsaturated amides. Cyclization of  $\delta,\gamma$ -unsaturated thioimides, derived from the corresponding olefinic amides, with bis(collidine)bromonium perchlorate<sup>4</sup> was found to give 2-(2'-bromoalkyl)pyrrolidin-5-ones with high regio and diastereoselectivity, though the cyclization of the olefinic amides under the same conditions gave the corresponding lactones. The results of our studies are described in this paper. The *E*- $\delta,\gamma$ -unsaturated acids (1 and 2) derived from 1-buten-3-ol and 1-penten-3-ol, respectively, through ortho ester-Claisen rearrangement procedure,<sup>5</sup> were converted to the amides (3a-f)<sup>6</sup> by the usual way. Treatment of 3a-f with *p*-methoxyphenylthionophosphine sulfide (Lawesson's reagent)<sup>7</sup> in benzene at room temperature gave the corresponding thioamides (4a-f), respectively. Methylation of 4a-f (methyl iodide, methylene chloride, room temperature, 10 h, then aqueous sodium hydrogen carbonate) afforded the corresponding thioimides (5a-f) in nearly quantitative yield from 3a-f in each cases. In a similar way, the *Z*- $\delta,\gamma$ -unsaturated acid (6), derived from *cis*-3-hexen-1-ol (i.  $\text{MeSO}_2\text{Cl}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{Et}_3\text{N}$ ; ii.  $\text{NaCN}$ , acetone, 18-crown-6; iii. 10 %  $\text{EtOH-KOH}$ , reflux, 15 h), was converted to the corresponding thioimide (9) through the amide (7) and thioamide (8). Cyclization of 5a with bis(collidine)bromonium perchlorate (1.2 equiv) was carried out in methylene chloride ( $-78^\circ\text{C}$ , 0.5 h), followed by quenching with 10 % aqueous sodium carbonate ( $-78^\circ\text{C}$ ) and

then further stirring at room temperature (12 h) to give the threo-2-(2'-bromoethyl)pyrrolidin-5-one (10a)<sup>8</sup> as an oil in 48 % yield as a single diastereomer, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.67 (3H, d, J=7 Hz), 2.81 (3H, s), 3.49 (1H, dt, J=3, 6 Hz), 4.46 (1H, dq, J=3, 7 Hz); MS, m/z 205 (M<sup>+</sup>), 207 (M<sup>+</sup>+2); IR (CHCl<sub>3</sub>) 1675 cm<sup>-1</sup>. In this reaction, the formation of 5-bromo-6-methylpiperidin-2-one (11) was not observed. In a similar way, the thioimidates (5b-f, 9) were also subjected to bromo-lactamization under the same conditions as above. Cyclization of 5b-f afforded the corresponding N-substituted threo-2-(2'-bromoalkyl)pyrrolidin-5-ones (10b-f)<sup>6</sup> along with a small quantity of amides (3b-f), respectively. Cyclization of 9 yielded the erythro-2-(2'-bromopropyl)pyrrolidin-5-one (12),<sup>8</sup> the stereoisomer of 10e, accompanied with a formation of a small quantity of 7. Separation of these bromocyclization products were easily achieved by column chromatography on silica gel by using AcOEt-hexane (3:1). In the mass spectra of 10a-f and 12, the characteristic peak due to the ion (13) was observed as the base peak in all cases.



The method of the bromolactamization described herein would be useful for a synthesis of a variety of aza-cyclic compounds.

## REFERENCES AND NOTES

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6. All new compounds gave satisfactory spectral data. Yields of 10a-f and 12 were not optimized. Characteristic spectral data of 10b-f and 12 are as follows.  
10b: 47 % yield, an oil,  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.13 (3H, t,  $J=7$  Hz), 1.70 (3H, d,  $J=7$  Hz), 3.50-3.83 (2H, m), 4.49 (1H, dq,  $J=2, 7$  Hz); IR ( $\text{CHCl}_3$ )  $1665\text{ cm}^{-1}$ ; MS,  $m/z$  219 ( $M^+$ ), 221 ( $M^+ + 2$ ),  
10c: 45 % yield, an oil,  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.37 (6H, d,  $J=7$  Hz), 1.67 (3H, d,  $J=7$  Hz), 3.52-3.73 (1H, m), 3.81-4.23 (1H, m), 4.48 (1H, dq,  $J=2, 7$  Hz); IR ( $\text{CHCl}_3$ )  $1660\text{ cm}^{-1}$ ; MS,  $m/z$  233 ( $M^+$ ), 235 ( $M^+ + 2$ ).  
10d: 45 % yield, an oil,  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.66 (3H, d,  $J=6$  Hz), 3.50-3.70 (2H, m), 4.43 (1H, dq,  $J=3, 6$  Hz); IR ( $\text{CHCl}_3$ )  $1650\text{ cm}^{-1}$ ; MS,  $m/z$  283 ( $M^+$ ), 285 ( $M^+ + 2$ ).  
10e: 48 % yield, an oil,  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.13 (1H, t,  $J=7$  Hz), 2.80 (3H, s), 3.57 (1H, dt,  $J=2, 5$  Hz), 4.22 (1H, dt,  $J=2, 7$  Hz); IR ( $\text{CHCl}_3$ )  $1675\text{ cm}^{-1}$ ; MS,  $m/z$  219 ( $M^+$ ), 221 ( $M^+ + 2$ ).  
10f: 48 % yield, an oil,  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.12 (6H, t,  $J=7$  Hz), 3.51-3.94 (2H, m), 4.21 (1H, dt,  $J=2, 7$  Hz); IR ( $\text{CHCl}_3$ )  $1665\text{ cm}^{-1}$ ; MS,  $m/z$  233 ( $M^+$ ), 235 ( $M^+ + 2$ ).

12: 45 % yield, an oil,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.10 (3H, t,  $J=7$  Hz), 2.83 (3H, s), 3.83-4.20 (2H, m); IR ( $\text{CHCl}_3$ )  $1675\text{ cm}^{-1}$ ; MS,  $m/z$  219 ( $\text{M}^+$ ), 221 ( $\text{M}^++2$ ).

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8. Since all bromolactamization products were obtained as a single diastereomer, the stereochemistry of the products derived from the E-olefinic thioimidates (5a-f) was assigned as threo and the product obtained from the Z-olefinic thioimide (9) was assigned as erythro.

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