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Sulfur Extrusion Reaction: A New β-Enamino Lactone Synthesis

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SYNTHETIC COMMUNICATIONS, 24(18), 2577-2584 (1994)

SULFUR EXTRUSION REACTION: A NEW β-ENAMINO LACTONE SYNTHESIS

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Abstract: Condensation of α-bromo lactones **4** with thiolactams **3** leads to the formation of β-enamino lactones **2a-g** through sulfide-contraction sequence.

Cyclic β-enamino esters are useful intermediates for natural products synthesis. In this field, we have recently published a synthetic method[1] to prepare cyclic β-enamino lactones **1** from 2-acetylbutyrolactones and lactim ethers, which permitted a new xenovenine synthesis[2].

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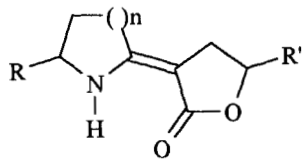

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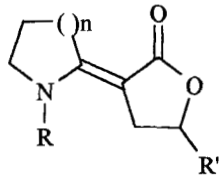
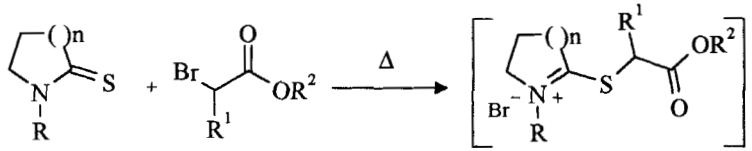
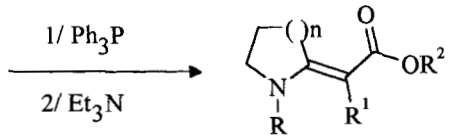


2a-g

The presence of two prochiral carbon atoms on enamino lactones **1** is interesting for asymmetric synthesis: the R or/and R' substituent(s) can be used to induce a facial differenciation during the carbon-carbon double bond reduction. However, in enaminic systems such as **2** (R' = H), a chiral R substituent on the



3 **4**



2

2	n	R	R^1	R^2
a	1	Bn	$-(CH_2)_2-$	
b	2	Bn	$-(CH_2)_2-$	
c	3	Bn	$-(CH_2)_2-$	
d	1	Bn	$-CH_2-CH(CH_3)-$	
e	2	Bn	$-CH_2-CH(CH_3)-$	
f	1	Me	$-(CH_2)_2-$	
g	2	Me	$-(CH_2)_2-$	
h	1	Bn	H	Et
i	2	Bn	H	Et
j	3	Bn	H	Et

Scheme **1**

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Table 1. β-Enamino Lactones **2a-g** and β-Enamino Esters **2h-j** prepared.

Pro-ducts	Salt Formation T (°C)	time (mn)	Yield[b] (%)	mp or Rf (EtOAc)	Molecular Formula or Lit. mp	IR ($CHBr_3$) ν(cm^{-1})
2a	100	10	82	90-91°C	$C_{15}H_{17}NO_2$ (243.1) [c]	1685, 1580
2b	100	10	84	87°C	$C_{16}H_{19}NO_2$ (257.1) [c]	1690, 1580
2c	100	20	39	0.1	$C_{17}H_{21}NO_2$ (271.1) [c]	1670, 1570
2d	100	10	89	0.5	$C_{16}H_{19}NO_2$ (257.1) [c]	1695, 1595
2e	100	10	79	0.5	$C_{17}H_{21}NO_2$ (271.1) [c]	1690, 1560
2f	100	10	78	98-99°C	$C_9H_{13}NO_2$ (167.1) [c]	1710, 1590
2g	100	10	86	0.2	$C_{10}H_{15}NO_2$ (181.1) [c]	1645, 1580
2h	100	3	70	58-60°C	60-61°C [6]	1665, 1590
2i	70[a]	3	69	66°C	$C_{16}H_{21}NO_2$ (259.1) [d]	1665, 1560
2j	100	3	87	74°C	$C_{17}H_{23}NO_2$ (273.1) [d]	1670, 1570

[a] Lower temperature is required to avoid thioiminium salt decomposition.

[b] isolated yields.

[c] Satisfactory HRMS obtained ± 5 ppm.

[d] Satisfactory microanalyses obtained: C ±0.34, H ±0.32, N ±0.15.

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Table 2. NMR data of β-Enamino Lactones **2a-g** and β-Enamino Esters **2h-i**

	^{1}H-NMR ($CDCl_3$) δ (ppm), J	^{13}C-NMR ($CDCl_3$) δ (ppm)
2a	7.13-7.40 (m, 5H), 4.64 (s, 2H), 4.13 (t, 2H, 8Hz), 3.25-3.39 (m, 4H), 2.98 (t, 2H, 8Hz), 1.85-2.10 (m, 2H).	174.7, 160.3, 137.8, 129.1, 127.7, 126.3, 81.8, 64.1, 53.9, 50.9, 33.0, 27.0, 21.5.
2b	7.17-7.40 (m, 5H), 4.55 (s, 2H), 4.02 (t, 2H, 7.5Hz), 3.24 (t, 2H, 6Hz), 3.14 (t, 2H, 6Hz), 2.89 (t, 2H, 7.5Hz), 1.60-1.80 (m, 4H).	174.4, 161.5, 138.2, 128.8, 127.4, 126.4, 87.6, 63.9, 56.2, 48.9, 30.0, 25.7, 22.5, 19.1.
2c	7.20-7.80 (m, 5H), 4.54 (s, 2H), 3.97 (t, 2H, 7Hz), 3.20-3.40 (m, 4H), 2.78 (t, 2H, 7.5Hz), 1.50-1.90 (m, 6H).	172.6, 165.8, 137.7, 128.6, 128.2, 126.2, 89.0, 63.1, 55.3, 50.5, 30.1, 29.2, 27.8, 27.0, 26.3.
2d	7.10-7.40 (m, 5H), 4.63 (dd, 2H, 28-17Hz), 4.35-4.50 (m, 1H), 3.25-3.45 (m, 4H), 3.11 (dd, 1H, 13-8Hz), 2.57 (dd, 1H, 13-8Hz), 1.90-2.10 (m, 2H), 1.28 (d, 3H, 6Hz).	173.7, 159.7, 137.5, 128.6, 127.2, 125.9, 82.3, 71.4, 53.4, 50.4, 34.4, 32.7, 21.9, 21.1.
2e	7.10-7.40 (m, 5H), 4.55 (dd, 2H, 24-16.5Hz), 4.33 (q, 1H, 6.5Hz), 3.20-3.40 (m, 2H), 3.15 (t, 2H, 6Hz), 3.02 (dd, 1H, 13.5-7Hz), 2.54 (dd, 1H, 13.5-7Hz), 1.55-1.80 (m, 4H), 1.27 (d, 3H, 6Hz).	173.5, 160.7, 137.8, 128.4, 126.9, 126.0, 88.0, 71.1, 55.7, 48.4, 37.2, 25.4, 22.1, 21.2, 18.8.

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2f	4.18 (t, 2H, 8Hz), 3.46 (t, 0.1H, 7Hz), 3.34 (t, 1.9H, 7Hz), 3.13 (s, 3H), 3.10-3.25 (m, 3.8H), 2.71 (t, 0.1H, 8Hz), 2.54 (t, 0.1H, 8Hz), 1.80-2.00 (m, 2H).	E-isomer: 174.3, 160.5, 80.0, 63.9, 56.0, 34.8, 32.6, 26.9, 20.9.
2g	4.20 (t, 0.7H, 7Hz), 4.12 (t, 1.3H, 7.5Hz), 3.28 (t, 0.7H, 6.5Hz), 3.21 (t, 1.3H, 6.5Hz), 3.17 (s, 1.05H), 3.00-3.15 (m, 4.65H), 3.07 (s, 1.95H), 2.79 (t, 0.7H, 7.5Hz), 2.40 (t, 0.7H, 6Hz), 1.50-1.90 (m, 4H).	E-isomer: 173.9, 160.7, 86.2, 63.6, 51.6, 41.8, 26.4, 22.4, 19.0, 29.6. Z-isomer: 169.0, 157.9, 83.6, 63.7, 49.4, 43.3, 30.08, 26.4, 22.4, 19.3.
2h	7.14-7.36 (m, 5H), 4.67 (s, 1H), 4.35 (s, 2H), 4.07 (q, 2H, 7Hz), 3.33 (t, 2H, 7Hz), 3.22 (t, 2H, 8Hz), 1.90-2.10 (m, 2H), 1.22 (t, 3H, 7Hz).	169.2, 164.9, 135.8, 128.5, 127.2, 126.9, 78.1, 58.0, 52.2, 49.7, 32.4, 20.8, 14.5.
2i	7.10-7.40 (m, 5H), 4.64 (s, 1H), 4.38 (s, 2H), 4.00 (q, 2H, 7Hz), 3.10-3.30 (m, 4H), 1.66-1.85 (m, 4H), 1.16 (t, 3H, 7Hz).	169.1, 162.6, 135.1, 128.8, 127.2, 126.6, 82.7, 58.2, 55.2, 49.8, 26.9, 23.4, 19.8, 14.6.
2j	7.20-7.60 (m, 5H), 4.52 (s, 1H), 4.35 (s, 2H), 4.05 (q, 2H, 7Hz), 3.20-3.30 (m, 4H), 1.40-1.80 (m, 6H), 1.14 (t, 3H, 7Hz).	169.4, 167.9, 136.9, 128.7, 127.2, 126.7, 83.6, 58.3, 56.2, 52.3, 29.6, 28.3, 27.4, 26.3, 14.3.

nitrogen atom is required to control the stereochemistry of the reduction[3] Unfortunately, N-alkylated β-enamino lactones **2** (R = Me, Bn, $CH(CH_3)Ph$...) are not accessible by the lactim ether procedure. The Eschenmoser reaction[4] could be an alternative route to this method. Usually, N-substituted thiolactams **3** are S-alkylated with primary α-bromoesters in a solvent (CH_2Cl_2, CH_3CN...) at room temperature, to afford thioiminium salts[5]. These intermediates lead, after sulfide--contraction, to the corresponding β-enamino esters **2** (R^1 = H) (Scheme 1). In the same conditions, the complete nucleophilic substitution with α-bromo lactones **4** [$R^1 = R^2 = -(CH_2)_2-$] requires 500 hours time, due to the more hindered α-bromo derivatives.

Herein, we report a new and rapid procedure permitting β-enamino lactones **2** synthesis. We have found that brief heating of thiolactams **3** and α-bromo lactones **4** during a few minutes, without solvent, gave the thioiminium salts. Usual work-up with Ph_3P and Et_3N afforded the expected β-enamino lactones **2a-g** in good yields (Table 1). These new conditions have been extended to ethyl α-bromoacetate: the alkylation required a few minutes instead of 24 hours[6]. ^{1}H-NMR assignments only showed E stereochemistry for N-benzyl β-enamino lactones and esters while N-methyl β-enamino lactones were a mixture of E and Z isomers in ratio 95:5 and 65:35 for **2f** and **2g** respectively.

This investigation is the first example of thiolactams condensation with α-bromolactones through sulfide contraction leading to β-enamino lactones formation.

EXPERIMENTAL

Melting points were determined on a Büchi 530 apparatus and were uncorrected. IR spectra were recorded on a Philips Model PU 9700 spectrophotometer. ^{1}H-

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and ^{13}C-NMR spectra were recorded on a Bruker AC200 spectrometer in $CDCl_3$ with TMS as internal standard. Column chromatography was performed on Merck Kieselgel 60, 0.063-0.2 mm.

Thiolactams **3**: n = 1 , R = Me,Bn ; n = 2 , R = Me ; n = 2,3 , R = Bn, were prepared according to the literature[7-9].

β-Enamino Lactones and Esters 2; General Procedure :

To thiolactam **3** (0.575 g, 3 mmol), heated to 70-100°C, α-bromobutyrolactone **4** or ethyl α-bromoacetate (6 mmol) was quickly added under stirring. Heating was continued for 3 to 20mn. The reaction was then stopped by cooling with a water bath, and a solution of Ph_3P (3.3 mmol) in CH_2Cl_2 (10 mL) was added, followed by Et_3N (3.3 mmol). The resulting mixture was stirred at room temperature for 30mn, excepted for compounds **2b,c,e** and **g** (7h), and washed with water (5 mL). The organic layer was dried over Na_2SO_4, the solvent was removed, and the residue was purified on silica gel (petroleum ether-EtOAc mixtures) to yield exocyclic enamine **2**. NMR data were reported in Table 2.

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