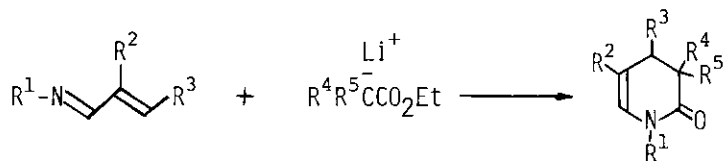


NEW SYNTHESIS OF FUNCTIONALIZED  $\beta$ -LACTAMS FROM AZABUTADIENE ANALOGUES  
AND ESTER ENOLATES

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**Abstract** - Reaction of the 2-azabutadiene **1** with  $\alpha$ -lithioesters **2a,b** gave N-styryl-2-azetidiones **3a,b** in high yields in contrast to the  $\delta$ -lactam formation of 1-azadienes with **2**. The azines **7a,b** also reacted with the enolate **2a** to result in  $\beta$ -lactam formation: N-alkylidenamino-2-azetidiones **8a,b** and/or 1,1'-bi(2-azetidione)s **9a,b** were obtained in good yields.

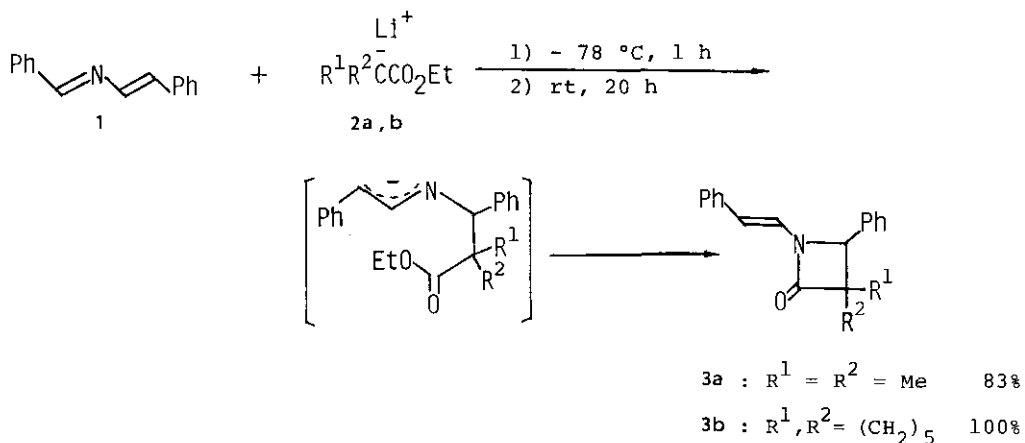
Azabutadienes are expected to be useful building blocks for nitrogen-containing heterocycles.<sup>1</sup> In the previous paper, we showed the facile synthesis of pyridone derivatives by the reaction of 1-azabutadienes with ester enolates.<sup>2</sup> The reaction seems to be better than cycloaddition of the 1-azadienes with ketenes<sup>3</sup> because of high chemoselectivity.



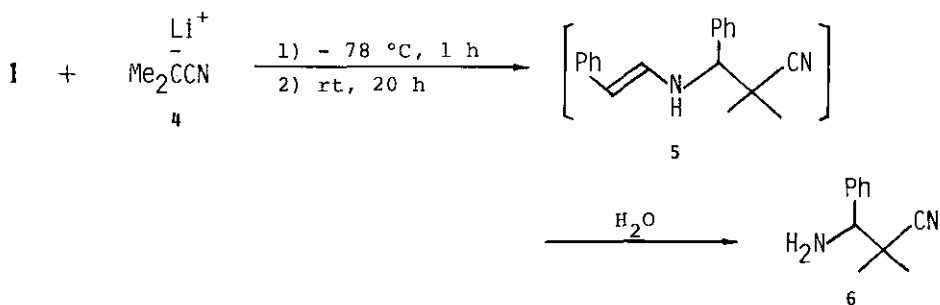
Here we wish to report a new reaction mode of azadienes with ester enolates giving  $\beta$ -lactams having a functional group. Recently functionalized monocyclic  $\beta$ -lactams renewed interest in biological activity,<sup>4</sup> and the following reaction can be employed as a useful synthetic method for  $\beta$ -lactam derivatives.

To a solution of lithium diisopropylamide (6.5 mmol) in THF (18 ml) was added ethyl isobutyrate (0.84 ml, 6.25 mmol) in THF (3 ml) at  $-78^\circ\text{C}$  and the mixture was stirred for 1 h. Then 1.05 g (5.0 mmol) of 1,4-diphenyl-2-aza-1,3-diene (**1**) in THF (3 ml) was added and was stirred for 1 h at the same temperature. The reaction mixture was allowed to stand at room temperature for 20 h. After usual work-up and concentration 1.15 g (83%) of 3,3-dimethyl-4-phenyl-1-styrylazetidion-2-one (**3a**) was

obtained as a colorless solid. Similarly, 3,3-pentamethylene-4-phenyl-1-styryl-azetidin-2-one (**3b**) was formed quantitatively from **1** and ethyl cyclohexanecarboxylate. The structures of the products were satisfactorily determined by spectral data (see Table 2). The results are in marked contrast to the  $\delta$ -lactam formation from 1-azadienes and **2**.<sup>2</sup>



The reaction of an azaallyl anion, formed by addition of a carbanion to a 2-azadiene, with a ketone is reported to result in C-C bond formation.<sup>5</sup> However, in the present case, N-C bond formation was exclusively observed partly because of steric reason. When the corresponding  $\alpha$ -cyanocarbanion **4** was employed instead of the enolate **2a**, no cyclization product but the  $\beta$ -aminonitrile **6**,<sup>6</sup> which was formed by hydrolysis of the acyclic 1:1 adduct **5**, was obtained in 63% yield.



The azines **7a, b**, 2,3-diazabutadienes, were also reacted with the ester enolate to give the mono- $\beta$ -lactams **8a, b** and/or the N,N'-bi- $\beta$ -lactams **9a, b** according to the reaction conditions. The results are summarized in Table 1. 1,2-Cycloadditions of azines are less known than 1,4-cycloadditions<sup>7,8</sup> and 1,3-cycloadditions (criss-cross reactions).<sup>7-11</sup> The azine **7b** is reported to react with diphenylketene to give an azetidinone derivative corresponding to **8**, while the azine **7a** reacts with

the ketene to give an oxazinone derivative via loss of propionitrile.<sup>12</sup>

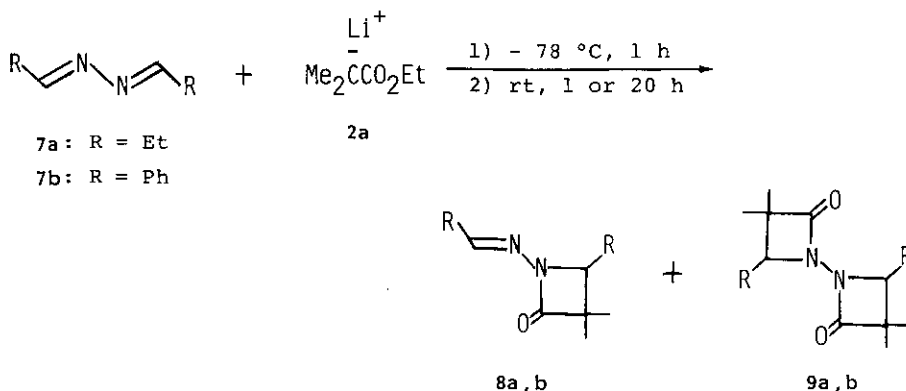


Table 1. The Reaction of the Azines 7 with the Enolate 2a.

Azine R	Mole Ratio 7/2a	Solvent	Reaction Time at r.t. (h)	Yield (%)	
				8	9
7a Et	1/1.2	THF	20	31	--
7a Et	1/1.2	THF	1	17	36
7a Et	1/2.2	THF	1	trace	76
7b Ph	1/1.2	THF	20	50	--
7b Ph	1/1.2	THF	1	59	18*
7b Ph	1/1.2	THF-HMPA**	1	85*	--
7b Ph	1/2.2	THF	1	22*	62*

\*Determined by NMR.

\*\*2.4 equiv. of HMPA was added per 1 equiv. of 7.

The reactions were carried out in a similar manner to those of the 2-azadiene 1 except that the reaction was quenched after one-hour stirring at room temperature. The prolonged reaction time (20 h) suppressed the formation of the bi-β-lactams 9. The mole ratio of the azine and the enolate affects on the ratio of the mono- and bis-adducts. Propionaldehyde azine 7a seems to be more susceptible to bi-β-lactam formation than benzaldehyde azine 7b. Furthermore, addition of HMPA as a co-solvent resulted in selective and more effective formation of the mono-β-lactam 8b.

#### ACKNOWLEDGEMENT

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Table 2. Spectral Data for the Compounds 3, 8, and 9.

Compd	mp (°C) or [bp] (°C/mmHg)	IR (cm <sup>-1</sup> )	<sup>1</sup> H-NMR (CDCl <sub>3</sub> , δ)	<sup>13</sup> C-NMR a) (CDCl <sub>3</sub> , ppm)	MS (m/e)
3a	121 (colorless needles from hexane)	1730 (C=O) <sup>b)</sup> 1630 (C=C)	0.78 (s, 3H, Me), 1.47 (s, 3H, Me), 4.67 (s, 1H, CH), 5.70 (d, J = 14.5 Hz, 1H, PhCH=), 6.9-7.3 (m, 11H, 2Ph and NCH=)	17.6 (q, Me), 22.5 (q, Me), 56.0 (s, Me <sub>2</sub> C), 66.8 (d, CH), 113.0 (d, PhCH=), 120.3 (d, NCH=), 170.4 (s, NC=O)	277 (M <sup>+</sup> )
3b	pale yellow <sup>d)</sup> liquid	1750 (C=O) <sup>c)</sup> 1640 (C=C)	0.7-2.1 (m, 10H, (CH <sub>2</sub> ) <sub>5</sub> ), 4.58 (s, 1H, PhCH), 5.63 (d, J = 15.0 Hz, 1H, PhCH=), 6.8-7.4 (m, 1H, 2Ph and NCH=)	22.1 (t), 23.4 (t), 25.2 (t), 27.6 (t), 33.4 (t), 60.6 (s, spiro-carbon), 66.9 (d, PhCH), 113.0 (d, PhCH=), 120.3 (d, NCH=)	317 (M <sup>+</sup> )
8a	[85/0.2] <sup>e)</sup> (colorless liquid)	1750 (C=O) <sup>c)</sup> 1640 (C=N)	1.01 (dd, 3H, Me), 1.03 (t, 3H, Me), 1.16 (s, 3H, Me), 1.27 (s, 3H, Me), 1.4-2.5 (m, 4H, 2CH <sub>2</sub> ), 3.50 (dd, 1H, EtCH), 8.00 (t, 1H, EtCH=)	10.8 (q, Me), 11.0 (q, Me), 16.6 (q, 2Me), 22.6 (t, CH <sub>2</sub> ), 22.9 (t, CH <sub>2</sub> ), 50.4 (s, Me <sub>2</sub> C), 50.5 (s, Me <sub>2</sub> C), 70.3 (d, NCH), 71.4 (d, NCH), 173.2 (s, C=O), 173.6 (s, C=O)	182 (M <sup>+</sup> )
9a	[140/0.2] <sup>e)</sup> (colorless liquid)	1790 (C=O) <sup>c)</sup> 1760 (C=O)	1.00 (t, 6H, 2Me) 1.20 (s, 6H, 2Me) 1.35 (s, 6H, 2Me) 1.70 (dq, 4H, 2CH <sub>2</sub> ) 3.52 (t, 2H, 2EtCH)	—	252 (M <sup>+</sup> )
8b	145-146 (colorless needles from hexane)	1760 (C=O) <sup>b)</sup> 1645 (C=N)	0.83 (s, 3H, Me), 1.53 (s, 3H, Me), 4.90 (s, 1H, PhCH), 7.0-7.8 (m, 11H, 2Ph and PhCH=)	—	278 (M <sup>+</sup> )
9b	154.5-155 (colorless plates from hexane)	1780 (C=O) <sup>b)</sup> 1750 (C=O)	0.78 (s, 6H, 2Me) 1.42 (s, 6H, 2Me) 4.78 (s, 2H, 2PhCH) 7.30 (s, 10H, 2Ph)	—	348 (M <sup>+</sup> )

a) Signals due to aromatic carbons are omitted.

b) In Nujol mull c) neat

d) Isolated by preparative TLC (SiO<sub>2</sub>-CHCl<sub>3</sub>).

e) Distilled by bulb-to-bulb

method.

Elemental analyses were satisfactory for all the compounds except for 8a, which was more susceptible to moisture than the others.

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6. The compound **6**: bp 150 °C/0.2 mmHg; IR 3150-3450 (NH) and 2240  $\text{cm}^{-1}$  (C≡N);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.17 (s, 3H, Me), 1.40 (s, 3H, Me), 2.09 (s, 2H,  $\text{NH}_2$ ), 3.15 (s, 1H, CH), 7.0-7.6 (m, 5H, Ph); MS ( $m/e$ ) 174 ( $\text{M}^+$ ), 173 ( $\text{M}^+ - 1$ ).
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