NEW SYNTHESIS OF FUNCTIONALIZED β-LACTAMS FROM AZABUTADIENE ANALOGUES AND ESTER ENOLATES

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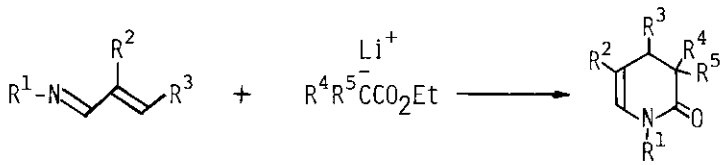
Abstract - Reaction of the 2-azabutadiene **1** with α-lithioesters **2a,b** gave N-styryl-2-azetidinones **3a,b** in high yields in contrast to the δ-lactam formation of 1-azadienes with **2**. The azines **7a,b** also reacted with the enolate **2a** to result in β-lactam formation: N-alkylidenamino-2-azetidinones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

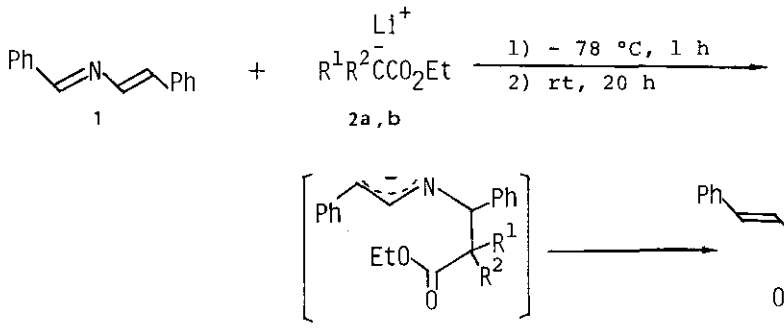
Azabutadienes are expected to be useful building blocks for nitrogen-containing heterocycles.[1] In the previous paper, we showed the facile synthesis of pyridone derivatives by the reaction of 1-azabutadienes with ester enolates.[2] The reaction seems to be better than cycloaddition of the 1-azadienes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



Here we wish to report a new reaction mode of azadienes with ester enolates giving β-lactams having a functional group. Recently functionalized monocyclic β-lactams renewed interest in biological activity,[4] and the following reaction can be employed as a useful synthetic method for β-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 °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-styrylazetidin-2-one (**3a**) was

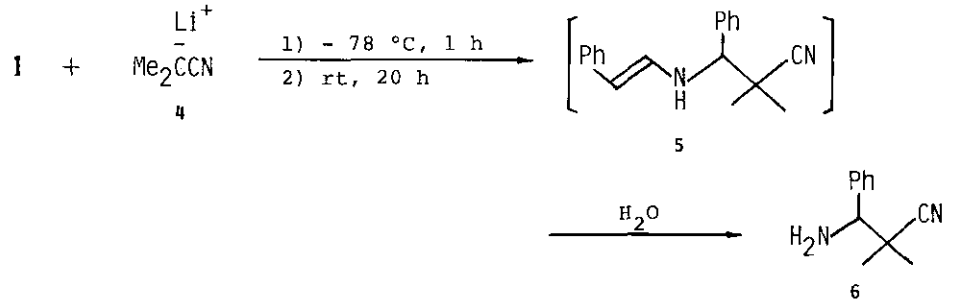
obtained as a colorless solid. Similarly, 3,3-pentamethylene-4-phenyl-1-styryl-azetidin-2-one (**3b**) was formed quantitatively from 1 and ethyl cyclohexanecarboxylate. The structures of the products were satisfactorily determined by spectral data (see Table 2). The results are in marked contrast to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



3a : $R^1 = R^2 = Me$ 83%

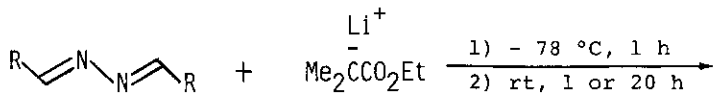
3b : $R^1, R^2 = (CH_2)_5$ 100%

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.[5] However, in the present case, N-C bond formation was exclusively observed partly because of steric reason. When the corresponding α-cyanocarbanion **4** was employed instead of the enolate **2a**, no cyclization product but the β-aminonitrile **6**,[6] which was formed by hydrolysis of the acyclic 1:1 adduct **5**, was obtained in 63% yield.



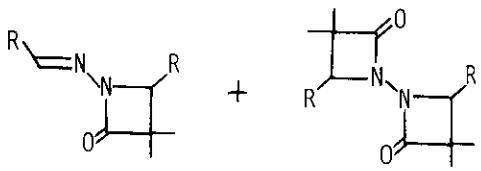
The azines **7a,b**, 2,3-diazabutadienes, were also reacted with the ester enolate to give the mono-β-lactams **8a,b** and/or the N,N'-bi-β-lactams **9a,b** according to the reaction conditions. The results are summarized in Table 1. 1,2-Cycloadditions of azines are less known than 1,4-cycloadditions[7,8]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

the ketene to give an oxazinone derivative via loss of propionitrile.[12]



7a: R = Et
7b: R = Ph

2a



8a,b 9a,b

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

Azine		Mole Ratio	Solvent	Reaction Time	Yield (%)	
	R	7/2a		at r.t. (h)	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^{-1})	^{1}H-NMR ($CDCl_3$, δ)	^{13}C-NMR a) ($CDCl_3$, ppm)	MS (m/e)
3a	121 (colorless needles from hexane)	1730 (C=O) b) 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_2C), 66.8(d, CH), 113.0 (d, PhCH=), 120.3(d, NCH=), 170.4(s, NC=O)	277 (M^+)
3b	pale yellow d) liquid	1750 (C=O) c) 1640 (C=C)	0.7-2.1(m, 10H, $(CH_2)_5$), 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^+)
8a	[85/0.2] e) (colorless liquid)	1750 (C=O) c) 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, $2CH_2$), 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_2), 22.9 (t, CH_2), 50.4(s, Me_2C), 50.5(s, Me_2C), 70.3(d, NCH), 71.4 (d,NCH), 173.2(s, C=O), 173.6(s, C=O)	182 (M^+)
9a	[140/0.2] e) (colorless liquid)	1790 (C=O) c) 1760 (C=O)	1.00(t, 6H, 2Me) 1.20(s, 6H, 2Me) 1.35(s, 6H, 2Me) 1.70(dq, 4H, $2CH_2$) 3.52(t, 2H, 2EtCH)	——	252 (M^+)
8b	145-146 (colorless needles from hexane)	1760 (C=O) b) 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^+)
9b	154.5-155 (colorless plates from hexane)	1780 (C=O) b) 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^+)

a) Signals due to aromatic carbons are omitted. b) In Nujol mull c) neat
d) Isolated by preparative TLC (SiO_2-$CHCl_3$). 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 cm^{-1} (C≡N); ^{1}H-NMR ($CDCl_3$) δ 1.17 (s, 3H, Me), 1.40 (s, 3H, Me), 2.09 (s, 2H, NH_2), 3.15 (s, 1H, CH), 7.0-7.6 (m, 5H, Ph); MS (m/e) 174 (M^+), 173 (M^+ - 1).

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