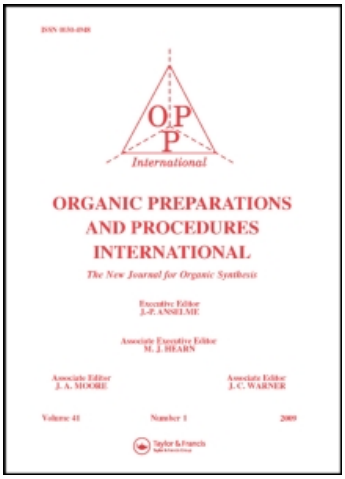

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SYNTHESIS AND REACTIONS OF β-SULTAMS. A REVIEW

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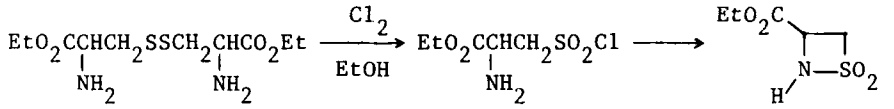
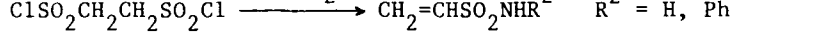
INTRODUCTION

β-sultams are 4-membered cyclic sulfonamides derived from 2-amino alkanesulfonic acids. The first member was synthesized by Baganz[1] in 1960 by chlorination of cystine diethyl ester followed by a dehydrochlorination.



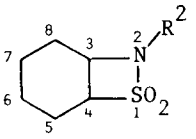
Le Berre[2] obtained ethanesultam in 1970 by a similar process. In a study of the chemistry of ethane-1,2-disulfonylchloride, Kohler[3] claimed the isolation of an "anhydrotaurine" and an "anhydrophenyltaurine" from the reaction of the chloride with ammonia or aniline. In contrast with Kohler's claim it was found that these reactions afforded isomers of ethenesulfonamides.[4]



It was thought that the substitution of the carbonyl group of the β-lactam by a sulfonyl group would render β-sultams more reactive and in recent years this attractive hypothesis has given rise to a recrudescence of activity in β-sultam chemistry.[5,6]

In the literature, monocyclic β-sultams are usually referred to thiazetidines. The first analogue (ethanesultam) is named 1,2-thiazetidine-1, 1-dioxyde. The numbering of ring atoms of bicyclic β-sultams may be the one used for thiazetidinone; all β-sultam show bands at ∿ 1330 and ∿ 1150 cm^{-1} in the infrared; the references should be consulted for more details.

A brief review of β-sultams has been given by Timberlake in a recent book.[7]



I. SYNTHESIS OF β-SULTAMS

The synthetic routes to β-sultams are, in many respects, comparable with those of β-lactams. At the present time, three processes may be used to synthesize β-sultam ring.

1. Cyclization of 2-Aminoalkanesulfonic Acid Derivatives (N-S Bond Formation)

Many variously N or C substituted β-sultams have been prepared by the cyclization of 1-halosulfonyl-2-aminoalkanes. Two processes using this strategy have been developed.

A. Cyclization of 1-Chlorosulfonyl-2-Aminoalkane Hydrochlorides

This method employs the cyclization of taurines,[8] β-aminothiols,[6,9] β-aminodisulfides[9] or 2-aminoalkanesulfonic acids[10] in the presence of base. Taurines 1 which are internal salts of 2-aminoethanesulfonic acids, have been prepared by sulfoethylation of primary amines by isopropylethenesulfonate[11] and their transformation to 1-chlorosulfonyl-2-aminoethane hydro-

$$CH_2{=}CHSO_3iPr \xrightarrow[2.\ MeOH,HCl]{1.\ R^2NH_2} R^{2+}NH_2CH_2CH_2SO_3^- \xrightarrow{PCl_5} \underline{2}$$

chloride (2), was effected with phosphorus pentachloride.[8] Treatment of these hydrochlorides 2 with excess sodium carbonate suspended in ethyl acetate results in cyclization to give 1,2-thiazetidine-1,1-dioxide (3).

$$\underset{\underline{2}}{R^{2+}NH_2CH_2CH_2SO_2Cl\ Cl^-} \xrightarrow[EtOAc]{Na_2CO_3} \underset{\underline{3}}{\begin{bmatrix} SO_2 \\ | \\ N \\ \diagdown R^2 \end{bmatrix}}$$

The sultams which have been obtained by this process are listed in Table 1. 1-Chlorosulfonyl-2-aminoethane hydrochlorides of type 5 can be prepared by chlorination of aminomercaptans[5,8,11] or aminodisulfides[9] in the presence of alcohol ($CCl_4/EtOH/Cl_2$, ~10°); oxidation to the hydrochlorides can be also effected by means of hypochlorous acid.[8]

In these processes aminomercaptans 4 were generally obtained either from thiiranes and primary amines or from aziridines and H_2S.[8,9] The sultams which have been synthesized by this process are listed in Table 2.

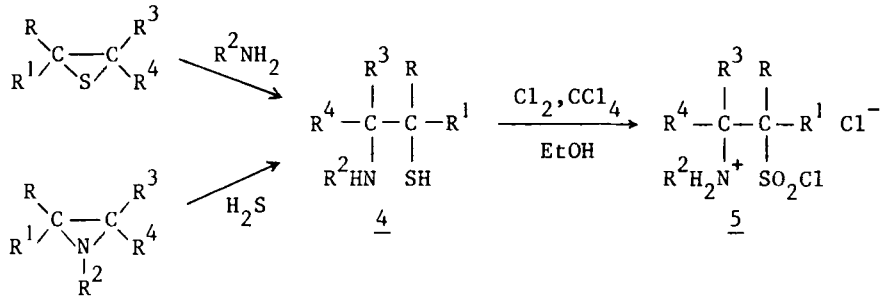
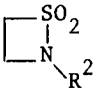


TABLE 1. Synthesis of β-Sultams by Cyclization of 2-Aminoalkanesulfonic Acid Derivatives 

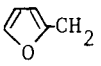
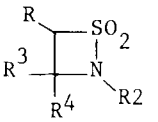
R^2	mp.(bp.)[b] (°C)	Yield (%)	^{1}H nmr (δ)	Method	Ref.[a]
H	53	90	5.60(s,1H), 4.30(t.2H), 3.35(t,2H)	1.A.a	3
Me	36	70	4.15(t,2H), 3.18(t,2H), 2.72(s,3H)	1.A.b	8,(9,10)
Et	(85/0.1)	70	4.15(t,2H), 3.20(t,2H), 3.10(q,2H), 1.22(t,3H)	1.A.a	8,(10)
n-Pr	(88/0.1)	75	4.10(t,2H), 3.20(t,2H), 3.00(t,2H), 1.95-1.25(m,2H), 0.98(t,3H)	1.A.a	8,(9)
i-Pr	(88/0.2)	90	4.05(t,2H), 3.40(q,1H), 3.17(t,2H), 1.20(d,6H)	1.A.a	8,(9,10)
n-Bu	(98-102)	82	4.11(t,2H), 3.18(t,2H), 3.04(d,2H), 1.75-1.25(m,4H), 0.95(t,3H)	1.A.a	8
t-Bu	68-68.5	74	4.00(t,2H), 3.20(t,2H), 1.35(s,9H)	1.B	8
Ph	132	50	7.60-6.80(m,5H), 4.22(t,2H), 3.65 (t,2H)	1.A.a	8,(10)
C_6H_{11}	62	94	4.00(t,2H), 3.15(t,2H), 2.00-1.00 (m,11H)	1.A.a	8,(10)
$PhCH_2$	71-72	70	7.38(s,5H), 4.20(s,2H), 4.10(t,2H), 3.15(t,2H)	1.A.a	8,(9,10)
$C_{10}H_{21}$	37	89	4.10(t,2H), 3.50-2.90(m,4H), 1.60-0.90(m,16H), 0.90(t,3H)	1.A.a	8
$C_{12}H_{25}$	51	85	4.08(t,2H), 3.15(t,2H), 3.03(t,2H), 1.80-1.10(m,20H), 0.90(t,3H)	1.A.a	8
	182	80	7.40(d,1H), 6.35(d,2H), 4.20(s,2H), 4.10(t,2H), 3.18(t,2H)	1.A.a	8
1-Naphtyl	115	76	-	1.A.a	8
CH_2CH_2OH	-	26	-	1.A.b	9

TABLE 1. (contd)

R^2	mp.(bp.)[b] (°C)	Yield (%)	^{1}H nmr (δ)	Method	Ref.[a]
$CH_2CH_2CO_2Ph$	-	96	-	1.A.b	9
CH_2CH_2Ph	-	95	-	1.A.b	9
CH_2CH_2CN	-	75	-	1.A.b	9

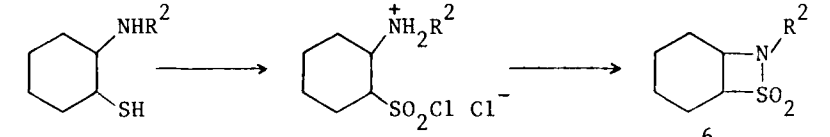
a. References in parenthesis should be consulted for other procedures.
b. Value given below bp. refers to pressure in mm Hg; if none given, then refers to atmospheric pressure.

TABLE 2. Synthesis of β-Sultams by Cyclization of 2-Aminoethanesulfonic Acid Derivatives



R	R^2	R^3	R^4	(bp.)[b] (°C)	Yield (%)	^{1}H nmr (δ)	Method	Ref.
Me	Me	H	H	(84-85) 0.1	88	4.43(sex,1H), 3.70-3.50 (m,1H), 2.70(s,3H), 2.50 (t,1H), 1.53(d,3H)	1.A.b	8
Me	Et	H	H	(100-101) 2.0	66	4.40(sex,1H), 3.50-3.30 (m,1H), 3.10(q,2H), 2.70 (t,1H), 1.53(d,3H), 1.20 (t,3H)	1.A.b	8
Me	n-Pr	H	H	(85-87) 0.1	81	4.40(sex,1H), 3.50-3.30 (m,1H), 3.15-2.50(m,2H), 2.65(t,1H), 1.90-1.30 (m,2H), 1.56(d,3H), 0.99 (t,3H)	1.A.b	8
Me	i-Pr	H	H	(92) 0.5	81	4.30(sex,1H), 3.60-3.10 (m,2H), 2.65(t,1H), 1.53 (d,3H), 1.25(d,3H), 1.15 (d,3H)	1.A.b	8
Me	n-Bu	H	H	(101-103) 0.4	81	4.40(sex,1H), 3.15-2.60) (m,2H), 2.70(t,2H), 1.90 -1.30(m,2H), 1.53(d,3H), 0.92(t,3H)	1.A.b	8
Me	C_6H_{11}	H	H	(132-134) 0.3	65	4.30(sex,1H), 3.50-3.20 m,1H), 3.00-2.85(m,1H), 2.65(t,1H), 2.00-1.00(m, 2H), 1.53(d,3H)	1.A.b	8
Me	$C_{10}H_{21}$	H	H	(140-145) 0.3	67	4.30(sex,1H), 3.50-2.60 (m,3H), 1.90-1.10(m,3H), 1.43(d,3H), 0.90(t,3H)	1.A.b	8
Me	$PhCH_2$	H	H	(142-145) 0.2	85	7.30(m,5H), 4.30(sex,1H), 4.10(s,2H), 3.50-3.20(m, 1H), 2.53(t,1H), 1.43(d,3H)	1.A.b	8
H	H	Me	Me	-	74	-	1.A.b	9
H	H	Me	H	-	69	-	1.A.b	9

These methods were successfully used for the preparation of bicyclic β-sultams (Table 3).[5,6,8] Thus cis- and trans-bicyclo-β-sultams 6 were obtained from cis and trans 1-amino-2-mercapto-2-cyclohexanes.[8] The reaction is stereospecific and the aminothiol configuration is conserved after cyclization.

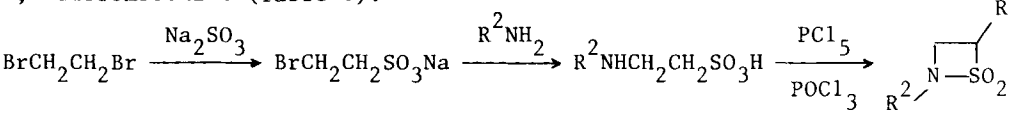


cis and trans

6

cis and trans

The synthesis of bicyclic β-sultams whose structure resembles that of the penicillins were recently reported;[5,6] thus β-sultams, analogous β-lactam penicillanic acid, were recently prepared by Koller et al.[5] Mesityl oxide was converted by regioselective bromination of the sylilenol ether 7 and subsequent reaction with benzylthiol into the benzylthiomesityl oxide (8) which gives the adduct 9 with N-benzylidene derivative of glycine methylester; the amine obtained by cleavage of 9 with hydrochloric acid was cyclized by potassium carbonate to give the pyrroline 10 which was then reduced to the pyrrolidine 11. Oxidation of 11 with chlorine in the presence of ethanol yielded the sulfonylchloride 13 which is converted into the non-hydrolysable β-sultam ester 12. Hydrolysis of 11 gave the acid 14 which can be reesterified with p-nitrobenzyl alcohol to 15; cyclization of 15 afforded a mixture of the diastereoisomers 16 which were separated by column chromatography. Catalytic hydrogenation of 16a and 16b yielded the sodium salts 17a and 17b. This latter compound – like the analogous β-lactam penicillanic acid – is devoid of antibacterial activity (Scheme 1). An analogous strategy was involved in the preparation of the unsubstituted parent structure of sultam analogs of penicillin and its higher homologs[6] (scheme 2); bicyclic sultams are listed in Table 3. It is also possible to synthesize 1-chlorosulfonyl-2-aminoethane hydrochloride by reaction of a mixture of phosphorus pentachloride and phosphorus oxychloride with 2-aminoethanesulfonic acid which is prepared from 1,2-dibromoethane (Table 1).[9]



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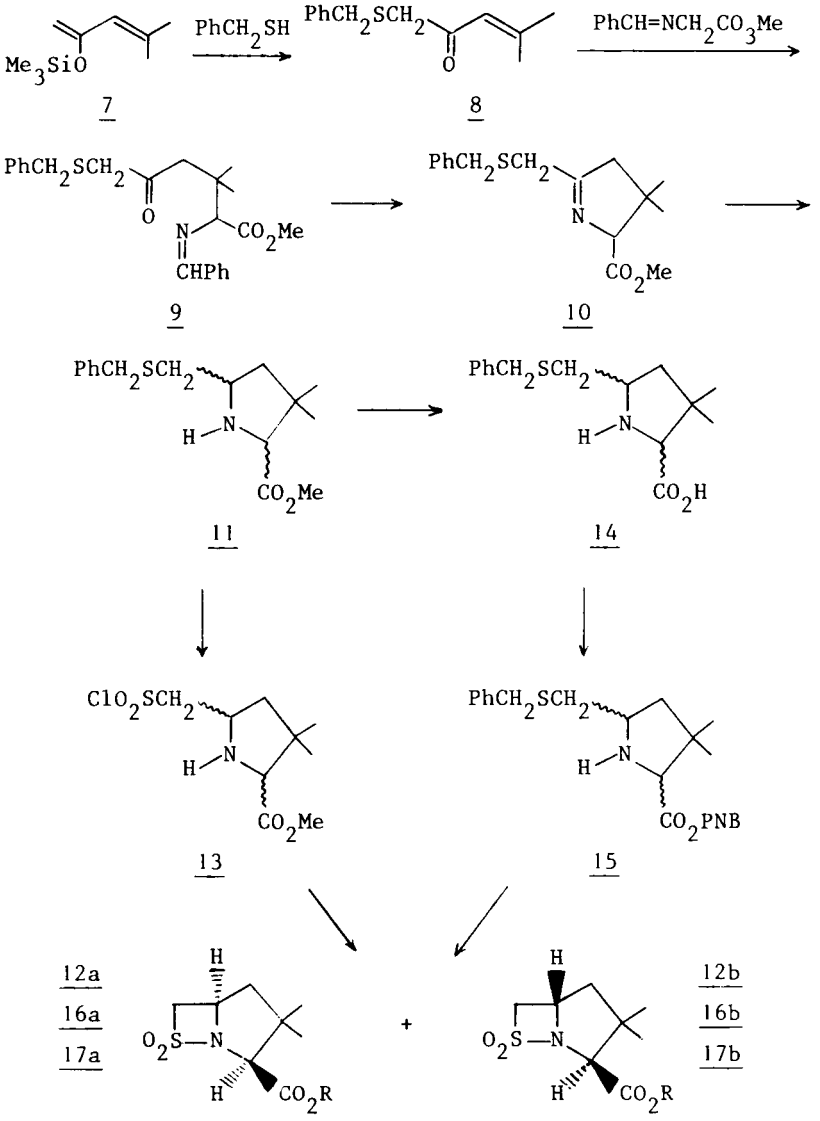
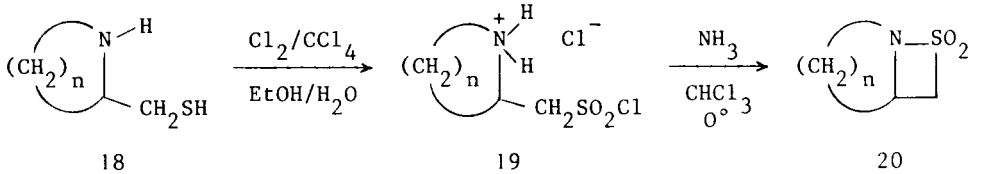


12 R = Me; 16 R = PNB; 17 R = Na

Scheme 1



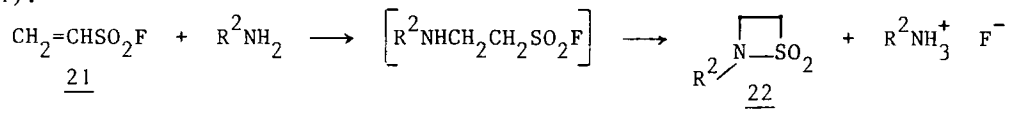
18 19 20

n = 3, 4, 5

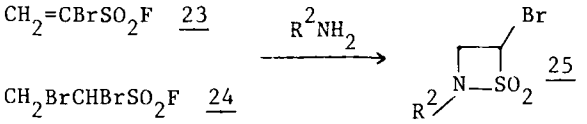
Scheme 2

B. Cyclization of 1-Fluorosulfonyl-2-Aminoalkanes[8]

The preceeding methods involved β-aminosulfonyl chloride; since chloride ion is a good leaving group, the ring closure requires that the chlorosulfonyl group be introduced on the carbon chain subsequent to amine function as the inverse strategy would lead to acyclic sulfonamide formation. On the other hand, when the reaction is carried out with fluorosulfonyl aminoethane, the amine group may be introduced after the formation of the fluorosulfonyl group since fluoride ion is a relatively poor leaving group. Thus the treatment of ethenesulfonyl fluoride (21) with two equivalents of a primary amine affords β-sultams 22 in high yields (Table 1).[8]

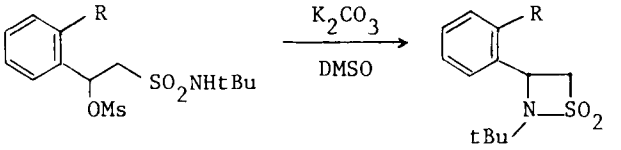


A similar cyclization was observed in the reaction of 2-bromoethenesulfonyl fluoride (23) or 1,2-dibromoethanesulfonyl fluoride (24) with primary amines; the β-bromosultams 25 were obtained (Table 4).



2. Cyclization of β-Hydroxysulfonamides (Formation of N-C Bond by Ring Closure)

Recently Thompson synthesized β-sultams 27 via N-C-3 bond formation by cyclization of β-hydroxysulfonamides mesylate (Table 5).[12] The reaction



may be viewed as involving abstraction of the amidic proton followed by an intramolecular nucleophilic substitution. β-Hydroxysulfonamides 29 are easily prepared by chemoselective C-alkylation of α,N-alkanesulfonamide dianions 28.[12] This synthesis is comparable with the preparation of β-lactams by cyclodehydrohalogenation of 3-halopropanamides in basic medium.[13]

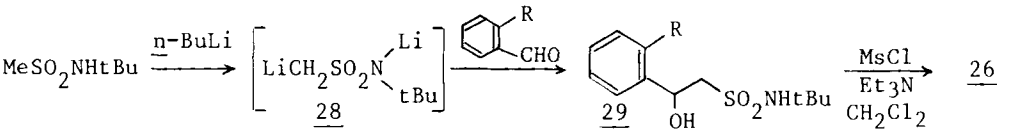


TABLE 3. Synthesis of Bicyclic β-Sultams by Cyclization of 2-Aminoalkanesulfonic Acid Derivatives

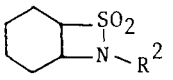
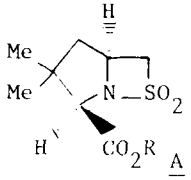
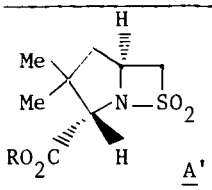
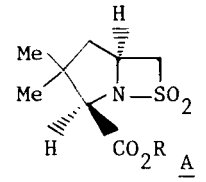
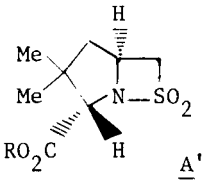
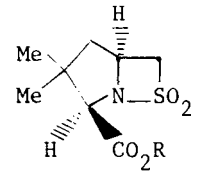
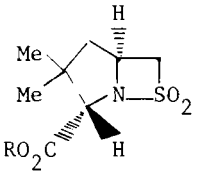
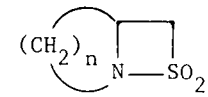
Compound	R, R^2 or n	mp. (°C)	Yield (%)	^{1}H nmr (δ)	Method	Ref.[a]
	H trans	58-59	30	5.35(s,1H), 4.00-3.50(sex, 1H), 3.40-2.80(sex,1H), 2.40-1.10(m,8H)	I.A.b	8
ibid.	H cis	83-84	92	5.60(s,1H), 4.50-4.10(sex, 1H), 3.90-3.50(sex,1H), 2.30-1.10(m,8H)	I.A.b	8
ibid.	Me trans	53	92	3.90-3.40(sex,1H), 2.59(s, 3H), 2.50-2.30(sex,1H), 2.30-1.10(m,8H)	I.A.b	8
ibid.	Me cis	92	75	4.07(q,1H), 3.30-2.90(q, 1H), 2.56(s,1H), 2.20(s, 1H), 2.20-1.20(m,8H)	I.A.b	8
ibid.	Et trans	oil	75	4.00-3.50(sex,1H), 3.30-2.50(m,3H), 2.50-1.10(m, 8H), 1.22(t,3H)	I.A.b	8
ibid.	Et cis	oil	88	4.06(q,1H), 3.40-3.10(q, 1H), 2.95(quint,2H), 2.30-1.20(m,8H), 1.23(t,3H)	I.A.b	8
ibid.	n-Pr trans	oil	78	4.00-3.50(sex,1H), 3.30-2.50(m,3H), 2.50-1.10(m, 8H), 0.97(t,3H)	I.A.b	8
ibid.	n-Pr cis	oil	84	4.05(q,1H), 3.40-2.50(m, 5H), 2.30-1.20(m,8H), 0.97 (t,3H)	I.A.b	8
ibid.	n-Bu trans	oil	62	4.00-3.50(sex,1H), 3.30-2.50(m,7H), 2.50-1.10(m, 8H), 0.92(t,3H)	I.A.b	8
ibid.	n-Bu cis	oil	92	4.05(q,1H), 3.40-3.10(m, 1H), 3.00-2.50(m,6H), 2.20-1.10(m,8H), 0.92(t,3H)	I.A.b	8
ibid.	$PhCH_2$ trans	oil	74	7.32(s,5H), 4.10-3.60(m,3H) 3.00-2.40(sex,1H), 2.40-1.10(m,8H)	I.A.b	8
ibid.	$PhCH_2$ cis	oil	95	7.30(s,5H), 4.28-3.10(m,4H) 2.20-1.10(m,8H)	I.A.b	8
	Me	131-133	54 A+A'	[c] 4.45(dd,1H), 4.30(s,1H), 4.10(m,1H), 3.90(dd,1H), 3.75(s,3H), 2.10(dd,1H), 1.85(dd,1H), 1.45(s,3H), 1.05(s,3H)	I.A.b	5

TABLE 3. (contd)

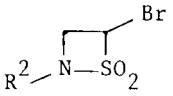
Compound	R, R^2 or n	mp. (°C)	Yield (%)	^{1}H nmr (δ)	Method	Ref.[a]
 A'	Me	87-88	54 A+A'	c 4.50-4.20(m,2H), 4.05(m,1H) 3.85(s,1H), 3.80(s,3H), 2.40-1.90(m,2H), 1.30(s,6H)	1.A.b	5
 A	f PNB	-	55 A+A'	d 8.25(d,2H), 7.57(d,2H), 5.35-5.25(AB system,2H), 4.94(dd,1H), 4.37(s,1H), 4.12(m,1H), 3.96(dd,1H), 2.12(dd,1H), 1.85(dd,1H), 1.43(s,3H), 1.00(s,3H)	1.A.b	5
 A'	f PNB	-	55 A+A'	d 8.25(d,2H), 7.60(d,2H), 5.40-5.25(AB system,2H), 4.41(dd,1H), 4.23(dd,1H), 4.05(m,1H), 3.90(s,1H), 2.25(dd,1H), 2.08(dd,1H), 1.27(s,3H), 1.25(s,3H)	1.A.b	5
	Na	-	90	e 4.05(dd,1H), 3.84(m,1H), 3.70(s,1H), 3.35(dd,1H), 1.93(dd,1H), 1.55(dd,1H), 1.30(s,3H), 0.95(s,3H)	1.A.b	5
	Na	-	96	4.22(dd,1H), 3.81(dd,1H), 3.69(m,1H), 3.52(s,1H), 2.00-1.90(AB system,2H), 1.27(s,3H), 1.17(s,3H)	1.A.b	5
	n=3	56	60	-	1.A.b	6 (9)
	n=4	57	82	-	1.A.b	6
	n=5	49-50	76	-	1.A.b	6

c. 100 MHz; d. 400 MHz; e. 400 MHz DMSO-d_6; f. PNB p.nitrobenzyl

3. Cycloaddition Reactions

Cycloaddition reactions of heterocumulenes have been widely used for the synthesis of different types of β-lactams;[13] the keteneimine interaction affords the simultaneous formation of N-C-2 and C-3-C-4 bonds while the addition of isocyanates on olefines allows the creation of C-2-C-3 and

TABLE 4. Synthesis of β-Bromosultams

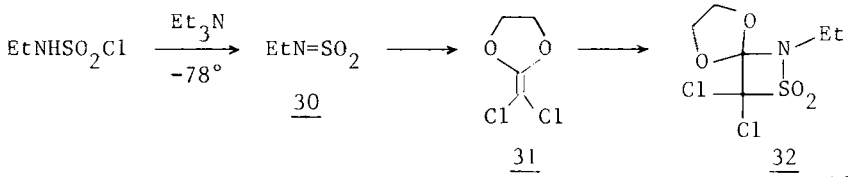


R^2	mp. (°C)	Yield (%)	^1H nmr (δ)	Method	Ref.
Et	oil	47	5.65(dd,1H), 3.70(dd,1H), 3.40-3.00 (m,3H), 1.30(t,3H)	1.B	8
i-Pr	43-44	50	5.60(dd,1H), 3.75(dd,1H), 4.00-3.00 (m,2H), 1.20(d,6H)	1.B	8
t-Bu	85-86	56	5.55(dd,1H), 3.80(dd,1H), 3.20(dd, 1H), 1.40(s,9H)	1.B	8
C_6H_{11}	60-60.5	38	5.60(dd,1H), 3.80(dd,1H), 3.20(dd, 1H), 2.20-1.00(m,11H)	1.B	8
$PhCH_2$	41-42	80	7.30(s,5H), 5.60(dd,1H), 4.20(s,2H), 3.60(dd,1H), 3.00(dd,1H)	1.B	8

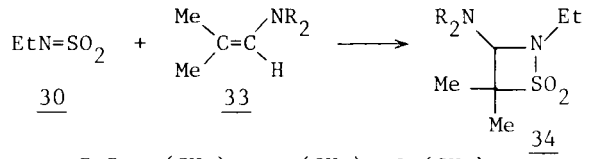
N-C-4 bonds. In the same way, β-sultams can be synthesized by sulfeneimine interaction (simultaneous formation of C-3-C-4 and S-N bonds) or sulfonylamine-olefin interaction (formation of S-C-4 and N-C-3 bonds).

A. Reaction of N-Sulfonylamines with Olefins

N-sulfonylamines, prepared by the action of triethylamine on sulfamoyl chlorides, react with nucleophilic olefins to give 1,2-thiazetidine-1,1-dioxides.[13-17] Ethylsulfamoyl chloride reacts rapidly with triethylamine to afford N-sulfonylethylamine (30). When 30 was generated in the presence of the dioxolane 31, the β-sultam 32 was isolated in 85% yield (Table 5).[16] This method was also successfully used with the pyrrolidine



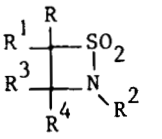
enamine or the morpholine enamine of isobutyraldehyde 33 (Table 5).[16,17]



R,R = $(CH_2)_4$ or $(CH_2)_2$-O-$(CH_2)_2$

If the enamines possess either a methylene group on the α-carbon or a hydrogen on the β-carbon, acyclic sulfonamides 38 or 39 are obtained.[17]

TABLE 5. Synthesis of Substituted β-Sultams by Cyclization of β-Hydroxysulfonamides or Cycloaddition Reactions

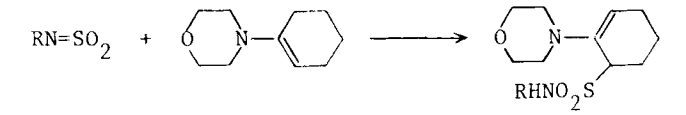


R	R^1	R^2	R^3	R^4	mp. (°C)	Yield (%)	^{1}H nmr (δ)	Method	Ref.
H	H	t-Bu	oPhNO$_2$	H	179-181	53	[g] 8.23(d,1H,J=3), 7.95(d, 1H,J=3), 7.73(t,1H,J=3), 7.50(t,1H,J=3), 5.05(dd, 1H,J=2,J=4), 4.69(dd,1H, J=4,J=12), 3.80(dd,1H,J= 2,J=12), 1.25(s,9H)	1.2	12
Cl	Cl	Et			74-75	85	4.27(m,4H), 3.28(q,2H, J=7), 1.33(t,3H,J=7)	1.3.A	16
Me	Me	Me		H	oil	-	3.83-3.60(m,4H), 3.31(s, 1H), 2.76(s,3H), 3.13-2.50(m,4H), 1.56(s,6H)	1.3.A	17
Me	Me	Et		H	oil	-	[h] 3.66(s,1H), 3.22(q,2H, J=7), 3.00-2.51(m,4H), 1.94-1.62(m,4H), 1.57(s, 6H), 1.28(t,3H,J=7)	1.3.A	16
Me	Me	Et		H	oil	-	1.26(t,3H,J=7), 1.56(s, 6H), 2.50-3.13(m,4H), 3.46(s,1H), 3.60-3.83(m, 4H), 3.25(q,2H,J=7)	1.3.A	17
H	H	PhCO	OEt	H	87-88	71	8.20-7.30(m,5H), 5.93(m, 1H), 4.38-3.20(m,2H), 4.15(q,2H,J=7), 1.38(t, 3H,J=7)	1.3.A	16
Me	H	CO_2Me	Me	Me	55-56	-	-	1.3.A	15
Me	Me	CO_2Me		H	122-123	-	-	1.3.A	15
H	H	CO_2Me	Ph	H	138-139.5	-	ABX system: 5.09(dd,1H, J=5,J=8.3), 4.66(dd,1H, J=8.3,J=12.5), 4.05(dd, 1H,J=5,J=12.5)	1.3.A	15
H	H	CO_2Me	pPhOMe	H	118-119	-	-	1.3.A	15
H	H	CO_2Me	Ph	Ph	175-176	-	-	1.3.A	15
PhCO	H	n-Pr	Ph	H	148	13	[i] 4.93(d,1H,J=6), 5.58(d, 1H,J=6)	1.3.A	18
PhCO	H	Ph	Ph	H	164-165	22	[i] 6.15(d,1H,J=6), 5.81(d, 1H,J=6)	1.3.A	18
PhCO	H	pPhOMe	Ph	H	138	10	[k] 6.10(d,1H,J=6), 5.68(d, 1H,J=6)	1.3.A	18

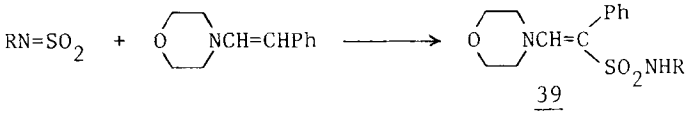
TABLE 5. (contd)

R	R^1	R^2	R^3	R^4	mp. (°C)	Yield (%)	^{1}H nmr (δ)	Method	Ref.
PhCO	H	$PhCH_2$	Ph	H	143	5	5.57(d,1H,J=6), 4.97(d, 1H,J=6)	1.3.A	18
PhCO	H	pPhMe	Ph	H	163	24	6.15(d,1H,J=6), 5.77(d, 1H,J=6) [i]	1.3.A	18
Ph	H	Me cis	pPhCl	H	154-155	}88	7.32-7.10(m,9H), 5.73(d, 1H,J=8.8), 4.72(d,1H,J= 8.8), 2.88(s,3H)	1.3.B	19
Ph	H	Me trans	pPhCl	H	89-90		7.52-7.33(m,9H), 5.16(d, 1H,J=7.5), 4.24(d,1H,J= 7.5), 2.78(s,3H)	1.3.B	19
Ph	H	Me cis	$pPhNO_2$	H	179-180	}52	8.18-7.10(m,9H), 5.82(d, 1H,J=9), 4.81(d,1H,J=9), 2.94(s,3H)	1.3.B	19
Ph	H	Me trans	$pPhNO_2$	H	170-171		8.39-7.43(m,9H), 5.18(d, 1H,J=7), 4.37(d,1H,J=7), 2.85(s,3H)	1.3.B	19
Ph	H	Me cis	Ph	H	147-148	}80	7.28-6.98(m,10H), 5.74 (d,1H,J=8.5), 4.75(d,1H, J=8.5), 2.89(s,3H)	1.3.B	19
Ph	H	Me trans	Ph	H	81-82		7.60-7.12(m,10H), 5.22 (d,1H,J=7), 4.28(d,1H, J=7), 2.80(s,3H)	1.3.B	19
Ph	H	Me cis	pPhOMe	H	132-133	}80	7.32-6.62(m,9H), 5.68 (d,1H,J=8.5), 4.73(d,1H, J=8.5), 3.70(s,3H), 2.88 (s,3H)	1.3.B	19
Ph	H	Me trans	pPhOMe	H	oil		7.58-6.78(m,9H), 5.18(d, 1H,J=7), 4.22(d,1H,J=7), 3.78(s,3H), 2.74(s,3H)	1.3.B	19

g. 200 MHz; h. in benzene; i. in CD_3NO_2; j. in CD_3CN; k. in dioxan



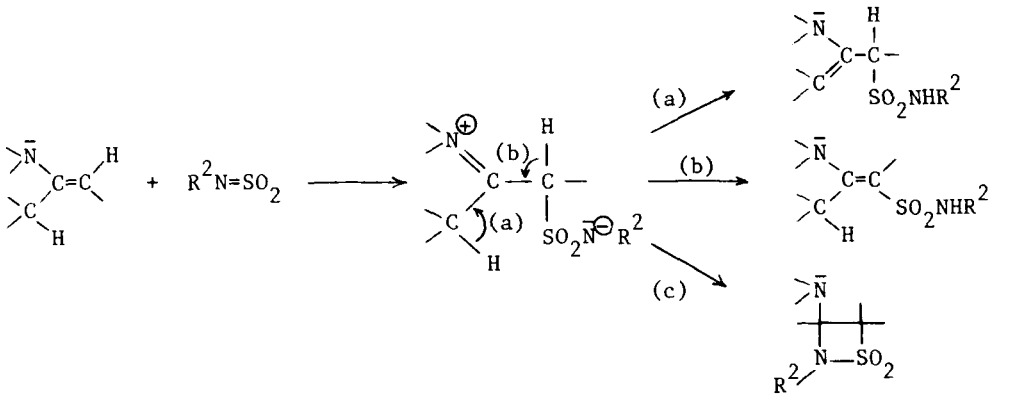
38



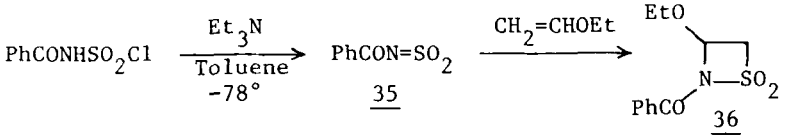
39

R = Me, Et

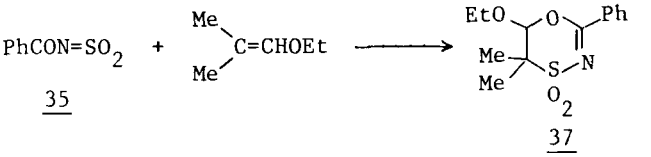
These results have been rationalized within the framework of a zwitterionic intermediate which may evolve in accord with three paths.[17] It is noteworthy that the cyclization fails with olefins of moderate nucleophi-



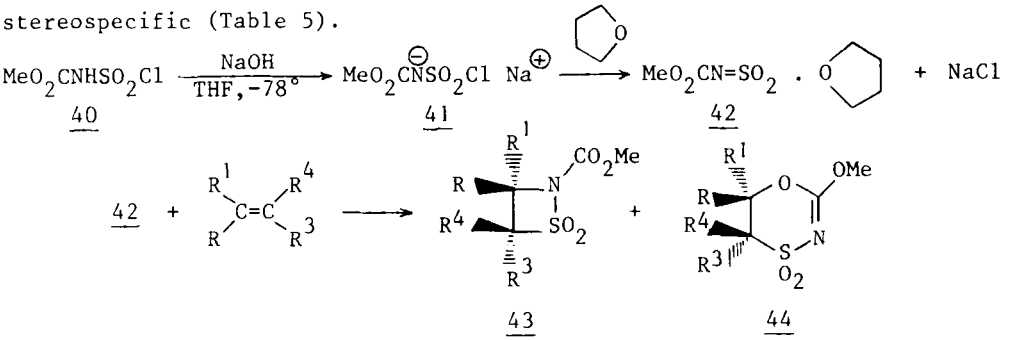
licity. These olefins give only the cycloaddition when N-sulfonylamines are of greater electrophilicity. For instance when N-sulfonylbenzamide (35) is generated in the presence of ethyl vinyl ether, β-sultam 36 was obtained in 70% yield (Table 5).[16] 1,2-Thiazetidine-1,1-dioxide formation



can partly or totally compete with 1,4-cycloaddition; this is the case when 35 was allowed to react with isobutenyl ethyl ether as the only cycloadduct isolated was the oxathiazine 37.[16] An alternative method[15]

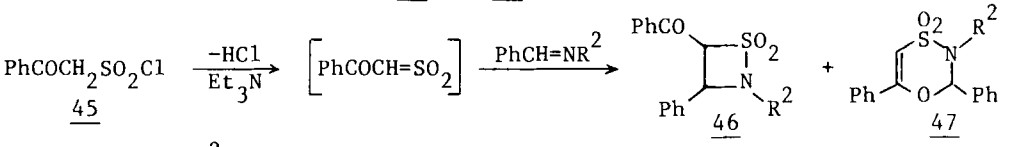


consists of the treatment of sulfamoyl chloride (40) with sodium hydride at -78° in tetrahydrofuran solution. At 30° the salt formed 41 was decomposed rapidly to give the solvated complex 42. This species demonstrates a high degree of electrophilic reactivity in cycloadditions with substituted alkenes to afford β-sultams 43 and oxathiazines 44; the reaction is stereospecific (Table 5).



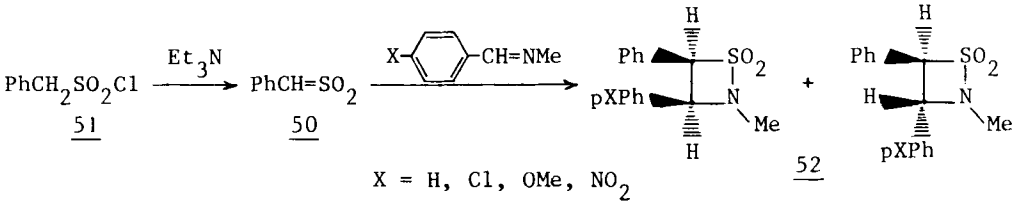
B. Reaction of Sulfenes with Imines

Usually, sulfenes are generated in situ by dehydrohalogenation of suitable methanesulfonyl chlorides derivatives in the presence of a tertiary base.[18,19] The reactions of benzoylmethanesulfonyl chloride (45) with various benzylidenamines were reported to afford the corresponding (2+2) and (4+2) cycloadducts 46 and 47 (Table 5).[18] The percentage of



R^2 = Pr, Ph, pMePh, pMeOPh, $PhCH_2$, cyclohexyl

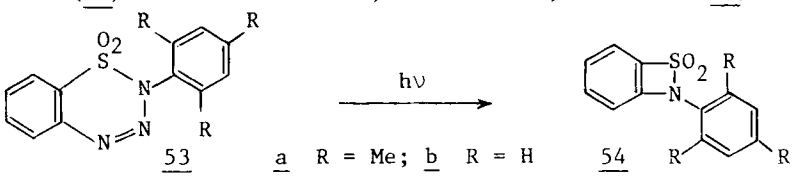
(2+2) and (4+2) cycloadducts depends on the nature of the substituents R in the anils and on the reaction conditions. In the absence of triethylamine, the sulfonyl chloride 45 gave only the (2+2) cycloadduct while the (4+2) cycloadduct was obtained exclusively in the presence of triethylamine.[18] The stereochemistry of the cycloaddition has been studied for the reaction of phenylsulfene with Schiff bases. Phenylsulfene (50) generated in THF from benzylsulfonyl chloride (51) and triethylamine reacted with N-(p-substituted)benzylidenemethylamine to give 2-methyl-4-phenyl-3-aryl-1,2-thiazetidine-1,1-dioxide 52 which were separated into cis and trans



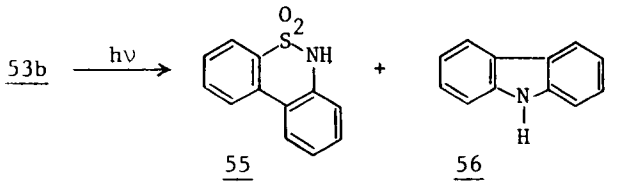
X = H, Cl, OMe, NO_2

isomers (Table 5). In all cases the preferred formation of the cis isomer over the trans isomer was observed. This result suggests that the reaction would be a concerted $[\pi^2s + \pi^2a]$ cycloaddition with some secondary effects.[19]

Outside the reactions regrouped in the three previously described processes it is worthy to note a photolysis reaction affording to a stable benzo-β-sultam. Photolysis of 2-mesityl-2-H-benzo[e]-1,2,3,4-thiatriazine-1,1-dioxide (53a) yields the benzo-β-sultam 54 whilst irradiation of 53b gives carbazole (56) and the dibenzo-1,2-thiazine-1,1-dioxide (55).[20]



a R = Me; b R = H



53b → 55 + 56

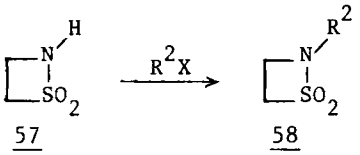
II. REACTIONS OF β-SULTAMS

The reactions which take place with β-sultams show that their chemical properties are in many respects comparable with those of β-lactams.

1. Reactions without Destruction of β-Sultam Ring

A. N-Alkylation

It is possible to alkylate the β-sultam 57 according to a phase-transfer method which had been developed for β-lactams.[9] Activated alkyl halides such as allyl bromide and benzyl bromide reacted rapidly; the β-sultams 58 obtained by this process are listed in Table 6.



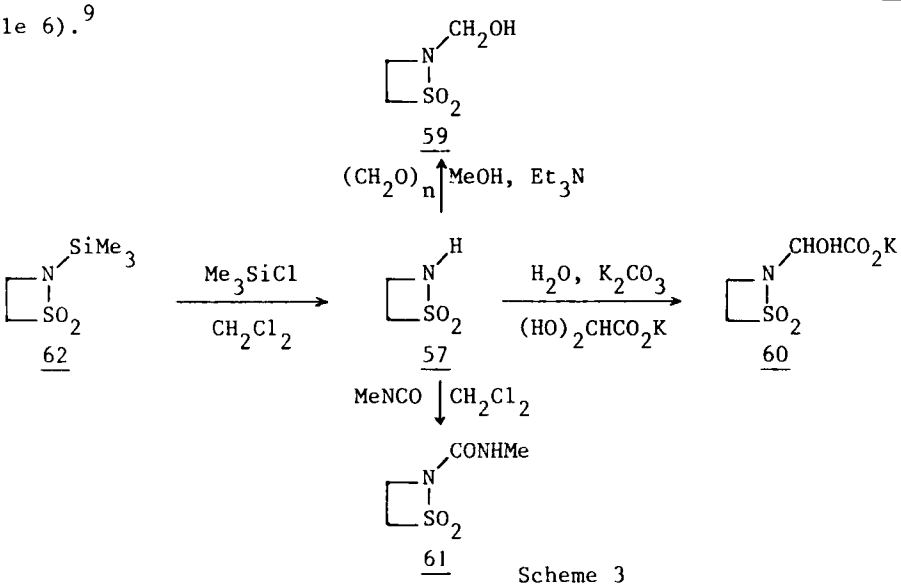
57 → 58 (R^2X)

B. N-Acylation

The introduction of a acyl group in 2-position results in destabilisation of the molecule and is thus relatively difficult; however introduction of a methoxycarbonyl group is easy by means of methyl chloroformate.[9]

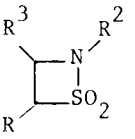
C. Various N-Substitutions

Scheme 3 summarizes various substitutions realized on N-atom of 57 (Table 6).[9]



Scheme 3

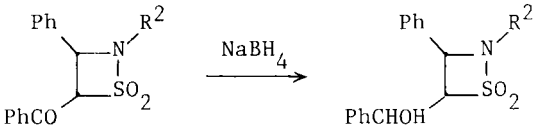
TABLE 6. Synthesis of β-Sultams by Various Reactions



R	R^2	R^3	mp. (°C)	Yield (%)	^{1}H nmr (δ)	Method	Ref.[a]
H	$CH_2CH=CH_2$	H	-	72	-	II.1.A	9
H	CH_2COMe	H	-	22	-	II.1.A	9
H	CH_2CO_2Et	H	-	31	-	II.1.A	9
H	n-C_6H_{13}	H	-	76	-	II.1.A	9
H	$CH_2CO_2CH_2Ph$	H	-	47	-	II.1.A	9
H	CH_2OH	H	-	100	-	II.1.C	9
H	$CHOHCO_2K$	H	-	57	-	II.1.C	9
H	COMe	H	-	27	-	II.1.C	9
H	CONHMe	H	-	87	-	II.1.C	9
H	CO_2Me	H	-	82	-	II.1.C	9
H	PhCO	H	-	2	-	II.1.C	9 (21)
H	$SiMe_3$	H	-	78	-	II.1.C	9
PhCHOH	Ph	Ph	195	83	7.60-6.70(m,15H), 5.35(q,1H) 4.80-4.50(m,2H), 4.14(d,1H)	II.1.D	18
PhCHOH	n-Pr	Ph	103-104	84	7.40-6.90(m,10H), 5.24(d,1H) 4.42(q,1H), 3.86(d,1H), 3.40-2.50(m,3H), 1.80-1.20 (m,2H), 0.90(t,3H)	II.1.D	18

D. Reduction

Ring cleavage of β-sultams 46 does not occur by treatment with sodium borohydride; only reduction of the carbonyl group is observed.[18]



46 R^2 = Pr, Ph 63

2. Reactions with Destruction of β-Sultam Ring

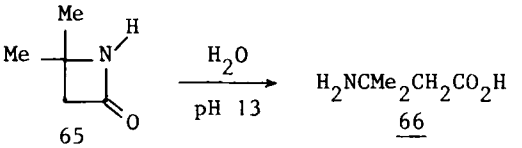
The various bonds in β-sultams can undergo cleavage to give acyclic intermediate which may further undergo transformation.

A. Cleavage of the N-S Bond

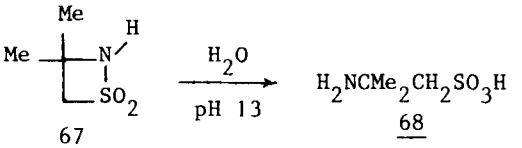
The β-sultam bond undergoes rupture in the presence of water, alkali or acid. Ethanesultam (57) readily dissolves in water and is slowly transformed in taurine (64).[2] The stability of β-sultams has been compared with

57 64

those of β-lactams in aqueous basic and acidic solutions.[9] At pH 13, β-lactam 65 was converted only half as fast as β-sultam 67. The difference in

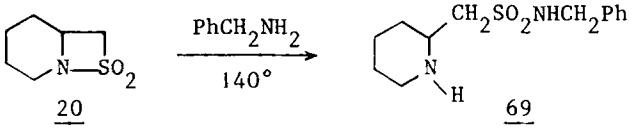


65 66



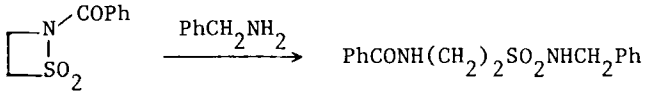
67 68

stability between the two 4-membered heterocycles is more dramatic in acidic solutions. The half life of 67 is 12 min. at pH 2.3 whereas 65 remains unchanged under these conditions for over 24 hours. Ethanesultam (57) is converted to chlorosulfonyl aminoethane with hydrogen chloride in anhydrous medium.[2] The bicyclic β-sultam 20 is converted to sulfonamide 69 by treatment with benzylamine at temperature above 140°.[9] Similarly, N-ben-



20 69

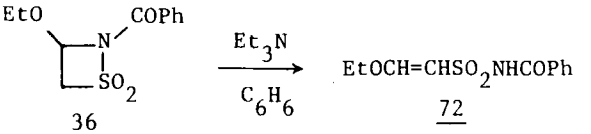
zoylethanesultam (70) reacts with benzylamine to give the 2-benzamido-N-benzylethanesulfonamide (71).[21]



70 71

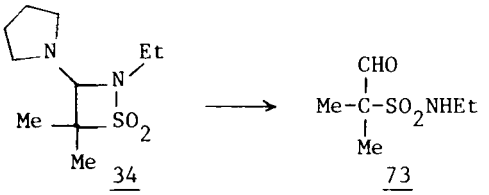
B. Cleavage of the N-C bond

Functionalized sultams which are often relatively unstable, are cleaved in nucleophilic medium, attack occuring on the C-3 of the ring. For example, the β-sultam 36 is converted in N-benzoyl ethoxy-2-ethenesulfonamide (72) by treatment with triethylamine in benzene at 30°.[14] 3-Aminosul-

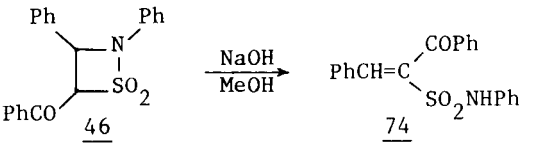


36 72

tam 34 is hydrolysed during chromatography over florisil with formation of α-(ethylsulfamoyl)isobutyraldehyde (73).[16] The treatment of the benzoyl-

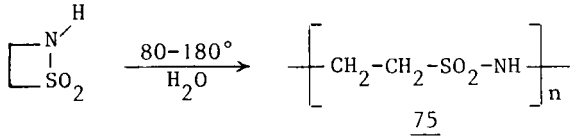


sultam 46 (R^2=Ph), with methanolic sodium hydroxide gives β-benzoyl-β-phenylsulfamoylstyrene (74).[18]

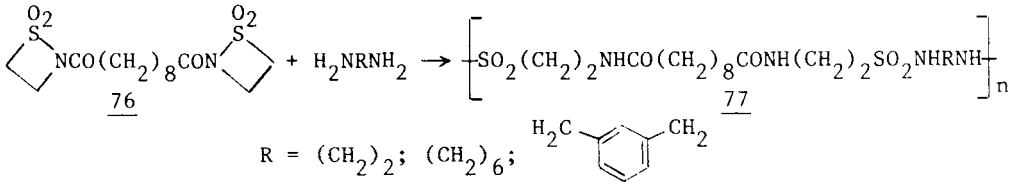


C. Reactions of Polymerization

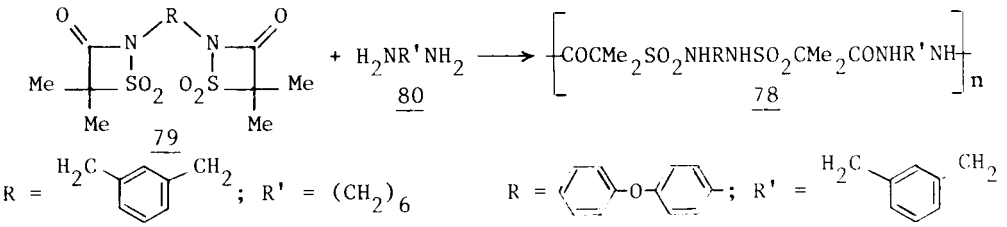
As many small heterocycles, β-sultams can give polymers by ring opening polymerization. While several investigations have dealt with the polymerization of propane and butanesultams,[22] only a few studies concern β-sultams. In 1972, Imai reported the synthesis of polyethanesultam 75, a polysulfonamide analogue to a Nylon-3, by ring opening polymerization of ethanesultam with water catalysis.[23] Aliphatic diamines react with bis-



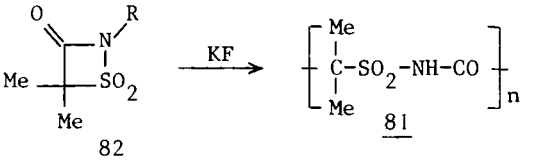
ethanesultam (76) to give polymers of ring opening polyaddition 77.[21]



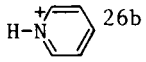
Polyamide-sulfonamides 78 were also obtained by ring opening polyaddition of aliphatic diamines with 2,2'-disubstituted-bis(thiazetidinone-1,1-dioxides).[24] Bis(thiazetidinone-1,1-dioxide) monomers 79 were synthesized by



condensation of 2-chlorosulfonyl-2-methylpropionyl chloride with diamines 80. Although 1,2-thiazetidine-3-one-1,1-dioxides strictly speaking do not belong to β-sultam family, it is noteworthy that these products are easily polymerized by ring opening in various conditions. For example, poly(acylsulfonamides) 81 were prepared with high yield by ring opening polymerization of 82, catalysed by potassium fluoride[25] or by anionic ring opening polymerization.[26]

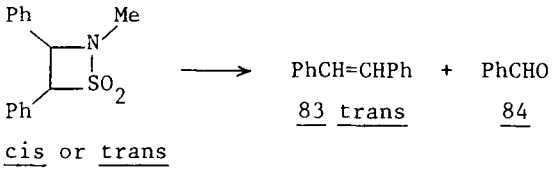


82 → 81

R = H,[25] K^+,[26b] $HNEt_3^+$,[26b]  [26b]

D. Thermolysis

Only one report deals with β-sultam thermolysis.[19] Pyrolysis of cis-sultam 52 at 220° in nitrogen atmosphere yielded trans-stilbene (83) and benzaldehyde (84); the yield of the latter compound is very low (∿5%); the same results were obtained from the trans-isomer 52. This fragmentation, which is non-stereospecific, is very different from that of β-lactams wherein cleavage leading to an olefinic compound proceeded with total retention of configuration.[27]



52 cis or trans → PhCH=CHPh (83 trans) + PhCHO (84)

In contrast to that of β-lactams, the chemistry of β-sultams is still being developed. This is probably because, until these recently there was a scarcity of good synthetic processes. However, their potential utility as biological active molecules, their usefulness as synthons and their tendency toward polymerization promise a rich future harvest from the study of these substances.

REFERENCES

1. H. Baganz and C. Bransch, Chem. Ber., 93, 784 (1960).
2. A. Le Berre and J. Petit, Tetrahedron Lett., 213 (1972).
3. E. Kohler, Am. Chem. J., 19, 728 (1897).

4. a) P. W. Clutter Buck and J. B. Cohen, J. Chem. Soc., 121, 120 (1922); b) W. Autenrieth and P. Rudolph, Ber., 34, 3469 (1901); c) W. Autenrieth and J. Kodurger, ibid., 36, 3626 (1963); d) U. Zoller, Phosphorus and Sulfur, 1, 305 (1976).

5. F. Cavagna, W. Koller, A. Linkies, H. Rehling and D. Reuschling, Angew. Chem. Int. Ed. Engl., 21, 548 (1982).

6. H. H. Otto and P. Schwenkkraus, Tetrahedron Lett., 23, 5389 (1982).

7. J. W. Timberlake and E. S. Elder, "Comprehensive Heterocyclic Chemistry", Vol. 7, p. 449, A. R. Katritzky and C. W. Rees, Eds., Pergamon Press, Oxford, New-York, 1984.

8. A. Champseix, J. Chanet-Ray, A. Etienne, A. Le Berre, J. C. Masson, C. Napierala and R. Vessière, Bull. Soc. Chim. France, 463 (1985).

9. W. Koller, A. Linkies, H. Rehling and D. Reuschling, Tetrahedron Lett., 24, 2131 (1983).

10. E. Meyle and H. H. Otto, Arch. Pharm., 316, 281 (1983).

11. A. Le Berre, A. Etienne and B. Dumaitre, Bull. Soc. Chim. France, 946 (1970).

12. M. E. Thompson, J. Org. Chem., 49, 1700 (1984).

13. A. K. Mukerjee and A. K. Singh, Tetrahedron, 34, 1731 (1978).

14. G. M. Atkins and E. M. Burgess, J. Am. Chem. Soc., 89, 2502 (1967).

15. E. M. Burgess and W. M. Williams, ibid., 94, 4386 (1972).

16. G. M. Atkins and E. M. Burgess, ibid., 94, 6135 (1972).

17. T. Nagai, T. Shingaki, M. Inagaki and T. Ohshima, Bull. Chem. Soc. Japan, 52, 1102 (1979).

18. O. Tsuge and S. Iwanami, ibid., 43, 3543 (1970).

19. T. Hiraoka and T. Kobayashi, ibid., 48, 480 (1975).

20. G. Ege and E. Beisiegel, Liebigs Ann. Chem., 763, 46 (1972).

21. Y. Imai, H. Hirukawa, K. Okuyama and M. Ueda, Makromol. Chem., 180, 25 (1979).

22. W. H. Libby, U.S. Patent 2,983,713, May 9, 1961; Chem. Abstr., 55, 19342c (1961).

23. Y. Imai and H. Hirukawa, Polymer Letters Edition, 11, 271 (1973).

24. Y. Imai, M. Ueda and K. Okuyama, Makromol. Chem., 180, 1413 (1979).

25. Y. Imai, M. Ueda and K. Okuyama, ibid., 179, 2327 (1978).

26. a) Y. Imai, M. Ueda and K. Okuyama, Polymer Journal, 10, 637 (1978); b) Y. Imai, M. Ueda and K. Okuyama, ibid., 11, 613 (1979).

27. L. A. Paquette, M. J. Wyvratt and G. R. Allen Jr, J. Am. Chem. Soc., 92, 1763 (1970).

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