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A STEREOSPECIFIC SYNTHESIS OF β-ALKOXY-β-LACTAMS (1)

Ajay K. Bose, J.C. Kapur, S.G. Amin and M.S. Manhas*

Department of Chemistry and Chemical Engineering
Stevens Institute of Technology
Hoboken, New Jersey 07030

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Since the discovery (2) of 7-methoxy cephalosporins and their biological activity considerable attention has been directed towards the synthesis of α-methoxy-β-lactams (3). For some time we have been interested in the synthesis of β-alkoxy-β-lactams and have reported the preparation of one such compound through a multi-step sequence of reactions in which isomeric products were obtained (4). In this communication we describe a facile method for the stereospecific synthesis of β-alkoxy-β-lactams in good yield.

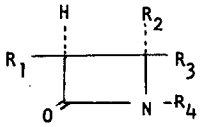
Attempts to synthesize 4-alkoxy-2-azetidinones 2 *via* the "acid chloride-imine" reaction were unsuccessful when an imino-ether 1 was employed as the imine component. The preparation of a β-alkoxy-β-lactam through the intermediacy of a β-chloro-β-lactam 4 also failed because the reaction of the imino-chloride 3 with an acid chloride did not produce a β-lactam. Advantage was then taken of the reaction between imino-thioethers and acid chlorides to afford β-lactams 5 with an SR group at C_4 (Scheme 1) and several compounds of this general structure were synthesized. This reaction led to a single isomer of the product with E configuration as had been previously noted by us (5).

The 4-methylthio-2-azetidinones could be converted to the corresponding 4-methoxy-2-azetidinones by treatment with bromine (1 mole) at -78° in dichloromethane followed by dropwise addition of methanol. The reaction mixture after quenching with aqueous sodium bicarbonate and usual work up gave about 60% of the product as a single isomer. By using this general procedure the β-lactams 7,8,9 and 11 were converted to the corresponding β-methoxy derivatives 12, 13, 14, and 16 respectively. We have found that $-S-CH_2Ph$ at C_4 in 10 can also be replaced by an $-OCH_3$ function to give 14 under similar conditions. Using ethanol instead of methanol, the β-ethoxy-β-lactam 15 could be synthesized from 7.

In order to explore the general applicability of this reaction a 4-phenylthio-2-azetidinone 24 was prepared by the reaction of the imino-thioether 23 with phenoxyacetyl chloride in the presence of triethylamine. This phenylthio-β-lactam 24 was found suitable as a substrate for introducing the methoxy group; the desired β-lactam 25 was obtained in 60% yield.

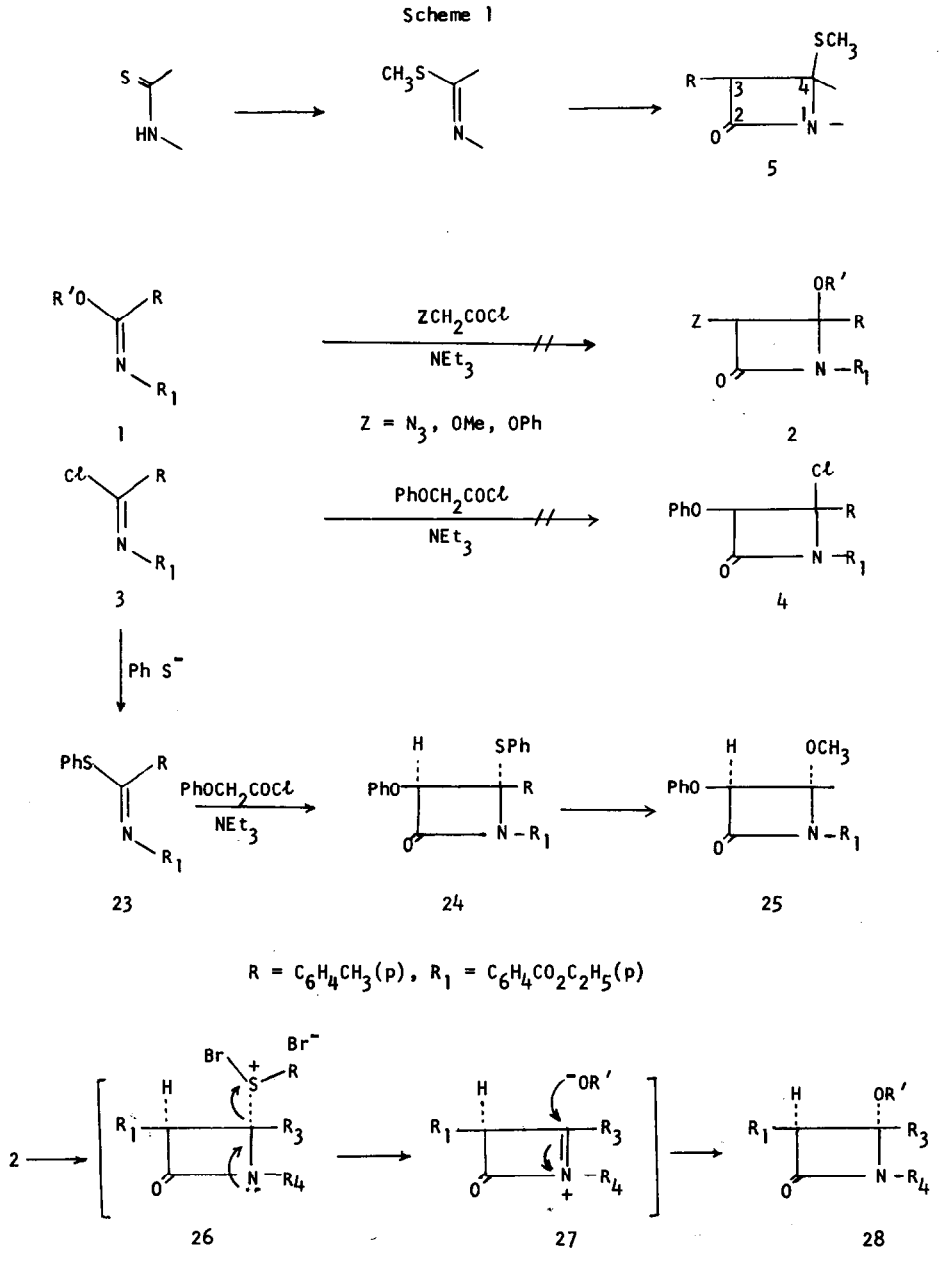
The presence of an azido group at C_3 in 17 did not interfere with this replacement reaction and the β-lactam 18 was formed. The α-azido-β-lactam 18 was used as an intermediate for incorporating the amide side chain through catalytic reduction to 19 and subsequent acylation to 20.

The E stereochemistry of 7 has been established (5) previously on the basis of its PMR spectrum (τ 7.8, $S\underline{CH_3}$) and Raney Ni desulfurization to the *cis* β-lactam 6. An examination of the PMR spectrum of the β-methoxy-β-lactam 12 derived from 7 shows a normal value (τ 6.38) for the $-OCH_3$ signal. This observation leads us to the conclusion that the methoxy β-lactam 12 also has an E configuration and that the C_4-OCH_3 and C_3-Ph are *trans* to each other (6). Furthermore the addition of Eu(FOD)$_3$ to 12 led to a down-



	R_1	R_2	R_3	R_4
6	Ph	H	Ph	Ph
7	Ph	SMe	Ph	Ph
8	OMe	SMe	Ph	Ph
9	OPh	SMe	Ph	Ph
10	OPh	SCH_2Ph	Ph	Ph
11	OPh	SMe	Ph	$C_6H_4CO_2Et$ (p)
12	Ph	OMe	Ph	Ph
13	OMe	OMe	Ph	Ph
14	OPh	OMe	Ph	Ph
15	Ph	OEt	Ph	Ph
16	OPh	OMe	Ph	$C_6H_4CO_2Et$ (p)
17	N_3	SMe	Ph	Ph
18	N_3	OMe	Ph	Ph
19	NH_2	OMe	Ph	Ph
20	$PhOCH_2CONH$	OMe	Ph	Ph
21	SCh_2Ph	H	Ph	Ph
22	OPh	H	$C_6H_4NMe_2$ (p)	C_6H_4SMe (p)

Scheme 1


S
HN
CH3S
N
SCH3
R
3
4
2
1
O
N –
5
R'O
R
N
R1
1
ZCH2COCℓ
NEt3
Z = N3, OMe, OPh
OR'
Z
R
O
N –R1
2
Cℓ
R
N
R1
3
PhOCH2COCℓ
NEt3
PhO
Cℓ
R
O
N –R1
4
Ph S–
PhS
R
N
R1
23
PhOCH2COCℓ
NEt3
H
SPh
PhO
R
O
N –R1
24
H
OCH3
PhO
O
N –R1
25
R = C6H4CH3(p), R1 = C6H4CO2C2H5(p)
2
Br
Br–
S+
R
H
R1
R3
O
N
R4
26
–OR'
N+
27
OR'
28

field shift of the C_4-OCH_3 and C_3-H signals. The magnitude of the C_3-H signal shifts was larger than that for the $-OCH_3$ group. This is indicative of the complex formation at the ether oxygen which causes a larger shift in the C_3-H signal - suggesting a *cis* disposition of these groups in the molecule. The PMR spectrum of 8 shows the $-SCH_3$ signal at τ 7.89 and the $-OCH_3$ signal at τ 6.76. This unusually high field value for the chemical shift of the $-OCH_3$ signal has been ascribed to the ring current effect of the *trans* phenyl group at C_4. Substitution of $-SCH_3$ in 8 by $-OCH_3$ resulted in 13 whose PMR spectrum showed two methoxy signals at τ 6.8 and 6.47 respectively. The normal value for the resonance signal of the incoming $-OCH_3$ group is clearly indicative of its *cis* geometry relative to the C_3-H. The NMR spectrum of other 4-alkoxy-β-lactams described here also showed the normal position of the alkoxy proton signals. It, thus, appears that the formation of 4-alkoxy-β-lactams from the corresponding alkylthio or arylthio compounds is a stereospecific reaction and proceeds *via* retention of configuration.

The replacement reaction leading to the β-alkoxy-β-lactams can be visualized as proceeding through the intermediacy of an unsaturated β-lactam 27 and a subsequent attack by the nucleophile. The formation of the unsaturated intermediate 27 envisages the participation of the nitrogen lone pair. The involvement of such an intermediate has also been postulated by Sheehan (7), Barton (8) and Kukolja (9). This mechanism finds further support from the failure of the β-lactams 21 and 22 to give the corresponding methoxy derivative. It is interesting to note that the reaction of a nucleophile on the unsaturated intermediate of type 27 postulated by Barton (8) results in inversion at C_4 of the azetidinone ring. Kukolja (9), however, reports the formation of isomeric products from the same type of intermediate.

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