A Convenient Synthesis of *N*-Benzyloxy-β-lactams *via* *N*-Benzyloxyimines

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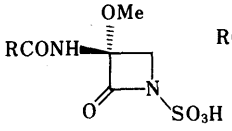
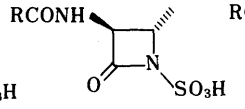
***N*-Benzyloxy-β-lactams were prepared from *N*-benzyloxyimines by reaction with ketene trimethylsilyl acetals in the presence of trimethylsilyl triflate followed by cyclization, or with lithium ester enolates in one step.**

Keywords *N*-benzyloxy-β-lactam; *N*-benzyloxyimine; monobactam; ketene silyl acetal; trimethylsilyl triflate; lithium ester enolate

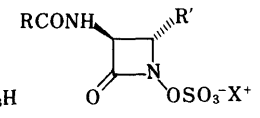
Novel monocyclic β-lactams such as sulfazecin (**1**),[1] azthreonam (**2**),[2] and monosulfactam (**3**)[3] have attracted much interest because of their potent antibacterial activities against gram-negative bacteria as well as their simple and unique structures. These antibiotics have a sulfo group on



1 sulfazecin



2 azthreonam



3 monosulfactam

the β-lactam nitrogen. The synthesis of *N*-unsubstituted and *N*-hydroxylated β-lactams has therefore become an important subject in connection with these antibiotics. A number of new methods have been developed for the construction of β-lactam rings having suitable substituents.[3,4]

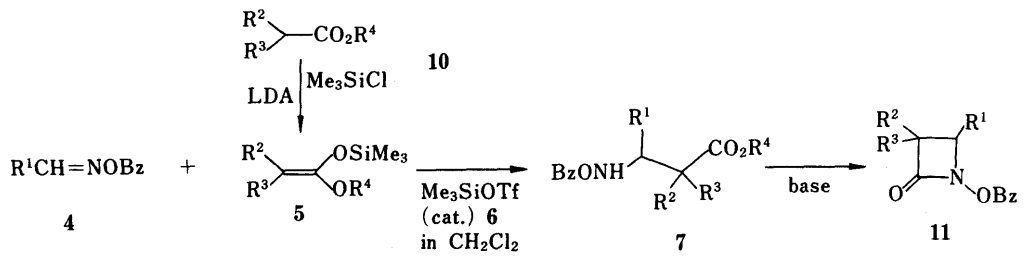
We have developed two efficient approaches using *N*-benzyloxyimines for the preparation of monocyclic *N*-benzyloxy-β-lactams which are convertible to *N*-hydroxylated β-lactams by catalytic hydrogenation and then to *N*-unsubstituted ones by treatment with titanium trichloride. We found that *N*-benzyloxyimines (**4**) reacted with ketene silyl acetals (**5**) in the presence of trimethylsilyl triflate (**6**) catalyst to give alkyl β-benzyloxyaminocarboxylates (**7**), which were cyclized to the corresponding β-lactams[5] (method A) (Chart 1). We also found an alternative method for synthesis of *N*-benzyloxy-β-lactams which involves the reaction of *N*-benzyloxyimines (**4**) with lithium enolates generated *in situ* from carboxylic esters[6] (method B) (Chart 1).

We now report the results of detailed investigations of the synthesis of *N*-benzyloxy-β-lactams.

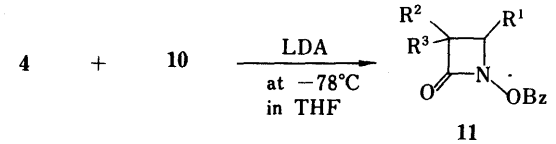
Reaction of *N*-Benzyloxyimines with Ketene Silyl Acetals In contrast to previous papers[4a-k] on the synthesis of *N*-benzyloxy-β-lactams through N–C_4 ring closure, we exploited a new route through N–C_2 ring closure, which involves synthesis of alkyl β-benzyloxyaminocarboxylates as key precursors. In the present study, we employed *N*-benzyloxyimines (**4**), prepared from benzyloxyamine and the corresponding aldehydes, for the introduction of benzyloxyaminoalkyl- ($PhCH_2ONHCH$-) or aminoalkyl- (NH_2CH-) groups into the α-position of carboxylates.

Treatment of *N*-benzyloxyimines (**4**) with ketene silyl acetals (**5**) in the presence of a catalytic amount of trimethylsilyl triflate (**6**) afforded alkyl β-benzyloxyaminocarboxylates (**7**), which were then cyclized to give *N*-

A. synthesis of *N*-benzyloxy-β-lactams through 1-benzyloxyaminoalkylation at the α-position of carboxylates



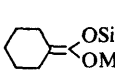
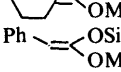
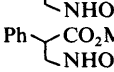
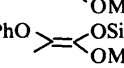
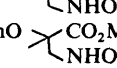
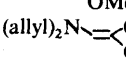
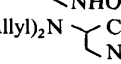
B. direct synthesis of *N*-benzyloxy-β-lactams



Bz : $PhCH_2$-

Chart 1

TABLE I. Production of Alkyl β-Benzyloxyaminocarboxylates

Entry	*N*-Benzyloxyimine	No.	Ketene silyl acetal	No.	Solvent, conditions	Product	No.	Yield[c] (%)
1	$CH_2=NOCH_2Ph$[a]	**4a**		**5a**	CH_2Cl_2, rt, 5 h		**7a**	89
2		**4a**		**5b**	CH_2Cl_2, rt, 3.5 h		**7b**	76
3		**4a**		**5c**	CH_2Cl_2, rt, 3 h		**7c**	42
4		**4a**		**5d**	CH_2Cl_2, rt, 6 h		**7d**	95
5		**4a**		**5e**	CH_2Cl_2, rt, 7 h		**7e**	93
6		**4a**		**5f**	CH_2Cl_2, rt, 6 h		**7f**	88
7		**4a**		**5g**	CH_2Cl_2, rt, 5 h		**7g**	52
8	$CH_3CH=NOCH_2Ph$[b]	**4b**		**5a**	CH_3CN, 30 °C, 18 h		**7h**	52
9		**4b**		**5c**	CH_3CN, 30 °C, 20 h		**7i**	61

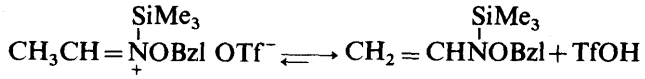
a) *N*-Benzyloxyimine–ketene silyl acetal = 1 : 1 (molar proportion), Me_3SiOTf: 10 mol%. *b*) *N*-Benzyloxyimine–ketene silyl acetal = 1.5 : 1, Me_3SiOTf: 10 mol% to *N*-benzyloxyimine. *c*) Based on the product isolated.

benzyloxy-β-lactams.

A similar condensation between ketene silyl acetals and Schiff bases has been reported to proceed in the presence of an equimolar amount of titanium tetrachloride to give β-lactams directly or to give the β-aminoesters after hydrolysis.[7]

The conditions and the results of this reaction of formaldoxime-*O*-benzyl ether (**4a**) and acetaldoxime-*O*-benzyl ether (**4b**) with a number of ketene silyl acetals (**5a**—**g**) are summarized in Table I. The physical and spectral properties and elemental analyses are summarized in Table II.

All the reactions of **4a** ($R^1=H$) with a variety of ketene silyl acetals proceeded smoothly in dichloromethane at room temperature in the presence of 0.1 mol eq of trimethylsilyl triflate (**6**). The reaction of **4b** ($R^1=CH_3$) did not proceed under the same conditions without the use of acetonitrile instead of dichloromethane. Presumably, enolizable *N*-benzyloxyimine (**4b**) exists in equilibrium with a significant amount of enamine in the presence of trimethylsilyl triflate in dichloromethane.



The structures of alkyl β-benzyloxyaminocarboxylates (**7a**—**i**) were determined on the basis of the elementary analyses, and infrared (IR), proton magnetic resonance (^{1}H-NMR) and carbon 13 magnetic resonance (^{13}C-NMR) spectra. The ^{1}H-NMR spectra of **7a**—**i** showed signals at 3.05—3.58 ppm due to methylene or methine protons adjacent to the nitrogen atom. In the ^{1}H-NMR spectrum of **7c**, the signals due to $HNCH_2$ and $COCH_2$ appeared as doublets at 3.19 ppm ($J=6.0$ Hz), and 2.59 ppm ($J=6.0$ Hz), respectively. The signals of methylene protons of **7e** appeared as two sets of doublet of doublets at 3.16 ppm ($J=13.2$, 6.3 Hz) and at 3.58 ppm ($J=13.2$, 8.5 Hz). The structure of **7i** was deduced from the ^{1}H-NMR spectrum, in

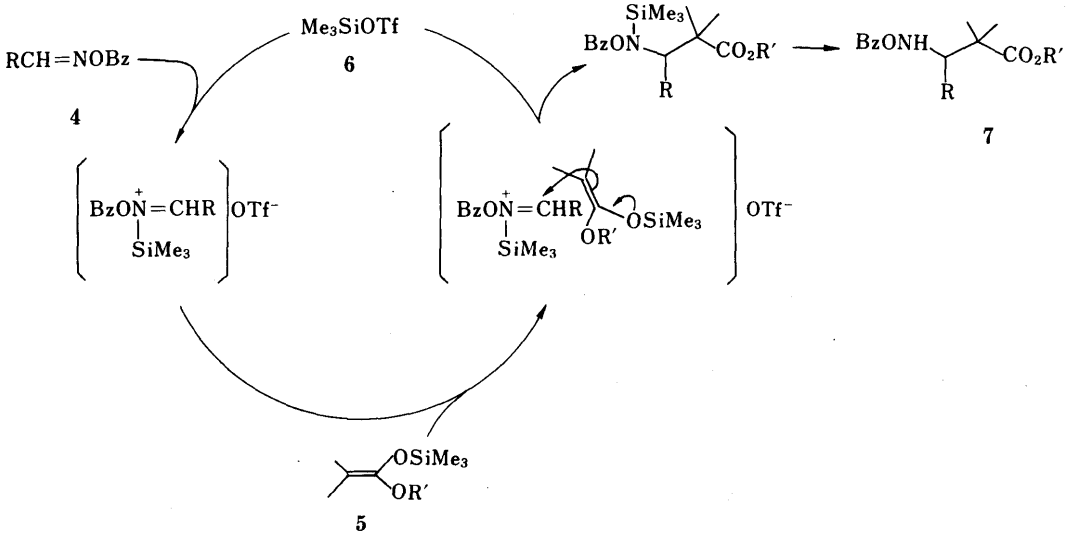


Chart 2

TABLE II. Spectral and Analytical Data for Alkyl β-Benzyloxyaminocarboxylates

Compd. No.	bp (°C) (mmHg)	IR $\nu_{max}^{liq.}$ cm^{-1} C=O	IR $\nu_{max}^{liq.}$ cm^{-1} NH	^{1}H-NMR ($CDCl_3$) δ ppm (J=Hz)	^{13}C-NMR ($CDCl_3$) δ ppm	Formula M_r	Analysis (%) Calcd (Found) C	H	N
7a	118 (0.50)	1740	3298	1.20 (6H, s, Me_2C), 3.05 (2H, s, NCH_2), 3.58 (3H, s, OMe), 4.62 (2H, s, CH_2Ph), 7.31 (5H, s, Ph)	23.9 (q, Me_2C), 42.2 (s, Me_2C), 51.7 (q, OMe), 60.4 (t, NCH_2), 75.9 (t, CH_2Ph), 127.7, 128.2, 128.5 (d, Ph), 137.9 (s, Ph), 177.4 (s, CO)	$C_{13}H_{19}NO_3$ 237.29	65.80 (65.87	8.07 8.02	5.90 5.90)
7b	125 (1.5)	1743	3280	1.15 (3H, d, J=6.8, $CHCH_3$), 2.62—3.32 (3H, m, $CHCH_3$, NCH_2), 3.64 (3H, s, OMe), 4.66 (2H, s, CH_2Ph), 7.32 (5H, s, Ph)	15.2 (q, MeCH), 37.8 (d, MeCH), 51.5 (q, OMe), 55.0 (t, NCH_2), 76.2 (t, CH_2-Ph), 127.8, 128.4 (d, Ph), 138.0 (d, Ph), 176.0 (s, CO)	$C_{12}H_{17}NO_3$ 223.26	64.55 (64.79	7.68 7.58	6.27 6.16)
7c	138 (0.40)	1736	3280	2.59 (2H, t, J=6.0, CH_2CO), 3.19 (2H, t, J=6.0, NCH_2), 4.35 (1H, brs, NH), 4.65 (2H, s, $NOCH_2Ph$), 5.09 (2H, s, CO_2CH_2Ph), 7.31 (10H, s, 2Ph)	44.5 (t, CH_2CO), 47.5 (t, NCH_2), 64.9 (t, CO_2CH_2Ph), 76.1 (t, $NOCH_2Ph$), 126.9, 127.3, 127.1, 128.1, 128.4, 128.5 (d, 2Ph), 136.0, 141.3 (s, 2Ph), 172.1 (s, CO)	$C_{17}H_{19}NO_3$ 285.33	71.56 (71.84	6.71 6.82	4.91 4.83)
7d	154 (0.30)	1732	3296	1.06—1.69 (6H, m, $-(CH_2)_3-$), 1.92—2.26 (4H, m, $-CH_2CCH_2-$), 3.06 (2H, s, NCH_2), 3.60 (3H, s, OMe), 4.61 (2H, s, CH_2Ph), 7.31 (5H, s, Ph)	22.8, 25.9, 32.6 (t, $-(CH_2)_3-$), 46.7 (s, >C<), 51.5 (q, OMe), 60.0 (t, NCH_2), 75.9 (t, CH_2Ph), 127.7, 128.2, 128.5 (d, Ph), 137.9 (s, Ph), 176.4 (s, CO)	$C_{16}H_{23}NO_3$ 277.35	69.28 (69.06	8.36 8.30	5.05 5.04)
7e	155 (0.20)	1736	3280	3.16 (1H, dd, J=13.2, 6.3, CHHCH), 3.58 (1H, dd, J=13.2, 8.5, CHHCH), 3.61 (3H, s, OMe), 4.06 (1H, dd, J=8.5, 6.3, CH_2CH), 4.67 (2H, s, CH_2Ph), 5.36 (1H, brs, NH), 7.27 (5H, s, PhCH), 7.30 (5H, s, CH_2Ph)	49.3 (d, CHPh), 51.9 (q, OMe), 54.4 (t, NCH_2), 76.0 (t, CH_2Ph), 127.5, 127.8, 128.1, 128.3, 128.5, 128.8 (d, 2Ph), 136.9, 137.8 (s, 2Ph), 173.4 (s, CO)	$C_{17}H_{19}NO_3$ 285.33	71.56 (71.78	6.71 6.60	4.91 4.86)
7f	165 (0.50)	1742	3292	1.51 (3H, s, MeC), 3.39 (2H, s, NCH_2), 3.62 (3H, s, OMe), 4.64 (2H, s, CH_2Ph), 5.58 (1H, brs, NH), 6.74—7.41 (5H, m, PhO), 7.30 (5H, s, CH_2Ph)	20.6 (q, MeC), 52.2 (q, OMe), 60.1 (t, NCH_2), 76.0 (t, CH_2Ph), 80.6 (s, >C<), 120.1, 122.7, 127.7, 128.2, 128.4, 129.1 (d, 2Ph), 137.7, 155.0 (s, 2Ph), 173.3 (s, CO)	$C_{18}H_{21}NO_4$ 315.36	68.55 (69.02	6.71 6.64	4.44 4.47)
7g	145 (0.30)	1736	3298	2.91—3.47 (6H, m, NCH_2, $2=CHCH_2$), 3.68 (3H, s, OMe), 3.77—4.02 (1H, m, NCH), 4.68 (2H, s, CH_2Ph), 4.97—5.31 (4H, m, $2CH_2=CHCH_2$), 5.46—6.02 (2H, m, $2CH_2=CHCH_2$), 7.32 (5H, s, Ph)	50.9 (t, $2=CHCH_2$), 51.1 (q, OMe), 54.0 (t, NCH_2), 59.1 (d, NCH), 75.7 (t, CH_2-Ph), 117.1 (t, $2CH_2=CHCH_2$), 127.7, 128.2, 128.3 (d, Ph), 136.4 (d, $2CH_2=CHCH_2$), 138.2 (s, Ph), 172.8 (s, CO)	$C_{17}H_{24}N_2O_3$ 304.38	67.08 (66.57	7.95 7.98	9.20 9.31)
7h	121 (0.30)	1736	3288	1.04 (3H, d, J=6.6, CHMe), 1.13 (6H, s, Me_2C), 3.38 (1H, q, J=6.6, CHMe), 3.57 (3H, s, OMe), 4.60 (2H, s, CH_2Ph), 6.94—7.08 (1H, brs, NH), 7.30 (5H, s, Ph)	13.5 (q, CHMe), 23.4 (q, Me_2C), 45.2 (s, Me_2C), 51.6 (q, OMe), 61.4 (d, CH-Me), 76.1 (t, CH_2Ph), 127.7, 128.2, 128.5 (d, Ph), 138.1 (s, Ph), 177.7 (s, CO)	$C_{14}H_{21}NO_3$ 251.32	66.90 (66.22	8.42 8.43	5.57 5.89)
7i	156 (0.30)	1735	3270	1.07 (3H, d, J=6.3, CHMe), 2.33 (1H, dd, J=14.2, 6.0, CHCHH), 2.63 (1H, dd, J=14.2, 6.8, CHCHH), 3.48 (1H, ddq, J=6.0, 6.8, 6.3, $CHCH_2$), 4.63 (2H, s, $NOCH_2Ph$), 5.05 (2H, s, CO_2CH_2Ph), 7.28 (10H, s, 2Ph)	17.9 (q, CHMe), 39.0 (t, CH_2CO_2), 53.0 (d, CHMe), 66.1 (t, CO_2CH_2Ph), 76.6 (t, $NOCH_2Ph$), 127.7, 128.1, 128.2, 128.5 (d, 2Ph), 136.0, 138.0 (s, 2Ph), 171.8 (s, CO)	$C_{18}H_{21}NO_3$ 299.36	72.21 (72.29	7.07 7.14	4.68 5.03)

which the signal of the methine proton adjacent to the nitrogen atom appeared as a doublet of doublets of quartets at 3.48 ppm (J=6.0, 6.8, 6.3 Hz). The ^{13}C-NMR spectrum of **7a**—**i** showed signals at 171.8—177.7 ppm due to the carbonyl carbon atom. The IR spectra of **7a**—**i** displayed bands indicative of a secondary amino group (NH) at 3270—3298 cm^{-1} and a carbonyl group (C=O) at 1732—1743 cm^{-1}.

Mechanistically in this reaction the catalytic cycle is presumably initiated by the formation of an intermediary silylated *N*-benzyloxyiminium salt [$\begin{matrix}Me_3Si\\BzlO\end{matrix}$>N=CHR]$^+OTf^-$ from *N*-benzyloxyimine (**4**) and trimethylsilyl triflate (**6**) as previously proposed for the reaction of hexahydro-1,3,5-triazines with ketene silyl acetals[8] (Chart 2).

Ring closure of β-benzyloxyaminocarboxylates to β-lactams was achieved. For example, treatment of **7a** with an equimolar amount of lithium bis(trimethylsilyl)amide in tetrahydrofuran (THF) gave **8** smoothly in 76% yield. While ring closure of **7i** did not proceed under the same conditions, presumably owing to the presence of α-hydrogen, conversion of **7i** to the corresponding β-lactam (**9**) could be achieved by the use of mesityl magnesium bromide as a base (Chart 3).

The lactam (**9**) thus obtained is regarded as a precursor of azthreonam, since **9** can be converted to *N*-sulfo-2-azetidinone stepwise by azidation at the C_3 carbon with tosyl azide, hydrogenation to amine with simultaneous debenzylation, removal of the *N*-hydroxyl group by titanium trichloride reduction, and *N*-sulfonation with pyridine–sulfur trioxide complex (Pyr·SO_3).[4e,f,9]

This method provides an efficient synthetic route to the preparation of azthreonam.

7a, 7i 8 (7a→) 9 (7i→)

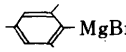
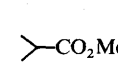
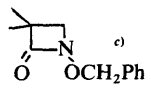
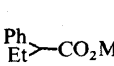
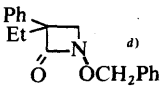
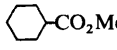
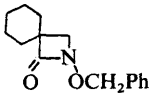
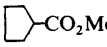
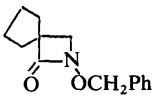
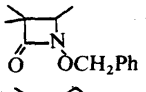
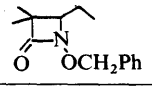
	R^1	R^2	R^3	R^4	conditions	yield (%)
8 :	H	Me	Me	Me	$(Me_3Si)_2NLi$, −78°C, 1 h, in THF	76
9 :	Me	H	H	Bz	 MgBr, 0°C, 1 h, in THF	28

Chart 3

TABLE III. Production of *N*-Benzyloxy-β-lactams[a]

Entry	*N*-Benzyloxyimine	No.	Ester	No.	Product	No.	Yield (%)[b]
1	$CH_2=NOCH_2Ph$	**4a**		**10a**	 [c]	**11a**	67
2		**4a**		**10b**	 [d]	**11b**	82
3		**4a**		**10c**		**11c**	65
4		**4a**		**10d**		**11d**	49
5	$CH_3CH=NOCH_2Ph$	**4b**		**10a**		**11e**	48
6	$C_2H_5CH=NOCH_2Ph$	**4c**		**10a**		**11f**	40

a) LDA–ester–*N*-benzyloxyimine = 1.2 : 1.0 : 1.0 (molar proportion). *b*) Based on the product isolated. *c*) P. G. Mattingly, J. F. Kerwin, Jr. and M. J. Miller, *J. Am. Chem. Soc.*, **101**, 3983 (1979). *d*) B. J. R. Nicolaus, E. Bellasio, G. Pagani and E. Testa, *Gazz. Chim. Ital.*, **93**, 618 (1963).

Reaction of *N*-Benzyloxyimines with Lithiated Carboxylic Esters The reaction of imines with lithiated carboxylic esters has been exploited as a method for the synthesis of the β-lactam ring.[4l-n] However, the applicable imines were limited to non-isomerizable arylimines and alkylimines with no α-hydrogen atom which would prevent their crucial isomerization to enamines. Therefore, this methodology was applicable only to the synthesis of 4-arylated and 4-*tert*-alkylated β-lactams.[4m,n] To overcome this critical limitation of the methodology, *N*-benzyloxyimines were expected to be the most suitable alkylimine derivatives with little tendency for imine-to-enamine isomerization owing to the imine bond deactivation resulting from the interaction of the lone pair electrons on the oxygen atom. *N*-Benzyloxyimines should provide biologically important 4-alkylated β-lactams such as azthreonam by the reaction with lithiated carboxylic esters.

N-Benzyloxyimines reacted with lithiated carboxylic esters, generated *in situ* from carboxylic esters (**10**) and lithium diisopropylamide (LDA) in THF, to give directly 4-unsubstituted and 4-alkylated *N*-benzyloxy-β-lactams in moderate yields.

The conditions and the results of this reaction of *N*-benzyloxyimines with a number of carboxylic esters are summarized in Table III. The physical and spectral properties and elemental analyses are summarized in Table IV.

The reactions of *N*-benzyloxyimines (**4a—c**) with an equimolar amount of lithiated carboxylic esters proceeded smoothly in THF at −78 °C. The structures of **11a—f** were determined on the basis of the elemental analyses, and IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectra of **11a—f** showed characteristic absorption bands at 1768—1772 cm^{-1} due to the β-lactam ring carbonyl group. The ^{1}H-NMR spectra of **11a—f** showed signals at 3.02—3.47 ppm due to the methylene or methine protons adjacent to the nitrogen atom. The ^{13}C-NMR spectra of **11a—f** showed signals at 167.1—170.0 ppm due to the carbonyl carbon atom. The ^{1}H-NMR spectrum of **11b** showed the signals of *gem*-methylene protons adjacent to the nitrogen atom as

TABLE IV. Analytical and Spectral Data for *N*-Benzyloxy-β-lactams

Compd. No.	bp (°C) (mmHg)	IR $\nu_{max}^{liq.}$ cm^{-1} β-lactam CO	^{1}H-NMR ($CDCl_3$) δ ppm (J = Hz) NCH or NCH_2	CH_2Ph	Others	^{13}C-NMR ($CDCl_3$) δ ppm NCH or NCH_2	CH_2Ph (t)	NCO (s)	Formula M_r	Analysis (%) Calcd (Found) C	H	N
11a	95 (0.03)	1772	3.03 (2H, s)	4.92	1.18 (6H, s, Me_2C), 7.37 (5H, s, Ph)	60.0 (t)	77.5	169.3	$C_{12}H_{15}NO_2$ 205.25	70.22 (69.72	7.37 7.54	6.82 6.60)
11b	163 (0.05)	1769	3.40 (1H, d, J = 4.0) 3.47 (1H, d, J = 4.0)	4.92	0.84 (3H, t, J = 7.2, CH_3-CH_2), 1.88 (2H, q, J = 7.2, CH_3CH_2), 7.28 (5H, s, Ph), 7.32 (5H, s, CH_2Ph)	57.2 (t)	77.7	167.1	$C_{18}H_{19}NO_2$ 281.34	76.84 (77.17	6.81 6.96	4.98 4.50)
11c	148 (0.15)	1768	3.02 (2H, s)	4.92	1.06—1.92 (10H, m, $-(CH_2)_5-$), 7.37 (5H, s, Ph)	58.5 (t)	77.5	169.5	$C_{15}H_{19}NO_2$ 245.13	73.44 (73.10	7.81 8.05	5.71 5.26)
11d	220 (0.15)	1771	3.12 (2H, s)	4.93	1.09—2.22 (8H, m, $-(CH_2)_4-$), 7.38 (5H, s, Ph)	60.6 (t)	77.4	169.9	$C_{14}H_{17}NO_2$ 231.28	72.70 (72.36	7.41 7.44	6.06 5.83)
11e	116 (0.15)	1768	3.29 (1H, q, J = 6.3)	4.93	1.00 (3H, d, J = 6.3, CH-Me), 1.05, 1.17 (6H, s, Me_2C), 7.37 (5H, s, Ph)	65.1 (d)	78.0	170.0	$C_{13}H_{17}NO_2$ 219.27	71.20 (70.78	7.82 8.00	6.39 5.88)
11f	129 (0.60)	1768	3.12 (1H, t, J = 6.7)	4.95, 4.96	0.90 (3H, t, J = 7.2, CH_3-CH_2), 1.10, 1.18 (6H, s, Me_2C), 1.26—1.67 (2H, m, CH_3CH_2), 7.38 (5H, s, Ph)	71.3 (d)	77.9	170.0	$C_{14}H_{19}NO_2$ 233.30	72.07 (71.34	8.21 8.23	6.00 5.36)

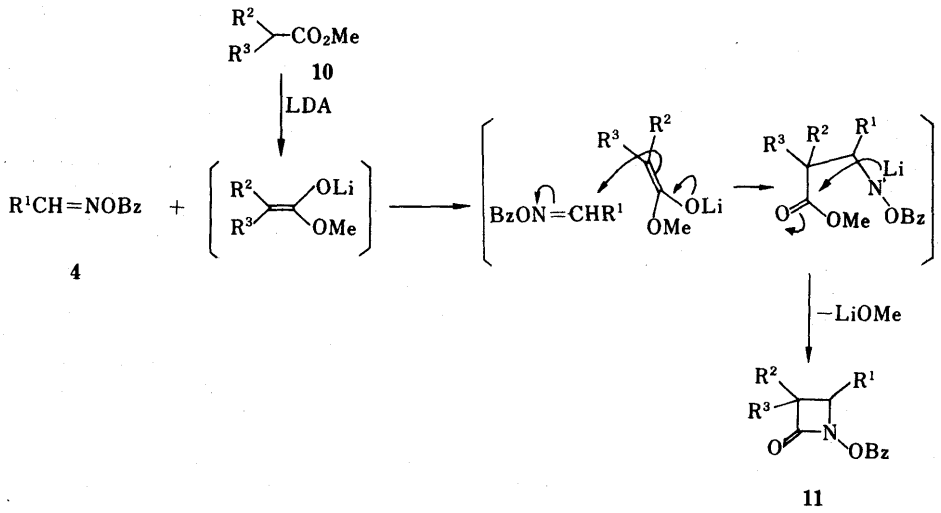


Chart 4

doublets at 3.40 ppm (J=4.0 Hz) and at 3.47 ppm (J=4.0 Hz).

This reaction can be explained in terms of the formation of intermediary lithiated *N*-benzyloxyaminocarboxylates from *N*-benzyloxyimines and lithiated carboxylic esters generated *in situ* from carboxylic esters and LDA in THF, followed by ring closure to β-lactams. Under these reaction conditions, only lithiated α,α-dialkylcarboxylate esters reacted to give the β-lactams (Chart 4).

This finding is in distinct contrast to previous reports,[4m,n] which indicated that the corresponding *N*-aryimines and *N*-silyl imines failed to react with lithiated carboxylic esters. It should also be noted that *N*-benzyloxy-β-lactams thus obtained may be easily convertible to *N*-hydroxy-β-lactams[4a] and then unsubstituted ones.[4f] These products are related to monosulfactams, monobactams and also some 3,3-dialkyl-β-lactams, which have been found to have antimicrobial activity.[10]

In summary, *N*-benzyloxy-β-lactams, which serve as general intermediates for the preparation of monobactam antimicrobial agents, are readily synthesized by the newly developed methodology described herein.

Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO A-202 spectrometer. ^{1}H-NMR spectra (90 MHz) and ^{13}C-NMR spectra (22.5 MHz) were taken on a JEOL JNM-90Q NMR spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard, and the chemical shifts are given in δ values. The abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Preparation of Ketene Silyl Acetals (5a—g) The ketene trimethylsilyl acetals were prepared from the corresponding carboxylic esters by the previously reported procedure.[11] **5a**, bp 76—77 °C/65 mmHg (lit.,[11] bp 35 °C/15 mmHg). **5b**, bp 68—69 °C/65 mmHg (lit.,[11] bp 70 °C/3 mmHg). **5c**, bp 98—99 °C/0.40 mmHg (lit.,[11] bp 63 °C/0.001 mmHg). **5d**, bp 105—106 °C/20 mmHg (lit.,[11] bp 80 °C/2.5 mmHg). **5e**, bp 100—101 °C/0.08 mmHg (lit.,[11] bp 95 °C/0.5 mmHg). **5f**, bp 90—91 °C/1.0 mmHg (lit.,[11] bp 86.5 °C/0.7 mmHg). **5g**, bp 92 °C/0.3 mmHg. A new compound, [[1-methoxy-2-(diallylamino)ethenyl]oxy]trimethylsilane (**5g**), was prepared from *N*,*N*-diallylglycine methyl ester and trimethylsilyl chloride according to the procedure described in the literature.[11] **5g**, bp 92 °C/0.3 mmHg. IR (film): 1643 (CH_2=$CHCH_2N$), 1680 (C=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.22 (9H, s, $SiMe_3$), 3.22 (4H, br d, J=6.0 Hz, CH_2=$CHC\underline{H}_2N$×2), 3.60 (3H, s, OMe), 4.22 (1H, s, >C$\underline{H}$=C<(OMe, $OSiMe_3$)), 5.32—4.82 (4H, m, $C\underline{H}_2$=$CHCH_2N$×2), 5.52—6.25 (2H, m, CH_2=$C\underline{H}CH_2N$×2).

Preparation of Formaldoxime-*O*-benzyl Ether (4a) Formalin (37%, 4.1 g, 0.05 mol) was added to a stirred solution of benzyloxyamine (6.2 g, 0.05 mol), 37.5% aqueous NaOH solution (1 ml) and benzene (20 ml), and the mixture was stirred for 1 h at room temperature. After separation of the organic layer, the aqueous layer was extracted with $CHCl_3$. The combined organic extracts were dried over $MgSO_4$. After removal of the solvent, the residue was distilled under reduced pressure to give formaldoxime-*O*-benzyl ether **4a** (6.0 g, 90%). **4a**, bp 76 °C/15 mmHg. IR (film): 1614 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.00 (2H, s, CH_2Ph), 6.27, 6.89 (2H, d, J=8.4 Hz, CH_2=N), 7.16 (5H, s, Ph).

Preparation of Acetaldoxime-*O*-benzyl Ether (4b) and Propionaldoxime-*O*-benzyl Ether (4c) Acetaldehyde (0.10 mol) was added to a stirred solution of benzyloxyamine (6.2 g, 0.05 mol), molecular sieves 4A (0.5 g) and benzene (20 ml) at 0 °C, and the mixture was stirred for 1 h at room temperature. The resulting suspension was filtered through Celite and the filtrate was evaporated. The residue was distilled under reduced pressure to give acetaldoxime-*O*-benzyl ether (**4b**) (yield 94%). **4b**, bp 95 °C/15 mmHg. IR (film): 1640 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.80, 1.83 (3H, d, J=6.0 Hz, $C\underline{H}_3CH$=N), 5.02, 5.08 (2H, s, OCH_2Ph), 6.27, 7.39 (1H, q, J=6.0 Hz, $CH_3C\underline{H}$=N), 7.25 (5H, s, Ph). In the same manner, propionaldoxime-*O*-benzyl ether (**4c**) was prepared (yield 82%). **4c**, bp 113 °C/23 mmHg. IR (film): 1633 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.2 Hz, $C\underline{H}_3CH_2$), 2.01—2.52 (2H, m, $CH_3C\underline{H}_2CH$=). 5.03 (2H, s, OCH_2Ph), 6.58, 7.24 (1H, t, J=5.1 Hz, $EtC\underline{H}$=N), 7.23 (5H, s, Ph).

Reaction of Aldoximes (4a, b) with Ketene Silyl Acetals (5a—g) (Table I) General Procedure A (in the Case of **4a**): Trimethylsilyl triflate (**6**) (0.5 mmol) was added as a catalyst to a stirred solution of 5 mmol of formaldoxime-*O*-benzyl ether (**4a**) and 5 mmol of a ketene silyl acetal in 10 ml of dry CH_2Cl_2 under cooling. After stirring for the requisite time at room temperature, the reaction mixture was washed with 10% aqueous $KHCO_3$. The separated organic layer was dried over $MgSO_4$. Removal of the solvent gave an oily residue, which was fractionally distilled under reduced pressure to give the corresponding product (**7a—g**). Yields, physical and analytical data of the products are listed in Tables I and II, respectively.

General Procedure B (in the Cases of **4b** and **4c**): Trimethylsilyl triflate (0.75 mmol) was added as a catalyst to a stirred solution of 7.5 mmol of acetaldoxime-*O*-benzyl ether (**4b**) or propionaldoxime-*O*-benzyl ether (**4c**) and 5 mmol of a ketene silyl acetal in 10 ml of CH_3CN under cooling, and the mixture was stirred for the requisite time at 30—35 °C. After removal of the solvent, the residue was treated with 30% aqueous K_2CO_3 and the aqueous layer was extracted with ether. The combined organic layers were dried over $MgSO_4$ and evaporated. The resulting residue was fractionally distilled under reduced pressure to give the corresponding products (**7a, i**). Yields, and physical and analytical data for the products are listed in Tables I and II, respectively.

Conversion of *N*-benzyloxy-β-aminocarboxylates (**7a, i**) to the corresponding *N*-benzyloxy-β-lactams (**8, 9**).

In the Case of **7a**: *N*-Benzyloxy-β-aminocarboxylate (**7a**) 1.19 g (5 mmol) was added to a stirred solution of lithium bis(trimethylsilyl)-

amide (6 mmol), freshly prepared from *n*-butyllithium (1.6 M) 3.75 ml (6 mmol) and hexamethyldisilazane 0.97 g (6 mmol), in dry THF (20 ml at −78 °C under argon. After 2 h at −78 °C, the reaction mixture was allowed to warm to room temperature and evaporated. The residue was dissolved in ether (20 ml) and the ethereal layer was washed with saturated aqueous NH_4Cl and brine and dried oved $MgSO_4$. The solvent was evaporated off and the residue was distilled under reduced pressure to give 1-benzyloxy-3,3-dimethyl-2-azetidinone (**8**) (0.78 g, 76%). The structure of the β-lactam (**8**) was consistent with that of **11a**.

In the Case of **7i**: *N*-Benzyloxy-β-aminocarboxylate (**7i**) 1.50 g (5 mmol) was added to a stirred solution of mesityl magnesium bromide (6 mmol), freshly prepared from magnesium 0.146 g (6 mmol) and mesityl bromide 1.19 g (6 mmol), in dry THF (20 ml) at 0 °C under argon. The mixture was stirred for 1 h at 0 °C, the solvent was removed and the resulting residue was dissolved in ether (20 ml). The ethereal layer was washed with 1.5 M HCl, water and 10% aqueous $KHCO_3$, and dried over $MgSO_4$. After removal of the solvent, the residue was distilled under reduced pressure to give 1-benzyloxy-4-methyl-2-azetidinone (**9**) (0.27 g, 28%). **9**, bp 200 °C/0.15 mmHg (bulb-to-bulb distillation). IR (film): 1770 (β-lactam C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, d, J=6.1 Hz, $CHC\underline{H}_3$), 2.20 (1H, dd, J=13.5, 5.0 Hz, $CHHC\underline{H}$), 3.46—3.75 (1H, m, $CH_2C\underline{H}$), 4.93 (2H, s, CH_2Ph), 7.37 (5H, s, Ph). ^{13}C-NMR ($CDCl_3$) δ: 17.8 (q), 39.5 (t), 53.6 (d), 78.2 (t), 128.5 (d), 128.8 (d), 129.1 (d), 135.7 (s), 164.1 (s). *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 7.33; N, 6.85. Found: C, 69.09; H, 7.01; N, 6.64.

Reaction of Aldoxime-*O*-benzyl Ether (4a—c) with Lithiated Alkyl Carboxylates (Generated from 10a—d) (Table III) A solution of a carboxylate (**10a—d**) (5 mmol) in dry THF (1 ml) was added to a solution of LDA, freshly prepared from *n*-butyllithium (1.6 M) 3.8 ml (6 mmol) and diisopropylamine 0.61 g (6 mmol), in dry THF (20 ml) dropwise with stirring at −78 °C under argon. Stirring was continued for 1 h at −78 °C, then a solution of aldoxime-*O*-benzyl ether (5 mmol) in dry THF (1 ml) was added dropwise. Stirring was further continued at −78 °C for 1 h and then at room temperature for a while. After removal of the solvent, an ethereal solution of the residue was washed with 3 M aqueous HCl and 10% aqueous $KHCO_3$, and dried over $MgSO_4$. Removal of the solvent gave the crude product, which was distilled under reduced pressure. Yields, physical and analytical data of the products (**11a—f**) are listed in Tables III and IV, respectively.

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