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FACILE SYNTHESIS OF ALKYL β-BENZYLOXYAMINOCARBOXYLATES RELATED TO MONOCYCLIC β-LACTAMS.

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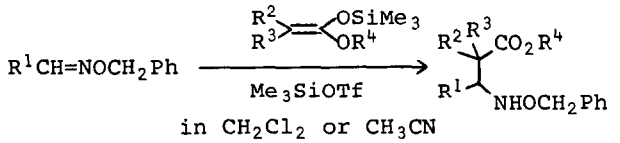
N-Benzyloxyimines have been shown to react with ketene silyl acetals in the presence of trimethylsilyl triflate catalyst to give alkyl β-benzyloxyaminocarboxylates. Conversion of them to β-lactams has been exemplified.

Synthesis of N-unsubstituted and N-hydroxylated β-lactams is an important subject in connection with the recently interesting monobactams such as sulfazecin[1] and azthreonam,[2] and monosulfactams[3f] as biologically active monocyclic β-lactams. A number of works[3a-g] have been reported for this purpose. One of the methods is, as previously reported,[3g] to synthesize 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. In contrast to the previous papers[3a-g] on the synthesis of N-benzyloxy-β-lactams through N-C_4 bond closure, the present paper has exploited a new route through N-C_2 bond closure, which involves synthesis of key precursors, alkyl β-benzyloxyaminocarboxylates. A series of this type of the compound, previously unknown, have been synthesized by a reaction of N-benzyloxyimines with ketene silyl acetals catalyzed by trimethylsilyl triflate. 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.[4]



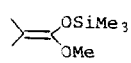
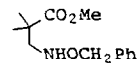
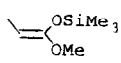
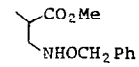
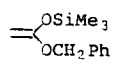
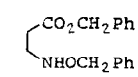
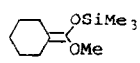
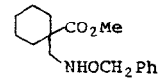
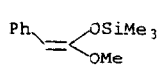
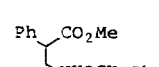
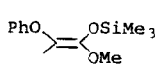
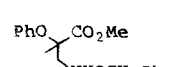
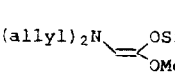
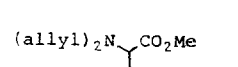
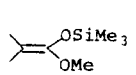
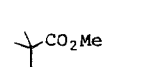
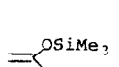
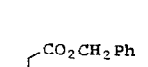
The conditions and the results of this reaction of formaldoxime-(1) and acetaldoxime-O-benzyl ether (2) with a number of ketene silyl acetals are summarized in Table 1. All the reaction of 1 proceeded smoothly in dichloromethane at room temperature in the presence of 0.1 molar equivalent of trimethylsilyl triflate. The reaction of 2 did not proceed under the same conditions other than the use of acetonitrile instead of dichloromethane.

A typical experiment (entry 1 in Table 1) is as follows. To a solution of 1 (5 mmol) and dimethylketene methyl trimethylsilyl acetal (5 mmol) in 10 ml of dichloromethane trimethylsilyl triflate (0.5 mmol) was added dropwise on cool. The mixture was stirred at room temperature for 5 hr. The reaction solution was washed with 10% potassium bicarbonate solution and dried over anhydrous magnesium sulfate. After removal of dichloromethane the resulting residue was distilled under reduced pressure to give methyl 3-(N-benzyloxyamino)-2,2-dimethylpropionate in 89% yield. A liquid: bp 118°C(0.50 mmHg); IR (film) 1740(ester C=O) and 3298 cm^{-1}(NH); ^{1}H-NMR ($CDCl_3$) δ=1.20[6H, s, $C(C\underline{H}_3)_2$], 3.05(2H, s, $C\underline{H}_2N$), 3.58(3H, s, $OC\underline{H}_3$), 4.62(2H, s, $C\underline{H}_2Ph$), and 7.31 (5H, s, $C_6\underline{H}_5$); ^{13}C-NMR ($CDCl_3$) δ=23.9(q), 42.2(s), 51.7(q), 60.4(t), 75.9(t), 127.7(d), 128.2(d), 128.5(d), 137.9(s), and 177.4(s).

Mechanistically in this reaction the catalytic cycle can be postulated to be initiated by the formation of an intermediary silylated N-benzyloxyiminium salt [$RCH=\overset{\oplus}{N}\overset{OBz}{\underset{SiMe_3}{}}\ \overset{\ominus}{}OTf$] from N-benzyloxyimine and trimethylsilyl triflate as recently proposed for the reaction of hexahydro-1,3,5-triazines with ketene silyl acetals.[5]

Ring closure of β-benzyloxyaminocarboxylates to β-lactams was realized by the use of 3 and 4 (entry 1 and 9) as representatives. The reaction of 3 proceeded smoothly in the presence of an equimolar amount of lithium bis(trimethylsilyl)amide in tetrahydrofuran, but 4 did not proceed under the same conditions, presumably owing to its structure possessing α-hydrogen. Conversion of 4 to the corresponding β-lactam (6) could be performed by the use of mesityl magnesium bromide as a base.

Table 1. PRODUCTION OF ALKYL β-BENZYLOXYAMINOCARBOXYLATES

Entry	N-Benzyloxy-imine	Ketene silyl acetal	Solvent, Conditions	Product[c]	Compd. No.	Yield(%)[d]
1	CH_2=NOCH$_2$Ph [a]		CH_2Cl_2, rt, 5 h		3	89
2	CH_2=NOCH$_2$Ph [a]		CH_2Cl_2, rt, 3.5 h			76
3	CH_2=NOCH$_2$Ph [a]		CH_2Cl_2, rt, 3 h			42
4	CH_2=NOCH$_2$Ph [a]		CH_2Cl_2, rt, 6 h			95
5	CH_2=NOCH$_2$Ph [a]		CH_2Cl_2, rt, 7 h			93
6	CH_2=NOCH$_2$Ph [a]		CH_2Cl_2, rt, 6 h			88
7	CH_2=NOCH$_2$Ph [a]		CH_2Cl_2, rt, 5 h			52
8	CH_3CH=NOCH$_2$Ph [b]		CH_3CN, 30°C, 18 h			52
9	CH_3CH=NOCH$_2$Ph [b]		CH_3CN, 30°C, 20 h		4	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) All products gave satisfactory elemental analyses and their spectral data were consistent with the proposal structures. d) Based on the product isolated.

R^1	R^2	R^3	R^4	Compd. No.	Conditions	β-Lactam No.	Yield(%)
H	Me	Me	Me	3	$(Me_3Si)_2NLi$, -78°C, 1 hr, in THF	5	76
Me	H	H	Me	4	 , 0°C, 1 hr, in THF	6	28

The β-lactam (6) obtained is regarded as a precursor of azthreonam, since 6 can be convertible to N-sulfo-2-azetidinone stepwise by azidation at the C_3 carbon with tosyl azide, hydrogenation to amine with simultaneous debenzylation, removal of N-hydroxy group by titanium trichloride reduction, and N-sulfonation with pyridine-sulfur trioxide complex ($Pyr \cdot SO_3$), according to the previous papers.[3e,3g,6] Therefore, a new synthetic route to azthreonam has been established.

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