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A New Route to 4-Unsubstituted β-Lactams through Ureidomethylation of Ketene Silyl Acetals

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α-Ureidomethylated carboxylates were obtained by the reaction of ketene silyl acetals with benzyl N-(chloromethyl)carbamates in the presence of titanium tetrachloride. Successive hydrogenolysis over palladium-on-charcoal followed by treatment with lithium diisopropylamide gave β-lactams.

Keywords——β-lactam; titanium tetrachloride; ureidomethylation; hexahydro-1,3,5-triazine; benzyloxycarbonyl chloride

Methods for synthesizing monocyclic β-lactams are of particular interest in connection with the synthesis of analogs of the naturally occurring antibiotics such as nocardicin A.[1)]

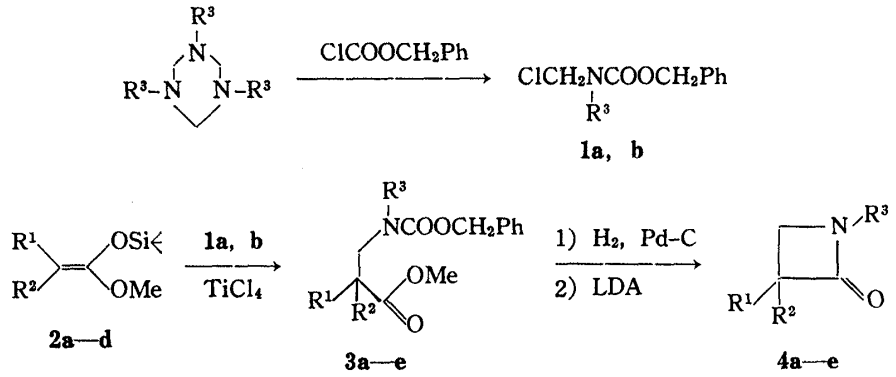

Chart 1

In very recent papers the titanium tetrachloride-aided reaction of silyl enol ethers has provided, at α to carbonyl, N-alkylamidoalkylation[2] in the 1,3,5-trialkylhexahydro-1,3,5-triazine–acetyl chloride system and ureidomethylation[3] with N-(chloromethyl)carbamates. As a continuation of this work, we examined the possibility of synthesizing β-lactams by extending the reaction to ketene silyl acetals.

The present paper reports a new route to β-lactam synthesis, as summarized in Chart 1. Ureidomethylation at α to an alkoxycarbonyl group was achieved by the reaction of ketene silyl acetals with benzyl N-(chloromethyl)carbamates in the presence of titanium tetrachloride. Benzyl N-(chloromethyl)carbamates[4] (**1a**, R^3=Me; **1b**, R^3=iso-Pr) were prepared by the

Table I. Syntheses of 4-Unsubstituted β-Lactams

2a—d $\xrightarrow[TiCl_4]{\textbf{1a, b}^{a)}}$ **3a—e** $\xrightarrow[2)\ LDA^{c)}]{1)\ H_2,\ Pd\text{-}C^{b)}}$ **4a—e**

R^1	R^2	Substrate No.	R^3	Product No.	Yield (%)[d] (2a—d→3a—e)	Product No.	Yield (%)[d] (3a—e→4a—e)
CH_3	CH_3	**2a**	CH_3	**3a**	86	**4a**	61
CH_3	CH_3	**2a**	$(CH_3)_2CH$	**3b**	90	**4b**	56
CH_3	H	**2b**	CH_3	**3c**	85	**4c**	5
$-(CH_2)_5-$		**2c**	CH_3	**3d**	83	**4d**	81
C_6H_5O	CH_3	**2d**	CH_3	**3e**	81	**4e**	24

a) Molar proportion of **2**: **1**: $TiCl_4$=1: 1.2: 1.2. Solvent: CH_2Cl_2 Temp.: 0—10°.
b) Under hydrogen at normal pressure and room temperature. Solvent: THF.
c) LDA: 1.2 mol equiv. Solvent: THF.
d) Based on the product isolated.

Table II. Physical and Spectral Data for the Products

Compd. No.	bp °C (mmHg)	IR ν_{max}^{liq} cm^{-1}[a] (C=O)	NMR δ (in $CDCl_3$)[b] (J=Hz) >NCH_2–	>NCH_3 or NCH $(CH_3)_2$	–OCH_3	Formula	Analysis (%) Calcd. (Found) C	H	N
3a	158—159(0.15)	1720 1695	3.49(s)	2.88(s)	3.65(s)	$C_{15}H_{21}NO_4$	64.49 (64.44	7.85 7.53	5.01 5.17)
3b	157—158(0.10)	1730 1700	3.45(s)	1.22 (d, J=6.6)	3.63(s)	$C_{17}H_{25}NO_4$	66.42 (66.59	8.20 8.15	4.56 4.51)
3c	151—152(0.20)	1740 1710	3.42 (d, J=7.0)	2.89(s)	3.59(s)	$C_{14}H_{19}NO_4$	63.38 (63.79	7.22 7.28	5.28 5.24)
3d	184—185(0.07)	1735 1710	3.38(s)	2.85(s)	3.59(s)	$C_{18}H_{25}NO_4$	67.69 (67.43	7.89 7.72	4.39 4.61)
3e	220—221(0.40)	1740 1710	3.82(s)	3.10(s)	3.65(s)	$C_{20}H_{23}NO_5$	67.21 (67.44	6.49 6.45	3.92 4.02)
4a	71—72(20) [lit.,[c] 50—52 (5)]	1760	3.03(s)	2.79(s)		$C_6H_{11}NO$	63.68 (63.43	9.80 9.64	12.39 12.00)
4b	72—73(20)	1750	2.96(s)	1.15 (d, J=6.6)		$C_8H_{15}NO$	68.04 (67.73	10.71 10.76	9.92 9.73)
4c	74—76(90) [lit[d]., 65—66 (12)]	1760	3.2—3.8(m)	2.79(s)		C_5H_9NO	60.58 (60.51	9.15 9.31	14.13 14.33)
4d	95—96(5)	1775	3.02(s)	2.79(s)		$C_9H_{15}NO$	70.55 (70.58	9.87 9.91	9.14 9.20)
4e	126—127(5)	1770	3.31 (d, J=5.4) 3.53 (d, J=5.4)	2.84(s)		$C_{11}H_{13}NO_2$	69.09 (69.46	6.85 7.06	7.33 7.21)

a) The IR spectra of **4a—e** were measured in CCl_4.
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reaction of 1,3,5-trialkylhexahydro-1,3,5-triazines with benzyloxycarbonyl chloride.

As summarized in Table I, various ketene silyl acetals were allowed to react with **1a** and **1b** in dichloromethane in the presence of titanium tetrachloride to give the corresponding β-amino acid derivatives (**3a—e**) in good yields. They exhibit satisfactory nuclear magnetic resonance (NMR) and infrared (IR) spectra (see Table II). To remove the benzyloxycarbonyl group, the products **3a—e** were catalytically reduced over palladium-on-charcoal at room temperature; subsequent treatment of the reaction mixture with 1.2 molar equivalents of lithium diisopropylamide (LDA) gave the corresponding β-lactams (**4a—e**), in the yields listed in Table I. The products, **4a—e**, gave absorption bands (1750—1775 cm^{-1}) characteristic of β-lactam carbonyl in their IR spectra and satisfactory NMR spectra. As can be seen in the run with **3c**, the yield was appreciably lowered when R=H.

The above process starting from 1,3,5-trialkylhexahydro-1,3,5-triazine should be useful for synthesizing 4-unsubstituted β-lactams, which are not accessible by the usual synthetic methods starting from Schiff bases.

Experimental

All boiling points are uncorrected. IR spectra were taken on a Hitachi EPI-G2 spectrophotometer and NMR spectra were recorded on a Hitachi R-24 spectrometer.

Benzyl N-(chloromethyl)carbamates[4] (**1a, b**) and ketene silyl acetals[5] (**2a—d**) were prepared according to the methods described in the literature, and their boiling points are as follows: **1a**, bp 125—126° (0.4 mmHg) [lit.,[4] bp 121—122° (0.35 mmHg)]; **1b**, bp 129—130° (0.1 mmHg), IR ν_{max}^{liq} cm^{-1} 1720 (C=O), NMR δ (in $CDCl_3$), 1.32 [6H, d, J=6.6 Hz, $CH(CH_3)_2$], 5.22 (2H, s, $ClCH_2$), 5.35 (2H, s, OCH_2), 7.36 (5H, s, C_6H_5); **2a**, bp 76—77° (65 mmHg) [lit.,[5] bp 35° (15 mmHg)]; **2b**, bp 68—69° (65 mmHg) [lit.,[5] bp 70° (3 mmHg)]; **2c**, bp 105—106° (20 mmHg) [lit.,[5] bp 80° (2.5 mmHg)]; **2d**, bp 90—91° (1.0 mmHg), IR ν_{max}^{liq} cm^{-1} 1722 (C=C), NMR δ (in $CDCl_3$), 0.13 [9H, s, $Si(CH_3)_3$], 3.59 (3H, s, OCH_3), 6.75—7.45 (5H, m, C_6H_5).

Syntheses of β-Amino Acid Derivatives (3a—e)——General Procedure: A stirred solution of 0.06 mol of benzyl N-(chloromethyl)carbamate (**1a, b**) in 200 ml of dry CH_2Cl_2 was treated dropwise with 0.05 mol of ketene silyl acetal (**2a—d**) under cooling, then 0.06 mol of titanium tetrachloride was added at 0—10°. After 1 hr of stirring the reaction mixture was washed with 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 product. Yields and physical and spectral data for the products are listed in Tables I and II, respectively.

Syntheses of β-Lactams (4a—e)——General Procedure: A suspension of 0.05 mol of **3a—e** and 1 g of 10% palladium-on-charcoal in 50 ml of THF was stirred under hydrgen at normal pressure and room temperature. After uptake of hydrogen had ceased, the catalyst was removed by filtration and the filtrate was added dropwise to a solution of LDA in dry THF (freshly prepared from 0.06 mol of *n*-butyllithium and 0.06 mol of diisopropyl amine) at 0° with stirring. After 1 hr of stirring at 0°, the reaction was quenched by adding a few drops of water and bubbling carbon dioxide through the mixture. The solvent was evaporated off under reduced pressure. The residue was extracted with ether and the ethereal layer was dried over anhydrous $MgSO_4$. Removal of the ether gave an oily residue, which was fractionally distilled under reduced pressure to give the product. Yields and physical and spectral data are recorded in Tables I and II, respectively.

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