Convenient Synthesis of β-Lactams by the Reaction of Ketene Silyl Acetals with Schiff Bases Promoted by Titanium(IV) Chloride

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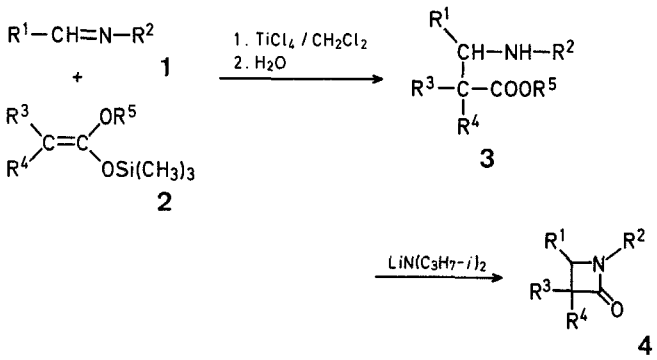
Preparative methods for the β-lactam ring system have been attracting much interest with regard to the development of the analogues of β-lactam antibiotics such as penicillins, cephalosporins, nocardicins, and thienamycins[1], and the following four methods are well known: (a) cycloaddition of ketene to Schiff base[2], (b) cycloaddition of ketene, generated *in situ* from acid chloride, to Schiff base[3], (c) Reformatsky reaction of Schiff base[4], and (d) cycloaddition of chlorosulfonyl isocyanate to olefin[5].

We found that ketene trimethylsilyl methyl acetals **(2)** added to Schiff bases in the presence of titanium(IV) chloride to give β-lactams directly or to give the β-amino esters after hydrolysis, depending upon the substituents of Schiff base, especially that on nitrogen[6]. However, the examples so far examined were restricted to the synthesis of β-lactams having alkyl or phenyl substituent(s). Here we describe the successful extension of our method to the synthesis of new β-lactams having heteroatom or heteroaromatic substituent(s).

In the present study, we employed the Schiff bases **(1)** of arylamines. Thus, β-amino esters **(3)** were obtained in good to excellent yield as initial products and were further cyclized to the corresponding β-lactams **(4)** by the action of lithium diisopropylamide.



Results for the preparation of the β-amino esters **(3)** and their physical and spectral properties are summarized in Table 1, and those for the β-lactams **(4)** are listed in Table 2. The reaction proceeded nicely in every case examined to give the corresponding new β-amino esters **(3)** and β-lactams **(4)**.

Dimethylketene Methyl Trimethylsilyl Acetal (2; R^3, R^4, $R^5 = CH_3$): Prepared according to the general method of Ref.[7].

Ketene Methyl Trimethylsilyl Acetals 2 Bearing Phenoxy or Phenylthio Substituents (R^3 or R^4); General Procedure:
To a solution of diisopropylamine (0.600 mol) in anhydrous tetrahydrofuran (400 ml) is added dropwise an equimolar amount of 15% *n*-

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butyllithium in *n*-hexane at 0 °C under argon with stirring. The solution of lithium diisopropylamide thus prepared is cooled to −78 °C, and then the methyl ester of phenoxyacetic acid, 2-phenoxypropanoic acid, or 2-phenylthiopropanoic acid (0.400 mol) is added slowly. After stirring for 30 min, chlorotrimethylsilane (1.2 mol) is added over a period of 10 min, and the mixture is stirred for 1 h at −78 °C. The mixture is warmed gradually up to ambient temperature and stirred overnight. After adding anhydrous ether, the precipitated lithium chloride is filtered off on a glass filter under argon and the filtrate is concentrated. Then, the residual solution is distilled under reduced pressure to give the corresponding ketene methyl trimethylsilyl acetal **2**.

Methylphenoxyketene methyl trimethylsilyl acetal (**2**; $R^3=C_6H_5O$, R^4, $R^5=CH_3$); yield: 75%; b.p. 79–87 °C/0.5 torr.

I.R. (film): ν = 1720 cm^{-1} (C=C).

^{1}H-N.M.R. ($CDCl_3$): δ = 0.35 (s, 9H); 1.84 (s, 3H); 3.62 (s, 3H); 6.9–7.5 ppm (m, 5H).

Phenoxyketene methyl trimethylsilyl acetal (**2**; $R^3=C_6H_5O$, $R^4=H$, $R^5=CH_3$); yield: 49%; b.p. 92–95 °C/0.6 torr.

I.R. (film): ν = 1700 cm^{-1} (C=C).

^{1}H-N.M.R. ($CDCl_3$): δ = 0.36 (s, 9H); 3.72 (s, 3H); 5.73 (s, 1H); 7.0–7.5 ppm (m, 5H).

Table 1. Preparation of β-Amino Esters **3**

Product	R^1	R^2	R^3	R^4	R^5	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (KBr) ν [cm^{-1}] NH	I.R. (KBr) ν [cm^{-1}] C=O	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
3a	2-furyl	C_6H_5	CH_3	CH_3	CH_3	62	107–109°	$C_{16}H_{19}NO_3$ (273.3)	3375	1720	1.24 (s, 6H); 3.63 (s, 3H); 4.43 (br s, 1H); 4.70 (s, 1H); 5.9–7.4 (m, 8H)
3b	2-thienyl	C_6H_5	CH_3	CH_3	CH_3	54	124–126°	$C_{16}H_{19}NO_2S$ (289.4)	3420	1720	1.28 (s, 6H); 3.64 (s, 3H); 4.60 (br s, 1H); 4.71 (s, 1H); 6.0–7.4 (m, 8H)
3c	2-pyridyl	C_6H_5	CH_3	CH_3	CH_3	81	112–114°	$C_{17}H_{20}N_2O_2$ (284.4)	3420	1725	1.22 (s, 6H); 3.63 (s, 3H); 4.74 (s, 1H); 5.13 (br s, 1H); 6.4–7.7 (m, 8H); 8.5 (m, 1H)
3d	C_6H_5	C_6H_5	C_6H_5O	CH_3	CH_3	98	138–141°[b]	$C_{23}H_{23}NO_3$ (361.4)	3425	1755	1.29, 1.48 (s, 3H); 3.60, 3.75 (s, 3H); 4.60 (br s, 1H); 4.80, 4.83 (s, 1H); 6.3–7.7 (m, 15H)
3e	C_6H_5	C_6H_5	C_6H_5O	H	CH_3	72	114–117°[b]	$C_{22}H_{21}NO_3$ (347.4)	3420, 3360	1760, 1730	3.57, 3.66 (s, 3H); 4.80 (br s, 1H); 4.98 (ABq, J=3 Hz), 5.00 (s, 2H); 6.4–7.7 (m, 15H)
3f	C_6H_5	C_6H_5	C_6H_5S	CH_3	C_2H_5	82	134–135°	$C_{24}H_{25}NO_2S$ (391.5)	3390	1710	1.13 (t, 3H, J=7 Hz); 1.30 (s, 3H); 4.09 (q, 2H, J=7 Hz); 4.63 (s, 1H); 5.64 (br s, 1H); 6.3–7.7 (m, 15H)
3g	2-furyl	C_6H_5	C_6H_5O	CH_3	CH_3	92	118–120°[b]	$C_{21}H_{21}NO_4$ (351.4)	3400	1750, 1730	1.36, 1.51 (s, 3H); 3.71, 3.74 (s, 3H); 4.60 (br s, 1H); 5.02, 5.05 (s, 1H); 6.2–7.8 (m, 13H)
3h	2-thienyl	C_6H_5	C_6H_5O	CH_3	CH_3	99	117–118°	$C_{21}H_{21}NO_3S$ (367.5)	3410	1755	1.34 (s, 3H); 3.73 (s, 3H); 4.87 (br s, 1H); 5.11 (s, 1H); 6.3–7.5 (m, 13H)
3i	2-furyl	C_6H_5	C_6H_5S	CH_3	C_2H_5	71	77–79°	$C_{22}H_{23}NO_3S$ (381.5)	3400	1720	1.18 (t, 3H, J=7 Hz); 1.43 (s, 3H); 4.14 (q, 2H, J=7 Hz); 4.92 (s, 1H); 5.00 (br s, 1H); 6.2–8.0 (m, 13H)
3j	2-thienyl	C_6H_5	C_6H_5S	CH_3	C_2H_5	90	110–111°	$C_{22}H_{23}NO_2S_2$ (397.6)	3380	1710	1.17 (t, 3H, J=7 Hz); 1.39 (s, 3H); 4.12 (q, 2H, J=7 Hz); 5.00 (s, 1H); 5.39 (br s, 1H); 6.5–7.6 (m, 13H)
3k	C_6H_5	3,4-di-Cl—C_6H_3	CH_3	CH_3	CH_3	86	116–118°	$C_{18}H_{19}Cl_2NO_2$ (352.3)	3430	1730	1.13 (s, 3H); 1.27 (s, 3H); 3.62 (s, 3H); 4.33 (s, 1H); 5.01 (br s, 1H); 6.2–7.4 (m, 8H)

[a] All products gave satisfactory microanalyses (C ±0.28%, H ±0.17%, N ±0.17%, S ±0.12%, Cl ±0.09%).

[b] Mixture of *threo* and *erythro* isomers.

Table 2. Preparation of β-Lactams **4**

Product[a]	Yield [%]	m.p. [°C]	Molecular formula[b]		I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
4a	84	107–109°	$C_{15}H_{15}NO_2$	(241.3)	1740	1.08 (s, 3H); 1.49 (s, 3H); 4.70 (s, 1H); 6.0–6.4 (m, 2H); 6.8–7.5 (m, 6H)
4b	79	111–112°	$C_{15}H_{15}NOS$	(257.4)	1740	1.30 (s, 3H); 1.50 (s, 3H); 5.00 (s, 1H); 6.7–7.5 (m, 8H)
4c	91	163–164°	$C_{16}H_{16}N_2O$	(252.3)	1745	0.89 (s, 3H); 1.62 (s, 3H); 4.93 (s, 1H); 7.0–7.8 (m, 8H); 8.5–8.7 (m, 1H)
4d	92	147–153°[c]	$C_{22}H_{19}NO_2$	(329.4)	1760	1.27, 1.77 (s, 3H); 5.03, 5.23 (s, 1H); 6.6–7.7 (m, 15H)
4e	87	193–195°	$C_{21}H_{17}NO_2$	(315.4)	1755	5.35 (d, 1H, J=5 Hz); 5.56 (d, 1H, J=5 Hz); 6.5–7.7 (m, 15H)
4f	98	120–121°	$C_{22}H_{19}NOS$	(345.5)	1760	1.10 (s, 3H); 4.88 (s, 1H); 6.8–8.0 (m, 15H)
4g	97	91–98°[c]	$C_{20}H_{17}NO_3$	(319.4)	1750, 1740	1.51, 1.76 (s, 3H); 5.16, 5.32 (s, 1H); 6.2–7.6 (m, 13H)
4h	90	115–117°	$C_{20}H_{17}NO_2S$	(335.4)	1755	1.72 (s, 3H); 5.19 (s, 1H); 6.9–7.5 (m, 13H)
4i	84	150–153°	$C_{20}H_{17}NO_2S$	(335.4)	1755	1.68 (s, 3H); 5.09 (s, 1H); 6.2–7.6 (m, 13H)
4j	93	101–104°	$C_{20}H_{17}NOS_2$	(351.5)	1740	1.32 (s, 3H); 5.19 (s, 1H); 6.7–7.8 (m, 13H)
4k	98	109–111°	$C_{17}H_{15}Cl_2NO$	(320.2)	1750	0.81 (s, 3H); 1.47 (s, 3H); 4.67 (s, 1H); 6.7–7.8 (m, 3H)

[a] For R^1, R^2, R^3, R^4, see Table 1.
[b] All products gave satisfactory microanalyses (C ±0.25%, H ±0.11%, N ±0.12%, S ±0.13%, Cl ±0.22%).
[c] Mixture of *cis* and *trans* isomers.

Methylphenylthioketene ethyl trimethylsilyl acetal (**2**; $R^3=C_6H_5S$, $R^4=CH_3$, $R^5=C_2H_5$); yield: 76%; b.p. 117–119°C/1.0 torr.

I.R. (film): ν=1645 cm^{-1} (C=C).

^{1}H-N.M.R. ($CDCl_3$): δ=0.18, 0.23 (2s, 9H); 1.16, 1.21 (2t, 3H); 1.77, 1.83 (2s, 3H); 3.88 (q, 2H); 6.8–7.3 ppm (m, 5H); mixture of (*E*)- and (*Z*)-isomers.

β-Amino Esters 3; General Procedure:
To a 1 molar solution of titanium chloride in dichloromethane (20 ml, 20 mmol) is added dropwise a dichloromethane solution (20 ml) of Schiff base **1** (20 mmol) at ambient temperature with stirring over a period of 10 min. Then, the ketene trimethylsilyl acetal **2** (20 mmol) in dichloromethane (10 ml) is added to the resulting dark-red solution and stirring is continued for 1–5 h. Then, the reaction mixture is poured into ice/water (200 ml), the organic layer is extracted with dichloromethane, washed with water, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. When pyridylmethylideneaniline is used as Schiff base (product **3c** in Table 1), neutralization of the reaction mixture with aqueous sodium hydroxide is necessary before extraction. The residue is treated with *n*-pentane to give the corresponding β-amino ester **3** as crystals, which are collected on a glass filter and further washed with *n*-pentane. Although the β-amino esters **3** thus obtained have sufficient purity for the subsequent cyclization reaction, samples for microanalysis are prepared by recrystallization from ethanol (Table 1).

β-Lactams 4; General Procedure:
The β-amino ester **3** (15 mmol) is dissolved in tetrahydrofuran (30 ml) and to this solution is slowly added a solution of lithium diisopropylamide (16 mmol) in *n*-hexane/tetrahydrofuran (1:1,25 ml), prepared from *n*-butyllithium and diisopropylamine, with cooling in an ice/water bath. After stirring for 15–30 min, the reaction mixture is poured into ice/water (50 ml) and extracted with dichloromethane (3 × 50 ml). The extract is dried with anhydrous magnesium sulfate and the solvent is removed under reduced pressure. The residue is treated with *n*-pentane to give the corresponding crystalline β-lactam **4**, which is further purified by recrystallization from ether to prepare the samples for microanalysis (Table 2).

When methyl 3-(*N*-phenyl)-amino-3-phenyl-2-phenoxypropanoate (**3e**) is used, the lithium diisopropylamide solution is slowly added at −78°C, and the reaction mixture is gradually warmed up to 0°C, and then submitted to hydrolysis by ice/water.

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