Novel Synthesis of α-Methylene-β-lactams

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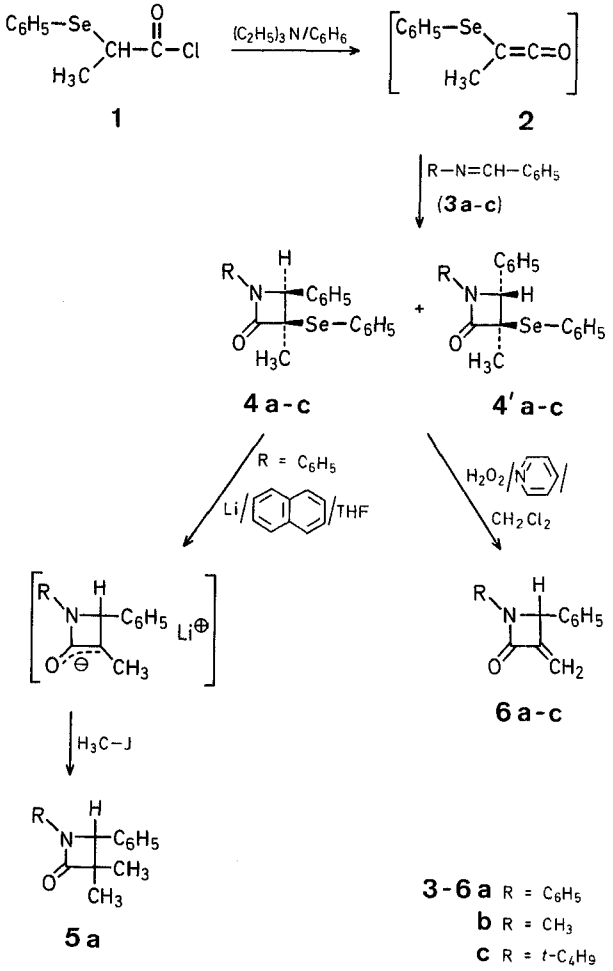
Considerable attention has been paid to the synthesis of α-methylene-β-lactams from the viewpoint of biological activities[1,2], and we have already proposed a method for their preparation by thermolysis of α-phenylthio-β-lactam derivatives[2]. Our method, however, required rather severe reaction conditions, so we have now developed a novel process for an effective preparation of α-methylene-β-lactams by use of methyl-phenylseleno-ketene, as a synthon of methyleneketene.

Methyl-phenylseleno-ketene (**2**) was produced *in situ* by dehydrochlorination of 2-phenylselenopropanoyl chloride (**1**) with triethylamine because of its unstability. The reaction of **2** with imines **3** gave a mixture of the *cis*- and *trans*-α-phenylseleno-β-lactams **4** and **4'**. The isomers were separated in the reaction of benzylidenaniline, but in the other cases, separations were not successful except for the isolation of the *cis*-isomer of the β-lactam **4c**. The results are summarized in Table 1.



The α-methylene-β-lactams **6** were derived effectively from the α-phenylseleno-β-lactams **4** by treatment with hydrogen peroxide[3]. In these reactions, except for the β-lactam **4a**, mixtures of isomers were used and satisfactory results obtained (Table 2).

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Table 1. Synthesis of α-Phenylseleno-β-lactams **4a–c**

Product No.	R	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (Nujol) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	M.S. (70 eV) *m/e* (^{80}Se; relative intensity %)
4a *(cis)*	C_6H_5	52	204.5–205.5°	$C_{22}H_{19}NOSe$ (392.4)	1730	1.77 (s, 3H, CH_3); 5.03 (s, 1H, CH); 7.0–7.8 (m, 15H_{arom})	393 (M^+, 12); 274 (14); 212 (52); 181 (100)
4'a *(trans)*	C_6H_5	4	130.0–132.0°	$C_{22}H_{19}NOSe$ (392.4)	1735	1.21 (s, 3H, CH_3); 5.03 (s, 1H, CH); 7.0–7.9 (m, 15H_{arom})	393 (M^+, 17); 274 (26); 212 (54); 181 (100)
4b	CH_3	50[b]	—	$C_{17}H_{17}NOSe$ (330.3)	1740	*cis:* 1.68 (s, 3H, CH_3); 2.88 (s, 3H, NCH_3); 4.51 (s, 1H, CH); 7.0–8.0 (m, 10H_{arom}) *trans:* 1.13 (s, 3H, CH_3); 2.54 (s, 3H, NCH_3); 4.48 (s, 1H, CH); 7.0–8.0 (m, 10H_{arom})	331 (M^+, 21); 274 (24); 212 (100); 174 (53)
4c	t-C_4H_9	52[c]	*cis:* 152–154°	$C_{20}H_{23}NOSe$ (372.4)	1725	*cis:* 1.32 (s, 9H, t-C_4H_9); 1.62 (s, 3H, CH_3); 4.54 (s, 1H, CH); 7.1–8.0 (m, 10H_{arom}) *trans:* 1.05 (s, 9H, t-C_4H_9); 1.13 (s, 3H, CH_3); 4.72 (s, 1H, CH); 7.1–8.0 (m, 10H_{arom})	373 (M^+, 10); 274 (100); 117 (50)

[a] Satisfactory microanalyses obtained: C ±0.22, H ±0.15, N ±0.07. [b] 76:24 *cis/trans* mixture. [c] 30:70 *cis/trans* mixture.

Table 2. Synthesis of α-Methylene-β-lactams **6a–c**

Product	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (Nujol) cm^{-1} $\nu_{C=O}$	$\nu_{C=CH_2}$	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	M.S. (70 eV) *m/e* (relative intensity %)
6a	92[b]	150.5–152.0°	$C_{16}H_{13}NO$ (235.7)	1730	930	5.17 (t, 1H, =CHH); 5.42 (t, 1H, CH); 5.86 (t, 1H, =CHH); 7.0–7.5 (m, 10H_{arom})	235 (M^+, 60); 116 (100)
6b	67	—	$C_{11}H_{11}NO$ (173.2)	1740	910	2.89 (s, 3H, NCH_3); 4.96 (t, 1H, CH or =CHH); 5.07 (t, 1H, =CHH or CH); 5.73 (t, 1H, =CHH); 7.2–7.7 (m, 5H_{arom})	173 (M^+, 62); 144 (11); 116 (100)
6c	85	138.0–140.0°	$C_{14}H_{17}NO$ (215.3)	1735	920	1.26 (s, 9H, t-C_4H_9); 4.91 (t, 1H, CH or CHH); 5.07 (t, 1H, =CHH or CH); 5.65 (t, 1H, =CHH); 7.2–7.5 (m, 5H_{arom})	215 (M^+, 5); 200 (100); 115 (54)

[a] Satisfactory microanalyses obtained: C ±0.16, H ±0.20, N ±0.10. [b] From *cis*-**4a**.

Substitution of the phenylseleno group of the β-lactam **4a** by the methyl group was achieved by treatment with lithium/naphthalene[4] followed by treatment with methyl iodide, to give the α,α-dimethyl-β-lactam **5a** in high yield.

2-Phenylselenopropanoyl Chloride (1):

Ethyl 2-Phenylselenopropanoate: To a solution of sodium benzeneselenolate (17.9 g, 0.1 mol) in ethanol (100 ml), ethyl 2-chloropropanoate (13.7 g, 0.1 mol) in ethanol (40 ml) is added. The mixture is stirred for 1 h at room temperature and an additional 1 h at reflux temperature. The mixture is then distilled to give ethyl 2-phenylselenopropanoate; yield: 77%; b.p. 91–93 °C/0.25 torr.

M.S. (70 eV): $m/e = 258$ (M^+).

I.R. (neat): $\nu = 1720$ cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.19 (t, 3H, CH_3); 1.51 (d, 3H, CH_3); 3.81 (q, 1H, CH); 4.12 (q, 2H, CH_2); 7.2–7.8 ppm (m, 5H_{arom}).

2-Phenylselenopropanoic Acid: To a solution of potassium hydroxide (5.5 g, 98 mmol) in ethanol/water (1/1; 100 ml), ethyl 2-phenylselenopropanoate (19.6 g, 77 mmol) in ethanol (100 ml) is added dropwise, and the resultant mixture is stirred under nitrogen for 8 h at reflux temperature. The mixture is acidified with conc. hydrochloric acid and extracted with ether (2 × 50 ml). The product is recrystallized from hexane; yield: 88%; m.p. 55–56 °C.

M.S. (70 eV): $m/e = 230$ (M^+).

I.R. (Nujol): $\nu = 1680$ cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.51 (d, 3H, CH_3); 3.78 (q, 1H, CH); 7.2–7.8 (m, 5H_{arom}); 11.91 ppm (s, 1H, COOH).

2-Phenylselenopropanoyl Chloride (**1**): 2-Phenylselenopropanoic acid (15.5 g, 68 mmol) in carbon tetrachloride (50 ml) is treated with thionyl chloride (12 g, 0.1 mol) for 3 h at reflux temperature. The product is isolated by distillation in vacuo; yield: 94%; b.p. 75.5–76.5 °C/0.2 torr.

M.S. (70 eV): $m/e = 212$ ($M^+ - Cl$).

I.R. (neat): $\nu = 1760$ cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.57 (d, 3H, CH_3); 4.01 (q, 1H, CH); 7.2–7.9 ppm (m, 5H_{arom}).

α-Phenylseleno-β-lactams 4; General Procedure:

To a refluxing benzene solution (50 ml) of 2-phenylselenopropanoyl chloride (**1**; 1.24 g, 5 mmol) and the imine **3** (10 mmol), triethylamine (0.51 g, 5 mmol) in benzene (40 ml) is added dropwise within 2 h. After standing overnight at room temperature, the mixture is extracted with diethyl ether (3 × 50 ml), the extract washed with water (50 ml), and dried with sodium sulfate. The condensate is crystallized from ethanol, chromatographed (silica gel, benzene/hexane, 1:1), or distilled in a Kugelrohr apparatus to isolate the product (Table 1).

α-Methylene-β-lactams 6; General Procedure:

To a dichloromethane solution (20 ml) of the β-lactam **4** (2 mmol) and pyridine (4 mmol), 28% aqueous hydrogen peroxide (6 mmol) is added dropwise at room temperature within 40 min. After addi-

tion of hydrogen peroxide, the reaction mixture is heated at 30–40 °C for 15–30 min and the product then separated from the mixture by column chromatography (silica gel, benzene as eluent for **6a**, or chloroform as eluent for **6b, 6c**) (Table 2).

3,3-Dimethyl-2-oxo-4-phenylazetidine (5a):
The *cis*-β-lactam **4a** is treated with 2.6 mol equivalents of lithium naphthylide[4] in tetrahydrofuran at −50 °C for 20 min followed by treatment with methyl iodide (4 mol equivalents) for 10 min, and the reaction mixture is allowed to stand for 12 h at room temperature. The α,α-dimethyl-β-lactam **5** is isolated by column chromatography (silicagel, benzene); yield: 86%; m.p. 156.5–158.0 °C.

$C_{17}H_{17}NO$	calc.	C 81.24	H 6.82	N 5.57
(251.3)	found	81.00	6.77	5.60

I.R. (Nujol): $\nu = 1740\ cm^{-1}$ (C=O).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.85$ (s, 3H, CH_3); 1.53 (s, 3H, CH_3); 4.82 (s, 1H, CH); 6.9–7.7 ppm (m, $10H_{arom}$).

M.S. (70 eV): $m/e = 251$ (M^+).

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