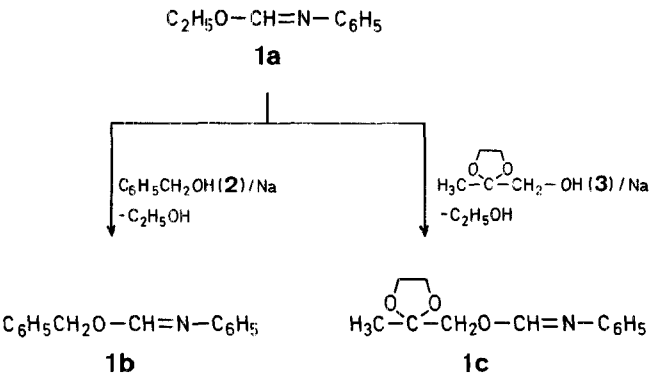
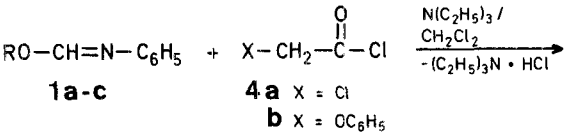
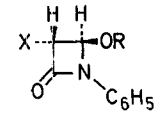


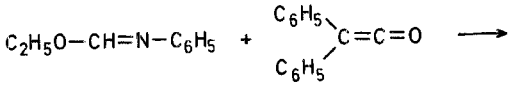
Thus, the reaction of formimidates **1** with chloro-**(4a)** or phenoxyacetyl chloride **(4b)** in the presence of triethylamine gave substituted β-lactams **5** in moderate to high yields. Furthermore, the β-lactam **7** was prepared from **1a** and diphenylketene **(6)**, generated externally. All β-lactams were characterized by microanalysis and spectral data (Table).

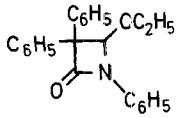




5

5	R	X
a	C_2H_5	Cl
b	C_2H_5	OC_6H_5
c	$C_6H_5CH_2$–	OC_6H_5
d	H_3C–C(O)(O)–CH_2–	OC_6H_5





7

Studies on β-Lactams; I. Stereospecific Synthesis of 4-Alkoxy-β-lactams from Imidates

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The 4-alkoxy-β-lactams, a scarcely investigated class of compounds, are usually prepared via substitution of a suitable leaving group at position 4 of a preformed β-lactam nucleus by an alkoxy group. Some examples are also reported where the title compounds were directly prepared from imidates, according to the classical acid chloride – imine cycloaddition route[1–5]. This reaction, however, has been reported to fail when imidates are used as the imine component[6].

As part of our research programme on the synthesis of β-lactam antibiotics, we have now checked the validity of this statement and report here that the direct synthesis of 4-alkoxy-β-lactams can be carried out via the acid chloride – imine route. For this purpose, ethyl *N*-phenylformimidate **(1a)**[7], benzyl- **(1b)** and 2-oxopropyl ethylene acetal *N*-phenylformimidates **(1c)** were reacted with various acid chlorides. The formimidates **1b** and **1c** were prepared from the ethyl derivative **1a** and the appropriate alcohols **2** and **3**, respectively, in the presence of sodium.

The result of this work points to a general applicability of the reaction between acid chlorides and imidates to afford 4-alkoxy-β-lactams. The major feature of this synthesis is the high stereoselectivity, only *trans*-4-alkoxy-β-lactams being formed, as inferred from the magnitude of the coupling constants (J = 1 Hz) of the C-3 and C-4 methine protons.

Ethyl-*N*-phenylformimidate **(1a)** is prepared as reported[7].

Benzyl *N*-Phenylformimidate (1b) and 2-Oxopropyl Ethylene Acetal *N*-Phenylformimidate (1c):

A mixture of ethyl *N*-phenylformimidate (**1a**; 5 g, 33.5 mmol) and either benzyl alcohol (**2**; 3.89 g, 36 mmol) or 1-hydroxypropan-2-one ethylene acetal (**3**; 4.3 g, 36 mmol) is heated in the presence of sodium (100 mg) for 2 h (at 160 °C with the former, at 130 °C with the latter) and distilled to give pure imidates.

1b: yield: 5.7 g (80%); b.p. 115 °C/0.04 torr; m.p. 27 °C (petroleum ether).

Table. β-Lactams **5** and **7** prepared

Product No.	Yield[a] [%]	m.p. [°C][b] (solvent)	Molecular formula[c]	I.R. (Film)[d] $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. (Acetone-d_6/TMS)[e] δ [ppm]	M.S.[f] *m/e* (M^+)
5a	10	oil	$C_{11}H_{12}ClNO_2$ (225.7)	1770	1.24 (t, 3H, J = 7.5 Hz, CH_3); 3.6–4.0 (m, 2H, OCH_2); 5.0 (d, 1H, J = 1 Hz, H-3); 5.52 (d, 1H, J = 1 Hz, H-4); 7.0–7.7 (m, 5H_{arom})	225
5b	90	45° (PE)	$C_{17}H_{17}NO_3$ (283.3)	1770	1.22 (t, 3H, J = 7.5 Hz, CH_3); 3.55–4.0 (m, 2H, OCH_2); 5.4 (d, 1H, J = 1 Hz, H-3); 5.6 (d, 1H, J = 1 Hz, H-4); 6.9–7.8 (m, 10H_{arom})	283
5c	98	oil	$C_{22}H_{19}NO_3$ (345.4)	1765	4.82 (d, 2H, J = 3 Hz, OCH_2); 5.42 (d, 1H, J = 1 Hz, H-3); 5.72 (d, 1H, J = 1 Hz, H-4); 6.8–7.7 (m, 10H_{arom})	345
5d	82	oil	$C_{20}H_{21}NO_5$ (355.4)	1765	1.32 (s, 3H, CH_3); 3.6–4.0 (m, 6H, OCH_2); 5.43 (d, 1H, J = 1 Hz, H-3); 5.75 (d, 1H, J = 1 Hz, H-4); 6.9–7.8 (m, 10H_{arom})	355
7	20	109–110° (PE)	$C_{23}H_{21}NO_2$ (343.3)	1740	0.92 (t, 3H, J = 7.5 Hz, CH_3); 3.3–4.0 (m, 2H, OCH_2); 6.07 (s, 1H, H-4); 7.0–7.8 (m, 15H_{arom})	343

[a] Yield of pure products.
[b] Uncorrected (PE = petroleum ether).
[c] Satisfactory microanalyses obtained: C ±0.44, H ±0.25, N ±0.15.
[d] Recorded on a Perkin-Elmer model 297 spectrophotometer, the solid samples were run as nujol mull.
[e] Recorded on a Varian EM-390 spectrometer.
[f] Recorded on a Hewlett-Packard 5980A low-resolution mass spectrometer.

I.R. (Film): ν = 1640 cm^{-1} (C=N).

^{1}H-N.M.R. (Acetone-d_6): δ = 5.3 (s, 2H, OCH_2); 6.9–7.6 (m, 10 H_{arom}); 7.9 ppm (s, 1H, CH).

1c: yield: 3.76 g (47%); b.p. 111 °C/0.2 torr.

I.R. (film): ν = 1640 cm^{-1} (C=N).

^{1}H-N.M.R. (Acetone-d_6): δ = 1.3 (s, 3H, CH_3); 3.8–4.1 (m, 4H, O—CH_2—CH_2—O); 4.17 (s, 2H, OCH_2); 6.9–7.5 (m, 5H_{arom}); 7.85 ppm (s, 1H, CH).

4-Alkoxy-1-phenyl-2-azetidinones (5); General Procedure:
To a stirred solution of imidate **1** (6.7 mmol) and triethylamine (2.02 g, 20 mmol) in dry dichloromethane (20 ml) maintained at room temperature and under nitrogen is added dropwise a solution of acid chloride **4a** or **4b** (20 mmol) in dry dichloromethane (15 ml). After stirring the reaction mixture for 12 h, the solvent is removed under reduced pressure and ether is added to the residue. The triethylamine hydrochloride is filtered off, and the solvent removed under reduced pressure. The oily residue is purified by column chromatography on silica gel [eluent: **5a**, benzene; **5b** and **5c**, cyclohexane/ethyl acetate (8/2); **5d**, benzene/ethyl acetate (9/1)].

4-Ethoxy-1,3,3-triphenyl-2-azetidinone (7):
To a solution of **1a** (1 g, 6.7 mmol) in dry dichloromethane (20 ml), maintained at room temperature under nitrogen, is added dropwise a solution of diphenylketene (**6**; 1.3 g, 6.7 mmol) in dry dichloromethane (15 ml). After stirring the mixture for 12 h, the solvent is removed under reduced pressure. Column chromatography of the residue on silica gel using benzene/cyclohexane (1/1) as eluent gives diphenylacetanilide as the first eluted fraction and compound **7** as the second. Compound **7** is further purified by crystallization from petroleum ether.

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