A One-Pot Synthesis of β-Lactams

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The synthesis of β-lactams has been achieved by a variety of methods, among which the acid chloride/imine method has been frequently employed[1]. Recently, the synthesis of β-lactams by the reaction of β-amino acids with methanesulfonyl chloride in chloroform/aqueous alkali solution in the presence of a phase transfer catalyst has been reported[2].

In connection with an earlier report[3] dealing with the reaction of acid anhydrides with imines, the present work was undertaken to synthesize some β-lactams by the one-pot reaction of mixed acid anhydrides with imines in the presence of triethylamine. The mixed anhydrides **3**, synthetic equivalents to acid chlorides, were prepared from phthalimido- or *p*-chlorophenoxyacetic acids **1** and *p*-toluenesulfonyl chloride **(2)** in the presence of triethylamine. Under the mild reaction conditions employed, the *in situ* formed **3** react with imines **4** to give corresponding monocyclic β-lactams **5** in moderate yields.

The structure of the β-lactams **5** were confirmed by their I.R. and ^{1}H-N.M.R. spectra, and microanalyses (Table). The stereochemistry at C-3 and C-4 of the β-lactam ring was deduced from the coupling constants of the protons attached to these carbon atoms in their ^{1}H-N.M.R. spectra. Compound **5d** has the *cis*-configuration ($J=5$ Hz) whereas **5a, 5b,** and **5c** are *trans*-isomers ($J=2$ Hz). No *cis/trans* isomeric mixture was observed in the ^{1}H-N.M.R. spectra of the products.

Since the advent of antibiotics exhibiting broad spectrum antibacterial activities, such as cephams and oxacephams, intensive synthetic studies have appeared in the literature. Tricyclic β-lactams have been synthesized[1] from azidoacetyl chloride and cyclic imines and cephams from substituted acetyl chlorides and dihydrothiazine derivatives[4]. The present procedure to prepare β-lactam compounds was then extended to the synthesis of some tricyclic β-lactams **7**, cephams **9**, and oxacephams **11**.

When a mixture of a 3,4-dihydroisoquinoline **(6)**, which was utilized as the imine component, a mixed anhydride **3**, and triethylamine in anhydrous dichloromethane was stirred at room temperature for 48 h, the corresponding β-lactam compound **7** was obtained. Similar treatment of 2-phenyl-5,6-dihydro-4*H*-1,3-thiazine **(8)** and -oxazine **(10)** with **3** afforded β-lactams **9** and **11**, respectively. Spectral data and microanalyses support the structure of the products **7, 9,** and **11** (Table).

The present method provides a simple and convenient preparation of the β-lactams under mild conditions. Further studies on the application of the method to organic synthesis are in progress.

The 3,4-dihydroisoquinolines **6a**[5], **6b**[6], **6c**[6], 2-phenyl-5,6-dihydro-4*H*-1,3-thiazine **(8)**[7] and 2-phenyl-5,6-dihydro-4*H*-1,3-oxazine **(10)**[8] were prepared according to literature procedures.

β-Lactams 5, Tricyclic β-Lactams 7, Cephams 9, and Oxacephams 11; General Procedure:

A solution of the substituted acetic acid **1** (1 mmol), *p*-toluenesulfonyl chloride **2** (1 mmol), and triethylamine (2 mmol) in anhydrous dichloromethane (5 ml) is stirred at room temperature for 10 min. To this solution is added the imine **4** or 3,4-dihydroisoquinoline **6** or 1,3-thiazine **8** or 1,3-oxazine **10** (1 mmol) in anhydrous dichloromethane (2 ml). The reaction mixture is stirred at room temperature for 48 h, washed with 5% sodium hydrogen carbonate solution (3 ml), water (3 ml), and dried with anhydrous sodium sulfate. Removal of the solvent and subsequent trituration with ethanol under ice-cooling gives crude crystals, which on recrystallization from dichloromethane/ethanol afford the pure product (Table).

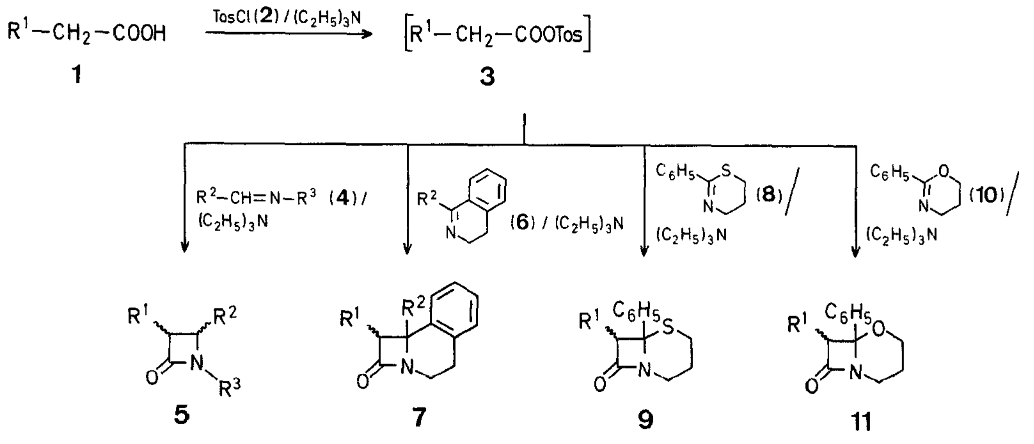
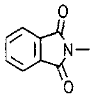
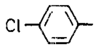
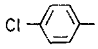
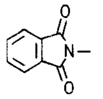
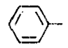
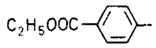
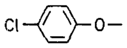
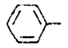
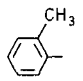
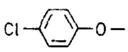
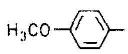
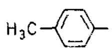
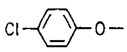
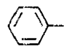
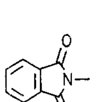
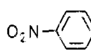
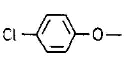
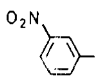
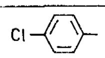
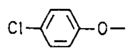
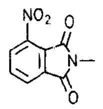
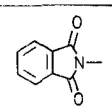
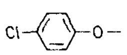
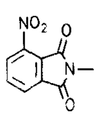


Table. β-Lactams **5**, Tricyclic β-Lactams **7**, Cephams **9**, and Oxacephams **11** prepared

Product No.	R^1	R^2	R^3	Yield [%]	m.p.[a] [°C]	Molecular formula[b]	I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
5a				48	217–218°	$C_{23}H_{14}Cl_2N_2O_3$ (437.3)	1710, 1760, 1780	5.23 (d, 1H, J=2 Hz); 5.33 (d, 1H, J=2 Hz); 7.22–7.81 (m, 12H)
5b				52	262–262.5°	$C_{26}H_{20}N_2O_5$ (440.4)	1700, 1720, 1765	1.38 (t, 3H, J=7 Hz); 4.35 (q, 2H, J=7 Hz); 5.32 (d, 1H, J=2 Hz); 5.48 (d, 1H, J=2 Hz); 6.95–8.45 (m, 8H)
5c				41	124–125°	$C_{22}H_{18}ClNO_2$ (363.8)	1750	2.42 (s, 3H); 5.11 (d, 1H, J=2 Hz); 5.2 (d, 1H, J=2 Hz); 6.9–7.5 (m, 13H)
5d				41	157–158°	$C_{23}H_{20}ClNO_3$ (393.9)	1740	2.25 (s, 3H); 3.74 (s, 3H); 5.29 (d, 1H, J=5 Hz); 5.37 (d, 1H, J=5 Hz); 6.62–7.41 (m, 12H)
7a			—	49	124–125°	$C_{23}H_{18}ClNO_2$ (375.8)	1750	2.5–3.0 (m, 2H); 3.55–3.98 (m, 2H); 5.42 (s, 1H); 6.65–7.51 (m, 13H)
7b			—	53	261–262°	$C_{25}H_{17}N_3O_5$ (439.4)	1710, 1760, 1780[c]	2.7–3.0 (m, 2H); 3.75–4.15 (m, 2H); 5.68 (s, 1H); 7.08–8.23 (m, 12H)
7c			—	55	135–136°	$C_{23}H_{17}ClN_2O_4$ (420.8)	1760[c]	2.5–3.15 (m, 2H); 3.6–4.0 (m, 2H); 5.52 (s, 1H); 6.75–8.36 (m, 12H)
9a		—	—	39	157–158°	$C_{18}H_{16}ClNOS$ (329.8)	1760	1.6–2.15 (m, 2H); 2.5–3.39 (m, 3H); 4.0–4.5 (m, 1H); 4.31 (s, 1H); 6.79–7.49 (m, 9H)
9b		—	—	46	121–121.5°	$C_{18}H_{16}NO_2S$ (345.8)	1780	1.6–2.15 (m, 2H); 2.55–3.3 (m, 3H); 3.85–4.4 (m, 1H); 5.27 (s, 1H); 6.5–7.71 (m, 9H)
9c		—	—	64	208–209°	$C_{20}H_{15}N_3O_5S$ (409.4)	1712, 1762, 1785[d]	1.65–2.2 (m, 2H); 2.5–2.9 (m, 2H); 3.05–3.6 (m, 1H); 4.1–4.6 (m, 1H); 5.5 (s, 1H); 7.0–8.2 (m, 8H)
11a		—	—	44	239–240°	$C_{20}H_{16}N_2O_4$ (348.3)	1710, 1760, 1790	1.25–2.25 (m, 2H); 3.0–4.32 (m, 4H); 5.35 (s, 1H); 7.14–7.72 (m, 9H)
11b		—	—	43	138–139°	$C_{18}H_{16}ClNO_3$ (329.8)	1760	1.2–2.69 (m, 3H); 2.7–3.5 (m, 1H); 3.52–4.38 (m, 2H); 5.25 (s, 1H); 6.5–7.68 (m, 9H)
11c		—	—	51	217–218°	$C_{20}H_{15}N_3O_6$ (393.3)	1712, 1780, 1795[d]	1.05–2.2 (m, 2H); 2.4–2.7 (m, 1H); 2.9–4.25 (m, 3H); 5.25 (s, 1H); 6.95–8.45 (m, 8H)[e]

[a] Not corrected.
[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.18, N ±0.30.
[c] ν_{NO_2} = 1520 cm^{-1}.
[d] ν_{NO_2} = 1540 cm^{-1}.
[e] Measured in DMSO-d_6.

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