A Convenient Annelation of Imines to α-Substituted β-Lactams[1]

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It is well known that multi-substituted β-lactams exhibit high chemical reactivity and are prone to molecular rearrangements. Therefore, attempts have been made to explore new methods for β-lactam synthesis that operate under milder conditions. Several methods[2-5] are available for the synthesis of β-lactams. In recent years, various phosphorus agents have been used for activating the carboxy group to achieve the amide bond formation. Manhas et al.[6] have utilised such compounds for the formation of β-lactam ring systems. These authors found that phosphorylating agents like diethyl phosphorochloridate, diphenyl phosphorochloridate, or *o*-phenylene phosphorochloridate led to the formation of β-lactams whereas diphenylphosphoryl azide, diethyl cyanophosphate, and diphenyl phosphite-pyridine failed to do so.

Palomo et al.[7] have recently described a new reagent *N,N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride **(1)** to activate the carboxy group for the synthesis of amides and esters. During our studies directed towards the semi-synthetic β-lactam antibiotics, we became interested in this reagent. In the present communication, we report on the use of this reagent in a new facile method for the conversion of imines to α-substituted β-lactams.

A mixture of imine **4** and an appropriately substituted acetic acid **2** in the presence of triethylamine was reacted with *N,N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride **(1)** at 10–20 °C for 7–8 h to give the β-lactam **6** in 40–80% yield. The structure of the β-lactam **6** was confirmed by microanalyses, I.R., and ^{1}H-N.M.R. spectrometry. A possible reaction pathway is shown in Scheme **A**.

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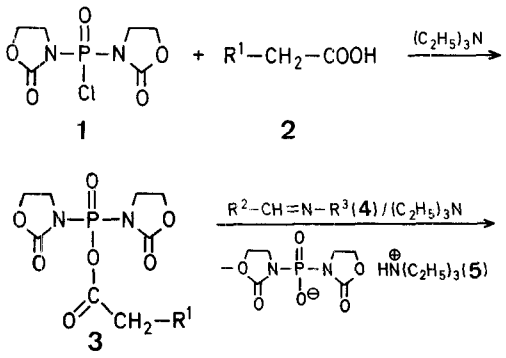
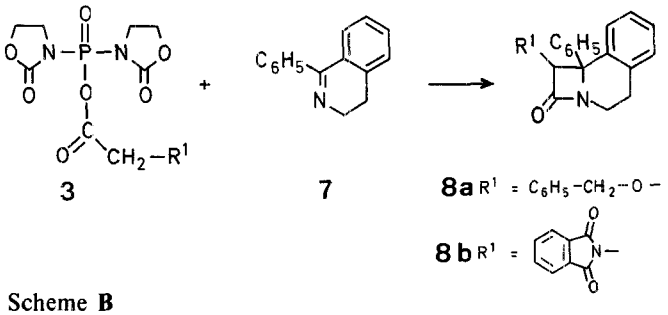


Scheme A

A variety of monocyclic β-lactams (Table) were prepared by this method. The stereochemistry was derived from their ^{1}H-N.M.R. spectra. The configuration of C-3 and C-4 protons in all these monocyclic β-lactams was observed to be *cis* ($J \approx 5$ Hz) except in case of the α-phthalimido-β-lactam which had *trans* disposition ($J \approx 2$ Hz). The reaction works equally well for the synthesis of polycyclic β-lactams **8a** and **8b** (Scheme B).

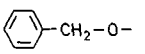
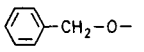
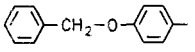
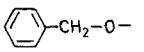
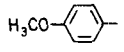
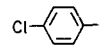
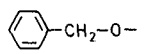
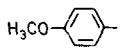
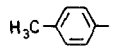
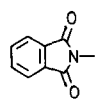
The new method works under mild conditions and gives yields comparable to the earlier known methods for the synthesis of β-lactams.



Scheme B

Melting points were determined in open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. I.R. spectra were taken on Perkin Elmer 237 or 577 spectrophotometer. ^{1}H-N.M.R. spectra were recorded on Varian A-60 and Jeol FX-100 instruments using TMS as internal standard. Microanalyses were performed using a Hösli microcombustion apparatus MK 101.

Table. β-Lactams **6** and **8** prepared

Product No.	R^1	R^2	R^3	Yield[a] [%]	m.p. [°C]	Molecular formula[b]	I.R. (nujol) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$ or CF_3COOH) δ [ppm]
6 a				50	156–158°	$C_{22}H_{18}ClNO_2$ (363.8)	1750	4.25 (br s, 2H); 4.95 (d, 1H, J=5 Hz); 5.15 (d, 1H, J=5 Hz); 6.8–7.5 (m, 14H)
6 b				55	269°	$C_{21}H_{16}ClNO_2$ (349.8)	1730	insufficiently soluble
6 c				50	137°	$C_{29}H_{24}ClNO_3$ (470.0)	1735	4.32 (q, 2H); 5.0–5.2 (m, 4H); 6.9–7.5 (m, 18H)
6 d				45	182°	$C_{23}H_{20}ClNO_3$ (393.9)	1730	3.75 (s, 3H); 4.19 (d, 1H, J=10 Hz); 4.36 (d, 1H, J=10 Hz); 5.10 (d, 1H, J=5 Hz); 5.20 (d, 1H, J=5 Hz); 6.8–7.4 (m, 13H)
6 e				40	246°	$C_{21}H_{15}Cl_2NO_2$ (384.3)	1730	5.56 (d, 1H, J=5 Hz); 5.80 (d, 1H, J=5 Hz); 6.7–7.3 (m, 13H)
6 f				45	160°	Ref.[8], m.p. 159–160 °C	1740	2.24 (s, 3H); 3.80 (s, 3H); 4.40 (s, 2H); 5.00 (d, 1H, J=5 Hz); 5.20 (d, 1H, J=5 Hz); 7.0–7.5 (m, 13H)
6 g				65	219°	$C_{23}H_{15}ClN_2O_3$ (402.8)	1770, 1750, 1710	5.20 (d, 1H, J=2.5 Hz); 5.28 (d, 1H, J=2.5 Hz); 6.9–7.8 (m, 13H)
8a	—	—	—	60	128°	$C_{24}H_{21}NO_2$ (355.4)	1750	2.7 (m, 2H); 3.6 (m, 2H); 4.50 (s, 2H); 5.02 (s, 1H); 7.0–7.6 (m, 14H)
8b	—	—	—	80	273°	$C_{25}H_{18}N_2O_3$ (394.4)	1770, 1750, 1710	2.7 (m, 2H); 3.7 (m, 2H); 5.50 (s, 1H); 6.9–7.9 (m, 13H)

[a] Yield of pure, crystallised product based on **4**.

[b] Satisfactory microanalyses obtained: C ±0.39, H ±0.34, N ±0.30; exceptions: **6c, e, 8a**, C ±0.50; **6c, d**, H ±0.50.

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β-Lactams 6 and 8; General Procedure:

A mixture of Schiff's base **4** or 1-phenyl-3,4-dihydroisoquinoline **7** (0.01 mol), triethylamine (0.04 mol), and substituted acetic acid **2** (0.01 mol) in dichloromethane (200 ml) is stirred under a nitrogen atmosphere at 10 °C and *N,N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride (**1**; 0.01 mol) is added. The resulting mixture is stirred at 20 °C for 7–8 h, washed with water (50 ml), followed by 5% sodium hydrogen carbonate solution (50 ml), and finally again with water (50 ml). The dichloromethane solution, on evaporation, gives crude **6** or **8**, which is purified by column chromatography on florisil using hexane/dichloromethane (1:1) as eluent. The solvent is evaporated and the residue crystallised from chloroform/ethanol mixture to give pure **6** or **8** (Table).

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[1] Communication No. 38 from IDPL Research Centre, Hyderabad, India.

[2] R. Graf, *Justus Liebigs Ann. Chem.* **661**, 111 (1963).

[3] A. K. Bose, M. S. Manhas, R. M. Ramer, *Tetrahedron* **21**, 449 (1965).

[4] B. G. Chatterjee, P. N. Moza, S. K. Roy, *J. Org. Chem.* **28**, 1418 (1963).

[5] J. C. Sheehan, J. J. Ryan, *J. Am. Chem. Soc.* **73**, 1204, 4367 (1951).

[6] M. S. Manhas, Bansi Lal, S. G. Amin, A. K. Bose, *Synth. Commun.* **6**, 435 (1976).

[7] J. Diago-Meseguer, A. L. Palomo-Coll, *Synthesis* **1980**, 547.

[8] M. S. Manhas, S. G. Amin, B. Ram, A. K. Bose, *Synthesis* **1976**, 689.

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