Synthesis of β-Lactams using a New Phosphorylating Agent[1], Phenyl *N*-Methyl-*N*-phenylphosphoramidochloridate

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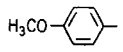
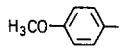
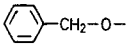
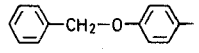
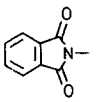
The discovery of nocardicins and monobactams has attracted the increased attention of scientists towards the synthesis of monocyclic β-lactams. Although several methods[2-5] are already known for the annellation of imines and substituted acetic acids to construct β-lactams, there is still a need to find new mild methods. Various phosphorylating agents[6,7,8] which form reactive mixed anhydride-type of intermediates with carboxylic acids have been used for the synthesis of β-lactams. Recently phenyl *N*-phenylphosphoramidochloridate (**1**; R = H) and phenyl *N*-methyl-*N*-phenylphosphoramidochloridate (**1**; R = CH_3) have been reported[9] to give good yields of carboxamides and anhydrides. Compound **1** (R = H), however, has been reported to give better yields of amides than phenyl *N*-methyl-*N*-phenylphosphoramidochloridate (**1**; R = CH_3).

We now report the use of phenyl *N*-methyl-*N*-phenylphosphoramidochloridate (**1**; R = CH_3) in a new mild method for the conversion of imines to α-substituted-β-lactams. Phenyl *N*-phenylphosphoramidochloridate (**1**; R = H), however failed to give β-lactams under varied conditions. The failure of the β-lactam formation by the reagent **1** (R = H) can be attributed to the excess triethylamine, required for the synthesis of β-lactams in the presence of a less nucleophilic imine **4**, which is detrimental to the mixed anhydride **3**. This was confirmed by a separate experiment where the use of 1 mol of triethylamine gave expected yields of carboxamide **9** with aniline (Scheme **A**), whereas the mixed anhydride **3**, when stirred with excess triethylamine overnight and then treated with aniline, gave no carboxamide. However, a solid (m.p. 133–135 °C) was isolated from the aqueous extract after acidification with mineral acid, which corresponds to phenyl *N*-phenylphosphoramidic acid (m.p. 134–136 °C)[10].

In the present one-pot reaction, a mixture of reagent **1**, (R = CH_3) substituted acetic acid **2**, triethylamine, and imine **4** is stirred at room temperature overnight to give the β-lactams **6** and **8** in good yields (Table). The possible reaction pathway for the β-lactam formation is shown in Scheme **A**.

Table. β-Lactams **6a–h** and **8a,b** prepared

Product No.	R^1	R^2	R^3	Yield[a] [%]	m.p. [°C]	Molecular Formula[b] or Lit. m.p. [°C]	I.R. (Nujol)[c] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$)[d] δ [ppm]
6a				66	215°	219°[4]	1770, 1750, 1710	5.55 (d, 1H, J = 1.5 Hz); 5.65 (d, 1H, J = 1.5 Hz); 7.3–8.2 (m, 13H)
6b				60	234°	$C_{22}H_{18}ClNO_3$ (379.5)	1740	3.85 (s, 3H); 5.50 (d, 1H, J = 5 Hz); 5.75 (d, 1H, J = 5 Hz); 6.7–7.4 (m, 13H)
6c				78	195°	$C_{24}H_{17}ClN_2O_4$ (432.5)	1760, 1750, 1710	3.78 (s, 3H); 5.25 (d, 1H, J = 1.5 Hz); 5.35 (d, 1H, J = 1.5 Hz); 6.8–7.9 (m, 12H)
6d				44	153–154°	156–158°[4]	1745	4.30 (q, 2H, J = 11 Hz); 5.00 (d, 1H, J = 5 Hz); 5.20 (d, 1H, J = 5 Hz); 7.0–7.5 (m, 14H)
6e				26	232°	$C_{28}H_{22}ClNO_3$ (455.3)	1730	–[e]
6f				46	268°	269°[4]	1730	–[e]
6g			$C_2H_5OOC-CH_2-$	76	144–146°	oil[11]	1780, 1760, 1715	1.13 (t, 3H); 4.07 (q, 2H); 3.57, 4.21 (2d, 2H, N—CH_2—COO); 5.10 (d, 1H, J = 1.5 Hz); 5.18 (d, 1H, J = 1.5 Hz); 7.1–7.9 (m, 9H)
6h	see Scheme **A**			41	273°	$C_{22}H_{20}N_2O_3$ (360.4)	1775, 1745, 1715	0.9–2.15 (m, 10H); 5.04 (s, 1H); 7.1–7.9 (m, 9H)
8a	see Scheme **A**			41	105°	$C_{23}H_{19}NO_2$ (341.4)	1730	3.40 (m, 2H); 4.30 (m, 2H); 6.06 (s, 1H); 7.3–8.0 (m, 14H)
8b	see Scheme **A**			70	273°	273°[4]	1770, 1750, 1710	2.70 (m, 2H); 3.7 (m, 2H); 5.5 (s, 1H); 7.9 (m, 13H)

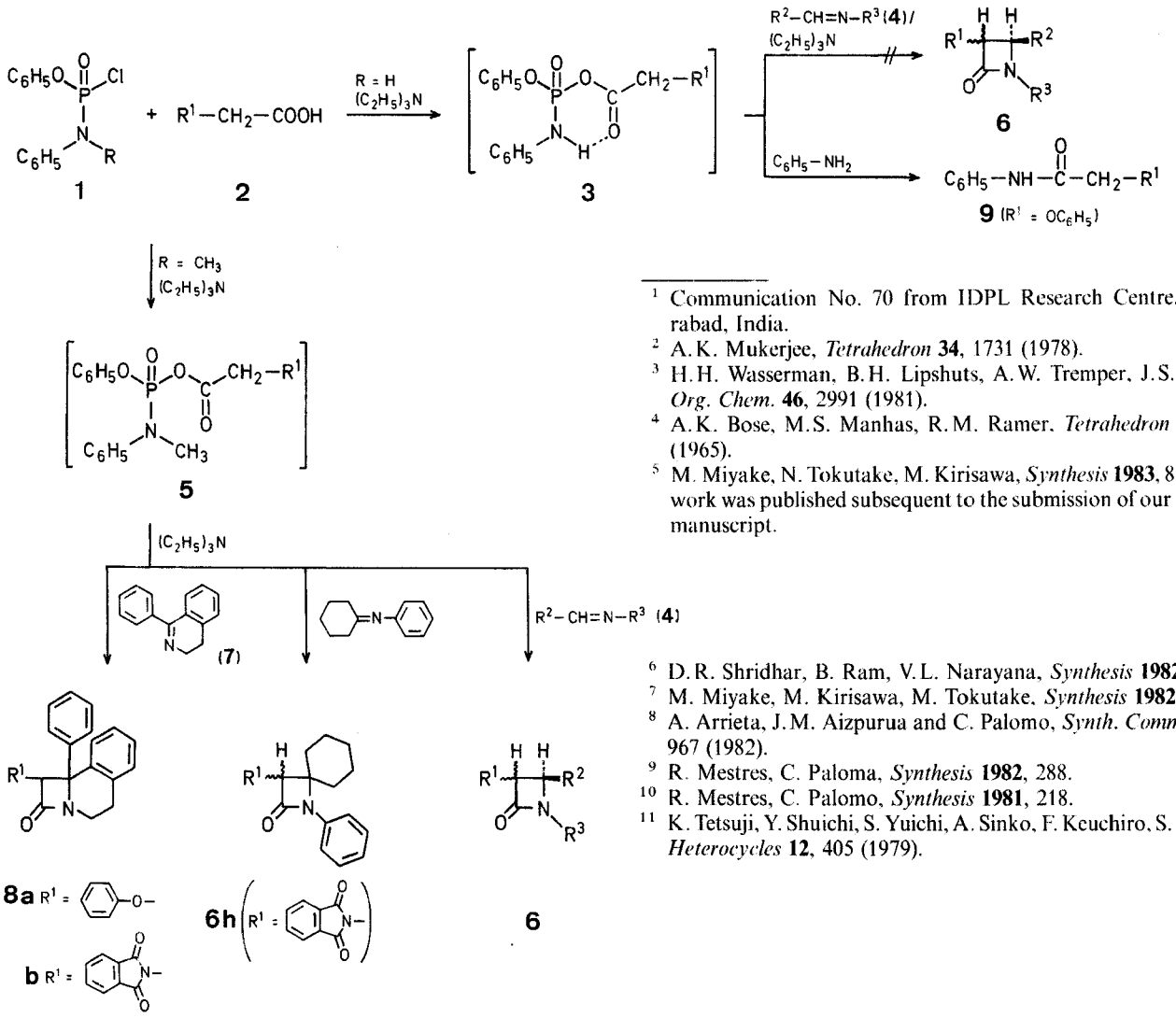
[a] Yield of pure, crystallised product based on **4**.

[b] The micro analyses of the new compounds were in satisfactory agreement with the calculated values (C ±0.38, H ±0.40, N ±0.49 except **6h** C ±0.62).

[c] Recorded on a Perkin-Elmer model 298 spectrometer.

[d] ^{1}H-N.M.R. measured at 90 MHz on Varian A-90 (EM-390) spectrometer using TMS as an internal standard.

[e] Insufficiently soluble.



Scheme A

The structures of **6** and **8**, thus obtained, were confirmed by microanalyses, I.R. and ^{1}H-N.M.R. spectroscopy. The configuration of C–3 and C–4 protons in **6** was determined by ^{1}H-N.M.R. and was found to be *cis* (J = 5 Hz) in all the β-lactams except in case of α-phthalimido-β-lactams which had *trans* (J = 1.5 Hz) disposition of these protons.

Phenyl *N*-methyl-*N*-phenylphosphoramidochloridate (**1**; R = CH_3) as a condensing agent works under mild conditions and gives yields comparable to those reported by earlier methods for the synthesis of β-lactams.

β-Lactams 6 and 8; General Procedure:

A mixture of carboxylic acid **2** (0.01 mol), triethylamine (0.011 mol), dichloromethane (100 ml), and reagent **1** (0.011 mol) is stirred for 30 min at 10–15 °C under nitrogen followed by the slow addition of a solution of imine **4** (0.01 mol) and triethylamine (0.02 mol) in dry dichloromethane (50 ml). The mixture is stirred at room temperature overnight, washed with water (3 × 50 ml), aqueous sodium hydrogen carbonate (50 ml) and finally with water (50 ml). The organic phase is dried with sodium sulphate and passed over a Florisil column. Evaporation of the solvent and recrystallisation from dichloromethane/hexane affords the pure β-lactam.

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