One-pot sequence synthesis of azetidin-2-one using diethyl chlorophosphate

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A simple and convenient synthesis of 2-azetidinone derivatives from the reaction of a pre-mixture of amines and aldehydes with carboxylic acids in the presence of diethyl chlorophosphate by [2+2] cycloaddition reaction is described. Separation and purification of imines as intermediates were not required. The methodology is convenient and good to excellent yields of products were obtained with simple purification.

Keywords: β-lactam, 2-azetidinone, Staudinger reaction**,** diethyl chlorophosphate**,** ketene, imine

The 2-azetidinone (β-lactam) unit is a crucial structural feature of β-lactam antibiotics. It forms the structural component of the widely used penicillin, cephalosporin, thienamycine, nocardicin, aztreonam and carumonam.[1–2] Ezetimibe, new cholesterol absorption inhibitor drug, has a β-lactam skeleton.[3] In addition, there are many other biological activities of β-lactams.[4,5] 2-Azetidinones (β-lactams) can be employed as useful intermediates in organic synthesis in the synthesis of several compounds (β-lactam synthon method) and as side-chain equivalents for the synthesis of Taxol and Taxotere.[6–9] Because of these applications and the growing resistance of bacteria against β-lactam antibiotics, it is necessary to synthesise new β-lactams.

Among many synthetic methods for the formation of the β-lactam ring[10,11] the [2+2] cycloaddition of ketenes and imines (Staudinger reaction) is the simplest and most convenient.[12–13] This reaction has very broad applications in the preparation of *β*-lactams. The convenience of the Staudinger cycloaddition arises from not only the mild reaction conditions but also the general availability of imines and ketenes. Also ketenes can be simply prepared by the treatment of acyl chlorides with triethylamine before the reaction or *in situ*.[14–24]

Because of instability and difficulty in the preparation of acyl chloride, the Staudinger [2+2] cycloaddition has been extensively modified. These modifications include the application of a variety of acid-activating agents for the generation of ketenes from carboxylic acids *in situ*.[25–39]

The high cost, unavailability, pollution and low yields are disadvantages of some of these acid activators. Furthermore in some cases, heating or cooling of the reaction is necessary and purification of imines in most cases has been performed.

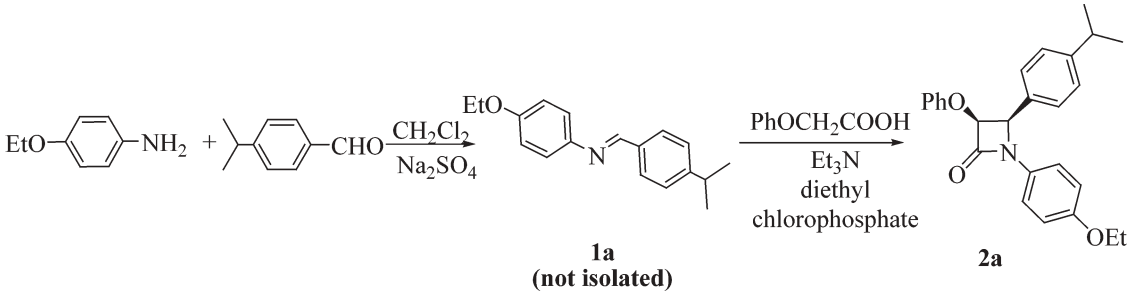
In this work, the one-pot sequence synthesis of β-lactams by the Staudinger reaction using diethyl chlorophosphate as a cheap and convenient method is described.

First, the condensation of 4-ethoxyaniline (1.0 mmol) and 4-isopropylbenzaldehyde (1.0 mmol) in dry CH_2Cl_2 in the presence of excess of anhydrous sodium sulfate was performed. After 24 hours, sodium sulfate was filtered and the resulting solution containing *N*-(4-isopropylbenzylidene)-4-ethoxyaniline **1a** (without isolation) was transferred to a round-bottomed flask equipped with a magnetic stirring bar and a calcium chloride tube. Then phenoxyacetic acid (1.0 mmol), dry triethylamine (3.0 mmol) and diethyl chlorophosphate (1.0 mmol) was added to the mixture at room temperature and the mixture was stirred overnight. After the usual work-up and purification by crystallisation from ethyl acetate the pure *cis*-1-(4-ethoxyphenyl)-4-(4-isopropylphenyl)-3-phenoxyazetidin-2-one **2a** was obtained as a white solid in 68% yield (Scheme 1). The 2-azetidinone **2a** was characterised by its spectral data. The *cis* stereochemistry was assigned by the comparison of the coupling constant H-3 and H-4 ($J_{3,4}$ = 4.8 Hz).

After this successful result, the optimisation of the reaction conditions was investigated by consideration of the effects of temperature and molar ratio of the reagent in the synthesis of β-lactam **2a** at dry CH_2Cl_2 (Table 1).

As shown in Table 1, the yield of **2a** increases when 1.5 mmol of diethyl chlorophosphate and 1.5 mmol of carboxylic acid react with 1.0 mmol of the mixture of amine and aldehyde instead of 1.0 or 1.3 mmol of diethyl chlorophosphate. Also the yields were better at room temperature than at 0 °C. The yield was not increased when the reaction stirred at 0 °C for 48 hours.

On the basis of above results, the 2-azetidinones **2a–k** were synthesised by treatment of 1.0 mmol of the corresponding amines and 1.0 mmol of the corresponding aldehydes in the presence of anhydrous sodium sulfate in dry dichloromethane for 24 hours, followed by addition of 1.5 mmol of substituted acetic acids, 1.5 mmol of diethyl chlorophosphate and 5.0 mmol triethylamine to the previous solution at room temperature and they were purified by crystallisation from EtOAc (Table 2). All products were obtained in good to excellent yields and were characterised by their spectral data and elemental analyses. The *cis* stereochemistry of all products was judged from the comparison of the coupling constant H-3 and H-4 ($J_{3,4}$> 4.4 Hz).



Scheme 1

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Table 1 Optimisation of conditions in the synthesis of β-lactam **2a**

Entry	Temp /°C	Diethyl chlorophosphate /mmol	Yield /%[a]
1	rt	1.0	68
2	rt	1.3	75
3	rt	1.5	88
4	rt	2.0	85
5	0 °C	1.5	76

[a] All reactions were stirred for 24 hours.

In conclusion, we have developed a simple procedure for the synthesis of 2-azetidinones in good to excellent yields by activated carboxylic acids using diethyl chlorophosphate and a mixture of amines and aldehydes at room temperature. All the steps of reaction are sequential and isolation and purification of imines is not required. The reaction has the advantages of mild conditions, simple purification, easy handling of the starting materials and high yields.

Experimental

All chemicals were purchased from Merck, Fluka and Acros. The melting points were determined on a Buchi 535 apparatus and are uncorrected. IR spectra were measured on a galaxy series FT-IR 5000 spectrometer. NMR spectra were recorded on a Bruker spectrophotometer (^{1}H NMR 300 MHz, ^{13}C NMR 75 MHz) using tetramethylsilane as an internal standard and coupling constants are given in Hz. Elemental analyses were run on a Vario EL III elemental analyser. TLC was carried out on silica gel 254 analytical sheets obtained from Fluka. Spectral data for **2i–k** have been previously reported.[31,40]

*Synthesis of 2-azetidinones (**2a-k**); general procedure*

To a stirred solution of corresponding aldehyde (1.0 mmol) in dry CH_2Cl_2 (20 mL) at room temperature were successively added the corresponding amine (1.0 mmol) and a large excess of anhydrous sodium sulfate (2.0 g). The resulting mixture was stirred for 24 hours at room temperature. The mixture was filtered and the resulted solution transferred to round-bottomed flask equipped with a magnetic stirring bar and calcium chloride tube. Then corresponding substituted acetic acids (1.5 mmol), dry triethylamine (5.0 mmol) and diethyl chlorophosphate (1.5 mmol) was added to the mixture at room temperature and it was stirred overnight. Then the solution was washed successively with HCl 0.5 M (20 mL), saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure to give the crude products. β-Lactams **2a–k** were purified by crystallisation from ethyl acetate.

1-(4-Ethoxyphenyl)-4-(4-isopropylphenyl)-3-phenoxyazetidin-2-one (**2a**): White solid; m.p. 161–163 °C. IR (KBr) cm^{-1}: 1751 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (2Me, d, 6H, *J* = 7.3), 1.35 (Me, t, 3H, *J* = 6.8), 2.82 (CH, septet, 1H), 3.92 (OCH_2, q, 2H, *J* = 6.8), 5.30 (H-4, d, 1H, *J* = 5.0), 5.69 (H-3, d, 1H, *J* = 5.0), 6.82–7.86 (ArH, m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (Me), 21.7 (Me), 32.5 (CH), 60.8 (OCH_2), 63.3 (C-4), 81.5 (C-3), 113.3, 117.3, 119.5, 122.1, 124.3, 125.9, 127.1, 127.9, 136.3, 144.8, 147.2, 158.2 (aromatic carbons), 161.9 (CO, β-lactam). Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.89; H, 6.92; N, 3.41%.

3-(2,4-Dichlorophenoxy)-1-(4-ethoxyphenyl)-4-(4-isopropylphenyl) azetidin-2-one (**2b**): White solid; m.p. 155–157 °C. IR (KBr) cm^{-1}: 1746 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (2Me, d, 6H, *J* = 7.0), 1.31 (Me, t, 3H, *J* = 6.7), 2.74 (CH, septet, 1H), 4.00 (OCH_2, q, 2H, *J* = 6.7), 5.47 (H-4, d, 1H, *J* = 5.1), 5.65 (H-3, d, 1H, *J* = 5.1), 6.88–7.73 (ArH, m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8 (Me), 23.3 (Me), 34.1 (CH), 61.4 (OCH_2), 63.1 (C-4), 82.9 (C-3), 111.3, 112.8, 116.0, 117.8, 120.6, 124.0, 126.2, 126.6, 129.3, 132.9, 137.1, 141.6, 145.8, 155.9 (aromatic carbons), 163.1 (CO, β-lactam). Anal. Calcd for $C_{26}H_{25}Cl_2NO_3$: C, 66.39; H, 5.36; N, 2.98. Found: C, 66.45; H, 5.348; N, 3.06%.

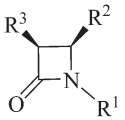
1-(4-Ethoxyphenyl)-4-(4-isopropylphenyl)-3-(naphthalen-2-yloxy) azetidin-2-one (**2c**): White crystalline solid; m.p. 182–184 °C. IR (KBr) cm^{-1}: 1744 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (2Me, d, 6H, *J* = 7.2), 1.39 (Me, t, 3H, *J* = 7.0), 2.66 (CH, septet, 1H), 4.06 (OCH_2, q, 2H, *J* = 7.0), 5.38 (H-4, d, 1H, *J* = 4.4), 5.59 (H-3, d, 1H, *J* = 4.4), 6.81–7.84 (ArH, m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9 (Me), 25.1 (Me), 32.8 (CH), 60.1 (OCH_2), 63.6 (C-4), 84.0 (C-3), 113.7, 115.1, 117.0, 117.4, 119.6, 122.3, 123.7, 124.1, 126.0, 126.9, 127.7, 131.4, 135.8, 139.2, 143.6, 144.0, 148.1, 157.4 (aromatic carbons), 162.3 (CO, β-lactam). Anal. Calcd for $C_{30}H_{29}NO_3$: C, 79.80; H, 6.47; N, 3.10. Found: C, 79.74; H, 6.59; N, 3.03%.

2-(1-(4-Ethoxyphenyl)-2-(4-isopropylphenyl)-4-oxoazetidin-3-yl) isoindoline-1,3-dione (**2d**): Light-yellow solid; m.p. 178–180 °C. IR (KBr) cm^{-1}: 1738, 1751 (CO, phth), 1774 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (2Me, d, 6H, *J* = 7.0), 1.33 (Me, t, 3H, *J* = 7.2), 2.61 (CH, septet, 1H), 4.12 (OCH_2, q, 2H, *J* = 7.2), 5.19 (H-4, d, 1H, *J* = 4.6), 5.57 (H-3, d, 1H, *J* = 4.6), 6.79-7.63 (ArH, m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1 (Me), 24.6 (Me), 31.5 (CH), 60.9 (OCH_2), 62.7 (C-4), 65.3 (C-3), 114.8, 118.2, 121.1, 125.9, 126.4, 127.3, 128.3, 135.5, 138.2, 147.1, 155.8 (aromatic carbons), 162.4 (CO, phth), 164.0 (CO, β-lactam). Anal. Calcd for $C_{28}H_{26}N_2O_4$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.11; H, 5.90; N, 6.24%.

1-Benzyl-3-(4-chlorophenoxy)-4-(4-nitrophenyl)azetidin-2-one (**2e**): Light-yellow solid; m.p. 123–125 °C IR (KBr) cm^{-1}: 1332, 1522 (NO_2), 1744 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92, 4.80 (CH_2-benzyl, 2d, 2H, *J* = 15.0), 4.91 (H-4, d, 1H, *J* = 4.8), 5.56 (H-3, d, 1H, *J* = 4.8), 6.74-8.21 (ArH, m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.8 (CH_2), 62.4 (C-3), 83.6 (C-4), 116.3, 120.6, 122.9, 127.8, 128.3, 129.4, 129.7, 131.0, 138.8, 140.2, 146.2, 155.3 (aromatic carbons), 163.7 (CO, β-lactam). Anal. Calcd for $C_{22}H_{17}ClN_2O_4$: C, 64.63; H, 4.19; N, 6.85. Found: C, 64.74; H, 4.32; N, 6.94%.

1-Benzyl-3-(4-chlorophenoxy)-4-(4-chlorophenyl)azetidin-2-one (**2f**): White solid; m.p. 109–111 °C IR (KBr) cm^{-1}: 1752 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85, 4.87 (CH_2-benzyl, 2d, 2H, *J* = 14.8), 4.93 (H-4, d, 1H, *J* = 5.1), 5.41 (H-3, d, 1H, *J* = 5.1),

Table 2 Synthesis of 2-azetidinones **2a–k**



Entry	R^1	R^2	R^3	Product	Isolated yield/%
1	4-$EtOC_6H_4$	4-$(Me_2CH)C_6H_4$	PhO	**2a**	88
2	4-$EtOC_6H_4$	4-$(Me_2CH)C_6H_4$	2,4-$Cl_2C_6H_3O$	**2b**	84
3	4-$EtOC_6H_4$	4-$(Me_2CH)C_6H_4$	2-naphthO	**2c**	82
4	4-$EtOC_6H_4$	4-$(Me_2CH)C_6H_4$	PhthN	**2d**	79
5	$PhCH_2$	4-$NO_2C_6H_4$	4-ClC_6H_4O	**2e**	87
6	$PhCH_2$	4-ClC_6H_4	4-ClC_6H_4O	**2f**	80
7	4-$MeOC_6H_4CH_2$	4-$NO_2C_6H_4$	4-ClC_6H_4O	**2g**	82
8	4-$MeOC_6H_4CH_2$	4-ClC_6H_4	4-ClC_6H_4O	**2h**	76
9	4-$MeOC_6H_4$	4-MeC_6H_4	MeO	**2i**	83
10	4-$MeOC_6H_4$	CH=CHPh	PhO	**2j**	79
11	4-$EtOC_6H_4$	4-$MeOC_6H_4$	2-naphthO	**2k**	88

6.84-7.57 (ArH, m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.7 (CH_2), 60.5 (C-3), 81.9 (C-4), 114.2, 118.7, 121.0, 124.6, 126.3, 127.5, 128.9, 132.4, 134.1, 138.7, 141.3, 153.8 (aromatic carbons), 161.4 (CO, β-lactam). Anal. Calcd for $C_{22}H_{17}Cl_2NO_2$: C, 66.34; H, 4.30; N, 3.52. Found: C, 66.29; H, 4.41; N, 3.46.

1-(4-Methoxybenzyl)-3-(4-chlorophenoxy)-4-(4-nitrophenyl)azetidin-2-one (**2g**): Light-yellow solid; m.p. 92–94 °C. IR (KBr) cm^{-1}: 1339, 1544 (NO_2), 1745 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (OMe, s, 3H), 3.93, 4.84 (CH_2-benzyl, 2d, 2H, *J* = 14.9), 4.89 (H-4, d, 1H, *J* = 4.8), 5.52 (H-3, d, 1H, *J* = 4.8), 6.71–8.24 (ArH, m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.4 (CH_2), 56.1 (OMe), 61.3 (C-3), 81.7 (C-4), 115.3, 116.8, 120.6, 124.0, 127.5, 128.2, 129.5, 130.3, 142.8, 145.1, 154.7, 157.9 (aromatic carbons), 162.7 (CO, β-lactam). Anal. Calcd for $C_{23}H_{19}ClN_2O_5$: C, 62.95; H, 4.36; N, 6.38. Found: C, 63.08; H, 4.46; N, 6.41%.

1-(4-Methoxybenzyl)-3-(4-chlorophenoxy)-4-(4-chlorophenyl)azetidin-2-one (**2h**): White solid; m.p. 83–85 °C. IR (KBr) cm^{-1}: 1749 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (OMe, s, 3H), 3.88, 4.78 (CH_2-benzyl, 2d, 2H, *J* = 15.0), 4.85 (H-4, d, 1H, *J* = 4.5), 5.42 (H-3, d, 1H, *J* = 4.5), 6.63–7.59 (ArH, m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.9 (CH_2), 55.7 (OMe), 62.4 (C-3), 81.1 (C-4), 114.8, 116.0, 118.3, 123.5, 126.9, 127.7, 129.1, 130.8, 136.4, 142.6, 153.1, 158.4 (aromatic carbons), 163.6 (CO, β-lactam). Anal. Calcd for $C_{23}H_{19}Cl_2NO_3$: C, 64.50; H, 4.47; N, 3.27. Found: C, 64.57; H, 4.62; N, 3.20%.

1-(4-Methoxyphenyl)-3-methoxy-4-p-tolylazetidin-2-one (**2i**): White solid; m.p. 153-155 °C (lit.[40] 151–153 °C).

1-(4-methoxyphenyl)-3-phenoxy-4-styrylazetidin-2-one (**2j**): White solid; m.p. 182–184 °C (lit.[31] 181–182 °C).

1-(4-Ethoxyphenyl)-4-(4-methoxyphenyl)-3-(naphthalen-2-yloxy)-azetidin-2-one (**2k**):White solid; m.p. 161–163 °C (lit.[40] 162–164 °C).

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