# Facile synthesis of ß-lactam derivatives by the Staudinger reaction using 3,6-dichlorotetrazine

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A versatile and convenient method for synthesis of β-lactams using 3,6-dichlorotetrazine as an acid activator in the ketene–imine cycloaddition is reported. Monocyclic and spirocyclic β-lactams are obtained in good to excellent yields. Easy purification of the products can be performed by aqueous workup and then crystallisation from ethyl acetate.

**Keywords:** β-lactam, 2-azetidinone, Staudinger reaction, 3,6-dichlorotetrazine, ketene, imine

β-Lactam antibiotics are a group of drugs used to counter infections caused by bacteria. Unfortunately, bacteria resistant to them are now widespread with the irregular use of the β-lactam antibiotics as one of the reasons for this resistance.[1] Biologically active substrates, based on the β-lactam (2-azetidinone) structure, have been reported recently such as ezetimibe which acts as a cholesterol absorption inhibitor, a new clinical use of 2-azetidinones.[2] β-Lactams have also been used as synthetic intermediates in organic synthesis and in the semisynthesis of taxol derivatives.[3]

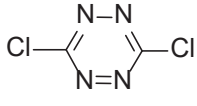
Many synthetic methods have been reported for the synthesis of the 2-azetidinone ring because of the tremendous importance of these β-lactams.[4,5] The Staudinger reaction ([2+2] ketene–imine cycloaddition) is the most commonly used method for the synthesis of 2-azetidinones.[6,7] Also, the reaction of acyl chlorides with triethyamine has been used for the generation of the ketenes.[8]

Acyl chlorides are unstable in the presence of moisture, some of them are not commercially available and their synthesis and purification can be difficult. Activation of a carboxylic acid with acid activator reagents followed by treatment with a base is another method for ketene generation without using acid halides.[9-18] Unfortunately, some of these acid activators are difficult to access and require harsh conditions and purification of the products is problematical.

3,6-Dichlorotetrazine **1** is a highly electron-deficient heterocycle and, therefore, undergoes nucleophilic substitution reactions. This reagent has been used previously for the synthesis of bis(triazidomethyl)methoxytetrazine[19] and in the synthesis of a tripodal *s*-tetrazine.[20]

To the best of our knowledge, β-lactams have not been synthesised using 3,6-dichlorotetrazine. We now present our synthesis of β-lactams from imine and carboxylic acids using 3,6-dichlorotetrazine through ketene–imine cycloaddition.

Schiff bases were synthesised by refluxing equimolar amounts of aldehydes and amines in 95% ethanol. Acid activator **1** was added to a solution of the Schiff base **2a**, carboxylic acid **3a** and triethylamine in dry toluene at room temperature. After usual work-up and crystallisation from ethyl acetate, 2-azetidinone **4a** was obtained in 55%. Therefore, this reaction was considered as the optimum model. Several dry solvents such as toluene, $CH_2Cl_2$, $CHCl_3$, THF and DMF were considered (Table 1). Among the solvents, dichloromethane was found to be the optimal, but low temperatures decreased the yield. As shown in Table 1, the highest yield of **4a** was obtained when 1.5 mmol of 3,6-dichlorotetrazine **1** and 1.5 mmol carboxylic acid **3a** react with 1.0 mmol of Schiff base **2a** in dry dichloromethane at room temperature(RT) (entry 8).

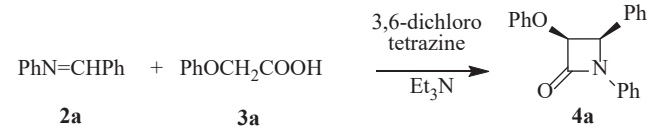


**1**

Using the optimal conditions, various β-lactams have been synthesised through cycloaddition of Schiff bases with ketenes (Scheme 1, Table 2). As can be seen from Table 2, different carboxylic acids and Schiff bases can all be converted into the corresponding 2-azetidinones using 3,6-dichlorotetrazine **1** in good to excellent yields and with high purity.

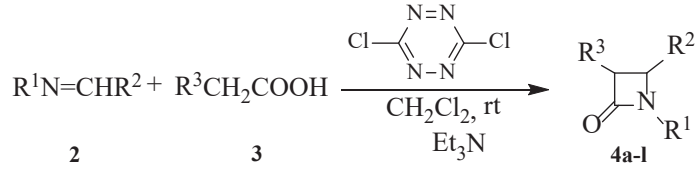
The purification of β-lactams **4a–l** was performed by crystallisation from EtOAc after simple aqueous work-up. This reaction is efficient and clean because the by-product of tetrazine and the resulting salts are water soluble and are easily removed by simple aqueous workup. All products were characterised by their spectral data and elemental analyses. The stereochemistry was judged by the comparison of the coupling constants H-3 and H-4 ($J_{3,4}$> 4.0 Hz) for the *cis* stereoisomer and ($J_{3,4}$≤ 3.0 Hz) for the *trans* stereoisomer.[21]

**Table 1** Reaction condition in the synthesis of 2-azetidinone **4a**




**2a** **3a** **4a**

| Entry | Solvent | Temp/°C | Quantity of reagent/mmol | Yield/% |
|---|---|---|---|---|
| 1 | Toluene | RT | 1.0 | 55 |
| 2 | THF | RT | 1.0 | 39 |
| 3 | $CH_2Cl_2$ | RT | 1.0 | 63 |
| 4 | $CHCl_3$ | RT | 1.0 | 61 |
| 5 | DMF | RT | 1.0 | 51 |
| 6 | $CH_2Cl_2$ | 0 | 1.0 | 36 |
| 7 | $CH_2Cl_2$ | RT | 1.3 | 79 |
| 8 | $CH_2Cl_2$ | RT | 1.5 | 90 |




**2** **3** **4a-l**

**Scheme 1** Synthesis of 2-azetidinones **4a–l**.

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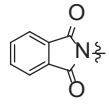
**Table 2** Synthesis of 2-azetidinones **4a–l** using 3,6-dichlorotetrazine

| Entry | $R^1$ | $R^2$ | $R^3$ | *cis/ trans* | Product | Isolated yield /% |
|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | $C_6H_5$ | PhO | *cis* | **4a** | 90 |
| 2 | 4-$MeOC_6H_4$ | 4-$ClC_6H_4$ | PhO | *cis* | **4b** | 87 |
| 3 | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | PhO | *cis* | **4c** | 86 |
| 4 | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | 4-$ClC_6H_4O$ | *cis* | **4d** | 75 |
| 5 | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | 2,4-$Cl_2C_6H_4O$ | *cis* | **4e** | 71 |
| 6 | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | MeO | *cis* | **4f** | 87 |
| 7 | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | PhthN[a] | *trans* | **4g** | 89 |
| 8 | 4-$ClC_6H_4$ | 4-($Me_2CH$) $C_6H_4$ | PhO | *cis* | **4h** | 93 |
| 9 | 4-$ClC_6H_4$ | 4-($Me_2CH$) $C_6H_4$ | 4-$ClC_6H_4O$ | *cis* | **4i** | 91 |
| 10 | 4-$ClC_6H_4$ | 4-($Me_2CH$) $C_6H_4$ | 2,4-$Cl_2C_6H_4O$ | *cis* | **4j** | 83 |
| 11 | 4-$ClC_6H_4$ | 4-($Me_2CH$) $C_6H_4$ | MeO | *cis* | **4k** | 81 |
| 12 | 4-$ClC_6H_4$ | 4-($Me_2CH$) $C_6H_4$ | PhthN[a] | *trans* | **4l** | 75 |

[a] PhthN = phthalimido group = 

Many different experimental factors, such as reaction temperature, solvent, electronic effect and the steric hindrance of the ketene and imine substituents may affect the stereochemistry of the β-lactams in the Staudinger reaction.[22] Ketenes generated from alkoxyacetic acids lead to *cis* β-lactam but ketenes derived from phthalimidoacetic acid (β-lactams **4g** and **4l**) lead to the *trans* isomer because of the greater steric hindrance of phthalimidoketene relative to that in alkoxyketenes.

The use of 3,6-dichlorotetrazine **1** was successfully extended to the synthesis of C-3 spiro-β-lactams. The treatment of xanthene-9-carboxylic acid **5** with imines **2** in the presence of reagent **1** and triethylamine afforded spiro-β-lactams **6a-b** which were purified by crystallisation from EtOAc (Scheme 2).

In conclusion, a simple and convenient method for one-pot synthesis of β-lactams from carboxylic acids and imines using 3,6-dichlorotetrazine has been reported. Good to excellent yields of the products, easy workup and purification, and the mild condition reactions are some advantages of this method.

## Experimental

All required chemicals were purchased from Merck, Fluka, and Acros Chemical Companies. The melting points were determined on a Buchi 535 apparatus. IR spectra were measured on a Shimadzu FTIR 8300 spectrophotometer. NMR spectra were recorded on a Bruker spectrometer ($^1$H NMR 250 MHz, $^{13}$C NMR 62.9 MHz) using tetramethylsilane as an internal standard and coupling constants (*J*) 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 **4a–c** have been previously reported[23-25] and β-lactams **4d–l** and **6a–b** are new compounds.

*Synthesis of 2-azetidinones (**4a–l** and **6a–b**); general procedure*

3,6-Dichlorotetrazine (1.5 mmol) was added to solutions of substituted acetic acids (1.5 mmol), imines (1.0 mmol) and triethylamine (5.0 mmol) in dry $CH_2Cl_2$ (15 mL) at room temperature and the mixture was stirred overnight. The reaction mixture was washed successively with saturated $NaHCO_3$ (15 mL) and brine (15 mL). The organic layer was dried ($Na_2SO_4$), filtered and the solvent was removed to give the crude product, which was purified by crystallisation from EtOAc to give pure β-lactams **4a–l** and **6a–b**.

*3-Phenoxy-1,4-diphenyl-2-azetindione* (**4a**): M.p 191–193 °C (lit.[23] 193–195 °C).

*4-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one* (**4b**): M.p. 181–183 °C (lit.[24] 180–182 °C).

*1,4-bis(4-Chlorophenyl)-3-phenoxyazetidin-2-one* (**4c):** M.p. 234–236 °C (lit.[25] 246 °C)**.**

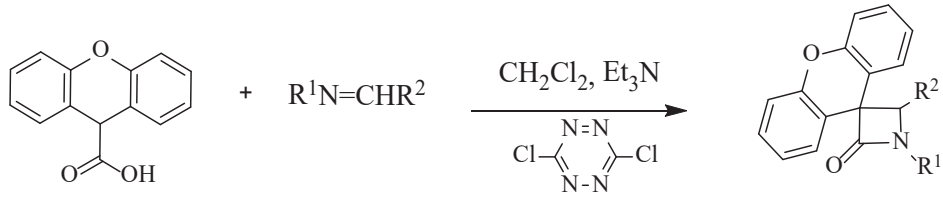
*3-(4-Chlorophenoxy)-1,4-bis(4-chlorophenyl)azetidin-2-one* (**4d**): White solid; m.p. >220 °C. IR (KBr) $cm^{-1}$: 1744 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 5.34 (H-4, d, 1H, *J* = 4.9), 5.65 (H-3, d, 1H, *J* = 4.9), 6.87–7.35 (ArH, m, 12H); $^{13}$C NMR δ 62.1 (C-4), 79.83 (C-3), 116.9, 120.6, 126.6, 128.3, 128.5, 128.6, 128.7, 128.8, 129.5, 136.1, 137.8, 156.0 (aromatic carbons), 162.4 (CO, β-lactam). Anal. calcd for $C_{21}H_{14}Cl_3NO_2$: C, 60.24; H, 3.37; N, 3.35; found: C, 60.32; H, 3.46; N, 3.30%.

*1,4-bis(4-Chlorophenyl)-3-(2,4-dichlorophenoxy)azetidin-2-one* (**4e**): Cream colour solid; m.p. >240 °C IR (KBr) $cm^{-1}$: 1743 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 5.29 (H-4, d, 1H, *J* = 5.0), 5.66 (H-3, d, 1H, *J* = 5.0 ), 6.91–7.43 (ArH, m, 11H); $^{13}$C NMR δ 61.1 (C-4), 81.8 (C-3), 119.3, 120.6, 126.8, 128.2, 128.3, 128.4, 128.5, 128.6, 131.3, 133.4, 135.8, 136.1, 137.8, 152.2, 161.1 (aromatic carbons), 161.1 (CO, β-lactam). Anal. calcd for $C_{21}H_{13}Cl_4NO_2$: C, 55.66; H, 2.89; N, 3.09; found: C, 55.79; H, 3.01; N, 3.01%.

*1,4-bis(4-Chlorophenyl)-3-methoxyazetidin-2-one* (**4f**): White solid; m.p. 160–162 °C. IR (KBr) $cm^{-1}$: 1754 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 3.40 (OMe, s, 3H), 5.04 (H-4, d, 1H, *J* = 4.6), 5.25 (H-3, d, 1H, *J* = 4.6), 7.12–7.33 (ArH, m, 8H); $^{13}$C NMR δ 58.5 (OMe), 62.9 (C-4), 82.0 (C-3), 120.6, 128.3, 128.5, 128.6, 128.8, 130.1, 131.9, 133.4, 137.8 (aromatic carbons), 163.8 (CO, β-lactam). Anal. calcd for $C_{16}H_{13}Cl_2NO_2$: C, 59.65; H, 4.07; N, 4.35; found: C, 59.75; H, 4.19; N, 4.42%.

*2-(1,2-bis(4-Chlorophenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione* (**4g**): Pale-yellow solid; m.p. 140–142 °C. IR (KBr) $cm^{-1}$: 1736, 1773 (CO, phth), 1784 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 5.45 (H-3, d, 1H, *J* = 2.5), 5.55 (H-4, d, 1H, *J* = 2.5), 7.18–7.59 (ArH, m, 12H); $^{13}$C NMR δ 61.2 (C-3), 62.3 (C-4), 120.2, 125.3, 128.8, 129.1, 129.4, 130.1, 131.2, 132.4, 133.1, 137.8, 137.9 (aromatic carbons), 165.5 (CO, phth), 167.8 (CO, β-lactam). Anal. calcd for $C_{23}H_{14}Cl_2N_2O_3$: C, 63.17; H, 3.23; N, 6.41; found: C, 63.12; H, 3.29; N, 6.36%.

*1-(4-Chlorophenyl)-4-(4-isopropylphenyl)-3-phenoxyazetidin-2-one* (**4h**): White solid; m.p. >240 °C. IR (KBr) $cm^{-1}$: 1757 (CO,




**5** **2**

**6a**: $R^1$= 4-$ClC_6H_4$, $R^2$= 4-$ClC_6H_4$ 86%
**6b**: $R^1$= 4-$ClC_6H_4$, $R^2$= 4-($Me_2CH$) $C_6H_4$ 87%

**Scheme 2**

β-lactam); $^1$H NMR ($CDCl_3$) δ 1.34 (Me, d, 6H), 3.04 (CH, Sept, 1H), 5.51 (H-4, d, 1H, *J* = 4.9), 5.67 (H-3, d, 1H, *J* = 4.9), 6.92–7.36 (ArH, m, 13H); $^{13}$C NMR δ 23.3 (Me), 34.0 (CH), 62.1 (C-4), 82.2 (C-3), 117.6, 120.6, 121.6, 125.5, 128.8, 128.9, 132.3, 133.2, 135.6, 137.8, 147.16, 157.9 (aromatic carbons), 162.0 (CO, β-lactam). Anal. calcd for $C_{24}H_{22}ClNO_2$: C, 73.56; H, 5.66; N, 3.57; found: C, 73.67; H, 5.73; N, 3.61%.

*3-(4-Chlorophenoxy)-1-(4-chlorophenyl)-4-(4-isopropylphenyl) azetidin-2-one* (**4i**): Cream colour solid; m.p. >210 °C. IR (KBr) cm$^{-1}$: 1755 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 1.32 (Me, d, 6H), 3.01 (CH Sept, 1H), 5.35 (H-4, d, 1H, *J* = 4.5), 5.66 (H-3, d, 1H, *J* = 4.5), 7.01–7.32 (ArH, m, 12H); $^{13}$C NMR δ 24.9 (Me ), 34.2 (CH), 62.7 (C-4), 80.68 (C-3), 115.9, 116.0, 120.6, 125.5, 127.4, 128.8, 129.4, 131.1, 133.3, 135.6, 147.2, 156.0 (aromatic carbons), 163.0 (CO, β-lactam). Anal. calcd for $C_{24}H_{21}Cl_2NO_2$: C, 67.61; H, 4.96; N, 3.29; found: C, 67.70; H, 5.09; N, 3.23%.

*1-(4-Chlorophenyl)-3-(2,4-dichlorophenoxy)-4-(4-isopropylphenyl)azetidin-2-one* (**4j**): Cream colour solid; m.p. 196–198 °C. IR (KBr) cm$^{-1}$: 1744 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 1.32 (Me, d, 6H), 3.05 (CH Sept, 1H), 5.35 (H-4, d, 1H, *J* = 4.7), 5.66 (H-3, d, 1H, *J* = 4.7), 7.01–7.39 (ArH, m, 11H); $^{13}$C NMR δ 22.2 (Me), 34.8 (CH),61.4 (C-4), 80.6 (C-3), 119.2, 120.5, 125.4, 126.4, 128.6, 132.3, 133.3, 135.5, 135.9, 137.3, 137.8, 138.2, 147.2, 152.2 (aromatic carbons), 163.0 (CO, β-lactam). Anal. calcd for $C_{24}H_{20}Cl_3NO_2$: C, 62.56; H, 4.37; N, 3.04; found: C, 62.63; H, 4.45; N, 2.97%.

*1-(4-Chlorophenyl)-4-(4-isopropylphenyl)-3-methoxyazetidin-2-one* (**4k**): White solid; m.p. 130–132 °C. IR (KBr) cm$^{-1}$: 1745.3 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 1.32 (Me, d, 6H), 3.02 (CH Sept, 1H), 5.04 (H-4, d, 1H, *J* = 4.5), 5.66 (H-3, d, 1H, *J* = 4.5), 7.01–7.31 (ArH, m, 8H); $^{13}$C NMR δ 23.0 (Me), 33.2 (CH), 57.9 (MeO), 63.4 (C-4), 83.0 (C-3), 120.6, 125.4, 128.7, 131.0, 133.3, 135.6, 137.3, 147.2 (aromatic carbons), 164.5 (CO, β-lactam). Anal. calcd for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.11; N, 4.25; found: C, 69.33; H, 6.25; N, 4.32%.

*2-(1-(4-Chlorophenyl)-2-(4-isopropylphenyl)-4-oxoazetidin-3-yl) isoindoline-1,3-dione* (**4l**): White solid; m.p. 170–172 °C. IR (KBr) cm$^{-1}$: 1731, 1758 (CO, phth), 1774 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 1.31 (Me, d, 6H), 3.04 (CH Sept, 1H), 5.46 (H-3, d, 1H, *J* = 2.5), 5.55 (H-4, d, 1H, *J* = 2.5), 7.01–7.80 (ArH, m, 11H); $^{13}$C NMR δ 24.1 (Me), 34.7 (CH), 60.8 (C-3), 61.8 (C-4), 121.0, 125.2, 126.3, 128.7, 131.0, 131.9, 133.2, 134.8, 137.3, 138.2, 145.8 (aromatic carbons), 166.2 (CO, phth), 167.5 (CO, β-lactam). Anal. calcd for $C_{26}H_{21}ClN_2O_3$: C, 70.19; H, 4.76; N, 6.30; found: C, 70.28; H, 4.85; N, 6.34%.

*1,2-bis(4-Chlorophenyl)spiro[azetidine-3,9'-xanthen]-4-one* (**6a**): White solid; m.p. 220–222 °C IR (KBr) cm$^{-1}$: 1748 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 5.60 (H-4, S, 1H), 6.86–7.34 (ArH, m, 16H); $^{13}$C NMR δ 62.7 (C-4), 71.7 (C-3), 116.8, 119.9, 121.8, 122.9, 123.9, 123.8, 125.9, 127.8, 129.05, 133.2, 134.4, 136.9, 137.2, 150.8 (aromatic carbons), 167.7 (CO, β-lactam). Anal. calcd for $C_{27}H_{17}Cl_2NO_2$: C, 70.75; H, 3.74; N, 3.06; found: C, 70.85; H, 3.83; N, 3.11%.

*1-(4-Chlorophenyl)-2-(4-isopropylphenyl)spiro[azetidine-3,9'-xanthen]-4-one* (**6b**): White solid; m.p. 156–158 °C. IR (KBr) cm$^{-1}$: 1746 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 1.28(Me, d, 6H), 2.97 (CH, sept, 1H), 5.5 (H-4, s, 1H), 6.81–7.32 (ArH, m, 16H); $^{13}$C NMR δ 22.9 (Me), 34.3 (CH), 63.0 (C-4), 77.0 (C-3), 117.4, 120.1, 122.1, 123.4, 124.6, 128.3, 129.0, 134.1, 135.3, 136.9, 137.3, 138.8, 145.8, 151.0 (aromatic carbons), 166.9 (CO, β-lactam). Anal. calcd for $C_{30}H_{24}ClNO_2$: C, 77.33; H, 5.19; N, 3.01; found: C, 77.42; H, 5.32; N, 3.09%.

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