Tosylimidazole-mediated one-pot synthesis of 2-azetidinones

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Cyclocondensation of Schiff bases and substituted acetic acid with tosylimidazole afforded 2-azetidinones in good to excellent yields. This reaction works reliably well for monocyclic and spirocyclic 2-azetidinones. This reaction is green and efficient and the products can be purified by simple crystallisation.

Keywords: β-lactam, 2-azetidinone, Staudinger reaction, tosylimidazole, ketene, imine

N-(*p*-Toluenesulfonyl)imidazole (tosylimidazole, TsIm; Fig. 1) is a highly efficient, cheap and stable reagent for the one-pot conversion of alcohols to alkyl azides and alkyl nitriles, and for esterification.[1] Although this reagent is commercially available, it can also be prepared by a reported method.[2]

Owing to the wide-ranging and important biological activities of 2-azetidinones[3] and their application in the synthesis of non-β-lactam products,[4] several methods have been developed for the synthesis of the 2-azetidinone ring.[5–7]

A well-established method for 2-azetidinone synthesis is the [2 + 2] ketene–imine cycloaddition (Staudinger reaction).[8–10] Ketenes can be generated *in situ* by reaction of acyl chlorides with triethylamine.[11,12] However, owing to their instability and the lack of availability of acyl chlorides and sometimes the low yield of products, direct generation of ketenes from carboxylic acids using acid activators has been considered.[12–20] Here, we report the use of tosylimidazole as a coupling reagent for the one-pot synthesis of 2-azetidinones from carboxylic acids and imines.

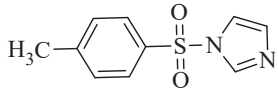


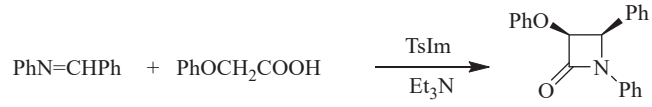
Fig. 1 Tosylimidazol, TsIm.

Results and discussion

Aldehydes and amines were refluxed in 95% ethanol for 2 h to give the corresponding Schiff bases. Then treatment of *N*-benzylideneaniline **1**, phenoxyacetic acid and tosylimidazole in dry benzene in the presence of triethylamine afforded 2-azetidinone **3** in 51% yield. This reaction was considered as a model reaction to permit the optimisation of the method. Several dry solvents, such as benzene, THF, DMF, $CHCl_3$, CH_2Cl_2 and CH_3CN, were examined (Table 1). It was found that the best yield was with CH_2Cl_2 (Table 1, entry 2). Also temperature and equimolar amounts of reagents were tested. The results showed that the highest yield of 2-azetidinone **3** was obtained when 1.3 mmol phenoxyacetic acid and 1.3 mmol TsIm were reacted with 1.0 mmol of Schiff base **1** in dry CH_2Cl_2 at room temperature (Table 1, entry 9).

After determining the optimum reaction conditions, several monocyclic 2-azetidinones were synthesised using this method. Simple aqueous work-up and purification by recrystallisation from ethanol afforded pure 2-azetidinones **3**–**11** (Scheme 1 and Table 2). All products were characterised from their spectra and physical data. The stereochemistry of products was deduced by the comparison of the coupling constant H-3 and H-4 ($J_{3,4} > 4.0$ Hz) for the *cis* stereoisomer and ($J_{3,4} \leq 3.0$ Hz) for the

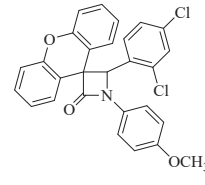
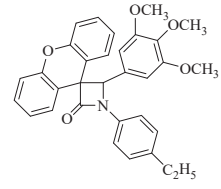
Table 1 Reaction conditions in the synthesis of 2-azetidinone **3**



1 **2** **3**

Entry	Solvent	Temperature/°C	Tosylimidazole/mmol	Yield/%
1	benzene	r.t.	1.0	51
2	CH_2Cl_2	r.t.	1.0	76
3	$CHCl_3$	r.t.	1.0	73
4	THF	r.t.	1.0	41
5	CH_3CN	r.t.	1.0	49
6	DMF	r.t.	1.0	55
7	CH_2Cl_2	0	1.0	67
8	CH_2Cl_2	40	1.0	70
9	CH_2Cl_2	r.t.	1.3	91
10	CH_2Cl_2	r.t.	1.5	88

Table 2 Synthesis of 2-azetidinones **3**–**13** using TsIm

Entry	R^1	R^2	R^3	*cis*/*trans*	Product	Isolated yield/%
1	C_6H_5	C_6H_5	PhO	*cis*	**3**	91
2	4-$MeOC_6H_4$	2,4-$Cl_2C_6H_3$	PhO	*cis*	**4**	94
3	4-$MeOC_6H_4$	2,4-$Cl_2C_6H_3$	PhthN	*trans*	**5**	85
4	4-$MeOC_6H_4$	3,4,5-$(MeO)_3C_6H_2$	2,4-$Cl_2C_6H_2O$	*cis*	**6**	77
5	4-$MeOC_6H_4$	3,4,5-$(MeO)_3C_6H_2$	PhthN	*trans*	**7**	91
6	4-EtC_6H_4	2,4-$Cl_2C_6H_3$	PhO	*cis*	**8**	85
7	4-EtC_6H_4	2,4-$Cl_2C_6H_3$	2,4-$Cl_2C_6H_2O$	*cis*	**9**	80
8	4-EtC_6H_4	3,4,5-$(MeO)_3C_6H_2$	2,4-$Cl_2C_6H_2O$	*cis*	**10**	81
9	4-EtC_6H_4	3,4,5-$(MeO)_3C_6H_2$	PhthN	*trans*	**11**	76
10				–	**12**	72
11				–	**13**	70

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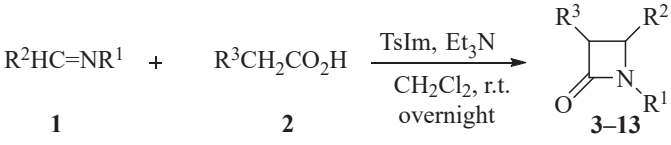

Scheme 1 Synthesis of 2-azetidinones **3–13**.

trans stereoisomer.[21] This method was extended to the synthesis of 3-spirocyclic-2-azetidinones **12** and **13** (Table 2, entries 10 and 11).

The stereochemistry of 2-azetidinones in the Staudinger reaction depends on reaction temperature, solvent, electronic effect and the steric hindrance of the ketene and imine substituents.[22,23]

In summary, the use of tosylimidazole for the one-pot synthesis of 2-azetidinones from Schiff bases and carboxylic acids under mild conditions is reported. The solvents, molar ratio of reagent, time and temperature have been optimised. The method is efficient and versatile.

Experimental

Melting points were measured by the capillary tube method with an opti-melt MPA100 apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Spectrospin Advance 400 spectrometer using TMS as an internal standard and $CDCl_3$ as a solvent. Chemical shifts were reported in ppm (δ) and coupling constants (*J*) were reported in Hz. IR spectra were recorded from KBr disks using the Shimadzu FT IR-8400S. Elemental analyses were recorded using a Thermo Finnigan Flash EA–1112. Commercial aluminium-backed plates of silica gel 60 F_{254} were used to monitor the progress of reactions by thin-layer chromatography.

Synthesis of 2-azetidinones (**3**–**13**)*; general procedure*

A mixture of Schiff base (1.0 mmol), triethylamine (5.0 mmol), carboxylic acid (1.3 mmol) and tosylimidazole (1.3 mmol) in dry CH_2Cl_2 (20 mL) was stirred at room temperature overnight. The mixture was washed successively with saturated $NaHCO_3$ (20 mL) and brine (15 mL). The organic layer was dried and the solvent was removed to give the crude product, which was purified by crystallisation from EtOH to give pure 2-azetidinones **3**–**13**.

3-Phenoxy-1,4-diphenyl-2-azetindione (**3**): M.p. 190–192 °C (lit.[24] 191–193 °C).

4-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (**4**): White solid; m.p. 132–135 °C; IR (KBr) (cm^{-1}): 1755 (CO, β-lactam); ^{1}H NMR ($CDCl_3$): δ 3.69 (s, 3H, OMe), 5.52 (d, 1H, *J* = 4.9, H-4), 5.71 (d, 1H, *J* = 4.9, H-3), 6.75–7.29 (m, 12H, ArH); ^{13}C NMR ($CDCl_3$): δ 54.4 (OMe), 57.0 (C-4), 80.3 (C-3), 113.5, 114.8, 117.6, 121.5, 124.8, 126.3, 127.7, 128.2, 128.7, 128.9, 133.2, 133.9, 155.7, 155.9 (aromatic carbons), 161.3 (CO, β-lactam). Anal. calcd for $C_{22}H_{17}Cl_2NO_3$: C, 63.78; H, 4.14; N, 3.38; found: C, 63.87; H, 4.28; N, 3.43.

2-(2-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**5**): White solid; m.p. 205–207 °C; IR (KBr) (cm^{-1}): 1772 (CO, β-lactam), 1762, 1726 (CO, phth); ^{1}H NMR ($CDCl_3$): δ 3.77 (s, 3H, OMe), 5.59 (d, 1H, *J* = 3.0, H-4), 5.80 (d, 1H, *J* = 3.0, H-3), 6.79–7.65 (m, 11H, ArH); ^{13}C NMR ($CDCl_3$): δ 56.71 (OMe), 57.86 (C-4), 60.6 (C-3), 113.5, 117.4, 122.6, 124.8, 126.0, 127.8, 128.9, 129.4, 130.1, 132.5, 133.4, 133.8, 155.6 (aromatic carbons), 159.7 (CO, phth), 165.3 (CO, β-lactam). Anal. calcd for $C_{24}H_{16}Cl_2N_2O_4$: C, 61.69; H, 3.45; N, 5.99; found: C, 61.61; H, 3.54; N, 6.03.

3-(2,4-Dichlorophenoxy)-4-(3,4,5-trimethoxyphenyl)-1-(4-methoxyphenyl)azetidin-2-one (**6**): White solid; m.p. 154–156 °C; IR (KBr) (cm^{-1}): 1755 (CO, β-lactam); ^{1}H NMR ($CDCl_3$): δ 3.76, 3.78, 3.80 (3 s, 12H, 4 OMe), 5.28 (d, 1H, *J* = 4.8, H-4), 5.53 (d, 1H, *J* = 4.8, H-3), 6.49–7.69 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$): δ 54.39, 55.14, 59.80 (OMe), 60.7 (C-4), 80.3 (C-3), 104.1, 113.4, 115.0, 115.9, 117.9, 122.9, 126.2, 126.3, 129.0, 129.2, 137.3, 150.3, 152.2, 155.7 (aromatic carbons), 160.5 (CO, β-lactam). Anal. calcd for $C_{25}H_{23}Cl_2NO_6$: C, 59.54; H, 4.60; N, 2.78; found: C, 59.62; H, 4.69; N, 2.71.

2-(1-(4-Methoxyphenyl)-2-oxo-4-(3,4,5-trimethoxyphenyl) azetidin-3-yl)isoindoline-1,3-dione (**7**): White solid; m.p. 118–120 °C; IR (KBr) (cm^{-1}): 1767 (CO, β-lactam), 1751, 1720 (CO, phth); ^{1}H NMR ($CDCl_3$): δ 3.62 (s, 3H, OMe), 3.70 (s, 6H, 2 OMe), 3.81 (s, 3H, OMe), 5.34 (d, 1H, *J* = 3.0, H-4), 5.62 (d, 1H, *J* = 3.0, H-4), 6.49–7.69 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$): δ 54.4, 55.1, 58.3 (OMe), 59.32 (C-4), 60.2 (C-3), 102.0, 113.3, 117.6, 122.3, 122.8, 126.7, 130.2, 133.3, 136.8, 152.1, 155.5 (aromatic carbons), 159.1 (CO, phth), 165.9 (CO, β-lactam). Anal. calcd for $C_{27}H_{24}N_2O_7$: C, 66.39; H, 4.95; N, 5.73; found: C, 66.48; H, 5.03; N, 5.79.

4-(2,4-Dichlorophenyl)-1-(4-ethylphenyl)-3-phenoxyazetidin-2-one (**8**): White solid; m.p. 129–131 °C; IR (KBr) (cm^{-1}): 1758 (CO, β-lactam); ^{1}H NMR ($CDCl_3$): δ 1.94 (t, 3H, *J* = 7.6, CH_3), 2.59 (q, 2H, *J* = 7.6, CH_2), 5.58 (d, 1H, *J* = 4.9, H-4), 5.80 (d, 1H, *J* = 4.9, H-3), 6.86–7.37 (m, 12H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.5 (CH_3), 27.3 (CH_2), 58.9 (C-4), 80.2 (C-3), 114.9, 116.3, 121.5, 126.3, 127.7, 128.3, 128.8, 129.0, 133.2, 133.2, 133.5, 133.9, 140.1, 155.9 (aromatic carbons), 161.7 (CO, β-lactam). Anal. calcd for $C_{23}H_{19}Cl_2NO_2$: C, 67.00; H, 4.65; N, 3.40; found: C, 67.12; H, 4.73; N, 3.35.

3-(2,4-Dichlorophenoxy)-4-(2,4-dichlorophenyl)-1-(4-ethylphenyl)azetidin-2-one (**9**): White solid; m.p. 148–150 °C; IR (KBr) (cm^{-1}): 1762 (CO, β-lactam); ^{1}H NMR ($CDCl_3$): δ 1.20 (t, 3H, *J* = 7.6, CH_3), 2.61 (q, 2H, *J* = 7.6, CH_2), 5.56 (d, 1H, *J* = 5.1, H-4), 5.81 (d, 1H, *J* = 5.1, H-3), 7.14–7. 44 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.5 (CH_3), 27.4 (CH_2), 56.8 (C-4), 80.5 (C-3), 115.7, 116.4, 123.2, 126.4, 126.6, 126.75, 127.8, 128.0, 128.4, 128.7, 128.9, 133.1, 133.3, 134.1, 140.4, 150.4 (aromatic carbons), 160.9 (CO, β-lactam). Anal. calcd for $C_{23}H_{17}Cl_4NO_2$: C, 57.41; H, 3.56; N, 2.91; found: C, 57.36; H, 3.66; N, 2.85.

3-(2,4-Dichlorophenoxy)-1-(4-ethylphenyl)-4-(3,4,5-trimethoxyphenyl)azetidin-2-one (**10**): White solid; m.p. 145–151 °C; IR (KBr) (cm^{-1}): 1720 (CO, β-lactam); ^{1}H NMR ($CDCl_3$): δ 1.19 (t, 3H, *J* = 7.5, CH_3), 2.59 (q, 2H, *J* = 7.5, CH_2), 3.77 (s, 6H, 2 OMe), 3.82 (s, 3H, OMe), 5.30 (d, 1H, *J* = 4.9, H-4), 5.53 (d, 1H, *J* = 4.9, H-4), 6.57–7.32 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.5 (CH_3), 27.3 (CH_2), 55.2, 59.8 (OMe), 60.6 (C-4), 80.2 (C-3), 104.2, 115.1, 116.6, 123.0, 126.3, 126.4, 126.6, 127.5, 129.1, 133.5, 137.4, 140.1, 150.3, 152.2 (aromatic carbons), 160.9 (CO, β-lactam). Anal. calcd for $C_{26}H_{25}Cl_2NO_5$: C, 62.16; H, 5.02; N, 2.79; found: C, 62.25; H, 5.13; N, 2.84.

2-(1-(4-Ethylphenyl)-2-(3,4,5-trimethoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**11**): White solid; m.p. 215–217 °C; IR (KBr) (cm^{-1}): 1767 (CO, β-lactam), 1718, 1759 (CO, phth); ^{1}H NMR ($CDCl_3$): δ 1.19 (t, 3H, *J* = 7.5, CH_3), 2.59 (q, 2H, *J* = 7.5, CH_2), 3.81, 3.85 (2 s, 9H, 3 OMe), 5.28 (d, 2H, *J* = 2.5, H-4 and H-3), 6.57–7.87 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.5 (CH_3), 27.3 (CH_2), 55.1, 59.8 (OMe), 60.6 (C-4), 61.7 (C-3), 101.8, 116.6, 122.8, 127.4, 130.5, 130.6, 133.6, 133.9, 137.3, 139.7, 152.9 (aromatic carbons), 160.93 (CO, phth), 165.8 (CO, β-lactam). Anal. calcd for $C_{28}H_{26}N_2O_6$: C, 69.12; H, 5.39; N, 5.76; found: C, 69.20; H, 5.51; N, 5.83.

2-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)spiro[azetidine-3,9'-xanthen]-4-one (**12**): White solid; m.p. 220–223 °C; IR (KBr) (cm^{-1}): 1757 (CO, β-lactam); ^{1}H NMR ($CDCl_3$): δ 3.81 (s, 3H, OMe), 5.28 (s, 1H, H-4), 6.72–8.89 (m, 15H, ArH); ^{13}C NMR ($CDCl_3$): δ 54.4 (OMe), 54.5 (C-4), 71.4 (C-3), 113.4, 113.6, 115.5, 117.8, 121.2, 123.0, 124.5, 126.5, 127.5, 128.2, 129.5, 133.2, 150.4, 150.9, 152.2, 155.7 (aromatic carbons), 165.1 (CO, β-lactam); Anal. calcd for $C_{28}H_{19}Cl_2NO_3$: C, 68.86; H, 3.92; N, 2.87; found: C, 68.94; H, 4.05; N, 2.95.

1-(4-Ethylphenyl)-4-(3,4,5-trimethoxyphenyl)spiro[azetidine-3,9'-xanthen]-2-one (**13**): White solid; m.p. 148–149 °C; IR (KBr) (cm^{-1}): 1760 (CO, β-lactam); ^{1}H NMR ($CDCl_3$): δ 1.14 (t, 3H, *J* = 7.6, CH_3), 2.54 (q, 2H, *J* = 7.6, CH_2), 3.63, 3.68 (2s, 9H, 3OMe), 4.98 (s, 1H, H-4), 6.84–7.48 (m, 14H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.5 (CH_3), 27.3 (CH_2), 55.1, 59.8 (3 OMe), 63.2 (C-4), 73.1 (C-4), 102.9, 115.1, 115.7,

116.1, 118.8, 122.8, 127.4, 127.5, 128.4, 128.7, 134.1, 139.8, 151.0, 151.2 (aromatic carbons), 164.8 (CO, β-lactam). Anal. calcd for $C_{32}H_{29}NO_5$: C, 75.72; H, 5.76; N, 2.76; found: C, 75.81; H, 5.89; N, 2.81.

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