SHORT PAPER

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Synthesis of β-lactams and oxazolidines from phenoxyacetic acid and ethanolimines promoted by benzenesulfonyl chloride†

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β-Lactams and oxazolidines have been synthesised by the reaction of phenoxyacetic acid with ethanolimines induced by benzenesulfonyl chloride under mild reaction conditions.

Keywords: azetidinones, oxazolidines, imines, β-lactams

β–Lactams show diverse and interesting antibiotic activity. The *N-(*2-hydroxyethyl) β-lactams are very important precursors of *N*-unsubstituted β-lactams. Literature reports show that their syntheses have been carried out by the annelation of ethanolimines with acetic acids in the presence of phenyl dichlorophosphate[1,2] and Vilsmeier reagents.[3] These β-lactams have also been synthesised using the acid chloride–imine method.[4] Oxazolidines are useful synthetic intermediates. They are usually obtained by the condensation of secondary β-aminoalcohols with either aldehydes or their corresponding acetals.[5] *N*-Acylated oxazolidines have been synthesised using very drastic conditions.[6-7]

Here we report the synthesis of some new β-lactams and *N*-acylated oxazolidines from ethanolimines and phenoxyacetic acid induced by benzenesulfonyl chloride under very mild reaction conditions.

Various imines (**3a–e)** have been synthesised by refluxing substituted primary β-aminoalcohols with aldehydes in methanol for 3–4 h in 93–94% yield. The ^{1}H NMR data (Table 1) clearly indicated them to exist as Schiff bases, azomethine protons appearing in the range δ 8–8.7 ppm. Further, these imines were protected by trimethylsilyl chloride in the presence of triethylamine by stirring the reactants at room temperature for 1h followed by successive addition of phenoxyacetic acid and benzenesulfonyl chloride at 0 °C. The contents were then stirred at room temperature for 19–20 h followed by quenching with water to afford the *N*-2-hydroxyethyl β-lactams **4a–d** in 60–70% yield (Scheme 1). The structures of the β-lactams were assigned on the basis of elemental analysis and spectroscopic (IR, ^{1}H NMR) data. The protons at C_3 and C_4 of all the βlactams were found to be in *cis*-orientation as evident from the coupling constants $J_{3,4} \sim$ 4–5 Hz. The IR spectra showed the presence of the β-lactam carbonyl peak in the range of 1740–1755 cm^{-1} (Table 3) Similar results were obtained when phenoxyacetyl chloride was used instead of mixed anhydride for the β-lactam synthesis.

However, the treatment of the unprotected imines with phenoxyacetic acid and benzenesulfonyl chloride in the presence of triethylamine in dichloromethane furnished *N*-acylated oxazolidines (**5a–c**) in 65–70% yield (Scheme 2). The IR spectra of these compounds showed amide carbonyl peak in the range of 1660–1670 cm^{-1}. NH, OH and β–lactam carbonyl stretching bands were found to be absent. 300 MHz ^{1}H NMR spectra indicated the presence of two singlets at δ 4.5–4.8 corresponding to the methylene protons adjacent to the phenoxy group and another at δ 6.4–6.7 from the C_2 proton of the oxazolidine which is flanked by N, O and aromatic group. In **5c**, C_2-H appeared as a doublet at δ 6.48. (Table 3)

This cyclisation reaction under the influence of the acylating species led us to suggest that the reaction proceeds through the intermediacy of iminium ion **6,** followed by nucleophilic attack by the hydroxyl group on the incipient carbonium ion to produce the oxazolidines.[8] However, when the hydroxyl group of the imine is protected as its trimethylsilyl ether, the iminium ion formation is followed by proton abstraction leading to the formation of zwitterionic intermediate followed by ring closure to furnish β-lactams **4a–d** (Scheme 3).

In conclusion, we have synthesised some new *N*-acylated oxazolidines and βlactams through the use of mixed carboxylic-sulfonic anhydride from the β-hydroxyethylimines and their *O*-silylated derivatives respectively.

Table 1 Spectral data of Schiff bases **3a–e**

Compound	R^1	R^2	Spectral data
3a	CH_3	2-thienyl	IR[a]: 1640 cm^{-1} ^{1}H NMR[b]: δ8.4 (s, 1H, -CH=N)
3b	CH_3	*o*-C_6H_4Br	IR[a]: 1640 cm^{-1} ^{1}H NMR[b]: δ8.73 (s, 1H, -CH=N)
3c	CH_3	$C_6H_3(OMe)_2$	IR[a]: 1635 cm^{-1} ^{1}H NMR[b]: δ8.36 (s, 1H, -CH=N)
3d	H	2-thienyl	IR[a]: 1640 cm^{-1} ^{1}H NMR[b]: δ8.4 (s, 1H, -CH=N)
3e	CH_3	-CH=CHPh	IR[a]: 1640 cm^{-1} ^{1}H NMR[b]: δ8.2 (s, 1H, -CH=N)

[a] In nujol. [b] In $CDCl_3$

Experimental

Melting points are uncorrected. The IR spectra were recorded on a Perkin- Elmer Model 430 spectrophotometer and the ^{1}H NMR spectra were recorded on a 300 MHz Bruker AC 300F spectrometer. The purity of the compounds was checked by TLC.

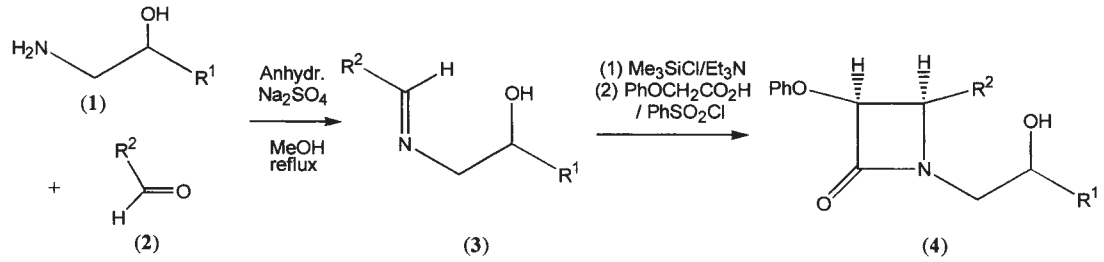
Preparation of the Schiff bases **3(a–e)**: In a round bottomed flask, the appropriate substituted ethanolamine (10 mmol) and aldehyde (10 mmol) were dissolved in methanol (30 ml) and refluxed for 3–4 h in

Table 2 Physical data for β-lactams **4a–d** and oxazolidines **5a–c**

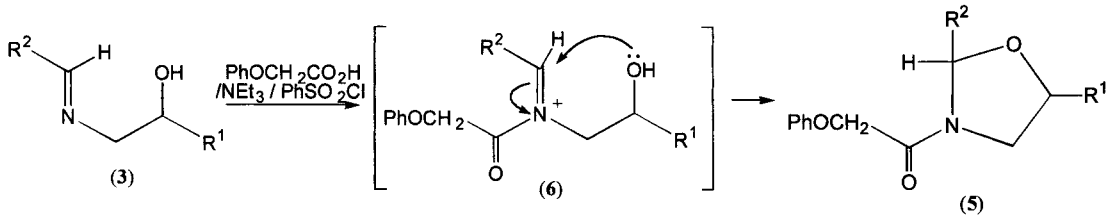
Compound	R^1	R^2	Yield %	M.p./°C
4a	CH_3	2-thienyl	70	115
4b	CH_3	o-C_6H_4Br	61	82–84
4c	CH_3	$C_6H_3(OMe)_2$	67	100
4d	H	2-thienyl	60	99–100
5a	CH_3	2-thienyl	70	Oil
5b	CH_3	$C_6H_3(OMe)_2$	62	Oil
5c	CH_3	-CH=CHPh	65	Oil

* To receive any correspondence.

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 1



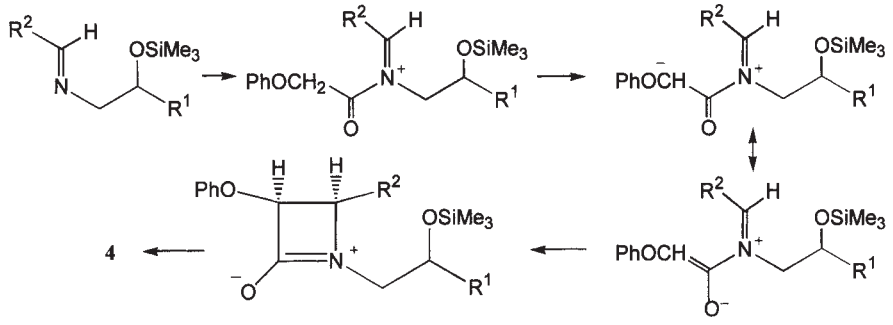
Scheme 2

the presence of anhydrous sodium sulfate (monitored by TLC). It was filtered and the solvent was removed under reduced pressure. The crude imine was used as such for the next step. (see Table 1)

Preparation of N-(2-hydroxyethyl) β-lactams (**4a–d**): To a solution of the imine (10 mmol) and triethylamine (40 mmol) in dry dichloromethane (40 ml) at 0°C was added trimethylsilyl chloride (10 mmol). The ice bath was then removed and the mixture stirred for about one hour until the complete conversion into trimethylsilyl ether (as monitored by TLC). Phenoxyacetic acid (10mmol) and benzenesulfonyl chloride (10 mmol) were added at 0 °C and the mixture was stirred for *ca* 1 h, then for a further 19–20 h at room temperature Water (20ml) was added and stirring was continued for a further 30 min. The organic layer was separated, washed with water (2 × 50 ml) and dried over anhydrous sodium sulfate, the solvent was removed on a water bath, and the product was purified by column chromatography on neutral Al_2O_3 (eluent 30% EtOAc – petroleum ether) to afford the desired β-lactam. (see Tables 2 and 3).

Table 3 Analytical and spectroscopic data for compounds **4a–d, 5a–c**

Compd	Molecular formula	Calculated (Found) (%) C	H	N	ν_{max}/cm^{-1}	δ_H ($CDCl_3$/DMSO-d_6)
4a	$C_{16}H_{17}NO_3S$	63.37 (62.92)	5.61 (5.77)	4.62 (4.83)	3400(O-H) 1740(C=O)	1.18(d,*J*=6.5Hz,3H,CH_3);3.03(m,1H,-NCH_2); 3.30(m,1H,-NCH_2); 3.36(br.s,1H,OH);4.10 (m,1H,-CH); 5.31(d,*J*=4.3Hz,1H,C_4-H); 5.49 (d,*J*=4.3Hz,1H,C_3-H); 6.80–7.31 (m,8H,Ar-H)
4b	$C_{18}H_{18}BrNO_3S$	57.44 (57.27)	4.78 (4.72)	3.72 (3.75)	3400(O-H) 1755(C=O)	1.13(d,*J*=6.38Hz,3H,CH_3);2.87(m,1H,-NCH_2); 3.52(m,1H,-NCH_2); 4.01(m,1H,-CH); 4.84 (br.s,1H,OH); 5.58 (d,*J*=5.1Hz,1H,C_4-H); 5.62 (d,*J*=5.1Hz,1H,C_3-H); 6.76–7.56 (m,9H,Ar-H)
4c	$C_{20}H_{23}NO_5$	67.22 (67.10)	6.44 (6.51)	3.92 (3.88)	3400(O-H) 1740(C=O)	1.22(d,*J*=6.1Hz,3H,CH_3);3.03(m,1H,-NCH_2); 3.26(m,1H,-NCH_2); 3.31 (br.s,1H,OH);3.82 (s,3H,-OCH_3); 3.84(s,3H, -OCH_3);4.10(m,1H,-CH); 4.94(d,*J*=4.3Hz,1H,C_4-H); 5.47 (d,*J*=4.3Hz,1H,C_3-H); 6.72–7.26 (m,8H,Ar-H)
4d	$C_{15}H_{15}NO_3S$	62.28 (62.07)	5.19 (5.22)	4.84 (4.89)	3450(O-H) 1740(C=O)	1.71 (br.s,1H,OH); 3.25 (m,1H,-NCH_2);3.3 (m,1H,-NCH_2);3.82 (t,2H,-OCH_2);5.27 (d,*J*=4.3Hz,1H,C_4-H); 5.49 (d,*J*=4.3Hz,1H,C_3-H); 6.80–7.35 (m,8H,Ar-H)
5a	$C_{16}H_{17}NO_3S$	63.37 (63.11)	5.61 (5.58)	4.62 (4.66)	1670(C=O)	1.17 (d,*J*=5.98Hz,3H,CH_3);3.37 (m,1H,-NCH_2); 3.92 (m,1H,-NCH_2);4.10 (m,1H,-CH);4.67 (s,2H,-OCH_2);6.67 (s,1H,-NCH-O);6.73–7.33 (m,8H,Ar-H)
5b	$C_{20}H_{23}NO_5$	67.22 (67.08)	6.44 (6.52)	3.92 (3.82)	1660(C=O)	1.20 (d,*J*=6.13Hz,3H,CH_3);3.24 (m,1H,-NCH_2); 351 (m,1H,-NCH_2); 3.95 (s,3H,-OCH_3); 3.9 7 (s,3H, -OCH_3);4.12 (m,1H,-CH);4.52 (s,2H,-OCH_2);642 (s,1H,-NCH-O);6.7–7.48 (m,8H, Ar-H)
5c	$C_{20}H_{21}NO_3$	74.30 (74.06)	6.50 (6.43)	4.33 (4.28)	1660(C=O)	1.21 (d,*J*=6.7Hz,3H,CH_3);323 (m,1H,-NCH_2); 3.69 (m,1H,-NCH_2);4.30(m,1H,-CH);4.50 (s,2H,-OCH_2);6.06 (m,1H,-CH);6.48 (d,*J*=6.4Hz,1H,-CH);6.76–7.37 (m,11H,Ar-H,=CH-Ph)



Scheme 3

Preparation of N-acylated oxazolidines ***(5a–c)****:* To a solution of phenoxyacetic acid (10 mmol) in dry dichloromethane (30 ml) was added triethylamine (30 mmol) followed successively by the imine (10 mmol) and benzenesulfonyl chloride (10 mmol) at 0° C. The resulting mixture was stirred for a further 19–20 h and washed with water (2 × 50 ml). The organic layer was separated, dried over anhydrous Na_2SO_4 and the product was purified by column chromatography (eluent 10% EtOAc-petroleum ether). See Tables 2 and 3.

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