Tetrahedron 65 (2009) 2927–2934

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The Vilsmeier reagent: a useful and versatile reagent for the synthesis of 2-azetidinones

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ARTICLE INFO

Article history:
Received 3 November 2008
Received in revised form 11 January 2009
Accepted 5 February 2009
Available online 11 February 2009

ABSTRACT

(Chloromethylene)dimethylammonium chloride (Vilsmeier reagent), prepared easily from *N*,*N*-dimethylformamide and oxalyl chloride or thionyl chloride, works as a versatile acid activator reagent for the direct [2+2] ketene–imine cycloaddition of substituted acetic acid and imines in one-pot synthesis under mild conditions. Monocyclic, spirocyclic and 3-electron-withdrawing group β-lactams were synthesized by this method and optimization of conditions were performed.

1. Introduction

(Chloromethylene)dimethylammonium chloride (Vilsmeier reagent) has been known as a formylating agent.[1] It has also emerged as an efficient synthetic auxiliary for the synthesis of some important class of organic compounds.[2] This white solid is easily synthesized by reaction of *N*,*N*-dimethylformamide (DMF) and chlorinating agents such as PCl_3 or $SOCl_2$.[3]

The interest in β-lactam compounds goes back to the 1940s, when the antibiotic properties of the first semisynthetic penicillins were discovered.[4] In recent years, their medicinal interest has been developed to other biological activities.[5] This four-membered cyclic amides have been extensively used as a synthon for the synthesis of several compounds[6] and some reviews have been published for β-lactam synthon method.[7]

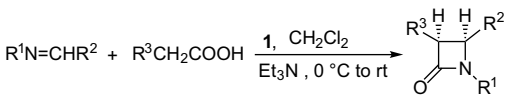
Among the several methods for the synthesis of β-lactams, the [2+2] cycloaddition reaction of Schiff bases with ketenes (Staudinger reaction)[8] is mostly applied. This method has been used for the synthesis of a large number of monocyclic, bicyclic, tricyclic and spirocyclic β-lactams.[9] The ketenes are commonly generated in situ from acyl halides in the presence of tertiary amines.[10] In addition to the utilization of acyl halides, a variety of other methods have been described to activate carboxylic acids.[11] These methods are conventionally useful when the acid halides are not commercially available, difficult to prepare or when they are unstable. Some acid activating agents include 1,1-carbonyldi-imidazole,[12] triphosgene,[13] ethyl chloroformate,[14] trifluoroacetic anhydride,[15] *p*-toluenesulfonyl chloride,[16] phosphorus-derived reagents,[17] cyanuric chloride,[18] the Mukaiyama reagent[19] and acetic anhydride.[20]

In our recent communication,[21] we reported an efficient use of the Vilsmeier reagent as an acid activator in the synthesis of 2-azetidinone ring by the Staudinger reaction. In this paper we wish to describe the versatility and utility of the Vilsmeier reagent for the activation of various carboxylic acids in β-lactam synthesis under simple and mild conditions.

2. Results and discussion

(Chloromethylene)dimethylammonium chloride **1** was prepared from DMF and oxalyl chloride or thionyl chloride in dry CH_2Cl_2.

We have successfully employed the Vilsmeier reagent for the one-step cycloaddition reaction of various imines **2** and substituted acetic acid **3** to obtain β-lactams **4** (Scheme 1). (Chloromethylene)dimethylammonium chloride **1** was added to a solution of mixture of acids **2**, imines **3** and triethylamine in CH_2Cl_2 at 0 °C and the reaction mixture was stirred at room temperature for 7–8 h. The usual work-up and the then crystallization from EtOAc gave pure β-lactams 4 in high yields (Table 1).



Scheme 1.

We found that this method was very simple and clean. The DMF and triethylammonium salt are two by-products, which were removed by simple aqueous work-up. In all cases the

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doi:10.1016/j.tet.2009.02.005

Table 1
Synthesis of β-lactams **4** from imines **2** and carboxylic acids **3**

Entry	R^1	R^2	R^3	Product[a]	Yield[b] (%)
1	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	PhO	**4a**	93
2	4-$EtOC_6H_4$	4-ClC_6H_4	PhO	**4b**	87
3	4-$EtOC_6H_4$	4-$MeOC_6H_4$	PhO	**4c**	81
4	4-$MeOC_6H_4$	4-MeC_6H_4	PhO	**4d**	88
5	4-$MeOC_6H_4$	3,4-$DiMeOC_6H_3$	PhO	**4e**	83
6	4-$MeOC_6H_4$	4-ClC_6H_4	PhO	**4f**	86
7	4-$MeOC_6H_4$	CH=CHPh	PhthN	**4g**	90
8	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	PhthN	**4h**	91
9	4-$EtOC_6H_4$	4-$MeOC_6H_4$	PhthN	**4i**	82
10	4-$EtOC_6H_4$	4-MeC_6H_4	PhthN	**4j**	89
11	4-$MeOC_6H_4$	3,4-$DiMeOC_6H_3$	3-NO_2PhthN	**4k**	80
12	4-$EtOC_6H_4$	4-MeC_6H_4	MeO	**4l**	84
13	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	MeO	**4m**	81
14	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	2,4-$DiClC_6H_3O$	**4n**	94
15	4-$EtOC_6H_4$	4-ClC_6H_4	2,4-$DiClC_6H_3O$	**4o**	92
16	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	2-NaphthO	**4p**	95
17	4-$EtOC_6H_4$	4-ClC_6H_4	2-NaphthO	**4q**	90

[a] All products were characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass and elemental analyses.
[b] Isolated yield of pure products.

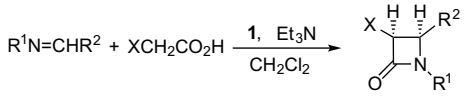
stereoselective cycloaddition afforded only *cis* β-lactams **4a**–**q**. Next, we decided to examine the effect of solvents and reaction conditions in the synthesis of β-lactam **4a**. According to Table 2, among the solvents examined (THF, CH_3CN, CH_2Cl_2), CH_2Cl_2 proved to be the best in all cases. The work-up in CH_2Cl_2 was much more comfortable than in THF and CH_3CN. It was also found that the yields were almost identical at 0 °C and room temperature. Best yields were obtained when 1.5 mmol of the Vilsmeier reagent and carboxylic acid was used relative to 1.0 mmol of imine.

On the basis of these successful results, the reaction of 5-norbornene-2,3-dicarboxyloylglycine **5**, prepared from 5-norbornene,2,3-dicarboxylic anhydride and glycine at 160–165 °C, and crotonic acid **6** with various imines were performed using 1.5 mmol of the Vilsmeier reagent in dry CH_2Cl_2 at rt to give β-lactams **7a**–**c** and **8a**–**c**, respectively (Scheme 2). *trans* β-Lactams **7a**–**c** were purified by crystallization from EtOAC but *trans* β-lactams **8a**–**c** were purified by filtration of the reaction mixture through a short silica gel column.

Spiro-β-lactams are interesting compounds due to their potential antiviral[22] and antibacterial properties.[23] Therefore, the Vilsmeier reagent was also successfully employed for the synthesis of C-3 and C-4 spiro-β-lactams. Treatment of Schiff base **9** (prepared from 2,4-dimethoxyaniline and *N*-benzylisatin in the presence of catalytic acetic acid in refluxing ethanol) with various acetic acids in the presence of the Vilsmeier reagent and triethylamine afforded pure spiro-β-lactams **10a**–**c** after crystallization from 96% ethanol. β-Lactam **10a**[24] has been previously prepared in our laboratory and its crystal structure has been reported.[25] Spiro-β-lactams **11a**–**c** were easily obtained by the cycloaddition of xanthene-9-carboxylic acid with imines using the Vilsmeier reagent and purified by crystallization from EtOAc (Scheme 3).

This method was also extended to the synthesis of 3-chloro and 3-cyano-β-lactams. In 2006, Melman[12] and Nahmany reported that 1,1-carbonyldi-imidazole was a useful reagent for the preparation of β-lactams bearing electron-withdrawing groups at C-3 from α-electron-withdrawing substituted carboxylic acids, but not useful for cyanoacetic acid.

3-Chloro-β-lactams **12a**–**d** and 3-cyano-β-lactams **13a**–**d** were synthesized from corresponding carboxylic acid and imines using the Vilsmeier reagent in the presence of Et_3N at room temperature in 19–38% yield. When these reactions were performed at −10 °C to room temperature, the yields increased to 41–60% (Table 3).



To compare the Vilsmeier reagent with other acid activators, the reactions of cyanoacetic acid and chloroacetic acid with *N*-(4-nitrobenzylidene)-4-ethoxyaniline were performed in the presence of some acid activators and triethylamine at −10 °C to room temperature. It is noteworthy that β-lactams **12a** and **13a** were obtained in good yields only when the Vilsmeier reagent was used as the acid activator. 3-Chloro β-lactam **12a** was obtained in 8% yield when the Mukaiyama reagent was used (Table 4).

Table 2
Optimizational reaction conditions for the synthesis of **4a**

Entry	Solvent	Temp (°C)	Quantity of reagent/mmol	Isolated yield (%)
1	CH_2Cl_2	0	1.0	63
		rt	1.0	60
		0	1.3	79
		rt	1.3	78
		0	1.5	93
		rt	1.5	94
2	CH_3CN	0	1.0	56
		rt	1.0	48
		0	1.3	66
		rt	1.3	68
		0	1.5	79
		rt	1.5	77
3	THF	0	1.0	33
		rt	1.0	25
		0	1.3	60
		rt	1.3	54
		0	1.5	72
		rt	1.5	61

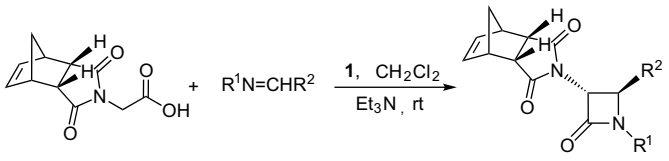
3. Conclusions

We have shown the application and versatility of (chloromethylene)dimethylammonium chloride (Vilsmeier reagent) as an acid activator for the synthesis of monocyclic and spirocyclic β-lactams under mild reaction condition via ketene–imine cycloaddition reactions. The Vilsmeier reagent was easily prepared from cheap and available materials. The effects of solvents, molar ratio of reagent and the temperature were investigated. Carboxylic acids bearing an α-withdrawing were converted into β-lactams by this method.

4. Experimental section

4.1. General

All needed chemicals were purchased from Merck, Fluka and Acros chemical companies. All reagents and solvents were dried prior to use according to standard methods.[26] IR spectra were run on a Shimadzu FT-IR 8300 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ using a Bruker Avance DPX instrument (^{1}H NMR 250 MHz, ^{13}C NMR 62.9 MHz). Chemical shifts were reported in parts per million (δ) downfield from TMS. All of the coupling constants (J) are in hertz. The mass spectra were recorded on a Shimadzu GC–MS QP 1000 EX instrument. Elemental analyses were run on a Thermo Finnigan Flash

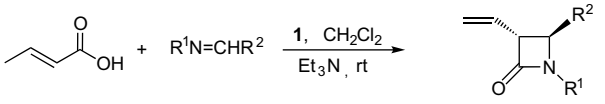


5 **7a-c**

a, R^1 = 4-$MeOC_6H_4$; R^2 = 4-$NO_2C_6H_4$ 78%

b, R^1 = 4-$MeOC_6H_4$; R^2 = 4-ClC_6H_4 83%

c, R^1 = 4-$EtOC_6H_4$; R^2 = 4-$NO_2C_6H_4$ 75%



6 **8a-c**

a, R^1 = 4-$EtOC_6H_4$; R^2 = 4-$NO_2C_6H_4$ 69%

b, R^1 = 4-$MeOC_6H_4$; R^2 = 4-ClC_6H_4 71%

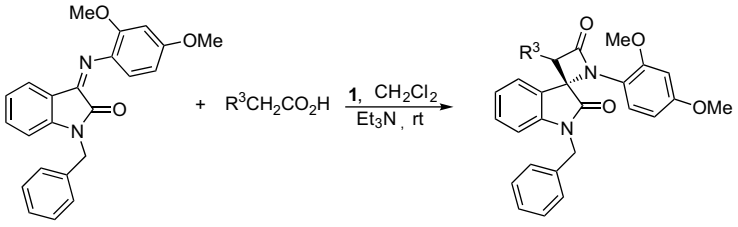
c, R^1 = 4-$MeOC_6H_4$; R^2 = 4-$MeOC_6H_4$ 77%

Scheme 2.

EA-1112 series. Melting points were determined in open capillaries with Buchi 510 melting point apparatus. Thin-layer chromatography was carried out on silica gel F_{254} analytical sheets obtained from Fluka. Column chromatography was performed on Merck Kiesel gel (230–270 mesh).

4.2. Preparation of (chloromethylene)dimethylammonium chloride (Vilsmeier reagent) 1

Oxalyl chloride (0.10 mmol) at 0 °C or thionyl chloride (0.10 mmol) at 40 °C was added dropwise with stirring to a solution

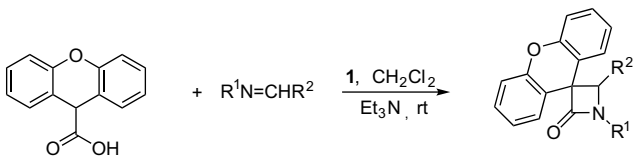


9 **10a-c**

a, R^3 = PhO 83%

b, R^3 = 2,4-$DiClC_6H_3O$ 76%

c, R^3 = 2-NaphthO 80%



11a-c

a, R^1 = 4-$MeOC_6H_4$; R^2 = 4-$MeOC_6H_4$ 82%

b, R^1 = 4-$EtOC_6H_4$; R^2 = 4-ClC_6H_4 78%

c, R^1 = 4-$EtOC_6H_4$; R^2 = 4-$NO_2C_6H_4$ 79%

Scheme 3.

Table 3
Synthesis of 3-electron-withdrawing β-lactams **12a–d** and **13a–d**

Entry	R^1	R^2	X	Temperature (°C)	Product	Yield (%)
1	4-$EtOC_6H_4$	4-ClC_6H_4	Cl	rt	**12a**	33
2	4-$EtOC_6H_4$	4-ClC_6H_4	Cl	−10	**12a**	59
3	4-$MeOC_6H_4$	C_6H_5	Cl	rt	**12b**	36
4	4-$MeOC_6H_4$	C_6H_5	Cl	−10	**12b**	57
5	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Cl	rt	**12c**	38
6	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Cl	−10	**12c**	60
7	4-$MeOC_6H_4$	C═CPh	Cl	rt	**12d**	35
8	4-$MeOC_6H_4$	C═CPh	Cl	−10	**12d**	56
9	4-$EtOC_6H_4$	4-ClC_6H_4	CN	rt	**13a**	27
10	4-$EtOC_6H_4$	4-ClC_6H_4	CN	−10	**13a**	53
11	4-$MeOC_6H_4$	C_6H_5	CN	rt	**13b**	22
12	4-$MeOC_6H_4$	C_6H_5	CN	−10	**13b**	51
13	4-$MeOC_6H_4$	4-$MeOC_6H_4$	CN	rt	**13c**	35
14	4-$MeOC_6H_4$	4-$MeOC_6H_4$	CN	−10	**13c**	49
15	4-$MeOC_6H_4$	C═CPh	CN	rt	**13d**	19
16	4-$MeOC_6H_4$	C═CPh	CN	−10	**13d**	41

of DMF (0.10 mmol) in dry CH_2Cl_2 (7 mL). After 5 min, the (chloromethylene)dimethylammonium chloride **1** was obtained as a white solid.

4.3. Synthesis of Schiff bases

Schiff bases from aldehydes, *N*-benzylisatin and corresponding amines were prepared by refluxing in ethanol and their spectral data have been previously reported.[16a,24,27]

4.4. Synthesis of 5-norbornene-2,3-dicarboxyloylglycine (5)

A mixture of glycine (1.88 g, 25.0 mmol) and 5-norbornene-2,3-dicarboxylic anhydride (4.2 g, 25.0 mmol) was placed in an oil bath, which has been previously heated to 160–165 °C. The mixture was stirred occasionally during the first 10 min and pushed down the 5-norbornene-2,3-dicarboxylic anhydride, which sublimed on the walls into the reaction mixture with a glass rod. The mixture was left for 5 min. Then, the test tube was removed from the bath when the liquid mass solidified; the residue was recrystallized from 10% ethanol to give the title compound **5** (4.6 g, 81%) as a white solid. Mp 150–152 °C; IR (KBr, cm^{-1}): 1749, 1781 (phthalimido, CO), 1736 (COOH), 2454–3378 (OH); GC–MS *m*/*z*=221 [M^+]. Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.88; H, 5.12; N, 6.20.

4.5. Typical procedure for the synthesis of β-lactams

(Chloromethylene)dimethylammonium chloride (1.5 mmol) was added to a solution of the substituted acetic acid (1.5 mmol), corresponding Schiff base (1.0 mmol) and triethylamine (5.0 mmol) in dry solvents (CH_3CN, THF and CH_2Cl_2) at the mentioned temperature and the mixture was stirred for 7–9 h at room temperature. In the case of acetonitrile and tetrahydrofuran, water was added and extraction by CH_2Cl_2 or $CHCl_3$ was performed. Then the organic solution was washed successively with 10% HCl (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 **4a–q**, **7a–c**, **11a–c** were purified by crystallization from ethyl acetate, β-lactams **10a–c** by crystallization from ethanol and β-lactams **8a–c**, **12a–d**, **13a–d** by short column chromatography.

Table 4
Comparison of acid activators in the synthesis of β-lactams **12a** and **13a**

X	Acid activator	Product	Yield (%)
Cl	Vilsmeier reagent	**12a**	59
Cl	$POCl_3$	**12a**	0
Cl	Tosyl chloride	**12a**	0
Cl	Cyanuric chloride	**12a**	0
Cl	Mukaiyama reagent	**12a**	8
CN	Vilsmeier reagent	**13a**	53
CN	$POCl_3$	**13a**	0
CN	Tosyl chloride	**13a**	0
CN	Cyanuric chloride	**13a**	0
CN	Mukaiyama reagent	**13a**	0

*4.5.1. 1-(4-Ethoxyphenyl)-4-(4-nitrophenyl)-3-phenoxy-azetidin-2-one (**4a**)*

Light-yellow solid. Yield: (0.38 g, 93%), mp: 180–182 °C; IR (KBr) cm^{-1}: 1340, 1517 (NO_2), 1744 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 1.30 (Me, t, 3H, *J*=7.0), 3.89 (OCH_2, q, 2H, *J*=7.0), 5.39 (H-4, d, 1H, *J*=4.8), 5.55 (H-3, d, 1H, *J*=4.8), 6.68–8.08 (ArH, m, 13H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.7 (Me), 61.1 (OCH_2), 63.7 (C-4), 81.2 (C-3), 115.2, 115.4, 118.7, 122.6, 123.6, 129.0, 129.5, 129.7, 140.5, 148.1, 156.3, 156.5 (aromatic carbons), 161.8 (CO, β-lactam); GC–MS *m*/*z*=404 [M^+]. Anal. Calcd for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93. Found: C, 68.28; H, 5.05; N, 6.88.

*4.5.2. 4-(4-Chlorophenyl)-1-(4-ethoxyphenyl)-3-phenoxy-azetidin-2-one (**4b**)*

White crystalline solid. Yield: (0.34 g, 87%), mp: 164–166 °C; IR (KBr) cm^{-1}: 1747 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 1.31 (Me, t, 3H, *J*=7.0), 3.87 (OCH_2, q, 2H, *J*=7.0), 5.24 (H-4, d, 1H, *J*=4.8), 5.45 (H-3, d, 1H, *J*=4.8), 6.68–7.23 (ArH, m, 13H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.8 (Me), 61.4 (OCH_2), 63.7 (C-4), 81.1 (C-3), 115.0, 115.6, 118.8, 122.3, 128.7, 129.4, 129.5, 130.0, 131.4, 134.6, 156.0, 156.8 (aromatic carbons), 162.3 (CO, β-lactam); GC–MS *m*/*z*=395 [M^+, ^{37}Cl], 393 [M^+, ^{35}Cl]. Anal. Calcd for $C_{23}H_{20}ClNO_3$: C, 70.14; H, 5.12; N, 3.56. Found: C, 70.24; H, 5.17; N, 3.50.

*4.5.3. 1-(4-Ethoxyphenyl)-4-(4-methoxyphenyl)-3-phenoxy-azetidin-2-one (**4c**)*

White crystalline solid. Yield: (0.32 g, 81%), mp: 168–170 °C; IR (KBr) cm^{-1}: 1754 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 1.30 (Me, t, 3H, *J*=6.9), 3.64 (OMe, s, 3H), 3.88 (OCH_2, q, 2H, *J*=6.9), 5.21 (H-4, d, 1H, *J*=4.7), 5.41 (H-3, d, 1H, *J*=4.7), 6.69–7.23 (ArH, m, 13H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.8 (Me), 55.2 (OMe), 61.8 (OCH_2), 63.7 (C-4), 81.2 (C-3), 113.8, 114.9, 115.7, 118.9, 122.1, 124.5, 129.2, 129.4, 130.4, 155.8, 157.0, 159.8 (aromatic carbons), 162.6 (CO, β-lactam); GC–MS *m*/*z*=389 [M^+]. Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 73.97; H, 5.90; N, 3.64.

*4.5.4. 1-(4-Methoxyphenyl)-3-phenoxy-4-p-tolylazetidin-2-one (**4d**)*

White solid. Yield: (0.32 g, 88%), mp: 165–167 °C; IR ($CHCl_3$) cm^{-1}: 1756.8 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 2.36 (Me, s, 3H), 3.71 (OMe, s, 3H), 5.16 (H-4, d, 1H, *J*=4.5), 5.52 (H-3, d, 1H, *J*=4.5), 6.68–7.51 (ArH, m, 13H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.7 (Me), 56.9 (OMe), 61.6 (C-4), 82.6 (C-3), 117.2, 113.2, 116.5, 117.1, 120.0, 123.5, 131.3, 131.9, 132.7, 150.2, 153.6, 156.2 (aromatic carbons), 161.5 (CO, β-lactam); GC–MS *m*/*z*=359 [M^+]. Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.77; H, 5.96; N, 3.85.

*4.5.5. 4-(3,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-3-phenoxy-2-azetidinone (**4e**)*

White solid. Yield: (0.34 g, 83%), mp: 158–160 °C; IR (KBr) cm^{-1}: 1755 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 3.62, 3.72, 3.76 (3OMe, 3s, 9H), 5.44 (H-4, d, 1H, *J*=5.8), 5.71 (H-3, d, 1H, *J*=5.8), 6.68–7.37 (ArH, m, 12H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 54.4, 54.7, 55.1 (OMe), 59.9 (C-4), 66.5 (C-3), 113.7, 115.2, 115.9, 119.1, 123.1, 126.7, 129.0, 130.4, 133.2, 135.9, 147.8, 154.3, 155.1, 156.3 (aromatic

carbons), 161.9 (CO, β-lactam); GC–MS m/z=405 [M^+]. Anal. Calcd for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 71.23; H, 5.78; N, 3.51.

*4.5.6. 4-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-phenoxy-azetidin-2-one (**4f**)*

White solid. Yield: (0.33 g, 86%), mp: 181–183 °C; IR (KBr) cm^{-1}: 1744 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 3.92 (OMe, s, 3H), 5.32 (H-4, d, 1H, J=4.6), 5.53 (H-3, d, 1H, J=4.6), 6.75–7.49 (ArH, m, 13H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 56.3 (OMe), 60.9 (C-4), 82.7 (C-3), 113.4, 115.8, 117.6, 119.3, 125.7, 129.4, 131.7, 136.0, 138.9, 145.6, 150.4, 158.5 (aromatic carbons), 161.7 (CO, β-lactam); GC–MS m/z=381 [M^+, ^{37}Cl], 379 [M^+, ^{35}Cl]. Anal. Calcd for $C_{22}H_{18}ClNO_3$: C, 69.57; H, 4.78; N, 3.69. Found: C, 69.49; H, 4.85; N, 3.61.

*4.5.7. 2-(1-(4-Methoxyphenyl)-2-oxo-4-styrylazetidin-3-yl)isoindoline-1,3-dione (**4g**)*

White solid. Yield: (0.38 g, 90%), mp: 189–191 °C; IR (KBr) cm^{-1}: 1732, 1753 (CO, phth), 1779 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 3.61 (OMe, s, 3H), 5.12 (H-4, dd, 1H, J=5.4, 8.8), 5.61 (H-3, d, 1H, J=5.4), 6.29 (H-5, dd, J=8.8, 15.9), 6.87 (H-6, d, 1H, J=15.9), 7.04–7.86 (ArH, m, 13H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 55.6 (OMe), 61.5 (C-4), 64.1 (C-3), 113.7, 115.1, 119.4, 120.6, 122.5, 124.3, 128.8, 130.1, 132.5, 138.9, 143.0, 151.6, 158.6 (C=C, aromatic carbons), 163.8 (CO, phth), 166.5 (CO, β-lactam); GC–MS m/z=424 [M^+]. Anal. Calcd for $C_{26}H_{20}N_2O_4$: C, 73.57; H, 4.75; N, 6.60. Found: C, 73.66; H, 4.81; N, 6.53.

*4.5.8. 2-(1-(4-Ethoxyphenyl)-2-(4-nitrophenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**4h**)*

Light-yellow crystalline solid. Yield: (0.42 g, 91%), mp: 179–181 °C; IR ($CHCl_3$) cm^{-1}: 1337, 1521 (NO_2), 1736, 1773 (CO, phth), 1784 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 1.26 (Me, t, 3H, J=7.0), 3.87 (OCH_2, q, 2H, J=7.0), 5.36 (H-4, d, 1H, J=4.8), 5.76 (H-3, d, 1H, J=4.8), 6.90–8.37 (ArH, m, 12H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.5 (Me), 58.3 (OCH_2), 60.7 (C-4), 63.2 (C-3), 113.4, 118.2, 123.9, 128.3, 129.5, 130.5, 134.9, 140.8, 143.6, 147.5, 157.5 (aromatic carbons), 162.3 (CO, phth), 165.4 (CO, β-lactam); GC–MS m/z=457 [M^+]. Anal. Calcd for $C_{25}H_{19}N_3O_6$: C, 65.64; H, 4.19; N, 9.19. Found: C, 65.71; H, 4.24; N, 9.11.

*4.5.9. 2-(1-(4-Ethoxyphenyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**4i**)*

White solid. Yield: (0.36 g, 82%), mp: 191–193 °C; IR (KBr) cm^{-1}: 1731, 1757 (CO, phth), 1774 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 1.18 (Me, t, 3H, J=7.0), 3.65 (OMe, s, 3H), 4.02 (OCH_2, q, 2H, J=7.0), 4.91 (H-4, d, 1H, J=4.7), 5.11 (H-3, d, 1H, J=4.7), 6.76–7.71 (ArH, m, 12H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.7 (Me), 54.5 (OCH_2), 59.1 (OMe), 62.3 (C-4), 63.6 (C-3), 117.6, 120.7, 123.4, 127.8, 130.0, 131.5, 134.6, 134.9, 154.7, 159.5, 160.6 (aromatic carbons), 164.2 (CO, phth), 166.4 (CO, β-lactam); GC–MS m/z=442 [M^+]. Anal. Calcd for $C_{26}H_{22}N_2O_5$: C, 70.58; H, 5.01; N, 6.33. Found: C, 70.66; H, 5.10; N, 6.35.

*4.5.10. 2-(1-(4-Ethoxyphenyl)-2-oxo-4-p-tolylazetidin-3-yl)isoindoline-1,3-dione (**4j**)*

White solid. Yield: (0.38 g, 89%), mp: 193–195 °C; IR (KBr) cm^{-1}: 1735, 1771 (CO, phth), 1783 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 1.26 (Me, t, 3H, J=7.0), 2.39 (Me, s, 3H), 3.85 (OCH_2, q, 2H, J=7.0), 5.36 (H-4, d, 1H, J=5.1), 5.43 (H-3, d, 1H, J=5.1), 6.59–7.54 (ArH, m, 12H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.5, 21.7 (2Me), 61.5 (OCH_2), 63.5 (C-4), 64.8 (C-3), 113.0, 118.6, 123.2, 125.7, 128.7, 130.1, 131.2, 132.4, 134.0, 138.5, 156.3 (aromatic carbons), 160.6 (CO, phth), 164.2 (CO, β-lactam); GC–MS m/z=426 [M^+]. Anal. Calcd for $C_{26}H_{22}N_2O_4$: C, 70.58; H, 5.01; N, 6.33. Found: C, 70.48; H, 5.07; N, 6.28.

*4.5.11. 2-[2-(3,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl]-4-nitroisoindole-1,3-dione (**4k**)*

White solid. Yield: (0.45 g, 80%), mp: 198–200 °C; IR (KBr) cm^{-1}: 1734, 1770 (CO, phth), 1780 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 3.65, 3.74, 3.78 (3OMe, 3s, 9H), 5.33 (H-4, d, 1H, J=5.2), 5.53 (H-3, d, 1H, J=5.2), 6.64–8.01 (ArH, m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 55.8, 56.1, 56.4 (OMe), 61.2 (C-4), 63.3 (C-3), 109.1, 112.7, 114.4, 115.2, 118.3, 119.7, 121.1, 123.5, 127.9, 129.0, 131.6, 132.8, 140.7, 144.2, 150.3, 157.0 (aromatic carbons), 161.2 (CO, phth), 163.5 (CO, β-lactam); GC–MS m/z=503 [M^+]. Anal. Calcd for $C_{26}H_{21}N_3O_8$: C, 62.03; H, 4.20; N, 8.35. Found: C, 62.12; H, 4.38; N, 8.40.

*4.5.12. 1-(4-Ethoxyphenyl)-3-methoxy-4-p-tolylazetidin-2-one (**4l**)*

White crystalline solid. Yield: (0.29 g, 92%), mp: 133–135 °C; IR (KBr) cm^{-1}: 1745 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 1.34 (Me, t, 3H, J=6.9), 2.34 (Me, s, 3H), 3.37 (OMe, s, 3H), 3.94 (OCH_2, q, 2H, J=6.9), 4.76 (H-4, d, 1H, J=4.7), 5.12 (H-3, d, 1H, J=4.7), 6.73–7.28 (ArH, m, 15H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.77, 21.24 (2 Me), 61.61 (OCH_2), 63.59 (C-4), 84.74 (C-3), 114.8, 118.7, 125.9, 127.9, 129.3, 130.3, 138.4, 155.6 (aromatic carbons), 163.8 (CO, β-lactam); GC–MS m/z=311 [M^+]. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.34; H, 6.85; N, 4.47.

*4.5.13. 1-(4-Ethoxyphenyl)-3-methoxy-4-(4-nitrophenyl)-azetidin-2-one (**4m**)*

Light-yellow solid. Yield: (0.28 g, 81%), mp: 118–120 °C; IR (KBr) cm^{-1}: 1342, 1519 (NO_2), 1749 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 1.41 (Me, t, 3H, J=6.9), 3.26 (OMe, s, 3H), 4.19 (OCH_2, q, 2H, J=6.9), 4.60 (H-4, d, 1H, J=4.4), 5.04 (H-3, d, 1H, J=4.4), 6.61–7.85 (ArH, m, 8H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 15.7 (Me), 57.8 (OMe), 62.6 (OCH_2), 64.8 (C-4), 85.5 (C-3), 117.5, 119.4, 124.8, 128.3, 129.9, 131.7, 137.7, 158.4 (aromatic carbons), 165.6 (CO, β-lactam); GC–MS m/z=342 [M^+]. Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.18; H, 5.37; N, 8.20.

*4.5.14. 3-(2,4-Dichlorophenoxy)-1-(4-ethoxyphenyl)-4-(4-nitrophenyl)-azetidin-2-one (**4n**)*

Light-yellow crystalline solid. Yield: (0.45 g, 94%), mp: 160–162 °C; IR (KBr) cm^{-1}: 1335, 1524 (NO_2), 1748 (250 MHz, CO, β-lactam); ^1H NMR ($CDCl_3$) δ 1.37 (Me, t, 3H, J=7.0), 3.96 (OCH_2, q, 2H, J=7.0), 5.52 (H-4, d, 1H, J=5.1), 5.56 (H-3, d, 1H, J=5.1), 6.78–8.22 (ArH, m, 11H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.7 (Me), 60.4 (OCH_2), 63.7 (C-4), 81.8 (C-3), 115.2, 116.7, 118.7, 123.7, 124.0, 127.7, 128.0, 129.0, 129.5, 130.1, 140.2, 148.2, 151.2, 156.4 (aromatic carbons), 161.3 (CO, β-lactam); GC–MS m/z=476 [M^+, ^{37}Cl], 472 [M^+, ^{35}Cl]. Anal. Calcd for $C_{23}H_{18}Cl_2N_2O_5$: C, 58.37; H, 3.83; N, 5.92. Found: C, 58.32; H, 3.88; N, 5.89.

*4.5.15. 4-(4-Chlorophenyl)-3-(2,4-dichlorophenoxy)-1-(4-ethoxyphenyl)-azetidin-2-one (**4o**)*

White solid. Yield: (0.43 g, 92%), mp: 182–184 °C; IR (KBr) cm^{-1}: 1746 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 1.38 (Me, t, 3H, J=7.0), 3.96 (OCH_2, q, 2H, J=7.0), 5.35 (H-4, d, 1H, J=5.0), 5.48 (H-3, d, 1H, J=5.0), 6.78–7.33 (ArH, m, 11H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.8 (Me), 60.9 (OCH_2), 63.7 (C-4), 81.7 (C-3), 115.1, 116.7, 118.9, 124.2, 127.5, 127.7, 128.8, 129.5, 129.9, 130.1, 131.0, 134.9, 151.4, 156.2 (aromatic carbons), 161.5 (CO, β-lactam); GC–MS m/z=468 [M^+, ^{37}Cl], 462 [M^+, ^{35}Cl]. Anal. Calcd for $C_{23}H_{18}C_{l3}NO_3$: C, 59.70; H, 3.92; N, 3.03. Found: C, 59.65; H, 4.01; N, 3.06.

*4.5.16. 1-(4-Ethoxyphenyl)-3-(naphthalen-2-yloxy)-4-(4-nitrophenyl)-azetidin-2-one (**4p**)*

Light-yellow crystalline solid. Yield: (0.43 g, 95%), mp: 174–176 °C; IR (KBr) cm^{-1}: 1345, 1527 (NO_2), 1751 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 1.39 (Me, t, 3H, J=7.0), 3.95 (OCH_2, q, 2H, J=7.0), 5.51 (H-4, d, 1H, J=4.8), 5.74 (H-3, d, 1H, J=4.8), 6.79–8.11

(ArH, m, 15H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.8 (Me), 61.1 (OCH_2), 63.7 (C-4), 81.2 (C-3), 109.0, 115.2, 118.0, 118.7, 123.6, 124.5, 126.7, 126.9, 127.7, 128.9, 129.6, 129.7, 129.8, 133.8, 140.5, 148.1, 154.4, 156.3 (aromatic carbons), 161.7 (CO, β-lactam); GC–MS m/z=454 [M^+]. Anal. Calcd for $C_{27}H_{22}N_2O_5$: C, 71.35; H, 4.88; N, 6.16. Found: C, 71.41; H, 4.92; N, 6.20.

4.5.17. 4-(4-Chlorophenyl)-1-(4-ethoxyphenyl)-3-(naphthalen-2-yloxy)-azetidin-2-one (**4q**)

Light-yellow solid. Yield: (0.42 g, 95%), mp: 140–142 °C; IR (KBr) cm^{-1}: 1748 (CO, β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.35 (Me, t, 3H, J=7.0), 3.90 (OCH_2, q, 2H, J=7.0), 5.35 (H-4, d, 1H, J=4.5), 5.64 (H-3, d, 1H, J=4.5), 6.67–8.08 (ArH, m, 15H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.9 (Me), 61.4 (OCH_2), 64.6 (C-4), 81.0 (C-3), 109.1, 114.8, 115.1, 118.3, 118.9, 123.9, 124.3, 126.5, 126.9, 127.7, 128.7, 129.5, 130.9, 131.4, 133.9, 134.6, 154.7, 156.1 (aromatic carbons), 162.2 (CO, β-lactam); GC–MS m/z=445 [M^+, ^{37}Cl], 443 [M^+, ^{35}Cl]. Anal. Calcd for $C_{27}H_{22}ClNO_3$: C, 73.05; H, 5.00; N, 3.16. Found: C, 73.13; H, 5.09; N, 3.11.

4.5.18. 1-(4-Methoxyphenyl)-3-(5-norbornene-2,3-dicarboxyloylimido)-4-(4-nitrophenyl)-azetidin-2-one (**7a**)

White solid. Yield: (0.36 g, 78%), mp: 235–237 °C; IR ($CHCl_3$) cm^{-1}: 1337, 1525 (NO_2), 1735, 1768. (CO, imide), 1778 (CO, β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.47, 1.67 (H-11, 2d, 2H, J=8.8), 3.04 (H-5, d, 1H, J=5.0), 3.13 (H-10, d, 1H, J=5.1), 3.29–3.40 (H-6 and H-9, m, 2H), 3.68 (OMe, s, 3H), 4.85 (H-4, d, 1H, J=2.5), 5.15 (H-3, d, 1H, J=2.5), 6.12–6.22 (H-7 and H-8, m, 2H), 6.69–8.13 (ArH, m, 8H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 44.7, 45.2 (C-5, C-10), 45.8, 46.2 (C-6, C-9), 52.1 (C-11), 55.4 (OMe), 59.1 (C-4), 62.5 (C-3), 114.5, 118.3, 123.5, 126.9, 130.2, 134.0, 140.0, 147.9, 148.2, 156.7 (C═C, aromatic carbons), 160.3 (CO, β-lactam), 176.2, 176.4 (CO, imide); GC–MS m/z=459 [M^+]. Anal. Calcd for $C_{25}H_{21}N_3O_6$: C, 65.35; H, 4.61; N, 9.15. Found: C, 65.27; H, 4.68; N, 9.06.

4.5.19. 4-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-(5-norbornene-2,3-dicarboxyloylimido)-azetidin-2-one (**7b**)

White crystalline solid. Yield: (0.37 g, 83%), mp: >245 °C; IR ($CHCl_3$) cm^{-1}: 1740, 1772 (CO, imide), 1781 (CO, β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.54, 1.75 (H-11, 2d, 2H, J=8.8), 3.30 (H-5, d, 1H, J=7.5), 3.35 (H-10, d, 1H, J=7.5), 3.40–3.48 (H-6 and H-9, m, 2H), 3.73 (OMe, s, 3H), 4.88 (H-4, d, 1H, J=2.5), 5.05 (H-3, d, 1H, J=2.5), 6.17–6.25 (H-7 and H-8, m, 2H), 6.75–7.49 (ArH, m, 8H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 45.3, 45.8 (C-5, C-10), 47.1, 47.9 (C-6, C-9), 52.1 (C-11), 55.4 (OMe), 59.4 (C-4), 62.7 (C-3), 114.4, 118.9, 123.9, 127.3, 129.6, 132.7, 134.5, 142.4, 148.3, 155.3 (C═C, aromatic carbons), 161.7 (CO, β-lactam), 177.0, 177.3 (CO, imide); GC–MS m/z=450 [M^+, ^{37}Cl], 448 [M^+, ^{35}Cl]. Anal. Calcd for $C_{25}H_{21}ClN_2O_4$: C, 66.89; H, 4.72; N, 6.24. Found: C, 66.95; H, 4.81; N, 6.30.

4.5.20. 1-(4-Ethoxyphenyl)-3-(5-norbornene-2,3-dicarboxyloylimido)-4-(4-nitrophenyl)-azetidin-2-one (**7c**)

Light-yellow solid. Yield: (0.35 g, 75%), mp: 209–211 °C; IR ($CHCl_3$) cm^{-1}: 1341, 1533 (NO_2), 1735, 1767 (CO, imide), 1776 (CO, β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.41 (Me, t, 3H, J=6.8), 1.57, 1.76 (H-11, 2d, 2H, J=8.9), 3.13 (H-5, d, 1H, J=5.4), 3.21 (H-10, d, 1H, J=5.2), 3.38–3.45 (H-6 and H-9, m, 2H), 3.98 (OCH_2, q, 2H, J=6.8), 4.93 (H-4, d, 1H, J=2.5), 5.24 (H-3, d, 1H, J=2.5), 6.21–6.30 (H-7 and H-8, m, 2H), 6.76–8.22 (ArH, m, 8H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.2 (Me), 44.7, 44.9 (C-5, C-10), 45.8, 46.2 (C-6, C-9), 52.2 (C-11), 59.0 (OCH_2), 62.4 (C-4), 63.7 (C-3), 115.0, 118.3, 123.5, 126.9, 129.8, 130.1, 134.5, 140.1, 143.7, 156.1 (C═C, aromatic carbons), 160.3 (CO, β-lactam), 176.2, 176.5 (CO, imide); GC–MS m/z=473 [M^+]. Anal. Calcd for $C_{26}H_{23}N_3O_6$: C, 65.95; H, 4.90; N, 8.87. Found: C, 66.03; H, 4.97; N, 8.85.

4.5.21. 1-(4-Ethoxyphenyl)-4-(4-nitrophenyl)-3-vinylazetidin-2-one (**8a**)

White crystalline solid. Yield: (0.22 g, 64%), mp: 60–62 °C; IR ($CHCl_3$) cm^{-1}: 1340, 1527 (NO_2), 1739 (CO, β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.24 (Me, t, 3H, J=6.9), 3.63 (H-3, dd, 1H, J=2.5, 7.5), 3.84 (OCH_2, q, 2H, J=6.9), 4.84 (H-4, d, 1H, J=2.5), 5.21–5.33 (vinilic H, m, 2H), 5.87–6.03 (vinilic H, m, 1H), 6.64–8.11 (ArH, m, 8H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.7 (Me), 60.2 (OCH_2), 63.6 (C-3), 64.0 (C-4), 115.0, 118.2, 121.6, 123.9, 126.8, 130.1, 140.0, 144.9, 147.9, 155.7 (C═C, aromatic carbons), 163.9 (CO, β-lactam); GC–MS m/z=338 [M^+]. Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.29; H, 5.40; N, 8.19.

4.5.22. 4-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-vinylazetidin-2-one (**8b**)

White solid. Yield: (0.22 g, 71%), mp: 73–75 °C; IR ($CHCl_3$) cm^{-1}: 1737 (CO, β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.54 (H-3, dd, 1H, J=2.4, 7.9), 3.61 (OMe, s, 3H), 4.65 (H-4, d, 1H, J=2.4), 5.16–5.27 (vinilic H, m, 2H), 5.84–5.90 (vinilic H, m, 1H), 6.63–7.41 (ArH, m, 8H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 55.4 (OMe), 60.5 (C-3), 64.0 (C-4), 113.9, 118.3, 121.7, 127.4, 129.3, 131.4, 134.3, 146.4, 147.5, 156.2 (C═C, aromatic carbons), 164.5 (CO, β-lactam); GC–MS m/z=315 [M^+, ^{37}Cl], 313 [M^+, ^{35}Cl]. Anal. Calcd for $C_{18}H_{16}ClNO_2$: C, 68.90; H, 5.14; N, 4.46. Found: C, 68.96; H, 5.27; N, 4.40.

4.5.23. 1,4-Bis(4-methoxyphenyl)-3-vinylazetidin-2-one (**8c**)

White solid. Yield: (0.24 g, 77%), mp: 77–79 °C; IR ($CHCl_3$) cm^{-1}: 1741.6 (CO, β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.66, 3.70 (2OMe, 2s, 6H), 3.74 (H-3, dd, 1H, J=2.5, 7.7), 4.75 (H-4, d, 1H, J=2.5), 5.24–5.37 (vinilic H, m, 2H), 5.94–6.08 (vinilic H, m, 1H), 6.72–7.26 (ArH, m, 8H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 55.2, 56.7 (2OMe), 62.9 (C-3), 63.8 (C-4), 114.1, 118.4, 121.7, 126.7, 128.3, 130.8, 132.0, 135.1, 147.6, 156.3 (C═C, aromatic carbons), 163.4 (CO, β-lactam); GC–MS m/z=309 [M^+]. Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.68; H, 6.11; N, 4.59.

4.5.24. 1′-Benzyl-1-(2,4-dimethoxyphenyl)-3-phenoxyspiro-[azetidine-2,3′-indoline]-2′,4-dione (**10a**)

Light-yellow crystalline solid. Yield: (0.42 g, 83%), mp: 169–171 °C; IR (KBr) cm^{-1}: 1725 (CO, isatin), 1765 (CO, β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.30, 3.34 (2OMe, s, 6H), 4.78, 5.13 (CH_2-benzyl, 2d, 2H, J=14.8), 5.55 (H-3, s, 1H), 6.37–8.01 (ArH, m, 17H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 43.8 (CH_2-benzyl), 55.3, 56.0 (2OMe), 68.1 (C-4), 84.8 (C-3), 101.2, 108.3, 113.2, 116.9, 122.6, 123.9, 124.0, 125.2, 126.9, 127.1, 128.4, 130.0, 130.9, 131.7, 135.0, 136.3, 141.9, 150.2, 151.5, 158.9 (aromatic carbons), 164.1 (CO, β-lactam), 172.6 (CO, isatin); GC–MS m/z=506 [M^+]. Anal. Calcd for $C_{31}H_{26}N_2O_5$: C, 73.50; H, 5.17; N, 5.53. Found: C, 73.43; H, 5.29; N, 5.50.

4.5.25. 1′-Benzyl-3-(2,4-dichlorophenoxy)-1-(2,4-dimethoxyphenyl)spiro[azetidine-2,3′-indoline]-2′,4-dione (**10b**)

Light-yellow solid. Yield: (0.44 g, 76%), mp: 155–157 °C; IR (KBr) cm^{-1}: 1723 (CO, isatin), 1767 (CO, β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.26, 3.32 (2OMe, s, 6H), 4.83, 5.19 (CH_2-benzyl, 2d, 2H, J=15.0), 5.62 (H-3, s, 1H), 6.52–8.11 (ArH, m, 15H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 44.6 (CH_2-benzyl), 54.7, 55.4 (2OMe), 67.9 (C-4), 82.1 (C-3), 107.0, 109.9, 115.2, 115.5, 123.8, 124.5, 124.8, 125.9, 127.6, 127.8, 128.8, 129.9, 130.4, 131.1, 136.3, 136.5, 143.2, 151.2, 152.4, 159.3, 159.5, 160.2 (aromatic carbons), 163.5 (CO, β-lactam), 171.9 (CO, isatin); GC–MS m/z=578 [M^+, ^{37}Cl], 574 [M^+, ^{35}Cl]. Anal. Calcd for $C_{31}H_{24}Cl_2N_2O_5$: C, 64.70; H, 4.20; N, 4.87. Found: C, 64.81; H, 4.33; N, 4.96.

*4.5.26. 1′-Benzyl-1-(2,4-dimethoxyphenyl)-3-(naphthalen-2-yloxy)spiro[azetidine-2,3′-indoline]-2′,4-dione (**10c**)*

Light-yellow solid. Yield: (0.45 g, 80%), mp: 175–177 °C; IR (KBr) cm^{-1}: 1726 (CO, isatin), 1762 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 3.24, 3.29 (2OMe, s, 6H), 4.69, 5.05 (CH_2-benzyl, 2d, 2H, *J*=14.6), 5.39 (H-3, s, 1H), 6.21–8.14 (ArH, m, 19H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 42.0 (CH_2-benzyl), 53.7, 54.9 (2OMe), 66.2 (C-4), 83.9 (C-3), 106.4, 107.6, 108.0, 109.7, 111.2, 114.4, 116.0, 121.0, 123.2, 123.9, 124.5, 126.2, 127.9, 128.3, 128.7, 129.6, 130.9, 131.7, 135.2, 137.4, 142.8, 150.7, 151.3, 154.7, 157.8, 160.7 (aromatic carbons), 165.3 (CO, β-lactam), 171.9 (CO, isatin); GC–MS *m*/*z*=556 [M^+]. Anal. Calcd for $C_{35}H_{28}N_2O_5$: C, 75.52; H, 5.07; N, 5.03. Found: C, 75.60; H, 5.18; N, 4.94.

*4.5.27. 1,2-Bis(4-methoxyphenyl)spiro[azetidine-3,9′-xanthen]-4-one (**11a**)*

Milky-colour solid. Yield: (0.37 g, 82%), mp: 161–163 °C; IR ($CHCl_3$) cm^{-1}: 1755 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 3.60, 3.73 (2OMe, 2s, 6H), 5.03 (H-4, s, 1H), 6.69–7.76 (ArH, m, 16H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 55.6, 56.9 (2OMe), 62.9 (C-4), 72.6 (C-3), 111.4, 114.4, 116.1, 116.9, 119.0, 1211.7, 124.2, 125.6, 127.9, 128.9, 130.9, 151.7, 152.1, 158.2 (aromatic carbons), 163.6 (CO, β-lactam); GC–MS *m*/*z*=449 [M^+]. Anal. Calcd for $C_{29}H_{23}NO_4$: C, 77.49; H, 5.16; N, 3.12. Found: C, 77.53; H, 5.27; N, 3.00.

*4.5.28. 2-(4-Chlorophenyl)-1-(4-ethoxyphenyl)spiro-[azetidine-3,9′-xanthen]-4-one (**11b**)*

White crystalline solid. Yield: (0.37 g, 78%), mp: 239–241 °C; IR ($CHCl_3$) cm^{-1}: 1757 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 1.31 (Me, t, 3H, *J*=6.9), 3.97 (OCH_2, q, 2H, *J*=6.9), 5.17 (H-4, s, 1H), 6.65–8.05 (ArH, m, 16H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.0 (Me), 61.8 (OCH_2), 63.7 (C-4), 74.4 (C-3), 109.6, 116.3, 116.7, 117.2, 118.9, 122.9, 124.3, 125.5, 126.9, 127.9, 128.3, 129.2, 129.7, 157.8 (aromatic carbons), 164.1 (CO, β-lactam); GC–MS *m*/*z*=469 [M^+, ^{37}Cl], 467 [M^+, ^{35}Cl]. Anal. Calcd for $C_{29}H_{22}ClNO_3$: C, 74.43; H, 4.74; N, 2.99. Found: C, 74.37; H, 4.81; N, 3.06.

*4.5.29. 1-(4-Ethoxyphenyl)-2-(4-nitrophenyl)spiro-[azetidine-3,9′-xanthen]-4-one (**11c**)*

Light-yellow crystalline solid. Yield: (0.38 g, 79%), mp: 186–188 °C; IR ($CHCl_3$) cm^{-1}: 1343, 1529 (NO_2), 1757 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 1.38 (Me, t, 3H, *J*=7.0), 4.05 (OCH_2, q, 2H, *J*=7.0), 5.12 (H-4, s, 1H), 6.87–7.89 (ArH, m, 16H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.8 (Me), 63.8 (OCH_2), 64.5 (C-4), 73.4 (C-3), 115.3, 116.8, 118.8, 120.0, 123.4, 126.9, 128.1, 129.8, 130.2, 142.5, 147.3, 151.7, 152.7, 156.3 (aromatic carbons), 164.8 (CO, β-lactam); GC–MS *m*/*z*=478 [M^+]. Anal. Calcd for $C_{29}H_{22}N_2O_5$: C, 72.79; H, 4.63; N, 5.85. Found: C, 72.84; H, 4.73; N, 5.78.

*4.5.30. 3-Chloro-4-(4-chlorophenyl)-1-(4-ethoxyphenyl)-azetidin-2-one (**12a**)*

Milky-colour solid. Yield: (0.20 g, 59%), mp: 91–93 °C; IR (KBr) cm^{-1}: 1745 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 1.27 (Me, t, 3H, *J*=7.0), 3.81 (OCH_2, q, 2H, *J*=7.0), 4.63 (H-4, d, 1H, *J*=5.2), 4.85 (H-3, d, 1H, *J*=5.2), 6.69–7.34 (ArH, m, 8H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 15.1 (Me), 60.6 (OCH_2), 63.8 (C-4), 67.1 (C-3), 108.4, 115.8, 120.1, 124.7, 127.2, 132.4, 148.5, 155.0 (aromatic carbons), 162.3 (CO, β-lactam); GC–MS *m*/*z*=339 [M^+, ^{37}Cl], 335 [M^+, ^{35}Cl]. Anal. Calcd for $C_{17}H_{15}Cl_2NO_2$: C, 60.73; H, 4.50; N, 4.17. Found: C, 60.79; H, 4.41; N, 4.25.

*4.5.31. 3-Chloro-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**12b**)*

White solid. Yield: (0.16 g, 57%), mp: 116–118 °C; IR (KBr) cm^{-1}: 1751 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 3.63 (OMe, s, 3H), 4.51 (H-4, d, 1H, *J*=4.5), 4.98 (H-3, d, 1H, *J*=4.5), 6.84–7.17 (ArH, m, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 54.7 (OMe), 62.5 (C-4), 68.3 (C-3), 106.0, 113.3, 119.1, 125.8, 126.0, 134.1, 149.6, 151.8 (aromatic carbons), 163.7 (CO, β-lactam); GC–MS *m*/*z*=289 [M^+, ^{37}Cl], 287 [M^+, ^{35}Cl]. Anal. Calcd for $C_{16}H_{14}NO_2Cl$: C, 66.78; H, 4.87; N, 4.87. Found: C, 66.69; H, 4.96; N, 4.73.

*4.5.32. 3-Chloro-1,4-bis(4-methoxyphenyl)-azetidin-2-one (**12c**)*

White solid. Yield: (0.19 g, 60%), mp: 121–123 °C; IR (KBr) cm^{-1}: 1747 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 3.61, 3.79 (2OMe, 2s, 6H), 4.69 (H-4, d, 1H, *J*=4.8), 5.04 (H-3, d, 1H, *J*=4.8), 6.80–7.43 (ArH, m, 8H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 55.2, 57.9 (2OMe), 60.5 (C-4), 67.9 (C-3), 110.7, 112.2, 120.7, 125.3, 128.3, 134.8, 149.8, 157.2 (aromatic carbons), 164.6 (CO, β-lactam); GC–MS *m*/*z*=319 [M^+, ^{37}Cl], 317 [M^+, ^{35}Cl]. Anal. Calcd for $C_{17}H_{16}ClNO_3$: C, 64.26; H, 5.08; N, 4.41. Found: C, 64.40; H, 5.16; N, 4.48.

*4.5.33. 3-Chloro-1-(4-methoxyphenyl)-4-styrylazetidin-2-one (**12d**)*

White solid. Yield: (0.18 g, 56%), mp: 139–141 °C; IR (KBr) cm^{-1}: 1758 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 3.69 (OMe, s, 3H), 5.08 (H-4, dd, 1H, *J*=4.6, 9.1), 5.04 (H-3, d, 1H, *J*=4.6), 6.36 (H-5, dd, *J*=9.1, 16.0), 6.75 (H-6, d, 1H, *J*=16.0), 6.84–7.59 (ArH, m, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 55.3 (OMe), 63.7 (C-4), 68.8 (C-3), 109.1, 116.3, 120.8, 122.5, 125.2, 128.7, 133.6, 149.5, 158.2 (C=C, aromatic carbons), 162.8 (CO, β-lactam); GC–MS *m*/*z*=315 [M^+, ^{37}Cl], 313 [M^+, ^{35}Cl]. Anal. Calcd for $C_{18}H_{16}ClNO_2$: C, 68.90; H, 5.14; N, 4.46. Found: C, 68.82; H, 5.28; N, 4.36.

*4.5.34. 2-(4-Chlorophenyl)-1-(4-ethoxyphenyl)-4-oxoazetidine-3-carbonitrile (**13a**)*

Light-yellow solid. Yield: (0.17 g, 53%), mp: 82–84 °C; IR (KBr) cm^{-1}: 1759 (CO, β-lactam), 2251 (CN); ^1H NMR (250 MHz, $CDCl_3$) δ 1.36 (Me, t, 3H, *J*=7.0), 3.88 (OCH_2, q, 2H, *J*=7.0), 4.95 (H-4, d, 1H, *J*=4.8), 5.21 (H-3, d, 1H, *J*=4.8), 6.83–7.59 (ArH, m, 8H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 17.0 (Me), 58.4 (OCH_2), 63.7 (C-4), 73.6 (C-3), 108.3, 114.8, 122.1, 126.7, 129.5, 134.1, 138.3, 147.0, 156.1 (CN, aromatic carbons), 165.1 (CO, β-lactam); GC–MS *m*/*z*=328 [M^+, ^{37}Cl], 326 [M^+, ^{35}Cl]. Anal. Calcd for $C_{18}H_{15}ClN_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.44; H, 5.16; N, 9.96.

*4.5.35. 1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidine-3-carbonitrile (**13b**)*

Light-yellow solid. Yield: (0.14 g, 51%), mp: 97–99 °C; IR (KBr) cm^{-1}: 1767 (CO, β-lactam), 2247 (CN); ^1H NMR (250 MHz, $CDCl_3$) δ 3.58 (OMe, s, 3H), 5.11 (H-4, d, 1H, *J*=5.0), 5.36 (H-3, d, 1H, *J*=5.0), 6.65–7.33 (ArH, m, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 56.5 (OMe), 59.3 (C-4), 70.2 (C-3), 110.4, 113.9, 118.4, 121.5, 126.6, 129.3, 133.5, 149.2, 155.8 (CN, aromatic carbons), 163.3 (CO, β-lactam); GC–MS *m*/*z*=278 [M^+]. Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.44; H, 5.16; N, 9.96.

*4.5.36. 1,2-Bis(4-methoxyphenyl)-4-oxoazetidine-3-carbonitrile (**13c**)*

Light-yellow solid. Yield: (0.15 g, 49%), mp: 117–119 °C; IR (KBr) cm^{-1}: 1776 (CO, β-lactam), 2250 (CN); ^1H NMR (250 MHz, $CDCl_3$) δ 3.55, 3.63 (2OMe, 2s, 6H), 5.08 (H-4, d, 1H, *J*=4.5), 5.27 (H-3, d, 1H, *J*=4.5), 6.80–7.53 (ArH, m, 8H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 57.4, 59.2 (2OMe), 61.7 (C-4), 75.1 (C-3), 109.5, 111.8, 115.2, 122.7, 126.3, 128.0, 133.6, 147.7, 158.0 (CN, aromatic carbons), 162.8 (CO, β-lactam); GC–MS *m*/*z*=308 [M^+]. Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.30; H, 5.39; N, 9.01.

*4.5.37. 1-(4-Methoxyphenyl)-2-oxo-4-styrylazetidine-3-carbonitrile (**13d**)*

Light-yellow solid. Yield: (0.12 g, 41%), mp: 135–137 °C; IR (KBr) cm^{-1}: 1759 (CO, β-lactam), 2246 (CN); ^1H NMR (250 MHz, $CDCl_3$)

δ 3.69 (OMe, s, 3H), 4.92 (H-4, dd, 1H, J=5.1, 8.3), 5.06 (H-3, d, 1H, J=5.1), 6.21 (H-5, dd, J=8.3, 15.5), 6.68 (H-6, d, 1H, J=15.5), 6.84–7.47 (ArH, m, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 56.2 (OMe), 60.0 (C-4), 72.5 (C-3), 107.3, 115.0, 119.3, 123.6, 128.9, 133.5, 136.2, 141.4, 148.8, 157.8 (C=C, CN, aromatic carbons), 163.5 (CO, β-lactam); GC–MS m/z=304 [M^+]. Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.86; H, 5.38; N, 9.12.

Acknowledgements

The authors thank the Shiraz University Research Council for financial support (Grant No. 87-GR-SC-23).

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