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Efficient one-pot synthesis of 2-azetidinones from acetic acid derivatives and imines using methoxymethylene-*N*,*N*-dimethyliminium salt

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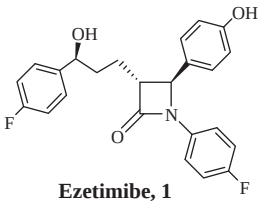
ABSTRACT

A cheap, versatile and convenient method for synthesis of β-lactams using methoxymethylene-*N*,*N*-dimethyliminium salt as an acid activator in Staudinger reaction is reported. This method is used for the preparation of monocyclic, spirocyclic, *N*-alkyl and three-electron-withdrawing group β-lactams. The products are obtained in good to excellent yields.

1. Introduction

β-Lactam antibiotics have played an important role in antibacterial drugs and in medicinal chemistry.[1] Ezetimibe **1** is a new and selective cholesterol absorption inhibitor.[2]



Ezetimibe, 1

Some other significant biological activities of β-lactams are inhibitors of human cytomegalovirus (HCMV),[3] human leukocyte elastase (HLE),[4] thrombin,[5] porcine pancreatic elastase (PPE),[6] HIV-1 protease[7] and cysteine protease.[8] Anticancer,[9] antifungal,[10] potential antimalarials,[11] anti-influenza virus,[12] antihyperglycemic,[13] central nervous system (CNS) active agents[14] and combat of neurological diseases[15] are also other new biological activities of these compounds.

The chemical basis of both the biological activity and the inhibition of β-lactam antibiotics is directly related to the reactivity of the four-membered β-lactam ring and in particular to the susceptibility of the carbonyl group towards nucleophilic attack.[16] It is widely accepted that the high reactivity of β-lactam antibiotics results from the lack of amide resonance in the 2-azetidinone ring.[17]

The major limitation to the potentials of β-lactam antibacterials is the ability of bacteria to produce a family of enzymes called β-lactamases. These enzymes hydrolyze the β-lactam ring, which is required for antibacterial activity. Thus, because of the alarming increase in bacterial resistance to β-lactam antibiotics and the need for medicines with a more specific antibacterial activity, several synthetic and semi-synthetic β-lactam antibiotics have been developed by the pharmaceutical industry.[18]

β-Lactams are not only useful fragments of antibiotics, but are also used as intermediates and synthons for the production of several organic compounds.[19] The side chain of Taxol (the antitumour agent) is preferentially prepared by nucleophilic ring opening of suitably substituted β-lactams.[20]

Due to importance of β-lactams several synthetic methods have been developed for the preparation of the β-lactam ring[21] and some reviews for this topic have been published.[22] The Staudinger reaction[23] ([2+2] ketene–imine cycloaddition reaction) is regarded as the most fundamental and versatile method for the synthesis of 2-azetidinone ring and are used for the synthesis of a large number of β-lactams.[24] Generally the coupling constant of H-3 and H-4 is used for indication of stereochemistry of 2-azetidinones ($J_{3,4}$>4.0 Hz for the cis and $J_{3,4}\leq$3.0 Hz for the trans stereoisomers).[22i]

Among the several methods for formation of ketenes,[25] they are generally generated via the in situ by reaction of acyl halides with tertiary amines.[26] The application of acyl halides for the generation of ketenes has some drawbacks such as low availability, instability and difficulty of preparation. For this, acid activators have been used for the synthesis of 2-azetidinones from imines and carboxylic acids.[27]

Alkoxymethylene-*N*,*N*-dimethyliminium salts have been prepared from DMF and *o*-alkylating agents [28] and they have been used in several reactions.[29]

In our recent communication,[30] we utilized alkoxymethylene-*N*,*N*-dimethyliminium salts as acid activators in the synthesis of 2-azetidinone ring by the ketene–imine cycloaddition. The versatility and efficiency of the methoxymethylene-*N*,*N*-dimethyliminium salt in β-lactam synthesis from carboxylic acids under mild conditions is demonstrated in this paper.

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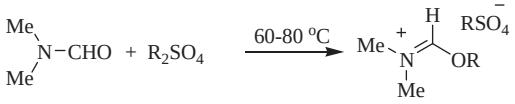
2. Results and discussion

Methoxy- and ethoxy-methylene-*N*,*N*-dimethyliminium salts **2** and **3** were formed by reacting *N*,*N*-dimethylformamide (DMF) with Me_2SO_4 and Et_2SO_4, respectively (Scheme 1).

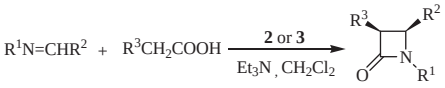


Scheme 1.

After generation in DMF, salts **2** and **3** were used after cooling without any further purification. To characterize the structure of **2**, the excess of DMF was removed under reduced pressure and a gel-like solid was obtained. The IR spectrum showed the characteristic absorption of C=N at 1721 cm^{-1}.

Then the iminium salts **2** or **3** were added to a mixture of imines **4a**,**b** and carboxylic acids **5** in dry dichloromethane. As is shown in Table 1, DMF or Me_2SO_4 alone was inactive and reagent **2** (DMF/Me_2SO_4) proved to be better than **3** (DMF/Et_2SO_4) for the synthesis of β-lactams **6a**,**b**. Also the yields were better at room temperature than 0 °C. The indicated cis stereochemistry for these monocyclic β-lactams was deduced from analysis of their ^1H NMR spectra.

Table 1
Reaction condition in the synthesis of **6a**,**b**



4a-b **5** **6a-b**

R^1	R^2	R^3	Reagent	Temp	Product	Yield (%)
4-$MeOC_6H_4$	4-MeC_6H_4	PhO	DMF	rt	—	—
4-$MeOC_6H_4$	4-MeC_6H_4	PhO	Me_2SO_4	rt	—	—
4-$MeOC_6H_4$	4-MeC_6H_4	PhO	**2**	0 °C	**6a**	31
4-$MeOC_6H_4$	4-MeC_6H_4	PhO	**2**	rt	**6a**	87
4-$MeOC_6H_4$	4-MeC_6H_4	PhO	**3**	0 °C	**6a**	26
4-$MeOC_6H_4$	4-MeC_6H_4	PhO	**3**	rt	**6a**	49
4-$EtOC_6H_4$	4-$NO_2C_6H_4$	MeO	**2**	0 °C	**6b**	53
4-$EtOC_6H_4$	4-$NO_2C_6H_4$	MeO	**2**	rt	**6b**	82
4-$EtOC_6H_4$	4-$NO_2C_6H_4$	MeO	**3**	0 °C	**6b**	18
4-$EtOC_6H_4$	4-$NO_2C_6H_4$	MeO	**3**	rt	**6b**	44

To optimize the solvent, the reaction for the synthesis of β-lactam **6a** by reagent **2** in dry solvents at room temperature was performed. Among the solvents considered, dichloromethane showed the best result (Table 2).

The molar optimization of **2** was determined for the production of **6a** (Table 3). As it is shown in the table, the yield of **6a** increases when 1.5 mmol of **2** and 1.5 mmol of carboxylic acid react with 1.0 mmol of imine instead of 1.0 or 1.3 mmol of **2**.

Based on the above results, the 2-azetidinones in Table 4 were synthesized by treatment of 1.0 mmol of imines, 1.5 mmol of substituted acetic acids and 1.5 mmol of **2** in the presence of triethylamine in dry dichloromethane at room temperature for 8–16 h. The β-lactams **6a**–**r** were synthesized by mild and simple reactions and byproducts (DMF and salts) were removed by a simple aqueous work-up. The purification of β-lactams was performed by crystallization from EtOAc and all products were characterized by their spectral data and elemental analyses.

Table 2
Solvent optimization in the synthesis of **6a**

Entry	Solvent	Yield (%)
1	*N*,*N*-Dimethylformamide	47
2	Acetonitrile	71
3	1,2-Dichloroethane	68
4	Dichloromethane	87
5	Toluene	33

Table 3
Molar optimization of **2** for the synthesis of **6a**

Entry	**2**	Carboxylic acid	Imine	Yield (%)
1	1.0	1.0	1.0	51
2	1.3	1.3	1.0	68
3	1.5	1.5	1.0	87

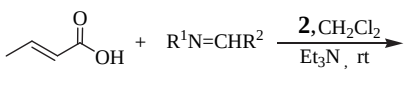
Table 4
Synthesis of 2-azetidinones **6a**–**r** by reagent **2**

Entry	R^1	R^2	R^3	Product	Isolated yield (%)
1	4-$MeOC_6H_4$	4-MeC_6H_4	PhO	**6a**	87
2	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	MeO	**6b**	82
3	4-$EtOC_6H_4$	4-ClC_6H_4	PhO	**6c**	91
4	4-$EtOC_6H_4$	4-$MeOC_6H_4$	PhthN	**6d**	82
5	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	2,4-$Cl_2C_6H_3O$	**6e**	94
6	4-$EtOC_6H_4$	4-ClC_6H_4	2,4-$Cl_2C_6H_3O$	**6f**	79
7	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	2-Naphtho	**6g**	88
8	4-$MeOC_6H_4$	4-ClC_6H_4	MeO	**6h**	85
9	4-$EtOC_6H_4$	CH=CHPh	PhthN	**6i**	90
10	4-$EtOC_6H_4$	4-ClC_6H_4	PhthN	**6j**	84
11	4-$EtOC_6H_4$	4-$MeOC_6H_4$	2-Naphtho	**6k**	94
12	4-$EtOC_6H_4$	3,4-$(MeO)_2C_6H_3$	PhO	**6l**	95
13	4-$EtOC_6H_4$	CH=CHPh	PhO	**6m**	91
14	4-$EtOC_6H_4$	4-MeC_6H_4	PhO	**6n**	94
15	4-$MeOC_6H_4$	2,3-$(MeO)_2C_6H_3$	PhO	**6o**	81
16	4-$MeOC_6H_4$	4-$MeOC_6H_4$	PhO	**6p**	88
17	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	2,4-$Cl_2C_6H_3O$	**6q**	86
18	4-$MeOC_6H_4$	4-MeC_6H_4	MeO	**6r**	92

β-Lactams **7a**–**c** were also synthesized from crotonic acid by this method and purified by short column chromatography on silica gel (Scheme 2). The trans stereochemistry was deduced from H-3 and H-4 coupling constants (J=2.3–2.5).

Treatment of imines with 5-norbornene-2,3-dicarboxyloylglycine in the presence of reagent **2** at room temperature gave *trans* 2-azetidinones **8a**–**c**, which were purified by crystallization from EtOAc (Scheme 3).

Then to check the generality of this method, we synthesized 2-azetidinones **9a**–**c** and **10a**,**b** from imines derived from aliphatic amines **4l**,**m** and **4r**, respectively (Scheme 4).



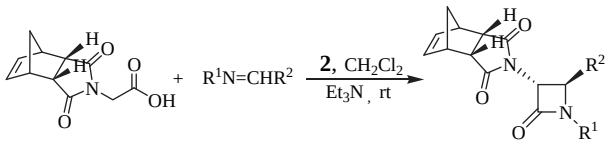
crotonic acid

7a, R^1 = 4-$EtOC_6H_4$; R^2 = 4-$NO_2C_6H_4$ 72%

7b, R^1 = 4-$MeOC_6H_4$; R^2 = 4-$MeOC_6H_4$ 68%

7c, R^1 = 4-$EtOC_6H_4$; R^2 = 4-MeC_6H_4 73%

Scheme 2.



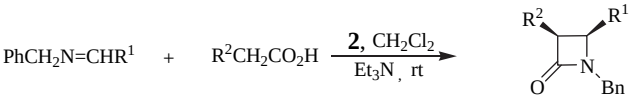
5-norbornene-2,3-dicarboxyloylglycine

8a, R^1 = 4-$MeOC_6H_4$; R^2 = 4-ClC_6H_4 78%

8b, R^1 = 4-$EtOC_6H_4$; R^2 = 4-$NO_2C_6H_4$ 83%

8c, R^1 = 4-$EtOC_6H_4$; R^2 = 3,4-$(MeO)_2C_6H_3$ 81%

Scheme 3.



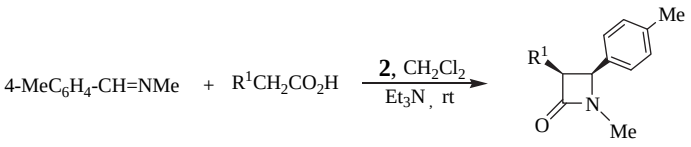
4l, R^1 = 4-ClC_6H_4

4m, R^1 = 4-$NO_2C_6H_4$

9a, R^1 = 4-ClC_6H_4 ; R^2 = PhO 93%

9b, R^1 = 4-ClC_6H_4 ; R^2 = 2,4-$Cl_2C_6H_3O$ 86%

9c, R^1 = 4-$NO_2C_6H_4$; R^2 = PhO 91%



4r

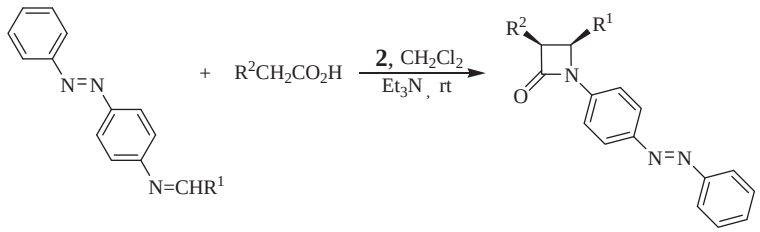
10a, R^1 = PhthN 79%

10b, R^1 = PhO 84%

Scheme 4.

Highly coloured 2-azetidinones **11a**–**c** were also synthesized from Schiff bases **4n**, **4o** and acetic acid derivatives via the methoxymethylene-*N*,*N*-dimethyliminium salt **2** (Scheme 5).

The cycloaddition reaction of xanthene-9-carboxylic acid and imines using the methoxymethylene-*N*,*N*-dimethyliminium salt **2** gave 3-spiro-β-lactams **12a**–**c** in excellent yields (Scheme 6).



4n, R^1 = 4-ClC_6H_4

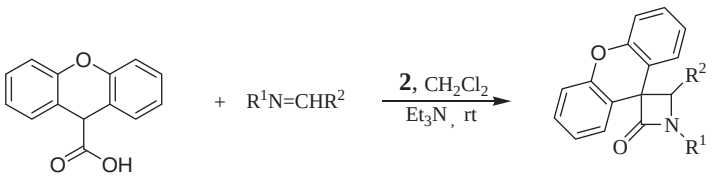
4o, R^1 = 4-$NO_2C_6H_4$

11a, R^1 = 4-ClC_6H_4 ; R^2 = PhO 90%

11b, R^1 = 4-$NO_2C_6H_4$; R^2 = 2,4-$Cl_2C_6H_3O$ 87%

11c, R^1 = 4-$NO_2C_6H_4$; R^2 = 2-naphthO 92%

Scheme 5.



xanthene-9-carboxylic acid

12a, R^1 = 4-$MeOC_6H_4$; R^2 = 4-$MeOC_6H_4$ 76%

12b, R^1 = 4-$EtOC_6H_4$; R^2 = 4-ClC_6H_4 74%

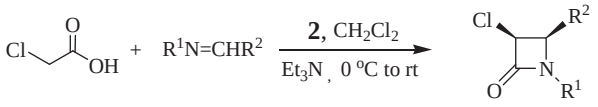
12c, R^1 = 4-$EtOC_6H_4$; R^2 = 4-$NO_2C_6H_4$ 81%

Scheme 6.

The [2+2] cycloaddition reaction of ketene–imine using α-electron-withdrawing substituted carboxylic acids generally fails for the synthesis of 2-azetidinones. We have used methoxymethylene-*N*,*N*-dimethyliminium salt **2** for preparation of 3-chloro and 3-azido β-lactams **13a**–**c** and **14a**–**c** from chloro and azidoacetic acids in dry CH_2Cl_2, respectively (Scheme 7). In the case of chloroacetic acid, the yields of β-lactams **13a**–**c** were low at room temperature, so the reactions were performed at 0 °C to room temperature.

Table 5
Comparison of different formamides in the synthesis of β-lactam **6a**

Amide	Time (h)	Yield (%)
N,*N*-Dimethylformamide	9	87
N,*N*-Dimethylacetamide	15	41
N,*N*-Diisopropylformamide	25	26
N,*N*-Dimethylthioformamide	22	50

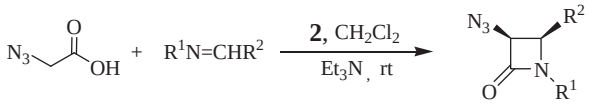


chloroacetic acid

13a, R^1 = 4-$EtOC_6H_4$; R^2 = 4-ClC_6H_4 57%

13b, R^1 = 4-$MeOC_6H_4$; R^2 = C_6H_5 45%

13c, R^1 = 4-$MeOC_6H_4$; R^2 = 4-$MeOC_6H_4$ 49%



azidoacetic acid

14a, R^1 = 4-$EtOC_6H_4$; R^2 = 4-$NO_2C_6H_4$ 69%

14b, R^1 = C_6H_5 ; R^2 = C_6H_5 64%

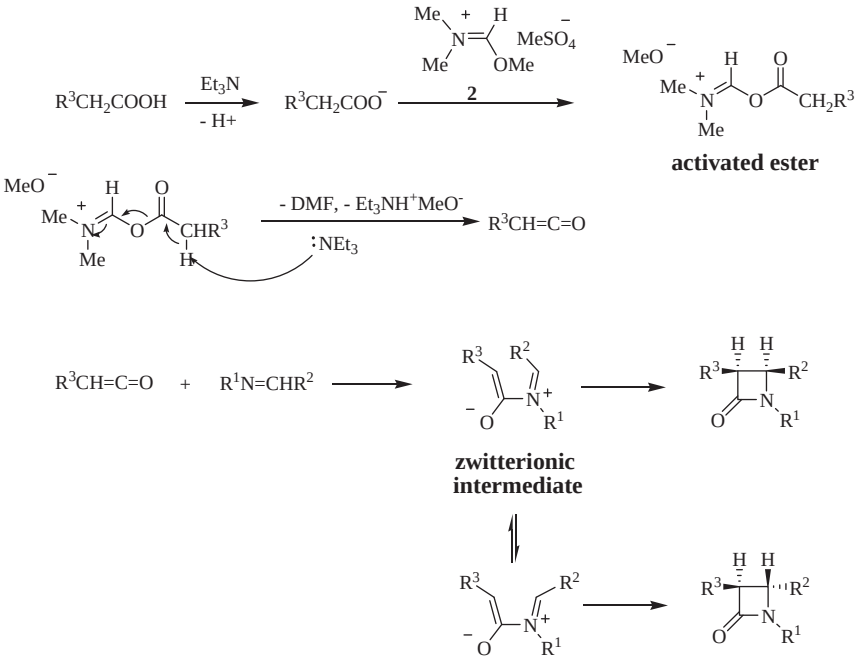
14c, R^1 = 4-$MeOC_6H_4$; R^2 = 4-ClC_6H_4 72%

Scheme 7.

As it is shown in Table 5, several amides other than DMF could also be alkylated to form active iminium salts in the synthesis of β-lactams. In all cases 1.5 mmol of the iminium salt was used at room temperature. The completion of the reaction was identified by TLC monitoring (disappearing of imine). Reagent **2** (DMF/Me_2SO_4) showed to be the most effective one for β-lactam synthesis.

The sharp decrease in the yield of **6a** using *N*,*N*-dimethylacetamide and *N*,*N*-diisopropylformamide is perhaps due to the increase of the steric hindrance of these reagents. On the basis of hard and soft acid and base principle (HSAB), *N*,*N*-dimethylthioformamide cannot react with Me_2SO_4 as well as *N*,*N*-dimethylformamide.

Finally a possible mechanism is proposed according to the reported mechanisms for the Staudinger reaction[31] (Scheme 8).



Scheme 8.

Treatment of a substituted acetic acid with methoxymethylene-*N*,*N*-dimethyliminium salt **2** in the presence of triethylamine provides the corresponding activated ester. The activated ester reacts with triethylamine to generate the desired ketene, which then reacts with imines to form a zwitterionic intermediate, which undergoes a conrotatory ring closure to produce the β-lactam. The stereochemistry is mainly dominated by the electronic effect and the steric hindrance of the ketene and imine substitutents.[31a]

3. Conclusions

This paper, which is an extension of our earlier communication describes the use of methoxymethylene-*N*,*N*-dimethyliminium salt to activate the substituted acetic acids in the synthesis of 2-azetidinones via a ketene–imine cycloaddition reaction. The remarkable versatility of this method avoids the use of chlorinating agents, the mild condition reactions, availability of the reagents, easy purification and high yield of the products. Compared to other amides, DMF has been found to be superior in terms of yield of product and time of reaction.

4. Experimental section

4.1. General

All required chemicals were purchased from Merck, Fluka and Acros chemical companies. All reagents and solvents were dried prior to use according to standard methods.[32]

IR spectra were run on a Shimadzu FT-IR 8300 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ 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 EA-1112 series. Melting points were determined in open capillaries with Buchi 510 melting point apparatus and are not corrected. Thin-layer chromatography was carried out on silica gel 254 analytical sheets obtained from Fluka. Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh). Azidoacetic acid[33] and 5-norbornene-2,3-dicarboxyloylglycine[27a] were synthesized via the reported procedures. Spectral data for **6a**–**g**, **6i**, **6l**–**p**, **7a**,**b**, **8a**,**b**, **12a**–**c** and **13a**–**c** have been previously reported.[27a,f,i,30,34]

4.2. Preparation of alkoxymethylene-*N*,*N*-dimethyliminium salts 2 and 3

A mixture of *N*,*N*-dimethylformamide (0.13 mL, 0.12 g, 1.7 mmol) and Me_2SO_4 or Et_2SO_4 (1.5 mmol) was stirred at 60–80 °C for 2 h to give reagents **2** and **3**, respectively [In the case of DMF/Me_2SO_4 by removal of excess of DMF and addition of 2 mL $CHCl_3$: IR ($CHCl_3$, cm^{-1}): 1246, 1068 (C–O–(C)) and 1721 (C=N)].

4.3. General procedure for the synthesis of 2-azetidinones using alkoxymethylene-*N*,*N*-dimethyliminium salts 2 and 3

After cooling, the solution containing reagent **2** or **3** was added to a mixture of imine (1.0 mmol) and substituted acetic acid (1.5 mmol). The reaction mixture was stirred for 10–15 min, and then dry triethylamine (0.15 mL, 0.11 g, 5.0 mmol) was added at 0 °C or at room temperature and it was stirred overnight at room temperature. Then the solution was washed successively with 10% HCl (20 mL), saturated $NaHCO_3$ (20 mL), brine (20 mL), dried over Na_2SO_4 and then filtered. The solvent was evaporated under reduced pressure to give the crude product. β-Lactams **6a**–**r**, **8a**–**c**, **9a**–**c**, **10a**,**b**, **11a**–**c**, **12a**–**c** were purified by crystallization from ethyl acetate and β-lactams **7a**–**c**, **13a**–**c**, **14a**–**c** by short column chromatography on silica gel.

*4.3.1. 4-(4-Chlorophenyl)-3-methoxy-1-(4-methoxyphenyl)-azetidin-2-one (**6h**).* White solid (0.27 g, 85%); mp: 119–121 °C. IR (KBr, cm^{-1}): 1750 (CO, β-lactam). ^{1}H NMR δ 3.28, 3.69 (2OMe, 2s, 6H), 4.88 (H-4, d, 1H, J=4.6), 5.37 (H-3, d, 1H, J=4.6), 6.72–7.64 (ArH, m, 8H). ^{13}C NMR δ 55.3, 57.5 (2OMe), 64.1 (C-4), 82.6 (C-3), 115.7, 118.8, 122.3, 127.1, 130.4, 142.7, 149.0, 159.3 (aromatic carbons), 161.8 (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, 64.15; H, 5.17; N, 4.46.

*4.3.2. 2-(2-(4-Chlorophenyl)-1-(4-ethoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**6j**).* White solid (0.38 g, 84%); mp: 185–187 °C. IR ($CHCl_3$, cm^{-1}): 1720, 1759 (CO, phth), 1787 (CO, β-lactam). ^{1}H NMR δ 1.37 (Me, t, 3H, J=7.0), 3.97 (OCH_2, q, 2H, J=7.0), 5.22 (H-4, d, 1H, J=4.5), 5.32 (H-3, d, 1H, J=4.5), 6.78–7.76 (ArH, m, 12H). ^{13}C NMR δ 14.8 (Me), 60.7 (OCH_2), 62.7 (C-4), 63.7 (C-3), 115.0, 118.7, 123.1, 127.9, 129.0, 130.3, 131.5, 133.8, 134.6, 135.1, 156.0 (aromatic carbons), 161.2 (CO, phth), 166.8 (CO, β-lactam). GC–MS m/z=448 [M$^+$, ^{37}Cl], 446 [M$^+$, ^{35}Cl]. Anal. Calcd for $C_{25}H_{19}ClN_2O_4$: C, 67.19; H, 4.29; N, 6.27. Found: C, 67.16; H, 4.27; N, 6.24.

*4.3.3. 1-(4-Ethoxyphenyl)-4-(4-methoxyphenyl)-3-(naphthalen-2-yloxy)-azetidin-2-one (**6k**).* White crystal (from EtOAc) (0.41 g, 94%); mp: 162–164 °C. IR (KBr, cm^{-1}): 1753 (CO, β-lactam). ^{1}H NMR δ 1.32 (Me, t, 3H, J=7.0), 3.62 (OMe, s, 3H), 3.91 (OCH_2, q, 2H, J=7.0), 5.29 (H-4, d, 1H, J=4.6), 5.56 (H-3, d, 1H, J=4.6), 6.57–7.96 (ArH, m, 15H). ^{13}C NMR δ 14.8 (Me), 55.1 (OMe), 61.8 (OCH_2), 63.7 (C-4), 81.1 (C-3), 109.2, 113.9, 115.0, 118.5, 119.0, 124.2, 124.5, 126.5, 127.0, 127.7, 129.4, 129.5, 129.9, 130.4, 134.0, 154.9, 155.9, 159.8 (aromatic carbons), 162.5 (CO, β-lactam). GC–MS m/z=439 [M$^+$]. Anal. Calcd for $C_{28}H_{25}NO_4$: C, 76.52; H, 5.73; N, 3.19. Found: C, 76.68; H, 5.80; N, 3.24.

*4.3.4. 3-(2,4-Dichlorophenoxy)-1-(4-methoxyphenyl)-4-(4-nitrophenyl)-azetidin-2-one (**6q**).* White solid (0.39 g, 86%); mp: 177–189 °C. IR (KBr, cm^{-1}): 1751 (CO, β-lactam). ^{1}H NMR δ 3.89 (OMe, s, 3H), 5.56 (H-4, d, 1H, J=4.5), 5.64 (H-3, d, 1H, J=4.5), 6.72–7.64 (ArH, m, 11H). ^{13}C NMR δ 57.9 (OMe), 64.4 (C-4), 82.7 (C-3), 113.4, 116.1, 117.9, 122.5, 124.7, 127.2, 128.5, 129.3, 129.8, 131.4, 142.6, 148.7, 150.2, 155.8 (aromatic carbons), 163.6 (CO, β-lactam). GC–MS m/z=463 [M$^+$, ^{37}Cl], 461, 459 [M$^+$, ^{35}Cl]. Anal. Calcd for $C_{22}H_{16}Cl_2N_2O_5$: C, 57.53; H, 3.51; N, 6.10. Found: C, 57.48; H, 3.63; N, 6.12.

*4.3.5. 1-(4-Methoxyphenyl)-3-methoxy-4-p-tolylazetidin-2-one (**6r**).* White solid (0.27 g, 92%); mp: 151–153 °C. IR (KBr, cm^{-1}): 1748 (CO, β-lactam). ^{1}H NMR δ 2.34 (Me, s, 3H), 3.25, 3.91 (2OMe, 2s, 6H), 4.63 (H-4, d, 1H, J=5.1), 4.81 (H-3, d, 1H, J=5.1), 6.68–8.26 (ArH, m, 8H). ^{13}C NMR δ 20.4 (Me), 56.7, 58.1 (2OMe), 61.9 (C-4), 83.5 (C-3), 111.7, 119.5, 123.9, 127.0, 129.1, 133.6, 139.6, 156.7 (aromatic carbons), 164.1 (CO, β-lactam). GC–MS m/z=297 [M$^+$]. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.76; H, 6.41; N, 4.66.

*4.3.6. 1-(4-Ethoxyphenyl)-4-(4-methylphenyl)-3-vinylazetidin-2-one (**7c**).* White crystal (from hexane/EtOAc 9:1) (0.22 g, 73%); mp: 68–70 °C. IR ($CHCl_3$, cm^{-1}): 1743 (CO, β-lactam). ^{1}H NMR δ 1.28 (Me, t, 3H, J=6.9), 2.27 (Me, s, 3H), 3.61 (H-3, dd, 1H, J=2.3, 7.5), 3.85 (OCH_2, q, 2H, J=6.9), 4.65 (H-4, d, 1H, J=2.3), 5.19–5.30 (vinilic H, m, 2H), 5.75–5.81 (vinilic H, m, 1H), 6.66–7.37 (ArH, m, 8H). ^{13}C NMR δ 14.7 (Me), 21.2 (Me), 61.2 (OCH_2), 63.6 (C-3), 64.0 (C-4), 114.9, 119.7, 122.2, 126.6, 129.8, 131.0, 134.4, 139.4, 146.7, 155.4 (C=C, aromatic carbons), 164.1 (CO, β-lactam). GC–MS m/z=307 [M$^+$]. Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.06; H, 6.95; N, 4.49.

*4.3.7. 1-(4-Ethoxyphenyl)-3-(5-norbornene-2,3-dicarboxyloylimido)-4-(3,4-dimethoxy)-azetidin-2-one (**8c**).* Milky-coloured

solid (0.40 g, 81%); mp: 214–216 °C. IR ($CHCl_3$, cm^{-1}): 1738, 1766 (CO, imide), 1778 (CO, β-lactam). ^1H NMR δ 1.26 (Me, t, 3H, J=6.7), 1.42, 1.61 (H-11, 2d, 2H, J=8.3), 3.07 (H-5, d, 1H, J=5.1), 3.24 (H-10, d, 1H, J=5.1), 3.41–3.57 (H-6 and H-9, m, 2H), 3.69, 3.74 (2OMe, 2s, 6H), 3.83 (OCH_2, q, 2H, J=6.7), 4.85 (H-4, d, 1H, J=2.5), 4.96 (H-3, d, 1H, J=2.5), 6.07–6.16 (H-7 and H-8, m, 2H), 6.64–7.34 (ArH, m, 7H). ^{13}C NMR δ 15.7 (Me), 44.1, 44.7 (C-5, C-10), 46.1, 46.7 (C-6, C-9), 52.0 (C-11), 55.3, 55.4 (2 OMe), 56.4 (OCH_2), 61.0 (C-4), 62.8 (C-3), 109.7, 112.8, 113.6, 116.1, 119.7, 120.2, 128.2, 130.5, 133.2, 135.9, 149.6, 155.7 (C=C, aromatic carbons), 161.2 (CO, β-lactam), 176.4, 176.5 (CO, imide). GC–MS m/z=474 [M^+]. Anal. Calcd for $C_{27}H_{26}N_2O_6$: C, 68.34; H, 5.52; N, 5.90. Found: C, 68.39; H, 5.63; N, 5.97.

*4.3.8. 1-Benzyl-4-(4-chlorophenyl)-3-phenoxyazetidin-2-one (**9a**).* White solid (0.34 g, 93%); mp: 104–106 °C. IR ($CHCl_3$, cm^{-1}): 1741 (CO, β-lactam). ^1H NMR δ 3.85, 4.83 (CH_2-benzyl, 2d, 2H, J=14.7), 4.71 (H-4, d, 1H, J=4.3), 5.37 (H-3, d, 1H, J=4.3), 6.88–7.76 (ArH, m, 14H). ^{13}C NMR δ 44.4 (CH_2), 60.8 (C-3), 82.0 (C-4), 115.4, 122.2, 128.1, 128.3, 128.5, 128.7, 129.0, 129.3, 130.1, 131.5, 134.6, 156.7 (aromatic carbons), 165.4 (CO, β-lactam). GC–MS m/z=365 [M^+, ^{37}Cl], 363 [M^+, ^{35}Cl]. Anal. Calcd for $C_{22}H_{18}ClNO_2$: C, 72.62; H, 4.99; N, 3.85. Found: C, 72.75; H, 5.10; N, 3.78.

*4.3.9. 1-Benzyl-4-(4-chlorophenyl)-3-(2,4-dichlorophenoxy)-azetidin-2-one (**9b**).* White solid (0.37 g, 86%); mp: 74–76 °C. IR ($CHCl_3$, cm^{-1}): 1744 (CO, β-lactam). ^1H NMR δ 3.90, 4.82 (CH_2-benzyl, 2d, 2H, J=14.7), 4.74 (H-4, d, 1H, J=4.7), 5.34 (H-3, d, 1H, J=4.7), 6.91–7.74 (ArH, m, 12H). ^{13}C NMR δ 44.4 (CH_2), 60.2 (C-3), 82.3 (C-4), 114.7, 115.9, 117.0, 123.8, 127.3, 127.7, 128.1, 128.6, 129.0, 129.9, 130.1, 130.9, 134.7, 151.5 (aromatic carbons), 164.6 (CO, β-lactam). GC–MS m/z=437 [M^+, ^{37}Cl], 431 [M^+, ^{35}Cl]. Anal. Calcd for $C_{22}H_{16}Cl_3NO_2$: C, 61.06; H, 3.73; N, 3.24. Found: C, 61.00; H, 3.81; N, 3.33.

*4.3.10. 1-Benzyl-4-(4-nitrophenyl)-3-phenoxyazetidin-2-one (**9c**).* White solid (0.34 g, 91%); mp: 130–132 °C. IR ($CHCl_3$, cm^{-1}): 1738 (CO, β-lactam). ^1H NMR δ 3.99, 4.84 (CH_2-benzyl, 2d, 2H, J=14.7), 4.87 (H-4, d, 1H, J=4.5), 5.48 (H-3, d, 1H, J=4.5), 6.68–8.1 (ArH, m, 14H). ^{13}C NMR δ 44.9 (CH_2), 60.7 (C-3), 82.2 (C-4), 115.2, 122.4, 123.3, 128.3, 128.7, 129.0, 129.4, 129.5, 134.1, 140.6, 1480, 156.4 (aromatic carbons), 165.1 (CO, β-lactam). GC–MS m/z=374 [M^+]. Anal. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.49; H, 4.77; N, 7.40.

*4.3.11. (1-Methyl-2-oxo-4-p-tolylazetidin-3-yl)isoindoline-1,3-dione (**10a**).* White solid (0.24 g, 79%); mp: 176–178 °C. IR ($CHCl_3$, cm^{-1}): 1731, 1764 (CO, phth), 1782 (CO, β-lactam). ^1H NMR δ 2.37 (Me, s, 3H), 2.90 (Me–N, s, 3H), 4.88 (H-4, d, 1H, J=4.4), 5.16 (H-3, d, 1H, J=4.4), 7.22–7.86 (ArH, m, 8H). ^{13}C NMR δ 21.2 (Me), 27.4 (Me–N), 62.1 (C-4), 62.9(C-3), 123.6, 126.5, 129.9, 131.7, 132.5, 134.5, 139.0 (aromatic carbons), 164.9 (CO, phth), 166.9 (CO, β-lactam). GC–MS m/z=320 [M^+]. Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.18; H, 5.16; N, 8.62.

*4.3.12. 1-Methyl-3-phenoxy-4-p-tolylazetidin-2-one (**10b**).* White solid (0.22 g, 84%); mp: 102–104 °C. IR (KBr, cm^{-1}): 1751 (CO, β-lactam). ^1H NMR δ 2.31 (Me, s, 3H), 2.96 (Me–N, s, 3H), 5.25 (H-4, d, 1H, J=4.8), 5.47 (H-3, d, 1H, J=4.8), 6.51–7.53 (ArH, m, 9H). ^{13}C NMR δ 22.5 (Me), 28.2 (Me–N), 61.3 (C-4), 80.9 (C-3), 111.9, 124.8, 128.5, 130.3, 132.0, 136.7, 138.1, 156.9 (aromatic carbons), 161.7 (CO, β-lactam). GC–MS m/z=267 [M^+]. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.31; H, 6.50; N, 5.11.

*4.3.13. 4-(4-Chlorophenyl)-3-phenoxy-1-(4-(phenyldiazenyl)-phenyl)-azetidin-2-one (**11a**).* Orange solid (0.41 g, 90%); mp: 204–206 °C. IR (KBr, cm^{-1}): 1756 (CO, β-lactam). ^1H NMR δ 5.45 (H-4, d, 1H, J=5.0), 5.62 (H-3, d, 1H, J=5.0), 6.79–7.90 (ArH, m, 18H). ^{13}C NMR δ 61.6 (C-4), 81.3 (C-3), 115.6, 117.9, 118.3, 120.6, 122.5, 122.8, 124.2, 128.9, 129.1, 129.4, 130.8, 131.0, 134.3, 146.5, 153.1, 160.5 (aromatic carbons), 166.2 (CO, β-lactam). GC–MS m/z=455 [M^+, ^{37}Cl], 453 [M^+, ^{35}Cl]. Anal. Calcd for $C_{27}H_{20}ClN_3O_2$: C, 71.44; H, 4.44; N, 9.26. Found: C, 71.50; H, 4.39; N, 9.35.

*4.3.14. 3-(2,4-Dichlorophenoxy)-4-(4-nitrophenyl)-1-(4-(phenyldiazenyl)-phenyl)-azetidin-2-one (**11b**).* Orange solid (0.46 g, 87%); mp: 191–193 °C. IR ($CHCl_3$, cm^{-1}): 1752 (CO, β-lactam). ^1H NMR δ 5.63 (H-4, d, 1H, J=5.0), 5.80 (H-3, d, 1H, J=5.0), 6.86–8.18 (ArH, m, 16H). ^{13}C NMR δ 62.8 (C-4), 80.6 (C-3), 114.3, 115.9, 116.4, 118.8, 121.1, 122.0, 122.6, 125.7, 128.5, 128.9, 129.7, 130.2, 131.4, 135.2, 138.0, 142.9, 150.4, 158.8 (aromatic carbons), 164.7 (CO, β-lactam). GC–MS m/z=536 [M^+, ^{37}Cl], 532 [M^+, ^{35}Cl]. Anal. Calcd for $C_{27}H_{18}Cl_2N_4O_4$: C, 60.80; H, 3.40; N, 10.50. Found: C, 60.88; H, 3.51; N, 10.56.

*4.3.15. 3-(Naphthalen-2-yloxy)-4-(4-nitrophenyl)-1-(4-(phenyldiazenyl)-phenyl)-azetidin-2-one (**11c**).* Orange solid (0.47 g, 92%); mp: 220–222 °C. IR ($CHCl_3$, cm^{-1}): 1755 (CO, β-lactam). ^1H NMR δ 5.66 (H-4, d, 1H, J=5.0), 5.85 (H-3, d, 1H, J=5.0), 6.88–8.18 (ArH, m, 20H). ^{13}C NMR δ 61.3 (C-4), 81.4 (C-3), 109.1, 110.5, 112.8, 115.3, 117.9, 118.0, 122.8, 123.8, 124.4, 124.7, 126.8, 126.9, 127.8, 129.0, 129.1, 129.8, 129.9, 131.1, 133.8, 146.3, 150.7, 154.3 (aromatic carbons), 162.9 (CO, β-lactam). GC–MS m/z=514 [M^+]. Anal. Calcd for $C_{31}H_{22}ClN_3O_2$: C, 72.36; H, 4.31; N, 10.89. Found: C, 72.42; H, 4.43; N, 10.81.

*4.3.16. 3-Azido-1-(4-ethoxyphenyl)-4-(4-nitrophenyl)-azetidin-2-one (**14a**).* Light-yellow solid (0.24 g, 69%); mp: 101–103 °C. IR ($CHCl_3$, cm^{-1}): 2100 (N_3), 1748 (CO, β-lactam). ^1H NMR δ 1.37 (Me, t, 3H, J=6.9), 3.94 (OCH_2, q, 2H, J=6.9), 5.17 (H-4, d, 1H, J=5.3), 5.43 (H-3, d, 1H, J=5.3), 6.76–8.29 (ArH, m, 8H). ^{13}C NMR δ 14.7 (Me), 59.8 (OCH_2), 63.7 (C-3), 67.6 (C-4), 114.7, 117.7, 122.1, 125.1, 128.7, 140.6, 148.2, 160.6 (C=C, aromatic carbons), 165.1 (CO, β-lactam). GC–MS m/z=353 [M^+]. Anal. Calcd for $C_{17}H_{15}N_5O_4$: C, 57.79; H, 4.28; N, 19.82. Found: C, 57.88; H, 4.40; N, 19.90.

*4.3.17. 3-Azido-1,4-diphenylazetidin-2-one (**14b**).* Pale-yellow solid (0.17 g, 64%); mp: 96–98 °C. IR ($CHCl_3$, cm^{-1}): 2130 (N_3), 1745 (CO, β-lactam). ^1H NMR δ 4.95 (H-4, d, 1H, J=5.1), 5.39 (H-3, d, 1H, J=5.1), 6.54–7.51 (ArH, m, 10H). ^{13}C NMR δ 60.0 (C-3), 64.2 (C-4), 112.8, 115.1, 118.8, 120.9, 123.5, 127.3, 139.0, 151.1 (C=C, aromatic carbons), 160.4 (CO, β-lactam). GC–MS m/z=264 [M^+]. Anal. Calcd for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.06; H, 4.69; N, 21.13.

*4.3.18. 3-Azido-4-(4-chlorophenyl)-1-(4-methoxyphenyl)-azetidin-2-one (**14c**).* Pale-yellow solid (0.27 g, 72%); mp: 81–83 °C. IR ($CHCl_3$, cm^{-1}): 2117 (N_3), 1748 (CO, β-lactam). ^1H NMR δ 3.71 (OMe, s, 3H), 5.02 (H-4, d, 1H, J=5.3), 5.25 (H-3, d, 1H, J=5.3), 6.70–7.37 (ArH, m, 8H). ^{13}C NMR δ 55.4 (OMe), 60.1 (C-3), 67.4 (C-4), 114.3, 118.7, 125.1, 127.2, 129.4, 131.4, 143.5, 156.7 (C=C, aromatic carbons), 160.8 (CO, β-lactam). GC–MS m/z=330 [M^+, ^{37}Cl], 328 [M^+, ^{35}Cl]. Anal. Calcd for $C_{16}H_{13}ClN_4O_2$: C, 58.45; H, 10.78; N, 17.04. Found: C, 58.53; H, 10.85; N, 16.97.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.05.009. These data include MOL files and InChiKeys of the most important compounds described in this article.

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