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On-column N-dearylation of 2-azetidinones by silica-supported ceric ammonium nitrate

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ABSTRACT

A modified traditional preparative chromatographic column can be used to achieve quantitative N-dearylation of *N*-(alkoxyphenyl), *N*-(alkoxynaphthyl), and *N*-(alkoxybenzyl)-2-azetidinones under mild conditions. Starting materials are charged on top of the column and the pure *N*-unsubstituted 2-azetidinones leave the column minutes later without need for other purifications. The yields are good-to-excellent and the reaction condition is mild, easy, efficient, and cheap.

1. Introduction

Ceric ammonium nitrate (CAN) is a one-electron oxidant with advantages, such as low toxicity, ease of handling, and solubility in a number of organic solvents.[1] Ceric ammonium nitrate has proved to be very useful to synthetic organic chemists for several decades. The enormous growth in the use of this reagent is evidenced by the publication of a large number of research papers and several reviews concerning CAN-mediated reactions.[1,2]

2-Azetidinones, commonly known as β-lactams, are heterocyclic compounds well known to organic and medicinal chemists.[3] The activities of widely used antibiotics, such as penicillins, cephalosporins, carbapenems, monobactams, and nocardicins are attributed to the presence of 2-azetidinone ring.[4] Ezetimibe is a new drug, which has the 2-azetidinone skeleton and selectively inhibits the absorption of cholesterol.[5] Besides the antibacterial and cholesterol absorption inhibitory activities, β-lactams possess various other biological activities.[6] β-Lactams are not only useful in medicinal applications, but are also used as intermediates and synthon for the production of several organic compounds.[7] Several synthetic methods have been developed for the preparation of the β-lactam ring.[8]

N-Unsubstituted 2-azetidinones offer major synthetic opportunities in the synthesis of β-lactam antibiotics and the glutamine synthetase inhibitor, tabtoxin.[9] Application of *N*-unsubstituted 2-azetidinones in the semi-synthesis of the anticancer agents Taxol and Taxotere has been also reported.[10]

Routes to *N*-unsubstituted 2-azetidinones involve the reaction of *N*-trimethylsilyl imines with the corresponding compounds,[11] reaction of chlorosulfonyl isocyanate with alkenes[12] and N-deprotection of *N*-functionalized β-lactams. Several groups are often used for N-protection of β-lactams and can be deprotected in different methods to give *N*-unsubstituted β-lactams.[13] With few exceptions the yields are poor. Furthermore some methods need expensive and unavailable materials. Toxic and non-safe byproducts obtained in some cases together with difficulties of the purification of main products are other problems of these methods. Among these methods, oxidative cleavage by ceric ammonium nitrate of *p*-alkoxyphenyl moiety attached to the nitrogen of the β-lactam ring offers the most direct synthesis of *N*-unsubstituted β-lactams.[14] This reaction commonly is performed in aqueous acetonitrile and involves oxidation of the aromatic ring to benzoquinone with the release of 1 mol equiv of corresponding alcohol and 1 mol equiv of the cyclic amide (Scheme 1). The mechanism of this reaction has been reported by several groups.[14g,15]

Alumina, silica, and clays are of the most widely employed supports, where surface hydroxyl groups play a major role in these reactions. Amongst them silica is widely used as a supporting material since it presents desirable properties and silica gel plays an important role in fine organic synthesis.[14g,16]

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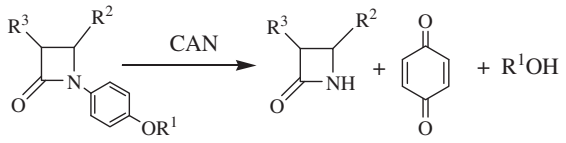


Scheme 1. Deprotection of β-lactams with CAN.

Ceric ammonium nitrate on silica gel (CAN–SiO_2) has been used for the removal of trityl and silyl groups,[17] oxidation of oxygenated aromatic compounds to quinones,[18] regeneration of carbonyl compounds from oximes, semicarbazones, phenylhydrazones,[19] nitration of aromatics, and heteroaromatics,[20] in the synthesis of 2,2-bis(*N*-methyl-3′-indolyl)-*N*-methylindoxyl[21] and oxidative deprotection of benzylic tetrahydropyranyl ethers.[22] High applications of ceric ammonium nitrate on silica gel (CAN–SiO_2) have made it commercially available.[23] In industry, reaction columns have been used for large-scale synthesis for quite some time; however, much of the technology is proprietary.[24]

In our recently reported letter,[25] we described the use of CAN–SiO_2 as an efficient reagent for N-dearylation of *N*-(*p*-methoxyphenyl) and *N*-(*p*-ethoxyphenyl) groups on β-lactams in solutions and on column reactions. The versatility and efficiency of the on column N-dearylation of several types of β-lactams is demonstrated in this paper.

2. Results and discussion

Ceric ammonium nitrate on silica gel was prepared as a yellowish solid by a reported method.[17] Based on earlier successful N-dearylations,[25,26] we decided to carry out these β-lactam N-dearylation reactions on a CAN–SiO_2 column. Also purification of the products was performed at the same time. The 10% CAN–SiO_2 column was chosen due to better filling height of the reaction zone. Our type A column was filled with silica gel and was topped with a band of 10% CAN–SiO_2, which conducted the reaction 'on-column', followed by 'in situ' purification of the products (Fig. 1). *cis*-β-Lactams **1a**–**i** were charged carefully onto the column in a little dichloromethane and the solvent was allowed to percolate down to the surface of silica gel. Then the column was eluted with THF/H_2O (19:1).

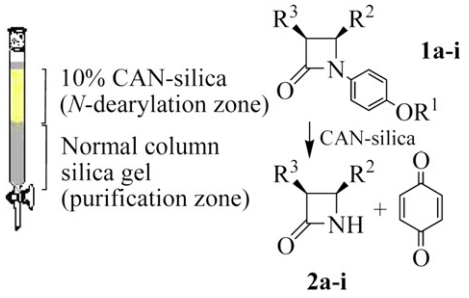


Fig. 1. Type A column.

After the addition of eluent the yellowish reaction zone turned to red. The resulting solution was collected in fractions (10–15 mL) and checked by TLC. At first *p*-benzoquinone eluted from the column and then, *N*-unsubstituted 2-azetidinones **2a**–**i** were isolated in excellent yields with high purities. The yields were comparable to those obtained in the solution phase reaction (Table 1).

Successful results obtained from type A on-column reaction and removal of *p*-benzoquinone by Na_2SO_3 solution by the general procedure, promoted us to create a type B on-column reaction. The type B column was packed from the bottom: a little silica gel (~1 cm), 10% SiO_2–Na_2SO_3, 10% CAN–SiO_2, and a little silica gel (Fig. 2).

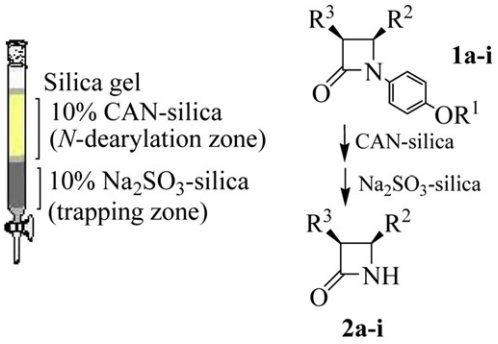


Fig. 2. Type B column.

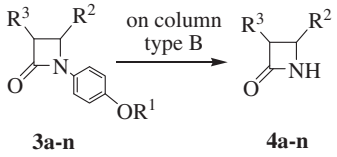
β-Lactams **1a**–**i** were charged onto the type B column and in the N-dearylation zone, they were converted to *N*-unsubstituted β-lactams **2a**–**i** and the benzoquinone byproduct was trapped in the trapping zone (Na_2SO_3–SiO_2). A clear and colorless solution was eluted from the column, which contained only *N*-unsubstituted β-lactam. The pure NH-β-lactams **2a**–**i** were obtained in excellent yields after removal of solvent under reduced pressure. A change of color from yellow to red in the N-dearylation zone and from white to dark-brown in the trapping zone was indicative of the deprotection and the trapping of benzoquinone, respectively.

On the basis of these successful results, the N-dearylation of β-lactams **3a**–**n** with 'on column type B' was performed and *N*-unsubstituted β-lactams **4a**–**n** were obtained in good-to-excellent yields without any further purification (Scheme 2, Table 2). β-Lactams **3h**–**n** containing electron withdrawing substituents on position 3 also resulted in excellent yields. Especially N-dearylation of 3-chloro β-lactams **3h**–**i** using 'on column type B' showed better results than AgO[13q] and CoF_3.[13p]

Encouraged by above successful results, we next investigated the oxidative N-dearylation of other types of *N*-alkoxyphenyl-β-

Table 1
Solution phase and 'on-column' synthesis of deprotected *cis*-β-lactams **2a**–**i**

Substrate	R^1	R^2	R^3	Product	Isolated yield (%) by 10% CAN–SiO_2				Isolated yield (%) by CAN
					CH_3CN/H_2O	CH_2Cl_2/H_2O	On column A	On column B	
1a	Me	3,4-$DiMeOC_6H_3$	PhO	**2a**	94	81	91	94	83
1b	Me	2,3-$DiMeOC_6H_3$	PhO	**2b**	86	73	83	88	77
1c	Me	3,4-$DiMeOC_6H_3$	3-NO_2PhthN	**2c**	88	68	90	87	79
1d	Et	CH=CHPh	PhthN	**2d**	91	74	87	93	71
1e	Et	4-$MeOC_6H_4$	PhO	**2e**	85	74	85	89	85
1f	Et	CH=CHPh	PhO	**2f**	93	79	91	90	78
1g	Et	4-$NO_2C_6H_4$	2-NaphthO	**2g**	82	71	88	92	80
1h	Et	4-$NO_2C_6H_4$	2,4-$DiClC_6H_3O$	**2h**	91	80	90	94	74
1i	Et	4-MeC_6H_4	MeO	**2i**	84	75	86	87	85

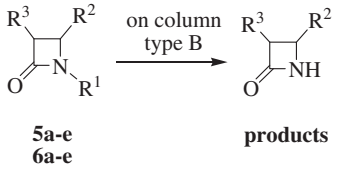


Scheme 2. N-Dearylation of β-lactams **3a**–**n** with 'on column type B'.

Table 2
N-Dearylation of β-lactams **3a**–**n** with 'on column type B'

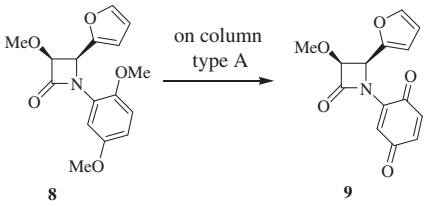
Substrate	R^1	R^2	R^3	Stereochemistry	Products	Isolated yield (%)
3a	Me	3-$NO_2C_6H_4$	2,4-$DiClC_6H_3O$	Cis	**4a**	80
3b	Et	4-ClC_6H_4	2,4-$DiClC_6H_3O$	Cis	**4b**	86
3c	Et	4-$NO_2C_6H_4$	MeO	Cis	**4c**	88
3d	Me	4-$NO_2C_6H_4$	4-ClC_6H_4O	Cis	**4d**	81
3e	Me	4-$MeOC_6H_4$		Trans	**4e**	78
3f	Et	4-$NO_2C_6H_4$		Trans	**4f**	80
3g	Me	4-ClC_6H_4		Trans	**4g**	74
3h	Me	4-$MeOC_6H_4$	Cl	Cis	**4h**	82
3i	Me	C_6H_5	Cl	Cis	**4i**	84
3j	Et	4-ClC_6H_4	Cl	Cis	**4j**	85
3k	Et	4-MeC_6H_4	N_3	Cis	**4k**	79
3l	Me	4-ClC_6H_4	N_3	Cis	**4l**	81
3m	Me	4-$MeOC_6H_4$	$MeSO_2$	Cis	**4m**	80
3n	Me	4-ClC_6H_4	$MeSO_2$	Cis	**4n**	77

lactams. Treatment of *N*-(2,4-dimethoxyphenyl)-β-lactams **5a**–**e** and *N*-(3,4-dimethoxyphenyl)-β-lactams **6a**–**e** with 'on column type B' afforded the pure corresponding NH-β-lactams in excellent yields (Scheme 3, Table 3). The mechanism is similar to 4-(methoxyphenyl)-β-lactams and the resulted benzoquinone derivatives were trapped in the trapping zone (Na_2SO_3–SiO_2).



Scheme 3. N-Dearylation of β-lactams **5a**–**e** and **6a**–**e** with 'on column type B'.

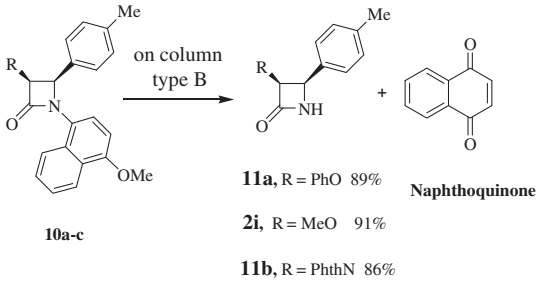
Treatment of *N*-(2,5-dimethoxyphenyl)-β-lactam **8** with 'on column type A' produced β-lactam **9** bearing a quinone moiety at N1-position and no NH-2-azetidinones were found (Scheme 4). 'On column type B' is not useful for β-lactams like **8** because the products will be trapped in the trapping zone (Na_2SO_3–SiO_2).



Scheme 4. Reaction of β-lactam **8** with 'on column type A'.

It is noteworthy that Alcaide and co-workers have synthesized β-lactams bearing a quinone moiety at N1, C3 or C4 positions from 2,5-dimethoxyphenyl substituted β-lactams using ceric ammonium nitrate (CAN) in aqueous acetonitrile.[27]

It is reasonable to assume that 4-methoxynaphthyl group resembles the 4-methoxyphenyl group. Therefore 2-azetidinones **10a**–**c** containing the 4-methoxynaphthyl group on N1-position were prepared using [2+2] ketene–imine cycloaddition. When 2-azetidinones **10a**–**c** were treated with 'on column type B', only the corresponding NH-2-azetidinones were obtained from the column. But treatment of 2-azetidinones **10a**–**c** with 'on column type A' resulted in both the corresponding NH-2-azetidinones and naphthoquinone (compared with authentic sample) (Scheme 5). The resulted naphthoquinone was trapped in the trapping zone (Na_2SO_3–SiO_2) of 'on column type B'. The 4-methoxynaphthyl group was oxidized better than the *p*-methoxyphenyl group (compare R=MeO in Scheme 3 and compound **1i** in Table 1).



Scheme 5. Removal of 4-methoxynaphthyl group from N1-position of β-lactams by 'on column type B'.

Treatment of Schiff bases derived from anthracene-9-carbaldehyde or 9*H*-fluoren-9-one with 9*H*-xanthene-9-carboxylic acid in the presence of triethylamine and tosyl chloride afforded polycyclic aromatic spiro-β-lactams **12a**–**c**[28] and dispiro-β-lactams **13a**,**b**,[29] respectively.

The crystal structure of β-lactam **12a**[30a] (Fig. 3) and **12b**[30b] have been reported previously. Using the 'on column type B', spiro-β-lactams **12a**–**c** and dispiro-β-lactams **13a**,**b** were converted into the corresponding NH-β-lactams **14** and **15**, in good-to-excellent yields (Scheme 6).

Table 3
N-Dearylation of β-lactams **5a**–**e** and **6a**–**e** with 'on column type B'

Substrate	R^1	R^2	R^3	Stereochemistry	Product	Isolated yield (%)
5a	2,4-$DiMeOC_6H_3$	3,4-$DiMeOC_6H_3$	PhO	Cis	**2a**	84
5b	2,4-$DiMeOC_6H_3$	2-$NO_2C_6H_4$	PhO	Cis	**7a**	78
5c	2,4-$DiMeOC_6H_3$	3-$MeOC_6H_4$	PhO	Cis	**7b**	81
5d	2,4-$DiMeOC_6H_3$	3-$NO_2C_6H_4$	PhthN	Trans	**7c**	80
5e	2,4-$DiMeOC_6H_3$	3-$MeOC_6H_4$	PhthN	Trans	**7d**	83
6a	3,4-$DiMeOC_6H_3$	4-$NO_2C_6H_4$	PhO	Cis	**7e**	85
6b	3,4-$DiMeOC_6H_3$	4-$MeOC_6H_4$	PhO	Cis	**2e**	80
6c	3,4-$DiMeOC_6H_3$	3,4-$DiMeOC_6H_3$	PhO	Cis	**2a**	84
6d	3,4-$DiMeOC_6H_3$	4-$NO_2C_6H_4$	PhthN	Trans	**7f**	78
6e	3,4-$DiMeOC_6H_3$	4-$MeOC_6H_4$	PhthN	Trans	**7g**	82

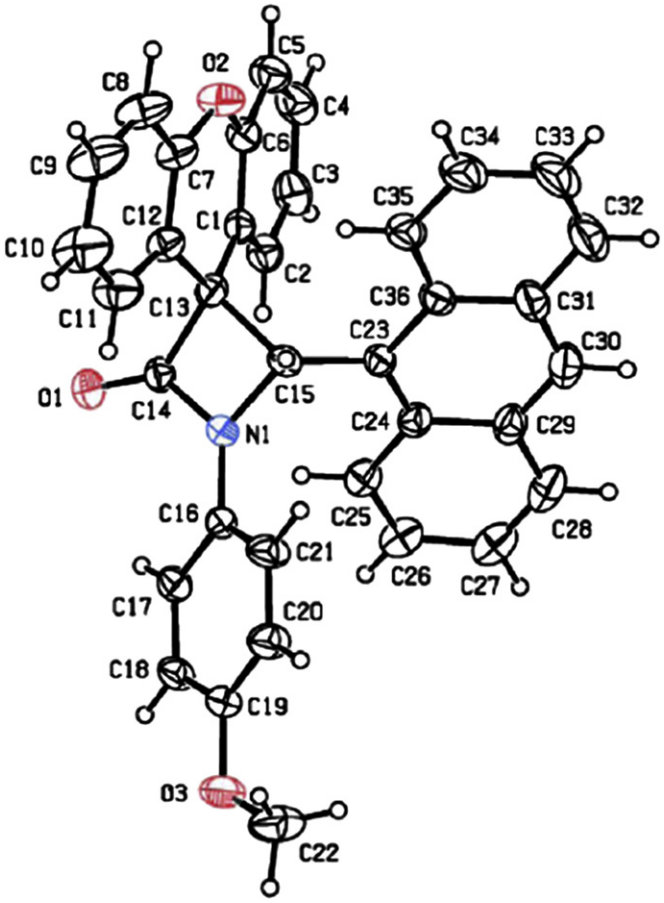


Fig. 3. ORTEP diagram of β-lactam **12a**.

Bisulfite addition products are formed from aldehydes upon treatment with sodium bisulfite. The reaction is reversible (by treatment of the addition product with either acid or base) and is useful for the purification of the starting compounds.[32] Treatment of β-lactams **16a**–**d** with 'on column type B' afforded a mixture of *N*-unsubstituted 2-azetidinones **17a**–**d** and *p*-methoxybenzaldehyde. The pure *N*-unsubstituted 2-azetidinones **17a**–**d** were obtained after evaporation of solvents and crystallization from Et_2O. The acidic property of silica gel is the cause of reversibility of bisulfite addition reaction. The above facts encouraged us to create 'on column type C' for the N-dearylation of *N*-(*p*-methoxybenzyl)-β-lactams **16a**–**d** without need to further purification. 'On column type C' was packed like 'on column type B', but the trapping zone is $NaHSO_3$ supported on neutral alumina ($NaHSO_3$–Al_2O_3) for the trapping of *p*-methoxybenzaldehyde (Fig. 4). The pure NH-β-lactams **17a**–**d** were obtained from *N*-(*p*-methoxybenzyl)-β-lactams **16a**–**d** in excellent yields using 'on column type C' after removal of solvent under reduced pressure (Table 4).

All products were characterized by spectral data and elemental analyses.

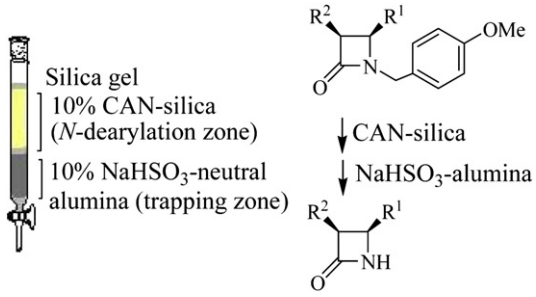
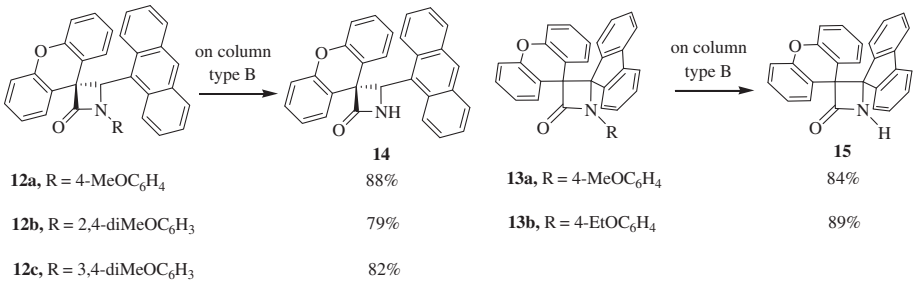


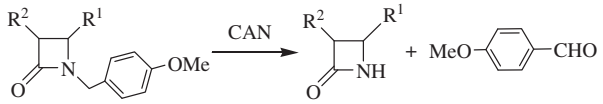
Fig. 4. Type C column.



	14		**15**
12a, R = 4-$MeOC_6H_4$	88%	**13a**, R = 4-$MeOC_6H_4$	84%
12b, R = 2,4-di$MeOC_6H_3$	79%	**13b**, R = 4-$EtOC_6H_4$	89%
12c, R = 3,4-di$MeOC_6H_3$	82%		

Scheme 6. N-Dearylation of spiro-β-lactams **12a**–**c** and dispiro-β-lactams **13a**,**b** using the 'on column type B'.

This method was also extended to the N-dearylation of *N*-(*p*-methoxybenzyl)-β-lactams. N-Dearylation of *N*-(*p*-methoxybenzyl)-β-lactams using ceric ammonium nitrate in aqueous acetonitrile has been reported.[31] *p*-Methoxybenzaldehyde is the byproduct of this reaction (Scheme 7). β-Lactams **16a**–**d** were synthesized by the [2+2] ketene–imine cycloaddition reaction and then charged to 'on column type A'. First *p*-methoxybenzaldehyde was eluted from the column and then *N*-unsubstituted 2-azetidinones **17a**–**d** were eluted with THF/H_2O (19:1).



16a-d **17a-d**

Scheme 7. N-Dearylation of *N*-(*p*-methoxybenzyl)-β-lactams **16a**–**d**.

Table 4
On-column N-dearylation of *N*-(*p*-methoxybenzyl)-β-lactams **16a**–**d**

Substrate	R^1	R^2	Product	Isolated yield (%) by 10% CAN-SiO_2		
				On column A	On column B	On column C
16a	4-$NO_2C_6H_4$	PhO	**17a**	77	69	75
16b	4-$NO_2C_6H_4$	PhthN	**17b**	80	78	84
16c	4-ClC_6H_4	MeO	**17c**	78	71	80
16d	4-ClC_6H_4	2-NaphthO	**17d**	85	76	88

3. Conclusion

In summary, silica-supported ceric ammonium nitrate (CAN–SiO_2) serves as a convenient and effective reagent for on column N-dearylation of β-lactams. 'On column type A' provides N-

dearylation and subsequent in situ separation to give NH-β-lactams. In addition, 'on column type B' and 'on column type C' containing the trapping zone for the removal of byproducts provide easy and efficient methods for obtaining pure NH-β-lactams in good-to-excellent yields.

4. Experimental section

4.1. Chemical reagents

All needed chemicals were purchased from Merck, Fluka, and Acros chemical companies. IR spectra were run on a Shimadzu FT-IR 8300 spectrophotometer or galaxy series FT-IR 5000 spectrometer. ^{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) or Bruker spectrophotometer (^{1}H NMR 300 MHz, ^{13}C NMR 75 MHz). Chemical shifts were reported in parts per million (δ) downfield from TMS. All of the coupling constants (J) are in Hertz. Elemental analyses were run on a Thermo Finnigan Flash EA-1112 series or on a Vario EL III elemental analyzer. Melting points were determined in open capillaries with Buchi 510 melting point apparatus. Thin-layer chromatography was carried out on silica gel 254 analytical sheets obtained from Fluka. Column chromatography was performed on Merck Kiesel gel (230–270 mesh). [2+2] Ketene–imine cycloaddition was chosen for preparation of β-lactams and spectral data for **1a**–**i**, **3a**–**n**, **12a**–**c**, and **13a**,**b** have been previously reported.[28,29,33] Spectral data for the NH-2-azetidinones **2a**–**i**, **4b**,**c**, **4e**,**g**–**i**, **7e**–**g**, **11a**, **17a**,**b**, and **17d** have been previously reported.[13e,p,q,14e–h,25]

4.2. General procedure for on-column N-dearylation reactions

(a) '*On column type A*'. A 48×2 cm^2 glass column was packed with silica gel (4.5 g, ~ 4.0 cm) and was topped up with 10% CAN–SiO_2 (12.0 g, ~11.5 cm). Then 2-azetidinone (1.0 mmol) in a little dichloromethane was charged onto the column and was allowed to stand at room temperature for 10–15 min. The column was then eluted with 19:1 THF–water to afford firstly *p*-benzoquinone followed by pure *N*-unsubstituted β-lactam.

(b) '*On column type B*'. A 48×2 cm^2 glass column was packed from the bottom: a little silica gel (~1 cm), 10% Na_2SO_3–SiO_2 (6.0 g, ~4.5 cm), 10% CAN–SiO_2 (12.0 g, ~ 11.5 cm), and a little of silica gel on top. β-Lactam (1.0 mmol) in dichloromethane (1.0–1.5 mL) was then charged onto the column. After 15 min the column was eluted with 19:1 THF–water to afford pure *N*-unsubstituted β-lactam and *p*-benzoquinone was trapped in the column.

(c) '*On column type C*'. A 48×2 cm^2 glass column was packed from the bottom: a little silica gel (~1 cm), 10% $NaHSO_3$–neutral Al_2O_3 (7.5 g, ~5.5 cm), 10% CAN–SiO_2 (12.0 g, ~11.5 cm), and a little of silica gel on top. β-Lactam (1.0 mmol) in dichloromethane (1.0–1.5 mL) was then charged onto the column. After 15 min the column was eluted with 19:1 THF–water to afford pure *N*-unsubstituted β-lactam and *p*-methoxybenzaldehyde was trapped in the column.

*4.2.1. cis-3-(2,4-Dichlorophenoxy)-4-(3-nitrophenyl)azetidin-2-one (**4a**).* Light-yellow solid (0.28 g, 80%). Mp: 156–158 °C. R_f=0.38 (3:7 hexane/EtOAc); IR (KBr) cm^{-1}: 1344, 1515 (NO_2), 1773 (CO, β-lactam), 3388 (NH); ^{1}H NMR (250 MHz, DMSO-d_6) δ 5.48 (H-3, d, 1H, J=4.7), 5.69 (H-4, dd, 1H, J=4.7, 2.8), 7.19–8.09 (ArH, m, 7H), 9.04 (NH, br s, 1H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 58.3 (C-4), 80.7 (C-3), 118.1, 120.3, 122.8, 126.0, 128.1, 129.0, 132.8, 133.5, 135.9, 143.7, 147.1, 158.3 (aromatic carbons), 163.8 (CO, β-lactam); Anal. Calcd for $C_{15}H_{10}Cl_2N_2O_4$: C, 51.01; H, 2.85; N, 7.93. Found: C, 51.10; H, 2.94; N, 7.86.

*4.2.2. cis-3-(4-Chlorophenoxy)-4-(4-nitrophenyl)azetidin-2-one (**4d**).* Light-yellow solid (0.26 g, 81%). Mp: 149–151 °C. R_f=0.34 (3:7 hexane/EtOAc); IR (KBr) cm^{-1}: 1338, 1529 (NO_2), 1770 (CO, β-lactam), 3375 (NH); ^{1}H NMR (250 MHz, DMSO-d_6) δ 5.29 (H-3, d, 1H, J=5.0), 5.69 (H-4, dd, 1H, J=5.0, 2.6), 7.05–8.11 (ArH, m, 8H), 9.10 (NH, br s, 1H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 56.2 (C-4), 82.6 (C-3), 116.3, 125.5, 127.3, 130.0, 134.9, 141.1, 145.8, 159.5 (aromatic carbons), 161.3 (CO, β-lactam); Anal. Calcd for $C_{15}H_{11}ClN_2O_4$: C, 56.53; H, 3.48; N, 8.79. Found: C, 56.61; H, 3.60; N, 8.84.

*4.2.3. trans-4-(4-Nitrophenyl)-3-vinylazetidin-2-one (**4f**).* White solid (0.17 g, 80%). Mp: 56–58 °C. R_f=0.45 (3:7 hexane/EtOAc); IR (KBr) cm^{-1}: 1346, 1518 (NO_2), 1761 (CO, β-lactam), 3370 (NH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.75 (H-3, dd, 1H, J=7.7, 2.4), 4.80 (H-4, dd, 1H, J=3.1, 2.4), 5.18–5.30 (vinilic H, m, 2H), 5.88–6.00 (vinilic H, m, 1H), 6.75–8.07 (ArH, m, 4H), 9.14 (NH, br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 66.1 (C-3), 67.9 (C-4), 114.6, 117.5, 127.0, 139.3, 141.8, 159.2 (C=C, aromatic carbons), 162.4 (CO, β-lactam); Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.47; H, 4.72; N, 12.76.

*4.2.4. cis-3-Chloro-4-(4-chlorophenyl)azetidin-2-one (**4j**).* White solid (0.18 g, 85%). Mp: 78–80 °C. R_f=0.48 (4:6 hexane/EtOAc); IR (KBr) cm^{-1}: 1761 (CO, β-lactam), 3436 (NH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.60 (H-4, dd, 1H, J=4.8, 2.3), 5.08 (H-3, d, 1H, J=4.8), 6.84–7.35 (ArH, m, 4H), 9.13 (NH, br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 60.9 (C-4), 67.1 (C-3), 112.7, 122.0, 130.3, 152.8 (aromatic carbons), 163.5 (CO, β-lactam); Anal. Calcd for $C_9H_7Cl_2NO$: C, 50.03; H, 3.27; N, 6.48. Found: C, 50.14; H, 3.42; N, 6.55.

*4.2.5. cis-3-Azido-4-p-tolylazetidin-2-one (**4k**).* Pale-yellow solid (0.16 g, 79%). Mp: 97–99 °C. R_f=0.44 (3:7 hexane/EtOAc); IR (KBr) cm^{-1}: 2129 (N_3), 1762 (CO, β-lactam), 3414 (NH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (Me, s, 3H), 4.96 (H-4, dd, 1H, J=5.0, 2.8), 5.47 (H-3, d, 1H, J=5.0), 6.93–7.41 (ArH, m, 4H), 9.03 (NH, br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.6 (Me), 61.8 (C-3), 67.5 (C-4), 120.5, 128.3, 140.9, 146.2 (aromatic carbons), 164.4 (CO, β-lactam). Anal. Calcd for $C_{10}H_{10}N_4O$: C, 59.40; H, 4.98; N, 27.71. Found: C, 59.47; H, 5.09; N, 27.63.

*4.2.6. cis-3-Azido-4-(4-chlorophenyl)azetidin-2-one (**4l**).* Pale-yellow solid (0.18 g, 81%). Mp: 86–88 °C. R_f=0.42 (3:7 hexane/EtOAc); IR (KBr) cm^{-1}: 2118 (N_3), 1758 (CO, β-lactam), 3402 (NH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.84 (H-4, dd, 1H, J=4.7, 3.1), 5.39 (H-3, d, 1H, J=4.7), 6.90–7.37 (ArH, m, 4H), 8.94 (NH, br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 63.6 (C-3), 66.2 (C-4), 122.4, 127.0, 138.6, 147.4 (aromatic carbons), 162.5 (CO, β-lactam). Anal. Calcd for $C_9H_7ClN_4O$: C, 48.55; H, 3.17; N, 25.17. Found: C, 48.51; H, 3.26; N, 25.12.

*4.2.7. cis-4-(4-Methoxyphenyl)-3-(methylsulfonyl)azetidin-2-one (**4m**).* White solid (0.20 g, 80%). Mp: 103–105 °C. R_f=0.39 (2:8 hexane/EtOAc); IR (KBr) cm^{-1}: 1154, 1322 (SO_2), 1768 (CO, β-lactam), 3357 (NH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.21 (SO_2–Me, s, 3H), 3.58 (OMe, s, 3H), 4.40 (H-4, dd, 1H, J=4.5, 2.8), 5.38 (H-3, d, 1H, J=4.5), 6.88–7.55 (ArH, m, 4H), 9.05 (NH, br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 35.1 (SO_2–Me), 55.9 (OMe), 65.1 (C-4), 81.7 (C-3), 113.4, 126.4, 137.9, 155.7 (aromatic carbons), 161.6 (CO, β-lactam). Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49. Found: C, 51.87; H, 5.31; N, 5.56.

*4.2.8. cis-4-(4-Chlorophenyl)-3-(methylsulfonyl)azetidin-2-one (**4n**).* White solid (0.20 g, 77%). Mp: 109–111 °C. R_f=0.38 (2:8

hexane/EtOAc); IR (KBr) cm^{-1}: 1149, 1330 (SO_2), 1764 (CO, β-lactam), 3344 (NH); ^1H NMR (300 MHz, DMSO-d_6) δ 3.29 (SO_2–Me, s, 3H), 4.35 (H-4, dd, 1H, J=4.7, 2.5), 5.28 (H-3, d, 1H, J=4.7), 6.93–7.36 (ArH, m, 4H), 9.11 (NH, br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 34.0 (SO_2-Me), 66.6 (C-4), 80.9 (C-3), 116.1, 127.7, 141.3, 153.9 (aromatic carbons), 162.8 (CO, β-lactam). Anal. Calcd for $C_{10}H_{10}ClNO_3S$: C, 46.25; H, 3.88; N, 5.39. Found: C, 46.38; H, 4.02; N, 5.31.

*4.2.9. cis-(2,4-Dimethoxyphenyl)-4-(3,4-dimethoxyphenyl)-3-phenoxyazetidin-2-one (**5a**).* White solid (0.40 g, 91%). Mp: 116–118 °C. R_f=0.51 (7:3 hexane/EtOAc); IR (KBr) cm^{-1}: 1758 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 3.64–3.70 (4OMe, 4s, 12H), 5.51 (H-3, 4s, 2H, J=4.4), 6.30–7.59 (ArH, m, 11H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 55.48, 55.55, 55.68, 55.86 (4OMe), 64.94 (C-4), 82.01 (C-3), 99.64, 104.46, 110.44, 111.22, 115.51, 117.75, 121.19, 121.88, 125.30, 126.44, 128.78, 129.20, 130.89, 148.47, 148.90, 153.00, 157.02, 158.89 (aromatic carbons), 164.58 (CO, β-lactam); Anal. Calcd for $C_{25}H_{25}NO_6$: C, 68.95; H, 5.79; N, 3.22. Found: C, 68.47; H, 5.93; N, 3.73.

*4.2.10. cis-4-(2-Nitrophenyl)-3-phenoxyazetidin-2-one (**7a**).* Light-yellow solid (0.22 g, 78%). Mp: 127–129 °C. R_f=0.40 (3:7 hexane/EtOAc); IR (KBr) cm^{-1}: 1355, 1532 (NO_2), 1771 (CO), 3240 (NH); ^1H NMR (250 MHz, DMSO-d_6) δ 5.12 (H-3, d, 1H, J=5.1), 5.40 (H-4, dd, 1H, J=5.1, 2.6), 6.81–8.06 (ArH, m, 9H), 9.10 (NH, br s, 1H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 55.2 (C-4), 84.6 (C-3), 114.6, 119.1, 122.8, 125.9, 127.3, 137.0, 139.4, 142.6, 146.3, 159.5 (aromatic carbons), 161.6 (CO, β-lactam); Anal. Calcd for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25; N, 9.85. Found: C, 63.30; H, 4.31; N, 9.79.

*4.2.11. cis-4-(3-Methoxyphenyl)-3-phenoxyazetidin-2-one (**7b**).* White solid (0.22 g, 81%). Mp: 137–139 °C. R_f=0.47 (4:6 hexane/EtOAc); IR (KBr) cm^{-1}: 1771 (CO), 3414 (NH); ^1H NMR (250 MHz, DMSO-d_6) δ 3.46 (MeO, s, 3H), 5.00 (H-3, d, 1H, J=4.3), 5.38 (H-4, dd, 1H, J=4.3, 1.7), 6.82–7.24 (ArH, m, 9H), 9.05 (NH, br s, 1H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 55.3 (OMe), 56.6 (C-4), 82.1 (C-3), 107.3, 110.5, 113.8, 126.3, 127.5, 133.8, 135.0, 139.3, 144.1, 158.1 (aromatic carbons), 161.6 (CO, β-lactam); Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.44; H, 5.73; N, 5.14.

*4.2.12. trans-2-(2-(3-Nitrophenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**7c**).* Light-yellow solid (0.27 g, 80%). Mp: 188–190 °C. R_f=0.35 (2:8 hexane/EtOAc); IR ($CHCl_3$) cm^{-1}: 1353, 1547 (NO_2), 1739, 1771 (CO, phth), 1783 (CO, β-lactam), 3367 (NH); ^1H NMR (250 MHz, DMSO-d_6) δ 4.81 (H-3, d, 1H, J=2.3), 5.62 (H-4, dd, 1H, J=2.3, 1.5), 7.02–8.00 (ArH, m, 8H), 9.04 (NH, br s, 1H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 56.7 (C-4), 63.8 (C-3), 117.1, 119.5, 125.3, 128.1, 130.6, 132.3, 141.4, 145.9, 150.4 (aromatic carbons), 161.5 (CO, phth), 165.8 (CO, β-lactam); Anal. Calcd for $C_{17}H_{11}N_3O_5$: C, 60.54; H, 3.29; N, 12.46. Found: C, 60.46; H, 3.39; N, 12.41.

*4.2.13. trans-2-(2-(3-Methoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**7d**).* White crystalline solid (0.27 g, 83%). Mp: 171–173 °C. R_f=0.42 (2:8 hexane/EtOAc); IR ($CHCl_3$) cm^{-1}: 1731, 1772 (CO, phth), 1784 (CO, β-lactam), 3342 (NH); ^1H NMR (250 MHz, DMSO-d_6) δ 3.68 (OMe, s, 3H), 5.08 (H-3, d, 1H, J=2.4), 5.14 (H-4, dd, 1H, J=2.4, 1.8), 7.16–8.19 (ArH, m, 8H), 9.06 (NH, br s, 1H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 56.4 (OMe), 57.9 (C-4), 63.5 (C-3), 109.8, 115.3, 123.8, 128.5, 133.1, 137.7, 142.9, 144.0, 157.3 (aromatic carbons), 165.7 (CO, phth), 166.5 (CO, β-lactam); Anal. Calcd for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.14; H, 4.47; N, 8.71.

*4.2.14. cis-1-(4-Methoxynaphthalen-1-yl)-3-phenoxy-4-p-tolyl-azetidin-2-one (**10a**).* White solid (0.38 g, 92%). Mp: 182–184 °C. R_f=0.53 (7:3 hexane/EtOAc); IR (KBr) cm^{-1}: 1751 (CO, β-lactam); ^1H NMR (300 MHz, $CDCl_3$) δ 2.44 (Me, s, 3H), 3.62 (OMe, s, 3H), 5.27 (H-4, d, 1H, J=4.8), 5.57 (H-3, d, 1H, J=4.8), 6.75–8.03 (ArH, m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5 (Me), 55.6 (OMe), 61.4 (C-4), 83.3 (C-3), 107.4, 109.7, 111.0, 112.8, 113.3, 115.9, 117.4, 118.5, 119.1, 122.4, 130.8, 131.5, 132.2, 137.9, 147.4, 150.8, 152.7, 157.5 (aromatic carbons), 163.4 (CO, β-lactam); Anal. Calcd for $C_{27}H_{23}NO_3$: C, 79.20; H, 5.66; N, 3.42. Found: C, 79.31; H, 5.80; N, 3.49.

*4.2.15. cis-3-Methoxy-1-(4-methoxynaphthalen-1-yl)-4-p-tolyl-azetidin-2-one (**10b**).* White solid (0.29 g, 84%). Mp: 135–137 °C. R_f=0.48 (7:3 hexane/EtOAc); IR (KBr) cm^{-1}: 1745 (CO, β-lactam); ^1H NMR (300 MHz, $CDCl_3$) δ 2.48 (Me, s, 3H), 3.29, 3.62 (2OMe, s, 6H), 4.84 (H-4, d, 1H, J=4.5), 5.26 (H-3, d, 1H, J=4.6), 6.72–7.85 (ArH, m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7 (Me), 56.3, 57.1 (OMe), 63.7 (C-4), 82.8 (C-3), 108.8, 110.6, 112.3, 112.8, 118.0, 119.1, 123.9, 124.5, 131.9, 133.4, 136.2, 143.9, 151.6, 154.6 (aromatic carbons), 162.1 (CO, β-lactam); Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.14; H, 6.17; N, 3.95.

*4.2.16. cis-2-(1-(4-Methoxynaphthalen-1-yl)-2-oxo-4-p-tolylazetidin-3-yl)-isoindoline-1,3-dione (**10c**).* White solid (0.40 g, 87%). Mp: 201–203 °C. R_f=0.43 (7:3 hexane/EtOAc); IR (KBr) cm^{-1}: 1738, 1776 (CO, phth), 1781 (CO, β-lactam); ^1H NMR (300 MHz, $CDCl_3$) δ 2.44 (Me, s, 3H), 3.58 (OMe, s, 3H), 5.26 (H-4, d, 1H, J=4.7), 5.39 (H-3, d, 1H, J=4.7), 6.77–7.94 (ArH, m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2 (Me), 56.7 (OMe), 61.2 (C-4), 64.2 (C-3), 106.4, 109.2, 111.4, 113.1, 113.6, 113.9, 120.3, 122.4, 122.9, 123.5, 124.1, 127.9, 132.3, 134.6, 139.7, 140.3, 149.4, 153.7 (aromatic carbons), 160.9 (CO, phth), 163.5 (CO, β-lactam); Anal. Calcd for $C_{29}H_{22}N_2O_4$: C, 75.31; H, 4.79; N, 6.06. Found: C, 75.40; H, 4.93; N, 6.13.

*4.2.17. cis-2-(2-Oxo-4-p-tolylazetidin-3-yl)isoindoline-1,3-dione (**11b**).* White solid (0.26 g, 86%). Mp: 193–195 °C. R_f=0.44 (2:8 hexane/EtOAc); IR (KBr) cm^{-1}: 1736, 1772 (CO, phth), 1781 (CO, β-lactam), 3486 (NH); ^1H NMR (300 MHz, DMSO-d_6) δ 2.32 (Me, s, 3H), 4.86 (H-4, dd, 1H, J=3.3, 4.9), 5.13 (H-3, d, 1H, J=4.9), 7.17–8.01 (ArH, m, 8H), 9.09 (NH, br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.0 (Me), 56.2 (C-4), 61.7 (C-3), 120.1, 125.6, 126.2, 129.8, 137.2, 139.5, 147.4 (aromatic carbons), 163.7 (CO, phth), 165.2 (CO, β-lactam); Anal. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.48; H, 4.73; N, 9.24.

*4.2.18. 2-(Anthracen-9-yl)spiro[azetidine-3,9′-xanthen]-4-one (**14**).* Light-yellow solid (0.36 g, 88%). Mp: 211–213 °C. R_f=0.47 (5:5 hexane/EtOAc); IR (KBr) cm^{-1}: 1769 (CO, β-lactam), 3447 (NH); ^1H NMR (300 MHz, DMSO-d_6) δ 6.11 (H-4, d, 1H, J=3.8), 6.73–8.29 (ArH, m, 17H), 9.17 (NH, br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 68.4 (C-4), 84.7 (C-3), 114.9, 116.1, 121.2, 123.5, 124.2, 128.9, 129.3, 131.7, 132.0, 137.7, 139.3, 141.2, 145.9, 155.6 (aromatic carbons), 166.1 (CO, β-lactam); Anal. Calcd for $C_{29}H_{19}NO_2$: C, 84.24; H, 4.63; N, 3.39. Found: C, 84.32; H, 4.79; N, 3.44.

*4.2.19. Dispiro[azetidine((2,9′-fluoren)(3,9′-xanthen))]-4-one (**15**).* Light-yellow solid (0.34 g, 89%). Mp >235 °C. R_f=0.45 (5:5 hexane/EtOAc); IR (KBr) cm^{-1}: 1762 (CO, β-lactam), 3432 (NH); ^1H NMR (300 MHz, DMSO-d_6) δ 6.64–8.18 (ArH, m, 16H), 9.02 (NH, br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 72.8 (C-3), 80.3 (C-4), 116.8, 118.2, 122.5, 125.7, 126.1, 127.9, 129.2, 134.6, 136.0, 140.4, 143.5, 158.2 (aromatic carbons), 165.8 (CO, β-lactam); Anal. Calcd for $C_{27}H_{17}NO_2$: C, 83.70; H, 4.42; N, 3.62. Found: C, 83.78; H, 4.57; N, 3.54.

*4.2.20. cis-1-(4-Methoxybenzyl)-4-(4-nitrophenyl)-3-phenoxy-azetidin-2-one (**16a**).* Light-yellow crystalline solid (0.37 g, 92%). Mp: 94–96 °C. R_f=0.42 (7:3 hexane/EtOAc); IR (KBr) cm^{-1}: 1335, 1538 (NO_2), 1748 (CO, β-lactam); ^1H NMR (300 MHz, $CDCl_3$) δ 3.78 (OMe,

s, 3H), 3.96, 4.80 (CH_2–benzyl, 2d, 2H, J=14.7), 4.86 (H-4, d, 1H, J=4.5), 5.46 (H-3, d, 1H, J=4.5), 6.68–8.11 (ArH, m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.3 (CH_2), 55.3 (OMe), 60.5 (C-3), 82.0 (C-4), 114.1, 115.2, 122.1, 123.3, 126.1, 128.9, 129.1, 129.4, 140.8, 147.9, 156.4, 159.5 (aromatic carbons), 164.9 (CO, β-lactam); Anal. Calcd for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93. Found: C, 68.24; H, 5.08; N, 6.98.

*4.2.21. cis-2-(1-(4-Methoxybenzyl)-2-(4-nitrophenyl)-4-oxoazetidin-3-yl)-isoindoline-1,3-dione (**16b**).* White solid (0.39 g, 85%). Mp: 124–126 °C. R_f=0.36 (7:3 hexane/EtOAc); IR (KBr) cm^{-1}: 1337, 1530 (NO_2), 1735, 1772 (CO, phth), 1788 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (OMe, s, 3H), 3.89, 4.84 (CH_2–benzyl, 2d, 2H, J=14.5), 5.22 (H-4, d, 1H, J=4.6), 5.64 (H-3, d, 1H, J=4.6), 6.81–8.25 (ArH, m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.1 (CH_2), 55.7 (OMe), 60.2 (C-4), 62.7 (C-3), 110.7, 114.5, 115.4, 127.7, 128.2, 128.5, 129.9, 144.6, 146.2, 148.5, 158.8 (aromatic carbons), 161.1 (CO, phth), 163.6 (CO, β-lactam); Anal. Calcd for $C_{25}H_{19}N_3O_6$: C, 65.64; H, 4.19; N, 9.19. Found: C, 65.72; H, 4.31; N, 9.27.

*4.2.22. cis-1-(4-Methoxybenzyl)-4-(4-chlorophenyl)-3-methoxyazetidin-2-one (**16c**).* White solid (0.30 g, 90%). Mp: 65–67 °C. R_f=0.49 (7:3 hexane/EtOAc); IR (KBr) cm^{-1}: 1752 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.30, 3.78 (2OMe, 2s, 6H), 3.88, 4.63 (CH_2–benzyl, 2d, 2H, J=15.0), 4.80 (H-4, d, 1H, J=4.9), 5.19 (H-3, d, 1H, J=4.9), 6.81–7.44 (ArH, m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.1 (CH_2), 55.3, 56.5 (2OMe), 63.7 (C-3), 83.9 (C-4), 115.7, 122.9, 123.1, 126.3, 128.0, 135.1, 144.9, 150.6 (aromatic carbons), 162.4 (CO, β-lactam); Anal. Calcd for $C_{18}H_{18}ClNO_3$: C, 65.16; H, 5.47; N, 4.22. Found: C, 65.11; H, 5.59; N, 4.27.

*4.2.23. cis-1-(4-Methoxybenzyl)-4-(4-chlorophenyl)-3-(naphthalen-2-yloxy)azetidin-2-one (**16d**).* Light-yellow crystalline solid (0.41 g, 93%). Mp: 137–139 °C. R_f=0.53 (7:3 hexane/EtOAc); IR (KBr) cm^{-1}: 1744 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (OMe, s, 3H), 3.92, 4.73 (CH_2–benzyl, 2d, 2H, J=14.9), 4.88 (H-4, d, 1H, J=4.4), 5.53 (H-3, d, 1H, J=4.4), 6.75–7.74 (ArH, m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.5 (CH_2), 56.2 (OMe), 59.9 (C-3), 83.7 (C-4), 110.5, 112.7, 118.8, 119.3, 122.6, 124.0, 127.3, 127.5, 127.9, 128.5, 129.0, 129.6, 130.1, 134.5, 135.8, 142.2, 144.9, 147.3 (aromatic carbons), 163.1 (CO, β-lactam); Anal. Calcd for $C_{27}H_{22}ClNO_3$: C, 73.05; H, 5.00; N, 3.16. Found: C, 73.16; H, 5.14; N, 3.22.

*4.2.24. cis-4-(4-Chlorophenyl)-3-methoxyazetidin-2-one (**17c**).* White solid (0.17 g, 80%). Mp: 74–76 °C. R_f=0.38 (3:7 hexane/EtOAc); IR (KBr) cm^{-1}: 1769 (CO), 3426 (NH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.32 (OMe, s, 3H), 4.56 (H-4, dd, 1H, J=4.5, 2.9), 4.71 (H-3, d, 1H, J=4.5), 6.73–7.25 (ArH, m, 4H), 8.94 (NH, br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.9 (OMe), 59.7 (C-4), 83.3 (C-3), 125.1, 128.4, 140.2, 142.5 (aromatic carbons), 165.9 (CO, β-lactam); Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.83; H, 4.90; N, 6.55.

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