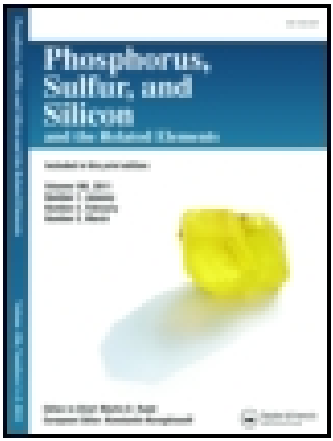


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Ceric Ammonium Nitrate on Silica Gel for Solid-Solid Phase N-Dearylation of β -Lactams

Aliasghar Jarrahpour [a] & Maaroof Zarei [a]
[a] Department of Chemistry, College of Sciences , Shiraz University , Shiraz, Iran
Published online: 22 Jun 2009.

To cite this article: Aliasghar Jarrahpour & Maaroof Zarei (2009) Ceric Ammonium Nitrate on Silica Gel for Solid-Solid Phase N-Dearylation of β -Lactams, Phosphorus, Sulfur, and Silicon and the Related Elements, 184:7, 1738-1749, DOI: 10.1080/10426500802336630

To link to this article: http://dx.doi.org/10.1080/10426500802336630

Phosphorus, Sulfur, and Silicon, 184:1738–1749, 2009

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802336630

Taylor & Francis
Taylor & Francis Group

Ceric Ammonium Nitrate on Silica Gel for Solid–Solid Phase *N*-Dearylation of β-Lactams

Aliasghar Jarrahpour and Maaroof Zarei
Department of Chemistry, College of Sciences, Shiraz University, Shiraz, Iran

Silica gel–supported ceric ammonium nitrate (CAN-SiO_2) has been found to be an effective reagent for the solid–solid phase and solvent-free N-dearylation of β-lactams. The results have been compared with CAN alone in solution and solid–solid phase.

Keywords 2-Azetidinones; ceric ammonium nitrate; *N*-dearylation; solid–solid phase; solvent-free; *N*-unsubstituted β-lactam

INTRODUCTION

The introduction of supported reagents for bringing about various chemical transformations has provided an attractive option for organic synthesis.[1] Supported reagents offer advantages such as simple work-up, purification of product, and enhanced or reduced reactivity of functional groups.[2] Silica gel plays an important role in fine organic synthesis.[3] Solid-state[4] or solvent-free[5] reactions have many advantages, such as reduced pollution, low costs, and simplicity in process and handling. These factors are especially important in industry. Furthermore, in many cases, solid-state reactions proceed much faster than reactions in solution, probably because the solid state reaction has a very high concentration reaction.[6] Among the various heterocyclic ring systems, β-lactams are possibly some of the best-known and most widely investigated.[7] This is primarily due to their antibacterial activity[8] and other new biological activities.[9] Also, this four-membered cyclic amide

Received 13 April 2008; accepted 1 July 2008.
The authors thank the Shiraz University Research Council for financial support (Grant No. 86-GR-SC-23).
Address correspondence to A. Jarrahpour, Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran. E-mail: jarrah@susc.ac.ir or aliasghar6683@yahoo.com

has been extensively used for the synthesis of several compounds[10] and in the semi-synthesis of Taxol derivatives.[11]

Some of the β-lactam antibiotics and tabtoxin, the glutamine synthase inhibitor, can be synthesized from *N*-unsubstituted β-lactams.[12] *N*-unsubstituted β-lactams have been obtained from the reaction of N-trimethylsilylimine with corresponding compounds,[13] *N*-deprotection of *N*-aryl or alkyl β-lactams,[14] and reaction of chlorosulfonyl isocyanate with alkenes.[15] *N*-Deprotection of *N*-alkoxyphenyl-β-lactams by several methods is an established method in β-lactam chemistry.[16]

Ceric ammonium nitrate (CAN) is one of the reagents that has been previously utilized for this purpose.[17] Commonly *N*-(4-alkoxyphenyl)-β-lactams are converted to NH-β-lactams with CAN in aqueous acetonitrile or THF.[18] Toxicity, high cost, and tedious work-up are some drawbacks of these methods, and environmentally benign processes try to minimize the use of hazardous solvents such as acetonitrile.

Silica-supported CAN has been used in some reactions.[19] In our laboratory, we have successfully developed *N*-dearylation of 2-azetidinones with CAN-SiO_2 in solution phase and on column reactions in which the columns were packed with CAN-SiO_2 (as the N-dearylation zone) and silica gel (as the purification zone).[20] Recently, we reported the solvent-free and solid–solid phase *N*-dearylation of β-lactams by CAN.[21] Here, a remarkably simple, effective, solvent-free, and solid–solid phase method for *N*-dearylation of *N*-(4-methoxy or 4-ethoxyphenyl)-β-lactams with CAN-SiO_2 is described. No solvents are utilized, and no further purifications are required.

RESULTS AND DISCUSSION

Ceric ammonium nitrate on silica gel (CAN-SiO_2) was prepared as a yellowish solid by a reported method.[19a] The [2+2] ketene-imine cycloaddition (Staudinger reaction) was chosen for the generation of the β-lactam ring.[22] 2-Azetidinones **1a–j** were synthesized, and the *cis* or *trans* stereochemistry was assigned by measuring coupling constants of H-3 and H-4 in their ^{1}H NMR spectra. Then the finely powdered β-lactam **1a** was ground with 40% CAN-SiO_2 (3.0 eq CAN) in a mortar for 1 min to afford the *N*-unsubstituted β-lactam **2a**. The color changed from yellow to orange.

Experiments were performed to find the optimized reaction condition. It was found to be 2.5 eq of CAN-SiO_2 using 20 min reaction time (Table I).

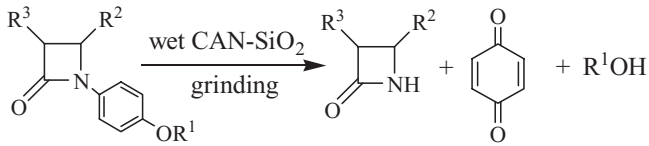
In view of this, β-lactams **1a–j** were converted to *N*-unsubstituted β-lactams **2a–j** by grinding with wet 40% CAN-SiO_2 (2.5 eq CAN)

TABLE I *N*-Dearylation of 1a by Grinding with 40% CAN-SiO_2

Molar eq. of CAN	Time (min)	Isolated yield (%)
3.0	30	82
	20	84
	15	76
2.5	30	84
	20	83
	15	79
2.0	45	51[a]
	30	48[a]
	20	46[a]
	15	33[a]

[a]Based on unreacted starting material.

for 20 min in high yields (Scheme 1, Table II). After completion of the reaction (TLC monitoring), the reaction mixture was poured into dichloromethane, and the silica gel was filtered off. The resulting solution contained the corresponding NH-β-lactams and *p*-benzoquinone (compared with authentic samples). *p*-Benzoquinone was easily removed by washing with 10% $NaHSO_3$ solution.[23]



1a-j **2a-j**

SCHEME 1

According to Table II, compared to the solution reaction, use of CAN-SiO_2 has the following merits: easy separation and purification, simple instruments, mild conditions, and no hazardous solvents.

Although the solid–solid phase *N*-dearylation by CAN alone is a good method, a larger amount of the reagent (3.5 eq) is needed to complete the reaction. In addition, CAN-SiO_2 is more convenient to handle than CAN alone, as the latter is hygroscopic.[24] The structures of *N*-unsubstituted β-lactams **2a–j** were confirmed by spectroscopic data and elemental analyses.

TABLE II Comparison of *N*-Dearylation of 1a–i by 40% CAN-SiO_2 and CAN Alone

						Isolated yield			
						CAN		CAN-SiO_2	
β–Lactam	R^1	R^2	R^3	cis/trans	Product	Solution[a]	Grinding[b]	Solution[c]	Grinding[d]
1a*	4-$EtOC_6H_4$	3,4-di$MeOC_6H_3$	PhO	cis	**2a**	84	81	76	83
1b	4-$MeOC_6H_4$	4-$MeOC_6H_4$	PhO	cis	**2b**	79	74	83	82
1c	4-$EtOC_6H_4$	4-MeC_6H_4	PhthN	trans	**2c**	81	83	80	81
1d	4-$MeOC_6H_4$	3,4-di$MeOC_6H_3$	3-NO_2PhthN	cis	**2d**	79	82	75	86
1e	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	2-naphthO	cis	**2e***	80	75	73	81
1f*	4-$EtOC_6H_4$	4-ClC_6H_4	2-naphthO	cis	**2f***	83	82	81	79
1g*	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	2,4-diClC_6H_3O	cis	**2g**	76	80	82	86
1h*	4-$EtOC_6H_4$	4-ClC_6H_4	2,4-diClC_6H_3O	cis	**2h***	82	74	78	80
1i*	4-$MeOC_6H_4$	4-MeC_6H_4	MeO	cis	**2i**	81	84	81	82
1j	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	MeO	cis	**2j***	77	80	82	78

[a]In CH_3CN/H_2O (3:1) by 3.0 eq. of CAN for 45 min.
[b]By 3.5 eq. of CAN for 30 min.
[c]In CH_3CN/ H_2O (3:1) by 2.5 eq. of CAN for 30 min.
[d]By 2.5 eq of CAN for 20 min.
*Compounds marked by an asterisk are new.

CONCLUSION

We found that CAN-SiO_2 is a rapid, easy, efficient reagent for solvent-free *N*-dearylation of β-lactams with high yields. This reagent can easily be prepared and handled. Use of silica gel–supported CAN allowed the *N*-dearylation reactions to proceed using less reagent than the other methods.

EXPERIMENTAL

All needed chemicals were purchased from Merck, Fluka, and Acros chemical companies. Dichloromethane and triethylamine were dried by distillation over CaH_2 and then stored over molecular sieve 4Å. 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 ppm (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.

Preparation of Silica Gel–Supported Ceric Ammonium Nitrate (CAN-SiO_2)[19a]

Silica gel (6.0 g, Merck Kieselgel 70–230 mesh) was mixed with a solution of CAN (4.0 g) in water (4.0 mL). Evaporation of water under reduced pressure gave a yellowish powder, which contained 40% (by weight) of CAN. This reagent was found to be active for at least 6 months if stored in a well-capped bottle.

General Procedure for the Solvent-Free *N*-Dearylation of β-Lactams 1a–j by CAN-SiO_2

$\beta-$Lactams **1a–i** (1 mmol) were mixed thoroughly with wet 40% CAN-SiO_2 (contained 2.5 eq of CAN) in a mortar. Then the mixture was ground together for 1 min and was kept for the mentioned times. After completion of the reaction (TLC monitoring), the mixture was poured into dichloromethane, and the solid was filtered off. The resulting solution was washed with 10% $NaHSO_3$ (2 $\times$ 20 mL) and brine, and

then dried (Na_2SO_4). Filtration and removal of solvent under reduced pressure afforded the *N*-unsubstituted β-lactams **2a–j**.

4-(3,4-Dimethoxyphenyl)-1-(4-ethoxyphenyl)-3-phenoxyazetidin-2-one (1a)

Mp 186–188°C IR (KBr) cm^{-1}:1758.2 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 1.36 (Me, t, 3H), 3.75, 3.81 (2OMe, 2s, 6H), 3.95 (OCH_2, q, 2H), 5.28 (H-4, d, 1H, $J = 4.2$), 5.52 (H-3, d, 1H, $J = 4.2$), 6.74–7.33 (ArH, m, 12H); ^{13}C NMR ($CDCl_3$) δ 14.8 (Me), 55.8, 55.9 (2OMe), 62.0 (OCH_2), 63.6 (C-4), 81.1 (C-3), 110.8, 110.9, 114.9, 115.6, 118.9, 120.9, 122.1, 125.0, 129.2, 130.4, 148.9, 149.3, 155.8, 156.9 (aromatic carbons), 162.5 (CO, β-lactam); GC-MS m/z = 419 [M^+]; Anal. Calcd for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.63; H, 5.98, N, 3.38.

1-(4-Methoxyphenyl)-4-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (1b)

Mp 168–170°C IR (KBr) cm^{-1}:1753.5 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 3.64, 3.71 (2OMe, 2s, 6H), 5.27 (H-4, d, 1H, $J = 4.5$), 5.46 (H-3, d, 1H, $J = 4.5$), 6.60–7.32 (ArH, m, 13H); ^{13}C NMR ($CDCl_3$) δ 55.2, 56.9 (2OMe), 61.4 (C-4), 81.6 (C-3), 113.2, 114.9, 115,7, 118.9, 122.1, 124.5, 129.3, 129.5, 130.4, 155.8, 157.1, 159.5 (aromatic carbons), 163.6 (CO, β-lactam); GC-MS m/z = 375 [M^+]; Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.65; H, 5.77; N, 3.72.

2-(1-(4-Ethoxyphenyl)-2-oxo-4-p-tolylazetidin-3-yl)-isoindoline-1,3-dione (1c)

Mp 202–204°C IR (KBr) cm^{-1}: 1744.2, 1776.2 (CO, phth), 1788.7 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 1.35 (Me, t, 3H), 2.33 (Me, s, 3H), 3.94 (OCH_2, q, 2H), 5.25 (H-4, d, 1H, $J = 2.5$), 5.32 (H-3, d, 1H, $J = 2.5$), 6.68–7.85 (ArH, m, 12H); ^{13}C NMR ($CDCl_3$) δ 14.3, 20.7 (2Me), 60.7 (OCH_2), 62.3 (C-4), 63.1 (C-3), 114.4, 118.6, 123.2, 125.7, 128.6, 129.5, 130.1, 131.2, 132.4, 133.6, 134.0, 138.5, 155.3 (aromatic carbons), 161.1 (CO, phth), 166.3 (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, 70.64; H, 5.05; N, 6.37.

2-[2-(3,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-4-oxo-azetidin-3-yl]-4-nitroisoindole-1,3-dione (1d)

Mp 198–200°C. IR (KBr) cm^{-1}: 1735.0, 1770.0 (CO, phth), 1778.0 (CO, β-lactam). ^1H NMR ($CDCl_3$) δ 3.65, 3.74, 3.78 (3 OMe, 3 s, 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 ($CDCl_3$) δ 55.8, 56.1, 56.4 (OMe), 61.2 (C-4), 63.3 (C-3),

109.1, 115.3, 117.8, 118.0, 123.1, 124.6, 126.2, 127.2, 128.7, 129.3, 129.9, 135.5, 142.8, 148.7, 153.6, 157.0 (aromatic carbons), 161.2 (CO), 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.

1-(4-Ethoxyphenyl)-3-(naphthalen-2-yloxy)-4-(4-nitrophenyl)-azetidin-2-one (1e)

Mp 174–176°C IR (KBr) cm^{-1}:1750.6 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 1.39 (Me, t, 3H), 3.95 (OCH_2, q, 2H), 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 ($CDCl_3$) δ 14.8 (Me), 61.1 (OCH_2), 63.7 (C-4), 81.2 (C-3), 109.0, 115.2, 118.1, 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-(4-Chlorophenyl)-1-(4-ethoxyphenyl)-3-(naphthalen-2-yloxy)-azetidin-2-one (1f)

Mp 140–142°C IR (KBr) cm^{-1}:1747.6 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 1.35 (Me, t, 3H), 3.90 (OCH_2, q, 2H), 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 ($CDCl_3$) δ 14.9 (Me), 61.4 (OCH_2), 64.6 (C-4), 81.0 (C-3), 109.1, 114.7, 115.1, 118.3, 123.9, 124.3, 126.6, 126.9, 127.7, 128.1, 128.7, 129.4, 129.6, 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.

3-(2,4-Dichlorophenoxy)-1-(4-methoxyphenyl)-4-(4-nitrophenyl)-azetidin-2-one (1g)

Mp 177–189°C IR (KBr) cm^{-1}:1751.1(CO, β-lactam); ^1H NMR ($CDCl_3$) δ 3.89 (OMe, s, 3H), 5.56 (H-4, d, 1H, J = 4.5), 5.64 (H-3, d, 1H, J = 4.5), 6.72–8.04 (ArH, m, 11H); ^{13}C NMR ($CDCl_3$) δ 57.9 (OMe), 64.4 (C-4), 82.7 (C-3), 113.4, 116. 3, 118.9, 123.1, 124.7, 127.0, 127.9, 129.1, 129.5, 130.1, 140.2, 148.2, 151.5, 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-(4-Chlorophenyl)-3-(2,4-dichlorophenoxy)-1-(4-ethoxyphenyl)-azetidin-2-one (1h)

Mp 182–184°C IR (KBr) cm^{-1}:1745.7 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 1.38 (Me, t, 3H), 3.96 (OCH_2, q, 2H), 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 ($CDCl_3$) δ 14.8 (Me), 60.9 (OCH_2), 63.7 (C-4), 81.7 (C-3), 115.1, 116.7, 118.8, 124.3, 127.5, 127.7, 128.8, 129.5, 129.8, 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], 466, 464, 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.

1-(4-Methoxyphenyl)-3-methoxy-4-p-tolylazetidin-2-one (1i)

Mp 151–153°C IR (KBr) cm^{-1}:1748.4 (CO, β-lactam); ^1H NMR ($CDCl_3$) 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, $J = 5.1$), 6.68–7.42 (ArH, m, 8H); ^{13}C NMR ($CDCl_3$) δ 20.4 (Me), 56.7, 58.1 (2OMe), 61.9 (C-4), 83.5 (C-3), 111.7, 113.6, 125.7, 127.3, 129.6, 130.4, 138.9, 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.

1-(4-Ethoxyphenyl)-3-methoxy-4-(4-nitrophenyl)-azetidin-2-one (1j)

Mp 118–120°C IR (KBr) cm^{-1}:1748.7 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 1.41 (Me, t, 3H), 3.26 (OMe, s, 3H), 4.19 (OCH_2, q, 2H), 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 ($CDCl_3$) δ 15.7 (Me), 57.8 (OMe), 62.6 (OCH_2), 64.8 (C-4), 85.5 (C-3), 117.5, 119.3, 121.5, 127.8, 133.1, 145.0, 151.2, 158.36 (aromatic carbons), 165.6 (CO, β-lactam); GC-MS m/z = 342 [M^+]; Anal. Calcd for C18H18N2O5: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.18; H, 5.37; N, 8.20.

4-(3,4-Dimethoxyphenyl)-3-phenoxyazetidin-2-one (2a)

Mp 140–142°C IR (KBr) cm^{-1}:1777.7 (CO), 3418.9 (NH); ^1H NMR (DMSO-d_6) δ 3.58, 3.66 (2MeO, 2s, 6H), 5.03 (H-3, d, 1H, $J = 4.0$), 5.58 (H-4, dd, 1H, $J = 2.2, 4.0$), 6.64–7.26 (ArH, m, 8H), 8.83 (NH, brs, 1H); ^{13}C NMR (DMSO-d_6) δ 55.2, 55.23 (2OMe), 56.4 (C-4), 81.1 (C-3), 111.0, 111.4, 115.0, 119.7, 121.4, 128.5, 129.2, 147.9, 148.3, 156.6 (aromatic carbons), 166.0 (CO, β-lactam); GC-MS m/z = 299 [M^+]; Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.31; H, 5.79; N, 4.73.

4-(4-Methoxyphenyl)-3-phenoxyazetidin-2-one (2b)

Mp 157–159°C IR ($CHCl_3$) cm^{-1}:1776.3 (CO), 3409.9 (NH); ^1H NMR (DMSO-d_6) δ 3.66 (MeO, s, 3H), 5.02 (H-3, d, 1H, $J = 4.3$), 5.52 (H-4, dd, 1H, $J = 1.8, 4.3$), 6.55–7.35 (ArH, m, 9H), 9.08 (NH, brs, 1H); ^{13}C NMR (DMSO-d_6) δ 54.83 (OMe), 56.4 (C-4), 81.8 (C-3), 113.19, 114.8, 121.7, 127.5, 128.8, 129.3, 156.2, 158.7 (aromatic carbons), 166.9 (CO, β-lactam); GC-MS m/z = 269 [M^+]; Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.42; H, 5.66; N, 5.24.

2-(2-Oxo-4-p-tolylazetidin-3-yl)-isoindoline-1,3-dione (2c)

Mp 197–199°C IR ($CHCl_3$) cm^{-1}: 1740.0, 1775.0 (CO, phth), 1785.0 (CO, β-lactam), 3480.5 (NH); ^1H NMR (DMSO-d_6) δ 2.35 (Me, s, 3H), 4.94 (H-4, dd, 1H, $J = 2.5, 3.5$), 5.04 (H-3, d, 1H, $J = 2.5$), 7.23–8.03 (ArH, m, 8H), 9.02 (NH, brs, 1H); ^{13}C NMR (DMSO-d_6) δ 20.7 (Me), 55.4 (C-4), 62.6 (C-3), 123.4, 125.8, 129.1, 131.3, 134.8, 136.0, 137.3 (aromatic carbons), 164.6 (CO, phth), 166.7 (CO, β-lactam); GC-MS m/z = 306 [M^+]; Anal. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.62; H, 4.58; N, 9.21.

2-[2-(3,4-Dimethoxyphenyl)-4-oxo-azetidin-3-yl]-4-nitroisoindole-1,3-dione (2d)

Mp 117–119°C. IR (KBr, cm^{-1}) 1735.0, 1770.2 (phth., CO), 1785.0 (CO, β-lactam), 3380.5 (NH); ^1H NMR (DMSO-d_6) δ 3.61, 3.75 (2 OMe, 2 s, 6H), 5.04 (H-4, dd, 1H, $J = 2.2, 5.5$), 5.53 (H-3, d, 1H, $J = 5.5$), 6.55 (NH, br s, 1H), 6.97–8.63 (ArH, m, 6H); ^{13}C NMR (DMSO-d_6) δ 55.4, 55.9 (OMe), 60.8 (C-4), 63.2 (C-3), 110.1, 114.6, 118.7, 122.5, 124.1, 126.4, 128.3, 129.4, 135.7, 143.0, 148.9, 150.1 (aromatic carbons), 163.4 (CO), 164.5 (CO, β-lactam); GC-MS m/z = 397 [M^+]; Anal. Calcd for $C_{19}H_{15}N_3O_7$: C, 57.43; H, 3.81; N, 10.58 Found: C, 57.37; H, 3.88; N, 10.55.

3-(Naphthalen-2-yloxy)-4-(4-nitrophenyl)-azetidin-2-one (2e)

Mp 172–174°C IR (KBr) cm^{-1}:1769.6 (CO), 3354.4 (NH); ^1H NMR (DMSO-d_6) δ 5.38 (H-3, d, 1H, $J = 4.5$), 5.86 (H-4, dd, 1H, $J = 2.3, 4.5$), 7.31–7.78 (ArH, m, 11H), 9.10 (NH, brs, 1H); ^{13}C NMR (DMSO-d_6) δ 56.0 (C-4), 82.7 (C-3), 117.5, 117.7, 122.9, 123.2, 124.1, 126.5, 126.7, 127.4, 128.8, 129.32, 130.6, 139.6, 144.5, 153.9 (aromatic carbons), 165.7 (CO, β-lactam); GC-MS m/z = 334 [M^+]; Anal. Calcd for $C_{19}H_{14}N_2O_4$: C, 68.26; H, 4.22; N, 8.38. Found: C, 68.23; H, 4.26; N, 8.42.

4-(4-Chlorophenyl)-3-(naphthalen-2-yloxy)-azetidin-2-one (2f)

Mp 122–124°C IR (KBr) cm^{-1}: 1765.8 (CO, β-lactam), 3358.3 (NH); ^1H NMR (DMSO-d_6) δ 5.18 (H-3, d, 1H, $J = 4.2$), 5.53 (H-4, dd, 1H, $J = 1.9, 4.2$), 6.46–7.96 (ArH, m, 15H), 8.87 (NH, brs, 1H); ^{13}C NMR (DMSO-d_6) δ 58.3 (C-4), 81.5(C-3), 106.8, 118.9, 122.7, 124.0, 126.3, 127.1, 128.9, 129.5, 129.8, 130.5, 133.4, 134.2, 155.6, 158.1 (aromatic carbons), 165.92 (CO, β-lactam); GC-MS m/z = 325 [M^+, ^{37}Cl], 323 [M^+, ^{35}Cl]; Anal. Calcd for $C_{19}H_{14}ClNO_2$: C, 70.48; H, 4.36; N, 4.33. Found: C, 70.40; H, 4.42; N, 4.28.

3-(2,4-Dichlorophenoxy)-4-(4-nitrophenyl)-azetidin-2-one (2g)

Mp 160–162°C IR (KBr) cm^{-1}:1775.5 (CO, β-lactam), 3320.5 (NH); ^1H NMR (DMSO-d_6) δ 5.34 (H-3, d, 1H, $J = 3.5$), 5.77 (H-4, dd, 1H, $J = 2.4, 3.5$), 7.32–8.22 (ArH, m, 7H), 9.20 (NH, brs, 1H); ^{13}C NMR (DMSO-d_6) δ 55.5 (C-4), 83.0 (C-3), 116.3, 122.2, 122.9, 125.8, 127.8, 128.8, 129.2, 143.9, 147.1, 150.7 (aromatic carbons), 165.0 (CO, β-lactam); GC-MS m/z = 356 [M^+, ^{37}Cl], 354, 352 [M^+, ^{35}Cl]; Anal. Calcd for $C_{15}H_{10}Cl_2N_2O_4$: C, 51.01; H, 2.85; N, 7.93. Found: C, 51.05; H, 2.92; N, 7.97.

4-(4-Chlorophenyl)-3-(2,4-dichlorophenoxy)azetidin-2-one (2h)

Mp 143–145°C IR (KBr) cm^{-1}:1770.1 (CO, β-lactam), 3324.6 (NH); ^1H NMR (DMSO-d_6) δ 5.23 (H-3, d, 1H, $J = 4.5$), 5.63 (H-4, dd, 1H, $J = 2.3, 4.5$), 6.94–8.13 (ArH, m, 7H), 9.06 (NH, brs, 1H); ^{13}C NMR (DMSO-d_6) δ 59.3 (C-4), 80.6 (C-3), 114.19, 117.3, 123.6, 126.7, 128.1, 129.9, 130.6, 135.4, 151.0, 156.9 (aromatic carbons), 163.2 (CO, β-lactam); GC-MS m/z = 348 [M^+, ^{37}Cl], 346, 344, 342 [M^+, ^{35}Cl]; Anal. Calcd for $C_{15}H_{10}C_{l3}NO_2$: C, 52.59; H, 2.94; N, 4.09. Found: C, 52.56; H, 3.07; N, 4.00.

3-Methoxy-4-p-tolylazetidin-2-one (2i)

Mp 92–94°C IR (KBr) cm^{-1}:1765.8 (CO, β-lactam), 3414.0 (NH); ^1H NMR (DMSO-d_6) δ 2.11 (Me, s, 3H), 2.82 (OMe, s, 3H), 4.51 (H-4, dd, 1H, $J = 2.2, 4.4$), 4.59 (H-3, d, 1H, $J = 4.4$), 6.69–7.07 (ArH, m, 4H), 8.41 (NH, brs, 1H); ^{13}C NMR (DMSO-d_6) δ 20.7 (Me), 56.2 (OMe), 57.1 (C-4), 86.3 (C-3), 127.3, 128.6, 134.1, 136.8 (aromatic carbons), 167.5 (CO, β-lactam); GC-MS m/z = 191 [M^+]; Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.14; H, 6.92; N, 7.28.

3-Methoxy-4-(4-nitrophenyl)-azetidin-2-one (2j)

Mp 101–103°C IR (KBr) cm^{-1}:1763.9 (CO, β-lactam), 3430.3 (NH); ^1H NMR (DMSO-d_6) δ 2.91 (OMe, s, 3H), 4.43 (H-4, dd, 1H, $J = 1.9,$

4.7), 4.50 (H-3, d, 1H, $J = 4.7$), 6.56–7.71 (ArH, m, 4H), 8.53 (NH, brs, 1H); ^{13}C NMR (DMSO-d_6) δ 57.1 (OMe), 59.1 (C-4), 84.4 (C-3), 124.7, 129.5, 136.3, 139.3 (aromatic carbons), 165.9 (CO, β-lactam); GC-MS m/z = 222 [M^+]; Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.11; H, 4.63; N, 12.58.

REFERENCES

[1] K. Smith, Ed., *Solid Supports and Catalysis in Organic Synthesis* (Ellis Horwood, New York, 1992).

[2] V. K. Yadav and K. K. Kapoor, *Tetrahedron Lett*., **35,** 9481–9484 (1994).

[3] A. K. Banerjee, M. S. L Mimo, and W. Vera Vegas, *Russ. Chem. Rev*., **70,** 971–990 (2001).

[4] F. Toda, *Acc. Chem. Res.*, **28,** 480–486 (1995).

[5] G. W. V. Cave, C. L. Raston, and J. L. Scott, *Chem. Commun.*, 2159–2169 (2001).

[6] F. Toda and K. Tanaka, *Chem. Rev.*, **100,** 1025–1074 (2000).

[7] A. Basak, K. Chandra, R. Pal, and S. C. Ghosh, *Synlett*, 1585–1588 (2007).

[8] (a) R. B. Morin and H. Gorman, Ed., *Chemistry and Biology of β-Lactam Antibiotics* (Acadamic Press, New York, 1982), Vol 1; (b) P. G. Sammes, Ed., *Topics in Antibiotic Chemistry* (Ellis Horwood Ltd., New York, 1980), Vol. 3; (c) J. O'Sullivan and E. P. Abraham, *Antibiotics* (Springer-Verlag, Berlin, 1981), Vol. IV; (d) G. Lukacs and M. Ohno, Eds., *Recent Progress in the Chemical Synthesis of Antibiotics* (Springer, Berlin, 1990).

[9] (a) R. M. Adlington, J. E. Baldwin, B. Chen, S. L. Cooper, W. McCoull, G. J. Pritchard, T. J. Howe, G. W. Becker, R. B. Hermann, A. M. McNulty, and B. L. Neubauer, *Bioorg. Med. Chem. Lett.*, **7,** 1689–1694 (1997); (b) J. C. Sutton, S. A. Bolton, K. S. Harti, M. H. Huang, G. Jacobs, W. Meng, G. Zhao, and G. S. Bisacchi, *Bioorg. Med. Chem. Lett.*, **14,** 2233–2239 (2004); (c) R. Gonzalez-Muniz, E. De Clercq, J. Balzarini, G. G. Navarro, J. P. De Vega, and C. Anderi, *Bioorg. Med. Chem. Lett.*, **14,** 2253–2256 (2004); (d) J. Tozsera, T. Sperka, J. Pitlik, and P. Bagossia, *Bioorg. Med. Chem. Lett.*, **15,** 3086–3090 (2005); (e) J. Marchand-Brynaert, G. Dive, M. Galleni, and and S. Gerard, *Bioorg. Med. Chem.*, **12,** 129–138 (2004); (f) X. Bai, X. Xu, R. Fu, J. Chen, and S. Chen, *Bioorg. Med. Chem. Lett.*, **17,** 101–104 (2007); (g) K. G. Desai and K. R. Desai, *Bioorg. Med. Chem.*, **14,** 8271–8279 (2006); (h) B. K. Banik, F. F. Becker, and I. Banik, *Bioorg. Med. Chem.*, **13,** 3611–3622 (2005).

[10] (a) B. Alcaide, P. Almendros, and C. Aragoncillo, *Chem. Rev.*, **107,** 4437–4492 (2007); (b) B. Alcaide and P. Almendros, *Synlett*, 381–393 (2002); (c) B. Alcaide and P. Almendros, *Chem. Soc. Rev.,* **30**, 226–240 (2001); (d) I. Ojima, *Acc. Chem. Res.,* **28**, 383–389 (1995).

[11] (a) H. Ge, J. T. Spletstoser, Y. Yang, M. Kayser, and G. I. Georg, *J. Org. Chem.,* **72,** 756–759 (2007); (b) M. Suffness, *Taxol Science and Applications* (CRC Press, Boca Raton, FL, USA, 1995).

[12] F. P. Cossio, B. Lecea, and C. Palomo, *J. Chem. Soc., Chem. Commun*., 1743–1744 (1987).

[13] (a) E. Bandini, G. Favi, G. Martelli, M. Panunzio, and G. Piersanti, *Org. Lett.*, **2,** 1077–1079 (2000); (b) D. J. Hart, K.-I. Kanai, D. G. Thomas, and T.-K. Yang, *J. Org. Chem.*, **48,** 289–294 (1983).

[14] (a) A. Jarrahpour and M. Zarei, *Molecules*, **12,** 2364–2379 (2007); (b) P. Imbach, M. Lang, C. Garcia-Echeverria, V. Guagnano, M. Noorani, J. Roesel, F. Bitsch, G. Rihs,

and P. Furet, *Bioorg. Med. Chem. Lett.*, **17,** 358–362 (2007); (c) E. Turos, B. Heldreth, T. E. Long, Jang, G. S. K. Reddy, S. Dickeyb, and D. V. Lim, *Bioorg. Med. Chem.*, **14,** 3775–3784 (2006); (d) P. Del Buttero, G. Molteni, and T. Pilati, *Tetrahedron*, **61,** 2413–2419 (2005); (e) R. Annunziata, M. Benaglia, M. Cinquini, and F. Cozzi, *J. Org. Chem.*, **68,** 2952–2955 (2003); (f) J. Podlech and M. R. Linder, *J. Org. Chem.*, **62,** 5873–5883 (1997); (g) K. Karupaiyan, V. Srirajan, A. R. A. S. Deshmukh, and B. M. Bhawal, *Tetrahedron Lett.*, **38,** 4281–4284 (1997).

[15] (a) X.-G. Li and L. T. Kanerva, *Adv. Synth. Catal.*, **348,** 197–205 (2006); (b) M. Ishiguro, R. Tanaka, K. Namikawa, T. Nasu, H. Inoue, T. Nakatsuka, Y. Oyama, and S. Imajo, *J. Med. Chem.*, **40,** 2126–2132 (1997).

[16] T. W. Green and P. G. M. Wuts, *Green's Protective Group in Organic Synthesis* (John Wiley & Sons, New Jersey, 2007), 4th ed., p. 903.

[17] D. K. Kronenthal, C. Y. Han, and M. K. Taylor, *J. Org. Chem.*, **47,** 2765–2768 (1982).

[18] J. C. Sutton, S. A. Bolton, K. S. Hartl, M.-H. Huang, G. Jacobs, W. Meng, M. L. Ogletree, Z. Pi, W. A. Schumacher, S. M. Seiler, W. A. Slusarchyk, U. Treuner, R. Zahler, G. Zhao, and G. S. Bisacchi, *Bioorg. Med. Chem. Lett.*, **12,** 3229–3233 (2002).

[19] (a) J. R. Hwu, M. L. Jain, F.-Y. Tsai, S.-C. Tsay, A. Balakumar, and G. H. Hakimelahi, *J. Org. Chem.*, **65,** 5077–5088 (2000); (b) M. H. Ali, M. Niedbalski, G. Bohnert, and D. Bryant, *Synth. Commun.*, **36,** 1751–1759 (2006); (c) A. Fisher and G. N. Henderson, *Synthesis*, 641–643 (1985); (d) H. M. Chawla and R. S. Mittal, *Synthesis*, 70–72 (1985); (e) M. Chakrabarty and A. Batabyal, *Synth. Commun.*, **24,** 1–10 (1994).

[20] A. Jarrahpour and M. Zarei, *Synlett*, 381–385 (2008).

[21] A. Jarrahpour and M. Zarei, *Synth. Commun.*, 1837–1845 (2008).

[22] (a) H. Staudinger, *Liebigs Ann. Chem.*, **356,** 51–123 (1907); (b) A. Jarrahpour and D. Khalili, *Tetrahedron Lett.*, **48,** 7140–7143 (2007); (c) A. Jarrahpour and M. Zarei, *Molecules*, **11,** 49–58 (2006).

[23] T. W. Green and P. G. M. Wuts, *Protective Group in Organic Synthesis* (John Wiley & Sons, New York, 1999), 3rd ed., p. 637.

[24] K. V. N. S. Srinivas and B. Das, *J. Chem. Res.*, 556–557 (2002).