From Solution-Phase to 'On-Column' N-Dearylation of β-Lactams by Silica-Supported Ceric Ammonium Nitrate (CAN–SiO_2)

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Abstract: It has been shown that *N*-(4-methoxy or 4-ethoxyphenyl) groups can be oxidatively removed by silica gel supported ceric ammonium nitrate (CAN–SiO_2) under mild conditions in solution and on column. The yields in these two methods were good to excellent and purification of products is simpler than the general method by CAN. Especially the 'on-column' reaction is mild, easy, efficient, and cheap. The lower mobility of CAN–SiO_2 makes it safer to handle.

Key words: on-column reaction, N-dearylation, N-unsubstituted 2-azetidinone, β-lactam, ceric ammonium nitrate, silica supported

The search for new syntheses of β-lactam derivatives represents an important field of research because of the unique biological activity of these molecules.[1] They are also being used increasingly as valuable intermediates in organic synthesis.[2] N-Unsubstituted 2-azetidinones offer major synthetic opportunities in the synthesis of β-lactam antibiotics such as the carbapenems, penams, monobactams, nocardicins, and the glutamine synthetase inhibitor, tabtoxin.[3]

Routes to N-unsubstituted β-lactams involve reaction of *N*-trimethylsilyl imines with corresponding compounds[4] or N-deprotection of N-functionalized β-lactams.[5] Several reports have studied the use of *p*-anisidine and its derivatives as the nitrogen source in the synthesis of 2-azetidinones.[6] These groups are then oxidatively cleaved with ceric ammonium nitrate (CAN).[7]

Alumina, silica, and clays are of the most widely employed supports, where surface hydroxyl groups play a major role in these reactions.[8] Amongst them, silica is widely used as a supporting material since it presents desirable properties[9] and silica gel plays an important role in fine organic synthesis.[10]

Ceric ammonium nitrate on silica gel (CAN–SiO_2) has been reported for removal of trityl and silyl groups,[11] oxidation of oxygenated aromatic compounds to quinones,[12] regeneration of carbonyl compounds from oximes, semicarbazones, phenylhydrazones,[13] and nitration of aromatics and heteroaromatics.[14] In industry, reaction columns have been used for large-scale synthesis for quite some time; however, much of the technology is proprietary.[15]

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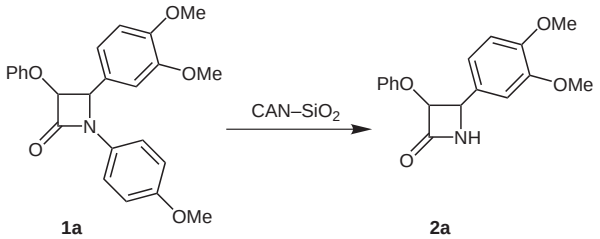
Herein we describe the use of CAN–SiO_2 as an efficient reagent for N-dearylation of *N*-(4-methoxyphenyl) and *N*-(4-ethoxyphenyl) groups on β-lactams in solutions. In addition, we demonstrate the use of silica–ceric ammonium nitrate in solid-phase 'on-column' N-dearylation of β-lactams.

Ceric ammonium nitrate on silica gel was prepared as a yellowish solid by a reported method.[11] N-Dearylation of β-lactam **1a** was carried out by CAN–SiO_2 in aqueous acetonitrile for 30 minutes at 0 °C and after filtration the N-unsubstituted 2-azetidinone **2a** was obtained in excellent yield. Then for optimizing the reaction different conditions were examined and it was noticed that MeCN–H_2O (3:1) at 25 °C are the optimal conditions (Table 1). As is shown in Table 1 and Table 2, the deprotection of β-lactams in CH_2Cl_2–H_2O is reported for the first time by us.

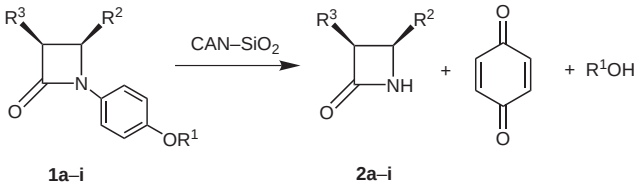
Table 1 Optimization of N-Dearylation of β-Lactam (**1a**) by CAN–SiO_2 in Solution



1a **2a**

	Temp (°C)	Time (min)	Isolated yield (%)	
			40% CAN–SiO_2	10% CAN–SiO_2
MeCN–H_2O (3:1)	0	25	84	82
	25	15	93	94
CH_2Cl_2–H_2O (18:1)	0	30	76	72
	25	15	80	81

Following on from the above results, 4-methoxyphenyl and 4-ethoxyphenyl β-lactams **1a**–**i** were converted to the corresponding NH-β-lactams **2a**–**i** by 10% CAN–SiO_2 in aqueous acetonitrile at room temperature in good-to-excellent yields (Scheme 1, Table 2). *p*-Benzoquinone was the only byproduct obtained in this reaction. The structures of NH-β-lactams **2a**–**i** were confirmed by spectral data and elemental analyses. This method has the follow-



Scheme 1 CAN–silica deprotection of β-lactams

ing merits: easy separation and purification, excellent yields, mild conditions, and a short reaction time.

Following on from the above results and the recently reported on-column reactions,[16] we decided to carry out these β-lactam N-dearylation reactions and purification of the products on a silica-supported ceric ammonium nitrate column 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 (Figure 1).

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). 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 the products, 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 2).

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

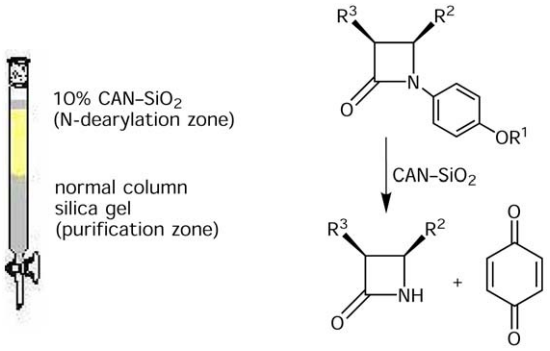


Figure 1 Type A column

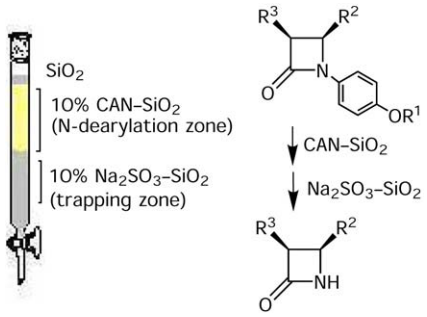


Figure 2 Type B column

β-Lactams **1a**–**i** were charged onto the type B column. In the N-dearylation zone, these were converted to N-unsubstituted β-lactams **2a**–**i** and benzoquinone which was trapped as sodium 2,5-dihydroxybenzenesulfonate[17] 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.

In conclusion, we have demonstrated for the first time that silica-supported CAN can be used in N-dearylation reaction of β-lactams with two different conditions: solution phase and reaction 'on column'. The main advantages of these methods are the ready availability, mild reaction conditions, ease of isolation of obtained products, short time reaction, and high yields. It is noteworthy that in the 'on-column' method, both N-dearylation and purification are performed at the same time.

Typical Procedure for Solution-Phase N-Dearylation Reactions

To a solution of β-lactams **1a**–**i** (1.0 mmol) in MeCN–H_2O (3:1) or CH_2Cl_2–H_2O (18:1) was added 40% or 10% CAN–SiO_2 (containing 2.5 equiv of CAN). The mixture was stirred at r.t. for the reported time. For reaction in aq MeCN, the mixture was extracted with EtOAc (2 × 20 mL) and washed with 10% of $NaHSO_3$ (30 mL), brine (20 mL), and then dried over Na_2SO_4. After filtration and evaporation of the solvent in vacuo, the products were obtained with satisfactory purity. For reaction in CH_2Cl_2, the reaction mixture was filtered and the silica gel was washed with $CHCl_3$. The resulting solution was washed with 10% of $NaHSO_3$ (30 mL), brine (20 mL), and then dried over Na_2SO_4. The solvent was removed under reduced pressure and pure N-unsubstituted β-lactams **2a**–**i** were obtained.

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, ca. 4.0 cm) and was topped up with 10% CAN–SiO_2 (12.0 g, ca. 11.5 cm). Then, 2-azetidinone (1.0 mmol) in a little CH_2Cl_2 was charged onto the column and was allowed to stand at r.t. for 10–15 min. The column was then eluted with THF–H_2O (19:1) to afford firstly *p*-benzoquinone followed by pure N-unsubstituted β-lactam.

Table 2 Solution-Phase and 'On-Column' Synthesis of Deprotected β-Lactams **2a–i**

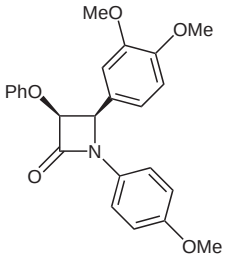
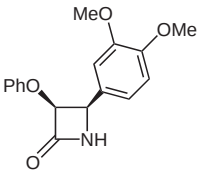
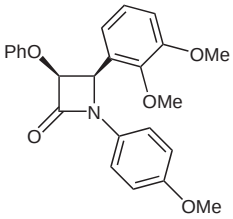
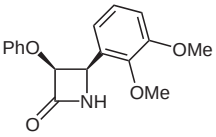
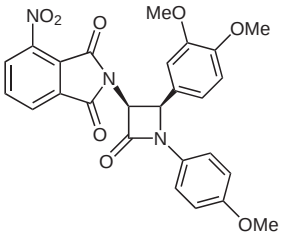
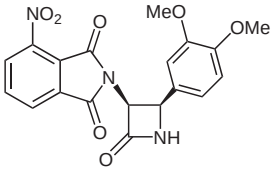
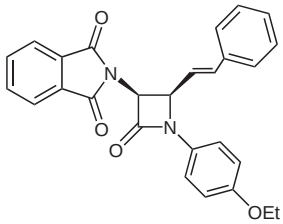
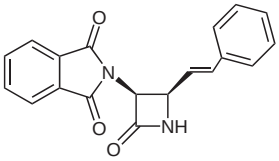
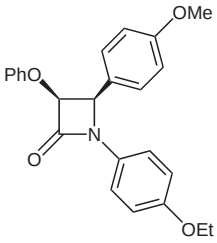
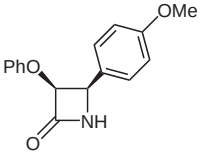
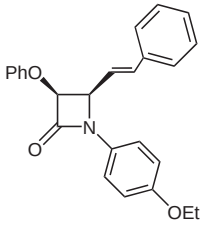
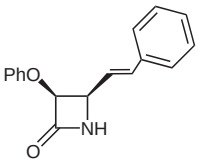
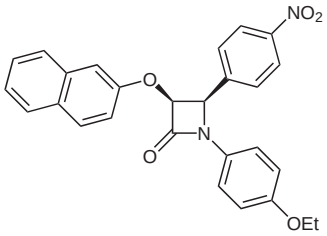
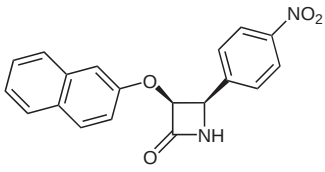
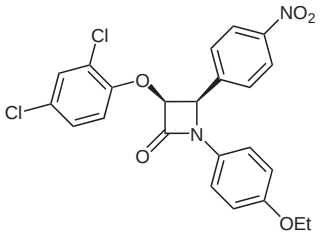
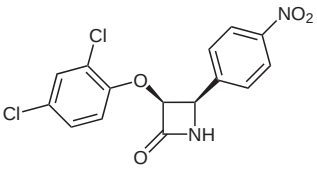
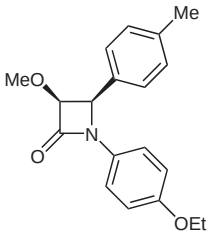
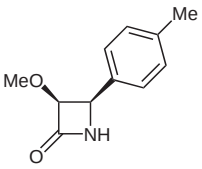
Substrate	Product	Isolated yield (%) by 10% CAN–SiO_2				Isolated yield (%) by CAN
		MeCN–H_2O	CH_2Cl_2/H_2O	Column A	Column B	
 **1a**	 **2a**	94	81	91	94	83
 **1b**	 **2b**	86	73	83	88	77
 **1c**	 **2c**	88	68	90	87	79
 **1d**	 **2d**	91	74	87	93	71
 **1e**	 **2e**	85	74	85	89	85
 **1f**	 **2f**	93	79	91	90	78

Table 2 Solution-Phase and 'On-Column' Synthesis of Deprotected β-Lactams **2a–i** (continued)

Substrate	Product	Isolated yield (%) by 10% CAN–SiO_2				Isolated yield (%) by CAN
		MeCN–H_2O	CH_2Cl_2/H_2O	Column A	Column B	
 **1g**	 **2g**	82	71	88	92	80
 **1h**	 **2h**	91	80	90	94	74
 **1i**	 **2i**	84	75	86	87	85

b) On Column Type B

A 48 × 2 cm^2 glass column was packed from the bottom: a little silica gel (ca. 1cm), 10% Na_2SO_3–SiO_2 (6.0 g, ca. 4.5 cm), 10% CAN–SiO_2 (12.0 g, ca. 11.5 cm), and a little of silica gel on top. β-Lactam (1.0 mmol) in CH_2Cl_2 (1.0–1.5 mL) was then charged onto the column. After 15 min the column was eluted with THF–H_2O (19:1) to afford pure N-unsubstituted β-lactam and *p*-benzoquinone was trapped in the column as sodium 2,5-dihydroxybenzene sulfonate.

4-(2,3-Dimethoxyphenyl)-3-phenoxy-2-azetidinone (2b)

IR (KBr): 1760.8 (CO, β-lactam), 3301.0 (NH) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.71, 3.79 (2 OMe, 2 s, 6 H), 5.14 (H-4, dd, 1 H, *J* = 8.3, 4.3 Hz), 5.29 (H-3, d, 1 H, *J* = 4.6 Hz), 6.73–7.83 (ArH, m, 8 H), 9.58 (NH, br s, 1 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 57.07, 61.14 (OMe), 81.99 (C-4), 83.65 (C-3), 112.81-157.65 (C_{arom}), 168.09 (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, 68.17; H, 5.81; N, 4.63.

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

Mp 172–174 °C. IR (KBr): 1769.6 (CO), 3354.4 (NH) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 5.38 (H-3, d, 1 H, *J* = 4.5 Hz), 5.86 (H-4, dd, 1 H, *J* = 2.3, 4.5 Hz), 7.31–7.78 (ArH, m, 11 H), 9.10 (NH, br s, 1 H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 56.05 (C-4), 82.71 (C-3), 117.51–147.53 (C_{arom}), 165.66 (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.

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

Mp 160–162 °C. IR (KBr): 1775.5 (CO), 3320.5 (NH) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 5.34 (H-3, d, 1 H, *J* = 3.5 Hz), 5.77 (H-4, dd, 1 H, *J* = 2.4, 3.5 Hz), 7.32–8.22 (ArH, m, 7 H), 9.20 (NH, br s, 1 H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 55.49 (C-4), 82.99 (C-3), 116.31–150.69 (C_{arom}), 165.00 (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.

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

Mp 92–94 °C. IR (KBr):1765.8 (CO), 3414.0 (NH) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.11 (Me, s, 3 H), 2.82 (OMe, s, 3 H), 4.51 (H-4, dd, 1 H, *J* = 2.2, 4.4 Hz), 4.59 (H-3, d, 1 H, *J* = 4.4 Hz), 6.97–7.07 (ArH, m, 4 H), 8.41 (NH, br s, 1 H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.65 (Me), 56.23 (OMe), 57.12 (C-4), 86.26 (C-3), 127.35–136.75 (C_{arom}), 167.48 (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.

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