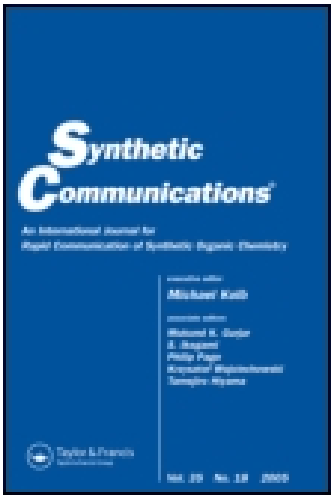

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Solid-Solid Phase and Solvent-Free Oxidative Removal of N-(4-Alkoxyphenyl) Groups of Monocyclic β-Lactams with Ceric Ammonium Nitrate as a Cheap, Simple, and Efficient Method

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Solid-Solid Phase and Solvent-Free Oxidative Removal of *N*-(4-Alkoxyphenyl) Groups of Monocyclic β-Lactams with Ceric Ammonium Nitrate as a Cheap, Simple, and Efficient Method

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Abstract: Five *N*-(4-methoxyphenyl)- and five *N*-(4-ethoxyphenyl)-β-lactams were prepared by ketene-imine [2 + 2] cycloaddition (Staudinger reaction). Then these 2-azetidinones were *N*-dearylated by grinding together with ceric ammonium nitrate without hazardous solvents in good to excellent yields. The solid-solid phase *N*-dearylation is easier, simpler, and more efficient than the general method in solution. The pure *N*-unsubstituted β-lactams obtained by a nontedious workup and without further purification.

Keywords: 2-Azetidinones, ceric ammonium nitrate, solvent-free, solid-solid phase, *N*-unsubstituted β-lactam

INTRODUCTION

It is remarkable that chemists still carry out their reactions in solution. Recently chemists have found that many reactions proceed efficiently in the solid state or solvent-free conditions.[1] The solid-state reactions[2] or solvent-free[3] reactions have many advantages: reduced pollution, low costs, and simplicity in process and handling. These factors are especially

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important in industry. Furthermore, in many cases, solid-state reactions proceed much faster than the solution reaction, probably because the solid-state reaction is a very high concentration reaction.[4] β-Lactam compounds really are "evergreen" bioactive molecules.[5] *N*-Unsubstituted β-lactams are intermediates in the synthesis of monocyclic and bicyclic β-lactam antibiotics.[6] Monocyclic β-lactams such as nocardicins **1** and monobactams **2** are of interest as they have been found to exhibit antibiotic properties.[7] These compounds can be synthesized by various routes, though the preparation of an *N*-unsubstituted β-lactam is a common feature.[8]

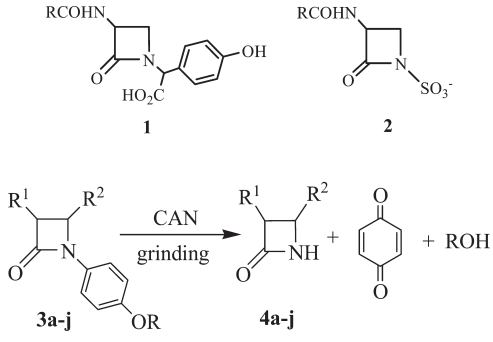
The importance of *N*-unsubstituted β-lactams for the semisynthesis of the novel anticancer agents Taxol and Taxotere is also well documented.[9] Several protecting groups are often used for N^1-protection of β-lactams and can be deproteced by different methods to give *N*-unsubstituted β-lactams.[10] Generally, the selection of N^1-protective groups in β-lactam synthesis is based on the ease of selective removal of these groups at the appropriate stage.[11] In solution-phase syntheses, ceric ammonium nitrate (CAN) has been utilized to remove the 4-methoxyphenyl,[12] 4-methoxybenzyl,[13] 4-(methoxymethoxy)-phenyl,[14] and benzloxy-aniline linker[15] group from the amide nitrogen of β-lactams to generate their *N*-unsubstituted analogs. Generally aqueous acetonitrile is used as solvent in these deprotection reactions.[16] However, these methods have some drawbacks that limit their applications: toxicity, high cost, and tedious workup. Acetonitrile is a toxic and expensive solvent. Because of the low partition coefficient between ethyl acetate and water, a large amount of the former is used repeatedly for workup.[17]

Our aim was to develop a simple and efficient synthetic strategy for the preparation of *N*-unsubstituted 2-azetidinones. In this study, we report the conversion of *N*-(4-alkoxyphenyl)-2-azetidinones to *N*-unsubstituted 2-azetidinones with ceric ammonium nitrate (CAN) in solid-solid phase and solvent-free medium.

RESULTS AND DISCUSSION

3,4-Disubstituted-2-azetidinones **3a–j** were prepared as described in Scheme 1. [2 + 2]-Ketene-imine cycloaddition reaction (Staudinger reaction) of corresponding acylchlorides and Schiff bases in the presence of triethylamine at −10 °C resulted in *cis* and *trans* 2-azetidinones **3a–j** in excellent yields. Subsequent treatment with ceric ammonium nitrate (CAN) converted β-lactams **3a–j** into the *N*-unsubstituted β-lactams **4a–j** (Scheme 1 and Table 1). The powdered β-lactams **3a–j** and CAN were mixed in a mortar. Then 2–3 drops of distilled cold water were added and ground into the mixture for 1 min at room temperature.

The reaction usually starts immediately with formation of the colored *p*-benzoquinone. The change of the color was a good indicator of its formation. The presence of water is necessary, and the reported mechanism[18] confirms it. After 15 min, the mortar was fully colored. Ethyl acetate was



Scheme 1. *N*-Dearylation of 2-azetidinones **3a–j** in solid-solid phase.

added to the reaction mixture, shaken well, and then filtered. The resulted solution was washed with 10% $NaHSO_3$ and brine. The released quinone was removed by forming the bisulfite adduct, which can be washed out with water.[19]

Removal of water by Na_2SO_4 and evaporation of the solvent in vacuo resulted in pure *N*-unsubstituted *β*-lactams **4a–j** in good to excellent yields. Both *N*-(4-methoxyphenyl)-2-azetidinones **3a–e** and *N*-(4-ethoxyphenyl)-2-azetidinones **3f–j** were dearylated rapidly and selectively with satisfactory purity without need for column chromatography or recrystallization.

The structures of the NH-*β*-lactams **4a–j** were confirmed by spectroscopic data and elemental analyses. The carbonyl function of these dearylated *β*-lactams was shifted to higher wave numbers in IR spectra. ^{1}H NMR spectra definitely showed the NH signals and H-4 as a doublet of doublets peak. The mass spectra showed the molecular ion for all synthesized molecules. This method is more convenient, more efficient, cheaper, and safer than the general reported methods.

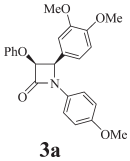
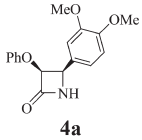
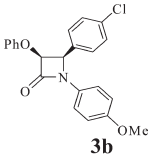
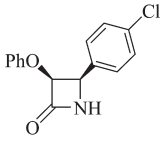
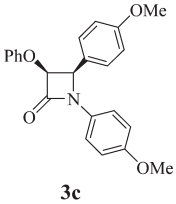
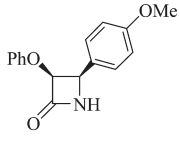
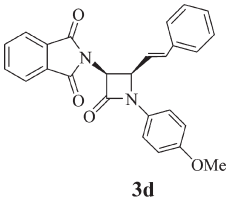
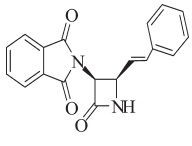
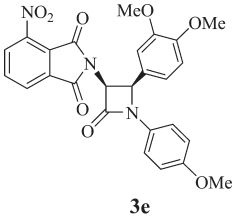
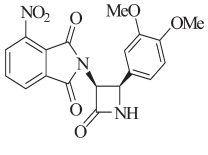
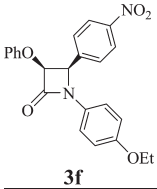
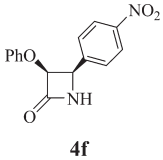
In summary, we have developed a simple and green procedure for the synthesis of *N*-unsubstituted *β*-lactams. For the first time, a solvent-free method for *N*-dearylation of 2-azetidinones in solid-solid phase by grinding with CAN has been reported by us. Cleavage of the electron-rich aryl groups with CAN occurs rapidly in mild and green conditions.

EXPERIMENTAL

Typical Experimental Procedure for the Solid-Solid Phase *N*-Dearylation of β-Lactams 3a–j

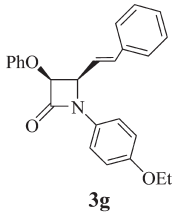
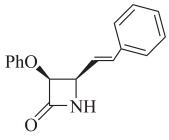
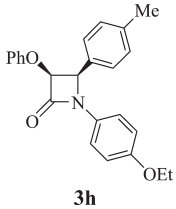
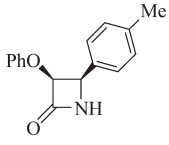
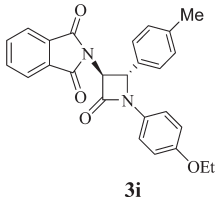
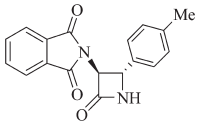
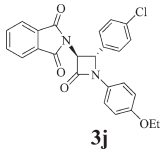
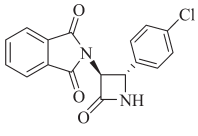
All solid–solid reactions were performed by grinding together 1.0 mmol of the pure 2-azetidinones **3a–j** with 3.5 mmol of CAN in the presence of 2–3 drops of cold water in a mortar for 1 min and keeping the mixture at room temperature for 15 min. Then the reaction mixture was poured into EtOAc, shaken well, and

Table 1. Comparison of the yields by use of CAN in solution with solvent-free *N*-dearylation of 2-azetidinones **3a–j**

Substrate	Products	Yield (%) by isolation	
		Solution phase[a]	Solid phase[b]
 **3a**	 **4a**	83	88
 **3b**	 **4b**	81	80
 **3c**	 **4c**	77	85
 **3d**	 **4d**	75	76
 **3e**	 **4e**	79	82
 **3f**	 **4f**	80	83

(*continued*)

Table 1. Continued

Substrate	Products	Yield (%) by isolation	
		Solution phase[a]	Solid phase[b]
 **3g**	 **4g**	76	79
 **3h**	 **4h**	84	85
 **3i**	 **4i**	78	83
 **3j**	 **4j**	74	78

[a]CH_3CN/H_2O (3:1) for 30–45 min.
[b]15 min.

filtered. The colored resulted solution was washed with 10% sodium bisulfite (until the aqueous layer remained colorless) and brine and then dried over dry sodium sulfate. After filtration and evaporation of solvent under reduced pressure, the *N*-unsubstituted β-lactams **4a–j** were obtained.

Data

4-(3,4-Dimethoxyphenyl)-3-phenoxyazetidin-2-one (4a). Yield: 88%. Mp: 140–142 °C. IR (KBr) cm^{-1}: 1777.7 (CO), 3418.9 (NH). ^1H NMR

(250 MHz, 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 (62.9 MHz, DMSO-d_6) δ 55.23, 55.25 (2OMe), 56.40 (C-4), 81.13 (C-3), 111.02–156.59 (aromatic carbons), 165.98 (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-Chlorophenyl)-3-phenoxyazetidin-2-one (4b). Yield: 80%. Mp: 188–190 °C. IR (KBr) cm^{-1}: 1773.5 (CO), 3420.0 (NH). ^{1}H NMR (250 MHz, DMSO-d_6) δ 5.09 (H-3, d, 1H, $J = 4.5$), 5.61 (H-4, dd, 1H, $J = 2.1$, 4.5), 6.77–7.32 (ArH, m, 9H), 8.89 (NH, brs, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 56.91 (C-4), 82.26 (C-3), 114.98–156.34 (aromatic carbons), 165.90 (CO, β-lactam). GC-MS $m/z = 275$ [M^+, ^{37}Cl], 273 [M^+, ^{35}Cl]. Anal. calcd. for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; N, 5.12. Found: C, 65.78; H, 4.46; N, 5.08.

4-(4-Methoxyphenyl)-3-phenoxyazetidin-2-one (4c). Yield: 85%. Mp: 157–159 °C. IR ($CHCl_3$) cm^{-1}: 1776.3 (CO), 3409.9 (NH). ^{1}H NMR (250 MHz, 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 (62.9 MHz, DMSO-d_6) δ 54.83 (OMe), 56.45 (C-4), 81.76 (C-3), 113.19–158.68 (aromatic carbons), 166.84 (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-styrylazetidin-3-yl)-isoindoline-1,3-dione (4d). Yield: 76%. Mp: 168–170 °C. IR ($CHCl_3$) cm^{-1}: 1726.2, 1768.6 (CO, phth), 1784.0 (CO, β-lactam), 3417.0 (NH). ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.72 (H-4, m, 1H), 5.60 (H-3, d, 1H, $J = 5.2$), 6.25 (H-5, dd, 1H, $J = 7.6$, 16.0), 6.70 (H-6, d, 1H, $J = 16.0$), 7.22–7.92 (ArH, m, 9H), 8.85 (NH, brs, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 55.38 (C-4), 58.69 (C-3), 123.42–135.69 (C=C, aromatic carbons), 164.06 (CO, phth), 166.93 (CO, β-lactam). GC-MS $m/z = 318$ [M^+]. Anal. calcd. for $C_{19}H_{14}N_2O_3$: C, 71.69; H, 4.43; N, 8.80. Found: C, 71.74; H, 4.49; N, 8.78.

2-[2-(3,4-Dimethoxyphenyl)-4-oxo-azetidin-3-yl]-4-nitroisoindole-1,3-dione (4e). Yield: 82%. Mp. 117–119 °C. IR (KBr, cm^{-1}) 1735.0, 1770.2 (phth., CO), 1785.0 (CO, β-lactam), 3380.5 (NH). ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.61, 3.75 (2 OMe, 2 s, 6H), 5.04 (H-4, dd, 1H, $J = 12.2$, 3.5), 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 (62.9 MHz, DMSO-d_6) δ 55.44, 55.85 (OMe), 60.81 (C-4), 63.16 (C-3), 110.08–150.07 (aromatic carbons), 163.36 (CO), 164.49 (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.

4-(4-Nitrophenyl)-3-phenoxyazetidin-2-one (4f). Yield: 83%. Mp: 160–162 °C. IR (KBr) cm^{-1}: 1774.4 (CO), 3247.9 (NH). ^1H NMR (250 MHz, DMSO-d_6) δ 5.33 (H-3, d, 1H, $J = 4.8$), 5.77 (H-4, dd, 1H, $J = 2.2, 4.8$), 6.77–8.20 (ArH, m, 9H), 9.10 (NH, brs, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 56.01 (C-4), 82.71 (C-3), 115.04–156.24 (aromatic carbons), 165.78 (CO, β-lactam). GC-MS $m/z = 284$ [M^+]. Anal. calcd. for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25; N, 9.85. Found: C, 63.44; H, 4.30; N, 9.87.

3-Phenoxy-4-styrylazetidin-2-one (4g). Yield: 79%. Mp: 190–192 °C. IR (KBr) cm^{-1}: 1775.7 (CO), 3310.0 (NH). ^1H NMR (250 MHz, DMSO-d_6) δ 4.64 (H-4, m, 1H,), 5.51 (H-3, d, 1H, $J = 4.3$), 6.18 (H-5, dd, 1H, $J = 7.4, 15.9$), 6.65 (H-6, d, 1H, $J = 15.9$), 6.90–7.33 (ArH, m, 9H), 8.96 (NH, brs, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 60.67 (C-4), 87.47 (C-3), 120.30–162.15 (C═C, aromatic carbons), 170.78 (CO, β-lactam). GC-MS $m/z = 265$ [M^+]. Anal. calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.92; H, 5.77; N, 5.24.

3-Phenoxy-4-*p*-tolylazetidin-2-one (4h). Yield: 85%. Mp: 180–182 °C. IR (KBr) cm^{-1}: 1773.9 (CO), 3300.0 (NH). ^1H NMR (250 MHz, DMSO-d_6) δ 1.95 (Me, s, 3H), 4.81 (H-3, d, 1H, $J = 4.4$), 5.32 (H-4, dd, 1H, $J = 2.2, 4.4$), 6.54–6.98 (ArH, m, 9H), 8.60 (NH, brs, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 20.62 (Me), 56.52 (C-4), 82.34 (C-3), 115.07–156.66 (aromatic carbons), 166.14 (CO, β-lactam). GC-MS $m/z = 253$ [M^+]. Anal. calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.84; H, 6.03; N, 5.48.

2-(2-Oxo-4-*p*-tolylazetidin-3-yl)isoindoline-1,3-dione (4i). Yield: 83%. 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 (250 MHz, 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 (62.9 MHz, DMSO-d_6) δ 20.68 (Me), 55.43 (C-4), 62.63 (C-3), 123.39–137.27 (aromatic carbons), 164.56 (CO, phth), 166.71 (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-(4-Chlorophenyl)-4-oxoazetidin-3-yl)-isoindoline-1,3-dione (4j). Yield: 78%. Mp: 196–198 °C. IR ($CHCl_3$) cm^{-1}: 1733.9, 1777.0 (CO, phth), 1785.0 (CO, β-lactam), 3373.5 (NH). ^1H NMR (250 MHz, DMSO-d_6) δ 4.92 (H-3, d, 1H, $J = 2.5$), 5.04 (H-4, dd, 1H, $J = 2.5, 3.2$), 7.41–7.92 (ArH, m, 8H), 9.01 (NH, brs, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 54.96 (C-4), 62.53 (C-3), 123.37–138.08 (aromatic carbons), 164.48 (CO, phth), 166.70 (CO, β-lactam). GC-MS $m/z = 328$ [M^+, ^{37}Cl], 326 [M^+, ^{35}Cl]. Anal. calcd. for $C_{17}H_{11}ClN_2O_3$: C, 62.49; H, 3.39; N, 8.57. Found: C, 62.55; H, 3.43; N, 8.54.

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