



On-column N-dearylation of 2-azetidiones 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-azetidiones under mild conditions. Starting materials are charged on top of the column and the pure *N*-unsubstituted 2-azetidiones 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.

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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-azetidione ring.⁴ Ezetimibe is a new drug, which has the 2-azetidione 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

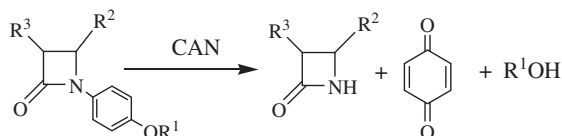
N-Unsubstituted 2-azetidiones offer major synthetic opportunities in the synthesis of β -lactam antibiotics and the glutamine

synthetase inhibitor, tabtoxin.⁹ Application of *N*-unsubstituted 2-azetidiones in the semi-synthesis of the anticancer agents Taxol and Taxotere has been also reported.¹⁰

Routes to *N*-unsubstituted 2-azetidiones involve the reaction of *N*-trimethylsilyl imines with the corresponding compounds,¹¹ reaction of chlorosulfonyl isocyanate with alkenes¹² 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–SiO₂) 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*-methylindoxyl²¹ and oxidative deprotection of benzylic tetrahydropyranyl ethers.²² High applications of ceric ammonium nitrate on silica gel (CAN–SiO₂) 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–SiO₂ 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–SiO₂ column. Also purification of the products was performed at the same time. The 10% CAN–SiO₂ 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–SiO₂, 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

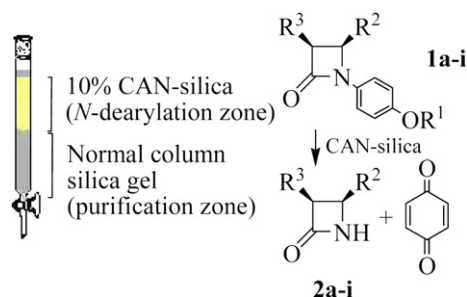


Fig. 1. Type A column.

dichloromethane and the solvent was allowed to percolate down to the surface of silica gel. Then the column was eluted with THF/H₂O (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, *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 Na₂SO₃ 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% SiO₂–Na₂SO₃, 10% CAN–SiO₂, and a little silica gel (Fig. 2).

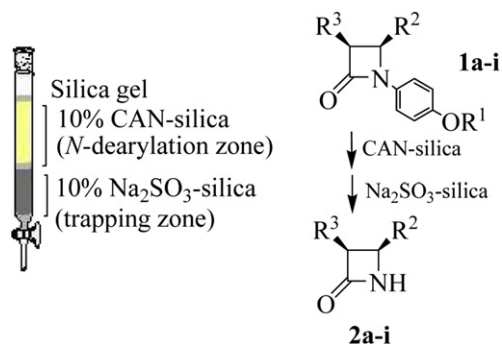


Fig. 2. Type B column.

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 (Na₂SO₃–SiO₂). 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 CoF₃.^{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 ₃ CN/H ₂ O	CH ₂ Cl ₂ /H ₂ O	On column A	On column B	
1a	Me	3,4-DiMeOC ₆ H ₃	PhO	2a	94	81	91	94	83
1b	Me	2,3-DiMeOC ₆ H ₃	PhO	2b	86	73	83	88	77
1c	Me	3,4-DiMeOC ₆ H ₃	3-NO ₂ PhthN	2c	88	68	90	87	79
1d	Et	CH=CHPh	PhthN	2d	91	74	87	93	71
1e	Et	4-MeOC ₆ H ₄	PhO	2e	85	74	85	89	85
1f	Et	CH=CHPh	PhO	2f	93	79	91	90	78
1g	Et	4-NO ₂ C ₆ H ₄	2-NaphthO	2g	82	71	88	92	80
1h	Et	4-NO ₂ C ₆ H ₄	2,4-DiClC ₆ H ₃ O	2h	91	80	90	94	74
1i	Et	4-MeC ₆ H ₄	MeO	2i	84	75	86	87	85

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