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Exploring a Benzyloxyaniline Linker Utilizing Ceric Ammonium Nitrate (CAN) as a Cleavage Reagent: Solid-Phase Synthesis of N-Unsubstituted β-Lactams and Secondary Amides

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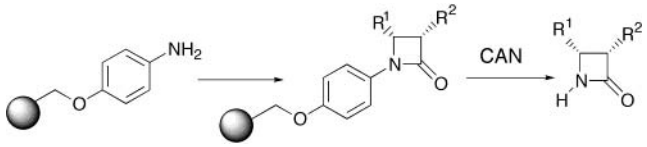
ABSTRACT



A novel benzyloxyaniline linker that uses ceric ammonium nitrate (CAN) as a cleavage reagent is described. Its application in the solid-phase synthesis of N-unsubstituted β-lactams and secondary amides furnishes compounds in moderate to excellent yield (45–91%) and high purity (93–99%).

There are a number of amide releasing linkers[1] that have been described that possess an amino group for incorporation as −NHCO− into their products. Such linkers include Rink,[2] Sieber amide,[3] PAL,[4] SASRIN,[5] BAL,[6] and MAMP.[7] These linkers rely on acid-induced S_N1 cleavage mechanisms and incorporate extended aromatic systems to stabilize the resulting cations. A drawback of such systems is that their amino groups are sterically hindered by methoxy groups included in their aromatic systems. For example, the acylation of Rink amide secondary amines with amino acids possessing bulky side chains was reported to occur in only modest yields (~60%).[8]

Herein we report a new amine linker of this category that is cleaved using ceric ammonium nitrate ($Ce(NO_3)_6(NH_4)_2$, CAN). The linker has been designed for the release of secondary amides and, in particular, β-lactams but will have broader application. Monocyclic β-lactams such as the nocardicins[9] and monobactams[10] are of interest as they have been found to exhibit antibiotic properties. These compounds can be synthesized by various routes, though the preparation of a *N*-unsubstituted β-lactam is a common feature.[8] In solution-phase syntheses CAN has been utilized to remove the *p*-methoxyphenyl group from the amide nitrogen of β-lactams to generate their *N*-unsubstituted analogues.[11,12] This reaction involves oxidation of the aromatic ring to benzoquinone with the release of 1 mole equiv of MeOH

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and 1 mole equiv of product amide. Deprotection is typically carried out in aqueous MeCN and is neither strongly acidic or basic. The reaction is generally rapid, requiring only a few minutes at room temperature, and exhibits high selectivity.[10]

Exploitation of CAN in a solid-phase cleavage strategy offers mild, rapid, and selective cleavage conditions. The linker is based on resin bound aniline and is free from steric hindrance and easy to prepare (Figure 1). The benzyloxy-

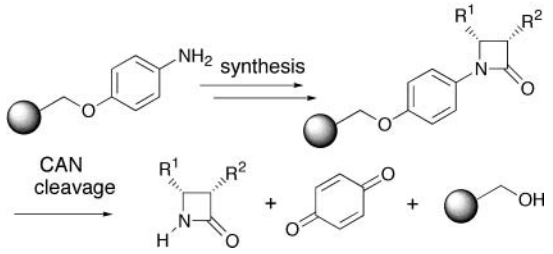
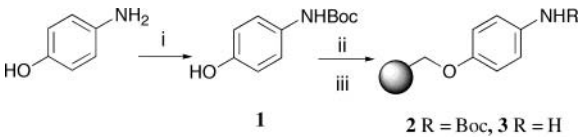


Figure 1. Linker construct that enables CAN cleavage.

aniline linker is also acid stable which contrasts with the CAN or TFA cleavable benzyloxybenzylamine (BOBA) linker.[23]

The linker was synthesized in three high yielding steps (Scheme 1) from *p*-aminophenol, which was first Boc-

Scheme 1. Synthesis of *p*-Benzyloxyaniline Resin[a]



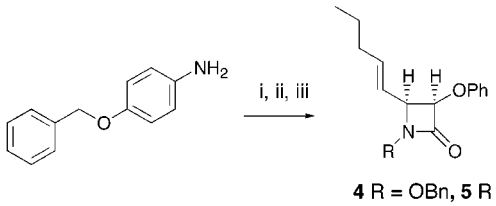
[a] (i) Et_3N (1 equiv), Boc_2O (1 equiv), DMF, 12 h, 0 °C to room temperature, 99%; (ii) NaH (3 equiv), **1** (3 equiv), DMF, 0 °C, 1 h then add to Br TentaGel resin (1 equiv), DMF, rt, 12 h, 97%; (iii) 10% TFA/DCM, rt, 12 h then filter and wash with Et_3N/DCM.

protected on the aniline nitrogen and then O-alkylated with bromomethyl TentaGel resin (Novabiochem, 0.28 mmol/g).

A TentaGel resin was selected for this initial work for its compatibility with the aqueous conditions required for CAN cleavage. Boc deprotection and neutralization gave the free amine resin **3** (97%, loading 0.28 mmol/g) as confirmed by the complete disappearance of the Boc trimethyl peak at 28.5 ppm in the ^{13}C gel-phase NMR spectrum.

To test whether CAN could cleanly remove the benzyloxyphenyl group, a solution-phase model synthesis was examined. Benzyloxyaniline, a resin mimic, was condensed with *trans*-hexenal in DCM with 4 Å molecular sieves. *trans*-Hexenal, an aldehyde with aliphatic carbons, was chosen to facilitate reaction monitoring by ^{13}C gel-phase NMR spectroscopy in the corresponding solid-phase reaction. The resultant imine underwent cycloaddition with phenoxyacetyl

Scheme 2. Solution-Phase Study of the CAN Cleavage Reaction on the *p*-Benzyloxyphenyl Group[a]



[a] (i) *t*-Hexenal (1 equiv), 4 Å molecular sieves, DCM, rt, 1 h; (ii) Et_3N (5 equiv), phenoxyacetyl chloride (2 equiv), DCM, 0 °C to room temperature, 18 h, 67% for two steps; (iii) CAN (3 equiv), MeCN/H_2O (2:1), 0 °C to room temperature, 1 h, 59%.

ketene, selected to exclusively furnish *cis* β-lactam, to afford **4** (67%, Scheme 2).[13] Lactam **4** was then reacted with CAN (3 equiv) in aqueous MeCN at ambient temperature for 0.5 h. A TLC of the crude reaction mixture indicated the presence of benzoquinone, which is a useful indicator for the reaction and can be easily removed by extraction into 20% aqueous Na_2SO_3. Subsequent removal of the final traces of CAN (detected by ^1H NMR spectroscopy) by filtration through a short plug of silica then furnished product **5** in 59% yield and greater than 95% purity (as judged by ^1H NMR spectroscopy).

Having demonstrated the ability of CAN to cleave the *p*-benzyloxyphenyl group, the solid-phase synthesis of β-lactams was examined. Although a number of papers have described the solid-phase synthesis of these pharmacologically renowned compounds,[14−17] only one has offered a route to N-unsubstituted derivatives[18] via the α-methyl-6-nitroveratrylamine photolabile linker.[19] Resin **3** was therefore condensed with an excess of *trans*-hexenal in DCM with 4 Å molecular sieves for 0.5 h and was washed with anhydrous DCM. A second condensation step was utilized to ensure complete imine formation for the subsequent cycloaddition with ketene, formed in situ from phenoxyacetyl chloride and Et_3N. Successful conversion to the β-lactam was confirmed by FTIR spectroscopy (υ cm^{-1} 1753) and ^{13}C gel-phase NMR spectroscopy.

The cleavage conditions were next examined by treatment of the resin bound β-lactam with either 5 or 10 equiv of CAN for 0.5, 2, or 5 h at ambient temperature. The resins were filtered and washed with several portions of DCM and H_2O, and the filtrates were extracted with DCM. The combined organics were then washed with saturated $NaHCO_3$, 20% aqueous Na_2SO_3, and brine. FTIR spectroscopy of all of the cleaved resins indicated quantitative release (disappearance of the β-lactam carbonyl at 1753 cm^{-1}), and

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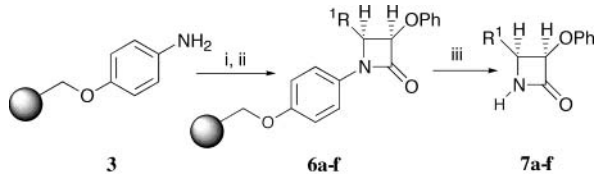
HPLC analysis of the resulting crude product **7a** revealed 5 equiv of CAN for 0.5 h to be effective cleavage conditions. When underivatized resin **3** was reacted with CAN (5 equiv) in aqueous MeCN for 0.5 h, benzoquinone was detected in the resin solvent, and a ^{13}C gel-phase NMR spectrum confirmed the formation of an alcohol resin

Having studied the conditions for β-lactam synthesis and cleavage, an array of β-lactams was synthesized using six aldehydes of varying stereoelectronic and steric character (Table 1). The mechanism of the Staudinger reaction involves

Table 1. CAN Cleavage of β-Lactams



3 **6a-f** **7a-f**

7	R^1	% purity[a]	% yield[b]
a	$CH_3(CH_2)_2CH{=}CH$-	98	83
b	4-nitrophenyl-	93	88
c	3-chlorophenyl-	98	62
d	2-bromophenyl-	99	56
e	$(CH_3)_3C$-	96	45
f	4-methoxyphenyl	97	85

[a] Determined by HPLC with UV detection at 220 nm. [b] Calculated from the loading of resin **3**.

initial nucleophilic attack of the imine nitrogen on the ketene carbonyl to form a zwitterionic intermediate, which cyclizes to form exclusively *cis* β-lactam, providing amines and acid chlorides are chosen such that they do not stabilize the zwitterionic charges.[20] The stereoelectronic nature of the aldehyde affects the nucleophilicity of the imine, with electron-donating and electron-withdrawing groups favoring and hindering reaction, respectively. In the second ring closure step, however, this trend is reversed and electron-withdrawing substituents are expected to enhance product formation. *p*-Anisaldehyde and *p*-nitrobenzaldehyde were therefore utilized to probe the sensitivity of the reaction to electronic character, while *m*-chlorobenzaldehyde was included as a "neutral" aldehyde being neither activated nor deactivated. *o*-Bromobenzaldehyde and trimethylacetaldehyde were also examined in the array to test for any steric effects in the reaction. Imine formation, for example, would be expected to be more difficult with sterically hindered carbonyl groups as would ring closure, which requires reaction at the aldehyde carbonyl carbon.

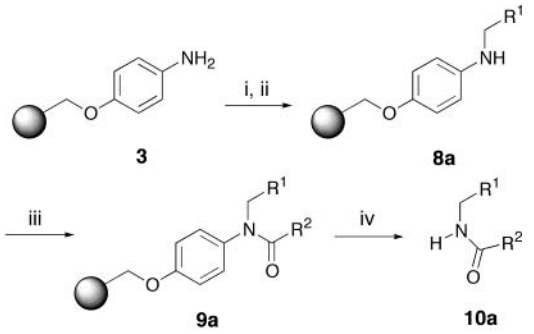
^{13}C gel-phase NMR and FTIR spectra of resins **6a**−**f** were obtained and indicated efficient transformations. Each of the resins was cleaved with 5 equiv of CAN for 0.5 h at room temperature, and the resin filtrates were extracted and washed as described earlier. Following filtration through a short plug of silica to remove the final traces of CAN, HPLC analysis of the crude products showed high levels of purity (Table 1). The yields obtained were also good to excellent (45−88%), with the lower yields deriving from the sterically hindered aldehydes *o*-bromobenzaldehyde and trimethylacetaldehyde. Their purity was not compromised, suggesting that the reduction in yield was most likely due to either incomplete imine formation or cycloaddition. This would result in reversion to aniline resin **3** during washing and release of MeOH, NH_3 and benzoquinone during CAN cleavage.

The mechanism of CAN deprotection of the *p*-methoxyphenyl group from amides has not been studied. Experiments on the oxidation of 1,4-dimethoxybenzenes and 1,4,5,8-tetramethoxynaphthalenes to their quinones have, however, shown that it is the aryl-oxygen bonds that are cleaved[21] and that 2 equiv of CAN are required.[22] The proposed mechanism thus involves two single electron oxidations of the electron rich aromatic ring.[22]

According to this mechanism cleavage of amide product from the benzyloxyaniline linker is accompanied by the release of 1 mole equiv of MeOH and benzoquinone, which are easily removed under vacuum and by extraction into Na_2SO_3, respectively. The amide product can therefore be obtained pure, without need for chromatography.

In β-lactams, the amide bond is less electron-withdrawing than in acyclic systems as a result of a decrease in delocalization of the nitrogen lone pair. To explore whether this effect is significant for CAN cleavage of the *p*-benzyloxyphenyl group, the synthesis and release of an acyclic secondary amide was investigated. Resin **3** was reacted with *p*-nitrobenzaldehyde to furnish the corresponding imine, which was reduced with $NaBH_4$ to **8a** (R^1 = *p*-nitrophenyl, Scheme 3). Subsequent acylation then furnished the acyclic amide **9a** (R^1 = *p*-nitrophenyl, R^2 = CH-$(CH_3)_2$), which was characterized by ^{13}C gel-phase NMR and

Scheme 3. Synthesis and Release of Acyclic Secondary Amides Using CAN as a Cleaving Agent[a]



[a] (i) R_1CHO (10 equiv), 4 Å molecular sieves, DCM, rt, 0.5 h, filter and wash with anhydrous DCM, repeat; (ii) $NaBH_4$ (5 equiv), MeOH/THF (1:1), rt, 10 h; (iii) DMAP (cat.), Et_3N (5 equiv), R_2COCl (5 equiv), DCM, rt, 10 h; (iv) CAN (5 equiv), MeCN/H_2O (2:1), rt, 0.5 h.

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Table 2. CAN Cleavage of Secondary Amides

10	R_1	R_2	% purity[a] (% yield)[b]
a	4-NO_2 phenyl-	$CH(CH_3)_2$	96 (83)
b	4-Me phenyl-	$CH(CH_3)_2$	93 (91)
c	2-Br phenyl-	$CH(CH_3)_2$	94 (64)
d	$(CH_3)_3C$-	Ph	95 (70)
e	4-MeO phenyl-	$CH(CH_3)_2$	*c*

[a] Determined by HPLC with UV detection at 220 nm. [b] Calculated from the loading of resin **3**. [c] Complex mixture of products produced.

FTIR spectroscopy. Exposure of resin **9a** to the cleavage conditions (5 equiv CAN, 0.5 h, room temperature) resulted in 83% product in high purity (96%).

Four more aldehydes were examined, with trimethylacetaldehyde and *o*-bromobenzaldehyde again being selected to examine the steric influences in the system. In this scheme the nature of the substituent at the imine carbon, deriving from the aldehyde, was found to have less effect on the efficiency of the reaction than in β-lactam synthesis as products were generally obtained in higher yields (64−91%) and purity (93−96%, Table 2). This suggests that it is the cyclization step of β-lactam formation (rather than imine formation) that is sensitive to steric encumbrance.

Utilization of *p*-anisaldehyde produced a complex mixture of products, presumably as a result of the opportunity for competitive *p*-methoxybenzyl cleavage. This result also contrasts with that obtained for the *p*-anisaldehyde derived β-lactam **7f** and may be due to the fact that this would have required cleavage of the β-lactam ring. *p*-Tolualdehyde was investigated to test the applicability of the cleavage conditions in the presence of a non-alkoxy-activated aromatic ring and yielded product in high yield (91%) and purity (93%).

To summarize, a new benzyloxyaniline linker utilizing CAN as a cleavage reagent has been developed for the synthesis and release of secondary amides, including β-lactams. The linker can be prepared in three steps in high yield (96%). Cleavage of the linker with CAN occurs rapidly (<0.5 h) in mild conditions (aqueous MeCN, room temperature) and compounds of high purity (typically >90%) are obtained after a simple extraction and filtration protocol. Application of this strategy for the release of secondary amines is currently under investigation.

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Supporting Information Available: Experimental procedures and characterization data for **2**, **3**, **6a**−**f**, **7a**−**f, 8a**−**e, 9a**−**e** and **10a**−**d**. ^{13}C NMR and ^{1}H NMR spectra of **6a** and **7a**, respectively. This material is available free of charge via the Internet at http://pubs.acs.org.

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