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Ceric ammonium nitrate-mediated detritylation of tritylated amines

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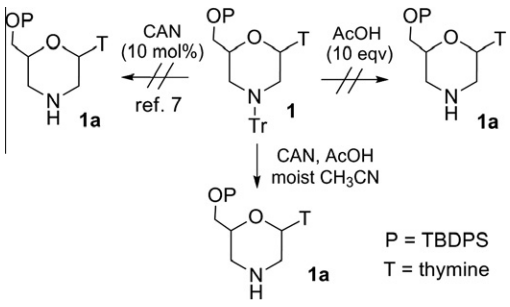
ABSTRACT

Efficient deprotection of tritylated amines to the corresponding amines mediated by 20 mol % ceric ammonium nitrate [$Ce(NH_4)_2(NO_3)_6$, CAN], 10 equiv of acetic acid and 15 equiv of water in dichloromethane is presented. This method equally worked well in the case of morpholino nucleosides.

The triphenylmethyl (trityl) moiety is a valuable protecting group for the hydroxyl, amine and thiol functionalities.[1] The bulky size of trityl gives high selectivity for protection and the derivatives are mostly crystalline solids which can be easily separated and purified by recrystallization. For *N*-detritylation, acidolysis with protonic acids (e.g., HCl, HBr, CF_3CO_2H, CCl_3CO_2H)[2] or Lewis acids (e.g., Yb(OTf)$_3$, $ZnBr_2$, diisopropylaluminum chloride)[3] is the widely used method but still HCl and CF_3CO_2H are the most common reagents.[4] In addition, Pd mediated hydrogenolysis,[5] harsh conditions like reductive demercuration,[6a] naphthalene catalyzed lithiation[6b] and Na/NH_3[6c] have also been employed to deprotect *N*-trityl compounds. Recently, ceric ammonium nitrate [$Ce(NH_4)_2(NO_3)_6$, CAN][7] or ceric triflate[8] have been used as suitable catalysts for the deprotection of trityl, monomethoxytrityl and dimethoxytrityl groups in wet acetonitrile under neutral conditions. However CAN-mediated deprotection has been reported for the hydroxy functionality of nucleosides and nucleotides whereas only three examples such as: *N*-tritylated phosphoramidate, *N*-tritylated-adenosine and *N*-tritylated-cytosine have been shown for *N*-detritylation.[7]

During our ongoing project we tried to deprotect *N*-trityl protected morpholino monomer **1** using 10 mol % of CAN in moist acetonitrile[7] (ACN) but unfortunately only a marginal conversion was observed (thin layer chromatography, TLC) even after stirring the reaction mixture for two days. According to the reaction mechanism,[7] the deprotected trityl cation converts into the corresponding trityl alcohol in the presence of water. We postulated that in case of *N*-detritylation, water might not be a good scavenger for trityl cation in comparison to the deprotected free amine.

Based on this postulation, we added a small amount (10 equiv) of acetic acid to the above reaction medium to protonate the deprotected amine. Interestingly, the reaction proceeded well and within one day, about 70% conversion was observed (Scheme 1). In order to confirm whether only acetic acid is responsible for the deprotection, the reaction was performed with only 10 equiv of AcOH in acetonitrile but almost no reaction was observed (TLC). Thus a combination of both CAN and AcOH is essential for the reaction. It is worth mentioning here that, during the synthesis of morpholino oligomers on solid support, *N*-detritylation of morpholino monomers was done with continuous flow of 2% acetic acid in trifluoroethanol[9] in order to remove the naked trityl cation and the reagent was used in large excess for complete deprotection.



Scheme 1. Deprotection of *N*-trityl morpholino monomer using 0.20 equiv CAN and 10 equiv AcOH.

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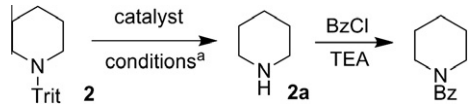
Encouraged by this result, we sought to find more appropriate conditions for the deprotection. We investigaed various conditions using CAN or CAN–SiO_2 as a catalyst in the presence of acetic acid to the readily available *N*-tritylpiperidine **2**[6a] and the results are summarized in Table 1. Typically, CAN was dissolved in minimum amount (roughly 15 equiv) of water followed by the addition of the substrate, solvent and acetic acid. The progress of the reaction was monitored by thin layer chromatography (TLC). In a dry solvent, without the addition of water, no reaction was observed. In the presence of CAN in dichloromethane (DCM), only a marginal progress of the reaction was observed (TLC) (entry 1). When the same reaction was performed in combination with 10 equiv of acetic acid, the reaction progressed well and 75% yield was isolated after in situ benzoyl protection (entry 3). Performing the reaction with only 10 equiv of acetic acid without CAN afforded good yield but the reaction took a longer period of time (entry 2). The tritylpiperidine **2** was then treated with 20 mol % of CAN in the presence of 10 and 5 equiv of acetic acid in DCM. In the presence of 10 equiv of acid, the reaction was completed in shorter time and 90% yield of the benzoyl-derivative was isolated (entry 4). GC analysis of the reaction mixture indicated complete disappearance of the starting material. Reduction of the amount of acid to 5 equiv did not help the reaction to reach completion and 63% benzoylated product was isolated (entry 5). The reaction was also done in acetonitrile but it took a longer period of time for completion (entry 6). Among the solvents tested, DCM was found to be superior to ACN, THF and DMF (entries 4 and 6–8). We attempted to remove trityl group using CAN–SiO_2 using the conditions reported by Hwu et al.[7] but CAN and CAN–SiO_2 were found to be almost comparable (entries 9–12). Again CAN–SiO_2 alone did not promote any transformation, and the starting material was almost completely recovered even after prolonged contact time whereas the deprotection went well in combination with 10 equiv of acetic acid (entries 9 and 10–12). The best results were obtained when 0.20 equiv of CAN or CAN–SiO_2 and 10 equiv of acetic acid were used in DCM (entries 4, 12).

In order to explore the generality of the present method we examined the deprotection on a number of substrates. The results are reported in Table 2. The trityl group was introduced readily by the treatment of parent amines with trityl chloride in the presence of triethylamine in dry DCM. The most unactivated long chain tritylamines **3** and **4** (Table 2, entries 1, 2) participated in this reaction and gave deprotected amines in excellent yield. Similarly the trityl protected benzyl amine **5** and its derivative **6** (Table 2, entries 3, 4) underwent clear deprotection and both the phenyl rings were intact in the presence of CAN and acetic acid. The deprotected 2-methoxybenzylamine was isolated as an acetyl-derivative in 87% yield after in situ acetylation with acetic anhydride and chromatographic purification. Heterocyclic ring containing substrate like *N*-trityl-2-picolylamine underwent complete deprotection within 5 min and the product was isolated in acetylated form (entry 5). As trityl is a useful protecting group in peptide chemistry, a trityl protected dipeptide (**8**) was subjected for deprotection under these conditions and the deprotected peptide was isolated as an acetyl-derivative in 84% yield (entry 6). Next we tried the deprotection reaction with methyl ester of trityl-protected proline because

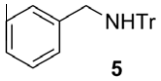
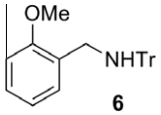
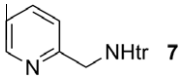
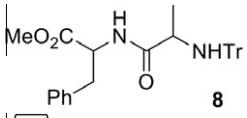
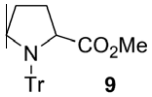
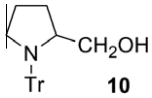
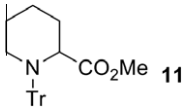
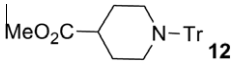
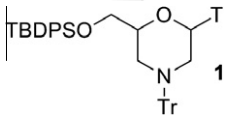
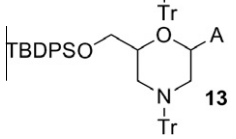
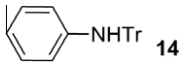
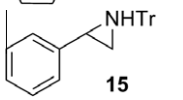
Table 1
Screening of reaction conditions for the deprotection of trityl amine **2**



Entry	Catalyst[c] (mol %)	AcOH (equiv)	Solvent	Time (h)	Yield[b] (%)
1	CAN (10)	—	DCM	20	Trace
2	—	10	DCM	40	76
3	CAN (10)	10	DCM	24	75
4	CAN (20)	10	DCM	4	90
5	CAN (20)	5	DCM	24	63
6	CAN (20)	10	ACN	18	88
7	CAN (20)	10	THF	20	80
8	CAN (20)	10	DMF	10	81
9	CAN–SiO_2 (10)	—	DCM	20	Trace
10	CAN–SiO_2 (10)	10	DCM	16	82
11	CAN–SiO_2 (20)	10	ACN	12	90
12	CAN–SiO_2 (20)	10	DCM	2	92

[a] Moist solvents were used.
[b] Yields were calculated based on benzoyl-derivative after silica gel column chromatography.
[c] 15 equiv H_2O was added to dissolve CAN before adding solvent.

Table 2
Yield of detritylation reactions[a]

Entry	Tritylated amine	Time	Yield (%)
1	$CH_3(CH_2)_{10}CH_2NHTr$ **3**	33 h	90[b]
2	$CH_3(CH_2)_{16}CH_2NHTr$ **4**	40 h	93[b]
3	 **5**	7.5 h	98[b]
4	 **6**	13 h	87[c]
5	 **7**	5 min	88[c]
6	 **8**	1.5 h	84[c]
7	 **9**	8 min	96[b]
8	 **10**	30 min	89[b]
9	 **11**	45 min	92[b]
10	 **12**	1 h	89[b]
11	 **1**	48 h	94[b]
12	 **13**	40 h	81[b]
13	 **14**	5 min	Oxidation
14	 **15**	2 h	Ring cleavage and oxidation

[a] Conditions: substrate (1.0 equiv), CAN (20 mol %), AcOH (10 equiv) and H_2O (15 equiv) in DCM.
[b] Yield based on work-up Method A (see footnote 14).
[c] Column purified yield by Method B (see footnote 14).

this substrate is an important building block for the stereoselective synthesis in organic chemistry.[4b] The detritylation of this substrate was earlier done by hexafluoroisopropanol or 5 M HCl[4b] or TFA[4c,d] whereas in our case the deprotection occurred under mild conditions just within 8 min (entry 7). Similarly we applied the reaction on trityl protected prolinol **10** which also gave a clean deprotected amine in excellent yield (entry 8). Encouraged by this finding, the method was extended to other amino acid derivatives like *N*-tritylpipecolinic acid methyl ester **11** and *N*-tritylisonipecotic acid methyl ester **12** which were deprotected to yield free amines (entries 9, 10). As pointed out earlier, *N*-trityl protected thymidine morpholino monomer **1** responded smoothly to the conditions although longer time is needed (entry 11). Adenosine morpholino monomer **13** was also similarly deprotected (entry 12). The TBDPS protection did survive under the reaction conditions. When we applied this methodology to aniline, an instant black colour appeared due to the formation of benzidine[10] as evidenced from the mass spectra of crude reaction mixture (entry 13). Present methodology cannot be applied on aziridines as unidentified products were formed presumably due to ring cleavage and oxidation (entry 14).[11]

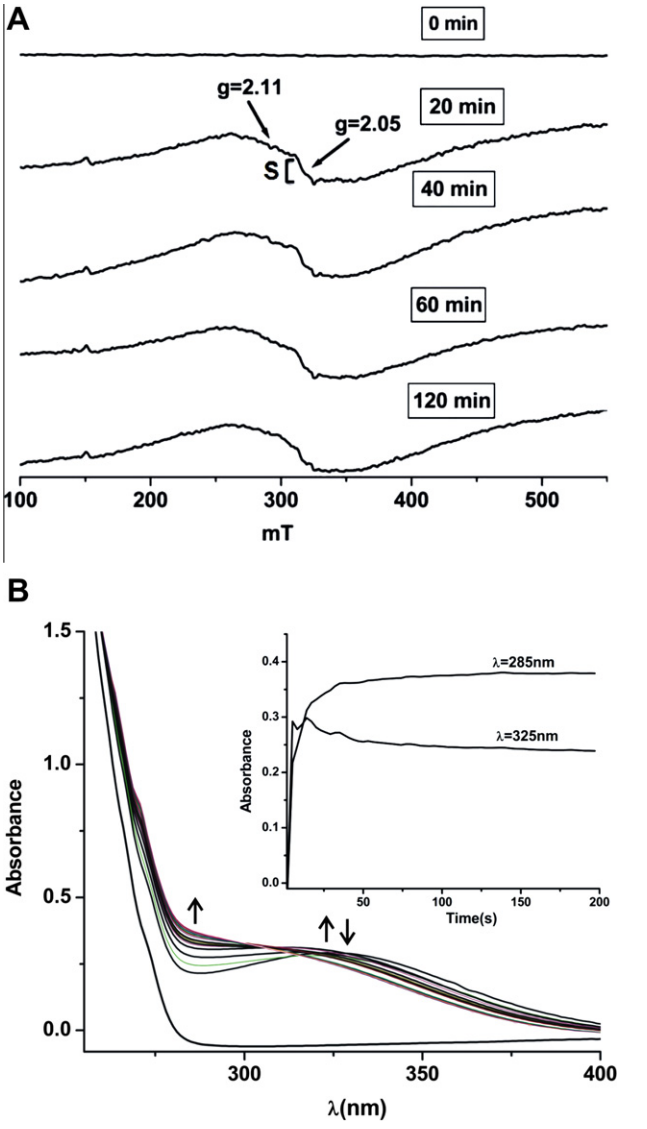


Figure 1. (A) The X-band EPR spectra of the detritylation reaction of **2** (0.15 mM solution in DCM) at different time intervals. (B) UV–vis spectra of the detritylation reaction (0.5 mM in ACN).

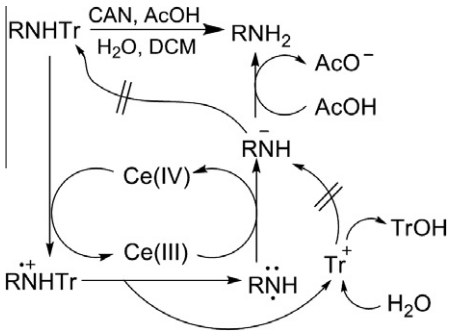


Figure 2. Proposed mechanism for CAN-mediated *N*-detritylation.

Proposed mechanisms[7] for deprotection of trityl ethers postulate the formation of Ce(III) and oxygen centred ion-radicals but no experimental evidences have been provided.

To investigate the mechanism of the reaction a set of preliminary experiments were conducted. Whereas Ce(IV) ion is diamagnetic, Ce(III) ion with a $^2F_{5/2}$ ground state is paramagnetic due to the presence of a single electron in the inner 4f shell. By electron paramagnetic resonance (EPR) spectroscopy, we monitored the progress of the detritylation of *N*-tritylpiperidine **2** in established reaction conditions at 120 K. Initially, at the commencement of the reaction, no EPR active species was found due to the presence of Ce(IV). A broad signal[12] having average *g* value 2.11 was obtained after few minutes confirming the formation of Ce(III) whose concentration remained almost constant during the course of the reaction (Fig. 1). The steep portion in the EPR spectrum labelled **S** (*g* value 2.05) may belong to one or more minor species (organic nitrogen centred ion-radicals[13]). Other features (e.g., hyperfine splitting) of the spectra of the minor species may be masked by the strong EPR signal of the major species, that is, Ce(III).

Guided by the EPR experiment results, we followed the kinetics of the same model reaction of **2** by UV–visible spectrometry to characterize the intermediates. At room temperature in ACN, no significant intermediates were observed. At low temperature (233 K) rapid first order formation and decay of two very short lived (2–3 s) intermediates were recorded (Fig. 2). The molar extinction coefficient ($\varepsilon = 528\ M^{-1}\ cm^{-1}$) indicates a charge transfer transition between cerium (IV) and the nitrogen centre. Our attempt to characterize these unstable intermediates by EPR at liquid nitrogen temperature remained unsuccessful.

Based on these observations we propose the following mechanism (Fig. 2). The initial step of detritylation is most likely a charge transfer complex which is followed by electron transfer to form the radical cation while reduction of Ce(IV) to Ce(III) takes place. The nitrogen centred radical cation then departs a trityl cation and in turn converts into the corresponding amine anion by taking one electron from Ce(IV). The naked trityl cation is scavenged by the water present. In the absence of acetic acid, reaction progression stops as trityl cation reacts with the anionic amine to give back the starting material.

In conclusion, we have developed a mild and efficient method for *N*-detritylation.[14] Applicability of the present method has been demonstrated on a variety of substrates. Preliminary investigations with the help of EPR and UV–visible spectroscopy have been carried out, suggesting the proposed mechanism.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.118.

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14. *General procedure*: The substrate (1 equiv) was added to a solution of CAN (20 mol %) in minimum amount of water (roughly 15 equiv). The reaction mixture was dissolved in dichloromethane and stirred magnetically. Acetic acid (10 equiv) was added to the solution and left to stir at rt for the required time mentioned in Table 2. Upon completion of the reaction, the solvent was evaporated under reduced pressure and worked up in the following methods. Method A: The solid residue was washed twice with petroleum ether to remove the by product trityl alcohol. The residue was then dissolved in methanol and filtered through a short pad of celite. Removal of the solvent under reduced pressure yielded the free amine. Method B: Water and acetic acid were removed from the reaction mixture in vacuo. The residue was dissolved in dry dichloromethane, followed by the addition of triethylamine (2.5 equiv) and acetic anhydride or benzoyl chloride (1.5 equiv). After the completion of the reaction, the solvent was evaporated. The residue was extracted with ethyl acetate twice. The combined organic layer was washed with water and brine and finally dried (Na_2SO_4). Solvent was removed under reduced pressure and the residue obtained was purified by silica gel column chromatography to afford the acylated amine.
15. *Selected spectral data:*
Compound **8**: white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (d, 3H, J = 7.0 Hz), 2.05 (br s, 1H), 3.10 (d, 2H, J = 5.7 Hz), 3.26 (q, 1H, J = 7.0 Hz), 3.72 (s, 3H), 4.56 (m, 1H), 7.19–7.22 (m, 2H), 7.25–7.36 (m, 18H), 7.68 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 21.2, 29.7, 38.0, 52.2, 52.7, 53.9, 72.0, 77.2, 126.2, 126.4, 127.1, 127.6, 128.0, 128.2, 128.4, 128.5, 128.8, 128.9, 129.4, 136.0, 145.5, 171.7, 175.4; HRMS calcd for $C_{32}H_{32}N_2O_3Na$ $(M+Na)^+$ 515.2311, found 515.2316.
Compound **9**: white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89–1.06 (m, 2H), 1.47–1.63 (m, 2H), 2.85 (dt, 1H, J = 11.0, 6.8 Hz), 3.38–3.46 (m, 1H), 3.49 (s, 3H), 3.90 (dd, 1H, J = 7.8, 1.8 Hz), 7.16 (t, 3H, J = 7.2 Hz), 7.23–7.32 (m, 6H), 7.57 (d, 6H, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 24.4, 31.4, 50.1, 51.7, 62.9, 126.3, 127.8, 129.4, 144.9, 177.4; HRMS calcd for $C_{25}H_{25}NO_2Na$ $(M+Na)^+$ 394.1783, found 394.1782.