# New detritylation method for nucleosides and nucleotides by ceric ammonium nitrate

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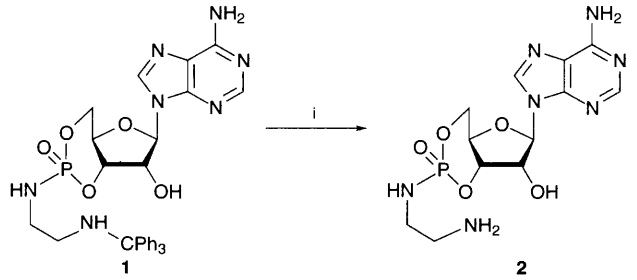
**The trityl and monomethoxytrityl groups are efficiently (80–98% yields) removed from protected nucleosides or nucleotides by use of 0.10 equivalent of $Ce(NH_4)_2(NO_3)_6$ in wet acetonitrile and DMF under neutral conditions.**

The triphenylmethyl (trityl) group is often used to protect the hydroxy functionality in carbohydrates because it can offer sterically controlled high selectivity.[1] Reagents used to remove the trityl group include hydrogen chloride, hydrogen bromide, acetic acid, trifluoroacetic acid,[2] sodium in liquid ammonia, hydrogen along with Pd/C and chlorine gas.[3] Detritylation under acidic conditions may cause acyl migration for ester-containing compounds[4] and cleavage of nucleobases in nucleosides and nucleotides.[5] The phosphoramidate linkage in the nucleotide derivative **1** does not survive during detritylation under mild acidic conditions.[6] On the other hand, use of sodium involving strong reducing conditions simultaneously destroys the ester and benzyl ether.[7] Hydrogenolysis of tritylated nucleosides proceeds somewhat sluggishly and often gives unsatisfactory results.[8] Removal of a trityl group with noxious chlorine gas is impractical on a large scale. Thus the discovery of an efficient detritylation method under mild conditions will broaden the use of the trityl group, especially in the chemistry of nucleic acids.

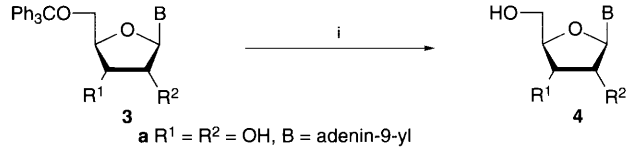
Ceric ammonium nitrate (CAN) functions as a one-electron transfer catalyst in various organic reactions.[9,10] Here we report our findings that CAN acts as a suitable catalyst for efficient detritylation of nucleosides and nucleotides.

Tritylated adenosine 3′,5′-monophosphoramide **1** (725 mg) in a wet mixture of acetonitrile (30 mL) and DMF (10 mL) was treated with a catalytic amount of CAN (64.6 mg, 0.10 equiv.) at 25 °C for 10 h. The solvent was then removed under reduced pressure and the residue washed with ether to remove triphenylmethanol. The product was recrystallized from methanol to afford detritylated nucleotide **2** (395 mg) in 90% yield (Scheme 1). We found that this method was widely applicable for the detritylation of nucleosides bearing a tritylated hydroxy group (*i.e.* **3a–f**) or a tritylated amino group (*i.e.* **3f**), as shown in Scheme 2. Completion of the detritylations took 1–15 h and yields of the isolated products ranged from 80–98% (Table 1). The same conditions were applied to the protected adenosine **5** and dinucleotide **6**[11] for removal of the 5′-*O*-mono(*p*-methoxy)-trityl group (MMTr) to give **4a** and **7** in 98 and 91% yields, respectively (Scheme 3 and Table 1).




**Scheme 1** *Reagents and conditions:* i, $Ce(NH_4)_2(NO_3)_6$ (0.10 equiv.), MeCN, DMF, $H_2O$, 25 °C, 90%

Our results indicate that some protecting groups sensitive to acids survived under the applied conditions; those groups include (dimethylamino)methylidene in **3b**, *tert*-butyldimethylsilyl in **3d**, and isopropylidene in **3e**. The *N*-glycosidic bond of nucleosides and nucleotides in **3a–f, 5** and **6** as well as the phosphoramidate linkage in **1** remained intact during detritylation by use of CAN. Furthermore, the acyl group in esters survived and yet migration to the adjacent hydroxy group did not occur in the conversion of 1-benzoyl-3-(triphenylmethyl)glycerol to 1-benzoylglycerol (94–98%) by use of CAN. In contrast, treatment of 1-benzoyl-3-(triphenylmethyl)glycerol with 5% $CF_3CO_2H$ in acetonitrile gave a mixture of 1-benzoylglycerol, 2-benzoylglycerol and glycerol in a ratio of 1.5 : 1 : 2.5. Isomerization of 1-benzoylglycerol to 2-benzoylglycerol was evidenced by $^1H$ NMR spectroscopy of




**a** $R^1 = R^2 = OH$, B = adenin-9-yl
**b** $R^1 = OH$, $R^2 = H$, B = $N^6$-(=$CHNMe_2$)-adenin-9-yl
**c** $R^1 = R^2 = OH$, B = uracil-1-yl
**d** $R^1 = OH$, $R^2 = OSiMe_2Bu^t$, B = uracil-1-yl
**e** $R^1 + R^2 = -OCMe_2O-$, B = uracil-1-yl
**f** $R^1 = OH$, $R^2 = H$, B = $N^4$-($CPh_3$)-cytosin-1-yl
**g** $R^1 = OH$, $R^2 = H$, B = cytosin-1-yl

**Scheme 2** *Reagents*: i, $Ce(NH_4)_2(NO_3)_6$ (0.10 equiv.), MeCN, DMF, $H_2O$, 80–98%

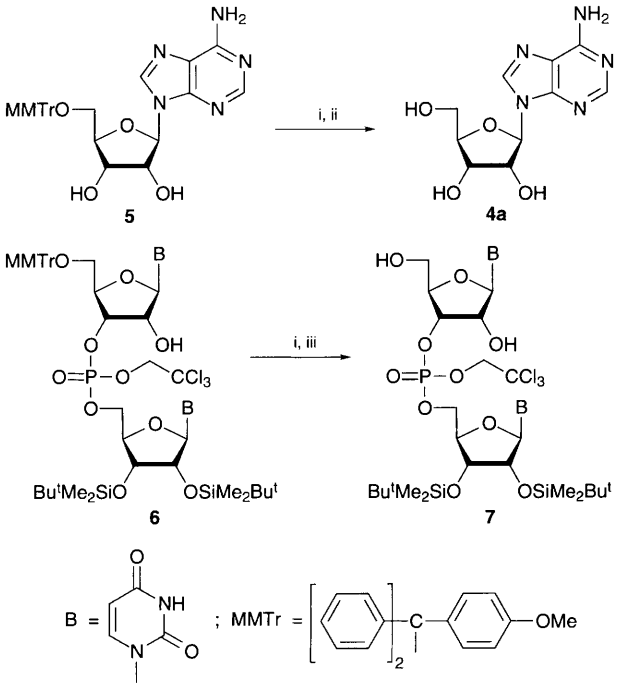
**Table 1** Detritylation of protected nucleosides and nucleotides by use of ceric ammonium nitrate (0.10 equiv.)

| Starting material | Solvent | *T*/°C | *t*/h | Product[a] | Yield (%) |
|---|---|---|---|---|---|
| **1** | MeCN/DMF (3 : 1) | 25 | 10 | **2**† | 90 |
| **1** | MeCN/DMF (3 : 1) | 82 | 1.5 | **2**† | 85 |
| **3a** | MeCN/DMF (3 : 1) | 25 | 13 | **4a** | 92 |
| **3a** | MeCN/DMF (3 : 1) | 82 | 1.5 | **4a** | 95 |
| **3b** | MeCN | 25 | 8 | **4b**[12] | 96 |
| **3b** | MeCN | 82 | 1 | **4b**[12] | 82 |
| **3c** | MeCN | 25 | 11 | **4c** | 88 |
| **3d** | MeCN | 25 | 12 | **4d**[11] | 80 |
| **3e** | MeCN | 25 | 10 | **4e**[13] | 90 |
| **3e** | MeCN | 82 | 1.2 | **4e**[13] | 98 |
| **3f** | MeCN | 25 | 15 | **4g** | 87 |
| **3f** | MeCN | 82 | 2 | **4g** | 93 |
| **5** | MeCN/DMF (5 : 1) | 25 | 1 | **4a** | 98 |
| **5** | MeCN | 82 | 0.1 | **4a** | 95 |
| **6** | MeCN | 25 | 1 | **7**[11] | 91 |

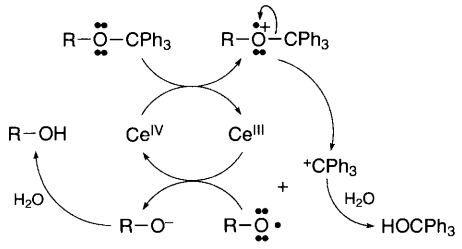
[a] The products were isolated and identified by comparison with authentic samples.

the above mixture. The C-2 proton appeared at lower field, δ 5.49 (t, *J* 5.2 Hz), in 2-benzoylglycerol in comparison with the corresponding regioisomer (*i.e.* 1-benzoylglycerol) at δ 4.00.†

A detritylation mechanism was proposed by using tritylated alcohols (Scheme 4). An essential step involves oxidation of trityl ether $ROCPh_3$ to the corresponding radical cation while reduction of $Ce^{IV}$ to $Ce^{III}$ takes place.[9] We found that the feasibility of deprotection by using CAN depended upon the stability of the resultant carbocation (*i.e.* $^+CPh_3$). At the same temperatures, deprotection of 5′-*O*-mono(*p*-methoxy)tritylated adenosine **5** and dinucleotide **6** proceeded about 10 times faster than deprotection of 5′-*O*-trityladenosine (**3a**,[6] Table 1). This is because the MMTr cation is more stable than $^+CPh_3$. In addition, regeneration of $Ce^{IV}$ from $Ce^{III}$ during the reduction of alkoxy radicals to alkoxides allows the use of a catalytic amount of CAN for detritylation.




**Scheme 3** *Reagents*: i, $Ce(NH_4)_2(NO_3)_6$ (0.10 equiv.), ii, MeCN, DMF, $H_2O$, 98%; iii, MeCN, $H_2O$, 91%




**Scheme 4**

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## Footnote

† *Spectral data* for **2**: mp 103–104 °C. $^1$H NMR [300 MHz, $(CD_3)_2SO$] δ 2.71 (2 H, s, $CH_2N$), 2.87 (2 H, s, $CH_2NP$), 3.03 (2 H, br s, $NH_2$), 4.36–4.61 (5 H, m, HC-2′ + HC-3′ + HC-4′ + $H_2C$-5′), 4.83 (1 H, br, OH), 6.07 (1 H, s, HC-1′), 7.84 (1 H, br, NH), 7.93 (2 H, br, $NH_2$), 8.03 (1 H, s, HC-2) and 8.11 (1 H, s, HC-8); $^{13}$C NMR [75 MHz, $(CD_3)_2SO$] δ 27.54 ($CH_2NH_2$), 35.76 ($CH_2NH$), 69.22 ($C_{2'}$), 71.94 ($C_{3'}$), 72.11 ($C_{4'}$), 76.53 ($C_{5'}$), 92.01 ($C_{1'}$), 118.24 ($C_5$), 140.21 ($C_8$), 147.73 ($C_4$), 151.42 ($C_2$) and 154.97 ($C_6$); UV(EtOH) $\lambda_{max}$ 260 nm (ε 15,300). For 1-benzoyl-3-(triphenylmethyl)glycerol: $^1$H NMR (300 MHz, $CDCl_3$) δ 3.25 (2 H, d, *J* 6.0 Hz, $CH_2OTr$), 3.89 (1 H, br, OH), 4.05 (1 H, br m, HC-2), 4.37 (2 H, d, *J* 6.0 Hz, $CH_2OCO$) and 7.12–8.04 (20 H, m, 4 × $C_6H_5$). For 1-benzoylglycerol: $^1$H NMR (300 MHz, $CDCl_3$) δ 2.45 (1 H, br, OH), 3.59–3.74 (2 H, m, $CH_2O$), 3.95 (1 H, d, *J* 6.2 Hz, OH), 4.00 (1 H, m, HC-2), 4.36 (2 H, m, $CH_2OCO$) and 7.36–8.01 (5 H, m, $C_6H_5$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 63.42 ($CH_2O$), 65.79 (CHO), 70.39 ($CH_2OCO$), 128.48, 129.74, 133.36 ($C_6H_5$) and 166.99 (CO).

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