



## A facile method for deprotection of trityl ethers using column chromatography

Ashish K. Pathak, Vibha Pathak, Laine E. Seitz, Kamal N. Tiwari, Mohammad S. Akhtar and Robert C. Reynolds\*

*Division of Organic Chemistry, Southern Research Institute, PO Box 55305, Birmingham, AL 35255-5305, USA*

Received 31 July 2001; accepted 28 August 2001

**Abstract**—A mild, efficient and inexpensive detritylation method is reported that uses trifluoroacetic acid on a silica gel column to obtain pure, detritylated compounds in one-step. This method is applicable to acid stable as well as acid sensitive compounds with only slight alterations in the procedure. Nineteen examples are given. © 2001 Elsevier Science Ltd. All rights reserved.

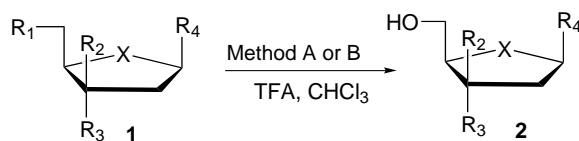
Triphenyl (Tr), monomethoxytriphenyl (MMTr) and dimethoxytriphenyl (DMTr) methylethers continue to be utilized as protecting groups for hydroxyl moieties in saccharide and nucleoside chemistry even after 50 years. Their utility is attributed to the high selectivity for primary hydroxyl groups in polyols as well as the ease and mildness in preparing and removing the trityl function.<sup>1–4</sup> These functionalities are typically removed using protic acids, Lewis acids or catalytic hydrogenation. The use of sodium involving strong reducing conditions destroy ester and benzyl ethers<sup>5</sup> and hydrogenation<sup>6</sup> of tritylated nucleosides proceeds sluggishly, often giving unsatisfactory results. In certain cases, the standard deprotection conditions are not suitable due to acid sensitivity of the starting material, resulting, for example, in deglycosylation. Classically, acids such as formic acid,<sup>7</sup> acetic acid and trifluoroacetic acid (TFA),<sup>8</sup> and acid-catalyzed reactions such as 1% methanolic solution of iodine<sup>9</sup> have been employed for deprotection, but in acid sensitive compounds such as deoxynucleosides and pentoses, several methods have been reported using ZnBr<sub>2</sub>,<sup>10</sup> AlClEt<sub>2</sub>,<sup>11</sup> Yb(OTf)<sub>3</sub>,<sup>12</sup> BCl<sub>3</sub>,<sup>13</sup> and Ce(NH<sub>4</sub>)<sub>2</sub>(NO<sub>3</sub>)<sub>6</sub><sup>14</sup> as Lewis acids.

Generally, even when a substrate deprotects efficiently, the product must be purified via crystallization or column chromatography. Herein, we report an efficient detritylation method that combines deprotection under acidic conditions with chromatography to supply a pure product in high yield in one simple process. For substrates that are acid labile, this technique can easily be adapted to further improve yields. The scale of the

reaction is limited only by available column sizes. Trityl and monomethoxytrityl deoxynucleosides are deprotected in excellent yields (77% to quantitative) using trifluoroacetic acid in chloroform:methanol solvent systems on a silica gel column using two different methods (A and B) as shown in Table 1 (entries 1–15). Method B typically gives better yields. This method uses less TFA for deprotection, and is useful for the deprotection of more acid sensitive molecules. For example, method B was applied to the dimer nucleosides **3a**<sup>16</sup> and **4a**<sup>16</sup> and gave excellent yields of detritylated products from the column (Fig. 1). A further modification has been adapted for extremely acid sensitive molecules (method C) such as certain pentoses (arabinofuranoside<sup>23</sup> and galactofuranoside<sup>24</sup>) (Fig. 1), resulting in further improvements in yields. The starting materials in Table 1 and Fig. 1 were either purchased commercially or were prepared by reported methods. As an example of a comparative yield see entry 15; an 88% yield of the deprotected product (method B) was obtained as compared to a 55% yield<sup>22</sup> using the conventional detritylation method (80% glacial acetic acid solution in water under reflux). The pure, detritylated products were compared to authentic samples using TLC and mass spectrometry (FAB-MS).

Three variations have been adapted for this process, and typical procedures are as follows: **Method A:** The sample (50 mg) was dissolved in CHCl<sub>3</sub> (5 mL) containing 5% TFA, and was promptly loaded onto a prepared silica gel column [silica gel (5.0 g) in CHCl<sub>3</sub> or hexane]. The detritylated product was eluted with the appropriate solvent system. **Method B:** The sample (50 mg) was dissolved in 5 mL of CHCl<sub>3</sub> and loaded onto a column of silica gel (5.0 g) first prepared in CHCl<sub>3</sub> or hexane to

\* Corresponding author. Tel.: +1-205-581-2454; fax: +1-205-581-2877; e-mail: reynolds@sri.org

**Table 1.** Detritylation reactions

Entry No.	Substitutions					Yields (%) methods		Ref.
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	X	R <sub>4</sub>	A	B	
1 <sup>a</sup>	Tr	H	OH	CH <sub>2</sub>	U	96	92	15
2 <sup>a</sup>	Tr	H	OH	CH <sub>2</sub>	T	88	92	15
4 <sup>b</sup>	Tr	H	NH <sub>2</sub>	O	T	83	86	16
5 <sup>c</sup>	Tr	H	OH	O	U	96	100	17
6 <sup>c</sup>	Tr	H	OH	O	T	100	100	<sup>e</sup>
7 <sup>c</sup>	Tr	H	OH	O	A	96	ND	<sup>e</sup>
8 <sup>a</sup>	MTr	OH	H	O	A	100	ND	<sup>e</sup>
9 <sup>d</sup>	Tr	OMs	H	O	T	60	77	18
10 <sup>d</sup>	Tr	H	OMs	O	T	94	ND	19
11 <sup>d</sup>	Tr	OH	H	O	T	97	ND	20
12 <sup>d</sup>	Tr	H	N <sub>3</sub>	O	T	95	ND	<sup>e</sup>
13 <sup>d</sup>	Tr	OMs	H	O	U	85	ND	21
14 <sup>c</sup>	DMTr	H	OH	O	A(N <sup>6</sup> -Bz)	83	89	<sup>e</sup>
15 <sup>d</sup>	Tr	H	N <sub>3</sub>	S	T	ND	88	22

ND=Not done; U=uracil, T=thymine, A=adenine.

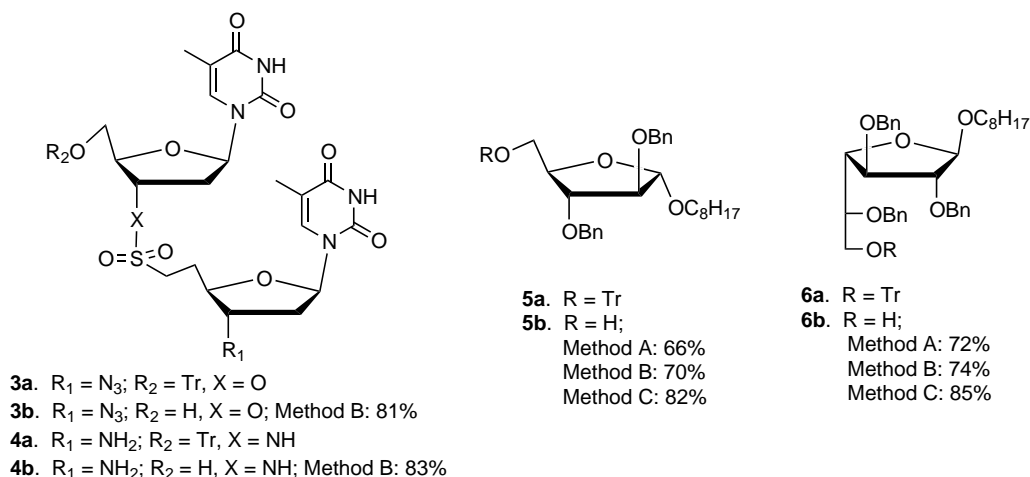
<sup>a</sup> CHCl<sub>3</sub>:MeOH (4:1).

<sup>b</sup> CHCl<sub>3</sub>:MeOH (2:1).

<sup>c</sup> CHCl<sub>3</sub>:MeOH (5:1).

<sup>d</sup> CHCl<sub>3</sub>:MeOH (7:1).

<sup>e</sup> Purchased commercially.

**Figure 1.** Detritylation yields of acid sensitive pentoses.

which was added a solution of 1% TFA in CHCl<sub>3</sub> or hexane (1.0 mL). The product was eluted with the appropriate solvent system. **Method C:** The column of silica gel (3.0 g) was first prepared in hexane containing 1% Et<sub>3</sub>N. This column was overlaid with a small buffer of sand followed by more silica gel (2.0 g) in hexane containing 1% TFA. The sample (50 mg) was then loaded in 5 mL of CHCl<sub>3</sub> and eluted with the appropriate solvent system.

In every case, a yellow-colored band representing the

cleaved triphenylmethyl moiety is eluted first followed by the deprotected compound. The column chromatography was performed using silica gel (230–400 mesh), and thin-layer chromatography (TLC) was performed using silica gel 60 F<sub>254</sub> plates.

In summary, we have developed a mild, efficient and inexpensive detritylation method using an acidic silica gel column that yields pure compounds in one-step. This approach can readily be altered further for more acid sensitive compounds.

### Acknowledgements

The authors are thankful to Dr. J. M. Riordan and Mr. M. D. Richardson for spectral work. This work was supported by NIH/NIAID grant R01 AI45317.

### References

1. Helferich, B. *Adv. Carbohydr. Chem.* **1948**, *3*, 79–111.
2. Smith, M.; Rammle, D. H.; Goldberg, I. H.; Khorana, H. G. *J. Am. Chem. Soc.* **1969**, *84*, 430–440.
3. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp. 102–104 583–584.
4. Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994.
5. Kovac, P.; Bauer, S. *Tetrahedron Lett.* **1972**, *23*, 2349.
6. Anderson, W.; Hayes, D. H.; Michelson, A. M.; Todd, A. R. *J. Chem. Soc.* **1954**, 1882.
7. Bessodes, M.; Komiotis, D.; Antonakis, K. *Tetrahedron Lett.* **1986**, *27*, 579–580.
8. MacCoss, M.; Cameron, D. J. *Carbohydr. Res.* **1978**, *60*, 206–209.
9. Wahlstrom, J. L.; Ronald, R. C. *J. Org. Chem.* **1998**, *63*, 6021–6022.
10. Kholi, V.; Blöcker, H.; Köster, H. *Tetrahedron Lett.* **1980**, *21*, 2683–2686.
11. (a) Köster, H.; Sinha, N. D. *Tetrahedron Lett.* **1982**, *23*, 2641–2644; (b) Fuentes, J.; Cuevas, T.; Pradera, M. A. *Synth. Commun.* **1994**, *24*, 2237.
12. Lu, R. J.; Liu, D.; Giese, R. W. *Tetrahedron Lett.* **2000**, *41*, 2817–2819.
13. Jones, G. B.; Hynd, G.; Wright, J. M.; Sharma, A. J. *Org. Chem.* **2000**, *65*, 263–265.
14. Hwu, J. H.; Jain, M. L.; Tsay, S.-C.; Hakimelahi, G. H. *Chem. Commun.* **1996**, 545–546.
15. Allen O'Dell, C.; Shealy, Y. F. *Nucleosides Nucleotides* **1994**, *13*, 1929–1937.
16. Reynolds, R. C.; Crooks, P. A.; Maddry, J. A.; Akhtar, M. S.; Montgomery, J. A.; Secrist, III, J. A. *J. Org. Chem.* **1992**, *57*, 2983–2985.
17. Pfitzner, K. E.; Moffatt, J. G. *J. Org. Chem.* **1964**, *29*, 1508–1511.
18. Horwitz, J. P.; Chua, J.; Noel, M. *J. Org. Chem.* **1964**, *29*, 2076–2078.
19. Michelson, A. M.; Todd, A. R. *J. Chem. Soc.* **1955**, 816.
20. Fox, J. J.; Miller, N. C. *J. Org. Chem.* **1964**, *28*, 936–941.
21. Lin, T.-S.; Mancini, W. R. *J. Med. Chem.* **1983**, *26*, 544–548.
22. Secrist, III, J. A.; Riggs, R. M.; Tiwari, K. N.; Montgomery, J. A. *J. Med. Chem.* **1992**, *35*, 533–538.
23. Pathak, A. K.; Pathak, V.; Maddry, J. A.; Suling, W. J.; Gurcha, S. S.; Besra, G. S.; Reynolds, R. C. *Biorg. Med. Chem.* **2001**, in press.
24. Pathak, A. K.; Pathak, V.; Seitz, L.; Maddry, J. A.; Gurcha, S. S.; Besra, G. S.; Suling, W. J.; Reynolds, R. C. *Biorg. Med. Chem.* **2001**, in press.