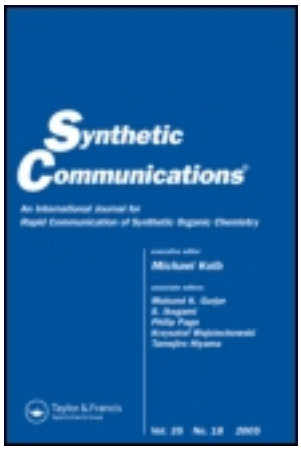


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Aqueous Trichloroacetic Acid: Another Useful Reagent for Highly Selective 5′-Desilylation of Multisilylated Nucleosides

Xue-Feng Zhu [a], Howard J. Williams [a] & A. Ian Scott [a]

[a] Center for Biological NMR, Department of Chemistry, Texas A&M University, College Station, Texas, USA

Published online: 17 Aug 2006.

To cite this article: Xue-Feng Zhu, Howard J. Williams & A. Ian Scott (2003) Aqueous Trichloroacetic Acid: Another Useful Reagent for Highly Selective 5′-Desilylation of Multisilylated Nucleosides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:12, 2011-2016, DOI: 10.1081/SCC-120021027

To link to this article: http://dx.doi.org/10.1081/SCC-120021027

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016



SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 12, pp. 2011–2016, 2003



# Aqueous Trichloroacetic Acid: Another Useful Reagent for Highly Selective 5′-Desilylation of Multisilylated Nucleosides

**Xue-Feng Zhu, Howard J. Williams, and A. Ian Scott***

Center for Biological NMR, Department of Chemistry,
Texas A&M University, College Station, Texas, USA

## ABSTRACT

Highly selective 5′-desilylation of multisilylated nucleosides can be achieved in excellent yield by treatment with 4.2 M aqueous trichloroacetic acid:THF (1:4) at 0°C.

*Key Words:* Nucleoside; Deprotection; Selective desilylation.

The protection and deprotection of free hydroxyl groups has become commonplace in chemical synthesis.[1] This is particularly true in synthetic nucleoside chemistry, where most of nucleosides possess two or three hydroxyl groups. Among numerous different types of protective

*Correspondence: A. Ian Scott, Center for Biological NMR, Department of Chemistry, Texas A&M University, P.O. Box 30012, College Station, TX 77842-3012, USA; E-mail: scott@mail.chem.tamu.edu.

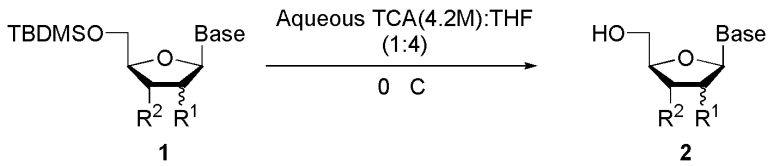


DOI: 10.1081/SCC-120021027 0039-7911 (Print); 1532-2432 (Online)

groups the silyl ethers are frequently used in nucleoside chemistry, the *tert*-butyldimethylsilyl (TBDMS) group being the most popular, mainly because TBDMS ethers are stable towards a variety of reaction conditions during nucleotide synthesis.[2]

Selective 5′-desilylation of multisilylated nucleosides is a very useful transformation, by which some important nucleosides such as 2′,3′-di-*O*-TBDMS, 2′- and 3′-mono-*O*-TBDMS protected nucleosides can be prepared simply from the corresponding 2′,3′,5′-trisilylated, 2′,5′- and 3′,5′-disilylated derivatives, respectively. Although some neutral reagents and conditions such as catalytic hydrogenation,[3] $NH_4F$/MeOH,[4] neutral alumina[5] and Lewis acids[6] have been reported for this transformation, the selective removal of the 5′-TBDMS group of mutisilylated nucleosides is normally achieved under acidic conditions. For example, acidic hydrolysis of 5′-TBDMS ethers has been carried out with aqueous or alcoholic mineral acids,[7] aqueous acetic acid,[8] aqueous trifloroacetic acid[9] and camphorsulfonic acids.[10] However, these methods often suffer from unsatisfactory yields because of concomitant side reactions such as acidic cleavage of glycosidic bonds and didesilylation. In a preceding communication, we modified Robins′ method[9] by adding THF as a co-solvent and found that highly selective 5′-desilylation of 2′,3′,5′-tri-*O*-TBDMS nucleosides can be achieved upon treatment with trifluoroacetic acid (TFA)–$H_2O$–THF (1:1:4) at 0°C.[11] The addition of THF as a co-solvent not only improves the selectivity of 5′-desilylation but avoids the unwanted depyrimidination and depurination side reactions seen in other procedures. We now report that another efficient 5′-desilylation reagent, 4.2 M aqueous trichloroacetic acid (TCA):THF (1:4), can be used as an economical alternative (Sch. 1). To the best of our knowledge, this is the first example of the use of aqueous TCA as a selective desilylation reagent. The results of 5′-desilylation are summarized in Table 1.

Under these novel conditions, 2′,3′,5′-tri-*O*-TBDMS nucleosides (Entries 1–2) and arabinonucleoside (Entry 3) are smoothly transformed into the expected 2′,3′-disilylated derivatives and excellent yields of pure products are obtained. More importantly, this milder reagent is superior




*Scheme 1.*

***Table 1.*** Selective 5′-desilylation of multisilylated nucleosides by aqueous TCA.

| Entry | Base[a] | $R^1$ | $R^2$ | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $A^{Bz}$ | OTBDMS | OTBDMS | 3 | 99 |
| 2 | $C^{Bz}$ | OTBDMS | OTBDMS | 8 | 93 |
| 3 | U | ara-OTBDMS | OTBDMS | 6 | 95 |
| 4 | $A^{Bz}$ | OH | OTBDMS | 3 | 94 |
| 5 | $A^{Bz}$ | OTBDMS | OH | 3 | 98 |
| 6 | U | OH | OTBDMS | 4.5 | 93 |
| 7 | U | OTBDMS | OH | 4 | 98 |
| 8 | $G^{Bz}$ | OH | OTBDMS | 2.5 | 90 |
| 9 | $G^{Bz}$ | OTBDMS | OH | 2.5 | 95 |
| 10 | $C^{Bz}$ | OH | OTBDMS | 6 | 85 |
| 11 | $C^{Bz}$ | OTBDMS | OH | 5.5 | 97 |

[a]$A^{Bz}$ = 6-*N*-benzoyladenine, $C^{Bz}$ = 4-*N*-benzoylcytosine, U=uracil, $G^{Bz}$=2-*N*-benzoylguanine.
[b]Isolated yield characterized by $^1$H NMR, $^{13}$C NMR, and MS.

to our previously reported TFA reagent in terms of the selectivity of 5′-desilylation of 2′,5′- or 3′,5′-disilylated nucleosides. Under our current conditions, 2′- or 3′-monosilyl nucleosides were obtained in good to excellent yields (Entries 4–11) in comparison with the relatively low yields generated by the TFA reagent. The monosilylated nucleosides were isolated as single products with no observed isomerization of TBDMS ether between two vicinal hydroxyl groups. Since 2′,5′- and 3′,5′-di-*O*-TBDMS nucleoside substrates can easily be prepared by a well-established selective disilylation procedure developed by Ogilvie et al,[9b,12,13] an improved 5′-desilylation method has become highly desirable in nucleoside chemistry. The ready availability of 2′(3′)-monosilyl nucleosides may afford an attractive alternative to prepare silyl phosphoramidite nucleosides **3** and **4**, two commonly used RNA building blocks[14] which now might simply be made from 2′ (3′)-monosilylated nucleosides via 5′-tritylation and 3′(2′)-phosphitylation. However, the currently available literature approach to **3** and **4** starts from 5′-DMTr nucleosides, and monosilylation of 5′-trityl nucleoside only gives a mixture of 5′-DMTr-2′-*O*-TBDMS protected nucleoside and its 5′-isomer even under conditions similar to those used by Ogilvie utilized for selective disilylation of nucleosides (Fig. 1).[12,15]

We also applied this novel method to the 5′-end partial cleavage of 3′,5′-TIPDS protected nucleosides, the expected products **6** and **8** being obtained in nearly quantitative yield (Sch. 2). In the case of 2′-deoxy nucleoside **9**, the steric differences between 3′-end and 5′-end silyl ethers

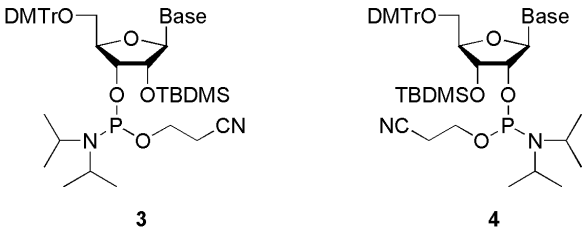
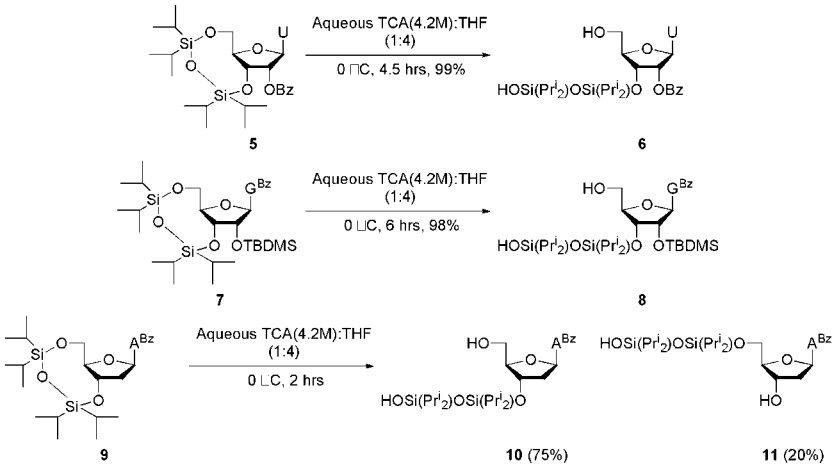



*Figure 1.*




*Scheme 2.*

are reduced because it lacks any functional group at the 2′-position, leading to a mixture of 5′-end and 3′-end partial cleavage products with the ratio of about 4:1. Once again, a variety of protecting groups such as the benzoyl group for the nucleobase and 2′-hydroxyl, and TBDMS ether for the 2′-hydroxyl group were found to be compatible with these mild reaction conditions.[16]

In conclusion, we have discovered another highly efficient and regioselective reagent (4.2 M aqueous TCA:THF = 1:4) for the 5′-desilylation of 2′,3′,5′-tri-*O*-TBDMS and 3′,5′-TIPDS protected nucleosides. Compared with the TFA reagent (TFA–$H_2O$–THF = 1:1:4), this novel reagent is particularly useful for the highly selective deprotection of 2′,5′- and 3′,5′-di-*O*-TBDMS protected nucleosides at the 5′-position. This mild deprotection method should find wide application in the

synthesis of nucleosides as well as carbohydrates and other complex molecules.

## EXPERIMENTAL

Typical procedure for 5′-desilylation of 2′,5′-di-*O*-TBDMS nucleosides (Entry 5 of Table 1): To a stirred solution of 2′,5′-di-*O*-TBDMS-$N^6$-benzoyladenosine **1e** (200 mg) in THF (4 mL) was added aqueous TCA (2.12 g in 1 mL $H_2O$) at 0°C. After stirring for 3 h at 0°C, the reaction mixture was neutralized with aqueous $NaHCO_3$ (1.1 g in 15 mL $H_2O$) and diluted with dichloromethane (50 mL). After separation, the aqueous phase was further extracted with dichloromethane ($3 \times 25$ mL). The combined extracts were dried over anhydrous $Na_2SO_4$ and evaporated at reduced pressure. The residue was subjected to flash chromatography ($CH_2Cl_2$:MeOH = 100:0.5 to 100:2) to provide 159 mg (98%) of 2′-monosilylated product **2e** as a white solid.

## ACKNOWLEDGMENTS

This work was supported by grants from the Texas Advanced Technology Research Program and the Robert A. Welch Foundation. X. F. Z. thanks members of the Scott group, especially Dr. Clotilde Pichon-Santander, for offering him invaluable help during his post-doctoral appointment at Texas A&M University.

## REFERENCES

1. (a) Gerhard, S.; Jochen, H. *Silylating Agents*; Fluka Chemie AG: Buchs, Switzerland, 1995; (b) Nelson, T.D.; Crouch, R.D. Synthesis **1996**, 1031; (c) Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Chemistry*, 3rd Ed.; John Wiley & Sons: New York, 1999; (d) Kocienski, P.J. *Protecting Groups*; Corrected Ed.; Thieme: Stuttgart, 2000.
2. Ogilvie, K.K. *Nucleosides*, *Nucleotides and their Biological Applications*; Henry, D.W., Beacham III, L.M., Eds.; Proceedings of the 5th International Round Table, Academic Press: 1982; 209.
3. (a) Cormier, J.F. Tetrahedron Lett. **1991**, *32*, 187; (b) Lee, K.; Wiemer, D.F. J. Org. Chem. **1993**, *58*, 7808.
4. Zhang, W.; Robins, M. Tetrahedron Lett. **1992**, *33*, 1177.
5. Feixas, J.; Capdevila, A.; Guerrero, A. Tetrahedron **1994**, *50*, 8539.

6. (a) Seela, F.; Ott, J.; Potter, B.V.L. J. Am. Chem. Soc. **1983**, *105*, 5879; (b) Seela, F.; Hißmann, E.; Ott, J. Lebigs Ann. Chem. **1983**, 1169; (c) Damha, M.J.; Ogilvie, K.K. J. Org. Chem. **1988**, *53*, 3710; (d) Tandon, M.; Begley, T.P. Synth. Commun. **1997**, *27*, 2953.
7. Halmos, T.; Montserrat, R.; Autonakis, K. Nucleic Acids Res. **1989**, *17*, 7663.
8. (a) Ogilvie, K.K.; Beaucage, S.L.; Schifman, A.L.; Theriault, N.Y.; Sadana, K. Can. J. Chem. **1978**, *56*, 2768; (b) Flockerzi, D.; Schlosser, W.; Pfleiderer, W. Helv. Chim. Acta **1983**, *66*, 2069.
9. (a) Robins, M.J.; Samano, V.; Johnson, M.D. J. Org. Chem. **1990**, *55*, 410; (b) Ichikawa, S.; Shuto, S.; Minakawa, N.; Matsuda, A. J. Org. Chem. **1997**, *62*, 1368.
10. Burlina, F.; Favre, A.; Fourrey, J.-L.; Thomas, M. Eur. J. Org. Chem. **2000**, 633.
11. Zhu, X.-F.; Williams, H.J.; Scott, A.I. J. Chem. Soc., Perkin Trans. 1 **2000**, 2305.
12. (a) Hakimelahi, G.H.; Proba, Z.A.; Ogilvie, K.K. Tetrahedron Lett. **1981**, *22*, 4775; (b) Hakimelahi, G.H.; Proba, Z.A.; Ogilvie, K.K. Tetrahedron Lett. **1981**, *22*, 5243; (c) Ogilvie, K.K.; Hakimelahi, G.H.; Proba, Z.A.; McGee, D.P.C. Tetrahedron Lett. **1982**, *23*, 1997; (d) Hakimelahi, G.H.; Proba, Z.A.; Ogilvie, K.K. Can. J. Chem. **1982**, *60*, 1106; (e) Ogilvie, K.K.; McGee, D.P.C.; Boisvert, S.M.; Hakimelahi, G.H.; Proba, Z.A. Can. J. Chem. **1983**, *61*, 1204.
13. Hakimelahi, G.H.; Moosavi-Movahedi, A.A.; Sadeghi, M.M.; Tsay, S.-C.; Hwu, J.R. J. Med. Chem. **1995**, *38*, 4648.
14. (a) Doudna, J.A.; Szostak, J.W.; Rich, A.; Usman, N. J. Org. Chem. **1990**, *55*, 5547; (b) Fu, D.-J.; McLaughlin, L.W. Biochemistry **1992**, *31*, 10941; (c) Beaucage, S.L.; Iyer, R.P. Tetrahedron **1992**, *48*, 2223; (d) Goodwin, J.T.; Osborne, S.E.; Scholle, E.J.; Glick, G.D. J. Am. Chem. Soc. **1996**, *118*, 5207; (e) Heidenhain, S.B.; Hayakawa, Y. Nucleosides & Nucleotides **1999**, *18*, 1771; (f) *Perspective in Nucleoside and Nucleic Acid Chemistry*; Kisakurek, M.V., Rosemeyer, H., Eds.; Wiley-VCH: Weinheim, 2000.
15. (a) Petersen, K.H.; Nielsen, J. Tetrahedron Lett. **1990**, *31*, 911; (b) Dreef-Tromp, C.M.; van Dam, E.M.A.; van den Elst, H.; van den Boogaart, J.E.; van der Marel, G.A.; van Boom, J.H. Recl. Trav. Chim. Pays-Bas **1991**, *110*, 378; (c) Milecki, J.; Zamaratski, E.; Maltseva, T.V.; Foldesi, A.; Adamiak, R.W.; Chattopadhyaya, J. Tetrahedron **1999**, *55*, 6603.
16. Zhu, X.-F.; Williams, H.J.; Scott, A.I. Tetrahedron Lett. **2000**, *41*, 9541.

Received in the USA September 16, 2002