Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 48 (2007) 5219–5222
Tetrahedron Letters

A catalytic method for chemoselective detritylation of 5′-tritylated nucleosides under mild and heterogeneous conditions using silica sulfuric acid as a recyclable catalyst

Ali Khalafi-Nezhad,[a,*] Abolfath Parhami,[a] Mohammad Navid Soltani Rad,[b] Mohammad Ali Zolfigol[c] and Abdolkarim Zare[d]

[a] *Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran*
[b] *Department of Chemistry, Faculty of Basic Sciences, Shiraz University of Technology, Shiraz 71555-313, Iran*
[c] *Faculty of Chemistry, Bu-Ali Sina University, Hamadan 65174, Iran*
[d] *Department of Chemistry, Payam Noor University of Bushehr, Bushehr 1698, Iran*

Received 10 April 2007; revised 12 May 2007; accepted 24 May 2007
Available online 31 May 2007

Abstract—A rapid, mild and highly efficient procedure for the chemoselective deprotection of triphenylmethyl (trityl, Tr), *p*-anisyldiphenylmethyl (monomethoxytrityl, MMT) and di-(*p*-anisyl)phenylmethyl (dimethoxytrityl, DMT) groups from nucleoside trityl ethers has been established. The deprotection was achieved at room temperature, using a catalytic amount of silica sulfuric acid (SSA) in acetonitrile. The trityl nucleosides were deprotected in 2–17 min without any depurination. These conditions are compatible with other acid sensitive hydroxyl protecting groups such as *p*-methoxybenzyl (PMB), isopropylidene, cyclohexylidene, di-(*p*-anisyl)methylidene, triisopropylsilyl (TIPS) and *t*-butyldimethylsilyl (TBDMS).

1. Introduction

Ether cleavage is a versatile transformation in organic chemistry and its importance for the deprotection of hydroxyl groups, especially in pharmaceuticals and other fine chemicals, has attracted the attention of synthetic chemists.[1] The triphenylmethyl (trityl) group, as a protecting group for the 5′-OH function of nucleosides is a desirable protecting group due to its stability.[2] The major problem with detritylation of nucleoside trityl ethers in acidic conditions is their depurination into the corresponding nucleobases and sugar residues.[3] Although various methods have been reported for removal of trityl groups from nucleosides without depurination,[1] methods for the selective removal of this protecting group in the presence of other acid sensitive protecting groups are scarce.

Several reagents or reagent systems such as HCO_2H in Et_2O[4] and I_2/MeOH[5] were used for the deprotection of the 5′-*O*-trityl moiety from nucleosides in the presence of isopropylidene and TBDMS protecting groups, respectively. Recently, Hwu et al. reported the use of CAN[6] and CAN/SiO_2[7] for the selective deprotection of a trityl group in the presence of isopropylidene, TBDMS and TIPS. The above mentioned methods have associated drawbacks, including long reaction times[5,6] and the use of hazardous reagents.[5] In recent years, heterogeneous catalysts have gained significant importance from environmental and economical standpoints.[8] Silica sulfuric acid is an inorganic solid acidic resin, which has recently been used in several organic transformations.[9]

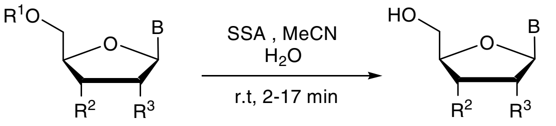
In continuation of our previous work on establishing new procedures for protection and deprotection of nucleosides,[10–14] herein we report silica sulfuric acid (SSA) as an efficient, mild and chemoselective catalyst for the deprotection of nucleoside trityl ethers (Scheme 1).

To obtain optimized reaction conditions, we examined the deprotection of 5′-dimethoxytrityl uridine (10 mmol)

Keywords: Detritylation; Nucleoside; Trityl; Heterogeneous; Silica sulfuric acid.

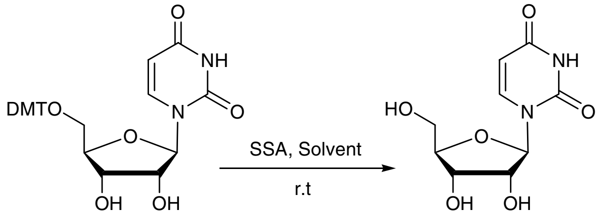
[*] Corresponding author. Tel.: +98 711 2282380; fax: +98 711 2280926; e-mail: khalafi@chem.susc.ac.ir

0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.05.153



B = *N*1-Uracil, *N*1-Thymine, *N*9-Adenine
R^1 = Tr, MMTr, DMTr
R^2/ R^3 = H, OH, OTBDMS, OTIPS, PMB, O-CR_2-O, O-CAr_2-O

Scheme 1.



Scheme 2.

in acetonitrile (10 mL) and water (0.36 g) as a model reaction (Scheme 2).

In the first experiment, the effect of different amounts of SSA on the efficiency of the model reaction in MeCN was studied. It was found that 2 mmol (20 mol %) of SSA was an appropriate amount for catalyzing the reaction. Using further amounts of SSA had no distinguishable effect on the efficiency of the model reaction. The choice of solvent was also important. Different solvents such as MeCN, CH_2Cl_2, $CHCl_3$, DMF, THF and CCl_4 were used in the reaction and among them, MeCN was the most efficient and thus was the solvent of choice (Table 1).

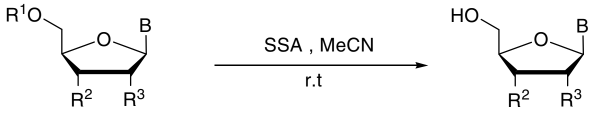
To investigate the generality and versatility of this method, the reaction was extended to various structurally diverse protected nucleosides. Using, the optimized reaction conditions, the deprotection of, trityl ethers of purine and pyrimidine nucleosides **1a**–**11a** were examined (Scheme 3).

Firstly, we examined the deprotection of 5′-*O*-Tr uridine, 5′-*O*-MMT uridine and 5′-*O*-DMT uridine (**1a**–**3a**). As shown in Table 2, the free nucleoside **1b** was obtained in excellent yields (88–91%).

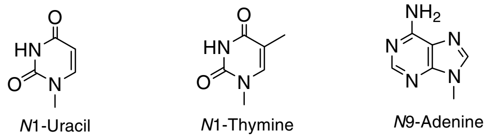
Table 1. Effect of solvent on the detritylation of 5′-dimethoxytrityl uridine (10 mmol) with a catalytic amount of SSA (0.76 g, 2 mmol, 20 mol %) at room temperature

Entry	Solvent	Time (min)	Yield[a] (%)
1	MeCN	2	91
2	CH_2Cl_2	4	70
3	$CHCl_3$	8	51
4	DMF	5	60
5	THF	12	72
6	CCl_4	140	26

[a] Isolated yield.



1a	B = *N*1-Uracil, R^1 = Tr, R^2 = R^3 = OH	**1b**
2a	B = *N*1-Uracil, R^1 = MMT, R^2 = R^3 = OH	**1b**
3a	B = *N*1-Uracil, R^1 = DMT, R^2 = R^3 = OH	**1b**
4a	B = *N*1-Thymine, R^1 = Tr, R^2 = R^3 = OH	**4b**
5a	B = *N*9-Adenine, R^1 = Tr, R^2 = OH, R^3 = H	**5b**
6a	B = *N*1-Uracil, R^1 = Tr, R^2 = OH, R^3 = OPMB	**6b**
7a	B = *N*1-Uracil, R^1 = Tr, R^2 = R^3 = O-$C(CH_2)_5$-O	**7b**
8a	B = *N*1-Uracil, R^1 = Tr, R^2 = R^3 = O-C(*p*-$MeOC_6H_4)_2$-O	**8b**
9a	B = *N*1-Uracil, R^1 = Tr, R^2 = R^3 = O-CMe_2-O	**9b**
10a	B = *N*1-Uracil, R^1 = Tr, R^2 = H, R^3 = OTBDMS	**10b**
11a	B = *N*1-Uracil, R^1 = Tr, R^2 = OH, R^3 = OTIPS	**11b**



Scheme 3.

As expected, the more acid sensitive mono- (MMT) and dimethoxytrityl (DMT) groups were removed more rapidly than trityl (Tr) with regard to the stability of their carbocationic species ($DMT^+ > MMT^+ > Tr^+$). Deprotection of 5′-*O*-Tr thymidine (**4a**) was also efficient (93%). In order to study the efficiency of the described catalyst for purine nucleosides, which are known to be more susceptible to depurination, the reaction was examined with 5′-*O*-Tr deoxyadenosine (**5a**). As shown in Table 2, the corresponding nucleoside (**5b**) was afforded in good yield (82%). To indicate the selectivity of our method, we also examined the detritylation reactions of a variety of nucleoside trityl ethers having other acid sensitive protecting groups within their structures (**6a**–**11a**). Various protecting groups such as PMB, isopropylidene, cyclohexylidene, di-(*p*-anisyl)methylidne, TIPS and TBDMS were chosen in order to study the selectivity in the presence of the Tr group (Scheme 3). The Tr group was chosen because it is the least reactive protecting group in comparison with MMT and DMT. Fascinatingly, excellent selectivity was observed for the removal of trityl moieties rather than other acid sensitive hydroxyl protecting groups. Reaction of **6a** with SSA afforded 2′-*p*-methoxybenzyloxy uridine (**6b**) in excellent yield (95%). When the same reaction was performed on **7a**, **8a** and **9a**, in which the 5′-OH was protected with Tr and the 2′-OH and 3′-OH groups were protected by acetal groups including cyclohexylidene, di(*p*-anisyl)methylidene and isopropylidene, it was observed that the Tr group was deprotected selectively, while the acetal moieties were maintained. Similar results were obtained when 5′-trityloxy-2′-*t*-butyldimethylsilyloxy uridine (**10a**) was exposed to detritylation, which afforded a good yield (83%) of 2′-*t*-butyldimethylsilyloxy uridine (**10b**). Furthermore, examination of the reaction of **11b** illustrated the selective deprotection of the Tr group in the presence of the acid sensitive TIPS group.

In an experiment to compare the catalytic effect of SSA with silica-supported sulfuric acid, we performed the deprotection of 5′-*O*-Tr uridne with SiO_2–H_2SO_4

Table 2. Selective detritylation of nucleoside trityl ethers (10 mmol) with SSA (0.76 g, 2 mmol, 20 mol %) in MeCN at room temperature

Entry	Substrate	Product	Time (min)	Yield[a] (%)	Mp, °C (lit.)[Ref.]	Eluent
1	**1a**	**1b**	17	88	164–165 (165)[15]	EtOAc–MeOH (4:1)
2	**2a**	**1b**	6	90	164–165 (165)[15]	EtOAc–MeOH (4:1)
3	**3a**	**1b**	2	91	164–165 (165)[15]	EtOAc–MeOH (4:1)
4	**4a**	**4b**	17	93	185–186 (186–187)[15]	EtOAc–MeOH (4:1)
5	**5a**	**5b**	17	82	233–235 (234–236)[15]	MeOH[b]
6	**6a**	**6b**	17	95	140–141 (141–143)[16]	*n*-Hexane–EtOAc (6:4)
7	**7a**	**7b**	17	90	164 (164–166)[17]	*n*-Hexane–EtOAc (7:3)
8	**8a**	**8b**	17	84	114–115 (112–114)[17]	MeCN[b]
9	**9a**	**9b**	17	89	172–173 (172–174)[7]	MeOH[b]
10	**10a**	**10b**	17	83	193–195 (192–194)[7]	*n*-Hexane–EtOAc (6:4)
11	**11a**	**11b**	17	85	154–155 (155–156)[7]	EtOAc–MeOH (9:1)

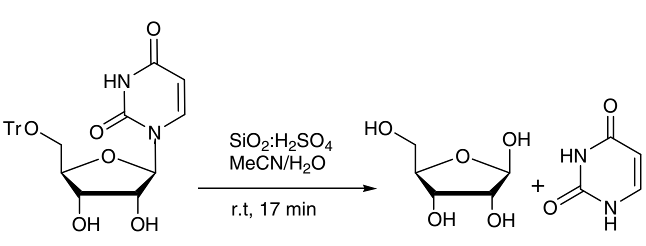
[a] Isolated yields.

[b] Recrystallization solvents.

(60 g:16 g) as the acidic catalyst. The reaction occurred with complete depurination of the nucleoside and the formation of uracil, which was confirmed by comparison with an authentic sample by TLC. As can be concluded from this experiment, SSA has completely different properties from SiO_2–H_2SO_4 (Scheme 4).

In another complementary experiment the deprotection of **1a** and **3a** was examined using unmodified SiO_2. No deprotection was observed even when the reaction time was prolonged up to 72 h. Furthermore, the catalytic activity of the recovered catalyst (SSA) was also examined. As shown in Table 3, the yields of 5′-*O*-DMT uridine (**3a**) deprotection in the second and third uses of the catalyst were almost the same in the reactivity as in the first use.

In summary, we have described an efficient, rapid and mild procedure for the chemoselective removal of the trityl groups from protected nucleosides. This method offers several advantages including: (i) The acid sensitive glycosidic bond in nucleosides is not cleaved by SSA. (ii) Chemoselective removal of the trityl moiety from nucleoside trityl ethers in the presence of other acid sensitive hydroxyl protecting groups was possible using a catalytic amount of SSA. (iii) SSA is an inexpensive and non toxic catalyst, which can be easily prepared, recycled and reused.

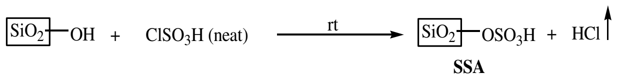


Scheme 4.

Table 3. Evaluation of recycled SSA for the detritylation of 5′-*O*-DMT uridine in MeCN at room temperature

Number of uses	Time (min)	Yield[a] (%)	% Recovery of SSA
1	2	91	95
2	2	87	92
3	2	85	90

[a] Isolated yield.



Scheme 5.

SSA was prepared according to the literature[18] by gradual addition of $ClSO_3H$ (23.3 g, 0.2 mol) to silica gel (60 g) over 30 min, which was accompanied by rapid evolution of HCl gas, affording SSA (76 g) as the product (Scheme 5).

The mass of HCl evolved can be calculated as follows:

$$\begin{aligned}\text{Mass of evolved HCl} &= 60.0\,\text{g (mass of } SiO_2)\\ &\quad +23.3\,\text{g (mass of 0.2 mol } ClSO_3H)\\ &\quad -76.0\,\text{g (mass of SSA obtained)}\\ &= 7.3\,\text{g}\end{aligned}$$

This amount of HCl (7.3 g) was exactly equimolar with $ClSO_3H$ (23.3 g, 0.2 mol) so the reaction progress was 100% and was completely stoichiometric.

2. General procedure for detritylation of trityl ethers

To a solution of the tritylated nucleoside (10 mmol) in acetonitrile (10 mL), were added a catalytic amount of silica sulfuric acid (0.75 g, 2 mmol, 20 mol %) and H_2O (0.36 g, 0.02 mol). The reaction mixture was allowed to stir at 25 °C until TLC monitoring did not show any remaining starting material. The silica sulfuric acid was removed by filtration and the catalyst was washed twice with hot MeCN (2 × 20 mL). The combined filtrates was dried over $MgSO_4$ and evaporated under reduced pressure. The product was recrystallized or purified by passing through a short column of silica gel (Table 2).

Acknowledgements

We acknowledge Shiraz University research council for partial support of this work. We also thank Mr. H. Sajedian Fard for running the NMR spectra.

References and notes

1. Green, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999.
2. Kasler, H.; Hoppe, N.; Kohli, V.; Kropline, M.; Kaut, H. *Nucleic Acids Symp. Ser.* **1980**, *7*, 39–60.
3. Beaucage, S. L.; Iyer, R. P. *Tetrahedron* **1992**, *48*, 2223–2311.
4. Bessodes, M.; Komiotis, D.; Antonakis, K. *Tetrahedron Lett.* **1986**, *27*, 579–580.
5. Wahlstrom, J. L.; Konald, R. C. *J. Org. Chem.* **1998**, *63*, 6021–6022.
6. Hwu, J. R.; Jain, M. L.; Tsay, S.; Hakimelahi, G. H. *Chem. Commun.* **1996**, 545–546.
7. Hwu, J. R.; Jain, M. L.; Tsay, F. Y.; Tsay, S. C.; Balakumar, A.; Hakimelahi, G. H. *J. Org. Chem.* **2000**, *65*, 5077–5088.
8. Sheldon, R. A.; Bekkum, H. V. In *Fine Chemicals Through Heterogeneous Catalysis*, 1st ed.; Wiley-VCH, ISBN 3527299513, 2001.
9. (a) Desai, U. V.; Thopate, T. S.; Pore, D. M.; Wadgaonkar, P. P. *Catal. Commun.* **2006**, *7*, 508–511; (b) Gawande, M. B. *Res. J. Chem. Environ.* **2006**, *10*, 93–94, and references cited therein; (c) Shaabani, A.; Rahmati, A. *J. Mol. Catal. A: Chem.* **2006**, *249*, 246–248; (d) Wu, H.; Shen, Y.; Fan, L.-Y.; Wan, Y.; Shi, D.-Q. *Tetrahedron* **2006**, *62*, 7995–7998; (e) Azizian, J.; Karimi, A. R.; Kazemzadeh, Z.; Mohammadi, A. A.; Mohammadizadeh, M. R. *Synthesis* **2005**, 1095–1098; (f) Khodæi, M. M.; Khosropour, A. R.; Fattahpour, P. *Tetrahedron Lett.* **2005**, *46*, 2105–2108; (g) Zolfigol, M. A.; Salehi, P. *J. Mol. Catal. A: Chem.* **2006**, *256*, 346–347, and references cited therein; For a comprehensive review see: (h) Salehi, P.; Zolfigol, M. A.; Shirini, F.; Baghbanzadeh, M. *Curr. Org. Chem.* **2006**, *10*, 2171–2189.
10. Khalafi-Nezhad, A.; Mokhtari, B. *Tetrahedron Lett.* **2004**, *45*, 6737–6739.
11. Khalafi-Nezhad, A.; Fareghi Alamdari, R. *Tetrahedron* **2001**, *57*, 6805–6807.
12. Khalafi-Nezhad, A.; Fareghi Alamdari, R.; Zekri, N. *Tetrahedron* **2000**, *56*, 7503–7506.
13. Khalafi-Nezhad, A.; Fareghi Alamdari, R. *Iran. J. Chem. Chem. Eng.* **1998**, *17*, 58–60.
14. Hakimelahi, G. H.; Khalafi-Nezhad, A. *Helv. Chim. Acta* **1983**, *66*, 757–759.
15. *The Combined Chemical Dictionaries on CD-ROM, Version 6.1*; Chapman and Hall, 2003.
16. Losse, G.; Pechstein, B. *J. Prakt. Chem.* **1989**, *331*, 46–54.
17. Reese, C. B.; Song, Q.; Yan, H. *Tetrahedron Lett.* **2001**, *42*, 1789–1791.
18. Zolfigol, M. A. *Tetrahedron* **2001**, *57*, 9509–9511.