

Selectivity in the Catalytic Transfer Hydrogenolysis of Silyl Ether Protecting Groups

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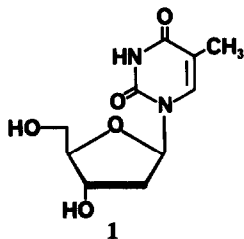
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Abstract: Catalytic transfer hydrogenolysis has been used to selectively cleave silyl protecting groups from primary and secondary alcohols, including from thymidine. Ease of cleavage is in the order triethyl >> *t*-butyldimethyl > triisopropyl > *t*-butyldiphenyl.

In the synthesis of complex molecules, it is frequently necessary to selectively protect and deprotect similar functional groups. For this purpose, many different protecting groups have been developed, along with methods for their selective removal.¹ One of the most common stages in such sequences is the masking of the hydroxyl group as its silyl ether. The *t*-butyldimethylsilyl (TBDMS) group² is widely employed, but *t*-butyldiphenylsilyl (TBDPS)³ and triisopropylsilyl (TIPS)⁴ ethers are also frequently used. In operating on polyhydroxy compounds, it is frequently desirable to use different silyl protecting groups, and remove them selectively. A variety of methods for desilylation have been developed, including fluoride ion,¹ and acid¹, which are fairly indiscriminating, and sodium hydride⁵ and diisobutylaluminum hydride⁶. Many groups desire milder and more specific routes. A recent example is the use of fluorosilicic acid⁷, which under certain conditions distinguishes TIPS and TBDMS. Some time ago, we reported⁸ the use of catalytic transfer hydrogenolysis (CTH) as a method for the removal of *t*-butyldimethylsilyl groups. We have now explored the selectivity of this reaction with respect to the steric bulk of the substituents at silicon and present our results in this communication.

Thymidine (1) was protected with various silyl groups, then treated with Pd(II)O in refluxing cyclohexene:methanol until TLC analysis revealed complete desilylation.⁹ As we expected, the bulkier silyl groups were removed more slowly. In particular, the triethylsilyl group is completely removed from the primary 5'-hydroxyl group in less than 30 minutes at reflux. A control experiment without catalyst gave no deprotection. On the other hand, the TBDMS group is cleaved under the same conditions in 2.5 hours. Bulkier silyl ethers are removed more slowly. Deprotection of 5'-TIPS thymidine was completed only after

three days at reflux. Similar treatment of 5'-TBDPS thymidine resulted in incomplete deprotection after two days (perhaps 20% consumption of starting material, as judged by TLC). Removal of the latter three protecting groups from the secondary 3'-hydroxyl group of thymidine is much slower. The TBDMS group is cleaved in 4-7 hours, while TLC analysis indicates that removal of the TBDPS and TIPS moieties is only *ca.* 5% complete after 24 hours.



Clearly, the reaction demonstrates a certain selectivity. We then proceeded to determine the reaction's ability to discriminate between different silyl ethers in identical positions in the same molecule. Thus, 1,6-hexanediol was mono- and disilylated with the TBDMS, TBDPS and TIPS groups. Results are presented in Table 1. There is a substantial difference in rate of silyl ether cleavage in the monosilylated molecules. Deprotection of the diol bearing TBDMS and *t*-butyldiphenyl groups leads to selective cleavage of the TBDMS group. Removal of the TIPS group is slightly less selective, with some of the fully deprotected diol being isolated.

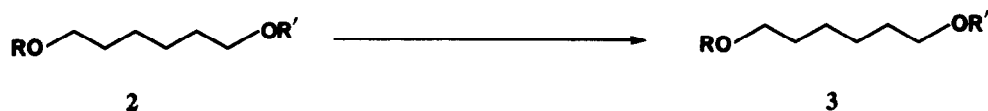


Table 1. Removal of silyl groups from 1,6-hexanediol.

2		3		Time (h)	Yield
R	R'	R	R'		
TBDMS	H	H	H	1.0	95%
TIPS	H	H	H	18	92%
TBDPS	H	H	H	21	93%
TBDMS	TIPS	H	TIPS	0.5	90% (3%) ^a
TBDMS	TBDPS	H	TBDPS	0.75	91%

^a, yield of fully deprotected material.

We also compared the removal of the same groups from benzylic alcohols. The substrate was 1,4-benzenedimethanol. The results of this series of reactions are presented in Table 2.

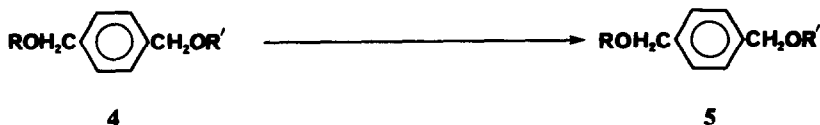


Table 2. Removal of silyl groups from 1,4-benzenedimethanol.

4		5		Time(h)	Yield
R	R'	R	R'		
TBDMS	H	H	H	0.67	94%
TIPS	H	H	H	23.5	85%
TBDPS	H	H	H	50	40%
TBDMS	TIPS	H	TIPS	0.67	70%
TBDMS	TBDPS	H	TBDPS	1.0	94%

The rate of deprotection appears to be sensitive to both the steric bulk of the substituents on silicon, and the accessibility of the scissile Si-O bond. For example, removal of any of the three bulky groups from the nucleoside primary hydroxyl group is slower than the same reaction on either of the two simpler diols. This may reflect the hindrance imparted by the rather large heterocyclic base. Removal of the TIPS and TBDPS groups from benzylic positions seems to be considerably more difficult than from simple primary alcohols.

In conclusion, the results presented here show that CTH can allow selective removal of the TBDMS group in the presence of the TIPS and TBDPS groups. The reaction occurs under mild, neutral conditions, with a simple workup. The relative rates of removal complement the observations of Shekhani *et al.*, wherein a TBDPS ether is cleaved in preference to a TBDMS ether, under reductive conditions.⁵

Acknowledgment: We thank Trent University and Employment and Immigration Canada's SEED Program for financial support. M.B.I. thanks the Trent International Program for a scholarship. We gratefully acknowledge Mr. Mike Feurth, University of Windsor, and Ms. Sue Blake, Queen's University, for running NMR spectra.

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9. In a typical procedure, 50-100 mg of the silylated alcohol was dissolved in methanol:cyclohexene (1:1, 10-20 ml). Pd(II)O hydrate (Aldrich, 10 wt%) was added and the mixture refluxed for the indicated time. Reaction progress was monitored by TLC. Reactions were considered complete when all starting material had disappeared from the TLC. TLCs of 1,6-hexanediol and 1,4-benzene dimethanol reactions were visualised by ammonium molybdate stain. For removal of TIPS and TBDPS groups from thymidine, extent of reaction was estimated by visual comparison of starting material and product spot intensities on TLC (visualised by UV). As noted in our previous communication, there is some variability in the time for removing a given silyl group (note the last two entries in each Table). Workup consisted of filtering off the catalyst through glass wool, and evaporation of solvents. In most cases, precipitation from hexanes yielded chromatographically pure products. In a few cases, short column silica gel chromatography was used to remove trace impurities. Isolated yields are reported. Compounds were identified by chromatographic comparison with authentic samples (thymidine), or by ^1H and ^{13}C NMR (1,6-hexanediol and 1,4-benzenedimethanol derivatives).

(Received in USA 28 August 1992; accepted 13 October 1992)