

## ALUMINA-MEDIATED CLEAVAGE OF *t*-BUTYLDIMETHYLSILYL ETHERS

Rajender S. Varma\*, Jagannath B. Lamture, and Manju Varma

The Center for Biotechnology, Baylor College of Medicine,  
4000 Research Forest Drive, The Woodlands, TX 77381, U. S. A.

**Key Words:** Deprotection; *t*-Butyldimethylsilyl ethers; Solid surface; Alumina; Microwave irradiation

**Abstract:** *A simple method for the cleavage of *t*-butyldimethylsilyl ethers is described which occurs on alumina surface under solvent free conditions within 10-15 minutes. Mild heating, using microwave irradiation facilitates the procedure.*

The *tert*-butyldimethylsilyl(TBDMS) group, is one of the most widely used protecting groups in organic synthesis and preparation of such silyl ethers is a method of choice for selectively protecting the hydroxy functionality.<sup>1</sup> The removal of *tert*-butyldimethylsilyl group has been accomplished using a variety of methods most of them involving fluoride ion.<sup>1</sup> Among these, tetramethylammonium fluoride (TBAF) in tetrahydrofuran,<sup>2</sup> potassium fluoride with crown ethers,<sup>3</sup> hydrogen fluoride in acetonitrile,<sup>4</sup> boron trifluoride etherate,<sup>5</sup> N-bromosuccinimide in DMF,<sup>6</sup> and more recently introduced, sodium azide in DMF,<sup>7</sup> sodium hydride in HMPA,<sup>8</sup> catalytic transfer hydrogenation,<sup>9</sup> ammonium fluoride in methanol,<sup>10</sup> tetrafluorosilane gas,<sup>11</sup> and potassium fluoride on alumina<sup>12</sup> are few of the prominent methods known. Although the selectivity<sup>11</sup> and compatibility issues for various functional groups during desilylation processes have been addressed,<sup>10-13</sup> the need for manipulatively easy and preferably solvent-free method of deprotection for TBDMS ethers still exists.

In connection with our improved synthesis of aurones on alumina surface,<sup>14</sup> we observed an interesting deacetylation reaction.<sup>15</sup> Consequently, we decided to explore the use of common solid supports (silica gel, aluminum oxide, etc.) for the deprotection of other functional groups. A recent report<sup>16</sup> on the use of partially deactivated alumina (with 1.5-3% water) to cleave TBDMS ethers in hexane solutions overnight prompts us to report our results on desilylation reaction. Interestingly, a recent study failed to detect any desilylation of TBDMS ethers on basic alumina in acetonitrile.<sup>12</sup>

The salient and distinctive feature of our approach is that deprotection is achieved on alumina surface without using any solvents. Further, moderate heating (~70-85°C) in domestic microwave oven generates alcohols in excellent yields within

10 minutes. That the effect is not purely *thermal*<sup>17,18</sup> is borne out by the fact that for similar yields longer time periods are required using alternative heating modes at the same temperature (oven or oil bath). Also, we find the use of microwave oven convenient and cleaner as compared to other means of heating (conventional ovens, oil baths or heating mantles). Microwave heating has been used for a wide variety of applications<sup>18-19</sup> and more recently accomplishment of reactions under "dry" conditions have been described.<sup>20-21</sup> Since the microwaves are only absorbed by the reactants on the surface of common inorganic oxides such as silica and alumina, numerous reagents supported on solid surfaces<sup>22</sup> can also be effectively utilized for conducting organic reactions under very safe and simple conditions. The use of domestic microwave ovens instead of specialized microwave systems designed for solution chemistry in sealed teflon bombs is yet another attractive feature of our method.

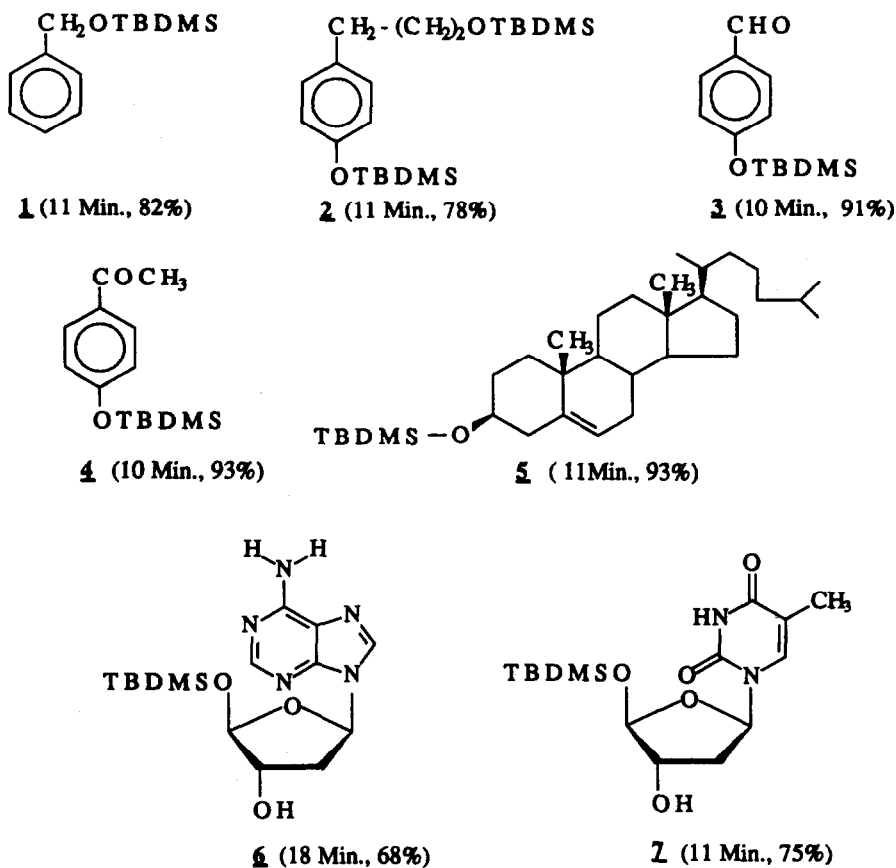


FIGURE : Structures of *t*-butyldimethylsilyl ethers deprotected by microwave irradiation on alumina

We conducted several reactions with a variety of compounds (see figure) using silica gel, as well as neutral and basic alumina.<sup>23</sup> We observed that the deprotection reactions for phenolic and alcoholic functionalities occurred efficiently on alumina surface. In the case of nucleoside analogues cleaner products are obtained only on basic alumina; no deprotection is observed on silica gel. Furthermore, deprotection of phenolic ethers is faster than the alcoholic ethers (as noticed by TLC examination of desilylation reaction with **2**) and consequently, selective deprotection of phenolic ethers in presence of alcoholic ethers is possible. Also, the reaction is fast enough that no undesirable byproducts originating from arylaldehyde via a concomitant Cannizzaro reaction<sup>24</sup> are observed in the reaction product involving carbonyl compounds.

The deprotection of 3-(4-hydroxyphenyl)-1-propanol-*t*-butyldimethylsilyl diether, **2**, is representative of the general procedure employed. Neutral alumina<sup>23</sup> (35g) is added to a solution of **2** (0.760g, 2mmol) dissolved in a minimum amount of dichloromethane (5ml) at room temperature and the reaction mixture is thoroughly mixed using a vortex mixer. The adsorbed material is dried in air (beaker) and placed in an alumina bath inside the microwave oven.<sup>17,20</sup> Upon completion of the reaction as followed by TLC examination (10 min.), the product is extracted into dichloromethane (4x15ml). Removal of the solvent, under reduced pressure yielded the product which is purified by crystallization from methanol-dichloromethane. Alternatively, the adsorbed material is charged directly on a silica gel column to afford the pure product, 3-(4-hydroxyphenyl)-1-propanol in 78% yield, mp 53-55°C, in ethyl acetate-methanol (4:1, v/v) as an eluent.

In conclusion, we have developed a simple method for the deprotection of *tert*-butyldimethylsilyl ethers that occurs under mild and solvent-free conditions using inexpensive aluminum oxide and household microwave oven. The deprotection of other functional groups on solid support surfaces is currently under investigation.

#### REFERENCES AND NOTES

1. a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, Wiley, New York, 2nd Edn., 1991, pp77-83.  
b) Lalonde, M.; Chan, T. H. *Synthesis* 1985, 817 and references cited therein.
2. Corey, E. J.; Venkateswarlu, A. *J Am. Chem. Soc.*, 1972, 94, 6190.
3. a) Liotta, C. L.; Harris, H. P. *J Am. Chem. Soc.*, 1974, 96, 2250.  
b) Torisawa, Y.; Shibasaki, M.; Ikegami, S. *Tetrahedron Lett.*, 1979, 20, 1865.
4. Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett.*, 1985, 26, 681.
5. Kelly, D. R.; Roberts, S. M.; Newton, R. F. *Synth. Commun.*, 1979, 9, 295..
6. Batten, R.J.; Dixon, A.J.; Taylor, R. J. K. *Synthesis*, 1980, 234.
7. Monger, S. J.; Parry, D. M.; Roberts, S. M. *J. Chem. Soc. Chem. Commun.*, 1989, 381.
8. Shekhani, M.S.; Khan, K. M.; Mahmood, K. *Tetrahedron Lett.*, 1988, 29, 6161.
9. Cormier, J. F. *Tetrahedron Lett.*, 1991, 32, 187.
10. Zhang, W.; Robins, M. J. *Tetrahedron Lett.*, 1992, 33, 1177.
11. Corey, E. J.; Yi, K. Y. *Tetrahedron Lett.*, 1992, 33, 2289.

12. Schmittling, E. A.; Sawyer, J. S. *Tetrahedron Lett.*, **1991**, *32*, 7207.
13. Corey, E. J.; Jones, G. B. *J. Org. Chem.* **1992**, *57*, 1028.
14. Varma, R. S.; Varma, M. *Tetrahedron Lett.*, **1992**, *33*, 5937.
15. Varma, R. S.; Varma, M.; Chatterjee, A. K. Unpublished observations.
16. Feixas, J.; Capdevila, A.; Camps, F.; Guerrero, A. *J. Chem. Soc. Chem. Commun.*, **1992**, 1451.
17. For a recent critical evaluation of activation process by microwaves see: Laurent, R.; Laporterie, A.; Dubac, J.; Berlan, J.; Lefeuvre, S.; Audhuy, M. *J. Org. Chem.* **1992**, *57*, 7099. The temperature of the alumina supporting the silyl ether is found to be ~85°C after 10 minutes of irradiation in an alumina bath (heat sink) inside a Sears Kenmore microwave oven equipped with turntable operated at full power (800Watts). Without the use of alumina bath,<sup>20</sup> temperature of only 65°C is reached in 11 minutes and is recommended for temperature-sensitive compounds e. g. pyrimidine nucleoside, **7**. Desilylation of purine nucleoside, **6**, adsorbed on basic alumina requires 3 hrs. at 90°C using an electric oven.
18. For recent reviews on Microwave Assisted Chemical Reactions see Abramovich, R. A. *Org. Prep. Proced. Int.*, **1991**, *23*, 683; Mingos, D. M. P.; Baghurst, D.R. *Chem. Soc. Rev.*, **1991**, *20*, 1.
19. a) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.*, **1986**, *27*, 279.  
b) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.*, **1986**, *27*, 4945.  
c) Giguere, R. J.; Namen, A. M.; Lopez, B. O.; Arepally, A.; Ramos, D. E.; Majetich, G.; Defrauw, J. *Tetrahedron Lett.*, **1987**, *28*, 6553.  
d) Bose, A. K.; Manhas, M. S.; Ghosh, M.; Raju, V. S.; Tabei, K.; Urbanczyk-Lipkowska, Z. *Heterocycles*, **1990**, *30*, 741.  
e) Bose, A. K.; Manhas, M. S.; Ghosh, M.; Shah, M.; Raju, V. S.; Bari, S. S.; Nawaz, S. N.; Banik, B. K.; Chaudhary, A. G.; Barakat, K. J. *J. Org. Chem.* **1991**, *56*, 6968.  
f) Banik, B. K.; Manhas, M. S.; Kaluza, Z.; Barakat, K. J.; Bose, A. K. *Tetrahedron Lett.*, **1992**, *33*, 3603.
20. Bram, G.; Loupy, A.; Majdoub, M.; Gutierrez, E.; Ruiz-Hitzky, E. *Tetrahedron*, **1990**, *46*, 5167.
21. For reactions under 'dry' conditions see a) Benalloum, A.; Labiad, B.; Villemin, D. *J. Chem. Soc. Chem. Commun.*, **1989**, 386.  
b) Villemin, D.; Labiad, B.; Ouhilal, Y. *Chem. Ind. (London)* **1989**, 607.  
c) Villemin, D.; Labiad, B. *Synth. Commun.*, **1990**, *20*, 3333 and 3325.  
d) Villemin, D.; Benalloum, A. *Synth. Commun.*, **1991**, *21*, 1 and 63.  
e) Villemin, D.; Lalaoui, M.; Benalloum, A. *Chem. Ind. (London)* **1991**, 176.
22. For leading reviews pertinent to organic reactions on solid supports see:  
a) Posner, G. H. *Angew. Chem. Int. Ed. Engl.*, **1978**, *17*, 487  
b) McKillop, A.; Young, D.W. *Synthesis*, **1979**, 401, and 481  
c) Cornellis, A.; Laszlo, P. *Synthesis*, **1985**, 909  
d) Laszlo, P. *Acc. Chem. Res.*, **1986**, *19*, 121  
e) Laszlo, P.; Cornellis, A. *Aldrichimica Acta*, **1988**, *21*, 97.
23. Aluminum oxide, basic, Brockmann I (Aldrich chem. Co., Cat. No. 19,944-3, ~150 mesh, 58A, surface area 155m<sup>2</sup>/g) and Aluminum oxide, neutral [80-200 mesh, for chromatographic analysis (Fisher, Cat. No. A540-500)] were used as received.
24. Varma, R. S.; Varma, M. Unpublished observations.