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A Desilylation and a One-Pot Desilylation−Oxidation of Aliphatic *tert*-Butyldimethylsilyl Ethers Using Catalytic Quantities of $PdCl_2(CH_3CN)_2$

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The *tert*-butyldimethylsilyl (TBDMS) protecting group[1] for alcohols has become widely used by many chemists due to the ease in which it can be attached to and removed from alcohols.[2] Although a large number of reagents have been used to remove the TBDMS group, only four methods have been reported in which a TBDMS group is removed and the resulting alcohol oxidized in one step.[3−7] Most chemists use a two-step procedure, wherein (1) the silyl ether is desilylated and (2) the resulting alcohol is then oxidized.[8] Since $PdCl_2(CH_3CN)_2$ has been reported to desilylate aliphatic[9] and phenolic[10] silyl ethers and palladium acetate has been used with 2-bromomesitylene to oxidize primary and secondary alcohols to aldehydes (or acids) and ketones,[11,12] respectively, we investigated whether the desilylation and oxidation reactions could be combined into a one-pot reaction using a Pd(II) catalyst. We report herein that $PdCl_2(CH_3CN)_2$ can be used catalytically to both desilylate and oxidize TBDMS-protected primary and secondary alcohols to aldehydes and ketones, respectively. In addition, the scope of the desilylation reaction of aliphatic TBDMS ethers has been expanded.

Optimized desilylation conditions involved heating **2** in acetone containing **5 equiv of water**[13] in the presence of 5 mol % $PdCl_2(CH_3CN)_2$ for 6 h at 75 °C; compound **6** was formed in 90% yield. Optimized oxidation conditions involved treating **6** with 5 mol % $PdCl_2(CH_3CN)_2$, 10 mol % PPh_3, and 2-bromomesitylene (1.1 equiv) in DMF **containing 5 equiv of water**[14] at 110 °C for 4 h. Acetophenone was formed in 90% yield. Unfortunately, we discovered the desilylation and the oxidation reactions would not proceed in wet DMF and wet acetone, respectively. Thus, neither solvent alone was suitable for the other reaction.

After many attempts with different solvents, temperatures, and catalysts, we found that a stepwise desilylation−oxidation was possible. The silyl group in **2** was first removed in wet acetone. After GC indicated no starting material was remaining (6 h, 75 °C), the acetone was removed on a rotoevaporator. DMF, 2-bromomesitylene, PPh_3, and K_2CO_3 were added, and the mixture was heated to 120 °C for 5 h. Acetophenone (**7**) was obtained in 80% yield. Although this procedure was satisfactory, we felt that removal of the acetone was a weak step in the above sequence. Finally, we found that a mixture of acetone and DMF (1:1) containing 5 equiv of water was an ideal combination for a stepwise desilylation−oxidation reaction.[15] Thus, treatment of compound **2** with 5 mol % $PdCl_2(CH_3CN)_2$ in acetone/DMF (1:1) containing 5 equiv of water for 9 h at 120 °C provided **6** (by GC). 2-Bromomesitylene (1.1 equiv), PPh_3 (10 mol %), and K_2CO_3 were then added to the reaction vessel, and the mixture was heated for 4 h to provide acetophenone (**7**) in 94% yield. Unfortunately, the desilylation−oxidation cannot be performed in the presence of the mesityl bromide, PPh_3, and K_2CO_3, since we found that the desilylation reaction was inhibited in the presence of a variety of bases like K_2CO_3.

The desilylation[16] and desilylation−oxidation[17] procedures were not limited to the *tert*-butyldimethylsilyl group or benzylic secondary alcohols. Trimethylsilyl protected ethers (**1**) were successfully cleaved (alcohol, 95%) and oxidized (acetophenone, 89%), while triisopropyl- (**4**), and *tert*-butyldiphenylsilyl ethers (**5**) were not removed under the optimized desilylation or desilylation−oxidation conditions. The triethylsilyl moiety (**3**)

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(13) Treatment of **2** according to the procedure reported by Lipshitz[9] provided **6** in 40% yield. The yield improved to 90% upon the addition of 5 equiv of water and increasing the temperature of the reaction to 75 °C. The best desilylation results were obtained with 5 equiv of water. Alcohol **6** was formed in 79%and 75% yield when 0.6 and 1.0 equiv of water was used, respectively (75 °C, 24 h). The byproduct from this desilylation reaction is t-BuMe$_2$SiOH by GC/MS.

(14) Although Tamaru and co-workers[11] emphasized that anhydrous conditions were necessary for the oxidation, we felt at the time that if the oxidation would proceed in wet DMF then the desilylation might also be possible in wet DMF. To our delight, the oxidation of **6** to **7** proceeded smoothly in DMF containing 5 equiv of water.

(15) At this time, we do not understand why the mixed solvent system works so well. For material on the use of and effects of mixed solvents with other systems, see: (a) Ta-Shma, R.; Rappoport Z. *Adv. Phys. Org. Chem.* **1992**, *27*, 239. (b) Watts, D. W. In *Physical Chemistry of Organic Solvent Systems*; Covington, A. V., Dickinson, T., Eds.; Plenum Press: New York, **1973**; pp 715−716.

(16) Optimized desilylation procedure: To a solution of **2** (100 mg, 0.42 mmol) in reagent-grade acetone (2.1 mL) and water (38 μL, 5 equiv) was added $PdCl_2(CH_3CN)_2$ (5.5 mg, 21 μmol). The reaction mixture was refluxed (75 °C) for 6 h (followed by GC) and cooled to rt and the acetone removed *in vacuo* to leave an oil. Purification by distillation provided 1-phenyl-1-ethanol (90%).

(17) Optimized desilylation−oxidation procedure: To a solution of **2** (60 mg, 0.25 mmol) in reagent-grade acetone (1.25 mL), DMF (1.25 mL), and water (23 μL, 5 equiv) was added $PdCl_2(CH_3CN)_2$ (3.3 mg, 13 μmol). The reaction mixture was heated at 110 °C until GC (or TLC) indicated the desilylation was complete (6 h). Triphenylphosphine (13.3 mg, 55 μmol), 2-bromomesitylene (39 μL, 0.27 mmol), and potassium carbonate (39 mg, 0.28 mmol) were added, and the reaction was heated at 110 °C for 4 h. The reaction mixture was cooled to rt, diluted with ether (2 mL), and washed with saturated NaCl (2 × 4 mL). The ether was dried ($MgSO_4$) and removed *in vacuo* to leave an oil which was distilled to provide acetophenone (94%).

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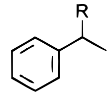
Table 1. Times and Yields for the Desilylation and Oxidation of TBDMS Ethers

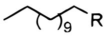
starting material	time for desilylation (h)	alcohol (% yield)	time for oxidation (h)	aldehyde or ketone (% yield)[b]
1. **8**	14	**9** (91)[a]	6	**10** (86)
2. **11**	14	**12** (80)[a]	6	**13** (76)
3. **14**	16	**15** (73)[a]	4	**16** (79)
4. **17**	12	**18** (82)[a]	10	**19** (69)
5. **20**	18	**21** (86)[a]	22	**22** (80)
6. **23**	13	**24** (80)[c]	7	**25** (75)
7. **26**	16	**27** (78)[c]	22	**28** (78)
8. **29**	14	**30** (78)[a]	20	**31** (70)
9. **32**	20	**33** (82)[c]	7[d]	**34** (10)

[a] Isolated yields using acetone, water (5 equiv), 75 °C, 6 h. [b] Isolated yields using DMF:acetone (1:1), water (5 equiv), 120 °C, 9 h, and then add 10 mol % PPh$_3$, 2-bromomesitylene (1.1 equiv). [c] GC yields using the procedure in footnote *b* above. [d] Addition of another 5 mol % catalyst did not affect the yield.

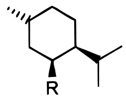
was found to be very capricious under the desilylation conditions; approximately 50% of the silyl group would fall off under the best of conditions. Primary and secondary silyl ethers were desilylated smoothly to provide alcohols in 73−91% yield (entries 1−4, Table 1). Similarly, primary, and secondary-protected alcohols were oxidized smoothly to the corresponding aldehydes (75−86%, entries 1, 5, and 6, Table 1) and ketones (70−78%, entries 2, 7, and 8, Table 1); over oxidation of aldehydes to their corresponding acids or esters was not detected.



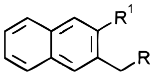
1 R= OSiMe$_3$
2 R= OSi(*t*-Bu)Me$_2$
3 R= OSiEt$_3$
4 R= OSi(i-Pr)$_3$
5 R= OSi(*t*-Bu)$_2$Ph
6 R= OH
7 R= =O



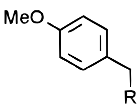
8 R= OSi(*t*-Bu)Me$_2$
9 R= OH
10 R= =O



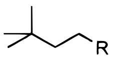
11 R= OSi(*t*-Bu)Me$_2$
12 R= OH
13 R= =O



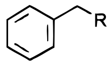
14 R= OSi(*t*-Bu)Me$_2$, R^1=Br
15 R= OH, R^1=Br
16 R= =O, R^1=H



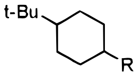
17 R= OSi(*t*-Bu)Me$_2$
18 R= OH
19 R= =O



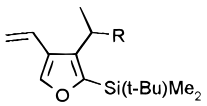
20 R= OSi(*t*-Bu)Me$_2$
21 R= OH
22 R= =O



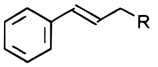
23 R= OSi(*t*-Bu)Me$_2$
24 R= OH
25 R= =O



26 R= OSi(*t*-Bu)Me$_2$
27 R= OH
28 R= =O



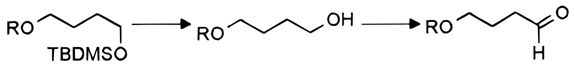
29 R= OSi(*t*-Bu)Me$_2$
30 R= OH
31 R= =O



32 R= OSi(*t*-Bu)Me$_2$
33 R= OH
34 R= =O

The oxidation of benzylic alcohols containing a bromine atom attached to the aromatic ring (**14**, entry 3, Table 1) and allylic alcohols (entry 9, Table 1) were the only two limitations observed. Although **14** desilylated smoothly to provide **15** (73%), the oxidation provided a good yield of 3-naphthaldehyde (**16**, 79%) in which the bromine atom was removed.[18] Similarly, allylic silyl ether **32** when treated with the desilylation−oxidation procedure provided allylic alcohol **33** and *trans*-cinnamaldehyde (**34**) in 82% and 10% yield, respectively (entry 9, Table 1). The addition of 5 mol % more catalyst, after desilylation was detected by GC, did not result in an increase in the yield of *trans*-cinnamaldehyde. Work is continuing to find a suitable method for the oxidation of allylic alcohols.

Table 2. Compatibility of the Desilylation−Oxidation Conditions with Other Protecting Groups of Alcohols



entry	starting material	alcohol (% yield)[a]	aldehyde (% yield)[a]
1	**35**, R = SiEt$_3$	**36** (56)	**37** (40)
2	**38**, R = Si(*i*-Pr)$_3$	**39** (80)	**40** (70)
3	**41**, R = Si(*t*-Bu)Ph$_2$	**42** (81)	**43** (78)
4	**44**, R = MOM	**45** (78)[b]	**46** (60)
5	**47**, R = Bn	**48** (80)	**49** (66)
6	**50**, R = THP	**51** (61)[b]	**52** (−)[c]
7	**53**, R = Ac	**54** (65)[b]	**55** (55)

[a] Isolated yields. [b] Diol was present by GC. [c] NMR indicated decomposition has occurred.

For the desilylation−oxidation procedure to be effective, it is important to know what other protecting groups can be tolerated. Table 2 indicates that a *tert*-butyldimethylsilyl ether was cleaved and the resulting alcohol oxidized in one step in the presence of triisopropylsilyl-, *tert*-butyldiphenylsilyl-, and benzyl-protected alcohols. While compounds with a MOM and acetate group provided the expected aldehydes (**46** and **55**), small amounts of diol (5 and 6%, respectively) were detected by GC after the desilylation had occurred. The desilylation−oxidation procedure should not be used when molecules contain a THP- or triethylsilyl-protecting group, since with the THP group, 27% of the diol was recovered,[9] and under the oxidation conditions, the reaction mixture decomposed. As mentioned previously, triethylsilyl ethers are also sensitive to the desilylation conditions, and lower yields of the aldehyde were obtained along with some diol (32%).

We have developed a mild one-pot procedure for the desilylation−oxidation of *tert*-butyldimethylsilyl ethers using catalytic amounts of PdCl$_2$(CH$_3$CN)$_2$, which provides aldehydes and ketones within 13−20 h (70−86%) and tolerates a variety of other protecting groups for alcohols. In addition, the scope of desilylation using catalytic amounts of PdCl$_2$(CH$_3$CN)$_2$ has been expanded. We are currently studying the mechanism of the desilylation reaction in the presence of water in more detail.

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[18] Presumably, the palladium(0) catalyst oxidatively inserts into the aryl−bromine bond in both 2-bromomestilyene and the substrate resulting in debrominated product. Most likely, aryl iodides would be removed under similar conditions.