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Operationally Simple and Efficient Workup Procedure for TBAF-Mediated Desilylation: Application to Halichondrin Synthesis

Yosuke Kaburagi and Yoshito Kishi*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

kishi@chemistry.harvard.edu

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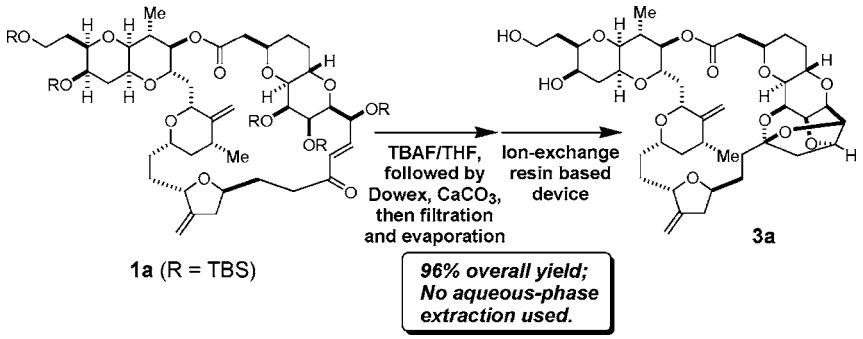
ABSTRACT



An operationally simple and efficient workup method for tetrabutylammonium fluoride (TBAF)-mediated *t*-butyldimethylsilyl (TBS) deprotection has been developed. The procedure includes addition of a sulfonic acid resin and calcium carbonate, followed by filtration and evaporation. This method eliminates the tedious aqueous-phase extraction process to remove excess TBAF and materials derived from TBAF, thereby making the protocol highly amenable to multiple TBS deprotections. Its efficiency and usefulness were demonstrated by using the transformation of 1a to 3a in the halichondrin synthesis.

The *t*-butyldimethylsilyl (TBS) group is one of the most widely used protecting groups for alcohols, phenols, carboxylic acids, and amines because it is (1) easy to introduce, (2) stable under various conditions, and (3) readily and selectively cleaved under the fluoride-mediated, typically tetrabutylammonium fluoride (TBAF), conditions.[1,2] However, deprotection with TBAF often requires an excess amount of the reagent, and an aqueous-phase extraction protocol is commonly used to remove excess TBAF and materials derived from TBAF. For the cases where deprotected products have a high water solubility, the protocol of aqueous-phase extraction is not ideal. Despite this concern, very limited TBAF workup methods are known to avoid an aqueous-phase extraction. Thus, a TBAF workup with no use of aqueous-phase extraction is potentially useful.

This need came to our attention for a slightly different reason. In conjunction with the synthesis of marine natural products halichondrins,[3−7] we recently reported an ion-exchange resin based device to achieve a complete conversion of the enone **2a** into the polycyclic ketal **3a** in an excellent chemical yield (Scheme 1).[4d] The enone **2a** was in turn obtained via TBAF deprotection of the penta-TBS enone **1a**; this deprotection was accomplished in the presence of 7.5−10.0 equiv of TBAF (1.5−2.0 equiv of TBAF per TBS ether), and **2a**[8] was isolated in a high yield by the standard aqueous-phase extraction workup. However, tediously ex-

(1) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190−6191.

(2) For example, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.

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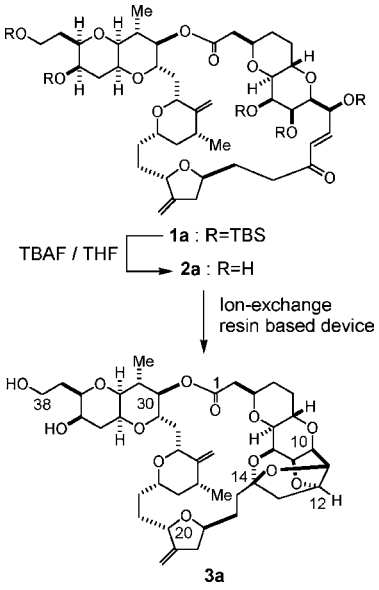
Scheme 1. Transformation of **1a** to **3a**

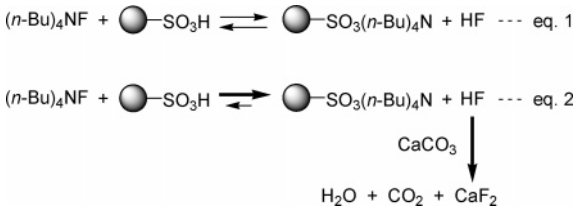


tensive extraction was required, to obtain **2a** free from excess TBAF and materials derived from TBAF. Thus, we recognized the need of developing a nonaqueous workup method of TBAF deprotection, not only because such a method should eliminate the labor-intensive step but also because such a method might allow us to achieve the conversion of the enone **1a** to the polycyclic ketal **3a** without isolation of the intermediate **2a**. Herein, we report an operationally simple, efficient, and versatile workup protocol for TBAF-mediated desilylation.

Related to the current work, we noticed two relevant methods known in the literature. First, Craig and Everhart used sodium perchlorate, to remove excess TBAF as the insoluble tetra-*n*-butylammonium perchlorate salt.[9] Second, Parlow, Vazquez, and Flynn reported the simultaneous use of a calcium sulfonate resin with a sulfonic acid resin.[10] We appreciated an appealing future for both methods but, at the same time, recognized some room for improvement.[11]

At the outset of our work, we envisioned the possibility of removing the tetrabutylammonium cation with the use of acidic ion-exchange resin. To test this possibility, we treated TBAF in THF with excess sulfonic acid resin at room temperature, removed the resin by filtration, and evaporated the filtrate. A ^{1}H NMR analysis of the residue showed that only a small portion of TBAF was removed by this operation, thereby suggesting that sulfonic acid resin alone cannot drive eq 1 toward the right side (Scheme 2). On the basis of this

Scheme 2. Reaction of TBAF and Sulfonic Acid Resin in the Absence (Eq 1) or Presence (Eq 2) of Calcium Carbonate



observation, we focused on a method to remove liberated HF from THF solution. Calcium carbonate (insoluble in THF) seemed to be an attractive HF scavenger for the following reasons: (1) the equilibrium should shift toward the right side because formed CaF_2 precipitates out from the system (CaF_2 is insoluble in THF) and (2) the products, i.e., CaF_2 (insoluble in THF), water, and CO_2, can be removed by filtration and evaporation (see eq 2 in Scheme 2). To test this possibility experimentally, we treated TBAF in THF in

(3) For the first isolation of the halichondrins from a marine sponge *Halichondria okadai* Kadota, see: (a) Uemura, D.; Takahashi, K.; Yamamoto, T.; Katayama, C.; Tanaka, J.; Okumura, Y.; Hirata, Y. *J. Am. Chem. Soc.* **1985**, *107*, 4796−4798. (b) Hirata, Y.; Uemura, D. *Pure Appl. Chem.* **1986**, *58*, 701−710. For isolation of the halichondrins from different species of sponges, see: (c) Pettit, G. R.; Herald, C. L.; Boyd, M. R.; Leet, J. E.; Dufresne, C.; Doubek, D. L.; Schmidt, J. M.; Cerny, R. L.; Hooper, J. N. A.; Rutzler, K. C. *J. Med. Chem.* **1991**, *34*, 3339−3340. (d) Pettit, G. R.; Tan, R.; Gao, F.; Williams, M. D.; Doubek, D. L.; Boyd, M. R.; Schmidt, J. M.; Chapuis, J. C.; Hamel, E.; Bai, R.; Hooper, J. N. A.; Tackett, L. P. *J. Org. Chem.* **1993**, *58*, 2538−2543. (e) Litaudon, M.; Hart, J. B.; Blunt, J. W.; Lake, R. J.; Munro, M. H. G. *Tetrahedron Lett.* **1994**, *35*, 9435−9438. (f) Litaudon, M.; Hickford, S. J. H.; Lill, R. E.; Lake, R. J.; Blunt, J. W.; Munro, M. H. G. *J. Org. Chem.* **1997**, *62*, 1868−1871.

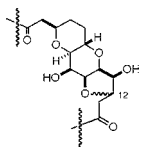
(4) For the synthetic work from this laboratory, see: (a) Aicher, T. D.; Kishi, Y. *Tetrahedron Lett.* **1987**, *28*, 3463−3466. (b) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K.; Kishi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 3162−3164. (c) Choi, H.; Demeke, D.; Kang, F-A.; Kishi, Y.; Nakajima, K.; Nowak, P.; Wan, Z.-K.; Xie, C. *Pure Appl. Chem.* **2003**, *75*, 1−17 and the references cited therein. (d) Namba, K.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7770−7771. (e) Namba, K.; Kishi, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15382−15383 and references cited therein.

(5) For synthetic work by Salomon, Burke, and Yonemitsu, see: (a) Kim, S.; Salomon, R. G. *Tetrahedron Lett.* **1989**, *30*, 6279−6782. (b) Cooper, A. J.; Pan, W.; Salomon, R. G. *Tetrahedron Lett.* **1993**, *34*, 8193−8196 and the references cited therein. (c) Lambert, W. T.; Hanson, G. H.; Benayoud, F.; Burke, S. D. *J. Org. Chem.* **2005**, *70*, 9382−9398 and the references cited therein. (d) Horita, K.; Hachiya, S.; Nagasawa, M.; Hikota, M.; Yonemitsu, O. *Synlett* **1994**, 38−39. (e) Horita, K.; Nagasawa, M.; Sakurai, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1998**, *46*, 1199−1216. (f) Horita, K.; Nishibe, S.; Yonemitsu, O. *Phytochem. Phytopharm.* **2000**, 386−397 and the references cited therein.

(6) For the mechanism of action, see: (a) Bai, R.; Paull, K. D.; Herald, C. L.; Malspeis, L.; Pettit, G. R.; Hamel, E. *J. Biol. Chem.* **1991**, *266*, 15882−15889. (b) Hamel, E. *Pharmacol. Ther.* **1992**, *55*, 31−51. (c) Dabydeen, D. A.; Burnett, J. C.; Bai, R.; Verdier-Pinard, P.; Hickford, S. J. H.; Pettit, G. R.; Blunt, J. W.; Munro, M. H. G.; Gussio, R.; Hamel, E. *Mol. Pharmacol.* **2006**, *70*, 1866−1875 and the references cited therein. (d) Luduena, R. F.; Roach, M. C.; Prasad, V.; Pettit, G. R. *Biochem. Pharmacol.* **1993**, *45*, 421−427.

(7) Recently, Jordan and co-workers reported that the primary antimitotic mechanism of action of halichondrin analogue E7389 is suppression of microtubule growth. For details, see: Jordan, M. A.; Kamath, K.; Manna, T.; Okouneva, T.; Miller, H. P.; Davis, C.; Littlefield, B. A.; Wilson, L. *Mol. Cancer Ther.* **2005**, *4*, 1086−1095.

(8) Compound **2** exists primarily as the intramolecular oxy-Michael adducts shown below.



(9) Craig, J. C.; Everhart, E. T. *Synth. Commun.* **1990**, *20*, 2147−2150.

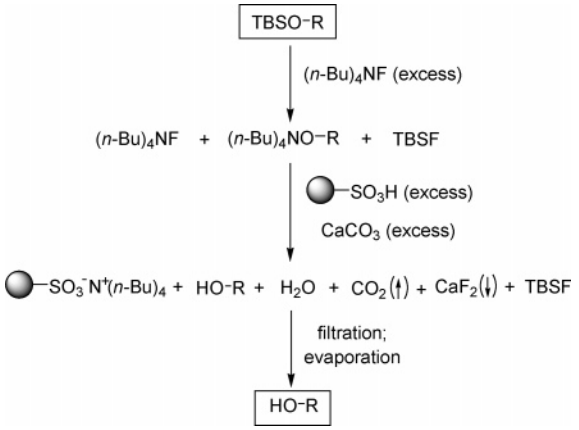
(10) Parlow, J. J.; Vazquez, M. L.; Flynn, D. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2391−2394.

(11) For instance, perchlorates are potentially hazardous, whereas calcium sulfonate resin is not commercially available.

the presence of calcium carbonate at room temperature, removed the insoluble materials by filtration, and evaporated the filtrate to dryness under reduced pressure. A ^{1}H NMR analysis of the residue showed that more than 98% of TBAF was removed via this simple operation. Among the sulfonic acid resins tested,[12] DOWEX 50WX8-400 was found to be the most effective for this purpose.

Having demonstrated that a combination of sulfonic acid resin and calcium carbonate can effectively remove TBAF from THF solution, we then studied the effectiveness of this workup method of TBAF-promoted TBS deprotection. The anticipated overall transformation is depicted in Scheme 3.

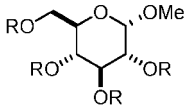
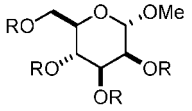
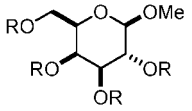
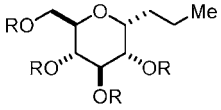
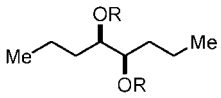
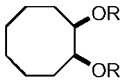
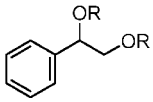
Scheme 3. Overall Transformation



TBS ether is treated with excess TBAF, followed by addition of DOWEX 50WX8-400 (H^+ form, excess) and calcium carbonate (powder, excess). The products formed in this transformation are the desired alcohol, DOWEX 50WX8-400 (n-Bu_4N^+ form), calcium fluoride, water, CO_2, and *t*-butyldimethylsilyl fluoride (TBSF). DOWEX 50WX8-400 (n-Bu_4N^+ form) and calcium fluoride, as well as excess DOWEX 50WX8-400 (H^+ form) and calcium carbonate, can be removed by filtration, whereas water and TBSF can be removed by evaporation. Thus, only the desired alcohol should be left after filtration and evaporation.

To test the feasibility of this method, we selected seven substrates that should furnish the deprotected products with a broad range of polarity (Table 1). According to the general procedure given below,[13] deprotection and workup were carried out. ^{1}H NMR analysis revealed that the crude product

Table 1. Substrates Used to Test the Feasibility and Efficiency of the TBAF Workup Protocol[a]

entry	substrate (R = TBS)/ product (R = H)	equiv of TBAF	crude yield (%)[b]	removed TBAF (%)[c]
1		8	111	99.3
2		8	110	99.5
3		8	107	99.5
4		8	106	99.5
5		4	95[d]	99.5
6		8	110	99.6
7		3	103	99.8

[a] Reaction conditions employed for desilylation: substrate (1 equiv), TBAF (3−8 equiv), THF, rt or heat, 4−28 h; $CaCO_3$, DOWEX 50WX8-400 (used as supplied), MeOH, rt, 1 h. [b]Based on the weight obtained after filtration and evaporation. [c]Estimated from ^{1}H NMR spectra of the crude compound. [d]Product was volatile.

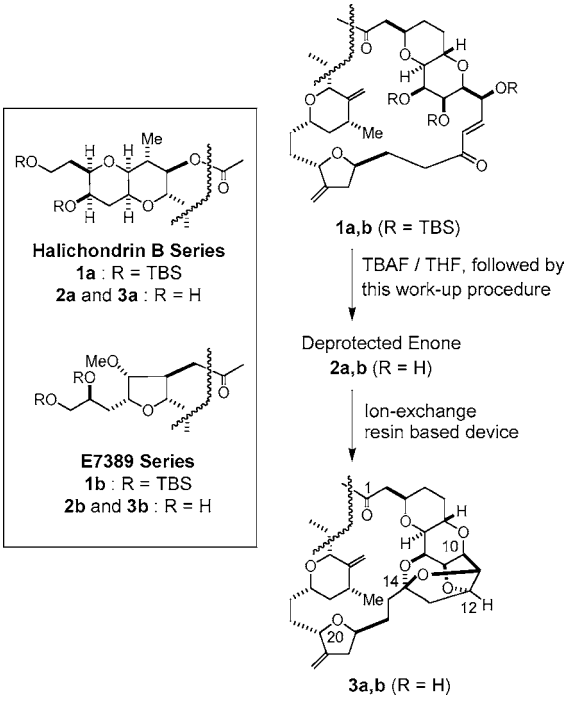
thus obtained was the expected deprotected alcohol only contaminated with a small amount of the TBAF-derived materials. On the basis of the signal intensity in the ^{1}H NMR spectrum of the crude product, at least 99% of the TBAF-derived materials was removed through this procedure for all the cases. Interestingly, practically no TBS-derived material was contaminated in the crude product. This procedure thus proved effective for all the seven substrates tested. In our view, this method offers an attractive option to deal with water-soluble products for which a conventional aqueous-phase workup is difficult to apply.

As mentioned earlier, we had one specific goal for this developmental work. Thus, the penta-TBS enone **1a** in the halichondrin B series was subjected to TBAF-promoted TBS removal in THF (TBAF: total of 10 equiv or 2.0 equiv per TBS, room temperature, 49 h), followed by this workup method, to furnish the crude desilylated enone **2a** (126% of the theoretical weight). Then, the crude product was directly applied to the ion-exchange resin device,[4d] to give the crude

(12) Other sulfonic acid resins tested included Rexyn 101 and Amberlyst 15.

(13) General workup procedure for removal of TBAF residue (Table 1, entry 1): A 10 mL flask containing a stirring bar was charged with substrate (110 mg, 0.169 mmol). TBAF (1.0 M in THF, 1.35 mL, 1.35 mmol) was added via syringe. After the solution was stirred at room temperature for 4 h (no SM nor partially deprotected intermediate detected by TLC), $CaCO_3$ (280 mg), DOWEX 50WX8-400. (840 mg, used as supplied), and MeOH (2.0 mL) were added. The suspension was stirred at room temperature for 1 h. All insoluble materials were removed by filtration through a pad of Celite, and the filter cake was washed with MeOH thoroughly. The combined filtrates were evaporated to dryness under reduced pressure to give the crude product (36.3 mg, 111%) as a white solid. ^{1}H NMR spectra of the crude product showed that 99.3% of tetrabutylammonium salt was removed by these operations.

Scheme 4. Application of This TBAF Workup Method to the Advanced Synthetic Stage in Both the Halichondrin B and E7389 Series



ketal **3a** (107% of the theoretical weight), which was passed through a short plug of silica gel to furnish the pure ketal **3a** in 96% overall yield from **1a** (Scheme 4). This protocol was also successfully applied to the transformation of the penta-TBS enone **1b** to the polycyclic ketal **3b** in the E7389 series.[14]

In summary, we developed an operationally simple and efficient workup method for TBAF-promoted desilylations, with the use of commercially available sulfonic acid resin (used as supplied) and calcium carbonate. This method eliminates the tedious aqueous-phase extraction protocol, to remove excess TBAF and TBAF-derived materials. The effectiveness and versatility of this method were demonstrated for the seven examples shown in Table 1. The usefulness of this method was further demonstrated by using the transformation of **1a**,**b** to **3a**,**b** in the halichondrin synthesis. We believe that this method offers an attractive option to deal with water-soluble products for which a conventional aqueous-phase workup is difficult to apply.

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Supporting Information Available: Experimental details and ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Zheng, W.; Seletsky, B. M.; Palme, M. H.; Lydon, P. J.; Singer, L. A.; Chase, C. E.; Lemelin, C. A.; Shen, Y.; Davis, H.; Tremblay, L.; Towle, M. J.; Salvato, K. A.; Wels, B. F.; Aalfs, K. K.; Kishi, Y.; Littlefield, B. A.; Yu, M. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5551−5554.