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Polymer-Assisted Dithane Hydrolysis with Minimum Workup

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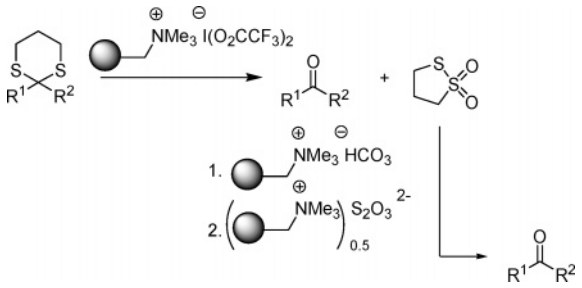
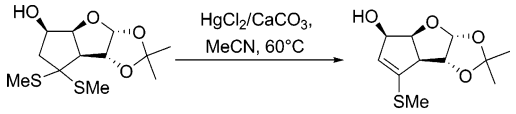


The first solid-phase-assisted protocol for the hydrolysis of dithioacetals is described using three different functionalized ion exchange resins. The hydrolysis and the purification proceed under milder conditions than common homogeneously employed reagents so that very reactive carbonyl compounds can be prepared.

Dithioacetals have recently experienced a renewed interest in synthetic organic chemistry partly because new, highly efficient methods for their preparation starting from propargylic carbonyl compounds and bis-ynones have been developed.[1] Furthermore, Schaumann and Kirschning[2] have developed a new tandem reaction that is based on the silyl dithioacetal moiety.[3,4] It has seen diverse applications in the synthesis of KDO,[5] apicularen A,[6] and polyketide chains found in the mycoticins and in spongistatin[7]

SCHEME 1. Problems Associated with the Hydrolytic Cleavage of Dithioacetals Like 1a



1a **2**

During the course of a synthetic project in the field of prostaglandin chemistry,[8] we had to find conditions for the hydrolytic cleavage of dithioacetals like **1a**, **1h**, and **1i**. Unfortunately, all common homogeneous conditions tested (transition metals, oxidative and alkylation conditions) failed or at best afforded vinyl sulfide **2** in maximum 22% yield (Scheme 1).[9]

Therefore, we had to search for a method for cleaving dithioacetals that only requires mild workup conditions. Ideally, chromatographic purification should be avoided. On the basis of our experience in the development of polymer-bound reagents and scavengers[10] we devised a concept that relies on a polymer-bound thiophilic reagent based on iodine and two scavenger resins (Scheme 2). In fact, the bistrifluoroacetoxy iodate(I) ion[11] is highly thiophilic as we demonstrated before for the activation of thioglycosides.[12] The anionic character can be used to create the corresponding exchange resin **3**. In this paper the first solid phase assisted concept of dithioacetal hydrolysis is disclosed

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(1) (a) Sneddon, H. F.; Gaunt, M. J.; Ley, S. V. *Org. Lett.* **2003**, *5*, 1147−1150. (b) Sneddon, H. F.; van den Heuvel, A.; Hirsch, A. K. H.; Booth, R. A.; Shaw, D. M.; Gaunt, M. J.; Ley, S. V. *J. Org. Chem.* **2006**, *71*, 2715−2725. (c) Gaunt, M. J.; Hook, D. F.; Tanner, H. R.; Ley, S. V. *Org. Lett.* **2003**, *5*, 4815−4818. (d) Gaunt, M. J.; Sneddon, H. F.; Hewitt, P. R.; Orsini, P.; Hook, D. F.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 15−16. (e) Ball, M.; Gaunt, M. J.; Hook, D. F.; Jessiman, A. S.; Kawahara, S.; Orsini, P.; Scolaro, A.; Talbot, A. C.; Tanner, H. R.; Yamanoi, S.; Ley, S. V. *Angew. Chem.* **2005**, *117*, 5569−5574; *Angew. Chem., Int. Ed.***2005**, *44*, 5433−5438.

(2) (a) Kirschning, A.; Kujat, C.; Luiken, S.; Schaumann, E. *Eur. J. Org. Chem.* **2007**, 2387−2400. (b) Schaumann, E.; Kirschning, A. *Synlett* **2007**, 177−190.

(3) Fischer, M.-R.; Kirschning, A.; Michel, T.; Schaumann, E. *Angew. Chem.* **1994**, *106*, 220−221; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 217−218.

(4) Tietze, L. F.; Geissler, H.; Gewert, J. A.; Jakobi, U. *Synlett* **1994**, 511−512.

(5) Bräuer, N.; Kirschning, A.; Schaumann, E. *Eur. J. Org. Chem.* **1998**, 2729−2732.

(6) Petri, A. F.; Bayer, A.; Maier, M. E. *Angew. Chem.* **2004**, *116*, 5945−5947; *Angew. Chem., Int. Ed.* **2004**, *43*, 5821−5823.

(7) (a) Smith, A. B., III; Pitram, S. M. *Org. Lett.* **1999**, *1*, 2001−2004. (b) Smith, A. B., III; Zhuang, L. L.; Brook, C. S. C. S.; Lin, Q. Q.; Moser, W. H.; Lee, W. H.; Trout, R. E.; Boldi, A. M. *Tetrahedron Lett.* **1997**, *38*, 8671−8674. (c) Smith, A. B., III; Lin, Q.; Nakayama, K.; Boldi, A. M.; Brook, C. S.; McBriar, M. D.; Moser, W. H.; Sobukawa, M.; Zhuang, L. *Tetrahedron Lett.* **1997**, *38*, 8675−8678. (d) Smith, A. B., III; Zhu, W.; Shirakami, S.; Sfouggatakis, C.; Doughty, V. A.; Bennett, C. S.; Sakamoto, Y. *Org. Lett.* **2003**, *5*, 761−764. (e) Smith, A. B., III; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukawa, M. *Angew. Chem.* **2001**, *113*, 197−201; *Angew. Chem., Int. Ed.* **2001**, *40*, 191−195. (f) Smith, A. B., III; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783−786. (g) Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2004**, *6*, 1493−1495.

(8) Michel, T. Ph.D. Thesis, Technical University Clausthal, 1995.

(9) Different methods were investigated including the most common strategy with mercury salts like mercury(II) chloride, red mercury oxide, and $HgO/BF_3{\cdot}OEt_2$. Further experiments were conducted with "claycop" (copper(II) nitrate and clay with the active species NO^+), NBS, DMSO, *hν* activated magnesium perchlorate, and alkylating reagents like methyl iodide. (a) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553−3560. (b) Seebach, D. *Synthesis* **1969**, 17−36. (c) Katzenellenbogen, J. A.; Bowlus, S. B. *J. Org. Chem.* **1973**, *38*, 627−632. (d) Woessner, W. D.; Ellison, R. A. *Tetrahedron Lett.* **1972**, *35*, 3735−3738. (e) Vedejs, E.; Fuchs, P. L. *J. Org. Chem.* **1971**, *36*, 366−367. Balogh, M.; Cornélis, A.; Laszlo, P. *Tetrahedron Lett.* **1984**, *25*, 3313−3316. (f) Cornelis, A.; Laszlo, P. *Synthesis* **1985**, 909−918. (g) Rao, C. S.; Chandrasekharam, M.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1992**, *33*, 8163−8164. (h) Epling, G. A.; Wang, Q. *Synlett* **1992**, 335−336. (i) Trost, B. M.; Preckel, M.; Leichter, L. M. *J. Am. Chem. Soc.* **1975**, *97*, 2224−2232.

(10) (a) Kirschning, A.; Wittenberg, R.; Monenschein, H. *Angew. Chem.* **2001**, *113*, 670−701; *Angew. Chem., Int. Ed.* **2001**, *40*, 650−679. (b) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815−4195.

(11) (a) Kirschning, A.; Jesberger, M.; Monenschein, H. *Tetrahedron Lett.* **1999**, *40*, 8999−9002. (b) Monenschein, H.; Sourkouni, G.; Schubothe, K. M.; O'Hare, T.; Kirschning, A. *Org. Lett.* **1999**, *1*, 2101−2104.

(12) (a) Jaunzems, J.; Sourkouni-Argirusi, G.; Jesberger, M.; Kirschning, A. *Tetrahedron Lett.* **2003**, *44*, 637−639. (b) Jaunzems, J.; Hofer, E.; Jesberger, M.; Sourkouni-Argirusi, G.; Kirschning, A. *Angew. Chem.* **2003**, *115*, 1198−1202; *Angew. Chem., Int. Ed.* **2003**, *42*, 1166−1170.

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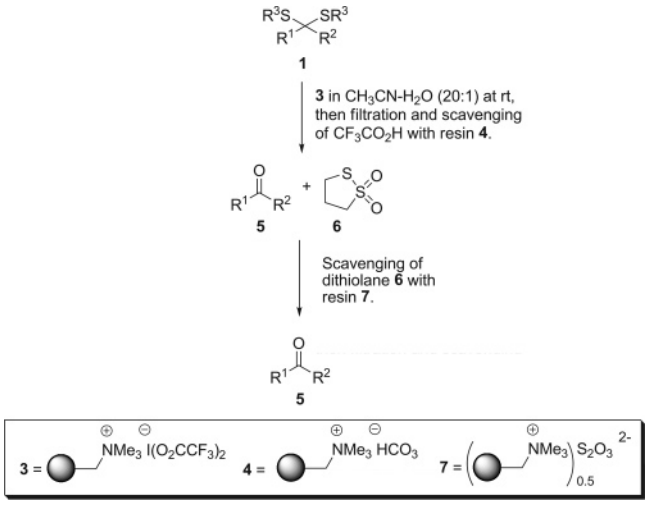
SCHEME 2. Concept of Polymer-Assisted Hydrolysis of Dithioacetals Combined with a Scavenging Protocol

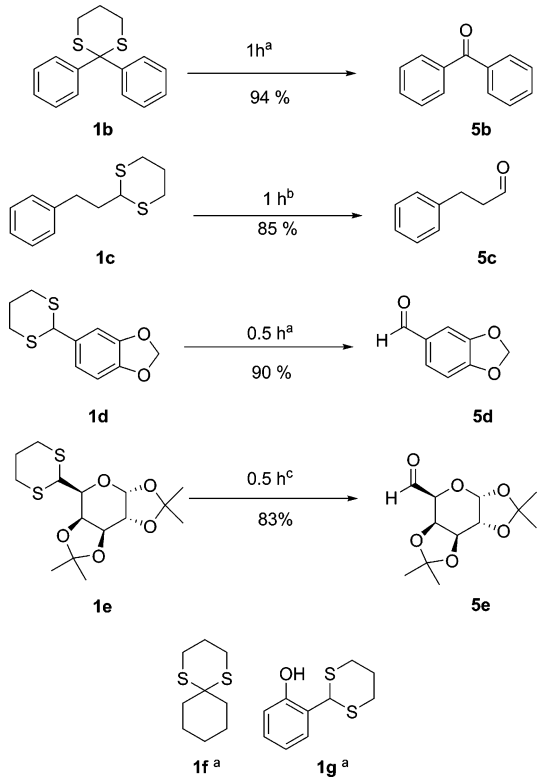


that utilizes **3** as an electrophilic activating agent. Besides the desired carbonyl compound **5**, trifluoroacetic acid (as judged by pH control) and 1,2-dithiolane 1,1-dioxide **6**[13] are formed as byproducts. Scavenging of the former is achieved by addition of bicarbonate exchange resin **4** while dithiolane **6** is removed from the reaction mixture by adding thiosulfate exchange resin **7**. The feasability of this concept that beneficially only relies on anion exchange resins was tested on several dithianes **1b**−**g** (Scheme 3).

The transformations were quantitative and in most cases the corresponding pure carbonyl compounds **5b**−**e** were isolated in very good yield. Additional purification was commonly not necessary. Because of its volatile character cyclohexanone, the hydrolysis product from dithiane **1f**, was analyzed by GC-MS. Salicylic aldehyde was obtained from dithiane **1g**. However, the phenolic group leads to removal from the reaction mixture by exchange on resins **4** or **7**, which hampers easy workup. The solvent of choice was acetonitrile that had to contain water (20:1). Other solvents like CH_2Cl_2, THF, or CH_3NO_2 did not afford rapid or quantitative hydrolysis of the dithioacetal moiety. Beneficially, both scavenging steps also proceeded well in acetonitrile so that no solvent switch needs to be carried out. It needs to be noted that the reagents are employed in equal molar amounts and in excess with respect to the theoretical loading.[14] After both scavenging steps product **5** was commonly pure. Although resin **7** was able to completely remove dithiolane **6** from the solution, we were unable to determine the exact structure of the scavenged species. Acidification of the resin only released a complex mixture of products of unknown nature. To date, it has been reported that dithiolane **6** undergoes ring-opening in the presence of thiolates to form the corresponding sulfinic acids.[15]

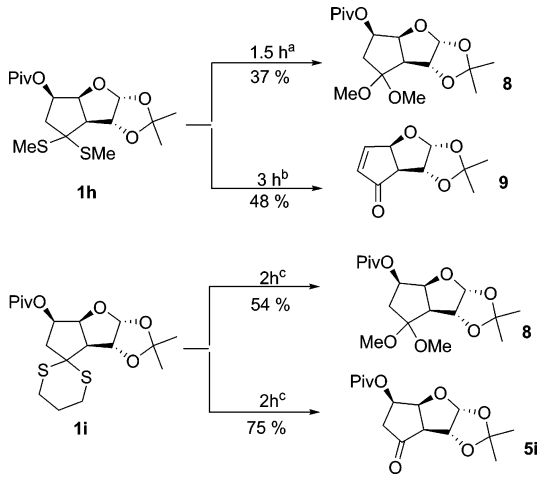
Returning to our initial goal, we tested the mildness of our cleavage and purification protocols on dithioacetals **1h** and **1i**

SCHEME 3. Polymer-Assisted Hydrolytic Cleavage and Purification of Simple Dithianes 1b−g (According to Scheme 2)[14]



[a] Conditions: resins **3**, **4**, and **7** (1:1:1; 5 equiv). [b]Conditions: resins **3**, **4**, and **7** (1:1:1; 4 equiv). [c]Conditions: resins **3**, **4**, and **7** (1:1:1; 10 equiv).

SCHEME 4. Polymer-Assisted Hydrolytic Cleavage and Purification of Complex Dithianes 1h and 1i (According to Scheme 2)[14]



[a] Conditions: resins **3**, **4**, and **7** (1:1:1; 10 equiv). [b]Conditions: resins **3**, **4**, and **7** (1:1:1; 6 equiv). [c]Conditions: resins **3**, **4**, and **7** (1:1:1; 5 equiv).

(Scheme 4). Thus, when dithioacetal **1h** was treated under the optimized conditions with methanol as solvent the dimethoxy acetal **8** was formed,which was purified by a flash gel filtration. In the absence of methanol the desired ketone was formed but it underwent β-elimination to enone **9** during chromatographic purification on silica. But the corresponding dithiane derivative **1i** turned out to be better suited than dithiomethyl acetal **1h**. In

(13) (a) Storck, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287−290. (b) Sheu, C.; Foote, C. S.; Gu, C.-L. *J. Am. Chem. Soc.* **1992**, *114*, 3015−3021. (c) Fleming, F. F.; Funk, L.; Altundas, R.; Tu, Y. *J. Org. Chem.* **2001**, *66*, 6502−6504.

(14) It is commonly experienced that more equivalents than expected are needed for full transformation with solid-bound reagents. This can be ascribed to the general observation that not all locations on the resin bearing the anion can be accessed by the substrate.

(15) Macke, J. D.; Field, L. *J. Org. Chem.* **1988**, *53*, 396−402.

the presence of methanol again acetal **8** was formed. Gratifyingly, the methanol-free protocol yielded the desired ketone **1i** in very good yield. After the scavenging protocol the crude product was pure enough for full characterization, which is crucial because **1i** does not withstand chromatographic purification on silica.

In conclusion, we have reported the first polymer-assisted protocol for the hydrolysis of dithioacetals to the corresponding carbonyl compounds. The method exclusively relies on anion exchange resins, which simplifies the procedure and guarantees straightforward regeneration of the resins by simple washing steps. Importantly, we demonstrated that the method also gives excellent results when reactive carbonyl compounds are generated.

Experimental Section

Additional experimental details can be found in the Supporting Information.

Bis(trifluoroacetoxy)iodate(I) Exchange Resin 3. Polymer-bound iodide Amberlyst (A-26, iodide form) was repeatedly washed with dry methanol and dry CH_2Cl_2. The resin was dried in vacuo for 10 h. The dry resin A-26 (iodide form; 5 g, 2.9 mmol/g) was suspended in dry CH_2Cl_2 (50 mL) and [bis(trifluoroacetoxy)iodo]-benzene (11.22 g, 26 mmol) was added. The suspension was shaken for 2 h in the dark. The resin was filtered and washed twenty times with small portions of dry CH_2Cl_2 and dried in vacuo for 10 h to afford 8.28 g of the title polymer. The loading was calculated to be 1.752 mmol/g.

Bicarbonate Exchange Resin 4. A patch of Amberlyst IRA 900 (5 g, 1 mmol/g Cl^-) was put in a Büchner funnel and a 1.0 M solution of sodium bicarbonate (300 mL) was rinsed through the funnel until no chloride could be detected in the filtrate. The resin was successfully washed twice with methanol, acetone, and diethyl ether then finally dried for 6 h in vacuo to afford the title polymer (5.13 g). The loading was calculated to be 0.98 mmol/g.

Thiosulfate Exchange Resin 7. A patch of Amberlyst IRA 900 (5 g, 1 mmol/g Cl^-) was put in a Büchner funnel and a semisaturated solution of sodium thiosulfate (300 mL) was rinsed through the funnel until no chloride could be detected in the filtrate. The resin was washed twice with methanol, acetone, and diethyl ether then finally dried for 6 h in vacuo to afford the title polymer (5.43 g). The loading was calculated to be 0.92 mmol/g.

Typical Procedure for the Hydrolytic Cleavage of Dithioacetals. Prior to use, the trifluoroacetoxyiodate(I)-resin **3** (0.5 mmol, 285 mg; 1.752 mmol/g) was washed with CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, and acetonitrile, respectively. This resin was added to a suspension of 1,3-dithioacetal (0.1 mmol) in acetonitrile/water (20:1; 4 mL). The reaction mixture was shaken for 1 h. After a reaction time of 0.5−2 h, the resin was filtered off from the deep orange solution and was washed (5×) with acetonitrile (2 mL). Bicarbonate exchange resin **4** (0.5 mmol, 510 mg) was added to the filtrate and the suspension was shaken for 15 min to afford a pale yellow solution, which was filtered, and the remaining polymer **4** was washed (5 × 2 mL) with acetonitrile. Finally, thiosulfate exchange resin **7** (prepared by a washing protocol as described for resin **3**; 0.5 mmol, 538 mg) was added to the solution and the suspension was shaken for 16 h. The reaction mixture was filtered and the resin was washed (5 × 2 mL) with acetonitrile. The solution was concentrated under reduced pressure to give the corresponding aldehyde or ketone, respectively. The resulting product was commonly pure enough for analytical characterization.

***O,O*-Acetal 8.** Preparation followed the general procedure except that methanol was used as solvent instead of acetonitrile: **1h** (20 mg, 0.053 mmol) afforded **8** (6.8 mg, 0.020 mmol; 37%) after gel filtration (silica gel; hexanes/EtOAc 5:1) and **1i** (18 mg, 0.046 mmol) afforded **8** (8.6 mg, 0.025 mmol; 54%) after gel filtration (silica gel; hexanes/EtOAc 5:1). $[\alpha]^{20}_D$ +39.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (d, J = 3.8 Hz, 1H), 4.92 (ddd, J = 10.8, 6.8, 4.2 Hz, 1H), 4.89 (d, J = 3.8 Hz, 1H), 4.87 (dd, J = 5.0, 4.2 Hz, 1H), 3.23 (s, 3H), 3.20 (s, 3H), 2.79 (d, J = 5.0 Hz, 1H), 2.24 (dd, J = 12.5, 6.8 Hz, 1H), 1.97 (dd, J = 12.5, 10.8 Hz, 1H), 1.50 (s, 3H), 1.33 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 111.7, 107.2, 105.7, 82.4, 81.8, 71.5, 54.6, 50.0, 48.5, 38.7, 37.6, 27.3, 27.1, 26.8; HRMS (ESI) (M + Na + acetonitrile)$^+$ calcd for $C_{19}H_{31}NO_7Na$ 408.1998, found 408.2004.

Hydrolysis Product 5i. Preparation followed the general procedure: **1i** (20.0 mg, 0.051mmol) afforded **5i** (11.5 mg, 0.039 mmol; 75%). ^{1}H NMR (400 MHz, C_6D_6) δ 5.50 (d, J = 3.8 Hz, 1H), 4.94 (dd, J = 9.1, 3.2 Hz, 1H), 4.92 (dd, J = 3.2, 3.2 Hz, 1H), 4.67 (d, J = 3.8 Hz, 1H), 2.46−2.24 (m, 3H), 1.32 (s, 3H), 1.17 (s, 9H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 208.8, 177.6, 111.8, 106.6, 83.2, 80.27, 69.6, 61.0, 40,2, 38.7, 27.1, 26.8, 26.3 ppm; HRMS (ESI and EI were not possible) calcd for $C_{15}H_{22}O_6$ 298.1416, fragments found 283.1172 (M − CH_3), 199, 181, 167, 149, 139, 85.

Enone 9. Preparation followed the general procedure: **1h** (19.1 mg, 0.051 mmol) afforded **9** (4.8 mg, 0.024 mmol; 48%) after gel filtration (silica gel; hexanes/EtOAc 10:1). $[\alpha]^{20}_D$ −50.0 (*c* 0.43, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 5.7, 2.6 Hz, 1H), 6.21 (d, J = 5.7 Hz, 1H), 5.70 (d, J = 3.4 Hz, 1H), 5.48 (dd, J = 5.7, 2.6 Hz, 1H), 4.72 (d, J = 3.4 Hz, 1H), 3.16 (d, J = 5.7 Hz, 1H), 1.56 (s, 3H), 1.36 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 161.3, 135.1, 113.2, 106.6, 82.4, 81.4, 54.8, 27.9, 27.0. HRMS calcd for $C_{10}H_{12}O_4$ 196.0736, fragments found 181.0497 (M − CH_3), 139, 121, 82, 59.

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Supporting Information Available: Details of the experimental procedures and spectroscopic data of the starting dithioacetals. This material is available free of charge via the Internet at http://pubs.acs.org.

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