ORGANIC LETTERS

2001
Vol. 3, No. 14
2185−2188

Chelation, Activation, and Proximity Effects in the Deprotection of Dithianes with $ZnBr_2$. Applications in the Polyketide Field

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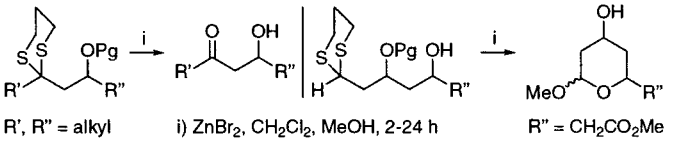
Received April 27, 2001

ABSTRACT



Double deprotection of dithiane aldol equivalents is feasible under mild conditions with $ZnBr_2$ and suitably placed MEM, BOM, and SEM groups which function as protecting, activating, and regiodirecting groups. The procedure is useful in natural product synthesis.

The role of 1,3-dithianes in the development of the synthon concept and of reactivity *umpolung* is well established. There are important reasons why cyclic *S*,*S*-acetals continue to attract the attention of synthetic chemists.[1] Dithianes are acyl anion equivalents which allow selective C−C couplings of complex building blocks, giving aldol segments with full protection of the carbonyl group and with full or partial protection of the hydroxy group. Furthermore, the choice of the electrophilic component allows direct control of absolute stereochemistry.[1,2]

On the other hand, selective removal of a protecting group in a multifunctional environment can be more troublesome than its introduction. The large number of methods which address the problem of dethioacetalization may be taken as evidence that deprotection often proves refractory and requires trial and error.

In general, three methods are used for deprotection of *S*,*S*-acetals: (i) heavy metal coordination, (ii) alkylation, and (iii) oxidation. In the course of deprotecting a variety of SEM ethers,[3] we have developed a new, chelation-guided deprotection method of dithianes. For example, deprotection of the SEM group in the masked aldol **1** was found to proceed smoothly (**1** → **2**) with $MgBr_2$ under homogeneous conditions ($Et_2O/MeNO_2$; Scheme 1). The use of $ZnBr_2$ (wet) instead of $MgBr_2$ furnished a further surprising result. In this case a double deprotection with both loss of the SEM group and regeneration of the carbonyl function took place to provide fully deprotected β-hydroxy ketone **3**.

We assume that deprotection of the dithiane is assisted by chelation of the zinc ion by the oxygen atoms of the

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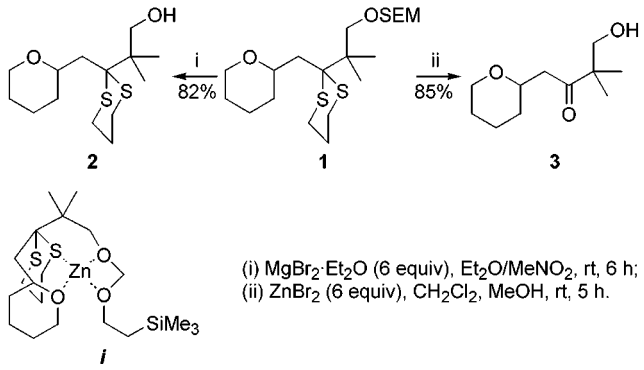
(1) (a) Smith, A. B.; Condon, S. M.; McCauley, J. A. *Acc. Chem. Res.* **1998**, *31*, 35. (b) Tietze, L. F.; Geissler, H.; Gewert, J. A.; Jakobi, U. *Synlett* **1994**, 511. (c) Hale, K. J.; Hummersone, M. G.; Bhatia, G. S. *Org. Lett.* **2000**, *2*, 2189. (d) Luh, T.-Y. *Acc. Chem. Res.* **1991**, *24*, 257. (e) Page, P. C. B.; van Niel, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643−7677. (f) Vakalopoulos, A.; Lampe, T. F. J.; Hoffmann, H. M. R. *Org. Lett.* **2001**, *3*, 929. (g) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. (h) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 639. (i) Corey, E. J.; Seebach, D.; Freedman, R. *J. Am. Chem. Soc.* **1967**, *89*, 434.

(2) (a) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Chemistry*, 3rd ed.; Wiley: New York, 1999. (c) Schelhaas, M.; Waldmann, H. *Angew. Chem.* **1996**, *108*, 2192; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2056. (d) Pearson, A. J., Roush, W. R. Eds. *Handbook of Reagents for Organic Synthesis, Activating Agents and Protecting Groups*; Wiley: New York, 2000.

(3) Vakalopoulos, A.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 1447.

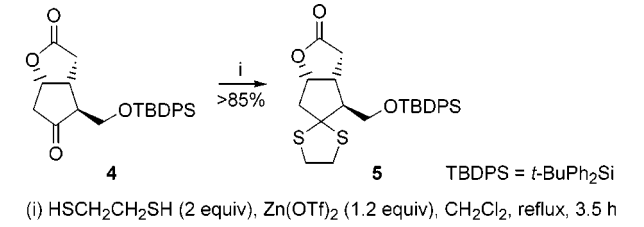
10.1021/ol016037l CCC: $20.00
Published on Web 06/09/2001

Scheme 1



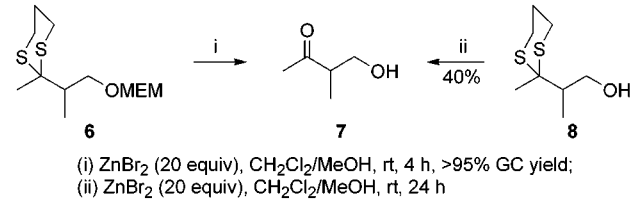
protecting SEM group and of the tetrahydropyran (cf. ***i***). Recombination of the liberated 1,3-propanedithiol with the sterically encumbered ketone **3** to the corresponding dithiane was not observed in this case, although this type of reaction may occur under these conditions with surprising ease (see below). For example, both $Zn(OTf)_2$ (1.2 equiv) and ZnI_2 (2 equiv) have been used for the thioacetalization of carbonyl compounds (Scheme 2).[4]

Scheme 2



The role of chelation and functionality distance is examined further in Scheme 3. We chose the more chelating MEM

Scheme 3

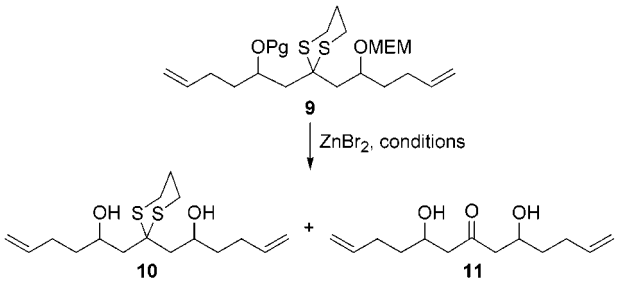


protecting group[5] to induce double deprotection[6] of the masked aldol **6** obtaining the desired β-hydroxy ketone **7**.[7] In contrast, a *free* hydroxy group in a 1,3-distance as in **8** was inefficient, giving **7** in 40% yield only.

(4) (a) Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* **1983**, *24*, 169. (b) Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009.

To investigate deprotection conditions for a more stable and more hindered *S,S*-acetal, we prepared masked aldol **9** by standard methods using epoxides (Table 1).

Table 1



entry	Pg	conditions	reaction time	yield of **10** + **11** [%]
1	H	15 equiv of $ZnBr_2$ CH_2Cl_2	21 h	53 + 30
2	H	15 equiv of $ZnBr_2$ CH_2Cl_2/30 equiv of MeOH	24 h	30 + 41
3	H	25 equiv of $ZnBr_2$ CH_2Cl_2/25 equiv of MeOH	12 h	26 + 56
4	H	40 equiv of $ZnBr_2$ CH_2Cl_2/40 equiv of MeOH	6 h	43 + 51
5	H	40 equiv of $ZnBr_2$ CH_2Cl_2/80 equiv of MeOH	5 h	35 + 63
6	H	40 equiv of $ZnBr_2$ CH_2Cl_2/80 equiv of MeOH[a]	5 h	19 + 76
7	MEM	12 equiv of $ZnBr_2$ CH_2Cl_2/12 equiv of MeOH	24 h	34 + 31[c]
8	BOM	40 equiv of $ZnBr_2$ CH_2Cl_2/80 equiv of MeOH[a]	10 d	nd[b] + 48[c]

[a] Addition of acetaldehyde (8 equiv), 0 °C, 1.5 h, then aqueous workup. [b] Not determined. [c] Not optimized.

Again, the MEM protecting group was chosen for a chelation-mediated deprotection. Variations of solvent mixtures and amounts of $ZnBr_2$ are shown for Pg = H (entries 1−5). Kinetically controlled double deprotection of the MEM and dithiane group was only achieved with a large excess of the Lewis acid to provide the desired keto diol **11**. To

(5) For the role of the MEM group to coordinate metal ions and even serve as a stereodirector, see: (a) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809. (b) Salomon, R. G.; Sachinvala, N. D.; Roy, S.; Basu, B.; Raychaudhuri, S. R.; Miller, D. B.; Sharma, R. B. *J. Am. Chem. Soc.* **1991**, *113*, 3085.

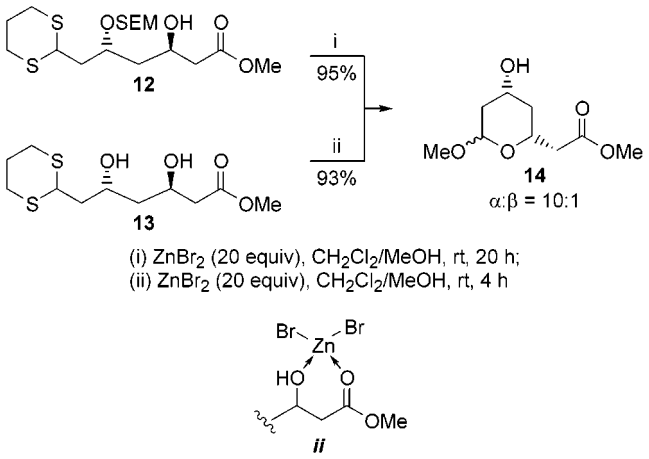
(6) For the use of $ZnBr_2$ in the deprotection of MEM ethers, see: (a) Reference 5a. (b) Guindon, Y.; Morton, H. E.; Yoakim, C. *Tetrahedron Lett.* **1983**, *24*, 3969. (c) $CeCl_3 \cdot 7H_2O$/MeCN: Sabitha, G.; Satheesh Babu, R.; Rajkumar, M.; Srividya, R.; Yadav, J. S. *Org. Lett.* **2001**, *3*, 1149.

(7) During the aqueous workup, a partial reaction of **7** to dithiane **8** (no MEM group) was observed.

circumvent recombination of 1,3-propanedithiol with the carbonyl function in **11** to diol **10** during workup, the reaction mixture was quenched with additional acetaldehyde. In this fashion the dithiol component (entry 6, footnote a) was scavenged via tranthioacetalization. The use of two flanking MEM groups in the aldol pattern **9** was not helpful (entry 7). Some decomposition was observed, presumably due to overactivation. The BOM group could be used as a further chelation group (entry 8).

We have also applied the deprotection protocol to terminal *S*,*S*-acetals (Scheme 4). Because of the high reactivity of

Scheme 4

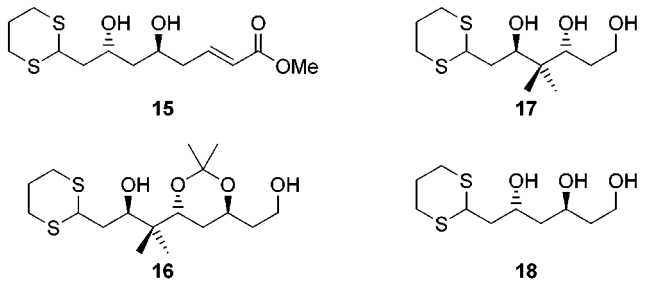


aldehydes toward liberated 1,3-propanedithiol under the reaction conditions, we chose a free hydroxy group in a 1,5-functionality distance hoping to obtain a methoxy acetal. In fact, SEM-protected dithiane **12** afforded masked lactol **14** in excellent yield: The double deprotection−cyclization involves at least three steps and is of interest in the synthesis of natural products.[8,9]

To our surprise, diol **13** without any hydroxy protecting group at all also cyclized to **14** under these conditions, although other 1,3-diols did not. We assume that the β-hydroxyester part of dithiane **13** serves as a bidentate ligand and is complexed first of all (cf. ***ii***), before a second molecule of Lewis acid removes the *S*,*S*-acetal.

As a test substrate, vinylogous β-hydroxyester **15** was prepared and unlike diol **13** was found to be stable to the deprotection conditions. The deprotection−cyclizing protection failed on diol **16** and triols **17** and **18**, as expected. Starting materials were recovered (Scheme 5), and in the

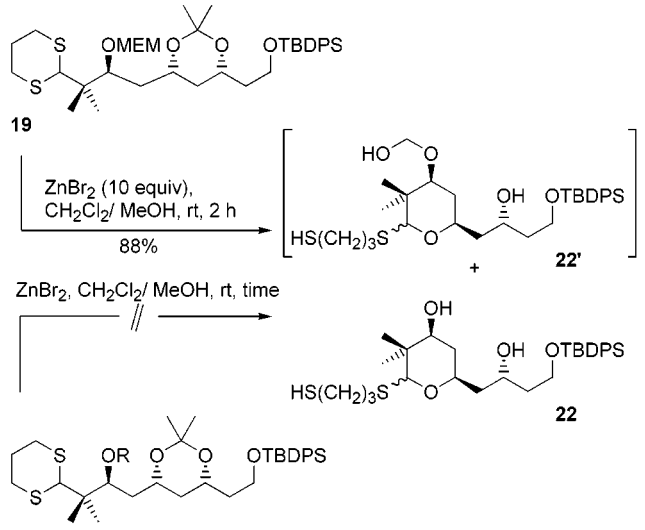
Scheme 5



case of acetonide **16** deprotection to the corresponding tetrol was observed in 99% yield.

The superiority of the MEM chelator is demonstrated in Scheme 6. MEM-protected dithiane **19** afforded a mixture

Scheme 6



of *O*,*S*-acetal **22** and a small amount of formaldehyde-derived unstable hemiacetal **22′**, which results from incomplete deprotection of the $MeOCH_2CH_2OCH_2$ group.

On slow isolation, hemiacetal **22′** was converted into **22**. Presumably the *gem*-dimethyl group prevents further reaction to the methoxy acetal which was observed for the parent system (Scheme 4). SEM-protected dithiane **20** and alcohol

(8) **Representive Experimental Procedure. Synthesis of 14.** Anhydrous $ZnBr_2$ (230 mg, 1.02 mmol) was added to a solution of dithiane **12** (21 mg, 0.051 mmol) in 0.5 mL of CH_2Cl_2 and MeOH (83 μL, 2.04 mmol). The resulting solution was stirred for 20 h at room temperature and then diluted with MTB ether and washed with 1 N HCl (10 mL). The organic layer was washed with 2 N NaOH (2 × 10 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL), the combined organic layers were washed with brine (2 × 20 mL) and dried (Na_2SO_4), and the solvent was removed. The crude product was purified by column chromatography (SiO_2; MTB/PE, 3:1 → MTB) to afford **14** (10 mg, 95%), colorless oil, $[\alpha]^{20}_D = -14.5°$ (*c* 0.25, $CHCl_3$): IR (neat) ν 3668, 2933, 1718, 1438, 1387, 1264, 1196, 1154, 1120, 1042, 972 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.83 (d, ^3J = 3.2 Hz, 1 H, C*H*OMe), 4.23−4.06 (m, 2 H, C*H*(OH)CH_2C*H*CH_2), 3.70 (s, 3 H, CO_2CH_3), 3.33 (s, 3 H, OCH_3), 2.57 (dd, ^2J = 15.5 Hz, ^3J = 8.9 Hz, 1 H, CH_2CO_2), 2.46 (dd, ^2J = 15.5 Hz, ^3J = 4.4 Hz, 1 H, CH_2-CO_2), 2.10−1.96 (m, 3 H, CH_2CH(O*H*)CH_2), 1.54−1.45 (m, 1 H, CH_2-CH(OH)CH_2), 1.28 (q, 1 H, $^{2/3}J$ = 11.7 Hz, 1 H, CH_2CH(OH)CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.49 (4°, CO_2), 98.93 (3°, *C*HOMe), 64.40 (3°, *C*HCH_2CO_2), 63.38 (3°, *C*HOH), 54.57 (1°, OCH_3), 51.64 (1°, CO_2CH_3), 40.54 (2°, CH_2CO_2), 40.18/38.85 (2°, CH_2*C*H(OH)CH_2); MS (170 °C) *m*/*z* 204 (M^+, 8), 187 (5), 159 (11), 155 (80), 133 (12), 123 (21), 107 (12), 85 (21), 81 (100), 69 (13).

(9) See also: Vakalopoulos, A.; Hoffmann, H. M. R. *Org. Lett.* **2001**, *3*, 177.

21 provided the corresponding triols, after removal of the sensitive protecting groups: the *S*,*S*-acetal group stayed intact.

In conclusion, removal of protecting groups and release of dissimilar functionality need not be a linear operation but can be simultaneous and part of an overall strategy, saving steps. MEM, SEM, and BOM groups in a 1,3-functionality distance to a dithiane induce a *double* deprotection when using $ZnBr_2$ distance in CH_2Cl_2/MeOH to give aldols. If a hydroxy group is present in a 1,5-distance, cyclic acetals and methoxyglycosides can be observed. The chelation tendency and activity of zinc ion depend on the number of oxygen atoms in the protecting-activating group: MEM > SEM, BOM. The MEM group was removed first, in preference to other protecting groups. In general, polyols are not deprotected unless selective precomplexation is feasible as in **13** which contains no protecting groups (Scheme 4). Transthioacetalization is a further possibility to improve reaction yields. Our protocol does not employ toxic agents [such as $Hg(ClO_4)_2$ with $CaCO_3$][10] or oxidizing agents [e.g., bis(trifluoroacetoxy)iodobenzene].[11] Together with our previous work[3] it provides simplified options for single-flask transformations in the polyketide and carbohydrate field.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft, Volkswagen Foundation, and Fonds der Chemischen Industrie for their support and Ulrike Eggert for her help.

OL016037L

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(11) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287. For *N*-haloamides see ref 2.