Oxidative Deprotection of 1,3-Dithiane Group Using $NaClO_2$ and NaH_2PO_4 in Aqueous Methanol

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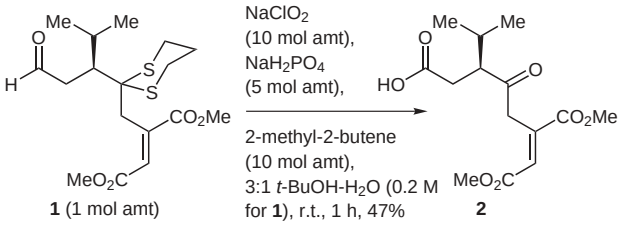
Abstract: The 1,3-dithiane group was oxidatively deprotected under the conditions of sodium chlorite, sodium dihydrogenphosphate, and 2-methyl-2-butene in 3:1 methanol–water at room temperature in good yield.

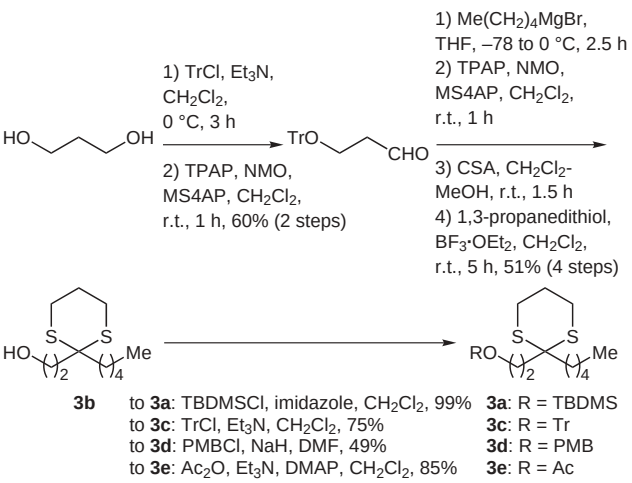
Key words: thioacetals, sodium chlorite, sodium dihydrogenphosphate, protecting groups, deprotection

1,3-Dithiane derivatives are versatile intermediates in organic synthesis. Since the introduction by Corey and Seebach in 1965,[1] the 2-metallo-1,3-dithiane derivatives have been used as excellent acyl anion equivalents for carbon-carbon bond formation.[2,3] Moreover, the 1,3-dithiane group is widely used as an important carbonyl protecting group because of its stability in both acidic and basic conditions.[4] However, it is necessary to use special conditions for deprotection of the 1,3-dithiane group to generate the parent carbonyl group.[4,5] Therefore, the development of new deprotection methods is still of continuous concern by synthetic organic chemists.[6] During the course of our synthetic studies on biscembranoid marine natural products, we found that dithiane aldehyde **1**[7] was converted to keto carboxylic acid **2** under normal oxidation conditions, i.e., $NaClO_2$, NaH_2PO_4, and 2-methyl-2-butene in 3:1 *t*-BuOH–H_2O at room temperature (Scheme 1).[8] We considered that this oxidation method would be a new, facile, and mild alternative for the deprotection of the 1,3-dithiane group. We describe in this letter the results of this research.



Scheme 1

We selected silyl ether **3a**, prepared from 1,3-propanediol via alcohol **3b** as shown in Scheme 2, as the model compound. First, solvent (0.2 M for **3a**) optimization was investigated (Table 1) using 6 molar amounts of $NaClO_2$,[9] 2 molar amounts of NaH_2PO_4,[10] and 10 molar amounts of 2-methyl-2-butene at room temperature for the indicated reaction time. As shown in Table 1, alcoholic solvents were suitable for this reaction (entries 7–10); among them, 3:1 MeOH–H_2O was the best choice (entry 10, 84% yield of **4a**).



Scheme 2 Preparation of 1,3-dithiane derivatives **3a**–**e**

Next, the substrate concentration was examined in 3:1 MeOH–H_2O. Data in Table 2 show that the lower the concentration for **3a**, the better the isolated yield of **4a**. From a synthetic point of view, the 0.1 M substrate concentration is suitable; therefore, the following experiments were conducted in the 0.1 M concentration.

Under these optimized conditions, several 1,3-dithiane derivatives, **3b**–**e** (Scheme 2) and **3f**–**r** (Figure 1; the preparation of **3f**–**r** is shown in Scheme 3),[11] were subjected to the deprotection reactions. These results are compiled in Table 3.

The 2,2-dialkyl-1,3-dithiane derivatives, **3b**–**h**, afforded the corresponding parent carbonyl compounds, **4b**–**h**, in good yields (entries 1–7). No α-epimerization occurred in the case of **3f** (entry 5). 2,2-Diphenyl-1,3-dithiane (**3i**) and

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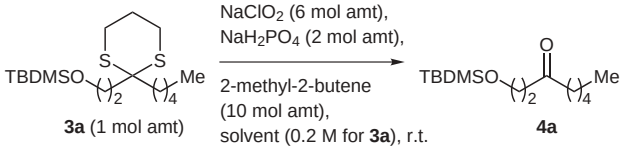
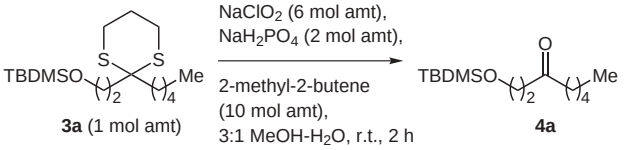
Table 1 Solvent Optimization for Deprotection of **3a**



Entry	Solvent	Time (h)	Yield (%) of **4a**[a]
1	3:1 EtOAc–H_2O	2	29
2	3:1 THF–H_2O	2	30
3	3:1 CH_2Cl_2–H_2O	2.5	31
4	3:1 Acetone–H_2O	2.5	39
5	3:1 DMF–H_2O	2	42
6	3:1 MeCN–H_2O	3	55
7	3:1 *t*-BuOH–H_2O	1	54
8	3:1 *i*-PrOH–H_2O	2	67
9	3:1 EtOH–H_2O	4	77
10	3:1 MeOH–H_2O	2	84

[a] Isolated yield after silica-gel column chromatography.

Table 2 Effect of Substrate Concentration for Deprotection of **3a**



Entry	Concentration (M) for **3a**	Yield (%) of **4a**[a]
1	0.2	84
2	0.1	92
3	0.05	97

[a] Isolated yield after silica-gel column chromatography.

the 2-aryl-2-pentyl-1,3-dithiane derivatives, **3j**–**m**, also gave the corresponding parent carbonyl compounds, **4i**–**m**, in good yields. The electronic nature of the substituent on the phenyl ring had only a small influence on the yields of **4i**–**m** (entries 8–12). In contrast, in the case of the ester-substituted 1,3-dithiane derivative **3n**, ketone **4n** was isolated in less than 10% yield (entry 13). Only a complex mixture was obtained when the aliphatic aldehyde- and benzaldehyde-derived 1,3-dithiane derivatives, **3o** and **3p**, were subjected to our conditions (entries 14 and 15). Interestingly and expected, the aromatic aldehyde-derived 1,3-dithiane derivatives having the methoxy substituent, **3q** and **3r**, gave a mixture of the carboxylic acids and their methyl esters in good yields (entries 16 and 17).

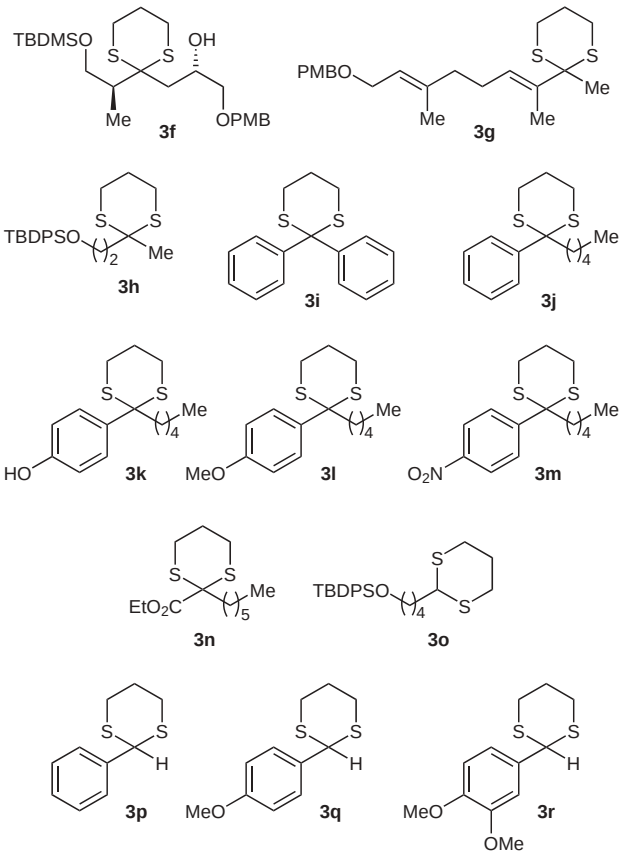


Figure 1

A possible rationale for the substituent dependence on the success of the reaction is as follows (Scheme 4). When the first mono-oxidized intermediate **I** is opened to give the intermediate **II** (path a),[12] deprotection smoothly proceeds to afford the parent carbonyl compound. However, when the intermediate **I** is further oxidized to give the intermediate **III** (path b), deprotection does not proceed under the given reaction conditions.[2b] The critical point is the electronic nature of the substituents at the C2 position of the 1,3-dithiane derivatives. Ketone-derived 1,3-dithiane derivatives prefer the path a route because the two substituents can stabilize the intermediate **II**. The electron-withdrawing ester substituent (**3n**) would prevent the path a route and only one alkyl or phenyl substituent (**3o** or **3p**) would be insufficient for the path a route.

It is noteworthy that the methyl esters were obtained in the case of **3q** and **3r** (Table 3, entries 16 and 17). With **3q**, an interesting disulfide **6** (Scheme 5) was also isolated in 12% yield. The structure of **6** was confirmed by ^{1}H NMR, ^{13}C NMR, and MS spectra. In addition, the following results also support the structure; reduction of **6** with Bu_3P gave thiol **8** (6:1 CH_2Cl_2–H_2O, r.t., 0.5 h, quantitative yield, Scheme 6) and thiol **8** was oxidized to **6** by treatment with I_2 (MeOH, Et_3N, r.t., 10 min, 77%). We considered that this *S*-alkyl thioate **6** would be the precursor of methyl ester **5**. To rationalize this assumption, we conducted an experiment using a 1 molar amount of **3q** and 2 molar amounts of $NaClO_2$, giving a 57:12:19:12 mixture

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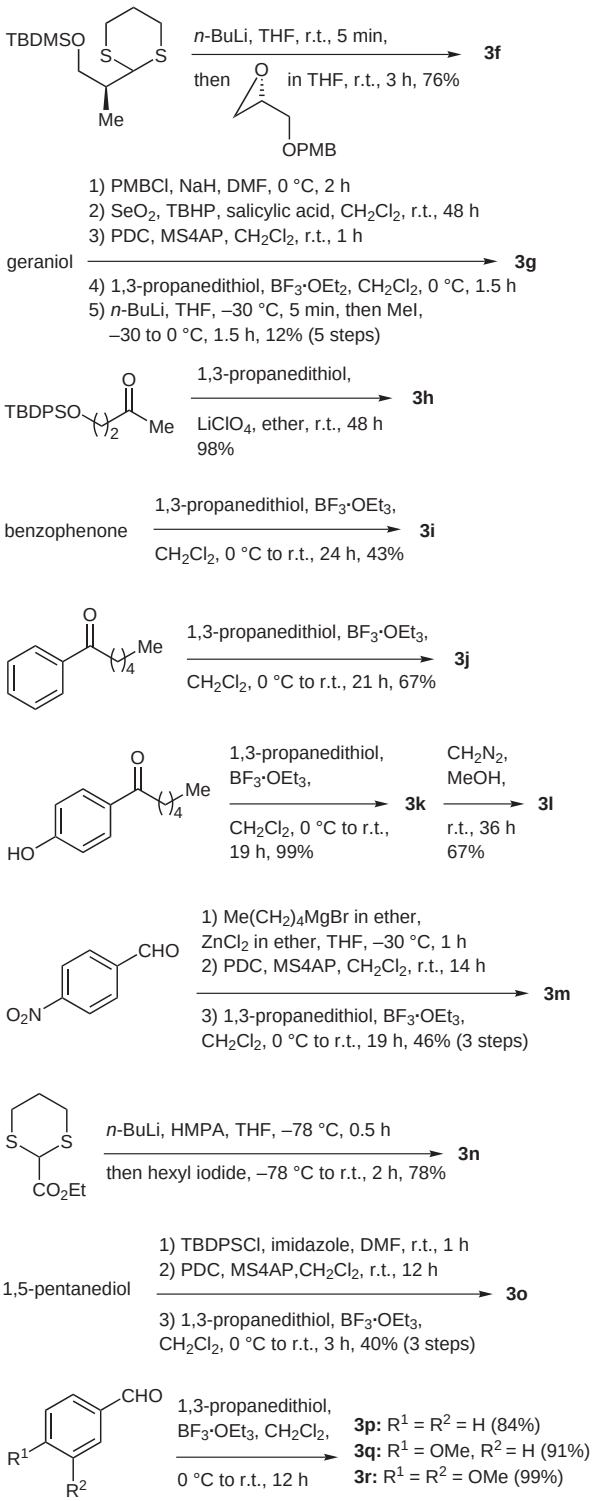
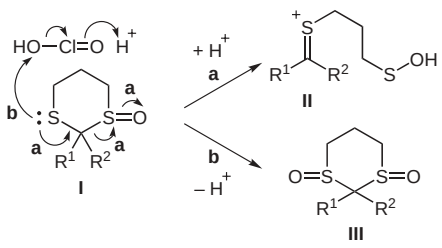


Scheme 3 Preparation of 1,3-dithiane derivatives **3f**–**r**



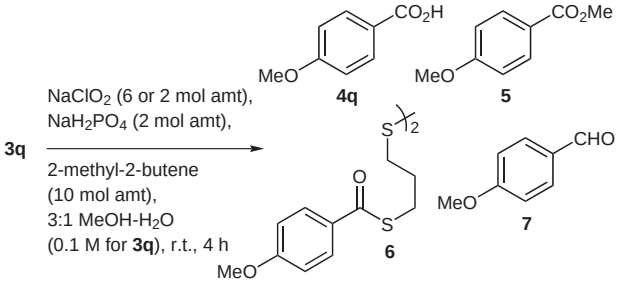
Scheme 4

Table 3 Deprotection of Several 1,3-Dithiane Derivatives **3b**–**r**

3b–3r (1 mol amt)
$NaClO_2$ (6 mol amt), NaH_2PO_4 (2 mol amt), 2-methyl-2-butene (10 mol amt), 3:1 MeOH-H_2O (0.1 M for **3**), r.t.
4b–4r

Entry	Substrate	Time (h)	Yield (%) of **4**[a]
1	**3b**	2	61
2	**3c**	2	80
3	**3d**	2	85
4	**3e**	2	88
5	**3f**	1	87
6	**3g**	3.5	85[b]
7	**3h**	2	75
8	**3i**	2	96
9	**3j**	3	94
10	**3k**	3	93
11	**3l**	4.5	97
12	**3m**	4	89
13	**3n**	3	<10
14	**3o**	4	–[c]
15	**3p**	2	–[c]
16	**3q**	2	83[d]
17	**3r**	2	94[e]

[a] Isolated yield after silica gel column chromatography.
[b] The reaction temperature was 0 °C.
[c] Complex mixture was obtained.
[d] Carboxylic acid (68%) and its methyl ester (15%) were obtained.
[e] Carboxylic acid (68%) and its methyl ester (26%) were obtained.



Scheme 5

of **3q**, **4q**, **6**, and **7** (Scheme 5).[13] A possible mechanism for the formation of **6** is depicted in Scheme 6. The highly reactive sulfenic acid **II**[14] is attacked by **3q** to give the disulfide intermediate **IV** that is oxidized with $NaClO_2$, affording *S*-alkyl thioate **6** via the intermediate **V**. The isolated **6** was subjected to the deprotection conditions, quantitatively giving a 76:24 mixture of carboxylic acid

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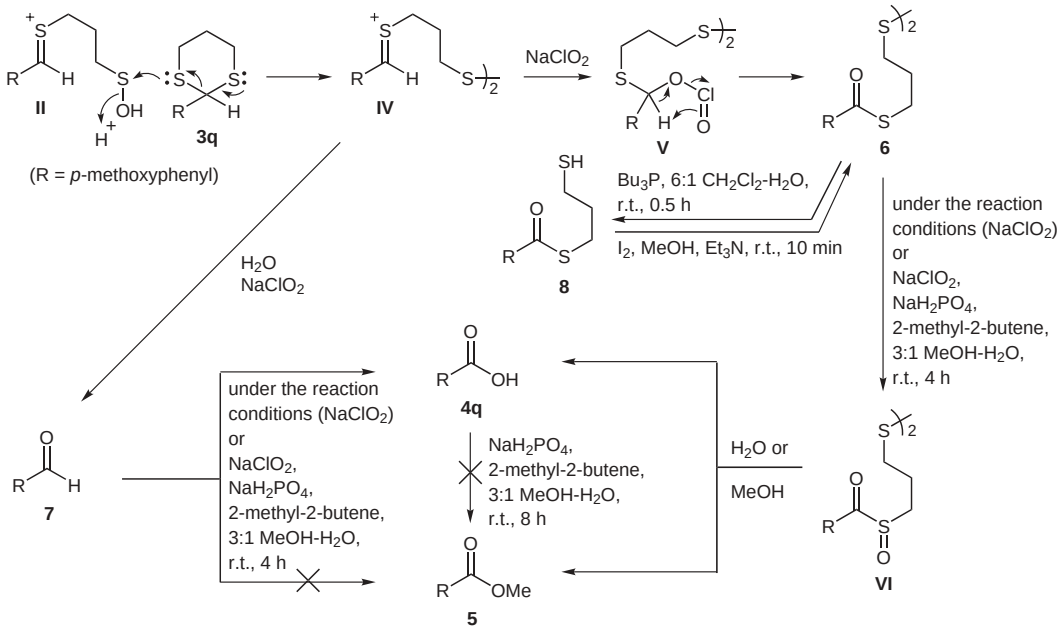

Scheme 6 Proposed mechanism for formation of **4q** and **5**

4q and methyl ester **5**. The probable intermediate in this case must be the acyl sulfoxide **VI**. Moreover, *p*-methoxybenzaldehyde (**7**) itself afforded carboxylic acid **4q** as the only oxidation product under the deprotection conditions, while **4q** itself did not afford methyl ester **5** under the deprotection conditions without $NaClO_2$. These facts indicate that *S*-alkyl thioate **6** must be the precursor of not only carboxylic acid **4q** but also methyl ester **5** in our deprotection reaction.

In summary, we developed new, facile, and mild deprotection conditions for 1,3-dithiane derivatives using 6 molar amounts of $NaClO_2$, 2 molar amounts of NaH_2PO_4, and 10 molar amounts of 2-methyl-2-butene in 3:1 MeOH–H_2O at room temperature. These conditions are suitable for the ketone-derived 1,3-dithiane derivatives and aromatic aldehyde-derived 1,3-dithiane derivatives. In the latter case, the products are a mixture of carboxylic acids and their methyl esters.[15]

Acknowledgment

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(9) The starting material **3a** remained when less than 6 molar amounts of $NaClO_2$ were used.

(10) In the absence of NaH_2PO_4, no reaction occurred.

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(12) The sulfenic acid part in **II** is a transient structure because of its high reactivity. See ref.[14]

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(15) **Representative Experimental Procedure (Table 2, Entry 2):**
To a mixture of **3a** (57.0 mg, 0.163 mmol) in MeOH (1.2 mL) and H_2O (0.400 mL) were added at r.t. 2-methyl-2-butene (0.172 mL, 1.630 mmol) and NaH_2PO_4 (39.0 mg, 0.326 mmol). After cooling to 0 °C, 86% $NaClO_2$ (103.0 mg, 0.978 mmol) was added and the resulting suspension was stirred at r.t. for 2 h. Then H_2O (1.5 mL) was added and the mixture was extracted with EtOAc (1.5 ml × 3); the extracts were washed with sat. aq NaCl, dried with Na_2SO_4, and concentrated. The residue was chromatographed on silica gel with 3:1 hexane–EtOAc to afford **4a** (38.7 mg, 92%) as a colorless oil. Compound **4a**: ^{1}H NMR (300 MHz, $CDCl_3$, $CHCl_3$ = 7.26): δ = 0.04 (6 H, s), 0.87 (9 H, s), 0.88 (3 H, t, *J* = 7.0 Hz), 1.18–1.40 (4 H, m), 1.57 (2 H, quint, *J* = 7.5 Hz), 2.44 (2 H, t, *J* = 7.5 Hz), 2.59 (2 H, t, *J* = 7.0 Hz), 3.88 (2 H, t, *J* = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$ = 77.16): δ = –5.35, 14.04, 18.34, 22.59, 23.34, 25.98, 31.52, 43.99, 45.70, 59.07, 210.42. HRMS (EI): *m/z* calcd for $C_{10}H_{21}O_2Si$ $[M - t\text{-Bu}]^+$ 201.1311; found: 201.1318.

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