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ORIGINAL PAPER

Nickel boride mediated cleavage of 1,3-oxathiolanes: a convenient approach to deprotection and reduction

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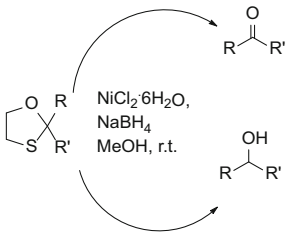
Abstract 1,3-Oxathiolanes are rapidly cleaved by nickel boride allowing regeneration of corresponding carbonyl compounds. Optimum reaction conditions have also been defined to obtain alcohols exclusively by reduction of oxathiolanes. Reactions are rapid at room temperature and do not require protection from atmosphere. Mild reaction conditions, simple work up, and high yields are some of the major advantages of the procedure.

Graphical abstract



Keywords Oxathiolanes · *O*,*S* Acetals · *O*,*S* Ketals · Alcohols

Introduction

The process of sequential protection and deprotection of diverse range of functionalities is inevitably involved in the course of chemical manipulation of polyfunctional molecules. Protecting carbonyl functionality from nucleophilic attack poses a crucial challenge unless its electrophilic properties are modified. Due to the remarkable stability exhibited by 1,3-oxathiolanes under usual acidic or basic conditions [1, 2], these compounds avail wide synthetic utility as carbonyl protecting groups. These oxathioacetals display umpolung reactivity and find synthetic applications for C–C bond formation [3–6] enjoying a distinct reputation in maneuvering the strategies for construction of complex molecules.

Many procedures are available for the preparation of oxathioacetals and ketals. Deprotection, however, is not always facile. Usually deprotection of acetals and ketals is accomplished by treatment with acids or Lewis acid. However, normal acid catalysed hydrolysis fails in case of thioacetals probably due to the fact that sulfur is less basic than oxygen and therefore the protonated species is lower in concentration at a given pH. 1,3-Oxathiolanes have been reportedly deprotected to the parent carbonyl compounds by Raney nickel [7], $AgNO_2$–I_2 and Al_2O_3–I_2 [8, 9], chloramines-T [10], TMSOTf [11], TMSOTf-*p*-nitrobenzaldehyde/polymer supported *p*-nitrobenzaldehyde [12, 13], glyoxal-Amberlyst [14], IBX-cyclodextrin [15], $Bi(NO_3)_3$ [16], V_2O_5–H_2O_2–NH_4Br [17], NBS [18], and H_2O_2–MeCN [19].

Nickel boride has been reported as a useful reagent in a number of important processes like reduction, deoxygenation and desulfurization [20, 21]. It can easily be generated in situ from nickel(II) chloride and sodium borohydride under different conditions in both protic and aprotic solvents and is convenient to handle. There is a continuing interest in studying its properties and

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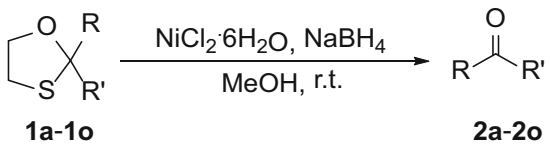
applications. We have reported the applications of nickel boride as a dynamic reagent [22–34]. As a part of our ongoing efforts to explore the various ambits where nickel boride can prove to be an efficient reagent, we had reported its application for reductive desulfurization of *S*,*S*-acetals and ketals [35], to give $-CH_2-$ groups. Recently, we have reported the application of nickel boride for reductive deprotection and reductive deprotection with concomitant reduction of acetals and ketals [36] to corresponding alcohols. Therefore it was a natural corollary to investigate the reactions of oxathiolanes in order to understand whether these would lead to reduced product or reductive deprotection.

Results and discussion

The appropriate conditions for deprotection of oxathiolanes to restore the original carbonyl group were investigated using 2-methyl-2-phenyl-1,3-oxathiolane (**1a**) as the model substrate. The activity of nickel boride is known to depend on the method of its preparation, source of metal used, solvents chosen, etc. [20, 21]. Therefore parameters had to be set out by carrying out the reactions of **1a** with nickel boride in different solvents and also reactions being examined for optimum molar ratios of substrate to nickel chloride to sodium borohydride.

Scheme 1



1a-1o **2a-2o**

The solvents THF and acetonitrile resulted in sluggish and incomplete reactions with a mixture of products. When 2-methyl-2-phenyl-1,3-oxathiolane was allowed to react with nickel(II) chloride to sodium borohydride in 1:6:6 molar ratio in methanol, the reaction was incomplete even after 24 h but acetophenone was observed to be formed as a result of deprotection by co-TLC analysis. Repeating the reaction with the same molar ratio in methanol under reflux resulted in a mixture of products. Only on increasing the molar ratio to 1:8:8, the reaction went to completion in 2 h at room temperature yielding 82 % of acetophenone, accompanied by a trace amount of 1-phenylethanol. Furthermore it could be undoubtedly concluded that the deprotection was proceeding due to in situ formation of the nickel boride as no reaction of **1a** was observed with nickel(II) chloride or sodium borohydride, independently. Subsequently, deprotection of a variety of 1,3-oxathiolanes could be smoothly effected with nickel boride in methanol at ambient temperature (Scheme 1). The deprotection reactions are believed to be proceeding through hydrogenolysis of C–O/C–S bond as reported earlier [36]. The reactions resulted in high yields of corresponding carbonyl compounds. The results are listed in Table 1. It can also be inferred from Table 1 that *O*,*S* acetals **1i**–**1o**

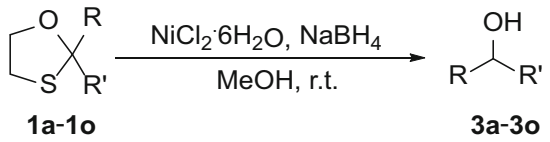
Table 1 Deprotection of 1,3-oxathiolanes using nickel boride in methanol at ambient temperature (Scheme 1)

R	R′	Molar ratio **1**:$NiCl_2{\cdot}6H_2O$:$NaBH_4$	Product	Time/h	Yield/%	M.p./°C	
						Obs	Lit [38, 39]
C_6H_5	CH_3	1:8:8	**2a**	2.0	82	–	–
p-$(CH_3)C_6H_4$	CH_3	1:8:8	**2b**	2.0	85	–	–
p-$(CH_3O)C_6H_4$	CH_3	1:8:8	**2c**	2.0	88	–	36–38
p-ClC_6H_4	CH_3	1:8:8	**2d**	2.0	87	–	14–18
p-BrC_6H_4	CH_3	1:8:8	**2e**	2.0	91	48–50	49–51
1-Naphthyl	CH_3	1:8:8	**2f**	45 min	88	–	–
C_6H_{13}	CH_3	1:8:8	**2g**	45 min	90	–	–
Cyclohexyl	–	1:8:8	**2h**	40 min	89	–	–
C_6H_5	H	1:6:6	**2i**	1.5	92	–	–
p-$(CH_3)C_6H_4$	H	1:6:6	**2j**	1.5	89	–	–
p-$(CH_3O)C_6H_4$	H	1:6:6	**2k**	1.5	84	–	–
p-ClC_6H_4	H	1:6:6	**2l**	1.5	88	50	45–50
p-BrC_6H_4	H	1:6:6	**2m**	1.5	90	56–57	55–58
m-ClC_6H_4	H	1:6:6	**2n**	1.5	87	–	–
p-FC_6H_4	H	1:6:6	**2o**	1.5	85	–	–

require lower molar ratios of substrate to nickel boride in comparison to the *O*,*S* ketals **1a**–**1h**.

The fact that the amount of adsorbed hydrogen in the crystal lattice of nickel boride depends upon the metal:-boron ratio [37], coupled with our initial observations on the formation of small amount of 1-phenylethanol in reaction of **1a** with nickel boride, prompted us to investigate the reduction of oxathiolanes to the corresponding alcohols with nickel boride by varying metal:boron ratio. It was observed that in the reaction of **1a** with nickel boride in methanol, using a molar ratio wherein sodium borohydride was in excess over nickel(II) chloride (1:6:18), the reaction was complete in 2.5 h and 1-phenylethanol was obtained exclusively in 87 % yield. **1a** did not give 1-phenylethanol on reaction with nickel chloride (6 mol equiv.) or sodium borohydride (18 mol equiv.) in independent reactions, thus confirming the involvement of nickel boride. Subsequently, a variety of oxathiolanes were subjected to reaction with nickel boride using 1:6:18 molar ratio of substrate:nickel chloride:sodium borohydride in methanol at room temperature (Scheme 2). All the oxathiolanes underwent reductive deprotection to give the corresponding alcohols in high yields. The results are summarized in Table 2. The alcohols were confirmed to be formed by a rapid reaction of initially formed aldehydes/ketones.

Scheme 2



Conclusion

We conclude that nickel boride as an efficient, easily prepared, cheap, and convenient to handle reagent for the deprotection and reduction of 1,3-oxathiolanes under non-acidic, mild, and protic conditions at ambient temperature. Good yields and easy workup procedures further add to the merits of the reagent.

Experimental

All products are reported compounds. Melting points were recorded on a Tropical Labequip apparatus. The ^{1}H NMR spectra are recorded on Hitachi FT-NMR (60 MHz) using TMS as internal standard. The products were identified by m.p. (wherever applicable) and superimposable IR and NMR spectra with authentic samples. Methanol (S. D Fine), nickel chloride hexahydrate (S. D Fine), and sodium borohydride (E. Merck) were used in all the reactions.

*General procedure: deprotection of 2-methyl-2-phenyl-1,3-oxathiolane (**1a**)*

In a typical reaction, a 50 cm^{3} round-bottomed flask fitted with a reflux condenser was mounted over a magnetic

Table 2 Reduction of 1,3-oxathiolanes using nickel boride in methanol at ambient temperature

R	R′	Molar ratio **1**:$NiCl_2·6H_2O$:$NaBH_4$	Product	Time/h	Yield/%	M.p./°C	
						Obs	Lit [38, 39]
C_6H_5	CH_3	1:6:18	**3a**	2.5	87	–	19-20
p-$(CH_3)C_6H_4$	CH_3	1:6:18	**3b**	2.5	88	–	–
p-$(CH_3O)C_6H_4$	CH_3	1:6:18	**3c**	3.5	82	–	–
p-ClC_6H_4	CH_3	1:6:18	**3d**	2.0	89	–	–
p-BrC_6H_4	CH_3	1:6:18	**3e**	2.0	90	–	36–38
1-Naphthyl	CH_3	1:6:18	**3f**	1.0	90	65	63–65
C_6H_{13}	CH_3	1:6:18	**3g**	1.0	86	–	–
Cyclohexyl	–	1:6:18	**3h**	1.0	90	–	20–22
C_6H_5	H	1:6:18	**3i**	2.0	85	–	–
p-$(CH_3)C_6H_4$	H	1:6:18	**3j**	2.0	84	58–60	59–61
p-$(CH_3O)C_6H_4$	H	1:6:18	**3k**	2.5	88	–	22–25
p-ClC_6H_4	H	1:6:18	**3l**	2.0	85	70	68–71
p-BrC_6H_4	H	1:6:18	**3m**	2.0	86	75–76	75–77
m-ClC_6H_4	H	1:6:18	**3n**	2.0	83	–	–
p-FC_6H_4	H	1:6:18	**3o**	2.0	80	–	–

stirrer and 0.2 g **1a** (1.11 mmol) dissolved in 10 cm^3 of methanol was placed in it. $NiCl_2 \cdot 6H_2O$ (2.1 g, 8.88 mmol) was added followed by 0.33 g $NaBH_4$ (8.88 mmol) cautiously. The reaction mixture was stirred vigorously at room temperature. The progress of the reaction was monitored by TLC using ethyl acetate:petroleum ether (5:95) as eluent. TLC showed complete disappearance of the starting material after 2 h. The reaction was quenched by adding 10 cm^3 of methanol. The reaction mixture was filtered through a Celite pad ($\sim$2.5 cm) and washed with methanol (2 $\times$ 10 cm^3). Water (20 cm^3) was added to the filtrate, which was extracted with ethyl acetate (3 $\times$ 10 cm^3). The combined extract was dried over anhyd. $MgSO_4$. After concentration, followed by column chromatography on neutral alumina using ethyl acetate:petroleum ether (3:97, v/v) as eluent, acetophenone was obtained in 82 % yield as characterized by superimposable IR spectra and ^1H NMR spectra.

*General procedure: reduction of 2-methyl-2-phenyl-1,3-oxathiolane (**1a**)*

In a typical reaction, a 50 cm^3 round-bottomed flask fitted with a reflux condenser was mounted over a magnetic stirrer and 0.2 g, **1a** (1.11 mmol) dissolved in 10 cm^3 of methanol was placed in it. $NiCl_2 \cdot 6H_2O$ (1.58 g, 6.66 mmol) was added followed by 0.71 g $NaBH_4$ (18.78 mmol) cautiously. The reaction mixture was stirred vigorously at room temperature. The progress of the reaction was monitored by TLC using ethyl acetate:petroleum ether (5:95) as eluent. TLC showed complete disappearance of the starting material after 2.5 h. The reaction was quenched by adding 10 cm^3 of methanol. The reaction mixture was filtered through a Celite pad ($\sim$2.5 cm) and washed with methanol (2 $\times$ 10 cm^3). Water (20 cm^3) was added to the filtrate, which was extracted with ethyl acetate (3 $\times$ 10 cm^3). The combined extract was dried over anhyd. $MgSO_4$, decanted through a cotton pad, and concentrated on a rotary evaporator to obtain 0.12 g of 1-phenylethanol (87 %) as characterized by superimposable IR spectra and ^1H NMR spectra.

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