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Synthesis and Deprotection of 1,3-Dithianes and 1,3-Dithiolanes by Polyphosphoric Acid

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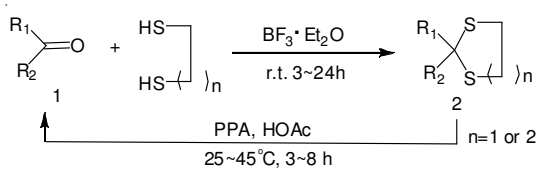
A simply, mild and efficient method for the deprotection of 1,3-dithianes and 1,3-dithiolanes to their corresponding carbonyl compounds using a mixture of polyphosphoric acid and acetic acid at 20-45 ºC is reported.

Key Words: 1,3-Dithianes, 1,3-Dithiolanes, Deprotection, Polyphosphoric acid.

INTRODUCTION

The protection of a carbonyl group is often a necessary step in organic synthesis, especially in the total synthesis of natural products and multifunctional organic compounds. Thioacetals and cyclic thioacetals (1,3-dithianes and 1,3-dithiolanes) are protecting groups commonly used due to their easy access and high stability under both acidic and basic conditions[1]. Furthermore, cyclic thioacetals are versatile synthetic reagents as acyl anion equivalents for C-C bond formation[2], which is a common and successful strategy for the construction of complex natural products.

Many procedures are available for the preparation of thioacetals or thioketals; dethioacetalization or dethioketalization, however, is not always an easy step[1]. Traditionally, deprotection of thioacetals or thioketals[3] has required drastic conditions, stoichiometric or an excess amount of toxic reactives such as Hg^{2+} salts and other heavy metal salts from Bi^{3+}, Zn^{2+}, Zr^{2+}, V^{5+}, Ce^{3+}, Ta^{5+}, $SbCl_5$[4] or SeO_2. In addition, there are methods of alkylation (such as MeI)[5] or oxidative hydrolysis[6]. Nevertheless, these methods have some disadvantages such as long reaction time, strong acids[7], toxic reagents and solvents, expensive catalysts or not readily available reactives and undesired side reactions. Therefore, it is still necessary to develop alternative milder and convenient methods for dethioacetalization and dethioketalization using inexpensive, not toxic and accessible reagents. Thus, we report herein a simple and convenient deprotection of thioketals/thioacetals by a mixture of polyphosphoric acid (PPA) and HOAc (**Scheme-I**).



Scheme-I: Synthesis and deprotection of 1,3-dithianes and 1,3-dithiolanes

EXPERIMENTAL

General procedures: All the solvents used were of analytical grade (Shanghai Chemical Co., Ltd.) and dried with molecular sieve (4A). All melting points were determined on an electrothermal P & S apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance II-300 spectrometer in $CDCl_3$ (Chemical Shifts are given as δ in ppm). ESI-MS were performed on a Finingan LCQ Deca XP MAX mass spectrometer. 1,3-Dithianes or 1,3-dithiolanes were prepared by literature methods[1]. The physical constants of the new 1,3-dithianes or 1,3-dithiolanes are listed below:

2-(4-Ethoxyphenyl)-1,3-dithiane (2b): White solid, m.p. 74-76 ºC (EtOH). 1.23-1.28 (3H, t, J = 7.5, $-CH_3$); 1.91-2.00 (1H, m, $-CH_2-$); 2.14-2.22 (1H, m, $-CH_2-$); 2.61-2.28 (2H, q, J = 7.5, $-CH_2CH_3$); 2.88-2.95 (2H, m, $-CH_2-$); 3.03-3.12 (2H, m, $-CH_2-$); 5.16 (1H, s, CH); 7.17-7.20 (2H, d, J = 8.1, Ar-H); 7.38-7.41 (2H, d, J = 8.1, Ar-H); ESI-MS M^+ = 241.6.

2-(3-Nitrophenyl)-1,3-dithiane (2c): White solid, m.p. 113-115 ºC, 2.02-2.11 (1H, m, $-CH_2-$); 2.26-2.34 (1H, m, $-CH_2-$); 3.00-3.07 (2H, m, $-CH_2-$); 3.12-3.22 ºC (EtOH). (2H, m, $-CH_2-$); 5.33(1H, s, CH); 7.59-7.64 (1H, t, J = 8.4, Ar-H);

7.89-7.93 (1H, m, Ar-H); 8.24-8.28 (1H, m, Ar-H); 8.43-8.46 (1H, q, Ar-H); ESI-MS M^- = 240.5.

2-(1,3-Dithian-2-yl)-2-methylpropan-1-ol (2e): White solid, m.p. 62-65 ºC (EtOH). 1.08 (6H, s, $-CH_3$); 1.80-1.88 (1H, m, -HCH-); 2.07-2.16 (1H, m, -HCH-); 2.17 (1H, s, -OH); 2.89-2.94 (4H, m, $-CH_2CH_2-$); 3.56 (2H, s, $-CH_2OH$), 4.22 (1H, s, CH); ESI-MS M^+ =193.5.

2-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-1,3-dithiane (2f): White solid, m.p. 119-121 ºC (EtOH). 1.99-2.02 (2H, m, $-CH_2-$); 2.77-2.82 (4H, m, $-SCH_2-$); 3.81(3H, s, $-OCH_3$); 3.85 (3H, s, $-OCH_3$); 3.89 (3H, s, $-OCH_3$); 6.81(1H, s, Ar-H); 6.85-6.89 (3H, m, Ar-H); 7.18-7.21 (1H, d, *J* = 8.4); 7.40 (1H, d, *J* = 2.4, Ar-H); 7.56-7.59 (2H, d, *J* = 9, Ar-H); ESI-MS M+H = 363.5.

6',7'-Dimethoxy-3',4'-dihydro-2'H-spiro[[1,3]dithiane-2,1'-naphthalene (2j): White solid, m.p. 120-122 ºC (EtOH). 1.65-2.04 (1H, m, $-CH_2-$); 2.13-2.21 (1H, m, $-CH_2-$); 2.56-2.62 (2H, m, $-CH_2-$); 2.64-2.76 (6H, m, $-CH_2-$); 3.15-3.25 (2H, m, $-CH_2-$); 3.85 (3H, s, $-OCH_3$); 3.92 (3H, s, $-OCH_3$); 6.52 (1H, s, Ar-H); 7.48 (1H, s, Ar-H); ESI-MS M^+ = 297.3.

2-(4-Chlorophenyl)-2-methyl-1,3-dithiane (2l): Oil (silica gel CC, petroleum ether: AcOEt = 15:1). 3.07(1H, s, $-CH_3$); 1.85-1.91 (2H, m, $-CH_2-$); 2.60-2.69 (4H m, $-CH_2-$); 7.24-7.28 (2H, m, Ar-H); 7.78-7.84 (2H, m, Ar-H); ESI-MS M^+ = 245.4.

Ethyl 3-(2-(3,4-dimethoxyphenyl)-1,3-dithian-2-yl)-propanoate (2m): Oil (silica gel CC, petroleum ether: AcOEt = 10:1).1.17-1.18 (3H, t, *J* = 7.2, $-CH_3$); 1.87-1.91 (1H, t, *J* = 5.7, $-CH_2-$); 2.20-2.26 (2H, m, $-CH_2-$); 2.30-2.36 (2H, m, $-CH_2-$); 2.65-2.69 (4H, m, $-CH_2CH_2-$); 3.81-3.83 (6H, m, $-OCH_3$); 3.94-4.01 (2H, q, *J* = 7.2, $-OCH_2-$); 6.77-6.80 (1H, d, *J* = 8.1, Ar-H); 7.33-7.33 (1H, d, *J* = 2.4, Ar-H); 7.35-7.70 (1H, m, Ar-H); ESI-MS M+H = 357.8.

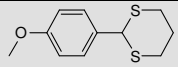
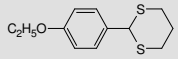
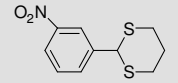
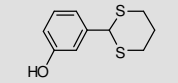
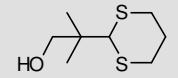
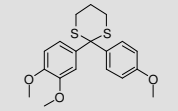
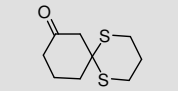
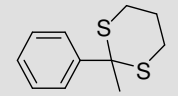
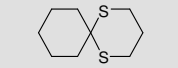
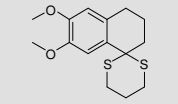
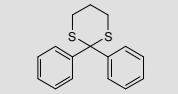
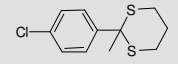
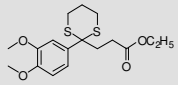
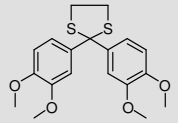
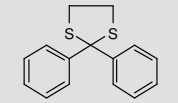
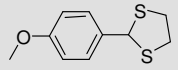
2,2-*Bis*(3,4-dimethoxyphenyl)-1,3-dithiolane (2n): White solid, m.p. 121-124 ºC (silica gel CC, petroleum ether: AcOEt = 3:1), 3.42 (4H, s, $-CH_2CH_2-$); 3.84 (6H, s, $-OCH_3$); 3.87 (6H, s, $-OCH_3$); 6.74 (1H, s, Ar-H); 6.77 (1H, s, Ar-H); 7.09-7.10 (1H, d, *J* = 2.1, Ar-H); 7.12-7.13 (1H, d, *J* = 2.4, Ar-H); 7.23 (1H, s, Ar-H); 7.23 (1H, s, Ar-H); ESI-MS $M+K^+$ = 417.5.

General procedures for deprotection: 1,3-Dithianes or 1,3-dithiolanes (50 mmol) were mixed with polyphosphoric acid (PPA, 1-10 g) and acetic acid (2-10 drops). The mixture was stirred at 25-45 ºC and the reaction end was estimated by TLC, usually for 3-8 h. After the reaction was completed, water was added to hydrolyze polyphosphoric acid. The corresponding aldehydes or ketones could be obtained by extraction with dichloromethane and purified by column chromatography on silica gel. The yields and details of reaction temperature and time were as shown in Table-1.

RESULTS AND DISCUSSION

Polyphosphoric acid (PPA) is usually used as a catalyst in Friedel-Crafts reaction, but interestingly, it could be used for deprotection of 1,3-dithianes and 1,3-dithiolanes in present study. In order to study the scope and limitations of deprotection in presence of polyphosphoric acid and HOAc, various 1,3-dithianes and 1,3-dithiolanes with different functional groups and different temperatures and times of reaction were investigated. Structures of synthesized 1,3-dithianes and 1,3-dithiolanes were assigned on the basis of mass and ^{1}H NMR spectra. The results of deprotection are summarized in Table-1. As shown in Table-1, the deprotection reaction can be simply accomplished by stirring the reactants at temperature of 25-45 ºC, in 3-8 h with good yields. Moreover, various functional groups such as esters, phenol, halides and nitro-group were unaffected in present method. But thioacetals were more sensitive than thioketals to polyphosphoric acid and AcOH. In thioacetals

TABLE-1
DEPROTECTION OF 1,3-DITHIANES OR 1,3-DITHIOLANES IN PRESENCE OF POLYPHOSPHORIC ACID AND AcOH

Entry	Thioacetals 2	Temp. (ºC)/Time (h)	Yield (%)
2a		25/7	68
2b		40/8	52
2c		35/8	73
2d		25/15	51
2e		35/8	42
2f		20/5	83
2g		35/8	81
2h		25/4	83
2i		20/6	82
2j		45/3	86
2k		35/4	84
2l		45/8	75
2m		25/8	62
2n		30/3	86
2o		40/4	85
2p		45/6	72

entry **2a-2e** and **2p**, the yields of deprotection were lower than 73 %; in contrast, thioketals entry **2f-2l** showed higher yields of more than 80 %.

In contrast to earlier methods involving metal-ion, alkylative, oxidants[2,6] or strong acids[7], both polyphosphoric acid and acetic acid are safe, cheap and easily available and the reaction was milder and completed in a short time. After simple aqueous workup without the addition of base, the product could be extracted to give easily handled waste liquid.

As polyphosphoric acid was very viscous, it was used in an appropriately excessive amount to make the reactants mixed well. It seemed that polyphosphoric acid was not only the key reactant, but also the solvent in this deprotection procedure. Not enough amount of polyphosphoric acid could result in low yields. We used some organic solvents added to the reactants to increase the liquidity. 5 mL of AcOH, trifluoroacetic acid, tetrahydrofuran, Et_2O and CH_2Cl_2 were added into the reaction mixture respectively as a solvent to examine their impact on the yields. Although these solvents we added could not dissolve polyphosphoric acid, they could make the reactants mix better. The experimental results were shown in Table-2. Except AcOH, other solvents caused low yields in the deprotection of compound **2k**.

TABLE-2
YIELDS OF DEPROTECTION OF COMPOUND **2k** IN PRESENCE OF POLYPHOSPHORIC ACID AND SOME ORGANIC SOLVENTS

Solvent	HOAc	THF	Ethyl ether	CH_2Cl_2
Time	4	12	12	12
Temp.	35	40	25	30
Yield	85	15	< 10	< 10

Interestingly, polyphosphoric acid could not complete the reaction very well without acetic acid. When 1,3-dithiolanes (**2h-2k**) were treated with polyphosphoric acid only and without acetic acid, corresponding ketones were obtained in a very low yield (< 10 %). Nevertheless, addition of 5-10 drops of acetic acid could increase the yield to 84 %. However, further addition of acetic acid could not increase the yield any more (Table-2).

Typically, acids are used to catalyze the reaction to produce 1,3-dithianes and 1,3-dithiolanes and seldom used in deprotection reactions. Glyoxalic acid and acetic acid were reported to be used to deprotect 1,3-dithiolanes[8]. We used two organic acids (propanoic acid and trifluoroacetic acid) and phosphoric acid instead of acetic acid but found they could not promote the reaction and the yields of the deprotection of **2j**-**2l** were less than 10 %. As a substitute for acetic acid, acetic anhydride, which could be possibly produced by dehydration of adding acetic acid to polyphosphoric acid, could not promote the reaction and the yields of deprotection were very low (< 10 %), too.

From these facts, acetic acid was very important in this deprotection procedure. The reaction mechanism was under further research. There might be an interaction between polyphosphoric acid and acetic acid and the intermediate promoted the deprotection reaction. Above all, both acetic acid and polyphosphoric acid played very important roles in our reported reaction.

Conclusion

We have developed a very simple, mild and convenient method for the deprotection of dithianes and dithiolanes, which involves the use of polyphosphoric acid and acetic acid. This protocol is a valuable alternative to the existing deprotection methods for economical and environmental reasons.

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