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Mild Deprotection of Dithioacetals by TMSCl/NaI Association in CH₃CN

Yunxin Yao, a Guangkuan Zhao, a Abdallah Hamze, a Mouad Alami, a and Olivier Provot a*  

a Université Paris-Saclay, CNRS, BioCIS, 92290, Châtenay-Malabry, France. Phone: +33 (0)146835847. Email: olivier.provot@universite-paris-saclay.fr

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Abstract. A mild process using a combination of TMSCl and NaI in acetonitrile is used to regenerate carbonyl compounds from a variety of dithiane and dithiolane derivatives. This easy to handle and inexpensive protocol is also efficient to deprotect oxygenated and mixed acetals as 1,3-dioxanes, 1,3-dioxolanes and 1,3-oxathianes quantitatively. As a possible extension of this method, it was also showed that nitrogenated-substrates as hydrazones, N-tosyldihydrazones and ketimes reacted well under these conditions to give the expected ketones in high yields. The methodology proposed herein is a good alternative to the existing methods since it does not use metals, oxidants, reducing agents, acidic or basic media, and keto-products were obtained in high to excellent yields.

Keywords: dithioacetal; deprotection; trimethylsilylchloride; sodium iodide; ketone

Introduction

Dithianes are commonly used in organic chemistry to mask the electrophilic nature of carbonyl groups in elaborated molecules and serve as acyl anions in syntheses according to the Umpolung concept. The main advantages of dithianes are their easy access from a carbonyl compound by using propane-1,3-dithiol and a Lewis acid and their stabilities in alkaline and acid conditions notably permitting their purification on a silica column. In counterparts to this stability, many procedures have been developed for their deprotection but generally require harsh conditions. Most of the time, toxic metal salts as Hg(II), Ag(I), Zn(II), Ga(III), Cu(II), Tl(V) and others are used in excess in harsh conditions with some success. The use of hypervalent-iodine reagents for the removal of dithianes has also been reported as an efficient process using periodic acid, diacetoxyiodobenzene, bis(trifluoracetoxy)iodo-benzene (BTI), Dess-Martin periodinane and N-halosuccinimides. However, a large variety of the methods mentioned before require the use of toxic metals, the need of oxidizing species in large amounts sometimes accompanied with co-oxidants mainly in harsh reaction conditions. In this context, we believe that an alternative milder process is still needed using for example inexpensive and soft reagents to achieve this transformation at room temperature in the presence of various functional groups.

Recently, we reported the interesting reducing properties of the TMSCl/NaI association in CH₂Cl₂ towards various functional groups as unsymmetrical α-diketones, α-ketoesters and hydrazones derivatives. Under similar reaction conditions, we next demonstrated that a variety of dithioacetals were cleanly desulfurized at rt in CH₂Cl₂ using this metal-free process in a Mozlingo-type reaction.

By replacing CH₂Cl₂ by CH₃CN as the reaction solvent, we surprisingly observed that dithianes derivatives were not reduced into methylene substrates but were totally and cleanly deprotected into ketones. It seemed interesting to study this method for the deprotection of thioacetals which does not use metal salts, oxidants, toxic or expensive reagents (Figure 1).

Table 1. Optimization of reaction conditions

Results and Discussion
with no trace of the reduced 2-ethynaphthalene obtained in CH₂Cl₂.\(^{[17]}\) Under same reaction conditions but without NaI, 1a was found unchanged showing the essential role of NaI (entry 17). Addition of water, NaOH\(_{aq}\) or HCl\(_{aq}\) had a deleterious effect on the reaction since a large part of 1a was recovered after 24 h of reaction (entries 9-12). The amount of TMSCl/NaI and the temperature of the reaction were next examined (entries 13-17) and the best result was obtained by achieving the deprotection reaction at 60 °C in the presence of 20 eq of TMSCl/NaI leading to ketone 2a in an excellent yield of 92% (entry 17). Under the same reaction conditions, the replacement of CH₃CN by PhCN provided 2a but in a low yield of 52% (entry 18). To examine the influence of solvents (deprotection vs reduction), 1a was reacted with TMSCl/NaI in CH₂CN/CH₃Cl₂ (1/1) for 24 h at 60 °C (entry 19). In this mixture of solvents, we have isolated only ketone 2a (85%) with no trace of the 2-ethynaphthalene (reduced compound) showing the predominant role of CH₃CN. Last, the reaction was also run in CH₃CN in the presence of TMSI (10 eq) at rt (entry 20) for comparison. After only 3 h of reaction, we observed by TLC the total disappearance of 1a but 2a was isolated, beside a large number of unidentified by-products, with a low yield of 10%\(^{[20]}\) showing the superiority of the TMSCl/NaI association compared to TMSI for carrying out these deprotection reactions in CH₃CN. The reasons for this difference in reactivity between TMSI and TMSCl/NaI in CH₃CN remains unclear.

Next, we were interested in evaluating this mild protocol with 1,3-dioxolane 3, 1,3-dioxane 4, 1,3-oxathiane 5 and dihydrobenzo[d]thiazole 6 (Scheme 1).

**Scheme 1.** Deprotection of cyclic ketal 3,4 and oxathiane 5 by TMSCl/NaI in MeCN

![Scheme 1](image-url)
(used in entry 7 of Table 1), we observed a clean and complete deprotection of ketals 3 and 4 as well as 1,3-oxathiane 5 into ketones (93% to 97%). The deprotection of benzothiazole 6 was also effective but required conditions B (entry 17, Table 1) to completely deprotect 6. For comparison, Jung reported that TMSI in CHCl₃ also deprotected ethylene ketals into ketones but with meager yields (20%) and that TMSI was unable to deprotect thioketals after 24 h of mixing at 75 °C.²¹

Encouraged by these results and by the simplicity of this process, the deprotection of a variety of thioacetals 1a-u was carried out with the TMSCl/NaI association in CH₂CN for 24 h. Table 2 summarizes the results of this study achieved using 10 eq of TMSCl/NaI at rt (conditions A) or 20 eq of TMSCl/NaI at 60 °C (conditions B) for less cooperative substrates. As observed, 1,3-dithianes and 1,2-dithiolanes of acetoephones 1a-h were deprotected into their parent ketones with good yields ranging from 54 to 94%. It is of note that, 1,3-dithianes 1b-d and 1f-h were more cooperative substrates than our model substrate 1a since the deprotection reaction required half quantity of TMSCl/NaI and was achieved at rt under conditions A. Examination of these results also shows that 1,3-dithianes seem easier to deprotect using TMSCl/NaI in CH₂CN than their 1,2-dithiolane counterparts (compare 1d with 1e) and that electron-donating groups on the aromatic nucleus allowed more efficient deprotection reactions (compare 1d with 1h). As expected, 1,3-dithianes prepared from aliphatic aryl (cyclic or not) ketones 1i-m reacted well with the TMSCl/NaI combination and furnished ketones 2i-m in good to excellent isolated yields (64 to 91%). Then we examined the deprotection reactions with dialkyldithianes 1n-q. We showed that these compounds were also cooperative substrates as they were rapidly and cleanly deprotected to give the desired ketones 2n-q with satisfactory yields (76% to 95%). Then, the case of diaryldithianes was examined. Under conditions A (TMSCl/NaI 10 equiv, rt, 24 h), we observed that 1,3-dithiane 1r having no Hα, reacted with TMSCl/NaI to give a mixture composed in almost equal parts of the expected ketone 2r (43%) accompanied by the reduction product 1-benzyl-4-methoxybenzene (40%). To avoid the formation of the reduction by-product, we successfully replaced NaI by NaBr, increased the quantity of TMSCl/NaBr and heated the solution at 60 °C for a prolonged time (TLC monitoring). Using these conditions, diaryketones 2r and 2s were then obtained with acceptable yields and without any traces of the reduced diarylmethane by-products. Next, 1,3-dithianes of aldehydes were also studied with compounds 1t and 1u. We noted that these 1,3-dithianes reacted rapidly using conditions A to give

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Table 2. Deprotection of 1a-u by TMSCl/NaI in MeCN
the corresponding aldehydes in variable yields. For the deprotection of dithioketals of aldehydes, it is crucial to examine the course of the deprotection reaction by TLC monitoring because prolonged reaction times resulted in a severe decrease in yields. Indeed, it has been reported that, at rt, aldehydes reacted rapidly with TMSI to give iodosilyl ethers. This suggests that, as soon as aldehydes are formed after thioacetal deprotection, they add nucleophilic iodes, which may arise from TMSI slowly generated in the media according to an exchange Finkelstein reaction.

To show the interest of this process with respect to other previously reported methods using for examples HgO associated with BF₃·Et₂O, 2,6-dicarboxypyridinium chlorochromate (DCPCC) or SbCl₅, we have deprotected dithiols 1v and 1w by TMSCl/NaI in CH₃CN (Scheme 2).

**Scheme 2.** Deprotection of dithianes 1v and 1w by TMSCl/NaI in CH₃CN.

The comparison of the yields obtained using the TMSCl/NaI mild association in CH₃CN vs toxic oxidizing agent as HgO (86% vs 65%), DCPCC (93% vs 70%) or SbCl₅ (93% vs 77%) supports well that this novel metal-free process is welcome since the yields in desired ketones are significantly higher and the reagents used for the deprotection are inexpensive, non-toxic and very easy to handle.

Next, as dithiaoacetals, the regeneration of carbonyl compounds from nitrogen-derivatives as hydrazones, N-tosylhydrazones, ketimines, and oximes required most of the time harsh reaction conditions including oxidative or reducing process, acidic or alkaline media, expensive reagents or hazardous experimental protocols. To find a milder process, we next examined if the TMSCl/NaI combination in CH₃CN process could be applied successfully to these robust nitrogen substrates. In Scheme 3 we present the results of the regeneration of carbonyl functions of diphenylhydrazone 7, N-tosylhydrazone 8, N-benzylimine 9, ketimine 10 and diphenylmethanone oxime 11, using TMSCl/NaI in CH₃CN.

**Scheme 3.** Reaction of 7-11 by TMSCl/NaI in MeCN

We were pleased to observe that the TMSCl/NaI combination in CH₃CN was able to transform imines and hydrazones into ketones with good yields (90 to 100%) as well as N-tosylhydrazone 8 which required the use of harsher reaction conditions. On the contrary, imine 9 and ketimine 10 were easily transformed into their ketones with high yields using the TMSCl/NaI association in CH₃CN at rt. When diphenylmethanone oxime 11 was reacted with the TMSCl/NaI association (10 eq), we isolated, after 24 h of reaction achieved at rt, 4-methoxy-N-(4-methoxyphenyl)benzamide 12 in good yield (84%) accompanied by only 4% of the bist(4-methoxyphenyl)methane 2r. The scope of this interesting Beckmann rearrangement, using the TMSCl/NaI combination, is currently under investigation in our lab with a range of oxime substrates.

A plausible reaction mechanism is proposed in (Scheme 4). First, TMSCl in the presence of NaI is slowly transformed by halogen exchange into TMSI which complexes with CH₃CN to give an intermediate of type I as previously proposed by Olah. Then, complex I reacts with a sulfur atom of dithioketal 1d to give a sulfonium species of type II. Further assistance from the neighboring dithioketal sulfur atom possibly leads to a fragmented sulfonium.
intermediate III which adds H$_2$O (from reagents, CH$_3$CN or during hydrolysis) to promote hemithioketal IV which is then activated into a sulfonium intermediate V (having or not Hα). With no Hα as in 1r or 1s, V finally rearranges into the desired ketone 2e.[32] For dithiolanes prepared from enolizable ketones as 1d, the same (a) pathway could be followed, but it is also reasonable to consider an additional pathway (b) in which an iodide deprotonates intermediate V to furnish an enol species which tautomerizes into ketone 2e. Since dithioacetals having Hα can evolve according to two different pathways, this can explain that these entities are more straightforward to deprotect than diarylthioketals counterparts. It is noted that Nicolaou has previously proposed a similar mechanism for the deprotection of S,S-acetals and ketals using IBX.[33]

### Conclusion

In this article we showed for the first time, the fundamental role of CH$_3$CN associated with TMSCl/NaI combination to deprotect S,S-ethylene- and S,S-propylene-ketones into ketones. Indeed, if the mild TMSCl/NaI association leads to the reduction of dithioketals in CH$_2$Cl$_2$, we have demonstrated that this association can be used to deprotect a large variety of various dithioketals into ketones in CH$_3$CN. Otherwise, under mild experimental conditions, O,O-acetals as well as O,S-oxathianes and S,N-acetals were cleanly depoetected with high yields. It is also possible to efficiently regenerate the carbonyl function of various hydrzones and imines using this novel protocol. We believe that this metal-free process is an excellent alternative to other known methodologies used to deprotect dithioketals into ketones.

### Experimental Section

A general experimental procedure is described as following: a mixture of thio-ketal (100 mg) and NaI (10 eq) was stirred in MeCN for 5 min. Then, TMSCl (10 eq) was added to the solution which was stirred for 24 h at rt. The reaction was then hydrolyzed for 5 min, with H$_2$O (5 mL) and extracted with CH$_2$Cl$_2$. Organic layers were dried over MgSO$_4$ and concentrated under reduced pressure to give a residue which was purified by chromatography on silica gel to give the expected carbonyl compound which have identical NMR spectra with starting ketones.

### Acknowledgements

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### References


[20] 2-(1-Iodoethyl)naphthalene resulting from the reduction of 1a was also identified in the crude mixture (< 10%).


[22] To a solution of ketone or aldehyde (1 mmol) in 20 mL of DCM was added the thiol derivative (1,2-ethanedithiol or 1,3-propanedithiol; 5 mmol), followed by 1 mL of BF3-Et2O. The solution was stirred at rt until disappearance of starting material (judged by TLC). Then, H2O (20 mL) and DCM (30 mL) were added to the solution. The organic layer was separated, washed with H2O (2 x 10 mL) and saturated NaCl solution (2 x 10 mL), dried over MgSO4, and concentrated under reduced pressure to give a dithioacetal which was purified by chromatography on silica gel.


[29] To our knowledge, only one paper reported the use of TMSCI in CH3CN to achieve at a high temperature of 100 °C, the Beckmann rearrangement of the cyclooctadecanone oxime into o-laurolactam (a single example having no functional groups was described in this letter; no isolated yield is mentioned), see: S. Sato, S. Hoshino, T.; Sugimoto, K. Kashiwagi, *Chem. Lett.* 2010, 39, 1319-1320.

[30] Analysis of 13C NMR spectra indicates that a complex of type I may be formed under the conditions used to deprotect dithioketals. Complex I can be obtained from the progressive formation of TMSI which complexes with CH3CN, which is not the case of TMSCI. (see NMR spectra in SI).


[32] With a dithioketal having no functional groups was described in this example: 100 °C, the Beckmann rearrangement of the cyclooctadecanone oxime into o-laurolactam (a single example having no functional groups was described in this letter; no isolated yield is mentioned), see: S. Sato, S. Hoshino, T.; Sugimoto, K. Kashiwagi, *Chem. Lett.* 2010, 39, 1319-1320.

Mild Deprotection of Dithioacetals by TMSCl / NaI Association in CH\textsubscript{3}CN


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- Ease of implementation
- Mild conditions, inexpensive and non-toxic reagents
- Applicable to S,S-acetals, O,O-acetals, S,O-acetals, S,N-acetals, hydrazones, ketimines
- 32 examples, high yields.