RESEARCH ARTICLE

Visible Light Thiyl Radical-Mediated Desilylation of Arylsilanes

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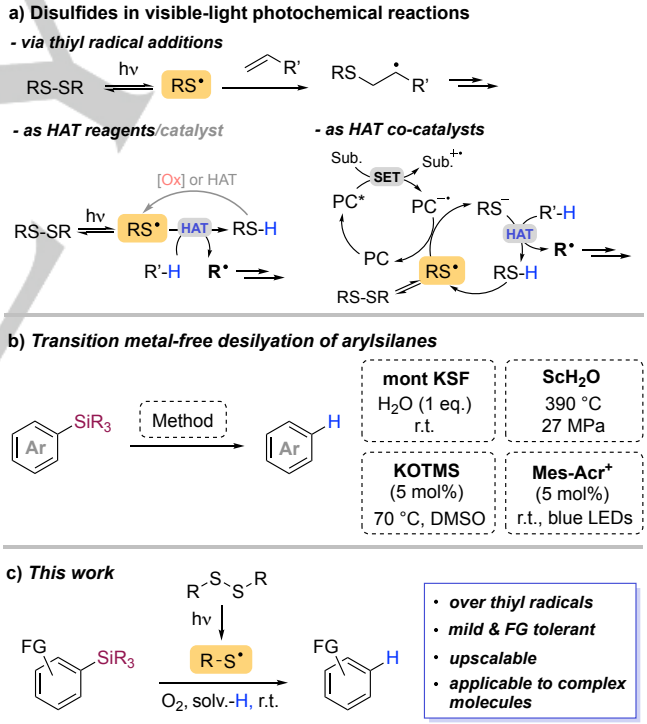
Abstract: A straightforward, visible-light triggered desilylation of arylsilanes by thiyl radicals is presented. Silyl groups are often used to block a reactive position in multi-step organic synthesis, for which a mild cleavage at a late-stage will provide new possibilities and disconnection routes by C_{Ar}-Si cleavage/deprotection. In this work, commercially available and cheap disulfides are employed for the first time in this type of C(sp^2)-Si bond cleavage reactions. Thus, upon irradiation with visible-light, homolytic cleavage of the disulfide give rise to the corresponding thiyl radical that allows for a radical chain mechanism. This methodology represents a mild, fast and simple approach suitable for a broad variety of simply substituted arylsilanes. Moreover, the procedure could be easily extended to natural products and therapeutic derivatives, showing its robustness and synthetic application potential.

Introduction

Thiyl radicals (RS•) occur frequently in enzymatic and biochemical processes,[1] leading to ubiquitous disulfide, S-C and S-heteroatom bonds in nature. Sulfur compounds are likewise widely used in synthesis, medicinal chemistry and material science.[2] The thiyl radicals formed *in situ* under light irradiation conditions have the ability to promote a broad variety of radical bond-forming reactions. Hence, they are well-known as radical starters or precursors in synthetic organic chemistry,[3] such as cycloadditions, oxidation reactions or boration of alkynes. The generation of thiyl radicals can occur in various ways. On the one hand, they can be generated from thiols by hydrogen atom transfer (HAT) to other radical initiators.[4] However, thiophenols suffer some disadvantages such as unpleasant smell and toxicity. On the other hand, light-induced homolytic bond cleavage of the easier to handle and less toxic disulfides, which present a lower binding dissociation energy than thiols (BDE_{S-S} ≈50 $kcal^{-1}mol^{-1}$ *vs.* e.g. BDE_{S-H} 79 $kcal^{-1}mol^{-1}$ for PhSH),[5] has become a common practice to gain *in situ* thiyl radicals.[3,4] As a consequence, disulfide-(co)catalyzed HAT type photo-induced reactions relying on thiyl radicals have been well established in organic synthesis (Scheme 1a).[6] However, disulfides have scarcely been used as thiyl precursors for photochemical C-heteroatom bond cleavage reactions.[6-8]

Organosilanes are of high synthetic importance in modern organic chemistry,[9] especially due to their wide-spread use as protecting groups. There are several approaches for the selective removal of silyl groups.[10] However, for the case of aromatic C-Si bond cleavage, most methods suffer from harsh conditions and thus limited functional group tolerance.[10,11] To overcome some of these issues, several research groups have reported new approaches towards desilylation of arylsilanes based on supercritical water,[12] montmorillonite KSF clay[13] or catalytic KOTMS, among others (Scheme 1b).[14] Moreover, our group has also recently contributed by the development of an alternative photocatalytic desilylation method using an acridinium photoredox system.[15] However, all these technologies present even now some incompatibilities and substrate limitations, and more efficient, mild and straightforward approaches for the removal of arylsilane protecting groups are still highly desirable.



Scheme 1. Uses of disulfides in photoreactions (a), transition metal-free desilylation of arylsilanes (b), and this work on thiyl radical mediated desilylation approach.

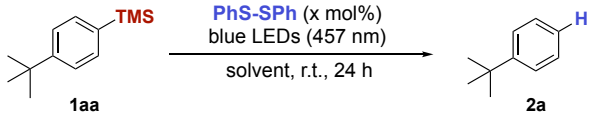
Following our program on visible light promoted reactions with organosilanes,[15,16] we envisioned a desilylation strategy relying on thiyl radicals formed *in situ* from readily available disulfides under visible light irradiation (Scheme 1c). Based on previous reports on Si-S bond formation of by radical-pathways,[17] we hypothesized the reaction of the thiyl radical with the silicon center and subsequent targeted C-Si bond cleavage. Herein, we are

pleased to report a simple, practical and efficient visible light induced thiyl radical mediated desilylation of arylsilanes.

Results and Discussion

We started our investigation with the optimization of the model desilylation reaction of (4-*tert*-butyl(phenyl))trimethylsilane (**1aa**) (Table 1). First, the loading of the diphenyldisulfide **I** as thiyl radical precursor in DCE under air at room temperature was studied (entries 1-3). It turned out, that the use 60 mol% of **I** was optimal, giving rise to the desired product **2a** in 70% yield. Next, we carried out an extensive solvent and concentration screening (entries 4-9; see also S.I., Tables S2 and S3). The use of DCE and TFE in a 3:1 mixture and a 0.1 M concentration led to a notable improvement of the yield to 79% (entry 7). To our delight, changing the atmosphere from air to pure oxygen led to a further increase in the yield to 86% (entry 11). Moreover, the reaction under argon atmosphere proved less efficient (66%, entry 10), while no irradiation or the absence of the disulfide led to no product formation.

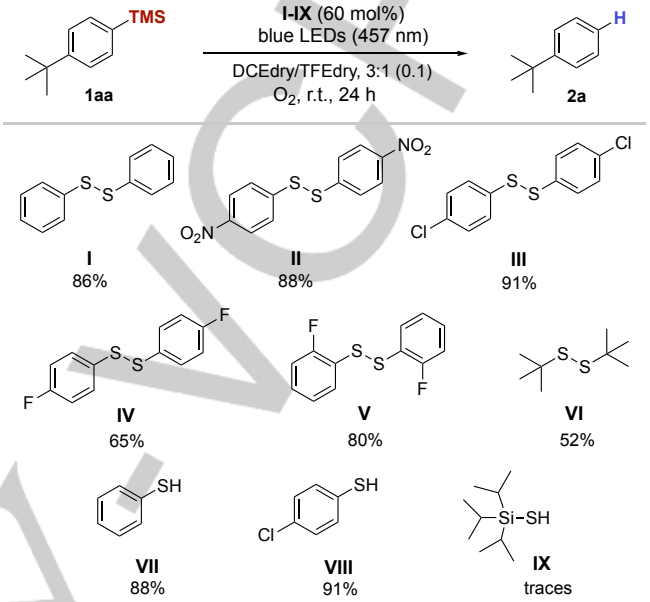
Table 1. Optimization of the thiyl radical-mediated desilylation of **1a**.[a]



Entry	PhSSPh (**I**) (mol%)	Solvent ([M])	Yield (%)[b]
1	10	DCE (0.1)	32
2	30	DCE (0.1)	34
3	60	DCE (0.1)	70
4	60	THF (0.1)	16
5	60	$CHCl_3$ (0.1)	4
6	60	MeOH (0.1)	trace
7	60	DCE_{dry}/TFE_{dry}, 3:1 (0.1)	79
8	60	DCE_{dry}/TFE_{dry}, 3:1 (0.03)	52
9	60	DCE_{dry}/TFE_{dry}, 3:1 (0.5)	67
10[c]	60	DCE_{dry}/TFE_{dry}, 3:1 (0.1)	66
11[d]	60	DCE_{dry}/TFE_{dry}, 3:1 (0.1)	86
12	--	DCE_{dry}/TFE_{dry}, 3:1 (0.1)	--
13[e]	60	DCE_{dry}/TFE_{dry}, 3:1 (0.1)	--

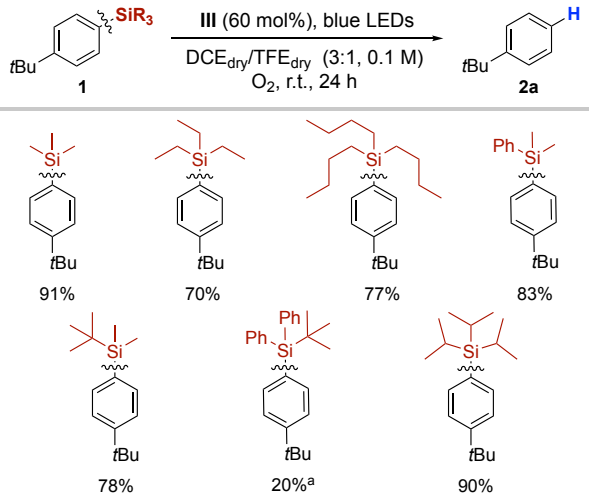
[a] Conditions: **1a** (0.1 mmol) and $(PhS)_2$ under air in the given solvent in a closed vial irradiated from the bottom for 18 h. [b] Yields were determined by GC-FID with naphthalene as an internal standard. [c] The reaction was performed under argon atmosphere. [d] The reaction was performed under O_2 atmosphere. [e] The reaction was performed without irradiation.

Next, a variety of commercially available disulfides and thiols was tested (Scheme 2). Therefore, different diaryl disulfides bearing electron withdrawing groups, such as nitro- (**II**) or halogen substituents (**III-V**) were investigated, providing the product in similar yields, while the dialkyl derivative **VI** showed lower reactivity. In this context, the chlorinated disulfide **III** led to the best result, building up the desired product **2a** in 91% yield. Interestingly, the often-used silylthiol **IX** as HAT reagent[18] was not suitable for this reaction. Conversely, the corresponding thiophenols **VII** and **VIII** were as effective and gave **2a** in comparable high yields (88% and 91%, respectively). However, we continued our study with disulfide **III** as it is easier to handle and less odor-nuisance than its thiol counterpart.



Scheme 2. Screening of the thiyl radical precursor **I-IX**. Yields were determined by GC-FID with naphthalene as an internal standard.

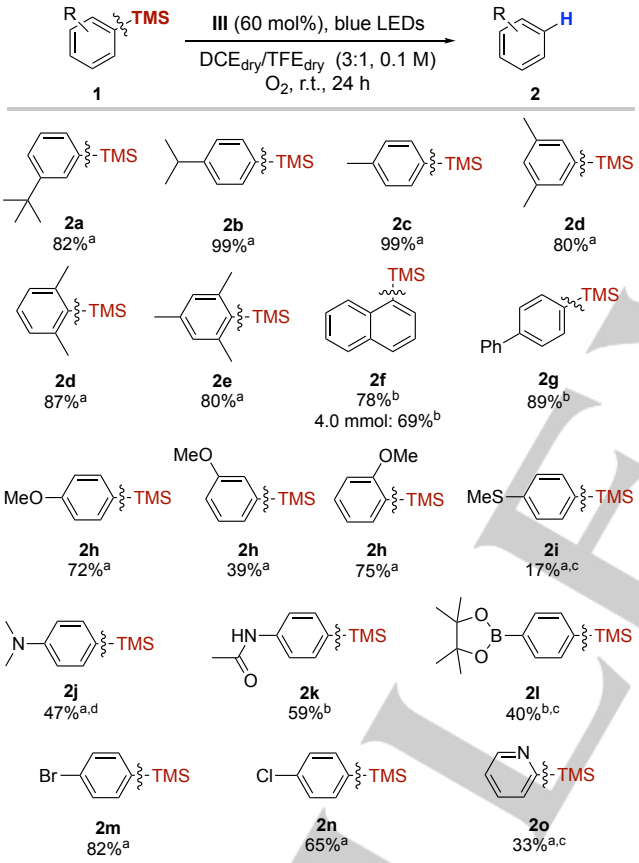
With the optimized conditions in hand, the reaction was first applied to different sterically demanding silyl protecting groups such as triethylsilyl (TES, **1ab**), tributylsilyl (**1ac**), phenyldimethylsilyl (DMPS, **1ad**), *tert*-butyldimethylsilyl (TBS, **1ae**), *tert*-butyldiphenylsilyl (TBDPS, **1af**) and triisopropyl (TIPS, **1ag**). It turned out, that these more sterically demanding groups than TMS are also well tolerated and gave the corresponding desilylated product in high to excellent yields (70-91% yield), except for TBDPS for which the yield decreased significantly.



Scheme 3. Scope of the Si-group. GC-FID yields determined with naphthalene as an internal standard. [a] No full conversion of **1** was observed.

After selecting TMS as silyl group due its good reactivity and aiming at less waste generation, the substrate scope of the

reaction was next evaluated (Scheme 4). The reaction with the arylsilane with the *meta-t*Bu substitution (**1aa'**) gave the same product **2a** in a good 82% yield. Other alkyl substitution was well-tolerated. Thus, *iso*-propyl, as well as mono-, di- or trimethyl substituted arylsilanes gave the corresponding products in excellent yields (**2b-2e**, 80-99%). The desilylation reaction was also applied to naphthalene and biphenylsilanes with high efficiency (**2f** and **2g**, 78% and 89% yield, respectively). Moreover, methoxy groups in *para* and *ortho* position led to **2h** in good yields (72-75%), while the *meta* substitution and the corresponding *para* thioether gave the products **2h** and **2i** in only moderate 39% and 17% yield, respectively. The scope was efficiently extended to other functional groups such as a tertiary amine (**2j**, 47%), amide (**2k**, 59%) and a boronic ester (**2l**, 40%). To our delight, also challenging halogenated and heteroaromatic substrates such as pyridine were well-tolerated, obtaining the protodesilylated products in moderate (**2o**, 33%) to good yields (**2m-2n**, 65-82%).



Scheme 4. Scope of the reaction. [a] GC-FID yields determined with naphthalene as an internal standard. [b] Isolated yields after column chromatogaphy. [c] No full conversion of **1** was observed. [d] Partial decomposition of **1** took place.

Furthermore, the applicability of our methodology was demonstrated by upscaling 40-times the reaction of the naphthyl derivative **1fa** while maintaining a good reactivity (**2f**, 69%; Scheme 4), as well as by the desilylation of complex derivatives and natural compounds (Figure 1). The adamantane *N*-arylamide provided the corresponding desilylated product **2p** in a good 63% yield, while the raspberry ketone **2q** and menthol **2r** derivatives were obtained in 59% and 42% yield, respectively. Moreover, medicinal drug derivates such as valproic acid, gemfibrozil and ibuprofen gave the desired products **2s-u** in moderate to good yields (37-78%), while a significant lower desilylation grade was observed for the ketoprofen derivative (**2v**, 19% yield).

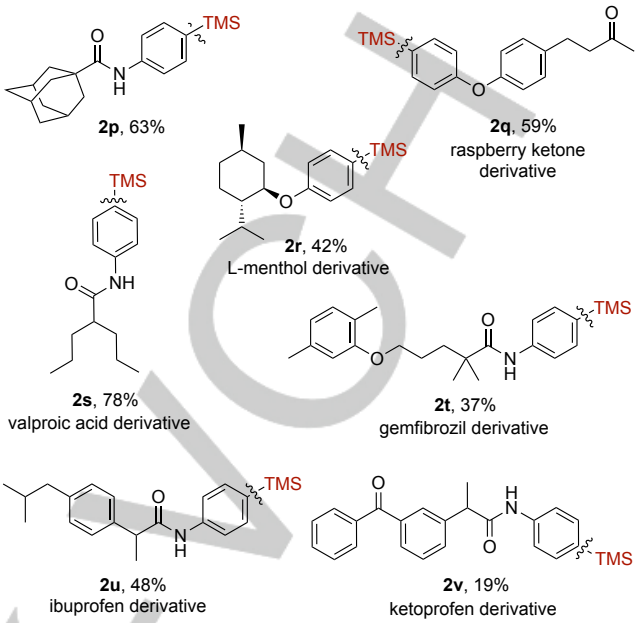
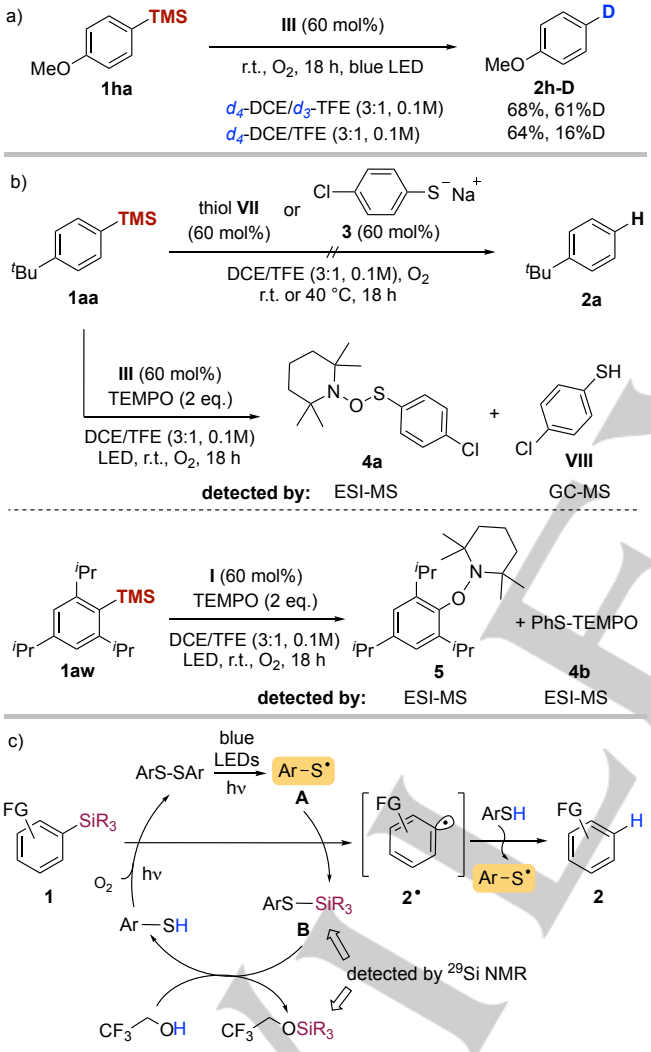


Figure 1. Deprotosilylation of complex molecules and therapeutic derivatives. Isolated yields after column chromatogaphy.

Finally, different mechanistic studies were carried out (Scheme 5). Firstly, we investigated the hydrogen atom source by running the reaction of **1ha** in d_4-DCE/d_3-TFE or d_4-DCE/TFE as deuterated solvent (Scheme 5a). It turned out that the solvent is the principal deuterium source as a 61%D incorporation was observed when using a d_4-DCE/d_3-TFE mixture. Moreover, a poor 16%D incorporation took place in d_4-DCE/TFE, also indicating that the TFE is the main H-atom source. Secondly, the generation of the hypothesized active thiyl radical vs. a thiol/thiolate nucleophilic Si-attack–desilylation mechanism was considered (Scheme 5b).[19] While the reaction of **1aa** with the thiol **VII** or the corresponding sodium thiolate in DCE:TFE at r.t. or 40 °C led to no product formation, the addition of TEMPO under standard photodesilylation conditions inhibited the reaction and the formation of the TEMPO-sulfide adduct **4** was observed by ESI-MS, which indicates the formation of the thiyl radical upon light-mediated homolytic cleavage of **III** and its subsequent radical trapping. Since the aryl radical-TEMPO adduct from **1aa** could not be detected, the reaction with **1aw** was performed, aiming at being able to trap the corresponding, more hindered aryl radical. In this case, the formation of the Ar-TEMPO species **5** could be observed by ESI-MS analysis of the crude reaction, suggesting the participation of the aryl radical in the process (see SI, section 8.1.). Additionally, the reaction under anaerobic conditions proceeds with a significantly lower yield for the disulfide **III** (66% vs. 86%. Table 1, entries 10 and 11) or more pronounced for the corresponding thiol **VIII** (29% vs. 88%; see S.I., Table S6), for which we assume that the oxygen atmosphere supports the process by (partially) oxidizing the formed arylthiol intermediate to the disulfide and then back into the thiyl radical under the applied light irradiation.[20,21] Taking all these observations into consideration, we propose that the generated thiyl radical acts as a starter to give rise to a radical chain reaction (Scheme 5c). Moreover, the measured quantum yield of ϕ = 11.4 supports the

radical chain mechanism (see S.I. for details). Accordingly, photochemical homolytic cleavage of the disulfide into the thiyl radical **A** takes first place. This species adds to the silane at the heteroatomic center, leading to fragmentation to the aryl radical **2**• and the thiosilane **B** (detected by ^{29}Si NMR). The Si-S bonds in thiosilanes are generally known to be very sensitive to hydrolysis,[22] and upon reaction with the polar solvent media (e.g. the alcohol TFE or water traces) lead to the thiol and corresponding Si-O compound(s) (TFE-SiR_3 or R_3Si-O-SiR_3, see S.I.). The thiyl radical is then regained by photoautooxidation of the thiol into the disulfide[20] and subsequent homolytic cleavage. Alternatively, the thiol intermediate acts as HAT, building the final product upon reaction with the aryl radical **2**• and re-generating the thiyl species.



Scheme 5. Mechanistic investigations: a) hydrogen-atom source study by deuteration, b) reaction with a thiolate as activator and TEMPO radical trapping experiment. c) Simplified thiyl radical chain mechanism.

Conclusion

In conclusion, we have developed a metal and base-free, straightforward thiyl radical-mediated methodology for the mild, photochemical desilylation of arylsilanes. We showed the broad applicability and functional group tolerance of the method by the effective reaction of simple arylsilanes, as well as to complex structures and therapeutic derivatives. Furthermore, mechanistic investigations supported the hypothesized radical chain mechanism, which is initiated by the photochemically *in situ* generated thiyl radicals from simple disulfide or thiol precursors. This simple and wide-ranging strategy might open new pathways towards late-stage C_{Ar}-Si cleavage/deprotection of silyl groups in complex and natural product synthesis.

Experimental Section

General procedure for the desilylation reaction: The corresponding TMS-aryl derivative **1** (0.1 mmol, 1.0 equiv.) and disulfide **III** (17.2 mg, 0.06 mmol, 60 mol%) were dissolved in a mixture of DCE and TFE (1 mL, 3:1) under oxygen. The closed vial was irradiated with a single 457 nm LED from the bottom plane for 24 h at room temperature and the crude mixture of volatile compounds was analyzed by GC-FID with naphthalene as internal standard and the identity confirmed by GC-MS. Isolable products were purified by flash column chromatography.

Acknowledgements

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Keywords: Thiyl radical • disulfide • photochemistry • arylsilane • desilylation

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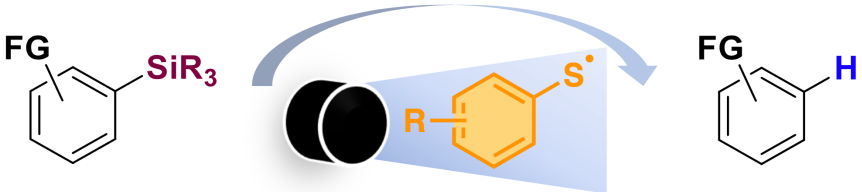

Commercially available and cheap disulfides proved to be excellent thiyl-radical sources for the mild desilylation of arylsilanes under visible-light irradiation. This method relying in a radical chain mechanism shows a broad applicability and functional group tolerance, allowing for the effective reaction of simple arylsilanes, as well as complex structures and therapeutic derivatives.

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