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Recent Applications of Hexamethyldisilathiane (TMS_2S) in Organic Synthesis

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Hexamethyldisilathiane (TMS_2S), also named bis(trimethylsilyl) sulfide, (CAS: 3385-94-2), was reported for the first time in the early 1950's.[1] This liquid compound (bp 160 °C) was prepared by the reaction between iodotrimethylsilane and silver sulfide. Alternatively, bis(trimethylsilyl) sulfide has been also prepared by the addition of disodium sulfide on chlorotrimethylsilane.[1,2] TMS_2S is nowadays commercially available (ca. 28 €/g).[3] This reagent can be viewed as a S1 source of sulfide that is less toxic, less flammable, and easier to handle than gaseous hydrogen sulfide (H_2S). On contact with water, TMS_2S releases H_2S and should be stored in a cold and dry place in an oxygen-free atmosphere. TMS_2S is used as a sulfur transfer agent for the synthesis of alkyl sulfides, thioaldehydes, or thioketones but also as a reducing agent.[4] TMS_2S is also employed in the synthesis of inorganic–organic hybrid clusters[5] or phosphinidene sulfide compounds.[6] It is noteworthy that the number of publications describing the use of TMS_2S has steadily increased since the 1950's to reach an average of 65 publications per year from 2015 to 2022.[7] This Spotlight article highlights the versatility of TMS_2S as a S1 source of sulfides and its recent applications in organic synthesis.

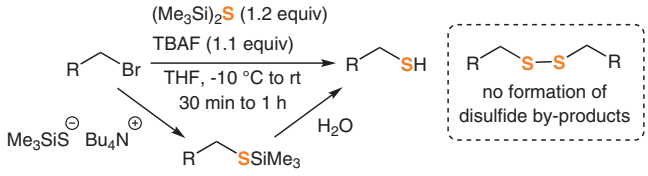
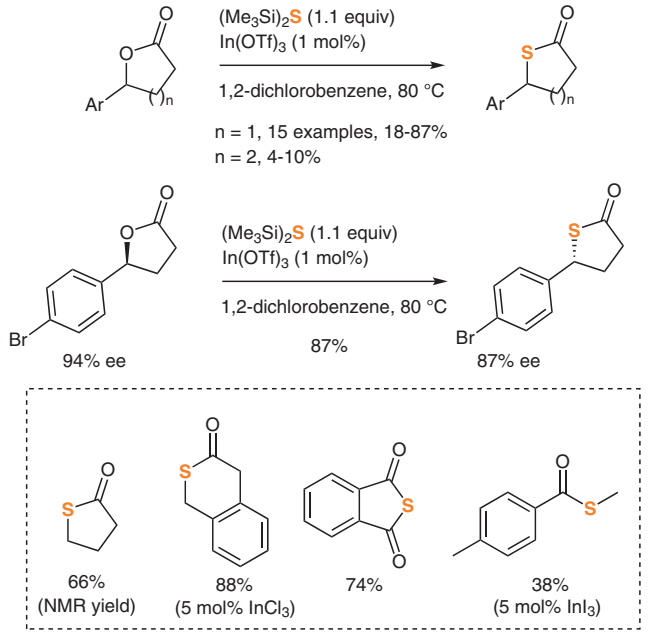
Dr Damien Hazelard (right) obtained his PhD in 2005 under the supervision of Dr A. Fadel (Paris-Sud University). In 2006, he performed a postdoctoral training in the field of organocatalysis in the group of Prof. Y. Hayashi at the Tokyo University of Science. Then he joined the group of Prof. F. Colobert to work on total synthesis at the University of Strasbourg. He was appointed in 2010 as assistant professor at the same university in the group of Prof. P. Compain. In July 2019, he defended his habilitation ('Habilitation à Diriger des Recherches'). His main research interests are the development of new synthetic methodologies for the synthesis of glycomimetics.

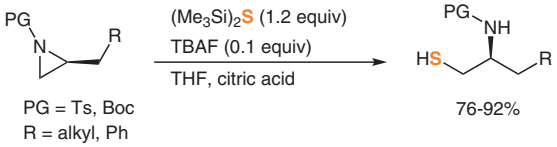
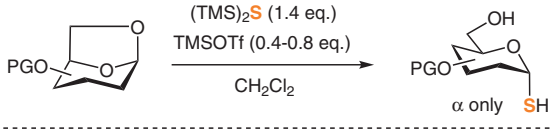
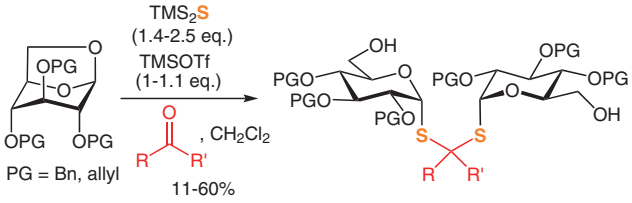
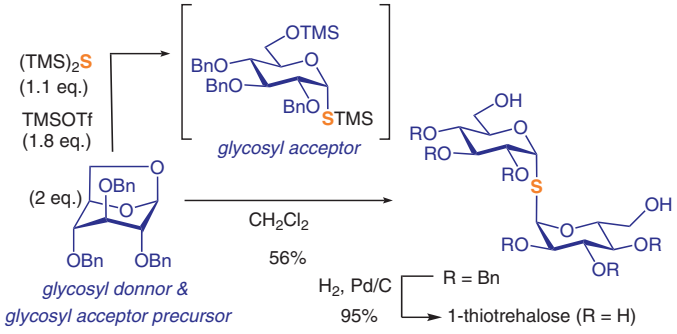
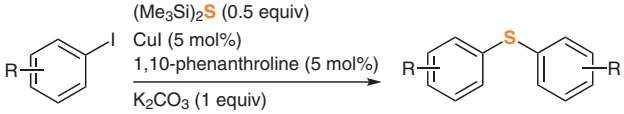
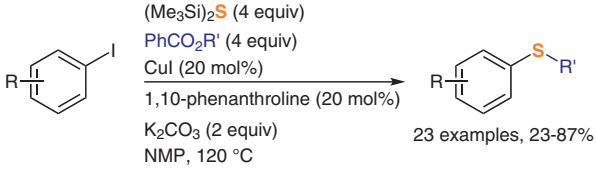
Philippe Compain (left) gained his engineering degree from CPE Lyon. In 1998, he was awarded the Dina Surdin Prize by the French Chemical Society for his PhD research on alkaloid synthesis (UCBL, Lyon). After a postdoctoral stay at Montreal with Prof. Hanessian, he was appointed as a Chargé de Recherche at CNRS (ICOA, Orléans). In 2008, he accepted a full professorship at the University of Strasbourg. His research interests span from synthetic methodologies to glycomimetics of therapeutic interest. Prof. Compain is a fellow of the Royal Society of Chemistry and an honorary member of the Institut Universitaire de France (IUF). He is currently president of the 'Groupe Français des Glycosciences' (GFG, the French network in glycosciences).

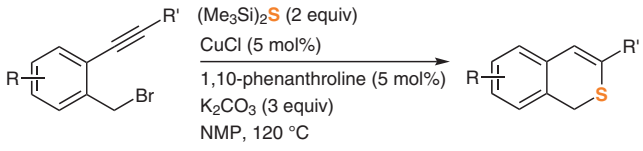
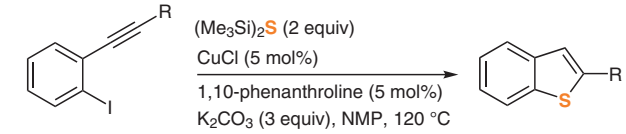
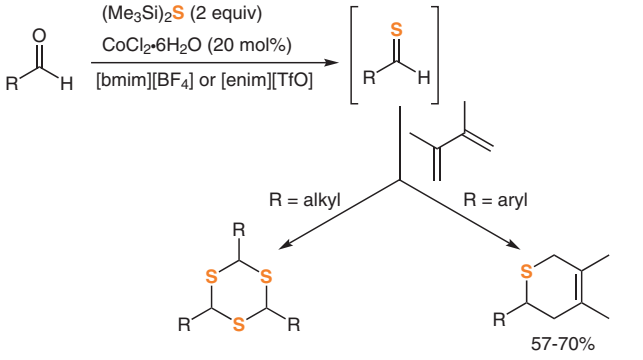
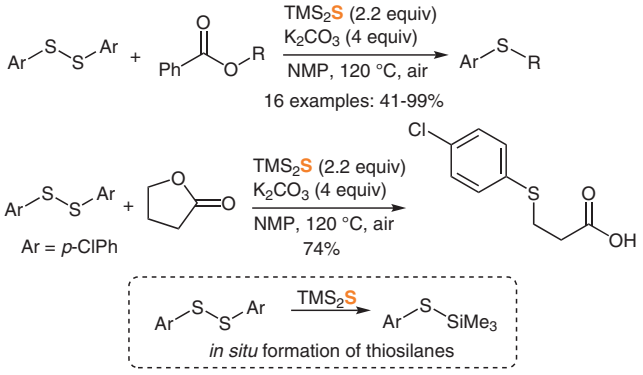
In 1999, Hu and Fox reported a trimethylsilylthioxy dehalogenation reaction for the synthesis of functionalized thiols (Table 1, A).[8] In this process, tetrabutylammonium trimethylsilylthiolate ($Me_3SiS^-Bu_4N^+$), generated *in situ*

from TMS_2S and tetrabutylammonium fluoride (TBAF), reacts with bromoalkanes to give the corresponding thiols without the formation of disulfide side products,[8,9] even though exceptions exist.[10,11] This chemoselectivity may be explained by mild reaction conditions (i. e., short reaction time, low temperature).[8] TMS_2S enables also the formation of thiolactones by way of indium-catalyzed nucleophilic ring opening of 5-aryl-lactones (Table 1, B)[12,13] Two mechanistic pathways have been proposed for this reaction. The first one is based on the attack of TMS_2S at the benzylic position of the indium-activated lactone followed by intramolecular cyclization.[14] In a second possible pathway, TMS_2S attacks the lactone carbonyl group. The formation of the thiolactone ring would then proceed by way of intramolecular nucleophilic substitution at the benzylic position. Following related studies on epoxide ring-opening reactions,[15] Capperucci et al. showed that aziridines can be converted into 1,2-mercaptoamines in the presence of TMS_2S and TBAF (Table 1, C).[16] TMS_2S has also found application in glycochemistry as a nucleophile. In 2011, Zhu et al. reported an efficient method for the synthesis of α-glycosyl thiols through TMS_2S ring opening of 1,6-anhydrosugars[17] in the presence of TMSOTf.[18] A few years later, it was discovered by serendipity that this process could be extended to the synthesis of dithioacetal-α,α-diglycosides by adding a ketone or an aldehyde to the reaction media (Table 1, D).[19] TMS_2S ring opening of 1,6 anhydrosugars has been also applied to the expeditious synthesis of 1-thiotrehalose derivatives (Table 1, E).[20] As a metabolically stable analogue of trehalose, this thiodisaccharide and its derivatives are potential fungicides and insecticides.[20] In the highly convergent approach designed, the commercially available 1,6-anhydrosugar starting material serves both as a glycosyl donor and as a direct precursor of the glycosyl acceptor. The modification of the initial thiolation protocol[18] led to the one-step synthesis of the 1-thiotrahalose skeleton in 56% yield.

Table 1 Recent Applications of Hexamethyldisilathiane (TMS_2S)

(A) Nucleophilic substitution of alkylbromides:[8–11] • access to thiols under mild conditions • broad synthetic scope	
(B) Nucleophilic substitution of 5-aryl-lactones:[12,13] • access to thiolactones from lactones • moderate to high yields with γ-lactones • low yields with δ-lactones • mechanistic proofs (inversion of configuration)	

(C) Ring opening of aziridines:[16] • access to enantioenriched 1,2-mercaptoamines • metal-free • high regioselectivity	 PG = Ts, Boc R = alkyl, Ph 76-92%
(D) Ring opening of 1,6-anhydrosugars in the presence of carbonyl compounds:[19] • access to dithioacetal-α,α-diglycosides • high α-stereoselectivity • one-pot formation of three covalent bonds	(TMS)2S ring opening of 1,6-anhydrosugar (2011)[18]   R = H, R' = aryl, alkyl; R, R' = cyclobutyl, cyclohexyl; R, R' = Et
(E) Double thioglycosylation:[20] • one-pot synthesis of protected 1-thiotrehalose • 2-step synthesis of 1-thiotrehalose • no need to prepare a glycosyl donor and acceptor	
(F) Copper-catalyzed coupling reactions of aryl iodides:[21] • synthesis of diaryl sulfides • double C–S bond formation • high functional group tolerance	 R = H, alkyl, OMe, SMe, NO_2, CN, Br, Cl, F... 17 examples, 29-99%
(G) Copper-catalyzed coupling reactions of aryl iodides in the presence of esters:[22] • synthesis of aryl alkyl sulfides • double C–S bond formation • high functional group tolerance	 23 examples, 23-87% R = H, alkyl, OMe, OEt, SEt, CN, Br, Cl, F; R' = alkyl R = NO_2 or R' = Ph, Bn, *i*-Pr => no reaction or complex mixture

(H) Copper-catalyzed synthesis of isothiochromenes and benzo[*b*]thiophenes:[23] • selective 6-*endo-dig* cyclization • mechanistic studies	 R = H, Me; R' = aryl: 52-77% R = H; R' = alkyl: trace or 0%  R = aryl, alkyl: 56-93%
(I) Generation of thioaldehydes using ionic liquids:[24] • mild conditions • *in situ* formation of thioaldehydes • one-pot synthesis of 3,6-dihydro-2*H*-thiopyrans from aryl aldehydes	
(J) TMS_2S-promoted cleavage of sulfur–sulfur bond in aromatic disilathianes:[26] • one-pot synthesis of alkyl aryl sulfides • alkyl carboxylates used as alkylation reagents • TMS_2S not acting as a S1 source but as a promoter of the S–S bond cleavage	

Cu-catalyzed coupling reactions of aryl iodide and TMS_2S afford symmetrical diaryl sulfides in moderate to excellent yields (Table 1, F).[21] Alkyl aryl sulfides can be obtained via the same catalytic process in the presence of alkyl benzoates (Table 1, G).[22] TMS_2S has been also used as a sulfur source in the copper-catalyzed synthesis of isothiochromenes and benzo[*b*]thiophenes via intramolecular *endo*-selective hydrothiolation of alkynes (Table 1, H).[23] The TMS_2S-based thionation[4] of aryl aldehydes in ionic liquid leads to the *in situ* formation of thials and to 3,6-dihydro-2*H*-thiopyran derivatives by Diels–Alder trapping with 2,3-dimethylbutadiene (Table 1, I).[24] In contrast, the same process applied to alkyl aldehydes provides the corresponding 1,3,5-trithianes.[25] TMS_2S promotes the cleavage of S–S bond in aromatic disulfides enabling the synthesis of the corresponding alkyl aryl sulfides through reaction of *in situ* generated thiosilanes with alkyl carboxylates (Table 1, J).[26] The scope of this reaction has been extended to the synthesis of alkyl aryl selenides from diaryl diselenides.[26]

In summary, TMS_2S has found broad applications as a S1 source in the synthesis of sulfur-containing compounds, from useful building blocks to aromatic heterocycles and thioglycosides. The recent finding that hexamethyldisilathiane can also promote the cleavage of S–S or Se–Se bonds suggests that the synthetic potential of this reagent has not yet been fully uncovered.

Conflict of Interest

The authors declare no conflict of interest.

References and Notes

(1) (a) Eaborn, C. *Nature* **1950**, *165*, 1686. (b) Eaborn, C. *J. Chem. Soc.* **1950**, *165*, 3077. (c) So, J.-H.; Boudjouk, P.; Hong, H. H.; Weber, W. P. *Inorg. Synth.* **1992**, *29*, 30.
(2) For others methods for the preparation of TMS_2S, see: Curphey, T. J. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2001**, *173*, 123.
(3) Sigma-Aldrich (accessed March 16, 2023): https://www.sigmaaldrich.com/FR/en/product/aldrich/283134
(4) For selected reviews, see: (a) Matulenko, M. A.; Degl'Innocenti, A.; Capperucci, A. *Bis(trimethylsilyl) sulfide*, In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: New York, **2007**. (b) Degl'Innocenti, A.; Capperucci, A.; Castagnoli, G.; Malesci, I. *Synlett* **2005**, 1965. (c) Degl'Innocenti, A.; Capperucci, A.; Nocentini, T.; Castagnoli, G.; Malesci, I.; Cerreti, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2005**, *180*, 1247.
(5) For recent examples, see: (a) Rojas-León, I.; Christmann, J.; Schwan, S.; Ziese, F.; Sanna, S.; Mollenhauer, D.; Rosemann, N. W.; Dehnen, S. *Adv. Mater.* **2022**, *34*, 2203351. (b) Liu, L. J.; Zhang, J. W.; Asas, M.; Whang, Z.-Y.; Zhang, S.-Q.; Mak, T. C. W. *Chem. Commun.* **2021**, *57*, 5586.
(6) See for examples: (a) Sato, Y.; Nishimura, M.; Kawaguchi, S.; Nomoto, A.; Ogawa, A. *Chem. Eur. J.* **2019**, *25*, 6797. (b) Graham, C. M. E.; Pritchard, T. E.; Boyle, P. D.; Valjus, J.; Tuononen, H. M.; Ragogna, P. J. *Angew. Chem. Int. Ed.* **2017**, *56*, 6236. (c) Graham, C. M. E.; Macdonald, C. L. B.; Boyle, P. D.; Wisner, J. A.; Ragogna, P. J. *Chem. Eur. J.* **2018**, *24*, 743.
(7) Search run on Scifinder March 16, 2023.
(8) Hu, J.; Fox, M. A. *J. Org. Chem.* **1999**, *64*, 4959.
(9) For recent examples, see: (a) Jayaraman, J.; Ganapathy, A. S.; Thanikachalam, V.; Palanivel, J.; Sekar, P. *J. Phys. Org. Chem.* **2018**, *31*, e3796. (b) Kong, R.; Xiao, Z.; Xie, F.; Jiang, J.; Ding, L. *New J. Chem.* **2017**, *41*, 2895. (c) Kothur, R. R.; Patel, B. A.; Cragg, P. J. *Chem. Commun.* **2017**, *53*, 9078. (d) Wójcik, M. M.; Wróbel, J.; Jańczuk, Z. Z.; Mieczkowski, J.; Górecka, E.; Choi, J.; Cho, M.; Pociecha, D. *Chem. Eur. J.* **2017**, *23*, 8912. (e) Rahman, M. L.; Biswas, T. K.; Sarkar, S. M.; Yusoff, M. M.; Yuvaraj, A. R.; Kumar, S. *J. Colloid Interface Sci.* **2016**, *478*, 384. (f) Sun, J.; Li, W.; Xiao, L.; Yu, G.; Shi, J. *RSC Adv.* **2016**, *6*, 62200. (g) Olshansky, J. H.; Ding, T. X.; Lee, Y. V.; Leone, S. R.; Alivisatos, A. P. *J. Am. Chem. Soc.* **2015**, *137*, 15567. (h) Liu, Y.; Najafabadi, B. K.; Fard, M. A.; Corrigan, J. F. *Angew. Chem. Int. Ed.* **2015**, *54*, 4832.
(10) Kizling, M.; Dzwonek, M.; Nowak, A.; Tymecki, L.; Stolarczyk, K.; Więckowska, A.; Bilewicz, B. *Nanomaterials* **2020**, *10*, 1434.
(11) See also: (a) Reddy, P. V. G.; Lin, Y.-W.; Chang, H.-T. *ARKIVOC* **2007**, *(xvi)*, 113. (b) Gopidas, K. R.; Whitesell, J. K.; Fox, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 14168.
(12) Ogiwara, Y.; Takano, K.; Horikawa, S.; Sakai, N. *Molecules* **2018**, *23*, 1339.
(13) Nie, Z.; Chiou, M.-F.; Cui, J.; Qu, Y.; Zhu, X.; Jian, W.; Xiong, H.; Li, Y.; Bao, H. *Angew. Chem. Int. Ed.* **2022**, *61*, e202202077.
(14) Sakai, N.; Horikawa, S.; Ogiwara, Y. *Synthesis* **2018**, *50*, 565.
(15) Degl'Innocenti, A.; Capperucci, A.; Cerreti, A.; Pollicino, S.; Scapecchi, S.; Malesci, I.; Castagnoli, G. *Synlett* **2005**, 3063.
(16) (a) Tanini, D.; Borgogni, C.; Capperucci, A. *New J. Chem.* **2019**, *43*, 6388. (b) Tanini, D.; Barchielli, G.; Benelli, F.; Degl'Innocenti, A.; Capperucci, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2015**, *190*, 1265.
(17) For a review on ring opening of 1,6-anhydrosugars, see: Hazelard, D.; Compain, P. *Eur. J. Org. Chem.* **2021**, 3501.
(18) Zhu, X.; Dere, R. T.; Jiang, J.; Zhang, L.; Wang, X. *J. Org. Chem.* **2011**, *76*, 10187.
(19) Céspedes, Dávila. M. F.; Schneider, J. P.; Godard, A.; Hazelard, D.; Compain, P. *Molecules* **2018**, *23*, 914.
(20) Tardieu, D.; Céspedes, Dávila. M. F.; Hazelard, D.; Compain, P. *Synthesis* **2018**, *50*, 3927.
(21) Ogiwara, Y.; Maeda, H.; Sakai, N. *Synlett* **2018**, *19*, 655.
(22) Sakai, N.; Maeda, H.; Ogiwara, Y. *Synthesis* **2019**, *51*, 2323.
(23) Nakajima, T.; Takeuchi, R.; Oomori, K.; Ishida, K.; Ogiwara, Y.; Sakai, N. *Synthesis* **2023**, *55*, 779.
(24) Tanini, D.; Angeli, A.; Capperucci, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2016**, *191*, 156.
(25) Tanini, D.; Trapani, F.; Capperucci, A. *J. Sulfur Chem.* **2020**, *41*, 635.
(26) Nakajima, T.; Takano, K.; Maeda, H.; Ogiwara, Y.; Sakai, N. *Chem. Asian J.* **2021**, *16*, 4103.