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Synthetic equivalents of benzenethiol and benzyl mercaptan having faint smell: odor reducing effect of trialkylsilyl group

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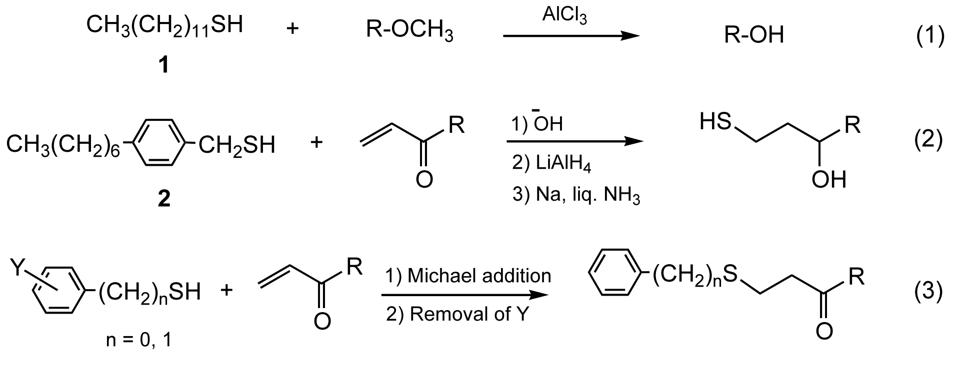
Abstract—Syntheses and odor tests of the trialkylsilylated benzyl mercaptans and benzenethiols have revealed that the trimethylsilyl substituent on the benzene ring has a remarkable effect in reducing the foul smell of the parent benzyl mercaptan and benzenethiol. Protodesilylation allowed these silylated thiols to function as odorless synthetic equivalents of benzyl mercaptan and benzenethiol. This discovery will greatly improve the physical environment of the researcher working with these malodorous compounds. © 2002 Elsevier Science Ltd. All rights reserved.

Introduction of a sulfur substituent into organic molecules is one of the basic reactions in organic synthesis. Unfortunately, sulfur-containing reagents generally have such a strong, foul smell that working with them can be extremely unpleasant. Recently, we have been involved in a program aimed at the development of odorless thiols[1] and sulfides[2] which can be substituted for malodorous reagents such as ethanethiol, benzyl mercaptan and dimethyl sulfide. Odorless substitutes for these foul-smelling molecules are always desirable from an environmental standpoint. Among the purified 1-alkanethiols tested, 1-dodecanethiol (**1**) was found to have no odor. An alkyl chain of over 12 carbon atoms in the thiol was crucial in reducing the offending smell. Consequently, we synthesized 4-alkylphenylmethanethiols, and discovered that the 4-heptylphenylmethanethiol (**2**), which has a 12-carbon chain, was also odorless. We next demonstrated that the alkanethiols **1** and **2** could be used as odorless substitutes for ethanethiol and benzyl mercaptan in dealkylation and thiol-introducing reactions, as shown in Eqs. (1) and (2), respectively (Scheme 1).[1] However, the odorless thiol **2** could not be used to introduce a benzylthio group because removal of the heptyl group on the benzene ring proved difficult. Therefore, we developed odorless thiols, which possessed a removable substituent on the phenyl and the benzyl groups, as shown in Eq. (3).

During our search for odorless thiols, we found that the 4-*tert*-butylphenylmethanethiol did not possess the odor of a thiol but rather that of an alcohol. We



Scheme 1.

Keywords: odorless benzyl mercaptan; odorless benzenethiol; trimethylsilyl group; odor scale; Michael addition; protodesilylation.

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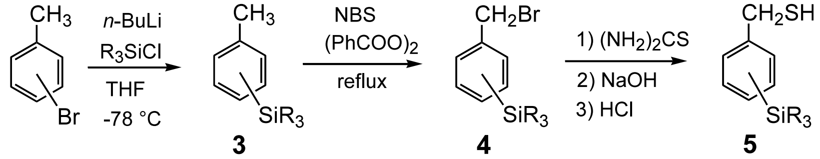
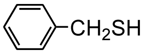
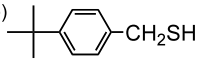
therefore envisioned introducing a more bulky trialkylsilyl group onto the benzene ring that would reduce the smell of the parent benzenethiol and benzyl mercaptan, if indeed the olfactory sense of the human nose recognizes the odor of a compound by its steric bulkiness. Although the sterically bulky *ortho*-trimethylsilylbenzenethiol[3] and 4-*tert*-butyl-benzenethiol[4] have been used for enantio- and diastereoselective Michael additions of α,β-unsaturated carbonyl compounds, there is no mention of their odor. Herein we report the effect of a trialkylsilyl substituent on the benzene ring in reducing the smell of the parent thiol, and their development as odorless synthetic equivalents of the parent benzyl mercaptan and benzenethiol by protodesilylation.

First, we synthesized the trialkylsilylphenylmethanethiols having a trialkylsilyl group at every position on the benzene ring. We adopted the reactions without foul-smell for their syntheses. The results are shown in Table 1. 1-Bromo-2-, 3-, and 4-methylbenzenes were converted to the corresponding trialkylsilylphenylmethanethiols (**5**) in satisfactory yields through silylation by lithium–halogen exchange, bromination at the benzylic position with *N*-bromosuccinimide (NBS), and thiolation with thiourea. All of the prepared thiols **5** were purified using high performance gel-permeation chromatography[5] after silica gel column chromatography. Their odors were scaled by the human nose of two test subjects in descending order of odor with benzyl mercaptan being the most foul-smelling (5) and the odorless thiol (0). The silylated benzyl mercaptans have considerably less odor than the parent benzyl mercaptan and slightly less than *tert*-butylphenylmethanethiol. The presence of a propyl group in the trialkylsilyl unit seems to cause a stronger thiol odor. Trimethylsilyl and triethylsilyl substituents were found to have a very faint odor and in some cases were virtually odorless, regardless of their position on the benzene ring.

Since the trimethylsilyl substituent on the benzene ring has been found to have a remarkable effect in reducing the smell of the parent benzyl mercaptan, we decided to prepare the trimethylsilylbenzenethiols[6] (from bromophenols as the starting material) and test their respective odors (Table 2). *ortho*-, *meta*- and *para*-Bromophenols were transformed into the trimethylsilylbenzenethiols (**9**) by silylation, *N*,*N*-dimethylaminothiocarbamoylation, the Newman–Kwart rearrangement,[7] and reduction. The cleavage of the O–Si bond of *ortho*-trimethylsilylphenyloxy trimethylsilyl ether required treatment with TBAF (Table 2, entry 3), whereas the bonds of the corresponding *para* and *meta* derivatives were easily cleaved by treatment with a 1N HCl solution (Table 2, entries 1 and 2). The Newman–Kwart rearrangement of *O*-(trimethylsilyl)phenyl *N*,*N*-dimethylaminothiocarbamates was greatly influenced by the position of the trimethylsilyl substituent. The yields of the rearrangement decreased as the silyl substituent was moved from *para* to *ortho*, indicating that the steric bulkiness of the *ortho*-trimethylsilyl substituent interferes with the intramolecular approach of the thiocarbamoyl group to the aromatic carbon attached to the trimethylsilyl group. All of the

Table 1. Syntheses and odor scales of trialkylsilylphenylmethanethiols **5**



Entry	Substrate	R_3SiCl	Yield (%)			Odor scale[a] of **5**	
		R	**3**	**4**	**5**	A	B
1	*para*	Me	93	75	71	0	1
2	*meta*	Me	80	87	56	1	1
3	*ortho*	Me	67	61	53	1	0
4	*para*	Et	61	78	98	1	1
5	*meta*	Et	66	100	89	0	1
6	*ortho*	Et	100	79	94	0	1
7	*para*	Pr	60	90	97	1	2
8	*meta*	Pr	97	94	64	2	2
9	*ortho*	Pr	100	64	72	1	1
	b) 					5	5
	b) 					1	1

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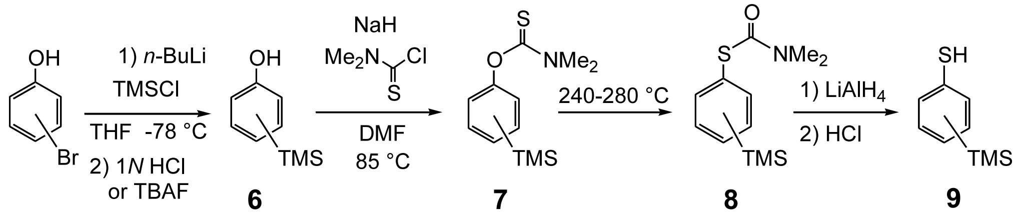
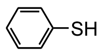
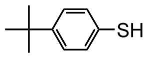
[a] Odor scale: foul-smelling 5 to odorless 0 by the human nose of two test subjects A and B.

[b] Cited from Ref. 1b.

Table 2. Syntheses and odor scales of trimethylsilylbenzenethiols **9**



Entry	Substrate	Yield (%)				Odor scale[a] of **9**	
		6	**7**	**8**	**9**	A	B
1	*para*	78	100	82	71	1	1
2	*meta*	90	100	53	83	1	1
3	*ortho*	89[b]	60	30	84	0	1
c. f.						5	5
						2	2

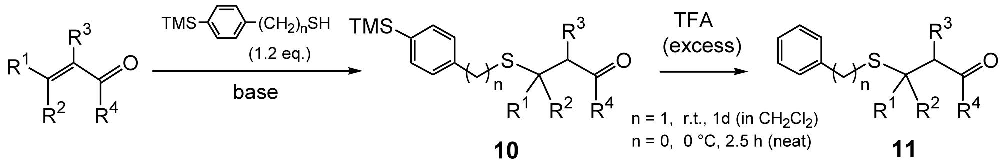
[a] Odor scale: foul-smelling 5 to odorless 0 by the human nose of two test subjects A and B.

[b] Treatment of TBAF was required for the cleavage of O–TMS bond. Overall yield.

trimethylsilylbenzenethiols (**9**) prepared had a faint odor or none at all. The trimethylsilyl group on the substituted benzenethiols had a remarkable effect in reducing the foul smell of the parent benzenethiol.

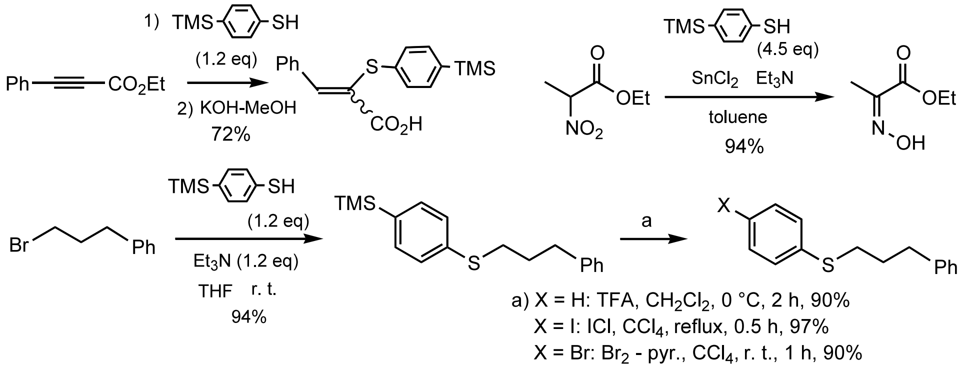
We substituted the odorless trimethylsilylated benzyl mercaptan and benzenethiol for the parent compounds in the Michael addition of α,β-unsaturated carbonyl compounds and the results are shown in Table 3. The benzyl mercaptan and benzenethiol silylated at the *para*-position[8] were selected because of the steric and electronic nature of the trimethylsilyl group.[9] Tetrabutylammonium fluoride (TBAF) in THF[10] successfully catalyzed the Michael addition of *para*-trimethylsilylated benzyl mercaptan (odd entries), whereas triethylamine or DBU in petroleum ether[11] catalyzed the reaction of *para*-trimethylsilylated benzenethiol (even entries). The efficiency of the Michael addition with α,β-unsaturated carbonyl compounds was dependent on the nucleophilicity of the thiols. A longer reaction time was necessary with 4-trimethylsilylbenzenethiol than with 4-trimethylsilylphenylmethanethiol. The β-substituents on the α,β-unsaturated carbonyl compounds significantly retarded the reaction of

Table 3. Michael addition and protodesilylation



Entry	α,β-Unsat. carb. compd				Thiol	Base (amount)	Solv.[a]	Temp.	Time	Yield (%)	
	R^1	R^2	R^3	R^4	n					**10**	**11**
1	H	H	H	OEt	1	TBAF (0.2 equiv.)	THF	rt	0.5 h	100	88
2	H	H	H	OEt	0	Et_3N (0.1 equiv.)	PE	0°C–rt	2.5 days	100	100
3	H	H	Me	OEt	1	TBAF (0.2 equiv.)	THF	rt	0.5 h	95	90
4	H	H	Me	OEt	0	DBU (1.2 equiv.)	PE	rt	0.5 h	57	100
5	Me	H	H	OEt	1	TBAF (0.2 equiv.)	THF	rt	0.5 h	98	100
6	Me	H	H	OEt	0	Et_3N (0.1 equiv.)	PE	50°C	2 days	91	85
7	Me	Me	H	OEt	1	TBAF (0.2 equiv.)	THF	rt	20 h	71	53
8	Me	Me	H	OEt	0	DBU (1.2 equiv.)	PE	rt	1 day	n.r.	–
9	Me	H	H	Et	1	TBAF (0.2 equiv.)	THF	rt	0.5 h	95	97
10	Me	H	H	Et	0	Et_3N (1.2 equiv.)	PE	rt	6 h	100	100

[a] THF: tetrahydrofuran, PE: petroleum ether.



Scheme 2.

4-trimethylsilylphenylmethanethiol (entry 7). Furthermore, the reaction with 4-trimethylsilylbenzenethiol did not proceed even under prolonged reaction times (entry 8). Protodesilylation[3a,9a] of the Michael adducts with trifluoroacetic acid[12] permitted the introduction of the benzylthio and phenylthio groups under odorless reaction conditions.

Several applications of 4-trimethylsilylbenzenethiol, not including the Michael addition, were also tested, as shown in Scheme 2. The radical addition of 4-trimethylsilylbenzenethiol to ethyl phenylpropiolate under neat reaction conditions (100°C, 15 min) followed by hydrolysis gave α-(4-trimethylsilylphenylthio)cinnamic acid, as does benzenethiol itself according to the literature.[13] 4-Trimethylsilylbenzenethiol can be used in the reduction of nitro groups to oximes under reductive conditions at room temperature for 1 h using stannous chloride (1.5 equiv.) and triethylamine (5.0 equiv.).[14] The 4-trimethylsilyl group on the benzene ring can tolerate even the acidic conditions of *p*-toluenesulfonic acid in benzene at reflux, 1N HCl–MeOH at room temperature, and 6N HCl–MeOH at 0°C for 24 h, but it decomposed to benzenethiol under stronger acidic conditions. Lewis acidic conditions, such as boron trifluoride etherate, dibutylboron triflate, and triethylborane were not suitable, whereas lanthanide(III) triflates (Yb, Sc, Sm, La) did not decompose 4-trimethylsilylbenzenethiol at room temperature. In addition to protodesilylation, 4-trimethylsilylbenzenethiol was useful for the introduction of the 4-bromo- or 4-iodophenylthio group under odorless conditions by electrophilic bromination or iodination using bromine–pyridine[12] or iodine monochloride,[15] respectively.

In conclusion, we have demonstrated the remarkable effect of a trimethylsilyl substituent in reducing the smell of the parent benzyl mercaptan and benzenethiol by systematic syntheses of silylated thiols. Protodesilylation of the Michael adducts having silylated benzyl mercaptan or benzenethiol allowed the introduction of the parent thiols into the substrates under odorless reaction conditions, namely, the silylated benzyl mercaptan and benzenethiol are useful as faintly malodorous or even odorless synthetic equivalents of the parent thiols. This feature has greatly improved the environmental working conditions in which foul-smelling thiols are used. In addition, other possible functional group manipulations[15d,16] of the trimethylsilyl group on the benzene ring could conceivably expand the synthetic value of these odorless silylated thiols.

Acknowledgements

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References

1. (a) Nishide, K.; Ohsugi, S.; Shiraki, H.; Tamakita, H.; Node, M. *Org. Lett.* **2001**, *3*, 3121–3124; (b) Node, M.; Kumar, K.; Nishide, K.; Ohsugi, S.; Miyamoto, T. *Tetrahedron Lett.* **2001**, *42*, 9207–9210.
2. Nishide, K.; Ohsugi, S.; Fudesaka, M.; Kodama, S.; Node, M. *Tetrahedron Lett.* **2002**, *43*, 5177–5179.
3. (a) Nishimura, K.; Tomioka, K. *J. Org. Chem.* **2002**, *67*, 431–434; (b) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 440–442; (c) Tomioka, K.; Okuda, M.; Nishimura, K.; Manabe, S.; Kanai, M.; Nagaoka, Y.; Koga, K. *Tetrahedron Lett.* **1998**, *39*, 2141–2144; (d) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 12974–12975; (e) Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675–8676.
4. Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043–4044.
5. Compounds were purified by a recycle HPLC (LC-908, Japan Analytical Industry Co., Ltd.) on GPC columns (JAIGEL 1H and 2H) after purification on silica gel.
6. The *ortho*-lithiation of benzenethiol was reported for a direct synthesis of *ortho*-trimethylsilylbenzenethiol: (a) Block, E.; Eswarakrishnan, V.; Gernon, M.; Ofori-Okai, G.; Saha, C.; Tang, K.; Zubieta, J. *J. Am. Chem. Soc.* **1989**, *111*, 658–665; (b) Smith, K.; Lindsay, C. M.; Pritchard, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 665–669; (c) Block, E.; Gernon, M.; Kanf, H.; Ofori-Okai, G.; Zubieta, J. *Inorg. Chem.* **1989**, *28*, 1263–1271; (d) Block, E.; Ofori-Okai, G.; Zubieta, J. *J. Am. Chem. Soc.* **1989**, *111*, 2327–2329.

7. (a) Kwart, H.; Evans, E. R. *J. Org. Chem.* **1966**, *31*, 410–413; (b) Newman, M. S.; Karnes, H. A. *J. Org. Chem.* **1966**, *31*, 3980–3984; (c) Delogu, G.; Fabbri, D.; Dettori, M. A. *Tetrahedron: Asymmetry* **1998**, *9*, 2819–2826.
8. The strength of the odor (in parentheses) measured by a Portable Odor Meter FPO-1 (Futaba Electronics, Yokohama, Japan) was as follows: benzenethiol (606), 4-trimethylsilylbenzenethiol (56), benzyl mercaptan (422), 4-trimethylsilylphenylmethanethiol (312) and the control nitrogen gas (38). The sampling method was as follows: each sample (10 mg) was diluted 100-fold in hexane, and the vapor of each sample was collected in a Flek-Sampler (1 L polyester sealed bag) by a flow of nitrogen gas after evaporation of hexane. Consequently, the strength of the odor between the human nose and an odor semiconductor sensor was not completely correlated, as in the case of the alkanethiols.[1b]
9. (a) Bailey, F. P.; Taylor, R. *J. Chem. Soc. (B)* **1971**, 1446–1449; (b) Alt, H.; Bock, H. *Tetrahedron* **1971**, *27*, 4965–4975; (c) Cornish, A. J.; Eaborn, C. *J. Chem. Soc., Perkin Trans. 2* **1975**, 874–878.
10. Hankovszky, H. O.; Hideg, K.; Jerkovich, G. *Synthesis* **1989**, 526–529.
11. Suzuki, K.; Ikegawa, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3277–3282.
12. For example, see: Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5245–5253.
13. Wadsworth, D. H.; Detty, M. R. *J. Org. Chem.* **1980**, *45*, 4611–4615.
14. Bartra, M.; Romea, P.; Urpi, F.; Vilarrasa, J. *Tetrahedron* **1990**, *46*, 587–594.
15. For example, see: (a) Lehmann, U.; Schlüter, A. D. *Eur. J. Org. Chem.* **2000**, 3483–3487; (b) Knölker, H.-J.; Braier, A.; Bröcher, D. J.; Jones, P. G.; Piotrowski, H. *Tetrahedron Lett.* **1999**, *40*, 8075–8078; (c) Hamon, D. P. G.; Massy-Westropp, R. A.; Newton, J. L. *Tetrahedron Lett.* **1993**, *34*, 5333–5336; (d) Félix, G.; Laguerre, M.; Dunoguès, J.; Calas, R. *J. Org. Chem.* **1982**, *47*, 1423–1427.
16. For example, see: Bennetau, B.; Krempp, M.; Dunoguès, J.; Ratton, S. *Tetrahedron* **1990**, *46*, 8131–8142.