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Odorless substitutes for foul-smelling thiols: syntheses and applications

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Abstract—Several alkanethiols and *p*-alkylphenylmethanethiols were synthesized, and their odors were compared with those of ethanethiol and benzyl mercaptan by human and instrumental sensors. Among the various thiols analyzed, 1-dodecanethiol (**1**) and *p*-heptylphenylmethanethiol (**3**) were revealed to be odorless. 1-Dodecanethiol (**1**) has been used instead of ethanethiol for dealkylation of ethers, and *p*-heptylphenylmethanethiol (**3**) can replace benzyl mercaptan in the preparation of a 1,3-mercapto alcohol from an α,β-unsaturated ketone. These odorless thiols will greatly improve the physical environment of the researcher working with these foul-smelling compounds.

Thiols are a fundamental and important functional group in organic chemistry, and the literature contains ample reports of organic and bioorganic chemistry on this group.[1] Commonly used thiols like ethanethiol and benzyl mercaptan have a foul smell making them difficult and unpleasant to use in the laboratory without fume hoods. The problem becomes even worse in industry where these malodorous reagents are used on a large scale. Odorless substitutes are therefore always required. While experimental assessment of human olfactory thresholds has been reported for four alkanethiols including 1-dodecanethiol,[2] there have been no serious attempts to pursue this research. We report here, for the first time, the synthesis of new odorless thiols to replace the usual foul-smelling ones, as well as various applications in organic reactions.

Recently, we published an asymmetric Michael addition to α,β-unsaturated carbonyl compounds using 10-mercaptoisoborneol as the hydrogen sulfide equivalent.[3] During the course of the study, we looked for an odorless thiol substitute for the foul-smelling ethanedithiol for the thiol exchange reaction of the vinyl sulfide. Two commercially available thiols, 1-dodecanethiol (**1**) and 1-hexadecanethiol (**2**), were selected for odor testing because it was thought that the smell of thiols was related to their volatility. Unexpectedly, **1** turned out to be an odorless liquid whereas **2** reeked in spite of being a crystalline compound, a result which seemed contradictory to the relationship between volatility and odor. To understand this apparent contradiction and to find other useful odorless thiol substitutes, we planned to test the odor of a number of alkanethiols. All of the alkanethiols were commercially available except for 1-tetradecanethiol which was prepared by reacting the tetradecyl Grignard reagent with sulfur[4] followed by lithium aluminum hydride reduction.

The relative odor index of these thiols with the foul-smelling ethanethiol perceived by the human nose of two test subjects is listed in Table 1. The index of the most malodorous thiol is 5; the index of the odorless thiol, 0. The odor of a thiol depends virtually entirely on its purity, i.e. 1-hexadecanethiol (**2**) purified by HPLC on a GPC column was found to be almost odorless,[5] while the commercial 1-hexadecanethiol had essentially the same odor as indicated in a chemical catalog. Therefore, purification of all these thiols was done on HPLC using a GPC column before analyzing their respective odors. Among the alkanethiols, 1-dodecanethiol (oil) was found to be odorless, while lower carbon-chain thiols were found to be malodorous. These facts suggest that the foul smell of thiol toward the human olfactory cell is related to the length of its carbon-chain.

Furthermore, these alkanethiols were subjected to a Fragrance and Flavor analyzer FF-1,[6] as shown in Fig. 1.[7] FF-1 consists of an odor concentration tube and 6 odor sensors (made by metal oxide semiconductors).

Keywords: odorless thiols; synthesis; odor scale; dealkylation; Michael addition.

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Table 1. The odour scale for alkanethiols

Entry	Thiols	Marker in Fig. 1	Carbon length	Bp (°C)[a]	Odor scale[b]	
					A	B
1	CH_3CH_2SH	□	2	35	5	5
2	$CH_3(CH_2)_2SH$	◇	3	67–68	5	5
3	$CH_3(CH_2)_3SH$	△	4	98	5	4
4	$CH_3(CH_2)_4SH$	▽	5	126	4	3
5	$CH_3(CH_2)_5SH$	◁	6	150–154	3	3
6	$CH_3(CH_2)_6SH$	▷	7	173–176	4	3
7	$CH_3(CH_2)_7SH$	+	8	197–200	2	1
8	$CH_3(CH_2)_8SH$	×	9	220	2	1
9	$CH_3(CH_2)_9SH$	★	10	114/13 mmHg	1	1
10	$CH_3(CH_2)_{10}SH$	■	11	103–104/3 mmHg[c]	1	0
11	$CH_3(CH_2)_{11}SH$ (**1**)	◆	12	266–283	0	0
12	$CH_3(CH_2)_{13}SH$	▼	14	298–320 (mp 7)[c]	0	1
13	$CH_3(CH_2)_{14}SH$	◀	15	125–128/0.1 mmHg[d]	0	0
14	$CH_3(CH_2)_{15}SH$ (**2**)	▶	16	184–191/7 mmHg (mp 18–20)	0	0

[a] Cited from the Aldrich chemical catalog unless otherwise noted.
[b] Odor scale: foul-smelling 5 to odorless 0 by the human nose of two test subjects A and B.
[c] Cited from *Dictionary of Organic Compounds*; 2nd ed.; Koudansya: Tokyo, 1989.
[d] Experimental data.

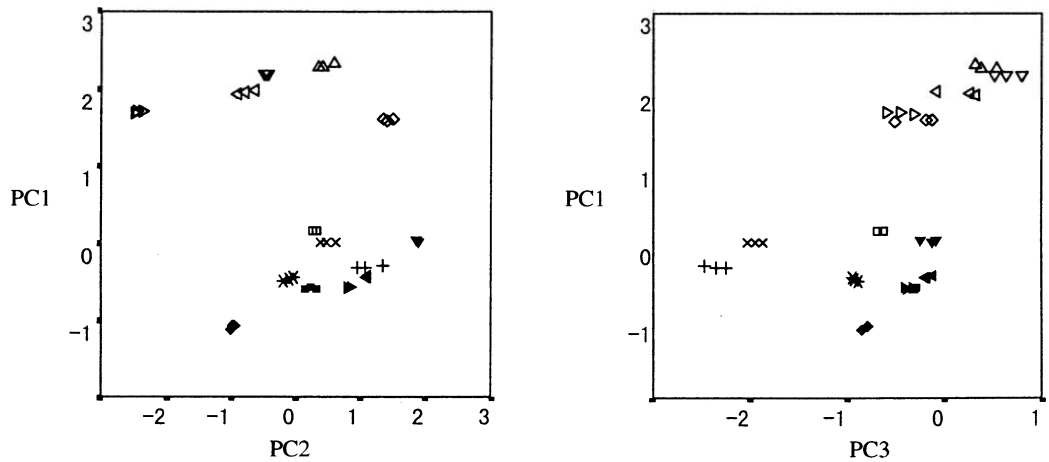


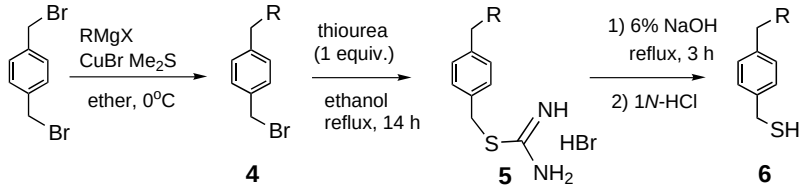
Figure 1. Results of a principal-component analysis of the response of the six odor semiconductor sensors to samples using the FF-1.

The first principal component was depicted as PC1. PC1 would be indicative of the odor intensity in the experiment because each sample has a minute odor quality difference. Although the odor index using the FF-1 instrument depends on the thiol's sensitivity to the detectors in the instrument and on the vapor pressure of each thiol, no appreciable linear correlation between odor index and the length of the carbon-chain of the thiols was observed in the FF-1 instrument. However, 1-dodecanethiol (**1**) was found to have the lowest value among the alkanethiols tested, which coincided with its odorlessness for the human nose.

Some *p*-alkylphenylmethanethiols were prepared having an alkyl chain length similar to 1-dodecanethiol. The syntheses of the new *p*-alkylphenylmethanethiols are described in Scheme 1. In order to prepare the *p*-alkylphenylmethanethiols, we chose *p*-xylylene dibromide as the starting material. Mono-alkylation with alkyl Grignard reagent in the presence of the cuprous bromide dimethyl sulfide complex[8] gave the *p*-alkylbenzylic bromides in moderate yields along with the radical coupling product, 1,2-(4,4′-dialkyl)diphenylethane. Substitution of the bromide with thiourea afforded the thiouronium salt, which was hydrolyzed to give the *p*-alkylphenylmethanethiols in high yields.[9] The whole process for the synthesis of thiols involves no foul-smelling reagents or intermediates and thus can be scaled up to an industrial level.

Results of the odor testing of various thiols are shown in Table 2. *p*-Heptylphenylmethanethiol (**3**) was chosen as the odorless substitute for benzyl mercaptan.

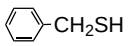
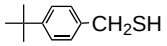
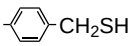
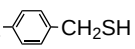
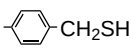
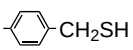
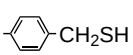
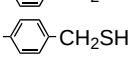
Some applications using odorless 1-dodecanethiol (**1**) and *p*-heptylphenylmethanethiol (**3**) are shown in Scheme 2. Previously, we developed useful reagent systems (hard Lewis acid and thiol) for demethylation of



R	X	RMgX (equiv.)	CuBr Me_2S (equiv.)	Time (h)	Yield of **4** (%)	Yield of **5** (%)	Yield of **6** (%)
propyl	Br	1.5	0.6	6	42	75	99
butyl	Cl	1.5	0.6	18	37	100	91
pentyl	Br	1.5	0.75	6	37	99	79
hexyl	Br	1.5	0.6	6	41	81	87
heptyl	Br	1.0	0.1	18	28	74	90
octyl	Br	1.5	0.6	6	41	90	78

Scheme 1. Synthesis of *p*-alkyl substituted benzylic mercaptans.

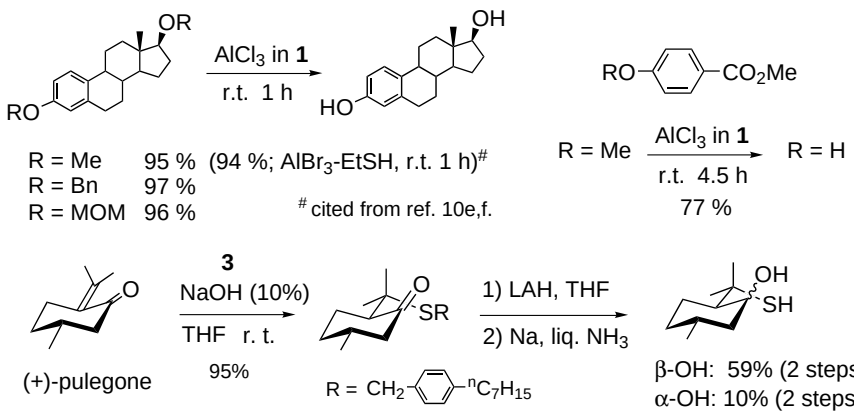
Table 2. The odor scale for benzylic mercaptans

Entry	Thiols	Odor Scale[a] A	B
1		5	5
2		1	1
3	$CH_3(CH_2)_3$ 	2	1
4	$CH_3(CH_2)_4$ 	2	1
5	$CH_3(CH_2)_5$ 	0	1
6	$CH_3(CH_2)_6$  (**3**)	0	0
7	$CH_3(CH_2)_7$ 	1	0
8	$CH_3(CH_2)_8$ 	1	1

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

aliphatic and aromatic methyl ethers.[10] The yields of the parent alcohols and phenols from methyl, benzyl, and MOM ethers using aluminum chloride and 1-dodecanethiol (**1**) were very high, similar to those using the previous reagent system. The selective demethylation of a phenolic methyl ether in the presence of methyl ester was observed using the new reagent system. We have also demonstrated that the odorless benzyl mercaptan **3** can be used instead of benzyl mercaptan in the Michael addition of a thiol to an α,β-unsaturated ketone. Reductive cleavage of the benzylic carbon–sulfur bond with sodium metal in liquid ammonia gave the 1,3-mercapto alcohol in good yield.

In conclusion, we have found that 1-dodecanethiol (**1**) and *p*-heptylphenylmethanethiol (**3**) are odorless thiols compared to the commonly used malodorous thiols. Although biological studies must be carried out to ultimately prove the relationship between the carbon length of the thiol and the biological mechanism in human olfactory cells, it is obvious that the twelve-carbon length of the thiol is crucial for the diminished odor of thiols. We have demonstrated that the foul-smelling ethanethiol and benzyl mercaptan can be replaced by 1-dodecanethiol and *p*-heptylbenzyl mercaptan in dealkylation and Michael addition, respectively. We believe that eliminating the stench of thiols is an important part of sulfur chemistry and that the use of these odorless thiols will greatly improve the physical environment of the researcher working with these foul-smelling compounds.



Scheme 2. Synthetic applications of odorless thiols **1** and **3**.

Acknowledgements

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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. Each sample (15 mg) and 2 L of nitrogen gas were placed into the sampling bag made of polyethylene terephthalate. A sample gas was generated until a saturated condition was achieved in the sample bag headspace at a room temperature of 25°C. The sample gas was analyzed by a Fragrance and Flavor analyzer FF-1 (made by Shimadzu Corporation) the 'electronic nose.'
7. A colony of the spots on a principal-component analysis shows an odor character of the samples. Each scale of coordinates indicates the intensity of the odor.
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