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ORGANIC PREPARATIONS WITH MOLAR AMOUNTS OF VOLATILE MALODOROUS THIOLS

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GRAPHICAL ABSTRACT



Abstract Thiols are indispensable for the preparation of many organic sulfur compounds. Their strong smell and use for gas leakage perception render it almost impossible to work with them without arousing public attention. Molar amounts of the very odoriferous thiol 2-methyl-2-propanethiol (t-butylthiol) are needed, for example, for the large-scale synthesis of two useful synthetic building blocks, 1,2,4,5-tetrakis(t-butylthio)benzene and tetramethylbenzo-2,2,6,6-[1,2-d;4,5-d']bis[1,3]dithiol. We investigated an array of alternatives to circumvent the problem: (1) alternative thiols (primary, long-chain, tertiary thiols of larger molar mass); (2) exhaust cleaning methods (adsorption, oxidation, conversion to a salt); and (3) thermal exhaust treatment. Only combustion of the fumehood exhaust with domestic gas at 900°C in a regenerative thermal oxidation unit was able to completely prevent the thiol smell from escaping.

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Keywords Exhaust air treatment; 2-methyl-2-propanethiol; odor of thiols; stench; thermal exhaust treatment

INTRODUCTION

Sulfur compounds fulfill key functions in both organisms and technical applications, including medicine. Of the drugs listed in the Merck index (drugs, pesticides, and physiological substances), almost 13% contain one or more sulfur atoms, 40% of which are in sulfidic binding and almost 4% are thiols. Access to most organic sulfur compounds requires a synthetic step with a strong-smelling bivalent sulfur

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species. The sulfur atoms often have to be introduced in the early stages of the synthetic routes, entailing the need to handle large quantities. This severely limits the accessibility of related starting materials and downstream products.

Typical thiols for the introduction of sulfur by nucleophilic substitution are methanethiol, ethanethiol, 2-propanethiol, and 2-methyl-2-propanethiol (t-butylthiol). They smell very unpleasantly and have a very low odor threshold. A mixture of as little as 3.8 mg/m^3 of three of them is added to domestic gas for the perception of leaks. The concentration level results from the requirement that they must be clearly perceived when the gas concentration in the air reaches 0.2 times the lower flammable limit.^[1] The smell will be interpreted as a gas leak even if it stems from their synthetic use.

Alkylthiols like the ones mentioned are key reagents for the synthesis of quite a few sulfur-substituted aromatic systems, for example, the tetraalkylthiobenzenes 9g, 9h, and 2a with methyl, isopropyl, and t-butyl substituents.^[2-11] We needed to prepare large amounts of 1,2,4,5-tetrakis(t-butylthio)benzene (2a) en route to tetramethylbenzo-2,2,6,6-[1,2-d;4,5-d']bis[1,3]dithiol (3). The latter is a basic building blocks for spin labels, that is, stable triarylmethyl (TAM) radicals^[12] tailored for modern pharmaceutical and medical imaging techniques,^[13–15] particularly electron spin resonance (ESR) spectroscopy. TAMs (Scheme 1) are formally derivatives of 1,2,4,5-benzenetetrathiols (10).^[16–18] Their synthesis begins by reacting 1,2,4,5tetrachlorobenzene (1) with an appropriate thiol to yield the respective 1,2,4,5-benzenetetrathioethers 2 or 9,^[19,20] followed by conversion to 3 (Scheme 2). The bivalent sulfur atoms are essential for the stability and ESR properties of the TAMs that are at the end of a multistep synthesis. For the synthesis of the basic building blocks 2 and 9 (which do not pose a particular problem for smell), molar amounts of 2-methyl-2-propanethiol need to be handled, posing a major challenge especially for academic research laboratories. We investigated the following techniques for avoiding thiol odor release: Use of thiols that are less volatile or odoriferous exhaust scrubbing, and exhaust combustion.



Scheme 1. Synthesis of TAM.^[31] Reagents and conditions: (a) Na, DMF, 2-methyl-2-propanethiol; (b) HBF₄ (54% in Et₂O), propane-2-one, toluene; (c) nBuLi (2.5 M in hexanes) 1 equiv. in Et₂O; then 0.3 equiv. of methyl chloroformate; (d) nBuLi (2.5 M in hexanes) and TMEDA 10 equiv, followed by excess DIBOC; and (e) CF₃COOH.



Scheme 2. Synthesis of 2,2,6,6-tetramethylbenzo[1,2-d;4,5-d]bis[1,3]dithiole (3). Reagents and conditions: (a) argon atmosphere, dry DMF, thiol, Na or NaH 60% (w/w) in mineral oil 0 °C, 2–12 h reflux; (b) HBF₄ (54% in Et₂O), propan-2-one, toluene; and (c) Na in NH₃.

RESULTS AND DISCUSSION

Less Volatile or Odoriferous Thiols

An alternative to 2-methyl-2-propanethiol would have to be less odoriferous, be still strongly S-nucleophilic, and bear an alkyl rest removable as a carbenium ion in the second step of the synthetic scheme depicted in Scheme 1. Table 1 lists

Table 1. Tertiary (7) and primary (8) thiols tested for the preparation of the sulfides 2 or 9 and the bis(thioketal) 3

Thiol	R1	R2	R3	Tetrakis(thioalkyl)benzene, ^a isolated yield (%)	3 , ^{<i>b</i>} isolated yield
7a	CH ₃	CH ₃	_	2a, 60	70
7b	C_9H_{19}	CH ₃		2b , — ^e	
7c	C_6H_{13}	CH ₃		2c , $-e^{e}$	
7d ^{<i>c</i>}	C_2H_5	C_2H_5		$2d^{f}$	
$7e^c$	C_3H_7	CH ₃	_	$2e^{f}$	
$7\mathbf{f}^d$	CH ₂ COOH	CH ₃		$2\mathbf{f}^{g}$	
8a		_	$C_{12}H_{25}$	9a , $-e^{e}$	
8b			C ₈ H ₁₇	9b , 85 ^{<i>h</i>}	e
8c			$C_{6}H_{13}$	9c , 80 ^h	e
8d			CH ₂ COOH	9d , $-i$	
8e			$CH_2C_6H_5$	9e , — ^{<i>i</i>}	
8f			CH ₂ C ₆ H ₄ OCH ₃	9 f, — ^{<i>i</i>}	
8g			CH ₃	$9g^{i}$	
8h	_		$CH(CH_3)_2$	9h ^{<i>i</i>}	_

^aScheme 2, method a.

^bScheme 2, method b.

^cSynthesis according to Ref. 22.

^dSynthesis according to Ref. 23.

^eUn-identifiable product mixture.

^fNot synthesized, thiol smell much too storng.

^gNot synthesized, thiol insoluble in toluene.

^hSynthesis according to Ref. 31.

'Incomplete substitution.

Not synthesized.

the thiols and alternative paths tested. In summary, (a) thiols with an alkyl chain of less than six carbon atoms are too strong smelling because of their low volatility. (b) Primary S-alkyl chains of whatever length were not transferable to toluene in the next step (Scheme 2). (c) To circumvent this step, but still use a long-chain, primary thiol, the preparation of 1,2,4,5-benzenetetrathiol (10) was attempted by reduction of various alkylarylsulfides with sodium in liquid ammonia.^[19] The alkylarylsulfides 2b, 2c, and 9a proved to be greasy materials that could not be extracted from the reaction mixtures. The sulfides 9b and 9c were isolable; however, they failed to be converted to 3 (Scheme 2, *f*) via 10. Judging from the physical properties of the reaction mixtures, 10 polymerized faster than it did react with 2-propanone. (d) The tertiary thiols 7d and 7e were prepared following published procedures.^[21,22] Though their smell did not suggest gas leakages, even their salts presented no improvement odorwise. Compound 7f^[23] could not be used because it was insoluble in toluene. Thiols 8d–f gave only incomplete substitution.

All alternative thiols either were no improvement over 2-methyl-2-propanethiol or yielded ill-defined reaction mixtures or products that were unsuitable for the next steps on the way to TAM radicals.

Exhaust Cleaning

The synthetic pathway depicted in Scheme 1, especially step a, necessitated a discontinued operational mode with strongly varying concentrations of substances in the exhaust air over time. The exhaust cleaning could not be guided by information on concentrations and changes over time. The total exhaust airstream to be cleaned was unknown. As is often the case in academic laboratories, for technical and financial considerations neither the temporary installation of an external pilot plant nor an exhaust air-cleaning plant within the building were possible. The parameters known for exhaust air cleaning were the following: carrying gas, air from a standard laboratory fumehood; standard air parameters (emission temperature 20-30 °C; 45-60% relative humidity); and no superimposed foreign matter, only components stemming from the process itself. The component to be separated primarily was 2-methyl-2-propanethiol. Its residual concentration before release of the exhaust air to the environment was defined as maximum of 0.01 mg/m^3 . In Germany, the Technische Regel G 280-1 "Gas odoration"^[1] demands a minimum concentration of gas odorant thiols of 0.03 mg/m^3 so that even people with a weakly developed olfactory sense are sure to notice the thiol smell in the air. Other exhaust air components of considerable concentrations were N,N-dimethylformamide, 1,2,4,5-tetrachlorobenzene, and reaction intermediates. According to technical rules on air pollution, they needed to be reduced to a maximum of $20 \text{ mg C}_{ges}/m^3$ in the washed exhaust air. The following preliminary experiments were undertaken. They did not lead to the basically required drop of the thiol concentration below the odor threshold. Their short description highlights the limits set by the local conditions and indicates what would have to be done to perhaps reach the goal by exhaust air cleaning. The main problem is that it would not be sufficient to absorb the odoriferous exhausts from the reactor. Most of the 2-methyl-2-propanethiol (or related thiol reagent) is set free during workup which includes long suction filtration of the reaction mixture after pouring onto ice. This (typical) workup necessitates cleaning all the fumehood air. Researchers who did related reactions in laboratory gloveboxes were not able to prevent the odor from escaping into the neighborhoods.^[24]

Adsorption. As adsorbents, two different pelletized active charcoal brands were used in a reactor tube of approximately 700 mm filling length and a diameter of approximately 50 mm. The reactor tube received the exhaust volatile material of the synthetic process. With an average bulk density of $300-400 \text{ kg/m}^3$, it contained approximately 500 g of active charcoal. If conditions for adsorption were ideal, (flow rate; 4:1 ratio of height and length of the filling; transport mechanisms of heat and materials; levels of temperature, humidity and partial pressures; no displacement processes and co-adsorption of water; etc.), and with a maximum load capacity of 20% by weight, up to 100 g of noxious substances could be adsorbed. In reality, a laboratory fumehood setup, with a minimum amount of exhaust air of 150 Nm³/h and a flow rate of at least 21 m/s resulted. In comparison with the theoretical optimum of 1 m/s, the adsorber will be overrun massively, leading to too short contact times.

An elaborate method for the determination of smell is described in technical rules.^[25] It was not carried out because the very strong and characteristic smell of the thiol allowed for subjective assessment of the released air. Over the whole time, the odor of the exhaust air was dominated by the typical thiol note. So even if the adsorber held back most of the material, the necessary effect—no odor at all—was not attained. It was therefore considered unnecessary to determine the exact amount adsorbed.

Scrubbing. In addition to the active charcoal adsober (see previous paragraph), two washing bottles were added before the adsorber, containing 500 ml of washing solution each. The exhaust air was introduced, finely divided by way of a glass sinter frit, using a standard method for the determination of gaseous harmful substances.^[26]

Oxidation. This aimed at destroying the thiol by oxidation with potassium permanganate (4%) or hydrogen peroxide (3%). Again, two washing flasks were arranged in series between the reaction flask and charcoal adsorber.

Salt formation. An aqueous sodium hydroxide solution (20%) was supposed to absorb the thiol by conversion to its nonvolatile sodium salt.

In all cases, the concentration of the thiol remained above the odor threshold. Concerning oxidation, this is partly connected with the well-known fact that tertiary thiols are very resistant oxidation.^[27] Since the experimental setup enforces a discontinuous gas flow and accompanying release of the odor, optimal conditions for gas washing could not be achieved, that is, very small flow rates with long contact times in the washing media and very large surface for interaction due to an optimal surface-to-volume ratio of the bubbles.

It was concluded that the relative chemical inertness of the thiol in connection with its very low odor threshold and the large (molar) amounts render exhaust air scrubbing and adsorption unsuitable under the (in terms of exhaust air purification) inadequate local conditions. **Thermal exhaust air treatment.** With the high amount of sulfur compounds and discontinued release of all components in the exhaust air, a process at lower temperatures supported by catalysts was not considered.

We resorted to a thermal exhaust air treatment on site of LTB (Luft- und Thermotechnik Bayreuth GmbH & Co. KG), Germany. This proved to be the most economical, fastest, most functional, and safest solution. The complete exhaust air from the fumehood the reaction was run under was transferred to a thermal after-burning unit. This was almost unaffected by fast and pronounced fluctuations of the noxious components, mode of operation (batch or continuous), and the composition of the exhaust air. There were almost no negative influences on air combustion through interactions of components, no displacement processes as in adsorption, etc. What needed to be taken into account were rules to explosion prevention and emission limits (e.g., for dioxines, furanes, aerosoles, total carbon).^[28] The physical and chemical properties of 2-methyl-2-propanethiol and other exhaust air components further suggested thermal after-burning to be the method of choice: all components had carbon skeletons; for 2-methyl-2-propanethiol the burning point was -24° C and ignition point, was 225° C. In an on-site (LTB) standard fumehood, the synthesis, workup, isolation, and preliminary purification of the target product were performed (2a, Scheme 2). The fumehood was connected to a regenerative thermal oxidation (RTO) unit so that the main ventilator of the RTO constantly created a flow rate from the fumehood set to 900 Nm³/h. This high (in relation to the fumehood and process size) flow rate was chosen to prevent any leakage of 2-methyl-2-propanethiol from the hood. Through another suction port, the RTO could have been fed with fresh air to dilute the air from the hood before combustion. This would have been necessary if the RTO exhaust would have smelled for the thiol or if the immission limit had exceeded 25% of the lower explosion limit.^[29] Both cases did not occur. The temperature in the combustion chamber was optimized so that the combustion of the starting material, 1,2,4,5-tetrachlorbenzene, would not lead to the formation of more dioxine than allowed. The times for opening and closing the valves for the crude gas flow and flushing had to be adjusted to the synthetic process. Because no thiol odor was detected, further exhaust air analyses were not undertaken.

In conclusion, exhaust air after-burning proved to be a successful way of working with an extremely malodorous substance that otherwise could not have been used in large quantities in the framework of academic research. The RTO unit used was mobile and for lease and can be set up next to a lab building. Even smaller units, suitable to be taken inside laboratories, could be manufactured.

EXPERIMENTAL

Full experimental details for the syntheses are provided in the Supplementary Material, available online, including NMR spectra and characterization data.

A Roxitherm RTO units, manufactured by Luft- und Thermotechnik Bayreuth GmbH & Co. KG, Goldkronach, Germany, was used.

Roxitherm from LTB is based on the thermal oxidation process with regenerative heat recovery to transform organic materials to the oxides of the respective elements. The energy required to preheat emission gasses is more than 90% regeneratively recovered. The exhaust air is transported into one of three chambers. After preheating by heat exchange to $800 \,^{\circ}$ C, it is led into the next chamber by way of the burner compartment. On its way to the RTO exhaust, it preheats the heat exchangers. With each cycle, the gas enters one of the three chambers and is led out by the neighboring one, with a detention period of 2 min per chamber and a purging time of approximatley 40 s for the third chamber. The purged gas is fed into the main exhaust gas flow for oxidation. In a typical repeat cycle, the chambers consecutively hold contaminated gas, decontaminated gas, and gas for purging.

Scale was 1.5 (for maximum volume flow of 1500 Nm³/h). Volume flow during synthesis and workup was 900 Nm³/h. Combustion medium was air oxygen with domestic gas. Domestic gas flow was 9.0 m^3 /h. Temperature of combustion chamber was 900 °C. Connection power was 11 kW. Floor space (length × breadth × height) was 7000 × 2500 × 3500 mm.

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