The First Stable Aromatic *S*-Nitrosothiol: Synthesis, Structure and Reactivity

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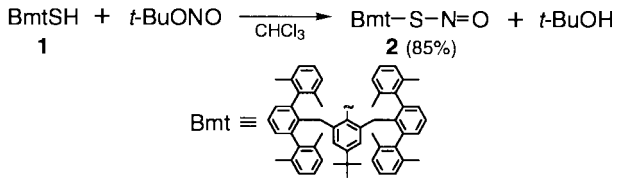
The first stable aromatic *S*-nitrosothiol, *S*-nitroso-4-*t*-butyl-2,6-bis[(2,2",6,6"-tetramethyl-*m*-terphenyl-2'-yl)methyl]benzenethiol, was synthesized by the nitrosation of the corresponding thiol and the structure was established by X-ray crystallography. Its oxidation and reactions with some nucleophiles were carried out.

Nitrites (R–O–N=O) are stable compounds and their chemistry is well established. By contrast *S*-nitrosothiols (R–S–N=O) are far less stable because of a weak S–N bond. *S*–Nitrosothiols have been of current interest since they are a precursor of nitric oxide, NO, which has a variety of important biological activities.[1] However, *S*-nitrosothiols are usually quite unstable, although some stable aliphatic *S*-nitrosothiols have been isolated[2–4] and are used for studies on biological activities of NO. No stable aromatic *S*-nitrosothiols have been reported so far most likely because thiolate or thiyl radical formed in their reactions is stabilized by delocalization due to an aromatic ring attached to it and hence decomposition is accelerated.

We have been interested in the synthesis of highly reactive species by kinetic stabilization.[5] We here report the synthesis, X-ray crystallographic analysis, and some reactions of the first stable aromatic *S*-nitrosothiols.[6,7]

Reaction of 4-*t*-butyl-2,6-bis[(2,2",6,6"-tetramethyl-*m*-terphenyl-2'-yl)methyl]benzenethiol, (BmtSH, **1**)[8] (502 mg, 0.658 mmol) with *t*-butyl nitrite (94 μL, 0.79 mmol) in chloroform (20 mL) at room temperature for 20 min gave the corresponding *S*-nitrosothiol (Bmt–S–N=O, **2**) (497 mg, 85%) as deep green crystals after reprecipitation from dichloromethane–ethanol.[9]



The structure of **2** was definitively established X-ray crystallography (Figure 1).[10] The SNO group is almost perpendicular to the benzene ring attached to it and adopts a syn configuration with regards to the S–N bond. While *S*-nitroso-DL-penicillamine (SNAP)[2] and Ph_3CSNO[3] adopt anti conformation with regards to the S–N bond, TrmSNO[11] exists as a mixture of the anti and syn isomers. It has been reported that also in a nitrite, R–O–N=O, a syn conformation with regards to the N–O bond is more stable than an anti conformer.[12] The bond lengths of N–O, S–N, and C–S in the C–S–N=O group of **2** are 1.204, 1.804, and 1.770 Å, respectively. It should be noted that the C–S bond length (1.770 Å,) is considerably shorter than those reported for SNAP (1.842 Å,), Ph_3CSNO (1.867 Å,) and TrmSNO (1.841 Å,) although the N–O and S–N bond lengths are similar to those for these aliphatic ones (1.206 and 1.762 Å, for SNAP,2 1.177 and 1.792 Å, for Ph_3CSNO,[3] and 1.205 (anti), 1.189 (syn) and 1.781 Å, for TrmSNO).[11]

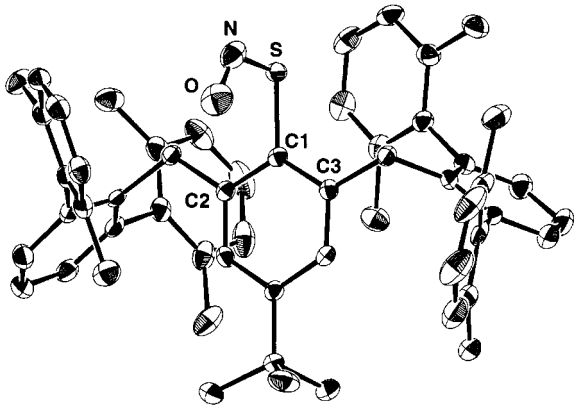
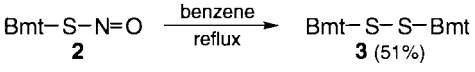


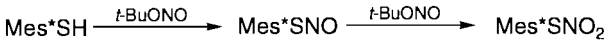
Figure 1. ORTEP drawing of **2**·2(CH_2Cl_2) with thermal ellipsoids (50% probability). Two CH_2Cl_2 molecules and hydrogen atoms are omitted for clarity. Selected bond lengths (Å), bond angles (deg), and torsion angles (deg): C1-S 1.770(3), S-N 1.804(3), N-O 1.204(4), C1-S-N 101.1(1), S-N-O 117.8(2), C1-S-N-O 1.1(3), N-S-C1-C2 85.5(2), N-S-C1-C3 –92.2(2).

It is known that aromatic *S*-nitrosothiols rapidly decompose to give the corresponding disulfide and NO.[13,14] For example, the half-life times of ArSNO (Ar = phenyl, *p*-methoxyphenyl, *p*-nitrophenyl, 3,5-di-*t*-butyl-4-phenyl) are 7–14 min in a dichloromethane solution at room temperature.[14] *S*-Nitrosothiol **2**, however, was quite stable. NMR monitoring indicated that no reaction took place in benzene-d_6 at 50 °C for 12 h, and the decomposition was completed in refluxing benzene for 75 h to give the corresponding disulfide **3** (51%). In view of the proposed thermolysis mechanism[1c] where the decomposition involves bimolecular reaction of an initially formed thiyl radical with a second molecule of *S*-nitrosothiol, the thermal stability of **2** suggests that the Bmt group is very effective in suppressing such type of bimolecular induced decomposition.

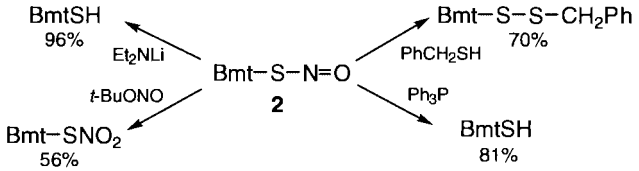


In order to know the efficiency of the Bmt group, we also synthesized *S*-nitrosothiol Mes*SNO (Mes* denotes 2,4,6-tri-*t*-butylphenyl) bearing another bulky aromatic substituent. The

reaction of thiol Mes*SH with *t*-butyl nitrite (1.1 equiv) in the presence of excess trifluoroacetic acid gave Mes*SNO (47%).[15] Mes*SNO was found to be much less stable than BmtSNO **2** and difficult to be obtained as pure specimen because of its facile further reaction with *t*-butyl nitrite giving the corresponding *S*-nitrothiol Mes*SNO_2. Mes*SNO was completely decomposed after 48 h at room temperature in chloroform, indicating that the stabilization by Bmt group is much more effective than that by Mes*.



We have already reported that Bmt group is very useful in stabilizing highly reactive functional groups such as BmtSOH, BmtSeOH, and BmtSI which decompose via a bimolecular mechanism while the intrinsic high reactivity of such functional groups with relatively small molecules is retained.[5a] Also in the case of *S*-nitrosothiol **2**, in spite of its high stability, it undergoes some reactions as shown in Scheme 1.[16]



Scheme 1.

The reaction with α-toluenethiol gave unsymmetric disulfide $BmtSSCH_2Ph$, while the reaction of triphenylphosphine and lithium diethylamide afforded thiol BmtSH **1**. Less reactive nitrogen nucleophiles such as *N*-methylaniline and diethylamine did not react with **2**. Oxidation of **2** with *t*-butyl nitrite gave *S*-nitrothiol, $BmtSNO_2$. The nitrothiol is quite stable in contrast to the reported instability of simple aromatic nitrothiols such as *p*-$XC_6H_4SNO_2$ (X = Cl, Br, CH_3) which decompose rapidly at room temperature.[1a] The reaction of $BmtSNO_2$ (for 5 min in chloroform) with triphenylphosphine gave *S*-nitrosothiol **2** in 94%, providing an alternative synthetic approach to **2**.

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Dedicated to Professor Hideki Sakurai on the occasion of his 70th birthday.

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9 **2**: mp 114 °C (dec); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9H), 1.87 (s, 24H), 2.99 (s, 4H), 6.60 (s, 2H), 6.81 (d, J = 7.6 Hz, 8H), 6.93–7.00 (m, 8H), 7.30 (t, J = 7.7 Hz, 2H). UV–vis (hexane) λ_{max} 372 (ε 320), 530 (26), 572 (68) nm. Found; C, 84.68; H, 7.15; N, 1.74; S, 4.11%. Calcd for $C_{56}H_{57}NOS$: C, 84.91; H, 7.25; N, 1.77; S, 4.05%.

10 Crystal data for **2**·2(CH_2Cl_2): Formula $C_{56}H_{57}NOS$·2(CH_2Cl_2), fw = 961.94, monoclinic, space group $P2_1/n$ (#14), Z = 4, a = 12.490(2) Å, b = 20.959(3) Å, c = 20.338(2) Å, β = 102.970(1)°, V = 5188(1) Å^3, D_{calcd} = 1.232 g/cm^3, μ = 3.08 cm^{-1}, $2\theta_{max}$ = 50.0°, T = 93 K, R_1 ($I > 2\sigma(I)$)= 0.0684, wR_2 (all data) = 0.1975, GOF = 1.042 for 9076 reflections and 607 parameters.

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15 Mes*SNO: red brick crystals; ^{1}H NMR δ 1.20 (s, 18H), 1.38 (s, 9H), 7.55 (s, 2H). Found; C, 66.42; H, 8.87; N, 4.33; S, 10.05%. Calcd for $C_{18}H_{29}NOS$: C, 70.31; H, 9.51; N, 4.55; S, 10.68%.

16 Reaction conditions (solvent, reaction temperature, reaction time) were as follows: 1) $PhCH_2SH$; $CHCl_3$, r.t., 21 h, 2) Et_2NLi; TMF, 0 °C, 5 min, 3) Ph_3P; $CHCl_3$, r.t., 2.5 h, 4) *t*-BuONO; $CHCl_3$, r.t., 1 h.