Modeling of the Bioactivation of an Organic Nitrate by a Thiol to Form a Thionitrate Intermediate

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Abstract: Thionitrates (R–SNO 2 ) have been proposed as key intermediates in the biotransformation of organic nitrates that have been used for the clinical treatment of angina pectoris for over 100 years. It has been proposed and widely accepted that a thiol would react with an organic nitrate to afford a thionitrate intermediate. However, there has been no example of an experimental demonstration of this elementary chemical process in organic systems. Herein, we report that aryl- and primary-alkyl-substituted thionitrates were successfully synthesized by the reaction of the corresponding lithium thiolates with organic nitrates by taking advantage of cavity-shaped substituents. The structure of a primary-alkyl-substituted thionitrate was unambiguously established by X-ray crystallographic analysis.

Keywords: thionitrates; reactive intermediates; kinetic stabilization; organic nitrates; nitric oxide; biotransformation; X-ray crystallographic analysis

1. Introduction

Organic nitrates such as nitroglycerin and isosorbide-5-mononitrate, have been widely used for the treatment of angina pectoris and congestive heart failure since the first clinical application of nitroglycerin in the late 19th century. They are regarded as nitric oxide (NO) prodrugs, and it has been assumed that they are converted to NO or an NO congener, which leads to vasorelaxation [1–4]. Although the mechanism of biotransformation of organic nitrates is still not fully understood, the potential chemical mechanism is a thiol-dependent pathway, for which several reaction pathways have been proposed as shown in Scheme 1 [5,6]. Importantly, all of them have the same first step in common, i.e., the formation of a thionitrate by the reaction of a cysteine thiol (Cys-SH) in protein with an organic nitrate. However, very little chemical evidence has been available for this elementary chemical transformation [7,8]. Recently, a thionitrate intermediate, which was formed in the active site of aldehyde dehydrogenase-2 by soaking with nitroglycerin, has been observed by protein X-ray crystallographic analysis and also detected by mass spectrometry [9]. In the artificial systems, thionitrates are highly reactive species and easily undergo bimolecular decomposition (Scheme 2) [10–12]. Hence, model studies on the chemical processes involving R–SNO 2 have been difficult and scarcely investigated [12–14].
In the course of our studies on biologically relevant highly reactive species containing sulfur and selenium, we have developed various cavity-shaped substituents and demonstrated that these substituents are very effective for kinetic stabilization of highly reactive species that otherwise undergo facile bimolecular decomposition [13–22]. Herein, we report a model study on the bioactivation of an organic nitrate by a thiol, which is the fundamental chemical process in the thiol-dependent biotransformation of nitrates. By taking advantage of the cavity-shaped aromatic and primary-alkyl substituents (Figure 1), denoted as Bpq and BpqCH₂, respectively, we demonstrated that thionitrates are formed by the reaction of the corresponding thiolates with organic nitrates. The first crystallographic analysis of a primary-alkyl-substituted thionitrate is also presented.

![Scheme 1. Proposed thiol-dependent pathways of biotransformation of organic nitrates.](image)

Scheme 2. Bimolecular decomposition of thionitrates.

In the course of our studies on biologically relevant highly reactive species containing sulfur and selenium, we have developed various cavity-shaped substituents and demonstrated that these substituents are very effective for kinetic stabilization of highly reactive species that otherwise undergo facile bimolecular decomposition [13–22]. Herein, we report a model study on the bioactivation of an organic nitrate by a thiol, which is the fundamental chemical process in the thiol-dependent biotransformation of nitrates. By taking advantage of the cavity-shaped aromatic and primary-alkyl substituents (Figure 1), denoted as Bpq and BpqCH₂, respectively, we demonstrated that thionitrates are formed by the reaction of the corresponding thiolates with organic nitrates. The first crystallographic analysis of a primary-alkyl-substituted thionitrate is also presented.

![Scheme 2. Bimolecular decomposition of thionitrates.](image)

2. Results and Discussion

Several stable thionitrates have been synthesized and isolated by taking advantage of kinetic stabilization utilizing appropriate bulky substituents such as tertiary alkyl groups [10,11,16] and cavity-shaped aromatic groups [17,23]. We previously reported the synthesis of a stable aryl thionitrate, BpqSNO₂ (I), by the reaction of the corresponding S-nitrosothiol with an excess amount of t-BuONO or N₂O₄ [17]. Thus, we first employed the Bpq group for a model study on the bioactivation of organic nitrates. Treatment of thiol 2 bearing a Bpq group with an excess amount of isoamyl nitrate in C₆D₆ resulted in no reaction (Scheme 3). To increase the nucleophilicity of the sulfur, 2 was deprotonated with n-BuLi to generate lithium thiolate 3, which was then allowed to react with an excess amount of isoamyl nitrate in benzene. This reaction sequence successfully afforded thionitrate 1 (64%) together with thiol 2 (36%). This is the first experimental demonstration of the formation of a thionitrate by the reaction of a thiolate with an organic nitrate.

![Figure 1. Molecular cavities utilized for the present model study.](image)
As a model compound for naturally occurring cysteine-derived thionitrites (Cys-SNO2), a primary-alkyl-substituted thionitrate is considered to be the most relevant. However, the steric demands of usual primary-alkyl groups are too small to protect such reactive species, and there has been no example of the synthesis of a thionitrate bearing a primary-alkyl group. Meanwhile, we have recently developed an effective primary-alkyl steric protection group, a BpqCH2 group (Figure 1), with a cavity-shaped framework and succeeded in the isolation of reactive species such as a sulfenic acid [18], a sulfenyl iodide [19], a selenenic acid [20], and a selenenyl iodide [21] by utilizing this substituent. Thus, a model study by utilizing the BpqCH2 group was examined. When lithium thiolate 5, prepared by the reaction of BpqCH2SH (4) with n-BuLi, was treated with an excess amount of isomyl nitrate in benzene, the corresponding thionitrate 6 was formed almost quantitatively and isolated as stable colorless crystals in 74% yield after recrystallization (Scheme 4). Characterization of 6 was performed by NMR and IR spectroscopies and elemental analysis. In the IR spectrum of 6, asymmetric and symmetric NO2 vibrational bands were observed at 1531 and 1297 cm⁻¹, respectively, which are almost identical to those of tertiary-alkyl-substituted thionitrites [16]. The 1H-NMR spectrum of 6 exhibited a singlet due to the methylene protons in the CH2SNO2 moiety at 5.10 ppm, which is shifted downfield by more than 1 ppm relative to that of thiol 4 (3.91 ppm). In the 13C-NMR spectrum of 6, the methylene carbon resonates at 41.3 ppm, which is also shifted downfield in comparison with 4 (30.5 ppm). The reaction of thiolate 5 with isosorbide-5-mononitrate (ISMN), which is widely used as a drug in treatment of angina pectoris, also afforded thionitrate 6 (Scheme 5), albeit in low yield (4%). Since thiol 4 was recovered in 95% yield in this reaction, it is probable that most of 5 was protonated and deactivated by the OH group in ISMN, resulting in the low yield of 6.

Scheme 3. Reactions of thiol 2 with isoamyl nitrate.

Scheme 4. Synthesis of thionitrate 6 by the reaction of thiolate 5 with isoamyl nitrate.

Scheme 5. Formation of 6 by the reaction of thiolate 5 with ISMN.

The structure of 6 was unambiguously established by X-ray crystallographic analysis (Figure 2), presenting the first example of the crystallographic analysis of a primary-alkyl-substituted thionitrate.
The CH₂SNO₂ moiety is incorporated within the cavity and effectively protected from the bimolecular decomposition by the peripheral moiety of the substituent. Selected structural parameters of 6 are summarized in Table 1, together with those of the aryl-substituted thionitrate 1 [14] and the tertiary-alkyl-substituted thionitrate 7 [16] reported by us as well as those of the aryl derivative 8 [24] reported by Itoh et al. In the crystalline state, 6 features disorder of the SNO₂ moiety with respect to a mirror plane perpendicular to the central benzene ring in the ratio of 0.8:0.2, both of which possess a similar structure. The structural parameters of the major component are discussed in the following. The CH₂SNO₂ moiety is well incorporated within the cavity of the Bpq group. The C=S–N–O dihedral angles are 4.8(5)° and −176.0(4)°, showing that the C–SNO₂ moiety is almost coplanar. The C–S bond length (1.803(3) Å) in 6 is slightly longer than those in the aromatic derivatives 1 (1.7651(15) Å) and 8 (1.764(2) Å) and similar to that of the tertiary-alkyl derivative 7 (1.789(6) Å). The C–S–N bond angles of 6 (100.5(2)°) are similar to those of 1 (100.47(7)°) and 8 (99.75(10)°) yet much smaller than that of 7 (107.9(5)°). The enlargement of the C–S–N bond angle was observed only in 7, which is probably due to the steric repulsion between the SNO₂ moiety and m-terphenyl groups. The structure of the primary-alkyl-substituted compound 6 shown here is expected to serve as reference data for X-ray crystallographic analysis of protein–SNO₂.

Table 1. Selected bond lengths and angles for thionitrate.

| Bond lengths (Å) | 6 (this work) | 1 [14] | 7 [16] | 8 [24] |
|------------------|---------------|--------|--------|--------|
| S(1)–N(1)        | 1.780 (6)     | 1.7898 (17) | 1.746 (9) | 1.795 (2) |
| N(1)–O(1)        | 1.205 (8)     | 1.2180 (19) | 1.229 (9) | 1.215 (3) |
| N(1)–O(2)        | 1.211 (6)     | 1.213 (2)   | 1.239 (9) | 1.228 (3) |
| C(1)–S(1)        | 1.803 (3)     | 1.7651 (15) | 1.789 (6) | 1.764 (2) |
| Bond angles (°)  |               |         |        |        |
| S(1)–N(1)–O(1)   | 121.7 (4)     | 120.25 (12) | 114.1 (9) | 121.19 (17) |
| S(1)–N(1)–O(2)   | 114.1 (9)     | 113.28 (13) | 119.7 (9) | 113.48 (18) |
| O(1)–N(1)–O(2)   | 124.00 (57)   | 126.44 (17) | 126.2 (11) | 125.3 (2) |
| C(1)–S(1)–N(1)   | 100.5 (2)     | 100.47 (7)  | 107.9 (5) | 99.75 (10) |

Figure 2. Oak Ridge thermal ellipsoid plot (ORTEP) drawing of 6 (50% probability).
3. Materials and Methods

Unless otherwise stated, all operations were performed in an MBraun UNIlab glovebox an argon atmosphere, in a Miwa 1ADB-3KTG glovebox under an argon atmosphere, or by using high-vacuum and standard Schlenk techniques under an argon atmosphere. Benzene (anhydrous) was purchased from Kanto Chemical (Tokyo, Japan) and distilled from benzophenone ketyl prior to use. Other chemicals were purchased from commercial sources and used as received. \(^1\)H-NMR spectra were recorded on a JEOL ECX-500, a JEOL ECX-400, or a JEOL ECS-400 spectrometer (JEOL, Tokyo, Japan), and the chemical shifts of \(^1\)H are referenced to the residual proton signal of CDCl\(_3\) (δ 7.25). \(^{13}\)C-NMR spectra were recorded on a JEOL ECX-500 or a JEOL ECX-400 spectrometer (JEOL, Tokyo, Japan), and the chemical shifts of \(^{13}\)C are referenced to the signal of CDCl\(_3\) (δ 77.0). All spectra were assigned with the aid of DEPT (distortionless enhancement by polarization transfer), COSY (correlated spectroscopy), HMQC (heteronuclear multi quantum correlation), and HMBC (heteronuclear multiple bond correlation) NMR experiments. IR spectra were recorded on a JASCO FT/IR-4100 (JASCO, Tokyo, Japan) by utilizing a JASCO ATR Pro550S unit. Melting points were measured with a Yanaco MP-S3 (Yanaco, Tokyo, Japan) and are uncorrected.

3.1. The Reaction of Thiol \(\mathbf{2}\) with Isoamyl Nitrate

To a solution of thiol \(\mathbf{2}\) (3.5 mg, 3.9 \(\mu\)mol) in \(\text{C}_6\text{D}_6\) (0.6 mL) was added isoamyl nitrate (30 \(\mu\)L, 0.23 mmol) at ambient temperature. The reaction was monitored by \(^1\)H-NMR spectroscopy in a screw-capped NMR tube, and no reaction was observed for 2 h.

3.2. Synthesis of Thionitrate \(\mathbf{1}\)

\(n\)-BuLi (1.6 mol/L in hexane, 0.30 mL, 0.48 mmol) was diluted with benzene (3 mL). To a solution of thiol \(\mathbf{2}\) (18.3 mg, 20 \(\mu\)mol) in benzene (6 mL) was added the diluted \(n\)-BuLi solution (0.15 mL, 22 \(\mu\)mol). The reaction mixture was stirred for 30 min at ambient temperature, and then isoamyl nitrate (30 \(\mu\)L, 0.23 mmol) was added at ambient temperature. After 10 min, the solvent was removed in vacuo, and the residue was washed with hexane to afford the mixture of thionitrate \(\mathbf{1}\) and thiol \(\mathbf{2}\). The yields of \(\mathbf{1}\) and \(\mathbf{2}\) were estimated to be 64% and 36%, respectively, by \(^1\)H-NMR spectroscopy.

3.3. Synthesis of Thionitrate \(\mathbf{6}\)

In a glovebox under an argon atmosphere, to a solution of thiol \(\mathbf{4}\) (20.3 mg, 22.1 \(\mu\)mol) in benzene (6.6 mL) in a Schlenk flask with a J-young valve was added \(n\)-BuLi (56 mM in hexane, 434 \(\mu\)L, 24 \(\mu\)mol) at ambient temperature. After 1 h, the flask was carefully sealed and transferred to a glovebox under a nitrogen atmosphere. To the reaction mixture was added isoamyl nitrate (27 \(\mu\)L, 0.20 mmol) at ambient temperature. After 30 min, the resulting yellow solution was evaporated in vacuo, followed by recrystallization from hexane to afford \(\mathbf{6}\) (14.2 mg, 16 \(\mu\)mol, 74%) as colorless crystals.

\(\mathbf{6}\): colorless crystals; mp 203.5–204.4 °C (dec); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) δ 1.07 (d, \(J = 6.9\) Hz, 24H), 1.13 (d, \(J = 6.9\) Hz, 24H), 2.80 (sept, \(J = 6.9\) Hz, 8H), 5.10 (s, 2H), 7.06 (t, \(J = 1.5\) Hz, 2H), 7.14–7.22 (m, 12H), 7.27–7.50 (m, 7H); \(^{13}\)C-NMR (126 MHz, CDCl\(_3\)) δ 24.0 (q), 24.1 (q), 30.6 (d), 41.3 (t), 122.5 (d), 128.0 (d), 128.4 (d), 128.6 (d), 129.8 (d), 130.5 (d), 138.5 (s), 141.1 (s), 143.9 (s), 146.67 (s), 146.72 (s); IR (ATR) \(\nu\) 1531 cm\(^{-1}\) (asym-NO\(_2\)), 1297 cm\(^{-1}\) (sym-NO\(_2\)). Anal. Calcd for C\(_{67}\)H\(_{79}\)NOS: C, 83.61; H, 8.27; N, 1.46; S, 3.33. Found: C, 83.37; H, 8.38; N, 1.33; S, 3.20.

3.4. Formation of \(\mathbf{6}\) by the Reaction with Isosorbide-5-Mononitrate (ISMN)

In a glovebox under an argon atmosphere, to a solution of thiol \(\mathbf{4}\) (18.5 mg, 20.2 \(\mu\)mol) in benzene (6 mL) in a Schlenk flask with a J-young valve was added \(n\)-BuLi (56 mM in hexane, 436 \(\mu\)L, 24 \(\mu\)mol) at ambient temperature. After 1 h, the flask was carefully sealed and transferred to a glovebox under a nitrogen atmosphere. To the reaction mixture was added a solution of ISMN (4.3 mg, 22 \(\mu\)mol) in
benzene (1 mL) at ambient temperature. After 30 min, the reaction mixture was evaporated in vacuo. The $^1$H-NMR analysis of the crude mixture confirmed the formation of 6 (4%) together with 4 (95%).

3.5. X-Ray Crystallography

Single crystals of 6·1.5CHCl$_3$ were grown in their hexane-CHCl$_3$ solution. A colorless crystal of 6·1.5CHCl$_3$ was mounted on a loop. All measurements were made on a Rigaku/MSC Mercury CCD (Charge Coupled Device) diffractometer (Rigaku, Tokyo, Japan) with graphite-monochromated Mo-K$_\alpha$ radiation ($\lambda = 0.71070$ Å) at –153 °C. The structures were solved by the direct method and refined by full-matrix least squares on $F^2$ using SHELXL 97 [25]. Crystal Data for 6·1.5CHCl$_3$ ($M = 1141.42$ g/mol): triclinic, space group $P\overline{1}$, $a = 11.6005(15)$ Å, $b = 15.8742(14)$ Å, $c = 18.923(2)$ Å, $\alpha = 99.399(3)^\circ$, $\beta = 105.607(4)^\circ$, $\gamma = 100.004(3)^\circ$, $V = 3223.0(6)$ Å$^3$, $Z = 2$, $D_{calc} = 1.176$ g/cm$^3$, 20857 reflections measured, 11040 unique ($R_{int} = 0.0148$). The final $R_1$ was 0.0941 ($I > 2\sigma(I)$) and $wR_2$ was 0.2475 (all data). CCDC 1518311 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk)

4. Conclusions

Formation of a thionitrate by the reaction of a thiolate with an organic nitrate was experimentally demonstrated for the first time by taking advantage of molecular cavities. The X-ray crystallographic analysis of a primary-alkyl-substituted thionitrate was also established. The present results provide chemical corroboration to the formation of a thionitrate intermediate proposed for the first step in the thiol-mediated bioactivation of an organic nitrate, which has long been suggested but not evidenced. Further investigations on the modeling of the bioactivation processes of organic nitrates are currently in progress.

**Supplementary Materials:** The following are available online at http://www.mdpi.com/1420-3049/22/1/19/s1.

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**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Fung, H.L. Biochemical mechanism of nitroglycerin action and tolerance: Is this old mystery solved? *Ann. Rev. Pharmacol. Toxicol.* 2004, 44, 67–85. [CrossRef] [PubMed]
2. Chen, Z.Q.; Stamler, J.S. Bioactivation of nitroglycerin by the mitochondrial aldehyde dehydrogenase. *Trends Cardiovasc. Med.* 2006, 16, 259–265. [CrossRef] [PubMed]
3. Mayer, B.; Beretta, M. The enigma of nitroglycerin bioactivation and nitrate tolerance: News, views and troubles. *Br. J. Pharmacol.* 2008, 155, 170–184. [CrossRef] [PubMed]
4. Daiber, A.; Münzel, T. Organic nitrate therapy, nitrate tolerance, and nitrate-induced endothelial dysfunction: emphasis on redox biology and oxidative stress. *Antioxid. Redox Signaling* 2015, 23, 899–942. [CrossRef] [PubMed]
5. Thatcher, R.G.J.; Weldon, H. NO problem for nitroglycerin: Organic nitrate chemistry and therapy. *Chem. Soc. Rev.* 1998, 27, 331–337. [CrossRef]
6. Wenzl, M.V.; Beretta, M.; Griesberger, M.; Russwurm, M.; Koessling, D.; Schmidt, K.; Mayer, B.; Gorren, A.C.F. Site-directed mutagenesis of aldehyde dehydrogenase-2 suggests three distinct pathways of nitroglycerin biotransformation. *Mol. Pharmacol.* 2011, 80, 258–266. [CrossRef] [PubMed]
7. Yeates, R.A.; Laufen, H.; Leitold, M. The reaction between organic nitrates and sulfhydryl compounds. A possible model system for the activation of organic nitrates. *Mol. Pharmacol.* **1985**, *28*, 555–559. [PubMed]

8. Yeates, R.A. Possible mechanism of activation of soluble guanylate-cyclase by organic nitrates. *Drug Res.* **1992**, *42*, 1314–1317.

9. Lang, B.S.; Gorren, A.C.F.; Oberdorfer, G.; Wenzl, M.V.; Furdui, C.M.; Poole, L.B.; Mayer, B.; Gruber, K. Vascular bioactivation of nitroglycerin by aldehyde dehydrogenase-2. *J. Biol. Chem.* **2012**, *287*, 38124–38134. [CrossRef] [PubMed]

10. Oae, S.; Shinhama, K. Organic thionitrites and related substances—A review. *Org. Prep. Proced. Int.* **1983**, *15*, 165–198. [CrossRef]

11. Oae, S.; Shinhama, K.; Fujimori, K.; Kim, Y.H. Physical-properties and various reactions of thionitrites and related substances. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 775–784. [CrossRef]

12. Artz, J.D.; Yang, K.X.; Lock, J.; Sanchez, C.; Bennett, B.M.; Thatcher, G.R.J. Reactivity of thionitrate esters: Putative intermediates in nitrovasodilator activity. *Chem. Commun.* **1996**, *927–928*. [CrossRef]

13. Goto, K.; Shimada, K.; Furukawa, S.; Miyasaka, S.; Takahashi, Y.; Kawashima, T. Formation of a stable sulfenic acid by hydrolysis of a thionitrate and a sulfenyl bromide. *Chem. Lett.* **2006**, *35*, 862–863. [CrossRef]

14. Goto, K.; Yoshikawa, S.; Ideue, T.; Sase, S. Transnitrosation from a stable thionitrate to an amine with concomitant formation of a sulfenic acid. *J. Sulfur Chem.* **2013**, *34*, 705–710. [CrossRef]

15. Goto, K. Synergy of reactivity and stability in nanoscale molecular architectures. In *Synergy in Supramolecular Chemistry*, Nabeshima, T., Ed.; CRC Press: Boca Raton, FA, USA, 2015; pp. 191–218.

16. Goto, K.; Hino, Y.; Kawashima, T.; Kaminaga, M.; Yano, E.; Yamamoto, G.; Takagi, N.; Nagase, S. Synthesis and crystal structure of a stable S-nitrosothiol bearing a novel steric protection group and of the corresponding S-nitrothiol. *Tetrahedron Lett.* **2000**, *41*, 8479–8483. [CrossRef]

17. Goto, K.; Hino, Y.; Takahashi, Y.; Kawashima, T.; Yamamoto, G.; Takagi, N.; Nagase, S. Synthesis, structure, and reactions of the first stable aromatic S-nitrosothiol bearing a novel dendrimer-type steric protection group. *Chem. Lett.* **2001**, *30*, 1204–1205. [CrossRef]

18. Ishihara, M.; Abe, N.; Sase, S.; Goto, K. Synthesis, structure, and reactivities of a stable primary-alkyl-substituted sulfenic acid. *Chem. Lett.* **2015**, *44*, 615–617. [CrossRef]

19. Sase, S.; Aoki, Y.; Abe, N.; Goto, K. Stable sulfenyl iodide bearing a primary alkyl steric protection group with a cavity-shaped framework. *Chem. Lett.* **2009**, *38*, 1188–1189. [CrossRef]

20. Sase, S.; Kakimoto, R.; Goto, K. Synthesis of a stable selenoaldehyde by self-catalyzed thermal dehydration of a primary-alkyl-substituted selenenic acid. *Angew. Chem. Int. Ed.* **2015**, *54*, 901–904. [CrossRef] [PubMed]

21. Sase, S.; Kakimoto, R.; Kimura, R.; Goto, K. Synthesis of a stable primary-alkyl-substituted selenenyl iodide and its hydrolytic conversion to the corresponding selenenic acid. *Molecules* **2015**, *20*, 21415–21420. [CrossRef] [PubMed]

22. Goto, K.; Sonoda, D.; Shimada, K.; Sase, S.; Kawashima, T. Modeling of the 5′-deiodination of thyroxine by iodothyronine deiodinase: Chemical corroboration of a selenenyl iodide intermediate. *Angew. Chem. Int. Ed.* **2010**, *49*, 545–547. [CrossRef] [PubMed]

23. Itoh, M.; Takenaka, K.; Okazaki, R.; Takeda, N.; Tokitoh, N. The first stable aromatic S-nitrosothiol: Synthesis, structure and reactivity. *Chem. Lett.* **2001**, *30*, 1206–1207. [CrossRef]

24. Itoh, M.; Takenaka, K.; Okazaki, R. Synthesis, structure, and reactivity of stable aromatic S-nitrosothiols bearing bulky substituents. *Nippon Joshi Daigaku Kiyo Rigakubu* **2004**, *12*, 33–38.

25. Sheldrick, G.M. *SHELXL-97, Computer Program for Crystal Structure Refinement*; University of Göttingen: Göttingen, Germany, 1997.

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