ly applied on the preparation of a monolithic forsterite-PMMA nanocomposite. The monolithic composite prepared had very good optical transparency, and largely improved mechanical characteristics relative to the inorganic counterpart, and most of all it was machinable. The mechanical property of the composite had hybrid characteristics of those inorganic and organic moieties. Doping of the optically active materials (either ions or macromolecules) into this new forsterite-PMMA nanocomposite is in progress, and some dopants have been successfully incorporated into this host material, which would be dealt in forthcoming report.

Acknowledgment. The support of the Korean Science and Engineering Foundation (K-N96048) is acknowledged with gratitude.

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Design and Synthesis of Furoxan Derivatives as Probe for the Nitric Oxide Generation

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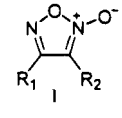
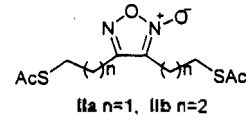
Received February 2, 1998

Nitric oxide (NO),[1] known to be the smallest biomolecule up-to-date, is involved in various physiological activities such as vasodilation[2] and tumoricidal and bactericidal activities.[3] More interestingly, it mediates a signal transduction in the brain.[4] Due to these diverse biological actions, the NO precursors have been a main subject of interest in the treatment of NO-related diseases. Furoxan (Furazan *N*-Oxide) **I** has been known to release NO by interacting with a thiol compound such as cysteine and glutathione *in vivo*.[5] We also reported the NO generation from various furoxan derivatives by the electron impacted fragmentation.[6] The biochemical mechanism for NO generation from the furoxan, however, is not explored exactly in the molecular level. To probe such a biochemical mechanism and to develop a potential NO-precursor for biomedical study, we designed thiol containing furoxan derivatives **IIa** and **IIb** expecting the NO generation by the intramolecular sulfide-nitronate interaction.[7] Here, we wish to report a synthetic method of the furoxans **IIa** and **IIb** containing protected thiol.

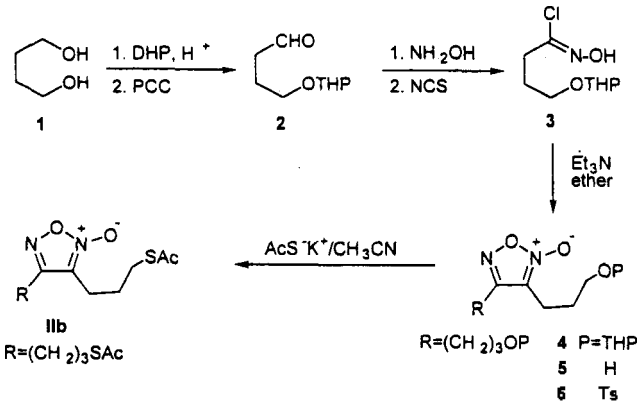


I



IIa n=1, IIb n=2

The furoxans **IIa** and **IIb** were prepared through dimerization of the corresponding nitrile oxide as a key step.



The synthetic scheme for the furoxan **IIb** is shown in the scheme. Initially, 1,4-butanediol (5 g, 50 mmol) was converted to the aldehyde **2** (2.7 g, 32%) by PCC oxidation following the selective protection of mono-hydroxyl group. The addition of hydroxylamine to the aldehyde **2** and a subsequent treatment with *N*-chlorosuccinimide in DMF generated the *N*-hydroxyiminoyl chloride **3** as reported by Howe and coworkers.[8] The furazan ring was formed by the dimerization of the nitrile oxide which was generated *in situ* from the iminoyl chloride **3** in 34% yield.[9] Since the isolation of the diol **5** was not easy due to its high solubility in water, the least amount of water was used for the deprotection of furoxan **4**. Through repeated column chromatography (5% MeOH/CH_2Cl_2), the diol **5** was obtained in 73% yield. The diol **5** was reacted with *p*-TsCl and potassium thiolaceatate by sequence to produce furoxan **IIb** in 65% yield.[10,11] The similar synthetic scheme was applied to prepare the furoxan (**IIa**).[12,13]

Treatment of the furoxan **IIb** with $NaBH_4$ (2.5 equivalent) generated the corresponding thiol-containing furoxan in low yield.[14] Also, the cleavage of furazan ring was confirmed by the NMR spectroscopic data. Currently, a mechanistic study for the potential NO-generation from the furoxans **IIa** and **IIb** is in progress.

As a conclusion, furoxan derivatives **IIa** and **IIb** containing protected thiol were designed and prepared for the first time as mechanistic probe of NO generation *via* the intramolecular thiol-nitronate interaction.

Acknowledgment. This research was supported by non-directed research fund, Korea Research Foundation 1996 (project No. 961030118).

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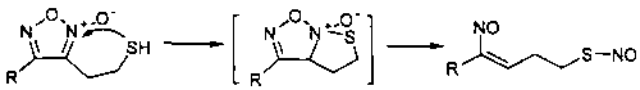
7. A proposed mechanism for the NO generation by the intramolecular sulfide-nitronate interaction from the thiol containing furoxan derivative.



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10. Spectroscopic data of the furoxan (**6**): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.8-2.2 (4H, m, CH_2CH_2O), 2.4 (6H, s, CH_3), 2.5 (2H, m, $N{=}CCH_2$), 2.7 (2H, m, $N{=}CCH_2$), 4.4 (2H, m, CH_2O), 4.1 (2H, m, CH_2O), 7.2-7.8 (8H, AB_q, J=8.2 Hz, ArH); ^{13}C NMR (200 MHz, $CDCl_3$) δ 17.1, 19.9, 20.0, 22.5, 23.7, 61.4, 67.2, 113.0, 128.6, 131.0, 143.8, 155.1.
11. Spectroscopic data of the furoxan (**IIb**): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.9-2.2 (4H, m, CH_2CH_2S), 2.0 (3H, s, CH_3), 2.1 (3H, s, CH_3), 2.6 (2H, t, J=7.8 Hz, $N{=}CCH_2$), 2.7 (2H, t, J=7.4 Hz, $N{=}CCH_2$), 4.1 (2H, t, J=6.0 Hz, CH_2S), 4.2 (2H, J=6.0 Hz, CH_2S); ^{13}C NMR (200 MHz, $CDCl_3$) δ 17.8, 19.1, 19.2, 20.8, 22.6, 23.8, 61.3, 61.4, 113.4, 155.4, 169.3, 169.4.
12. ^{1}H NMR (200 MHz, $CDCl_3$) for the furoxan (**IIa**): δ 2.05 (3H, s, CH_3), 2.06 (3H, s, CH_3), 2.9 (2H, t, J=6.0 Hz, $N{=}CCH_2$), 3.0 (2H, t, J=6.0 Hz, $N{=}CCH_2$), 4.3 (2H, t, J=6.0 Hz, CH_2S), 4.4 (2H, t, J=6.0 Hz, CH_2S).
13. Spectroscopic data of 3,4-bis-[2-(toluene-4-sulfonic acid) ethyl-ester]furoxan: ^{1}H NMR (200 MHz, $CDCl_3$), δ 2.4 (6H, s, CH_3), 2.8 (2H, t, J=5.9 Hz, $N{=}CCH_2$), 3.0 (2H, t, J=6.1 Hz, $N{=}CCH_2$), 4.2 (2H, t, J=5.9 Hz, CH_2S), 4.3 (2H, t, J=6.1 Hz, CH_2S), 7.3-7.8 (8H, AB_q, ArH); ^{13}C NMR (200 MHz, $CDCl_3$), δ 20.0, 20.1 21.5, 24.1, 62.7, 64.8, 111.1, 126.2, 126.4, 128.6, 128.7, 130.5, 144.1, 152.9.
14. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.69 (br, SH), 1.9-2.1 (4H, m, CH_2CH_2S), 2.6-2.75 (4H, m, $N{=}CCH_2$), 3.74 (4H, m, CH_2S).