DOI 10.5012/bkcs.2010.31.12.3583

Synthesis and E-Beam-Mediated Gas Phase Fragmentation of Thiol-Containing Furoxans for Nanopatterned Alkyne Formation on Gold Surface

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Received August 10, 2010, Accepted September 28, 2010

Furoxanthiols **PFT** and **BPFT** possessing thiomethyl or thiobenzyl groups in the furoxan ring were designed and synthesized as potential light-sensitive alkyne precursors on a gold surface. The synthesis of thiofuroxans **PFT** and **BPFT** was performed from the corresponding halofuroxans **1b** and **2c**, respectively, by the substitution with potassium thioacetate in ethyl acetate/ethanol or DMF, followed by basic hydrolysis as the key reactions. Electron-beam-mediated fragmentation of furoxans **1c** and **2d** in a mass spectrometer afforded the corresponding aryl alkyne fragments, with the evolution of NO in high preference. In the cases of thiofuroxans **PFT** and **BPFT**, carbon-sulfur bond cleavage was observed as a representative fragmentation, producing M-SH and M-SAc peaks, which competed with the release of NO. In the fragmentation of mono-aryl furoxan **1c**, the release of molecule of NO was predominately observed to produce an M-NO fragment as a base peak by the formation of trimembered thiiranium or azirine intermediate.

Key Words: Alkyne, Furoxanthiol, Fragmentation, Electron-beam, Gold

Introduction

An alkyne group on a solid surface can play the role of an anchor for the attachment of diverse agents useful in biomedical device coating, fluorescence sensing films, and surface reforming.[1-4] For example, the 1,3-dipolar cycloaddition of alkynes with organic azides on a surface has been known to be a pertinent method of connecting DNA, protein and fluorophores on the solid surface.[5-8] In particular, selectively immobilized alkynes on a surface can be useful to nanoarrays and nanopatternings of a surface. For the selective immobilization of alkynes on a surface, alkynes can be introduced by covalent bonding with the prearrayed functional group.[6] In addition the photochemical transformation of a potential alkyne precursor can lay alkynes on the surface in an arrayed manner. To generate arrayed alkynes on a solid surface, we have focused on the fragmentation of furoxan (furazan *N*-oxide) derivatives as potential alkyne precursors in the gas or solid phase (Fig. 1).[9-14] Furoxan has been known to the first alkyne precursor to form self-assembled alkyne on silica or a gold surface *via* light induced NO release.[9-10]

In the previous study, furoxan self-assembeld monolayers (SAMs) were prepared by imine bonding between furoxan-aldehyde and an amino group on a solid surface.[10] However, the imine linkage was limited in its usage because of air-instability-induced decomposition and a reductive response due to the irradiating light.[10,15] Continuing this effort with furoxan SAM, for the sake of convenience, we considered the CVD method to be a useful technique. Thus, we designed and synthesized furoxan derivatives **PFT** and **BPFT** (Fig. 2). In our design, a thiol group is required for the attachment of furoxans through sulfur-gold bond formation, and an aryl group at 3- or 4-position of the furoxan ring is introduced for the elongated conjugation with an anticipated triple bond resulting from the furoxan fragmentation.[11,12] Further, the minimization of molecular weight was considered to manage vaporization at as low a temperature as possible. In the synthesis of furoxans containing a thiol group, the intrinsic reactivity of thiol group with a furoxan ring is a serious drawback. The thiol group or thiolate that might be generated in the reaction medium interacted with the furoxan ring, resulting in the occurrence of side reactions.[16,17] The synthetic experiment involving thiol-containing furoxans required careful handling to maintain oxygen-free, neutral conditions. Thus, the liberation of a thiol group was planned at the end of the synthetic route. Here, we report the synthesis of furoxanthiols **PFT** and **BPFT** containing a thiol group for SAM formation on a gold surface, as well as their fragmentation in the gas phase *via* electron impact.

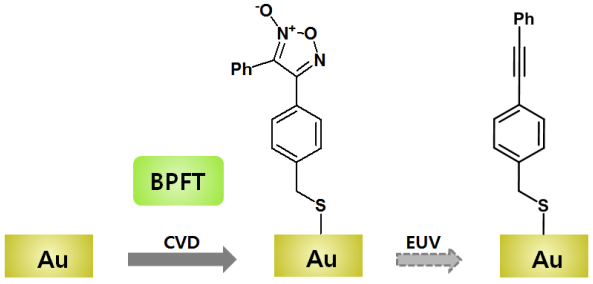


Figure 1. Diagram for the alkyne formation by the fragmentation of thiofuroxan deposited on gold surface (EUV: Extreme UV Light).

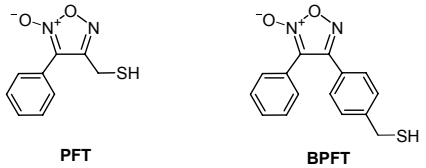


Figure 2. Structure of thiofuroxan derivatives.

Experimental Section

Reactions requiring anhydrous conditions were carried out with the usual precautions for the rigorous exclusion of air and moisture. Thin-layer chromatography was performed on precoated silica gel $60F_{254}$ plates (Merck), and column chromatography was performed on silica gel (Merck, 230 ~ 400 mesh). The spots were monitored with UV light (wave length: 254 nm or 365 nm) and TLC staining using anisaldehyde in acidic solution as needed. Methylene chloride (MC) and dimethylformamide (DMF) were distilled from calcium hydride before use. ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer at 200 MHz and 50 MHz, respectively. Mass spectra were recorded with an Autospec mass spectrometer (Varian 1200 L). When necessary, chemicals were purified according to the reported procedure.

3-(Hydroxymethyl)-4-phenyl-1,2,5-oxadiazole 2-oxide (1a). $NaNO_2$ (50.72 g, 735 mmol) was add to a solution of cinnamyl alcohol (14.1 g, 105 mmol) in a mixture of AcOH (12 mL) and 1,4-dioxane (12 mL) in deionized (DI) water (20 mL); the resulting mixture was then refluxed for 3 days at 50 °C. The reaction mixture was neutralized with $NaHCO_3$, extracted with EtOAc, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography, eluting with 10% EtOAc/*n*-hexane, to obtain furoxanalcohol **1a** (7.31 g, 37%) as a pale yellow solid. ^{1}H-NMR δ_H ($CDCl_3$, ppm): 7.54-7.83 (m, 5H, Ar-H), 4.74-4.76 (d, 2H, CH_2): ^{13}C-NMR δc ($CDCl_3$, ppm): 53.45 (-CH_2-OH), 115.01 (-C=N^+-O^-), 126.29, 127.92, 129.54, 131.50 (Ph-C), 156.98 (-C=N); MS *m*/*z* (relative intensity); 192 (M+, 30), 162 (M-30, 22), 131 (M-60, 100), 115 (M-77, 13), 103 (M-103, 38), 89 (M-103, 6), 77 (M-116, 26), 63 (M-129, 7).

3-(Chloromethyl)-4-phenyl-1,2,5-oxadiazole 2-oxide (1b). Et_3N (1.79 mg, 15.6 mmol) was added to a solution of furoxan alcohol **1a** (2 g, 10 mmol) in CH_2Cl_2 (10 mL). After stirring the resulting solution for 10 min at room temperature, methansulfonyl chloride (1.58 g, 15.6 mg) was added to it dropwise at 0 °C and stirred for 2 h at room temperature. The reaction mixture was neutralized with $NaHCO_3$, extracted with Et_2O, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography, eluting with 10% EtOAc/*n*-hexane, to obtain furoxanchloride **1b** (1.69 g, 80%) as a pale yellow solid. ^{1}H-NMR δ_H ($CDCl_3$, ppm): 7.58-7.80 (m, 5H, Ar-H), 4.60 (s, 2H, CH_2); ^{13}C-NMR δc ($CDCl_3$, ppm): 32.80 (-CH_2-OH), 113.05 (-C=N^+-O^-), 125.97, 127.74, 129.71, 131.72 (Ph-C), 156.10 (-C=N); MS *m*/*z* (relative intensity); 210 (M+, 35), 179.9 (M-30, 42), 150 (M-60, 100), 115 (M-95, 83).

3-(Acetylthiomethyl)-4-phenyl-1,2,5-oxadiazole 2-oxide (1c). A mixture of KSAc (906 mg, 6.6 mmol) in D.I. water (10 mL) was added into a solution of furoxan chloride **1b** (1.27 g, 6.6 mmol) in EtOAc (10 mL) and EtOH (5 mL) at 0 °C and stirred for 2 h at room temperature. The reaction mixture was extracted with EtOAc, dried over $MgSO_4$, and concentrated to obtain furoxanthioactate **1c** (1.27 g, 78%) as a pale white oil. ^{1}H-NMR δ_H ($CDCl_3$, ppm): 7.57- 7.67 (m, 5H, Ar-H), 4.21 (s, 2H, CH_2), 2.36 (s, 3H, CH_3); MS *m*/*z* (relative intensity): 249.9 (M+, 1), 220 (M-30, 100), 189.9 (M-60, 40), 146.9 (M-103, 91) 114.9 (M-135, 83).

3-(Mercaptomethyl)-4-phenyl-1,2,5-oxadiazole 2-oxide (PFT). K_2CO_3 (464 mg, 3.4 mmol) was added to a solution of furoxan thioactate **1c** (700 mg, 2.8 mmol) in MeOH; the resulting mixture was then stirred for 3 h at room temperature. The reaction mixture was acidified with 1 M HCl solution to a pH of 6, extracted with EtOAc, dried over $MgSO_4$, and concentrated. Sublimation of the residue at 120 °C gave furoxanthiol **PFT** (435 mg, 78%) as a brown solid. ^{1}H-NMR δ_H ($CDCl_3$, ppm): 7.26-7.76 (m, 5H, Ar-H), 3.93 (s, 2H, CH_2); MS *m*/*z* (relative intensity): 208.0 (M+, 10), 191 (M-17, 22), 178.0 (M-30, 6), 148.0 (M-60, 41).

3-(4-Formylphenyl)-4-phenyl-1,2,5-oxadiazole 2-oxide (2a). $NaNO_2$ (6.96 g, 100.8 mmol) was added to a solution of *trans*-4-stilbene-carboxaldehyde (3 g, 14.4 mmol) in a mixture of AcOH (12 mL) and 1,4-dioxane (30 mL) stirred for 30 min at 50 °C, in DI water (20 mL); the resulting mixture was then refluxed for 2 days at 50 °C. The reaction mixture was neutralized with $NaHCO_3$, extracted with EtOAc, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography, eluting with 10% EA/*n*-hexane, to obtain furoxanaldehyde **2a** (1.77 g, 46%) as a pale red-yellow solid. ^{1}H-NMR δ_H ($CDCl_3$, ppm): 10.1 (t, 1H, CHO), 7.26-8.05 (m, 9H, Ar-H); MS *m*/*z* (relative intensity): 266 (M+, 12), 206 (M-60, 100), 176 (M-80, 34), 151 (M-115, 13).

3-(4-(Hydroxymethyl)phenyl)-4-phenyl-1,2,5-oxadiazole 2-oxide (2b). $NaBH_4$ (28.44 mg, 752 mmol) was added to a solution of biphenyl furoxan alcohol **2a** (400 mL, 1.50 mmol), and EtOH (25 mL); the resulting mixture was then stirred for 3 h at room temperature. The reaction mixture was extracted with EtOAc, dried over $MgSO_4$, and concentrated to obtain furoxanalcohol **2b** (165 mg, 41%) as a pale yellow oil. ^{1}H-NMR δ_H ($CDCl_3$, ppm): 7.26-7.54 (m, 9H, Ar-H), 4.76 (d, 2H, CH_2); *m*/*z* (relative intensity): 268 (M+, 41), 208 (M-60, 100), 179 .0 (M-89, 30), 120 (M-148, 18).

3-(4-(Chloromethyl)phenyl)-4-phenyl-1,2,5-oxadiazole 2-oxide (2c). Et_3N (283 mg, 2.80 mmol) was added to a solution of biphenyl furoxanalcohol **2b** (412 mL, 1.53 mmol) in CH_2Cl_2 (25 mL). After stirring the resulting solution for 10 min at room temperature, methansulfonyl chloride (320 mg, 2.80 mmol) was added to it and stirred for 18 h at room temperature. The reaction mixture was extracted with EtOAc, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography, eluting with 10% EA/*n*-hexane, to obtain furoxanchloride **2c** (413 mg, 94%) as a pale yellow solid. ^{1}H-NMR δ_H ($CDCl_3$, ppm): 7.26-7.56 (m, 9H, Ar-H), 4.62 (d, 2H, CH_2): *m*/*z* (relative intensity); 288.0 (M+2, 7), 286.1 (M+, 20), 226.1 (M-60, 100), 191 (M-95, 73).

3-(4-(Acetylthiomethyl)phenyl)-4-phenyl-1,2,5-oxadiazole 2-oxide (2d). KSAc (296 mg, 2.59 mmol) was added to a solution of biphenyl furoxanchloride **2c** (492 mg, 1.72 mmol) in DMF (25 mL); the resulting solution was stirred for 2 h at 50 °C. The reaction mixture was extracted with EtOAc, dried over $MgSO_4$, and concentrated to obtain furoxan thioactate **2d** (460 mg, 82%) as a pale yellow oil. ^{1}H-NMR δ_H ($CDCl_3$, ppm): 7.34-7.51 (m, 9H, Ar-H), 4.13-4.15 (d, 2H, CH_2), 2.38 (s, 3H, CH_3): *m*/*z* (relative intensity); 326.0 (M+, 17), 266.1 (M-60, 53), 191.1 (M-135, 100).

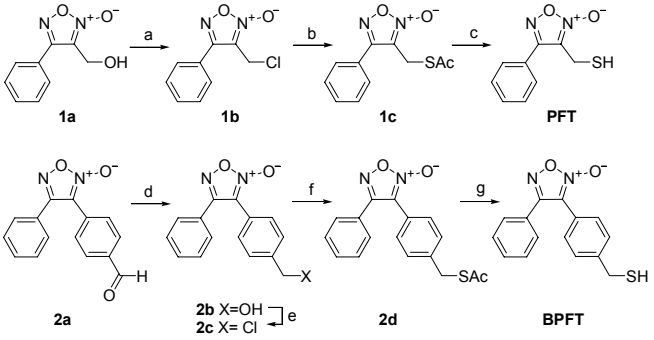
3-(4-(Mercaptomethyl)phenyl)-4-phenyl-1,2,5-oxadiazole 2-oxide (BPFT). K_2CO_3 (203 mg, 1.5 mmol) was added to a

solution of biphenyl furoxanthioacete **2d** (400 mg, 1.2 mmol) in MeOH (10 mL); the resulting solution was stirred for 3 h at 50 °C. After the treatment with 1 M HCl solution to a pH of 6, it was extracted with EtOAc, dried over $MgSO_4$, and concentrated. The residue was purified by dry loading column chromatography, eluting with 10% EA/*n*-hexane to obtain **BPFT** (113 mg, 32%) as a pale brown oil. ^{1}H-NMR δ_H ($CDCl_3$, ppm): 7.26-7.52 (m, 9H, Ar-H), 3.64-3.65 (d, 2H, CH_2); *m*/*z* (relative intensity): 284.0 (M+, 2), 251.0 (M-33, 100), 222.0 (M-62, 23), 191 (M-93, 58).

Results and Discussion

Synthesis. Thiofuroxans **PFT** and **BPFT** are designed as potential light sensitive alkyne precursors. A thiol group is necessary to form a gold-sulfur bond on a surface.[18] The aromatic substituent is introduced to the 3- or 4-position of the furoxan ring to facilitate the fragmentation of furoxan, producing stabilized alkynes *via* the conjugation effect.[12] For the facile vaporization of thiofuroxan by low-temperature CVD on gold, the molecular weight of those thiofuroxans was minimized as much as possible. Because of the intrinsic reactivity of a thiol group with a furoxan ring, the thiol group liberation was planned as the last step of the synthetic route (Scheme 1).[14]

Thiofuroxans **PFT** and **BPFT** were synthesized by the key step of a conversion of chlorofuroxans **1b** and **2c** to a thioacetate, followed by basic hydrolysis. Furoxans **1a** and **2a** were initially prepared *via* a reaction with sodium nitrate in acetic acid and 1,4-dioxane, from the corresponding alkenes, crotonalcohol and stilbenealdehyde, respectively.[12-14] In the synthesis of furoxan **1a**, multiple extractions of the aqueous layer were required because of its high polarity and it was finally isolated using column chromatography. Furoxanalcohol **1a** and **2b** were converted to chlorofuroxans **1b** and **2c** in one step *via* a reaction with methanesulfonyl chloride then reacted with potassium thioacetate in EA-EtOH or DMF, produced thioacetates **1c** and **2d**. Basic hydrolysis using potassium carbonate in methanol[19] liberated thiol group from the thioacetate of **1c** (78%) and **2d** (82%) yield with disulfide of **PFT** and **BPFT**. Direct conversion of halofuroxans **1b** and **2c** to the corresponding thiols using sodium hydrosulfide in DMF or Lawesson's reagent, was unsuccessful because of the interaction of sulfur with the furoxan ring.[20] Reductive deacetylation using sodium brohydride also failed to convert thioacetate **1b** and **2c** to a thiofuroxan. It was considered that *in-situ*-generated thiolate interacts with the furoxan ring to give an unidentified by-product.[17] A similar procedure used in the synthesis of **PFT** was applied for the synthesis of **BPFT**, with a minor modification. The conversion of chlorofuroxan **2c** to **2d** was required to take place under more vigorous conditions (in DMF at 50 °C) than in the case of **1b**.



Scheme 1. Synthetic route for thiofuroxans: (a) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C → rt, 2 h. (b) $KSCOCH_3$, EA-EtOH, 0 °C → rt, 2 h. (c) K_2CO_3, MeOH, 0 °C → rt, 3 h. (d) $NaBH_4$, EtOH, rt, 3 h, (e) CH_3SO_2Cl, Et_3N, CH_2Cl_2, rt, 18 h (f) $KSCOCH_3$, DMF, 50 °C, 2 h (g) K_2CO_3, MeOH, 0 °C → rt, 3 h

Fragmentation of thiofuroxans. To exploit the cleavage tendency of thiofuroxans, E-beam-mediated fragmentation in the gas phase was analyzed, as shown in Fig. 3-6. Fragmentation was performed at 20 eV, which is the lowest value allowed in the MS instrument. The fragmentation tendency for alkyne formation or carbon-sulfur bond cleavage was focused in the MS data analysis. Generally, the mass spectra of furoxan **PFT** and **BPFT** containing a thiol group showed a quite complicated fragmentation pattern with many peaks having low intensity. The mass spectra of furoxans with thioacetate **1c** and **2d** showed a simpler fragmentation pattern than those of furoxanthiol **PFT** and **BPFT**.

The mass spectrum of furoxan thioacetate **2d** (Fig. 3) with biphenyl substituents at the furoxan ring showed peaks at *m*/*z* = 266.1 (M-2NO), 191.1 (M-2NO-SAc) as shown Fig. 3. The M-60 (*m*/*z* = 266) peak, derived from the loss of 2NO is characteristic of furoxans with aryl groups. This is because of the conjugation of biphenyl groups with the triple bond.[12,13] Unlike the case of furoxans,[13] the peak, M-2NO-SAc (*m*/*z* = 191.1) appeared as the base peak in the mass spectrum of thioacetate (**2d**). Presumably, a benzylic cation that is stabilized by conjugation with an aromatic ring facilitates the cleavage of thioacetyl group of furoxan **2d** with the loss of two equivalent of NO.

In the mass spectrum of furoxan thioacetate **1c**, characteristic peaks were observed at *m*/*z* = 249.9 (M+), 220 (M-NO),

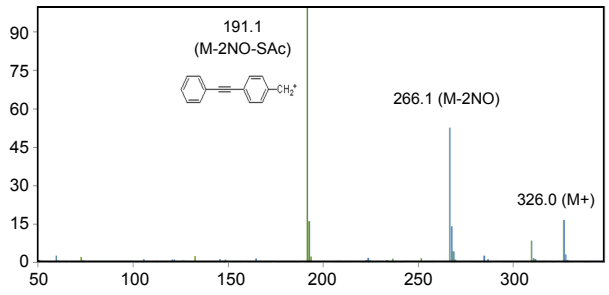


Figure 3. EI mass spectrum of furoxan thioacetate (**2d**).

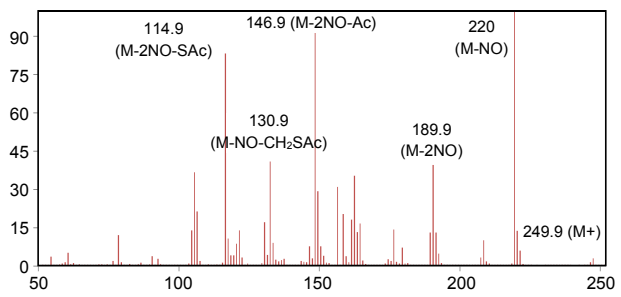


Figure 4. EI mass spectrum of furoxan thioacetate (**1c**).

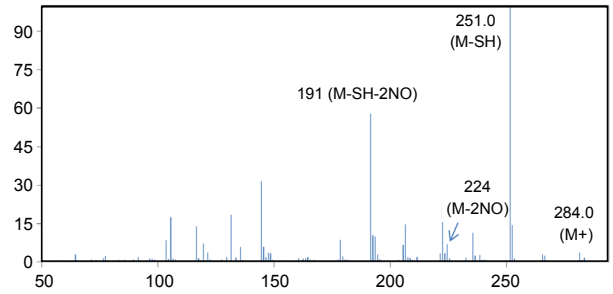


Figure 5. EI mass spectrum of **BPFT**.

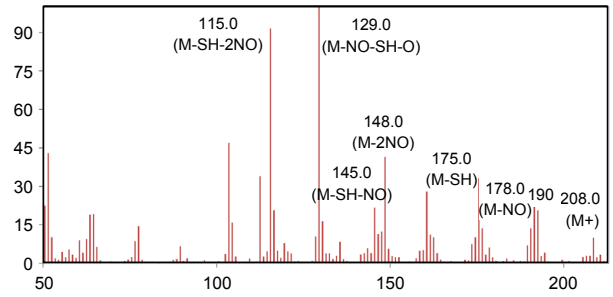


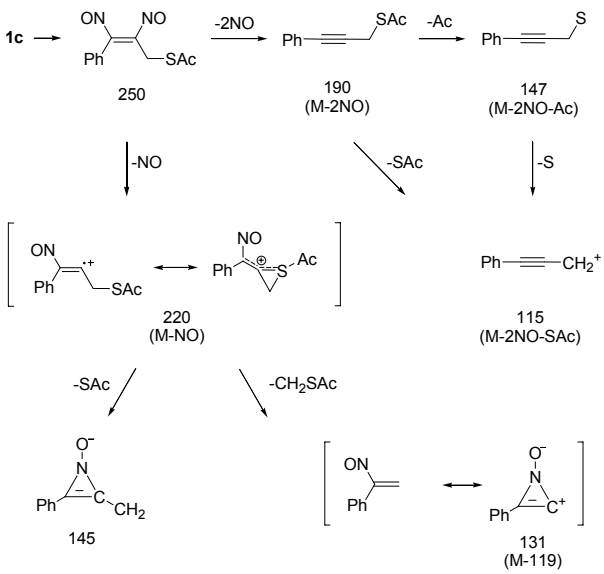
Figure 6. EI mass spectrum of **PFT**.

189.9 (M-2NO), 146.9 (M-2NO-Ac) and 114.9 (M-2NO-SAc) as shown in Figure 4. Under the electron impact of thiofuroxan **1c**, 2NO was released, affording alkyne functionality, and the desulfurization or deacetylation appeared as the main disruption route as shown in Scheme 2. Notably, characteristic fragmentation was observed, in which one molecule of NO was released to give M-NO intermediate as base peak. The M-NO fragment, as base peak, dominated over the M-2NO peak. The high intensity of the M-NO fragment was considered to be attributed to the resonance stabilization consisting of a trimembered thiiranium cation (Scheme 2). Further fragmentation of the M-NO intermediate generated m/z = 145 (-SAc, 8) and m/z = 131 (-CH_2SAc, 41). The structure of the fragment, m/z = 131, was proposed to be 2-phenyl-azirine *N*-oxide originating from the loss of CH_2SAc from the M-NO peak (m/z = 220).

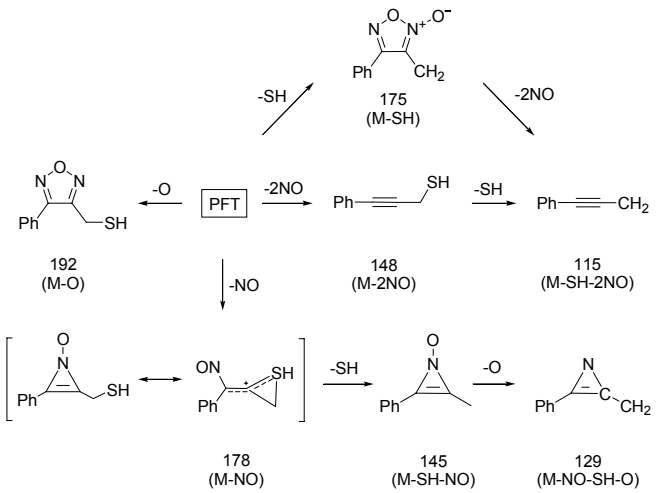
The mass spectra of furoxan **PFT** and **BPFT** containing a thiol group showed a quite complicated fragmentation pattern with many tiny peaks having intensity, as shown in Figs. 5 and 6. The base peak of the mass spectrum of **BPFT** (Fig. 5) appeared at m/z = 251.0 (M-SH), derived from the loss of the thiol group (dethiolation). The M-2NO peak (m/z = 224), which usually appears with high intensity in furoxan derivatives,[13] showed a quite low intensity. The resonance stabilized benzylic cation might facilitate dethiolation of **BPFT** under EI-mode. After dethiolation, releasing of 2NOs dominated over other fragmentations, producing an m/z = 191 peak (M-SH-2NO) with the second highest intensity.

In the mass spectrum of **PFT**, M-SH, M-NO, M-2NO, m/z = 129, and M-2NO peaks were observed as representative peaks (Fig. 6). Among them, the fragment m/z = 129 appeared as the base peak which is assumed as azirine as shown in Scheme 3. As in the case of thiofuroxan **1c**, the release of one molecule of NO release followed by azirine formation was competed with the release of 2NO. Trimembered azirine intermediate is considered to maintain high stability in EI-mode fragmentation. The intensity of the M-2NO peak of **PFT** was higher than that of the M-NO peak. It was supposed that loss of 2NO was preferred to the trimembered azirine formation, originating from the one NO (Scheme 3).

To summarize, furoxanthiols **PFT** and **BPFT** were synthesized in order to study their fragmentation pattern in the gas phase, for consideration as potential alkyne precursors on a gold surface. The thiol group of furoxans **PFT** and **BPFT** was liberated *via* of reaction of the corresponding chlorofuroxans **1a** and **2b** with KSAc in EtOH or DMF followed by hydrolysis with K_2CO_3/MeOH. In the gas phase, E-beam induced fragmentation of thiofuroxan derivatives produced an M-2NO fragment corresponding to the alkyne functionality as expected. However, many fragments derived from the cleavage of carbon-sulfur bond of furoxans were observed at high intensity. This result suggests that the carbon-sulfur bond cleavage competes



Scheme 2. Proposed fragmentation pathway of thiofuroxan **1c** under EI mode in gas phase (all intermediates are assumed in cationic status)



Scheme 3. Proposed fragmentation pathway of thiofuroxan **PFT** under EI mode in gas phase (all intermediates are assumed in cationic status)

with the NO evolution, leading to alkyne formation depending on the substituent in the furoxan ring. Notably, one molecule of NO release leading to the formation of thiiranium or azirine, was observed as a main fragmentation route in the E-beam mediated fragmentation of **PFT** or thiofuroxan **1c** with the thiomethyl substituent at the furoxan ring. In collaboration with the Pohang Accelerator Lab, SAM of furoxan thiols **PFT** and **BPFT** were prepared on the gold surface and irradiated with EUV, resulting in a diverse photoproduct on the surface. These results will be reported elsewhere.

Acknowledgments. This work was supported by a National Research Foundation of Korea Grant funded by the Korean Government (2009).

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