Synthesis and Fragmentation of Furoxanaldehydes in the Gas Phase for Nanopatterned Alkyne Formation on a Solid Surface

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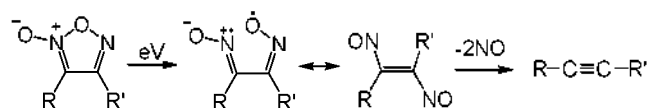*Chonnam National University, Gwangju 500-757, Korea*

Furoxanaldehydes possessing phenyl or alkenyl groups at the 3- or 4-position of the furoxan ring were designed for alkyne formation on a solid surface. Furoxans **2** and **3** were prepared from the corresponding alkenes **2a** and **3a** by the reaction with $NaNO_2$ in acetic acid. Furoxan **4**, in which the furoxan ring is conjugated with a double bond, was prepared from *bis*(bromomethyl)benzene **4a** in 5 steps using the Wittig reaction of aldehyde **1** as the key step. The electron beam-mediated fragmentation of furoxanaldehydes **1-4** in a mass spectrometer was exploited by focusing on alkyne formation on the solid surface. The fragmentation of furoxan **3** possessing diaryl groups afforded diaryl-acetylene at high efficiency, suggesting that the aryl group conjugated with the furoxan ring could facilitate alkyne formation with the evolution of NO.

Key Words: Alkyne, Furoxan, Furoxanaldehyde, E-beam, Fragmentation

Introduction

The functionality of alkyne, which can act as an anchor for the attachment of diverse agents on solid surfaces through the 1,3-dipolar cycloaddition[1-4] with organic azides, is applicable to biochips, fluorescence sensing films and surface reforming.[5-8] The cycloaddition of alkyne with azide compounds, known as click chemistry,[4] can be performed in physiological environments in which many other chemical functional groups are tolerated, thereby facilitating its application to the study of proteins, biochips and biocompatibility on solid surfaces. The immobilization of alkyne groups onto a solid surface has been attained by either the direct attachment[1-2] of alkyne compounds through covalent bonding or the spin coating of polymers having alkyne groups.[3] Instead of the direct introduction of alkynes, if a potential alkyne functionality is attached and then followed by subsequent transformation to alkyne *via* selective chemical- or light-mediated cleavage reactions, it might be useful to nanoarrays and nanopatternings of a surface. In light of such applications, we focused on the synthesis and fragmentation of furoxan(furazan *N*-oxide) derivatives in a gas or solid phase as a potential alkyne precursor on the solid surface.

Furoxan is a well known nitric oxide (NO) precursor involved in diverse physiological activities such as vasodilation,[9] tumoricidal and bactericidal activities,[10] and signal transduction in neurotransmission.[11] Beside these physiological properties arising from NO evolution in a physiological environment, furoxans cleave to alkynes by thermal,[12] light[13] or electronic[14]

energy mediation (Scheme 1). We have previously reported for the first time alkyne formation on a solid surface from the self-assembled furoxans on silica or gold substrates[15] (Scheme 2).

Alkyne formation from a furoxan in the solid phase by soft-X ray or electron beam (e-beam) only achieved in low efficiency. This low efficiency of alkyne formation was attributed to the photosensitivity, stability and assembling orientation of the furoxans on the surface.[16] The fragmentation of furoxan into alkyne is affected by its substituents on irradiation with e-beam in the gas phase.[14,17] In other words, the fragmentation pathway of furoxan, as well as the alkyne formation efficiency in the solid phase, can be escorted by the substitutes of the furoxan ring. In an effort to increase alkyne formation efficiently *via* the fragmentation of the furoxan on the solid surface, furoxan derivatives **1-4** were designed. In these derivatives, a formyl group is required for the attachment of furoxans through the imine bond onto the amino-surface, and a phenyl or alkenyl group is introduced to improve the conjugation with the anticipated triple bond resulted from the fragmentation of the furoxan. Here, we report the synthesis of furoxanaldehydes **1-4** and the e-beam-mediated fragmentation for the alkyne generation in the gas phase.

Scheme 1. Alkyne formation from furoxans with NO release.
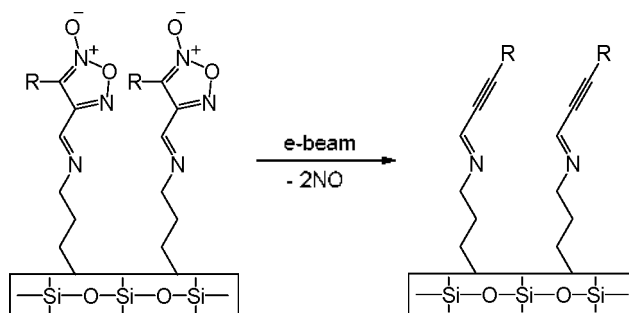
Scheme 2. Fragmentation of self-assembled furoxan for alkyne formation on a silica substrate.
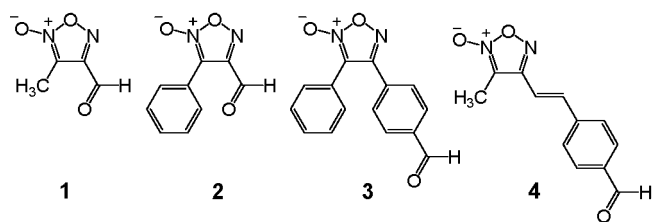
Figure 1. Furoxan derivatives containing a formyl group.

Experimental Section

Reactions requiring anhydrous condition were performed with the usual precautions for rigorous exclusion of air and moisture. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Thin-layer chromatography was performed on precoated silica gel 60F$_{254}$ plates (Merck) and column chromatography (CC) on silica gel 60 (Merck, 230~400 mesh). ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded on a Varian Gemini at 200 MHz and 50 MHz, respectively. Mass spectra were recorded with an Autospec mass spectrometer (Micromass, U.K., Manchester). When necessary, chemicals were purified according to the reported procedure.

4-Formyl-3-methyl furoxan (1). To a solution of NaNO$_2$ (17.2 g, 0.285 mol) in water (100 mL) was added crotonaldehyde (5.91 ml, 71 mmol) in AcOH (20 mL). The resulting solution was stirred for 12 h at 25 °C. The reaction mixture was neutralized with NaHCO$_3$, extracted with CH$_2$Cl$_2$, dried over anhydrous MgSO$_4$ and concentrated. The residue was purified by column chromatography (CC) eluting with CHCl$_3$, and then recrystallized from petroleum ether (5 ml) to give furoxan derivative **1** (3.0 g, 33%) as a white crystal.[18] Mp 44-46 °C; ^{1}H NMR (CDCl$_3$) δ2.38 (s, 3H, CH$_3$), 10.10 (s, 1H, CHO); MS m/z (relative intensity) 128 (M$^+$, 100), 98 (M-30, 59), 67 (M-61, 33).

4-Hydroxymethyl-3-phenyl furoxan (2b). To a solution of NaNO$_2$ (36.0 g, 0.522 mol) in water (150 ml) was added cinnamyl alcohol (10 g, 74.5 mmol) in AcOH (30 mL). The resulting solution was stirred for 4 h at 50 °C. The reaction mixture was neutralized with NaHCO$_3$, extracted with CH$_2$Cl$_2$, dried over anhydrous MgSO$_4$ and concentrated. The residue was purified by CC eluting with CHCl$_3$ to give furoxan alcohol **2b** (4.19 g, 29%) as a pale yellowish oil. Mp 44-46 °C; ^{1}H NMR (CDCl$_3$) δ3.80 (s, 1H, OH), 4.69 (s, 2H, CH$_2$), 7.49~7.81 (m, 5H, Ph); ^{13}C NMR (CDCl$_3$) δ53.3, 114.9, 126.1, 127.8, 129.4, 131.4, 156.8; MS m/z (relative intensity) 192 (M$^+$, 100), 162 (M-30, 99), 131 (M-61, 98).

4-Formyl-3-phenyl furoxan (2). To a solution of hydroxymethyl furoxan **2b** (4.18g, 21.8 mmol) in CH$_2$Cl$_2$ (20 mL) was added pyridinium dichromate (PDC; 9.00g, 23.9 mmol). After stirring at 25 °C for 2 h, the reaction mixture was filtered and concentrated. The residue was purified by CC eluting with a 5% EtOAc/hexane solution to give furoxanaldehyde **2** (2 g, 48%) as a pale yellowish oil. ^{1}H NMR (CDCl$_3$) δ 7.54-7.93 (m, 5H, Ph), 9.98 (s, 1H, HC=O); ^{13}C NMR (CDCl$_3$) δ98.2, 122.4, 128.4, 131.4, 155.2, 191.2; MS m/z (relative intensity) 190 (M$^+$, 58), 160 (M-30, 39), 129 (M-61, 100).

4-(4-Formylphenyl)-3-phenyl furoxan (3). To a stirred solu-

tion of (E)-4-styrylbenzaldehyde (2 g, 9.6 mmol) in a mixture solvent of AcOH (6 mL) and 1,4-dioxane (10 mL) at 50 °C, a solution of NaNO$_2$ (5.64 g, 67.2 mmol) in water (5 mL) was added dropwise. The reaction mixture was stirred further for 17 h at 50 °C and poured into ice water. The resulting mixture was neutralized with NaHCO$_3$ and extracted with EtOAc. The extract was dried over anhydrous MgSO$_4$ and concentrated. The residue was purified by CC eluting with a 13% EtOAc/hexane solution to give furoxan **3** (0.51 g, 20%) as a white crystal. Mp 102-105 °C; ^{1}H NMR (CDCl$_3$) δ7.40-7.60 (m, H, C$_6$H$_5$), 7.72 (d, J = 8.0 Hz, 2H, C$_6$H$_4$), 7.97 (d, J = 8.0 Hz, 2H, C$_6$H$_4$), 10.09 (s, 1H, CHO); ^{13}C NMR (CDCl$_3$) δ114.1, 122.5, 128.4, 128.8, 129.24, 129.9, 130.9, 131.4, 137.8, 155.3, 191.4; MS m/z (relative intensity); 266 (M$^-$, 13), 206 (M-60, 100), 176 (M-90, 26) 151 (M-115, 11).

4-(Bromomethyl)benzyl acetate (4b). A mixture of 1,4-bis(bromomethyl)benzene **4a** (26.2 g, 0.1 mol) and NaOAc (0.9 g, 0.11 mol) in DMF (200 mL) was stirred for 15 h at 30 °C. The reaction mixture was poured into ice water and extracted with EtOAc (100 mL × 3). The combined extracts were washed with water, dried over anhydrous MgSO$_4$, and concentrated. The residue was purified by CC eluting with a 13% EtOAc/hexane solution to give furoxan **4b** (11.89 g, 49%) as a pale yellowish oil. ^{1}H NMR (CDCl$_3$) δ2.09 (s, 3H, CH$_3$), 4.47 (s, 2H, BrCH$_2$), 5.08 (s, 2H, OCH$_2$), 7.5-7.3 (m, 4H, Ar).

(E)-4-[4-(Acetoxymethyl)styryl]-3-methyl furoxan (4d). A solution of benzyl ester **4b** (20.7 g, 85.2 mmol) and triphenylphosphine (24.7 g, 93.7 mmol) in toluene (250 mL) was stirred for 48 h at 30 °C. The reaction mixture was filtered and the filter cake was washed with toluene. The product **4c** (39.96 g, 79 mmol, 93%) was dried in an oven at 100 °C. A suspension of NaH (2.1 g, 87 mmol) in THF (250 ml) was added dropwise to a solution of compound **4c** (39.96 g, 79 mmol) in THF at -78 °C. After further stirring at 0 °C for 0.5 h, a solution of aldehyde compound **1** (10.1 g, 79 mmol) in THF (15 ml) was slowly added at -78 °C. Stirring was continued for another 10 h at 25 °C. The reaction mixture was extracted with CH$_2$Cl$_2$ (three times), dried over anhydrous MgSO$_4$ and concentrated. The residue was purified by CC eluting with a 20% EtOAc/hexane solution to give furoxan **4d** (8.45 g, 35%) as a pale yellowish oil. ^{1}H NMR (CDCl$_3$) δ7.27-7.34 (m, 4H, Ar), 7.13 (d, J = 12.0 Hz, 1H, HC=C-Ar), 6.38 (d, J = 12.0 Hz, 1H, furoxan-C=CH), 5.10 (s, 2H, CH$_2$O), 2.12 (s, 3H, furoxan-CH$_3$), 1.65 (s, 3H, CH$_3$).

(E)-4-[4-(Hydroxymethyl)styryl]-3-methyl furoxan (4e). A mixture of furoxan **4d** (3.37 g, 12.3 mmol) and Na$_2$CO$_3$ (1.43 g, 13.5 mmol) in MeOH (30 ml) was stirred for 3 h at 25 °C. The resulting mixture was poured into water and extracted with CH$_2$Cl$_2$ (three times), dried over anhydrous MgSO$_4$ and concentrated. The residue was purified by CC eluting with a 13% EtOAc/hexane solution to give furoxan compound **4e** (2 g, 70%) as a white crystal. Mp 65-67 °C; ^{1}H NMR (CDCl$_3$) δ 1.62 (s, 3H, CH$_3$), 3.45 (s, 1H, OH), 4.59 (s, 2H, Ar-CH$_2$), 6.31 (d, J = 12.0 Hz, 1H, furoxan-CH=CH), 7.10 (d, J = 12.0 Hz, 1H, CH=CH-Ar), 7.26 (s, 4H, Ar); ^{13}C NMR (CDCl$_3$) δ 7.8, 64.0, 112.6, 113.0, 126.9, 128.7, 133.9, 139.7, 142.1, 154.9; MS m/z (relative intensity); 232 (M$^+$, 12), 215 (M-17, 83), 202 (M-30, 4), 172 (M-60, 67), 141 (M-91, 97), 135 (M-97, 57), 128 (M/2, 100), 115 (M-117, 89).

Furoxanaldehydes for Alkyne Formation

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(*E*)-4-(4-Formylstyryl)-3-methyl furoxan (4). To a solution of compound 4e (2 g. 8.6 mmol) in CH₂Cl₂ (5 ml) was added PDC (9.00g. 23.9 mmol). After stirring for 5 h at 25 °C. the reaction mixture was filtered and concentrated. The residue was purified by CC eluting with a 33% EtOAc/hexane solution to give furoxan aldehyde 4 (1.5 g; 65%) as a yellow solid. Mp 78-79 °C; ¹H NMR (CDCl₃) δ 1.75 (s. 3H. C*H₃*). 6.48 (d. *J* = 12.0 Hz. 1H. furoxan-*H*C=CH). 7.18 (d. *J* = 12.0 Hz, 1H. CH = C*H*-Ar). 7.52 (d. *J* = 8.0 Hz. 2H. Ar). 7.86 (d. *J* = 8.0 Hz. 2H. Ar). 10.01 (s. 1H. C*H*O); ¹³C NMR (CDCl₃) δ 6.5. 110.5. 114.4. 127.9, 128.4, 134.7. 137.1. 139.4. 152.6, 189.9; MS *m/z* (relative intensity) 230 (M⁺. 1). 213 (M-17, 48). 200 (M-30. 3). 170 (M-60, 28), 141 (M-89, 100), 115 (M/2. 54).

Results and Discussion

Synthesis. In furoxanaldehydes 1-4, designed for alkyne formation on the solid surface *via* fragmentation of the furoxan ring. a formyl group is required to form an imine linkage with the amine groups on the surface.[15,16] In addition. either an aromatic ring or alkene functionality was introduced to the 3- or 4-position of the furoxan ring to stabilize the corresponding alkyne by conjugation effect. In a synthetic review of furoxans 1-4. dimerization of nitrile oxide[19] or oxidation of 1.2-dioxime[20] were initially considered. However. the cross coupling between different nitrile oxides (R₁CNO and R₂CNO) gave a low yield of furoxan formation. Thus, the unsymmetrical furoxans 1-4 were prepared using dinitrogen trioxide (N₂O₃. generated from NaNO₂/H⁺) addition to alkene as the key step following Gasco's method[18] with minor modification.

Furoxans possessing a formyl group 1, 2b and 3 were formed by the reaction of NaNO₂ in acetic acid with the corresponding alkenes. crotonaldehyde. 2a and 3a. respectively. In the synthesis of furoxan 1. multiple extractions from the aqueous reaction mixture were required due to its high polarity and it was finally isolated using column chromatography followed by recrystallization in petroleum ether. In addition, furoxan 1 was easily vaporized under low pressure and converted to a hydrate.
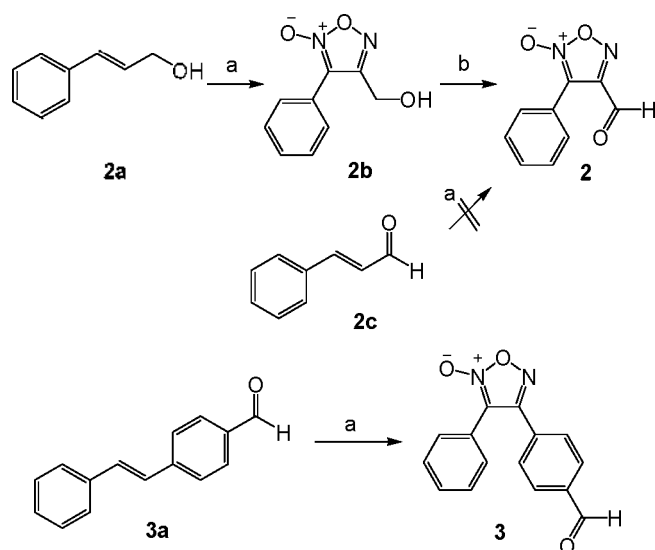
which therefore necessitated refrigerated storage. The formation of the furoxan ring was confirmed by the characteristic ¹³C NMR peaks assigned to the furoxan ring carbons at around δ 155 and 115 ppm.

PDC-mediated oxidation of alcohol 2b readily afforded furoxanaldehyde 2. Because of the similar R*f* values of 2 and 2b. aldehyde 2 was isolated at 48% yield from alcohol 2b by using repeated column chromatography. The direct conversion of cinnamaldehyde (2c) to furoxan 2 using NaNO₂/AcOH was unsuccessful. even under various reaction conditions. such as the variation of reaction temperature (50-150 °C). solvents (DMF. THF. MeOH. dioxane. CH₂Cl₂). pH and the equivalent reagent ratios. The retardation of cinnamaldehyde to react with N₂O₃ was attributed to the conjugation of a double bond with a carbonyl group causing a reduction of nucleophilicity of the double bond in 2c.

4-Formylphenyl-substituted furoxan 3 was prepared from styrylbenzaldehyde 3a using NaNO₂/AcOH in a minor modification to the known method.[21] Addition of dioxane to the reaction mixture afforded a homogenous solution and a better yield of product 3. whose structure was confirmed by two characteristic ¹³C-NMR peaks for the furoxan ring near δ 155 and 114 ppm, as well as a molecular ion peak at *m/z* 266. Synthetic efforts for the direct formylation[22] of the 3.4-diphenylfuroxan (5) using POCl₃-DMF, TiCl₄-dichloromethyl methyl ether. or CHCl₃-*t*-BuOK were unsuccessful. and instead led to deoxygenation into furazan 6 as a major product (Scheme 5).

Furoxan 4 substituted with an alkenyl group was produced from 1.4-*bis*(bromomethyl)benzene in 5 steps using the Wittig reaction[23] of phosphine ylide 4c with furoxanaldehyde 1 as the key step (Scheme 4). Initially. 1,4-*bis*(bromomethyl)benzene was mono-protected by NaOAc/DMF to give acetate 4b. which was converted to phosphonium bromide 4c by the treatment with Ph₃P in toluene. After treating with NaH, phosphonium bromide 4c was reacted with aldehyde 1 to give the conjugated furoxan 4d at 35% yield. Furoxanaldehyde 4 was finally obtained from the acetate 4d by deprotection with Na₂CO₃ in MeOH and the subsequent PDC oxidation.

Fragmentation of furoxanaldehydes. To exploit the fragmentation tendency of furoxans immobilized on a solid surface, e-beam-mediated fragmentation of furoxanaldehydes 1-4 in the gas phase was analyzed. as shown in Figs. 2-5. The fragmentation experiment was performed at 20 eV as the lowest value allowed in the MS instrument.

Fragmentation of furoxanaldehyde (1). The mass spectrum of furoxanaldehyde 1 (Fig. 2) without a double bond or aryl group at the furoxan ring showed characteristic peaks at *m/z* 128 (M⁺. rel. intensity 100%). 98 (M-30). 67 (M-61). The appearance of the molecular ion peak as a base peak suggested

Scheme 3. Syntheses of furoxans 2 and 3: (a) NaNO₂, AcOH, 50 °C and (b) PDC, CH₂Cl₂, 25 °C.
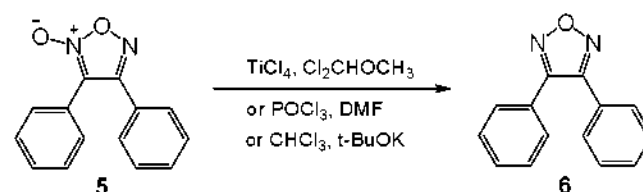
Scheme 4. Deoxygenation of furoxan to furazan
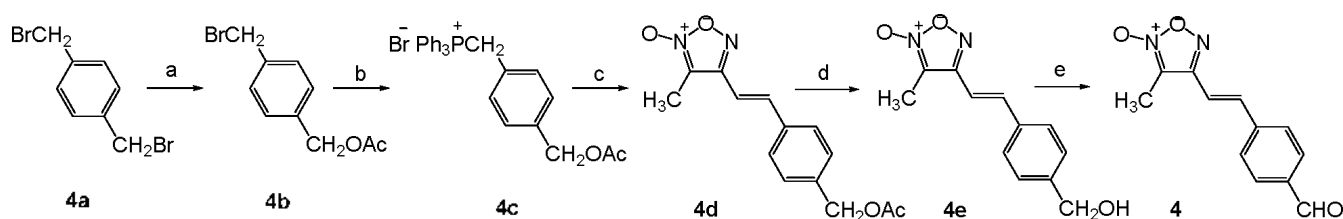
Scheme 5. Synthesis of furoxan **4**: (a) NaOAc. DMF: (b) PPh₃. toluene. 30 °C (c) NaH. 1. THF, -78 °C (d) Na₂CO₃. MeOH. 25 °C and (e) PDC. CH₂Cl₂, 25 °C.

that furoxan **1** is reluctant to cleave in comparison with other aldehydes **2-4** at a low energy electron impact. The lower fragmentation tendency of furoxan **1** indicates that the higher intensity at *m/z* 98 (M-30) in comparison to that at *m/z* 67 (M-61) originated from the initial loss of two equivalents of NO. Usually, the MS spectra of other furoxans[11,17] showed apparent M-60 peaks over M-30. Instead of an M-60 peak, the M-61 peak was clearly observed in Fig. 2. The propynyl acylium ion [CH₃CCCO]⁻ corresponding to the M-61 (M-60-H) peak is quite stable because the octet valency of all atoms has been satisfied. Thus, the losses of 2NO and one proton of the formyl group from furoxan **1** were considered to be facilitated by e-beam.

Fragmentations of furoxanaldehydes (2,3). The mass spectra of aldehydes **2** and **3** substituted with phenyl group(s) at the ring are shown in Figs. 3 and 4, respectively. The spectrum of

furoxan **3** substituted with phenyl groups at the 3,4-positions of the ring showed a distinctive peak at *m/z* 206 (M-60, rel. intensity 100%) with a molecular ion peak at *m/z* 266 (M⁺, rel. intensity 12%). Unlike the case of furoxan **1**, an M-30 (*m/z* 236) peak was not shown at all. This observation indicated the stability of the phenyl groups conjugated with a triple bond, so that the fragmentation to alkyne is highly facilitated and evolves two equivalents of NO from the furoxan.

In the fragmentation of furoxan **2**, a similar phenyl substituent effect was observed as in the case of furoxan **3**. The MS peaks of furoxan **2** appeared at *m/z* 190 (M⁺), 160 (M-30), 129 (M-61, rel. intensity 100%). As in the case of furoxan **1**, the M-61 peak showed a higher intensity than that of M-60 due to the high stability of the phenylethynyl acylium ion, [PhCCCO]⁻, generated by the loss of a formyl proton from the phenylethynyl aldehyde (M-60).
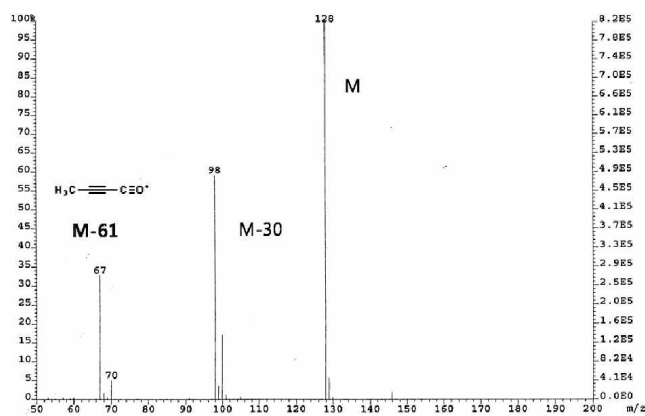

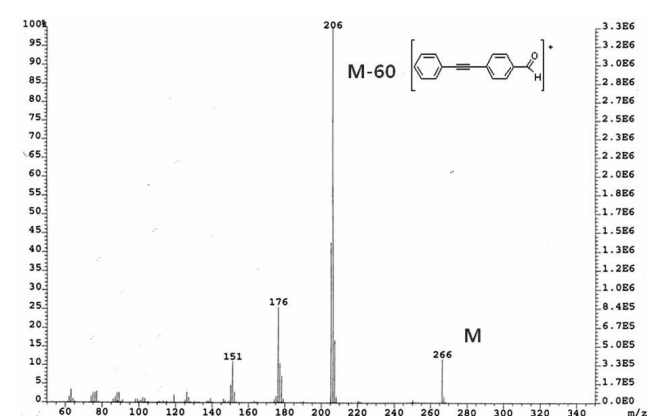**Figure 2.** EI mass spectrum of furoxanaldehyde **1**.

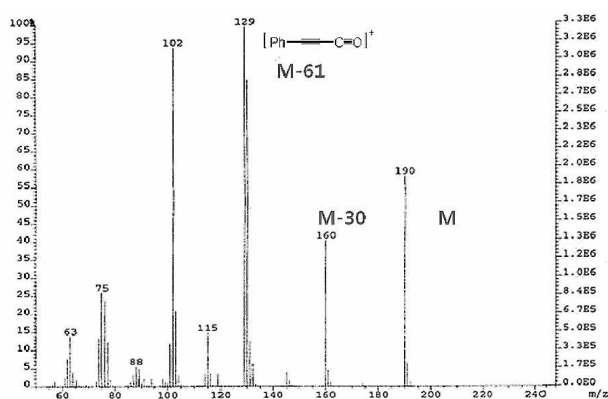**Figure 4.** EI mass spectrum of furoxanaldehyde **3**.

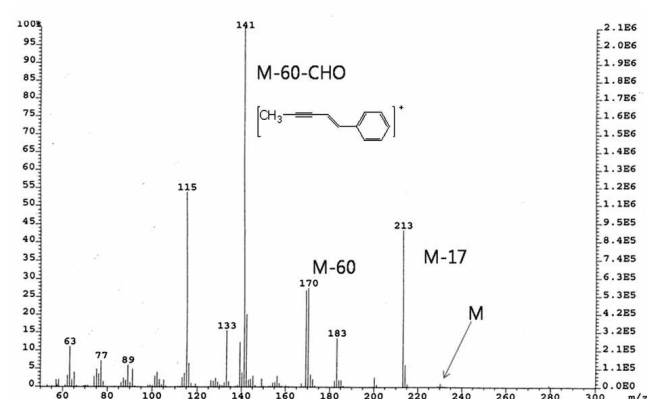**Figure 3.** EI mass spectrum of furoxanaldehyde **2**.

Figure 5. EI mass spectrum of furoxan **4**.

Furoxanaldehyde (4). The mass spectrum of furoxan **4** with a double bond conjugated with the furoxan ring showed peaks at m/z 230 (M^+, rel. intensity 1%), 213 (M-17, 48%), 200 (M-30, 3%), 170 (M-60, 28%), and 141 (M-60-CHO, 100%). As shown in Fig. 5, the fragmentation pattern was more complicated to interpret than those for furoxans **1-3**. A molecular ion peak barely appeared and a base peak was assigned to m/z 141. The origin of the base peak was attributed to the loss of both equivalents of NO and a CHO group (M-60-CHO). Considering the relative intensities of the M-60 (28%) and M-60-CHO (100%) peaks, the CHO cleavage was assumed to be more favored over the loss of NOs.

Conclusion

Furoxanaldehydes **1-4** were synthesized to study their fragmentation in the gas phase for alkyne generation on a solid surface applicable to nanopatterning. The furoxan ring of aldehydes **2** and **3** was prepared by the reaction of the corresponding alkenes **2a** and **3a** with $NaNO_2$ in acetic acid. Furoxan **4**, possessing a conjugated double bond, was prepared *via* the Wittig reaction of phosphonium bromide **4c** with aldehyde **1** as the key step. E-beam-mediated fragmentation of furoxan **3** containing diphenyl substituents afforded diphenylacetylene as the main fragmentation at higher efficiency than in the case of furoxans without the phenyl or double bond substituents. This result suggests that the aryl group could facilitate alkyne formation with the evolution of NO when it conjugated with the furoxan ring. In collaboration with the Pohang Accelerator Lab, a self-assembled monolayer (SAM) of furoxanaldehyde **3** was prepared on the silica and gold surface, after which furoxan **3** on the SAM was irradiated with extreme ultraviolet to give the corresponding alkyne at high efficiency, as expected in the gas phase fragmentation. These results will be reported soon.

References

1. Zhang, Y.; Luo, S.; Tang, Y.; Yi, L.; Hou, K. Y.; Cheng, J. P.; Zeng, X.; Wang, P. G. *Anal. Chem.* **2006**, *78*, 2001.

2. a) Sun, X. L.; Stabler, C. L.; Cazalis, C. S.; Chaikof, E. L. *Bioconjugate Chem.* **2006**, *17*, 52. b) Lee, J. K.; Chi, Y. S.; Choi, I. S. *Langmuir* **2004**, *20*, 3844.

3. Nandivada, H.; Chen, H.-Y.; Bondarenko, L.; Lehann, J. *Angew. Chem.* **2006**, *45*, 3360.

4. a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004. b) Zhao, Y. B.; Yan, Z. Y.; Liang, Y. M. *Tetrahedron Lett.* **2006**, *47*, 1545.

5. a) Murcia, M. J.; Naumann, C. A. *Biofunctionalization of Fluorescent Nanoparticles* in *Biofunctionalization of Nanomaterials*; Kumar, C., Ed.; WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2005; Chap 1, p 1. b) Meziani, M. J.; Lin, Y.; Sun, Y. P. *Conjugation of Nanomaterials with Proteins* in *Biofunctionalization of Nanomaterials*; Kumar, C., Ed.; WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2005; Chap 7, p 183.

6. He, P.; Dai, L. *Carbon Nanotube Biosensors* in *Biological and Biomedical Nanotechnology*; Lee, A. P.; Lee, L. J.; Ferrari, M., Eds.; Springer Science+Business Media, LCC: New York, 2006; Chap 6, p 171.

7. Soelhner, M. B.; Dickson, B. L.; Nilsson, R. T. *J. Am. Chem. Soc.* **2003**, *125*, 11790.

8. Cui, Y.; Wei, Q.; Park, H.; Lieber, C. M. *Science* **2001**, *293*, 1289.

9. a) Moncada, S.; Palmer, R. M. J.; Higgs, E. A. *Pharmacol. Rev.* **1991**, *43*, 109. b) Palmer, R. M. J.; Ferrige, A. G.; Moncada, S. *Nature* **1987**, *327*, 524. c) Furchagott, R. F.; Zawadzki, J. V. *Nature* **1980**, *288*, 373.

10. a) Sexton, D. J.; Muruganandam, A.; Mckenney, D. J.; Mutus, B. *Photochem. Photobiol.* **1994**, *59*, 463. b) Nathan, C. F.; Hibbs Jr., J. B. *Curr. Opin. Immunol.* **1991**, *3*, 65. c) Marletta, M. A.; Yoon, P. S.; Lyengar, R.; Leaf, C. D.; Wishnok, J. S. *Biochemistry* **1988**, *27*, 8706. d) Hibbs Jr., J. B.; Vavrin, Z.; Taintor, R. R. *J. Immunol.* **1987**, *138*, 550.

11. a) Montague, P. R.; Gancayco, C. D.; Winn, M. J.; Marchase, R. B.; Friedlander, M. J. *Science* **1994**, *263*, 973. b) Snyder, S. H. *Science* **1992**, *257*, 494.

12. a) Curran, D. P.; Fenk, C. *J. Am. Chem. Soc.* **1985**, *107*, 6023. b) Mitchell, W. R.; Paton, R. M. *Tetrahedron Lett.* **1979**, 2443.

13. Hwang, K.-J.; Kim, S. K.; Shim, S. C. *Chem. Lett.* **1998**, *8*, 859.

14. Hwang, K.-J.; Jo, I.; Shin, Y. A.; Yoo, S.; Lee, J. H. *Tetrahedron Lett.* **1995**, *36*, 3337.

15. Kim, C. O.; Jung, J. W.; Kim, M.; Kang, T. H.; Ihm, K.; Kim, K. J.; Kim, B.; Park, J. W.; Nam, H. W.; Hwang, K.-J. *Langmuir* **2003**, *19*, 4504.

16. a) Jung, Y. J.; La, Y. H.; Kim, H. J.; Kang, T. H.; Ihm, K.; Kim, K. J.; Kim, B. S.; Park, J. W. *Langmuir* **2003**, *19*, 4512. b) La, Y. H.; Kim, H. J.; Maeng, I. S.; Jung, Y. J.; Park, J. W.; Kang, T. H.; Kim, K. J.; Ihm, K.; Kim, B. *Langmuir* **2002**, *18*, 301.

17. a) Kim, G. Y. *Synthesis of Furoxan Derivatives for Cleavage Reaction on Solid Surface*, MS thesis; Hongik University: December, 2005. b) Heo, J.-M.; Kim, G. Y.; Hwang, K.-J. *J. Korean Chem. Soc.* **2007**, *51*, 160.

18. a) Calvino, R.; Gasco, A.; Menziani, E.; Serafino, A. *J. Heterocyclic Chem.* **1983**, *20*, 783. b) Fruttero, R.; Ferrarotti, B.; Serafino, A.; Stilo, A. D.; Gasco, A. *J. Heterocyclic Chem.* **1989**, *26*, 1345.

19. a) Hwang, K.-J.; Park, Y. C.; Kim, H. J.; Lee, J. H. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 1693. b) Hwang, K.-J.; Kang, H. *Bull. Kor. Chem. Soc.* **1998**, *19*, 506.

20. Das, O.; Paria, S.; Paine, T. K. *Tetrahedron Lett.* **2008**, *49*, 5924.

21. Velazquez, C.; Rao, P. N. P.; McDonald, R.; Knaus, E. E. *Bioorg. Med. Chem.* **2005**, *13*, 2749.

22. a) Mundy, B. P.; Ellerd, M. G. *Name Reactions and Reagents in Organic Synthesis*; Wiley: New York, 1988; pp 214-215. b) Witiak, D. T.; Williams, D. R.; Kakodkar, S. V.; Hite, G.; Shen, M.-S. *J. Org. Chem.* **1974**, *39*, 1242.

23. Dambacher, J.; Zhao, W.; El-Batta, A.; Anness, R.; Jiang, C.; Bergdahl, M. *Tetrahedron Lett.* **2005**, *46*, 4473.