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

Gi Young Kim, Jucheon Kim, Seung Hee Lee, Hyung Jin Kim,† and Kwang-Jin Hwang*

Department of Chemical System Engineering, Hongik University, Jochiwon, Chungnam 339-701, Korea
† E-mail: kjhwang@hongik.ac.kr

Center for Functional Nano Fine Chemicals, School of Applied Chemical Engineering, Chonnam National University, Gwangju 500-757, Korea
Received January 14, 2009, Accepted January 29, 2009

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 NaNO₂ 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 cycloaddition1-4 with organic azides, is applicable to biochips, fluorescence sensing films and surface conforming.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 attachment12 of alkyne compounds through covalent bonding or the spin coating of polymers having alkyne groups.13 Instead of the direct introduction of alkynes, if a potential alkyne functionality is attached and then followed by subsequent transformation to alkyne via 1,3-dipolar cycloaddition- or light-mediated cleavage reactions, it might be useful to nanoarrays and nanopatterning of a surface. In light of such applications, we focused on the synthesis and fragmentation of furoxanaldehydes (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 light13 or electronic14 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 substrates15 (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 substituents 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.
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 60F254 plates (Merck) and column chromatography (CC) on silica gel 60 (Merck, 230–400 mesh). 1H nuclear magnetic resonance (NMR) and mass spectra were recorded on 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 NaNO2 (17.2 g, 0.285 mol) in water (100 mL) was added crotonaldehyde (3.91 ml, 71 mmol) in AcOH (20 mL). The resulting solution was stirred for 12 h at 25 °C. The reaction mixture was neutralized with NaHCO3, extracted with CH2Cl2, dried over anhydrous MgSO4 and concentrated. The residue was purified by CC eluting with a 20% EtOAc/hexane solution to give furoxan 1 (17.2 g, 70%) as a white crystal. Mp 65–67 °C; 1H NMR (CDCl3) δ 2.38 (s, 3H, C-H3), 5.10 (s, 2H, C=O), 7.49–7.81 (m, 5H, Ph); MS m/z (relative intensity) 128 (M+, 100), 115 (M-117, 90), 102 (M-134, 26) 92 (M-155, 3); 13C NMR (CDCl3) δ 122.4, 128.4, 131.4, 137.8, 155.2, 191.2; MS m/z (relative intensity); 266 (M+, 13), 206 (M-60, 100), 176 (M-90, 26) 151 (M-115, 11).

4-(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 MgSO4, 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. 1H NMR (CDCl3) δ 2.09 (s, 3H, CH3), 4.47 (s, 2H, BrC=CH2), 5.08 (s, 2H, OCH2), 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 4d (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 4b (13.5 mmol) in AcOH (6 mL) and 1,4-dioxane (10 mL) at 50 °C. The resulting mixture was stirred for 4 h at 50 °C. The reaction mixture was neutralized with NaHCO3, extracted with CH2Cl2, dried over anhydrous MgSO4 and concentrated. The residue was purified by CC eluting with CH2Cl2 (three times), dried over anhydrous MgSO4, and concentrated. The residue was purified by CC eluting with an 80% EtOAc/hexane solution 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 NaNO2 (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 NaHCO3 and extracted with EtOAc. The extract was dried over anhydrous MgSO4 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; 1H NMR (CDCl3) δ 6.40–7.60 (m, H, C6H5), 7.72 (d, J = 8.0 Hz, 2H, C6H4), 7.97 (d, J = 8.0 Hz, 2H, C6H4), 10.09 (s, 1H, CHO); 13C NMR (CDCl3) δ 114.1, 122.5, 128.4, 128.8, 129.2, 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-(4-Formylphenyl)-3-phenyl furoxan (4c). A mixture of NaOH (19.6 g, 0.495 mol) and Na2CO3 (0.93 g, 10.8 mmol) in MeOH (30 ml) was stirred for 3 h at 25 °C. The resulting mixture was poured into water and extracted with CH2Cl2 (three times), dried over anhydrous MgSO4, and concentrated. The residue was purified by CC eluting with a 20% EtOAc/hexane solution 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 NaNO2 (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 NaHCO3 and extracted with EtOAc. The extract was dried over anhydrous MgSO4 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; 1H NMR (CDCl3) δ 6.40–7.60 (m, H, C6H5), 7.72 (d, J = 8.0 Hz, 2H, C6H4), 7.97 (d, J = 8.0 Hz, 2H, C6H4), 10.09 (s, 1H, CHO); 13C NMR (CDCl3) δ 114.1, 122.5, 128.4, 128.8, 129.2, 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-(4-Formylphenyl)-3-phenyl furoxan (3). To a stirred solution 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 NaNO2 (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 NaHCO3 and extracted with EtOAc. The extract was dried over anhydrous MgSO4 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; 1H NMR (CDCl3) δ 6.40–7.60 (m, H, C6H5), 7.72 (d, J = 8.0 Hz, 2H, C6H4), 7.97 (d, J = 8.0 Hz, 2H, C6H4), 10.09 (s, 1H, CHO); 13C NMR (CDCl3) δ 114.1, 122.5, 128.4, 128.8, 129.2, 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).
Furoxanaldehydes for Alkyne Formation

(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 (9.00 g, 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 of furoxan recrystallization in petroleum ether. In addition, furoxan finally isolated using column chromatography followed by mixture were required due to its high polarity and it was purified by CC eluting with a 33% EtOAc/hexane solution of furoxan formation. Thus, the unsymmetrical furoxans were initially considered. However, the cross coupling between different nitrile oxides (R₁CNO and R₂CNO) gave a low yield of product 3, whose structure was confirmed by two characteristic ¹³C-NMR peaks for the furoxan ring near 128 (M⁺, rel. intensity 100%), 98 (M-30), 67 (M-61). The fragmentation pattern of furoxanaldehydes was confirmed by the characteristic ¹³C-NMR peaks assigned to the furoxan ring carbons at around 155 and 115 ppm.

PDC-mediated oxidation of alcohol 2b readily afforded furoxanaldehyde 2. Because of the similar R₁ 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 furoxanaldehyde 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/MeOH in a minor modification to the known method. 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 155 and 114 ppm, as well as a molecular ion peak at m/z 266. Synthetic efforts for the direct formylation 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 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 tolane. After treating with NaH, phosphonium bromide 4c was reacted with aldehyde 1 to give the conjugated furoxan 4d at 35% yield. Furoxanaldehyde 4d 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, 3,4-disubstituted 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.
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\textsuperscript{14,17} 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 \([\text{CH}_3\text{C}==\text{CO}]^+\) 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, \([\text{PhCC}==\text{CO}]^+\), generated by the loss of a formyl proton from the phenylethynyl aldehyde (M-60).
Furoxanaldehydes for Alkyne Formation

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 NaN3 in acetic acid. Furoxan 4, possessing a conjugated double bond, was prepared via the Wittig reaction of phosphonium bromide 4e 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.

Acknowledgments. This work was supported by the “System IC 2010” project of the Korea Ministry of Knowledge Economy.

References