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Notes

Synthesis and Characterization of Bisimidazolylfuroxan Derivatives

Tae Keun Kim, Byung Woo Lee, Hai Whang Lee, Kyoo-Hyun Chung,* and Jin Seuk Kim†

High Energy Material Research Center, Department of Chemistry, Inha University, Incheon 402-751, Korea
**E-mail: kyoohyun@inha.ac.kr*
†Agency for Defense Development, Yuseong P.O. Box 35-5 (TRC-3-6), Daejeon 305-600, Korea
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Since TNT and its mixture were introduced into warfare technology, various explosives have been continuously developed. Consequently, there has been remarkable success to synthesize much higher energetic materials such as RDX, HMX, HNIW and so on. However, recent interest in munitions system focused on lower sensitivities to impact, shock and friction to reduce accidental initiation, along with higher performance.[1] Since most compounds containing *N*-heterocycles have high nitrogen content in their structures, high crystal density, and good thermal stability, nitro and amino derivatives were plausible energetic materials as explosives and propellants.[2]

Nitroazoles have been studied for their high energetic performance as well as biological activities. Most of nitroimidazoles, such as 2,4-dinitroimidazole, 2,4,5-trinitroimidazole, and 4,4',5,5'-tetranitro-2,2'-bisimidazole (TNBI) were readily synthesized with relatively low cost.[3]

2,4-Dinitroimidazole was regarded as some high energetic compound with insensitive characteristics. Meanwhile, 2,4,5-trinitroimidazole and TNBI have higher energetic performance, but were too hygroscopic to be used as practical explosives.[3c,4]

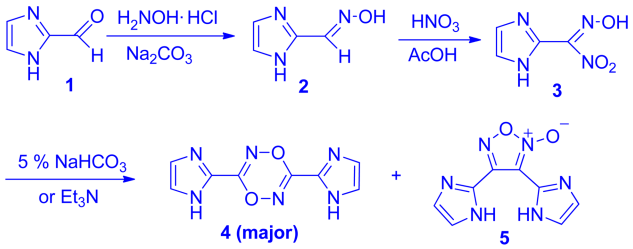
1,2,5-Oxadiazole-2-oxide (furoxan) compounds also have been regarded as potent explosives and propellants. Because of high nitrogen contents, high energy density and good oxygen balance, bis(nitrofurazano)furoxan (BNFF) and its derivatives were prepared to study their explosive properties.[2,5] On the bases of thermal properties and calculated densities, BNFF was expected to exhibit the best explosive performance among the related compounds.[5d] In line with continuous efforts to prepare novel molecular explosives, we describe syntheses of a bisimidazolylfuroxan and its nitro derivatives.

Since a 1,3-dipolar cyclization of a nitrile oxide was one of the most valuable methods to give a furoxan, we tried to find a good method to synthesize imidazolyl nitrile oxides. Generally, a nitrile oxide was generated from hydroximinoyl halides, oximes, nitrolic acids and primary nitroalkanes. Without the isolation of the corresponding nitrile oxide, the further reaction took place to afford several products such as furoxans, 1,4-dioxa-2,5-diazines, and nitrile oxide derived polymers.[6]

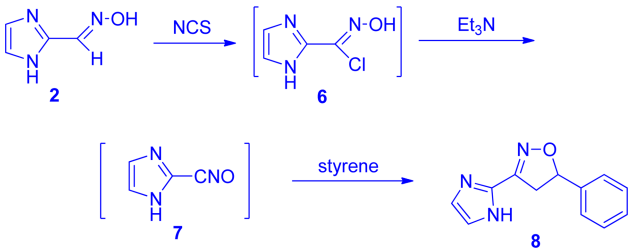
Nitrolic acids were extensively studied for donation of nitric oxide, which was involved in a wide range of biological activities. Imidazole 2- and 5-nitrolic acids were prepared from the commercially available corresponding imidazolecarboxaldehydes for ocular effects.[7] Meanwhile, the corresponding chloroximes were not synthesized yet. Therefore, we first tried to employ imidazole 2-nitrolic acid (**3**) for the generation of the nitrile oxide to synthesize bisimidazolylfuroxan.[8]

When the reaction of nitrolic acid **3** with K_2CO_3 in the presence of various solvents, the major product was the corresponding 1,4-dioxa-2,5-diazine derivative **4**, the 6-membered isomer. Regardless of other bases like Et_3N or homogeneity in the reaction media, furoxan **5**, the 5-membered isomer was not yielded (Scheme 1).[5,8]

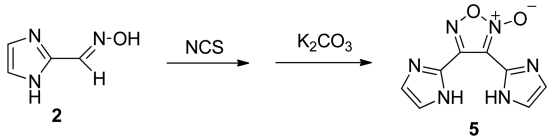
A chloroxime was usually prepared in the reaction of an oxime with NCS, NaOCl, or *t*BuOCl.[9] When oxime **2** was treated with NCS and the resulting mixture was extracted



Scheme 1. Dimerization of nitrolic acid **3**.



Scheme 2. Confirmation of nitrile oxide **7**.



Scheme 3. Formation of furoxan **5**.

with ether and concentrated *in vacuo*, chloroxime **6** seemed to be major in the crude mixture. However, the number of spots on TLC increased within a few hours because of decomposition. When the etheral solution was reacted with Et_3N without evaporation, and styrene was added into the mixture, isoxazoline **8** was afforded and furoxan compounds were not observed. As a result, nitrile oxide **7** was generated and 1,3-dipolar cyclization with the alkene dipolarophile proceeded faster than the dimerization (Scheme 2).[5b,10]

Because chloroxime **6** could be prepared and converted to nitrile oxide **7** upon treatment with a base, the etheral mixture was poured into aqueous K_2CO_3. The dimerization proceeded to give bisimidazolylfuroxan **5** which has a peak around 115 ppm in ^{13}C NMR, indicating a furoxan moiety (Scheme 3).

Dioxadiazine **4**, the isomer of bisimidazolylfuroxan **5** exhibited major exothermic peak at 136.94 °C on DSC analysis. It has significantly lower decomposition point than that of bisimidazolylfuroxan **5** which exhibited major exothermic peak at 237.01 °C (Figure 1). As previously reported, the

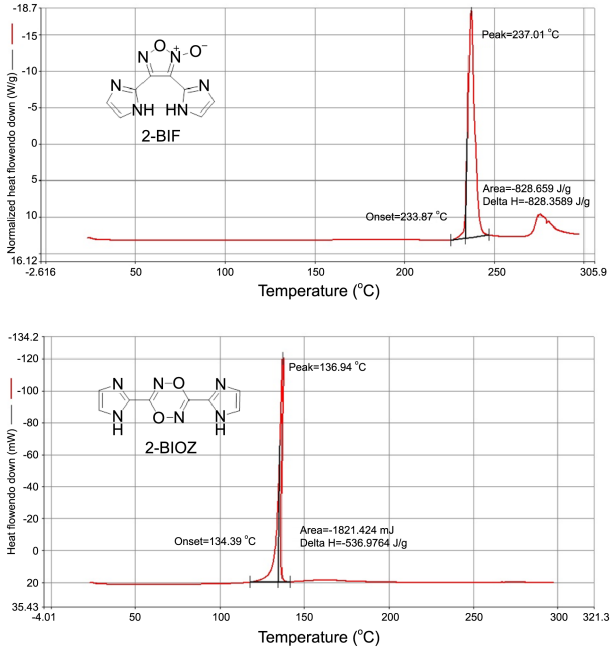
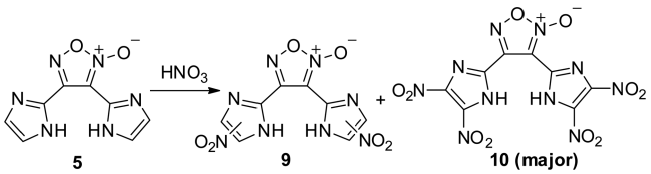
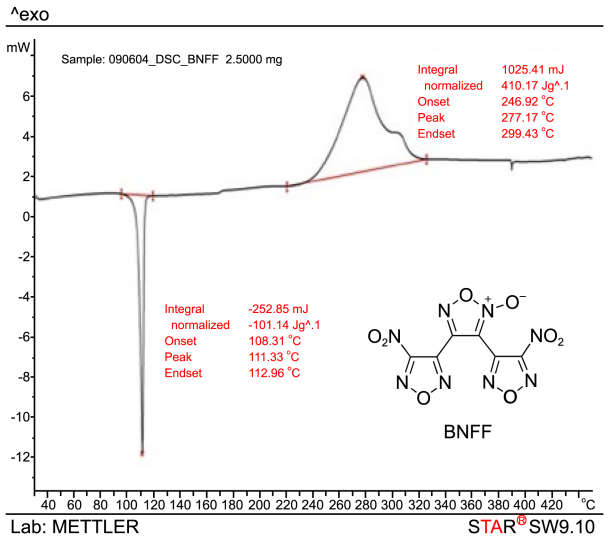


Figure 1. DSC of dioxadiazine **4** and furoxan **5**.



Scheme 4. Nitration of furoxan **5**.



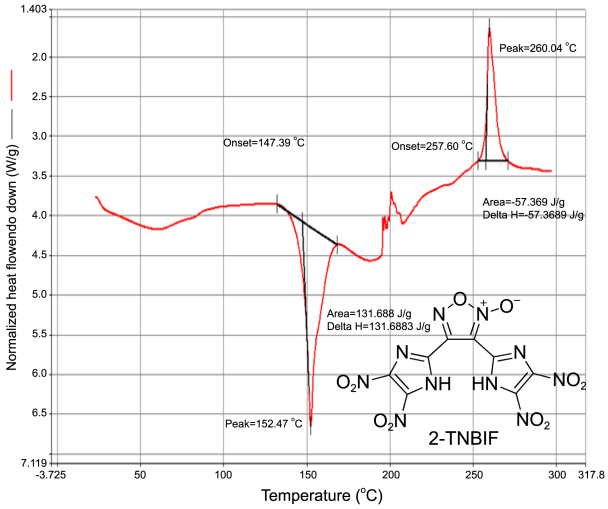


Figure 2. DSC of furoxan derivatives.

dioxadiazine ring, the structural isomer of furoxan generally causes a significant decrease of thermal stabilities.[5c]

Next, the nitration of compound **5** was tried to afford nitrofuroxan. In the reaction of furoxan **5** with anhydrous HNO_3, the major product was not dinitrofuroxan **9**, but tetranitrobisimidazolylfuroxan (2-TNBIF, **10**, Scheme 4).

As shown in Figure 2, DSC curve for 2-TNBIF showed that an endothermic peak began at 147.39 °C with summit peak at 152.47 °C and major exothermic peak at 260.04 °C. From this and previous results, we found out some similar thermal stabilities in a series of furoxan derivatives.[5d]

In conclusion, the imidazole derivatives containing furoxan and dioxadiazine moieties were synthesized *via* the dimerization of the corresponding nitrile oxide. However, the major compound was selectively given, depending on the nitrile oxide sources, obtained from the nitrolic acid or the chloroxime. On the basis of the thermal properties of DSC, the nitroimidazole derivative showed significant thermal unstability and lower decomposition temperature compared to BNFF. Moreover, the tetranitro derivatives were very

soluble in water, presumably because of high acidity. This methodology could be applied for the synthesis of furoxan derivatives of nitroazoles, such as pyrazole, triazole, and tetrazole.

Experimental Section

General. $^{1}H/^{13}C$ NMR spectra were recorded on Unitynova 400 instrument. Melting points were performed on recrystallized solids and recorded on a SRS Optimelt or electrothermal 9100 melting point apparatus and were uncorrected.

Caution: Imidazole and furoxan derivatives are suspected explosives. Should be treated with appropriate precaution.

Imidazole-2-carboxaldehyde Oxime (2).[7] Sodium carbonate (1.10 g, 10.4 mmol) was added to a solution of hydroxylamine hydrochloride (1.44 g, 20.7 mmol) in water (5 ml) and adjusted to pH 7. Imidazole-2-carboxaldehyde (**1**, 1.00 g, 10.4 mmol) was added potionwise to resulting reaction mixture. After being stirred for 1 h at 70 ºC, the product was filtered, washed with cold water and dried *in vacuo* to give a white solid (0.83 g, 72%). mp 178 ºC (dec.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.97 (1H, s), 7.14 (1H, s), 7.09 (1H, s); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 140.9, 140.3, 138.6, 136.9.

Imidazole-2-nitrolic Acid (3).[7] To a solution of imidazole-2-carboxaldehyde oxime (**2**, 0.25 g, 2.25 mmol) in acetic acid (1.5 mL), 98% nitric acid (0.3 mL, 7.20 mmol) was added dropwise at 0-4 ºC. After being stirred for 3 h at ambient temperature, the reaction mixture was filtered, washed with diethyl ether and dried *in vacuo* to give a yellow solid (0.32 g, 91%). mp 116 ºC; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.60 (2H, s); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 149.8, 129.2, 124.1.

3,6-Bis(imidazol-2-yl)-1,4,2,5-dioxadiazine (4). Imidazole-2-nitrolic acid (**3**, 0.62 g, 8.33 mmol) was added potionwise to 5% sodium bicarbonate (14 mL, 8.33 mmol) at 4 ºC. After being stirred for 30 min at 0-4 ºC, the reaction mixture was filtered, washed with cold water and dried *in vacuo* to give a brown solid (0.32 g, 91%). mp 130 ºC; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.35 (4H, s); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 153.1, 131.2, 126.2; ESI-MS (pos.): 240.94 ($[M+Na]^+$, $C_8H_6N_6O_2^+$; calc. 218.14).

3,4-Bis(imidazol-2-yl)furoxan (5). To a solution of *N*-chlorosuccinimide (3.40 g, 24 mmol) in 50% aqueous methanol (150 mL), imidazole-2-carboxaldehyde oxime (**2**, 2.24 g, 20.2 mmol) in methanol (100 mL) was added dropwise at 0-4 ºC. After being stirred for 2 h at 0-4 ºC, 3% aqueous potassium carbonate (100 mL, 25 mmol) was added slowly to the mixture at 0-4 ºC. After being stirred 2 h at ambient temperature, the reaction mixture was concentrated *in vacuo* and extracted with diethyl ether (50 mL) four times. The organic layer was washed with distilled water, dried with $MgSO_4$ and concentrated *in vacuo* to give a crude product as a brown solid. The crude product was purified by flash silica gel chromatography (THF/Chloroform = 1:9) to give a white solid (2.5 g, 58%). mp 224 ºC (dec.); ^{1}H NMR (CD_3OD, 400 MHz) δ 7.87 (2H, s), 7.05 (2H, s); ^{13}C NMR (CD_3OD, 400 MHz) δ 142.0, 139.7, 130.4, 126.2, 115.5; ESI-MS (pos.): 241.91 ($[M+Na]^+$, $C_8H_6N_6O_2^+$; calc. 218.14).

3,4-Bis(4,5-dinrtoimidazol-2-yl)furoxan (10). 3,4-Bis (imidazol-2-yl)furoxan (**5**, 0.5 g, 23 mmol) was added potionwise to 100% nitric acid (7 mL) at 0 ºC. After being stirred for 2 h at ambient temperature, the reaction mixture was quenched with acetic acid (70 mL) and concentrated *in vacuo* to give a crude yellow liquid. The crude product was recrystallized from methanol/MC to give an ivory solid (0.62 g, 68%). mp 147 ºC (melt), 257 (dec.); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 163.2, 159.5, 137.1, 129.6, 118.1; ESI-MS (pos.): 437.18 ($[M+K]^+$, $C_8H_2N_{10}O_{10}^+$; calc. 398.16).

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10. Compound **8** was exclusively given in the reaction of nitrolic acid **3** with styrene in the presence of a base.