Regular Article

Development of Nitrolactonization Mediated by Iron(III) Nitrate Nonahydrate

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The nitrolactonization of alkenyl carboxylic acids mediated by $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ has been developed. Nitrolactones were obtained in up to 93% yield by treatment of alkenyl carboxylic acids with $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$. Mechanistic studies disclosed that the reaction proceeded through a radical intermediate generated from addition of NO_2 to alkenyl carboxylic acids.

Key words nitrolactonization; iron(III) nitrate nonahydrate; nitrogen dioxide; radical intermediate

Introduction

Nitro compounds are useful synthons in synthetic organic chemistry due to their availability for various transformations. The strong electron-withdrawing property of the nitro group plays an important role in C–C bond formation reactions^{1,2)} including the nitro–aldol reaction (Henry reaction),^{3–5)} Michael reaction,^{6–11)} and alkylation.^{12,13)} Nitrones and nitrile oxides generated from nitro compounds undergo 1,3-dipole cycloaddition reaction to give various heterocycles.^{14–16)} The nitro group can be converted into a carbonyl or amino group through the Nef reaction^{17,18)} or reduction, respectively.¹⁹⁾ For these reasons, nitro compounds are heavily used as versatile starting materials in the synthesis of natural products and drugs.^{20–25)} Nitration mediated by iron(III) nitrate nonahydrate ($\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$) has been recently reported.^{26–35)} The use of $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ has attracted attention as a source of nitrogen dioxide in organic synthesis due to its properties as a readily available reagent of low toxicity and cost. It has been suggested that these nitrations proceed *via* a radical intermediate derived by addition of nitrogen dioxide generated from $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ with heating.³⁶⁾ We envisioned the novel development of a nitrolactonization of styrene derivative **1** mediated by $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (Chart 1). Because nitrolactone **2** could lead to 1,2-aminoalcohol and amino acid derivatives bearing a tetrasubstituted carbon center, the development of a new nitrolactonization reaction leading to substituted nitrolactones would be useful not only in natural product synthesis but in medicinal chemistry.

Precursor **3a** for nitrolactonization was prepared from benzene by Friedel–Crafts acylation with succinic anhydride followed by a Wittig reaction of the resultant ketone **4a** (Chart 2).

Nitrolactonization of carboxylic acid **3a** was investigated according to the reported method of generating NO_2 from $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ ³⁷⁾ (Table 1). Treatment of **3a** with 0.5 equivalent (equiv.) of $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ in 1,2-dichlorobenzene at 130 °C for 4 h afforded nitrolactone **5a**, hydroxylactone **6a**, and lactone **7a** in 48, 3, and 7% yields, respectively (entry 1). The nitration regioselectively took place at the olefinic moiety of **3a** to produce **5a**, with the product structure confirmed by X-ray crystallographic analysis.³⁸⁾ Hydroxylactone **6a** was en-

visioned to be produced *via* a nitrite lactone intermediate due to the ambident property of NO_2 while lactone **7a** was likely produced *via* proto-lactonization mediated by HNO_3 that was generated from NO_2 gas and water.³⁹⁾ The effect of the metal nitrate was investigated by use of copper(II) nitrate, zinc nitrate, and silver nitrate in the reaction (entries 2–4). These metal nitrates afforded nitrolactone **5** in lower yield when compared to the reaction with $\text{Fe}(\text{NO}_3)_3$ (entry 1 vs. entries 2–4). Reducing or increasing the number of equivalents of $\text{Fe}(\text{NO}_3)_3$ resulted in diminished yields (entry 1 vs. entries 5 and 6). The differences in the yields of products involved in the number of equivalent of $\text{Fe}(\text{NO}_3)_3$ would attribute the concentration of NO_2 generated for $\text{Fe}(\text{NO}_3)_3$. Lower equivalent of $\text{Fe}(\text{NO}_3)_3$ would not be enough to undergo NO_2 addition reaction but lead to decomposition of **5a** probably due to the equilibrium mixture between NO_2 and its various reactive isomers of N_2O_4 (entry 5).^{40–43)} Higher equivalent of $\text{Fe}(\text{NO}_3)_3$ would generate a high concentration of HNO_3 , which lead to proto-lactonization rather than radical addition of NO_2 (entry 6). To investigate the assumption that the heating-up time and reaction temperature would affect the reaction progress and yield, the reaction mixture was quickly heated (entries 7–9). When the reaction was conducted in a pre-heated oil bath at 130 °C, nitrolactone **5a** was produced in an improved yield of 58% and the reaction time was shortened (entry 1 vs. entry 7). Addition of KHCO_3 as a base to suppress the formation of byproduct **7a** did not result in an improved yield of **5a** (entry 8). Addition of proton-sponge[®] resulted in a complex product

Chart 1. Nitrolactonization Mediated by $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ Chart 2. Synthesis of Precursor **3a**

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Table 1. Optimization of Reaction Conditions^{a)}

Entry	Metal nitrate	X	Time (h)	Yield (%)		
				5a	6a	7a
1	Fe(NO ₃) ₃ ·9H ₂ O	0.5	4	48	3	7
2	Cu(NO ₃) ₂ ·3H ₂ O	0.75	5	36	12	4
3	Zn(NO ₃) ₂ ·6H ₂ O	0.75	3	8	8	30
4	AgNO ₃	1.5	3	3	4	0
5	Fe(NO ₃) ₃ ·9H ₂ O	0.34	4	7	4	5
6	Fe(NO ₃) ₃ ·9H ₂ O	0.67	4.5	24	3	49
7 ^{b)}	Fe(NO ₃) ₃ ·9H ₂ O	0.5	1.5	58	5	13
8 ^{b,c)}	Fe(NO ₃) ₃ ·9H ₂ O	0.5	2.5	54	approx. 10 ^{d)}	7
9 ^{b,e)}	Fe(NO ₃) ₃ ·9H ₂ O	0.5	24	0	0	0

a) A stirring mixture of metal nitrate and **3** in 1,2-dichlorobenzene was heated gradually from room temperature (r.t.) to 130 °C and after temperature reached at 130 °C, the reaction was run for the indicated time. b) The reaction was performed in pre-heated oil bath (130 °C). c) 0.3 equiv. of KHCO₃ was added. d) A small amount of 4-phenyl-4-oxobutanoic acid was contained. e) 1.0 equiv. of proton-sponge[®] was added.

Table 2. Effects of Substituent at Phenyl Group

Entry	Starting material	R	Time (h)	Products	Yield (%)	
					5	7
1	3b	OMe	3	5b , 7b	12	69
2	3c	NO ₂	2	5c	16	0
3	3d	CN	4	5d	26	0

Table 3. Nitrolactonization of Benzoic Acid Derivatives **8**

9a (R = H): 22 h, 93%	9b (R = OMe): 0.5 h, 65% (10b : 30%)	9c (R = Me): 0.5 h, 89% (10c : 11%)	9d (R = Br): 0.5 h, 67%
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mixture (entry 9).

The effect of substitution at the phenyl group of starting material **3** was examined (Table 2). Treatment of **3b** with Fe(NO₃)₃·9H₂O in 1,2-dichlorobenzene at 130 °C afforded nitrolactone **5b** and lactone **7b** in 12 and 69% yields, respectively, without production of hydroxylactone. The yield of **7b** was higher than that of **5b** because the electron-donating effect of the methoxy group prompted a protonation reaction instead of the radical addition of nitrogen dioxide (entry 1). Substituents bearing electron-withdrawing groups such as NO₂ and CN at phenyl group resulted in low yields of **5c** and **5d** due to com-

plication in reaction (entries 2 and 3).

The nitrolactonization of benzoic acid derivatives **8a–d** was investigated to determine whether yields would improve due to acceleration of the cyclization rate and stabilization of the radical intermediate (*vide infra*) (Table 3). The reaction of **8a** for 22 h proceeded smoothly to give **9a**⁴⁴⁾ as a sole product in 93% yield. Nitrolactonization of compounds **8b** and **8c** bearing electron-donating substituents at the aromatic ring produced not only **9b** (65% yield) and **9c** (89% yield), respectively, but also **10b** (30% yield) and **10c** (11% yield), respectively, as a result of addition of nitrogen dioxide and the

Chart 3. Plausible Mechanism

Chart 4. Effect of BHT for Nitrolactonization

competing formation of a stable cation at the double benzylic position. Substitution of a bromo group at the aromatic ring, which can be converted into various functional groups, resulted in a reduced yield of nitrolactone **9d** (67%) but lactone **10d** was not observed.

A plausible mechanism is shown in Chart 3. Nitrogen dioxide generated from $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ by pyrolysis would react with **3a** at nitrogen atom to lead to radical intermediate **A**. Oxidation of **A**, which might be mediated by $\text{Fe}(\text{NO}_3)_3$ and/or HNO_3 , would give carbocation **B**, which would undergo cyclization to form **5a**. This radical mechanism is supported by the fact that nitrolactonization of **8a** in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical scavenger reduced the yield of **9a** (12%) (Table 3, entry 1 vs. Chart 4) and recovered **8a** in 16% yield. Isolation of **8a** and **9a** was possible although other products could be unidentified because of complication in the reaction. Through a similar process leading to production of **5a**, hydroxylactone **6a** would be obtained through nitrite radical intermediates **C**, carbocation **D**, and nitrite **E**, sequentially. It was assumed that cleavage of the O–NO bond of **E** took place in the reaction media or by addition of water during the workup stage. The ambident property of NO_2 might produce nitrite intermediate **C**. It had been reported not only that partial pressure of oxygen influenced the production of nitrite adducts in the reaction of isobutylene and N_2O_4 which has been regarded as an equilibrium mixture with NO_2 ,^{40–43,45} but also that oxidative cleavage of a tetra-substituted olefin catalyzed by $\text{Fe}(\text{NO}_3)_3$ would proceed *via* a dinitrite intermediate in the presence of molecular oxygen.³⁷ We speculated that production of **6a** might be related to the amount of dissolved oxygen in the reaction media, however the detailed effect of the dissolved oxygen on the production of **6a** was unclear. Lactone **7a** was obtained *via* carbocation **F** by catalysis of nitric acid generated from H_2O and NO_2 in the reaction media.

The nitrolactonization of carboxylic acids mediated by $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ was developed. Mechanistic studies disclosed that the reaction proceeded *via* a radical intermediate derived from addition of NO_2 , which was generated by pyrolysis of $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$, at the olefin moiety. These results demon-

strate the utility of $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ as a source of nitrogen dioxide and could lead to the development of new reactions mediated by $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$.

Experimental

General ^1H -NMR were measured in CDCl_3 or dimethyl sulfoxide ($\text{DMSO}-d_6$) solution and referenced from tetramethylsilane (TMS) (0.00 ppm) using JEOL JNM ECA-600 (600 MHz) or JEOL JNM ECA-400 (400 MHz) spectrophotometer, unless otherwise noted. ^{13}C -NMR were measured in CDCl_3 solution and referenced to CDCl_3 (77.0 ppm), $\text{DMSO}-d_6$ ($(\text{CD}_3)_2\text{SO}$) (39.5 ppm) or CD_3OD (49.0 ppm) using JEOL JNM ECA-600 (150 MHz) or JEOL JNM ECX-400 (100 MHz) spectrophotometer, unless otherwise noted. Chemical shifts are reported in ppm. When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. IR spectra were recorded on Horiba IR-710 spectrometer. Mass spectra were obtained on JEOL JMS-T100TD. Flash column chromatography was performed on Silica Gel (SiliaFlash® F60). TLC was performed on precoated plates (0.25 mm, silica gel Merck Kieselgel 60F₂₄₅), and compounds were visualized with UV light and *p*-anisaldehyde stain or phosphomolybdic acid stain. Melting points were measured with Yanaco MICRO MELTING POINT APPARATUS. 1,2-Dichlorobenzene was purchased from TOKYO CHEMICAL INDUSTRY CO., LTD. (Japan) and used without any purifications. $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ was purchased from FUJIFILM Wako Pure Chemical Corporation (Japan) and used without any purifications.

Compounds **3a**,⁴⁶⁾ **3c**,⁴⁷⁾ **3d**,⁴⁸⁾ and **8a–d**⁴⁹⁾ were prepared according to the literatures and identified with ^1H -NMR by comparison with the reported ones.

General Procedure 1: Optimization of Reaction Conditions (Table 1) A mixture of **3a** (47.0 mg, 0.27 mmol) and metal nitrate in 1,2-dichlorobenzene (2.7 mL) was stirred at 130 °C. After being stirred for the indicated time in Table 1, the reaction was quenched by addition of sat. aq. NaHCO_3 and the resulting mixture was filtered through a pad of Celite. The filtrate was extracted with CH_2Cl_2 . The extracts were washed with brine, and dried over Na_2SO_4 , filtered, and concentrated. The residue was purified through silica gel column chromatography (hexane/AcOEt = 8/2 to 7/3) to give **5a**, **6a**, and **7a**, respectively.

Entry 1

According to the general procedure 1, the reaction was performed with $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (54.0 mg, 0.13 mmol) for 4 h to give **5a** (28.6 mg, 48%), **6a** (1.7 mg, 3%), and **7a** (3.5 mg, 7%),

respectively.

Entry 2

According to the general procedure 1, the reaction was performed with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (48.3 mg, 0.2 mmol) for 5 h to give **5a** (21.0 mg, 36%), **6a** (6.4 mg, 12%), and **7a** (1.7 mg, 4%), respectively.

Entry 3

According to the general procedure 1, the reaction was performed with $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (59.5 mg, 0.2 mmol) for 3 h to give **5a** (4.6 mg, 8%), **6a** (3.9 mg, 8%), and **7a** (14.2 mg, 30%), respectively.

Entry 4

According to the general procedure 1, the reaction was performed with AgNO_3 (68.0 mg, 0.4 mmol) for 3 h to give **5a** (1.6 mg, 3%), **6a** (1.9 mg, 4%), and recovered **3a** (1.2 mg, 3%), respectively.

Entry 5

According to the general procedure 1, the reaction was performed with $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (36.7 mg, 0.09 mmol) for 4 h to give **5a** (4.3 mg, 7%), **6a** (2.1 mg, 4%), and **7a** (2.3 mg, 5%), respectively.

Entry 6

According to the general procedure 1, the reaction was performed with $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (72.0 mg, 0.18 mmol) for 4.5 h to give **5a** (14.4 mg, 24%), **6a** (1.5 mg, 3%), and **7a** (23.2 mg, 49%), respectively.

Entry 7

A mixture of **3a** (44.0 mg, 0.25 mmol) and $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (50.5 mg, 0.13 mmol) in 1,2-dichlorobenzene (2.5 mL) was lowered into pre-heated oil bath (130 °C). After being stirred for 1.5 h at same temperature, the mixture was cooled to r.t. and quenched by addition of sat. aq. NaHCO_3 . The resulting mixture was filtered through a pad of Celite. The filtrate was extracted with CH_2Cl_2 . The extracts were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified through silica gel column chromatography (hexane/ AcOEt = 9/1 to 3/2) to give **5a** (31.8 mg, 58%), **6a** (2.6 mg, 5%), and **7a** (5.6 mg, 13%), respectively.

Entry 8

A mixture of **3a** (44.0 mg, 0.25 mmol), $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (50.5 mg, 0.13 mmol), and KHCO_3 (7.5 mg, 0.075 mmol) in 1,2-dichlorobenzene (2.5 mL) was lowered into pre-heated oil bath (130 °C). After being stirred for 2.5 h at same temperature, the mixture was cooled to r.t. and quenched by addition of sat. aq. NaHCO_3 . The resulting mixture was filtered through a pad of Celite. The filtrate was extracted with CH_2Cl_2 . The extracts were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified through silica gel column chromatography (hexane/ AcOEt = 9/1 to 3/2) to give **5a** (29.6 mg, 54%), **6a** (4.8 mg, a small amount of 4-phenyl-4-oxobutanoic acid was contaminated, approx. 10%), and **7a** (3.2 mg, 7%), respectively.

5-Nitromethyl-5-phenyloxolan-2-one (**5a**)

White solid; mp: 95.0–95.5 °C; IR (CHCl_3) cm^{-1} : 1790, 1560; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 7.47–7.38 (5H, m), 4.81 (1H, d, J = 12.6 Hz), 4.75 (1H, d, J = 12.6 Hz), 3.00–2.91 (1H, m), 2.75–2.66 (2H, m), 2.58–2.49 (1H, m); $^{13}\text{C-NMR}$ (CDCl_3 , 150 MHz) δ : 174.7, 138.7, 129.1, 124.6, 84.6, 81.9, 31.8, 27.8; $^{13}\text{C-NMR}$ (CD_3OD , 150 MHz) δ : 177.5, 141.0, 129.9, 129.7, 125.9, 86.6, 82.9, 33.6, 28.5; high resolution (HR)MS (DART) m/z Calcd for $\text{C}_{11}\text{H}_{12}\text{NO}_4$ [(M + H) $^+$]: 222.07663. Found

222.07629.

5-Hydroxymethyl-5-phenyloxolan-2-one (**6a**)⁵⁰

White solid; mp: 108.5–109.5 °C; IR (CHCl_3) cm^{-1} : 3953, 1716, 1686; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 7.40–7.34 (5H, m), 3.88 (1H, dd, J = 5.2, 12.4 Hz), 3.73 (1H, dd, J = 8.4, 12.4 Hz), 2.84–2.70 (2H, m), 2.57–2.49 (1H, m), 2.43–2.39 (1H, m), 1.91 (1H, dd, J = 5.2, 8.4 Hz); MS (DART) m/z : 193 [(M + H) $^+$]. The spectral data were identified with the reported ones.

5-Methyl-5-phenyloxolan-3-one (**7a**)⁵¹

Yellow oil; IR (CHCl_3) cm^{-1} : 1764, 1683; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 7.38–7.29 (5H, m), 2.64–2.41 (4H, m), 1.73 (3H, s); MS (DART) m/z : 177 [(M + H) $^+$]. The spectral data were identified with the reported ones.

Nitrolactonization of 3b A mixture of **3b** (51.6 mg, 0.25 mmol) and $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (50.5 mg, 0.13 mmol) in 1,2-dichlorobenzene (2.5 mL) was lowered into pre-heated oil bath (130 °C). After being stirred for 3 h at same temperature, the mixture was cooled to r.t. and the reaction was quenched by addition of sat. aq. NaHCO_3 . The resulting mixture was filtered through a pad of Celite. The filtrate was extracted with CH_2Cl_2 . The extracts were washed with brine, and dried over Na_2SO_4 , filtered, and concentrated. The residue was purified through silica gel column chromatography (hexane/ AcOEt = 8/1 to 6/4) to give **5b** (7.8 mg, 12%) and **7b** (35.7 mg, 69%), respectively.

5-(4'-Methoxyphenyl)-5-nitromethyloxolan-2-one (**5b**)

Pale yellow solid; mp: 130.0–131.0 °C; IR (CHCl_3) cm^{-1} : 1790, 1558; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 7.33 (2H, d, J = 9.0 Hz), 6.94 (2H, d, J = 9.0 Hz), 4.78 (1H, d, J = 12.4 Hz), 4.71 (1H, d, J = 12.4 Hz), 3.83 (3H, s), 2.92–2.87 (1H, m), 2.73–2.64 (2H, m), 2.58–2.51 (1H, m); HRMS (DART) m/z Calcd for $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_5$ [(M + NH_4) $^+$]: 269.11375. Found 269.11193.

5-(4'-Methoxyphenyl)-5-methyloxolan-2-one (**7b**)⁵²

Pale yellow oil; IR (CHCl_3) cm^{-1} : 1770, 1513, 1249; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 7.30 (2H, d, J = 8.8 Hz), 6.90 (2H, d, J = 8.8 Hz), 3.81 (3H, s), 2.63–2.37 (4H, m), 1.70 (3H, s). The spectral data were identified with the reported ones.

Nitrolactonization of 3c A mixture of **3c** (52.0 mg, 0.24 mmol) and $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (48.5 mg, 0.12 mmol) in 1,2-dichlorobenzene (2.4 mL) was lowered into pre-heated oil bath (130 °C). After being stirred for 2 h at same temperature, the mixture was cooled to r.t. and the reaction was quenched by addition of sat. aq. NaHCO_3 . The resulting mixture was filtered through a pad of Celite. The filtrate was extracted with CH_2Cl_2 . The extracts were washed with brine, and dried over Na_2SO_4 , filtered, and concentrated. The residue was purified through silica gel column chromatography (hexane/ AcOEt = 5/1 to 6/4) to give 5-(4'-nitrophenyl)-5-nitromethyloxolan-2-one (**5c**) (10.1 mg, 16%) as pale yellow needles; mp: 141.0–142.0 °C (recrystallized from AcOEt /hexane); IR (KBr) cm^{-1} : 1795, 1731, 1606, 1556, 1378; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 600 MHz) δ : 8.29 (2H, d, J = 9.0 Hz), 7.75 (2H, d, J = 9.0 Hz), 5.52 (1H, d, J = 14.4 Hz), 5.39 (1H, d, J = 14.4 Hz), 2.80 (1H, ddd, J = 6.6, 9.6, 17.4 Hz), 2.71 (1H, ddd, J = 6.6, 9.6, 13.8 Hz), 2.55 (1H, ddd, J = 6.0, 10.2, 17.4 Hz), 2.39–2.35 (1H, m); $^{13}\text{C-NMR}$ ($\text{DMSO}-d_6$, 150 MHz) δ : 175.3, 147.6, 147.3, 126.3, 123.7, 84.3, 81.4, 32.9, 27.2; HRMS (DART) m/z Calcd for $\text{C}_{11}\text{H}_{11}\text{N}_2\text{O}_6$ [(M + H) $^+$]: 267.06171. Found 267.06153.

Nitrolactonization of 3d A mixture of **3d** (41.5 mg, 0.21 mmol) and $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (41.6 mg, 0.11 mmol) in 1,2-di-

chlorobenzene (2.1 mL) was lowered into pre-heated oil bath (130 °C). After being stirred for 4 h at same temperature, the mixture was cooled to r.t. and the reaction was quenched by addition of sat. aq. NaHCO₃. The resulting mixture was filtered through a pad of Celite. The filtrate was extracted with CH₂Cl₂. The extracts were washed with brine, and dried over Na₂SO₄, filtered, and concentrated. The residue was purified through silica gel column chromatography (hexane/AcOEt = 6/4 to 1/1) to give 5-(4'-cyanophenyl)-5-nitromethylloxolan-2-one (**5d**) (13.3 mg, 26%) as pale yellow solid; mp: 174.5–175.0 °C; IR (neat) cm⁻¹: 2231, 1788, 1631, 1612, 1556; ¹H-NMR (methanol-*d*₄, 400 MHz) δ: 7.81 (2H, d, *J* = 8.8 Hz), 7.66 (2H, d, *J* = 8.8 Hz), 5.20 (1H, d, *J* = 13.6 Hz), 5.14 (1H, d, *J* = 13.6 Hz), 2.88–2.70 (2H, m), 2.61–2.51 (2H, m); ¹³C-NMR (DMSO-*d*₆, 150 MHz) δ: 175.4, 145.6, 132.6, 125.8, 118.4, 111.1, 84.3, 81.3, 32.8, 27.1; HRMS (DART) *m/z* Calcd for C₁₂H₁₄N₃O₄ [(M + NH₄)⁺]: 264.09843. Found 264.09788.

Nitrolactonization of 8a A mixture of **8a** (56.0 mg, 0.25 mmol) and Fe(NO₃)₃·9H₂O (50.5 mg, 0.13 mmol) in 1,2-dichlorobenzene (2.5 mL) was lowered into pre-heated oil bath (130 °C). After being stirred for 22 h at same temperature, the mixture was cooled to r.t. and the reaction was quenched by addition of sat. aq. NaHCO₃. The resulting mixture was filtered through a pad of Celite. The filtrate was extracted with CH₂Cl₂. The extracts were washed with brine, and dried over Na₂SO₄, filtered, and concentrated. The residue was purified through silica gel column chromatography (hexane/AcOEt = 9/1 to 3/1) to give 3-(nitromethyl)-3-phenylisobenzofuran-1(3*H*)-one (**9a**)⁴⁴ (62.8 mg, 93%) as a white solid; mp: 128.5–130.0 °C; IR (CHCl₃) cm⁻¹: 1782, 1562; ¹H-NMR (CDCl₃, 400 MHz) δ: 7.96–7.40 (9H, m), 5.26 (1H, d, *J* = 12.8 Hz), 5.17 (1H, d, *J* = 12.8 Hz); ¹³C-NMR (CDCl₃, 150 MHz) δ: 168.1, 147.5, 136.0, 134.7, 130.5, 129.6, 129.3, 126.5, 125.7, 125.1, 122.9, 85.5, 80.2; HRMS (DART) *m/z* Calcd for C₁₅H₁₂NO₄ [(M + H)⁺]: 270.07663. Found 270.07407.

Nitrolactonization of 8b A mixture of **8b** (35.6 mg, 0.14 mmol) and Fe(NO₃)₃·9H₂O (28.3 mg, 0.07 mmol) in 1,2-dichlorobenzene (1.4 mL) was lowered into pre-heated oil bath (130 °C). After being stirred for 30 min at same temperature, the mixture was cooled to r.t. and the reaction was quenched by addition of sat. aq. NaHCO₃. The resulting mixture was filtered through a pad of Celite. The filtrate was extracted with CH₂Cl₂. The extracts were washed with brine, and dried over Na₂SO₄, filtered, and concentrated. The residue was purified through silica gel column chromatography (hexane/AcOEt = 9/1 to 7/3) to give 3-nitromethyl-3-(4'-methoxyphenyl)-isobenzofuran-1(3*H*)-one (**9b**) (26.9 mg, 65%) and 3-methyl-3-(4'-methoxyphenyl)isobenzofuran-1(3*H*)-one (**10b**) (10.5 mg, 30%), respectively.

3-Nitromethyl-3-(4'-methoxyphenyl)isobenzofuran-1(3*H*)-one (**9b**)

White solid; mp: 49.0–50.0 °C; IR (CHCl₃) cm⁻¹: 1780, 1560; ¹H-NMR (CDCl₃, 400 MHz) δ: 7.96–7.60 (4H, m), 7.45 (2H, d, *J* = 9.2 Hz), 6.92 (2H, d, *J* = 9.2 Hz), 5.23 (1H, d, *J* = 13.0 Hz), 5.14 (1H, d, *J* = 13.0 Hz), 3.80 (3H, s); ¹³C-NMR (CDCl₃, 150 MHz) δ: 168.2, 160.3, 147.6, 134.6, 130.9, 127.7, 126.7, 126.3, 125.7, 123.0, 114.5, 85.5, 80.2, 55.3; HRMS (DART) *m/z* Calcd for C₁₆H₁₄NO₅ [(M + H)⁺]: 300.08720. Found 300.08665.

3-Methyl-3-(4'-methoxyphenyl)isobenzofuran-1(3*H*)-one (**10b**)⁴⁹

Pale yellow oil; IR (CHCl₃) cm⁻¹: 1759, 1514, 1255;

¹H-NMR (CDCl₃, 400 MHz) δ: 7.91 (1H, d, *J* = 8.0 Hz), 7.66 (1H, t, *J* = 7.6 Hz), 7.52 (1H, t, *J* = 7.6 Hz), 7.42 (1H, d, *J* = 8.0 Hz), 7.33 (2H, d, *J* = 9.0 Hz), 6.86 (2H, d, *J* = 9.0 Hz), 3.79 (3H, s), 2.03 (3H, s); ¹³C-NMR (CDCl₃, 150 MHz) δ: 170.0, 159.5, 154.4, 134.2, 132.5, 129.0, 126.6, 125.8, 125.2, 122.0, 113.9, 87.6, 55.3, 27.1; HRMS (DART) *m/z* Calcd for C₁₆H₁₅O₃ [(M + H)⁺]: 255.10212. Found 255.10299. The spectral data were identified with the reported ones.

Nitrolactonization of 8c A mixture of **8c** (59.6 mg, 0.25 mmol) and Fe(NO₃)₃·9H₂O (50.5 mg, 0.13 mmol) in 1,2-dichlorobenzene (2.5 mL) was lowered into pre-heated oil bath (130 °C). After being stirred for 30 min at same temperature, the mixture was cooled to r.t. and the reaction was quenched by addition of sat. aq. NaHCO₃. The mixture was filtered through a pad of Celite and the filtrate was extracted with CH₂Cl₂. The extracts were washed with brine, and dried over Na₂SO₄, filtered, and concentrated. The residue was purified through silica gel column chromatography (hexane/AcOEt = 9/1 to 7/3) to give 3-nitromethyl-3-(*p*-tolyl)-isobenzofuran-1(3*H*)-one (**9c**) (63.0 mg, 89%) and 3-methyl-3-(*p*-tolyl)isobenzofuran-1(3*H*)-one (**10c**) (7.0 mg, 11%), respectively.

3-Nitromethyl-3-(*p*-tolyl)isobenzofuran-1(3*H*)-one (**9c**)

White solid; mp: 99.0–100.5 °C; IR (CHCl₃) cm⁻¹: 1780, 1560; ¹H-NMR (CDCl₃, 400 MHz) δ: 7.94 (1H, d, *J* = 7.6 Hz), 7.78–7.74 (1H, m), 7.72 (1H, d, *J* = 7.6 Hz), 7.63–7.59 (1H, m), 7.43 (2H, d, *J* = 8.2 Hz), 7.23 (2H, d, *J* = 8.2 Hz), 5.24 (1H, d, *J* = 13.0 Hz), 5.16 (1H, d, *J* = 13.0 Hz), 2.35 (3H, s); ¹³C-NMR (CDCl₃, 150 MHz) δ: 168.2, 147.7, 139.6, 134.6, 133.0, 130.3, 129.9, 126.3, 125.6, 124.9, 122.9, 85.5, 80.1, 21.0; HRMS (DART) *m/z* Calcd for C₁₆H₁₄NO₄ [(M + H)⁺]: 284.09228. Found 284.09152.

3-Methyl-3-(*p*-tolyl)isobenzofuran-1(3*H*)-one (**10c**)

Pale yellow oil; IR (CHCl₃) cm⁻¹: 1759, 1514; ¹H-NMR (CDCl₃, 400 MHz) δ: 7.90 (1H, d, *J* = 7.6 Hz), 7.67–7.63 (1H, m), 7.53–7.49 (1H, m), 7.44 (1H, d, *J* = 7.6 Hz), 7.32 (2H, d, *J* = 7.8 Hz), 7.16 (2H, d, *J* = 7.8 Hz), 2.33 (3H, s), 2.03 (3H, s); ¹³C-NMR (CDCl₃, 150 MHz) δ: 170.0, 154.4, 138.2, 137.7, 134.2, 129.3, 129.0, 125.8, 125.08, 125.06, 122.0, 87.6, 27.2, 21.0; HRMS (DART) *m/z* Calcd for C₁₆H₁₅O₂ [(M + H)⁺]: 239.10720. Found 239.10637.

Nitrolactonization of 8d A mixture of **8d** (33.2 mg, 0.11 mmol) and Fe(NO₃)₃·9H₂O (22.1 mg, 0.06 mmol) in 1,2-dichlorobenzene (1.1 mL) was lowered into pre-heated oil bath (130 °C). After being stirred for 30 min at same temperature, the mixture was cooled into r.t. and the reaction was quenched by addition of sat. aq. NaHCO₃. The resulting mixture was filtered through a pad of Celite and the filtrate was extracted with CH₂Cl₂. The extracts were washed with brine, and dried over Na₂SO₄, filtered, and concentrated. The residual oil was purified through silica gel column chromatography (hexane/AcOEt = 9/1 to 7/3) to give 3-(4'-bromophenyl)-3-nitromethylisobenzofuran-1(3*H*)-one (**9d**) as white solid; mp: 104.0–104.5 °C; IR (CHCl₃) cm⁻¹: 1784, 1558; ¹H-NMR (CDCl₃, 400 MHz) δ: 7.96 (1H, d, *J* = 7.6 Hz), 7.80–7.76 (1H, m), 7.70 (1H, d, *J* = 7.6 Hz), 7.66–7.62 (1H, m), 7.57 (2H, d, *J* = 8.6 Hz), 7.45 (2H, d, *J* = 8.6 Hz), 5.22 (1H, d, *J* = 13.2 Hz), 5.12 (1H, d, *J* = 13.2 Hz); ¹³C-NMR (CDCl₃, 150 MHz) δ: 167.8, 147.1, 135.1, 134.9, 132.5, 130.7, 126.8, 126.7, 125.5, 124.0, 122.7, 84.9, 80.0; HRMS (DART) *m/z* Calcd for C₁₅H₁₄BrN₂O₄ [(M + NH₄)⁺]: 365.01369. Found 365.01524.

Experiment for Chart 4 Di-*tert*-butylhydroxytoluene (BHT) (132.2 mg, 0.6 mmol) was added to a mixture of **8a** (44.9 mg, 0.2 mmol) and Fe(NO₃)₃·9H₂O (40.4 mg, 0.1 mmol) in 1,2-dichlorobenzene (2.0 mL). The mixture was lowered into pre-heated oil bath (130 °C). After being stirred for 19 h at same temperature, the mixture was cooled to r.t. and the reaction was quenched by addition of sat. aq. NaHCO₃. The resulting mixture was filtered through a pad of Celite. The filtrate was acidified the 4N HCl and extracted with CH₂Cl₂. The extracts were washed with water, brine, and dried over Na₂SO₄, filtered, and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt = 9/1 to 8/2) to give a mixture of **9a** (12%) and **8a** (16%), respectively. The yields of **9a** and **8a** were determined by qNMR using 1,4-dinitrobenzene as an internal standard.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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