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Copper(II)-mediated oxidation of 1,2-dioxime to furoxan

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ABSTRACT

1,2-Dioximes undergo oxidative transformation mediated by copper(II) ions in acetonitrile to form the corresponding furoxans in high yields. A series of 1,2-dioximes including aliphatic, aromatic, and heterocyclic dioximes were oxidized using these mild conditions.

1. Introduction

Furoxans (1,2,5-oxadiazole-2-oxides) and benzofuroxans represent an important class of NO donors.[1] Furoxans show a variety of NO-related bioactivities, including cytotoxicity, mutagenicity, immunosuppression, central muscle relaxant properties, anticonvulsive effects, monoamino oxidase inhibition, and direct vasodilator and blood pressure lowering activities.[2–4] Benzofuroxans are potent antileukemic and immunosuppressive drugs, and can be used as in vitro inhibitors of RNA synthesis in sheep lymphocytes.[5–7] Furoxans are widely used in organic chemistry as intermediates for the synthesis of many heterocycles.[8]

Furoxans can be synthesized easily by ring closure or cycloaddition reactions. Monocyclic furoxans are normally prepared by oxidative cyclization of 1,2-dioximes. Many different oxidizing agents such as hypohalite, ferricyanide, ceric ions, nitric acid and nitrogen oxides, manganese dioxide, lead tetraacetate, *N*-iodosuccinimide, and phenyliodine(III) bistrifluoroacetate have been used for cyclization reactions.[9,10] Alumina-promoted cyclization of α-nitrooximes has also been reported for the synthesis of furoxans.[11] Typical methods for the synthesis of benzofuroxans involve oxidation of benzoquinone dioxime, thermolysis of *ortho*-nitroaryl azides, and oxidation of *ortho*-nitroanilines.[12–14]

In spite of the presence of a large number of transition metal complexes,[15] particularly copper(II) complexes of 1,2-dioximes, there is no report on copper(II)-mediated oxidation of dioximes. We report herein the preparation of a new 1,10-phenanthroline-based furoxan from the corresponding dioxime by an oxidative transformation reaction mediated by copper(II) ions in the presence of a base and subsequent formation of a mononuclear copper(II) complex of the furoxan. The synthesis and characterization of the copper(II)-1,10-phenanthrolinefuroxan complex is reported along with the isolation and characterization of free furoxan. We have further extended this procedure to other 1,2-dioximes and found it to be a general method for the synthesis of furoxans. We report here, for the first time, the oxidation of 1,2-dioximes to furoxans mediated by copper(II) in acetonitrile.

2. Results and discussion

Reaction of dioxime L^1, copper(II) chloride, and sodium perchlorate in acetonitrile in the presence of triethylamine leads to oxidative transformation of dioxime L^1 to furoxan L^2 (Scheme 1) with concomitant formation of $[Cu^I(CH_3CN)_4]ClO_4$. Formation of furoxan is very much dependent on the presence of a base during the reaction. In the absence of any base, the dioxime ligand is not oxidized. The furoxan ligand reacts with excess copper(II) in solution to form a mononuclear complex $[Cu(L^2)_2Cl]^+$ (**1**) (Scheme 1). The extent of formation of **1** depends on the molar ratio of copper(II)/dioxime (L^1), and a maximum yield of 95% for **1** was observed when they react in a molar ratio of 3:1. The oxidation of L^1 to L^2 is a two-electron process and requires 2 equiv of copper(II) salt to generate 1 equiv of L^2. The excess of copper(II) salt then forms a complex with L^2.

To establish this oxidative transformation reaction further, it was deemed important to characterize the free furoxan. Free furoxan L^2 was isolated by treating complex **1** with excess aqueous ammonia. A cream colored solid was isolated from the reaction mixture and was characterized by spectroscopic methods. ESI-MS in positive ion mode (in acetonitrile) showed molecular ion peaks at *m*/*z* 261.08 (100%) and 239.09 (23%) with expected isotope distribution patterns calculated for $[L^2+Na]^+$ and $[L^2+H]^+$, respectively. In

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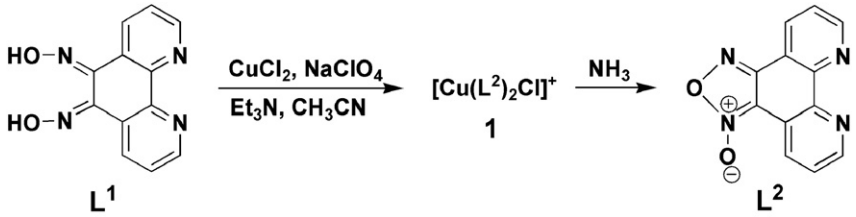


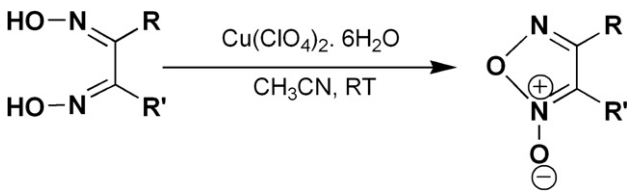
Scheme 1. Oxidation of 1,10-phenanthroline 5,6-dioxime to 1,10-phenanthrolinefuroxan.

comparison with L^1 showed molecular ion peaks at *m*/*z* 262.94 (47%) and 240.96 (100%) with expected isotope distribution patterns calculated for $[L^1+Na]^+$ and $[L^1+H]^+$, respectively. This indicates the formation of furoxan L^2 with a loss of two hydrogen atoms from L^1 and was strongly supported by ^1H NMR spectroscopy. The ^1H NMR spectrum of L^2 in DMSO-d_6 did not show any oxime-OH peaks in the region 12–14 ppm as observed in L^1. However, the six aromatic protons of the phenanthroline backbone were observed in the region 7.80–9.20 ppm and the signal positions and splitting patterns were considerably different from those in L^1. Additionally, two doublets were observed at 9.16 and 9.08 ppm for the *ortho*-protons of the pyridine rings of L^2. Two doublets due to the *para*-protons in the region 8.78–8.84 ppm and a multiplet at 7.86 ppm for the *meta*-protons were also observed. The NMR integration and splitting patterns of the peaks indicated that the two pyridine rings of L^2 are chemically different. All these experimental data corroborate with the formulation of furoxan L^2.

This methodology was further extended to the oxidation of other 1,2-dioximes including alkyl, aryl, and heterocycle susbstituted dioximes (Scheme 2, Table 1). The reactions were carried out using $Cu(ClO_4)_2{\cdot}6H_2O$ and 1,2-dioximes in acetonitrile at room temperature. The typical reaction time was about 12 h, except for 1,2-cyclohexanedionedioxime which required 24 h for complete conversion to the corresponding furoxan. Unlike the oxidation of L^1, no base was needed to carry out the oxidation of the other dioximes. After the reaction, the solution was concentrated and treated with ammonia to remove copper ions from the reaction solution and then extracted with organic solvents. The ratio of copper(II)/dioximes varied with the nature of the dioxime. Dioxime L^1 requires a 3:1 ratio of copper/dioxime for complete conversion to the furoxan, whereas for other dioximes a ratio of 2:1 was sufficient for the oxidative transformation.

All the furoxans showed very strong ν(C=N–O) peaks at 1590–1620 cm^{-1} in their IR spectra. Liquid furoxans **3a**, **4a**, and **6a** did not show characteristic molecular ion peaks in their ESI-MS spectra; however, the other furoxans showed peaks corresponding to $[M+H]^+$ and/or $[M+Na]^+$ with expected isotope distribution patterns. The furoxans were further characterized by ^1H and ^{13}C NMR spectroscopy. Interestingly, the NMR spectrum of unsymmetrical furoxan **4a** showed the presence of two different isomers in solution (Scheme 3). This was established clearly by ^1H NMR spectroscopy in $CDCl_3$, which showed two isomers in a 3:1 ratio at 298 K (see Section 3).

The oxidation of 1,2-dioxime to furoxan in acetonitrile is associated with the transfer of two electrons and two protons. The



Scheme 2. General method for the oxidation of 1,2-dioximes to furoxans.

probable mechanism of the oxidation reaction involves initial formation of a copper(II)–oxime complex. The oxime complex is probably strongly oxidizing, and therefore intramolecular electron transfer from the oxime to copper(II) leads to the formation of furoxan and a $[Cu(CH_3CN)_4]^+$ complex via the one electron oxidized form of dioxime, that is, an iminoxyl radical. Furoxans without a donor atom cannot form a complex with copper ions, while furoxans having ligating properties can easily form complexes with excess copper(II) ions present in the reaction medium.

In conclusion, we have developed a new copper(II)-mediated oxidative transformation of 1,2-dioximes to furoxans. The method is applicable to a wide range of dioxime substrates and demonstrates the role played by copper(II) ions in directing the course of an oxidative transformation reaction.

3. Experimental

Dioxime L^1 was synthesized from 1,10-phenanthroline-5,6-dione,[16] according to a literature procedure.[17] Dioxime **2** was synthesized according to procedure described in the literature.[18] Other dioximes were either purchased commercially or synthesized from the corresponding 1,2-diketones.

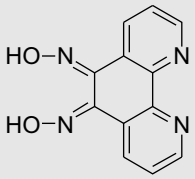
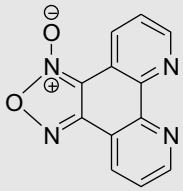
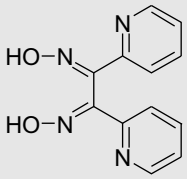
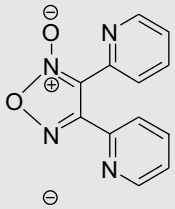
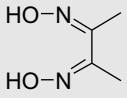
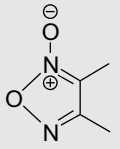
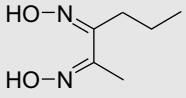
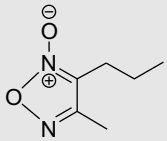
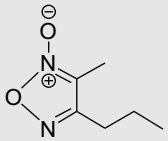
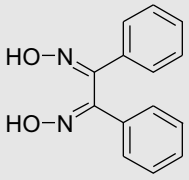
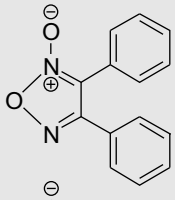
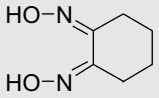
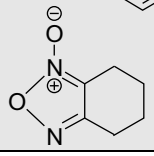
3.1. Complex 1

To a suspension of L^1 (0.24 g, 1 mmol) and triethylamine (0.27 mL, 2 mmol) in acetonitrile (20 mL) was added a mixture of $CuCl_2{\cdot}2H_2O$ (0.51 g, 3 mmol) and $NaClO_4{\cdot}H_2O$ (0.84 g, 6 mmol). The resulting greenish brown mixture was allowed to stir at room temperature for 12 h. A green solid ([**1**]Cl) was then isolated by filtration, washed with acetonitrile, and dried. Initially, a white crystalline solid of $[Cu^I(CH_3CN)_4]ClO_4$ was isolated from the filtrate followed by green crystals of [**1**]ClO_4. Total yield of **1**: 0.29 g (95%). Anal. Calcd for $C_{24}H_{12}Cl_2CuN_8O_8{\cdot}H_2O$: C, 41.60; H, 2.04; N, 16.17. Found: C, 41.9; H, 2.1; N, 16.1. IR (KBr disk, cm^{-1}): 3433(br), 3085, 1633(s), 1510(s), 1415(s), 1091(s), 820, 732, 623. UV–vis in acetonitrile (λ, nm; ε, $M^{-1}\,cm^{-1}$): 530(420), 400(470), 320(3400), 335(sh), 350(sh). MS-ESI (positive ion mode, acetonitrile): *m*/*z* 574.25 (6%, [**1**]$^+$), 539.26 (13%, [**1**−Cl]$^+$), 261.14 (100%, $[L^2+Na]^+$) and 239.15 (23%, $[L^2+H]^+$).

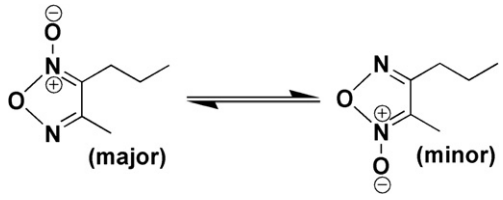
3.2. Isolation of L^2 from 1

To a suspension of complex [**1**]Cl (0.122 g, 0.2 mmol) in water was added an excess amount of aqueous ammonia (45 mL) in small portions with vigorous stirring. A blue colored solution was formed immediately along with precipitation of a cream colored solid. The solid was isolated by filtration, washed with aqueous ammonia, and air dried. Yield: 0.09 g (94%). Anal. Calcd for $C_{12}H_6N_4O_2{\cdot}0.5H_2O$: C, 58.30; H, 2.85; N, 22.66. Found: C, 58.5; H, 2.3; N, 21.8. MS-ESI (positive ion mode, acetonitrile): *m*/*z* 261.08 (100%, $[L^2+Na]^+$) and 239.09 (23%, $[L^2+H]^+$). IR (KBr disk, cm^{-1}): 3433(br), 3078-2972, 1624(s), 1585(s), 1500(s), 1400(s), 1074, 985, 814, 743, 675. UV–vis in DMSO (λ, nm; ε, $M^{-1}\,cm^{-1}$): 343(9200), 327(13200), 314(13800). ^1H NMR [$(CD_3)_2SO$, 300 MHz, 25 °C], δ, ppm: 9.16 (d,

Table 1
Oxidative transformation of various 1,2-dioxime derivatives to furoxans

Entry	Substrate	Time (h)	Product	Yield[a] (%)
1	 **L¹**	12	 **L²**	89[b]
2	 **2**	12	 **2a**	83
3	 **3**	12	 **3a**	88
4	 **4**	12	 (major) +  (minor) **4a**	96
5	 **5**	12	 **5a**	91
6	 **6**	24	 **6a**	92

[a] For pure isolated product.
[b] In the presence of triethylamine as base.



Scheme 3. Two different isomers of furoxan **4a** in solution.

1H, J = 2.8 Hz); 9.08 (d, 1H, J = 2.7 Hz); 8.84 (d, 1H, J = 7.9 Hz); 8.78 (d, 1H, J = 8.0 Hz); 7.86 (m, 2H). ^{13}C NMR [$(CD_3)_2SO$, 75 MHz], δ, ppm: 153.92, 152.26, 150.21, 148.47, 147.28, 132.29, 131.02, 125.77, 125.55, 119.39, 116.79, 108.78.

3.3. General method for the oxidation of 1,2-dioximes (2–6) to furoxans (2a–6a)

1,2-Dioxime (0.5 mmol) was dissolved in acetonitrile (15 mL) at room temperature and $Cu(ClO_4)_2{\cdot}6H_2O$ (1 mmol) was added. The solution turned green immediately and slowly to blue after about 2 h. The mixture was further stirred for 10 h (22 h for 1,2-cyclohexanedionedioxime) at room temperature. The solution was kept for several hours at room temperature during which slow evaporation of the solvent afforded a white crystalline solid of $[Cu(CH_3CN)_4](ClO_4)$. The solid was isolated by filtration, and the filtrate was concentrated to dryness. To this was added excess aqueous ammonia solution (25%), and the solution was stirred for several hours and the resulting blue solution was extracted with chloroform (3×25 mL). The combined organic layer was dried over magnesium sulfate and evaporated under reduced pressure to obtain the furoxan. In the case of furoxan **5a**, a white solid was precipitated from ammonia solution, which was isolated by filtration, washed with water, and dried.

3.3.1. Compound 2a

Off-white solid. Yield: 0.10 g (83%). Anal. Calcd for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.32. Found: C, 59.7; H, 3.8; N, 23.4. MS-ESI (positive ion mode, acetonitrile): m/z 263.04 (100%, $[\mathbf{2a}+Na]^+$) and 241.06 (35%, $[\mathbf{2a}+H]^+$). IR (KBr disk, cm^{-1}): 3433(br), 3049–

2852(s), 1595(s), 1566(s), 1487(s), 1406(s), 1221(s), 1087(s), 800(s), 746. ^{1}H NMR [$CDCl_3$, 300 MHz, 25 °C], δ, ppm: 8.57 (d, 1H, J = 4.7 Hz); 8.53 (d, 1H, J = 4.3 Hz); 8.0 (d, 1H, J = 7.9 Hz); 7.99–7.83 (m, 3H); 7.41–7.40 (m, 1H); 7.36–7.32 (m, 1H). ^{13}C NMR [$CDCl_3$, 75 MHz], δ, ppm: 156.96, 150.33, 146.46, 143.63, 138.01, 137.83, 126.15, 125.69, 125.24, 124.36, 114.96.

3.3.2. Compound 3a

Yellow oil. Yield: 0.05 g (88%). Anal. Calcd for $C_4H_6N_2O_2$: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.1; H, 5.1; N, 24.3. IR (KBr disk, cm^{-1}): 2925(s), 1612(s), 1468(s), 1379(s), 1163(s), 1040(s), 993(s), 848(s), 756, 646(s). ^{1}H NMR [$CDCl_3$, 300 MHz, 25 °C], δ, ppm: 2.32 (s, 3H); 2.13 (s, 3H). ^{13}C NMR [$CDCl_3$, 75 MHz], δ, ppm: 154.74, 113.16, 10.63, 7.44.

3.3.3. Compound 4a

Yellow oil. Yield: 0.068 g (96%). Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.6; H, 6.8; N, 19.2. IR (KBr disk, cm^{-1}): 2966–2876(s), 1610(s), 1468(s), 1153(s), 1015(s), 848, 605. ^{1}H NMR [$CDCl_3$, 300 MHz, 25 °C], δ, ppm: The major isomer shows peaks at 2.62 (t, 2H, J = 7.5 Hz); 2.14 (s, 3H); 1.78–1.64 (m, 2H); 1.03 (t, 3H, J = 7.4 Hz). The minor isomer shows peaks at 2.49 (t, 2H, J = 7.5 Hz); 2.32 (s, 3H); 1.78–1.64 (m, 2H); 0.97 (t, 3H, J = 7.5 Hz). ^{13}C NMR [$CDCl_3$, 75 MHz], δ, ppm: 158.03, 27.59, 24.19, 20.10, 13.65, 7.77 (for the major isomer). 154.45, 29.75, 22.74, 19.06, 11.18 (for the minor isomer).

3.3.4. Compound 5a

White solid. Yield: 0.11 g (91%). Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.1; H, 4.3; N, 11.5. MS-ESI (positive ion mode, acetonitrile): m/z 261.06 (100%, [**5a**+Na]$^+$). IR (KBr disk, cm^{-1}): 3416(br), 3063–2972(w), 1594–1576(s), 1504(s), 1421(s), 1115(m), 962(s), 833(s), 773(s), 693(s), 656(s). ^{1}H NMR [$CDCl_3$, 300 MHz, 25 °C], δ, ppm: 7.46–7.43 (m, 5H); 7.39–7.18 (m, 5H). ^{13}C NMR [$CDCl_3$, 75 MHz], δ, ppm: 156.30, 131.07, 130.63, 129.09, 129.03, 128.77, 128.37, 126.75, 122.96.

3.3.5. Compound 6a

Yellow oil. Yield: 0.065 g (92%). Anal. Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.7; H, 5.6; N, 19.4. IR (KBr disk, cm^{-1}): 3362(br), 2924–2853(s), 1618(s), 1467(s), 1425(s), 1168, 1132, 1003, 953, 924, 825, 760. ^{1}H NMR [$CDCl_3$, 300 MHz, 25 °C], δ, ppm: 2.82–2.78 (m, 2H); 2.62–2.58 (m, 2H); 1.85–1.80 (m, 4H). ^{13}C NMR [$CDCl_3$, 75 MHz], δ, ppm: 156.19, 116.51, 22.15, 21.18, 19.83, 16.44.

Acknowledgments

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