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Cyclization of α-Oxo-oximes to 2-Substituted Benzoxazoles

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Reactions of oximes **9**, **17**, and **19** with electrophiles **15a**−**f** and **24** in the presence of anhydrous potassium carbonate or triethylamine give 2-substituted condensed ring oxazoles **10**, **16a**−**c**, **18a**−**d**, **20a**−**c**, and **25** in a new general route to these compounds.

Introduction

The benzoxazole ring system occurs occasionally in nature,[1] and benzoxazole derivatives have achieved importance in pharmacology as antibacterial or antifungal agents,[2] HIV-1 reverse transcriptase inhibitors,[3] topoisomerase I inhibitors,[4] and antitumor agents.[5]

Known syntheses of benzoxazoles and other annulated oxazoles include the thermal dehydration of *o*-acylaminophenols[6] (eq 1), the Beckmann rearrangement of oximes of *o*-hydroxybenzophenones[6] (eq 2), oxidative ring closure of phenolic Schiff bases[7] (eq 3), and reactions of *o*-aminophenols with cyanogen bromide[6] (eq 4) or benzil[8] (eq 5). Reaction of tetrabromobenzo-1,2-quinone 1-(*O*-methyloxime) with benzyltriphenylphosphonium chloride[9] (eq 6), reactions of *o*-quinones with a variety of amines[10] (e.g., eq 7), and reaction of α-nitroso-*β*-naphthol with a pyridinium betaine (eq 8)[11] also give oxazoles (Scheme 1).

This paper discloses a new preparative route to annulated oxazoles through reactions of quinone monoximes with alkyl halides, aralkyl halides, or dimethyl sulfate in DMF in the presence of anhydrous potassium carbonate.

Results and Discussion

We reported recently that methylation of 2,1-benzisoxazole-4,5-dione 4-oxime (**1**) using dimethyl sulfate in DMF in the presence of anhydrous potassium carbonate gave isoxazolo[3,4-*e*][2,1]benzisoxazole (**2**).[12] It is now known, however, that the true structure is in fact [1,3]-oxazolo[4,5-*e*][2,1]benzoisoxazole (**3**), as shown by the following evidence (Scheme 2).

In an experiment designed to halt the reaction at the methylation stage, reaction of **1** with diazomethane was found to give two compounds, the *N*-methyl nitrone **4** and *trans*-2,1-benzisoxazole-4,5-dione 4-(*O*-methyloxime) **5** (in 52% and 11% isolated yields, respectively). Structures **4** and **5** were assigned unambiguously by X-ray crystallography (Figure 1), although the methyl group of **5** is disordered over two conformations with equal occupancies. The *N*-methyl nitrone **4** on stirring in DMF with 1.1 equiv of K_2CO_3 at room temperature gave the same product as formed from the reaction of **1** with dimethyl sulfate, which immediately suggested that it might in fact be [1,3]oxazolo[4,5-*e*][2,1]benzisoxazole **3** formed from **4** via **6** and **7** (Scheme 2). This is mechanistically reasonable because the methyl protons of **4** should be much more acidic than the *O*-methyl group of **5**.

Despite much effort, it has not proved possible to obtain a crystal of **3** suitable for X-ray crystallography, but

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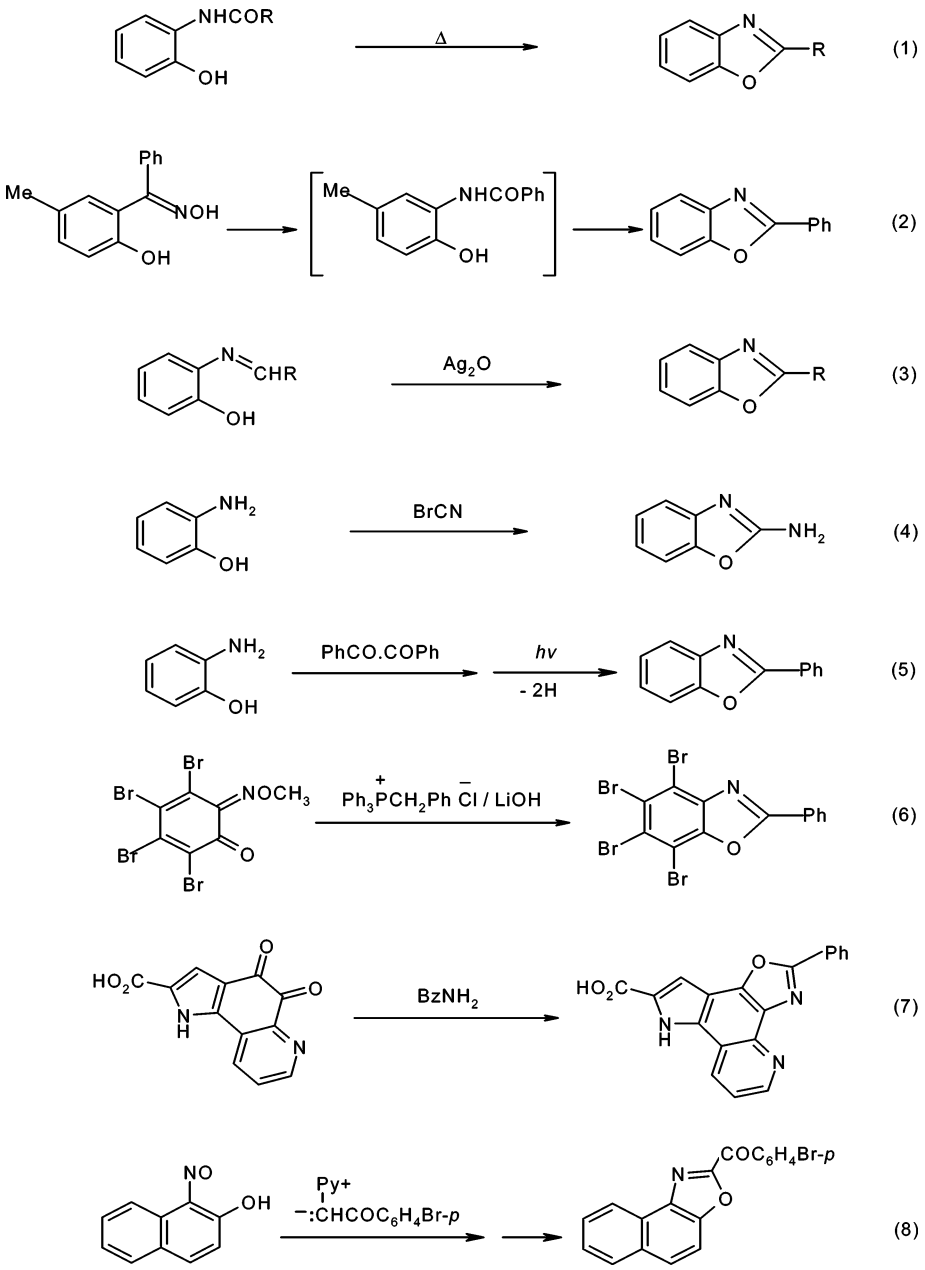
SCHEME 1



reexamination of the NMR data fits the oxazole structure **3** better than the isoxazole structure **2**. Thus the δ values for H-2 (8.19 ppm in $CDCl_3$) and C-2 (152.2 ppm) compare well with the published values[13] for H-2 (8.1 ppm) and C-2 (152.6 ppm) of 1,3-benzoxazole. Furthermore $^1J_{H-C}$ values for C-8 and C-2 of **3** are very different at 208 and 233 Hz, respectively, which reflects the published values for isoxazole[14] (203 Hz) and 1,3-benzoxazole[15] (233 Hz) ring carbons. Finally, the NMR spectrum in deuterated benzene shows separated signals for H-4 and H-5 (which overlap in $CDCl_3$), thus allowing detailed analysis of the ^{1}H coupling pattern and a series of HETCOR and HMBC spectra. Thus H-8 at 8.50 ppm couples with H-5 (1.05 Hz) and H-4 (0.17 Hz) to give a doublet of doublets; H-4 couples with H-5 (10.4 Hz) and H-8, H-5 couples with H-4, H-8, and H-2 (0.43 Hz) to give an octet; and H-2 gives an unresolved broad singlet. This coupling pattern is not consistent with structure **2**, which would require significant coupling between H-3 and H-4. In the HETCOR and HMBC spectra, H-8 correlates with C-8 (one bond), C-8b and C-5a (3 bonds in each case). Likewise, H-5 correlates with C-5 (one bond) and C-3a and C-8a (3 bonds), and both sets of correlations are consistent with either **2** or **3**. On the other hand, H-2 (in **3**) correlates with C-2 (one bond), C-8b and C-3a (3 bonds), and H-4 (of **3**) correlates with C-8b and C-5a (3 bonds) but not with the carbon atom of the alleged isoxazole ring in **2** (C-3). Thus our mistake in the structural assignment **2** in an earlier paper[12] is corrected to **3**.

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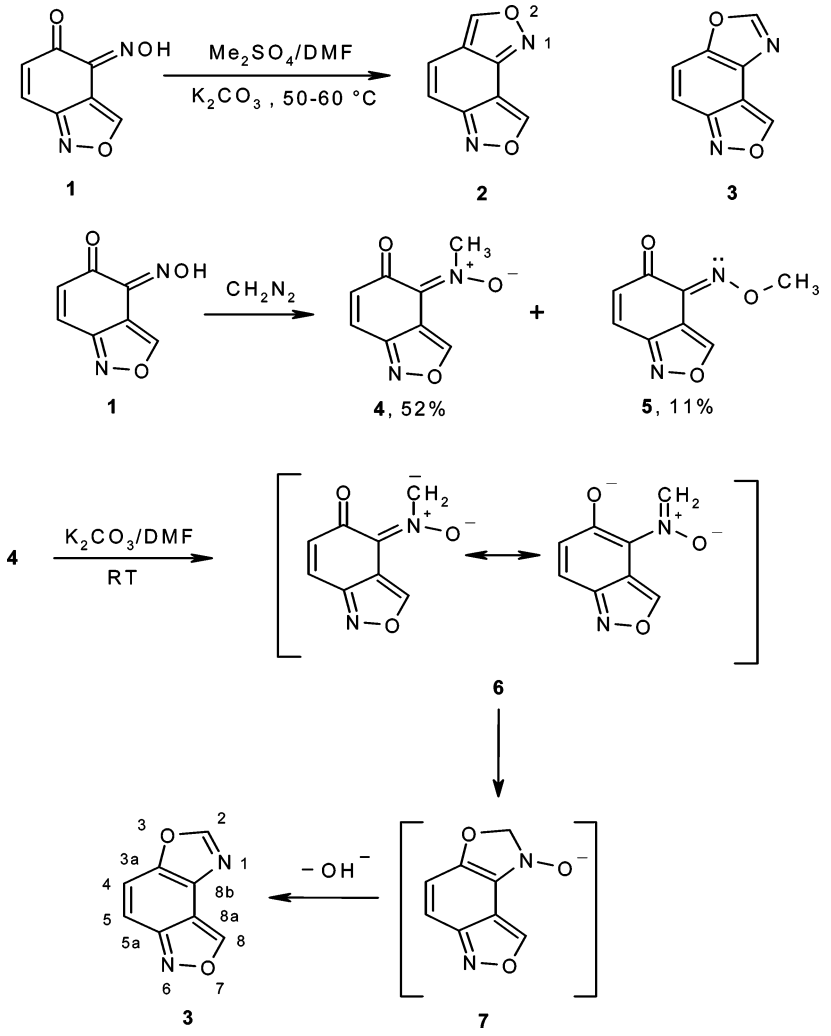
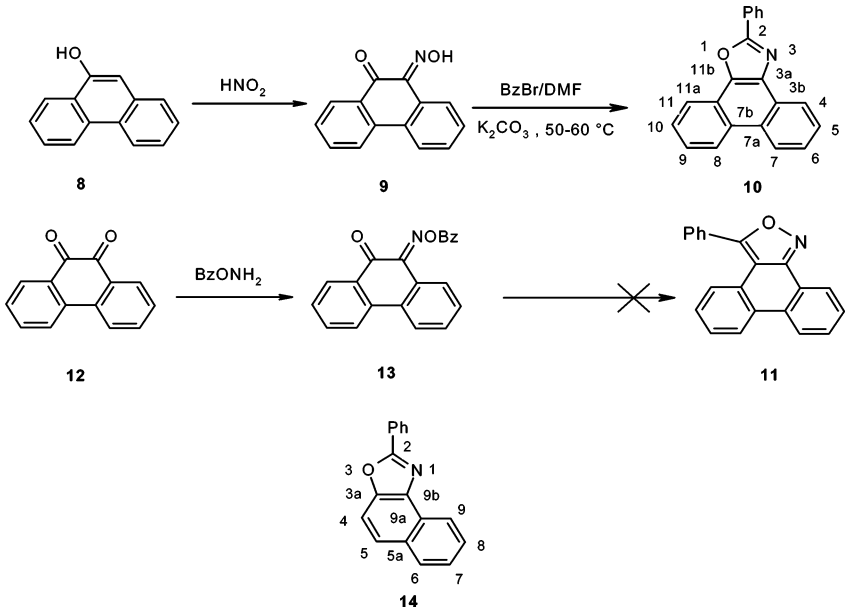
SCHEME 2

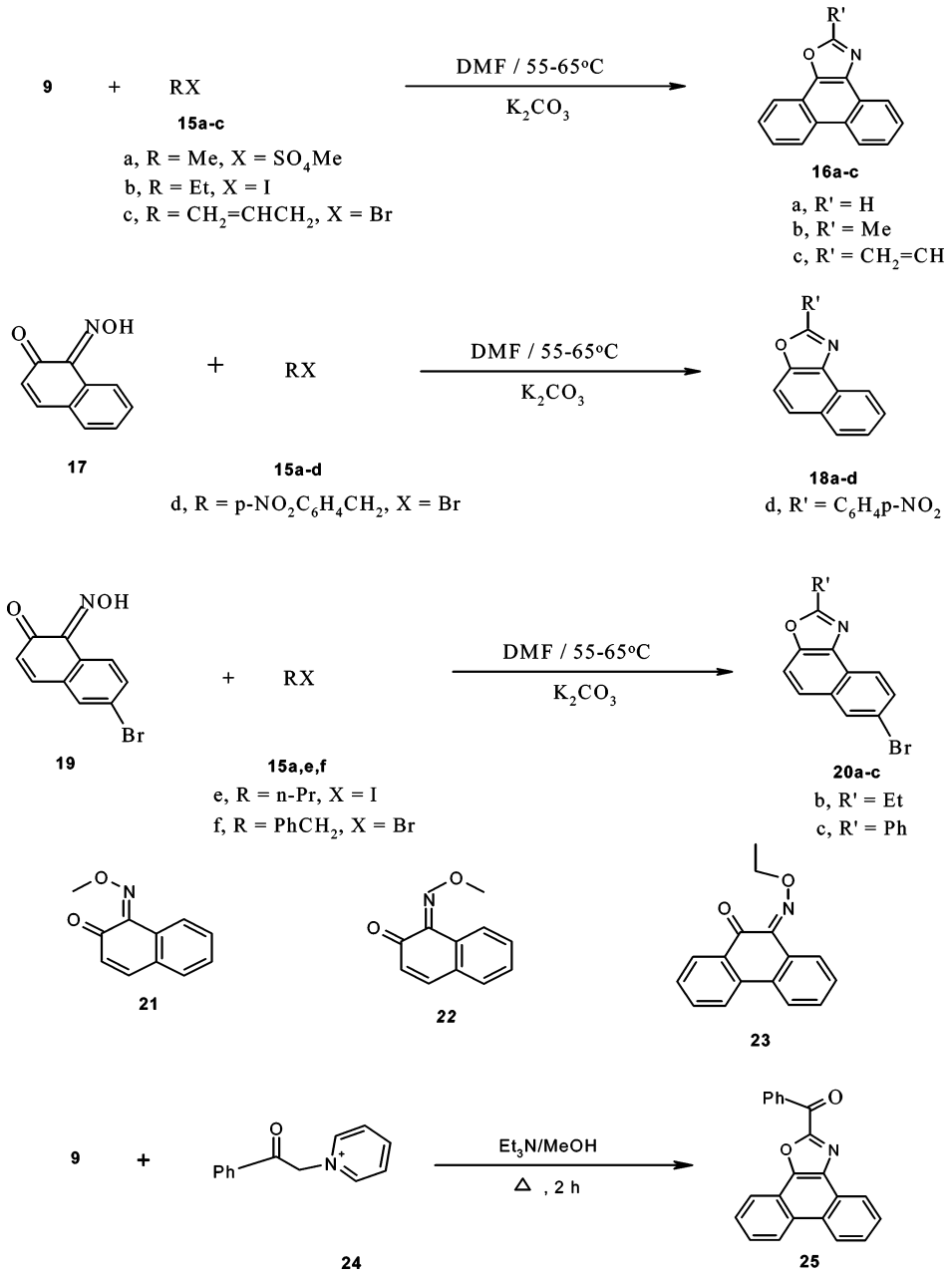


SCHEME 3



Further confirmation of the revised structure was obtained as follows (Scheme 3). 9,10-Phenanthrenedione 9-oxime **9**, derived from the nitrosation of 9-phenanthrol **8**, on heating with benzyl bromide in DMF in the presence of K_2CO_3, gave a compound first thought to be 3-phenylphenanthro[9,10-*c*]isoxazole **11** by analogy with

SCHEME 4



the supposed transformation **1** → **2**. However heating 9,10-phenanthrenedione 9-(*O*-benzyloxime) **13** (from **12** and *O*-benzylhydroxylamine) with K_2CO_3 in DMF failed to give the product obtained from **9** and benzyl bromide even under forcing conditions. In fact the product obtained from **9** and benzyl bromide was shown to be the known oxazole[16] **10** by observation of ^{13}C signals at 162.1 ppm (for C-2), 144.8 ppm (C-11b), and 126.1 ppm (C-3a), which are analogous to those for C-2, C-3a, and C-9b in **14**.[17]

Clearly this result offered an opportunity to extend the synthetic method to a range of annulated oxazoles, which was achieved by reactions of **9** (derived either by nitrosation of **8** or reaction of **12** with hydroxylamine) with **15a**−**c** to give **16a**−**c** (Scheme 4). Further examples were provided by reactions of 1,2-naphthalenedione 1-oxime **17** with **15a**−**d** to give **18a**−**d** and 6-bromo-1,2-naphthalenedione 1-oxime **19** with **15a,e,f** to give **20a**−**c**, and the results are summarized in Table 1. As an example of the

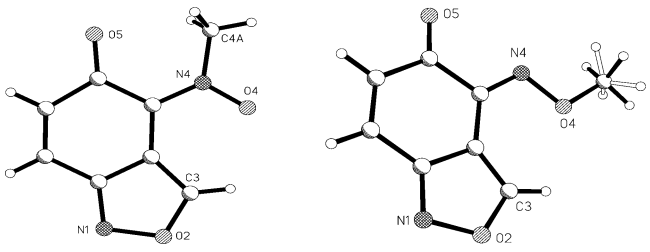


FIGURE 1. Structures of **4** and **5**.

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TABLE 1. Reaction of Oximes 9, 17, and 19 with Electrophiles (E) 15a−f in DMF at 54−60 °C in the Presence of K_2CO_3 over 1.5 h

substrate	E	product	yield (%)
9	Me_2SO_4 (**15a**)	**16a**, R′ = H	61
9	EtI (**15b**)[a]	**16b**, R′ = Me	51
9	CH_2=$CHCH_2Br$ (**15c**)	**16c**, R′ = CH_2=CH	24
9	$PhCH_2Br$ (**15f**)[a]	**10**, R′ = Ph	43
17	**15a**	**18a**, R′ = H	55
17	**15b**	**18b**, R′ = Me	40
17	**15c**	**18c**, R′ = CH_2=CH	32
17	*p*-$NO_2C_6H_4CH_2Br$ (**15d**)	**18d**, R′ = *p*-$NO_2C_6H_4$	24
19	**15a**	**20a**, R′ = H	54
19	*n*-PrI (**15e**)	**20b**, R′ = Et	34
19	**15f**	**20c**, R′ = Ph	41

[a] Reaction carried out at 20 °C over 17h.

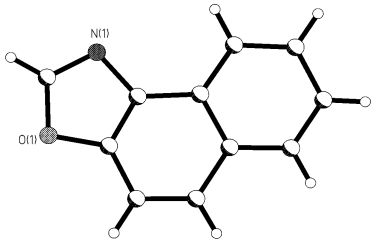

FIGURE 2. Structure of **18a**.

oxazoles prepared, structure **18a** was unambiguously confirmed by X-ray crystallography (Figure 2). We believe that the mechanisms for the formation of **10**, **16**, **18**, and **20** are analogous to those discussed above for the formations of compounds **3** and **4**.

Annulated oxazoles were the major isolated products in all of these reactions, albeit in modest yields, but oxime ethers were also isolated as byproducts. For example, *cis*-1,2-naphthalenedione 1-(*O*-methyloxime) **21** and *trans*-1,2-naphthalenedione 1-(*O*-methyloxime) **22** were isolated from the reaction mixture of **17** and **15a** and characterized by their $^1H/^{13}C$ NMR spectra and HRMS. Attempted purification of **21** and **22** failed because they were easily interconverted, with the *trans*-isomer **22** being favored at equilibrium. After column chromatography the *cis*-isomer **21** predominated (87:13, *cis*:*trans* as determined by ^1H NMR), but **21** gradually isomerized to the *trans* form **22** (47:53, *cis*:*trans* after 15 days), while the *trans*-isomer **22** changed from 80% to 72% during the same period. Likewise, 9,10-phenanthrenedione 9-(*O*-ethyloxime) **23** was separated from the reaction mixture affording **16b** and was identified by its $^1H/^{13}C$ NMR spectra and elemental analysis. The *O*-ethyloxime **23** was isolated as a single isomer, which isomerized to a mixture of *cis*- and *trans*-isomers (∼1:1) when kept in deuterated chloroform at room temperature for ca. 12 h but reverted to one isomer when heated to 60 °C.

On heating with 1-(2-oxo-2-phenyl-ethyl)-pyridinium bromide **24** in the presence of triethylamine, **9** gave phenanthro[9,10-*d*]oxazol-2-yl-phenyl-methanone **25** in 91% yield, probably following a similar process as in **6** → **7** after the corresponding nitrone was formed.[11]

The synthesis[9] of 2-phenylphenanthro[9,10-*d*][1,3]-oxazole from 9,10-phenanthrenedione 9-(*O*-methyloxime) and benzyl bromide by Nicolaides and co-workers probably follows a mechanism similar to those presented here rather than that originally proposed,[9] and in this respect is a precedent for the present approach to oxazoles.

In summary, a range of annulated oxazoles was prepared by unprecedented cyclizations of α-oxo-oximes on heating with dimethyl sulfate, alkyl or aralkyl halides in DMF and in the presence of anhydrous potassium carbonate. The reaction utilizes readily available starting materials and easily prepared intermediate oximes. The present method extends those previously reported for the synthesis of oxazoles and provides an experimentally convenient general procedure for the preparation of these compounds.

Experimental Section

General Methods and Materials. Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard for ^1H (300 MHz) or $CDCl_3$ as the internal standard for ^{13}C (75 MHz). Elemental and mass spectrometry analyses were performed by Analytical Laboratories, Department of Chemistry, University of Florida. DMF was dried over molecular sieves. Column chromatography was performed with silica gel 200−425 mesh or alumina adsorption 80−200 mesh. All reactions with air-sensitive compounds were carried out under nitrogen atmosphere.

Experimental details of the reaction of **1** with dimethyl sulfate in DMF in the presence of anhydrous potassium carbonate have been described earlier.[12]

Synthesis of Compounds 4 and 5. 2,1-Benzisoxazole-4,5-dione 4-oxime **1** (1.0 g, 6.1 mmol) was dissolved in anhydrous MeOH (100 mL), and the solution was cooled in an ice bath. A solution of diazomethane (0.51 g, 12 mmol) in ether (70 mL) was added in small portions, and the reaction mixture was stirred at 0 °C for 5 h. The solvent was removed under reduced pressure at room temperature. Purification of the solid residue by column chromatography on silica gel using hexanes/AcOEt as eluent gave first a yellow solid, methyl[5-oxo-2,1-benzisoxazole-4(5*H*)-ylidene]ammoniumolate **4** (0.56 g, 3.17 mmol, 52%), mp 140.0−141.0 °C, and then a second yellow solid, *trans*-2,1-benzisoxazole-4,5-dione 4-(*O*-methyloxime) **5** (0.12 g, 0.67 mmol, 11%), mp 159.0−161.0 °C. Data for **4**: ^1H NMR of (300 MHz, $CDCl_3$) δ 4.42 (d, J = 0.4 Hz, 3H), 6.70 (d, J = 9.9 Hz, 1H), 7.69 (dd, J = 9.9, 0.8 Hz, 1H), 9.56 (dq, J = 0.8, 0.4 Hz, 1H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 55.4, 111.3, 128.8, 132.8, 135.2, 154.2, 158.4, 178.4. Anal. Calcd for $C_8H_6N_2O_3$: C, 53.95; H, 3.40; N, 15.73. Found: C, 54.06; H, 3.25; N, 15.60. Data for **5**: ^1H NMR (300 MHz, $CDCl_3$) δ 4.39 (s, 3H), 6.64 (d, J = 10.2 Hz, 1H), 7.67 (dd, J = 10.2, 0.9 Hz, 1H), 9.10 (d, J = 0.9 Hz, 1H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 65.2, 108.5, 130.5, 134.3, 139.8, 154.0, 160.5, 181.4. Anal. Calcd for $C_8H_6N_2O_3$: C, 53.95; H, 3.40; N, 15.73. Found: C, 54.31; H, 3.44; N, 15.47. Crystal data for **4**: $C_8H_6N_2O_3$, FW 178.15, monoclinic, space group $P2_1$, a = 4.009(3), b = 6.794(6), c = 14.123(12) Å, β = 95.894(10)°, V = 382.6(6) Å^3, F(000) = 184, Z = 2, T = −105 °C, μ(Mo Kα) = 0.122 mm^{-1}, D_{calcd} = 1.546 g cm^{-3}, crystal size 0.46 × 0.31 × 0.29 mm, $2\theta_{max}$ 53° (CCD area detector, Mo Kα radiation), 119 parameters, GOF = 1.04, wR(F^2) = 0.0798 (all 1490 data), R = 0.0311 (1318 data with $I > 2\sigma I$). Crystal data for **5**: $C_8H_6N_2O_3$, FW 178.15, monoclinic, space group $P2_1/c$, a = 8.787(4), b = 9.798(4), c = 8.702(4) Å, β = 93.830(6)°, V = 747.6(6) Å^3, F(000) = 368, Z = 4, T = −105 °C, μ(Mo Kα) = 0.124 mm^{-1}, D_{calcd} 1.583 g cm^{-3}, crystal size 0.45 × 0.40 × 0.25 mm, $2\theta_{max}$ 53° (CCD area detector, Mo Kα radiation), 119 parameters, GOF = 0.99, wR(F^2) = 0.1006 (all 1504 data), R = 0.0359 (1177 data with $I > 2\sigma I$).

Synthesis of Compound 3. A mixture of nitrone **4** (0.040 g, 0.225 mmol) and potassium carbonate (0.034 g, 0.247 mmol) in dry DMF (1.7 mL) was stirred under nitrogen at room temperature for 3 h. Water (30 mL) was added with stirring,

the mixture was extracted with ether (3 × 30 mL), and the combined ether extract was washed with water (3 × 20 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent and purification of the residue by column chromatography on silica gel using hexanes/AcOEt (6/1−3/1) as eluent gave **3** (0.018 g, 0.112 mmol, 51%), mp 155−157 °C (lit.[12] 155−157 °C). Details of the $^1H/^{13}C$ NMR data for **3**, originally assigned structure **2**, are given in ref 12.

General Procedure for Preparation of Oximes 9, 17, and 19. 9-Phenanthrol or naphthol (20 mmol) was dissolved in a mixture of concentrated HCl (9.8 mL) and THF (9.8 mL) contained in a flask. and finely crushed ice was added until the temperature fell below 5 °C. The contents in the flask were stirred, and a solution of sodium nitrite (1.47 g, 20.8 mmol) in water (15.6 mL) was added slowly. The temperature was maintained between 0 and 5 °C by ice-bath. When all of the nitrite solution had been added, the mixture was stirred at this temperature for 1 h. Water (60 mL) was added, and the mixture was extracted with ethyl acetate (3 × 60 mL). The extract was dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexanes/ethyl acetate as eluent (6/1, v/v) to give the pure oximes.

***cis*-9,10-Phenanthrenedione 9-Oxime (9).** This oxime can be prepared either by the method described above (60%) or an alternative one as follows. A mixture of phenanthrenequinone (3.0 g, 14.4 mmol), hydroxylamine hydrochloride (1.0 g, 14.4 mmol), ethanol (90 mL), and pyridine (3 mL) was heated under reflux on an oil bath for 1 h. Pyridine and ethanol were removed in vacuo at 75 °C. Water (30 mL) was added to the cooled residue, and the mixture was cooled in an ice-bath with stirring until the oxime crystals formed. Filtration of the crystals, followed by washing with cold water and drying gave the pure product (3.23 g, 14.4 mmol): orange prisms (from ethanol); yield 100%; mp 156−158 °C (lit.[18] 157−158 °C); ^1H NMR ($CDCl_3$) δ 7.40−7.54 (m, 3H), 7.73−7.79 (m, 1H), 8.05 (d, J = 7.8 Hz, 1H), 8.12 (d, J = 8.1 Hz, 1H), 8.28−8.37 (m, 2H), 17.03 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 123.3, 123.4, 123.9, 128.2, 128.3, 128.8, 129.0, 129.1, 129.3, 130.0, 136.2, 137.5, 144.0, 182.3.

1,2-Naphthalenedione 1-oxime (17): brown prisms (from hexanes/ethyl acetate); yield 48% (lit.[18] 36%); mp 102−104 °C (lit.[18] 107−108 °C); ^1H NMR ($CDCl_3$) δ 6.57 (d, J = 9.8 Hz, 1H), 7.48−7.59 (m, 3H), 7.70 (d, J = 9.8 Hz, 1H), 8.32 (d, J = 7.3 Hz, 1H), 17.49 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 123.1, 125.7, 128.5, 129.6, 129.7, 130.7, 131.0, 144.8, 147.9, 182.8.

6-Bromo-1,2-naphthalenedione 1-oxime (19): yellow prisms (from hexanes/ethyl acetate); yield 67%; mp 145−146 °C; ^1H NMR ($CDCl_3$) δ 6.62 (d, J = 9.8 Hz, 1H), 7.61−7.66 (m, 3H), 8.19 (d, J = 9.0 Hz, 1H), 17.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 123.7, 124.7, 127.1, 129.4, 129.9, 132.0, 133.8, 144.4, 146.2, 182.3. Anal. Calcd for $C_{10}H_6BrNO_2$: C, 47.64; H, 2.40; N, 5.56. Found: C, 47.50; H, 2.20; N, 5.25.

General Procedure for Preparation of Phenanthro-[9,10-*d*][1,3]oxazoles (10), (16a−c). A mixture of the starting oxime (4.48 mmol), anhydrous potassium carbonate (1.15 g, 8.35 mmol), the electrophile (7.49 mmol, **15f** and **15a**−**c**), and dry DMF (44 mL) was stirred at 20−60 °C for 1−20 h under nitrogen. The mixture was cooled to 20 °C, and water (60 mL) was added. The mixture was extracted with ether (3 × 60 mL), and the combined ether extracts were washed with aqueous NaOH solution (1N, 60 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo and purification of the residue by column chromatography (for **16a**, on silica gel; **10**, **16b,c**, alumina) gave the corresponding products.

2-Phenylphenanthro[9,10-*d*][1,3]oxazole (10): 20 h, room temperature; colorless prisms after chromatography on alumina using hexanes/ethyl acetate as eluant (100/1, v/v); yield 43%; mp 199−201 °C; ^1H NMR ($CDCl_3$) δ 7.50−7.57 (m, 3H), 7.60−7.74 (m, 4H), 8.25−8.28 (m, 1H), 8.32−8.36 (m, 2H), 8.59 (dd, J = 8.1, 1.2 Hz, 1H), 8.64−8.69 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 120.8, 121.0, 122.9, 123.4, 123.7, 126.1, 126.2, 126.3, 127.1, 127.2, 127.4, 127.5, 128.8, 128.9, 129.2, 130.9, 135.5, 144.8, 162.1. Anal. Calcd for $C_{21}H_{13}NO$: C, 85.41; H, 4.44; N, 4.74. Found: C, 85.02; H, 4.49; N, 4.66.

Phenanthro[9,10-*d*][1,3]oxazole (16a): 6 h, 60 °C; yellow needles after chromatography on silica gel using hexanes/methylene chloride as eluant (100/1−20/1, v/v); yield 61%; mp 137−139 °C; ^1H NMR ($CDCl_3$) δ 7.63−7.75 (m, 4H), 8.21−8.23 (m, 1H), 8.24 (s. 1H), 8.51−8.54 (m, 1H), 8.66−8.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 120.9, 121.0, 122.7, 123.4, 123.6, 126.0, 126.2, 126.7, 127.3, 127.5, 128.9, 129.4, 133.3, 144.6, 151.2. Anal. Calcd for $C_{15}H_9NO$: C, 82.19; H, 4.14; N, 6.39. Found: C, 81.85; H, 4.00; N, 6.78.

2-Methylphenanthro[9,10-*d*][1,3]oxazole (16b): 1 h 50 min, 54−60 °C; colorless prisms after chromatography on alumina using hexanes/methylene chloride as eluant (10/1, v/v); yield 51%; mp 125−127 °C; ^1H NMR ($CDCl_3$) δ 2.76 (s, 3H), 7.58−7.72 (m, 4H), 8.13−8.16 (m, 1H), 8.46 (br d, J = 7.8 Hz, 1H), 8.64−8.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.6, 120.5, 120.9, 122.5, 123.3, 123.6, 125.8, 125.9, 126.0, 127.1, 127.3, 128.6, 128.8, 134.3, 144.8, 162.5. Anal. Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.00. Found: C, 81.99; H, 4.80; N, 5.93.

9,10-Phenanthrenedione 9-(*O*-ethyloxime) (23): yellow prisms; yield 24%; mp 53−55 °C; ^1H NMR ($CDCl_3$) δ 1.44 (t, J = 7.2 Hz, 3 H), 4.57 (q, J = 7.2 Hz, 2 H), 7.33−7.41 (m, 2 H), 7.45 (td, J = 7.6, 1.5 Hz, 1 H), 7.61 (td, J = 7.7, 1.5 Hz, 1 H), 7.90−7.96 (m, 2 H), 8.14 (dd, J = 7.7, 1.5 Hz, 1 H), 8.60 (dd, J = 8.0, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.5, 73.1, 123.2, 123.9, 125.5, 127.9, 128.2, 128.3, 130.4, 130.7, 130.9, 131.2, 134.5, 136.5, 146.3, 184.2. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.22; H, 5.41; N, 5.33.

2-Vinylphenanthro[9,10-*d*][1,3]oxazole (16c):1 h, 54−60 °C; colorless prisms after chromatography on alumina using hexanes/methylene chloride as eluant (10/1, v/v); yield 24%; mp 113−115 °C; ^1H NMR ($CDCl_3$) δ 5.83 (dd, J = 11.2, 1.0 Hz, 1H), 6.51 (dd, J = 17.7, 1.0 Hz, 1H), 6.86 (dd, J = 17.7, 11.2 Hz, 1H), 7.57−7.71 (m, 4H), 8.16−8.19 (m, 1H), 8.47 (dd, J = 8.0, 1.1 Hz, 1H), 8.60−8.63 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 120.7, 120.8, 122.6, 123.3, 123.5, 123.6, 123.7, 125.9, 126.1, 126.4, 127.1, 127.4, 128.8, 129.3, 135.0, 144.4, 161.2. Anal. Calcd for $C_{17}H_{11}NO$: C, 83.25; H, 4.25; N, 5.71. Found: C, 82.99; H, 4.65; N, 5.58.

General Procedure for Preparation of Naphtho[1,2-*d*][1,3]oxazoles (18a−d). A mixture of the starting oximes (6.06 mmol), anhydrous potassium carbonate (1.57 g, 11.36 mmol), the electrophile (10.18 mmol, **15a**−**d**), and dry DMF (42 mL) was stirred at 54−60 °C for 1.5 h under nitrogen (**18b**, 25 °C for 17 h). The mixture was cooled to 20 °C, and water (70 mL) was added with stirring. The mixture was extracted with ether (3 × 50 mL), and the combined extracts were dried over anhydrous $MgSO_4$. Evaporation of the solvent and purification of the residue by column chromatography on silica gel gave the corresponding products.

Naphtho[1,2-*d*][1,3]oxazole (18a): 1.5 h, 54−60 °C; colorless prisms after chromatography on silica gel using hexanes/methylene chloride as eluant (10/1, v/v); yield 55%; mp 61−63 °C; ^1H NMR ($CDCl_3$) δ 7.52−7.57 (m, 1 H), 7.64−7.70 (m, 1H), 7.69 (d, J = 8.9 Hz, 1H), 7.81 (d, J = 8.9 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 8.22 (s, 1H), 8.52 (br d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 110.9, 121.9, 125.4, 126.5, 126.6, 127.1, 128.5, 131.1, 135.4, 147.4, 151.5. Anal. Calcd for $C_{11}H_7NO$: C, 78.08; H, 4.18; N, 8.28. Found: C, 77.78; H, 3.96; N, 8.26.

Crystal data for 18a: $C_{11}H_7NO$, FW 169.18, monoclinic, space group $P2_1/n$, a = 9.413(7), b = 7.138(5), c = 12.329(9) Å, β = 103.842(10)°, V = 804.2(10) Å^3, $F(000)$ = 352, Z = 4, T = −105 °C, μ(Mo Kα) = 0.091 mm^{-1}, D_{calcd} 1.397 g cm^{-3}, crystal size 0.56 × 0.39 × 0.01 mm, $2\theta_{max}$ 45° (CCD area detector, Mo Kα radiation), 119 parameters, GOF = 1.14, wR(F^2) = 0.0864 (all 1060 data), R = 0.0548 (779 data with $I > 2\sigma I$).

(18) Chow, Y. L.; Wu, Z.-Z. *J. Am. Chem. Soc.* **1987**, *109*, 5260−5267.

***cis*-1,2-Naphthalenedione 1-(*O*-methyloxime) (21):** yellow oil; yield 8%; ^{1}H NMR ($CDCl_3$) δ 4.31 (s, 3H), 6.35 (d, J = 10.0 Hz, 1H), 7.33−7.44 (m, 4 H), 8.06−8.11 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 65.8, 124.5, 128.3, 128.9, 129.6, 129.7, 129.9, 131.6, 143.0, 143.6, 179.0; HRMS (EI) calcd for $C_{11}H_9NO_2$ 187.0633, found 187.0640.

***trans*-1,2-Naphthalenedione 1-(*O*-methyloxime) (22):** oil; yield 7%; ^{1}H NMR ($CDCl_3$) δ 4.36 (s, 3H), 6.41 (d, J = 9.9 Hz, 1H), 7.35−7.47 (m, 4H), 8.67−8.70 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 65.2, 126.9, 127.6, 129.8, 130.2, 130.9, 131.2, 131.9, 144.6, 145.2, 184.5; HRMS (EI) calcd for $C_{11}H_9NO_2$ 187.0633, found 187.0633.

2-Methylnaphtho[1,2-*d*][1,3]oxazole (18b): 17 h, 25 °C; colorless oil after chromatography on silica gel using hexanes/methylene chloride as eluant (100/1−7/1, v/v); yield 40%; ^{1}H NMR ($CDCl_3$) δ 2.72 (s, 3H), 7.47−7.53 (m, 1H), 7.59−7.65 (m, 2H), 7.72 (d, J = 8.9 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 8.44 (br d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.6, 110.6, 121.8, 125.0, 125.2, 126.2, 126.8, 128.4, 130.9, 136.5, 148.0, 162.8. Anal. Calcd for $C_{12}H_9NO$: C, 78.67; H, 4.96; N, 7.65. Found: C, 78.40; H, 5.09; N, 7.89.

2-Vinylnaphtho[1,2-*d*][1,3]oxazole (18c): 1.5 h, 54−60 °C; colorless oil after chromatography on silica gel using hexanes/ethyl acetate as eluant (100/1−6/1, v/v); yield 32%; ^{1}H NMR ($CDCl_3$) δ 5.85 (dd, J = 11.1, 1.0 Hz, 1H), 6.49 (dd, J = 17.7, 1.0 Hz, 1H), 6.86 (dd, J = 17.7, 11.1 Hz, 1H), 7.51−7.57 (m, 1H), 7.63−7.69 (m, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 8.49 (br d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 110.7, 122.0, 123.8, 124.1, 125.4, 126.4, 127.1, 128.6, 131.1, 137.1, 147.6, 161.4; HRMS (EI) calcd for $C_{13}H_9NO$ 195.0684, found 195.0682.

2-(4-Nitrophenyl)naphtho[1,2-*d*][1,3]oxazole (18d): 1.5 h, 54−60 °C; yellow prisms after chromatography on silica gel using hexanes/ethyl acetate as eluant (100/1−10/1, v/v); yield 24%; mp 215−217 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (t, J = 7.9 Hz, 1H), 7.72 (t, J = 7.3 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 8.39 (d, J = 8.8 Hz, 2H), 8,49 (d, J = 8.8 Hz, 2H), 8.59 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 110.8, 122.2, 124.2, 125.9, 126.6, 127.5, 127.9, 128.7, 131.3, 133.0, 137.7, 148.6, 149.0, 159.8; HRMS (EI) calcd for $C_{17}H_{10}N_2O_3$ 290.0691, found 290.0693.

General Procedure for Preparation of 7-Bromonaphtho[1,2-*d*][1,3]oxazoles (20a−c). A mixture of the starting oxime (3.97 mmol), anhydrous potassium carbonate (1.02 g, 7.40 mmol), the electrophile (6.64 mmol, **15a**, **15e**, or **15f**), and dry DMF (30 mL) was stirred at 54−60 °C for 1.5 h under nitrogen. The mixture was cooled to 20 °C, and water (70 mL) was added slowly. The resultant solution was extracted with ether (3 × 60 mL), and the combined extracts were dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo and purification of the residue by column chromatography on silica gel gave the corresponding products.

7-Bromonaphtho[1,2-*d*][1,3]oxazole (20a): 1.5 h, 54−60 °C; colorless prisms after chromatography on silica gel using hexanes/ethyl acetate as eluant (100/1−6/1, v/v); yield 54%; mp 111−112 °C; ^{1}H NMR ($CDCl_3$) δ 7.68−7.78 (m, 3H), 8.12 (d, J = 2.7 Hz, 1H), 8.23 (s, 1H), 8.37 (dd, J = 8.6, 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 112.1, 119.4, 123.7, 125.0, 125.5, 130.4, 130.5, 132.2, 135.5, 147.5, 151.8. Anal. Calcd for $C_{11}H_6BrNO$: C, 53.25; H, 2.44; N, 5.65. Found: C, 53.11; H, 2.27; N, 5.65.

7-Bromo-2-ethylnaphtho[1,2-*d*][1,3]oxazole (20b): 1.5 h, 54−60 °C; pale yellow prisms after chromatography on silica gel using hexanes/ethyl acetate as eluant (100/1−5/1, v/v); yield 34%; mp 59−61 °C; ^{1}H NMR ($CDCl_3$) δ 1.50 (t, J = 7.6 Hz, 3H), 3.06 (q, J = 7.6 Hz, 2H), 7.61 (d, J = 8.7 Hz, B part of AB system, 1H), 7.64 (d, J = 8.7 Hz, A part of AB system, 1H), 7.68 (dd, J = 8.7, 1.8 Hz, 1H), 8.07 (d, J = 1.8 Hz, 1H), 8.32 (dt, J = 8.7, 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.3, 22.3, 111.8, 118.9, 123.7, 124.1, 124.7, 130.0, 130.4, 132.0, 136.6, 148.0, 167.6. Anal. Calcd for $C_{13}H_{10}BrNO$: C, 56.55; H, 3.65; N, 5.07. Found: C, 56.39; H, 3.54; N, 4.73.

7-Bromo-2-phenylnaphtho[1,2-*d*][1,3]oxazole (20c): 1.5 h, 54−60 °C; reddish needles after chromatography on silica gel using hexanes/methylene chloride as eluant (100/1−5/1, v/v) and recrystallization from ethanol/methylene chloride (1/1); yield 41%; mp 175−176 °C; ^{1}H NMR ($CDCl_3$) δ 7.51−7.57 (m, 3H), 7.66−7.75 (m, 3H), 8.11 (d, J = 1.8 Hz, 1H), 8.26−8.34 (m, 2H), 8.44 (d, J = 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 112.0, 119.3, 124.0, 124.9, 125.0, 127.2, 127.4, 128.9, 130.2, 130.6, 131.3, 132.3, 137.7, 148.1, 162.7; HRMS (FAB) calcd for $C_{17}H_{11}BrNO$ 324.0018, found 324.0024.

Synthesis of 9,10-Phenanthrenedione 9-(*O*-benzyloxime) (13, two isomers). A mixture of phenanthraquinone **12** (0.92 g, 4.4 mmol), *O*-benzylhydroxylamine hydrochloride (0.80 g, 4.4 mmol), pyridine (0.93 mL), and EtOH (25 mL) was stirred at 73−75 °C for 1 h. EtOH and pyridine were removed under reduced pressure at 60−70 °C. About 15 mL of water was added into the residue, the mixture was extracted with ether (3 × 60 mL), and the combined extracts were dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure and purification by column chromatography on silica gel using hexane/AcOEt (12/1−6/1, v/v) as eluent gave two isomers of 9,10-phenanthrenedione 9-(*O*-benzyloxime) **13**. Isomer 1: yellow solid (0.28 g, 0.89 mmol, 20%), mp 77−78 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.47 (s, 2H), 7.35−7.62 (m, 8H), 7.76−7.82 (m, 1H), 7.96−8.06 (m, 2H), 8.24−8.32 (m, 2H); ^{13}C NMR (75 Hz, DMSO-d_6) δ 79.6, 123.5, 124.1, 125.5, 128.1, 129.0, 128.5, 128.6, 128.6, 128.8, 130.1, 131.0, 131.3, 131.7, 134.4, 136.1, 136.9, 146.7, 182.3. Anal. Calcd for $C_{21}H_{15}NO_2$: C, 80.48; H, 4.82; N, 4.47. Found: C, 80.12; H, 4.89; N, 4.45. Isomer 2: yellow solid (0.7 g, 2.23 mmol, 51%), mp 73−75 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.51 (s, 2H), 7.35−7.63 (m, 8H), 7.81 (t, J = 7.8 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 8.27−8.31 (m, 2H), 8.56 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 79.6, 123.4, 124.1, 125.6, 128.2, 128.4, 128.5, 128.6 (2C), 128.8, 130.6, 131.0, 131.3, 131.7, 134.7, 136.1, 136.7, 147.0, 184.4. Anal. Calcd for $C_{21}H_{15}NO_2$: C, 80.48; H, 4.82; N, 4.47. Found: C, 80.36; H, 4.85; N, 4.31.

Synthesis of Phenanthro[9,10-*d*]oxazol-2-yl-phenylmethanone (25). A mixture of the starting oxime **9** (0.223 g, 1.00 mmol), 1-(2-oxo-2-phenyl-ethyl)-pyridinium bromide **24** (0.306 g, 1.1 mmol), and triethylamine (0.35 mL) was refluxed in methanol for 1.5 h. The yellow precipitate was filtered and washed with methanol and hexane to give the product (0.295 g, 0.91 mmol): yield 91%; mp 188−189 °C (lit.[19] 201−203 °C); ^{1}H NMR ($CDCl_3$) δ 7.61 (t, J = 7.1 Hz, 2H), 7.66−7.77 (m, 5H), 8.41−8.44 (m, 1H), 8.59−8.62 (m, 1H), 8.65−8.70 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 120.5, 122.2, 123.0, 123.5, 123.7, 125.9, 127.0, 127.6, 127.8, 128.2, 128.5, 129.4, 130.9, 131.1, 134.0, 135.0, 135.3, 146.2, 156.8, 179.3. Anal. Calcd for $C_{22}H_{13}NO_2$: C, 81.72; H, 4.05; N, 4.33. Found: C, 81.40; H, 4.01; N, 4.28.

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Supporting Information Available: Crystallographic data (excluding structure factors) for structures **4**, **5,** and **18a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 204291, 204292, and 210734. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Rd., Cambridge CB2 1EZ, U.K (Fax 44(0) 1223-336033) or e-mail deposit@ccdc.cam.ac.uk.

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