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1,3-Dipolar Cycloaddition Reaction of Nitrile *N*-Oxides to 6-(2-Phenylethenyl)fulvene

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This paper is dedicated to Dr K. Nagarajan on the occasion of his 70th birthday

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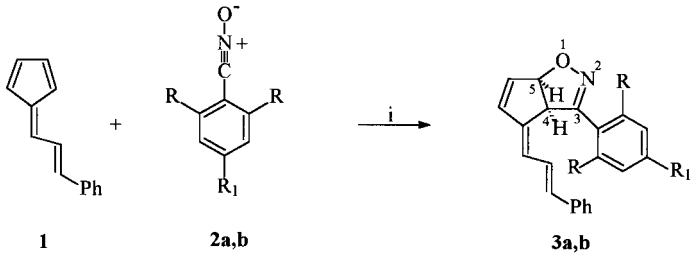
Abstract—Dipolar cycloaddition reactions of aryl nitrile oxides to 6-(2-phenylethenyl)fulvene leading to isoxazolines are described.

The chemistry of pentafulvenes, their cycloaddition reactions in particular, has been the subject of extensive investigations.[1,2] 6-(2-Phenylethenyl)fulvene **1** obtainable from cinnamaldehyde and cyclopentadiene can be viewed as an 8π conjugated system, which offers the possibility of multiple modes of cycloadditions including higher order cycloadditions. Prinzbach has reported the [4+2] cycloaddition reactions of 6-(2-phenylethenyl)fulvene **1** with DMAD.[3] We have recently shown that **1** can participate both as a 2π and 4π component in cycloaddition reactions.[4] In this context, it was of interest to study the reactions of 1,3-dipoles with **1**, especially because of the intriguing possibility of higher order dipolar cycloaddition offered by the latter. As far as we know, there has been no report on the addition of dipoles to **1** or similar compounds. The results of our investigations involving **1** and aryl nitrile oxides are reported here.

Results and Discussion

The reaction of 6-(2-phenylethenyl)fulvene **1**[5] with stable nitrile oxides **2a**,**b**[6] in dry benzene under reflux conditions afforded [3+2] adducts **3a**,**b** in good yields. The structures of the products were assigned on the basis of spectral and analytical data (Scheme 1).

In the ^{1}H NMR spectrum of **3a**, the proton on C-4 resonated as a doublet at δ 5.13 (J=7.4 Hz) and the proton on C-5 appeared as a double doublet at δ 6.01 (J=7.4 Hz, 0.9 Hz).



i. C_6H_6, Ar, reflux, 30 min.

a R = Cl, R_1 = H, 67%

b R = R_1 = CH_3, 50%

Scheme 1.

Keywords: fulvenes; cycloadditions; isoxazolines; nitrile oxides.
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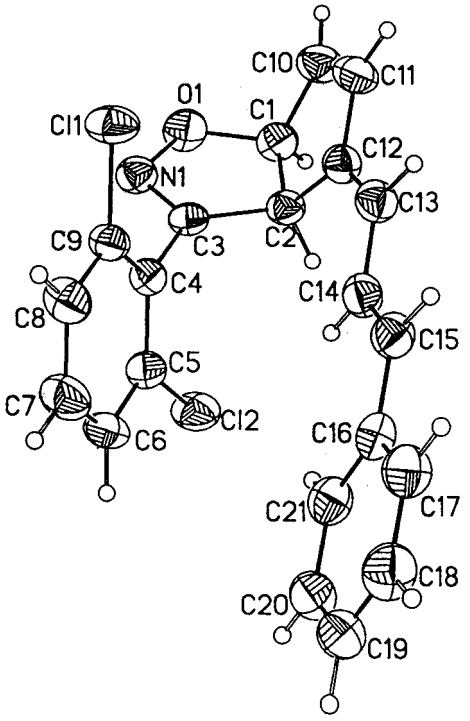


Figure 1. X-Ray crystal structure of **3a**.

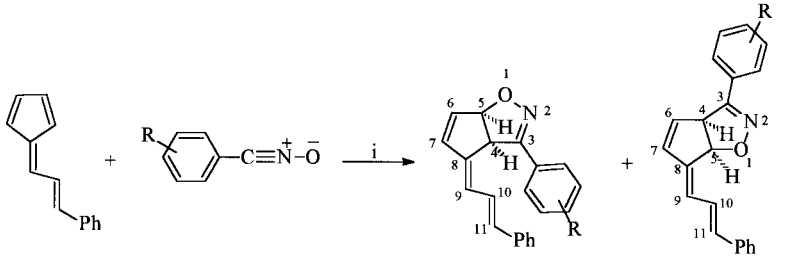
In the ^{13}C NMR spectrum, C-3 resonated at δ 153.10. The C-4 and C-5 signals were visible at δ 54.65 and 89.20 respectively. The structure was finally established unequivocally by single crystal X-ray analysis (Fig. 1).

Similar reactions were observed with 6-(2-phenylethenyl)-fulvene **1** and other substituted benzonitrile oxides **4a–d** generated in situ from the benzohydroximoyl chlorides and triethylamine in dry benzene; the regioisomeric mixtures of [3+2] adducts were obtained in good yields (Scheme 2).

The structures of the products **5a–d** were established by spectral analysis.[4,7] In the ^1H NMR spectrum of **5a**, the proton adjacent to the oxygen resonated as a double doublet at δ 5.91 (J=8.3 Hz, 1.4 Hz), whereas the other ring junction proton resonated as a doublet at δ 4.75 (J=8.3 Hz). The proton geminal to the phenyl group resonated as a doublet at δ 6.17 (J=11.1 Hz) while the styrenic proton appeared as a double doublet at δ 6.95 (J=15.4 Hz, 11.1 Hz) and the C-9 proton was visible as a doublet at δ 6.47 (J=15.4 Hz). The C-6 proton resonated as a double doublet at δ 6.27 (J=5.6 Hz, 1.4 Hz) and the signal due to C-7 proton was visible as a doublet at δ 6.87 (J=5.6 Hz). In the ^{13}C NMR spectrum, the carbon bound to oxygen resonated at δ 89.16 and the other sp^3 carbon signal appeared at δ 54.99. The C=N carbon resonated at δ 156.30.

The structures of the products **6a–d** were assigned on the basis of spectral and analytical data. In the ^1H NMR spectrum of **6a**, the protons on C-4 and C-5 resonated as double doublets at δ 4.89 (J=7.9, 1.6 Hz) and 5.90 (J=7.9, 1.2 Hz) respectively. The C-7 and C-9 protons appeared together as a multiplet at δ 6.45 whereas the styrenic proton resonated as a double doublet at δ 6.59 (J=15.2 Hz, 10.9 Hz). In the ^{13}C NMR spectrum, the C-4 and C-5 signals were visible at δ 55.03 and 89.81 respectively. The C=N carbon resonated at δ 156.31.

In order to explain the observed mode of cycloaddition and periselectivity in the above cycloaddition reactions, we have carried out some AM1 calculations using PC SPARTAN Graphical Interface Package for Molecular Mechanics and Molecular Orbital Models.[8] The correlation diagram for the



1 **4a-d** **5a-d** **6a-d**

i. Generated from the corresponding hydroximoyl chloride (C_6H_6, Ar, Et_3N, rt, 3 h)

Entry	Substituents	[3+2] adducts [ratio]	Yield (%)
1	**4a** R = 4-Cl	**5a:6a,** [1.4:1]	67
2	**4b** R = 2-Cl	**5b:6b,** [3:1]	47
3	**4c** R = 4-CH_3	**5c:6c,** [2.5:1]	62
4	**4d** R = 3-NO_2	**5d:6d,** [1.1:1]	53

Scheme 2.

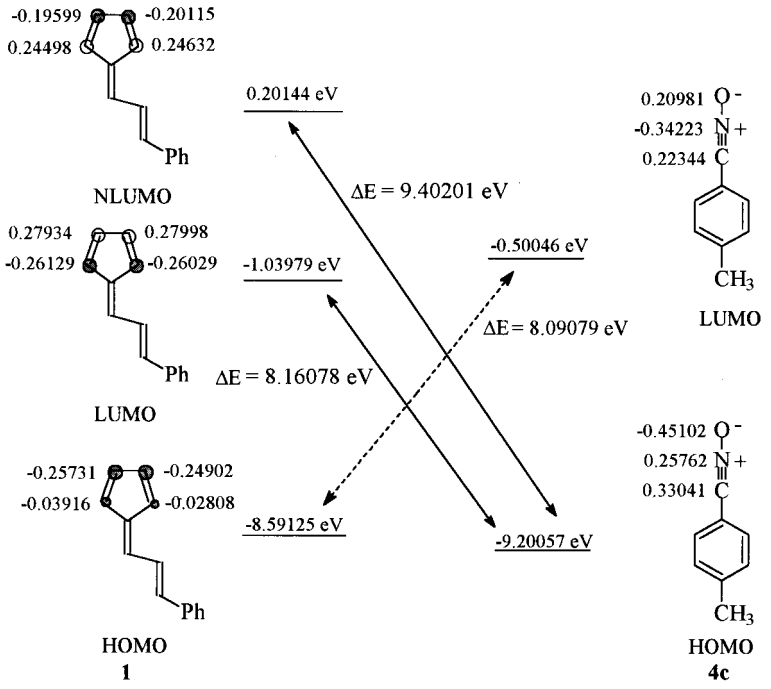


Figure 2. Molecular orbital correlation diagrams of **1** and **4c**.

reaction of 6-(2-phenylethenyl)fulvene **1** with **4c** is illustrated as an example in Fig. 2.

The exclusive formation of [3+2] adducts from **1** and **4c** can be explained in terms of the coefficients of the Frontier Orbitals at the reacting centers. It is clear from the correlation diagram that the interactions of HOMO(**4c**)–LUMO(**1**) and HOMO(**4c**)–NLUMO(**1**) are symmetry allowed. The interaction of HOMO(**1**)–LUMO(**4c**) is unimportant because the orbital coefficients are not matching at the reacting centers. Therefore, the interactions of HOMO(**4c**) with LUMO(**1**) and NLUMO(**1**) control the [3+2] cycloaddition, accounting for regioisomeric products.

On the basis of AM1 calculation the correlation diagram for the reaction of 6-(2-phenylethenyl)fulvene **1** with stable nitrile oxide **2a** was constructed and is presented in Fig. 3.

From the above correlation diagram it is evident that the size and sign of the orbital coefficients of the reacting carbon centres show that the interaction of HOMO(**1**) with LUMO(**2a**) is favored, more over the energy gap between HOMO(**1**)–LUMO(**2a**) is considerably smaller than that of HOMO(**2a**)–LUMO(**1**). From such considerations it can be concluded that the HOMO(**1**)–LUMO(**2a**) controls the cycloaddition.

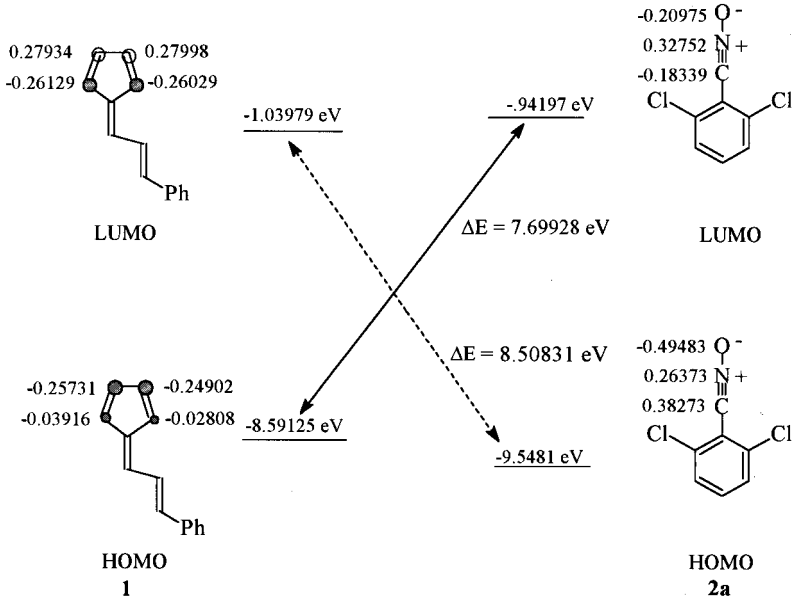


Figure 3. Molecular orbital correlation diagrams of **1** and **2a**.

It is worthy of note that the reaction of 6-(2-phenylethenyl)-fulvene 1 with stable nitrile oxide **2b**, generated in situ from the corresponding benzohydroxinoyl chloride and triethylamine in dry benzene, also afforded 50% of **3b**, indicating that the differing reaction conditions play no role in these reactions.

In conclusion, it has been observed that 6-(2-phenylethenyl)fulvene **1** participates as a 2π addend in 1,3-dipolar cycloaddition reactions with benzonitrile oxides.

Experimental

All reactions were carried out in oven dried glassware under argon atmosphere. Analytical thin layer chromatography was performed on silica gel plates. Purification by gravity column chromatography was carried out using silica gel (100–200). Mixtures of ethyl acetate–hexane and chloroform–methanol were used as eluents. All the compounds were recrystallised from ethyl acetate–hexane solvent system. Melting points are uncorrected. The IR spectra were recorded on a Nicolet impact 400D infrared spectrophotometer. NMR spectra were recorded on Jeol Ex-90 and Brüker 300 spectrophotometer using chloroform-d as solvent. The chemical shifts are given in the δ scale with tetramethylsilane as internal standard. Elemental analyses were done using Perkin–Elmer 2400 CHN analyzer. High-resolution mass spectra were obtained using Finnigan MAT model 8430.

2-Isoxazoline derivative 3a. A solution of 6-(2-phenylethenyl)fulvene **1** (0.180 g, 1 mmol) and 2,6-dichloro benzonitrile oxide **2a** (0.28 g, 1.5 mmol) in benzene (5 mL) was refluxed under argon for 30 min. The reaction mixture was concentrated in vacuo and the residue purified on silica gel column chromatography (2% ethyl acetate–hexane) to afford **3a** (0.246 g, 0.67 mmol, 67%) as a colorless crystalline solid (mp 175–177°C). IR (KBr): 3051, 1974, 1881, 1826, 1763, 1699, 1636, 1599, 1550, 1504, 1426, 1362, 1308, 1203, 1153, 1109, 1077, 1030, 965, 893, 851, 781 cm^{-1}. ^1H NMR: δ 7.27–6.99 (m, 8H), 6.45 (d, J=5.4 Hz, 1H), 6.32 (m, 2H), 6.23 (m, 2H), 6.01 (dd, J=7.4 Hz, J=0.9 Hz, 1H), 5.13 (d, J=7.4 Hz, 1H). ^{13}C NMR: δ 153.10, 142.31, 137.33, 136.81, 134.46, 133.47, 130.97, 128.77, 128.49, 128.45, 127.69, 127.56, 126.33, 124.67, 124.63, 89.20, 54.65. Anal. Calcd for $C_{21}H_{15}NOCl_2$: C- 68.65%, H- 4.12%, N- 3.81%. Found: C- 68.54%, H- 4.19%, N- 3.59%.

Crystal data of 3a: $C_{21}H_{15}NOCl_2$. Crystal size 0.30×0.22×0.20 mm. Monoclinic. Space group $P2_1/n$. Unit cell dimensions a=9.4179(2) Å, α=90°; b=15.8033(3) Å, β=90.247(1)°; c=11.8769(2) Å, γ=90°. Final R indices [I>2σ (I)] $R1$=0.0356, $wR2$=0.0848. R indices (all data) $R1$=0.0547, $wR2$=0.0924. Volume Z=1767.67(6) $Å^3$, 4. D_{calc}=1.311 Mg/m^3. F (000)=724. Absorption Coefficient=0.229 mm^{-1}. Reflections collected=27573. (Sheldrick, G. M., Siemens, Analytical X-ray Division, Madison, WI, 1995).

2-Isoxazoline derivative 3b. Reaction of **1** (0.180 g, 1 mmol) with **2b** (0.242 g, 1.5 mmol), as described earlier for **3a** yielded **3b** (0.171 g, 0.5 mmol, 50%) as a colorless crystalline solid (mp 136–138°C). IR (KBr): 3037, 2937, 1744, 1580, 1545, 1463, 1370, 1033, 964, 852, 752 cm^{-1}. ^1H NMR: δ 7.36–7.02 (m, 7H), 6.91 (m, 1H), 6.42 (d, J=5.4 Hz, 1H), 6.22 (m, 2H), 6.17 (d, J=11.2 Hz, 1H), 5.54 (dd, J=7.2 Hz, J=1.0 Hz, 1H), 4.80 (d, J=7.2 Hz, 1H), 2.43 (s, 3H), 2.28 (s, 3H), 2.03 (s, 3H). ^{13}C NMR: δ 156.17, 142.45, 139.13, 137.83, 136.14, 134.95, 133.69, 131.90, 128.44, 127.83, 126.42, 125.31, 124.71, 88.48, 56.42, 21.21, 20.89, 19.85. Anal. Calcd for $C_{24}H_{23}NO$: C- 84.42%, H- 6.79%, N- 4.10%. Found: C- 84.38%, H-6.81%, N- 4.22%.

2-Isoxazoline derivatives 5a and 6a. 4-Chloro benzohydroximoyl chloride **4a** (0.285 g, 1.5 mmol) in benzene (5 mL) was added to a solution of 6-(2-phenylethenyl)-fulvene **1** (0.180 g, 1.0 mmol) and triethylamine (0.152 g, 1.5 mmol) in benzene (5 mL) and was stirred at room temperature for 3 h. The reaction mixture was filtered to remove triethylamine hydrochloride and the solvent was evaporated in vacuo. The residue was chromatographed on a silica gel column. Elution of the column with 5% ethyl acetate–hexane afforded **5a** (0.135 g, 0.4 mmol, 40%, mp 170–173°C) and **6a** (0.089 g, 0.27 mmol, 27%, mp 186–188°C) as colorless solids.

Data for 5a: IR (KBr): 3070, 3036, 2201, 1600, 1499, 1485, 1398, 1337, 1094, 1020, 973, 912, 831, 751, 697 cm^{-1}. ^1H NMR: δ 7.62–7.18 (m, 9H), 6.95 (dd, J=15.4 Hz, 11.1 Hz, 1H), 6.87 (d, J=5.6 Hz, 1H), 6.47 (d, J=15.4 Hz, 1H), 6.27 (dd, J=5.6 Hz, 1.4 Hz, 1H), 6.17 (d, J=11.1 Hz, 1H), 5.91 (dd, J=8.3 Hz, J=1.4 Hz, 1H), 4.75 (d, J=8.3 Hz, 1H). ^{13}C NMR: δ 156.30, 141.93, 136.87, 135.84, 134.91, 133.57, 132.37, 128.96, 128.92, 128.67, 128.17, 127.90, 126.42, 124.71, 124.40, 89.16, 54.99. HRMS: Calcd for $C_{21}H_{16}NOCl$: 333.092042, Found: 333.090459.

Data for 6a: IR (KBr): 3049, 3029, 2942, 1735, 1593, 1506, 1485, 1445, 1411, 1330, 1222, 1094, 906, 845, 757, 703 cm^{-1}. ^1H NMR: δ 7.50–7.16 (m, 9H), 6.59 (dd, J=15.2 Hz, 10.9 Hz, 1H), 6.45 (m, 2H), 6.34 (d, J=10.9 Hz, 1H), 6.14 (dd, J=5.3 Hz, 1.6 Hz, 1H), 5.90 (dd, J=7.9 Hz, J=1.2 Hz, 1H), 4.89 (dd, J=7.9 Hz, J=1.6 Hz, 1H). ^{13}C NMR: δ 156.31, 142.18, 137.38, 136.82, 135.85, 134.46, 133.80, 129.55, 128.70, 128.00, 126.39, 125.34, 125.18, 89.81, 55.03. Anal. Calcd for $C_{21}H_{16}NOCl$: C- 75.56%, H- 4.83%, N- 4.20%. Found: C- 75.68%, H- 4.81%, N- 4.18%.

2-Isoxazoline derivatives 5b and 6b. Reaction of **1** (0.180 g, 1.0 mmol) with **4b** (0.285 g, 1.5 mmol) and triethylamine (0.152 g, 1.5 mmol), as described earlier afforded **5b** (0.120 g, 0.36 mmol, 36%, mp 167–170°C) and **6b** (0.038 g, 0.11 mmol, 11.4%, mp 127–129°C) as colorless solids.

Data for 5b: IR (KBr): 3062, 3010, 1588, 1476, 1432, 1326, 1251, 1201, 1033, 958, 889, 746 cm^{-1}. ^1H NMR: δ 7.28–7.10 (m, 10H), 6.43 (m, 2H), 6.19 (m, 2H), 5.98 (dd, J=7.9 Hz, J=1.3 Hz, 1H), 5.16 (d, J=7.9 Hz, 1H). ^{13}C NMR: δ 156.13, 141.70, 136.86, 135.42, 134.25, 133.79, 132.93, 131.69, 130.75, 129.48, 128.60, 127.77, 126.93,

126.57, 126.45, 124.74, 123.78, 88.56, 56.28.Anal. Calcd for $C_{21}H_{16}NOCl$: C- 75.56%, H- 4.83%, N- 4.20%. Found: C- 75.72%, H- 4.88%, N- 4.25%.

Data for 6b: IR, (KBr): 3062, 3047, 1713, 1595, 1560, 1472, 1432, 1320, 1201, 1033, 948, 859, 726 cm^{-1}. ^1H NMR: δ 7.30–7.12 (m, 10H), 6.43 (m, 2H), 6.17 (m, 2H), 5.95 (dd, J=8.3 Hz, J=1.2 Hz, 1H), 5.19 (dd, J=8.3 Hz, J=1.0 Hz, 1H). ^{13}C NMR: δ 156.06, 141.80, 136.92, 136.75, 134.15, 133.68, 132.83, 131.60, 130.65, 129.37, 129.17, 128.32, 127.56, 126.84, 126.35, 124.97, 124.78, 89.22, 54.64. Anal. Calcd for $C_{21}H_{16}NOCl$: C- 75.56%, H- 4.83%, N- 4.20%. Found: C- 75.65%, H- 4.85%, N- 4.30%.

2-Isoxazoline derivatives 5c and 6c. Reaction of **1** (0.180 g, 1.0 mmol) with **4c** (0.254 g, 1.5 mmol) and triethylamine (0.152 g, 1.5 mmol), as described earlier afforded **5c** (0.139 g, 0.44 mmol, 44.5%, mp 190–193°C) and **6c** (0.055 g, 0.18 mmol, 18%, mp 175–178°C) as colorless solids.

Data for 5c: IR (KBr): 2925, 2855, 1924, 1748, 1604, 1587, 1501, 1439, 1402, 1337, 1212, 1124, 1031, 968, 890 cm^{-1}. ^1H NMR: δ 7.41–7.10 (m, 9H), 6.57 (dd, J=15.1 Hz, 11.3 Hz, 1H), 6.43 (m, 2H), 6.30 (d, J=11.3 Hz, 1H), 6.14 (dd, J=5.2 Hz, 1.7 Hz, 1H), 5.93 (dd, J=7.8 Hz, J=1.7 Hz, 1H), 4.81 (d, J=7.8 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR: δ 157.20, 143.00, 139.96, 135.20, 133.35, 132.33, 129.46, 128.74, 127.88, 127.72, 126.49, 125.06, 124.42, 88.81, 55.28, 21.62. Anal. Calcd for $C_{22}H_{19}NO$: C- 84.31%, H- 6.11%, N- 4.47%. Found: C- 84.47%, H- 6.03%, N- 4.64%.

Data for 6c: IR (KBr): 3070, 2935, 2348, 1613, 1604, 1506, 1452, 1351, 1216, 1034, 973, 899, 818, 757, 697 cm^{-1}. ^1H NMR: δ 7.41–7.10 (m, 9H), 6.57 (dd, J=15.2 Hz, 11.1 Hz, 1H), 6.42 (m, 2H), 6.30 (d, J=11.1 Hz, 1H), 6.13 (dd, J=5.2 Hz, 1.8 Hz, 1H), 5.92 (d, J=7.9 Hz, 1H), 4.88 (dd, J=7.9 Hz, 1.8 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR: δ 157.27, 142.60, 139.68, 137.39, 137.06, 133.90, 129.15, 128.50, 128.09, 127.71, 127.17, 126.46, 125.79, 125.10, 89.46, 55.50, 21.20. Anal. Calcd for $C_{22}H_{19}NO$: C- 84.31%, H- 6.11%, N- 4.47%. Found: C- 84.51%, H- 6.18%, N- 4.68%.

2-Isoxazoline derivatives 5d and 6d. Reaction of **1** (0.180 g, 1.0 mmol) with **4d** (0.30 g, 1.5 mmol) and triethylamine (0.152 g, 1.5 mmol), as described earlier afforded 5d (0.096 g, 0.28 mmol, 28%, mp 193–195°C) and **6d** (0.086 g, 0.25 mmol, 25%, mp 143–145°C) as light yellow solids.

Data for 5d: IR (KBr): 3089, 2363, 1778, 1714, 1599, 1541, 1479, 1346, 1205, 1169, 1100, 1011, 959, 916, 820, 750, 692 cm^{-1}. ^1H NMR: δ 8.43–7.12 (m, 9H), 6.59 (dd, J=15.1 Hz, 11.1 Hz, 1H), 6.47 (m, 2H), 6.34 (d, J=11.1 Hz, 1H), 6.15 (dd, J=5.3 Hz, 1.9 Hz, 1H), 6.01 (dd, J=7.8 Hz, J=1.9 Hz, 1H), 4.98 (d, J=7.8 Hz, 1H). ^{13}C NMR: δ 155.22, 147.96, 141.56, 137.27, 136.32, 134.95, 134.11, 133.67, 131.97, 129.34, 128.62, 128.13, 126.18, 124.46, 124.18, 123.05, 90.08, 54.54. HRMS: Calcd for $C_{21}H_{16}N_2O_3$: 344.11609, Found: 344.11588.

Data for 6d: IR (KBr): 3080, 3037, 1592, 1528, 1351, 1225, 1085, 962, 921, 907, 820, 752 cm^{-1}. ^1H NMR: δ 8.60–7.27 (m, 9H), 6.95 (m, 2H), 6.56 (d, J=15.3 Hz, 1H), 6.35 (m, 2H), 5.98 (d, J=8.2 Hz, 1H), 4.80 (d, J=8.2 Hz, 1H). ^{13}C NMR: δ 155.64, 148.31, 141.73, 137.48, 134.23, 134.15, 133.23, 132.38, 129.64, 128.56, 127.93, 126.40, 124.81, 124.24, 122.33, 89.51, 54.70. Anal. Calcd for $C_{21}H_{16}N_2O_3$: C- 73.25%, H- 4.65%, N- 8.13%. Found: C- 73.00%, H- 4.65%, N- 8.05%.

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