3',4'-Diarylspiro[isobenzofuran-1(3H),5'(4'H)-isoxazol]-3-ones. Reaction of Nitrile Oxides with 3-Benzylidenephthalides

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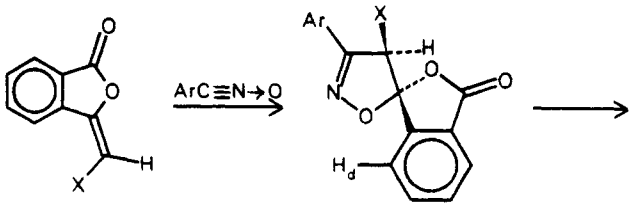
We previously reported[1] that 1,3-dipolar cycloaddition of aromatic nitrile oxides to 3-methylenephthalide (1) produced 3'-arylspiro[isobenzofuran-1(3H),5'(4'H)-isoxazol]-3-ones **3** in fair to good yields. The spiro heterocycles **3** are readily converted to 2-(3-aryl-5-isoxazolyl)benzoate derivatives, which are of considerable interest in pharmaceutical and agricultural industries.[2-6] The spiro heterocycles **3** themselves possess good herbicidal and plant growth regulant activity,[7] possibly as a result of in vivo conversion to **5**. This report presents our further work in definition of the scope and nature of the reaction of aromatic nitrile oxides with 3-methylenephthalides substituted on the vinyl group.

An attempted reaction of benzonitrile oxide (from benzohydroxamoyl chloride and triethylamine) with 3-ethylidenephthalide in ether failed to give any detectable adduct (NMR analysis) and resulted in complete disappearance of the nitrile oxide (IR analysis) through dimerization. Similarly, nitrile oxide cycloadducts were not obtained from (*Z*)-3-benzylidenephthalide, (*E*)- and (*Z*)-3-phenacylidenephthalide, and ethyl (*E*)- and (*Z*)-phthalylideneacetate. Evidently, the increased steric effects[8] in these trisubstituted olefins relative to **1** result in slower cycloaddition rates and consumption of the nitrile oxide through the competing dimerization route.

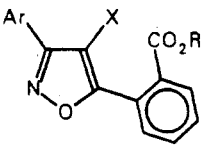
Spiro heterocycles **4** were formed, however, from reaction of nitrile oxides with (*E*)-3-benzylidenephthalides **2**. Although one might expect to obtain a mixture of regioisomers in this cycloaddition reaction, no evidence for spiro adducts with the spirolactone at the 4-position of the isoxazoline ring could be obtained. Evidence that the spiro heterocycle products possess the structure **4** derives from IR, ^1H and ^{13}C NMR, and mass spectral data. The IR spectra of **4** show the expected strained lactone carbonyl absorption at 1770–1780 cm^{-1}. The mass spectra of **4a–e** all have a prominent $M^+ - 148$ peak due to loss of phthalic anhydride, consistent only with the spirolactone being at the 5-position of the isoxazoline ring. Other major mass spectral fragmentation patterns result in production of aromatic nitrile radical cation and in benzylidenephthalide radical cation from loss of aromatic nitrile oxide. The ^{13}C NMR spectrum ($CDCl_3$) of **4a** shows the spiro carbon at 114.4 ppm, consistent with the 112-ppm shift[1] of the spiro carbon of **3** and inconsistent with the spirolactone being at the isoxazoline 4-position. As expected from past observations of exclusive cis additions of nitrile oxides to olefins,[8] the spiro heterocycles **4** formed from nitrile oxides and **2** retain the cis relationship of the phthalide aromatic ring and the vicinal aromatic ring. This product stereochemistry is revealed by the abnormally high shift of H_d (δ 6.20–6.37) observed in the proton NMR spectra[9] of **4a–e**. This upfield shift of H_d is a direct result of H_d lying in the shielding face[10] of the aromatic ring at the 4-position of the isoxazoline ring.

Scheme I



1, X = H
2, X = Ar

3, X = H
4a, X = Ar = C_6H_5 (31%)
b, X = 4-ClC_6H_4, Ar = C_6H_5 (35%)
c, X = 3-$CF_3C_6H_4$, Ar = C_6H_5 (42%)
d, X = 4-$CF_3C_6H_4$, Ar = C_6H_5 (43%)
e, X = 4-ClC_6H_4, Ar = 4-ClC_6H_4 (43%)



5, X = R = H
6a, X = Ar = C_6H_5, R = CH_3 (69%)
b, X = 3-$CF_3C_6H_4$, Ar = C_6H_5, R = CH_3 (61%)
c, X = 4-ClC_6H_4, Ar = 4-ClC_6H_4, R = CH_3 (76%)

Steric strain relief is considered to be an important factor in the relatively high dipolarophilic activity of norbornene.[11] Molecular models indicate little strain in (*Z*)-3-benzylidenephthalide and considerable steric congestion in (*E*)-3-benzylidenephthalide (**2**). Apparently, some relief of steric strain occurs in the transition state in reaction of nitrile oxides with **2**, and this accounts for the reactivity of the *E* isomer **2** relative to other strain-free 3-(substituted-methylene)phthalides.

Three of the spiro adducts **4** were converted to the isoxazolyl benzoates **6** with sulfuric acid and methanol. Benzoates **6** lack appreciable herbicidal and plant growth regulant activity, perhaps due to steric effects (nonplanarity and/or too large for proper bonding at active sites).

Experimental Section

Melting points were determined in open capillaries with a Mel-Temp apparatus and are corrected. IR spectra were obtained with a Perkin-Elmer Model 727B IR spectrometer. NMR spectra were obtained at 60 MHz with Varian T-60 NMR spectrometers, at 100 MHz with a JEOL FX-100 FT-NMR spectrometer, and

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(9) The assignment of the high-field aromatic proton of **4a** as H_d (Scheme I) was confirmed by homonuclear proton decoupling experiments at 360 MHz which showed H_d to be the M part of an ABCM spin pattern with appropriate ^3J, ^4J, and ^5J H–H coupling constants. Furthermore, protons H-2 and H-6 of the aryl ring at the isoxazoline 4-position of **4a**, **4b**, and **4e** appear at 60 MHz as a doublet, $J \simeq 9$ Hz, with further fine splittings, at δ 7.0 (slightly shielded by the phthalide aromatic ring). At 100 MHz, some broadening of the H-2, H-6 multiplet occurs. At 360 MHz, the H-2, H-6 signal is a broad singlet with width at half-height of about 40 Hz. This broadening is due to sterically hindered rotation of the 4-aryl ring and chemical shift nonequivalence of H-2, H-6. The coalescence temperature depends on the chemical shift separation in hertz and thus increases with field strength.
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at 360 MHz with a Bruker WM-360 superconducting FT-NMR spectrometer. Medium pressure liquid chromatography (MPLC) was performed on an EM LOBAR size C silica gel column at an eluent flow rate of 15 mL/min.

The method of Howe[12] was employed for preparation of the (*E*)-3-benzylidenephthalides.

(*E*)-3-Benzylidenephthalide: white crystals, mp 94.5–97 °C (lit.[13] mp 96 °C and olefinic H NMR signal at δ 6.8), 50% yield; NMR ($CDCl_3$) δ 7.83 (m, 1), 7.4 (m, 8), 6.8 (s, 1); IR (Nujol) 1770 cm^{-1}.

(*E*)-3-(4-Chlorobenzylidene)phthalide: white solid, mp 147.5–148.5 °C; 50% yield; NMR ($CDCl_3$) δ 7.83 (m, 1), 7.55–7.43 (m, 7), 6.86 (s, 1). Anal. Calcd for $C_{15}H_9ClO_2$: C, 70.19; H, 3.53. Found: C, 70.09; H, 3.53.

(*E*)-3-[3-(Trifluoromethyl)benzylidene]phthalide: white solid; mp 77.5–79 °C; 40% yield; NMR ($CDCl_3$) δ 8.0–7.4 (m, 8), 6.86 (s, 1). Anal. Calcd for $C_{16}H_9F_3O_2$: C, 66.21; H, 3.13. Found: C, 66.45; H, 3.16.

(*E*)-3-[4-(Trifluoromethyl)benzylidene]phthalide: 50% yield of 90:10 *E*:*Z* mixture; mp 101–111.5 °C. Three recrystallizations of a small amount of the mixture from cyclohexane gave 99% *E* isomer (GC analysis), mp 113.5–115 °C. Anal. Calcd for $C_{16}H_9F_3O_2$: C, 66.21; H, 3.13. Found: C, 66.06; H, 3.01.

3′,4′-Diphenylspiro[isobenzofuran-1(3*H*),5′(4′*H*)-isoxazol]-3-one (4a). To a solution of 9.40 g (0.0423 mol) of (*E*)-3-benzylidenephthalide and 6.54 g (0.0423 mol) of benzohydroxyamoyl chloride in 150 mL of ether stirred under nitrogen at 5 °C was added dropwise a solution of 4.28 g (0.0423 mol) of triethylamine in 20 mL of ether. The mixture was then stirred at 20 °C. After 42 h, no nitrile oxide remained (IR analysis), but NMR analysis of the ether solution showed residual (*E*)-3-benzylidenephthalide; no *Z* isomer had formed. The mixture was filtered. The collected solid was dissolved in 150 mL of chloroform, and the solution was washed twice with water, dried ($CaSO_4$), and concentrated to 3.55 g (24.6%) of solid that appeared to be pure spiro product (NMR analysis). This material was crystallized from toluene–methylcyclohexane to give 2.57 g (17.8%) of white, analytically pure spiro product: mp 187.5–188.5 °C; NMR ($CDCl_3$) δ 7.9–7.0 (m, 13), 6.27 (d, J = 7 Hz, of fine multiplets, 1), 5.06 (s, 1); IR (Nujol) 1780 cm^{-1}; MS, *m/e* (relative intensity) 341 (2.5), 222 (29), 194 (44.5), 193 (95.8), 192 (12.6), 166 (31.7), 165 (77.6), 116 (16.9), 105 (40), 104 (87.2), 103 (62.1), 91 (25.2), 90 (54.4), 89 (66.1), 77 (86.4), 76 (100.0). Anal. Calcd for $C_{22}H_{15}NO_3$: C, 77.41; H, 4.43. Found: C, 77.25; H, 4.46.

The ether filtrate from filtration of the reaction mixture was washed twice with water, dried ($CaSO_4$), and concentrated under vacuum to 9.0 g of oil; NMR, IR, and TLC analyses of the oil showed it to consist primarily of (*E*)-3-benzylidenephthalide and diphenylfurazan oxide, with a small amount of spiro adduct. A 2.0-g sample of the oil was separated by MPLC with toluene as eluent. The first material off the column consisted of 0.48 g of diphenylfurazan oxide, which corresponds to 2.16 g (43% yield) total in the 9.0 g of oil. The next material off the column was 1.10 g of (*E*)-3-benzylidenephthalide, which corresponds to 4.95 g (53% recovery) of starting material. Finally, 0.20 g of spiro adduct was obtained which corresponds to 0.90 g (6.2%) of spiro adduct. A total isolated yield of 30.8% of spiro adduct is thus indicated.

3′-Phenyl-4′-(4-chlorophenyl)spiro[isobenzofuran-1-(3*H*),5′(4′*H*)-isoxazol]-3-one (4b). (*E*)-3-(4-Chlorobenzylidene)phthalide in methylene chloride solution was treated with an equivalent of benzonitrile oxide (from benzohydroxamoyl chloride and triethylamine) for 4 days at 20 °C and then with another equivalent of benzonitrile oxide for several days. The mixture then was diluted with methylene chloride to dissolve all solids and was washed twice with water, dried ($CaSO_4$), and concentrated under vacuum to an oil. MPLC of the oil with methylene chloride gave pure spiro adduct, mp 179–181.5 °C, in 35% yield: NMR ($CDCl_3$) δ 7.9–7.0 (m, 12), 6.37 (d, *J* = 7 Hz, of fine multiplets, 1), 5.02 (s, 1); IR (Nujol) 1770 cm^{-1}; MS, *m/e* (relative intensity) 377 (0.6, $M^+ + 2$), 375 (2, M^+), 256 (9.3), 229 (23.9), 227 (56.5). Anal. Calcd for $C_{22}H_{14}ClNO_3$: C, 70.31; H, 3.75. Found: C, 70.37; H, 3.83.

3′-Phenyl-4′-[3-(trifluoromethyl)phenyl]spiro[isobenzofuran-1(3*H*),5′(4′*H*)-isoxazol]-3-one (4c). Treatment of (*E*)-3-[3-(trifluoromethyl)benzylidene]phthalide in methylene chloride solution with a total of 3 equiv of benzonitrile oxide (1 equiv every 3 days) followed by workup as for **4b** and MPLC with toluene gave spiro adduct **4c**, mp 194.5–196 °C, in 42% yield: NMR ($CDCl_3$) δ 7.96–7.26 (m, 12), 6.20 (d, *J* = 7 Hz, of fine multiplets, 1), 5.15 (s, 1); IR (Nujol) 1780 cm^{-1}. Anal. Calcd for $C_{23}H_{14}F_3NO_3$: C, 67.48; H, 3.45. Found: C, 67.52; H, 3.56.

3′-Phenyl-4′-[4-(trifluoromethyl)phenyl]spiro[isobenzofuran-1(3*H*),5′(4′*H*)-isoxazol]-3-one (4d). A 90:10 mixture of (*E*)- and (*Z*)-3-[4-(trifluoromethyl)benzylidene]phthalides was treated with 3 equiv of benzonitrile oxide in nearly identical fashion with that employed in the preceding experiment. The spiro adduct, isolated by MPLC with toluene eluent, had mp 174–175.5 °C and was isolated in 43% yield: NMR ($CDCl_3$) δ 7.92–7.23 (m, 12), 6.27 (d, *J* = 7 Hz, of fine multiplets, 1), 5.16 (s, 1); IR (Nujol) 1780 cm^{-1}. Anal. Calcd for $C_{23}H_{14}F_3NO_3$: C, 67.48; H, 3.45. Found: C, 67.38; H, 3.54.

3′,4′-Bis(4-chlorophenyl)spiro[isobenzofuran-1(3*H*),5′-(4′*H*)-isoxazol]-3-one (4e). Treatment of (*E*)-3-(4-chlorobenzylidene)phthalide in methylene chloride solution with a total of 4 equiv of 4-chlorobenzonitrile oxide (1 equiv every 24 h) gave, after workup and MPLC with toluene, solid spiro adduct, mp 136.5–144 °C, in 43% yield. Crystallization of this solid from cyclohexane gave 3.92 g (39.3%) of white solid: mp 155.5–157.5 °C; NMR ($CDCl_3$) δ 7.94–7.00 (m, 11), 6.36 (d, *J* = 7 Hz, of fine multiplets, 1), 5.00 (s, 1); IR (Nujol) 1780 cm^{-1}. The product tended to retain traces of solvent; for analysis, a sample was powdered and dried at 80 °C (0.1 torr) for several h. Anal. Calcd for $C_{22}H_{13}Cl_2NO_3$: C, 64.41; H, 3.19. Found: C, 64.48; H, 3.23.

Methyl 2-(3,4-Diphenyl-5-isoxazolyl)benzoate (6a). A solution of 1.80 g (0.005 27 mol) of 3′,4′-diphenylspiro[isobenzofuran-1(3*H*),5′(4′*H*)-isoxazol]-3-one, 125 mL of methanol, and 0.5 mL of concentrated H_2SO_4 was stirred at reflux for 40 h, cooled, and added to 400 mL of ice water. The mixture was extracted with 300 mL of ether. The ether was washed twice with aqueous sodium bicarbonate and once with water, dried ($CaSO_4$), and concentrated under vacuum to 1.7 g of clear viscous oil. Addition of a small amount of toluene and hexane caused the oil to crystallize to a white solid, mp 100.5–101.5 °C, which was recrystallized from toluene–hexane to give 1.29 g (69%) of white solid: mp 101.5–102.5 °C; NMR ($CDCl_3$) δ 7.93 (m, 1), 7.6–7.16 (m, 13), 3.73 (s, 3); IR (Nujol) 1730 cm^{-1}. Anal. Calcd for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82. Found: C, 77.57; H, 4.93.

Methyl 2-[3-Phenyl-4-[3-(trifluoromethyl)phenyl]-5-isoxazolyl]benzoate (6b). Similar conditions starting with **4c** gave 1.17 g (61%) of white solid, mp 97–98 °C. A small amount was recrystallized from ether–hexane to give solid: mp 97.5–98.5 °C; NMR ($CDCl_3$) δ 8.0 (m, 1), 7.66–7.26 (m, 12), 3.73 (s, 3); IR (Nujol) 1730 cm^{-1}. Anal. Calcd for $C_{24}H_{16}F_3NO_3$: C, 68.08; H, 3.81. Found: C, 68.03; H, 3.89.

Methyl 2-[3,4-Bis(4-chlorophenyl)isoxazol-5-yl]benzoate (6c). The crude product was crystallized once from ether–hexane to give 1.01 g (76%) of white solid: mp 146–147 °C; NMR ($CDCl_3$) δ 7.93 (m, 1), 7.73–6.9 (m, 11), 3.76 (s, 3); IR (Nujol) 1725 cm^{-1}. Anal. Calcd for $C_{23}H_{15}Cl_2NO_3$: C, 65.11; H, 3.56. Found: C, 65.30; H, 3.70.

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Regioselectivity of 1,3-Dipolar Cycloaddition Reactions of Nitrilimines with Aryl Vinyl Sulfones

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Nitrilimines have been known to react with various types of monosubstituted olefins to give predominantly 5-sub-

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