Nitrile Oxide Cycloaddition Routes to 2-(Isoxazolyl)-benzoates and 2-(1,2,4-Oxadiazol-3-yl)benzoates

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Cycloaddition of aromatic nitrile oxides to methyl *o*-vinylbenzoate produced methyl 2-(3-aryl-2-isoxazolin-5-yl)benzoates; the isoxazolines were converted to methyl 2-(3-arylisoxazol-5-yl)benzoates. Reaction of the nitrile oxide from *o*-methoxycarbonylbenzohydroximinoyl chloride (**11**) with phenylacetylene, styrenes, and aromatic nitriles resulted in methyl 2-(5-phenylisoxazol-3-yl)benzoate, methyl 2-(5-aryl-2-isoxazolin-3-yl)-benzoates (**15**), and methyl 2-(5-aryl-1,2,4-oxadiazol-3-yl)benzoates, respectively. The isoxazolines **15** were converted to the corresponding isoxazoles **16**.

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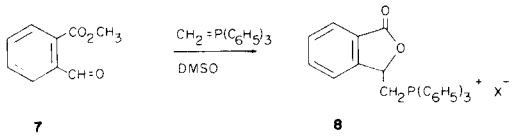
Several classes of 2-[aryl(heteroaryl)]benzoic acids inhibit *in vivo* transport of auxin, with resultant plant growth regulant and herbicidal activity (1-4). These classes include 2-(3-arylisoxazol-5-yl)benzoates, 2-(5-arylisoxazol-3-yl)benzoates, and 2-(3-aryl-1,2,4-oxadiazol-5-yl)benzoates, which possess moderate to excellent levels of biological activity (2,4). We reported recently the synthesis of 2-(1,2,4-thiadiazolyl)benzoates *via* 1,3-dipolar cycloaddition reactions of nitrile sulfides to benzonitriles (5). This account reports new routes to the two isomeric classes of 2-(arylisoxazolyl)benzoates and to the hitherto unreported 2-(5-aryl-1,2,4-oxadiazol-3-yl)benzoates *via* 1,3-dipolar cycloaddition reactions of nitrile oxides; in addition, syntheses of 2-(3-aryl-2-isozazolin-5-yl)benzoates and 2-(5-aryl-2-isoxazolin-3-yl)benzoates (dihydro analogs of the isoxazoles) are reported.

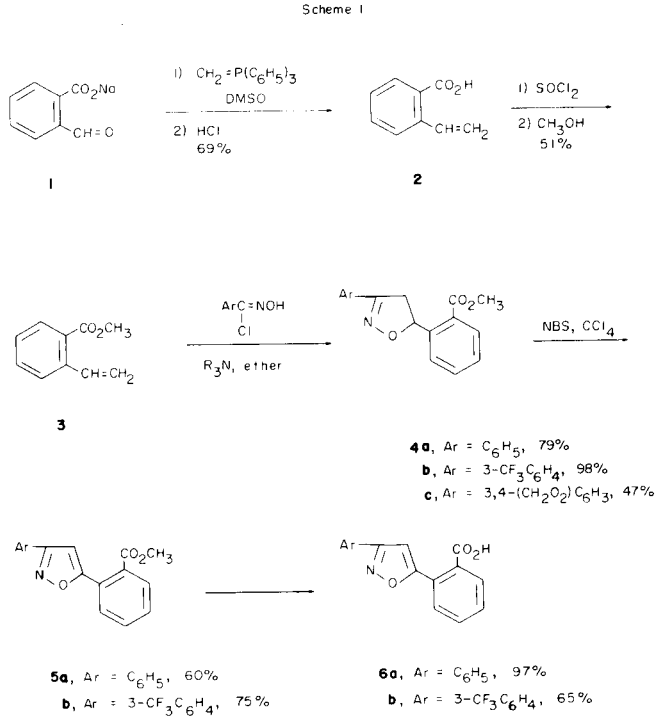
2-(3-Aryl-2-isoxazolin-5-yl)benzoates and 2-(3-aryl-isoxazol-5-yl)benzoates were prepared as shown in Scheme 1. Attempts to prepare methyl *o*-vinylbenzoate from methyl *o*-formylbenzoate and methylenetriphenylphosphorane resulted only in water soluble materials, presumably derived from the (phthalidylmethyl)phosphonium salt **8**. Use of the sodium salt of *o*-formylbenzoic acid in the Wittig reaction prevented formation of **8** and resulted in *o*-vinylbenzoic acid (**2**).



7 8

Cycloadditions of nitrile oxides, generated by *in situ* dehydrochlorination of chloro oximes, to methyl *o*-vinylbenzoate proceeded regioselectively (6) (within the limits of detection by nmr analysis) to produce isoxazolines **4a-c**. The structures of these isoxazolines were confirmed by nmr analyses (7). Bromination-dehydrobromination (8) of **4a,b** gave isoxazoles **5a,b**, whose structures were confirmed by hydrolysis of **5a** to the known acid **6a** and by nmr analyses which revealed the H-4 isoxazole ring proton (9) of **5a** and **5b** at δ 6.8. A primary advantage of this synthetic route is that a variety of analogs of **5** may be prepared in two steps from a common intermediate, **3**, and the readily accessible (10) chloro oximes.

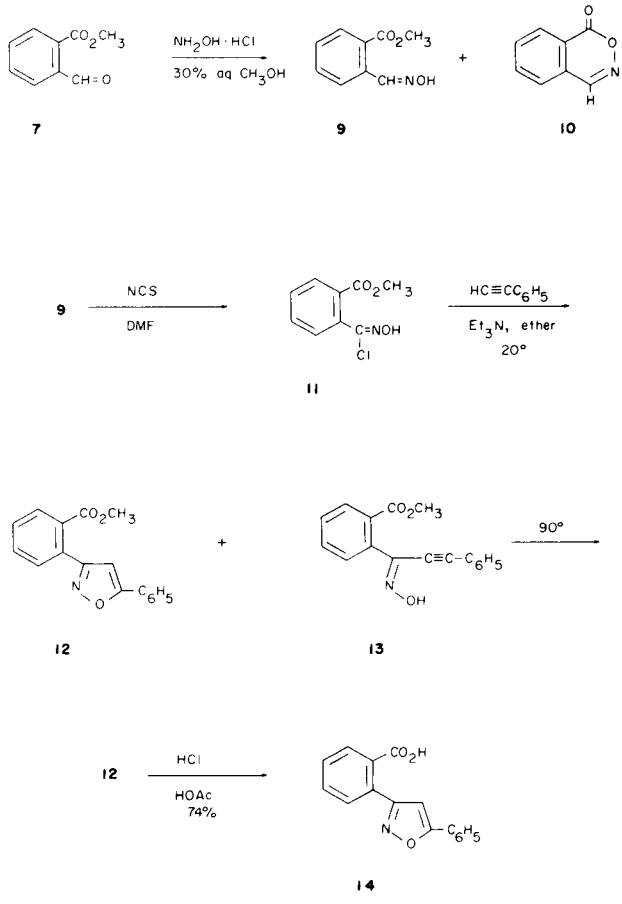
Scheme I



1 2 3

The key to preparation of 2-(5-aryl-2-isoxazolin-3-yl)-benzoates and 2-(5-arylisoxazol-3-yl)benzoates resided in the successful synthesis of the unstable oxime **9** and chloro oxime **11** (Scheme 2). Use of 30% aqueous methanol (11) as solvent in the condensation of hydroxylamine with **7** allowed preparation of **9** with only slight ($\leq$ 10%) contamination with 1*H*-2,3-benzoxazin-1-one (12) (**10**); use of less aqueous solvents led to increased percentages of **10**. Immediately after preparation, oxime **9** was converted with *N*-chlorosuccinimide-DMF (10) to **11**, which was employed without purification in the cycloaddition reactions.

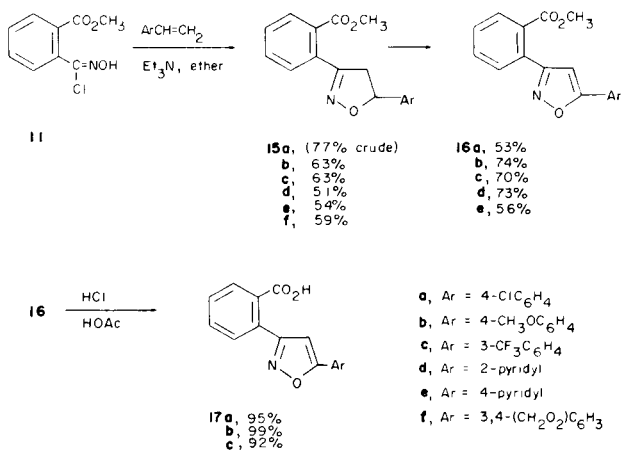
Scheme 2



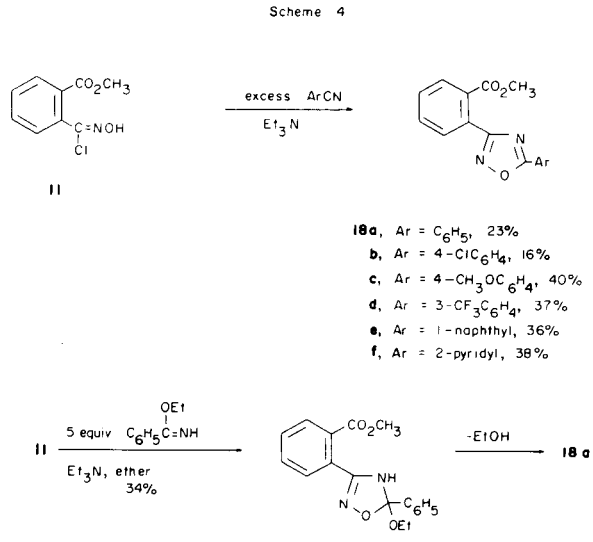
Reaction of the nitrile oxide from **11** with phenylacetylene was incomplete after 1 hour at 20°; an ir spectrum of the reaction mixture showed strong nitrile oxide absorption and also NOH absorptions attributable to the presence of **13** (13). Reaction was complete after thirty minutes at 90° (conditions which sufficed also to convert **13** to **12**) and produced isoxazole **12** (45% yield after purification). Hydrolysis of **12** gave the known (2) acid **14** (Scheme 2).

The 2-(5-arylisoxazolin-3-yl)benzoates and further examples of 2-(5-arylisoxazol-3-yl)benzoates were prepared as shown in Scheme 3. The structures of **15** were confirmed by nmr analyses (7) and by conversions to **16**. The structures of **16** were confirmed by nmr analyses (9) and by conversion of **16a** to the known (2) acid **17a**.

Scheme 3



Scheme 4



2-(3-Aryl-1,2,4-oxadiazol-5-yl)benzoic acids are readily prepared from the reaction of amide oximes with phthalic anhydride and have been known since 1885 (14). The isomeric 2-(5-aryl-1,2,4-oxadiazol-3-yl)benzoates appear not to have been made previously; we synthesized them from reaction of **11**, triethylamine, and aromatic nitriles as shown in Scheme 4. In addition, the imino ester variation of oxadiazole synthesis (15) was employed in one case to prepare **18a**.

The isomeric 2-(aryl-2-isoxazolinyl)benzoates **4a-c** and **15a-f** possess plant growth regulant activity but are not quite as active as the 2-(arylisoxazolyl)benzoates **5a-b, 12,** and **16a-e.** The 2-(5-aryl-1,2,4-oxadiazol-3-yl)benzoates **18a-f** possess plant growth regulant activity comparable to that of the isomeric 2-(3-aryl-1,2,4-oxadiazol-5-yl)benzoates.

EXPERIMENTAL

Melting points were taken in open capillaries in a Mel-Temp apparatus and are corrected; boiling points are uncorrected.

o-Vinylbenzoic Acid (2).

The sodium salt of 2-carboxybenzaldehyde was prepared by addition of 129.6 g (0.60 mole) of 25% sodium methoxide in methanol to a solution of 90 g (0.6 mole) of 2-carboxybenzaldehyde in 900 ml of methanol, followed by concentration under vacuum to 90° at 0.5 torr.

Sodium hydride dispersion, 50% in mineral oil, 29.04 g (0.605 mole), was washed three times with pentane and dried under nitrogen in a

2-liter 4-necked flask. Then, 600 ml of dry DMSO was added under dry nitrogen, and the mixture was stirred at 67° until hydrogen evolution was complete (30 minutes; the temperature must *not* exceed 70°) and was cooled to 25°. Then 216 g (0.605 mole) of methyltriphenylphosphonium bromide was added, followed by 600 ml of dry DMSO. The mixture was stirred under nitrogen and cooled to maintain the temperature below 35°.

The sodium carboxylate was added with stirring under nitrogen. After a few minutes, the solution was concentrated under oil pump vacuum (45° maximum bath temperature), and water was added to the residue. The mixture was filtered, and to the filtrate was added 57 ml of concentrated hydrochloric acid with stirring. The resultant mixture was extracted with ether. The ether solution was extracted with 5% sodium hydroxide. The aqueous layer was acidified with hydrochloric acid and then extracted with ether. The ether solution was dried and concentrated under vacuum to 61 g (69%) of sticky solid product. A 2.5 g portion was recrystallized from petroleum ether to give 1.5 g of solid, mp 89-90° [lit (16) mp 94-95°].

Methyl *o*-Vinylbenzoate (**3**).

A mixture of 58.5 g (0.395 mole) of crude *o*-vinylbenzoic acid and 127.3 g (1.08 moles) of thionyl chloride was heated on a steam bath until gas evolution subsided (40 minutes). The solution was concentrated, and 270 ml of methanol was added slowly. The mixture was held at reflux for 10 minutes and then was concentrated. Ether was added to the residue, and the solution was extracted three times with water. The ether layer was dried, a little hydroquinone was added, and the solution was distilled to give 32.3 g (51%) of liquid, bp 64-78°/0.2 torr [lit (17) bp 71-73°/0.1 torr]; nmr (deuteriochloroform): δ 8.07-7.17 (m, 5, ArH + vinyl H), 5.83-5.23 (m, 2, vinyl H), 3.87 (s, 3, OCH_3).

Methyl 2-(3-Phenyl-2-isoxazolin-5-yl)benzoate (**4a**).

To a stirred solution of 9.4 g (0.0604 mole) of benzohydroximinoyl chloride and 10.76 g (0.0664 mole) of methyl *o*-vinylbenzoate in 100 ml of ether at 0-5° was added dropwise a solution of 7.81 g (0.0604 mole) of ethyldiisopropylamine in 35 ml of ether during 30 minutes. The mixture was stirred in an ice bath for 4 hours, diluted with another 400 ml of ether, extracted three times with water, dried (calcium sulfate) and concentrated under vacuum to a solid. This solid was washed with 200 ml of hexane. The undissolved solid product, 14.21 g (84%), mp 90-94°, was crystallized from 100 ml of methanol to give 13.50 g (79%) of white solid, mp 93.5-95°; nmr (deuteriochloroform): δ 7.97 (m, 1), 7.83-7.17 (m, 8), 6.43 (dd, 1, $J_{4,5}$ = 11.3 Hz, $J_{4',5}$ = 6.7 Hz, H-5), 4.08 (dd, 1, $J_{4,5}$ = 11.3 Hz, $J_{4,4'}$ = 18 Hz, H-4), 3.92 (s, 3, OCH_3), 3.14 (dd, 1, $J_{4',5}$ = 6.7 Hz, $J_{4,4'}$ = 18 Hz, H-4'); ir (chloroform): 1710 cm^{-1}.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37. Found: C, 72.50; H, 5.38.

Methyl 2-{3-[3-(trifluoromethyl)phenyl]-2-isoxazolin-5-yl}benzoate (**4b**).

In similar fashion, reaction of equimolar amounts of 3-(trifluoromethyl)benzohydroximinoyl chloride (18), **3**, and triethylamine in ether at 20° for 21 hours gave, after workup (aqueous extraction, drying, and concentration under vacuum), fairly pure product (nmr analysis) as an oil in 98% yield; nmr (deuteriochloroform): δ 8.18-7.23 (m, 8), 6.53 (dd, 1, H-5), 4.10 (dd, 1, H-4), 3.93 (s, 3, OCH_3), 3.13 (dd, 1, H-4'); ir (film): 1720 cm^{-1}.

Methyl 2-[3-(3,4-Methylenedioxyphenyl)-2-isoxazolin-5-yl]benzoate (**4c**).

To a stirred solution of 17.0 g (0.0852 mole) of 3,4-methylenedioxybenzohydroximinoyl chloride (19) and 15 g (0.0926 mole) of methyl *o*-vinylbenzoate in 250 ml of ether was added dropwise during 40 minutes a solution of 8.61 g (0.0852 mole) of triethylamine with stirring at 0-5°. The mixture was stirred at 0-5° for 1 hour and then was allowed to stand overnight. Tetrahydrofuran, 500 ml, was added, and the mixture was stirred and then extracted twice with water. The water layers were combined and extracted once with fresh tetrahydrofuran-ether solution. The organic layers were combined, washed twice with aqueous sodium chloride, and concentrated under vacuum to 29.3 g of solid. Crystallization of the solid from methylcyclohexane gave 13.12 g (47%) of white solid, mp 125-127°. Recrystallization of 5.37 g of the solid from methylcyclohexane gave 4.49 g of solid, mp 126.5-127.5°; nmr (deuteriochloroform): δ 8.03-6.6 (m, 7), 6.33 (dd, 1, H-5), 5.92 (s, 2, CH_2O_2), 4.00 (dd, 1, H-4), 3.90 (s, 3, OCH_3), 3.05 (dd, 1, H-4'); ir (chloroform): 1710 cm^{-1}.

Anal. Calcd. for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.65. Found: C, 66.41; H, 4.66.

Methyl 2-[3-Phenylisoxazol-5-yl]benzoate (**5a**).

To a mixture of 11.05 g (0.0409 mole) of methyl 2-(3-phenyl-2-isoxazolin-5-yl)benzoate and 7.28 g (0.0409 mole) of *N*-bromosuccinimide in 150 ml of carbon tetrachloride heated at reflux was added 0.3 g of benzoyl peroxide. The mixture was held at reflux for 3 hours, at which time gas evolution had ceased, cooled to 20°, filtered free of solid, and concentrated to 9.8 g of oil. The solid was boiled twice with carbon tetrachloride. The supernatants were combined and concentrated to 4.0 g of oil. The oils were combined and subjected to Kugelrohr distillation; pure product was collected at 157-160°/0.2 torr, 7.30 g (60%) of oil; nmr (deuteriochloroform): δ 8.07-7.4 (m, 9, ArH), 6.8 (s, 1, H-4), 3.87 (s, 3, OCH_3); ir (chloroform): 1720 cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.01; H, 4.70; N, 4.98.

Methyl 2-{3-[3-(trifluoromethyl)phenyl]isoxazol-5-yl}-benzoate (**5b**).

In similar fashion, product **5b** was obtained as a viscous oil in 98% purity (gc analysis) and 75% yield after two Kugelrohr distillations (the second one at 155°/0.5 torr). Crystallization of the oil from ether-hexane at 0° gave solid (mp 46.5-48.5°, 52% yield), which was passed through a short silica gel column with benzene to give pure product as a white solid, mp 48-50° (48% yield); nmr (deuteriochloroform): δ 8.13-7.37 (m, 8), 6.77 (s, 1, H-4), 3.87 (s, 3, OCH_3), ir (chloroform): 1725 cm^{-1}.

Anal. Calcd. for $C_{18}H_{12}F_3NO_3$: C, 62.25; H, 3.48; N, 4.03. Found: C, 62.33; H, 3.49; N, 4.09.

2-(3-Phenylisoxazol-5-yl)benzoic Acid (**6a**).

A mixture of 1.0 g of ester **5a**, 1.0 g of sodium hydroxide, 3 ml of water, and 10 ml of methanol was heated on a steam bath for 30 minutes and then was concentrated under vacuum. The residue was dissolved in water, and the clear solution was acidified with concentrated hydrochloric acid to give 0.92 g of beige solid, mp 190-192° (97%). Recrystallization of the solid from 1,2-dichloroethane gave 0.76 g of beige solid, mp 192-193.5° [lit (2) mp 193-195°].

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18. Found: C, 72.35; H, 4.19.

The product was identical to that prepared in 24% yield overall from phenacylphthalide by the method of Harris and Huppatz (2) and also to that prepared in 29% yield from phthalic anhydride and acetophenone oxime by the method of Nadelson (20).

2-{3-[3-(Trifluoromethyl)phenyl]isoxazol-5-yl}benzoic Acid (**6b**).

A solution of 6.20 g of methyl 2-{3-[3-(trifluoromethyl)phenyl]isoxazol-5-yl}benzoate, 75 ml of acetic acid, and 50 ml of concentrated hydrochloric acid was held at reflux for 4 hours, cooled, and poured into 450 ml of cold water to give 5.29 g of white solid, mp 163-170°. This solid was recrystallized from acetonitrile to give 3.87 g (65%) of white solid, mp 176-177°. Recrystallization of 0.50 g of this latter material gave 0.35 g of white solid, mp 176.5-178°.

Anal. Calcd. for $C_{17}H_{10}F_3NO_3$: C, 61.27; H, 3.02. Found: C, 61.25; H, 3.03.

Methyl *o*-Formylbenzoate (**7**).

Methyl *o*-formylbenzoate was prepared in 81% yield from 2-carboxybenzaldehyde by the procedure of Brown and Sargent (21); nmr (deuteriochloroform): δ 10.57 (s, 1, CHO), 8.03-7.50 (m, 4, ArH), 3.93 (s, 3, CH_3).

Methyl 2-(Hydroximinomethyl)benzoate (**9**).

A solution of 82 g (0.50 mole) of methyl *o*-formylbenzoate and 35.0 g (0.50 mole) of hydroxylamine hydrochloride in 2500 ml of 30% aqueous

methanol was stirred at 10-20° for 1 hour and then at 0-5° for 1 hour to give 65.4 g (73%) of white solid product, mp 72-74.5°; nmr (deuteriochloroform): δ 9.03 (s, 1, CH=N), 8.60 (br s, 1, NOH), 8.18-7.42 (m, 4, ArH), 3.99 (s, 3, OCH_3); ir (mineral oil mull): 3200, 1710 cm^{-1}.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06. Found: C, 60.55; H, 5.12.

This material is not particularly stable; two preparations decomposed violently upon standing overnight at 20°.

o-Methoxycarbonylbenzohydroximinoyl Chloride (**11**).

To a stirred solution of 22.4 g (0.125 mole) of methyl 2-(hydroximinomethyl)benzoate in 124 ml of dimethylformamide was added about one-fourth of 16.7 g (0.125 mole) of *N*-chlorosuccinimide. Six ml of gas from the head space of a concentrated hydrochloric acid bottle was bubbled into the solution to initiate the reaction (as indicated by an exotherm). The rest of the *N*-chlorosuccinimide was added over several minutes, with intermittant cooling to keep the temperature at 35°. The solution was stirred an additional 15 minutes, cooled to 10°, and poured into 500 ml of cold water. The mixture was extracted with 300 ml of ether. The ether extract was washed twice with water, dried (calcium sulfate), and concentrated under vacuum to 22.0 g of white semisolid. This material was stirred with 40 ml of methylene chloride; the mixture was filtered, and the filtrate was concentrated under vacuum to give 21.1 g (79%) of white oil that was 85% pure product (nmr analysis based on OCH_3 integration versus the aromatic region). This material was stored in a refrigerator and was employed in subsequent reactions without further purification.

Methyl 2-(5-Phenylisoxazol-3-yl)benzoate (**12**).

To a solution of 7.0 g (0.0329 mole) of *o*-methoxycarbonylbenzohydroximinoyl chloride and 6.74 g (0.066 mole) of phenylacetylene in 200 ml of ether was added dropwise a solution of 3.32 g (0.033 mole) of triethylamine in 50 ml of ether during 35 minutes with stirring at -5° to 0°. This mixture was stirred at -5 to 0° for another 30 minutes and then was allowed to warm to 20° during 1 hour with stirring. The reaction mixture was washed twice with water, dried (calcium sulfate), examined by ir spectroscopy (which showed residual nitrile oxide absorption at 2290 cm^{-1} and NOH absorptions at 3550 and 3200 cm^{-1}), concentrated under vacuum, and held at 90° for 30 minutes to give 7.52 g of oil that was greater than 80% of the desired product (gc, tlc, ir, nmr analyses).

Chromatography of the oil on 450 g of silica gel (Woelm, for dry column chromatography) with benzene gave in the purest fractions 4.14 g (45%) of >99% pure product (gc analysis) as a viscous oil which crystallized after about three weeks, mp 62-67°. Crystallization of 1.0 g of this material from methanol at 0° gave 0.90 g of white solid, mp 68-69.5°; nmr (deuteriochloroform): δ 8.03-7.33 (m, 9, ArH), 6.62 (s, 1, H-4), 3.77 (s, 3, OCH_3); ir (chloroform): 1725 cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.22; H, 4.45; N, 4.99.

2-(5-Phenylisoxazol-3-yl)benzoic Acid (**14**).

A solution of 1.0 g of ester in 4 ml of acetic acid and 4 ml of concentrated hydrochloric acid was heated at reflux for 4 hours and was concentrated under vacuum. The solid residue was triturated with water, collected, and died to give 0.85 g (90%) of solid, mp 144-147°. Recrystallization of this solid from benzene gave 0.70 g (74%) of white solid, mp 147.5-149° [lit (2) mp 145-146°]; ir (mineral oil mull): 2400-3300, 1720 cm^{-1}.

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.60; H, 4.14; N, 5.22.

Methyl 2-[5-(4-Chlorophenyl)-2-isoxazolin-3-yl]benzoate (**15a**).

To a stirred solution of 10.7 g (0.050 mole) of *o*-methoxycarbonylbenzohydroximinoyl chloride and 13.9 g (0.10 mole) of *p*-chlorostyrene in 150 ml of ether was added dropwise 5.25 g (0.052 mole) of triethylamine in 20 ml of ether during 45 minutes with stirring at 0-5°. The mixture was stirred at 20° for 20 hours and then extracted with three 100-ml portions of water; the ether layer was dried (calcium sulfate) and concentrated under vacuum to 85°/0.2 torr to give 12.1 g (77% yield) of crude isoxazoline (about 80% pure by gc analysis) as an oil. A small sample of the oil obtained in the same way in another experiment was chromatographed on silica gel with 5% ether in benzene. The purest fractions were cyrstallized from methanol at -70° to give pure **15a**, mp 49.5-50.5°; nmr (deuteriochloroform): δ 7.97 (m, 1), 7.53 (m, 3), 7.43 (s, 4), 5.78 (dd, 1, $J_{4,5}$ = 10.6 Hz, $J_{4',5}$ = 9.4 Hz, H-5), 3.83 (s, 3, OCH_3), 3.74 (dd, 1, $J_{4,4'}$ = 17 Hz, $J_{4,5}$ = 10.6 Hz, H-4), 3.26 (dd, 1, $J_{4,4'}$ = 17 Hz, $J_{4',5}$ = 9.4 Hz, H-4'); ir (mineral oil mull): 1720 cm^{-1}.

Anal. Calcd. for $C_{17}H_{14}ClNO_3$: C, 64.67; H, 4.47. Found: C, 64.48; H, 4.50.

Methyl 2-[5-(4-Methoxyphenyl)-2-isoxazolin-3-yl]benzoate (**15b**).

Methyl 2-[5-(4-methoxyphenyl)-2-isoxazolin-3-yl]benzoate was obtained in similar fashion as a viscous oil, about 85% pure, 77% yield. Chromatography of a 5.0 g sample of the oil on 275 g of Woelm silica gel with 5% ether in benzene gave 4.07 g (corresponded to 63% yield) of pure product, which was crystallized from methanol at 0° to give 3.23 g of solid, mp 71-72°; nmr (deuteriochloroform): δ 8.1-6.83 (m, 8), 5.77 (t, 1, H-5), 3.97-3.03 (m, 2), 3.87 (s, 3, OCH_3), 3.38 (s, 3, OCH_3); ir (mineral oil mull): 1720 cm^{-1}.

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50. Found: C, 69.37; H, 5.50.

Methyl 2-{5-[3-(Trifluoromethyl)phenyl]-2-isoxazolin-3-yl}benzoate (**15c**).

Methyl 2-{5-[3-(trifluoromethyl)phenyl]-2-isoxazolin-3-yl}benzoate was obtained as an oil, 85% purity, 74% yield. Chromatography of a 4.0 g sample of the oil on 150 g of Woelm silica gel with 2% ether in benzene gave 3.38 g (corresponded to 63% yield) of pure product as an oil; n_D^{25} = 1.5412; nmr (deuteriochloroform): δ 8.0-7.33 (m, 8), 5.80 (dd, 1, H-5), 4.07-3.05 (m, 2), 3.8 (s, 3, OCH_3); ir (chloroform): 1720 cm^{-1}.

Anal. Calcd. for $C_{18}H_{14}F_3NO_3$: C, 61.89; H, 4.04. Found: C, 62.07; H, 4.07.

Methyl 2-[5-(2-Pyridyl)-2-isoxazolin-3-yl]benzoate (**15d**).

A solution of 7.38 g (0.0702 mole) of 2-vinylpyridine and 9.07 g (0.0702 mole) of ethyldiisopropylamine in 60 ml of ether was added dropwise during 20 minutes to a solution of 15.0 g (0.0702 mole) of *o*-(methoxycarbonyl)benzohydroximinoyl chloride in 200 ml of ether stirred at 0-5°. The mixture was stirred at 0-5° for another 2 hours and then at 20° for 72 hours, washed twice with aqueous sodium bicarbonate solution and once with aqueous sodium chloride solution, dried (calcium sulfate), and concentrated to 90°/0.15 torr to give 14.23 g (72%) of slightly impure **15d** as a viscous oil.

A 3.23 g sample of the oil was chromatographed on 150 g of Woelm silica gel with 10% ether in benzene to give 2.28 g (corresponded to 51% yield) of pure **15d** as an oil; nmr (deuteriochloroform): δ 8.53 (m, 2, pyridyl H-6), 7.97-7.07 (m, 7), 5.83 (dd, 1, isoxazoline H-5), 4.13-3.32 (m, 2), 3.72 (s, 3, OCH_3); ir (chloroform): 1725 cm^{-1}. A small sample was subjected to Kugelrohr distillation at 145°/0.03 torr for analysis.

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.15; H, 5.00. Found: C, 67.89; H, 5.10.

Methyl 2-[5-(4-Pyridyl)-2-isoxazolin-3-yl]benzoate (**15e**).

Methyl 2-[5-(4-pyridyl)-2-isoxazolin-3-yl]benzoate was prepared by the method used for **15d**, except that triethylamine was employed as the base. Chromatography of all of the crude product (73% yield) on Woelm silica gel with 60% ether in benzene and then ethyl acetate gave pure **15e** as a viscous oil in 54% yield. The oil darkened on heating above 65°, so the chromatography fractions were concentrated to a maximum temperature of 65°/0.2 torr. Nmr (deuteriochloroform): δ 8.73 (m, 2), 8.05 (m, 1), 7.53 (m, 5), 5.83 (dd, 1, H-5), 4.1-3.07 (m, 2), 3.83 (s, 3, OCH_3); n_D^{25} = 1.5876.

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00. Found: C, 67.80; H, 5.09.

Methyl 2-[5-(3,4-Methylenedioxyphenyl)-2-isoxazolin-3-yl]benzoate (**15f**).

Methyl 2-[5-(3,4-methylenedioxyphenyl)-2-iosoxazolin-3-yl]benzoate

was prepared by the method employed for **15a**. The crude product (77% yield) was crystallized from methanol at 0° to give pure **15f** as a white solid, mp 106-108.5°, in 59% yield. A 2.0 g sample of the solid was crystallized from methanol and then from methylcyclohexane to give 1.20 g of white solid, mp 108-109°; nmr (deuteriochloroform): δ 7.87 (m, 1), 7.45 (m, 3), 7.03-6.77 (m, 3), 5.95 (s, 2, CH_2O_2), 5.70 (t, 1, H-5), 3.97-3.0 (m, 2), 3.86 (s, 3, OCH_3); ir (chloroform): 1725 cm^{-1}.

Anal. Calcd. for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.65. Found: C, 66.46; H, 4.66.

Methyl 2-[5-(4-Chlorophenyl)-3-isoxazolyl]benzoate (**16a**).

The crude isoxazoline **15a** (12.1 g, 0.0383 mole), 6.9 g (0.0383 mole) of *N*-bromosuccinimide, and a trace of benzoyl peroxide in 150 ml of carbon tetrachloride was held at reflux for 1 hour and 10 minutes, allowed to cool, filtered, and concentrated under vacuum to 12.8 g of oil. The oil was crystallized from methanol to give 5.0 g of yellow solid, mp 81-112°. Trituration of the solid with 200 ml of ether, filtration, and concentration of the ether filtrate gave 4.70 g (39%) of pale yellow solid, mp 83-85°. This solid was crystallized from heptane (charcoal) to give 3.3 g of **16a** as a white solid, mp 85-86°; nmr (deuteriochloroform): δ 8.03-7.36 (m, 8, ArH), 6.60 (s, 1, H-4), 3.83 (s, 3, OCH_3); ir (chloroform): 1720 cm^{-1}.

Anal. Calcd. for $C_{17}H_{12}ClNO_3$: C, 65.08; H, 3.86; N, 4.46. Found: C, 65.06; H, 3.67; N, 4.34.

Concentration of the methanol filtrate and Kugelrohr distillation of the residue at 190°/0.2 torr gave 4.0 g of solid. The solid was triturated with ether; the ether was filtered and concentrated under vacuum. The residue was crystallized from methanol to give 1.70 g (14%) of white solid **16a**, mp 83-85°.

Methyl 2-[5-(4-Methoxyphenyl)-3-isoxazolyl]benzoate (**16b**).

A mixture of 6.2 g (about 0.0199 mole) of the crude isoxazoline **15b** and 9.08 g (0.04 mole) of dichlorodicyanobenzoquinone in 50 ml of chlorobenzene was held at reflux for 2.5 hours, allowed to cool, filtered free of 3.8 g of dichlorodicyanohydroquinone (ir identification), and concentrated under vacuum to 11.3 g of black solid. This material was chromatographed on 250 g of silcia gel (Woelm, for dry column chromatography) with benzene to give 4.55 g (74%) of solid product, mp 96.5-98°; nmr (deuteriochloroform): δ 7.8-6.88 (m, 8), 6.53 (s, 1, H-4), 3.88 (s, 3, OCH_3), 3.83 (s, 3, OCH_3); ir (chloroform): 1725 cm^{-1}.

Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.88; H, 4.98; N, 4.38.

Methyl 2-[5-[3-(Trifluoromethyl)phenyl]isoxazol-3-yl]benzoate (**16c**).

The method of **16a** was employed with a reflux time of 4 hours. Two Kugelrohr distillations (the second one at 148°/0.1 torr) of the crude product gave pure **16c** as an oil in 70% yield; nmr (deuteriochloroform): δ 7.9 (m, 8), 6.83 (s, 1, H-4), 3.87 (s, 3).

Anal. Calcd. for $C_{18}H_{12}F_3NO_3$: C, 62.25; H, 3.48; N, 4.03. Found: C, 62.27; H, 3.50; N, 4.09.

Methyl 2-[5-(2-Pyridyl)isoxazol-3-yl]benzoate (**16d**).

A mixture of 41.9 g (0.149 mole) of crude isoxazoline **15d**, 85.0 g (0.346 mole) of chloranil, and 370 ml of chlorobenzene was held at reflux for 24 hours, cooled, filtered, and concentrated under vacuum. Trituration of the resiude with 700 ml of ether, filtration, extraction of the filtrate with three 150-ml portions of a solution of 5% sodium hydroxide and 5% sodium dithionite and then with water, drying (magnesium sulfate), and concentration of the ether solution under vacuum to 95°/0.5 torr gave 31.5 g of brown oil. Crystallization of the oil from 30 ml of toluene at -60° gave 30.5 g (73%) of solid **16d**, mp 58.5-60°; nmr (deuteriochloroform): δ 8.63 (m, 1), 8.0-7.1 (m, 7), 7.0 (s, 1, H-4), 3.80 (s, 3).

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.41; H, 4.35; N, 9.93.

Methyl 2-[5-(4-Pyridyl)isoxazolyl-3-yl]benzoate (**16e**).

A mixture of 6.1 g (0.0216 mole) of pure methyl 2-[5-(4-pyridyl)-2-isoxazolin-3-yl]benzoate, 3.85 g (0.0216 mole) of *N*-bromosuccinimide, and 0.4 g of benzoyl peroxide in 80 ml of carbon tetrachloride was heated at reflux for 2 hours, cooled, diluted with 200 ml of methylene chloride and 100 ml of carbon tetrachloride, extracted three times with 200-ml portions of aqueous sodium carbonate solution and once with aqueous sodium chloride solution, dried (calcium sulfate), and concentrated to 5.64 g of black viscous residue that appeared to be 40% product and 60% of starting material. This mixture was treated with 3.85 g (0.0216 mole) of *N*-bromosuccinimide and 0.3 g of benzoyl peroxide in 280 ml of carbon tetrachloride at reflux for 1.75 hours. The reaction mixture was worked up as before to give 5.48 g of crude product. Chromatography of the crude product on silica gel with ethyl acetate gave 3.38 g (56%) of solid, mp 84-85.5°; nmr (deuteriochloroform): δ 8.85 (m, 2), 8.03 (m, 1), 7.7 (m, 5), 7.23 (s, 1, H-4), 3.83 (s, 3).

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.32. Found: C, 68.43; H, 4.23.

Acids **17a-c** were prepared by the method employed for **6b: 17a**, 95% yield, mp 175.5-177.5° [lit (2) mp 174-175°]. (*Anal.* Calcd. for $C_{16}H_{10}ClNO_3$: C, 64.12; H, 3.36. Found: C, 63.98; H, 3.40); **17b**, 99% yield, mp 186-187.5° (*Anal.* Calcd. for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44. Found: C, 69.11; H, 4.44); **17c**, 92% yield, mp 165-167° (*Anal.* Calcd. for $C_{17}H_{10}F_3NO_3$: C, 61.27; H, 3.02; N, 4.20. Found: C, 61.05; H, 3.02; N, 4.24).

Methyl 2-(5-Phenyl-1,2,4-oxadiazol-3-yl)benzoate (**18a**), and 3,4-Bis(2-methoxycarbonylphenyl)furazan Oxide.

A. To a solution of 10.0 g (0.0468 mole) of *o*-methoxycarbonylbenzohydroximinoyl chloride in 145 g (0.141 mole, 30 equivalents) of benzonitrile was added dropwise, with stirring at 0°, a solution of 5.05 g (0.050 mole) of triethylamine in 25 ml of ether during 1 hour. The mixture was stirred for 1 hour at 0° and for 2 days at 20-25°, filtered, and concentrated under vacuum at 5 torr. To the residue was added 100 ml of ether, and the mixture was extracted three times with water. The ether layer way dried (calcium sulfate) and concentrated under vacuum to 90° at 0.5 torr to 8.2 g of oil. The oil was chromatographed on 380 g of silica gel (Woelm, for dry column chromatography). Elution with 5% ether in benzene gave 5.0 g of 87% pure oxadiazole and then 0.17 g of 3,4-bis(2-methoxycarbonylphenyl)furazan oxide (nitrile oxide dimer). The 5 g of product was crystallized from hexane at 0° to give 3.0 g (23) of white solid, mp 55-56.5°. A small sample was recrystallized from hexane to give **18a**, mp 57-59°; nmr (deuteriochloroform): δ 8.43-7.53 (m, 9), 3.87 (s, 3); ir (chloroform): 1715 cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.47; H, 4.38; N, 10.04.

The furazan oxide, 0.17 g, was crystallized from heptane to give 0.15 g of solid, mp 134-135°; nmr (deuteriochloroform): δ 8.03 (m, 2), 7.60 (m, 6), 3.83 (s, 3), 3.77 (s, 3); ir (chloroform): 1725 cm^{-1}, 1600 cm^{-1}.

Anal. Calcd. for $C_{18}H_{14}N_2O_6$: C, 61.02; H, 3.98; N, 7.91; Found: C, 61.31; H, 3.82; N, 7.79.

B. To a solution of 30.9 g (0.21 mole) of ethyl iminobenzoate in 200 ml of ether stirred at 0-5° was added dropwise during 30 minutes a solution of 9.0 g (0.0421 mole) of *o*-methoxycarbonylbenzohydroximinoyl chloride in 100 ml of ether. The mixture was stirred at 0-5° for 2 hours at 20° for 4 days, extracted three times with 5% hydrochloric acid and once with water, dried (calcium sulfate), and concentrated under vacuum to 7.8 g of oil. Two Kugelrohr distillations of the oil at 135°/0.55 torr gave 4.0 g (34%) of oil that was 96% pure **18a** (gc, nmr analyses).

Methyl 2-[5-(4-Methoxyphenyl)-1,2,4-oxadiazol-3-yl]benzoate (**18c**).

Triethylamine (15.15 g, 0.150 mole) was added dropwise during 15 minutes to a stirred solution of 30.0 g (0.140 mole) of *o*-methoxycarbonylbenzohydroximinoyl chloride and 201 g (1.50 moles) of *p*-anisonitrile in 700 ml of chloroform. The solution was held at reflux for 22 hours, washed with three 400-ml portions of water, filtered through chloroform-prewet filter paper, and concentrated under vacuum. The residue was Kugelrohr distilled at 100°/2 torr and then at 100°/0.1 torr to remove excess *p*-anisonitrile. After a forerun collected at 110°/0.1 torr, 23.7 g

(54%) of 98% pure (gc assay) product was collected at 140°/0.1 torr.

This material was dissolved in warm methanol (total solution volume was 45 ml) and seeded to give 17.28 g (40%) of white solid, mp 73-75°; nmr (deuteriochloroform): δ 8.33-7.03 (m, 8), 3.94 (s, 3); ir (chloroform): 1725 cm^{-1}.

Anal. Calcd. for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.56; H, 4.48; N, 8.97.

Methyl 2-[5-(3-Trifluoromethylphenyl)-1,2,4-oxadiazol-3-yl]benzoate (**18d**).

To a solution of 8.0 g (0.0374 mole) of *o*-methoxycarbonylbenzohydroximinoyl chloride and 64 g (0.374 mole) of *m*-trifluoromethylbenzonitrile in 150 ml of ether was added, with stirring at 20-25°, a solution of 4.0 g (0.0396 mole) of triethylamine in 15 ml of ether during 1 hour. The reaction mixture was stirred at 20-25° for 10 days, washed three times with water, dried (calcium sulfate), and concentrated under vacuum to 63.5 g of residue. This material was subjected to Kugelrohr distillation; excess nitrile was removed at 80-90°/8 torr. After a small fraction collected up to 150°/0.1 torr, about 98% pure product was collected at 150°/0.15 torr as an oil. This oil was crystallized from methanol to give 4.88 g (37%) of white solid, mp 84.5-86.5°; nmr (deuteriochloroform): δ 8.33-7.23 (m, 8), 3.89 (s, 3); ir (chloroform): 1725 cm^{-1}.

Anal. Calcd. for $C_{17}H_{11}F_3N_2O_3$: C, 58.63; H, 3.18; N, 8.04. Found: C, 58.63; H, 3.16; N, 7.96.

Methyl 2-[5-(1-Naphthyl)-1,2,4-oxadiazol-3-yl]benzoate (**18e**).

A solution of 5.05 g (0.050 mole) of triethylamine in 60 ml of ether was added dropwise during 30 minutes to a stirred solution of 76.6 g (0.50 mole) of 1-naphthonitrile and 10.7 g (0.050 mole of *o*-(methoxycarbonyl)-benzohydroximinoyl chloride in 250 ml of ether at 0-10°. The mixture was stirred at 0-5° for 2 hours and then was allowed to stand for 56 days. The mixture was washed three times with water, dried (calcium sulfate), concentrated under aspirator vacuum, and then concentrated on a Kugelrohr apparatus to 110°/0.3 torr to remove excess naphthonitrile. The resultant 9.96 g of viscous, oily pot residue was chromatographed on 250 g of Woelm silica gel with 2.5% ether in benzene to give 7.47 g of solid, which gave 5.97 g (36%) of white solid, mp 87.5-88.5°, upon crystallization from methanol.

Anal. Calcd. for $C_{20}H_{14}N_2O_3$: C, 72.72; H, 4.27. Found: C, 72.48; H, 4.33.

Methyl 2-[5-(2-Pyridyl)-1,2,4-oxadiazol-3-yl]benzoate (**18f**).

To a solution of 156 g (1.50 moles) of 2-cyanopyridine in 470 ml of chloroform was added first 32.1 g (0.15 mole) of *o*-methoxycarbonylbenzohydroximinoyl chloride and then 15.2 g (0.150 mole) of triethylamine with swirling. The solution was heated at reflux for 21 hours, washed with three 350-ml portions of water and once with saturated sodium chloride, and filtered through a chloroform-prewet filter paper. The filtrate was concentrated under vacuum up to 90° (bath temperature) at 2 torr. The black pot residue was Kugelrohr distilled. After a forerun collected at 20-150°/0.2 torr, 24.66 g (58%) of 97% pure (gc analysis) product was collected at 170-175°/0.15 torr as a viscous oil. The oil was crystallized from ethyl acetate-methylcyclohexane to give 15.95 g (38%) of white solid, mp 76.5-78°; ir (chloroform): 1725 cm^{-1}.

Anal. Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94. Found:C, 64.06; H, 3.95.

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