3'-Arylspiro[isobenzofuran-1(3*H*),5'(4'*H*)-isoxazol]-3-ones and Their Conversion to 2-(3-Arylisoxazol-5-yl)benzoates

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A new, convenient route to the biologically active 2-(3-arylisoxazol-5-yl)benzoates **4** is reported. This route consists of 1,3-dipolar cycloaddition of aromatic nitrile oxides to 3-methylenephthalide to form the novel 3'-arylspiro[isobenzofuran-1(3*H*),5'(4'*H*)-isoxazol]-3-ones **3** and subsequent high-yield conversions of **3** to **4**.

Recently, there has been considerable interest in 2-(3-arylisoxazol-5-yl)benzoic acids and their derivatives in pharmaceutical and agricultural industries.[1-4] Previous synthetic routes to the 2-(isoxazol-5-yl)benzoates include the following: (1) reaction of acetophenone oxime dianion with phthalic anhydride and subsequent acid-promoted ring closure of the adduct;[1] (2) bromination of α-phenacylphthalide and subsequent reaction with hydroxylamine;[3] (3) oxidation of 3-aryl-5-(2-methylphenyl)isoxazoles prepared via a four-step synthesis,[3] (4) addition of aromatic nitrile oxides to methyl 2-vinylbenzoate and aromatization of the resultant isoxazolines;[4] (5) acid-promoted rearrangement of 2-[aryl(hydroxyimino)methyl]-1,3-indandiones.[5]

We report here a new route to 2-(3-arylisoxazol-5-yl)-benzoates that is particularly convenient because it proceeds from very readily accessible starting materials, possesses fairly general scope, and is efficacious for large-scale preparations. This route consists of 1,3-dipolar cycloaddition of aromatic nitrile oxides to 3-methylene phthalide to form the novel, isolable 3'-arylspiro[isobenzofuran-1(3*H*),5'(4'*H*)-isoxazol]-3-ones **3** and subsequent easy, high-yield conversion of spiro heterocycles **3** to the 2-(3-arylisoxazol-5-yl)benzoates **4** (Scheme I).

3-Methylenephthalide (**1**) has been obtained in 65% yield from reaction of thionyl chloride with 2-acetylbenzoic acid in DMF;[6,7] an improved workup procedure (see Experimental Section) gave **1** in 79–89% yields. Although **1** polymerizes readily in the absence of inhibitors, it can be kept for a few weeks in a refrigerator when admixed with a little hydroquinone. Chloro oximes **2** (Scheme I) are quite easily obtained from aldehydes according to a recently reported method,[8] in which aldehydes are converted to oximes and the crude oximes are treated with NCS/DMF to produce **2**.

Dehydrochlorination of the chloro oximes **2** with triethylamine produced nitrile oxides.[9] The nitrile oxides underwent 1,3-dipolar cycloaddition to 3-methylenephthalide to produce the novel spiro heterocycles **3**. The cycloaddition is regioselective (within the limits of NMR detection) and is in accordance with the regioselectivity observed in the reported[9] nitrile oxide cycloadditions to 1,1-disubstituted olefins. Yields of spiro adducts **3** (see Table I) depend on the competition between nitrile oxide dimerization and cycloaddition to 3-methylenephthalide. The spiro heterocycles **3** tend to be insoluble in ether, which facilitates their isolation and purification.

Confirmation of the structure of the spiro heterocycles **3** derives from ^{13}C NMR spectra (spiro carbon at 112 ppm), ^1H NMR spectra (H-4 and H-4' appear as an AB quartet with J = 18 Hz in Me_2SO),[10,11] IR spectra (lactone carbonyl absorption at 1780 cm^{-1}), and essentially quantitative conversion of **3** to 2-(3-arylisoxazol-5-yl)benzoates, a few

Scheme I

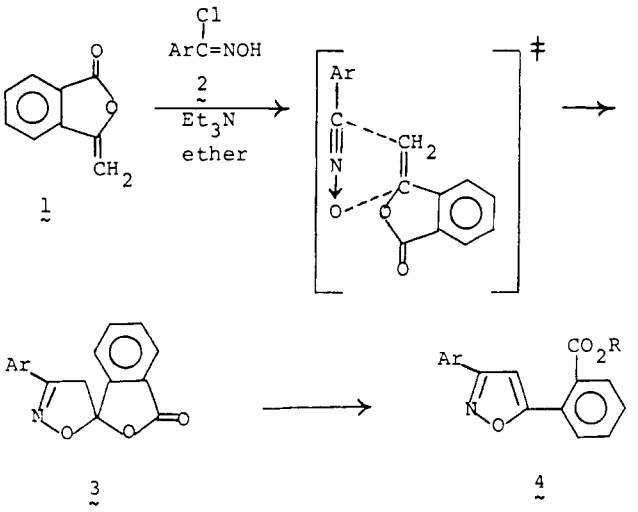

Table I. Yields and Melting Points for 3'-Arylspiro[isobenzofuran-1(3*H*),5'(4'*H*)-isoxazol]-3-ones[a] **3**

compd	Ar	% yield[b]	mp,[c] °C
3a	C_6H_5	79	120-122
b	4-FC_6H_4	65	142-145
c	4-ClC_6H_4	53	166-167
d	4-$CF_3C_6H_4$	72	177-178
e	4-$C_6H_5C_6H_4$	52	178-180
f	3-$O_2NC_6H_4$	20	183-186
g	3-$CF_3C_6H_4$	56	170
h	3-ClC_6H_4	56	127-129
i	3-NCC_6H_4	63	165-167
j	3-$C_6H_5OC_6H_4$	73	118-120
k	2-$CH_3C_6H_4$	65	159-163
l	2-$CF_3C_6H_4$	90	156-158
m	2,4-$Cl_2C_6H_3$	65	165-167
n	C_6F_5	54	157-159

[a] All compounds in this table gave satisfactory C and H analyses (carbon within 0.27% and hydrogen within 0.05% absolute of theoretical values). [b] Yield of isolated product that was ≥95% pure based on NMR analysis. [c] Melting point of analytical sample.

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(2) Nadelson, J. U.S. Patent 3987179, 1976; *Ger. Offen.* 2604119; *Chem. Abstr.* **1976**, *85*, 143087*z*.
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(4) Howe, R. K.; Schleppnik, F. M. *J. Heterocycl. Chem.* **1982**, *19*, 721.
(5) Gejta, L.; Germane, S.; Dalberga, I.; Lavrinovich, E. S. USSR SU 792872, 1981; *Chem. Abstr.* **1982**, *96*, 20087*u*.

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Table II. Yields and Melting Points for 2-(3-Arylisoxazol-5-yl)benzoic Acids 4 (R = H)

Ar	method[a]	% yield	mp, °C crude prdt	mp, °C pure prdt
3-$CF_3C_6H_4$	A	100	173-175	177-178[b]
3-$CF_3C_6H_4$	B	89	176.5-178[b]	
3-$CF_3C_6H_4$	C	98	175-176	
3-NCC_6H_4[c]	C	60	192-194	195-196
4-$CF_3C_6H_4$[c]	A	100	198-202	205-207
2,4-$Cl_2C_6H_3$[c]	A	100	181-183	182-183
2-$CH_3C_6H_4$	B	92	162-163.5	
2-$CH_3C_6H_4$[c]	C	96	158.5-159.5	162-163.5
2-$CF_3C_6H_4$[c]	B	98	159.5-163	162.5-165

[a] A, thermolysis; B, H_2SO_4-H_2O-dioxane at reflux; C, NaOH-H_2O-EtOH and then HCl. [b] Lit.[4] mp 176.5-178 °C. [c] This new compound gave satisfactory C and H analyses (carbon within 0.25% and hydrogen within 0.05% absolute of theoretical values).

Table III. Yields and Melting Points for Alkyl 2-(3-Arylisoxazol-5-yl)benzoates[a] 4 (R = alkyl)

Ar	R	% yield	mp, °C	n^{25}_D, deg
3-$CF_3C_6H_4$	CH_3	96	46-48[b]	
3-$CF_3C_6H_4$	Et	98	28-30	
3-$CF_3C_6H_4$	n-Bu	95		1.5419
3-$CF_3C_6H_4$	n-C_5H_{11}	99		1.5370
4-$CF_3C_6H_4$	CH_3	82	90.5-92	
4-ClC_6H_4	CH_3	88	89.5-91	
3-$C_6H_5OC_6H_4$	CH_3	95		1.6225
2-$CH_3C_6H_4$	CH_3	95		1.6021
2,4-$Cl_2C_6H_3$	Et	97	85-86	
C_6F_5	CH_3	97	97-98	

[a] All compounds in this table gave satisfactory C and H analyses (carbon within 0.19% and hydrogen within 0.07% absolute of theoretical values). [b] Lit.[4] mp 48-50 °C.

of which have been reported[3,4] previously.

Thermal conversion of the spiro heterocycles **3** to 2-(3-arylisoxazol-5-yl)benzoic acids occurred quantitatively within a few minutes at 200–225 °C; the reaction is quite clean as evidenced by NMR analysis and from the fact that the melting points of the acids thus produced were only 0–5 °C lower than that of the analytically pure acids. This thermal reaction accounted for the imprecise melting points (which were heating rate dependent) of the higher melting spiro heterocycles. Essentially quantitative conversion of the spiro heterocycles to 2-(3-arylisoxazol-5-yl)benzoic acids could be effected also with base or aqueous acids (see Table II and the Experimental Section). Treatment of the spiro heterocycles with primary alcohols and sulfuric acid gave alkyl 2-(3-arylisoxazol-5-yl)benzoates (see Table III), apparently via ring opening first to the 2-(3-arylisoxazol-5-yl)benzoic acids and subsequent esterification. An isoxazolylbenzoic acid was obtained from treatment of **3g** with isopropyl alcohol and sulfuric acid due to the esterification step being slow.

Treatment of **3l** with piperidine in inert solvents gave the piperidinium salt of 2-[3-[2-(trifluoromethyl)-phenyl]isoxazolyl-5-yl]benzoic acid, most reasonably by proton abstraction from the isoxazoline methylene group with ring opening via cleavage of the bond between the spiro carbon and the lactone oxygen atom. An alternative ring-opening mechanism involving nucleophilic attack on **3** at the lactone carbonyl atom followed by dehydration of the resultant 5-hydroxy-Δ^2-isoxazoline would have produced the *N*-benzoylpiperidine **5**; this amide was not formed in a detectable amount in the reaction of **3l** with piperidine.

Experimental Section

Melting points were taken in open capillaries with a Mel-Temp apparatus and are corrected. IR spectra were determined with a Perkin-Elmer Model 727B spectrometer. ^{13}C NMR spectra were obtained with a JEOL FX-100 FT NMR instrument at 25.05 MHz.

3-Methylenephthalide. Thionyl chloride (130.5 g, 1.096 mol) was added dropwise to a solution of 150.0 g (0.9137 mol) of 2-acetylbenzoic acid (purchased from Aldrich Chemical Co.) in 600 mL of reagent grade *N,N*-dimethylformamide stirred under dry nitrogen; the solution temperature rose to 50 °C. The solution was stirred at 60 °C for 2 h, allowed to cool to 30 °C, and poured into a mechanically stirred mixture of 1.2 L of ice–water and 1 L of methylene chloride. The layers were separated. The aqueous layer was extracted once with 500 mL of fresh methylene chloride. The organic layers were combined, 0.5 g of hydroquinone was added, and the solution was added to vigorously stirred 1.2 L of 5% aqueous K_2CO_3. The organic layer was separated and added again to 1.2 L of vigorously stirred 5% aqueous K_2CO_3. The organic layer then was washed with three 1-L portions of water and dried ($CaSO_4$), and 0.5 g of hydroquinone was added. The solution was concentrated under vacuum (maximum bath temperature = 30 °C) to 122.8 g of yellow solid 3-methylenephthalide that contained 3 wt % DMF (NMR analysis); 89% yield. An air-dried sample had a melting point of 54–56 °C (lit.[6] mp 56–58 °C).

General Procedure. Preparation of 3'-Arylspiro[isobenzofuran-1(3*H*),5'(4'*H*)-isoxazol]-3-ones 3. To a solution of 10.0 g (0.0684 mol) of 3-methylenephthalide, 0.1 g of hydroquinone, and 1.0–1.5 molar equiv of chloro oxime **2** in 250 mL of ether stirred under nitrogen in an ice bath was added dropwise a solution of 1.0–1.5 molar equiv of triethylamine in 50 mL of ether during 30–45 min. The reaction mixture was stirred at 22 °C for 17–24 h (reaction can be worked up when the nitrile oxide absorption at 2290 cm^{-1} in the IR spectrum has disappeared) and filtered. The collected precipitate (spiro heterocycle and triethylamine hydrochloride) was washed with fresh ether and then was dissolved completely in chloroform. The chloroform solution was washed with three portions of water, dried ($CaSO_4$), and concentrated under vacuum to give fairly pure product (NMR analysis). In several instances, a small sample of the product was recrystallized rapidly from ethanol for elemental analysis.

On a large scale with well-crystallized spiro heterocycles, the ether-insoluble precipitate was stirred and triturated well twice with water to remove the triethylamine hydrochloride and then air-dried to give a spiro heterocycle of good purity.

Compound **3a** was obtained initially as a sticky, low-melting solid (mp <65 °C) that occluded traces of solvent. The crystalline, higher melting form (mp 120–122 °C) of **3a** was obtained by agitation of molten **3a** at 80 °C under oil pump vacuum and intermittent scratching of the oil at 80 °C. Seed crystals of the higher melting form of **3a** caused crystallization of the higher melting form from concentrated solutions of the lower melting form. The ^{13}C NMR ($CDCl_3$) data (in parts per million) for **3a** are as shown below.

(6) Vinogradova, S. V.; Korshak, V. V.; Salazkin, S. N.; Chelidze, G. S. *J. Appl. Chem USSR (Engl. Transl.)* **1971**, *44*, 1405.

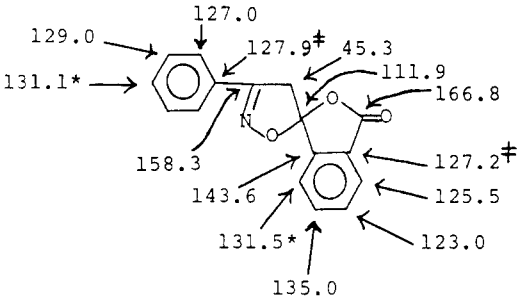
(7) A literature report (Lonsky, W.; Traitler, H. *Chem. Ber.* **1977**, *10*, 2601) claimed quantitative conversion of 2-acetylbenzoic acid to 3-methylenephthalide with HCl gas in chloroform solution; in our hands, treatment of 2-acetylbenzoic acid with HCl gas in chloroform or methylene chloride gave *no* detectable 3-methylenephthalide even after 5 h, either before or after aqueous washes.

(8) Liu, K.-C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916.

(9) Grundmann, C.; Grunanger, P. "The Nitrile Oxides"; Springer-Verlag: New York, 1971.

(10) Most of **3** gave a 2-proton singlet for H-4 and H-4' in $CDCl_3$ solution.

(11) For representative ^1H NMR data for Δ^2-isoxazolines, see: (a) Witczak, Z. *Heterocycles* **1980**, *14*, 1319. (b) Sustmann, R.; Huisgen, R.; Huber, H. *Chem. Ber.* **1967**, *100*, 1802.



2-(3-Arylisoxazol-5-yl)benzoic Acids 4 (R = H). (A) Thermolysis of 3. A sample of **3** is heated in a test tube at 200–225 °C until NMR shows the reaction to be complete (a few minutes).

(B) Acid Treatment of 3. A mixture of 0.28 g of **3**, 0.1 mL of concentrated sulfuric acid (or 0.5 mL of concentrated hydrochloric acid), 10 mL of water, and 6 mL of dioxane was heated at reflux for 1 h, cooled, diluted with water, and filtered to give the acid product.

(C) Base Treatment of 3. To 1 g of **3** in 25 mL of ethanol was added 20 mL of 1 N sodium hydroxide solution. The solution was stirred at room temperature for 2–5 h, acidified with concentrated hydrochloric acid, and extracted with ether. The ether layer was washed twice with water, dried ($CaSO_4$), and concentrated under vacuum to give the acid product.

***n*-Alkyl 2-(3-Arylisoxazol-5-yl)benzoates 4 (R = alkyl).** A solution of 6 g of spiro heterocycle **3**, 2 mL of concentrated sulfuric acid, and 300 mL of appropriate *n*-alkyl alcohol was held at reflux for 17–30 h, cooled, and poured into ice–water. The mixture was extracted with ether. The ether layer was washed twice with water, dried ($CaSO_4$), and concentrated under vacuum to give the ester product.

Attempted Preparation of Isopropyl 2-[3-[3-(Trifluoromethyl)phenyl]-5-isoxazolyl]benzoate. A solution of 8 g (0.024 mol) of **3g**, 0.3 mL of H_2SO_4, and 140 mL of isopropyl alcohol was held at reflux for 20 h, cooled, poured into 2000 mL of H_2O, and filtered. The collected solid material was dissolved in 800 mL of ether. The ether solution was washed twice with water, dried ($CaSO_4$), and concentrated under vacuum to give 7.82 g of white solid, mp 165–169 °C. Recrystallization of 5 g of the solid from 75 mL of acetonitrile gave 3.37 g of 2-[3-[3-(trifluoromethyl)phenyl]-5-isoxazolyl]benzoic acid as colorless crystals, mp 178–179 °C. NMR and IR spectra of this material were identical with those of authentic material.

***N*-[2-[3-[2-(Trifluoromethyl)phenyl]isoxazol-5-yl]benzoyl]piperidine (5).** A mixture of 12.2 g (0.0366 mol) of 2-[3-[2-(trifluoromethyl)phenyl]isoxazol-5-yl]benzoic acid and 60 mL of thionyl chloride was heated at reflux on a steam bath for 40 min and concentrated under vacuum. The warm, viscous oil residue was dissolved in 100 mL of carbon tetrachloride, and this solution was added slowly to a stirred solution of 18.2 g (0.214 mol) of piperidine in 200 mL of methylene chloride. The solution was stirred for 30 min and then washed with two 200-mL portions of water, with two 200-mL portions of dilute hydrochloric acid, and with 200 mL of water. The organic solution was dried ($CaSO_4$) and concentrated under vacuum to 13.3 g (91%) of light amber residue. This material was crystallized from methanol (seed crystals of pure product were employed) to give 9.17 g of white solid, mp 88–90 °C. A second crop (3.1 g; mp 84–88 °C) was recrystallized from aqueous methanol (charcoal) to give 1.52 g of light beige solid: mp 88–90 °C (total yield 73%); IR ($CHCl_3$) 1620 cm^{-1}; NMR ($CDCl_3$) δ 8.13–7.23 (m,8), 6.80 (s, 1, H-4), 3.77 (br s,2), 3.13 (br s,2), 1.63 (br, 6). Anal. Calcd for $C_{22}H_{19}F_3N_2O_2$: C, 65.99; H, 4.78. Found: C, 66.06; H, 4.81.

Reaction of Piperidine with 3′-[2″-(Trifluoromethyl)phenyl]spiro[isobenzofuran-1(3*H*),5′(4′*H*)-isoxazol]-3-one. (A) Reaction in 1,2-Dimethoxyethane. A solution of 2.00 g (0.0060 mol) of spiro compound and 0.51 g (0.0060 mol) of piperidine in 75 mL of dry 1,2-dimethoxyethane was held at reflux for 2.5 h, at which time TLC analysis (silica gel, 2% acetic acid in 1,2-dichloroethane) showed no residual spiro compound. The solution was concentrated under vacuum to give 2.75 g of orange oil that contained residual 1,2-dimethoxyethane. Further concentration at 2.3 mm at 90 °C (bath temperature) gave 1.90 g of viscous oil. This oil consisted of a mixture of piperidinium carboxylate and carboxylic acid, with no detectable amount of amide (based on the absence of significant broad absorption at δ 3.6–4.0 where authentic amide has absorption due to two protons). The oil was triturated twice with 50-mL portions of hot 1 N HCl and then crystallized twice from toluene to give 0.64 g (32%) of 2-[3-[2-(trifluoromethyl)phenyl]isoxazol-5-yl]benzoic acid, mp 162.5–165 °C (authentic acid has mp 162.5–165 °C).

(B) Reaction in Methylene Chloride. A solution of 1.00 g (3.0 mmol) of spiro compound **3l** and 0.25 g (3.0 mmol) of piperidine in 50 mL of methylene chloride was held at reflux for 14 days. During this time, TLC analyses (silica gel, 10% CH_3CN in 1,2-dichloroethane) showed formation of the piperidinium carboxylate (R_f = 0.0) and no detectable amount of amide (R_f = 0.18); the spiro compound had R_f = 0.54. The reaction mixture was concentrated under vacuum. The residue was analyzed by NMR; based on integration of the isoxazole H-4 vs. the aromatic region, the reaction was 70% complete.

Registry No. 1, 3453-63-2; **2a**, 698-16-8; **2b**, 42202-95-9; **2c**, 28123-63-9; **2d**, 74467-05-3; **2e**, 42202-94-8; **2f**, 33512-94-6; **2g**, 69053-93-6; **2h**, 29203-59-6; **2i**, 20680-35-7; **2j**, 76272-18-9; **2k**, 74467-03-1; **2l**, 74467-04-2; **2m**, 29203-60-9; **2n**, 27318-29-2; **3a**, 76272-20-3; **3b**, 76272-21-4; **3c**, 76272-11-2; **3d**, 74423-19-1; **3e**, 76272-10-1; **3f**, 87413-28-3; **3g**, 74423-18-0; **3h**, 76272-19-0; **3i**, 76272-13-4; **3j**, 76272-17-8; **3k**, 76272-12-3; **3l**, 76272-14-5; **3m**, 74423-21-5; **3n**, 76272-22-5; **4** (R = H; Ar = 3-$CF_3C_6H_4$), 69053-90-3; **4** (R = H; Ar = 3-NCC_6H_4), 76764-71-1; **4** (R = H; Ar = 4-$CF_3C_6H_4$), 74423-20-4; **4** (R = H; Ar = 2,4-$Cl_2C_6H_3$), 74423-22-6; **4** (R = H; Ar = 2-$CH_3C_6H_4$), 76272-33-8; **4** (R = H; Ar = 2-$CF_3C_6H_4$), 87413-29-4; **4** (R = CH_3; Ar = 3-$CF_3C_6H_4$), 69053-89-0; **4** (R = Et; Ar = 3-$CF_3C_6H_4$), 76272-32-7; **4** (R = *n*-Bu; Ar = 3-$CF_3C_6H_4$), 76272-30-5; **4** (R = *n*-C_5H_{11}; Ar = 3-$CF_3C_6H_4$), 76272-31-6; **4** (R = CH_3; Ar = 4-$CF_3C_6H_4$), 76272-24-7; **4** (R = CH_3; Ar = 4-ClC_6H_4), 76272-26-9; **4** (R = CH_3; Ar = 3-$C_6H_5OC_6H_4$), 76272-29-2; **4** (R = CH_3; Ar = 5-$CH_3C_6H_4$), 76272-25-8; **4** (R = Et; Ar = 2,4-$Cl_2C_6H_3$), 76272-28-1; **4** (R = CH_3; Ar = C_6F_5), 76272-23-6; **5**, 87413-30-7; 2-acetylbenzoic acid, 577-56-0; piperidine, 110-89-4.