Spiroheterocycles from Reaction of Nitrile Oxides with 3-Methylenephthalimidines

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In explorations of syntheses and chemistry of spiroheterocycles, we found that reaction of aromatic nitrile oxides with 3-methylenephthalimidines **8** produced spiroheterocycles **9**. When *N*-benzyl-3-methylenephthalimidine (**8c**) was employed, oximes **10** and **11** were formed in addition to the spiroheterocycles. Solvent effects on the reaction rates and on product ratios indicate that the product mixtures result from competition between a 1,3-cycloaddition reaction of nitrile oxide with **8** to produce a spiroheterocycle and a diradical reaction of nitrile oxide with **8** to produce the oximes. Spiroheterocycles **9b** and **9f** were converted cleanly to 2-(3-phenyl-5-isoxazolyl)benzanilide **12a** and benzamide **12b**, respectively, with base catalysis.

Aromatic nitrile oxides cycloadd to 3-methylenephthalide (**1**) and (*E*)-3-benzylidenephthalides **2** to produce spiroheterocycles **3** and **4**, respectively;[1,2] see Scheme I. These spiroheterocycles can be converted cleanly with heat, acid, or base to 2-(3-aryl-5-isoxazolyl)benzoic acids **5** and **6**. Acids **5** and esters thereof possess good herbicidal and plant growth regulant activity.[1,2] Spiroheterocycles **3** also possess herbicidal and plant growth regulant activity.[3]

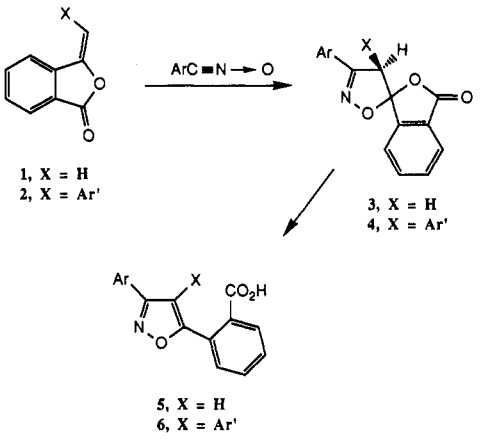
In explorations of the synthesis and chemistry of other spiroheterocycles, we have studied the reaction of aromatic nitrile oxides with 3-methylenephthalimidines. We report the results here.

Results and Discussion

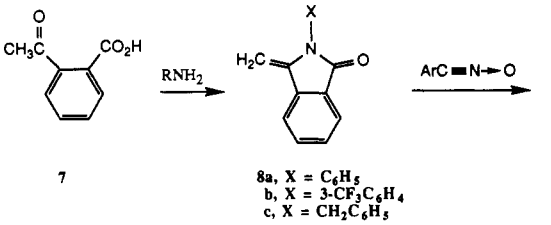
Aromatic nitrile oxides reacted readily with 2-aryl-3-methylenephthalimidines (**8**, X = aryl) to form spiroheterocycles **9a–e** in good yields (66–78% after recrystallization; Scheme II). The nitrile oxides were prepared in situ by dehydrochlorination of benzohydroximinoyl chlorides (chloro oximes)[4] with triethylamine. Dimerization of the nitrile oxides competed to a minor extent with reaction of the nitrile oxides with the phthalimidines. In these reactions, no firm evidence was found for formation of oxime products **10** or **11** from **8a,b**, although a few percent of the oximes could have formed on the basis of unassigned small singlets observed in the vinyl region in NMR analyses of the reaction mixtures. Reaction of nitrile oxides with 2-benzyl-3-methylenephthalimidine (**8c**) produced **9f–h** (40–57% yields after purification) as the major products and the oximes **10f–h** and **11f–h** as minor products.

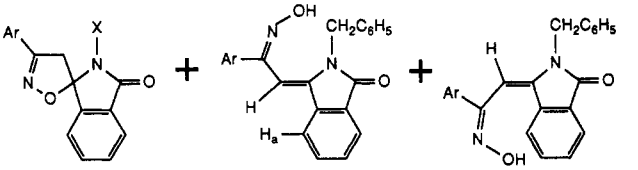
The spiroheterocycle structure **9** was confirmed by IR, ^{1}H NMR, and ^{13}C NMR analyses and by conversions of **9b** and **9f** to **12a** and **12b**, respectively; Scheme III. The IR spectra of the spiroheterocycles exhibited the strained lactam absorption at 1700–1720 cm^{-1}, and no OH or NH absorption was present. The proton NMR spectrum showed the isoxazoline[5] ring 4-H and 4′-H protons in the regions δ 3.5–3.8 and 3.1–3.6, with J = 18 Hz, which is completely consistent with a Δ^2-isoxazoline unsubstituted at the 4-position. If the spiro atom were at the 4-position of the isoxazoline ring, the protons at the 5-position would appear at lower fields than δ 4, and the coupling constant between the 5-H and 5′-H would be ca. 10 Hz.[5] The ^{13}C NMR spectra exhibit the spiro carbon atom at 101 ppm, at slightly higher field than the 112 ppm shift for the spiro carbon atom in **3**; this is as expected on the basis of the relative deshielding effects[6] of O and N in ^{13}C NMR.

Scheme I



Scheme II





(1) Liu, K.-C.; Howe, R. K. *J. Org. Chem.* **1983**, *48*, 4590.
(2) Howe, R. K.; Shelton, B. R.; Liu, K.-C. *J. Org. Chem.* **1985**, *50*, 903.
(3) Howe, R. K.; Liu, K.-C. U.S. Pat. 4 364 768; *Chem. Abstr.* **1981**, *94*, 47311h.
(4) Liu, K.-C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916.
(5) For representative ^{1}H 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.
(6) Levy, G. C.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*; Wiley-Interscience: New York, 1972; p 42.

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Scheme III

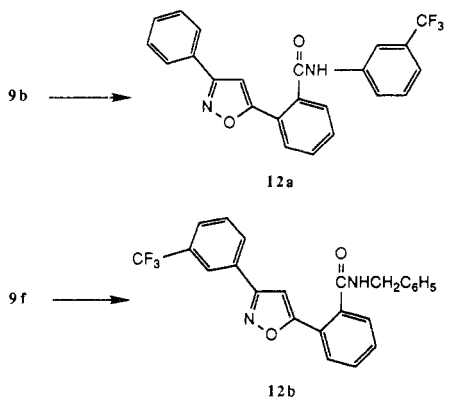


Table I. NOE Effects[a] in Oxime 10f

	NOE effect, %		
irradiated proton	vinyl *H*	Ar *H*[b]	NO*H*
NCH_2	0	0	+15
vinyl *H*		+15	0
Ar *H*[a]	+20		0

[a] DMSO-d_6 solvent. [b] Lowest field doublet between δ 8.05 and 8.31.

Formation of the 2-(5-isoxazolyl)benzamides from the spiroheterocycles further confirms that the spiro carbon is at the 5-position of the isoxazoline ring. That the benzamides are 5-isoxazolyl substituted instead of 4-isoxazolyl substituted is demonstrated by the observed NMR shifts of the isoxazolyl ring proton at δ 6.73 and 6.70 for **12a** and **12b**, respectively, which are similar to that (δ 6.80) observed previously[1] for a 2-(5-isoxazolyl)benzamide and that (δ 6.8–7.2) observed for 3,5-diarylisoxazoles;[7] this shift is at higher field than the shift of δ 8.0–8.4 that would be expected[8] for a proton at the 5-position of an isoxazole ring.

The proton NMR spectra of **9f–h** exhibited an unusual feature in that the doublet (one-half of an AB quartet) for the downfield benzyl proton was slightly broadened and, as a result, the peak heights of this doublet were less than those of the corresponding upfield doublet for the other benzyl proton. This evidently results from complex kinetic events in interconversions of conformers arising from rotation about the *N*-benzyl bond.[9] The AB quartet due to the geminal protons at the 4-position of the isoxazoline ring in **9** showed no selective broadening effect.

The (*Z*)-oxime structure **10** was confirmed by IR, ^1H NMR, ^{13}C NMR, and MS analyses; see the Experimental Section. The stereochemistry in the major oxime isomer **10f**, which was isolated in pure form, was determined by NOE NMR experiments at 100 MHz; Table I. The positive NOE effects between the methylene protons of the benzyl group and the NOH proton establish the closeness of these protons. Use of DMSO-d_6 as the solvent for this NMR experiment resulted in a sufficiently slow exchange rate of the NOH proton that the NOE effect on the NOH proton was observable. Irradiation of the vinyl proton gave a +15% enhancement of the lowest field aromatic doublet, which presumably is due to H_a.

We did not isolate pure **11** in any of the reactions. The structural assignment is based on cochromatography of **10f** with **11f** and of **10h** with **11h** and on IR and ^1H NMR spectra of the oxime mixtures. In particular, the NMR spectrum of the oxime mixtures exhibited singlets for the vinyl proton and methylene protons of the benzyl group of two different compounds (e.g., see Experimental Section under **9h**). An NOE NMR experiment conducted on a 58:42 mixture of **10f** and **11f** in $CDCl_3$ solution at 300 MHz confirmed the cis relationship of the vinyl proton and the methylene protons of the benzyl group in **11f**; irradiation of the methylene protons in **11f** gave a +18% NOE effect on the vinyl proton.

Thermally, **9b** is converted largely but not completely to **12a** within 5 min at 275 °C. Under these conditions, **9f** showed no change. In contrast to these results with the spirolactams, spirolactones **3** are converted quantitatively to benzoic acids **5** within a few minutes at 200–225 °C.[1] The difference in thermal stability of these two classes of spiroheterocycles probably results from the benzoate moiety being a better leaving group than the benzamide moiety and from autocatalysis in the lactone conversion by the product benzoic acid.

No reaction occurred upon heating 100 mg of **9b** with 30 mg of *p*-toluenesulfonic acid in 5 mL of 1,2-dichloroethane at reflux (84 °C) for 1 h (NMR analysis). Heating the same amounts of reagents in chlorobenzene at reflux (132 °C) for 2 h gave extensive (if not complete) conversion of **9b** to benzamide **12a**. Both **9b** and **9f** were converted completely and cleanly to the corresponding benzamides upon heating the spiroheterocycles with a little DBU (1,5-diazabicyclo[5.4.0]undec-5-ene) at 135–190 °C for a few minutes.

We studied effects of solvent polarity on the rate of reaction of 3-(trifluoromethyl)benzonitrile oxide with **8c** in order to gain a better understanding of the mechanism of formation of the spiroheterocycles and oximes. The Dimroth–Reichardt parameter E_t was employed as the measure of solvent polarity.[10] The nitrile oxide was generated by the nearly instantaneous dehydrochlorination of the hydroximinoyl chloride with triethylamine. The kinetics of the reactions of equimolar amounts (0.1 M each) of 3-(trifluoromethyl)benzonitrile oxide and phthalimidine **8c** in deuteriochloroform, acetone-d_6, and acetonitrile-d_3 were determined at 24 °C by 360-MHz proton NMR spectroscopy. In the reactions studied here, a minor amount of dimerization of the nitrile oxide competed with reaction of the nitrile oxide with **8**. This dimerization reduced the total yield of spiroheterocycle and oximes. Competing bimolecular reactions with equimolar amounts of reagents are difficult to analyze kinetically. It was sufficient for our purposes to obtain simple estimates of the relative rates of the cycloaddition reaction in the various solvents. We did this by the expedient of plotting the concentration of methylenephthalimidine as a function of time and determining the time (DT50) required for the concentration to decrease halfway between the initial and final concentration of methylenephthalimidine. This was done for each of the three solvents investigated. Since the same concentrations of reagents were employed in each run, the relative rates for the various solvents then were determined as the relative ratios of 1/DT50. In addition, the reaction of 3-(trifluoromethyl)benzonitrile oxide with **8a** in deuteriochloroform was studied in identical fashion. The results are given in Table II. The amounts of unreacted methylenephthalimidine (indicative of the amount of dimerization of nitrile oxide) in these NMR experiments ranged from 16 to 25%. The ratio of (*Z*)-oxime to spiro-

(7) Beam, C. F.; Dyer, M. C. D.; Schwarz, R. A.; Hauser, C. R. *J. Org. Chem.* **1970**, *35*, 1806.
(8) Barber, G. N.; Olofson, R. A. *J. Org. Chem.* **1978**, *43*, 3015.
(9) For a complete discussion of this type of phenomenon, see: Berg, U.; Roussel, C. *J. Am. Chem. Soc.* **1980**, *102*, 7848.
(10) Reichardt, C. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 29.

Table II. Solvent and Substituent Effects on the Reaction of 3-(Trifluoromethyl)benzonitrile Oxide with 3-Methylenephthalimidines

phth[a]	solvent	E_t[b]	time for 50% reactn, min	rel rate	ratio (Z)-oxime: spirohet.	ratio (E)-:(Z)-oximes
8c	$CDCl_3$	39.1	28	1.0	0.25	0.16
8c	$(CD_3)_2C{=}O$	42.2	14	2.0	0.22	0.16
8c	CD_3CN	46.0	7.5	3.7	0.18	0.22
8a	$CDCl_3$	39.1	14	2.0		

[a] Phth: 2-substituted-3-methylenephthalimidine. [b] E_t: Dimroth–Reichardt parameter for solvent polarity.

heterocycle did not change during the course of the reaction of 3-(trifluoromethyl)benzonitrile oxide with **8c** in any given solvent. There appeared to be no change in ratio of (*E*)- to (*Z*)-oximes during the course of the reactions for any given solvent. Since the spiroheterocycle is quite stable and the (*Z*)-oxime is reasonably stable, the constancy of the product ratios indicates that interconversions of products did not occur during the course of the reaction.

Formation of zwitterionic intermediates in 2 + 2 cycloaddition reactions results in large changes of rate constant with changes in solvent polarity.[11] The results in Table II reveal that the reaction rate of 3-(trifluoromethyl)benzonitrile oxide with **8c** increased only slightly as the solvent polarity increased. This appears to rule out a zwitterionic intermediate in the reaction pathway that produces the spiroheterocycle, the major product.

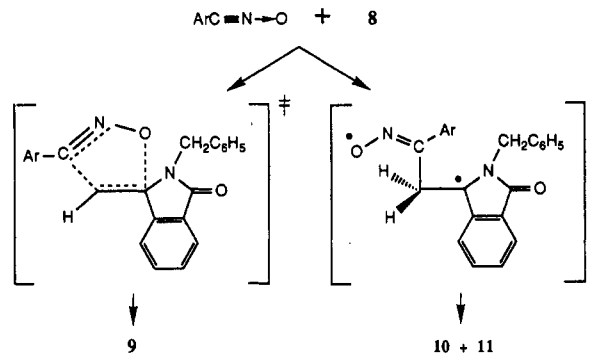
There was a slight trend toward lower ratios of (*Z*)-oxime and of total oximes to spiroheterocycle as the solvent polarity increased. The very minor changes in ratios with solvent polarity indicate that the polarities of the transition states for the competing reaction pathways do not differ much. Thus, zwitterionic intermediates appear unlikely for formation of the oximes also.

Reaction of benzonitrile oxide with phenylacetylene produces an isoxazole and an acetylenic oxime via competing pathways.[12] For this reaction, Huisgen had concluded that formation of the isoxazole occurs via 1,3-cycloaddition of the nitrile oxide to the acetylene and that the oxime is formed in a competing reaction either via a diradical or a zwitterionic intermediate.[12]

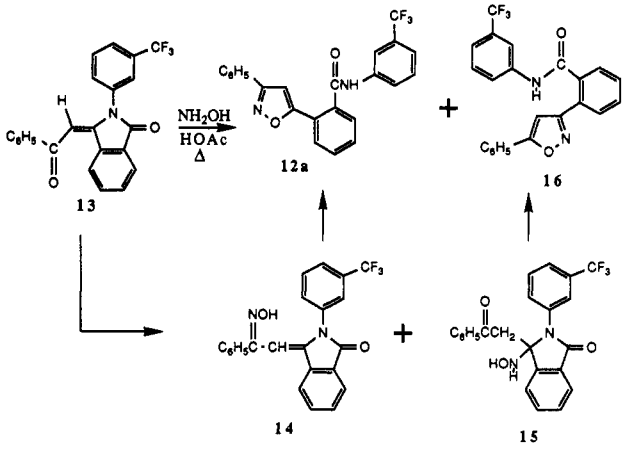
As stated by Houk et al.,[13] "The mechanism of 1,3-cycloadditions has been a topic of lively debate." The results of Houk et al.[13] confirm that the reaction of *p*-nitrobenzonitrile oxide with ethylene to form isoxazole proceeds via 1,3-cycloaddition with a concerted transition state, rather than through a stepwise mechanism involving a diradical intermediate. Although the reaction is concerted, "calculations indicate that the concerted transition state is asynchronous, with somewhat more CC than CO bonding in the single transition state separating reactants from products".[13]

Our results are best explained by a concerted but asynchronous 1,3-dipolar cycloaddition of nitrile oxide to the methylenephthalimidine to form the spiroheterocycle in competition with a diradical pathway for formation of the oximes[14] as depicted in Scheme IV. The effect of substituent on the reaction rate, *N*-phenyl resulting in slightly faster reaction rate than *N*-benzyl, is too small to interpret but is consistent with nonzwitterionic mechanisms.

Scheme IV



Scheme V



Attempts to prepare oximes related to **10** and **11** by the route shown in Scheme V were unsuccessful. Reaction of **13** with hydroxylamine required forcing conditions that resulted in a mixture of isoxazolylbenzamides **12a** and **16**. These probably arose via **14**, the desired oxime, and **15**, the Michael addition product from **13**.

Experimental Section

Melting points were determined in open capillaries in a Laboratory Devices Mel-Temp apparatus and are corrected. ^1H NMR spectra were determined with Varian T-60 (60 MHz), Varian EM-360L (60 MHz), JEOL FX-100 (100 MHz), Bruker WM-360 (360 MHz), and Varian VXR-300 (300 MHz) spectrometers. ^{13}C NMR spectra were determined with the JEOL and Bruker spectrometers. IR spectra were determined with a Perkin-Elmer 727B spectrometer. Elemental analyses were done by Atlantic Microlab, Inc., Atlanta, GA.

General Procedure for 2,3-Dihydro-3-methylene-2-substituted-1*H*-isoindol-1-ones (3-Methylenephthalimidines). A solution of 0.100 mol of substituted aniline or benzylamine and 0.100 mol of *o*-acetylbenzoic acid in 100 mL of *o*-dichlorobenzene was held at reflux for 1.5–6 h under a modified Dean–Stark trap that allowed the heavier distillate layer to return to the pot, and then ca. 80 mL of *o*-dichlorobenzene was distilled off. The solution in the pot was allowed to cool. The residue was crystallized from isopropyl alcohol.

(11) Huisgen, R. *Pure Appl. Chem.* **1980**, *52*, 2283.
(12) Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403 and references therein.
(13) Houk, K. N.; Firestone, R. A.; Munchausen, L. L.; Mueller, P. H.; Arison, B. H.; Garcia, L. A. *J. Am. Chem. Soc.* **1985**, *107*, 7227.
(14) Small increases of rate with increased polarity of solvent have been noted previously in generation of a free radical from a perester; the rate increased by a factor of 5 attending the solvent change from chlorobenzene (E_t 37.5) to acetonitrile (E_t 46.0): Martin, J. C.; Tuleen, D. L.; Bentrude, W. G. *Tetrahedron Lett.* **1962**, 229.

2,3-Dihydro-3-methylene-2-phenyl-1*H*-isoindol-1-one (8a). The solid product, mp 100–101 °C (lit.[15] mp 99–100 °C), was obtained in 46% yield.

2,3-Dihydro-3-methylene-2-[3-(trifluoromethyl)phenyl]-1*H*-isoindol-1-one (8b). The product (70% yield) was a yellow solid, mp 78.5–81 °C: NMR ($CDCl_3$) δ 8.02–7.5 (m, 8), 5.26 (d, 1, J = 2 Hz), 4.8 (d, 1, J = 2 Hz); IR (Nujol) 1700, 1680, 1640 cm^{-1}. Anal. Calcd for $C_{16}H_{10}F_3NO$: C, 66.44; H, 3.48. Found: C, 66.49; H, 3.54.

2,3-Dihydro-3-methylene-2-(phenylmethyl)-1*H*-isoindol-1-one (8c). The product (86% yield) was obtained as beige crystals, mp 118–120.5 °C: NMR ($CDCl_3$) δ 7.96–7.26 (m, 9), 5.15 (d, 1, J = 2 Hz), 5.0 (s, 2), 4.78 (d, 1, J = 2 Hz); IR (Nujol) 1700, 1680, 1640 cm^{-1}. Anal. Calcd for $C_{16}H_{13}NO$: C, 81.67; H, 5.57. Found: C, 81.61; H, 5.70.

General Procedure for Spiro[1*H*-isoindole-1,5′(4′*H*)-isoxazol]-3(2*H*)-ones 9. To a solution of 0.0425 mol of substituted 3-methylenephthalimidine and 0.0425 mol of substituted benzohydroximinoyl chloride[4] in 200 mL of methylene chloride stirred under nitrogen was added dropwise a solution of 0.0425 mol of triethylamine in 20 mL of methylene chloride during 30 min. The solution was stirred at room temperature for a few hours until IR analysis revealed the nitrile oxide had all reacted. The mixture was diluted with methylene chloride until all the solids had dissolved. The solution was extracted three times with water, dried ($CaSO_4$), and concentrated under vacuum to give crude product as a solid, glass, or oil. Purification methods are given in the individual examples below.

2,3′-Diphenylspiro[1*H*-isoindole-1,5′(4′*H*)-isoxazol]-3-(2*H*)-one (9a). The crude product from reaction of 0.0362-mol quantities each of 3-methylenephthalimidine, benzohydroximinoyl chloride, and triethylamine was dried under vacuum at 60 °C (bath temperature) to remove residual methylene chloride; this gave 11.1 g of solid (90% yield if it were all spiroadduct). NMR analysis indicated this solid to be fairly pure spiroadduct on the basis of the ratio of integration (20.5 mm) of the AB quartet for the two protons of the isoxazoline ring versus the integration (168 mm; 158 mm theory) of the aromatic protons region. The NMR spectrum showed a trace of residual methylenephthalimidine (ca. 5% of the amount of spiroadduct), based on the weak olefinic signals at δ 4.77 and 5.17. The only other impurity signals evident were very weak singlets at δ 6.50, 5.70, and 5.20 (ca. 0.5 mm integration each).

Crystallization of the solid from toluene gave a white solid (67% yield), mp 192–193.5 °C: NMR ($CDCl_3$) δ 7.87 (m, 1, Ar *H*), 7.7–7.16 (m, 13, Ar *H*), 3.77 (d, 1, J = 18 Hz), 3.56 (d, 1, J = 18 Hz); IR (Nujol) 1710 cm^{-1}. Anal. Calcd for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74. Found: C, 77.59; H, 4.77.

3′-Phenyl-2-[3-(trifluoromethyl)phenyl]spiro[1*H*-isoindole-1,5′(4′*H*)-isoxazol]-3(2*H*)-one (9b). Crystallization of the crude product from isopropyl alcohol gave white crystals (78%), mp 134–138 °C, that gave one spot upon TLC on silica gel in four different solvents (ethyl acetate, chloroform, 1,2-dichloroethane, and toluene). Anal. Calcd for $C_{23}H_{15}F_3N_2O_2$: C, 67.76; H, 3.70. Found: C, 67.66; H, 3.74.

Recrystallization of a small sample from ethanol gave a different crystal form, mp 150–151 °C. Dissolution of 1.05 g of the solid of mp 134–138 °C in hot ethanol and seeding with solid of mp 150–151 °C gave 0.94 g of white solid of mp 150–151 °C. Anal. Found: C, 67.63; H, 3.75.

The solution IR and NMR spectra of both crystal forms were identical. The mixture melting point of the two crystal forms was 150–151 °C. NMR ($CDCl_3$): δ 8.0–7.2 (m, 13), 3.83 (d, 1, J = 18 Hz), 3.49 (d, 1, J = 18 Hz). IR ($CHCl_3$): 1720 cm^{-1}. The ^{13}C NMR spectrum ($CDCl_3$ solvent) of **9b** exhibited signals at 166.3 ppm (carbonyl carbon), 157.6 (C=N carbon), 101.0 (spiro carbon), and 42.2 (carbon 4 of the isoxazoline ring), among the many other signals.

2-Phenyl-3′-[3-(trifluoromethyl)phenyl]spiro[1*H*-isoindole-1,5′(4′*H*)-isoxazol]-3(2*H*)-one (9c). The crude product, a viscous oil, was triturated with four 50-mL portions of ether, and the resultant undissolved beige solid (72%) was collected, mp 178.5–180 °C. The solid was recrystallized from 50 mL of toluene to give beige crystals (60%), mp 179.5–181 °C: NMR ($CDCl_3$) δ 8.0–7.2 (m, 13), 3.81 (d, 1, J = 18 Hz), 3.57 (d, 1, J = 18 Hz); IR (Nujol) 1720 cm^{-1}. Anal. Calcd for $C_{23}H_{15}F_3N_2O_2$: C, 67.65; H, 3.70. Found: C, 67.67; H, 3.80.

3′-(3-Chlorophenyl)-2-phenylspiro[1*H*-isoindole-1,5′-(4′*H*)-isoxazol]-3(2*H*)-one (9d). Trituration of the crude solid product with 100 mL of ether gave undissolved beige solid (66% yield), mp 172–174.5 °C. Recrystallization of the solid from a large volume of ethanol gave crystals (60%), mp 176–177 °C: NMR ($CDCl_3$) δ 8.06–7.1 (m, 13), 3.78 (d, 1, J = 18 Hz), 3.54 (d, 1, J = 18 Hz). Anal. Calcd for $C_{22}H_{15}ClN_2O_2$: C, 70.50; H, 4.03. Found: C, 70.56; H, 4.10.

2-Phenyl-3′-[4-(trifluoromethyl)phenyl]spiro[1*H*-isoindole-1,5′(4′*H*)-isoxazol]-3(2*H*)-one (9e). Trituration of the crude solid product with ether resulted in a white solid (69%), mp 115.5 °C, followed by resolidification and final melting at 156.5–158.5 °C. Apparently there are different crystalline forms of this compound. A 2.00-g sample was recrystallized from ethanol to give 1.47 g of solid, mp 170–172.5 °C: NMR ($CDCl_3$) δ 8.0–7.2 (m, 13), 3.78 (d, 1, J = 18 Hz), 3.54 (d, 1, J = 18 Hz); IR (Nujol) 1705 cm^{-1}. Anal. Calcd for $C_{23}H_{15}F_3N_2O_2$: C, 67.65; H, 3.70. Found: C, 67.64;, H, 3.74.

2-(Phenylmethyl)-3′-[3-(trifluoromethyl)phenyl]spiro-[1*H*-isoindole-1,5′(4′*H*)-isoxazol]-3(2)-one (9f) and 2,3-Dihydro-3-[2-(hydroxyimino)-2-[3-(trifluoromethyl)phenyl]-ethylidene]-2-(phenylmethyl)-1*H*-isoindol-1-one (10f). Reaction of 0.0425-mol quantities each of *N*-benzyl-3-methylenephthalimidine, 3-(trifluoromethyl)benzohydroximinoyl chloride, and triethylamine gave a "cotton-candy-like" oil that contained ca. 9 mol % of residual starting phthalimidine and a 78:22 mixture of spiroadduct and (*Z*)-oxime, as well as a trace of (*E*)-oxime ((*E*)/(*Z*)-oxime ratio of 0.2 based on vinyl signals at δ 5.8 and 5.9, respectively) and a little residual methylene chloride (NMR analysis). Trituration of the oil with 50 mL of ether gave 8.9 g of white solid (a mixture of spiroadduct and (*Z*)-oxime), mp 118–125.5 °C, in the first crop and 2.32 g of a 73:27 mixture of spiroadduct and (*Z*)-oxime as a second crop, mp 117–144 °C.

The 8.9 g of solid was crystallized from ethanol to give 7.25 g (40%) of solid, mp 119.5–126 °C, that appeared to be pure spiroadduct by NMR analysis; TLC analysis, however, showed a trace contaminant with a lower R_f value. The 7.25 g of solid was triturated twice with 30-mL portions of ether to give 6.27 g of solid, mp 124.5–127 °C. This latter material was dissolved in 10 mL of hot 1,2-dichloroethane; the solution was cooled and diluted with 30 mL of ether to give 4.76 g (26%) of white solid, mp 126.5–128.5 °C, that was pure spiroadduct (NMR, TLC analyses): NMR ($CDCl_3$) δ 7.9 (m, 1, Ar *H*), 7.77–7.50 (m, 7), 7.26–7.07 (m, 5), 5.37 (d, 1, J = 16 Hz, NCH_aH_b), 4.03 (d, 1, J = 16 Hz, NCH_aH_b), 3.55 (d, 1, J = 18 Hz), 3.17 (d, 1, J = 18 Hz); IR (Nujol) 1705 cm^{-1}. Anal. Calcd for $C_{24}H_{17}F_3N_2O_2$: C, 68.24; H, 4.05. Found: C, 68.21; H, 4.10.

The 2.32 g of 73:27 mixture of spiroadduct and oxime was subjected to HPLC on a 1 × 13 in. column of 70–230-mesh silica gel with 5% ether in 1,2-dichloroethane at 5 mL/min. After elution of 1.57 g of spiroadduct, 0.03 g of a mixture was obtained. Then, 0.57 g of white solid, mp 164–166.5 °C, eluted; NMR and TLC analyses showed this to be pure (*Z*)-oxime **10f**. Recrystallization of 0.20 g of the oxime from aqueous ethanol gave 0.15 g of white solid, mp 175–176.5 °C: NMR ($CDCl_3$ + 10% DMSO-d_6, 60 MHz) δ 8.0–7.16 (m, 8), 6.8 (s, 5), 5.97 (s, 1), 4.95 (s, 2); NMR (DMSO-d_6, 99.6 MHz) 12.09 (s, 1, NO*H*), 8.16 (m, 1), 7.9–7.3 (m, 7), 6.9–6.7 (m, 5), 6.43 (s, 1), 4.90 (s, 2, NCH_2); ^{13}C NMR (DMSO-d_6) 167.6 ppm (carbonyl carbon), 149.8 (C=N carbon), 96.8 (exocyclic double bond carbon), 42.1 (methylene carbon of benzyl group) among the other carbon signals; IR (Nujol) 3160, 1685, 1655 cm^{-1}; MS (EI, direct probe) m/z (rel intensity, ion) 422 (1.6, M^+), 405 (30.4, M^+ – OH), 327 (16.1), 234 (19.4, M^+ – $CF_3C_6H_4C(=NOH)$), 146 (21.8), 145 (18.8), (100, $C_6H_5CH_2^+$). Anal. Calcd for $C_{24}H_{17}F_3N_2O_2$: C, 68.24; H, 4.05; N, 6.63. Found: C, 68.25; H, 4.08; N, 6.64.

In another experiment designed to isolate the oxime mixture, 0.034-mol quantities of **8c**, 3-(trifluoromethyl)benzohydroximinoyl chloride, and triethylamine were allowed to react in acetonitrile solution for 3 h. The mixture was concentrated under vacuum to dryness. The residue was dissolved in ca. 200 mL of methylene

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chloride; this solution was washed three times with water, dried ($CaSO_4$), and concentrated under vacuum to 100 mL. The solution was chromatographed on silica gel (Water's Prep 500A preparative chromatograph). Elution of the column with methylene chloride gave 8.8 g of mixture of spiroadduct and starting phthalimidine. Further elution with 15% ether in methylene gave 6.16 g of a mixture of spiroadduct and oximes. Rechromatography of the latter mixture with 5% ether in methylene chloride as the elution solvent gave 4.3 g of spiroadduct (≥98% pure by reverse-phase HPLC with UV detection at 254 nm) and 1.8 g of solid oxime mixture (≥99% pure by HPLC analysis). Crystallization of the oxime mixture from ethanol gave 0.80 g of (*Z*)-oxime **10f**, mp 178–180 °C. Dilution of the filtrate with water gave 0.61 g of a 58:42 mixture of (*Z*)- and (*E*)-oximes, mp 171–179 °C. This latter mixture was employed for NOE NMR experiments to confirm the stereochemistry of the minor oxime isomer.

2-(Phenylmethyl)-3′-[4-(trifluoromethyl)phenyl]spiro-[1*H*-isoindole-1,5′(4′*H*)-isoxazol]-3(2*H*)-one (9g). Reaction of 0.0425-mol quantities each of 2-benzyl-3-methylenephthalimidine, 4-(trifluoromethyl)benzohydroximinoyl chloride, and triethylamine resulted in 17.6 g of orange oil that consisted of a 83:17 mixture of spiroadduct and oximes (oximes were a ca. 78:22 mixture of *Z* and *E* isomers), as well as ca. 9% starting phthalimidine and a little methylene chloride (NMR analysis). Trituration of the oil with 100 mL of ether gave 11.32 g (63%) of white solid, mp 164–167.5 °C. The solid was recrystallized from 175 mL of ethanol to give 9.22 g (51%) of analytically pure white solid, mp 167.5–169 °C: NMR ($CDCl_3$) δ 7.83 (m, 1), 7.73–6.8 (m, 12), 5.30 (d, 1, J = 16 Hz), 4.03 (d, 1, J = 16 Hz), 3.53 (d, 1, J = 18 Hz), 3.17 (d, 1, J = 18 Hz); IR (Nujol) 1700 cm^{-1}. Anal. Calcd for $C_{24}H_{17}F_3N_2O_2$: C, 68.24; H, 4.05. Found: C, 68.13; H, 4.10.

3′-(4-Chlorophenyl)-2-(phenylmethyl)spiro[1*H*-isoindole-1,5′(4′*H*)-isoxazol]-3(2*H*)-one (9h). Reaction of 0.0425-mol quantities each of *N*-benzyl-3-methylenephthalimidine, 4-chlorobenzohydroximinoyl chloride, and triethylamine gave 15.7 g of orange oil that consisted of an 82:18 mixture of spiroadduct and oximes (oximes were a ca. 77:23 mixture of *Z* and *E* isomers) and ca. 9% of starting phthalimidine. Trituration of the solid with 100 mL of ether gave 12.04 g of white solid, mp 148.5–156.5 °C, that consisted of a 82:18 mixture of spiroadduct and oximes. The solid was subjected to HPLC on 470 g of 70–230-mesh silica gel. Elution with 1,2-dichloroethane at 20 mL/min gave 9.36 g (57%) of pure spiroadduct as a white solid, mp 159.5–161 °C. The melting point changed to 184.5–186.5 °C upon storage of the sample for 2.5 months, but the NMR spectrum remained the same; evidently, there are two crystalline forms of this material. NMR ($CDCl_3$): δ 7.77 (m, 1), 7.47 (m, 3), 7.23 (s, 4), 7.03 (s, 5), 5.2 (d, 1, J = 16 Hz), 3.97 (d, 1, J = 16 Hz), 3.47 (d, 1, J = 18 Hz), 3.07 (d, 1, J = 18 Hz). IR (Nujol): 1710 cm^{-1}. Anal. Calcd for $C_{23}H_{17}ClN_2O_2$: C, 71.04; H, 4.41. Found: C, 71.05; H, 4.43.

Further elution of the column with 5% acetonitrile in 1,2-dichloroethane at 40 mL/min gave 1.57 g (10%) of oximes as a light yellow solid; NMR analysis revealed this to be an 83:17 mixture of *Z* and *E* double-bond isomers of the oxime (**10h** and **11h**, respectively). NMR ($CDCl_3$ + DMSO-d_6): δ 7.9–6.57 (m, 14), 6.03 (s, 0.83 H), 5.87 (s, 0.17 H), 5.08 (s, 0.34 H), 4.82 (s, 1.66 H). IR (Nujol): 3500–3000, 1710, 1675 cm^{-1}.

2-(3-Phenyl-5-isoxazolyl)-*N*-[3-(trifluoromethyl)-phenyl]benzamide (12a). A mixture of 5.27 g of spiroheterocycle **9b** and 0.20 g of DBU was held at 190 °C with swirling for 2 min under nitrogen, was allowed to cool, and was crystallized from aqueous ethanol to give 4.3 g (82%) of white solid, mp 146–147.5 °C: IR ($CHCl_3$) 3410, 3250, 1675, 1610 cm^{-1}; NMR ($CDCl_3$) δ 9.00 (bs, 1, N*H*), 8.10–7.73 (m, 2), 7.43 (m, 11), 6.73 (s, 1, 4-*H*). Anal. Calcd for $C_{23}H_{15}F_3N_2O_2$: C, 67.76; H, 3.70. Found: C, 67.62; H, 3.71.

***N*-(Phenylmethyl)-2-[3-[3-(trifluoromethyl)phenyl]-5-isoxazolyl]benzamide (12b).** A mixture of 3.0 g of spiroheterocycle **9f** and 0.2 g of DBU was held at 135–145 °C for 4.3 min with swirling under nitrogen, was cooled, and was crystallized from aqueous ethanol to give 2.72 g (91%) of white solid, mp 118–119.5 °C: NMR ($CDCl_3$) δ 7.93–7.33 (m, 8), 7.13 (s, 5), 6.70 (s, 1, 4-*H*), 6.33 (br s, 1, N*H*), 4.50 (d, 2, J = 6 Hz, HNCH_2); IR ($CHCl_3$) 3425, 1660 cm^{-1}. Anal. Calcd for $C_{24}H_{17}F_3N_2O_2$: C, 68.24; H, 4.05. Found: C, 68.25; H, 4.07.

Attempted Preparation of 14. A mixture of 4.00 g (0.0102 mol) of (*E*)-3-phenacylidene-*N*-[3-(trifluoromethyl)phenyl]-phthalimidine[16] (**13**), 0.74 g (0.0106 mol) of hydroxylamine hydrochloride, and 0.85 g (0.0104 mol) of sodium acetate in 40 mL of acetic acid was heated on a steam bath for 3.75 h. After this time, NMR and TLC analyses revealed that only a trace of reaction had occurred and that ca. 15% isomerization of the *E* isomer of the phenacylidenephthalamidine to the *Z* isomer[16] had occurred. Another 1.44 g (0.0207 mol) of hydroxylamine hydrochloride and 10 mL of acetic acid was added, and the mixture was heated at reflux. Periodic NMR analyses indicated that reaction was occurring slowly with formation of two new singlets just to lower field of the vinyl signal of the *Z* isomer of the starting phthalimidine. After the reaction mixture was heated for 9 h at reflux, NMR analysis indicated the presence of residual phenacylidenephthalimidines (mostly *E* isomer) and the two lower field singlets mentioned above. The mixture was cooled, filtered to remove a water-soluble solid, and concentrated under vacuum to 4.4 g of oil. TLC analysis indicated two major spots (fast moving) and five minor, slower moving spots (10% acetonitrile in 1,2-dichloroethane on silica gel). The 4.4 g of oil was chromatographed on 170 g of 70–230-mesh silica gel with 10% acetonitrile in 1,2-dichloroethane at 20 mL/min. The first major fraction consisted of 2.67 g of oily solid; this was a mixture of materials (NMR analysis). Subsequently, a total of 0.37 g of fairly insoluble, unidentified solid eluted. The 2.67 g of oily solid was rechromatographed on 330 g of 40–63-mesh silica gel with 1,2-dichloroethane. Two separate, resolved fractions were obtained. The first consisted of 0.5 g of yellow solid, mp 163–168 °C, that was starting (*E*)-phthalimidine based on TLC and NMR analyses. The second fraction, 1.6 g (38% yield) of light yellow solid, was a 70:30 mixture of isoxazolylbenzamides **12a** and **16** (NMR, TLC, IR analyses). This solid was recrystallized from aqueous ethanol to give 0.90 g of white solid, a 65:35 mixture of **12a** and **16**; the IR spectra of this solid and of authentic **12a** were identical. NMR ($CDCl_3$): δ 8.83 (br s, 0.65 H, N*H*), 8.72 (br s, 0.3 H, N*H*), 8.0–7.17 (m, 13), 6.70 (s, 0.65 H, 4-*H* of **12a**), 6.60 (s, 0.35 H, 4-*H* of **16**). The TLC R_f of this mixture and of authentic **12a** were the same in three different solvent systems on silica gel. Anal. Calcd for $C_{23}H_{15}F_3N_2O_2$: C, 67.64; H, 3.70. Found: C, 67.66; H, 3.73.

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