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The synthesis of novel thiophene-2-carboxylic acids bearing alkyl and aryl-substituted oxazole and oxadiazole rings is reported. Sequential functionalization of the key precursor, 5-formyl-2-thiophenecarboxylic acid furnished the intermediate carboxylic acid esters which were converted into desired acids by basic cleavage.

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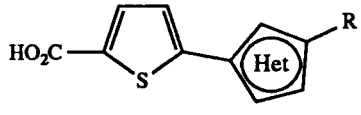
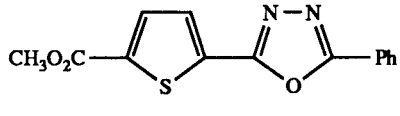
Introduction.

Publications from these laboratories over the past several years have documented the use of oxindoles and their derivatives as antiinflammatory agents [1a-f]. In connection with some related efforts and others designed to provide materials for empirical screening, we required samples of 5-heteroaryl-2-thiophenecarboxylic acids. Specifically of interest to us were a variety of 5-membered-ring heterocycles positionally-substituted with alkyl and aryl groups **1**.



1

In order to evaluate fully several aspects of our program a diversity of structural variants was required but surprisingly the literature provides few examples which completely satisfied our needs. For example, ostensibly related series of 5-(benzoxazo [2], benzimidazo [3] and imidazopyrido [4])-2-thiophenecarboxylic acids are known, as are a number of cardiotonic agents derived from 5-(thiazo)-2-thiophenecarboxylic acids and their corresponding alkyl esters [5a,b]. There were, in fact, only two compounds which ultimately proved to be of general interest: methyl 5-(5-phenyl-1,3,4-oxadiazol-2-yl)-2-thiophenecarboxylate (**2**), an intermediate used in the manufacture of optical brighters [6], and 5-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-2-thiophenecarboxylic acid (**3**), employed in regioselective metallation studies of thiophene derivatives [7].



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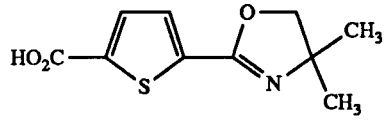


3

Although **2** would prove suitable as the penultimate precursor to a desired acid it was apparent that simple heterocyclic congeners were poorly known. This initial paper describes the synthesis of oxazole and oxadiazole representatives of **1**.

Results and Discussion.

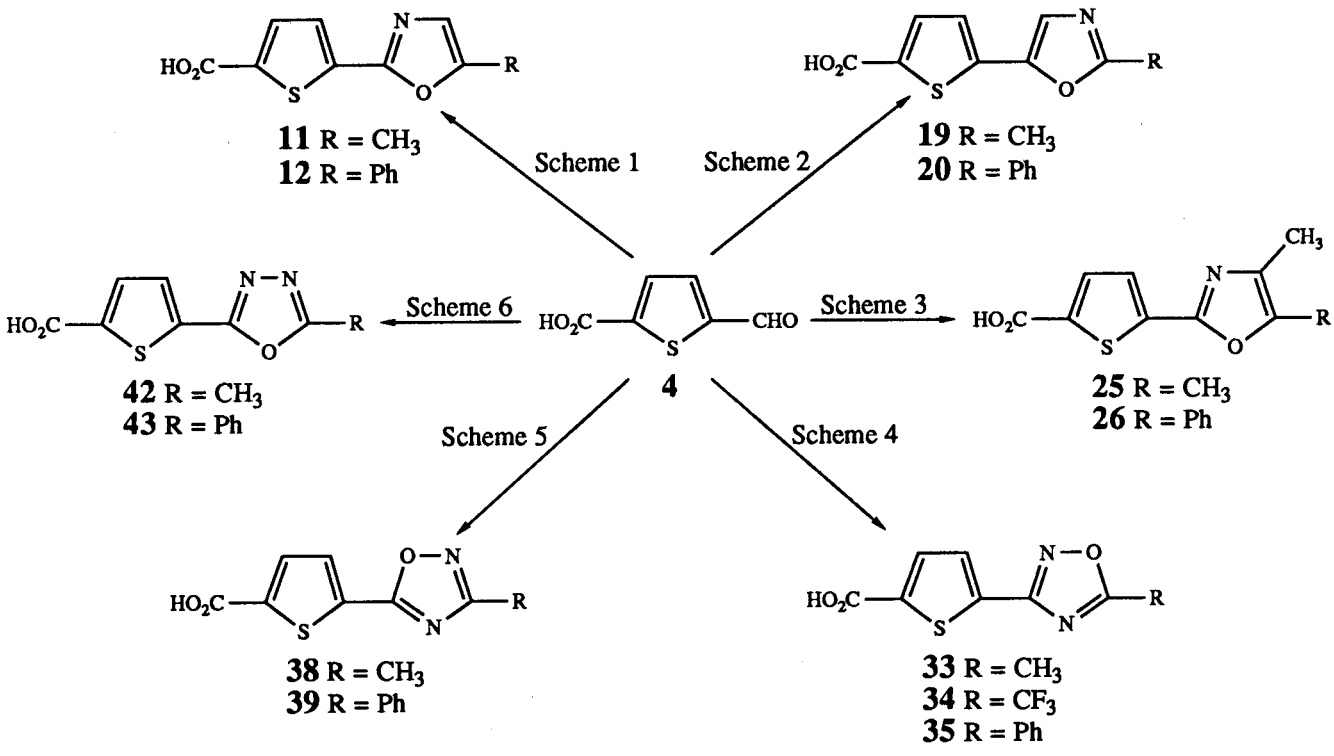
Of several conceptually applicable synthetic pathways to these compounds, the simplest and most attractive would be ring formation sequences based on appropriately functionalized thiophene-2-carboxylic acid ester auxiliaries. Our synthetic approach was therefore predicated on the selection of pivotal intermediates which, with minimal manipulation, would allow the synthesis of a wide variety of desired heterocycles. Well suited for this role is 5-formyl-2-thiophenecarboxylic acid (**4**) [8] whose exploitable bi-functionality and ease of synthesis make it a strategically useful synthon.

Oxazoles.

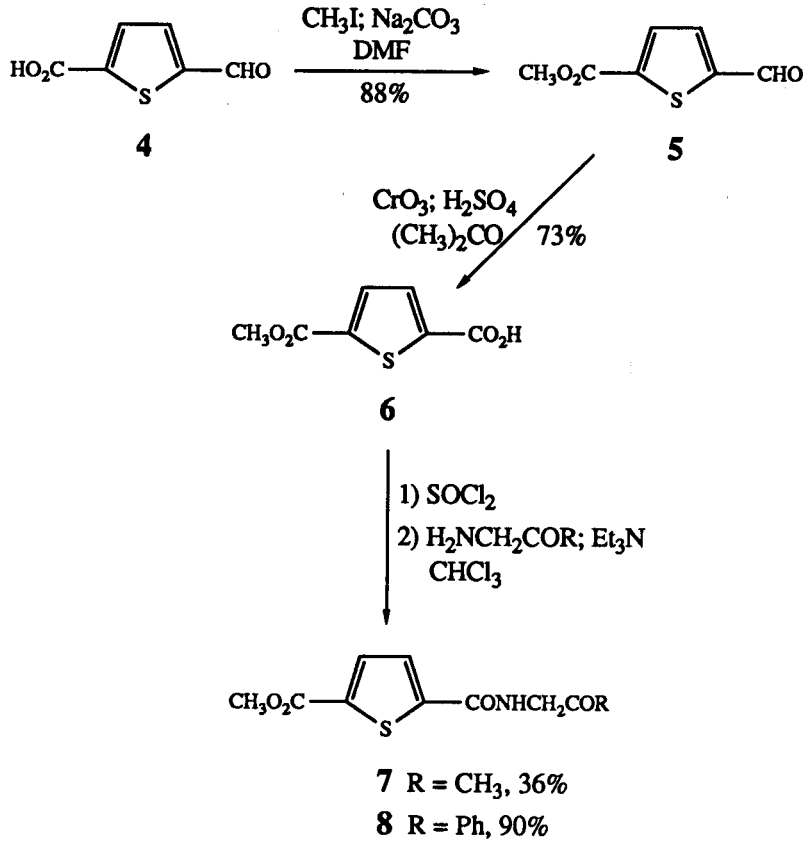
The synthesis of thiophene-2-carboxylic acids containing regioisomeric, mono-substituted oxazole nucleii is outlined below in Schemes 1 and 2. The oxazole ring formation step in each case is a Robinson-Gabriel cyclodehydration [9] [10] of an appropriate α-acylaminoketone.

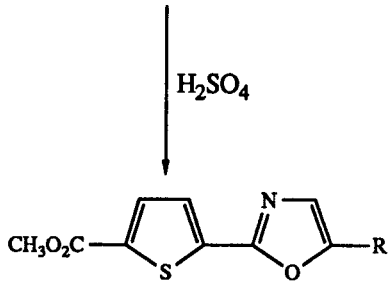
In Scheme 1 esterification of **4** to the known formyl ester **5** [11] followed by oxidation gave acid **6** [12]. Treatment with thionyl chloride gave the crude acid chloride which was immediately condensed with aminoacetone [13] or α-aminoacetophenone hydrochlorides to furnish amides **7** and **8**. Sulfuric acid-mediated cyclization to esters **9** and **10** followed by saponification with aqueous base gave carboxylic acids **11** and **12** in fair to good overall yields.

In Scheme 2 the requisite α-acylaminoketones **15** and **16** were synthesized beginning with acid **6**. Conversion to the acid chloride, homologation with diazomethane and functionalization with hydrogen bromide [14] yielded the known bromoketone **13** [4]. A modified Delepine reaction [15] [16] led to aminoketone salt **14** which was acylated with acetyl and benzoyl chlorides under standard conditions. While **14** was not appreciably hygroscopic and could

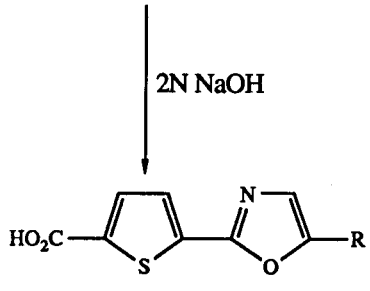

11 R = CH3
12 R = Ph
Scheme 1
Scheme 2
19 R = CH3
20 R = Ph
Scheme 6
Scheme 3
42 R = CH3
43 R = Ph
4
25 R = CH3
26 R = Ph
Scheme 5
Scheme 4
38 R = CH3
39 R = Ph
33 R = CH3
34 R = CF3
35 R = Ph

Scheme 1


CH3I; Na2CO3
DMF
88%
4
5
CrO3; H2SO4
(CH3)2CO
73%
6
1) SOCl2
2) H2NCH2COR; Et3N
CHCl3
7 R = CH3, 36%
8 R = Ph, 90%

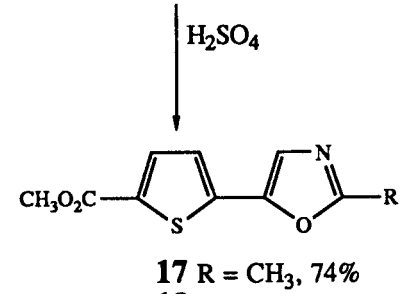


9 R = CH_3, 85%
10 R = Ph, 93%

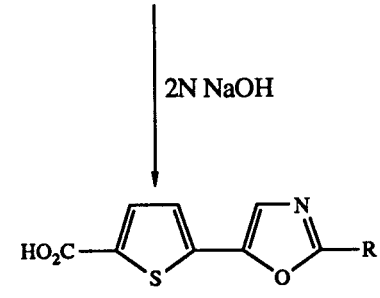


11 R = CH_3, 89%
12 R = Ph, 98%

Scheme 2

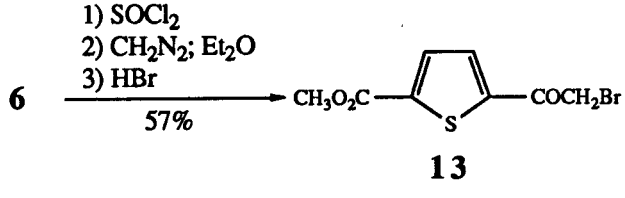


17 R = CH_3, 74%
18 R = Ph, 75%



19 R = CH_3, 87%
20 R = Ph, 89%

Scheme 3



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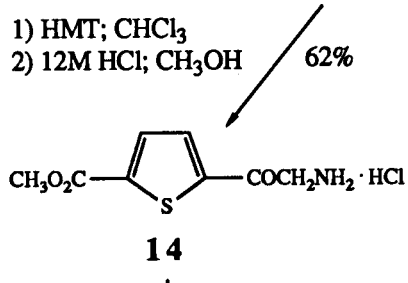

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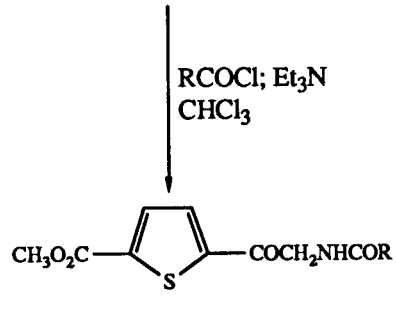
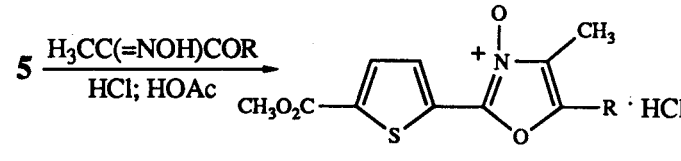
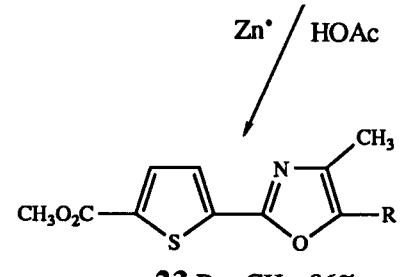


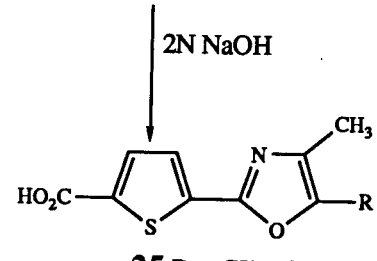
15 R = CH_3, 65%
16 R = Ph, 91%



21 R = CH_3, 66%
22 R = Ph, 20%



23 R = CH_3, 86%
24 R = Ph, 50%

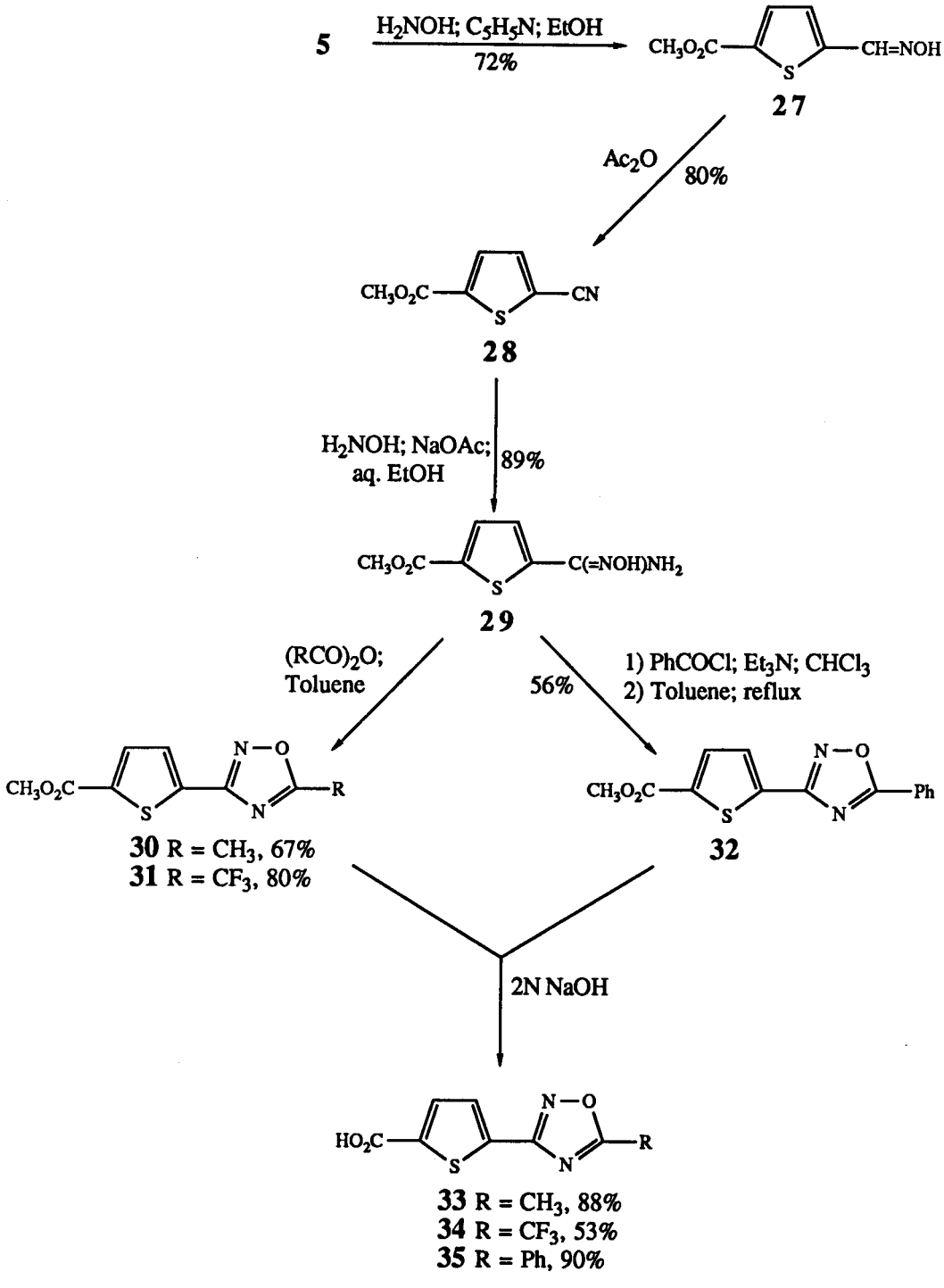


25 R = CH_3, 91%
26 R = Ph, 93%

be stored indefinitely at room temperature, it proved rather heat sensitive especially when in solution. Not suprisingly, solutions of the free base darken rapidly at ambient temperature. Dehydration of amides **15** and **16** with warm sulfuric acid gave esters **17** and **18** in 74% and 75% yields respectively. Cleavage to acids **19** and **20** with aqueous base was performed as previously described.

A different approach was employed for the synthesis of thienyl acids which incorporate a 2,3-disubstituted oxazole moiety. The reaction of diketone monoximes with aromatic aldehydes to give oxazole *N*-oxides, originally reported by Diels and Riley [17] and elaborated by other workers [18] [19], formed the basis for the synthesis of acids **25** and **26** shown in Scheme 3. The acid catalyzed

Scheme 4

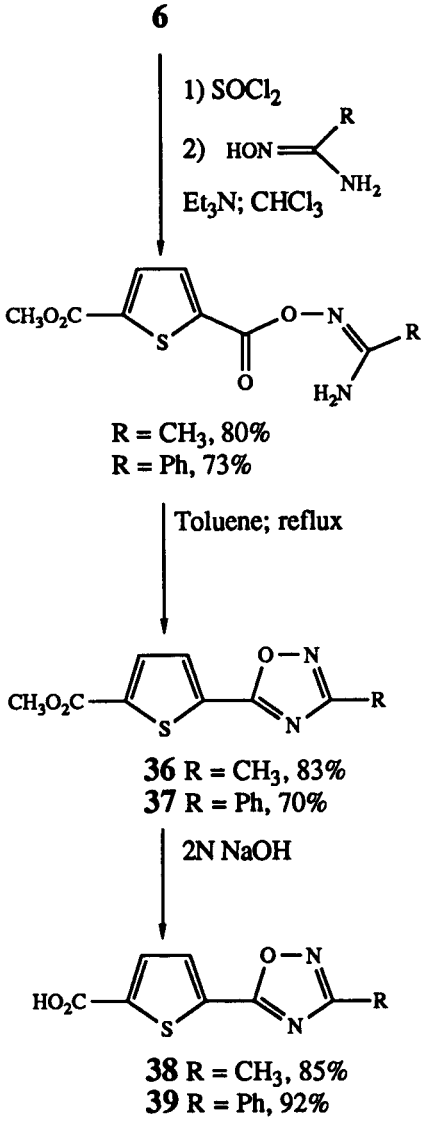


cyclocondensation of aldehyde **5** with 2,3-butanedione monoxime and 1-phenyl-1,2-propanedione 2-oxime was straightforward and gave *N*-oxides **21** and **22**. Because of the low yield in the cyclization step, **22** was used directly without complete characterization. Reduction of the intermediate *N*-oxides to esters **23** and **24** with zinc/acetic acid [20] followed by basic cleavage furnished final products **25** and **26**.

Oxadiazoles.

The chemical literature notes several synthetic routes leading to the formation of 3,5-disubstituted-1,2,4-oxadiazoles. In the present study the generation and thermal cyclization of *O*-acylamidoximes [21] was determined to be the most applicable preparative approach to this ring system.

Scheme 5



Pursuant to the synthesis of 3-thienyl-1,2,4-oxadiazoles **33**, **34** and **35** in Scheme 4, it was necessary to prepare a suitable nitrile precursor for amidoxime conversion and acylation. The required methyl 5-cyano-2-thiophenecarboxylate **28** has been reported previously [22] but the synthesis is not easily amenable to multigram scale production. Therefore a simpler method based on an acetic anhydride mediated dehydration of methyl 5-formyl-2-thiophenecarboxylate oxime **27** was utilized and gave cyanoester **28** in 80% yield.

Reaction of **28** with hydroxylamine furnished amidoxime **29**. Cyclization to thienyl esters **30** and **31** was effected by the *in-situ* formation and ring-closure of their corresponding *O*-acyloximes in refluxing toluene. During the preparation of ester **32** it was found preferrable, especially in terms of product purity and yield, to isolate and purify the intermediate *O*-benzoylamidoxime before cyclodehydration. To varying degrees all thiophene-2-carboxylates incorporating 1,2,4- and 1,3,4-oxadiazole rings exhibited an unfortunate tendency to sublime with apparent decomposition on warming under vacuum. For this reason the esters were carried directly into the saponification step with structural assignment based on high resolution mass spectrometry.

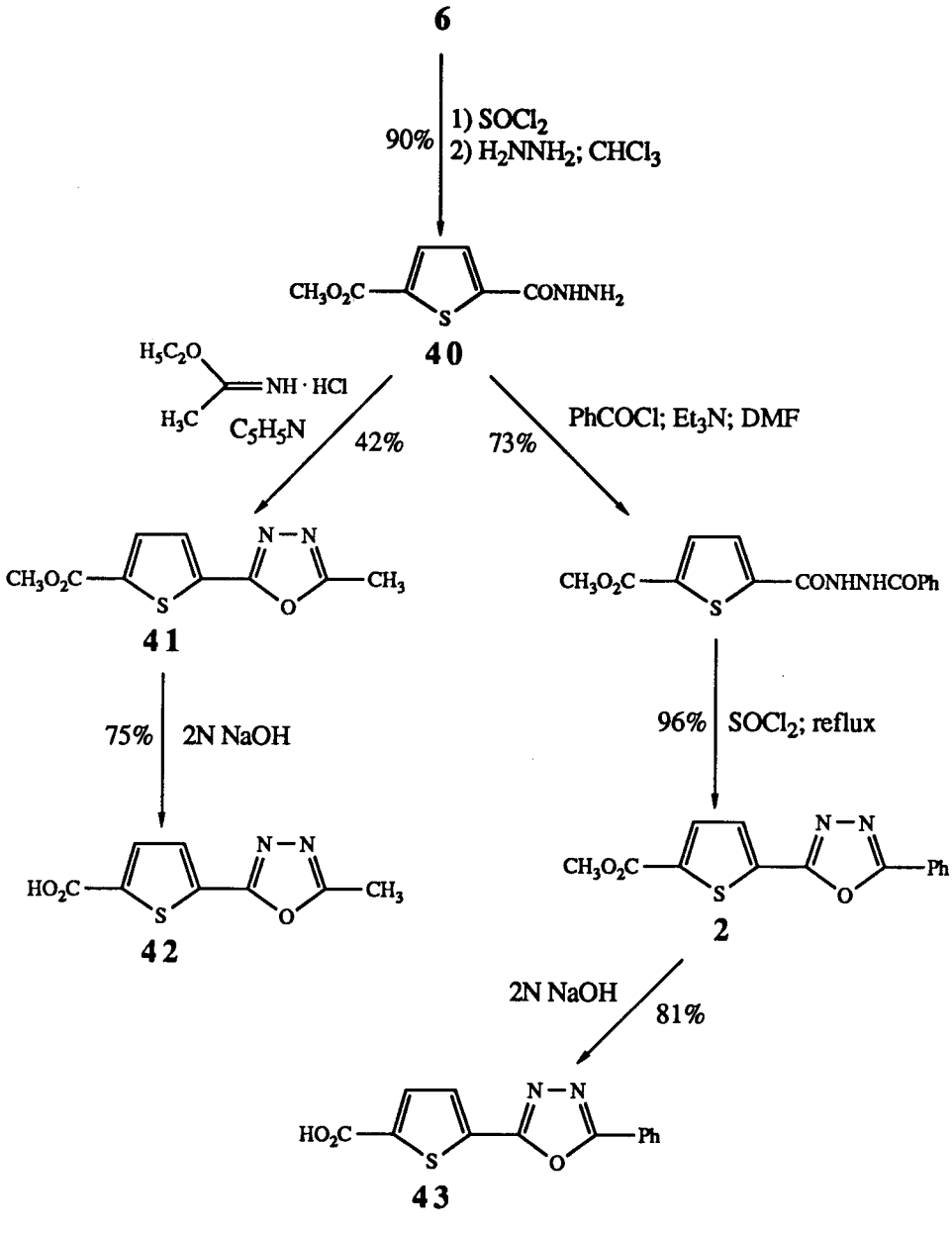
Preparation of the regioisomeric 5-thienyl-1,2,4-oxadiazoles **38** and **39** (Scheme 5) begins with the functionalization of acetamide [21] and benzamide [23] oximes with the acid chloride of **6**. The resulting *O*-acyloximes furnished esters **36** and **37** after ring closure in refluxing toluene. As in the case of ester **32** it was advantageous to isolate and superficially purify the respective acylated oxime intermediates before ring-closure. Although this approach requires an additional step it does afford products of greater purity than a recently reported, one-pot method [24] using pyridine as an acylation solvent.

Although separate preparative procedures were used in the synthesis of thiophene esters **41** and **2** from Scheme 6, both pathways utilize hydrazide **40** as a common intermediate. In the former case ring formation was effected through the reaction of **40** with ethyl acetimidate hydrochloride in pyridine [25] and in the latter through benzoylation and cyclization in neat thionyl chloride. The original procedure used in the synthesis of ester **2** [6] describes the formation of the intermediate diacylhydrazide by the interaction of **6** and benzoic acid hydrazide in chlorobenzene. No physicochemical data are furnished for this substance which was subsequently treated *in situ* with thionyl chloride and cyclized. Hydrolytic cleavage with aqueous base as before gave acids **42** and **43**.

Summary

During the course of the present study to total of thirteen thiophene-2-carboxylic acids bearing alkyl and aryl-

Scheme 6



substituted oxazole and oxadiazole rings were synthesized through the modification of 5-formyl-2-thiophenecarboxylic acid, **4**. Although **4** has seen only limited mention since its initial synthesis in 1967, we have found it to be an exceptionally versatile preparative synthon whose potential for synthetic manipulation should ensure its future popularity in the field of thiophene chemistry.

EXPERIMENTAL

Melting points, given in degrees celcius, were determined with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by John W. Greene of the Pfizer Central Research Analytical Department. The ^{1}H nmr spectra were obtained in deuteriodimethyl sulfoxide on Varian XL-300 and Bruker AM-300 instruments. Electron impact mass spectral measurements were made on Finnegan 4510 (70 eV) and Kratos AEI M30 spectrometers. Fourier Transform infrared spectra were recorded in potassium bromide on a Nicolet 510 instrument using the DRIFTS technique [26].

Unless noted, all reagents employed were purchased commercially and used without further purification.

Methyl 5-Formyl-2-thiophenecarboxylate (**5**).

Methyl iodide (4.36 g, 30.72 mmoles) was added to a stirred suspension of 5-formyl-2-thiophenecarboxylic acid [8] (4.00 g,

25.61 mmoles) and sodium carbonate (9.50 g, 89.63 mmoles) in 75 ml of *N,N*-dimethylformamide. After stirring overnight at room temperature the mixture was poured into water, saturated with solid sodium chloride and extracted with ethyl acetate. The extracts were washed with brine, dried (magnesium sulfate) and concentrated to a light yellow solid (3.83 g, 88% yield), mp 85-87°, lit [11] mp 88-89°; ^{1}H nmr: δ 10.01 (s, 1H), 8.05 (d, 1H, J = 4.0 Hz), 7.92 (d, 1H, J = 4.0 Hz), 3.87 (s, 3H); ms: m/z relative intensity) 170 (M^+, 95%), 139 (100), 111 (64).

5-Methoxycarbonyl-2-thiophenecarboxylic Acid (**6**).

A stirred solution of **5** (2.00 g, 11.75 mmoles) in 100 ml of acetone was treated dropwise with Jones' reagent until a persistant orange color resulted. The mixture was then stirred at room temperature for one hour, the excess oxidant decomposed with isopropanol and the mixture filtered. The residue obtained on evaporation was dissolved in ethyl acetate, dried over magnesium sulfate and evaporated to ~10 ml. Filtration furnished the pure title compound as a white solid (1.60 g, 73% yield), mp 186-189°; lit [12] mp 187-190°; ^{1}H nmr: δ 7.78 (d, 1H, J = 4.0 Hz), 7.72 (d, 1H, J = 4.0 Hz), 3.85 (s, 3H); ms: m/z (relative intensity) 186 (M^+, 70), 169 (7), 155 (100), 111 (20).

N-(5-Methoxycarbonyl-2-thenoyl)-α-aminoacetone (**7**).

A stirred suspension of **6** (3.00 g, 16.11 mmoles) in 20 ml of thionyl chloride was refluxed for one and one-half hours. The solution was cooled to room temperature and concentrated *in vacuo* to give the crude acid chloride as a pale yellow oil which crystallized under vacuum. This solid was dissolved in 20 ml of chloroform and added dropwise to an ice bath-cooled solution of aminoacetone hydrochloride [13] (1.77 g, 16.15 mmoles) and triethylamine (3.42 g, 33.80 mmoles) in 55 ml of chloroform. Once addition was complete the solution was stirred at room temperature for thirty minutes, washed with 25 ml of water, dried (magnesium sulfate) and evaporated to a reddish-orange solid. The crude product was flash chromatographed (silica gel; chloroform) to give 1.40 g (36% yield) of pure title compound as a pale yellow solid, mp 122-124°; ^{1}H nmr: δ 9.02 (t, 1H, J = 5.5 Hz), 7.81 (s, 2H), 4.10 (d, 2H, J = 5.5 Hz), 3.84 (s, 3H), 2.12 (s, 3H); ms: m/z (relative intensity) 241 (M^+, 12), 210 (21), 199 (79), 169 (100); ir: 3341 (br), 3096, 1723, 1633, 1565, 1264, 1100, 752 cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}NO_4S$: C, 49.78; H, 4.60; N, 5.81. Found: C, 49.92; H, 4.44; N, 5.72.

N-(5-Methoxycarbonyl-2-thenoyl)-α-aminoacetophenone (**8**).

A sample of **6** (1.50 g, 8.06 mmoles) was converted into the acid chloride as described in the previous example. This was dissolved in 10 ml of chloroform and added dropwise at ice bath temperature to a stirred solution of α-aminoacetophenone hydrochloride (1.45 g, 8.45 mmoles) and triethylamine (1.71 g, 16.90 mmoles) in 15 ml of chloroform. The resulting suspension was stirred cold for fifteen minutes and then evaporated to dryness *in vacuo*. The residual solid was stirred with 40 ml of 1*N* hydrochloric acid for fifteen minutes and recrystallized from ethanol to give 2.20 g (90% yield) of **8** as a light tan solid, mp 170-172°; ^{1}H nmr: δ, 9.19 (t, 1H, J = 5.6 Hz), 8.03 (m, 2H), 7.88 (d, 1H, J = 4.0 Hz), 7.83 (d, 1H, J = 4.0 Hz), 7.63 (m, 3H), 4.80 (d, 2H, J = 5.6 Hz), 3.85 (s, 3H); ms: m/z (relative intensity) 303 (M^+, 4), 198 (2), 169 (41), 137 (17), 105 (100); ir: 3393 (br), 1725, 1632, 1261, 747 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}NO_4S$: C, 59.39; H, 4.32; N, 4.62. Found: C, 59.46; H, 3.96; N, 4.61.

Methyl 5-(5-Methyloxazol-2-yl)-2-thiophenecarboxylate (**9**).

A stirred suspension of **7** (1.24 g, 5.14 mmoles) in 10 ml of concentrated sulfuric acid was warmed to 65° for thirty minutes and the resulting solution poured into 100 ml of water. The mixture was neutralized with solid sodium bicarbonate and the mixture extracted with ethyl acetate. The dried (magnesium sulfate) extracts were evaporated *in vacuo* to a tan solid which was purified by flash chromatography (silica gel; chloroform) to furnish 980 mg (85% yield) of **9** as an off-white solid, mp 107-109°; ^{1}H nmr: δ, 7.81 (d, 1H, J = 3.9 Hz), 7.63 (d, 1H, J = 3.9 Hz), 7.04 (t, 1H, J = 1.6 Hz), 3.85 (s, 3H), 2.37 (d, 3H, J = 1.6 Hz); ms: m/z (relative intensity) 223 (M^+, 99), 192 (100), 180 (45); ir: 3097, 1711, 1442, 1337, 1225, 1102, 750 cm^{-1}.

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.28. Found: C, 53.47; H, 3.90; N, 6.21.

Methyl 5-(5-Phenyloxazol-2-yl)-2-thiophenecarboxylate (**10**).

A 1.50 g (4.95 mmoles) portion of **8** was added in small portions to 20 ml of concentrated sulfuric acid with vigorous stirring. Once a complete solution had been achieved the solution was stirred at room temperature for fifteen minutes and then poured into 300 ml of water. Filtration and drying gave 1.31 g (93% yield) of analytically pure **10** as a light yellow solid, mp 139-141°; ^{1}H nmr: δ, 7.91 (s, 1H), 7.89 (d, 1H, J = 4.0 Hz), 7.86 (d, 1H, J = 4.0 Hz), 7.84 (m, 2H), 7.53 (m, 2H), 7.44 (m, 1H), 3.86 (s, 3H); ms: m/z (relative intensity) 285 (M^+, 100), 254 (20); ir: 1171, 1262, 743 cm^{-1}.

Anal. Calcd. for $C_{15}H_{11}NO_3S$: C, 63.14; H, 3.89; N, 4.91. Found: C, 62.92; H, 3.63; N, 4.86.

5-(5-Methyloxazol-2-yl)-2-thiophenecarboxylic Acid (**11**).

A stirred suspension of **9** (975 mg, 4.37 mmoles) in 20 ml of 2*N* sodium hydroxide was diluted with 3 ml of ethanol and warmed to 75° for ten minutes. The resulting solution was cooled briefly and acidified to *p*H 2 with concentrated hydrochloridic acid. The precipitated solid was collected, dried and recrystallized from methanol to furnish **11** (816 mg, 89% yield) as a peach-colored crystalline solid, mp 220-222°; ^{1}H nmr: δ, 7.72 (d, 1H, J = 4.0 Hz), 7.60 (d, 1H, J = 4.0 Hz), 7.02 (t, 1H, J = 1.5 Hz), 2.37 (d, 3H, J = 1.5 Hz), ms: m/z (relative intensity) 209 (M^+, 100), 194 (22), 180 (35), 166 (85), 155 (40); ir: 3300 (br), 1691, 1610, 1442, 1287, 1121, 1030, 804 cm^{-1}.

Anal. Calcd. for $C_9H_7NO_3S$: C, 51.66; H, 3.37; N, 6.70. Found: C, 51.55; H, 3.39; N, 6.58.

5-(5-Phenyloxazol-2-yl)-2-thiophenecarboxylic Acid (**12**).

A stirred suspension of **10** (1.29 g, 4.52 mmoles) in 35 ml of 2*N* sodium hydroxide was diluted with 10 ml of ethanol and refluxed for fifteen minutes. Acidification and workup as described for **11** and recrystallization from ethanol gave pure **12** (1.21 g, 98% yield) as a light yellow solid, mp 224-226°; ^{1}H nmr: δ, 7.90 (s, 1H), 7.85 (m, 2H), 7.84 (d, 1H, J = 3.9 Hz), 7.80 (d, 1H, J = 3.9 Hz), 7.53 (m, 2H), 7.42 (m, 1H); ms: m/z (relative intensity) 271 (M^+, 100), 171 (70); ir: 3233 (br), 2460, 1723, 1457, 1233 cm^{-1}.

Anal. Calcd. for $C_{14}H_9NO_3S$: C, 61.98; H, 3.34; N, 5.16. Found: C, 61.64; H, 3.48; N, 4.81.

Methyl 5-(α-Bromoacetyl)-2-thiophenecarboxylate (**13**).

A 500 mg (2.69 mmoles) sample of **6** was converted into the acid chloride as described for **7**. This solid was added in small portions at ice bath temperature to a dry ethereal solution of

diazomethane which had been prepared from 1.58 g (10.74 mmoles) of 1-methyl-3-nitro-1-nitrosoguanidine. Once addition was complete the light yellow slurry was stirred cold for one hour and then stored overnight at 0°. The suspension was placed in an ice bath and gaseous hydrogen bromide was bubbled into the mixture for a period of twenty minutes. The solution was filtered from some trace insolubles, evaporated and the residue recrystallized from methanol to give the title compound (405 mg, 57% yield) as a pale yellow crystalline solid, mp 117-119°; lit [4] mp 122-123°; ^{1}H nmr: δ 8.07 (d, 1H, J = 4.0 Hz), 7.89 (d, 1H, J = 4.0 Hz), 4.91 (s, 2H), 3.87 (s, 3H); ms: m/z (relative intensity) 262/264 (M^+, 15) 231/233 (9), 200 (29), 169 (100).

Methyl 5-(α-Aminoacetyl)-2-thiophenecarboxylate Hydrochloride (**14**).

A solution of 2.02 g (7.68 mmoles) of **13** and 1.13 g (8.06 mmoles) of hexamethylenetetramine (HMT) is 30 ml of chloroform was stirred overnight at room temperature and the precipitated quaternary salt was collected by filtration. This material (finely powdered) was suspended in 20 ml of methanol and concentrated hydrochloric acid (5 ml) was added. The resulting clear solution was stirred overnight at room temperature, the product which precipitated was collected, washed well with ethanol and dried. There was obtained 1.13 g (62% yield) of **14** as a white solid which was sufficiently pure for direct use. Satisfactory elemental analyses were difficult to obtain for this material due to its thermal sensitivity when in solution. A sample was recrystallized from methanol, mp >300° dec; ^{1}H nmr: δ, 8.51 (br s, 2H), 8.13 (d, 1H, J = 4.2 Hz), 7.92 (d, 1H, J = 4.2 Hz), 4.57 (s, 2H), 3.87 (s, 3H); ms: m/z (relative intensity) 199 (M^+, 40), 169 (100), 142 (81), 111 (76); ir: 3200 (br), 1719, 1679, 1269, 751 cm^{-1}.

Anal. Calcd. for $C_8H_9NO_3S$·HCl: C, 40.76; H, 4.28; N, 5.94. Found: C, 40.05; H, 4.05; N, 5.73.

Methyl 5-[*N*-Acetyl-(α-aminoacetyl)]-2-thiophenecarboxylate (**15**).

A stirred suspension of **14** (1.95 g, 8.27 mmoles) in 50 ml of chloroform was cooled to ice bath temperature and triethylamine (1.67 g, 16.50 mmoles) was added. The resulting solution was treated dropwise with acetyl chloride (682 mg, 8.69 mmoles) and then stirred cold for five minutes. The solution was washed with 30 ml of water, dried over magnesium sulfate and evaporated in volume to ~10 ml. The mixture was filtered and the residual solid dried to give pure **15** (1.30 g, 65% yield) as a light yellow solid, mp 170-172°; ^{1}H nmr: δ, 8.33 (t, 1H, J = 5.5 Hz), 8.05 (d, 1H, J = 4.2 Hz), 7.87 (d, 1H, J = 4.2 Hz), 4.53 (d, 2H, J = 5.5 Hz), 3.86 (s, 3H), 1.89 (s, 3H); ms: m/z (relative intensity) 241 (M^+, 65), 210 (35), 182 (62), 169 (100); ir: 3322, 1726, 1546, 1269, 749 cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}NO_4S$: C, 49.78; H, 4.60; N, 5.81. Found: C, 49.51; H, 4.27; N, 5.67.

Methyl 5-[*N*-Benzoyl-(α-aminoacetyl)]-2-thiophenecarboxylate (**16**).

A stirred suspension of **14** (1.25 g, 5.30 mmoles) in 30 ml of chloroform was cooled in an ice bath and treated with triethylamine (1.07 g, 10.57 mmoles). A 746 mg (5.31 mmoles) portion of benzoyl chloride was added dropwise and the resulting solution was stirred cold for fifteen minutes. The solution was washed with water (20 ml), 1*N* hydrochloric acid (20 ml), dried over magnesium sulfate and evaporated. The residual solid was triturated with hexanes, filtered and recrystallized from methanol to give **16** (1.46 g, 91% yield) as a light yellow solid, mp 134-136°; ^{1}H nmr: δ, 8.99 (t, 1H, J = 5.6 Hz), 8.15 (d, 1H, J = 4.3 Hz), 7.91 (d, 1H, J = 4.3 Hz), 7.89 (m, 2H), 7.52 (m, 3H), 4.73 (d, 2H, J = 5.6 Hz), 3.87 (s, 3H); ms: m/z (relative intensity) 303 (M^+, 27), 272 (3), 198 (2), 169 (25), 134 (27), 105 (100); ir: 3269 (br), 1721, 1260, 751 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}NO_4S$: C, 59.39; H, 4.32; N, 4.62. Found: C, 59.27; H, 4.28; N, 4.61.

Methyl 5-(2-Methoxyoxazol-5-yl)-2-thiophenecarboxylate (**17**).

A 1.23 g (5.10 mmoles) sample of **15** was added in small portions to 10 ml of concentrated sulfuric acid and stirred until a complete solution had been achieved. The solution was warmed to 60° for one hour, poured into 100 ml of water and carefully neutralized with solid sodium bicarbonate. The mixture was extracted with ethyl acetate, the extracts dried over magnesium sulfate and evaporated to a yellow solid which was purified by flash chromatography (silica gel; chloroform). This furnished the pure title compound (848 mg, 74% yield) as an off-white solid, mp 121-123°; ^{1}H nmr: δ, 7.79 (d, 1H, J = 4.0 Hz), 7.60 (s, 1H), 7.46 (d, 1H, J = 4.0 Hz), 3.83 (s, 3H), 2.47 (s, 3H); ms: m/z (relative intensity) 223 (M^+, 100), 192 (83), 168 (44), 137 (72); ir: 3099, 1718, 1277, 1098, 745 cm^{-1}.

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.28. Found: C, 53.70; H, 3.96; N, 6.12.

Methyl 5-(2-Phenyloxazol-5-yl)-2-thiophenecarboxylate (**18**).

A 1.10 g (3.63 mmoles) portion of **16** was dissolved in 35 ml of concentrated sulfuric acid and warmed to 65° for twenty minutes. The solution was poured into 100 ml of water with ice cooling and the formed solid extracted with ethyl acetate. The organic layer was washed with 5% sodium bicarbonate, dried (magnesium sulfate) and evaporated. The residue was recrystallized from methanol to furnish 770 mg (75% yield) of pure **18** as a greenish-yellow crystalline solid, mp 131-133°; ^{1}H nmr: δ, 8.05 (m, 2H), 7.90 (s, 1H), 7.84 (d, 1H, J = 4.2 Hz), 7.63 (d, 1H, J = 4.2 Hz), 7.56 (m, 3H), 3.85 (s, 3H); ms: m/z (relative intensity) 285 (M^+, 100), 254 (14); ir: 3101, 1706, 1449, 1327, 1106, 713 cm^{-1}.

Anal. Calcd. for $C_{15}H_{11}NO_3S$: C, 63.14; H, 3.89; N, 4.91. Found: C, 63.17; H, 3.86; N, 4.91.

5-(2-Methyloxazol-5-yl)-2-thiophenecarboxylic Acid (**19**).

A 772 mg (3.46 mmoles) portion of **17** was treated with 2*N* sodium hydroxide and worked up as described for **11**. Recrystallization from ethanol gave 632 mg (87% yield) of **19** as an off-white solid, mp 264-266°; ^{1}H nmr: δ, 7.70 (d, 1H, J = 4.0 Hz), 7.56 (s, 1H), 7.42 (d, 1H, J = 4.0 Hz), 2.47 (s, 3H); ms: m/z (relative intensity) 209 (M^+, 100), 154 (68), 137 (28); ir: 3200 (br), 1688, 1455, 1277, 748 cm^{-1}.

Anal. Calcd. for $C_9H_7NO_3S$: C, 51.66; H, 3.37; N, 6.70. Found: C, 51.54; H, 3.31; N, 6.61.

5-(2-Phenyloxazol-5-yl)-2-thiophenecarboxylic Acid (**20**).

A 635 mg (2.23 mmoles) sample of **18** was saponified as described for **12** to furnish 540 mg (89% yield) of title compound as a light yellow solid, mp 245-247° (ethanol); ^{1}H nmr: δ, 8.06 (m, 2H), 7.87 (s, 1H), 7.76 (d, 1H, J = 4.0 Hz), 7.60 (d, 1H, J = 4.0 Hz), 7.57 (m, 3H); ms: m/z (relative intensity) 271 (M^+, 59), 204 (100), 171 (45); ir: 3134 (br), 1725, 1453, 1242, 1225, 740 cm^{-1}.

Anal. Calcd. for $C_{14}H_9NO_3S$: C, 61.98; H, 3.34; N, 5.16. Found: C, 61.75; H, 3.39; N, 5.15.

2,3-Dimethyl-5-(5-methoxycarbonyl-2-thenoyl)oxazole *N*-oxide Hydrochloride (**21**).

A stirred solution of **5** (2.80 g, 16.45 mmoles) and 2,3-butanedione monoxime (1.83 g, 18.10 mmoles) in 15 ml of glacial acetic acid was treated with gaseous hydrogen chloride for a period of two hours. The resulting solution was poured into 350 ml of ether and the precipitated oil scratched until solidification was complete. Filtration and drying furnished the crude title compound (3.17 g, 66% yield) as a yellow solid. Recrystallization from ethanol gave the pure free base, mp 201-203°; ^{1}H nmr: δ, 7.84 (d, 1H, J = 3.8 Hz), 7.66 (d, 1H, J = 3.8 Hz), 3.85 (s, 3H), 2.39 (s, 3H), 2.10 (s, 3H); ms: m/z (relative intensity) 253 (M^+, 100), 236 (68), 222 (27), 169 (94); ir: 3083, 1708, 1252, 1105, 752 cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}NO_4S$: C, 52.16; H, 4.38; N, 5.53. Found: C, 52.21; H, 4.30; N, 5.50.

Methyl 5-(2,3-Dimethyloxazol-5-yl)-2-thiophenecarboxylate (**23**).

A stirred solution of crude hydrochloride **21** (2.78 g, 9.59 mmoles) in 15 ml of glacial acetic acid was treated with zinc dust (2.78 g, 42.53 mmoles) in small portions with ice bath cooling so as to keep the internal temperature at ~50°. Once addition had been completed, the mixture was stirred at room temperature for thirty minutes, filtered and poured into 200 ml of water. The precipitated product was collected, dried and recrystallized from methanol to give **23** (1.95 g, 86% yield) as a white solid, mp 118-120°; ^{1}H nmr: δ, 7.79 (d, 1H, J = 3.9 Hz), 7.59 (d, 1H, J = 3.9 Hz), 3.85 (s, 3H), 2.30 (s, 3H), 2.08 (s, 3H); ms: m/z (relative intensity) 237 (M^+, 100), 206 (95), 194 (28), 178 (32), 169 (48); ir: 2957, 1714, 1438, 1255, 1100, 749 cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90. Found: C, 55.59; H, 4.59; N, 5.84.

Methyl 5-(2-Phenyl-3-methyloxazol-5-yl)-2-thiophenecarboxylate (**24**).

The crude intermediate 2-phenyl-3-methyl-5-(5-methoxycarbonyl-2-thenoyl)oxazole *N*-oxide hydrochloride (**22**) (1.10 g, 20% yield) was prepared from **5** (2.65 g, 15.57 mmoles) and 1-phenyl-1,2-propanedione-2-oxime (2.80 g, 17.16 mmoles) as described for **21**. A portion of this crude solid (767 mg, 2.18 mmoles) was treated with zinc dust (767 mg, 11.73 mmoles) and worked up as described for **23**. The pure title compound (325 mg, 50% yield) was obtained as a bright yellow solid, mp 110-112°; ^{1}H nmr: δ, 7.86 (d, 1H, J = 4.0 Hz), 7.80 (d, 1H, J = 4.0 Hz), 7.73 (m, 2H), 7.54 (m, 2H), 7.42 (m, 1H), 3.87 (s, 3H), 2.43 (s, 3H); ms: m/z (relative intensity) 299 (M^+, 100), 268 (10), 230 (15), 199 (21), 171 (68); ir: 2955, 1716, 1452, 1318, 1259, 1098, 746 cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}NO_3S$: C, 64.19; H, 4.38; N, 4.68. Found: C, 64.33; H, 4.33; N, 4.62.

5-(2,3-Dimethyloxazol-5-yl)-2-thiophenecarboxylic Acid (**25**).

A stirred mixture of **23** (1.20 g, 5.06 mmoles) in 30 ml of 2*N* sodium hydroxide was reacted as described for **12** and gave pure title compound (1.03 g, 91% yield) as a light yellow solid after recrystallization from glacial acetic acid, mp 238-240°; ^{1}H nmr: δ, 7.70 (1H, J = 3.7 Hz), 7.56 (d, 1H, J = 3.7 Hz), 2.29 (s, 3H), 2.06 (s, 3H); ms: m/z (relative intensity) 223 (M^+, 100), 180 (36), 155 (66); ir: 3200 (br), 1686, 1241, 749 cm^{-1}.

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.28. Found: C, 53.72; H, 4.00; N, 6.23.

5-(2-Phenyl-3-methyloxazol-5-yl)-2-thiophenecarboxylic Acid (**26**).

A 725 mg (2.42 mmoles) amount of **24** was reacted with aqueous base as described for **12** and furnished 643 mg (93% yield) of a tan solid after recrystallization from ethanol, mp 246-248°; ^{1}H nmr: 7.76 (s, 2H), 7.71 (m, 1H), 7.59 (m, 2H), 7.42 (m, 1H), 2.42 (s, 3H); ms: m/z (relative intensity) 285 (M^+, 100), 216 (23), 171 (99); ir: 3400 (br), 3075, 1698, 1459, 1250, 1100, 746 cm^{-1}.

Anal. Calcd. for $C_{15}H_{11}NO_3S$: C, 63.14; H, 3.89; N, 4.91. Found: C, 63.04; H, 3.93; N, 4.93.

Methyl 5-Formyl-2-thiophenecarboxylate Oxime (**27**).

A solution of **5** (6.26 g, 36.78 mmoles), hydroxylamine hydrochloride (3.07 g, 44.18 mmoles) and pyridine (3.49 g, 44.12 mmoles) in 200 ml of ethanol was refluxed for two hours and then evaporated to dryness. The residue was dissolved in ether and washed with water. The organic layer was dried over magnesium sulfate, evaporated and the residue triturated with a small amount of ether to give pure oxime **27** (4.93 g, 72% yield) as a white solid, mp 164-167°; oxime (*Z*:*E*) ratio: (0.82:0.18); ^{1}H nmr: δ, *Z* isomer 12.52 (br s, 1H), 7.99 (s, 1H), 7.77 (d, 1H, J = 4.0 Hz), 7.50 (d, 1H, J = 4.0 Hz), 3.83 (s, 3H); *E* isomer 11.66 (s, 1H), 8.38 (s 1H), 7.74 (d, 1H, J = 4.0 Hz), 7.34 (d, 1H, J = 4.0 Hz), 3.82 (s, 3H); ms: m/z (relative intensity) 185 (M^+, 95), 154 (100), 137 (20); ir: 3400 (br), 1649, 918 cm^{-1}.

Anal. Calcd. for $C_7H_7NO_3S$: C, 45.39; H, 3.81; N, 7.56. Found: C, 45.41; H, 3.69; N, 7.48.

Methyl 5-Cyano-2-thiophenecarboxylate (**28**).

A stirred mixture of **27** (4.87 g, 26.29 mmoles) in 60 ml of acetic anhydride was refluxed overnight. The solution was cooled to room temperature, poured into 400 ml of water and shaken vigorously. The mixture was extracted with ether (3 x 100 ml) and the extracts were backwashed with 10% potassium hydroxide (3 x 50 ml). The organic layer was dried (magnesium sulfate) and concentrated to 3.50 g (80% yield) of an off-white solid, mp 76-78°; lit [22] 79°. ^{1}H nmr: δ, 8.03 (d, 1H, J = 4.2 Hz), 7.88 (d, 1H, J = 4.2 Hz), 3.87 (s, 3H); ms: m/z (relative intensity) 167 (M^+, 34), 136 (100).

Methyl 5-(*N*-Hydroxy)carboximidamido-2-thiophenecarboxylate (**29**).

A stirred mixture of **28** (2.40 g, 14.35 mmoles), hydroxylamine hydrochloride (1.20 g, 17.27 mmoles) and sodium acetate (1.59 g, 19.38 mmoles) in 60 ml of 5:1 ethanol-water was refluxed for one hour. The ethanol was evaporated, the crystalline residue triturated with water and filtered to furnish amidoxime **29** (2.54 g, 89% yield) as an off-white solid, mp 144-146°; ^{1}H nmr: δ, 9.97 (s, 1H), 7.72 (d, 1H, J = 4.0 Hz), 7.51 (d, 1H, J = 4.0 Hz), 6.11 (br s, 2H), 3.80 (s, 3H), ms m/z (relative intensity) 200 (M^+, 100), 185 (83), 169 (60); ir: 3491 (br), 1725, 1636 cm^{-1}.

Anal. Calcd. for $C_7H_8N_2O_3S$: C, 41.99; H, 4.03; N, 13.99. Found: C, 42.24; H, 3.91; N, 13.59.

Methyl 5-(5-Methyl-1,2,4-oxadiazol-3-yl)-2-thiophenecarboxylate (**30**).

A stirred slurry of **29** (734 mg, 3.67 mmoles) and acetic anhydride (1.12 g, 10.97 mmoles) in 25 ml of toluene was refluxed for twenty-four hours. The solution was evaporated almost to dryness and the solid collected by filtration to furnish the title compound as an off-white solid (547 mg, 67% yield), mp 134-136°; ^{1}H nmr: δ, 7.77 (d, 1H, J = 4.0 Hz), 7.69 (d, 1H, J = 4.0 Hz), 3.89 (s, 3H), 2.64 (s, 3H); ms: m/z (relative intensity) 224 (M^+,

99), 193 (100), 183 (58), 152 (89); ir: 1720, 1597, 887 cm^{-1}.

Exact mass. Calcd. for $C_9H_8N_2O_3S$: m/z 224.0255. Found: m/z 224.0291.

Methyl 5-(5-Trifluoromethyl-1,2,4-oxadiazol-3-yl)-2-thiophenecarboxylate (**31**).

A mixture of **29** (1.50 g, 7.49 mmoles) and trifluoroacetic anhydride (4.72 g, 22.47 mmoles) in 50 ml of toluene was warmed to 90° for five minutes and then worked up as described for **30**. There was obtained 1.67 g, (80% yield) of white crystalline solid, mp 126-127°; ^1H nmr: δ, 7.98 (d, 1H, J = 4.0 Hz), 7.93 (d, 1H, J = 4.0 Hz), 3.89 (s, 3H); ms: m/z (relative intensity) 278 (M^+, 67), 247 (100), 152 (41); ir: 1712, 1255, 912 cm^{-1}.

Exact mass. Calcd. for $C_9H_5F_3N_2O_3S$: m/z 277.9974. Found: m/z 277.9998.

Methyl 5-(5-Phenyl-1,2,4-oxadiazol-3-yl)-2-thiophenecarboxylate (**32**).

To a stirred mixture of **29** (2.25 g, 11.24 mmoles) and triethylamine (1.19 g, 11.76 mmoles) in 100 ml chloroform was added a solution of benzoyl chloride (1.66 g, 11.81 mmoles) in 10 ml of chloroform dropwise at room temperature. After stirring for forty-five minutes, the mixture was evaporated to small volume (~15 ml) and the precipitated solid collected. This gave the intermediate methyl 5-(*N*-benzoyloxy)carboximidamido-2-thiophenecarboxylate (2.49 g, 73% yield) as a white solid, mp 183-185°; ^1H nmr: δ, 8.17 (m, 2H), 7.83 (d, 1H, J = 3.9 Hz), 7.79 (d, 1H, J = 3.9 Hz), 7.67 (m, 1H), 7.55 (m, 2H), 7.29 (br s, 2H), 3.85 (s, 3H).

The crude benzoylamidoxime (2.20 g, 7.23 mmoles) was suspended in 100 ml of toluene and refluxed for forty-eight hours. The solvent was evaporated and the residue purified by flash chromatography (silica gel-chloroform) to furnish pure **32** as an off-white solid, mp 1.81 g 87% yield), mp 153-155°; ^1H nmr: δ, 8.14 (m, 2H), 7.89 (s, 2H), 7.72 (m, 1H), 7.65 (m, 2H), 3.87 (s, 3H); ms: m/z (relative intensity) 286 (M^+, 100), 255 (73), 183 (69), 152 (77); ir: 3110, 1680, 1571, 1445, 1310, 940, 745 cm^{-1}.

Exact mass. Calcd. for $C_{14}H_{10}N_2O_3S$: 286.0412. Found: C, 286.0380.

5-(5-Methyl-1,2,4-oxadiazol-3-yl)-2-thiophenecarboxylic Acid (**33**).

An 800 mg (3.57 mmoles) sample of **30** was saponified as described for **11** and furnished 663 mg (88% yield) of pure title compound after acidification and workup, mp 218-220°; ^1H nmr: δ, 7.77 (s, 2H), 2.65 (s, 3H); ms: m/z (relative intensity) 210 (M^+, 89), 169 (100), 152 (27); ir: 3429 (br), 1668, 889 cm^{-1}.

Anal. Calcd. for $C_8H_6N_2O_3S$: C, 45.70; H, 2.88; N, 13.33. Found: C, 45.69; H, 2.81; N, 13.06.

5-(5-Trifluoromethyl-1,2,4-oxadiazol-3-yl)-2-thiophenecarboxylic Acid (**34**).

A mixture of **31** (1.37 g, 4.92 mmoles) in 20 ml of 2*N* sodium hydroxide was diluted with 2 ml of methanol and warmed at 40° for fifteen minutes. The solution was cooled to room temperature, diluted with 5 ml of water and acidified to *p*H 2 with concentrated hydrochloric acid. The solution gradually deposited a crystalline solid on standing for one hour. The product was collected and dried to furnish pure **34** (690 mg, 53% yield) as an off-white solid, mp 175-177°; ^1H nmr: δ, 7.94 (d, 1H, J = 4.0 Hz), 7.83 (d, 1H J = 4.0 Hz); ms: m/z (relative intensity) 264 (M^+, 100), 247 (43), 169 (24); ir: 3430 (br), 1661, 1208, 847 cm^{-1}.

Anal. Calcd. for $C_8H_3F_3N_2O_3S$: C, 36.37; H, 1.14, 10.61. Found: C, 36.65; H, 1.18; N, 10.24.

5-(5-Phenyl-1,2,4-oxadiazol-3-yl)-2-thiophenecarboxylic Acid (**35**).

The title compound (1.28 g, 90% yield) was obtained by treating 1.50 g (5.24 mmoles) of ester **32** with aqueous base as described for **12**, mp 238-240° (ethanol); ^1H nmr: δ, 8.15 (m, 2H), 7.88 (d, 1H, J = 4.0 Hz), 7.81 (d, 1H, J = 4.0 Hz), 7.73 (m, 1H), 7.65 (m, 2H); ms: m/z (relative intensity) 272 (M^+, 100), 169 (96); ir: 3108 (br), 1681, 1559, 1365, 1307, 919, 735 cm^{-1}.

Anal. Calcd. for $C_{13}H_8N_2O_3S$: C, 57.34; H, 2.96; N, 10.29. Found: C, 57.25; H, 2.88; N, 10.13.

Methyl 5-(3-Methyl-1,2,4-oxadiazol-5-yl)-2-thiophenecarboxylate (**36**).

A 1.50 g (8.06 mmole) sample of **6** was converted into the acid chloride as described for **7**. This solid was dissolved in 5 ml of chloroform and added dropwise at room temperature to a stirred mixture of acetamide oxime [21] (657 mg, 8.87 mmoles) and triethylamine (898 mg, 8.87 mmoles) in 30 ml of chloroform. Once addition was complete the solution was stirred for one hour and then washed with water (2 x 20 ml). The solution was dried over magnesium sulfate, evaporated and the residue triturated with a small amount of toluene to afford 1.55 g (80% yield) of the intermediate *O*-(2-methoxycarbonyl-5-thenoyl)acetamide oxime, mp 150-152°; ^1H nmr: δ, 8.03 (d, 1H, J = 3.9 Hz), 7.83 (d, 1H, J = 3.9 Hz), 6.54 (br s, 2H), 3.85 (s, 3H), 1.80 (s, 3H).

The above oxime (1.43 g, 5.90 mmoles) was slurried in 75 ml of toluene and warmed to reflux overnight. The solution was evaporated almost to dryness and the off-white crystalline precipitate collected to give 1.10 g (83% yield) of the title ester, mp 154-156°; ^1H nmr: δ, 8.01 (d, 1H, J = 4.3 Hz), 7.92 (d, 1H, J = 4.3 Hz), 3.88 (s, 3H), 2.41 (s, 3H); ms: m/z (relative intensity) 224 (M^+, 98), 193 (100), 167 (30), 152 (32), 136 (82).

Exact mass. Calcd. for $C_9H_8N_2O_3S$: m/z 224.0255. Found: m/z 224.0241.

Methyl 5-(3-Phenyl-1,2,4-oxadiazol-5-yl)-2-thiophenecarboxylate (**37**).

A 1.75 g (9.40 mmoles) portion of **6** was converted into the acid chloride as described for **7**. This material was dissolved in 10 ml of chloroform and added dropwise at room temperature to a stirred of benzamide oxime [23] (1.34 g, 9.84 mmoles) and triethylamine (999 mg, 9.87 mmoles) in 50 ml of chloroform. The thick mixture was stirred for ten minutes and filtered to give *O*-(2-methoxycarbonyl-5-thenoyl)benzamide oxime (2.08 g, 73% yield) as an off-white solid, mp 189-191°; ^1H nmr: δ, 8.16 (d, 1H, J = 3.9 Hz), 7.87 (d, 1H, J = 3.9 Hz), 7.73 (m, 2H), 7.49 (m, 3H), 7.07 (br s, 2H), 3.86 (s, 3H).

The title compound (1.35 g, 70% yield) was obtained by the cyclization of 2.05 g (6.74 mmoles) of the above oxime in toluene as described for **36**, mp 104-106°; ^1H nmr: δ, 8.10 (d, 1H, J = 4.5 Hz), 8.05 (m, 2H), 7.94 (d, 1H, J = 4.5 Hz), 7.60 (m, 3H), 3.89 (s, 3H); ms: m/z (relative intensity) 286 (M^+, 100), 255 (46), 169 (72), 119 (99); ir: 3071, 2992, 1782, 1449, 1240, 1097, 748 cm^{-1}.

Exact mass. Calcd. for $C_{14}H_{10}N_2O_3S$: m/z 286.0412. Found: m/z 286.0395.

5-(3-Methyl-1,2,4-oxadiazol-5-yl)-2-thiophenecarboxylic Acid (**38**).

A 1.09 g (4.86 mmoles) sample of **36** was converted into 870 mg (85% yield) of title compound by the method described for **11**. The sample was recrystallized from methanol, mp 226-228°; ^1H

nmr: δ, 7.97 (d, 1H, J = 3.9 Hz), 7.82 (d, 1H, J = 3.9 Hz), 2.40 (s, 3H); ms: m/z (relative intensity) 210 (M^+, 100), 153 (99), 136 (52); ir: 3112 (br), 1699, 1289, 1112, 840 cm^{-1}.

Anal. Calcd. for $C_8H_6N_2O_3S$: C, 45.70; H, 2.88; N, 13.33. Found: C, 45.57; H, 2.75; N, 13.37.

5-(3-Phenyl-1,2,4-oxadiazol-5-yl)-2-thiophenecarboxylic Acid (**39**).

The title compound was obtained by basic cleavage of 1.19 g (4.16 mmoles) of **37** by the method used for **11**. Following ethanol recrystallization there was obtained 1.04 g (92% yield) of pure **39**, mp 222-224°; ^1H nmr: δ, 8.07 (d, 1H, J = 4.0 Hz), 8.06 (m, 2H), 7.86 (d, 1H, J = 4.0 Hz), 7.60 (m, 3H); ms: m/z (relative intensity) 272 (M^+, 100), 155 (18), 119 (72); ir: 3230 (br), 1740, 1561, 1362, 1265, 1101, 741 cm^{-1}.

Anal. Calcd. for $C_{13}H_8N_2O_3S$: C, 57.34; H, 2.96; N, 10.29. Found: C, 57.31; H, 2.86; N, 10.23.

5-Methoxycarbonyl-2-thiophenecarboxylic Acid Hydrazide (**40**).

A 1.86 g, (10.0 mmoles) sample of **6** was converted into the acid chloride as outlined for **7**. This material was dissolved in 25 ml of chloroform and added dropwise to an ice bath cooled solution of anhydrous hydrazine (800 mg, 25.0 mmoles) in 25 ml of chloroform under argon. Once addition was complete, the mixture was allowed to stir at room temperature for one hour and the solvent evaporated. The residual solid was suspended in 25 ml of water, stirred for fifteen minutes, filtered and recrystallized from ethanol to give 1.79 g (90% yield) of pure hydrazide **40**, mp 198-200°; ^1H nmr: δ, 10.05 (br s, 1H), 7.77 (d, 1H, J = 3.9 Hz), 7.71 (d, 1H, J = 3.9 Hz), 4.56 (br s, 2H), 3.82 (s, 3H); ms: m/z (relative intensity) 200 (M^+, 26), 169 (100); ir: 3319 (br), 3285, 1723, 1618, 1264, 746 cm^{-1}.

Anal. Calcd. for $C_7H_8N_2O_3S$: C, 41.99; H, 4.03; N, 13.99. Found: C, 41.88; H, 3.91; N, 13.86.

Methyl 5-(5-Methyl-1,3,4-oxadiazol-2-yl)-2-thiophenecarboxylate (**41**).

A 1.50 g (7.49 mmoles) amount of **40** and ethyl acetimidate hydrochloride (1.02 g, 8.25 mmoles) in 30 ml of pyridine was refluxed for four hours, cooled to room temperature and evaporated to dryness. The residual solid was dissolved in ethyl acetate and washed with water, 1*N* hydrochloric acid and 5% sodium bicarbonate. The organic layer was dried (magnesium sulfate) and evaporated to 706 mg (42% yield) of an off-white solid, mp 142-145°; ^1H nmr: δ, 7.88 (d, 1H, J = 3.9 Hz), 7.80 (d, 1H, J = 3.9 Hz), 3.87 (s, 3H), 2.58 (s, 3H); ms: m/z (relative intensity) 224 (M^+, 100), 193 (33), 169 (83), 154 (53), 137 (31); ir: 1705, 1571, 1291, 1101, 751 cm^{-1}.

Exact mass. Calcd. for $C_9H_8N_2O_3S$: m/z 224.0255. Found: m/z 224.0256.

Methyl 5-(5-Phenyl-1,3,4-oxadiazol-2-yl)-2-thiophenecarboxylate (**2**).

A stirred suspension of **40** (1.50 g, 7.49 mmoles) and triethylamine (834 mg, 8.24 mmoles) in 30 ml of *N,N*-dimethylformamide was treated dropwise with a solution of 1.16 g (8.25 mmoles) of benzoyl chloride in 5 ml of *N,N*-dimethylformamide. The mixture was stirred at room temperature for one hour, poured into 125 ml of 1*N* hydrochloric acid and extracted with ethyl acetate. The extracts were backwashed with brine, dried over magnesium sulfate and reduced in volume to ~20 ml. The precipitated solid was collected to give the intermediate *N*-(5-methoxycarbonyl-2-thenoyl)-*N'*-benzoylhydrazide (1.67 g, 73% yield) as an off-white solid, mp 184-186°.

A suspension of the above intermediate hydrazide (1.60 g, 5.26 mmoles) in 50 ml of thionyl chloride was refluxed for five hours. The excess thionyl chloride was evaporated and the residual solid triturated with hexane to furnish ester **2** as a light yellow solid (1.44 g, 96% yield), mp 163-165°, lit [6] mp 164.5°; ^1H nmr: δ, 8.09 (m, 2H), 7.97 (d, 1H, J = 3.9 Hz), 7.92 (d, 1H, J = 3.9 Hz), 7.64 (m, 3H), 3.88 (s, 3H); ms: m/z (relative intensity) 286 (M^+, 76), 255 (5), 171 (72), 105 (100).

5-(5-Methyl-1,3,4-oxadiazol-2-yl)-2-thiophenecarboxylic Acid (**42**).

A mixture of **41** (800 mg, 3.57 mmoles) in 25 ml of 2*N* sodium hydroxide was diluted with 9 ml of methanol and stirred at room temperature for two and one-half hours. The solution was filtered to remove some trace insolubles and acidified to *p*H 2 with concentrated hydrochloric acid. The precipitate was collected and dried to give 561 mg (75% yield) of pure acid **43**, mp 281-284°; ^1H nmr: δ, 7.79 (d, 1H, J = 3.9 Hz), 7.77 (d, 1H, J = 3.9 Hz), 2.57 (s, 3H); ms: m/z (relative intensity) 210 (M^+, 100), 193 (3), 155 (56), 140 (57); ir: 3443 (br), 1693, 1599, 1574, 1264, 744 cm^{-1}.

Anal. Calcd. for $C_8H_6N_2O_3S$: C, 45.70; H, 2.88; N, 13.33. Found: C, 45.81; H, 2.81; N, 13.26.

5-(5-Phenyl-1,3,4-oxadiazol-2-yl)-2-thiophenecarboxylic Acid (**43**).

The title compound (1.08 g, 81% yield) was prepared by the saponification of ester **2** (1.41 g, 4.92 mmoles) by the method described for **12**, mp 239-241° (2-propanol); ^1H nmr: δ, 8.09 (m, 2H), 7.94 (d, 1H, J = 4.0 Hz), 7.84 (d, 1H, J = 4.0 Hz), 7.64 (m, 3H); ms: m/z (relative intensity) 272 (M^+, 55), 171 (45), 155 (32), 105 (100); ir: 3246 (br), 3067, 1681, 1453, 1278, 719 cm^{-1}.

Anal. Calcd. for $C_{13}H_8N_2O_3S$: C, 57.34; H, 2.96; N, 10.29. Found: C, 57.18; H, 3.06; N, 10.18.

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