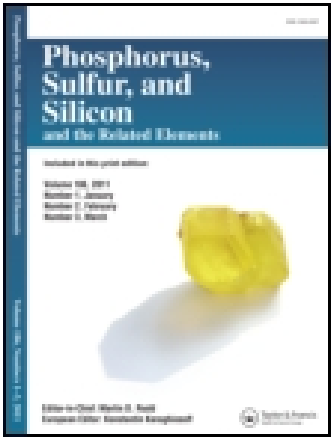

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Thiophene-Substituted 1,2,4-Oxadiazoles and Oxadiazines

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Thiophene-Substituted 1,2,4-Oxadiazoles and Oxadiazines

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Twenty one new thiophene-substituted 1,2,4-oxadiazol-5(4H)-ones, 1,2,4-oxadiazol-5(4H)-thiones, and 1,2,4-oxadiazin-5(6H)-ones were synthesized by the reaction of thiophene-ring substituted amidoximes with ethyl chloroformate, thiophosgene, and chloroacetylchloride, respectively. Their structure elucidation was performed by means of spectral measurements (IR, NMR, and MS) and physical data.

Keywords Oxadiazine; oxadiazole; spectroscopy; thiadiazole; thione; thiophene

INTRODUCTION

The amidoximes are versatile in organic synthesis as starting materials that have been widely used in assembling many heterocyclic compounds.[1–3] In particular, they and their derivatives have been reported to be used as drugs and to have considerable biological activity (antifungal, antibacterial, and antitumoral).[4–10] Synthetic procedures for substituted amidoximes, oxadiazoles, oxadiazines, and thiadiazoles have been reported by some of us previously.[11–16]

Thiophene is the most aromatic of the five-membered ring heterocycles and thus is unique in terms of reactivity, stability, and chemical and electronic properties that make it the subject of intense study. An increase in the number of thiophene derivatives was observed in superconductor research and clinical applications of potentially therapeutic products.[17] Amidoximes have also found numerous technological applications, such as uranium recovery and pharmacological uses.[18]

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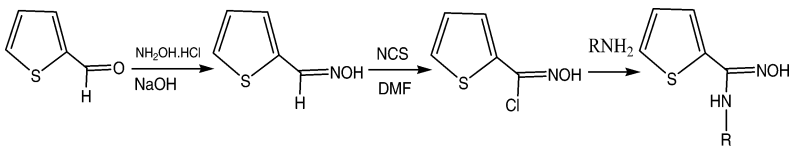
The fact that various oxadiazolones and thiones are known to show various biological activities[19–21] and also because thiophene itself has a considerable effect to enhance the previously discussed properties of the various class of potential bioactive compounds, we focused on synthesizing thiophene bearing 1,2,4-oxadiazol-5(4*H*)-one and thiones. Pharmacological and biological activities of the title compounds will be assayed in a future work.

We have previously reported the first examples of some *N*-substituted thiophene-2-carboxamidoximes[22] and data related to their acid–base equilibria.[23] In the present study, we report the first examples, to our best knowledge, of five-and six-membered thiophene substituted heterocycles (1,2,4-oxadiazol-5(4*H*)-ones) 1,2,4-oxadiazol-5(4*H*)-thiones, and (1,2,4-oxadiazin-5(6*H*)-ones) derived by the action of *N*-substituted thiophene-2-carboxamidoximes with ethyl chloroformate, thiophosgene, and chloroacetylchloride, respectively.

RESULTS AND DISCUSSION

N-substituted thiophene-2-carboxamidoximes **(4a–g)**, including a new one, **(4e)**, were obtained according to the procedure described in the literature[22] and were purified by flash chromatography (Scheme 1). Their structures were identified by means of IR, NMR, MS data, and melting points.

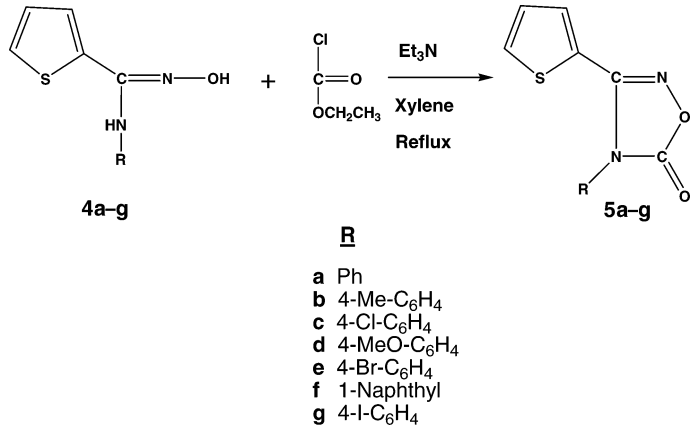


R

a Ph
b 4-Me-C_6H_4
c 4-Cl-C_6H_4
d 4-MeO-C_6H_4
e 4-Br-C_6H_4
f 1-Naphthyl
g 4-I-C_6H_4

SCHEME 1

Thiophene substituted-1,2,4-oxadiazol-5(4*H*)-ones **(5a–g)** were obtained by reacting amidoximes with ethyl chloroformate in the presence of triethylamine as a base in refluxing xylene (Scheme 2). Progress of the ring-closure reaction of amidoximes **(4a–g)** and ethylchloroformate was monitored by TLC.



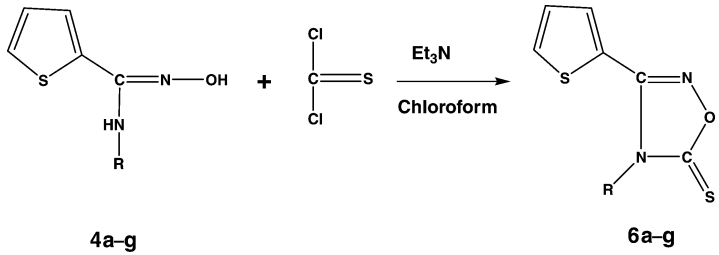
SCHEME 2

Common features of these compounds are their strong carbonyl absorptions around 1760–1780 cm^{-1} in IR spectra and the chemical shift position of a carbon atom of the carbonyl group at *ca* 165 ppm, along with the iminic carbon chemical shifts at around 155 ppm. The proton NMR spectra of these new compounds also revealed the necessary proof to elucidate their structures providing aromatic protons and methyl protons in the case of *N*-p-tolyl substitution. The data obtained are in accord with the literature values reported previously for similar structures.[24]

N-substituted thiophene-2-carboxamidoximes **(4a–g)** were reacted with thiophosgene in the presence of triethylamine as a base by cooling initially in an ice-salt bath and then standing to mix at r.t. until all the starting materials disappeared, which were monitored by TLC. After the usual workup, the crude reaction products were subjected to flash column chromatographic separation on silica gel with the specified eluants to give the thiophene substituted 1,2,4-oxadiazol-5(4*H*)-thiones **(6a–g)** (Scheme 3).

The new thiophene substituted 1,2,4-oxadiazol-5(4*H*)-thiones **(6a–g)** were identified based on their spectroscopic and physical data (IR, NMR, MS, m.p., and R_f). The disappearance of the broad hydrogen-bonded NOH absorption of the starting amidoxime and the arising of the N—C═S absorption in the IR spectra around 1350–1140 cm^{-1} is accepted as proof of the title compounds.

Upon a careful investigation of the mass spectra of **6a–g**, we can conclude that a thermal rearrangement process, thione-thiol rearrangement, occurred during mass spectral measurement as described previously.[25–27] Since the pure compounds were injected into a GC inlet of the GC-MS instrument, the account for the appearance of two peaks



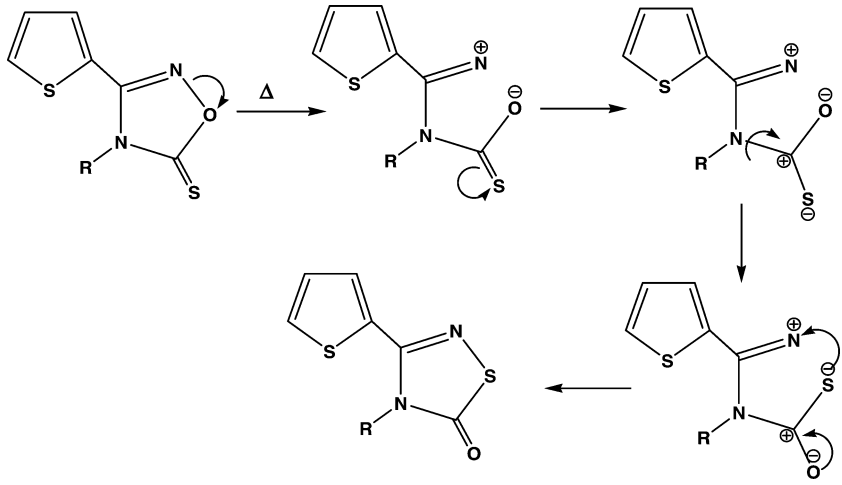
R

a Ph
b 4-Me-C_6H_4
c 4-Cl-C_6H_4
d 4-MeO-C_6H_4
e 4-Br-C_6H_4
f 1-Naphthyl
g 4-I-C_6H_4

SCHEME 3

in the total ion chromatograms of **6a, 6b, 6c, 6f**, and **6g**: 4-*N* substitution with phenyl, 4-methylphenyl, 4-chlorophenyl, 1-naphthyl, and 4-iodophenyl, respectively, is that there has been a thermal rearrangement of oxadiazolone into thiadiazolone (Scheme 4).[28]

Figures 1 and 2 show the representative total ion chromatogram of thione **(6a)** with two peaks showing both thione (retention time



SCHEME 4

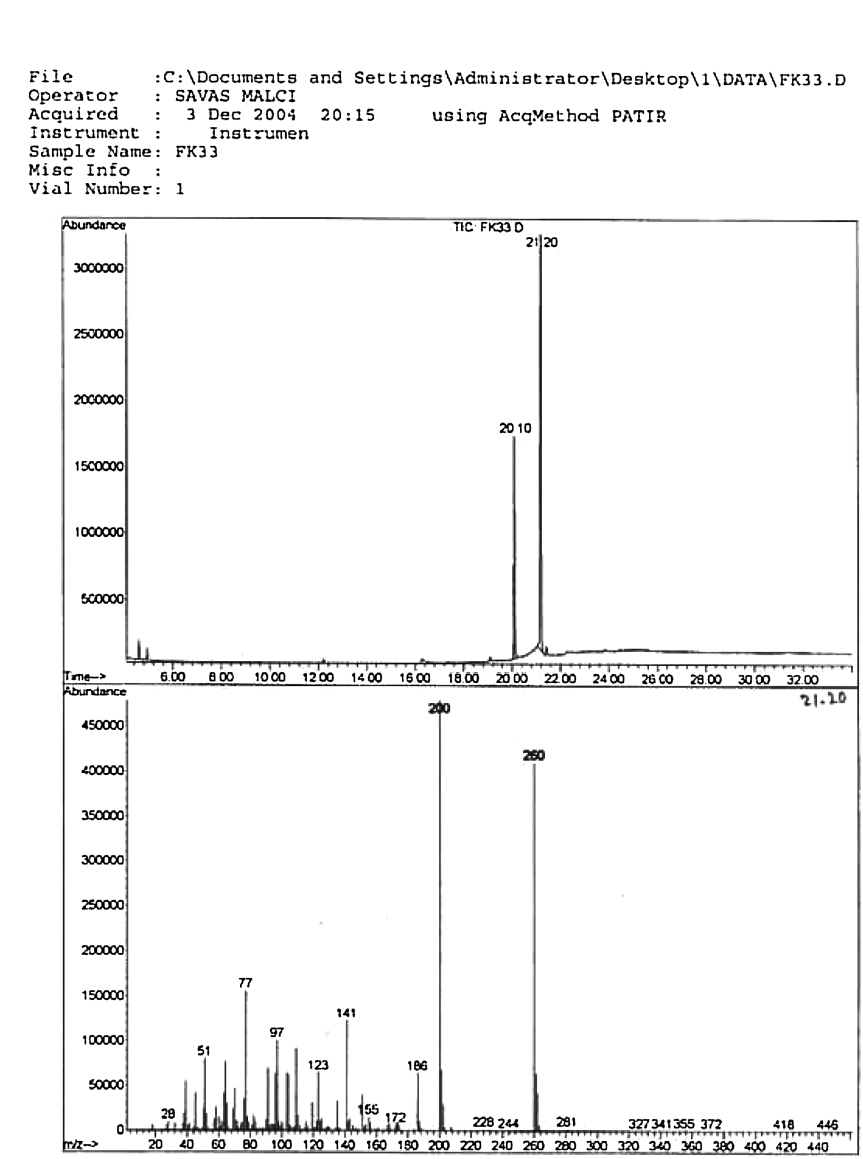


FIGURE 1

21.20 min) and the rearranged product thiadiazol-one (retention time 20.10 min).

The new thienyl substituted six-membered 1,2,4-oxadiazin-5(6*H*)-ones **(7e)** were synthesized by reacting the amidoximes **(4a–g)** with chloroacetylchloride in the presence of triethyl amine as a base (Scheme 5).

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Sample Name: FK33
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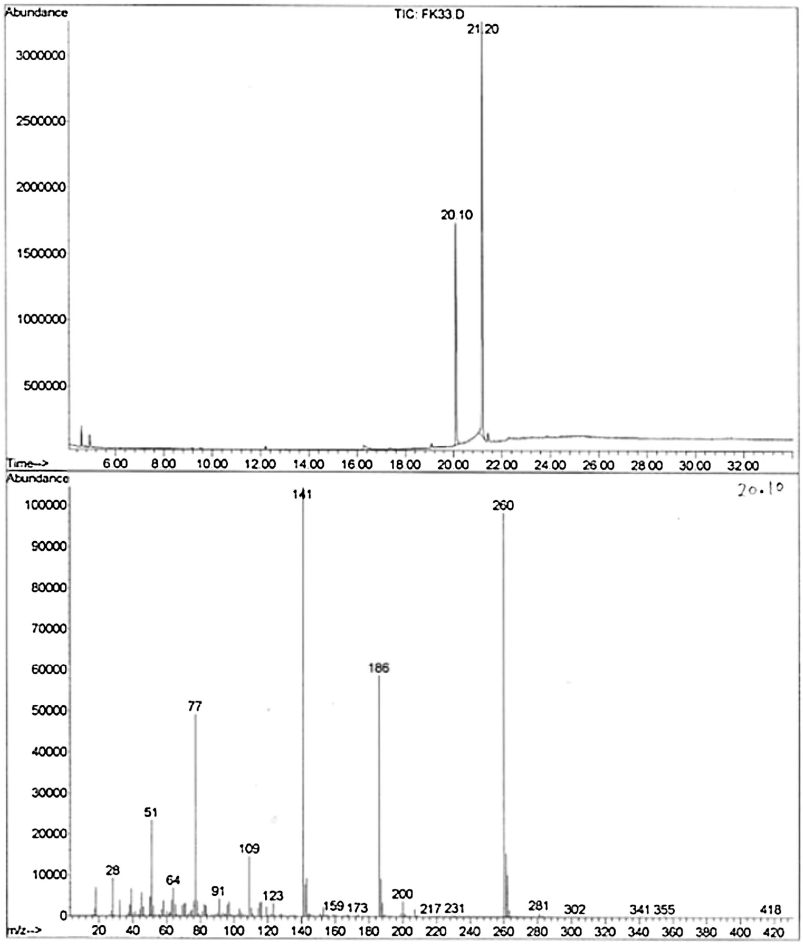
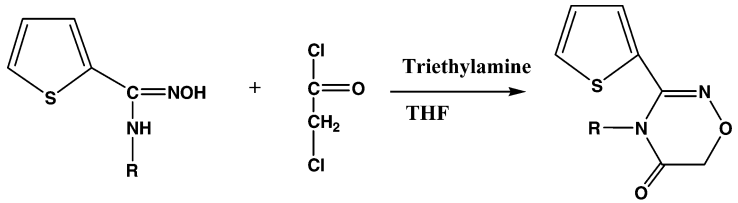


FIGURE 2

Despite the easy conversion of amidoximes into five-membered heterocyles, namely oxadiazolones and oxadiazolethiones, the ring closure leading to six-membered heterocycles, 1,2,4-oxadiazinones **(7a–g)** did not occur smoothly even if the various reaction conditions, including microwave irradiation and catalyst incorporation were tried. In this regard, we were able to obtain six-membered heterocyclic compounds



	R
7a	Ph
7b	4-Me-C_6H_4
7c	4-Cl-C_6H_4
7d	4-MeO-C_6H_4
7e	4-Br-C_6H_4
7f	1-Naphthyl
7g	4-I-C_6H_4

SCHEME 5

(7a–g) in low yields in comparison to the five-membered rings. Their structures were confirmed by spectroscopic and physical data.

EXPERIMENTAL

Thiophene-2-carbaldehyde, *N*-chlorosuccinimide, chloroacetylchloride, triethyl amine, and aromatic primary amines were purchased from Merck and Fluka. NMR data were recorded on Varian 300 and 400 MHz instruments (Palo Alto, CA). Mass spectra were recorded by a GC inlet of a Hewlett-Packard 5790 series instrument. IR spectra were run on a JASCO 430 FTIR spectrophotometer. Elemental analyses were performed on a LECO CHNS-932 (St. Joseph, MI). Melting points were determined on a Meltemp apparatus and are uncorrected. Silica gel (Merck (Darmstadt, Germany) or Fluka (Buchs SG, Switzerland), 230-400 Mesh ASTM) was used for flash column chromatography and precoated plastic plates with a fluorescent indicator for TLC. The stain solutions of permanganate, *p*-anisaldehyde, and iodine were used for visualization of the TLC spots.

Thiophene-2-carboxaldehyde oxime**(2)**, thiophene-2-hydroximoyl chloride**(3)**, *N*-phenyl thiophene-2-carboxamidoxime **(4a)**, *N*-p-tolyl thiophene-2-carboxamidoxime **(4b)**, *N*-(4-chlorophenyl) thiophene-2-carboxamidoxime **(4c)**, *N*-(4-methoxyphenyl) thiophene-2-carboxamidoxime **(4d)**, *N*-(4-bromophenyl) thiophene-2-carboxamidoxime **(4e)**, *N*-(1-naphthyl) thiophene-2-carboxamidoxime **(4f)**, and *N*-(4-iodo-

phenyl) thiophene-2-carboxamidoxime **(4g)** were obtained according to the methods described previously,[22] and their purity was checked by means of TLC, spectral, and physical data (NMR, IR and MS).

General Procedure for the Preparation of 1,2,4-Oxadiazol-5(4*H*)-ones (5a–g)

To a stirred solution of *N*-substituted thiophene-2-carboxamidoxime **4** (1.0 mmol) in xylene (25 mL) at r.t. was added triethylamine (1.0 mmol), and then ethyl chloroformate was added dropwise (1.1 mmol) in xylene (5 mL) to the previously mentioned mixture on an ice-salt bath. Then the mixture was heated under reflux for 3 h. The reaction mixture was filtered through filter paper, and the solution was evaporated at reduced pressure. The crude reaction product was crystallized from an appropriate solvent or solvent mixture specified to give pure products **(5a–g)**.

4-Phenyl-3-(2-thienyl)-1,2,4-oxadiazol-5(4*H*)-one (5a)

Yield 62%, m.p. 144–146°C (Cylohexane). R_f:0.42 (Eluant:hexane:ethyl acetate; 3:2). IR (KBr) ν (cm^{-1}): 1764 (C=O), 1573, 1546 (C=N). Anal. calcd. for $C_{12}H_8N_2O_2S$: (F.W.244.27): C, 59.00%; H, 3.30%; N, 11.47%; S, 13.13%. Found: C, 58.62%; H, 3.17%; N, 10.87%; S, 12.58%. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.56$–7.48 (m, 3H), 7.38–7.35 (m, 2H), 7.00–6.95 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 158.4$ (C=O), 153.6 (C=N), 131.6, 130.9, 130.8, 130.3, 128.2, 128.0, 123.4. MS (m/z, %): 244 (M^+, 100), 125 (19), 97 (53), 77 (51), 51 (28).

3-(2-Thienyl)-4-p-tolyl-1,2,4-oxadiazol-5(4*H*)-one (5b)

Yield 50%, m.p. 125–126°C (Cyclohexane). R_f:0.67 (Eluant:hexane:ethyl acetate; 3:2) IR (KBr) ν (cm^{-1}): 1774(C=O), 1577, 1516 (C=N). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.50$ (s, 1H), 7.32(d, 2H, $J = 8.2$ Hz), 7.25 (d, 2H, $J = 8.2$ Hz), 6.98 (s, 2H), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 157.7$ (C=O), 152.9 (C=N), 141.2, 130.9, 130.8, 21.6. MS (m/z, %): 258 (M^+, 100), 234 (95), 137 (51), 97 (49).

4-(4-Chlorophenyl)-3-(2-thienyl)-1,2,4-oxadiazol-5(4*H*)-one (5c)

Yield 42%, m.p. 111–112°C (Hexane). R_f:0.70 (Eluant:hexane:ethyl acetate; 3/2). IR (KBr) ν (cm^{-1}): 1786 (C=O), 1575, 1511 (C=N). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.54$–7.49 (m, 3H), 7.32–7.29 (m, 2H), 7.04–7.02

(m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 158.4$ (C=O), 153.3 (C=N), 136.9, 130.1, 129.4, 128.5, 128.1, 131.1, 130.6, 123.0, 131.0. MS (m/z, %): 278 (M^+, 100), 234 (95), 137 (51), 97 (49).

4-(4-Methoxyphenyl)-3-(2-thienyl)-1,2,4-oxadiazol-5(4*H*)-one (5d)

Yield 60%, m.p. 118–120°C (Cyclohexane). R_f:0.43 (Eluant:hexane:ethyl acetate; 3:2). IR (KBr) ν (cm^{-1}): 1769 (C=O), 1606, 1576, 1515 (C=N). Anal. calcd. for $C_{13}H_{10}N_2O_3S$: (F.W.274.30): C, 56.92%; H, 3.67%; N, 10.21%; S, 11.69%. Found: C, 57.30%; H, 3.33%; N, 9.55%; S, 11.16%. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.49$ (d, 1H, $J = 6.44$ Hz), 7.28(d, 2H, $J = 9.08$ Hz), 7.03 (m, 4H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 161.2$ (C=O), 158.7 (C=N), 153.8, 130.9, 130.8, 129.6, 128.0, 124.0, 123.5, 115.5, 55.9 (O-$\underline{C}H_3$). MS (m/z, %): 274 (M^+, 100), 230 (100), 216 (100), 187 (42), 149 (14), 133 (17), 106 (24), 97 (6), 78 (27).

4-(4-Bromophenyl)-3-(2-thienyl)-1,2,4-oxadiazol-5(4*H*)-one (5e)

Yield 63%, m.p. 112–113°C (Diethylether/hexane). R_f:0.41 (Eluant:hexane:ethyl acetate; 3:1). IR (KBr)ν (cm^{-1}): 1784 (C=O), 1574, 1510 (C=N). Anal. calcd. for $C_{12}H_7BrN_2O_2S$: (F.W.323.17): C, 44.60%; H, 2.18%; N, 8.67%; S, 9.92%. Found: C, 45.16%; H, 1.82%; N, 8.12%; S, 9.44%. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.67$ (d, 2H, $J = 9.0$ Hz), 7.53 (dd, 1H, $J = 6.6$, 5.1 Hz), 7.25(d, 2H, $J = 5.7$ Hz), 7.02 (m, 2H). ^{13}C NMR ($CDCl_3$, 75MHz): $\delta = 158.0$(C=O), 153.3 (C=N), 131.0, 130.6, 129.7, 128.2, 131.2, 133.6, 125.0, 123.0. MS (m/z, %): 322 (M^+, 100), 280 (100), 199 (18), 181 (32), 155 (19), 97 (45).

4-(1-Naphthyl)-3-(2-thienyl)-1,2,4-oxadiazol-5(4*H*)-one (5f)

Yield 54%, m.p. 187–188°C (Cyclohexane). R_f:0.40 (Eluant:hexane: ethyl acetate; 3:2). IR (KBr) ν (cm^{-1}): 1769 (C=O), 1597, 1576, 1555, 1525, 1508 (C=N). Anal. calcd. for $C_{16}H_{10}N_2O_2S$: (F.W.294.33): C, 65.29%; H, 3.42%; N, 9.52%; S, 10.89%. Found: C, 66.02%; H, 3.66%; N, 9.31%; S, 10.53%. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.08$ (d, 1H, $J = 6.9$ Hz), 7.96 (d, 1H, $J = 8.4$ Hz), 7.67–7.55 (m, 5H), 7.35 (t, 1H), 6.82 (t, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 158.6$ (C=O), 154.4 (C=N), 134.7, 131.9, 130.9, 130.5, 130.3, 129.1, 128.7, 128.0, 127.9, 127.8, 127.6, 125.7, 123.2, 121.5. MS (m/z, %): 294 (M^+, 100), 250 (76), 205 (19), 153 (68), 97 (14).

4-(4-Iodophenyl)-3-(2-thienyl)-1,2,4-oxadiazol-5(4*H*)-one (5g)

Yield 40%, m.p. 181–183°C (Cyclohexane). R_f:0.66 (Eluant:hexane:ethyl acetate; 3:2) IR (KBr) ν (cm^{-1}): 1769 (C=O), 1577, 1508 (C=N). ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 8.02$ (d, 1H, $J = 9.08$ Hz), 7.58–7. 45 (m, 3H), 7.25 (m, 1H) 7.01 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 157.9$ (C=O), 153.1 (C=N), 140.8, 134.4, 132.8, 131.1, 130.6, 130.4, 128.1, 123.4, 99.5. MS (m/z, %): 370 (M^+ could not be observed), 326 (M^+-CO_2, 100), 199 (60), 172 (43), 63 (16).

General Procedure or the Preparation of 1,2,4-Oxadiazole-5(4*H*)-thiones (6a–g)

To a solution of *N*-substituted thiophene-2-carboxamidoxime **4** (0.40 mmol) in chloroform (10 mL) at r.t. was added triethylamine (0.80 mmol), and thiophosgene (0.40 mmol) in chloroform (5 mL) was added dropwise on an ice-salt bath. The reaction mixture was stirred for 5 h at r.t. The solvent was evaporated at reduced pressure. The reaction mixture was extracted with acetone and filtered. Acetone was evaporated, and the remaining solid was crystallized from a solvent specified to give pure products **(6a–g)**.

4-Phenyl-3-(2-thienyl)-1,2,4-oxadiazole-5(4*H*)-thione (6a)

Yield 40%, m.p. 156–157°C (cyclohexane). R_f:0.72 (Eluant:benzene: ethyl alcohol; 5:1). IR (KBr) ν (cm^{-1}): 1578, 1556(C=N), 1348, 1141cm^{-1}(N–C=S). Anal. calcd. for $C_{12}H_8N_2O_2S$: (F.W.244.27): C, 59.00%; H, 3.30%; N, 11.47%; S, 13.13%. Found: C, 58.62%; H, 3.17%; N, 10.87%; S, 12.58%. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.66$–7.60 (m, 3H), 7.53 (dd, 1H, $J = 4.04$, 2.04 Hz), 7.43–7.39 (m, 2H), 7.03 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 187.2$ (C=S), 154.5 (C=N), 133.2, 131.4, 131.1, 130.3, 128.5, 127.9, 121.8. MS (thione) (m/z, %): 260 (M^+, 88), 200 (100), 141 (26), 97 (21), 77 (33). MS (thia) (m/z, %): 260 (M^+, 94), 186 (56), 141 (100), 77 (47).

3-(2-Thienyl)-4-p-tolyl-1,2,4-oxadiazol-5(4*H*)-thione (6b)

Yield 59%. m.p. 127–128°C (Hexane). R_f:0.47 (EtOH:Benzene; 1:6). IR (KBr) ν (cm^{-1}): 1575, 1512, 1332, 1227, 1144 (N–C=S). ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.54$ (d, 1 H, $J = 6.9$ Hz), 7.42 (d, 2H, $J = 8.0$ Hz), 7.29 (d, 2H, $J = 8.4$ Hz), 7.01 (m, 2H), 2.50 (s, 3H). ^{13}C NMR $\delta = (CDCl_3$, 100 MHz): 186.4 (C=S), 141.3 (C=N), 130.7, 130.8, 21.4. MS (thione)

(m/z, %): 274 (M^+, 94), 214 (100), 200 (11), 104 (14), 91 (30), 77 (12). MS (thia) (m/z, %): 274 (M^+, 100), 200 (72), 91 (32), 65 (28).

4-(4-Chlorophenyl)-3-(2-thienyl)-1,2,4-oxadiazole-5(4*H*)-thione (6c)

Yield 57%, m.p. 160–161°C (Hexane). R_f:0.74 (Eluant:EtOH:benzene; 1:5). IR (KBr) ν (cm^{-1}): 1575(C=N), 1351, 1231, 1157(N–C=S). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.61$(d, 2H, $J = 8.6$ Hz), 7.57 (dd, 1H, $J = 5.1$, 1.4 Hz), 7.36 (d, 2H, $J = 8.6$ Hz), 7.10 (dd, 1H, $J = 3.8$, 1.2 Hz), 7.06(t, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 187.1$ (C=O), 154.4 (C=N), 137.4, 131.6, 131.6, 131.4, 131.0, 130.3, 129.9, 129.8, 128.3, 128.1. MS (thione) (m/z, %): 294 (M^+, 68), 234 (100), 141 (55), 109 (28). MS (thia) (m/z, %): 294 (M^+, 78), 220 (60), 141 (100), 111 (22).

4-(4-Methoxyphenyl)-3-(2-thienyl)-1,2,4-oxadiazole-5(4*H*)-thione (6d)

Yield 58%, m.p. 136–137°C (Hexane). R_f:0.73 (Eluant:EtOH:benzene; 1:6). IR (KBr) ν (cm^{-1}): 1578(C=N), 1334, 1254, 1148 (N–C=S). Anal. calcd. for $C_{13}H_{10}N_2O_2S_2$: (F.W.290.36): C, 53.77%; H, 3.47%; N, 9.65%; S, 22.09%. Found: C, 54.30%; H, 3.43%; N, 10.48%; S, 22.09%. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.54$ (dd, 1H, $J = 3.8$, 0.9 Hz), 7.30 (d, 2H, $J = 8.8$ Hz), 7.12 (dd, 1H, $J = 3.8$, 1.2 Hz), 7.10 8d, 2H, $J = 8.8$ Hz), 7.04(dd, 1H, $J = 4.8$, 3.8 Hz), 3.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 187.5$(C=S), 161.4 (C=N), 154.8, 131.4, 131.2, 129.7, 127.9, 125.4, 121.9, 115.5, 55.6. MS (thione) (m/z, %) 290 (M^+, 88), 216 (83), 149 (52), 141 (100).MS (thia) not observed.

4-(4-Bromophenyl)-3-(2-thienyl)-1,2,4-oxadiazole-5(4*H*)-thione (6e)

Yield 47%, m.p. 151–152°C (Hexane). R_f:0.72 (Eluant:EtOH:benzene; 1/5). IR (KBr) ν (cm^{-1}):1575 (C=N), 1337, 1297, 1157 (N–C=S). Anal. calcd. for $C_{12}H_7BrN_2OS_2$: (F.W.339.23): C, 42.49%; H, 2.08%; N, 8.26%; S, 18.90%. Found: C, 43.19%; H, 2.11%; N, 8.06%; S, 18.88%. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.76$ (d, 2H, $J = 8.7$ Hz), 7.56 (dd, 1H, $J = 4.9$, 1.3 Hz), 7.28 (d, 2H, $J = 8.7$ Hz), 7.10 (dd, 1H, $J = 3.9$, 1.2 Hz), 7.06 (dd, 1H, $J = 5.0$, 3.9 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 186.8$ (C=S), 154.3(C=N), 133.8, 133.7, 131.4, 131.2, 129.7, 127.9, 125.4, 121.9, 115.5, 55.6.MS (thione) (m/z, %), 340 (M^+, 52), 266 (36), 199 (13), 183 (35), 155 (21), 141 (100), 97 (24).MS (thia) not observed.

4-(1-Naphthyl)-3-(2-thienyl)-1,2,4-oxadiazole-5(4*H*)-thione (6f)

Yield 48%, m.p. 172–173°C (Hexane). R_f:0.74 (Eluant:EtOH:benzene; 1:5). IR (KBr) ν (cm^{-1}): 1580, 1503 (C=N), 1333, 1149, 1108 (N—C=S). Anal. calcd. for $C_{16}H_{10}N_2OS_2$: (F.W.310.39): C, 61.91%; H, 3.25%; N, 9.03%; S, 20.66%. Found: C, 61.56%; H, 3.36%; N, 8.48%; S, 19.49%. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.18$ (d, 1H, $J = 8.1$ Hz), 8.05 (d, 1H, $J = 7.8$ Hz), 7.70–7.55 (m, 5H), 7.40 (dd, 1H, $J = 9.5$, 1.2 Hz), 6.91 (dd, 1H, $J = 4.7$, 1.0 Hz), 6.87 (t, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 187.2$ (C=S), 155.3 (C=N), 134.5, 131.9, 131.3, 131.0, 129.5, 129.3, 128.9, 128.5, 127.8, 127.7, 127.6, 127.5, 125.6, 121.6, 121.4. MS (thione) (m/z, %): 310 (M^+, 1), 250 (100), 207 (12), 140 (10). MS (thia) (m/z, %): 310 (M^+, 100), 236 (94), 169 (46), 141 (60).

4-(4-Iodophenyl)-3-(2-thienyl)-1,2,4-oxadiazole-5(4*H*)-thione (6g)

Yield 74%, m.p. 206–207°C (Hexane). R_f:0.68 (Eluant:EtOH:benzene; 1:5). IR (KBr) ν (cm^{-1}): 1577(C=N), 1334, 1155, 1055 (N—C=S). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.07$ (d, 1H, $J = 8.1$ Hz), 7.62 (t, 1H), 7.54(m, 1H), 7.37(t, 2H), 7.11–7.03 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 185.9$ (C=S), 154.0 (C=N), 140.8, 135.8, 132.7, 131.5, 130.4, 130.1, 128.0, 121.7, 98.6.MS (thione) (m/z, %): 386 (M^+, 36), 326 (69), 259 (71), 245 (48), 231 (100), 109 (38), 90 (48). MS (thia)(m/z, %): 386 (M^+, 100), 312 (36), 259 (13), 231 (32), 150 (61), 141 (55), 109 (13).

General Procedure for the Preparation of 1,2,4-oxadiazin-5(6*H*)-ones (7a–g)

To a solution of *N*-substituted thiophene-2-carboxamidoxime **(4)** (0.5 mmol) in THF (10 mL) at r.t. was added triethylamine (1.1 mmol), and chloroacetyl chloride (0.6 mmol) in THF(5 mL) was added dropwise on an ice-salt bath. Then the mixture was stirred and heated under the reflux for 2 d. The reaction mixture was filtered, and the solution was evaporated at a reduced pressure. The residual solid was subjected to flash column chromatography (eluant:dichloromethane-hexane, 1:1). The column-separated product was recrystallized from hexane to give pure products **(7a–g)**.

4-Phenyl-3-(2-thienyl)-4*H*-1,2,4-oxadiazin-5(6*H*)-one (7a)

Yield 40%, m.p. 173–174°C (Hexane). R_f:0.74 (EtOH:Benzene; 1:6). IR (KBr) ν (cm^{-1}): 1726 (C=O), 1551 (C=N), 1433, 1346, 1303, 1016. Anal.

calcd. for $C_{13}H_{10}N_2O_2S$: (F.W.258.30): C, 60.45%; H, 3.90%; N, 10.85%; S, 12.41%. Found: C, 60.51%; H, 3.84%; N, 11.19%; S, 11.96%. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.25$–7.41 (m, 6H), 6.76–6.83 (m, 2H), 4.65 (s, 2H, OCH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 163.9$ (C=O), 150.8 (C=N), 135.1, 130.9, 130.5, 129.3, 129.2, 128.8, 128.3, 127.1, 68.4. MS (m/z,%): 258 (M^+, 100), 200 (59), 186 (16), 105 (14), 97 (21), 77 (39).

4-(4-Methylphenyl)-3-(2-thienyl)-4*H*-1,2,4-oxadiazin-5(6*H*)-one (7b)

Yield 43%, m.p. 154–156°C (Hexane). R_f:0.76 (EtOH:Benzene; 1:6). IR (KBr) ν (cm^{-1}): 1730 (C=O), 1558 (C=N), 1440, 1361, 1283. Anal. calcd. for $C_{13}H_9ClN_2O_2S$: (F.W.292.74): C, 54.34%; H, 3.10%; N, 9.57%; S, 10.95%. Found: C, 54.01%; H, 3.39%; N, 9.58%; S, 10.96%. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.32$ (d, 1H, $J = 1.1$ Hz), 7.21 (d, 2H, $J = 8.6$ Hz), 7.14 (d, 2H, $J = 9.0$ Hz), 6.78–6.85 (m, 2H), 4.62 (s, 2H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 163.5$ (C=O), 150.3 (C=N), 138.4, 131.9, 130.4, 130.1,129.4, 128.8, 127.4, 126.6, 67.9 (O-$\underline{C}H_2$), 20.6 ($\underline{C}H_3$). MS (m/z, %): 272 (M^+, 100), 214 (52), 200 (23), 105 (15).

4-(4-Chlorophenyl)-3-(2-thienyl)-4*H*-1,2,4-oxadiazin-5(6*H*)-one (7c)

Yield 50%, m.p. 124–126°C (Hexane). R_f:0.80 (EtOH:Benzene; 1:6). IR (KBr) ν (cm^{-1}): 1732 (C=O), 1571, 1522 (C=N), 1493, 1306, 1221, 1090, 1016. ^{1}HNMR ($CDCl_3$, 400 MHz): $\delta = 7.30$–6.72 (m, 7H), 4.53 (s, 2H). ^{13}CNMR ($CDCl_3$, 100 MHz): $\delta = 163.8$ (C=O), 150.7 (C=N), 130.5, 129.4, 129.3, 127.5, 127.1, 114.5, 68.4, 55.4. MS (m/z, %): 292 (M^+, 100), 234 (47), 220 (14), 105 (23).

4-(4-Methoxyphenyl)-3-(2-thienyl)-4*H*-1,2,4-oxadiazin-5(6*H*)-one (7d)

Yield 53%, m.p. 131–132°C (Hexane). R_f:0.70 (EtOH:Benzene: 1:6). IR (KBr) ν (cm^{-1}): 1726 (C=O), 1608, 1564, 1511 (C=N). Anal. calcd. for $C_{14}H_{12}N_2O_3S$: (F.W.288.32): C, 58.32%; H, 4.20%; N, 9.72%; S, 11.12%. Found: C, 58.32%; H, 3.66%; N, 10.09%; S, 10.86%. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.31$ (d, 2H, $J = 3.9$ Hz), 7.17 (d, 1H, $J = 6.8$ Hz), 6.91 (d, 2H, $J = 8.6$ Hz), 6.85 (t, 1H), 6.65 (dd, 1H, $J = 9.3$, 1.1 Hz), 4.62 (s, 2H, OCH_2), 3.83 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 164.1$ (C=O), 159.6 (C=N), 150.9, 130.9, 130.5, 129.4, 129.3,127.5, 127.1,

114.5, 68.4 (O<u>C</u>H$_2$), 55.4 (O<u>C</u>H$_3$). MS (m/z, %): 288 (M$^+$, 100), 230 (45), 215 (100), 135 (17).

4-(4-Bromophenyl)-3-(2-thienyl)-4*H*-1,2,4-oxadiazin-5(6*H*)-one (7e)

Yield 50%, m.p. 155–156°C (Hexane). R$_f$:0.87 (EtOH:Benzene; 1:6). IR (KBr) ν (cm^{-1}): 1731 (C=O), 1570 (C=N). Anal. calcd. for $C_{13}H_9BrN_2O_2S$: (F.W.337.19): C, 46.31%; H, 2.69%; N, 8.31%; S, 9.51%. Found: C, 46.52%; H, 1.96%; N, 9.53%; S, 8.9%. ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.44$ (d, 2H, $J = 8.4$ Hz), 7.25 (dd, 1H, $J = 5.0$, 1.1 Hz), 7.04 (d, 2H, $J = 8.7$ Hz), 6.78 (dd, 1H, $J = 8.9$, 5.1 Hz), 6.72 (dd, 1H, $J = 9.3$, 1.1 Hz), 4.50 (s, 2H, OCH$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz): $\delta = 163.8$ (C=O), 150.5 (C=N), 134.2, 132.5, 131.0, 130.2, 129.6, 127.3, 122.7, 68.4. MS (m/z, %): 336 (M$^+$, 100), 280 (83), 183 (33), 155 (20), 97 (28).

4-(1-Naphthyl)-3-(2-thienyl)-4*H*-1,2,4-oxadiazin-5(6*H*)-one (7f)

Yield 35%, m.p. 158–159°C (Hexane). R$_f$:0.73 (EtOH:Benzene; 1:6). IR (KBr) ν (cm^{-1}): 1726 (C=O), 1604, 1572 (C=N). ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.89$–6.44 (m, 10H), 4.85 (q, 2H, OCH$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz): $\delta = 164.0$ (C=O), 148.9 (C=N), 135.5, 134.2, 130.4, 130.1, 129.2, 128.4, 128.3, 127.6, 127.0, 126.9, 126.8, 126.7, 126.4, 126.3, 125.3,125.2, 125.1, 122.1, 121.8, 68.5 (O<u>C</u>H$_2$).MS (m/z, %): 308 (M$^+$, 100), 249 (65), 153 (52), 140 (24), 127 (36).

4-(4-Iodophenyl)-3-(2-thienyl)-4*H*-1,2,4-oxadiazin-5(6*H*)-one (7g)

Yield 26%, m.p. 152–154°C (Hexane). R$_f$:0.65 (EtOH:Benzene; 1:6). IR (KBr) ν (cm^{-1}): 1730 (C=O), 1572 (C=N). ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.91$ (d, 1H, $J = 1.3$ Hz), 7.36–6.83 (m, 6H), 4.69 (q, 2H,OCH$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz): $\delta = 162.7$ (C=O), 149.6 (C=N), 140.2, 137.7, 130.9, 130.8, 130.6, 129.7, 129.5, 129.3, 127.1, 99.5, 68.3 (O<u>C</u>H$_2$). MS (m/z, %): 384(M$^+$,100), 326 (25), 312 (20), 257 (27), 199 (28), 155 (18), 132 (59), 90 (32), 76 (36).

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