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SYNTHESIS OF 2-SUBSTITUTED THIOPYRANO[3,2-*b*][1,4]BENZOXAZINE-2,3-DICARBOXYLIC ACID DIMETHYL ESTERS

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Abstract – The titled compounds were prepared by the reaction of 4*H*-benzo[1,4]-oxazin-3-thiones with dimethyl acetylenedicarboxylate. The 3-thione intermediates were obtained by treating 4-methyl-4*H*-benzo[1,4]oxazin-3-ones with P_2S_5 followed by piperidine-mediated condensation of the resulting 4-methyl-4*H*-benzo[1,4]oxazin-3-thiones with various aromatic and heteroaromatic aldehydes. Oxazine-3-thiones, however, failed to react with several benzyne intermediates.

INTRODUCTION

During the course of our ongoing investigation of the use of arynes in heterocyclic synthesis, we prepared a wide variety of benzo and naphtho fused heterocycles possessing at least two hetero ring atoms by the reaction of arynes or 2,3-didehydronaphthalene with potential cyclic-forming reagents. For example, various arynes and 2,3-didehydronaphthalene react with Barton sulfur esters to give benzo[4,5]thieno[2,3-*b*]pyridines[1] and naphtho[2',3':4,5]thieno[2,3-*b*]pyridines,[2] respectively, and with Barton selenium esters to give the corresponding benzo[4,5]selenolo[2,3-*b*]pyridines[3] and naphtho[2',3':4,5]thieno[2,3-*b*]pyridines.[2] Thiazadienes also react with 2,3-didehydronaphthalene to give 4*H*-naphtho[*2,3-b*][1,3]-thiazines, whereas selenoazadienes react with 2,3-didehydronaphthalene and various benzynes to give 4*H*-naphtho[2,3-*b*]- and 4*H*-1,3-benzoselenazines, respectively.[2]

We subsequently investigated the reaction of dienophiles with dienes in which one of the double bonds of the diene was part of or attached to a heterocyclic ring. We were first attracted to 3*H*-benzo[*b*]indolin-2-ones since several members of this ring system exhibit inhibitory properties against various receptor tyrosinekinases.[5] However these heterocyclic dienes did not undergo [4+2] cycloaddition reactions with

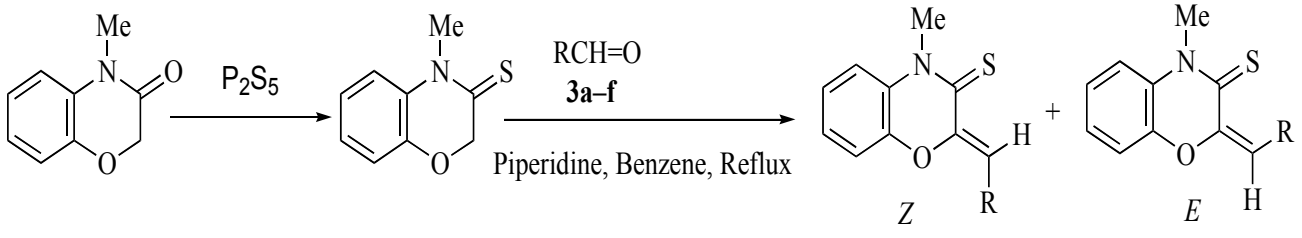
strong dienophiles such as arynes and dimethyl acetylenedicarboxylate. However, we found that the thio analogs, *i.e*. 3*H*-benzo[*b*]thiophen-2-ones,[6] in which C=O group has been converted to a C=S group, did react with a variety of arynes and dimethyl acetylenedicarboxylate to give benzothiopyrano[2,3-*b*]indoles in good yields.[7]

We next sought heterocyclic dienes that would deliver a 1,4-benzoxazine or 1,4-benzothiazine moiety *via* a [4+2] cycloaddition reaction. This basic ring structure is found in molecules which exhibit plant resistance factors against microbial diseases and insects,[8] analgesic,[9] antimicrobial,[10] and potassium channel modulating[11] properties, while 1,4-benzothiazin-3-(4*H*)-ones, like semotiadial, are antihypertensive drugs,[12] calcium antagonists[13] and highly potent inhibitors of LDL-oxidation.[14] Indeed, the diverse biological activity and desirable pharmacokinetics of these compounds has spurred the synthesis of compounds with the 1,4-benzoxazin and 1.4-benzothiazine skeleton.[15,16]

Although 1,4-benzoxazin-3-(4*H*)-ones and 1,4-benzothiazin-3-(4*H*)-ones might be worthy candidates for study, previous workers[17] have shown that the former ketones, which possess a C=O functional group attached to C-3 of the oxazine ring, are unaffected by nucleophiles, dienophiles and dienes, indicating the lack of α,β-unsaturated carbonyl character in the enone. However, they did react with nitrones in a [2+2] cycloaddition process to give a mixture of two diastereomeric cycloadducts. We subsequently found that 1,4-benzothiazin-3-(4*H*)-ones, which possess a thio carbonyl group attached to C-3 of the oxazine ring, do behave as α,β-unsaturated carbonyl moieties by undergoing [4+2] cycloaddition reactions with dimethyl acetylenedicarboxylate to give titled compounds. The results are reported herein.

RESULTS AND DISCUSSION

As shown in Scheme 1, the starting 4-methyl-4*H*-benzo[1,4]oxazine-3-thiones (**4** and **5**) were prepared by



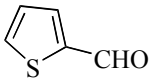
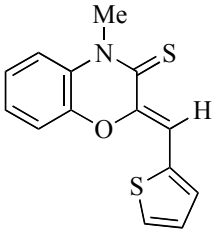
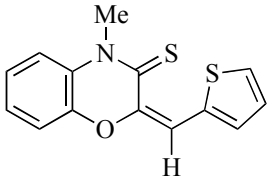
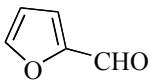
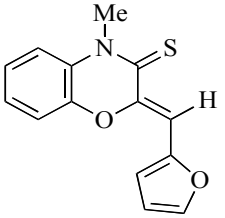
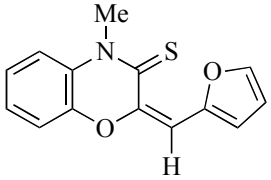
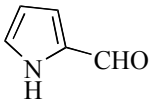
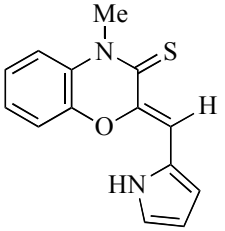
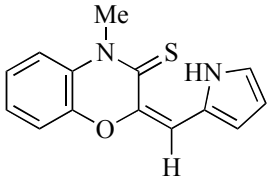
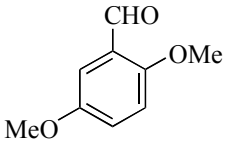
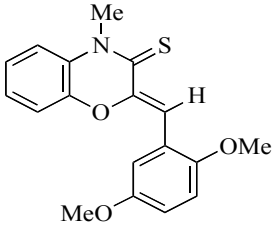
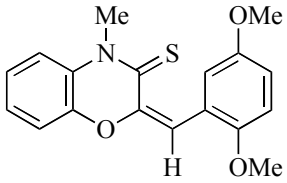
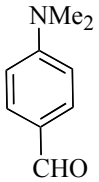
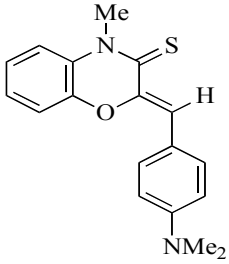
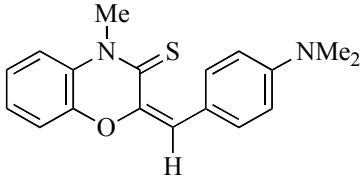
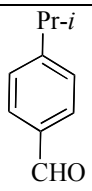
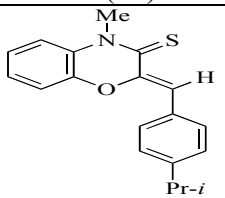
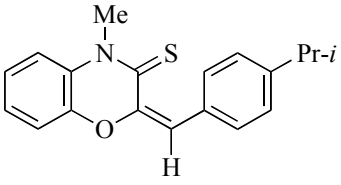
1 **2** **4** **5**

SCHEME 1

converting 4-methyl-4*H*-benzo[1,4]oxazin-3-one (**1**) to 4-methyl-4*H*-benzo[1,4]oxazin-3-thione (**2**) with P_2S_5 followed by piperidine mediated condensation of **2** with various aldehydes (**3a–f**) (Scheme 1) in refluxing benzene.[18] The results are listed in Table 1.

The *Z*- configuration was assigned to the three 3-substituted aryl derivatives (Entries 4–6) (**4d–f**) and the

Table 1

Entry	3	**4** (yield, %)	**5** (yield, %)	Ratio of **4**:**5** in EtOH[a]
1	 **3a**	 **4a** (88)	 **5a** (trace)	2.7: 1
2	 **3b**	 **4b** (trace)	 **5b (**79)	3.5:1
3	 **3c**	 **4c** (86)	 **5c** (trace)	1.1:1
4	 **3d**	 **4d** (84)	 **5d** (trace)	-
5	 **3e**	 **4e** (78)	 **5e (trace)**	1.1:1
6	 **3f**	 **4f** (76)	 **5f** (trace)	-

a. Ratio of **4** to **5** determined by HPLC analysis.

3-substituted thiophen-2-yl derivative (Entry 1) (**4a**) since the ^{1}H NMR spectrum of derivative exhibited an alkenic hydrogen chemical shifts in the range 7.78–7.90 ppm. These chemical shifts are in the same range as those previously reported for similarly configured 3*H*-benzo[*b*]thiophen-2-ones[6] and indolin-2-ones.[19] Furthermore, the structure of **4a** was determined by X-Ray analysis; an ORTEP for **4a** in shown in Figure 1. The preference of the three aryl derivatives (**4d–f)** for the *Z* configuration is most likely due

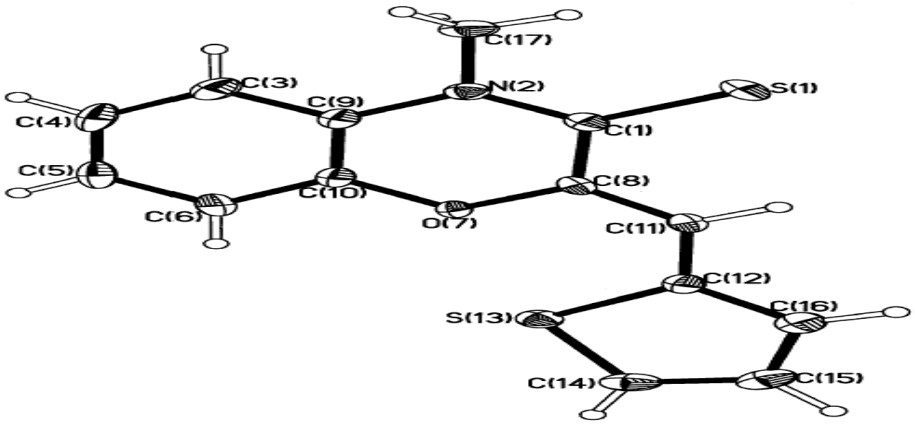


Figure 1 ORTEP of Compound (**4a)**

to the lack of steric hindrance between the 2-benzylidine ring and C-3 thiocarbonyl sulfur atom that would be present in **5d–f**, respectively. Similarly compound (**4a**) resists adopting the *E* configuration due to repulsion between the lone pair electrons on the sulfur atom of the C=S group and the sulfur atom of the thiophene ring (probably further enhanced by the mesomeric effect of the N-Me lone pair of electrons). Interestingly, ^{1}H NMR spectroscopy indicates that the 3-pyrrol-2-yl derivative (**5c**) is the *E* isomer since its alkenic proton chemical shift occurs at 7.50 ppm, which is in the range of previously reported *E* isomers. However, single-crystal X-Ray analysis, indicates that **4c** (ORTEP is shown in Figure 2) exists in the *Z* configuration. One must remember that X-Rays only tell one about the crystal lattice (solid phase) where lattice forces may favor one isomer over the other; this may not necessarily extend to solution phase where the molecules are more free.

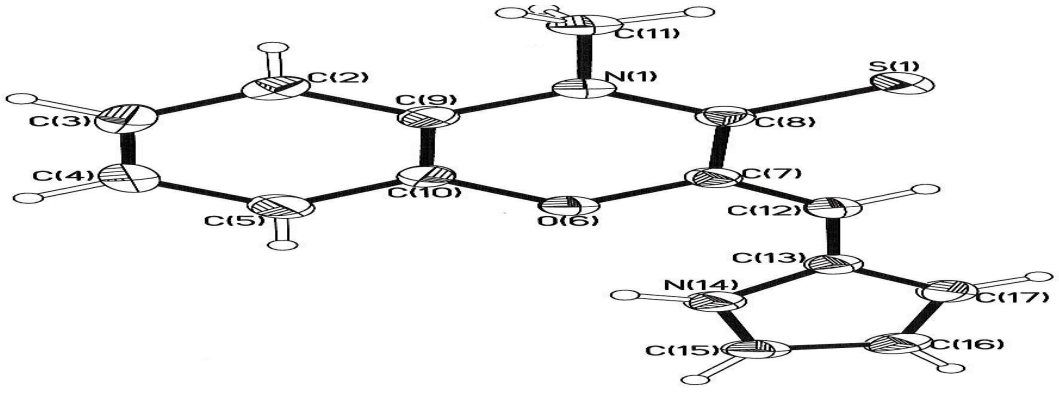
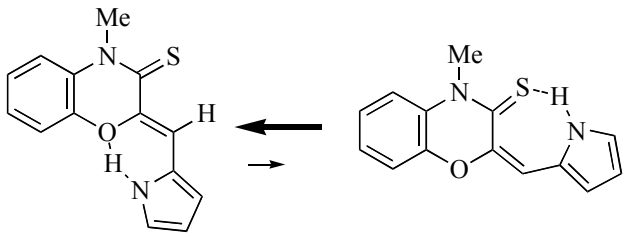


Figure 2 ORTEP Drawing of Compound (**4c**)

As shown in Figure 3, that crystalline (**4c)** exists in the *Z* configuration is probably due to stronger

hydrogen bonding involving the 6-membered ring to oxygen in **4c** as compared to that involving the 7-membered ring to sulfur in **5c**. At this time we do not know why the molecule adopts the *E*-configuration in solution.



4c **5c**

Figure 3 Relative Stabilities of **4c** and **5c** Based on Relative Hydrogen Bonding Strength in Each Configuration

In the exceptional case, the furan-2-yl derivative (**5b**) was assigned the *E*-configuration since its alkenic proton chemical shift occurs at 7.50 ppm. The preference of **5b** for the *E* configuration may be due to favorable electrostatic interactions between the C-3 thiocarbonyl sulfur atom of the oxazine ring with the oxygen atom of the furan ring shown in Figure 4. The mesomeric effect of the lone pair electrons on the

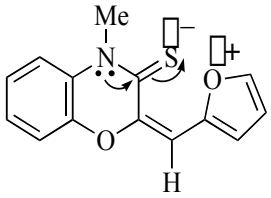


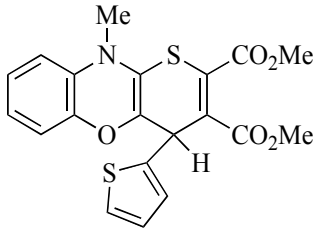
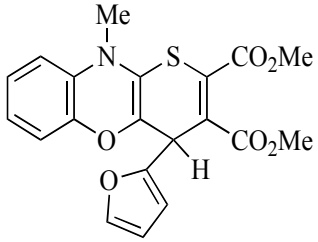
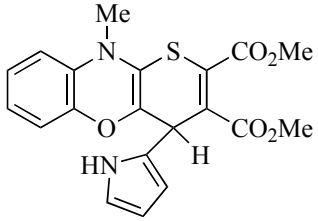
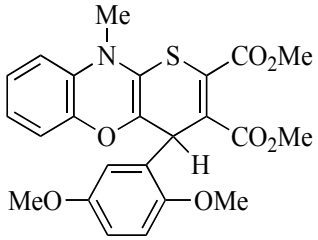
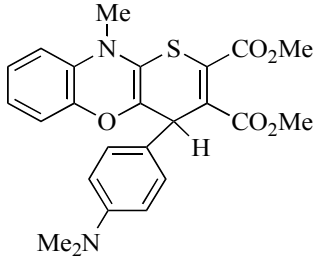
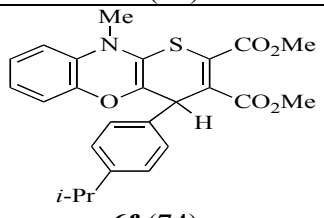
Figure 4 Electrostatic Interactions in **5b**

4-N atom would further increase the stability of the *E* configuration of **5b**. A similar explanation has been presented for the stability of the *Z* configuration of 3-[(thien-2-yl)(methylidenyl]indolin-2-ones (note: the order of priorities in the indolin-2-system is opposite to that in the oxazin-3-one system).[19]

The yields of **4** and **5** listed in Table 1 represent isolated yields of compounds after purification by column chromatography. GC/MS analysis revealed the isolated products to be pure. Intriqued by Tang's[19] observation of an equilibrium between the *Z* and *E* isomer forms in polar solvents, such as methanol, we dissolved samples of pure 3-thien-2-yl- (**4a**), 3-furan-2-yl- (**5b**) and 3-pyrrol-2-yl (**4c**) in ethanol and subjected the resulting solutions to HPLC analysis. The data revealed in Table 1 show that an equilibrium between the *Z* and *E* isomers was present in each case. The *Z* isomers had the larger R_f value which is consistent with their greater polarity as compared to that of the *E* isomers.

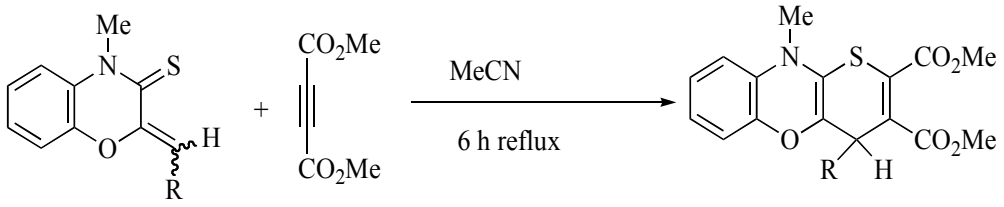
With the oxazine-3-thiones on hand, we turned our attention to investigating their use as dienes in [4+2] cycloaddition reactions. Since both *Z* and *E* diastereomers would give the same adduct, the mixtures of **4**

Table 2 Preparation of Compounds (**6a–f**)

Entry	**4** or **5**	**6** (yield, %)
1	**4a**	 **6a** (73)
2	**5b**	 **6b** (69)
3	**5c**	 **6c** (78)
4	**4d**	 **6d** (81)
5	**4e**	 **6e** (79)
6	**4f**	 **6f** (74)

and **5** prepared from the reactions shown in Scheme 1 were used without further purification. As shown in

eq. 1, the 4*H*-benzo[1,4]oxazine-3-thiones (**4** or **5**) reacted readily with dimethyl acetylenedicarboxylate to give the new nitrogen-oxygen-sulfur containing heterocyclic compounds (**6a–f**) in 69–81% yields. The results are listed in Table 2.



4 or **5** **6** eq. 1

The structures of compounds (**6a-f**) were ascertained by ^{1}H NMR and ^{13}C NMR spectroscopy. For example, each compound exhibited a singlet (corresponding to one proton) in its ^{1}H NMR spectrum in the range of 3.94–4.00 ppm, corresponding to the hydrogen at the 4-position.

We next attempted to treat **4** and **5** with arynes, however these reactions failed to yield benzyne cycloaddition products; only inextractible tars were obtained. Methods that were used to generate arynes include: heating 2-diazoniobenzenecarboxylate hydrochlorides in refluxing benzene;[20] adding isoamyl nitrite to a refluxing benzene solution (~80 °C);[21] and adding Me_4NF to a solution of (phenyl)[*o*-(trimethylsilyl)phenyl]iodonium triflate at room temperature.[22]

In conclusion, we have prepared a variety of 2-substitued thiopyrano[3,2-*b*][1,4]benzoxazine-2,3-dicarboxylic acid dimethyl esters in good yields by the reaction of 4*H*-benzo[1,4]oxazine-3-thiones with dimethyl acetylenedicarboxylate.

EXPERIMENTAL

General Data: Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker ADVANCE DRX-400 Multinuclear NMR spectrometer. Chemical shifts are reported in reference to TMS as internal standard. SMU Analytical Service Laboratories performed elemental analyses. All chemicals were purchased from Fisher Scientific. HPLC analysis were carried out a Waters Delta prep 4000 instrument equipped with a Whelk-01 (25 cm x 4.6 nm) column (purchased from Regis Technologies, Inc.) and UV detector at 254 nm. The eluent, hexane/isopropanol (70/30,v/v), was run at flow rate of 1 mL/min.

Preparation of 4-Methyl-4*H*-benzo[1,4]oxazine-3-thione (2). To a stirred solution of 4-methyl-4*H*-benzo[1,4]oxazin-3-one (**1**) (5 g, 37 mmol) in 30 mL of dry THF was added P_2S_5 (16.6 g, 37 mmol) and the resulting mixture was stirred at rt for 45 min. After $NaHCO_3$ (10.41 g, 123 mmol) was added in three portions, the mixture was stirred an additional 3 h at rt during which time a precipitate formed. The

precipitate was collected by vacuum filtration, and the mother liquor was concentrated to dryness. The residue was treated with 100 mL of ice water, extracted with $CHCl_3$ (3 X 60 mL) and purified by column chromatography on SiO_2 using EtOAc-hexanes as eluent to give **2** (4.5 g, 82%) as a light yellow solid (EtOAc–hexane), mp 79–82 °C. (lit.,[23] 80–82 °C).

Preparation of 2-Substituted 4-Methyl-4*H*-benzo[1,4]oxazine-3-thiones (4, 5).

A reaction mixture containing **2** (0.5 g, 2.7 mmol), an appropriate aldehyde (3.3 mmol) and piperidine (26 mg, 3 mmol) in dry benzene (6 mL) was stirred at 90 °C for 4 h then cooled to rt. The crude product which precipitated during cooling was collect by vacuum filtration, washed with benzene, dried, and then purified by column chromatography on SiO_2 using EtOAc–hexane (1:4,v/v). The physical and spectral properties of the oxazine-3-thiones (**4** and **5)** are given below.

(*Z*)-4-Methyl-2-[(thiophen-2-yl)(methylidenyl)]-4*H*-benzo[1,4]oxazine-3-thione (4a)

This compound was isolated as a yellow solid (CH_2Cl_2–hexane), mp 139–141 °C. ^{1}H NMR ($CDCl_3$) δ 3.9 (s, 3H), 7.06–7.16 (m, 4H), 7.19 (d, *J* = 6.8 Hz, 1H), 7.34 (s, 1H), 7.44 (d, *J* = 6.8 Hz, 1H), 7.78 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 37.5, 114.6, 115.8, 116.6, 123.7, 126.1, 127.4, 129.1, 131.1, 137.6, 144.0, 144.3, 183.4. *Anal.* Calcd for $C_{14}H_{11}NOS_2$: C, 61.51; H, 4.06; N, 5.12. Found: C, 61.55; H, 4.11; N, 5.15.

(*E*)-2-[(Furan-2-yl)(methylidenyl)]-4-methyl-4*H*-benzo[1,4]oxazine-3-thione (5b)

This compound was isolated as a light yellow solid (CH_2Cl_2–hexane), mp 135–136 °C. ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H), 6.54 (s, 1H), 7.02 (d, *J* = 6.8 Hz, 2H), 7.06–7.20 (m, 4 H), 7.50 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 37.6, 109.0, 112.8, 113.3, 115.9, 116.4, 123.7, 126.0, 127.3, 143.6, 143.8, 144.4, 151.0, 183.0. *Anal.* Calcd for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44. Found: C, 65.45; H, 4.33; N, 5.50.

(*Z*)-4-Methyl-2-[(pyrrol-2-yl)(methylidenyl)]-4*H*-benzo[1,4]oxazine-3-thione (4c)

This compound was isolated as a light red solid, mp 190–191 °C. ^{1}H NMR ($CDCl_3$) δ 3.97 (s, 3H), 6.33 (s, 1H), 6.63 (s, 1H), 7.01 (s, 1H), 7.07–7.09 (m, 2 H), 7.10–7.12 (m, 2H), 7.55 (s, 1H), 9.41 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 37.5, 110.9, 112.4, 113.1, 115.9, 116.0, 121.8, 123.8, 125.8, 128.0, 142.0, 143.0, 144.2, 184.3. *Anal.* Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72: N, 10.93. Found: C, 65.02; H, 4.79; N, 11.04.

(*Z*)-2-(2,5-Dimethoxybenzylidenyl)-4-methyl-4*H*-benzo[1,4]oxazine-3-thione (4d)

This compound was isolated as a light yellow solid (CH_2Cl_2–hexane), mp 123–124 °C. ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H), 3.88 (s, 3H), 4.02 (s, 3H), 6.87 (d, *J* = 7.8 Hz, 2H), 7.13–7.27 (m, 4H), 7.27 (d, *J* = 2.5 Hz, 1H), 7.98 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 37.9, 56.1, 56.7, 111.8, 114.4, 115.4, 115.6, 115.8, 116.4, 123.6, 124.3, 125.9, 127.8, 144.3, 146.7, 153.0, 153.5, 184.0. *Anal.* Calcd for $C_{18}H_{17}NO_3S$: C, 66.03; H, 4.28; N, 4.28. Found: C, 66.14; H, 4.21; N, 4.23.

(*Z*)-4-Methyl-2-(4-*N,N*-dimethylaminobenzylidenyl)-4*H*-benzo[1,4]oxazine-3-thione (4e)

This compound was isolated as a light red solid (CH_2Cl_2–hexane), mp 218–220 °C. ^{1}H NMR ($CDCl_3$) δ

2.85 (s, 6H), 4.03 (s, 3H), 7.02 (d, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.31–7.35 (m, 4H), 7.98 (s, 1H). ^{13}C NMR ($CDCl_3$) 40.3, 42.6, 113.1, 113.2, 114.5, 114.7, 117.4, 123.1, 124.3, 125.7, 126.0, 127.9, 153.5, 154.8, 184.5. *Anal.* Calcd for $C_{18}H_{17}NO_3S$: C, 73.19; H, 5.80; N, 4.74. Found: C, 73.31; H, 5.72; N, 4.80.

(*Z*)-2-(4-Isopropylbenzylidenyl)-4-methyl)-4*H*-benzo[1,4]oxazine-3-thione (4f)

This compound was isolated as a light yellow viscous oil. ^{1}H NMR ($CDCl_3$) 1.12 (d, *J* = 8.0 Hz, 6H), 2.80 (m, 1H), 4.04 (s, 3H), 6.82 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.23–7.35 (m, 4H), 7.86 (s, 1H). ^{13}C NMR ($CDCl_3$) 24.2, 33.9, 40.4, 114.5, 117.2, 117.3, 123.1, 125.2, 125.8, 125.9, 126.2, 126.5, 126.7, 127.9, 154.1, 154.3, 184.0. *Anal.* Calcd for $C_{19}H_{19}NOS$: Found: C, 73.75; H, 6.19; N, 4.53. Found: C, 73.72; H, 6.17; N, 4.54.

General Procedure for the Preparation of Substituted 10-Methylthiopyrano[3,2-*b*][1,4]benzoxazine-2,3-dicarboxylic Acid Dimethyl Esters (6)

To a well-stirred solution of compound (**4)** (0.35 mmol) in dry MeCN (5 mL) kept in a round-bottom flask fitted with a reflux condenser under argon atmosphere, a solution of dimethyl acetylenedicarboxylate (0.92 g, 1.7 mmol) in MeCN (1 mL) was added through a needle syringe system. The mixture was heated to reflux for 6 h and then cooled. Evaporation of solvent under reduced pressure afforded the crude product which was purified by column chromatography using SiO_2 with EtOAc–hexane (1:4, v/v). The physical and spectral properties of **6-a-f** are given below.

10-Methyl-4-(thien-2-yl)thiopyrano[3,2-*b*][1,4]benzoxazine-2,3-dicarboxylic Acid Dimethyl Ester (6a)

This compound was isolated as a light yellow viscous oil. ^{1}H NMR ($CDCl_3$) 3.79 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 3.96 (s, 1H), 7.02–7.04 (m, 3H), 7.28 (dd, *J* = 7.8 Hz, 8.0 Hz, 1H), 7.37 (dd, *J* = 2.1 Hz, 7.8 Hz, 1H), 7.56 (d, *J* =7.5 Hz, 1H), 7.58 (d, *J* =7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) 37.6, 38.5, 52.5, 52.6, 112.9, 116.7, 117.5, 117.8, 119.5, 123.4, 123.5, 125.3, 125.9, 131.2, 135.9, 139.1, 140.2, 140.2, 164.5. *Anal.* Calcd for $C_{20}H_{17}NO_5S_2$: C, 57.82; H, 4.12; N, 3.37. Found: C, 57.71; H, 4.20; N, 3.44.

4-(Furan-2-yl)-10-methylthiopyrano[3,2-*b*][1,4]benzoxazine-2,3-dicarboxylic Acid Dimethyl Ester (6b)

This compound was isolated as a viscous oil. ^{1}H NMR ($CDCl_3$) 3.83 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 3.95 (s, 1H), 6.55 (s, 1H), 7.03 (d, *J* = 6.8 Hz, 2H), 7.01–7.06 (m, 4H). ^{13}C NMR ($CDCl_3$) 32.9, 37.8, 104.9, 111.5, 113.0, 114.9, 117.5, 117.8, 120.1, 122.8, 132.5, 136.5, 140.3, 141.1, 144.2, 165.4. *Anal.* Calcd for $C_{20}H_{17}NO_6S$: C, 60.14; H, 4.29; N, 3.51. Found: C, 60.20; H, 4.36; N, 3.60.

10-Methyl-4-(pyrrol-2-yl)thiopyrano[3,2-*b*][1,4]benzoxazine-2,3-dicarboxylic Acid Dimethyl Ester (6c)

This compound was isolated as light red viscous oil. ^{1}H NMR ($CDCl_3$) □ 3.80 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 3.94 (s, 1H), 6.12 (d, *J* = 6.5 Hz, 1H), 6.35 (s, 1H), 7.05–7.09 (m, 4H), 7.56 (d, *J* = 6.5 Hz, 1H), 8.9 (br s, 1H). ^{13}C NMR ($CDCl_3$) □ 34.6, 37.9, 51.2, 51.9, 109.9, 110.5, 113.3, 114.9, 116.9, 117.6, 117.7, 120.3, 122.9, 130.3, 133.2, 136.9, 140.5, 165.9. *Anal.* Calcd for $C_{20}H_{18}N_2O_5S$: C, 60.29; H, 4.55; N, 7.03. Found: C, 60.33; H, 4.60; N, 7.14.

4-(2,5-Dimethoxyphenyl)-10-methylthiopyrano[3,2-*b*][1,4]benzoxazine-2,3-dicarboxylic Acid Dimethyl Ester (6d)

This compound was isolated as a colorless oil. ^{1}H NMR ($CDCl_3$) □ 3.85 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 3.98 (s, 3H), 4.00 (s, 1H), 6.88 (d, *J* = 7.8 Hz, 2H), 7.02–7.09 (m, 4H), 7.28 (d, *J* = 2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) □ 33.2, 38.1, 50.1, 50.9, 55.2, 55.6, 111.1, 113.3, 114.9, 115.6, 115.9, 117.3, 117.6, 120.9, 123.4, 124.9, 132.5, 136.9, 140.2, 140.5, 154.2, 155.1, 165.0. *Anal.* Calcd for $C_{24}H_{23}NO_7S$: C, 63.70; H, 5.35; N, 6.19. Found: C, 63.79; H, 5.40; N, 6.28.

10-Methyl-4-(4-*N*,*N*-dimethylaminophenyl)thiopyrano[3,2-*b*][1,4]benzoxazine-2,3-dicarboxylic Acid Dimethyl Ester (6e)

This compound was isolated as light red oil. ^{1}H NMR ($CDCl_3$) □ 2.86 (s, 6H), 3.78 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.98 (s, 1H), 7.01–7.03 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.38 (dd, *J* = 2.1 Hz, 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) □ 37.5, 38.4, 43.2, 52.6, 52.7, 112.5, 113.5, 113.1, 113.2, 115.9, 117.5, 117.6, 120.2, 123.4, 127.1, 130.0, 130.3, 130.5, 131.7, 136.9, 141.4, 141.5, 164.3. *Anal.* Calcd for $C_{24}H_{24}N_2O_5S$: C, 63.70; H, 5.35; N, 6.19. Found: C, 63.88; H, 5.40; N, 6.27.

4-(4-Isopropylphenyl)-10-methylthiopyrano[3,2-*b*][1,4]benzoxazine-2,3-dicarboxylic Acid Dimethyl Ester (6f)

This compound was isolated as a light viscous oil. ^{1}H NMR ($CDCl_3$) □ 1.18 (d, *J* = 8.0 Hz, 6H), 2.84–2.86 (m, 1H), 3.76 (s, 3H), 3.96 (s, 1H), 6.99 –7.02 (m, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.39 (dd, *J* = 2.1 Hz, 7.9 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) □ 24.2, 31.5, 34.2, 38.3, 51.9, 52.0, 112.5, 114.5, 117.6, 117.9, 120.5, 123.1, 126.5, 126.7, 128.3, 132.1, 134.1, 136.7, 140.1, 165.0. *Anal.* Calcd for $C_{25}H_{25}NO_5S$: C, 66.50; H, 5.58; N, 3.10. Found: C, 66.64; H, 5.70; N, 5.70; N, 3.18.

Selected R_f Values: 4a, 9.0; **5a**, 11.4; **4b**, 7.5; **5b**, 9.0; **4c**, 13.0; **5c** 9.0; **4e**, 10.8; **5e**, 13.7.

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