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Research Article

Synthesis of Benzothiophene-Fused Pyran Derivatives via Piperidine Promoted Domino Reaction

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A new domino reaction between thioaurones and malononitrile has been reported. This reaction allows efficient access to benzothiophene-fused pyran derivatives in good yields under mild reaction conditions. The substrate scope is broad; a series of benzothiophene-fused pyran derivatives have been synthesized.

1. Introduction

Fused pyran ring existing in both numerous natural products and synthetic compounds is an important heteroatom framework [1–5], which demonstrate great function on pharmacological activities, antibacterial, antiviral, anticoagulant, antianaphylactic, anticancer, diuretic activities, neurodegenerative disorders, and so on [6–10]. Recently, 2-aminochromenes are found to be employed as pigments, cosmetics, and agrochemicals [11–13]. Furthermore, the therapeutically effect on immune system diseases and diabetic complications entitled by substituted 2-amino-benzochromenes have been proved [14]. To date, there have been only limited methods to construct of a 2-amino-3-cyan-pyranskeleton. Klimochkin's group developed a convenient one-step synthesis of 4-unsubstituted 2-amino-4H-chromene-2-carbonitriles from quaternary ammonium salts (Scheme 1(a)) [15].

Subsequently, Takaki's research group was given an efficient synthetic strategy for 2-amino-4H-chromenes from photochemical generated *o*-quinone methides and malononitrile (Scheme 1(b)) [16]. After that, Rao's group also designed and synthesized a series of pyran derivatives in good yields by utilizing Baylis–Hillman chemistry (Scheme 1(c)) [17]. For the past decades, there was a rapid development on the organic small molecule catalyzed domino reaction. During our ongoing investigation of domino reactions, our research group has developed many domino reactions on thioaurone. Many benzothiophene-fused heterocycles were synthesized (Scheme 2(a)) [18–22]. Herein, we will report another new domino reaction between thioaurone and malononitrile. To our surprise, a series of benzothiophene-fused pyran derivatives were obtained (Scheme 2(b)).

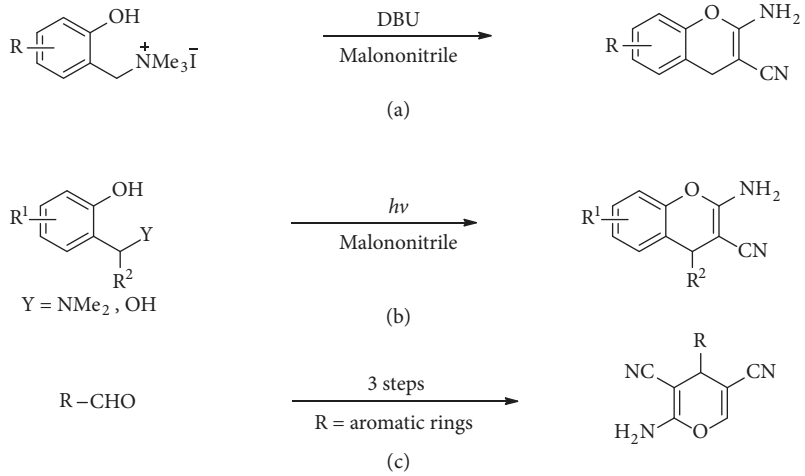
2. Materials and Methods

Material **1** was synthesized and reported in our previous work [18, 19] and **2** was purchased from commercial access.

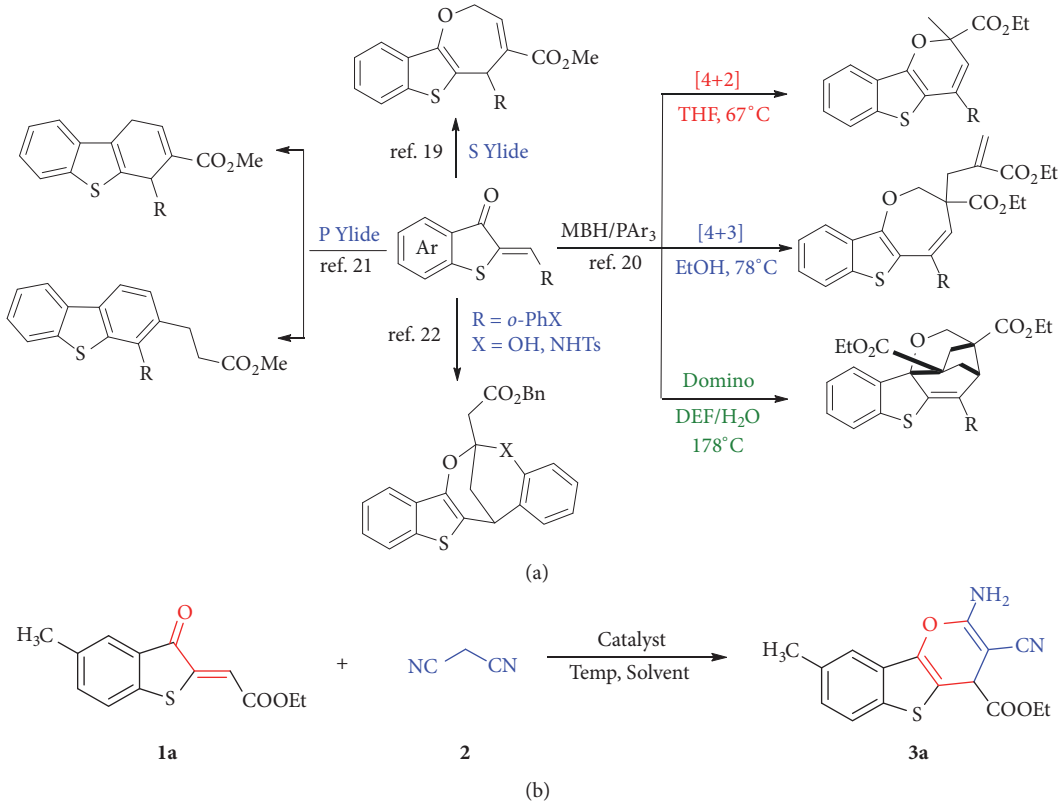
General synthetic procedure for **3** was as follows: under Ar atmosphere, to a solution of **1** (0.2 mmol) in dichloromethane (DCM) (2.0 mL) **2** (0.4 mmol) and piperidine (10 mol%) were added and the mixture was stirred at room temperature for 2 h. After extraction with DCM, the organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified through flash column chromatography on silica gel (petroleum ether/ethyl acetate = 1:1 to 5:1) to afford the desired product **3**.

3. Results and Discussion

The reaction between thioaurone **1a** and malononitrile **2** in dichloromethane as the solvent under reflux was first performed. Unfortunately, no product was detected by TLC (Table 1, entry 1). Then piperidine was added as a catalyst to promote the reaction. To our surprise, the reaction could



Scheme 1: Previous methods to establish a 2-amino-3-cyan-pyran skeleton.

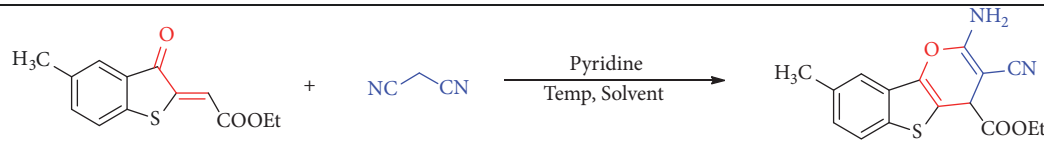


Scheme 2: Our works of domino reaction on thioaurone.

give a quickly and cleanly conversion and the product was obtained in a 70% yield (Table 1, entry 2). The structure of the product **3a** was established by X-ray crystallography (Figure 1) [23]. Encouraged by this result, the solvent effect was examined to optimize the reaction condition. There was only a feebly variation of the yield given by the different solvent such as chloroform, acetonitrile, tetrahydrofuran, and ethyl alcohol; the reaction afforded the yields of 68%-73% after stirring at the corresponding reflux temperature (Table 1, entries 3-6). When selecting toluene as the solvent, there was a negative effect on the conversion; the yield dropped to 57% (Table 1, entry 7). In the screening process, the additive effect of acetic acid was also screened. Insignificantly, there was no visible fluctuation on the yield (Table 1, entry 8). As the reflux temperature provided a moderate yield, the reaction was performed at room temperature (Table 1, entries 9-11). After attempting the above studies, the best reaction condition is at room temperature using piperidine as catalyst, and the yield up to 83% (entry 10).

With the best reaction conditions in hand, the substrate scope was examined with a series of thioaurone **1**. Firstly, the ethyl ester on the R^2 functional group switched to a

Table 1: Optimization of condition[a].

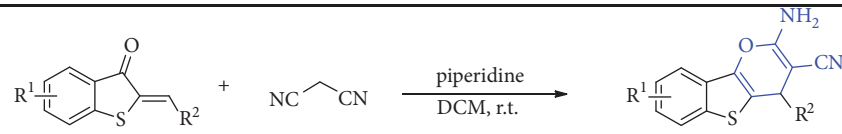


1a **2a** **3a**

Entry	Solvent	Temp [°C]	Time [min]	Yield [%][b]
1[c]	DCM	40	20	NR
2	DCM	40	10	70
3	$CHCl_3$	61	20	68
4	THF	66	15	71
5	CH_3CN	84	15	70
6	EtOH	80	10	73
7	Toluene	110	20	57
8[d]	EtOH	80	10	72
9	EtOH	r.t.	15	74
10	DCM	r.t.	15	83
11	THF	r.t.	10	63

[a]Reaction conditions: 0.2 mol thioaurone **1a**, 0.4 mol malononitrile **2a**, 2.0 mL solvent at the corresponding temperature, and 10% mol piperidine as catalyst. [b]Isolated yields. [c]No catalyst. [d]Acetic acid as an additive.

Table 2: Scope of the domino reaction[a].



1 **2a** **3**

Entry	R^1	R^2	Time [min]	Yield [%][b]
1	5-CH_3(**1a**)	COOEt	15	83 (**3a**)
2	5-CH_3(**1b**)	COOBn	20	52 (**3b**)
3	5-CH_3(**1c**)	*o*-PhCl	10	84 (**3c**)
4	5-CH_3(**1d**)	*m*-PhCl	10	99 (**3d**)
5	5-CH_3(**1e**)	*p*-PhMe	15	69 (**3e**)
6	5-F(**1f**)	COOEt	15	60 (**3f**)
7	5-Br(**1g**)	COOEt	20	59 (**3g**)
8	6-OMe(**1h**)	COOMe	15	71 (**3h**)
9	7-Cl(**1i**)	Phenyl	10	80 (**3i**)

[a]Reaction conditions: 0.2 mol thioaurone **1**, 0.4 mol malononitrile **2a**, 2.0 mL DCM at room temperature, and 10% mol piperidine as the catalyst. [b]Isolated yields.

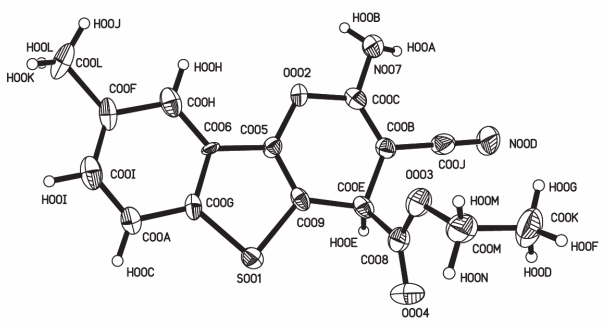
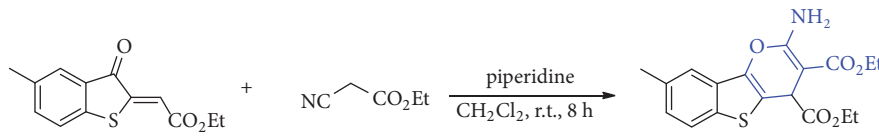


Figure 1: X-ray crystal structure of **3a**.

benzyl ester, leading to the desired product in yield of 52% (Table 2, entry 2). Subsequently, thioaurone **1** with aromatic groups on the **1** was also examined, for example, o- and m-chloro substituted **1c** and **1d**, p-methyl substituted **1e**. And as a consequence, the *para* methyl-substituted substrate was not given an optimistic effect, but the other two were tolerated well and excellent; the yield was reached to 83% and 99%, respectively (Table 2, entries 3-5). Furthermore, the effect of R^1 was also studied. When using halogen atom to replace the methyl on the C5 position, the fluoro and bromo substituted substrates were given the corresponding products in 60% and 59% yields, respectively (Table 2, entries 6-7). Substrate **1h**, bearing a 6-MeO group (R^1), also worked well and furnished



Scheme 3: Domino reaction between **1a** and **2b**.

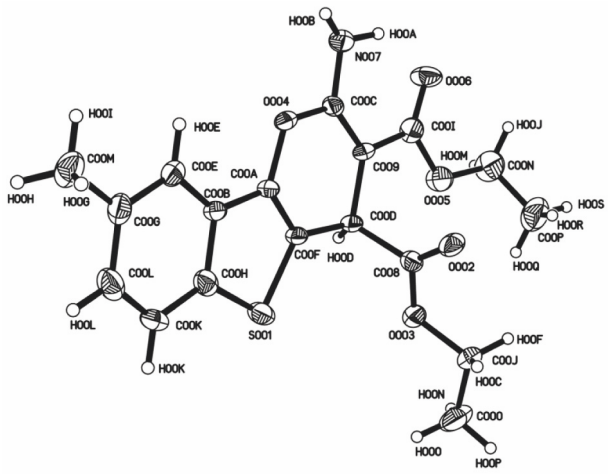


Figure 2: X-ray crystal structure of **4**.

the desired product in 71% yield. In addition, 7-Cl-substituted substrate **1i** was also screened in this domino reaction. The corresponding product **3i** was obtained in yield of 80% (Table 2, entry 9).

In order to explore the domino reaction scope, ethyl 2-cyanoacetate (**2b**) was used in this domino reaction (Scheme 3). To our surprise, the corresponding product **4** was obtained in yield of 63%. The structure of **4** was confirmed by X-ray crystal structure analysis (Figure 2) [23].

4. Conclusions

In conclusion, a novel piperidine-catalyzed [4+2] domino reaction between thioaurone and malononitrile was developed. A number of benzothiophene ring fused 2-amino-3-cyano-pyran derivatives were obtained in good yields. The product structure was identified by NMR, HRMS, and X-ray crystal structure.

5. Experimental

The ^{1}H- and ^{13}C-NMR spectrum were recorded at ambient temperature on Bruker 400 instruments. All spectra were referenced to $CDCl_3$ (^{1}H δ 7.26 ppm and ^{13}C NMR δ 77.00 ppm) and DMSO-d_6 (^{1}H δ 2.50 ppm and ^{13}C NMR δ 39.52 ppm). HRMS were obtained on Waters Xevo Q-TOF MS with ESI resource. Melting points were measured on a RY-I apparatus and are reported to be uncorrected.

*Ethyl 2-amino-3-cyano-8-methyl-4H-benzo[4,5]thieno[3,2-b]pyran-4-carboxylate (**3a**).* Yellow solid, m.p. 182-184°C; IR (KBr): 3411, 3332, 2362, 2336, 2192, 1719, 1653, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (d, J = 8.3 Hz, 1H, Ar-*H*), 7.45 (s, 1H, Ar-*H*), 7.20 (d, J = 8.3 Hz, 1H, Ar-*H*), 4.91 (s, 2H, NH_2), 4.62 (s, 1H, C*H*), 4.33 – 4.22 (m, 2H, OCH_2CH$_3$), 2.46 (s, 3H, Ar-CH_3), 1.34 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.8 (*C*OOEt), 160.8, 139.4, 134.8, 133.8, 129.0, 127.6, 122.4, 119.7, 119.1, 110.9, 62.3 (OCH_2CH$_3$), 55.0 (*C*CN), 40.3 (*C*H), 21.4 (Ar-CH_3), 14.2 (OCH$_2$CH_3) ppm; ESI-HRMS [M+H] calcd. for $C_{16}H_{15}N_2O_3S$ 315.0798, found 315.0801.

*Benzyl2-amino-3-cyano-8-methyl-4H-benzo[4,5]thieno[3,2-b]pyran-4-carboxylate (**3b**).* White solid, m.p. 177-179°C; IR (KBr): 3378, 3325, 3211, 2360, 2342, 2205, 1739, 1587, 1540, 734, 799 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (d, J = 8.3 Hz, 1H, Ar-*H*), 7.46 (s, 1H, Ar-*H*), 7.37 (m, 5H, Ar-*H*), 7.20 (d, J = 8.3 Hz, 1H, Ar-*H*), 5.23 (s, 2H, PhCH_2), 4.90 (s, 2H, NH_2), 4.69 (s, 1H, C*H*), 2.45 (s, 3H, Ar-CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.7 (*C*OOBn), 160.8, 139.4, 135.0, 134.8, 133.82, 129.0, 128.6, 128.5, 128.4, 127.7, 122.4, 119.7, 110.7, 68.0 (OCH_2Bn), 54.9 (*C*CN), 40.3 (*C*H), 21.4 (Ar-CH_3) ppm; ESI-HRMS [M+H] calcd. for $C_{21}H_{17}N_2O_3S$ 377.0954, found 377.0957.

*2-amino-4-(2-chlorophenyl)-8-methyl-4H-benzo[4,5]thieno[3,2-b]pyran-3-carbonitrile (**3c**).* Red solid, m.p. 236-238°C; IR (KBr): 3482, 3321, 3284, 2360, 2200, 1650, 1581, 863, 800, 763, 745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58 – 7.50 (m, 2H, Ar-*H*), 7.40 (d, J = 8.3 Hz, 1H, Ar-*H*), 7.33 – 7.29 (m, 1H, Ar-*H*), 7.25 – 7.16 (m, 3H, Ar-*H*), 5.58 (s, 1H, C*H*), 4.79 (s, 2H, NH_2), 2.47 (s, 3H, Ar-CH_3) ppm; ^{13}C NMR (100 MHz, DMSO) δ = 161.5, 140.9, 138.7, 135.0, 133.3, 132.4, 130.7, 130.3, 129.8, 129.2, 128.5, 127.8, 123.5, 120.4, 119.6, 117.0, 54.8 (*C*CN), 37.4 (*C*H), 21.5 (Ar-CH_3) ppm; ESI-HRMS [M+H] calcd. for $C_{19}H_{14}N_2OSCl$ 353.0510, found 353.0515.

*2-amino-4-(3-chlorophenyl)-8-methyl-4H-benzo[4,5]thieno[3,2-b]pyran-3-carbonitrile (**3d**).* White solid, m.p. 204-205°C; IR (KBr): 3470, 3322, 2360, 2342, 2199, 1661, 1581, 807, 799 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 – 7.47 (m, 2H, Ar-*H*), 7.28 (d, J = 7.8 Hz, 2H, Ar-*H*), 7.25 (s, 1H, Ar-*H*), 7.19 (d, J = 7.3 Hz, 2H, Ar-*H*), 4.93 (s, 1H, C*H*), 4.80 (s, 2H, NH_2), 2.48 (s, 3H, Ar-CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.8, 144.8, 138.4, 134.9, 133.8, 130.2, 129.2, 128.2, 127.8, 127.4, 125.9, 122.6, 119.8, 119.3, 117.3, 60.2 (*C*CN), 39.9 (*C*H), 21.5 (Ar-CH_3) ppm; ESI-HRMS [M+H] calcd. for $C_{19}H_{14}N_2OSCl$ 353.0510, found 353.0513.

*2-amino-8-methyl-4-(p-tolyl)-4H-benzo[4,5]thieno[3,2-b]pyran-3-carbonitrile (**3e**).* White solid, m.p. 249-251°C; IR (KBr): 3466, 3314, 2360, 2199, 1660, 1584, 1400, 872, 804 cm^{-1}; ^{1}H

NMR (400 MHz, $CDCl_3$) δ = 7.57 – 7.48 (m, 2H, Ar-*H*), 7.21 – 7.10 (m, 5H, Ar-*H*), 4.92 (s, 1H, C*H*), 4.71 (s, 2H, NH_2), 2.48 (s, 3H, Ar-CH_3), 2.32 (s, 3H, Ar-CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.9, 138.1, 137.6, 134.7, 133.8, 129.6, 129.3, 127.4, 127.1, 122.56 119.7, 119.5, 118.5, 61.2 (*C*CN), 39.7 (*C*H), 21.5 (Ar-*C*H_3), 21.1 (Ar-*C*H_3) ppm; ESI-HRMS [M+H] calcd. for $C_{20}H_{17}N_2OS$ 333.1056, found 333.1058.

*Ethyl 2-amino-3-cyano-8-fluoro-4H-benzo[4,5]thieno[3,2-b]pyran-4-carboxylate (**3f**).* Gray solid, m.p. 165-167°C; IR (KBr): 3424, 3372, 3327, 2198, 1739,1720, 1659, 1586, 854 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (dd, *J* = 8.8, 4.5 Hz, 1H, Ar-*H*), 7.31 (dd, *J* = 8.7, 2.2 Hz, 1H, Ar-H), 7.13 (td, *J* = 8.8, 2.4 Hz, 1H, Ar-*H*), 4.97 (s, 2H, NH_2), 4.64 (s, 1H, C*H*), 4.36 – 4.21 (m, 2H, OCH_2CH$_3$), 1.35 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ =169.6 (*C*OOEt), 160.8 (d, *J* = 242.3 Hz), 160.6, 139.3 (d, *J* = 4.3 Hz), 131.8 (d, *J* = 1.7 Hz), 129.7 (d, *J* = 9.8 Hz), 124.1 (d, *J* = 9.2 Hz), 118.9, 114.7 (d, *J* = 25.2 Hz), 113.3, 105.7 (d, *J* = 24.5 Hz), 62.5 (OCH_2CH$_3$), 54.7 (*C*CN), 40.3 (*C*H), 14.2 (OCH_2CH_3) ppm; ESI-HRMS [M+H] calcd. for $C_{15}H_{12}N_2O_3SF$ 319.0547, found 319.0551.

*Ethyl 2-amino-8-bromo-3-cyano-4H-benzo[4,5]thieno[3,2-b]pyran-4-carboxylate (**3g**).* Yellow solid, m.p. 195-197°C; IR (KBr): 3460, 3366, 3314, 2194, 1740, 1720, 1652, 1583, 859, 874 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (s, 1H, Ar-*H*), 7.58 (d, *J* = 8.6 Hz, 1H, Ar-*H*), 7.45 (d, *J* = 8.6 Hz, 1H, Ar-*H*), 4.99 (s, 2H, NH_2), 4.64 (s, 1H, C*H*), 4.37 – 4.23 (m, 2H, OCH_2CH$_3$), 1.36 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.5 (*C*OOEt), 160.5, 138.8, 135.2, 130.2, 129.0, 124.1, 122.6, 118.9, 112.8, 62.5 (OCH_2CH$_3$), 54.9 (*C*CN), 40.2 (*C*H), 14.2 (OCH_2CH_3) ppm; ESI-HRMS [M+H] calcd. for $C_{15}H_{12}N_2O_3SBr$ 378.9747, found 378.9751.

*Methyl2-amino-3-cyano-7-methoxy-4H-benzo[4,5]thieno[3,2-b]pyran-4-carboxylate (**3h**).* Red solid, m.p. 187-189°C; IR (KBr): 3447, 3384, 3350, 2196, 1743, 1651, 1584, 848, 831 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 7.19 (d, *J* = 2.1 Hz, 1H, Ar-*H*), 7.00 (dd, *J* = 8.8, 2.1 Hz, 1H, Ar-*H*), 4.90 (s, 2H, NH_2), 4.61 (s, 1H, C*H*), 3.86 (s, 3H, Ar-OCH_3), 3.82 (s, 3H, COOCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.4 (*C*OOCH$_3$), 160.8, 158.6, 139.4, 138.3, 122.7, 120.5, 119.1, 114.9, 107.7, 105.4, 55.7 (COO*C*H$_3$), 55.0 (*C*CN), 53.0 (Ar-OCH$_3$), 40.1 (*C*H) ppm; ESI-HRMS [M+H] calcd. for $C_{15}H_{13}N_2O_4S$ 317.0591, found 317.0598.

*2-amino-6-chloro-4-phenyl-4H-benzo[4,5]thieno[3,2-b]pyran-3-carbonitrile (**3i**).* Yellow solid, m.p. 231-233°C; IR (KBr): 3345, 3314, 3282, 2205, 1647, 1584, 1172, 817, 784 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (dd, *J* = 6.6, 2.2 Hz, 1H, Ar-*H*), 7.37 (m, 4H, Ar-*H*), 7.30 (m, 3H, Ar-*H*), 4.99 (s, 1H, C*H*), 4.78 (s, 2H, NH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.5, 142.3, 138.6, 135.7, 130.6, 129.0, 128.4, 128.1, 127.6, 126.1, 125.2, 119.7, 119.1, 118.3, 60.9 (*C*CN), 40.1 (*C*H) ppm; ESI-HRMS [M+H] calcd. for $C_{18}H_{12}N_2OSCl$ 339.0353, found 339.0354.

*Diethyl 2-amino-8-methyl-4H-benzo[4,5]thieno[3,2-b]pyran-3,4-dicarboxylate (**4**).* White solid, m.p. 139-141°C, IR (KBr): 3367, 3271, 2979, 2913, 1724, 1685, 1631, 804, 874 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.38 (s, 1H, Ar-*H*), 7.12 (dd, *J* = 8.4, 2.0 Hz, 1H, Ar-*H*), 6.64 (br, 2H, NH_2), 4.78 (s, 1H, C*H*), 4.10-4.29 (m, 4H, 2 × OCH_2CH$_3$), 2.41 (s, 3H, Ar-CH_3), 1.31 (t, *J* = 7.2 Hz, 3H, OCH$_2$CH_3), 1.26 (t, *J* = 7.2 Hz, 3H, OCH$_2$CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.2 (*C*OOEt), 169.0 (*C*OOEt), 160.6, 139.1, 134.3, 133.5, 129.4, 127.0, 122.2, 119.5, 112.8, 72.8 (*C*COOEt), 61.4 (OCH$_2$CH$_3$), 59.7 (OCH$_2$CH$_3$), 40.4 (*C*H), 21.3 (Ar-*C*H$_3$), 14.3 (OCH$_2$*C*H$_3$), 14.3 (OCH$_2$*C*H$_3$) ppm; ESI-HRMS [M+H] calcd. for $C_{18}H_{20}NO_5S$ 362.1057, found 362.1068.

Data Availability

The copies of NMR spectra data used to support the findings of this study are included within the supplementary information file(s) (available here).

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

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Supplementary Materials

NMR spectra of all new compound (PDF) and crystallographic data for compound **3a** and **4** (CIF). *(Supplementary Materials)*

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[23] CCDC 1882373 (**3a**) and 1888259 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/.