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Boron Trifluoride-Promoted Indium(III) Triflate-Catalyzed Sequential One-Pot Synthesis of (1,2-Diaryl-2-oxoethyl)malonates from *trans*-2-Aryl-3-nitrocyclopropane-1,1-dicarboxylates and Activated Arenes

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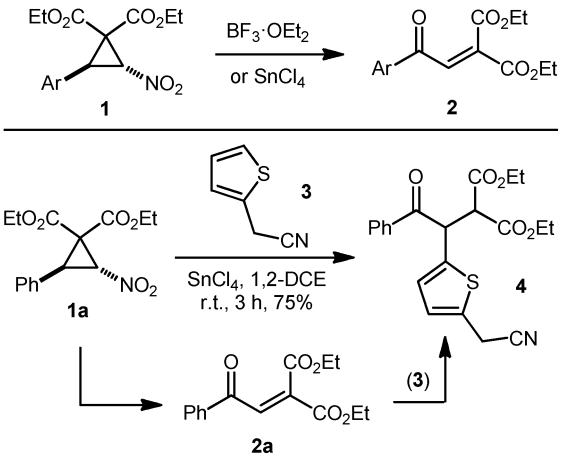
Abstract: A sequential one-pot synthesis of Michael adducts of aroylmethylidenemalonates with activated aromatics is described. The method involves treatment of *trans*-2-aryl-3-nitro-cyclopropane-1,1-dicarboxylates with boron trifluoride etherate to form aroylmethylidenemalonates *in situ* and then addition of activated aromatics such as indoles, carbazole, pyrrole, thiophenes, methoxybenzenes and benzodioxole followed by a catalytic amount of indium(III) triflate to the same reaction vessel. To prove the synthetic potential of the resulting Michael adducts, one of the adducts was transformed into a pharmaceutically interesting dihydropyridazinone derivative.

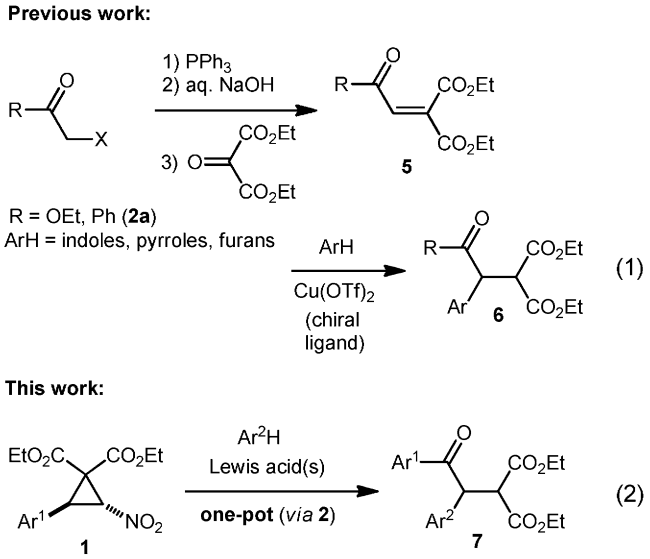
Keywords: aromatic substitution; C–C bond formation; (1,2-diaryl-2-oxoethyl)malonates; Lewis acids; Michael addition; synthetic methods

Introduction

The rich and diverse reactivity of donor-acceptor cyclopropanes has made them one of the most popular building blocks in organic synthesis.[1] They undergo numerous ring-opening,[2] ring-enlargement[3] and annulation reactions[4] providing access to an assortment of useful acyclic and cyclic compounds including natural products. Among various donor-acceptor cyclopropanes, nitro-substituted ones exhibit unique reactivity and they often undergo ring-opening/expansion reactions and rarely take part in annulation reactions.[5] Nevertheless, a considerable amount of attention has been paid to exploit the synthetic potential of different types of nitro-substituted donor-acceptor cyclopropanes. Charette and co-workers have studied the nucleophilic ring-opening reactions of 2-aryl-1-nitrocyclopropanecarboxylates for the synthesis of α-chiral ethers and amines[6] and pyrroles.[7] The Werz group has investigated the ring-enlargement reactions of this type of cyclopropanes for the preparation of cyclic nitronates (isooxazoline *N*-oxides).[8] Recently, Mattson et al., have reported the first ever annulation reaction of these cyclopropanes with nitrones as an access to highly functionalized oxazinanes.[9] In this line, our group is focusing attention on exploring the synthetic applications of 2-aryl-3-nitro-cyclopropane-1,1-dicarboxylates **1** (Scheme 1).[10] Upon treatment with $BF_3{\cdot}OEt_2$ or $SnCl_4$, these nitrocyclopropanedicarboxylates form aroylmethylidenemalonates (**2**) which serve as potential building blocks for various heterocycles.[10] During the course of our research, we observed that nitrocyclopropanedicarboxylate **1a** when



Scheme 1. Formation of aroylmethylidenemalonates and subsequent Michael addition reaction.



Scheme 2. Methods of synthesis of Michael adducts of aroylmethylidenemalonates with activated aromatics.

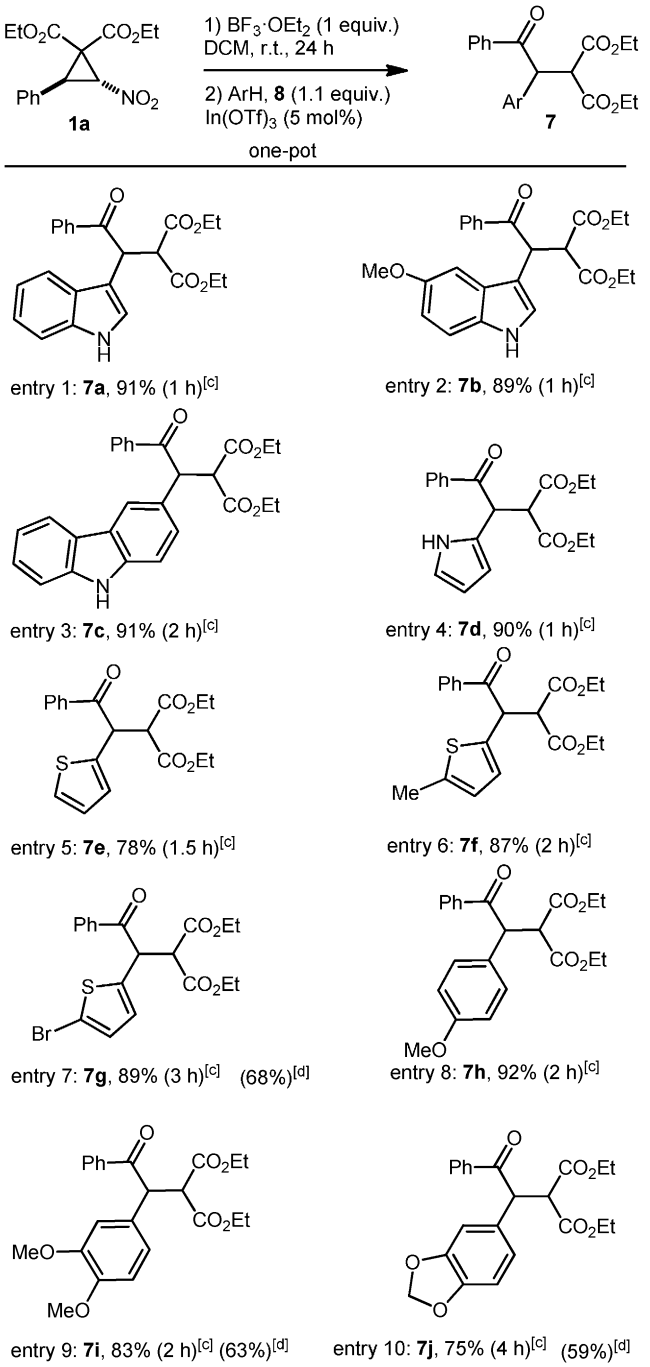
reacted with thiophene-2-acetonitrile (**3**) in the presence of $SnCl_4$ gave a β-ketomalonate **4** by the Michael addition reaction of **3** to the *in situ* generated diethyl benzoylmethylidenemalonate (**2a**) (Scheme 1).[10b]

Yamazaki and co-workers have extensively investigated the synthetic potential of ethenetricarboxylates **5**, including related aroylmethylidenemalonate **2a** [Scheme 2, Eq. (1)].[11] In their study, the ene tri(di)esters **5/2a**, prepared by the Wittig reaction of oxomalonates with the corresponding triphenylmethylenephosphoranes, have been subjected to asymmetric Michael addition reactions with activated aromatic compounds such as indoles, pyrroles and furans in the presence of $Cu(OTf)_2$ and chiral ligands to obtain the Michael adducts **6**.[11c,f] Obviously, our observation outlined in Scheme 1 suggested to us that similar Michael adducts **7** could be obtained in a sequential one-pot manner by the treatment of nitrocyclopropanedicarboxylates **1** with activated aromatics in the presence of Lewis acids [Scheme 2, Eq. (2)]. Inspired by the fact that β-ketomalonates are resourceful synthetic intermediates,[12] we set out to investigate the scope of the one-pot synthesis in detail as such a study could furnish a number of synthetically useful Michael adducts of aroylmethylidenemalonates with activated aromatics.

Results and Discussion

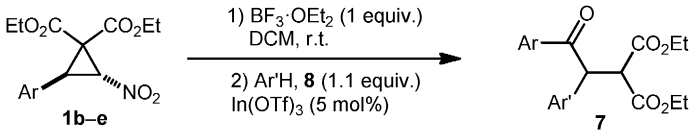
We began the study by reacting nitrocyclopropanedicarboxylate **1a** with indole (**8a**) (Table 1, entry 1). When an equimolar mixture of **1a** and **8a** is heated under reflux in the presence of $SnCl_4$ (1 equiv.) in 1,2-dichloroethane [as per the conditions reported earlier for thiophene-2-acetonitrile (**3**), Scheme 1],[10b] to our surprise, the starting materials did not undergo any change even after 24 h. We reasoned that this might be due to the strong coordination of $SnCl_4$ to the

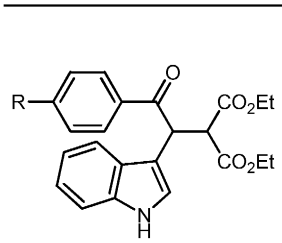
Table 1. Synthesis of Michael adducts from **1a** using various activated aromatics.[a,b]



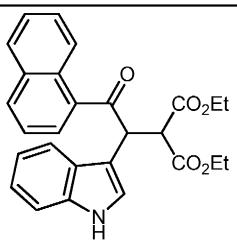
[a] Isolated yields.
[b] Furan gave a complicated mixture.
[c] Time in parenthesis indicates the time required for the second step.
[d] Yield obtained using $SnCl_4$ (24 h).

Table 2. Synthesis of Michael adducts from various nitrocyclopropanedicarboxylates and representative activated aromatics.[a]

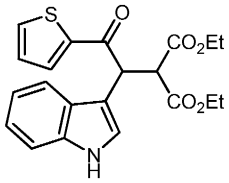




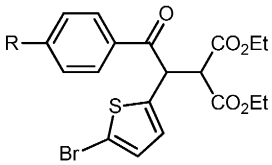
7k: R = Me, 82% (15 h)[b]
7l: R = Cl, 75% (25 h)[b]



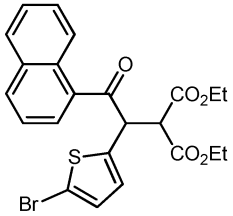
7m, 78% (24 h)[b]



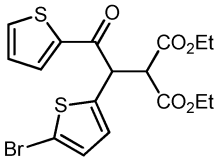
7n, 89% (3 h)[b]



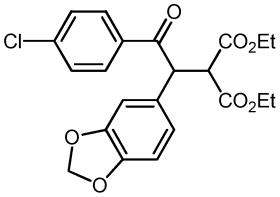
7o: R = Me, 62% (13 h)[b]
7p: R = Cl, 68% (28 h)[b]



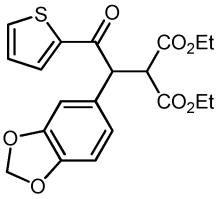
7q, 61% (11 h)[b]



7r, 75% (3 h)[b]



7s, 68% (28 h)[b]

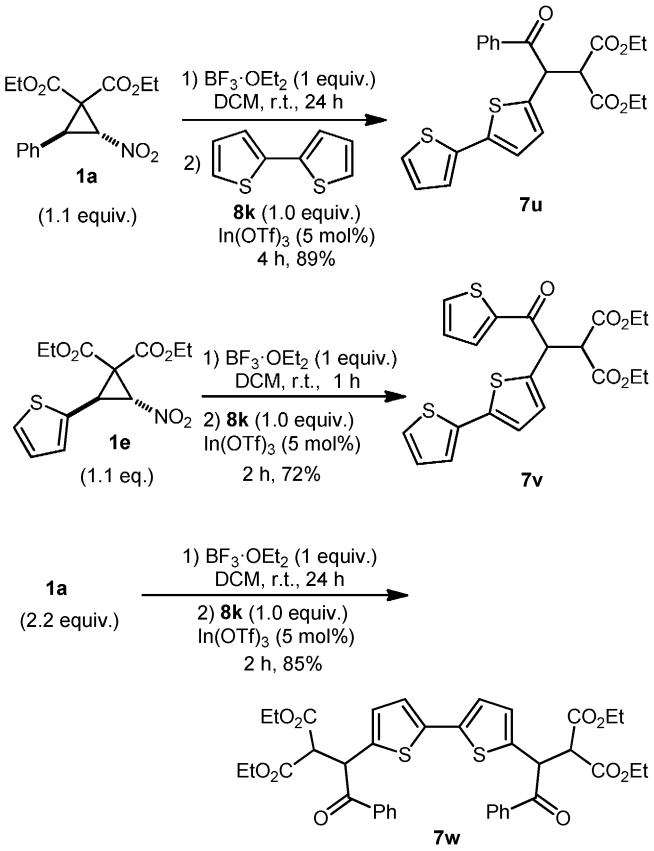


7t, 75% (10 h)[b]

[a] Isolated yields.
[b] Time in parenthesis indicates the total time required for both the steps.

indole nitrogen and hence we switched the Lewis acid to $BF_3{\cdot}OEt_2$ for effecting the reaction. Although **1a** was completely converted into diethyl benzoylmethylidenemalonate (**2a**) with $BF_3{\cdot}OEt_2$, the subsequent Michael addition reaction did not take place. Since $In(OTf)_3$ is a well-known catalyst for various organic transformations,[13] we envisaged that by adding a catalytic amount of $In(OTf)_3$ to the reaction mixture after the formation of **2a**, the desired result could be achieved. Accordingly, when **1a** was treated with $BF_3{\cdot}OEt_2$ (1 equiv.) in DCM, it formed **2a** *in situ* after 24 h (judged by TLC) and then indole was added to the same reaction flask followed by $In(OTf)_3$ (5 mol%). Pleasingly, the reaction furnished the expected Michael adduct **3a** in an excellent yield of 91% (Table 1, entry 1). Satisfied with the results, we started reacting **1a** with other activated aromatics such as 5-methoxyindole (**8b**), carbazole (**8c**), pyrrole (**8d**), thiophene (**8e**), 2-methylthiophene (**8f**), 2-bromothiophene (**8g**), anisole (**8h**), 1,2-dimethoxybenzene (**8i**) and benzodioxole (**8j**) under the reaction conditions (entries 2–10). In all cases, the expected Michael adducts **7b–j** were produced in good to excellent yields. We also repeated the reaction between **1a** and thiophene-2-acetonitrile (**3**) (see Scheme 1) under the present reaction conditions. The reaction afforded a higher yield of **4** (88%) as compared with the yield (75%) obtained earlier using $SnCl_4$ (Scheme 1). We also tested the reactions of **1a** with 2-bromothiophene (**8g**) and benzodioxole (**8j**) (entries 7 and 10) using $SnCl_4$; even though the expected Michael adducts **7g** and **7j** were produced in both cases, their yields (68% and 59%, respectively) were consistently low. Thus, the use of $BF_3{\cdot}OEt_2$ and then $In(OTf)_3$ seems to effect the transformation more efficiently than using $SnCl_4$ alone. We also screened a number of other Lewis acids [$AlCl_3$, $FeCl_3$, $InCl_3$, $TiCl_4$, $ZnCl_2$, AgOTf, $Cu(OTf)_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, $Zn(OTf)_2$] under different conditions, but none of them gave any reasonable results. It is worthwhile to mention that Yamazaki and co-workers had not used carbazole, thiophenes and benzodioxole previously as Michael partners in their work.[11]

Next, we examined the scope of the reaction for nitrocyclopropanedicarboxylates **1** having different aromatic rings with representative activated aromatics, namely, indole (**8a**), 2-bromothiophene (**8g**) and benzodioxole (**8j**) (Table 2). The reactions tolerated phenyl rings substituted with electron-releasing and halogen substituents, bulky naphthyl ring and hetero-

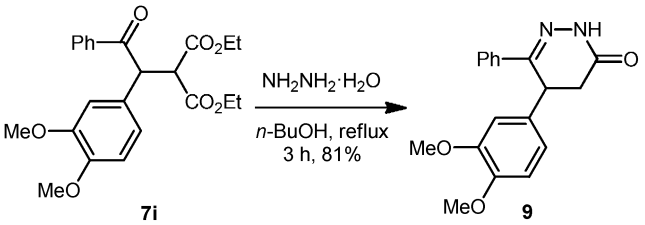


Scheme 3. Synthesis of mono-and bis-Michael adducts using 2,2′-bithiophene.

aromatic thienyl ring on the nitrocyclopropanedicarboxylates. It may be noted that indole, thiophene and benzodioxole ring systems are found in numerous natural products, drug/drug candidates and functional materials.[14]

We envisaged that when 2,2′-bithiophene is used as an activated aromatic in the one-pot synthesis, mono- and bis-Michael adducts could be obtained by varying the amount of nitrocyclopropanedicarboxylates. Thus, when 1.1 equiv. of phenylnitrocyclopropanedicarboxylate **1a** or 2-thienylnitrocyclopropanedicarboxylate **1e** was employed in the transformation, the mono-Michael adducts **7u** and **7v** were produced in 89 and 72% yields, respectively (Scheme 3). On the other hand, when 2.2 equiv. of **1a** were used, the corresponding bis-Michael adduct **7w** was produced in 85% yield. It is worthy to note that many bithiophene derivatives find use as active materials in organic electronics.[15]

With the availability of a variety of Michael adducts of aroylmethylidenemalonates with activated aromatics, we next focused our attention on probing their synthetic potential. The dihydropyridazinone is an important heterocyclic motif found in numerous cardiotonic agents including the drugs, levosimendan and pimobendan.[16] The Michael adducts prepared in the present study could serve as potential precursors for this class of heterocycles. To prove this point, we treated the Michael adduct **7i** with hydrazine hydrate in refluxing *n*-BuOH for 3 h, which afforded the dihydropyridazinone derivative **9** in 81% yield through cyclocondensation and decarbethoxylation (Scheme 4).



Scheme 4. A synthetic application of Michael adduct **7i**.

Conclusions

In summary, we have developed a sequential one-pot synthesis of Michael adducts of aroylmethylidenemalonates with the activated aromatics in the presence of Lewis acids. Accordingly, the treatment of *trans*-2-aryl-3-nitrocyclopropane-1,1-dicarboxylates with boron trifluoride etherate generates aroylmethylidenemalonates *in situ* and the addition of activated aromatics such as indoles, carbazole, pyrrole, thiophenes, methoxybenzenes and benzodioxole followed by a catalytic amount of indium(III) triflate to the same reaction vessel gives Michael adducts of aroylmethylidenemalonates. These Michael adducts are versatile synthetic precursors as exemplified by the synthesis of a pharmaceutically interesting dihydropyridazinone derivative. Work is underway to develop a chiral version of the methodology.

Experimental Section

General Methods

Melting points were determined by the open capillary tube method and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer. High resolution mass spectra (ESI) were recorded on a Q-TOF mass spectrometer. IR spectra were recorded on an FT-IR spectrometer. Low resolution mass spectra (ESI) were recorded on an LC mass spectrometer. Elemental analyses were performed on a CHN analyzer. Thin layer chromatography (TLC) was performed on pre-coated alumina sheets and detected under UV light. Silica gel (100–200 mesh) was used for column chromatography.

General Procedure for the Synthesis of Michael Adducts 7a–w

To a solution of nitrocyclopropane **1** (1 mmol) (in the case of **7w**, 2.2 equiv, of **1a** were used) in dichloromethane

(5 mL) was added $BF_3{\cdot}OEt_2$ (0.13 mL; 1 mmol) at room temperature. The reaction mixture was stirred at room temperature until the starting material disappeared completely (as judged by TLC). To the same reaction flask, activated aromatic **8** (1.1 mmol) was added followed by $In(OTf)_3$ (28 mg; 5 mol%) and the reaction mixture was stirred at room temperature. After completion of the reaction, it was quenched with water. The organic layer was separated, washed with water, dried (anhydrous Na_2SO_4) and the solvent was removed under reduced pressure. The crude product **7** was purified by column chromatography using 5–10% ethyl acetate/hexane.

Diethyl 2-[1-(1*H*-indol-3-yl)-2-oxo-2-phenylethyl]malonate (7a):[11c] yellow oil; yield: 357 mg (91%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (s, 1H), 7.98 (t, J = 4.4 Hz, 2H), 7.79–7.76 (m, 1H), 7.44–7.40 (m, 1H), 7.33–7.25 (m, 3H), 7.17–7.14 (m, 2H), 7.03 (d, J = 2.4 Hz, 1H), 5.64 (d, J = 11.6 Hz, 1H), 4.54 (d, J = 11.6 Hz, 1H), 4.21–4.15 (m, 2H), 3.85–3.74 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H), 0.80 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.3, 168.5, 136.3, 136.0, 132.9, 128.7, 128.5, 126.1, 124.0, 122.4, 120.1, 119.0, 111.3, 109.2, 61.8, 61.4, 55.8, 44.1, 14.0, 13.5.

Diethyl 2-[1-(5-methoxy-1*H*-indol-3-yl)-2-oxo-2-phenylethyl]malonate (7b): dark brown oil; yield: 376 mg (89%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (s, 1H), 7.98 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.4 Hz, 1H), 7.31 (t, J = 7.6 Hz, 2H), 7.19 (d, J = 2.0 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 6.80 (q, J = 6.4 Hz, 1H), 5.59 (d, J = 11.2 Hz, 1H), 4.54 (d, J = 11.6 Hz, 1H), 4.21–4.13 (m, 2H), 3.87 (s, 3H), 3.85–3.78 (m, 2H), 1.21 (t, J = 7.0 Hz, 3H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.3, 168.7, 168.6, 154.4, 136.1, 132.9, 131.5, 128.7, 128.5, 126.6, 124.8, 112.7, 112.2, 108.6, 100.6, 61.8, 61.4, 55.9, 55.6, 44.4, 14.0, 13.5; IR (KBr): ν = 3394 (N-H), 1732 (C=O, ester), 1679 (C=O) cm^{-1}; MS (ESI): m/z = 446.07 [M + Na$^+$]; anal. calcd. for $C_{24}H_{25}NO_6$: C 68.07, H 5.95, N 3.31; found: C 68.26, H 5.89, N 3.36.

Diethyl 2-[1-(9*H*-carbazol-3-yl)-2-oxo-2-phenylethyl]malonate (7c): yellow semisolid; yield: 403 mg (91%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (s, 1H), 8.01 (t, J = 15.6 Hz, 4H), 7.41–7.18 (m, 8H), 5.50 (d, J = 11.6 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 4.20–4.13 (m, 2H), 3.90–3.82 (m, 2H), 1.22 (t, J = 7.4 Hz, 3H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.9, 168.5, 168.3, 139.9, 139.1, 136.1, 133.0, 129.0, 128.5, 126.5, 126.2, 125.2, 123.9, 122.9, 120.9, 120.4, 119.6, 111.2, 110.7, 61.9, 61.4, 56.6, 53.2, 14.0, 13.8; IR (KBr): ν = 3394 (N-H), 1733 (C=O, ester), 1677 (C=O) cm^{-1}; HR-MS (ESI): m/z = 444.1809, calcd. for $C_{27}H_{25}NO_5$: 444.1806 [M + H$^+$].

Diethyl 2-[2-oxo-2-phenyl-1-(1*H*-pyrrol-2-yl)-ethyl]malonate (7d): dark brown oil; yield: 309 mg (90%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (s, 1H), 8.01 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.8 Hz, 2H), 6.68 (q, J = 2.4 Hz, 1H), 6.07–6.03 (m, 2H), 4.95 (d, J = 11.2 Hz, 1H), 4.40 (d, J = 11.2 Hz, 1H), 4.18–4.04 (m, 4H), 1.18 (t, J = 7.2 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 168.4, 168.0, 135.9, 133.3, 128.8, 128.6, 123.4, 119.1, 109.2, 109.0, 61.9, 61.7, 55.5, 46.0, 13.9; IR (KBr): ν = 3392 (N-H), 1731 (C=O, ester), 1676 (C=O) cm^{-1}; MS (ESI): m/z = 366.13 [M + Na$^+$]; anal. calcd. for $C_{19}H_{21}NO_5$: C 66.46, H 6.16, N 4.08; found: C 66.56, H 6.29, N 4.16.

Diethyl 2-(2-oxo-2-phenyl-1-thiophen-2-yl-ethyl)malonate (7e): yellow oil; yield: 281 mg (78%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.4 Hz, 2H), 7.51 (t, J = 7.2 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.17 (d, J = 4.8 Hz, 1H), 6.95 (d, J = 3.2 Hz, 1H), 6.88 (t, J = 4.4 Hz, 1H), 5.61 (d, J = 11.2 Hz, 1H), 4.46 (d, J = 11.6 Hz, 1H), 4.19–4.11 (m, 2H), 4.09–4.01 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.3, 167.8, 136.3, 135.6, 133.3, 128.9, 128.6, 127.6, 127.3, 126.2, 62.0, 61.6, 56.5, 47.4, 13.9, 13.85; IR (KBr): ν = 1733 (C=O, ester), 1684 (C=O) cm^{-1}; MS (ESI): m/z = 383.09 [M + Na$^+$]; anal. calcd. for $C_{19}H_{20}O_5S$: C 63.32, H 5.59; found: C 63.40, H 5.73.

Diethyl 2-[1-(5-methylthiophen-2-yl)-2-oxo-2-phenylethyl]malonate (7f): yellow oil; yield: 325 mg (87%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.71 (t, J = 3.2 Hz, 1H), 6.49 (t, J = 1.6 Hz, 1H), 5.45 (d, J = 11.2 Hz, 1H), 4.40 (d, J = 11.2 Hz, 1H), 4.17–4.02 (m, 4H), 2.33 (s, 3H), 1.17 (t, J = 7.2 Hz, 3H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.7, 167.94, 167.85, 163.7, 140.6, 134.2, 131.3, 128.5, 127.3, 125.3, 113.8, 61.8, 61.6, 56.4, 47.3, 15.3, 13.91, 13.87; IR (KBr): ν = 1740 (C=O, ester), 1674 (C=O) cm^{-1}; HR-MS (ESI): m/z = 375.1261, calcd. for $C_{20}H_{22}O_5S$: 375.1261 [M + H$^+$].

Diethyl 2-[1-(5-bromothiophen-2-yl)-2-oxo-2-phenylethyl]malonate (7g): yellow oil; yield: 390 mg (89%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 7.6 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 6.84 (d, J = 3.2 Hz, 1H), 6.72 (d, J = 3.2 Hz, 1H), 5.51 (d, J = 11.2 Hz, 1H), 4.41 (d, J = 11.2 Hz, 1H), 4.18–4.07 (m, 4H), 1.21–1.13 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.8, 167.6, 167.5, 137.9, 135.4, 133.6, 130.1, 128.9, 128.7, 128.1, 112.8, 62.1, 61.8, 56.3, 47.5, 13.9; IR (KBr): ν = 1745 (C=O, ester), 1679 (C=O) cm^{-1}; HR-MS (ESI): m/z = 439.0209, calcd. for $C_{19}H_{19}BrO_5S$: 439.0209 [M + H$^+$].

Diethyl 2-[1-(4-methoxyphenyl)-2-oxo-2-phenylethyl]malonate (7h): yellow oil; yield: 353 mg (92%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 8.4 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.38 (t, J = 7.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 5.27 (d, J = 11.2 Hz, 1H), 4.41 (d, J = 11.2 Hz, 1H), 4.21–4.12 (m, 2H), 4.00 (q, J = 7.2 Hz, 2H), 3.72 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.5, 168.2, 168.1, 159.3, 136.0, 133.0, 130.1, 128.9, 128.5, 126.4, 114.5, 61.8, 61.4, 56.0, 55.2, 52.1, 13.9, 13.8; IR (KBr): ν = 1733 (C=O, ester), 1681 (C=O) cm^{-1}; MS (ESI): m/z = 407.13 [M + Na$^+$]; anal. calcd. for $C_{22}H_{24}O_6$: C 68.74, H 6.29; found: C 68.68, H 6.19.

Diethyl 2-[1-(3,4-dimethoxyphenyl)-2-oxo-2-phenylethyl]-malonate (7i): brown oil; yield: 344 mg (83%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, J = 8.4 Hz, 2H), 7.48 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 6.87 (d, J = 8.4 Hz, 1H), 6.76 (t, J = 1.0 Hz, 2H), 5.28 (d, J = 11.6 Hz, 1H), 4.42 (d, J = 11.6 Hz, 1H), 4.21–4.14 (m, 2H), 3.98 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H), 1.03 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.6, 168.2, 168.1, 149.3, 148.8, 136.1, 133.1, 128.8, 128.5, 126.8, 121.7, 111.54, 111.50, 61.8, 61.4, 56.01, 55.96, 55.8, 52.5, 13.93, 13.88; IR (KBr): ν = 1733 (C=O, ester), 1680 (C=O) cm^{-1}; MS (ESI): m/z = 437.16 [M + Na$^+$]; anal. calcd. for $C_{23}H_{26}O_7$: C 66.61, H 6.32; found: C 66.80, H 6.16.

Diethyl 2-(1-benzo[1,3]dioxol-5-yl-2-oxo-2-phenylethyl)-malonate (7j): yellow oil; yield: 298 mg (75%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7. 98 (d, J = 8.0 Hz, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7. 40 (t, J = 7.4 Hz, 2H), 6.78 (s, 2H), 6.69 (d, J = 8.4 Hz, 1H), 5.89 (d, J = 6.8 Hz, 2H), 5.23 (d, J = 11.2 Hz, 1H), 4.37 (d, J = 11.2 Hz, 1H), 4.20–4.13 (m, 2H), 4.01 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.3, 168.1, 168.0, 148.1, 147.4, 135.9, 133.1, 128.9, 128.6, 128.0, 122.7, 109.0, 108.7, 101.2, 61.9, 61.4, 56.0, 52.4 13.93, 13.90; IR (KBr): ν = 1738 (C=O, ester), 1670 (C=O) cm^{-1}; HR-MS (ESI): m/z = 399.1440, calcd. for $C_{22}H_{22}O_7$: 399.1438 [M + H$^+$].

Diethyl 2-[1-(1*H*-indol-3-yl)-2-oxo-2-(4-methylphenyl)-ethyl]malonate (7k): yellow oil; yield: 334 mg (82%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (s, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.77 (t, J = 4.4 Hz, 1H), 7.28 (d, J = 3.6 Hz, 1H), 7.16–7.11 (m, 4H), 7.05 (q, J = 2.4 Hz, 1H), 5.63 (d, J = 11.2 Hz, 1H), 4.53 (d, J = 11.2 Hz, 1H), 4.24–4.14 (m, 2H), 3.85–3.74 (m, 2H), 2.30 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H), 0.81 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.9, 168.54, 168.49, 143.7, 136.2, 133.5, 129.2, 128.8, 126.2, 123.9, 122.4, 120.1, 119.0, 111.3, 109.6, 61.7, 61.3, 55.8, 44.0, 21.5, 14.0, 13.5; IR (KBr): ν = 3389 (N-H), 1732 (C=O, ester), 1675 (C=O) cm^{-1}; MS (ESI): m/z = 430.16 [M + Na$^+$]; anal. calcd. for $C_{24}H_{25}NO_5$: C 70.74, H 6.18, N 3.44; found: C 70.60, H 6.29, N 3.53.

Diethyl 2-[2-(4-chlorophenyl)-1-(1*H*-indol-3-yl)-2-oxo-ethyl]malonate (7l): dark brown oil; yield: 320 mg (75%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (s, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.73 (q, J = 3.2 Hz, 1H), 7.23 (d, J = 8.4 Hz, 3H), 7.13 (q, J = 3.2 Hz, 2H), 6.95 (d, J = 2.4 Hz, 1H), 5.58 (d, J = 11.2 Hz, 1H), 4.54 (d, J = 11.2 Hz, 1H), 4.22–4.12 (m, 2H), 3.84–3.74 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H), 0.79 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.2, 168.6, 168.5, 139.4, 136.3, 134.3, 130.1, 128.8, 126.0, 124.2, 122.5, 120.2, 118.7, 111.6, 108.6, 61.9, 61.5, 55.7, 44.3, 14.0, 13.5; IR (KBr): ν = 3395 (N-H), 1731 (C=O, ester), 1680 (C=O) cm^{-1}; MS (ESI): m/z = 449.93 [M + Na$^+$]; anal. calcd. for $C_{23}H_{22}ClNO_5$: C 64.56, H 5.18, N 3.27; found: C 64.63, H 5.29, N 3.32.

Diethyl 2-[1-(1*H*-indol-3-yl)-2-naphthalen-1-yl-2-oxo-ethyl]malonate (7m): yellow oil; yield: 346 mg (78%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36–8.33 (m, 1H), 8.15–8.13 (m, 2H), 7.84 (d, J = 8.0 Hz, 1H), 7.75–7.73 (m, 2H), 7.44–7.21 (m, 3H), 7.20–7.08 (m, 4H), 5.68 (d, J = 11.2 Hz, 1H), 4.68 (d, J = 11.2 Hz, 1H), 4.27–4.21 (m, 2H), 3.84–3.79 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H), 0.80 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.4, 168.7, 168.4, 136.2, 135.5, 133.8, 132.4, 130.8, 128.2, 127.6, 126.3, 126.2, 125.6, 124.4, 124.0, 122.4, 120.0, 119.1, 111.2, 108.6, 61.9, 61.4, 55.5, 47.6, 14.1, 13.5; IR (KBr): ν = 3392 (N-H), 1730 (C=O, ester), 1678 (C=O) cm^{-1}; MS (ESI): m/z = 466.02 [M + Na$^+$]; anal. calcd. for $C_{27}H_{25}NO_5$: C 73.12, H 5.68, N 3.16; found: C 73.30, H 5.65, N 3.05.

Diethyl 2-[1-(1*H*-indol-3-yl)-2-oxo-2-thiophen-2-ylethyl]-malonate (7n): yellow semisolid; yield: 355 mg (89%); mp 86–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (s, 1H), 7.77–7.74 (m, 2H), 7.43 (d, J = 4.4 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 2.4 Hz, 2H), 7.04 (s, 1H), 6.90 (d, J = 3.6 Hz, 1H), 5.46 (d, J = 11.6 Hz, 1H), 4.54 (d, J = 11.2 Hz, 1H), 4.20–4.16 (m, 2H), 3.84–3.73 (m, 2H), 1.20 (t, J = 7.0 Hz, 3H), 0.78 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.3, 168.4, 168.3, 142.6, 136.3, 133.7, 132.7, 128.1, 126.2, 124.2, 122.4, 120.1, 118.9, 111.6, 109.2, 61.9, 61.5, 55.5, 45.5, 14.0, 13.5; IR (KBr): ν = 3390 (N-H), 1730 (C=O, ester), 1657 (C=O) cm^{-1}; MS (ESI): m/z = 422.00 [M + Na$^+$]; anal. calcd. for $C_{21}H_{21}NO_5S$: C 63.14, H 5.30, N 3.51; found: C 63.29, H 5.29, N 3.65.

Diethyl 2-[1-(5-bromothiophen-2-yl)-2-oxo-2-tolylethyl]-malonate (7o): yellow oil; yield: 290 mg (62%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, J = 7.6 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 3.6 Hz, 1H), 6.71 (d, J = 3.6 Hz, 1H), 5.49 (d, J = 11.2 Hz, 1H), 4.40 (d, J = 11.2 Hz, 1H), 4.18–4.05 (m, 4H), 2.38 (s, 3H), 1.19 (t, J = 7.0 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.4, 167.7, 167.5, 144.6, 138.3, 132.8, 130.0, 129.5, 129.0, 128.0, 112.7, 62.0, 61.8, 56.2, 47.4, 21.7, 13.9; IR (KBr): ν = 1745 (C=O, ester), 1679 (C=O) cm^{-1}; MS (ESI): m/z = 475.02 [M + Na$^+$]; anal. calcd. for $C_{20}H_{21}BrO_5S$: C 52.99, H 4.67; found: C 53.10, H 4.49.

Diethyl 2-[1-(5-bromothiophen-2-yl)-2-(4-chlorophenyl)-2-oxo-ethyl]malonate (7p): yellow oil; yield: 321 mg (68%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.4 Hz, 2H), 7.41 (t, J = 8.4 Hz, 2H), 6.84 (d, J = 4.0 Hz, 1H), 6.70 (d, J = 3.6 Hz, 1H), 5.44 (d, J = 11.2 Hz, 1H), 4.39 (d, J = 11.2 Hz, 1H), 4.19–4.06 (m, 4H), 1.20 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.7, 167.5, 167.4, 140.1, 137.5, 133.7, 130.3, 130.1, 129.1, 128.2, 113.0, 62.2, 61.9, 56.2, 47.5, 13.9; IR (KBr): ν = 1735 (C=O, ester), 1680 (C=O) cm^{-1}; MS (ESI): m/z = 494.96 [M + Na$^+$]; anal. calcd. for $C_{19}H_{18}BrClO_5S$: C 48.17, H 3.83; found: C 48.40, H 3.69.

Diethyl 2-[1-(5-bromothiophen-2-yl)-2-naphthalen-1-yl-2-oxoethyl]malonate (7q): yellow oil; yield: 297 mg (61%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, J = 7.2 Hz, 1H), 8.17 (d, J = 7.2 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.57–7.47 (m, 3H), 6.80 (d, J = 4.0 Hz, 1H), 6.72 (d, J = 3.6 Hz, 1H), 5.56 (d, J = 11.2 Hz, 1H), 4.50 (d, J = 11.2 Hz, 1H), 4.20 (q, J = 5.2 Hz, 2H), 4.16–4.07 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.5, 167.8, 167.5, 137.5, 134.4, 133.9, 133.30, 133.29, 130.8, 130.0, 128.4, 128.3, 126.5, 125.5, 124.3, 112.8, 62.2, 61.9, 56.1, 51.1, 14.0, 13.9; IR (KBr): ν = 1745 (C=O, ester), 1658 (C=O) cm^{-1}; HR-MS (ESI): m/z = 489.0369, calcd. for $C_{23}H_{21}BrO_5S$: 489.0366 [M + H$^+$].

Diethyl 2-[1-(5-bromothiophen-2-yl)-2-oxo-2-thiophen-2-yl-ethyl]malonate (7r): white solid; yield: 333 mg (75%); mp 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, J = 3.6 Hz, 1H), 7.64 (d, J = 4.8 Hz, 1H), 7.11 (t, J = 4.4 Hz, 1H), 6.84 (d, J = 3.6 Hz, 1H), 6.76 (d, J = 3.6 Hz, 1H), 5.30 (d, J = 11.2 Hz, 1H), 4.53 (d, J = 11.2 Hz, 1H), 4.21–4.03 (m, 4H), 1.18 (t, J = 7.2 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.4, 167.4, 167.3, 141.9, 138.0, 134.8, 133.4, 130.0, 128.4, 128.1, 112.8, 62.2, 61.9, 55.8, 49.0, 13.89, 13.87; IR (KBr): ν = 1745 (C=O, ester), 1655 (C=O) cm^{-1}; MS (ESI): m/z = 466.96 [M + Na$^+$]; anal. calcd. for $C_{17}H_{17}BrO_5S_2$: C 45.85, H 3.85; found: C 45.90, H 3.99.

Diethyl 2-[1-benzo[1,3]dioxol-5-yl-2-(4-chlorophenyl)-2-oxoethyl]malonate (7s): yellow oil; yield: 293 mg (68%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 6.76–6.67 (m, 3H), 5.87 (d, J = 6.8 Hz, 2H), 5.15 (d, J = 11.6 Hz, 1H), 4.34 (d, J = 11.2 Hz, 1H), 4.19–4.09 (m, 2H), 4.03–3.97 (m, 2H), 1.19 (t, J =

7.2 Hz, 3H), 1.04 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.2, 168.1, 167.8, 148.2, 147.6, 139.6, 134.2, 130.3, 128.9, 127.6, 122.7, 108.9, 108.8, 101.3, 61.9, 61.5, 55.9, 52.4, 13.93, 13.89; IR (KBr): ν=1740 (C=O, ester), 1658 (C=O) cm^{-1}; MS (ESI): m/z=455.09 [M+Na$^+$]; anal. calcd. for $C_{22}H_{21}ClO_7$: C 61.05, H 4.89; found: C 61.20, H 5.01.

Diethyl 2-(1-benzo[1,3]dioxol-5-yl-2-oxo-2-thiophen-2-yl-ethyl)malonate (7t): yellow oil; yield: 303 mg (75%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.54 (d, J=0.8 Hz, 1H), 7.22 (q, J=3.2 Hz, 1H), 6.83–6.79 (m, 2H), 6.72–6.69 (m, 1H), 6.48 (q, J=2.0 Hz, 1H), 5.90 (d, J=6.8 Hz, 2H), 5.03 (d, J=12.0 Hz, 1H), 4.36 (d, J=11.6 Hz, 1H), 4.19–4.13 (m, 2H), 4.03–3.97 (m, 2H), 1.20 (t, J=7.2 Hz, 3H), 1.04 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=186.1, 168.0, 167.8, 151.6, 148.0, 147.5, 146.9, 127.8, 122.7, 118.6, 112.5, 109.1, 108.6, 101.2, 62.0, 61.5, 55.0, 52.4, 13.87, 13.85; IR (KBr): ν=1732 (C=O, ester), 1684 (C=O) cm^{-1}; MS (ESI): m/z=427.08 [M+Na$^+$]; anal. calcd. for $C_{20}H_{20}O_7S$: C 59.40, H 4.98; found: C 59.51, H 5.10.

Diethyl 2-(1-[2,2′]bithiophenyl-5-yl-2-oxo-2-phenylethyl)-malonate (7u): yellow semisolid; yield: 393 mg (89%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.05 (d, J=7.6 Hz, 2H), 7.53 (t, J=7.4 Hz, 1H), 7.44 (t, J=7.6 Hz, 2H), 7.17 (d, J=5.2 Hz, 1H), 7.08 (d, J=3.6 Hz, 1H), 6.95 (q, J=4.2 Hz, 2H), 6.87 (d, J=3.6 Hz, 1H), 5.56 (d, J=11.2 Hz, 1H), 4.48 (d, J=11.2 Hz, 1H), 4.22–4.05 (m, 4H), 1.20 (t, J=7.2 Hz, 3H), 1.13 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.0, 167.7, 167.7, 138.4, 136.9, 135.5, 135.1, 133.5, 129.0, 128.7, 128.4, 127.8, 124.6, 123.9, 123.7, 62.1, 61.8, 56.3, 47.5, 13.9; IR (KBr): ν=1752 (C=O, ester), 1654 (C=O) cm^{-1}; MS (ESI): m/z=465.08 [M+Na$^+$]; anal. calcd. for $C_{23}H_{22}O_5S_2$: C 62.42, H 5.01; found: C 62.49, H 5.12.

Diethyl 2-(1-[2,2′]bithiophenyl-5-yl-2-oxo-2-thiophen-2-yl-ethyl)malonate (7v): yellow oil; yield: 323 mg (72%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.81 (dd, J=0.8 & 4.0 Hz, 1H), 7.62 (dd, J=1.2 & 4.8 Hz, 1H), 7.16 (dd, J=1.2 & 5.2 Hz, 1H), 7.10–7.18 (m, 2H), 6.96–6.94 (m, 2H), 6.90 (d, J=3.6 Hz, 1H), 5.36 (d, J=11.6 Hz, 1H), 4.45 (d, J=11.6 Hz, 1H), 4.18–4.07 (m, 4H), 1.19 (t, J=7.0 Hz, 3H), 1.10 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=188.6, 167.54, 167.52, 142.1, 138.3, 136.8, 135.2, 134.7, 133.4, 128.39, 128.36, 127.8, 124.7, 123.9, 123.6, 62.1, 61.8, 55.9, 48.9, 14.0, 13.9; IR (KBr): 1746 (C=O, ester), 1655 (C=O) cm^{-1}; MS (ESI): m/z=471.04 [M+Na$^+$]; anal. calcd. for $C_{21}H_{20}O_5S_3$: C 56.23, H 4.49; found: C 56.40, H 4.63.

Diethyl 3-[5′-(1-benzoyl-2,2-bis-ethoxycarbonyl-ethyl)-[2,2′]bithiophenyl-5-yl]-2-ethoxycarbonyl-4-oxo-4-phenylbutyrate (7w): white solid; yield: 610 mg (85%); mp 166–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.00 (d, J=7.6 Hz, 2H), 7.49 (t, J=6.8 Hz, 1H), 7.40 (t, J=7.6 Hz, 2H), 6.86–6.82 (m, 2H), 5.53 (d, J=11.2 Hz, 1H), 4.43 (d, J=11.2 Hz, 1H), 4.17–4.06 (m, 4H), 1.17 (t, J=7.2 Hz, 3H), 1.10 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=195.9, 167.6, 137.8, 135.5, 135.4, 133.5, 128.9, 128.7, 128.5, 123.8, 62.1, 61.8, 56.3, 47.5, 13.9; IR (KBr): ν=1749 (C=O, ester), 1675 (C=O) cm^{-1}; MS (ESI): m/z=741.18 [M+Na$^+$]; anal. calcd. for $C_{38}H_{38}O_{10}S_2$: C 63.49, H 5.33; found: C 63.60, H 5.29.

5-(3,4-Dimethoxyphenyl)-6-phenyl-4,5-dihydro-2*H*-pyridazin-3-one (9)

To a solution of Michael adduct **7i** (1 mmol) in *n*-BuOH (5 mL) was added hydrazine hydrate (1.1 mmol) and the reaction mixture was heated under reflux. After completion of the reaction (3 h), the solvent was removed under reduced pressure and the residue was extracted with DCM. The organic layer was washed with water, dried (anhydrous Na_2SO_4) and the solvent was removed. The crude product was purified by column chromatography using 20–30% ethyl acetate/hexane as eluent to afford **9** as a pale yellow solid; yield: 251 mg (81%); mp 141–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.83 (s, 1H), 7.71–7.68 (m, 2H), 7.37–7.34 (m, 3H), 6.77–6.71 (m, 3H), 4.42 (dd, J=1.2 Hz, & 7.6 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.99 (dd, J=7.6 Hz & 16.8 Hz, 1H), 2.80 (dd, J=1.2 Hz & 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.1, 151.8, 149.6, 148.7, 135.3, 129.92, 129.86, 128.6, 126.2, 119.2, 111.8, 110.2, 55.91, 55.90, 39.5, 35.4; IR (KBr): ν=3436 (N-H), 1693 (C=O), 1592 (C=N) cm^{-1}; MS (ESI): m/z=311.1 [M+H$^+$]; anal. calcd. for $C_{18}H_{18}N_2O_3$: C 69.66, H 5.85, N 9.03; found: C 69.50, H 5.90, N 9.22.

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References

[1] a) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151–1196; b) M. Yu, B. L. Pagenkopf, *Tetrahedron* **2005**, *61*, 321–347; c) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev.* **2009**, *38*, 3051–3060; d) M. Y. Mel′nikov, E. M. Budynina, O. A. Ivanova, I. V. Trushkov, *Mendeleev Commun.* **2011**, *21*, 293–301; e) F. De Simone, T. Saget, F. Benfatti, S. Almeida, J. Waser, *Chem. Eur. J.* **2011**, *17*, 14527–14538; f) P. Tang, Y. Qin, *Synthesis* **2012**, 2969–2984; g) Z. W. Wang, *Synlett* **2012**, 2311–2327; h) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev.* **2014**, *43*, 804–818; i) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem.* **2014**, *126*, 5608–5628; *Angew. Chem. Int. Ed.* **2014**, *53*, 5504–5523; j) H. K. Grover, M. R. Emmett, M. A. Kerr, *Org. Biomol. Chem.* **2015**, *13*, 655–671.

[2] a) M. R. Emmett, M. A. Kerr, *Org. Lett.* **2011**, *13*, 4180–4183; b) S. S. So, T. J. Auvil, V. J. Garza, A. E. Mattson, *Org. Lett.* **2012**, *14*, 444–447; c) M. R. Emmett, H. K. Grover, M. A. Kerr, *J. Org. Chem.* **2012**, *77*, 6634–6637; d) S. M. Wales, M. M. Walker, J. S. Johnson, *Org. Lett.* **2013**, *15*, 2558–2561; e) M. C. Martin, D. V. Patil, S. France, *J. Org. Chem.* **2014**, *79*, 3030–3039; f) K. L. Ivanov, E. V. Villemson, E. M. Budynina, O. A. Ivanova, I. V. Trushkov, M. Y. Melnikov, *Chem. Eur. J.* **2015**, *21*, 4975–4987.

[3] a) P. E. O'Bannon, W. P. Dailey, *Tetrahedron* **1990**, *46*, 7341–7358; b) E. M. Budynina, O. A. Ivanova, E. B. Averina, T. S. Kuznetsova, N. S. Zefirov, *Tetrahedron Lett.* **2006**, *47*, 647–649; c) G.-Q. Li, L.-X. Dai, S.-L. You, *Org. Lett.* **2009**, *11*, 1623–1625; d) T. F. Schneider, J. Kaschel, B. Dittrich, D. B. Werz, *Org. Lett.* **2009**, *11*, 2317–2320; e) J. Kaschel, T. F. Schneider, D. Kratzert, D. Stalke, D. B. Werz, *Angew. Chem.* **2012**, *124*, 11315–11318; *Angew. Chem. Int. Ed.* **2012**, *51*, 11153–11156; f) G. Sathishkannan, K. Srinivasan, *Adv. Synth. Catal.* **2014**, *356*, 729–735.

[4] a) V. K. Yadav, V. Sriramurthy, *Angew. Chem.* **2004**, *116*, 2723–2725; *Angew. Chem. Int. Ed.* **2004**, *43*, 2669–2671; b) C. A. Carson, M. A. Kerr, *J. Org. Chem.* **2005**, *70*, 8242–8244; c) Y.-B. Kang, Y. Tang, X.-L. Sun, *Org. Biomol. Chem.* **2006**, *4*, 299–301; d) K. Sapeta, M. A. Kerr, *J. Org. Chem.* **2007**, *72*, 8597–8599; e) O. A. Ivanova, E. M. Budynina, Y. K. Grishin, I. V. Trushkov, P. V. Verteletskii, *Angew. Chem.* **2008**, *120*, 1123–1126; *Angew. Chem. Int. Ed.* **2008**, *47*, 1107–1110; f) A. T. Parsons, J. S. Johnson, *J. Am. Chem. Soc.* **2009**, *131*, 3122–3123; g) F. de Nanteuil, J. Waser, *Angew. Chem.* **2011**, *123*, 12281–12285; *Angew. Chem. Int. Ed.* **2011**, *50*, 12075–12079; h) G. Sathishkannan, K. Srinivasan, *Org. Lett.* **2011**, *13*, 6002–6005; i) G. Yang, Y. Shen, K. Li, Y. Sun, Y. Hua, *J. Org. Chem.* **2011**, *76*, 229–233; j) J.-P. Qu, Y. Liang, H. Xu, X.-L. Sun, Z.-X. Yu, Y. Tang, *Chem. Eur. J.* **2012**, *18*, 2196–2201; k) H. Xiong, H. Xu, S. Liao, Z. Xie, Y. Tang, *J. Am. Chem. Soc.* **2013**, *135*, 7851–7854; l) S. Chakrabarty, I. Chatterjee, B. Wibbeling, C. G. Daniliuc, A. Studer, *Angew. Chem.* **2014**, *126*, 6074–6078; *Angew. Chem. Int. Ed.* **2014**, *53*, 5964–5968; m) K. S. Halskov, F. Kniep, V. H. Lauridsen, E. H. Iversen, B. S. Donslund, K. A. Jørgensen, *J. Am. Chem. Soc.* **2015**, *137*, 1685–1691.

[5] a) R. Ballini, A. Palmieri, D. Fiorini, *Arkivoc* **2007**, *vii*, 172–194; b) E. B. Averina, N. V. Yashin, T. S. Kuznetsova, N. S. Zefirov, *Russ. Chem. Rev.* **2009**, *78*, 887–902.

[6] a) O. Lifchits, A. B. Charette, *Org. Lett.* **2008**, *10*, 2809–2812; b) O. Lifchits, D. Alberico, I. Zakharian, A. B. Charette, *J. Org. Chem.* **2008**, *73*, 6838–6840.

[7] R. P. Wurz, A. B. Charette, *Org. Lett.* **2005**, *7*, 2313–2316.

[8] C. D. Schmidt, J. Kaschel, T. F. Schneider, D. Kratzert, D. Stalke, D. B. Werz, *Org. Lett.* **2013**, *15*, 6098–6101.

[9] A. M. Hardman, S. S. So, A. E. Mattson, *Org. Biomol. Chem.* **2013**, *11*, 5793–5797.

[10] a) T. Selvi, K. Srinivasan, *J. Org. Chem.* **2014**, *79*, 3653–3658; b) T. Selvi, K. Srinivasan, *Chem. Commun.* **2014**, *50*, 10845–10848.

[11] a) S. Yamazaki, H. Kumagai, T. Takada, S. Yamabe, K. Yamamoto, *J. Org. Chem.* **1997**, *62*, 2968–2974; b) S. Yamazaki, H. Kataoka, S. Yamabe, *J. Org. Chem.* **1999**, *64*, 2367–2374; c) S. Yamazaki, Y. Iwata, *J. Org. Chem.* **2006**, *71*, 739–743; d) S. Morikawa, S. Yamazaki, Y. Furusaki, N. Amano, K. Zenke, K. Kakiuchi, *J. Org. Chem.* **2006**, *71*, 3540–3544; e) S. Morikawa, S. Yamazaki, M. Tsukada, S. Izuhara, T. Morimoto, K. Kakiuchi, *J. Org. Chem.* **2007**, *72*, 6459–6463; f) S. Yamazaki, S. Kashima, T. Kuriyama, Y. Iwata, T. Morimoto, K. Kakiuchi, *Tetrahedron: Asymmetry* **2009**, *20*, 1224–1234.

[12] G. Liu, M. E. Shirley, K. N. Van, R. L. McFarlin, D. Romo, *Nat. Chem.* **2013**, *5*, 1049–1057.

[13] a) C. G. Frost, J. P. Hartley, *Mini-Rev. Org. Chem.* **2004**, *1*, 1–7; b) R. Ghosh, S. Maiti, *J. Mol. Catal. A: Chem.* **2007**, *264*, 1–8.

[14] For indoles, see: a) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2004**, *21*, 278–311; b) F. Rodrigues de Sá Alves, E. J. Barreiro, C. A. M. Fraga, *Mini-Rev. Med. Chem.* **2009**, *9*, 782–793; c) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489–4497; d) M. S. Park, D. H. Choi, B. S. Lee, J. Y. Lee, *J. Mater. Chem.* **2012**, *22*, 3099–3104. For thiophenes, see: e) Y. Tian, X. Wei, H. Xu, *J. Nat. Prod.* **2006**, *69*, 1241–1244; f) C. J. O'Connor, M. D. Roydhouse, A. M. Przybyl, M. D. Wall, J. M. Southern, *J. Org. Chem.* **2010**, *75*, 2534–2538; g) Y. Chen, X. Wan, G. Long, *Acc. Chem. Res.* **2013**, *46*, 2645–2655. For benzodioxole, see: h) J. Yang, F. Xu, S. Shi, J. Nie, *Photochem. Photobiol. Sci.* **2012**, *11*, 1377–1382; i) H.-Y. Yu, Z.-Y. Chen, B. Sun, J. Liu, F.-Y. Meng, Y. Liu, T. Tian, A. Jin, H.-L. Ruan, *J. Nat. Prod.* **2014**, *77*, 1311–1320; j) A. Schöffmann, L. Wimmer, D. Goldmann, S. Khom, J. Hintersteiner, I. Baburin, T. Schwarz, M. Hintersteininger, P. Pakfeifer, M. Oufir, M. Hamburger, T. Erker, G. F. Ecker, M. D. Mihovilovic, S. Hering, *J. Med. Chem.* **2014**, *57*, 5602–5619.

[15] a) J. A. Merlo, C. R. Newman, C. P. Gerlach, T. W. Kelley, D. V. Muyres, S. E. Fritz, M. F. Toney, C. D. Frisbie, *J. Am. Chem. Soc.* **2005**, *127*, 3997–4009; b) X. Guo, R. P. Ortiz, Y. Zheng, Y. Hu, Y.-Y. Noh, K.-J. Baeg, A. Facchetti, T. J. Marks, *J. Am. Chem. Soc.* **2011**, *133*, 1405–1418; c) Y. Yamaguchi, Y. Maruya, H. Katagiri, K. Nakayama, Y. Ohba, *Org. Lett.* **2012**, *14*, 2316–2319.

[16] a) D. W. Robertson, J. H. Krushinski, E. E. Beedle, V. Wyss, G. D. Pollock, H. Wilson, R. F. Kauffman, J. S. Hayes, *J. Med. Chem.* **1986**, *29*, 1832–1840; b) Y. Nomoto, H. Takai, T. Ohno, K. Nagashima, K. Yao, K. Yamada, K. Kubo, M. Ichimura, A. Mihara, H. Kase, *J. Med. Chem.* **1996**, *39*, 297–303; c) H. A. Kasikcioglu, N. Cam, *Vasc. Health. Risk Manag.* **2006**, *2*, 389–400; d) I. M. Robertson, O. K. Baryshnikova, M. X. Li, B. D. Sykes, *Biochemistry* **2008**, *47*, 7485–7495; e) J. Häggström, A. Boswood, M. O'Grady, O. Jöns, S. Smith, S. Swift, M. Borgarelli, B. Gavaghan, J.-G. Kresken, M. Patteson, B. Åblad, C. M. Bussadori, T. Glaus, A. Kovačević, M. Rapp, R. A. Santilli, A. Tidholm, A. Eriksson, M. C. Belanger, M. Deinert, C. J. L. Little, C. Kvart, A. French, M. Rønn-Landbo, G. Wess, A. V. Eggertsdottir, M. L. O'Sullivan, M. Schneider, C. W. Lombard, J. Dukes-McEwan, R. Willis, A. Louvet, R. DiFruscia, *J. Vet. Intern. Med.* **2008**, *22*, 1124–1135.

