Aryl Alkyl Ketones in a One-Pot Gewald Synthesis of 2-Aminothiophenes

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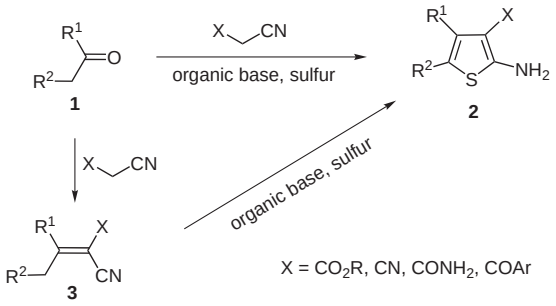
Abstract: 2-Aminothiophene-3-carboxylates bearing various aryl groups at the 4-position are readily obtained in good to moderate yields by the one-pot Gewald reaction of aryl alkyl ketones with ethyl cyanoacetate and elemental sulfur in the presence of morpholinium acetate and excess morpholine.

Key words: Gewald reaction, aryl alkyl ketones, 4-aryl-2-aminothiophene-3-carboxylates

Polysubstituted 2-aminothiophenes **2** prepared via the Gewald reaction[1] of ketones or aldehydes **1** with activated nitriles and elemental sulfur (Scheme 1) provide important polyfunctional starting materials for the synthesis of dyes,[1c] agrochemicals,[2] and conducting polymers.[3] Their core heterocycle forms an internal part of numerous natural products.[4] They have found application as selective site-directed inhibitors of various biological targets[5] and as synthetic pharmaceuticals, which show a broad range of biological activities.[1c] The Gewald method, which combines the benefits of multi-component reactions and the ability to generate highly diverse compound libraries, finds an ideal application in combinatorial chemistry.[5d,6] In addition, polyfunctional thiophenes show potential as efficient and cost effective starting templates for further parallel syntheses.[5a,7]

To continue our studies, we needed to synthesize a series of 2-aminothiophene-3-carboxylates bearing functionalized aryl groups at the C-4 position of the ring so as to provide several points of further structural variation including those located on the aryl. Towards this end, we required a straightforward, convenient, and general synthetic method, which could be directly used both in preparative syntheses and small-scale operations, typical of combinatorial chemistry. However, a search of the literature revealed that aryl ketones were unreactive in the direct one-pot Gewald synthesis, and the normal method by which 4-aryl-substituted 2-aminothiophene-3-carboxylates could be prepared involved a two-step technique (Scheme 1): synthesis and isolation of α,β-unsaturated nitriles **3** by Knoevenagel–Cope condensation followed by their thiolation with elemental sulfur in the presence of *sec*- or *tert*-amines with subsequent ring closure.[1c,8]



Scheme 1 Polysubstituted 2-aminothiophenes via the classical Gewald one-pot synthesis and its two-step modification

The two-step synthesis of 4-phenyl-2-aminothiophene-3-carboxylic acid ethyl ester (**2a**; Scheme 1, X = CO_2Et, R^1 = Ph, R^2 = H) with acetophenone as the starting material was reported to occur in yields not higher than 43% over two steps.[1b,9] Having applied the conditions reported by Cope[9] and Gewald[1b] for the two-step route, we were able to prepare thiophene **2a** in 34% overall yield.[10] *p*-Hydroxyacetophenone was even worse; we did not obtain the final heterocycle whatsoever, because the first step of the Knoevenagel–Cope condensation gave no measurable product under a variety of conditions.[9,11] These unpromising results and the strong interest in obtaining a variety of polyfunctional thiophenes **2** prompted us to conduct further studies of the Gewald reaction with the objective to extend the process to aryl alkyl ketones as starting materials in a direct one-pot preparation of various 4-arylthiophenes.

We speculated that the low reactivity of aryl ketones could hinder the formation of α,β-unsaturated nitriles **3**, thus limiting the rate of the whole multi-step process. To enhance the reaction rate, it seemed rational to probe highly concentrated solutions of ketone, cyanoacetic ester, and acid–base catalyst, which in turn could play the part of a polar solvent analogous to ionic liquids.[12] In order to facilitate the thiolation of nitriles **3**, an excess of free amine was required.[1c] We tested this suggestion with the reaction of acetophenone. Several ammonium salts (acetates and trifluoroacetates of ammonium, *n*-pentylammonium, cyclohexylammonium, diethylammonium, piperidinium, and morpholinium) and amines (piperidine, diethylamine, triethylamine, diisopropylethylamine, ethylenediamine, and morpholine) were selected as 'catalyst' and free organic base, respectively.

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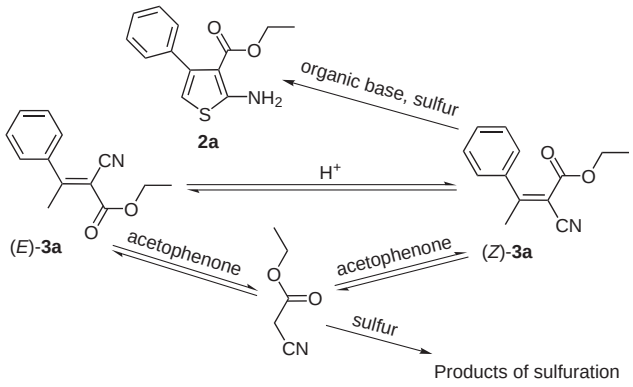

Scheme 2 Hypothetical scheme of one-pot Gewald reaction with aryl alkyl ketones

Typically, a solution of acetophenone, cyanoacetic ester, elemental sulfur (1 mmol of each), ammonium salt (0.5–1 mmol), and amine (1–2 mmol) was stirred in a 5 mL Wheaton® V-vial at 55 °C for 24 hours.[13] The course of the reaction was followed by ^{1}H NMR spectroscopy and GCMS. Experimental data showed that the acid–base 'catalytic' system composed of morpholine (3 equiv) and acetic acid (1 equiv), with acetophenone (1 equiv), cyanoacetate (1 equiv), and sulfur (1 equiv) gave the best results in terms of the homogeneity of the crude product and conversion of initial acetophenone to thiophene **2a**, which was obtained as the only product (61 mol%) with starting acetophenone being the only contaminant (39 mol%);[14] under these conditions cyanoacetic ester was completely consumed. These observations led us to believe that only a part of the initial ester participated in the formation of α,β-unsaturated nitriles **3a** (Scheme 2), while another was consumed leading to previously reported sulfurated species of ethyl cyanoacetate.[15]

Time-course experiments with the reaction performed analogously but in the absence of sulfur [morpholine (3 equiv), AcOH (1 equiv), acetophenone (1 equiv), and cyanoacetate (1 equiv)] proved that a reaction time of 1.5 hours was sufficient to establish the equilibrium between substrates and nitriles (*Z*)- and (*E*)-**3a** shown in Scheme 2. The progress of the reaction was followed by GCMS and ^{1}H NMR spectroscopy by following the peak at 2.67 pm for (*E*)-**3a** and 2.52 pm for (*Z*)-**3a**.[16] The equilibrium, though notably shifted towards initial acetophenone (82% mol) clearly allowed us to see the respective concentrations of nitriles **3a**, with (*E*)-**3a** being in excess of (*Z*)-**3a** (11% mol vs 7% mol).[17]

The remarkable fact is that having applied standard Cope conditions[9] to the condensation of acetophenone with cyanoacetic ethyl ester, we prepared a product, which in fact was the same mixture of (*Z*)- and (*E*)-nitriles **3a** obtained in a ratio of 1.7:1, similar to that observed above. Acid–base 'catalyst' [morpholine (3 equiv) and AcOH (1 equiv)] and elemental sulfur (1 equiv) afforded the required thiophene **2a** in 99% crude yield and in excellent crude purity of 97%, after a reaction time of 6 hours. This implied that the interconversion of isomers (*E*)-**3a** and (*Z*)-**3a** and further transformation of (*Z*)-**3a** to the title heterocycle were relatively fast on the time scale of this experiment.

Knowledge of the existence of two independent channels of cyanoacetate consumption and experimental data on the reactions outlined in Scheme 2 led us to the suggestion that an improvement in the yield of the desired thiophenes could follow from small alterations of the primary reaction protocol. Firstly, to compensate for the wastage of ethyl cyanoacetate it would be expedient to load an excess with the same parallel excess of sulfur. Secondly, to let the reaction reach equilibrium between isomeric nitriles **3a**, it seemed reasonable to begin the addition of sulfur with a 2–3 hour delay. Thirdly, the portion-wise addition of sulfur to the mixture at regular time intervals of 8–12 hours could diminish the side-reaction of cyanoacetate and lead to additional nitriles **3a** after complete exhaustion of the current portion of sulfur. To substantiate these arguments, we performed the synthesis of thiophene **2a** using the revised protocol.[18] Indeed the reaction resulted in 92% conversion of acetophenone to the title compound, with **2a** being isolated as the only product in 68% yield (Table 1, entry 1).

To establish the scope of this reaction, a variety of ring-substituted acetophenones and indanones were investigated. *p*-Chloro- and *p*-bromoacetophenones gave good results under these conditions, showing high and selective conversions to 2-aminothiophenes, which could be isolated in 52–56% yield (Table 1, entries 2 and 3). A significant increase in activity was observed when acetophenone was substituted in the *meta*-position with nitro, cyano, and ethoxycarbonyl groups. The reaction of these substrates resulted in highly homogenous crude materials, composed mostly of the title thiophenes isolated in good yields (52–70%, Table 1, entries 4–6).

p-Hydroxyacetophenone was found to be far less reactive. In addition to the low conversion of the substrate to the title 2-aminothiophene **2g**, ^{1}H NMR spectroscopy also showed that the reaction afforded less homogeneous crude material contaminated by initial ketone together with high molecular weight by-products resulting, apparently, from oxidation of the aryl moiety. However, they did not prevent the nitrile **2g** from being isolated in an acceptable yield of 37% (Table 1, entry 7), which compared favorably to our own results obtained for the two-step Gewald synthesis affording no measurable product (see above). Contrastingly, *m*-hydroxy- and *p*-methoxyacetophenones performed better in this reaction, resulting in both higher conversions of initial ketones and fairly good isolated yields (45% both, Table 1, entries 8 and 9).

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Table 1 Aryl Ketones in One-Pot Gewald Synthesis of 2-Aminothiophene-3-carboxylates

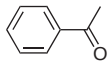
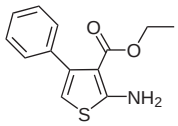
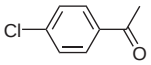
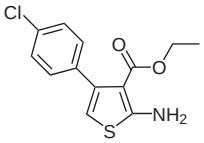
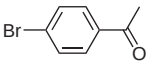
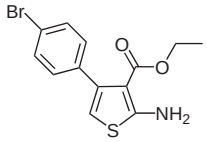
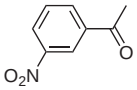
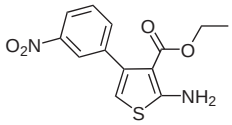
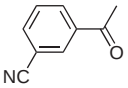
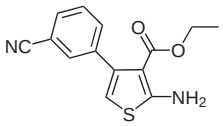
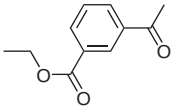
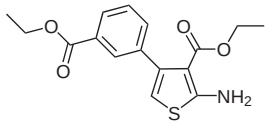
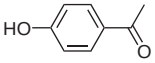
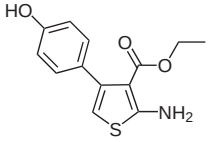
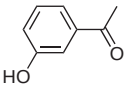
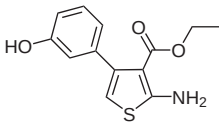
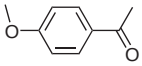
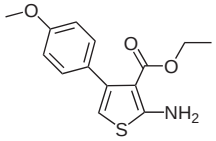
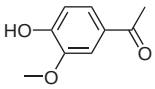
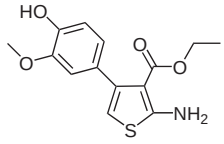
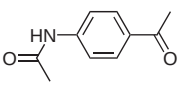
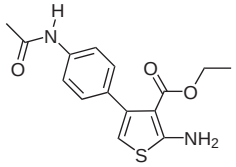
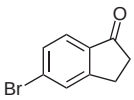
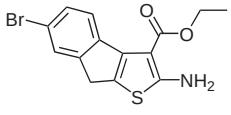
Entry	Ketone	2-Aminothiophene (**2a**–**n**)		Conversion (%)	Isolated yield (%)
1			**2a**	92	68
2			**2b**	76	56
3			**2c**	78	52
4			**2d**	91	70
5			**2e**	83	52
6			**2f**	85	64
7			**2g**	48	37
8			**2h**	67	45
9			**2i**	58	45
10			**2j**	39	20
11			**2k**	91	63
12			**2l**	69	44

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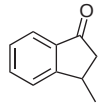
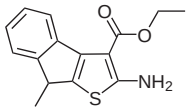
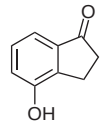
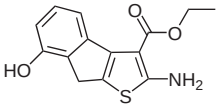
Table 1 Aryl Ketones in One-Pot Gewald Synthesis of 2-Aminothiophene-3-carboxylates (continued)

Entry	Ketone	2-Aminothiophene (**2a**–**n**)		Conversion (%)	Isolated yield (%)
13			**2m**	80	49
14			**2n**	41	25

[a] The conversion of ketone to 2-aminothiophene was monitored by ^{1}H NMR spectroscopy.

Addition of an *m*-methoxy group to *p*-hydroxyacetophenone led to drastic inhibition of the reaction rate with a respective decrease in isolated yield (20%). However, when a new portion of cyanoacetic ester (1.5 equiv per initial ketone) was added to the reaction mixture and the process was repeated once again, with a reaction time of 36 hours in accordance with the general procedure,[18] the yield rose to a more acceptable value (31%) (Table 1, entry 10).

The lowest reactivity was observed in the case of *p*- and *o*-aminoacetophenones, for which conversions to the required products were found to be low (18% and 0%, respectively). N-Acetylation could not help in the case of *o*-aminoacetophenone, but *N*-acetyl-4-aminoacetophenone smoothly gave the title product in good isolated yield (63%, Table 1, entry 11).

In addition to acyclic aryl ketones, we studied the suitability of this synthetic method for indanones, typical cyclic aryl ketones (Table 1, entries 12–14). All three substrates readily gave the required products in yields varying from good to acceptable, with the lowest yield observed for thiophene **2n** (25%). Compared with known literature data (25% for heterocyclization of the α,β-unsaturated nitrile obtained from 1-indanone[19]), even this, our worst result, was acceptable.

We mainly studied the potential of this synthetic method at a semi-preparative scale i.e. using 10–20 mmol of initial aryl ketones.[18] So finally, we investigated the application of this reaction to the preparation of 2-aminothiophene-3-carboxylates on a small scale typical of combinatorial chemistry (1–2 mmol). Experimental results showed that numerous products (**2a**–**e**, **2h**, **2l**, and **2n**) could be readily prepared in yields similar to those shown in Table 1.

In conclusion, we have extended the Gewald synthesis to the preparation of a variety of 2-aminothiophene-3-carboxylates substituted by aryl groups at the thiophene 4-position. The title products are readily obtained with yields from moderate to good by the one-pot Gewald reaction of aryl alkyl ketones with ethyl cyanoacetate and elemental sulfur in the presence of morpholinium acetate and excess morpholine.

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(13) To dissolve crystalline ammonium salts a small amount of 95% ethanol was added (0.5 mL per 1 mmol of acetophenone). DMF was also shown to be a good choice.
(14) Replacement of morpholine with alternative amines or acetic acid with TFA caused a substantial drop in the conversion of acetophenone. Thus, changing the amine from morpholine to diethylamine produced a heavily contaminated reaction mixture with only 18% conversion. At the same time employing half the amount of morpholine (1.5 equiv) and acetic acid (0.5 equiv) with acetophenone cyanoacetate (1 equiv) and sulfur (1 equiv) resulted in only a small decrease in ketone conversion (57%).
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(17) We were also interested in investigating if the combination of organic base and acid were essential for the formation of **3a** and if we could reach a similar equilibrium in the absence of acetic acid, that is, under conditions generally used in classical one-pot Gewald reaction (see ref. 1). In contrast to the former experiment, even heating for 12 hours was insufficient for the mixture of acetophenone, ethyl cyanoacetate, and morpholine (1:1:3) to give any condensation products at detectable concentrations. The same result was obtained for the reaction of acetophenone, ethyl cyanoacetate, and acetic acid in the absence of morpholine. Kinetic measurements and further experiments made it possible to consider that the acid–base 'catalyst', morpholinium acetate, was required in high concentrations to enhance the rate of the process leading to nitriles **3a**, which in turn was a key intermediate for the latter steps of thiolation and ring closure.
(18) **Heterocyclization; Typical Conditions**: A 25-mL round-bottomed two-necked flask equipped with a magnetic stirring bar and argon inlet tube was charged with acetophenone (2.40 g, 20.0 mmol), ethyl cyanoacetate (3.39 g, 30.0 mmol), 95% EtOH (5 mL), morpholine (2.61 g, 30.0 mmol), and glacial AcOH (0.60 g, 10 mmol). The mixture was stirred at 55 °C (temperature of bath) for 3 h. Finely powdered sulfur (3 × 0.32 g, 10 mmol) was then added in equal portions. After addition of each new portion the mixture was flushed with argon and left stirring at 55 °C for 10–12 h (overall reaction time 36–40 h). The mixture was transferred to a separating funnel containing CH_2Cl_2 (30 mL) and H_2O (30 mL). The organic layer was separated, washed with brine (4 × 10 mL), filtered through a short plug of silica, and concentrated in vacuo to give 4.62 g of the crude product. ^{1}H NMR spectroscopy indicated 92% conversion of acetophenone to **2a**.
Purification; Method A: Column chromatography (silica gel; $CHCl_3$) gave **2a** (3.38 g, 68%); off-white plates; mp 98–99 °C (hexane, Lit.[1b] mp 98 °C).
Method B: The crude product was dissolved in EtOAc (10 mL), and a solution of anhyd HCl (2.2 M) in anhyd EtOAc (15 mL, 33 mmol of HCl) was added to furnish a resinous cake. The cake was thoroughly triturated until crystallization began. The mixture was allowed to stand in a refrigerator overnight. The crystalline hydrochloride was collected by filtration, then washed with EtOAc (3 × 3 mL), and dried in air to give 3.92 g of crude hydrochloride. The residue was suspended in 5% aq NH_3 (10 mL) in CH_2Cl_2 (20 mL). The organic layer was separated, filtered through a short plug of silica, and concentrated in vacuo to give **2a** (3.14 g, 64%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, 3 H, *J* = 7.2 Hz, CH_3CH_2O), 4.02 (q, 2 H, *J* = 7.2 Hz, CH_3CH_2O), 5.58 (br s, 2 H, NH_2), 6.04 (s, 1 H, thiophene-CH), 7.28 (app s, 5 H, ArH). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.61 (q), 59.38 (t), 105.47 (d), 106.31 (s), 126.74 (d), 127.18 (d), 128.91 (d), 138.46 (s), 141.68 (s), 163.70 (s), 165.66 (s). HRMS: *m*/*z* calcd for $C_{13}H_{13}NO_2S$ [M^+]: 247.0667; found: 247.0678.
Thiophenes **2b**–**n** were prepared analogously.
Compound **2b**: Purified by method A (CH_2Cl_2); yield: 56%; white powder; mp 105–107 °C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, 3 H, *J* = 7.2 Hz, CH_3CH_2O), 4.04 (q, 2 H, *J* = 7.2 Hz, CH_3CH_2O), 5.94 (br s, 2 H, NH_2), 6.04 (s, 1 H, thiophene-CH), 7.21 (d, AB system, 2 H, *J* = 8.8 Hz, ArH), 7.25 (d, AB system, 2 H, *J* = 8.8 Hz, ArH). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.63 (q), 59.40 (t), 105.64 (d), 105.76 (s), 127.23 (d), 130.14 (d), 132.59 (s), 136.82 (s), 140.21 (s), 163.86 (s), 165.34 (s). HRMS: *m*/*z* calcd for $C_{13}H_{12}NO_2SCl$ [M^+]: 281.0277; found: 281.0281.
Compound **2c**: Purified by method B; yield: 52%; white powder; mp 120–121 °C (hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, 3 H, *J* = 7.2 Hz, CH_3CH_2O), 4.04 (q, 2 H, *J* = 7.2 Hz, CH_3CH_2O), 5.88 (br s, 2 H, NH_2), 6.02 (s, 1 H, thiophene-CH), 7.14 (d, 2 H, *J* = 8.4 Hz, ArH), 7.41 (d, 2 H, *J* = 8.4 Hz, ArH). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.67 (q), 59.44 (t), 105.65 (d), 105.73 (s), 120.72 (s), 130.21 (d), 130.51 (d), 137.31 (s), 140.23 (s), 163.89 (s), 165.35 (s). HRMS: *m*/*z* calcd for $C_{13}H_{12}NO_2SBr$ [M^+]: 324.9773; found: 324.9791.
Compound **2d**: Purified by method B; yield: 70%; white powder; mp 105–106.5 °C (toluene). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, 3 H, *J* = 7.2 Hz, CH_3CH_2O), 4.03 (q, 2 H, *J* = 7.2 Hz, CH_3CH_2O), 6.08 (br s, 2 H, NH_2), 6.11 (s, 1 H, thiophene-CH), 7.45 (dd, 1 H, *J* = 8.4, 8.4 Hz, ArH), 7.62 (ddd, 1 H, *J* = 8.4, 1.2, 1.2 Hz, ArH), 8.12 (ddd, 1 H, *J* = 8.4, 1.2, 1.2 Hz, ArH), 8.16 (dd, 1 H, *J* = 1.2, 1.2 Hz, ArH). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.56 (q), 59.51 (t), 105.14 (s), 106.67 (d), 121.57 (d), 123.96 (d), 127.92 (d), 134.96 (d), 138.77 (s), 139.87 (s), 147.35 (s), 164.36 (s), 165.04 (s). HRMS: *m*/*z* calcd for $C_{13}H_{12}N_2O_4S$ [M^+]: 292.0518; found: 292.0519.
Compound **2e**: Purified by method A ($CHCl_3$); yield: 52%; white powder; mp 126–127 °C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, 3 H, *J* = 7.2 Hz, CH_3CH_2O), 4.03 (q, 2 H, *J* = 7.2 Hz, CH_3CH_2O), 6.04 (br s, 2 H, NH_2), 6.06 (s, 1 H, thiophene-CH), 7.39 (ddd, 1 H, *J* = 8.4, 8.4, 0.6 Hz, ArH), 7.51 (ddd, 1 H, *J* = 8.4, 1.2, 1.2 Hz, ArH), 7.56 (ddd, 1 H, *J* = 8.4, 1.2, 1.2 Hz, ArH), 7.59 (ddd, 1 H, *J* = 1.2, 1.2, 0.6 Hz, ArH). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.59 (q), 59.46 (t), 105.27 (s), 106.42 (d), 111.29 (s), 118.74 (s), 127.93 (d), 130.18 (d), 132.54 (d), 133.31 (d), 138.96 (s), 139.59 (s), 164.28 (s), 165.04 (s). HRMS: *m*/*z* calcd for $C_{14}H_{12}N_2O_2S$ [M^+]: 272.0619; found: 272.0621.
Compound **2f**: Purified by method A (CH_2Cl_2–hexane, 1:2); yield: 64%; white powder; mp 102–103 °C (hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, 3 H, *J* = 7.2 Hz, CH_3CH_2O), 1.37 (t, 3 H, *J* = 7.1 Hz, CH_3CH_2O), 4.01 (q, 2 H, *J* = 7.2 Hz, CH_3CH_2O), 4.36 (q, 2 H, *J* = 7.1 Hz, CH_3CH_2O), 5.95 (br s, 2 H, NH_2), 6.07 (s, 1 H, thiophene-CH), 7.36 (dd, 1 H, *J* = 7.6, 7.6 Hz, ArH), 7.47 (ddd, 1 H, *J* = 7.6, 1.0, 1.0 Hz, ArH), 7.97 (ddd, 1 H, *J* = 7.6, 1.0, 1.0 Hz, ArH), 7.98 (dd, 1 H, *J* = 1.0, 1.0 Hz, ArH). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.53 (q), 14.20 (q), 59.36 (t), 60.75 (t), 104.67 (s), 105.89 (d), 127.12 (d), 127.89 (d), 129.57 (s), 130.06 (d), 133.26 (d), 138.58 (s), 140.47 (s), 163.99 (s), 165.45 (s), 166.45 (s). HRMS: *m*/*z* calcd for $C_{16}H_{17}NO_4S$ [M^+]: 319.0878; found: 319.0869.

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Compound **2g**: Prepared using EtOH–DMF (1:1) as the solvent and purified by method B; yield: 37%; white powder; mp 127–128 °C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, 3 H, *J* = 7.2 Hz, C*H*$_3$CH$_2$O), 4.06 (q, 2 H, *J* = 7.2 Hz, CH$_3$C*H*$_2$O), 5.65 (br s, 1 H, OH), 5.99 (s, 1 H, thiophene-CH), 6.06 (br s, 2 H, NH_2), 6.75 (d, 2 H, *J* = 8.4 Hz, ArH), 7.14 (d, 2 H, *J* = 8.4 Hz, ArH). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.72 (q), 59.58 (t), 105.11 (d), 105.94 (s), 114.11 (d), 130.08 (d), 130.80 (s), 141.16 (s), 154.72 (s), 163.82 (s), 165.84 (s). HRMS: *m*/*z* calcd for $C_{13}H_{13}NO_3S$ [M^+]: 263.0616; found: 263.0624.

Compound **2h**: Purified by method A ($CHCl_3$); yield: 45%; white powder; mp 115–116 °C (hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, 3 H, *J* = 7.2 Hz, C*H*$_3$CH$_2$O), 4.03 (q, 2 H, *J* = 7.2 Hz, CH$_3$C*H*$_2$O), 5.80 (br s, 3 H, NH_2, OH), 6.04 (s, 1 H, thiophene-CH), 6.74 (dd, 1 H, *J* = 1.0, 1.0 Hz, ArH), 6.75 (ddd, 1H, *J* = 8.5, 1.0, 1.0 Hz, ArH), 6.84 (ddd, 1 H, *J* = 8.5, 1.0, 1.0 Hz, ArH), 7.15 (dd, 1 H, *J* = 8.5, 8.5 Hz, ArH). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.56 (q), 59.49 (t), 105.56 (d), 106.32 (s), 113.69 (d), 115.95 (d), 121.48 (d), 128.32 (d), 139.83 (s), 141.01 (s), 154.61 (s), 163.70 (s), 165.74 (s). HRMS: *m*/*z* calcd for $C_{13}H_{13}NO_3S$ [M^+]: 263.0616; found: 263.0626.

Compound **2i**: Purified by method B; yield: 45%; white powder; mp 73–75 °C (toluene–hexane, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, 3 H, *J* = 7.2 Hz, C*H*$_3$CH$_2$O), 3.81 (s, 3 H, OCH_3), 4.05 (q, 2 H, *J* = 7.2 Hz, CH$_3$C*H*$_2$O), 5.99 (s, 1 H, thiophene-CH), 6.04 (br s, 2 H, NH_2), 6.84 (d, 2 H, *J* = 8.8 Hz, ArH), 7.21 (d, 2 H, *J* = 8.8 Hz, ArH). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.72 (q), 55.14 (q), 59.29 (t), 104.92 (d), 105.40 (s), 112.57 (d), 129.89 (d), 130.90 (s), 141.12 (s), 158.56 (s), 163.72 (s), 165.61 (s). HRMS: *m*/*z* calcd for $C_{14}H_{15}NO_3S$ [M^+] : 277.0773; found: 277.0778.

Compound **2j**: Purified by method B; yield: 20%; white powder; mp 123–124 °C (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, 3 H, *J* = 7.2 Hz, C*H*$_3$CH$_2$O), 3.87 (s, 3 H, OCH_3), 4.06 (q, 2 H, *J* = 7.2 Hz, CH$_3$C*H*$_2$O), 5.55 (br s, 1 H, OH), 5.95 (br s, 2 H, NH_2), 6.06 (s, 1 H, thiophene-CH), 6.81 (d, AB system, 1 H, *J* = 8.6 Hz, ArH), 6.82 (s, 1 H, ArH), 6.86 (d, AB system, 1 H, *J* = 8.6 Hz, ArH). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.82 (q), 55.80 (q), 59.35 (t), 105.02 (d), 105.96 (s), 111.79 (d), 113.19 (d), 121.82 (d), 130.55 (s), 141.27 (s), 144.59 (s), 145.29 (s), 163.72 (s), 165.66 (s). HRMS: *m*/*z* calcd for $C_{14}H_{15}NO_4S$ [M^+]: 293.0722; found: 293.0710.

Compound **2k**: Prepared using DMF as the solvent; purified by recrystallization (EtOH); yield: 63%; white powder; mp 193–195 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.94 (t, 3 H, *J* = 7.2 Hz, C*H*$_3$CH$_2$O), 2.05 (s, 3 H, C*H*$_3$CO), 3.97 (q, 2 H, *J* = 7.2 Hz, CH$_3$C*H*$_2$O), 6.11 (s, 1 H, thiophene-CH), 7.15 (d, 2 H, *J* = 8.4 Hz, ArH), 7.34 (s, 2 H, NH_2), 7.50 (d, 2 H, *J* = 8.4 Hz, ArH), 9.88 (s, 1 H, NHCO). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 13.77 (q), 23.92 (q), 58.56 (t), 102.89 (s), 104.62 (d), 117.73 (d), 128.76 (d), 132.89 (s), 137.84 (s), 140.17 (s), 164.68 (s), 165.00 (s), 168.08 (s). HRMS: *m*/*z* calcd for $C_{15}H_{16}N_2O_3S$ [M^+]: 304.0882; found: 304.0892.

Compound **2l**: Purified by method A ($CHCl_3$); yield: 44%; white powder; mp 189–190 °C ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (t, 3 H, *J* = 7.2 Hz, C*H*$_3$CH$_2$O), 3.61 (s, 2 H, CH_2), 4.44 (q, 2 H, *J* = 7.2 Hz, CH$_3$C*H*$_2$O), 6.12 (br s, 2 H, NH_2), 7.40 (dd, 1 H, *J* = 8.4, 0.8 Hz, ArH), 7.52 (d, 1 H, *J* = 0.8 Hz, ArH), 8.06 (d, 1 H, *J* = 8.4 Hz, ArH). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.56 (q), 34.09 (t), 60.05 (t), 101.15 (s), 118.03 (s), 122.99 (d), 125.54 (s), 126.97 (d), 129.39 (d), 138.82 (s), 141.28 (s), 148.05 (s), 165.41 (s), 167.02 (s). HRMS: *m*/*z* calcd for $C_{14}H_{12}NO_2SBr$ [M^+]: 336.9773; found: 336.9764.

Compound **2m**: Purified by method B; yield: 49%; white powder; mp 96–97 °C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (d, 3 H, *J* = 7.2 Hz, C*H*$_3$CH), 1.49 (t, 3 H, *J* = 7.2 Hz, C*H*$_3$CH$_2$O), 3.73 (q, 1 H, *J* = 7.2 Hz, CH$_3$C*H*), 4.45 (q, 2 H, *J* = 7.2 Hz, CH$_3$C*H*$_2$O), 6.12 (br s, 2 H, NH_2), 7.17 (m, 1 H, ArH), 7.27 (m, 1 H, ArH), 7.36 (br d, 1 H, *J* = 7.6 Hz, ArH), 8.16 (br d, 1 H, *J* = 7.2 Hz, ArH). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.59 (q), 18.61 (q), 40.40 (d), 59.96 (t), 101.24 (s), 121.78 (d), 122.69 (d), 124.23 (d), 126.52 (d), 132.62 (s), 138.88 (s), 139.79 (s), 151.76 (s), 165.75 (s), 166.85 (s). HRMS: *m*/*z* calcd for $C_{15}H_{15}NO_2S$: 273.0823; found: [M^+] 273.0821.

Compound **2n**: Purified by method B; yield: 25%; white powder; mp 187–188 (dec., EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.38 (t, 3 H, *J* = 7.2 Hz, C*H*$_3$CH$_2$O), 3.52 (s, 2 H, CH_2), 4.34 (q, 2 H, *J* = 7.2 Hz, CH$_3$C*H*$_2$O), 6.64 (dd, 1 H, *J* = 8.0, 0.8 Hz, ArH), 7.09 (dd, 1 H, *J* = 8.0, 8.0 Hz, ArH), 7.44 (s, 2 H, NH_2), 7.69 (dd, 1 H, *J* = 8.0, 0.8 Hz, ArH), 9.25 (s, 1 H, OH). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 14.42 (q), 31.22 (t), 59.07 (t), 98.07 (s), 111.71 (d), 113.38 (d), 124.44 (s), 127.33 (d), 130.77 (s), 141.02 (s), 141.13 (s), 152.27 (s), 164.63 (s), 168.32 (s). HRMS: *m*/*z* calcd for $C_{14}H_{13}NO_3S$ [M^+]: 275.0616; found: 275.0611.

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