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Truly Catalytic Gewald Synthesis of 2-Aminothiophenes Using Piperidinium Borate (Pip Borate), a Conjugate Acid–Base Pair

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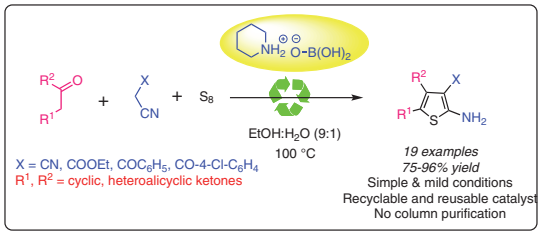

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Abstract The Gewald reaction has been well-known for more than half a century as an excellent method to provide bioactive 2-aminothiophene heterocycles from the reaction of carbonyl compounds, α-cyanoacetates, and elemental sulfur, in the presence of amines, in stoichiometric amounts. This work describes the use of salts of boric acid as conjugate acid-base pairs in a truly catalytic amount for the cyclocondensation of ketones with active methylenes such as malononitrile, ethyl cyanoacetate, and benzoyl acetonitrile with sulfur to give 2-aminothiophenes *via* the Gewald reaction. The present protocol is also applied for synthesizing Tinoridine, an anti-peroxidative NSAID, with excellent yield. Additionally, the catalyst has great recyclability and reusability.

Key words conjugate acid-base catalyst, Gewald reaction, 2-aminothiophenes, recyclable, piperidinium borate

Substituted 2-aminothiophenes are important intermediates in the synthesis of a variety of dyes[1] agrochemicals, and pharmacologically active compounds.[2] The condensation of ketones with active methylenes and elemental sulfur, initially reported in 1960 by Gewald and colleagues, is the simplest and most convergent synthesis of this class of compounds.[3] Many of the 2-aminothiophene structural motif-based compounds exhibit a variety of biological characteristics and have been identified as strong pan-serotype dengue virus inhibitors,[4] allosteric modulators of the A1 adenosine receptor,[5] antimicrobials,[6] antiproliferative agents,[7] and antitubercular agents.[8,9] The pharmaceutical industry has already benefited from using Gewald three-component reactions.[10] A selection of drugs and bioactive molecules containing 2-aminothiophenes are shown in Figure 1; these include olanzapine,[11] a typical antipsychotic drug; tinoridine,[12] a NSAID; T-62,[13] allosteric modulators of adenosine A1 receptors; TPCA-1,[14] a selective inhibitor of human IκB kinase 2; bentazepam,[15] anxiolytic, anticonvulsant, sedative and skeletal muscle relaxant; and brotizolam,[16] a sedative-hypnotic drug.

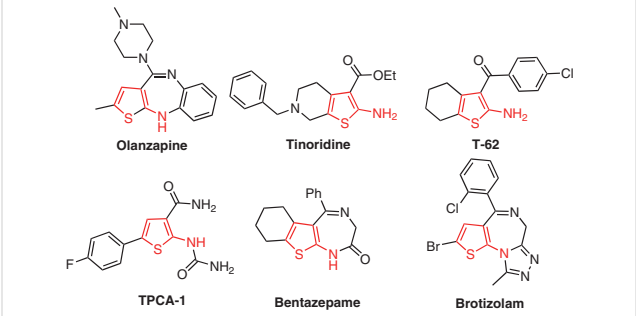
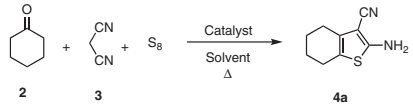


Figure 1 Selected biologically active 2-aminothiophenes

Although the one-pot method is well known, it has been discovered that a two-step method that involves first preparing an α,β-unsaturated nitrile by Knoevenagel condensation of a ketone with active methylenes, followed by a base-promoted reaction with sulfur, generally produces higher yields.[17] Substituted 2-aminothiophenes have been effectively synthesized using an organic base,[18] specifically amines such as morpholine,[19] diethylamine,[20] piperidine,[21] and triethylamine.[22] Alternative basic catalysts such as ionic liquids,[23] DES,[24] cesium carbonate,[25] and calcined Mg-Al hydrotalcite[26] have also been utilized for the Gewald reaction. However, it is difficult to develop the Gewald reaction further because of the drawbacks of current methods, which include excess catalyst loading, complex methods, and potentially hazardous solvents. We recently developed and applied piperidinium borate[27] to catalyze the Knoevenagel

condensation; we herein explore its application for synthesizing 2-aminothiophenes via the Gewald reaction. However, 2-aminothiophenes have been synthesized by various methods involving strong bases. Although many reports used a base in stoichiometric or excess amounts, we herein report the synthesis of 2-aminothiophenes *via* the Gewald reaction using truly catalytic amounts of a conjugate acid-base pair.

The catalyst significantly influences the reaction rate and yield. To determine optimized reaction conditions, such as catalyst loading, temperature, and solvent, a model reaction of cyclohexanone (1 equiv) with malononitrile (1 equiv), and sulfur (1 equiv) was initially examined (Scheme 1). The three salts of boric acid shown in Figure 2 were used for this reaction. To select the most suitable salt, pyrrolidine, piperidine, and morpholine salts of boric acid (20 mol%) were applied to the model reaction (Table 1). The 2-aminothiophene yields from the pyrrolidinium borate (Pyrr borate) and morpholinium borate (Mo borate) were good and the reaction took a shorter time (entries 1 and 3). With the shortest reaction time, the piperidinium borate (Pip borate) produced excellent product yields (entry 2). Pip borate showed superior results to other salts, so it was subsequently used as the catalyst for synthesizing 2-aminothiophenes via the Gewald reaction.



Scheme 1 Synthesis of 2-aminothiophene **4a**

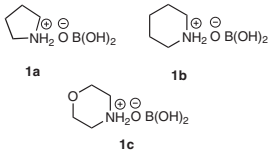


Figure 2 Salts of boric acid

Table 1 Catalyst Selection[a]

Entry	Cat. (20 mol%)	Time (min)	Yield (%)[b]
1	**1a**	30	85
2	**1b**	25	96
3	**1c**	90	74

[a] Reaction conditions: Cyclohexanone (5.09 mmol, 1 equiv), malononitrile (5.09 mmol, 1 equiv), sulfur (5.09 mmol, 1 equiv), EtOH/H_2O (10 mL, 9:1), 100 °C.
[b] Isolated yield.

After preliminary screening of salts, it was decided to perform catalyst loading studies for the Gewald reaction of 2-aminothiophenes using Pip borate (Table 2). Without a catalyst, the reaction did not proceed even after 24 hours (entry 1). With 10 and 15 mol% catalyst loading, the yield was very good with short reaction times (entries 2 and 3). With 20 mol% catalyst loading, complete conversion was achieved in 20 minutes with 96% yield (entry 4).

Table 2 Catalyst Loading Studies[a]

Entry	Cat. loading (mol%)	Time	Yield (%)[b]
1	0	>24 h	NR
2	10	45 min	69
3	15	25 min	78
4	20	25 min	96

[a] Reaction conditions: Cyclohexanone (5.09 mmol, 1 equiv), malononitrile (5.09 mmol, 1 equiv), sulfur (5.09 mmol, 1 equiv), **1b**, EtOH/H_2O (10 mL, 9:1), 100 °C.
[b] Isolated yield.

The model reaction was studied at three different temperatures (Table 3). At room temperature, traces of the product were obtained even after 24 hours (entry 1). After 3 hours, 84% of the product was obtained at 70 °C (entry 2), while at 100 °C, 96% yield of the product was obtained in 25 minutes (entry 3).

Table 3 Temperature Studies[a]

Entry	Temp. (°C)	Time	Yield (%)[b]
1	RT	>24 h	trace
2	70	3 h	84
3	100	25 min	96

[a] Reaction conditions: Cyclohexanone (5.09 mmol, 1 equiv), malononitrile (5.09 mmol, 1 equiv), sulfur (5.09 mmol, 1 equiv), **1b** (20 mol%), EtOH/H_2O (10 mL, 9:1).
[b] Isolated yield.

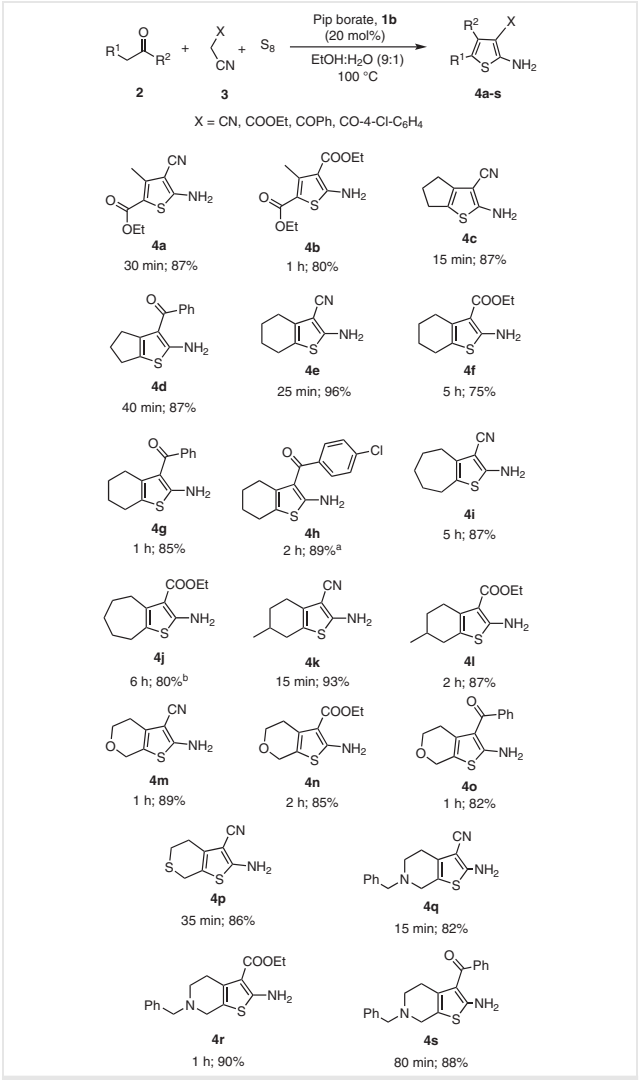
Various polar and nonpolar solvents were used to check the effects of the solvent on the reaction (Table 4). The results showed that ethanol/water (9:1) worked as an excellent solvent for eco-friendly and clean workup processes with an excellent yield in a shorter time (entry 5). The reaction took longer and gave lower yield in water (entry 1). The product gave good yields in methanol and ethanol but required longer reaction times (entries 2 and 3). Using a mixture of methanol and water (9:1) gave very good product yield with a shorter time than in methanol (entry 4). At the same time, with a 1:1 mixture of ethanol and water, the reaction completed in longer reaction time but in good yield (entry 6). The reactions in dimethyl sulfoxide and dimethylformamide proceeded rapidly, but the product yield was low (entries 7 and 8). As a result, ethanol with water in a ratio of 9:1 was chosen for further reactions.

Table 4 Solvent Studies[a]

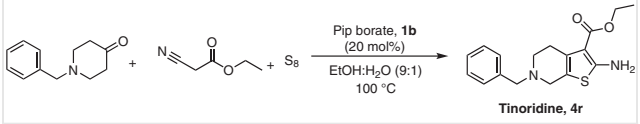
Entry	Solvent	Time (min)	Yield (%)[b]
1	H_2O	150	68
2	MeOH	85	82
3	EtOH	30	86
4	MeOH/H_2O (9:1)	45	79
5	EtOH/H_2O (9:1)	25	96
6	EtOH/H_2O (1:1)	45	88
7	DMSO	20	65
8	DMF	25	71

[a] Reaction conditions: Cyclohexanone (5.09 mmol, 1 equiv), malononitrile (5.09 mmol, 1 equiv), sulfur (5.09 mmol, 1 equiv), **1b** (20 mol%), solvent (10 mL), 100 °C.
[b] Isolated yield.

To evaluate the efficiency of the developed catalytic Gewald reaction using Pip borate, a series of ketones were screened with active methylenes such as malononitrile, ethyl cyanoacetate, and benzoyl acetonitrile, and sulfur (Scheme 2). When different active methylenes were compared, malononitrile had significantly greater activity. Ethyl acetoacetate reacted very well with malononitrile (**4a**) and ethyl cyanoacetate (**4b**) with a very good yield. The ring size of cyclic ketones with different active methylene moieties had a significant impact on the reaction; both cyclopentanone (**4c**) and cyclohexanone (**4e**) showed similar reactivities with malononitrile and offered very good yields, whereas cycloheptanone took much longer to react with malononitrile (**4i**). Cyclopentanone (**4d**) and cyclohexanone (**4g**) reacted with benzoyl acetonitrile with very good yields in 40 and 60 minutes, respectively. Cyclohexanone also reacted with 4-chlorobenzoyl acetonitrile with a very good yield in 2 hours (**4h**). The reactivity of ethyl cyanoacetate was lower than malononitrile in the reaction with cyclohexanone and cycloheptanone, but the yield was still good (**4f**, **4j**). Similarly, 4-methylcyclohexanone reacted well with malononitrile and took much longer with ethyl cyanoacetate (**4k**, **4l**). Heteroalicyclic ketones such as 4-oxotetrahydropyran and tetrahydrothiopyran-4-one showed higher reactivities with different active methylenes (**4m**–**p**). *N*-Benzyl-4-piperidone reacted briskly in 15 minutes with malononitrile and gave a very good yield of **4q**. *N*-Benzyl-4-piperidone also reacted well with benzoyl acetonitrile to give a very good yield of **4s**. All the synthesized products were characterized by their melting points and by NMR spectroscopy. Synthesis of tinoridine (**4r**), a NSAID and analgesic drug, was also realized under the optimized reaction conditions with a very good yield from starting materials *N*-benzyl-4-piperidone, ethyl acetoacetate and sulfur (Scheme 3).



Scheme 2 Synthesis of 2-aminothiophene derivatives. *Reagents and conditions*: Carbonyl compound (1 equiv), active methylene compound (1 equiv), sulfur (1 equiv), **1b** (20 mol%), EtOH/H_2O (10 mL, 9:1).
[a] Recrystallized from DCM/hexanes. [b] Recrystallized from ethanol.



Scheme 3 Synthesis of the NSAID Tinoridine (**4r**)

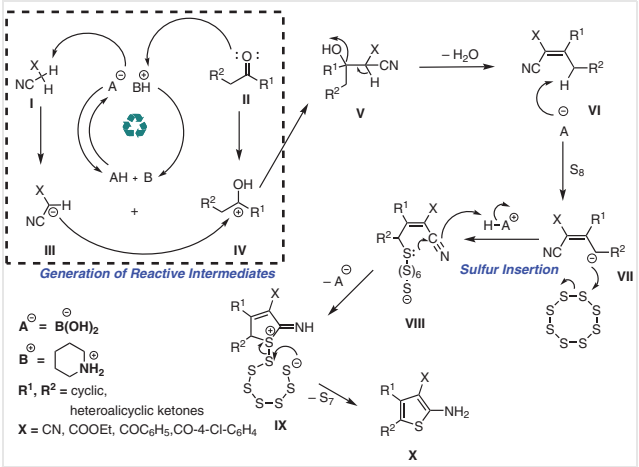
To assess the recyclability of the catalyst, the model reaction was conducted on a 1-gram scale with cyclohexanone, malononitrile, and sulfur. After the reaction was completed as indicated by TLC, the product was filtered. To remove organic material, the filtrate was washed with ethyl acetate and the aqueous layer was used in four cycles for the synthesis of 2-aminothiophene while maintaining good catalytic activity. The yield for recyclability studies of **1b** are summarized in Table 5.

Table 5 Recyclability of **1b** for the Synthesis of 2-Aminothiophenes[a]

Entry	Number of cycles	Yield (%)[b]
1	batch	96
2	1	96
3	2	95
4	3	92
5	4	90

[a] Reaction conditions: Cyclohexanone (5.09 mmol, 1 equiv), malononitrile (5.09 mmol, 1 equiv), sulfur (5.09 mmol, 1 equiv), **1b** (20 mol%), EtOH/H_2O (10 mL, 9:1), 100 °C.
[b] Isolated yield.

The Gewald reaction mechanism for synthesizing 2-aminothiophenes involves several key steps, including Knoevenagel condensation as the first step. The postulated mechanism for synthesizing the 2-aminothiophenes is shown in Scheme 4. The piperidinium cation (conjugate acid) protonates the carbonyl group of the ketone (II) to generate a carbocation (IV), which is then transformed into free base (B). The borate anion (conjugate base) abstracts a proton from the active methylene, forming carbanion (III) and returning to the acid state (AH). The carbocation (IV) is then attacked by the carbanion (III), forming intermediate (V), which dehydrates to produce the Knoevenagel product (VI). Acid (AH) and free base (B) recombine to make A^- BH^+, which is recycled for the next conversion. The conjugate base abstracts a proton from the γ-methylene of the Knoevenagel product (VI) to produce intermediate (VII). After this, the nucleophilic addition of elemental sulfur at the γ-methylene of intermediate (VII) produces sulfurated molecule (VIII), which undergoes ring closure by nucleophilic mercaptide attack at the cyano group, to produce intermediate (IX). Finally, a prototropic rearrangement produces 2-amino thiophene (X).



Scheme 4 Plausible mechanism for the synthesis of 2-aminothiophene via Gewald reaction

In conclusion, we have developed a straightforward and environmentally friendly approach for synthesizing 2-aminothiophenes via Gewald reaction using Pip borate in a truly catalytic amount in ethanol/water as a green solvent with excellent product yields. The advantages of this approach are low catalyst loading, eco-friendly solvent, readily available starting materials, recyclability and reusability of catalyst, and simple product isolation with good to excellent yields in short reaction time. To our knowledge, this is the first time that a conjugate base of a weak acid has been used as a catalyst for synthesizing 2-aminothiophenes. The catalyst was recycled after a simple workup and reused in four runs without appreciable reduction in catalytic activity. This protocol was also used to synthesize tinoridine, a NSAID and analgesic drug, with excellent yield in a short reaction time.

All solvents and reagents were obtained from Avra Synthesis, Spectrochem, or SD Fine Chemicals, and were utilized without purification. All reactions were carried out in oven-dried glassware, under a fume-hood; where required, reaction mixtures were magnetically agitated and heated in an oil bath. The reactions were monitored by TLC on Merck silica gel G F254 plates. Melting points were recorded with an Analab ThermoCal instrument in open glass capillaries and are uncorrected. ^{1}H and ^{13}C{^{1}H} NMR spectra are recorded with a MR500 NMR spectrometer, Agilent Technologies in $CDCl_3$ or DMSO-d_6 with tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in delta (δ) units in parts per million (ppm). The peak patterns are indicated as s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet.

Gewald Reaction; General Procedure

A mixture of ketone (1 equiv), active methylene (1 equiv), sulfur (1 equiv), and Pip borate (20 mol%), in ethanol/water (10 mL, 9:1) was stirred at 100 °C. Reaction progress was monitored using TLC (8:2 hexanes/EtOAc). After completion of the reaction, water was added (5 mL), and the solid product was filtered and washed with water (5 mL). Products were dried well in an oven and characterized using melting points and NMR spectroscopic analysis. In the case of compound **4h**, the reaction mixture was extracted with EtOAc (3 × 10 mL), and the combined EtOAc layer was dried over sodium sulfate and evaporated to obtain a sticky material that was then recrystallized (DCM/hexanes), to give a solid product.

Ethyl 5-Amino-4-cyano-3-methylthiophene-2-carboxylate (4a)

Yield: 0.70 g (87%); light-yellow solid; mp 205–207 °C (lit.[28] 202 °C).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.95 (s, 2 H), 4.16 (q, J = 7.1 Hz, 2 H), 2.37 (s, 3 H), 1.23 (t, J = 7.1 Hz, 3 H).

Diethyl 5-Amino-3-methylthiophene-2,4-dicarboxylate (4b)

Yield: 0.88 g (89%); yellow solid; mp 107–109 °C (lit.[23] 108–109 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.55 (s, 2 H), 4.28 (dq, J = 24.5, 7.1 Hz, 4 H), 2.69 (s, 3 H), 1.34 (dt, J = 22.6, 7.1 Hz, 6 H).

2-Amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carbonitrile (4c)

Yield: 0.85 g (87%); brown solid; mp 145–147 °C (lit.[29] 147–148 °C).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.02 (s, 2 H), 2.65 (dd, *J* = 9.7, 4.5 Hz, 2 H), 2.55 (dd, *J* = 10.1, 4.2 Hz, 2 H), 2.29–2.22 (m, 2 H).

(2-Amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-3-yl)(phenyl)-methanone (4d)

Yield: 1.18 g (87%); yellow solid; mp 170–172 °C (lit.[30] 176–177 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48–7.45 (m, 2 H), 7.44–7.42 (m, 1 H), 7.39 (dd, *J* = 11.3, 4.6 Hz, 2 H), 6.95 (s, 2 H), 2.69–2.63 (m, 2 H), 2.18–2.10 (m, 2 H), 2.08–2.02 (m, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 191.24, 169.44, 140.66, 140.43, 128.92, 126.82, 126.16, 120.75, 110.75, 30.20, 27.77, 26.50.

2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (4e)

Yield: 0.87 g (96%); yellow solid; mp 147–149 °C (lit.[29] 147–148 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.63 (s, 2 H), 2.49 (q, *J* = 4.1 Hz, 4 H), 1.85–1.72 (m, 4 H).

Ethyl 2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4f)

Yield: 0.86 g (75%); yellow solid; mp 114–116 °C (lit.[29] 114–115 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.93 (s, 2 H), 4.25 (q, *J* = 7.2 Hz, 2 H), 2.70 (dt, *J* = 9.9, 3.9 Hz, 2 H), 2.53–2.44 (m, 2 H), 1.82–1.69 (m, 4 H), 1.34 (q, *J* = 7.2 Hz, 3 H).

(2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)(phenyl)-methanone (4g)

Yield: 1.94 g (85%); yellow solid; mp 150–152 °C (lit.[31] 150–155 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47 (t, *J* = 7.0 Hz, 2 H), 7.43 (d, *J* = 6.9 Hz, 1 H), 7.39 (t, *J* = 7.3 Hz, 2 H), 6.70 (s, 2 H), 2.51 (t, *J* = 6.1 Hz, 2 H), 1.80 (t, *J* = 5.7 Hz, 2 H), 1.73 (dd, *J* = 10.8, 5.5 Hz, 2 H), 1.51–1.43 (m, 2 H).

(2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)(4-chloro phenyl)methanone (4h)

Yield: 1.32 g (89%); yellow solid; mp 123–125 °C (lit.[32] 124–125 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.5 Hz, 2 H), 7.37 (d, *J* = 8.5 Hz, 2 H), 6.72 (s, 2 H), 2.51 (t, *J* = 6.3 Hz, 2 H), 1.80 (t, *J* = 6.1 Hz, 2 H), 1.74 (dt, *J* = 12.3, 6.3 Hz, 2 H), 1.49 (dt, *J* = 11.8, 6.1 Hz, 2 H).

2-Amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophene-3-carbonitrile (4i)

Yield: 0.75 g (87%); light-brown solid; mp 123–125 °C (lit.[33] 125 °C).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.78 (s, 2 H), 2.48 (dd, *J* = 14.3, 8.4 Hz, 5 H), 1.74 (dd, *J* = 10.8, 5.5 Hz, 2 H), 1.59–1.51 (m, 4 H).

Ethyl 2-Amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophene-3-carboxylate (4j)

Yield: 0.85 g (80%); light-brown solid; mp 85–87 °C (lit.[33] 87 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.76 (s, 2 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 3.00–2.94 (m, 2 H), 2.60–2.54 (m, 2 H), 1.80 (dd, *J* = 10.6, 5.3 Hz, 2 H), 1.69–1.57 (m, 4 H), 1.34 (t, *J* = 7.1 Hz, 3 H).

2-Amino-6-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (4k)

Yield: 0.80 g (93%); light-brown solid; mp 125–127 °C (lit.[7] 124–126 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.68 (s, 2 H), 2.67–2.57 (m, 2 H), 2.56–2.47 (m, 1 H), 2.26–2.11 (m, 1 H), 2.00–1.84 (m, 2 H), 1.49–1.36 (m, 1 H), 1.10 (d, *J* = 6.6 Hz, 3 H).

Ethyl 2-Amino-6-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4l)

Yield: 0.93 g (87%); yellow solid; mp 113–115 °C (lit.[7] 112–114 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.93 (s, 2 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 2.93–2.80 (m, 1 H), 2.67–2.49 (m, 2 H), 2.13 (dd, *J* = 14.1, 11.4 Hz, 1 H), 1.83 (ddd, *J* = 12.8, 8.5, 3.9 Hz, 2 H), 1.40–1.28 (m, 4 H), 1.04 (d, *J* = 6.6 Hz, 3 H).

2-Amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carbonitrile (4m)

Yield: 0.79 g (89%); light-yellow solid; mp 216–218 °C (lit.[29] 215–218 °C).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.09 (s, 2 H), 4.42 (s, 2 H), 3.82 (t, *J* = 5.5 Hz, 2 H), 2.43 (t, *J* = 5.3 Hz, 2 H).

Ethyl 2-Amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylate (4n)

Yield: 0.96 g (85%); light-yellow solid; mp 118–120 °C (lit.[29] 117–118 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.02 (s, 2 H), 4.55 (s, 2 H), 4.26 (q, *J* = 7.1 Hz, 2 H), 3.90 (t, *J* = 5.6 Hz, 2 H), 2.81 (t, *J* = 5.3 Hz, 2 H), 1.33 (t, *J* = 7.1 Hz, 3 H).

(2-Amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-yl)(phenyl)methanone (4o)

Yield: 1.05 g (82%); yellow solid; mp 168–170 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50–7.43 (m, 3 H), 7.40 (dd, *J* = 11.3, 4.4 Hz, 2 H), 6.84 (s, 2 H), 4.56 (t, *J* = 1.9 Hz, 2 H), 3.63 (t, *J* = 5.4 Hz, 2 H), 1.97–1.91 (m, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 192.40, 165.15, 141.77, 130.47, 129.29, 128.13, 127.37, 115.27, 115.04, 64.78, 64.76, 28.20.

2-Amino-4,7-dihydro-5*H*-thieno[2,3-*c*]thiopyran-3-carbonitrile (4p)

Yield: 0.73 g (86%); yellow solid; mp 207–209 °C (lit.[29] 205–207 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.71 (s, 2 H), 3.56 (t, *J* = 1.7 Hz, 2 H), 2.89 (t, *J* = 5.8 Hz, 2 H), 2.80 (t, *J* = 5.7 Hz, 2 H).

2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carbonitrile (4q)

Yield: 0.68 g (82%); light-brown solid; mp 140–142 °C (lit.[34] 138–141 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.24 (m, 5 H), 4.76 (s, 2 H), 3.69 (s, 2 H), 3.40 (s, 2 H), 2.80 (t, *J* = 5.7 Hz, 2 H), 2.62 (t, *J* = 5.4 Hz, 2 H).

Ethyl 2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate (4r)

Yield: 0.75 g (90%); yellow solid; mp 107–109 °C (lit.[34] 110–111 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.19 (m, 5 H), 5.97 (s, 2 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 3.68 (s, 2 H), 3.41 (s, 2 H), 2.79 (dt, *J* = 37.5, 5.7 Hz, 4 H), 1.31 (t, *J* = 7.1 Hz, 3 H).

(2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-3-yl)-(phenyl)methanone (4s)

Yield: 0.81 g (88%); light-brown solid; mp 180–182 °C (lit.[35] 178–180 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.28 (m, 4 H), 7.27–7.22 (m, 4 H), 7.21–7.16 (m, 2 H), 6.76 (s, 2 H), 3.54 (s, 2 H), 3.34 (t, *J* = 1.8 Hz, 2 H), 2.39 (t, *J* = 5.7 Hz, 2 H), 1.85 (t, *J* = 5.7 Hz, 2 H).

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2189-3334.

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