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Reaction Pathways to 2-Aminothiophenes and Thiophene-3-carbonitriles

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Over the past two decades 2-amino-3-benzoylthiophenes have been found to act as allosteric enhancers of the adenosine A_1 receptor (A_1AR). As such, compounds of this type have potential applications in the therapy of a variety of disorders by enhancing A_1AR activation. Initial studies in this field identified various 2-amino-3-benzoylthiophenes as potential leads and of these PD 81723 **1a** has become the benchmark for comparative studies due to its favourable ratio of allosteric enhancement to antagonism. Surprisingly the synthesis and characterization of PD 81723 **1a** has not been previously reported. Herein we report the synthesis and characterization of this important A_1AR allosteric enhancer. As part of this study we also found an unexpected reaction pathway to 2-phenylthiophene-3-carbonitriles.

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Our group has been actively involved in the synthesis and pharmacological characterization of allosteric enhancers of the human adenosine A_1 receptor.[1–4] Research in the field of allosteric enhancers of the A_1AR has been well established over the past two decades. The seminal work of Bruns et al. identified a series of 2-amino-3-benzoylthiophenes which act as allosteric enhancers of the adenosine A_1 receptor.[5,6] Of the lead compounds found in that study, (2-amino-4,5-dimethylthiophen-3-yl)(3-(trifluoromethyl)phenyl)methanone **1a**, designated as PD 81723 (Fig. 1), was found to have the most favourable ratio of allosteric enhancement to antagonism and has since been the benchmark in the discovery of new allosteric enhancers. In our pursuit of improved allosteric enhancers we required a supply of PD 81723 **1a** for our pharmacological studies. Despite this compound being commercially available,[7] we attempted to synthesize it ourselves as the simplicity of its structure suggested that its synthesis would be straightforward with large quantities readily obtainable. The first and only report on the synthesis of PD 81723 **1a** was published in 1973 by Nakanishi et al.[8] via the one-pot Gewald procedure.[9] In this study, a series of 2-amino-3-benzoylthiophenes were prepared as intermediates in the synthesis of thienodiazepinones, but were not fully characterized. Compound **1a** was not isolated and no yield, melting point or spectroscopic data were described. Bruns et al. reported that the 2-amino-3-benzoylthiophenes used in their studies were synthesized at Parke-Davis via the method of Tinney et al.[10] Although Tinney and co-workers did synthesize a variety of 2-amino-3-benzoylthiophenes, they do not report the synthesis of PD 81723 **1a**. In fact to the best of our knowledge, none of the literature which describes PD 81723 **1a** (~44 papers in the Chemical Abstracts database) provides any synthetic or characterization details for this compound. This anomaly was intriguing because PD 81723 **1a** is the bench mark compound utilized in A_1AR studies and warrants characterization. We now report the synthesis and full characterization of such an important lead compound.

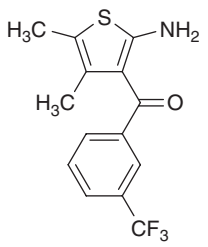

Fig. 1. Structure of PD 81723 **1a**.

We had initially attempted the one-pot Gewald procedure for the synthesis of 2-amino-3-benzoylthiophenes as outlined by Nakanishi et al. (Scheme 1).[8] *m*-Trifluoromethylbenzoyl acetonitrile **2a** was reacted with 2-butanone and sulfur in the presence of base (morpholine) to afford the desired product. However, the reaction did not go to completion and chromatographic purification was required to obtain the pure product in only 12% yield. The ^{1}H NMR spectrum of the crude product of this one-pot synthesis showed no sign of the isomeric thiophene **5**. This suggested that the *Z* isomer of the intermediate olefin (*Z*-**4a**) may isomerize under basic conditions to the more stable enolate ion before cyclization or possibly decompose under the reaction conditions.

In search of an improved synthesis of **1a**, we evaluated the corresponding two step procedure which involved a Knoevenagel condensation followed by the Gewald reaction. The rate-limiting step in the one-pot Gewald reaction is the formation of the olefinic intermediate which proceeds via the Knoevenagel condensation. In our experience, if a one-pot Gewald procedure returns starting materials, it is most likely due to the Knoevenagel condensation not proceeding. The standard method for the

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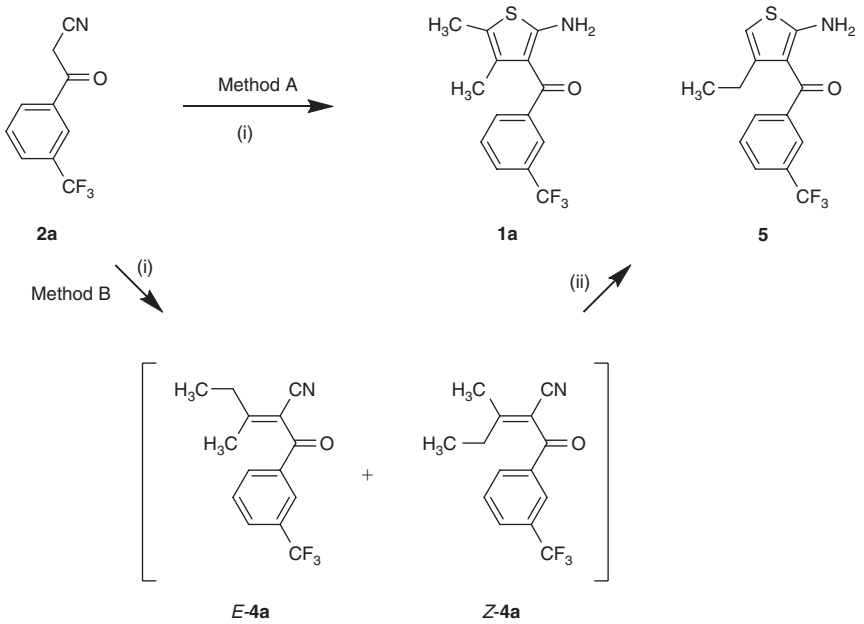
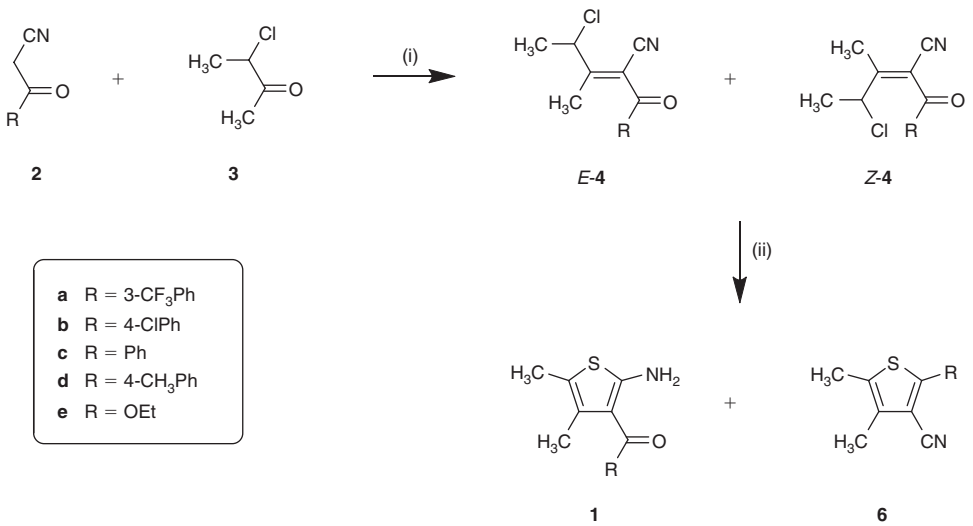


Scheme 1. Synthetic routes to PD 81723 (**1a**). Method A (One-pot method): (i) 2-butanone, S_8, morpholine, EtOH, reflux; 12% yield. Method B (Two-step method): (i) 2-butanone, $TiCl_4$, pyridine, CH_2Cl_2 then (ii) Et_2NH, THF, S_8; 23% yield (over two steps).



Scheme 2. Reagents and conditions. (i) $TiCl_4$, pyridine, CH_2Cl_2, (ii) EtOH, NaSH −78 to 10°C.

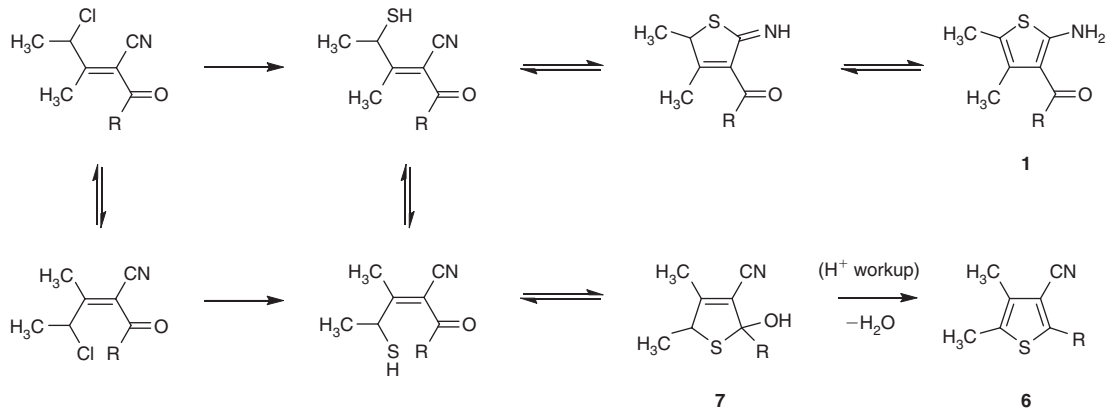
formation of the Knoevenagel product is to condense a nitrile and ketone/aldehyde in the presence of a catalytic amount of β-alanine and azeotropically remove water.[10] Although high yields can be obtained on fairly large scales, we have found that, on a smaller scale, this technique returns lower yields due to inefficient removal of water. An alternative approach to the Knoevenagel condensation was reported using titanium(IV) chloride[11] providing high yields of Knoevenagel products. We applied this technique and obtained quantitative conversion of the nitrile and ketone to the *E*/*Z* mixture of **4a**. Subjecting this mixture to basic conditions in the presence of elemental sulfur provided **1a** in a much cleaner state than the one-pot procedure and in moderate yield. Pure PD 81723 **1a** was obtained in an overall yield of 23% following a chromatographic purification and one recrystallization from petroleum spirits. The full characterization of this compound appears for the first time in the Experimental section of this manuscript.

It has been previously reported that improved yields of 2-aminothiophenes can be obtained by incorporating a leaving group α to the carbonyl of unsymmetrical ketones, which can subsequently be displaced by NaSH.[12–15] Therefore, commercially available 3-chloro-2-butanone **3** (Scheme 2) was submitted to Knoevenagel condensation with nitrile **2a** to produce the *E*/*Z* mixture of the olefin **4a**. This mixture was then treated at −78°C with an excess of NaSH and upon work-up providing what initially looked like the required thiophene **1a**, by virtue of two methyl singlets at 2.30 and 2.41 ppm in the ^{1}H NMR spectrum. However, by comparison with results from previous procedures where the methyl singlets for **1a** are at 1.50 and 2.14 ppm, and as only a trace amount could be detected by NMR in the crude

Table 1. Product ratios of 2-aminothiophenes and thiophene-3-carbonitriles

Entry	Nitrile	Ketone	R	Temp. [°C][A]	Product ratio[A]	Isolated yield[B]
1	**2a**	**3**	3-CF_3Ph	−78	**1a**:**6a** = 9:91	**6a** 45%
2	**2a**	**3**	3-CF_3Ph	rt	**1a**:**6a** = 65:35	nd
3	**2b**	**3**	4-ClPh	−78	**1b**:**6b** = 0:100	**6b** 61%
4	**2b**	**3**	4-ClPh	rt	**1b**:**6b** = 33:67	nd
5	**2c**	**3**	Ph	−78	**1c**:**6c** = 5:95	**6c** 50%
6	**2c**	**3**	Ph	rt	**1c**:**6c** = 9:91	nd
7	**2d**	**3**	4-CH_3Ph	−78	**1d**:**6d** = 0:100	**6d** 40%
8	**2d**	**3**	4-CH_3Ph	rt	**1d**:**6d** = 38:62	nd
9	**2d**	**3**	4-CH_3Ph	55	**1d**:**6d** = 18:82	nd
10	**2e**	**3**	OEt	−78	**1e**:**6e** = 100:0	**1e** 54%

[A]Product ratios of crude isolated material as determined by ^{1}H NMR spectroscopy.
[B]Isolated yield of the major product after chromatography.



Scheme 3. Pathways to 2-aminothiophenes versus 3-cyanothiophenes.

spectrum of the required 2-aminothiophene **1a**, full characterization of this product determined that it was in fact 4,5-dimethyl-2-(3-trifluoromethyl)phenylthiophene-3-carbonitrile (**6a**). The ^{13}C NMR spectra of the product revealed the absence of a keto group and retention of the nitrile. The IR spectra confirmed this observation with a CN stretching frequency at 2215 cm^{-1} and the absence of a carbonyl stretching frequency at 1576 cm^{-1}. The Knoevenagel products from the corresponding reactions with 4-chlorobenzoylacetonitrile, benzoylacetonitrile, and 4-methylbenzoylacetonitrile with 3-chloro-2-butanone **3** cyclized in a similar fashion to afford the corresponding 2-substituted 4,5-dimethylthiophene-3-carbonitriles. Only trace amounts of the 2-aminothiophenes **1b**–**d** (0–9%) were detected when these reactions were conducted at −78°C. However, at room temperature the product ratios increased considerably, with higher amounts of 2-aminothiophene formed. The amount of 2-aminothiophenes varied from substrate nitriles **2a**–**d** with up to 65% of 2-aminothiophene detected by NMR (Table 1, entries 2, 4, 6, and 8). We note also that the percentage of 2-aminothiophene obtained using the same substrate varied slightly from run to run. When heating the reaction at 55°C before addition of the sodium hydrosulfide in the case of nitrile **2d**, the product ratio actually decreased the amount of 2-aminothiophene, relative to the reaction run at room temperature (Table 1; entry 9).

In contrast, the Knoevenagel intermediate formed from the reaction of ethyl cyanoacetate **2e** with 3-chlorobutan-2-one **3** cyclized to give ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate **1e** exclusively at −78°C (Table 1, entry 10). The reaction of benzoylacetonitrile **2c** with phenacyl chloride also afforded solely the corresponding 2-aminothiophene at this temperature (outcome not shown in Table).

The mode of cyclization and predominance of the 2-substituted 4,5-dimethylthiophene-3-carbonitrile products may be influenced by base mediated isomerization of the intermediate olefin (before or after nucleophilic substitution of the chloride by NaSH) (Scheme 3). The predominance of the thiophene-3-carbonitrile from reactions between benzoylacetonitriles and 2-chlorobutan-2-one at −78°C suggests this is the kinetically favoured pathway. More specifically, the 2-hydroxydihydrothiophene-3-carbonitrile **7** may be the kinetically favoured species at this temperature, which then undergoes a dehydration step during the acid quench to give **6**. At room temperature, the establishment of an equilibrium between **7** and the 2-aminothiophene would account for the formation of a significant amount of the latter. The reduction of the proportion of this 2-aminothiophene observed when the reaction was conducted at 55°C may have resulted from dehydration of the 2-hydroxydihydrothiophene-3-carbontrile **7**, occurring before the acid quench. Accordingly, a larger percentage of more thermodynamically stable thiophene-3-carbonitrile would be expected relative to the reaction performed at room temperature.

Meth-Cohn and Narine have reported that 2-amino-3-benzoyl-4,5-dimethylthiophene rearranges to form 4,5-dimethyl-2-phenylthiophene-3-carbonitrile **6c** under relatively harsh basic conditions (NaOEt-EtOH, reflux, 4 h).[16] While a mechanism in which the 2-aminothiophenes formed first can not be ruled out in our case, this seems less likely under the reactions conditions that were employed.

We note that benzoylacetonitriles were not utilized in previously published studies on the modified Gewald procedure,[12–15] with cyanoacetates and malononitriles used instead. To the best of our knowledge the only published report on the use of a benzoylacetonitrile and an α-chloroketone (2-chlorocyclohexanone) was that by Gewald,[17] and 2-aminothiophene was reported as the sole product isolated. Furthermore, a literature search revealed that these thiophene-3-carbonitriles are novel structures except for 4,5-dimethyl-2-phenylthiophene-3-carbonitrile **6c** which was reported by Meth-Cohn and Narine.[16]

To conclude, we have synthesized the important benchmark A_1AR allosteric enhancer, PD 81723 **1a**, via a two-step procedure involving a Knoevenagel condensation and Gewald reaction. The target compound was obtained in adequate yield and has been fully characterized. In our pursuit to improve the yield of **1a** with 3-chloro-2-butanone **3a** we have observed the formation of an unexpected product and synthesized a small set of novel thiophenes. We are currently investigating the effect of different α-chloro ketones and benzoyl acetonitriles in this modified Gewald reaction and will report these findings in due course.

Experimental

Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. All ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer at 300.13 MHz and 75.49 MHz, respectively. Unless otherwise stated ^{13}C NMR spectra were recorded on a Varian Unity Inova 600 spectrometer at 150.8 MHz. Samples were dissolved in $CDCl_3$. Infrared spectra were recorded with a Scimitar Series Varian 800 FT-IR Spectrometer fitted with a PIKE Technologies MIRacle ATR and samples were run as pure solids. Solvents were dried over standard drying agents[18] and freshly distilled before use except for ethanol which was reagent grade and not dried. Reagents were purchased from Sigma-Aldrich and used without further purification. Benzoylacetonitriles **2a**–**d** were synthesized via the method of Ridge et al.[19] TLC was conducted on 0.2 mm plates using Merck silica gel 60 F_{254}. Column chromatography was achieved using Merck silica gel 60 (particle size 0.063–0.200 μm, 70–230 mesh). High resolution mass spectra were obtained on a Waters LCT Premier XE (TOF) mass spectrometer fitted with an ESI ion source.

(2-Amino-4,5-dimethylthiophen-3-yl) (3-(trifluoromethyl)phenyl)methanone ***1a***

Method A. *m*-Trifluoromethylbenzoyl acetonitrile (**2a**) (0.94 mmol) and 2-butanone (1.03 mmol) were dissolved in EtOH (0.5 mL) and elemental sulfur (1.03 mmol) was added to the mixture followed by morpholine (94 μL). The mixture was refluxed for 3 h. The cooled mixture was diluted with ether washed with dilute HCl, water (×2) and finally with brine, dried ($MgSO_4$), filtered, and concentrated providing a dark brown resin that was chromatographed on silica gel eluting with 10% EtOAc:pet ether (40–60°C). The appropriate fractions were collected and concentrated to give a bright yellow resin that crystallizes upon standing (80 mg). Recrystallization (petroleum ether) of this material afforded the title compound **1a** (33 mg, 12%) as a bright yellow powder.

Method B. *m*-Trifluoromethylbenzoyl acetonitrile **2a** (4.69 mmol) and 2-butanone (5.16 mmol) were dissolved in dry CH_2Cl_2 (20 mL) in a two-necked flask fitted with a rubber septum and nitrogen inlet. The mixture was cooled with an ice-water bath and neat $TiCl_4$ (515 μL) was added dropwise to the mixture. After stirring for 1 h at 0°C dry pyridine (335 μL) was added dropwise and the ice-water bath was removed. After stirring at room temperature for 1 h, a further aliquot of dry pyridine was added (1 mL) and the mixture was allowed to stir overnight. The mixture was partitioned between CH_2Cl_2 and 2 M HCl. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (×2). The combined organics were washed with water, dried ($MgSO_4$), filtered, and concentrated providing the *E*/*Z* mixture of **4a** in a 54:46 ratio (determined by NMR) as an amber/brown resin (1.24 g, 99%). δ_H 8.17–8.08 (m, 4H, ArH), 7.89–7.86 (m, 2H, ArH), 7.68–7.63 (m, 2H, ArH), 2.68 (q, 2H, $J = 7.6$ Hz, OCH_2CH_3), 2.43 (q, 2H, $J = 7.5$ Hz, OCH_2CH_3), 2.36 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 1.28 (t, 3H, $J = 7.5$ Hz, OCH_2CH_3), 1.16 (t, 3H, $J = 7.5$ Hz, OCH_2CH_3).

The resin is dissolved in THF (10 mL) elemental sulfur (5.16 mmol) was added followed by Et_2NH (3 mL) dropwise and the mixture allowed to stir at room temperature for 2 h. The mixture was concentrated to a resin and taken up in CH_2Cl_2 and washed with dilute HCl, water (×2) and finally with brine, dried ($MgSO_4$), filtered, and concentrated providing a dark brown resin that is chromatographed on silica gel eluting with 10% EtOAc:pet ether (40–60°C). The appropriate fractions were collected and concentrated to give a bright yellow resin that crystallizes upon standing (541 mg). Recrystallization (petroleum ether) of this material afforded the title compound **1a** (325 mg, 23%) as bright yellow powder, mp 100–104°C. (Found: [M + H] 300.0664 $C_{14}H_{13}F_3NOS$ requires [M + H] 300.0664. Found: C 56.1, H 4.0, N 4.6, Calc. for $C_{14}H_{12}F_3NOS$: C 56.2, H 4.0, N 4.7%). ν_{max}/cm^{-1} 3345, 3239 (NH_2), 3123, 3040, 3010 (ArH), 3000–2800 (CH, saturated), 1576 (CO), 1428, 1387, 1337, 1322, 1260, 1164, 1117, 1097, 1069, 909, 815, 705, 690. δ_H 7.78–7.67 (m, 3H, ArH), 7.58–7.50 (m, 1H, ArH), 6.15 (bs, 2H, NH_2), 2.13 (s, 3H, CH_3), 1.49 (s, 3H, CH_3). δ_C 190.9, 164.1, 142.5, 131.1, 130.6 (q, $J = 32.7$ Hz), 128.8, 128.1, 126.9 (q, $J = 3.5$ Hz), 124.9 (q, $J = 3.5$ Hz), 123.9 (q, $J = 272.5$ Hz), 116.8, 115.5, 15.5, 12.6.

General Procedure for the Synthesis of 4,5-Dimethyl-2-phenylthiophene-3-carbonitriles ***6a–d*** *and 2-Aminothiophenes* ***1c,e***

The appropriate nitrile **2a**–**e** (0.94 mmol) and 3-chlorobutan-2-one **3** (1.03 mmol) were dissolved in dry CH_2Cl_2 (4 mL) in a two-necked flask fitted with a rubber septum and nitrogen inlet. The mixture was cooled with an ice-water bath and neat $TiCl_4$ (206 μL) was added dropwise. After 0.5 h dry pyridine (67 μL) was added dropwise and the ice-water bath was removed. After stirring a further 1 h another aliquot of dry pyridine (200 μL) was added dropwise and the reaction mixture left to stir overnight. The reaction mixture was partitioned between 2 M HCl (50 mL) and CH_2Cl_2 (20 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with water and finally brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the *E*/*Z* mixture of olefins **4a**–**e** as an amber resin or oil. The crude mixtures were used directly in the next reaction without purification.

The *E*/*Z* mixture was dissolved in EtOH (5 mL) and cooled to −78°C (MeOH/dry ice) and a solution of NaSH (2.0–2.2 mmol) in EtOH (8 mL) was added dropwise over 30–60 s. The reaction mixture was left to stir while the MeOH/dry ice-bath was

kept in place but no further additions of dry ice were made. The MeOH/dry ice-bath slowly warmed up to 10°C (~1 h) and a small amount of precipitate was observed. The mixture was diluted with CH_2Cl_2 and while stirring 2 M HCl (20 mL) was added slowly with gas evolution occurring (CAUTION! H_2S is generated which is highly toxic!). The organic layer is separated and the aqueous layer extracted with CH_2Cl_2. The aqueous layer is treated with ~4% sodium hypochlorite to oxidize residual H_2S. The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure in a fume cupboard, to a solid or resin. Solids were recrystallized with isopropyl alcohol, whereas resins were chromatographed on silica gel with CH_2Cl_2 before recrystallization with isopropyl alcohol.

4,5-Dimethyl-2-(3-(trifluoromethyl)phenyl)thiophene-3-carbonitrile ***6a***

Pale yellow long needles (120 mg, 45%), mp 36–37°C. ν_{max}/cm^{-1} 3049 (ArH), 3000–2800 (CH, saturated), 2215 (CN), 1495, 1329, 1251, 1200, 1116, 1073, 890, 879, 798, 695, 663. δ_H 7.96–7.89 (m, 2H, ArH), 7.67–7.56 (m, 2H, ArH), 2.41 (s, 3H, CH_3), 2.30 (s, 3H, CH_3). δ_C (150.8 MHz) 147.2, 136.0, 134.6, 132.6, 131.6 (q, $J = 32.6$ Hz), 130.5, 129.7, 125.7 (q, $J = 3.5$ Hz), 124.3 (q, $J = 3.8$ Hz), 123.7 (q, $J = 273.3$ Hz), 115.7, 109.2, 13.3, 12.9. *m/z* (APCI) 282 ([M + H], 34%), 212 (100), 170 (32), 145 (26). Found: C 59.7, H 3.6, N 4.9, Calc. for $C_{14}H_{13}NS$: C 59.8, H 3.6, N 5.0%.

2-(4-Chlorophenyl)-4,5-dimethylthiophene-3-carbonitrile ***6b***

Off white powder (142 mg, 61%), mp 82–83°C. ν_{max}/cm^{-1} 3055, 3030, 3021 (ArH), 3000–2800 (CH, saturated), 2216 (CN), 1503, 1463, 1401, 1200, 1181, 1096, 1013, 967, 823, 692. δ_H 7.64 (d, $J = 8.7$ Hz, 2H, ArH), 7.41 (d, $J = 8.7$ Hz, 2H, ArH), 2.38 (s, 3H, CH_3), 2.27 (s, 3H, CH_3). δ_C (150.8 MHz) 147.9, 135.7, 135.2, 133.8, 130.3, 129.3, 128.5, 116.0, 108.5, 13.2, 12.9. *m/z* (APCI) 248 ([M + H], 34%), 212 (100), 199 (90), 171 (22).

4,5-Dimethyl-2-phenylthiophene-3-carbonitrile ***6c***

Off white needles (100 mg, 50%), mp 55–56°C (lit.[17] 38–40). ν_{max}/cm^{-1} 3058, 3023 (ArH), 3000–2800 (CH, saturated), 2210 (CN), 1506, 1466, 1385, 1363, 1179, 1083, 960, 759, 686. δ_H 7.74–76.71 (m, 2H, ArH), 7.48–7.37 (m, 3H, ArH), 2.38 (s, 3H, CH_3), 2.28 (s, 3H, CH_3). δ_C (150.8 MHz) 149.5, 135.5, 133.4, 131.9, 129.2, 129.1, 127.3, 116.3, 108.1, 13.2, 12.9. *m/z* (APCI) 214 ([M + H], 55%), 199 (92), 198 (100), 187 (10), 166 (56).

4,5-Dimethyl-2-(4-(methyl)phenyl)thiophene-3-carbonitrile ***6d***

Long thick needles (86 mg, 40%), mp 83–84°C. ν_{max}/cm^{-1} 3053, 3020 (ArH), 3000–2800 (CH, saturated), 2211 (CN), 1515, 1464, 1442, 1381, 1363, 1320, 1191, 1177, 1129, 956, 811, 709, 671, 639. δ_H 7.61 (d, $J = 8.1$ Hz, 2H, ArH), 7.24 (d, $J = 8.1$ Hz, 2H, ArH), 2.39 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.27 (s, 3H, CH_3). δ_C (150.8 MHz) 149.8, 139.4, 135.3, 132.8, 129.8, 129.1, 127.2, 116.4, 107.7, 21.3, 13.2, 12.9. *m/z* (APCI) 228 ([M + H], 63%), 213 (100), 212 (75), 198 (40), 180 (40). Found: C 73.9, H 5.7, N 6.1, Calc. for $C_{14}H_{13}NS$: C 74.0, H 5.8, N 6.2%.

(2-Amino-4-phenylthiophen-3-yl)(phenyl)methanone ***1e***

Yellow powder (157 mg, 60%), mp 152–154°C (lit.[10] 154–156). Found: [M + H] 280.0791 $C_{17}H_{14}NOS$ requires [M + H] 280.0792. ν_{max}/cm^{-1} 3354, 3242 (NH_2), 3143, 3050, 3026 (ArH), 3000–2800 (CH, saturated), 1584 (CO), 1563, 1524, 1483, 1447, 1432, 1395, 1329, 1280, 909, 770, 738, 716, 699, 659, 599, 592. δ_H 7.34–7.32 (m, 2H, aromatic), 7.15–7.09 (m, 1H, aromatic), 7.02–6.92 (m, 7H, aromatic), 6.55 (bs, 2H, NH_2), 6.19 (s, 1H, 5-H). δ_C (150.8 MHz) 192.9, 165.7, 141.8, 140.0, 137.3, 130.6, 128.9, 128.5, 127.6, 127.3, 126.4, 115.1, 105.5.

Ethyl 2-Amino-4,5-dimethylthiophene-3-carboxylate ***1e***

Off white powder (101 mg, 54%), mp 90–92°C (lit.[9] 91–92). Found: [M + H] 200.0747 $C_9H_{14}NO_2S$ requires [M + H] 200.0740. ν_{max}/cm^{-1} 3400, 3298 (NH_2), 3000–2800 (CH, saturated), 1646 (CO), 1594, 1575, 1492, 1407, 1376, 1321, 1272, 1169, 1059, 1027, 781. δ_H 5.31 (bs, 2H, NH_2), 4.28 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 2.18 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 1.35 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3). δ_C (150.8 MHz) 166.1, 161.0, 130.3, 113.8, 106.9, 59.4, 14.8, 14.4, 12.28.

Acknowledgements

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