

## Studies with enamines: Functionally substituted enamines as aldehyde equivalents in Gewald reactions

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### Abstract

Several aryl and functionally substituted enamines reacted with ethyl cyanoacetate and elemental sulfur to form 2-aminothiophene-3-carboxylic acid derivatives that proved to be excellent precursors for a variety of thiophenes.

**Keywords:** Gewald reaction, enamines, elemental sulfur, thiophenes

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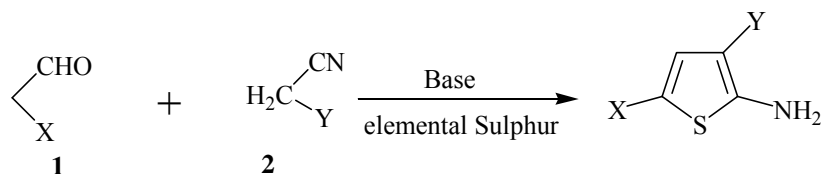
### Introduction

In 1966 Gewald<sup>1</sup> reported that aliphatic ketones, aldehydes or 1,3-dicarbonyl compounds react with activated nitriles and sulfur in the presence of a base at room temperature to give 2-aminothiophenes.<sup>1-4</sup> Since aminothiophenes are important intermediates in dye preparations,<sup>5,6</sup> in the pharmaceutical industry and as a precursors for other thiophenes employed in several high technology applications,<sup>7</sup> this methodology has been extensively utilized for the preparation of a variety of aminothiophenes *via* reacting ketones and aldehydes with active methylene carbonitriles and sulfur in presence of a base.<sup>8-11</sup> In the context of our interest in aminothiophenes as precursors to arylazo dyes<sup>12,13</sup> we became interested in 2-amino-4-unsubstituted thiophenes with a functional substituent at C-5.

### Results and Discussion

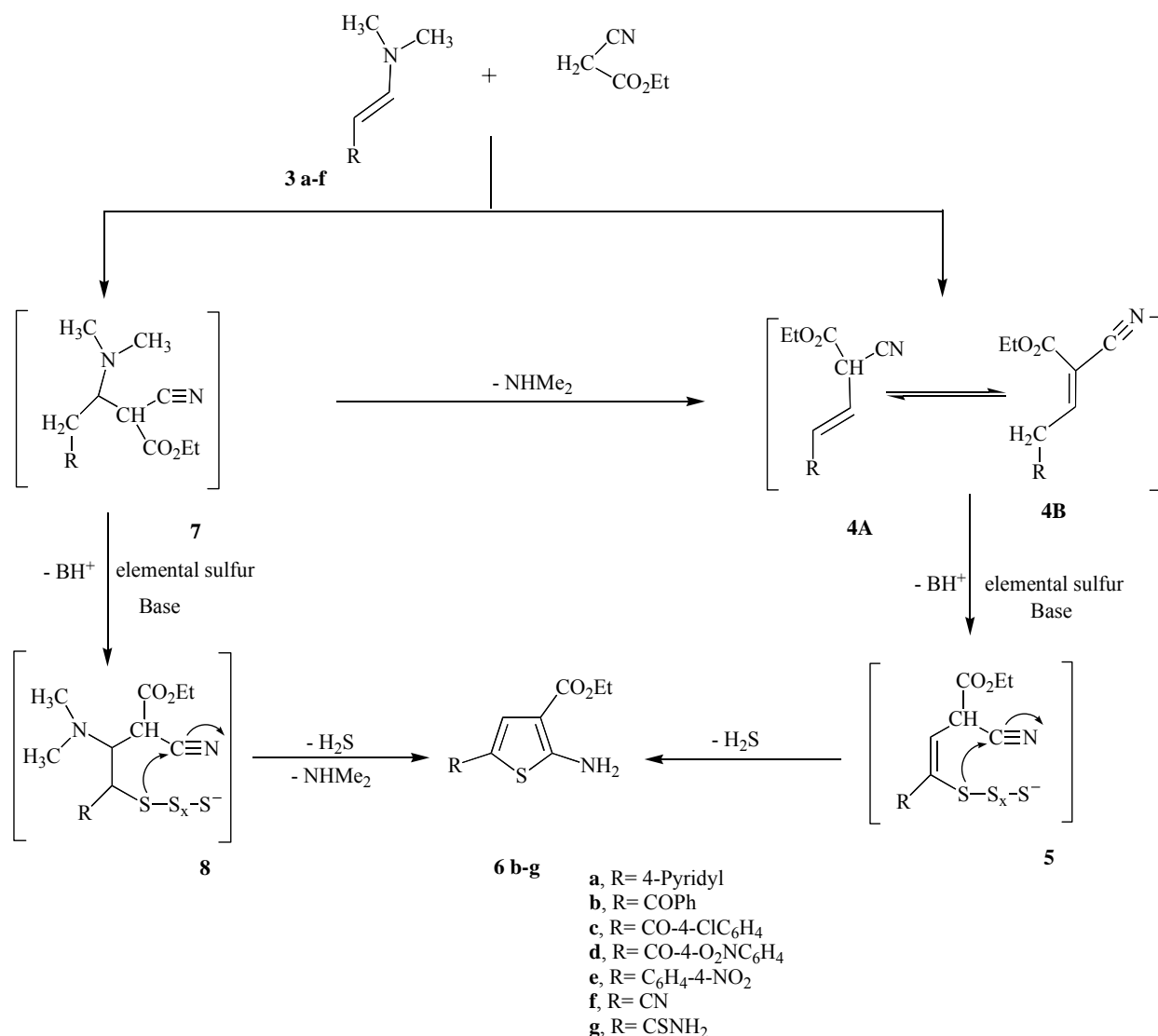
The logical starting materials for such thiophenes would be  $\beta$ -functional aldehydes **1**, active methylene nitriles **2** and elemental sulfur (cf. equation 1). However as  $\beta$ -functionalized aldehydes are rather unstable compounds therefore, we considered the possible use of functionally substituted enamines as their synthetic equivalents. We have, in the last decade, utilized such functionally substituted enamines extensively as precursors to functionally

substituted aromatic compounds<sup>14,15</sup> and heteroaromatic compounds.<sup>16–20</sup> We noted that only a few examples of the use of enamines **3a** as precursors to aminothiophenes have been reported.<sup>9,21</sup>



### Equation 1

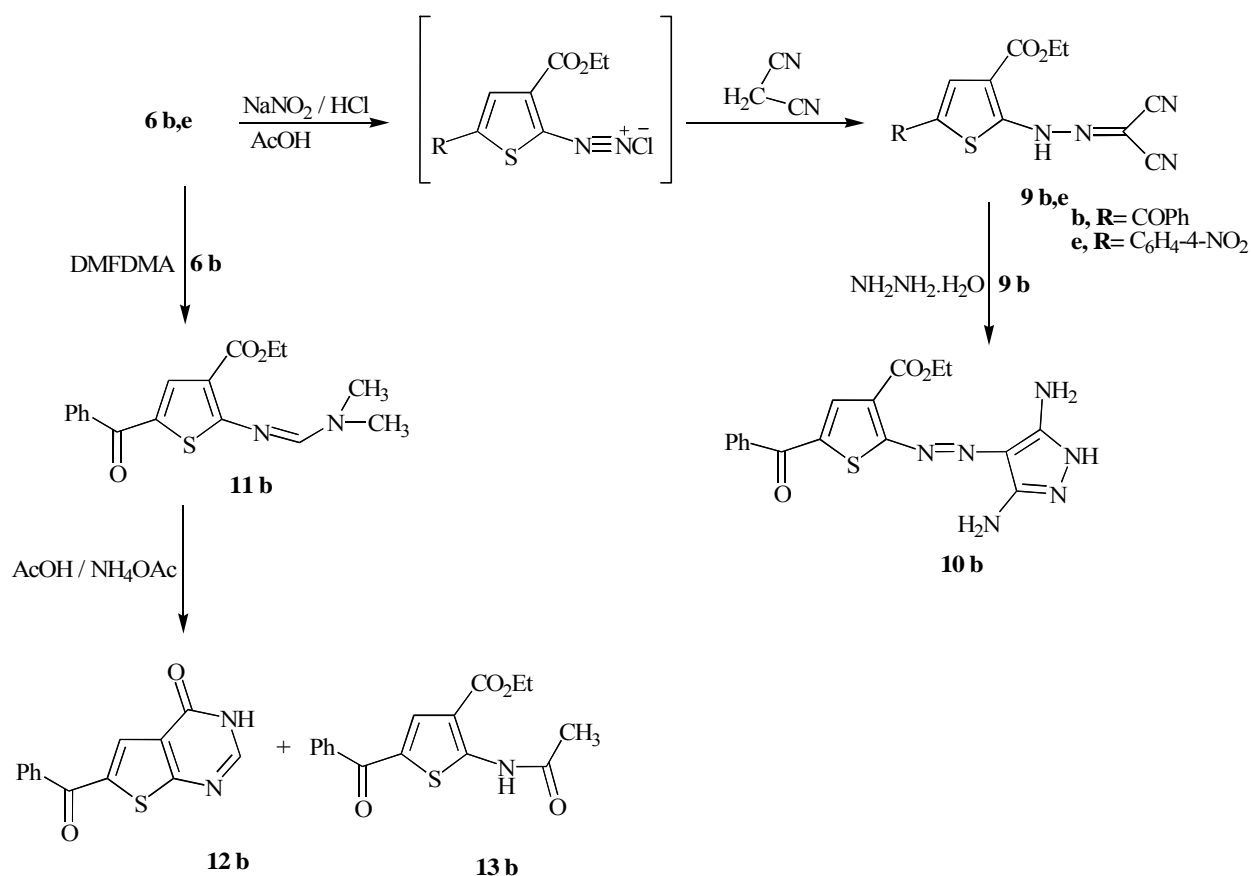
We envisioned that the initial step in this sequence would be the addition of an active methylenitrile to the  $\alpha,\beta$ -unsubstituted moiety in **3** with subsequent elimination of diethylamine to yield **4A** or **4B**. Alternatively, reaction of adduct **7** with sulfur in the presence of an equivalent amount of piperidine would yield **8** that would cyclise and aromatize to yield **6**. This sequence is quite similar to the reported general mechanism of the Gewald reaction.<sup>9</sup> In support of this we noted the elimination of H<sub>2</sub>S during the reaction. In either case, the activity of methylene moiety in either **4** or **7** is essential for the success of reaction. Consequently we selected enamines **3b-f** with electron attracting substituents to fulfill this prerequisite. We found that, **3b-e** reacted smoothly with elemental sulfur and ethyl cyanoacetate in the presence of equivalent amounts of piperidine (cf. Experimental Section) to yield amino thiophenes **6b-e**, **6b** in 70%, **6c**, 73%, **6d**, 76% and **6e**, 79% yields. Treating **3f** similarly with sulfur and ethyl cyanoacetate resulted in the formation of 2-aminothiophene-5-thiocarboxamide **6g** in 60% yield. We believe that initially **6f** is formed and this reacted further with the hydrogen sulfide produced during the reaction to yield the thioamide **6g** (cf. Scheme 1). Attempts to replace ethyl cyanoacetate by malononitrile failed in our hands to yield pure isolable products. An oily mixture of several products was produced with this reactant. Structures **6**, taking **6c** as a typical example, are supported by spectral and analytical evidence. Thus the MS of the typical example showed an M<sup>+</sup> peak at 309 (100), two intense peaks at 263 (100) (M<sup>+</sup> – OC<sub>2</sub>H<sub>5</sub>), and 139 (100) (P-chlorobenzoyl cation). Its <sup>13</sup>C NMR spectrum showed two signals for sp<sup>3</sup> carbons of the ester group at  $\delta = 15.05$  ppm and  $\delta = 60.99$  ppm; a benzyl carbonyl carbon at  $\delta = 186.61$  ppm, ester carbonyl carbon and C-2 at  $\delta = 169.32$  ppm and  $\delta = 165.64$  ppm (not necessarily respectively) and seven carbons at  $\delta = 138.56$ , 137.37, 136.81, 130.68, 129.35, 125.26, 109.21 ppm. The <sup>1</sup>H NMR spectrum also showed the expected signals for ethyl ester as triplets and quartets at  $\delta = 1.35$  and  $\delta = 4.31$  ppm respectively. The thiophene C-4 proton signal appeared as a singlet at  $\delta = 7.57$  ppm and an amino, D<sub>2</sub>O exchangeable, signal at  $\delta = 6.74$  ppm. The other analogues had spectra in complete agreement with proposed structure. The analytical data fits perfectly the proposed structures.



### Scheme 1

The 2-aminothiophene-5-carboxylic acid esters **6b-g** proved to be excellent precursors for the synthesis of arylazothiophenes as well as thieno[2,3-*d*]pyrimidines. Thus diazotizing **6b,e** in the presence of hydrochloric acid in acetic acid solution afforded diazonium salts that readily coupled with malononitrile to yield a thienylhydrazonomesoxalonitriles **9b,e**. Reacting **9b** with hydrazine hydrate gave the 3,5-diaminopyrazoles **10b**. Arylazopyrazol-3,5-diamines prepared long ago<sup>22</sup> in our laboratories have recently been shown to have interesting antiproliferative<sup>23</sup> activity and were also patented for possible utility as oxidative dyes for keratin fiber and for hair.<sup>24</sup> Thienylpyrazole-3,5-diamines merit testing in both these areas and this will be carried out. Aminothiophenes **6b** also condensed with dimethylformamide dimethylacetal to yield amidines **11b** that reacted in turn with acetic acid and ammonium acetate to yield a 1:1 mixture of

thienopyrimidine **12b** and acetylaminothiophene **13b**. The latter could also be obtained *via* acylation of **6b** with acetic anhydride (cf. Scheme 2).



**Scheme 2**

## Conclusions

In conclusion we have shown that functionally substituted enamines are excellent precursors for the synthesis of 2-amino-5-functionally-substituted thiophene carboxylic acid esters that can be readily used as precursors to potentially interesting thiophenes.

## Experimental Section

**General Procedures.** All melting points are uncorrected and were determined with a Sanyo (Gallaenkamp) instrument. Infrared spectra were recorded in KBr and were determined on a Perkin-Elmer 2000 FT-IR system. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were determined on a Bruker

DPX at (400 MHz for  $^1\text{H}$  NMR and 100 MHz for  $^{13}\text{C}$  NMR) spectrometer in  $\text{CDCl}_3$  or  $\text{DMSO-d}_6$  as solvent and TMS as internal standard; chemical shifts are reported in  $\delta$ (ppm). Mass spectra were measured on VG Autospec Q MS 30 and MS 9 (AEI) spectrometers, with EI 70 EV. Elemental analyses were measured by means of LEOCHNS-932 Elemental Analyzer.

### General procedure to synthesis compounds 6b-e

A mixture of **3b** (1.75 g, 0.010 mol), ethyl cyanoacetate (1.13 g, 0.010 mol) and elemental sulfur (0.32 g, 0.010 mol) in dry *N,N*-dimethylformamide as solvent (10 mL) was treated with an equivalent amounts of piperidine (2 mL). The reaction mixture was refluxed for 6-8 h, cooled and then poured onto ice-water. The residue, so formed, was extracted by dichloromethane. The organic layer was dried and the solvent was evaporated. The residue was purified through column chromatography on silica gel using a mixture of petroleum ether (60-80) and ethyl acetate (3 : 1) as an eluent.

**Ethyl 2-amino-5-benzoylthiophene-3-carboxylate (6b)**. Formed as yellow crystals in 70% yield; mp. 141-42 °C. Anal. Calcd. for  $\text{C}_{14}\text{H}_{13}\text{NO}_3\text{S}$  (275.06): C, 61.0; H, 4.7; N, 5.0; S, 11.7% Found: C, 60.8; H, 4.7; N, 5.1; S, 11.9% IR (KBr,  $\text{cm}^{-1}$ ): 3298, 3262 ( $\text{NH}_2$ ), 1686 (CO), 1620 (CO);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ , ppm = 1.28 (t, 3H,  $\text{CH}_3$ ,  $J = 8$  Hz), 4.31 (q, 2H,  $\text{CH}_2$ ,  $J = 8$  Hz), 6.60 (br, 2H,  $\text{NH}_2$ )  $\text{D}_2\text{O}$  exchangeable, 7.49-7.81 (m, 6H, Ar-H, CH-thiophene);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ , ppm = 15.1 ( $\text{CH}_3$ ), 60.5( $\text{CH}_2$ ), 107.3, 123.5, 128.9, 129.3, 164.7, 170.2 (CO), 186.8 (CO). MS:  $m/z$  (%) 275 ( $\text{M}^+$ , 100), 229 (95), 198 (20), 152 (40), 105 (80), 77 (60).

**Ethyl 2-amino-5-(4-chlorobenzoyl)thiophene-3-carboxylate (6c)**. Formed as yellow crystals in 73% yield; mp. 151-52 °C. Anal. Calcd. for  $\text{C}_{14}\text{H}_{12}\text{ClNO}_3\text{S}$  (309.77): C, 54.2; H, 3.9; N, 4.5; S, 10.3% Found: C, 54.3; H, 3.9; N, 4.8; S, 10.3% IR (KBr,  $\text{cm}^{-1}$ ): 3396, 3297 ( $\text{NH}_2$ ), 1677 (CO), 1600 (CO);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ , ppm = 1.35 (t, 3H,  $\text{CH}_3$ ,  $J = 8$  Hz), 4.31 (q, 2H,  $\text{CH}_2$ ,  $J = 8$  Hz), 6.74 (br, 2H,  $\text{NH}_2$ )  $\text{D}_2\text{O}$  exchangeable, 7.49 (d, 2H, Ar-H,  $J = 8$  Hz), 7.57 (s, 1H, CH-thiophene), 7.74 (d, 2H, Ar-H,  $J = 8$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ , ppm = 15.0 ( $\text{CH}_3$ ), 60.9( $\text{CH}_2$ ), 109.2, 125.2, 129.3, 130.6, 136.8, 137.3, 138.5, 165.6, 169.3 (CO), 186.6 (CO). MS:  $m/z$  (%) 309 ( $\text{M}^+$ , 100), 263 (100), 228 (20), 198 (20), 152 (55), 139 (100), 111 (80), 97 (15), 75 (30).

**Ethyl 2-amino-5-(4-nitrobenzoyl)thiophene-3-carboxylate (6d)**. Formed as yellow crystals in 76% yield; mp. 205-07 °C. Anal. Calcd. for  $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_5\text{S}$  (320.32): C, 52.5; H, 3.7; N, 8.7; S, 10.0% Found: C, 52.6; H, 3.9; N, 8.7; S, 10.0% IR (KBr,  $\text{cm}^{-1}$ ): 3401, 3273 ( $\text{NH}_2$ ), 1689 (CO), 1623 (CO);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ , ppm = 1.33 (t, 3H,  $\text{CH}_3$ ,  $J = 8$  Hz), 4.31 (q, 2H,  $\text{CH}_2$ ,  $J = 8$  Hz), 6.79 (br, 2H,  $\text{NH}_2$ )  $\text{D}_2\text{O}$  exchangeable, 7.54 (s, 1H, CH-thiophene), 7.93 (d, 2H, Ar-H,  $J = 8$  Hz), 8.37 (d, 2H, Ar-H,  $J = 8$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ , ppm = 14.5 ( $\text{CH}_3$ ), 60.6( $\text{CH}_2$ ), 109.1, 123.8, 124.2, 129.5, 137.6, 143.4, 149.5, 164.9, 169.3 (CO), 185.1 (CO). MS:  $m/z$  (%) 320 ( $\text{M}^+$ , 100), 274 (70), 229 (20), 152 (30), 104 (20), 96 (15), 76 (15).

**Ethyl 2-amino-5-(4-nitrophenyl)thiophene-3-carboxylate (6e).** The solid product, so formed, was crystallized from ethanol to yield a brown product, 79% yield; mp. 164-65 °C. *Anal.* Calcd. for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>S (292.05): C, 53.4; H, 4.1; N, 9.5; S, 10.9% Found: C, 53.2; H, 4.2; N, 9.7; S, 10.8% IR (KBr, cm<sup>-1</sup>): 3443, 3232 (NH<sub>2</sub>), 1671 (CO); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ, ppm = 1.29 (t, 3H, CH<sub>3</sub>, *J* = 8 Hz), 4.29 (q, 2H, CH<sub>2</sub>, *J* = 8 Hz), 7.59 (s, 1H, CH-thiophene), 7.68 (d, 2H, Ar-H, *J* = 8 Hz), 7.82 (br, 2H, NH<sub>2</sub>) D<sub>2</sub>O exchangeable, 8.14 (d, 2H, Ar-H, *J* = 8 Hz); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ, ppm = 15.31, 60.25, 106.76, 120.25, 124.92, 125.36, 126.82, 141.31, 145.33, 164.91, 166.06. MS: *m/z* (%) 292 (M<sup>+</sup>, 85), 246 (95), 215 (25), 171 (20), 144 (15).

**Synthesis of ethyl 2-amino-5-carbamothioylthiophene-3-carboxylate (6g).** A mixture of **3d** (1.36 g, 0.010 mol), ethyl cyanoacetate (1.13 g, 0.010 mol) and elemental sulfur (0.32 g, 0.010 mol) in *N,N*-dimethylformamide as solvent (10 mL) was treated with a few drops of piperidine. The reaction mixture was refluxed for 6-8 h., cooled and then poured onto ice-water. The residue, so formed, was extracted by dichloromethane. After evaporation of dichloromethane the residue was purified by column chromatography using a mixture of petroleum ether (60-80) and ethyl acetate (5 : 1) as an eluent. The afforded solid product was crystallized from diethyl ether to give yellow product; yield 60%; mp 214-15 °C. *Anal.* Calcd. for C<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub> (230.01): C, 42.3; H, 4.3; N, 12.1; S, 27.8% Found: C, 42.3; H, 4.5; N, 12.3; S, 27.7% IR (KBr, cm<sup>-1</sup>): 3376, 3193 (NH<sub>2</sub>), 3273, 3153 (NH<sub>2</sub>), 1679 (CO); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ, ppm = 1.26 (t, 3H, CH<sub>3</sub>, *J* = 8 Hz), 4.20 (q, 2H, CH<sub>2</sub>, *J* = 8 Hz), 7.68 (s, 1H, CH-thiophene), 7.85 (br, 2H, NH<sub>2</sub>) D<sub>2</sub>O exchangeable, 9.08 (br, 2H, NH<sub>2</sub>) D<sub>2</sub>O exchangeable; <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ, ppm = 15.4, 60.3, 106.9, 126.5, 165.5, 170.3, 170.5, 189.3. MS: *m/z* (%) 230 (M<sup>+</sup>, 100), 197 (35), 184 (90), 168 (20), 151 (60), 123 (15), 96 (30), 69 (20).

#### General procedures for preparation of compounds 9b,e

A solution of **6b** or **6e** (0.010 mol) in acetic acid (8 mL), was treated with concentrated hydrochloric acid (3 mL) and sodium nitrite (0.69 g, 0.010 mol) at 0 °C. This mixture was added gradually with stirring, to a cooled solution of malononitrile (0.66 g, 0.010 mol) in ethanol (10 mL) and sodium acetate (1.0 g). After complete addition, the reaction mixture was kept at room temperature for one hour. The solid product, so formed, was collected by filtration.

**5-Benzoyl-2-(*N'*-dicyanomethylene-hydrazino)-thiophene-3-carboxylic acid (9b).** The collected solid product was crystallized from ethanol to yield yellow product, 86% yield; mp. 181-82 °C. *Anal.* Calcd. for C<sub>17</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>S (352.06): C, 57.9; H, 3.4; N, 15.9; S, 9.1% Found: C, 57.7; H, 3.6; N, 15.9; S, 8.9% IR (KBr, cm<sup>-1</sup>): 3437 (NH), 2235 (CN), 2212 (CN), 1679 (CO), 1631 (CO); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ, ppm = 1.42 (t, 3H, CH<sub>3</sub>, *J* = 8 Hz), 4.45 (q, 2H, CH<sub>2</sub>, *J* = 8 Hz), 7.55-7.87 (m, 6H, Ar-H, CH-thiophene), 12.7 (br, 1H, NH) D<sub>2</sub>O exchangeable; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ, ppm = 14.7, 62.8, 93.3, 107.6, 111.3, 115.0, 129.2, 129.4, 133.2, 133.8, 136.2, 137.0, 158, 164.5, 187.6. MS: *m/z* (%) 352 (M<sup>+</sup>, 60), 306 (75), 275 (20), 105 (100), 77 (40).

**5-(4-Amino-phenyl)-2-(*N'*-dicyanomethylene-hydrazino)-thiophene-3-carboxylic acid (9e).**

As in the previous (above) procedures the products was crystallized from ethyl acetate to yield a dark brown product, 86% yield; mp. 216-17 °C. Anal. Calcd. for C<sub>16</sub>H<sub>11</sub>N<sub>5</sub>O<sub>4</sub>S (269.05): C, 52.0; H, 3.0; N, 18.9; S, 8.6% Found: C, 52.1; H, 3.0; N, 18.8; S, 8.8% IR (KBr, cm<sup>-1</sup>): 3299 (NH), 2226 (CN), 2208 (CN), 1677 (CO); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ, ppm = 1.36 (t, 3H, CH<sub>3</sub>, *J* = 8 Hz), 4.36 (q, 2H, CH<sub>2</sub>, *J* = 8 Hz), 7.85 (s, 1H, CH-thiophene), 7.94 (d, 2H, Ar-H), 8.22 (d, 2H, Ar-H), 10.9 (br, 1H, NH) D<sub>2</sub>O exchangeable; <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ, ppm = 14.16, 60.77, 133.8, 123.14, 124.4, 125.5, 126.0, 129.5, 139.6, 145.8, 148.6, 163.66, 168.2. MS: *m/z* (%) 269 (M<sup>+</sup>, 60), 334 (40), 292 (95), 246 (100), 215 (20), 172 (20), 120 (15), 72 (20).

**Synthesis of 3-5-Diamino-4-[(5-benzoyl-3-ethoxycarbonyl-2-thienyl)azo]-1*H*-pyrazole (10b).**

Equimolar amounts of **9b** (2.52 g, 0.010 mol) and hydrazine hydrate (0.5 g, 0.010 mol) in ethanol (10 mL) were heated at reflux for 5 h. After cooling, the reaction mixture was poured onto ice-water. The solid, so formed, was collected by filtration and crystallized from ethanol to give a red product; 85% yield; mp. 169-70 °C. Anal. Calcd. for C<sub>17</sub>H<sub>16</sub>N<sub>6</sub>O<sub>3</sub>S (384.1): C, 53.1; H, 4.2; N, 21.8; S, 8.35% Found: C, 53.0; H, 4.0; N, 21.9; S, 8.1% IR (KBr, cm<sup>-1</sup>): 3422 (NH), 3317, 3201 (NH<sub>2</sub>), 3217, 3159 (NH<sub>2</sub>), 1702 (CO), 1617 (CO); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ, ppm = 1.31 (t, 3H, CH<sub>3</sub>, *J* = 8 Hz), 4.26 (q, 2H, CH<sub>2</sub>, *J* = 8 Hz), 4.28 (br, 2H, NH<sub>2</sub>) D<sub>2</sub>O exchangeable, 4.29 (br, 2H, NH<sub>2</sub>) D<sub>2</sub>O exchangeable, 7.28-7.85 (m, 6H, Ar-H, CH-thiophene), 11.28 (br, 1H, NH) D<sub>2</sub>O exchangeable; <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ, ppm = 15.2, 61.2, 122.2, 123.4, 129.3 (2C), 129.4 (2C), 133.1, 133.6, 134.1, 137.2, 138.3, 162.2, 162.9, 173.4, 188.0. MS: *m/z* (%) 384 (M<sup>+</sup>, 50), 368 (10), 274 (65), 228 (70), 151 (20), 104 (100), 77 (80).

**Synthesis of ethyl 5-benzoyl-2-[(dimethylamino)methyleneamino]thiophene-3-carboxylate (11b).**

A mixture of compound **6b** (2.75 g, 0.010 mol) and *N,N*-dimethylformamide dimethylacetal (1.19 g, 0.010 mol) in toluene (20 mL) was refluxed for 6 h. The reaction mixture was evaporated under reduced pressure in vacuum yielding a crude product, which was crystallized from ethanol to give yellow crystals; yield 85%; mp. 130-31 °C. Anal. Calcd. for C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>S (330.1): C, 61.8; H, 5.4; N, 8.4; S, 9.7% Found: C, 62.0; H, 5.4; N, 8.6; S, 9.8% IR (KBr, cm<sup>-1</sup>): 1711 (CO), 1622 (CO); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ, ppm = 1.22 (t, 3H, CH<sub>3</sub>, *J* = 8 Hz), 3.06 (s, 3H, CH<sub>3</sub>), 3.16 (s, 3H, CH<sub>3</sub>), 4.15 (q, 2H, CH<sub>2</sub>, *J* = 8 Hz), 7.54-7.75 (m, 6H, Ar-H, CH-thiophene), 8.09 (s, 1H, CH); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ, ppm = 15.0, 35.0, 40.3, 60.5, 118.2, 128.7, 129.2, 129.5, 132.7, 138.4, 139.0, 157.7, 163.2, 172.2, 187.0. MS: *m/z* (%) 330 (M<sup>+</sup>, 65), 285 (20), 242 (20), 216 (10), 105 (95), 77 (100).

**General procedures for preparation of compounds 12b, 13b**

A mixture of compound **11b** (3.30 g, 0.010 mol), ammonium acetate (2.30 g, 0.03 mol) and acetic acid (7 mL) was refluxed for 4-6 h (monitored by TLC). The reaction mixture was cooled and poured onto ice-water. The solid product, so formed, was collected by filtration and washed with petroleum ether to extract the yellow product **12**. The residue was crystallized from ethyl acetate to yield white product **11**.

**6-Benzoylthieno[2,3-d]pyrimidin-4(3H)-one (12b).** Yield 45%, mp. 266-68 °C. Anal. Calcd. for C<sub>13</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>S (256.1): C, 60.9; H, 3.1; N, 10.9; S, 12.5% Found: C, 60.9; H, 3.2; N, 10.7; S, 12.6% IR (KBr, cm<sup>-1</sup>): 3149 (NH), 1657 (CO), 1628 (CO); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ, ppm = 7.59-7.89 (m, 6H, Ar-H, CH-thiophene), 8.32 (s, 1H, CH-Pyrimidine), 12.85 (br, 1H, NH) D<sub>2</sub>O exchangeable; <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ, ppm = 126.1, 129.3, 129.5, 130.6, 133.7, 137.1, 139.0, 149.5, 158.3, 169.0, 188.6. MS: *m/z* (%) 256 (M<sup>+</sup>, 100), 229 (40), 179 (80), 105 (100), 77 (80).

**Ethyl 2-acetamido-5-benzoylthiophene-3-carboxylate (13b).** Yield 45%; mp. 133-35 °C. Anal. Calcd. for C<sub>16</sub>H<sub>15</sub>NO<sub>4</sub>S (317.0): C, 60.5; H, 4.7; N, 4.4; S, 10.1. Found: C, 60.6; H, 4.8; N, 4.6; S, 10.2. IR (KBr, cm<sup>-1</sup>): 3264 (NH), 1674 (CO), 1633 (CO); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ, ppm = 1.23 (t, 3H, CH<sub>3</sub>, *J* = 8 Hz), 2.36 (s, 3H, CH<sub>3</sub>), 4.19 (q, 2H, CH<sub>2</sub>, *J* = 8 Hz), 7.41-7.80 (m, 6H, Ar-H, CH-thiophene), 11.13 (br, 1H, NH) D<sub>2</sub>O exchangeable; <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ, ppm = 15.1, 61.8, 107.3, 114.3, 123.5, 129.3, 129.6, 132.4, 133.5, 138.1, 154.4, 164.7, 169.8, 186.8. MS: *m/z* (%) 317 (M<sup>+</sup>, 30), 275 (100), 299 (85), 152 (25), 105 (80), 77 (55).

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