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Preparation of thieno[2,3-*b*]pyrroles starting from ketene-*N*,*S*-acetals

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Abstract—Thieno[2,3-*b*]pyrroles **4** can easily be synthesised in two different ways by using phenyl isothiocyanate and activated methylene compounds. The priority of the formation of the thiophene or pyrrole ring is investigated.

1. Introduction

Many thieno-fused bicyclic compounds have been recently prepared and tested for their biological properties, among them nitrogen containing heterocyclic systems such as thienopyridines[1], thienopyrimidines[2] and thienopyrroles[3,4] as well as more complex structures.[5,6]

Blair et al.[4] have reviewed some cases for which the thiophene replacement of the annulated benzene ring in some biologically active compounds maintains the activity but modifies the selectivity of these bioisosteres. These observations led them to investigate the activity of thienopyrroles, bioisosteric analogues of tryptamine derivatives.

Generally described synthetic access required appropriate thiophenes obtained after multi-step synthesis. Due to the interesting biological properties of thienopyrroles, we decided to develop new preparation methods based on the use of methylene active compounds and isothiocyanates.

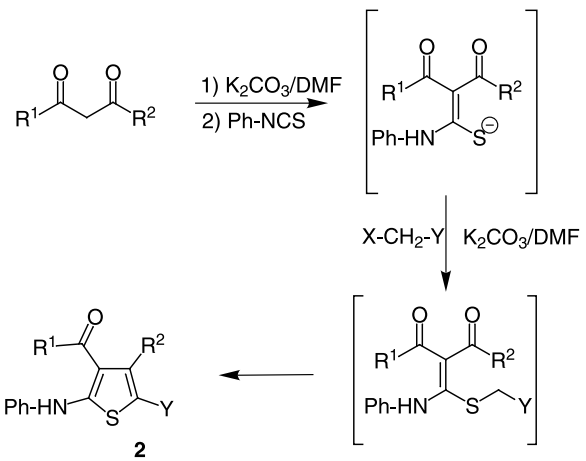
2. Results and discussion

We have recently reported a one-pot method[7] for the preparation of aminothiophenes **2**, precursors of thieno[2,3-*b*]pyrroles **4**.

The first step is the condensation of activated methylene compounds with alkyl or aryl isothiocyanates in a basic medium, which is well documented in the literature.[8–11]

Potassium carbonate has been used as the base in order to obtain the intermediate ketene aminothioacetals. The addition of two or more equivalents of alkyl bromoacetate, chloroacetonitrile, chloracetone or α-bromoacetophenone leads only to the thiophenes **2** in moderate to good yields (Scheme 1 and Table 1).

Condensation of the intermediate salt ketene-*N*,*S*-acetal with the halide currently leads to the corresponding aminothioacetal which smoothly undergoes a Dieckmann or Thorpe–Ziegler cyclisation in basic medium at room temperature. Formation of the pyrrole fused ring was achieved by prolonged reflux of **2** in acetone for 4–5 days in the presence of 1.5 equiv. of an alkyl bromoacetate.[12]



Scheme 1. Preparation of thiophenes **2**: Method A.

Keywords: thieno[2,3-*b*]pyrroles; ketene-*N*,*S*-acetals; thieno-fused bicyclic compounds.

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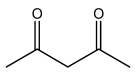
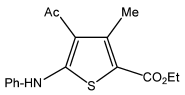
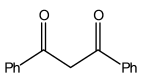
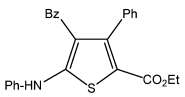
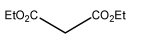
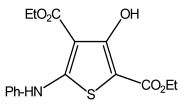
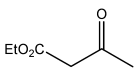
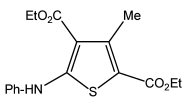
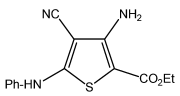
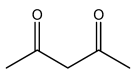
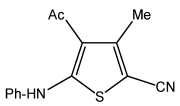
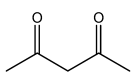
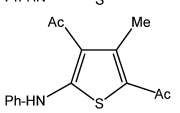
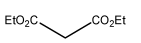
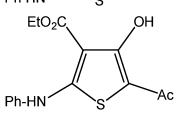
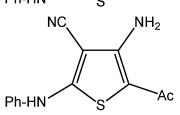
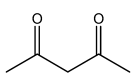
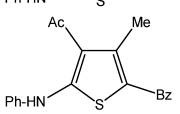
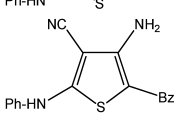
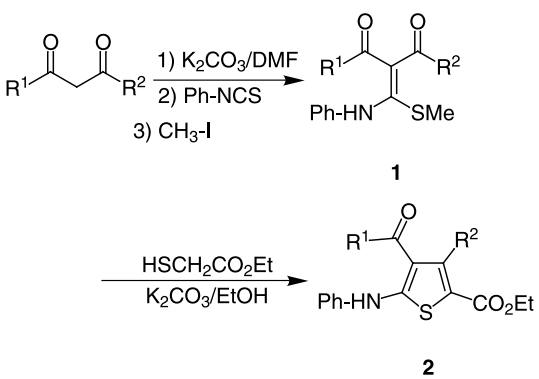
Table 1. One-pot method for the preparation of thiophenes **2** from 1,3-diketones or related compounds and phenyl isothiocyanate (Method A)

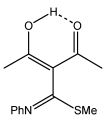
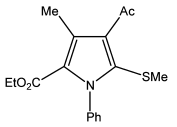
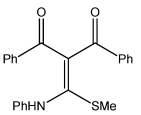
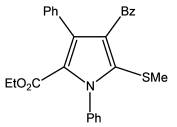
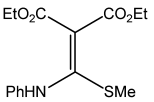
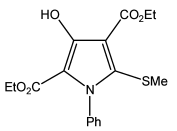
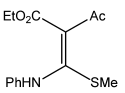
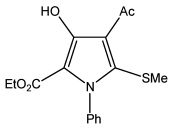
Entry	Starting compound	Product	Yield (%)
2a			47
2b			71
2c			34
2d			46
2e			19
2h			34
2i			94
2j			30
2k			82
2l			99
2m			82

We have also shown[13] that the preparation of these aminothiophenes **2** can be achieved in two steps with good yields when the one-pot method failed or gave the expected products in low yields. The first step consists in the



Scheme 2. Preparation of thiophenes **2**: Method B.

Table 2. Preparation of pyrroles **3** starting from **1**

Entry	Starting compound	Product	Yield (%)
3a			81
3b			43
3c			98
3d			10

formation of the N-phenyl S-methyl ketene-*N*,*S*-acetals **1**, obtained in one-pot from methylene active compounds, phenyl isothiocyanate and methyl iodide under the previously used basic conditions (K_2CO_3/DMF). These compounds were easily obtained in yields around 90% in all cases. In a second step, the ability of thioglycolate to react with compounds **1**, which is poorly related in the literature,[14] was therefore investigated (Scheme 2).

Although two steps are required for the preparation of the thiophenes **2** the yields for the two steps, in some cases, have been increased by a factor 2 to 3 (Tables 2 and 3).

On the other hand, thiophenes **2f**,**g** could be obtained by this way in moderate yields when our one step method completely failed.

We must note that in some cases our previous one step method remains attractive (see **2b**) and is the only easy way we currently have to introduce a substituent at the 2-position different from the carbethoxy group, which can be achieved in moderate (**2f**, **2g**) to excellent yields (almost quantitative for **2l**).

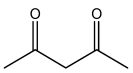
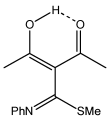
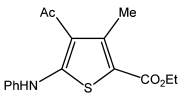
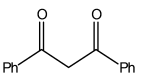
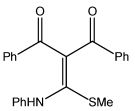
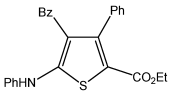
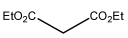
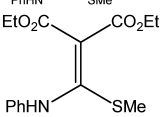
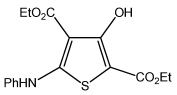
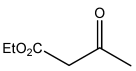
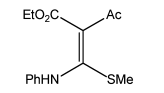
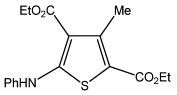
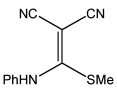
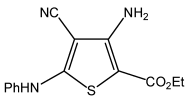
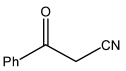
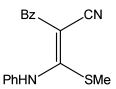
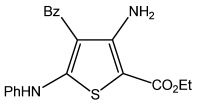
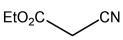
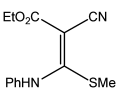
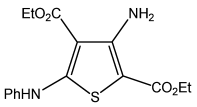
In a last step, we decided to investigate which of the thiophene or pyrrole rings should be prepared first in order to optimize this method (Scheme 3).

Starting from intermediates **1**, the corresponding 2-phenylamino-thiophenes **2** and 2-methylsulfanylpyrroles **3** have been obtained in moderate to good yields (10–98%) (Table 4).

We have already described[7] the preparation of thieno[2,3-*b*]pyrroles **4** from thiophenes **2** but the replacement of a methylsulfanyl group with a thiol on substituted pyrroles have not been related in the literature.

We have established that this strategy could be applied to

Table 3. Comparison of the two methods for the preparation of thiophenes **2** starting from **1**

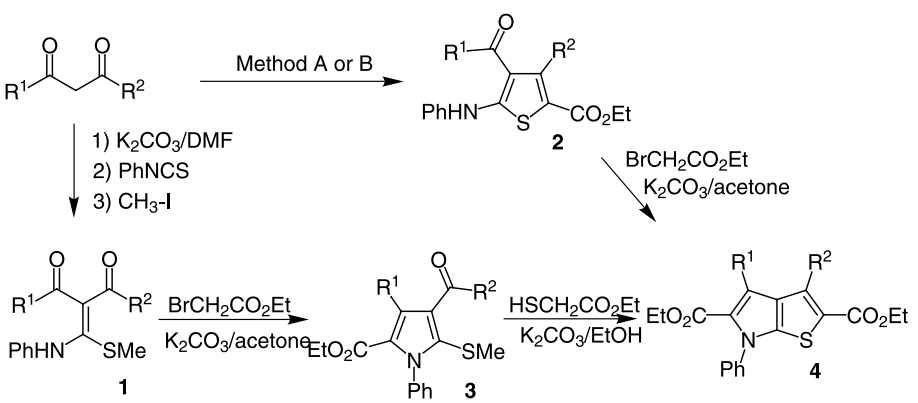
Entry	Starting Compound	Product 1	Yield (%)	Product 2	Yield (%)	
					Method A	Method B
a			96		47	79
b			58		71	21
c			98		34	88
d		 Mixture of two isomers	97		46	62
e			91		19	64
f			80		–	32
g			87		–	28

ketene aminothioacetal **1**. Although the ketene aminothioacetals moiety is still present in the pyrrole **2** skeleton, it was not obvious that a nucleophilic aromatic substitution reaction with thioglycolates was still feasible.

According to the results we report here, we clearly show that the methylsulfanyl group of some pyrroles can act as a leaving group in the presence of thioglycolate and lead to the expected thienopyrroles **4** (Table 4).

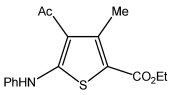
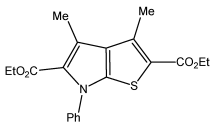
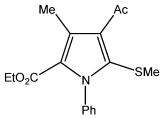
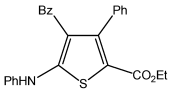
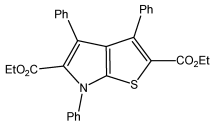
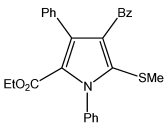
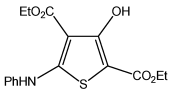
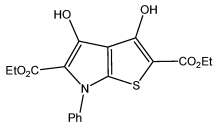
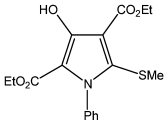
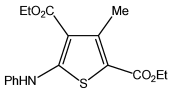
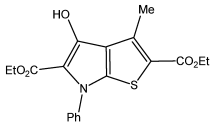
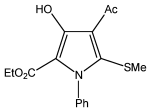
Nevertheless, it is currently not possible to predict whether the thiophene or pyrrole ring has to be synthesized first. In some cases, it appears to be independent from the preparation method chosen (**4a**,**c**) but for another case (**4d**), we were not able to continue the synthesis from the pyrrole **3d** even when we did not encounter major problems to prepare thiophenes **2d** and to finally obtain thieno[2,3-*b*]pyrroles **4d**.

In fact, it should be stressed that a thiol must react to replace the methylsulfanyl group from the pyrroles **3** even when a halide is required to obtain the compounds **4** from the thiophenes **2**. As a consequence, it becomes much more interesting to implement on account of the higher reliability of the latter, whether it is commercial or not.



Scheme 3.

Table 4. Comparative study for the preparation of thieno[2,3-*b*]pyrroles **4**

Entry	Yield (%)	Entry	Yield (%)
	79[a]		73
	81		72
	36[b]		61
	43		26
	92[a]		59
	98		43
	62[a]		32
	10		–

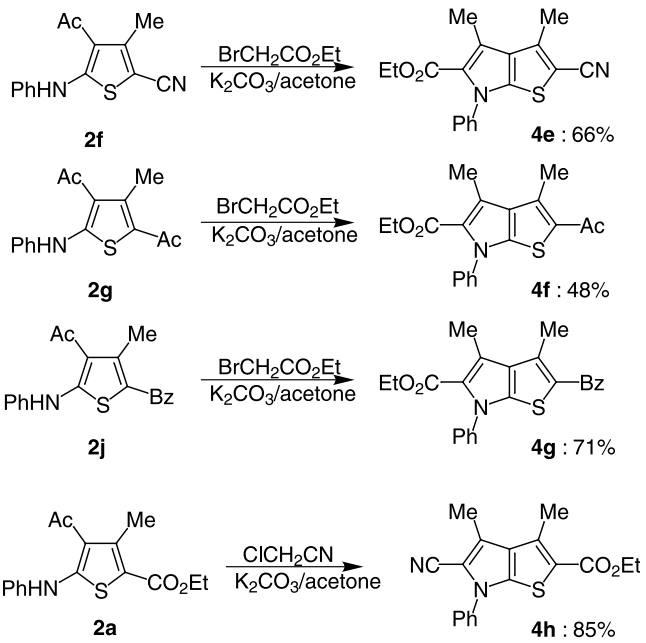
[a] Method B.
[b] Method A.

Finally, we want to report the preparation of thieno[2,3-*b*]pyrroles **4e**–**g** (see Scheme 4) obtained from thiophenes **2f**, **2g** and **2j** by treatment with ethyl bromacetate under the same conditions described for the preparation of compounds **4** from thiophenes **2**. Obviously, the use of our one-pot method to prepare the thiophene ring prior to the pyrrole one is required for the preparation of these bicyclic compounds.

Compound **4h**, isomer of **4e**, has been prepared from thiophenes **2a** following the same method with chloracetonitrile instead of bromacetate. This example clearly shows that our strategy allows to choose the position of all the desired substituents on the thieno[2,3-*b*]pyrrole framework, which demonstrates the generality and reliability of our method.

To sum up, we have developed a new synthetic pathway for the preparation of thieno[2,3-*b*]pyrroles.

Therefore, we have shown that, except for some rare cases,



Scheme 4. Preparation of thieno[2,3-*b*]pyrroles **4e**–**h**.

the best way to prepare these bicyclic compounds is the formation of the appropriate thiophenes, in one or two steps, prior to the pyrrole. The one-pot condensation with the appropriate halides followed by a Dieckman-type cyclisation allows to readily obtain the expected products in good yields.[12]

3. Experimental

3.1. General

NMR spectra were recorded at 250 and 62.5 MHz for ^{1}H and ^{13}C, respectively on a Bruker AC 250 spectrometer. IR spectra were recorded on a Mattson FTIR galaxy 3000 spectrophotometer using samples as KBr plates. Melting points were recorded on a Stuart Scientific SMP3 capillary melting point apparatus and were uncorrected. Elemental analysis were recorded on a Carlo Erba 1106 analyzer.

3.2. General procedure for the preparation of 1 and 2 (Method A)

A 100 mL three-necked round-bottom flask equipped with a magnetic stirrer, condenser and septum was charged with a solution of 1,3-diketone (10.0 mmol, 1 equiv.) in DMF (30 mL). Dried potassium carbonate (10.0 mmol, 1 equiv.) was added and the mixture was stirred for 1 h at room temperature. Phenyl isothiocyanate (10.0 mmol, 1 equiv.) was then added dropwise and the mixture was stirred for 2 h at room temperature before adding the appropriate halide (methyl iodide for **1**, ethyl bromacetate for **2a**–**g**, chloracetonitrile for **2h**, chloracetone for **2i**–**k** or α-bromacetophenone for **2l**,**m**)(10.0 mmol, 1 equiv.) and dried potassium carbonate (10.0 mmol, 1 equiv., not needed for **1**). The reaction was quenched with 100 mL of water after having stirred for 4 h at room temperature. The crude product precipitated and was purified by filtration followed by crystallisation in ethanol.

3.2.1. 2-Acetyl-3-hydroxy-*N*-phenyl-but-2-enimidothioic acid methyl ester (1a). Mp: 72°C (ethanol); IR (KBr): 1597 (L) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.12 (s, 6H), 2.50 (s, 3H), 6.69–7.39 (m, 5H), 15.04 (sl, 1H); ^{13}C NMR ($CDCl_3$): δ 14.3(2C), 23.8, 111.6, 120.6(2C), 123.9, 128.8(2C), 149.6, 164.8, 190.3(2C); Anal. calcd for $C_{13}H_{15}NO_2S$: C 62.62; H 6.06; N 5.62. Found: C 62.74; H 6.20; N 5.58.

3.2.2. 2-(Methylsulfanyl-phenylamino-methylene)-1,3-diphenyl-propane-1,3-dione (1b). Mp: 97°C (ethanol); IR (KBr): 1654 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.92 (s, 3H), 7.13–7.57 (m, 15H), 13.41 (sl, 1H); ^{13}C NMR ($CDCl_3$): δ 17.3, 112.2, 123.5, 125.8, 127.9(8C), 128.8(2C), 129.5(2C), 131.3(2C), 139.4, 140.8, 166.2, 187(2C); Anal. calcd for $C_{23}H_{19}NO_2S$: C 73.97; H 5.13; N 3.75. Found: C 74.00; H 5.12; N 3.80.

3.2.3. 2-(Methylsulfanyl-phenylamino-methylene)-malonic acid diethyl ester (1c). Mp: 56°C (ethanol); IR (KBr): 1715(L) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.31 (t, 6H, J=7.2 Hz), 1.95 (s, 3H), 4.25 (q, 4H, J=7.2 Hz), 7.22–7.33 (m, 5H), 10.61 (sl, 1H); ^{13}C NMR ($CDCl_3$): δ 13.6, 13.8, 16.0, 60.3, 61.8, 101.7, 123.2(2C), 124.9, 129.2(2C), 139.1, 159.3, 166.5(2C); Anal. calcd for $C_{15}H_{19}NO_4S$: C 58.23; H 6.19; N 4.53. Found: C 58.34; H 6.41; N 4.68.

3.2.4. 2-(Methylsulfanyl-phenylamino-methylene)-malononitrile (1e). Mp: 169°C (ethanol); IR (KBr): 2196, 2182 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.71 (s, 3H), 7.25–7.46 (m, 5H), 8.09 (sl, 1H); ^{13}C NMR ($CDCl_3$): δ 16.8, 114.1, 114.4, 124.3, 127.7(2C), 128.2, 129.8(2C), 137.1, 172.4; Anal. calcd for $C_{11}H_9N_3S$: C 61.37; H 4.21; N 19.52. Found: C 61.22; H 4.29; N 19.46.

3.2.5. 2-Benzoyl-3-methylsulfanyl-3-phenylamino-acrylonitrile (1f). Mp: 132°C (ethanol); IR (KBr): 2195, 1591 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.33 (s, 3H), 7.34–7.88 (m, 10H), 13.95 (sl, 1H); ^{13}C NMR ($CDCl_3$): δ 17.3, 85.5, 119.8, 124.6(2C), 127.3, 127.8(2C), 128.1(2C), 129.3(2C), 131.6, 137.1, 138.1, 172.7, 191.5; Anal. calcd for $C_{17}H_{14}N_2OS$: C 69.36; H 4.79; N 9.52. Found: C 69.53; H 4.74; N 9.46.

3.2.6. 2-Cyano-3-methylsulfanyl-3-phenylamino-acrylic acid ethyl ester (1g). Mp: 86°C (ethanol); IR (KBr): 2203, 1658 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.35 (t, 3H, J=7.2 Hz), 2.24 (s, 3H), 4.25 (q, 2H, J=7.2 Hz), 7.26–7.41 (m, 5H), 11.52 (sl, 1H); ^{13}C NMR ($CDCl_3$): δ 14.2, 17.2, 61.2, 117.4, 124.8(2C), 127.1(2C), 129.3, 129.4, 137.6, 167.7, 170.1; Anal. calcd for $C_{13}H_{14}N_2O_2S$: C 59.52; H 5.38; N 10.68. Found: C 59.61; H 5.49; N 10.89.

3.2.7. 4-Acetyl-3-methyl-5-phenylamino-thiophene-2-carboxylic acid ethyl ester (2a). Mp: 125°C (ethanol); IR (KBr): 1680, 1700, 2990 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.34 (t, 3H, J=7.1 Hz), 2.58 (s, 3H), 2.82 (s, 3H), 4.28 (q, 2H, J=7.1 Hz), 7.35–7.42 (m, 5H), 12.1 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.3, 16.5, 31.3, 60.5, 108.9, 119.2, 120.5, 124.7(2C), 129.5(2C), 139.6, 145.8, 162.7, 163.4, 195.7; Anal. calcd for $C_{16}H_{17}NO_3S$: C 63.34; H 5.65; N 4.62. Found: C 63.47; H 5.46; N 4.61.

3.2.8. 4-Benzoyl-3-phenyl-5-phenylamino-thiophene-2-carboxylic acid ethyl ester (2b). Mp: 222°C (ethanol); IR (KBr): 1495, 1602 cm^{-1}; ^1H NMR (DMSO): δ 1.14 (t, 3H, J=7.3 Hz), 4.13 (q, 2H, J=7.3 Hz), 6.95–7.47 (m, 15H), 11.19 (sl, 1H); ^{13}C NMR (DMSO): δ 14.0, 60.6, 110.2, 119.0, 120.2(2C), 124.7(2C), 126.8, 127.2(2C), 127.4(2C), 128.1, 128.3(4C), 129.7, 130.4, 134.6, 139.5, 148.3, 155.9, 163.0, 194.7; Anal. calcd for $C_{26}H_{21}NO_3S$: C 73.04; H 4.95; N 3.28. Found: C 73.00; H 5.02; N 3.32.

3.2.9. 3-Hydroxy-5-phenylamino-thiophene-2,4-dicarboxylic acid diethyl ester (2c). Mp: 96°C (ethanol); IR (KBr): 2982, 2932, 1733, 1663, 1596, 1577, 1234, 1189, 1151, 1030 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.10 (t, 3H, J=7.2 Hz), 1.22 (t, 3H, J=7.2 Hz), 3.96 (q, 2H, J=7.2 Hz), 4.22 (q, 2H, J=7.2 Hz), 7.14–7.55 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.0(2C), 60.0, 60.3, 98.3, 120.2(2C), 123.2, 124.8, 128.8(2C), 138.8, 161.7, 163.6, 165.3, 165.8; Anal. calcd for $C_{16}H_{17}NO_5S$: C 57.30; H 5.11; N 4.18. Found: C 57.20; H 5.12; N 4.20.

3.2.10. 3-Methyl-5-phenylamino-thiophene-2,4-dicarboxylic acid diethyl ester (2d). Mp: 119°C (ethanol); IR (KBr): 2984, 1693, 1656, 1593, 1560, 1521, 1250, 1230, 1195 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.34 (t, 3H, J=7.2 Hz), 1.41 (t, 3H, J=7.2 Hz), 2.77 (s, 3H), 4.27 (q, 2H, J=7.2 Hz), 4.35 (q, 2H, J=7.2 Hz), 7.11–7.44 (m, 5H), 10.60 (sl, 1H); ^{13}C NMR ($CDCl_3$): δ 14.0, 14.1, 15.7, 60.2, 108.6, 109.0, 119.5(2C), 124.0, 129.4(2C), 139.7, 147.2, 162.0, 162.5, 166.6; Anal. calcd for $C_{17}H_{19}NO_4S$: C 61.24; H 5.74; N 4.20. Found: C 61.25; H 5.70; N 4.17.

3.2.11. 3-Amino-4-cyano-5-phenylamino-thiophene-2-carboxylic acid ethyl ester (2e). Mp: 219°C (ethanol); IR (KBr): 1720, 2200, 3420 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.29 (t, 3H, J=7.2 Hz), 4.25 (q, 2H, J=7.2 Hz), 5.79 (sl, 2H), 7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.6(CH_3), 60.1(CH_2), 80.0, 89.4, 113.6(CN), 120.5, 125.6(2C), 129.9(2C), 138.8, 152.8, 161.9(CO_2), 162.0; Anal. calcd for $C_{14}H_{13}N_3O_2S$: C 58.52; H 4.56; N 14.62. Found: C 58.60; H 4.50; N 14.72.

3.2.12. 3-Amino-4-benzoyl-5-phenylamino-thiophene-2-carboxylic acid ethyl ester (2f). Mp: 232°C (ethanol); IR (KBr): 1665, 1619, 1417, 1330, 1285cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.04 (t, 3H, J=7.1 Hz), 3.98 (q, 2H, J=7.1 Hz), 7.22–7.59 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.1, 60.1, 118.1, 118.2, 127.8, 128.0, 129.0(2C), 129.3(2C), 129.4(2C), 129.6(2C), 130.4, 137.0, 139.6, 159.8, 161.3(CO_2), 187.3(CO); Anal. calcd for $C_{20}H_{18}N_2O_3S$: C 65.55; H 4.95; N 7.64. Found: C 65.40; H 5.11; N 7.52.

3.2.13. 3-Amino-5-phenylamino-thiophene-2,4-dicarboxylic acid diethyl ester (2g). Mp: 140°C (ethanol); IR (KBr): 3507, 3379, 2977, 1696, 1664, 1596, 1569, 1505, 1288, 1252, 1030 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.18 (t, 3H, J=7.1 Hz), 1.32 (t, 3H, J=7.2 Hz), 4.09 (q, 2H, J=7.1 Hz), 4.34 (q, 2H, J=7.2 Hz), 7.24–7.45 (m, 5H), 10.05 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.4(CH_3), 13.6(CH_3), 58.3(CH_2), 59.5(CH_2), 96.8, 101.0, 119.6(2C), 123.9, 128.6(2C), 138.3, 147.4, 162.0(CO_2), 163.1, 164.1(CO_2); Anal. calcd for $C_{16}H_{18}N_2O_4S$: C 57.47; H 5.43; N 8.38. Found: C 57.55; H 5.29; N 8.45.

3.2.14. 4-Acetyl-3-methyl-5-phenylamino-thiophene-2-carbonitrile (2h). Mp: 86°C (ethanol); IR (KBr): 3292,

2201, 1621, 1590, 1548, 1519 cm^{-1}; ^1H NMR (DMSO): δ 2.56 (s, 3H), 2.61 (s, 3H), 7.23–7.43 (m, 5H), 12.10 (sl, 1H); ^{13}C NMR (DMSO): δ 18.2, 30.9, 115.0, 117.3, 121.2(2C), 125.8, 130.0(2C), 130.1, 139.5, 150.2, 163.5, 194.9; Anal. calcd for $C_{14}H_{12}N_2OS$: C 65.60; H 4.72; N 10.93. Found: C 65.78; H 4.50; N 11.13.

3.2.15. 1-(5-Acetyl-4-methyl-2-phenylamino-thiophen-3-yl)-ethanone (2i). Mp: 115°C (ethanol); IR (KBr): 3180, 1650, 1614, 1533, 1485, 1399, 1218 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H), 2.59 (s, 3H), 2.80 (s, 3H), 7.16–7.45 (m, 5H), 11.99 (sl, 1H); ^{13}C NMR ($CDCl_3$): δ 17.3, 30.4, 31.6, 119.9, 120.0, 120.8(2C), 125.1, 129.6(2C), 139.5, 144.6, 163.3, 190.2, 196.5; Anal. calcd for $C_{15}H_{15}NO_2S$: C 65.91; H 5.53; N 5.12. Found: C 66.17; H 5.65; N 5.21.

3.2.16. 5-Acetyl-4-hydroxy-2-phenylamino-thiophene-3-carboxylic acid ethyl ester (2j). Mp: 109°C (ethanol); IR (KBr): 1549, 1587, 1665 cm^{-1};^1H NMR ($CDCl_3$): δ 1.41 (t, 3H, J=7.2 Hz), 2.26 (s, 3H), 4.42 (q, 2H, J=7.2 Hz), 7.13–7.59 (m, 5H), 10.89 (sl, 1H); ^{13}C NMR ($CDCl_3$): δ 14.4, 30.3, 60.4, 106.2, 121.6(2C), 124.9, 129.2(2C), 138.4, 145.2, 151.0, 152.2, 165.9, 180.5; Anal. calcd for $C_{15}H_{15}NO_4S$: C 59.00; H 4.95; N 4.59. Found: C 59.13; H 4.97; N 4.62.

3.2.17. 5-Acetyl-4-amino-2-phenylamino-thiophene-3-carbonitrile (2k). Mp: 212°C (ethanol); IR (KBr): 3379, 3266, 3191, 2204, 1588 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.07 (s, 3H), 7.18–7.57 (m, 5H), 10.44 (sl, 1H); ^{13}C NMR (DMSO): δ 028.0, 113.8, 114.8, 121.9(2C), 124.2, 125.6, 129.7(2C), 140.2, 155.1, 163.2, 186.9; Anal. calcd for $C_{13}H_{11}N_3OS$: C 60.68; H 4.31; N 16.33. Found: C 60.79; H 4.32; N 16.31.

3.2.18. 1-(5-Benzoyl-4-methyl-2-phenylamino-thiophen-3-yl)-ethanone (2l). Mp: 110°C (ethanol); IR (KBr): 1621, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.56 (s, 3H), 2.58 (s, 3H), 7.16–7.72 (m, 5H), 12.10 (sl, 1H); ^{13}C NMR ($CDCl_3$): δ 18.5, 31.5, 120.7(2C), 125.1(2C), 128.2, 128.4(2C), 128.6(2C), 129.6, 131.8, 132.8, 139.5, 140.6, 144.9, 164.5, 196.3, 199.4; Anal. calcd for $C_{20}H_{17}NO_2S$: C 71.62; H 5.11; N 4.18. Found: C 71.69; H 5.09; N 4.25.

3.2.19. 4-Amino-5-benzoyl-2-phenylamino-thiophene-3-carbonitrile (2m). Mp: 267°C (ethanol); IR (KBr): 3420, 2207, 1624 cm^{-1}; ^1H NMR (DMSO): δ 7.18–7.56 (m, 10H), 8.05 (sl, 2H), 10.57 (sl, 1H); ^{13}C NMR (DMSO): δ 80.5, 94.0, 113.7, 122.3(2C), 125.9, 127.0(2C), 128.7(2C), 129.8(2C), 130.8, 139.9, 141.0, 157.7, 165.2, 184.8; Anal. calcd for $C_{18}H_{13}N_3OS$: C 67.69; H 4.10; N 13.16. Found: C 67.67; H 3.94; N 12.98.

3.3. General procedure for the preparation of thiophenes 2 (Method B) from 1

A 100 mL three-necked round-bottom flask equipped with a magnetic stirrer, condenser and septum was charged with a solution of the aminothioacetals **1** (10.0 mmol, 1 equiv.) in ehanol (30 mL). Dried potassium carbonate (10.0 mmol, 1 equiv.) and ethylthioglycolate (10.0 mmol, 1 equiv.) was added. The reaction was quenched with 100 mL of water after having stirred 6 h in refluxing ethanol. The crude product precipitated and was purified by filtration followed by crystallisation in ethanol.

3.4. General procedure for the preparation of pyrroles 3

A 100 mL three-necked round-bottom flask equipped with a magnetic stirrer, condenser and septum was charged with a solution of aminothioacetals **1** (10.0 mmol, 1 equiv.) in acetone (30 mL). Dried potassium carbonate (10.0 mmol, 1 equiv.) and ethyl bromoacetate (or chloroacetonitrile) (10.0 mmol, 1 equiv.) was added. The reaction was quenched with 100 mL of water after having stirred 4–5 days in refluxing acetone. The crude product when precipated was purified by filtration followed by crystallisation in ethanol, when it was an oil the aqueous phase was washed 3× with dichloromethane and dried over magnesium sulfate and evaporated.

3.4.1. 4-Acetyl-3-methyl-5-methylsulfanyl-1-phenyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (3a). Yellow oil; ^1H NMR ($CDCl_3$): δ 1.00 (t, 3H, J=7.2 Hz), 2.08 (s, 3H), 2.53 (s, 3H), 2.73 (s, 3H), 4.04 (q, 2H, J=7.2 Hz), 7.20–7.46 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 12.3, 13.8, 20.6, 31.3, 60.2, 120.0(2C), 123.0, 123.9, 128.3, 128.4(2C), 128.5, 128.8, 150.8, 160.9, 196.5; Anal. calcd for $C_{17}H_{19}NO_3S$: C 64.33; H 6.03; N 4.41. Found: C 64.30; H 6.12; N 4.50.

3.4.2. 4-Benzoyl-5-methylsulfanyl-1,3-diphenyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (3b). Mp: 107°C (ethanol); IR (KBr): 1706, 1652 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.76 (t, 3H, J=7.3 Hz), 2.06 (s, 3H), 3.89 (q, 2H, J=7.3 Hz), 7.11–7.51 (m, 15H); ^{13}C NMR ($CDCl_3$): δ 13.1, 20.2, 60.2, 123.9, 127.0, 127.2(2C), 127.8(2C), 128.2(2C), 128.4(2C), 128.6, 129.6(2C), 130.0(2C), 132.6, 133.3, 138.1, 138.5, 160.1, 193.2; Anal. calcd for $C_{27}H_{23}NO_3S$: C 73.44; H 5.25; N 3.17. Found: C 73.45; H 5.25; N 3.15.

3.4.3. 3-Hydroxy-5-methylsulfanyl-1-phenyl-1*H*-pyrrole-2,4-dicarboxylic acid diethyl ester (3c). Yellow oil; IR (NaCl): 1738, 1687 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.20 (t, 3H, J=7.2 Hz), 1.34 (t, 3H, J=7.2 Hz), 1.80 (s, 3H), 3.27 (s, 1H), 4.10 (q, 2H, J=7.2 Hz), 4.30 (q, 2H, J= 7.2 Hz), 7.00–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 13.8, 13.9, 16.4, 60.7, 62.2, 119.3(2C), 124.2, 128.0, 128.7(2C), 129.5, 129.7, 147.9, 159.9, 167.7, 169.8; Anal. calcd for $C_{17}H_{19}NO_5S$: C 58.44; H 5.48; N 4.01. Found: C 58.55; H 5.50; N 4.00.

3.4.4. 4-Acetyl-3-hydroxy-5-methylsulfanyl-1-phenyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (3d). Mp: 76°C (ethanol); IR (KBr): 1757, 1693 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.27 (t, 3H, J=7.2 Hz), 2.25 (s, 3H), 2.47 (s, 3H), 4.26 (q, 2H, J=7.2 Hz), 4.52 (s, 1H), 6.78–7.19 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 13.7, 14.0, 17.5, 66.0, 119.4, 120.0, 119.8(2C), 123.1, 123.8, 128.1(2C), 128.8, 150.8, 167.9, 195.6; Anal. calcd for $C_{16}H_{17}NO_4S$: C 60.17; H 5.37; N 4.39. Found: C 60.36; H 5.15; N 4.49.

3.5. General procedure for the preparation of thieno[2,3-*b*]pyrroles 4

Formation of the pyrrole fused ring. Alkyl bromoacetate (or chloroacetonitrile) (15.0 mmol, 1.5 equiv.) was added to a stirred solution of thiophenes **2** (10.0 mmol, 1 equiv.) in

30 mL of dry acetone and dried potassium carbonate (10.0 mmol, 1 equiv.). The reaction mixture was heated at reflux for 5 days before quenching in 100 mL of water. The crude product precipitated and was purified by filtration followed by crystallisation in ethanol.

Formation of the thiophene fused ring. A 100 mL three-necked round-bottom flask equipped with a magnetic stirrer, condenser and septum was charged with a solution of the pyrroles **3** (10.0 mmol, 1 equiv.) in ehanol (30 mL). Dried potassium carbonate (10.0 mmol, 1 equiv.) and ethylthioglycolate (10.0 mmol, 1 equiv.) was added. The reaction was quenched with 100 mL of water after having stirred 6 h in refluxing ethanol. The crude product precipitated and was purified by filtration followed by crystallisation in ethanol.

3.5.1. 3,4-Dimethyl-6-phenyl-6*H*-thieno[2,3-*b*]pyrrole-2,5-dicarboxylic acid diethyl ester (4a). Mp: 127°C (ethanol); IR (KBr): 2985, 2974, 1697(L), 1597, 1505, 1369, 1268, 1238, 1159, 1111 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.08 (t, 3H, J=7.2 Hz), 1.33 (t, 3H, J=7.2 Hz), 2.71 (s, 3H), 2.83 (s, 3H), 4.14 (q, 2H, J=7.2 Hz), 4.16 (q, 2H, J=7.2 Hz), 7.30–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 11.7, 13.8, 14.3, 14.5, 60.1, 60.5, 120.3, 124.8, 125.0, 126.1, 127.5(2C), 128.9(2C), 130.7, 139.7, 139.9, 143.5, 161.1, 163.1; Anal. calcd for $C_{20}H_{21}NO_4S$: C 64.67; H 5.70; N 3.77. Found: C 64.84; H 5.58; N 3.90.

3.5.2. 3,4,6-Triphenyl-6*H*-thieno[2,3-*b*]pyrrole-2,5-dicarboxylic acid diethyl ester (4b). Mp: 156°C (ethanol); IR (KBr): 1706, 1651, 1596, 1492, 1237, 1150 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, J=7.2 Hz), 1.14 (t, 3H, J=7.2 Hz), 3.95 (q, 2H, J=7.2 Hz); 4.14 (q, 2H, J=7.2 Hz), 6.97–7.54 (m, 15H); ^{13}C NMR ($CDCl_3$): δ 13.4, 13.9, 60.3, 60.7, 119.1, 124.8(2C), 125.4(2C), 126.5(2C), 126.7, 126.9(2C), 127.1(2C), 128.2(2C), 129.1(2C), 129.4, 129.9, 130.6, 133.6, 138.4, 139.1, 140.2, 148.5, 161.2, 163.4; Anal. calcd for $C_{30}H_{25}NO_4S$: C 72.71; H 5.08; N 2.83. Found: C 72.72; H 5.06; N 2.72.

3.5.3. 3,4-Dihydroxy-6-phenyl-6*H*-thieno[2,3-*b*]pyrrole-2,5-dicarboxylic acid diethyl ester (4c). Orange oil; IR (KBr): 2982, 1739, 1629, 1593, 1211, 1029 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.21 (t, 3H, J=7.2 Hz), 1.32 (t, 3H, J=7.2 Hz), 4.09 (q, 2H, J=7.2 Hz), 4.27 (q, 2H, J=7.2 Hz), 6.97–7.44 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 13.8, 13.9, 60.6, 62.2, 119.3(2C), 120.6, 124.2, 128.9(2C), 133.6, 140.0, 147.9, 160.0, 162.1, 162.2, 167.7, 169.8; Anal. calcd for $C_{18}H_{17}NO_6S$: C 57.59; H 4.56; N 3.73. Found: C 57.40; H 4.50; N 3.60.

3.5.4. 4-Hydroxy-3-methyl-6-phenyl-6*H*-thieno[2,3-*b*]pyrrole-2,5-dicarboxylic acid diethyl ester (4d). Yellow oil; IR (KBr): 2982, 2930, 1720, 1628, 1597, 1368, 1272, 1135, 1031 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.10 (t, 3H, J=7.2 Hz), 1.28 (t, 3H, J=7.2 Hz), 2.81 (s, 3H), 4.13 (q, 2H, J=7.2 Hz), 4.27 (q, 2H, J=7.2 Hz), 4.88 (s, 1H), 7.33–7.46 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 13.8, 14.2, 14.4, 60.3, 60.7, 125.4(2C), 128.0, 129.2(2C), 139.2, 147.8, 160.5, 161.1, 162.5, 168.7, 170.2; Anal. calcd for $C_{19}H_{19}NO_5S$: C 61.11; H 5.13; N 3.75. Found: C 61.22; H 5.04; N 3.80.

3.5.5. 2-Cyano-3,4-dimethyl-6-phenyl-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylic acid ethyl ester (4e). Mp: 125°C (ethanol); IR (KBr): 2201, 1635 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.35 (t, 3H, J=7.2 Hz), 2.55 (s, 3H), 2.60 (s, 3H), 4.35 (q, 2H, J=7.2 Hz), 7.19–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 18.7, 60.1, 108.4, 115.0, 116.2, 117.2, 120.9, 121.0, 125.3, 125.8(2C), 129.9(2C), 133.4, 135.1, 139.0, 150.8, 166.7(CO_2).; Anal. calcd for $C_{18}H_{16}N_2O_2S$: C 66.64; H 4.97; N 8.64. Found: C 66.54; H 4.86; N 8.70.

3.5.6. 2-Acetyl-3,4-dimethyl-6-phenyl-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylic acid ethyl ester (4f). Mp: 146°C(ethanol); IR (KBr): 1730, 1629 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.18 (t, 3H, J=7.2 Hz), 1.74 (s, 3H), 2.41 (s, 3H), 2.51 (s, 3H), 4.16 (s, 2H, J=7.2 Hz), 7.05–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 13.8, 22.9, 28.2, 28.5, 60.5, 114.4(2C), 121.3, 127.2, 129.4(2C), 132.4, 139.4, 139.7, 140.1, 153.3, 167.0, 168.2, 188.4; Anal. calcd for $C_{19}H_{19}NO_3S$: C 66.84; H 5.61; N 4.10. Found: C 66.78; H 5.55; N 4.12.

3.5.7. 2-Benzoyl-3,4-dimethyl-6-phenyl-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylic acid ethyl ester (4g). Mp: 155°C(ethanol); IR (KBr): 2982, 1720, 1628, 1597, 1499, 1446, 1272, 1135, 1031 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.10 (t, 3H, J=7.2 Hz), 2.64 (s, 3H), 2.72 (s, 3H), 4.16 (q, 2H, J=7.2 Hz), 7.29–7.75 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 13.8, 14.1, 15.9, 60.2, 120.9, 125.4(2C), 127.9, 128.2(2C), 128.4(2C), 128.7(2C), 128.9, 129.0, 129.2, 129.7, 131.7, 133.6, 140.3, 142.4, 162.0, 191.4; Anal. calcd for $C_{24}H_{21}NO_3S$: C 71.44; H 5.25; N 3.47. Found: C 71.40; H 5.30; N 3.55.

3.5.8. 5-Cyano-3,4-dimethyl-6-phenyl-6*H*-thieno[2,3-*b*]pyrrole-2-carboxylic acid ethyl ester (4h). Mp: 115°C(ethanol); IR (KBr): 2202, 1696, 1530 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.34 (t, 3H, J=7.2 Hz), 2.58 (s, 3H), 2.82 (s, 3H), 4.29 (q, 2H, J=7.2 Hz), 7.14–7.44 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 18.5, 60.2, 108.0(CN), 115.4, 115.9, 117.8, 121.0, 121.1, 125.0, 125.8(2C), 130.0(2C), 132.9, 135.1, 139.2, 148.8, 164.7(CO_2); Anal. calcd for $C_{18}H_{16}N_2O_2S$: C 66.64; H 4.97; N 8.64. Found: C 66.48; H 4.95; N 8.62.

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