A Novel Route to the 5,6-Dihydro-4-H-thieno[3,2-b]pyrrol-5-one Ring System Involving an Intermediate Substituted-thiophene Synthesis

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A novel route to electron-deficient thienopyrrolones is disclosed. The target heterocycles are concisely constructed by condensation of activated α- or β-halo-substituted acrylonitriles, or *ortho*-substituted halo, cyano heterocycles with mercaptopyruvate, followed by reduction and subsequent lactamization.

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Thienopyrroles have been introduced into a range of biologically active compounds. These include protein tyrosine phosphatases and CCK antagonists [1,2], as well as inhibitors of glycogen phosphorylase [3-5], cyclooxygenase, lipoxygenase, and MCP-1 [6,7]. In addition, the thienopyrrole ring system has been incorporated into bioisosteric analogs of the serotonin agonist *N*,*N*-dimethyltryptamine [8], and has been utilized as an isosteric replacement for tryptophan in physicochemical profiling studies of modified peptides [9].

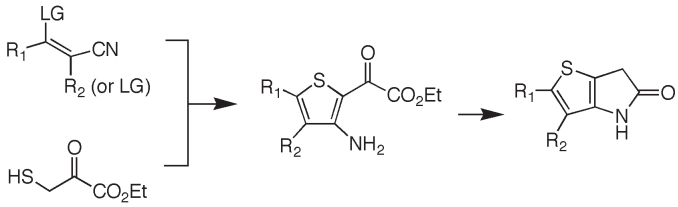
In our ongoing efforts to synthesize bioisosteres of functionalized indoles such as oxindole, we became interested in the thienopyrrolone ring system. While an extensive literature exists on the synthesis of the related thienopyrroles [10,11], only a few groups discuss the preparation of thienopyrrolones [12–16]. A common feature in many of these reports is the need to employ highly substituted thiophenes as starting materials, many of which are difficult to prepare.

In an attempt to address this issue, Lee *et al*., [17] described a methodology that involved construction of 3-aryl-5-alkoxycarbonyl-thienopyrrolones from thioaryolketene S,N-acetals and 2-diazo-3-trimethylsilyoxy-3-butenates *via* a Rhodium(II)-mediated Wolff Rearrangement. This approach obviated the need for the synthesis of the customary intermediate thiophene.

Herein, we report a complementary protocol that constitutes a more concise route to mono- and di-substituted thienopyrrolones and related ring-fused derivatives. The methodology employs readily available substituted acrylonitriles or suitably derivatized heterocycles in a condensation reaction with ethyl mercaptopyruvate. The final target heterocycles are generated efficiently *via* a subsequent reduction and lactamization process.

This approach takes advantage of a key transformation utilized previously in the synthesis of Urothione [18]. This involved the condensation of methyl mercaptopyruvate with a Michael acceptor embedded within a 2-chloro-3-cyanopyrazine moiety. The resultant thiophene product retained latent functionality that we anticipated could be used to generate the thienopyrrolone heterocycle. For our purposes, we would require the substitution of the reported pyrazine with a di- or tri-substituted acrylonitrile in which one of the substituents would function as a leaving group as depicted in Scheme 1.

Scheme 1

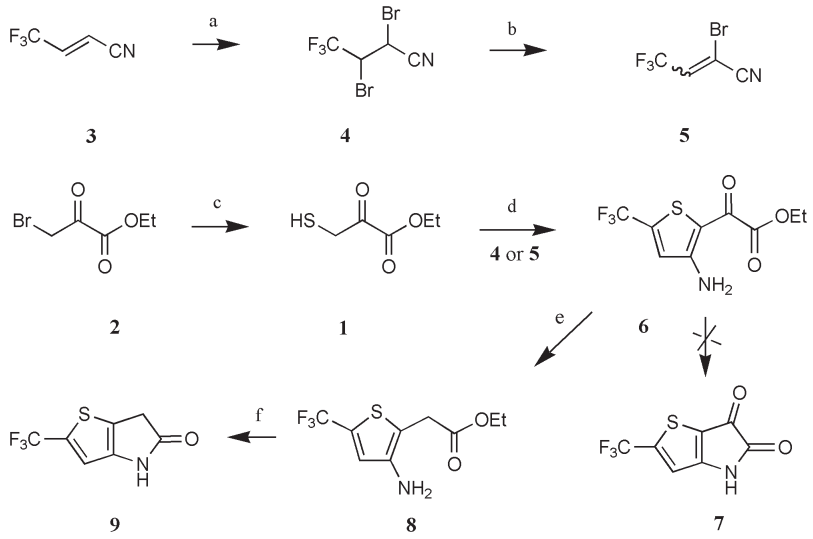


We considered this methodology would be attractive due to its conciseness and utilization of readily synthesized or commercially available starting materials.

Our initial investigations into this approach are described in Scheme 2. Ethyl mercaptopyruvate **1** was prepared according to literature procedures [18,19]. Alternative attempts to access this material by treatment of bromopyruvate **2** with sodium mercaptoacetate were unsuccessful, as the thiol group was found not only to displace the bromide, but also to react with the ketone present, leading to the formation of ethyl 2,3-bis-acetylsulfanyl-acrylate as the major product. In a separate step, 3-trifluoromethylacrylonitrile **3** was treated with bromine using minor modifications of previously reported methods [20] to generate the 2,3-dibromo-4,4,4-trifluorobutanenitrile **4**. This derivative was obtained as a viscous oil that was used directly in subsequent steps. However, in a parallel reaction sequence, the dibromide **4** was converted to the 2-bromo-3-trifluoromethylacrylate derivative **5** by exposure to base. It was subsequently found that treatment of either of these compounds with ethyl mercaptopyruvate under ambient conditions in the presence of triethylamine resulted in the generation of the thiophene **6** in almost identical yields, suggesting that elimination of HBr from **4** precedes reaction with the thiol.

Subsequent attempts to cyclize the amino ketoester **6** to generate the thienopyrrolidinedione **7** proved unsuccessful, a finding consistent with the limited number of reports extant in the literature for this type of vinylogous amide-ester cyclization [21-23]. In an attempt to increase the nucleophilicity of the amino functionality in **6**, the arylketone moiety was reduced using triethylsilane under acidic conditions [24] to give the aminoester **8** in 77% yield. The ester **8** was then hydrolyzed and attempts were made to cyclize the intermediate amino acid. This process proved to be very inefficient, with the best yield of 20% being observed when EEDQ was used as the coupling agent. More productively, it was found possible to directly cyclize **8** to the thienopyrrolone **9** using trimethylaluminum as the promoter. Using this reaction sequence the heterocycle **9** could be isolated in 51% yield.

Scheme 2



Reagents and conditions: (a) 1 Equiv. Br_2 ,CCl_4, reflux, 5 h, quantitative; (b) Et_3NH, THF, RT; (c) NaOEt, saturated with H_2S, 4°C, 1 h, 74%; (d) Et_3N, EtOH, 50°C or RT; (e)10 Equivs. Et_3SiH, 30 Equivs. TFA, RT, 24 h, 77%; (f) 2 Equivs. $AlMe_3$, PhMe, 4°C, 30 min, 51%.

Having developed an efficient route to the desired target heterocycle **9** we next sought to establish the generality of the protocol by investigating the reactivity of mercaptopyruvate **1** with a range of α- or β-halo-substituted acrylonitriles (Table 1). This step was anticipated to be the key determinant of the overall efficiency of the methodology since the subsequent reduction and lactamization should be influenced less by variation of relatively remote functionality attached to the intermediate thiophene.

It should be noted that the substituted acrylonitriles used in these investigations were either commercially available, or prepared from acrylonitriles *via* a two-step bromination-dehydrobromination sequence. In the latter case, the dibromo-derivatives were used directly and it was assumed that α-bromoacrylonitriles were generated *in-situ* as indicated above.

In one of the first experiments conducted we attempted to synthesize the unsubstituted parent compound **11** using the α-chloro-acrylonitrile **10.** Although a variety of reaction times and temperatures were explored the formation of **11** was not observed. This was attributed to the relatively low reactivity of the α-chloro-acrylonitrile **10**, in conjunction with the known instability of mercaptopyruvate **1** under basic conditions [25].

Scheme 3

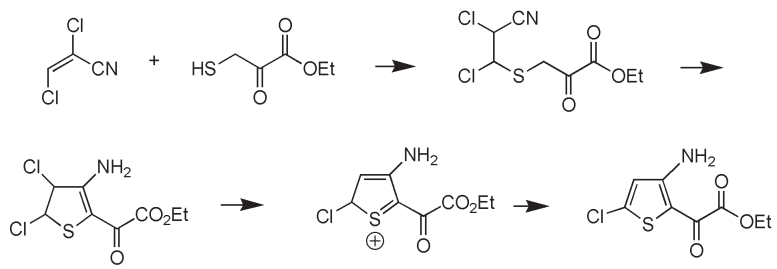
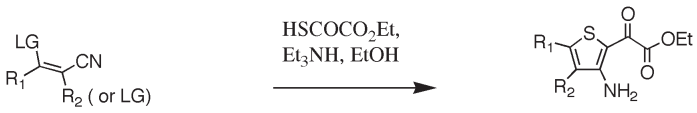


Table 1



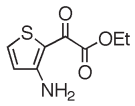
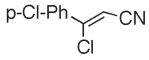
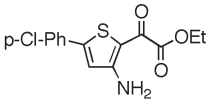
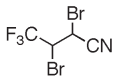
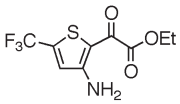
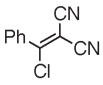
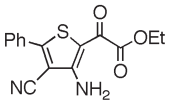
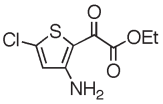
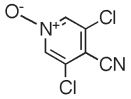
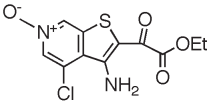
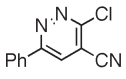
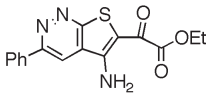
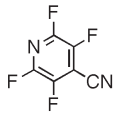
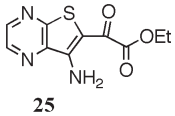
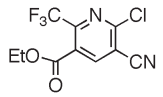
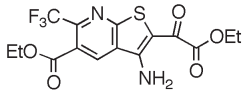
Michael Acceptor or Precursor	Reaction conditions	Product	Isolated Yield
 **10**	rt or 80°C, overnight	 **11**	no product
 **12**	rt or 70°C, overnight	 **13**	trace
 **4**	50°C to rt, 1.5 h	 **8**	54%
 **14**	rt, 5 min	 **15**	98%
 **16**	60°C, 30 min	 **17**	18%
 **18**	rt, overnight	 **19**	76%
 **20**	60°C, 1 h	 **21**	53%
 **22**	rt, overnight	 **23**	64%
 **24**	rt, overnight	 **25**	44%

Table 1 (continued)



26

rt, instantly



27

68%

With this perspective, we next explored the more highly substituted and reactive 2,3-dichloroacrylonitrile **16**. Consistent with the above hypothesis, when this was treated with ethyl mercaptopyruvate we succeeded in isolating the corresponding 2-chlorothiophene **17** in 18% yield. Interestingly, only one regioisomer was formed, presumably as a result of the pathway depicted in Scheme 3, wherein the 3-Cl substituent is preferentially eliminated as a result of participation of the electron density on the sulfur atom.

We next attempted to introduce functionality at the β-position of the acrylonitrile and examined the reactivity of the *p*-chlorophenyl derivative **12**. In this case, we anticipated activation of the Michael acceptor mediated by the electron withdrawing characteristics of the *p*-chlorophenyl group. However, with this reagent only traces of product were formed, an observation we attributed to the dominance of steric effects over the moderate electron withdrawing properties of the aryl substituent.

Conversely, in the case of the tetra-substituted acrylonitrile **14** that is strongly activated by the presence of an additional α-cyano group, we observed a near quantitative formation of thiophene on treatment with ethyl mercaptopyruvate. This clearly demonstrates that bulky substituents can be accommodated at the β-position provided the electrophile is sufficiently activated.

On review, it is apparent that a major aspect of this approach to thienopyrrolones is the need for the utilization of strongly electron-deficient acrylonitriles. This is required to ensure a sufficiently fast rate of reaction in the Michael addition to obviate the loss of the mercaptopyruvate nucleophile by alternative decompositon pathways [25].

Recognizing this limitation, and in an attempt to explore the full scope of the current methodology, we next examined the possibility of utilizing halo-substituted heterocyclic nitriles as the electrophilic component in the thiophene annulation reaction. Given the propencity of many of these systems to efficiently react with thiolate nucleophiles [*vide supra*], we anticipated that the current protocol could be successfully extended to the synthesis of ring-fused thienopyrrolones.

Indeed, the *ortho*-substituted halo, cyano heterocycles; **18**, **20**, **22**, **24** and **26**, all formed the corresponding thieno keto esters in good to moderate yields under relatively mild conditions. Consistent with previous observations, the yields of the reactions correlated with the predicted reactivity of the heterocycles.

In summary, a concise, three-step synthetic route to thienopyrrolones and related ring-fused derivatives has been established that utilizes readily accessible starting materials, and allows for the construction of a diverse range of electron defficient thienopyrrolones.

EXPERIMENTAL

Unless otherwise noted, all starting materials are commercially available and were used without further purification. ^{1}H NMR and ^{13}C NMR were recorded on a Brucker Avence 300 MHz or Brucker Avence 500 MHz spectrometer using tetramethylsilane as an internal reference. Chemical shifts are reported in δ units in ppm. High resolution mass spectra were performed on a Macromass LCT mass spectrometer with a TOF detector. Elemental analysis were performed on a Perkin-Elmer Model 2400 elemental analyzer.

Ethyl (3-Amino-5-trifluoromethyl-thiophen-2-yl)-2-oxoacetate (**6**).

Bromine (33 g, 0.207 mol) was added to a solution of 4,4,4-trifluorocrotononitrile (25 g, 0.207 mol) in carbon tetrachloride (600 ml). The mixture was refluxed for 5 hours and then cooled to room temperature before being quenched by the addition of water (40 ml). The organic layer was separated, washed with water, and then repeatedly washed with 5% aqueous sodium thiosulfate solution until it turned colorless. The organic solution was then washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in-vacuo* to give 56.6 grams of a yellow colored oil. This material gave a clean ^{1}H NMR spectrum consistent with the structure of 2,3-dibromo-4,4,4-trifluoro-butanenitrile. This oil was subsequently mixed with ethyl mercaptopyruvate (29.8 g, 0.201 mol) in absolute ethanol (3000 ml) and the mixture was heated until all of the ethyl mercaptopyruvate had dissolved. The resultant solution was then cooled to 50 °C, and neat triethylamine (40.6 g, 0.402 mol) was added through a dropping funnel over a period of 1.5 hours. This mixture was cooled to room temperature, and then filtered through silica (1000 g) to remove triethylammonium bromide salt. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel flash chromatography using 20% ethyl acetate in hexanes as eluant. Homogeneous fractions were combined and evaporated *in-vacuo*, to afford **6** as a yellow amorphous solid (27.9 g 52%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.07 (s, 2 H), 7.16 (s, 1 H), 4.31 (q, J = 7.0 Hz, 2 H), 1.30 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (500 MHz, DMSO-d_6):

δ 173.5, 161.7, 158.3, 138.7 (q, J_{CCF} = 37.4 Hz), 121.7 (q, J_{CF} = 270.6 Hz), 120.4, 105.6, 62.3, 13.7; HRMS [ESI, MH^+] *m/z* calcd for $C_9H_9NSO_3F$ 268.0255, found 268.0258; LCMS (ES^+): 2.67 min (RT), 100% (area); *m/z* 268.02 ($M+H^+$), 289.99 ($M+Na^+$).

Anal. Calcd. for $C_9H_8F_3NO_3S$: C, 40.45; H, 3.01; N, 5.24. Found: C, 40.17; H, 3.00; N, 5.13.

Ethyl (3-Amino-5-trifluoromethyl-thiophen-2-yl)-acetate (**8**).

Ethyl (3-Amino-5-trifluoromethyl-thiophen-2-yl)-oxoacetate **6** (27.9 g, 0.105 mol) was suspended in triethylsilane (122 g, 1.05 mol) and trifluoroacetic acid (357 g, 3.14 mol) was added. The resultant two-phase mixture was stirred vigorously at room temperature for 24 hours, whereupon the mixture homogenized. The resultant solution was then evaporated *in-vacuo* to remove excess TFA and Et_3SiH, and the residual oil was redissolved in ethyl acetate (700 ml). Solid $NaHCO_3$ was then added and the mixture stirred at room temperature until no further carbon dioxide evolution was observed. This suspension was then filtered, and the filtrate washed once with brine and then dried over anhydrous sodium sulfate. This suspension was filtered and the filtrate concentrated under reduced pressure. The residue was then purified by silica gel flash chromatography using 20% ethyl acetate in hexanes as eluant. Homogeneous fractions were combined and evaporated to afford **8** as a yellow, amorphous solid (24.2 g 77%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.91 (s, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 3.58 (s, 1 H), 3.70-3.30 (bs, 2 H), 1.27 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.1, 142.4, 127.7 (q, J_{CCF} = 39.1 Hz), 122.7, 122.4 (q, J_{CF} = 268.4 Hz), 111.8, 61.7, 32.7, 14.2; HRMS [ESI, MH^+] *m/z* calcd for $C_9H_{11}NSO_2F_3$ 254.0463, found 254.0453.

2-Trifluoromethyl-4,6-dihydro-thieno[3,2-*b*]pyrrol-5-one (**9**).

Ethyl (3-amino-5-trifluoromethyl-thiophen-2-yl)-acetate **9** (2 g, 7.9 mmol) was dried by dissolution in anhydrous toluene and evaporation to dryness under reduced pressure. This process was repeated three times before the residue was dissolved in anhydrous toluene (100 ml). The reaction vessel was then evacuated and flushed with nitrogen before being cooled to 0 °C. Trimethylaluminum (2 *M* in toluene, 7.9 ml, 15.8 mmol) was then added *via* syringe over 10 minutes. The resultant reaction mixture was then stirred at 0 °C for an additional 30 minutes, and then quenched by the addition of methanol (2 ml). The reaction mixture was poured onto a slurry of ice (200 g) and saturated aqueous NH_4Cl solution (200 ml), and the product extracted immediately using ethyl acetate (total 500 ml). The organic layer was washed with brine, dried over sodium sulfate, filtered and then concentrated *in-vacuo*. The residue was then purified by silica gel flash chromatography using 30% ethyl acetate in hexanes as eluant. Homogeneous fractions were combined and evaporated to afford the product **9** as a yellow, amorphous solid (840 mg 51%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.531 (s, 1 H), 7.35 (s, 1 H), 3.66 (s, 2 H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 178.0, 144.3, 128.9 (q, J_{CCF} = 38.4 Hz), 122.7 (q, J_{CF} = 267.8 Hz), 120.1, 114.71, 36.4; HRMS [ESI, $(M-H)^-$] *m/z* calcd for $C_7H_3NSOF_3$ 205.9887, found 205.9885.

Anal. Calcd. for $C_7H_4F_3NOS$: C, 40.58; H, 1.94; N, 6.76; S, 15.47. Found: C, 40.69; H, 1.80; N, 6.54; S, 15.44.

Ethyl (3-Amino-4-cyano-5-phenyl-thiophen-2-yl)-2-oxoacetate (**15**).

α-Chlorobenzylidenemalononitrile (500 mg, 2.65 mmol) and ethyl mercaptopyruvate (470 mg, 3.18 mmol) were suspended in anhydrous ethanol (20 ml) at room temperature, and the mixture stirred vigorously while neat Et_3N (268 mg, 2.65 mmol) was added *via* syringe. The reaction mixture was stirred for an additional 5 minutes at room temperature before being diluted with CH_2Cl_2 (100 ml). The resultant solution was then washed once with brine, dried over anhydrous sodium sulfate, filtered and then concentrated *in-vacuo*. The residue was purified by silica gel flash chromatography using 20% acetone in CH_2Cl_2 as eluant. Homogeneous fractions were combined and evaporated under reduced pressure to afford **15** as a bright-yellow, amorphous solid (782 mg, 98%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 7.50, 2.01 Hz, 2 H), 7.53 (m, 3 H), 7.30- 6.80 (bs, 2 H), 4.42 (q, *J* = 6.95 Hz, 2 H),1.43 (t, *J* = 7.14 Hz, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 173.5, 163.4, 162.2, 159.6, 131.8, 130.7, 129.6 (2 C), 127.7 (2 C), 113.7, 106.6, 96.8, 63.2, 14.1; HRMS [ESI, MH^+] *m/z* calcd for $C_{15}H_{13}N_2SO_3$ 301.0647, found 301.0652.

Anal. Calcd, for $C_{15}H_{12}N_2O_3S$: C, 59.98; H, 4.02; N, 9.32; S, 10.67. Found: C, 59.97; H, 3.97; N, 9.20; S, 10.54.

Ethyl (3-Amino-5-chloro-thiophen-2-yl)-2-oxoacetate (**17**).

A mixture of 2,3-dichloroacrylonitrile (42 mg, 0.34 mmol) and ethyl mercaptopyruvate (151 mg, 1.02 mmol) in absolute ethanol was heated at 60 °C and neat Et_3N (93 mg, 0.92 mmol) was added in a single portion. The mixture was stirred for an additional 30 minutes before being cooled to room temperature and concentrated *in vacuo*. The residue was then purified by silica gel flash chromatography using 20% ethyl acetate in hexanes as eluant. Homogeneous fractions were combined and evaporated under reduced pressure to give **17** as a light-yellow, amorphous solid (14 mg 18%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.04 (s, 1 H), 7.80 (s, 2 H), 4.30 (q, *J* = 7.0 Hz, 2 H), 1.30 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 172.8, 161.8, 154.7, 134.4, 113.6, 104.8, 62.1, 13.8; HRMS [ESI, MH^+] *m/z* calcd for $C_8H_9NSClO_3$ 233.9992, found 233.9986. The structure was further confirmed by the observed NOE between the amino group and the thiophene ring proton.

Anal. Calcd. for $C_8H_8ClNO_3S$: C, 41.12; H, 3.45; N, 5.99; Found: C, 41.39; H, 3.33; N, 5.87.

Ethyl 2-(1-*N*-oxo-3-amino-4-chlorothieno[2,3-*c*]pyridinium)-2-oxoacetate (**19**).

3,5-Dichloro-4-cyanopyridinium-1-olate (73 mg, 0.39 mmol) was suspended in ethanol (20 ml) and heated to 80 °C until the bulk of the material had dissolved. The resultant mixture was then cooled to room temperature, and ethyl mercaptopyruvate (80 mg, 0.58 mmol) was added followed immediately by triethylamine (50.7 mg, 0.50 mmol). This mixture was then stirred at room temperature overnight, after which an orange precipitate formed. This was collected by filtration, washed with cold ethanol, and then dried under vacuum to give 87.5 mg of the desired product as an amorphous, orange solid (76%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.90 (s, 1 H), 8.90 – 7.90 (bs, 2 H), 8.43 (s, 1 H), 4.37 (q, *J* = 7.0 Hz, 2 H),1.28 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 173.8, 162.1, 153.4, 142.1, 135.4, 132.5, 127.9, 121.0, 105.7, 62.3, 13.7; HRMS [ESI, MH^+] *m/z* calcd for $C_{11}H_{10}N_2SClO_4$ 301.0050, found 301.0044.

Anal. Calcd. for $C_{11}H_9ClN_2O_4S$: C, 43.93; H, 3.01; N, 9.31; S, 10.66. Found: C, 43.80; H, 2.99; N, 9.17; S, 10.37.

Ethyl 2-(5-Amino-3-phenylthieno[2,3-*c*]pyridazin-6-yl)-2-oxoacetate (**21**).

3-Chloro-6-phenylpyridazine-4-carbonitrile (100 mg, 0.464 mmol) was suspended in ethanol and briefly sonicated before being heated to 60 °C. Ethyl mercaptopyruvate (83.2 mg, 0.603 mmol) was then added, followed immediately by neat triethylamine (56 mg, 0.557 mmol). The resultant mixture was maintained at 60 °C for one hour during which time a red precipitate was observed to form. The reaction mixture was cooled to room temperature, and the solid collected by filtration and washed with cold ethanol. The filtrate was then concentrated, and more precipitate formed. This material was collected, washed with cold ethanol and combined with the original filtrate and then dried under vacuum. The product was obtained as a reddish-orange, amorphous solid (80.5 mg, 53%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.15(s, 1 H), 8.99 (bs, 2 H), 8.16 (d, *J* = 7.5 Hz, 1 H), 7.62 (t, *J* = 7.5 Hz, 2 H), 7.56 (t, J = 7.5 Hz, 1 H) 4.37(q, *J* = 7.0 Hz, 2 H), 1.35 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 175.2, 163.0, 161.8, 153.7, 152.4, 135.9, 129.7, 129.1 (2C), 126.8, 126.5 (2C), 118.0, 102.8, 62.3, 13.8; HRMS [ESI, M+H$^+$] *m/z* calcd for $C_{16}H_{14}SN_3O_3$ 327.0756, found 328.0766.

Anal. Calcd. for $C_{16}H_{13}N_3O_3S$: C, 58.70; H, 4.00; N, 12.83; S, 9.79. Found: C, 58.60; H, 3.82; N, 12.66, S, 9.72.

Ethyl 2-(3-Amino-4,5,7-trifluorothieno[2,3-*c*]pyridin-2-yl)-2-oxoacetate (**23**).

2,3,5,6-Tetrafluoroisonicotinonitrile (60 mg, 0.34 mmol) was suspended in ethanol and heated to 60 °C until the bulk of the material had dissolved. The resultant fine suspension was then cooled to room temperature before ethyl mercaptopyruvate (65 mg, 0.442 mmol) was added, followed immediately by neat triethylamine (41 mg, 0.408 mmol). This mixture was stirred at room temperature overnight before being concentrated *in vacuo*. The residue was then purified by silica gel flash chromatography using 10% ethyl acetate in hexanes as eluant. Homogenous fractions were combined and concentrated under reduced pressure to give 66 mg of the desired product as a yellow, amorphous solid (64%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.36 (bs, 2 H), 4.34 (q, *J* = 7.0 Hz, 2 H), 1.34 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 174.9, 161.3, 151.2, 147.9 (dd, *J* = 960 Hz, 50 Hz,), 143.66 (ddd, *J* = 940 Hz, 65 Hz, 55 Hz), 138.81 (ddd, *J* = 1035 Hz, 110 Hz, 30 Hz), 131.06, 121.57 (dd, *J* = 155 Hz, 15 Hz), 106.0, 103.94, 62.6, 13.7; HRMS [ESI, M-H$^-$] *m/z* calcd for $C_{11}H_6F_3SN_2O_3$ 303.0051, found 303.0054.

Anal. Calcd. for $C_{11}H_7F_3N_2O_3S$: C, 43.42; H, 2.31; N, 9.20. Found: C, 43.18; H, 2.10; N, 9.16.

Ethyl 2-(7-Aminothieno[2,3-*b*]pyrazin-6-yl)-2-oxoacetate (**25**).

3-Chloropyrazine-2-carbonitrile (95 mg, 0.68 mmol) and ethyl mercaptopyruvate (130 mg, 0.88 mmol) were dissolved in ethanol (10 ml). Triethylamine (79 mg, 0.78 mmol) was added and the resultant mixture was stirred overnight at room temperature. After concentration, the residue was purified by silica gel flash chromatography using 25% ethyl acetate in hexanes as eluant. Homogeneous fractions were combined and evaporated *in vacuo* to give 75 mg of the desired product as a yellow, amorphous solid (44%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.83 (d, *J* = 2.0 Hz,1 H), 8.77 (d, *J* = 2 Hz, 1 H), 8.61 (bs, 1 H), 4.33(q, *J* = 7.0 Hz, 2 H), 1.33 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 174.7, 161.8, 157.4, 152.1, 146.9, 141.8, 130.0, 102.2, 62.2, 13.7; HRMS [ESI, M+H$^+$] *m/z* calcd for $C_{10}H_{10}SN_3O_3$ 252.0443, found 252.0445.

Anal. Calcd. for $C_{10}H_9SN_3O_3$: C, 47.80; H, 3.61; N, 16.72. Found: C, 47.61; H, 3.10; N, 16.54.

Ethyl 3-Amino-2-(2-ethoxy-2-oxoacetyl)-6-(trifluoromethyl)-thieno[2,3-*b*]pyridine-5-carboxylate (**27**).

Ethyl 6-chloro-5-cyano-2-(trifluoromethyl)nicotinate (48 mg, 0.17 mmol) and ethyl mercaptopyruvate (38 mg, 0.255 mmol) were dissolved in ethanol (5 ml) and triethylamine (22 mg, 0.22 mmol) was added in a single portion at room temperature. An orange precipitate formed immediately. After a further 5 minutes of stirring, the reaction mixture was concentrated and the residue purified by silica gel flash chromatography using 10% - 15% ethyl acetate in hexanes as eluant. Homogeneous fractions were combined and evaporated *in vacuo* to give 45 mg of the desired product as an orange, amorphous solid (68%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.29(s, 1 H), 9.03 (bs, 1 H), 4.40 (q, *J* = 7.0 Hz, 2 H), 4.34(q, *J* = 7.0 Hz, 2 H), 1.34 (m, 6 H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 174.4, 164.3, 162.8, 161.9, 152.7, 145.4 (q, *J* = 145 Hz), 135.9, 125.5, 122.3, 120.8(q, *J* = 1096 Hz); HRMS [ESI, M-H$^-$] *m/z* calcd for $C_{15}H_{12}F_3SN_2O_5$ 389.0419, found 389.0419.

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