The Synthesis of Thienopyridines from *ortho*-Halogenated Pyridine Derivatives; Part 2

D.H. Bremner,[a] A.D. Dunn,[b] K.A. Wilson,[a] K.R. Sturrock,[a] G. Wishart[a]

[a] University of Abertay Dundee, Department of Molecular and Life Sciences, Bell Street, Dundee DD1 1HG, Scotland
Fax +44(1382)308663; E-mail: d.h.bremner@tay.ac.uk

[b] Beilstein-Institut, Carl-Bosch-Haus, Varrentrappstraße 40–42, D-6000 Frankfurt/Main 90, Germany

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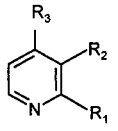
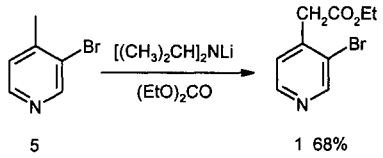
Synthetic routes to the *ortho*-halogenated pyridine derivatives, ethyl 2- and 4-chloro-3-pyridylacetate, ethyl 3-bromo-4-pyridylacetate and ethyl 3-bromo-2-pyridylacetate, which have methylene groups activated by the ester functionality are reported. Reaction of these pyridines with carbon disulfide in the presence of sodium hydride, followed by quenching with iodomethane, results in the formation of the corresponding thienopyridines in moderate yields.

We have previously reported[1] the preparation of pyridine derivatives containing halogens *ortho* to a methylene group activated by a nitrile function and their subsequent conversion to the corresponding thienopyridines. As a continuation of our synthetic programme, we required similar pyridine derivatives **1–4** which contained an ethyl ester function in place of the nitrile function, in order to investigate their conversion into thienopyridines.



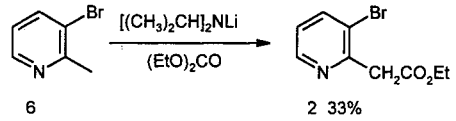
	R_1	R_2	R_3
1	H	Br	CH_2COOEt
2	CH_2COOEt	Br	H
3	Cl	CH_2COOEt	H
4	H	CH_2COOEt	Cl

Ethyl 3-bromo-4-pyridylacetate **(1)** had been prepared[2] previously by treatment of 3-bromo-4-methylpyridine[3] **(5)** with lithium diisopropylamide in THF followed by the addition of diethyl carbonate (Scheme 1). The reported yield[2] for this reaction was 82%, however in our hands the highest yield obtained was 68% with 13% starting material recovered unreacted.



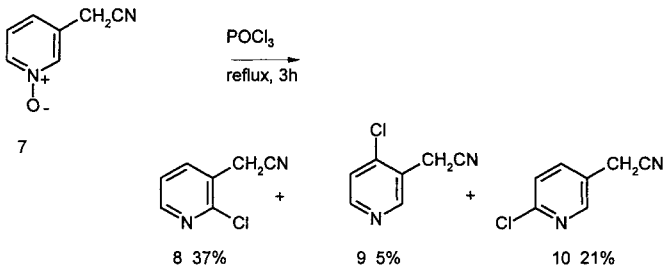
Scheme 1

The reaction used in the preparation of **1** was adapted for the synthesis of pyridine derivative **2**. Thus, treatment of 3-bromo-2-methylpyridine[4] **(6)** with lithium diisopropylamide, followed by the addition of diethyl carbonate gave ethyl 3-bromo-2-pyridyl acetate **(2)** in 33% yield (Scheme 2) with starting material recovered in 55% yield. Attempts to increase the yield did not afford any improvements on this figure. The starting material and reagents in this reaction are sufficiently inexpensive to allow the reaction to be carried out on a large enough scale to produce sufficient quantities of the product to overcome the disappointing yield.



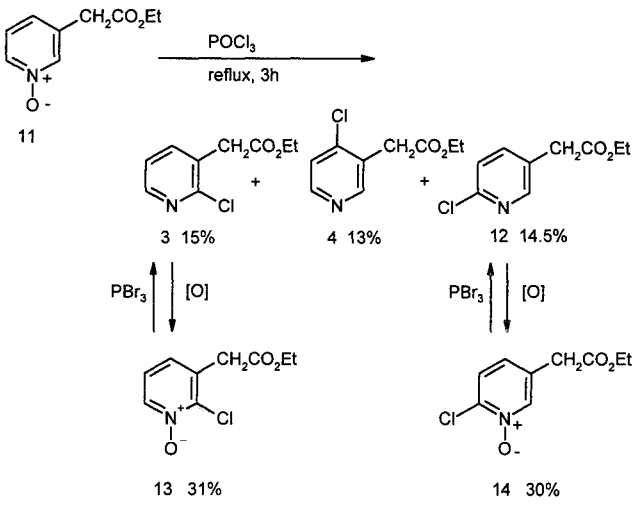
Scheme 2

As we previously reported[1] 3-cyanomethylpyridine *N*-oxide **(7)** had been found to react with phosphoryl chloride[5] to give the chlorinated derivatives **8, 9** and **10** (Scheme 3).



Scheme 3

In order to prepare pyridine derivatives **3** and **4** by the same method, we required ethyl 3-pyridylacetate *N*-oxide **(11)** which had been previously prepared[6] by the oxidation of ethyl 3-pyridylacetate with hydrogen peroxide and glacial acetic acid. The best yield we obtained from this method was 69%, so, after investigating several alternative reagents, we utilised a procedure[7] involving *m*-chloroperoxybenzoic acid (*m*-CPBA) which led to production of **11** in 93% yield. Chlorination of **11** with phosphoryl chloride produced the desired pyridine de-

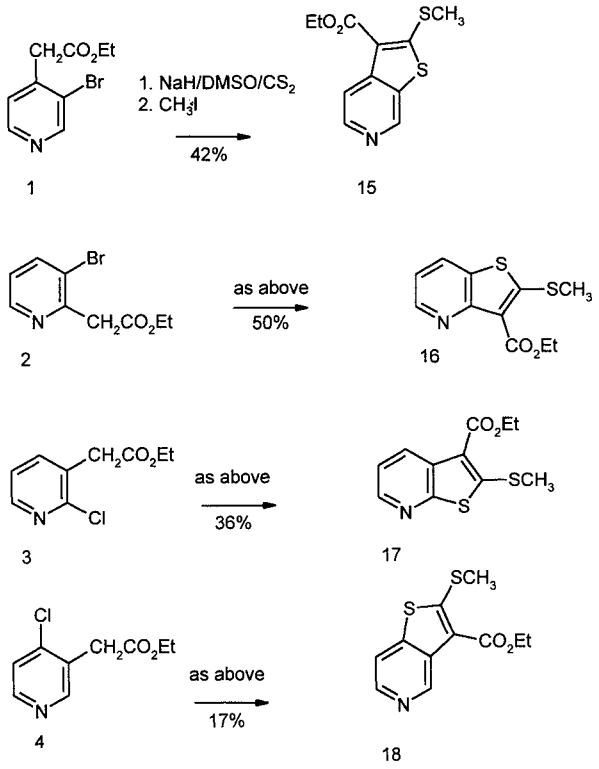


Scheme 4

rivatives **3** and **4** together with ethyl 2-chloro-5-pyridylacetate **(12)** (Scheme 4). Column chromatography only allowed the complete separation of **4**, with **3** and **12** being eluted together as a mixture. However, oxidation of this latter mixture with *m*-CPBA allowed easy separation of the respective *N*-oxides **13** and **14** by column chromatography. Deoxygenation with phosphorus tribromide gave the desired pyridines in almost quantitative yields. The overall yields of pyridines **3** and **12** from **11** were 15% and 14.5% respectively after the mixture of **3** and **12** had been oxidised, separated and deoxygenated. Surprisingly, the oxidation reaction, under the conditions used, did not go to completion and 25% of the mixture of **3** and **12** was recovered unreacted and subsequently recycled.

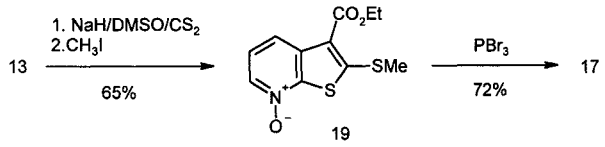
A comparison of the chlorination of both the nitrile **7** and ester **11** derivatives with phosphoryl chloride provided some interesting observations. This reaction is known[8] to proceed by two competing mechanistic routes derived from a complex of the *N*-oxide function and the inorganic acid halide. An intramolecular mechanism leads to chlorination at the 2-position, while an intermolecular chlorination favours the 4-position. Examination of the relative yields obtained in the two reactions strongly indicates that the intramolecular mechanism predominates. It was also noted that the relative polarities of the isomers varied. For the nitrile isomers, the 2,3-isomer **8** was the least polar, followed by pyridine **10**, then isomer **9**, while for the ester isomers, the least polar was the 2,5-isomer **12**, followed by compounds **3** and **4** which were virtually identical in polarity.

It is well known[9] that benzyl cyanides possessing an *ortho*-halogen atom react with carbon disulfide, in the presence of base, to form benzo[*b*]thiophenes. Since pyridine derivatives containing a methylene group activated by a nitrile, and *ortho* to a halogen atom undergo similar transformations,[1] we wished to study the corresponding reaction on pyridine derivatives activated by an ethyl ester function. When the *ortho*-halogenated derivatives **1–4** were reacted with carbon disulfide in the presence of sodium hydride in dimethyl sulfoxide, followed by quenching with iodomethane, the corresponding thienopyridines **15–18** were obtained in moderate yields (Scheme 5). It is again[1] believed that the reaction involves the intermediacy of a ketene dithioacetal dianion,[10] where displacement of the halogen by one sulfur anion of the ketene dithioacetal dianion forms the bicyclic bond, and the other anion is alkylated by iodomethane.



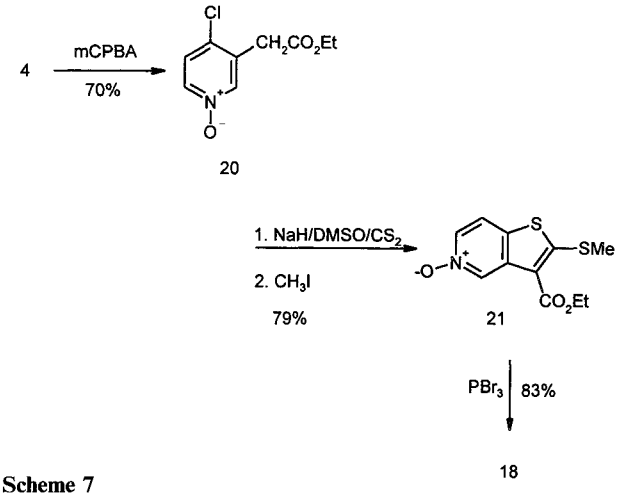
Scheme 5

It was thought that improvements to the overall yield of thienopyridine **17** might be achieved by carrying out the cyclisation reaction on the corresponding pyridine *N*-oxide **13** followed by deoxygenation, but in the event it was found that the overall yields of the two routes: **13** to **3** to **17**, and **13** to **19** to **17**, were essentially the same at approximately 45% (Scheme 6).



Scheme 6

The preparation of 3-carboethoxy-2-methylthiothieno-[3,2-*c*]pyridine **(18)** invariably gave poor yields. This was considered to be partly due to the instability of the pyridine precursor **4** which was found to decompose readily in air even when cold. It was hence converted to the *N*-oxide **20**, a stable crystalline solid, with *m*-CPBA in 70% yield. Conversion of **20** to the thienopyridine *N*-oxide **21** followed by deoxygenation gave **18** in an overall yield of 65% (Scheme 7). This is a significant improvement to the yield of **18** achieved by cyclisation of **4**.



Scheme 7

IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrophotometer and NMR spectra were recorded in $CDCl_3$ (except where otherwise stated) on a Joel PMX 60si spectrometer using TMS as internal reference. Melting points were determined using

an Electrothermal melting point apparatus and are uncorrected. Column chromatography was performed using pressurised short path columns with Kieselgel 60, particle size <0.063 mm (Merck #7729). Reactions were monitored by TLC on Merck DC-Alufolien Kieselgel 60 F254 (Merck #5554) plates which were visualised under ultraviolet irradiation. Reagents and appropriate starting materials were purchased from Aldrich Chemical Co. Petroleum ether used had bp 60–80 °C.

Ethyl 3-bromo-4-pyridylacetate **(1)** was prepared according to the literature procedure.[2]

Ethyl 3-Bromo-2-pyridylacetate (2):

To a solution of diisopropylamine (2.5 mL, 0.018 mol) in anhyd THF (25 mL) was added PhLi [1.8 M solution in cyclohexane/Et_2O (70:30); 10 mL, 0.018 mol] under N_2 at r.t. over 30 min. The mixture was stirred for 30 min and 3-bromo-2-methylpyridine (**6**;[4] 1.4 g, 0.008 mol) was added over 10 min. The mixture was stirred for 5 min, diethyl carbonate (2 mL, 0.018 mol) was added and stirring was continued for a further 1 h and then the mixture was poured onto Et_2O (50 mL). The organic layer was washed with H_2O (3 × 25 mL), dried ($MgSO_4$) and the solvent removed in vacuo to afford a dark oil (2.3 g). The oil was chromatographed on silica gel (100 g) and gradient elution with petroleum ether/Et_2O (10–50%) afforded starting material (770 mg, 55%). Further elution afforded **2** (650 mg, 33%) as a colourless liquid, bp 100 °C/0.7 mbar.

IR (film): ν = 2981, 1737 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.24 (t, 3 H, J = 7.2 Hz, CH_3), 3.98 (s, 2 H, CH_2), 4.15 (q, 2 H, J = 7.2 Hz, CH_2), 6.98 (dd, 1 H, J = 4.8, 7.2 Hz, H-5), 7.75 (dd, 1 H, J = 2.0, 7.2 Hz, H-4), 8.38 (dd, 1 H, J = 2.0, 4.8 Hz, H-6).

Analysis: found C 44.3, H 4.1, N 5.6, Br 32.7; $C_9H_{10}NBrO_2$ requires C 44.3, H 4.1, N 5.7, Br 32.7.

Ethyl 3-Pyridylacetate *N*-Oxide (11):

To a stirred solution of ethyl 3-pyridylacetate (25 g, 0.151 mol) in $CHCl_3$ (100 mL) was added *m*-CPBA (70%, 37.3 g, 0.151 mol) portionwise over 15 min at r.t. The mixture was stirred for 24 h, then any excess *m*-CPBA destroyed (wet starch-iodide paper) by the addition of solid $Na_2S_2O_5$. Dissolved *m*-chlorobenzoic acid was removed from solution by the addition of solid K_2CO_3 with stirring. The solids were removed by filtration and the solution dried ($MgSO_4$), filtered and the solvent removed in vacuo to give a pale yellow solid. Recrystallisation from toluene afforded **11** (26.8 g, 93%); mp 95–97 °C (Lit.[6] mp 97–98 °C).

IR (KBr): ν = 3081, 3051, 2990, 1731, 1271 cm^{-1}.

Reaction of Ethyl 3-pyridylacetate *N*-Oxide (11) with Phosphoryl Chloride:

Ethyl 3-pyridylacetate *N*-oxide (**11**; 2.8 g, 0.015 mol) was added to $POCl_3$ (35 mL) and the mixture was warmed slowly with vigorous shaking until all solid had dissolved and then refluxed for 3 h. Excess $POCl_3$ was removed in vacuo, the residue poured onto ice (100 g), neutralised with a dilute solution of ammonia and extracted with EtOAc (3 × 100 mL). The organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo to afford a dark oil. The oil was chromatographed on silica gel (100 g) and gradient elution with petroleum ether/Et_2O (10–50%) afforded an unresolved mixture of pyridine derivatives **3** and **12** (2.37 g). Further elution gave ethyl 4-chloro-3-pyridylacetate **(4)** as a clear liquid (350 mg, 13%). No bp obtained due to decomposition.

Compound **4**:

IR (film): ν = 2982, 1737 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.24 (t, 3 H, J = 7.2 Hz, CH_3), 3.76 (s, 2 H, CH_2), 4.16 (q, 2 H, J = 7.2 Hz, CH_2), 7.28 (d, 1 H, J = 4.8 Hz, H-5), 8.36 (d, 1 H, J = 4.8 Hz, H-6), 8.56 (s, 1 H, H-2).

Analysis: found C 54.0, H 5.1, N 7.0, Cl 17.8; $C_9H_{10}NClO_2$ requires C 54.1, H 5.0, N 7.0, Cl 17.8.

Ethyl 4-Chloro-3-pyridylacetate N-Oxide **(20)**:

Starting from **4**, the same experimental procedure as for the preparation of **11** was employed, except recrystallisation of the crude product from EtOAc gave **20** (70%) as a white crystalline solid; mp 110–112 °C.

IR (KBr): ν = 2980, 1250 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.25 (t, 3 H, J = 7.0 Hz, CH_3), 3.60 (s, 2 H, CH_2), 4.20 (q, 2 H, J = 7.0 Hz, CH_2), 7.25 (d, 1 H, J = 6.0 Hz, H-5), 8.03 (dd, 1 H, J = 6.0, 2.0 Hz, H-6), 8.15 (d, 1 H, J = 2.0 Hz, H-2).

Analysis: found C 50.0, H 4.9, N 6.5, Cl 16.4; $C_9H_{10}NClO_3$ requires C 50.1, H 4.7, N 6.5, Cl 16.4.

Oxidation of a Mixture of **3** *and* **12**:

The same experimental procedure as for the preparation of **11** was employed, except a dark oil was produced. The oil was chromatographed on silica gel and elution with petroleum ether/EtOAc afforded, as a colourless oil, a mixture of unoxidised pyridine derivatives **3** and **12** (0.85 g, 25%). Elution with EtOAc gave ethyl 2-chloro-5-pyridylacetate *N*-oxide **(14)** (0.77 g, 30%) as a white crystalline solid; mp 104–105 °C.

Compound **14**:

IR (KBr): ν = 2975, 1710, 1270 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.2 (t, 3 H, J = 6.0 Hz, CH_3), 3.47 (s, 2 H, CH_2), 4.03 (q, 2 H, J = 6.0 Hz, CH_2), 6.97 (dd, 1 H, J = 8.0, 2.0 Hz, H-4), 7.25 (d, 1 H, J = 8.0 Hz, H-3), 8.07 (d, 1 H, J = 2.0 Hz, H-6).

Analysis: found C 49.8, H 4.5, N 6.4, Cl 16.2; $C_9H_{10}NClO_3$ requires C 50.1, H 4.7, N 6.5, Cl 16.4.

Also isolated was ethyl 2-chloro-3-pyridylacetate *N*-oxide **(13)** (0.81 g, 31%), as a white crystalline solid; mp 59–60 °C.

Table. Compounds **15–19, 21** Prepared

Product	Yield (%)	mp (°C) (EtOAc)	IR (KBr) ν (cm^{-1})	^1H NMNR ($CDCl_3$/TMS) δ, J (Hz)
15	42	138–139	2980, 1681	1.38 (t, 3 H, J = 7.2, CH_3), 2.70 (s, 3 H, SCH_3), 4.32 (q, 2 H, J = 7.2, CH_2), 7.95 (d, 1 H, J = 3.0, H-4), 8.36 (d, 1 H, J = 3.0, H-5), 9.00 (s, 1 H, H-7)
16	50	85–86	2977, 1680	1.44 (t, 3 H, J = 7.2, CH_3), 2.70 (s, 3 H, SCH_3), 4.44 (q, 2 H, J = 7.2, CH_2), 7.08 (dd, 1 H, J = 7.6, 2.4, H-6), 7.93 (dd, 1 H, J = 7.6, 1.0, H-7), 8.68 (dd, 1 H, J = 2.4, 1.0, H-5)
17	36	109–110	2947, 1682	1.48 (t, 3 H, J = 7.1, CH_3), 2.72 (s, 3 H, SCH_3), 4.50 (d, 2 H, J = 7.1, CH_2), 7.56 (dd, 1 H, J = 8.3, 4.6, H-5), 8.24 (dd, 1 H, J = 4.6, 1.7, H-4), 8.63 (dd, 1 H, J = 8.3, 1.7, H-6)
18	17	119–120	2984, 1681	1.40 (t, 3 H, J = 7.2, CH_3), 2.70 (s, 3 H, SCH_3), 4.35 (q, 2 H, J = 7.2, CH_2), 7.90 (d, 1 H, J = 4.8, H-7), 8.34 (d, 1 H, J = 4.8, H-6), 9.34 (s, 1 H, H-4)
19	65	158–159	2950, 1680	1.44 (t, 3 H, J = 7.2, CH_3), 2.70 (s, 3 H, SCH_3), 4.38 (q, 2 H, J = 7.2, CH_2), 7.22 (dd, 1 H, J = 8.0, 6.5, H-5), 8.22 (m, 2 H, H-4 and H-6)
21	79	221–224	2969, 1680	1.47 (t, 3 H, J = 7.2, CH_3), 2.70 (s, 3 H, SCH_3), 4.47 (q, 2 H, J = 7.2, CH_2), 7.62 (d, 1 H, J = 6.9, H-7), 8.13 (dd, 1 H, J = 6.9, 1.4, H-6), 9.22 (d, 1 H, J = 1.4, H-4)

[a] Satisfactory microanalysis obtained: C ± 0.2, H ± 0.3, N ± 0.1.

Compound **13**:

IR (KBr): $\nu = 2960, 1700, 1250\ cm^{-1}$.

^1H NMR ($CDCl_3$): $\delta = 1.24$ (t, 3 H, $J = 6.0$ Hz, CH_3), 3.74 (s, 2 H, CH_2), 4.03 (q, 2 H, $J = 6.0$ Hz, CH_2), 7.11 (m, 2 H, H-4, H-5), 8.18 (m, 1 H, H-2).

Analysis: found C 49.8, H 4.8, N 6.5, Cl 16.3; $C_9H_{10}NClO_3$ requires C 50.1, H 4.7, N 6.5, Cl 16.4.

Deoxygenation of Ethyl 2-Chloro-3-pyridylacetate *N*-Oxide (13) to Ethyl 2-Chloro-3-pyridylacetate (3); Typical Procedure:

Ethyl 2-chloro-3-pyridylacetate *N*-oxide (**13**; 0.1 g, 0.46 mmol) and DMF (20 mL) were stirred together at r.t. PBr_3 (0.2 mL, 0.74 mmol) was added and stirring continued for 1 h. The mixture was poured onto sat. aq $NaHCO_3$ and extracted with EtOAc (3 × 20 mL). The extracts were combined, washed with sat. aq $NaHCO_3$, then brine, dried ($MgSO_4$), filtered and the solvent removed in vacuo to give **3** (0.092 g, 99%) as a colourless oil; bp 85 °C/0.5 mbar.

IR (KBr): $\nu = 2983, 1735\ cm^{-1}$.

^1H NMR ($CDCl_3$): $\delta = 1.26$ (t, 3 H, $J = 7.2$ Hz, CH_3), 3.74 (s, 2 H, CH_2), 4.16 (q, 2 H, $J = 7.2$ Hz, CH_2), 7.16 (dd, 1 H, $J = 7.0$, 4.8 Hz, H-5), 7.50 (dd, 1 H, $J = 7.0$, 2.0 Hz, H-4), 8.26 (dd, 1 H, $J = 4.8$, 2.0 Hz, H-6).

Analysis: found C 54.0, H 5.1, N 7.0, Cl 17.8; $C_9H_{10}NClO_2$ requires C 54.1, H 5.0, N 7.0, Cl 17.8.

Ethyl 2-Chloro-5-pyridylacetate **(12)**: yield (97%); a colourless oil; bp 75 °C/0.2 mbar.

IR (film): $\nu = 2982, 1732\ cm^{-1}$.

^1H NMR ($CDCl_3$): $\delta = 1.24$ (t, 3 H, $J = 7.2$ Hz, CH_3), 3.58 (s, 2 H, CH_2), 4.18 (q, 2 H, $J = 7.2$ Hz, CH_2), 7.23 (d, 1 H, $J = 8.4$ Hz, H-3), 7.57 (dd, 1 H, $J = 8.4$, 1.5 Hz, H-4), 8.24 (d, 1 H, $J = 1.5$ Hz, H-6).

Analysis: found C 54.0, H 5.1, N 7.0, Cl 17.8; $C_9H_{10}NClO_2$ requires C 54.1, H 5.0, N 7.0, Cl 17.8.

3-Ethoxycarbonyl-2-methylthiothieno[2,3-*c*]pyridine (15); Typical Procedure:

CS_2 (748 mg, 9.83 mmol) was added to a stirred solution of **1** (2.0 g, 8.19 mmol) in DMSO (40 mL), under N_2. NaH (433 mg, 18.02 mmol) was added portionwise and the mixture was stirred for 1 h at r.t., warmed to 90 °C for 1.5 h, allowed to cool to r.t. and MeI (2.6 g, 18.02 mmol) added. The mixture was then stirred for a further 1 h at r.t., poured onto ice (300 g), and the crude product was obtained by filtration. The solid was dissolved in EtOAc and some insoluble material was filtered. The organic extracts were dried ($MgSO_4$), decolourised with charcoal, filtered and the solvent removed in vacuo. Recrystallisation from EtOAc afforded **15** (882 mg, 42%); mp 138–139 °C (Table).

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