The Synthesis of Thienopyridines from ortho-Halogenated Pyridine Derivatives

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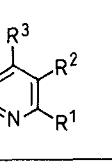
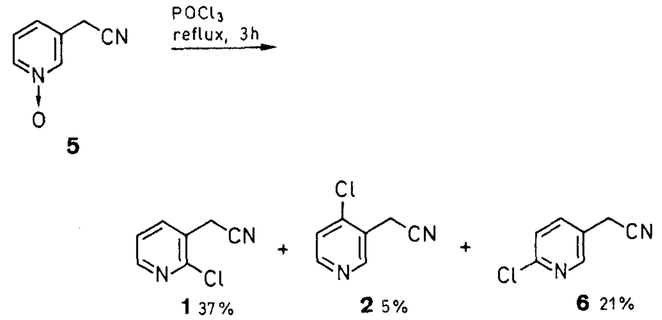
The synthesis of 2- and 4-chloro-3-cyanomethylpyridine, 3-bromo-2-cyanomethylpyridine and 3-bromo-4-cyanomethylpyridine containing methylene groups activated by the nitrile functionality is reported. Reaction of these compounds with sodium hydride and carbon disulfide, followed by iodomethane gives the corresponding thienopyridines.

Recent reports[1,2] concerning the synthesis and use of ketene dithioacetals derived from pyridines have prompted us to describe our results in this area. As part of our synthetic programme[3] we required the ortho-halogenated pyridine derivatives **1**–**4**, which contain active methylene groups, for further conversion into thienopyridines.

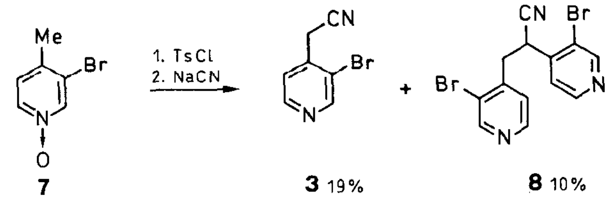


	R^1	R^2	R^3
1	Cl	CH_2CN	H
2	H	CH_2CN	Cl
3	H	Br	CH_2CN
4	CH_2CN	Br	H

Of the four possible isomers only 2-chloro-3-cyanomethylpyridine (**1**) had been prepared[4] previously from the reaction of 3-cyanomethylpyridine *N*-oxide (**5**) and phosphoryl chloride. According to the authors, three products were obtained from this reaction: 2-chloro-3-cyanomethylpyridine (**1**) in 37 % yield, 2-chloro-5-cyanomethylpyridine (**6**) in 14 % yield, and 3-cyanomethyl-5-hydroxypyridine in 8 % yield. When we repeated this reaction the product mixture differed from that produced above. Compounds **1** and **6** were still obtained, in 37 % and 21 % yields respectively, but the third product we isolated, in 5 % yield, was 4-chloro-3-cyanomethylpyridine (**2**). The formation of this last product allowed direct access to one of the desired cyanomethylpyridines in a single step from **5**, albeit in very low yield.

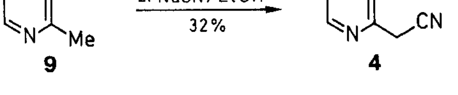


The third derivative, 3-bromo-4-cyanomethylpyridine (**3**) was synthesised, in 19 % yield, starting from 3-bromo-4-methylpyridine *N*-oxide (**7**)[5] by reaction with *p*-toluenesulfonyl chloride[6] followed immediately by sodium cyanide.

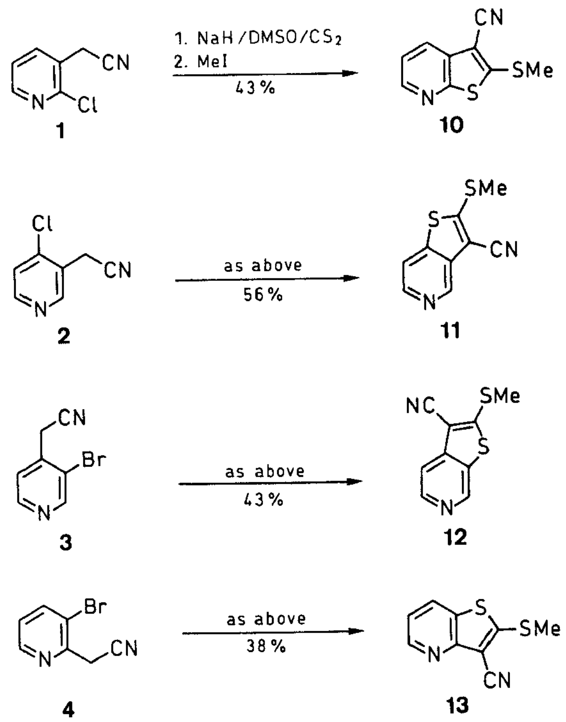


The low yield obtained in this reaction may be a result of the poor conversion of starting material into the chloromethyl intermediate allied to the fact that 3-bromo-4-[1-cyano-2-(3-bromo-4-pyridyl)ethyl]pyridine (**8**) was obtained as a byproduct in 10% yield. Dimer **8** is probably produced by abstraction of a proton from the relatively acidic benzylic position of **3** followed by reaction of the resulting anion with 3-bromo-4-chloromethylpyridine generated in the previous step of the reaction.

The final compound, 3-bromo-2-cyanomethylpyridine (**4**), was synthesised in 32% yield from the reaction of 3-bromo-2-methylpyridine (**9**)[7] with *N*-bromosuccinimide (NBS), followed by sodium cyanide. However, the ^{1}H NMR spectrum of the crude reaction mixture indicated that with 1.1 molar equivalents of *N*-bromosuccinimide the reaction only proceeded to approximately 40% completion and this accounts for the low yield of **4**. Optimisation of this synthesis is currently under investigation.



Since benzyl cyanides possessing an ortho-halogen atom have been shown to react with carbon disulfide in the presence of base to afford benzo[*b*]thiophenes,[8] we wished to study the corresponding reaction in the pyridine series. When the ortho-halogenated pyridine 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 **10–13** were obtained in good to moderate yields. In each case the reaction is believed to proceed via the intermediacy of a ketene dithioacetal dianion[9] where one of the thiolate anions displaces the halogen to produce the bicyclic product and the other is alkylated with the iodomethane.



The analytical and spectroscopic data for thienopyridines **10–13** are consistent with the proposed structures. The thiomethyl group in these compounds may be displaced by nucleophiles and reactions to produce novel tricycles will be reported later.

Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded either at 60 MHz on a Jeol PMX 60si spectrometer or at 90 MHz with a Jeol FX 90q spectrometer, using either $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. IR spectra were recorded using KBr discs on a Perkin-Elmer 1600 FT-IR spectrophotometer. Mass spectra were recorded with an AEI MS 920S spectrometer operating at 70 eV. Reactions were monitored by TLC using Merck DC Alufolien Kieselgel 60 F_{254} (Merck #5554) plates and were visualised under UV irradiation. Column chromatography was performed with Kieselgel 60 (Fluka; particle size 0.063–0.2 mm). Reagent quality solvents were used without further

Table. Thienopyridines **10–13** Prepared

Product	Yield[a] (%)	mp (°C) (EtOAc)	Molecular Formula[b]	IR (KBr) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) *m/z* (%)
10	43	143–143.5	$C_9H_6N_2S_2$ (206.3)	2996, 2924, 2213	2.79 (s, 3H, CH_3), 7.41 (dd, 1H, J = 4.6, 8.1, H-4), 8.03 (dd, 1H, J = 1.5, 8.1, H-5), 8.54 (dd, 1H, J = 1.5, 4.6, H-6)	206 (M$^+$, 100), 191 (47), 173 (23), 147 (32)
11	56	145–146	$C_9H_6N_2S_2$ (206.3)	3050, 2960, 2217	2.79 (s, 3H, SCH_3), 7.70 (d, 1H, J = 5.7, H-5), 8.53 (d, 1H, J = 5.7, H-6), 9.09 (s, 1H, H-2)	206 (M$^+$, 100), 191 (58), 173 (20), 147 (16)
12	43	137–138	$C_9H_6N_2S_2$ (206.3)	3060, 2922, 2214	2.89 (s, 3H, SCH_3), 7.66 (d, 1H, J = 5.7, H-5), 8.57 (d, 1H, J = 5.7, H-6), 9.25 (s, 1H, H-2)	206 (M$^+$, 100), 191 (19), 173 (34), 147, (19)
13	38	125–126	$C_9H_6N_2S_2$ (206.3)	3057, 2936, 2213	2.79 (s, 3H, SCH_3), 7.28 (dd, 1H, J = 4.8, 8.3, H-4), 8.03 (dd, 1H, J = 1.3, 8.3, H-5), 8.74 (dd, 1H, J = 1.3, 4.8, H-6)	206 (M$^+$, 100), 191 (28), 161 (17), 147 (27), 136 (54)

[a] Yield of pure crystallized products.

[b] Satisfactory microanalyses obtained: C ± 0.35, H ± 0.25, N ± 0.30, S ± 0.35.

purification. Reagents and appropriate starting materials were purchased from Aldrich Chemical Co. Petroleum ether used had bp 60–80 °C.

Reaction of 3-Cyanomethylpyridine *N*-Oxide (5) with Phosphoroyl Chloride:

3-Cyanomethylpyridine *N*-oxide (**5**; 10 g, 74.5 mmol) was added to $POCl_3$ (100 mL) and the mixture was warmed slowly with vigorous shaking. After all of the solid had dissolved the mixture was refluxed for 3 h. The excess $POCl_3$ was removed in vacuo and the residue poured onto ice (150 g), neutralized with a dilute solution of ammonia, and extracted with EtOAc (3 x 100 mL). The EtOAc extracts were dried ($MgSO_4$) and evaporated in vacuo to afford an oil, which was chromatographed on silica gel (100 g). Gradient elution with petroleum ether/Et_2O (10 to 50 %) afforded products **1**;[4] yield: 4.21 g (37 %) and **6**;[4] yield: 2.40 g (21 %). 4-Chloro-3-cyanomethylpyridine (**2**) was also isolated; yield: 0.05 g (5 %); mp 53–55 °C (petroleum ether/Et_2O).

$C_7H_5ClN_2$	calc.	C 55.1	H 3.3	Cl 23.2	N 18.4
(152.6)	found	55.3	3.5	23.4	18.0

IR (KBr): ν = 2887, 2247 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.82 (s, 2 H, CH_2), 7.28 (d, 1 H, J = 8 Hz, H-5), 8.40 (d, 1 H, J = 8 Hz, H-6), 8.56 (s, 1 H, H-2).

MS (%): m/z = 154 (M^+, 32), 152 (100), 125 (47), 117 (53), 90 (36).

3-Bromo-4-cyanomethylpyridine (3):

3-Bromo-4-methylpyridine *N*-oxide[5] (**7**; 10 g, 53.2 mmol) and TsCl (20.3 g, 106 mmol) were refluxed in dioxane (50 mL) for 4 h. The cooled mixture was treated with 10 % HCl (100 mL) and stirred for 15 min, extracted with Et_2O (4 x 50 mL) to remove the excess TsCl, neutralised with $NaHCO_3$, and extracted with Et_2O (3 x 100 mL). The solvent was removed in vacuo and a mixture of water (10 mL) and EtOH (40 mL) was added to the residue. This, in turn, was added to a refluxing solution of NaCN (13 g) in water (25 mL) and EtOH (125 mL) and reflux was continued for 1 h. Charcoal was added to the cooled reaction mixture which was then filtered. The solvent was removed in vacuo and water (50 mL) was added to the residue, which was extracted with EtOAc (3 x 100 mL). The EtOAc extracts were dried ($MgSO_4$), evaporated in vacuo, and the residue chromatographed on silica gel (120 g). Gradient elution with petroleum ether/Et_2O (10 to 50 %) afforded **3**; yield: 2.0 g (19 %); mp 93–94 °C (Et_2O/petroleum ether).

$C_7H_5BrN_2$	calc.	C 42.7	H 2.6	Br 40.6	N 14.2
(197.0)	found	43.0	2.9	40.8	13.9

IR (KBr): ν = 2859, 2250 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.82 (s, 2 H, CH_2), 7.42 (d, 1 H, J = 4.8 Hz, H-5), 8.48 (d, 1 H, J = 4.8 Hz, H-6), 8.66 (s, 1 H, H-2).

MS (%): m/z = 198 (M^+, 97), 196 (100), 117 (46), 116 (74), 90 (30).

Also isolated from this rection was 3-bromo-4-[1-cyano-2-(3-bromo-4-pyridyl)ethyl]pyridine (**8**); yield: 1.05 g (10 %); mp 120–122 °C (EtOAc/petroleum ether).

$C_{13}H_9Br_2N_3$	calc.	C 42.5	H 2.5	N 11.5
(367.1)	found	42.4	2.4	11.4

IR (KBr): ν = 3039, 2921, 2246 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.39 (m, 1 H, H_a of CH_2), 3.48 (m, 1 H, H_b of CH_2), 4.91 (m, 1 H, CHCN), 7.50 (d, 1 H, J = 5.5 Hz, H-5), 7.62 (d, 1 H, J = 4.8 Hz, H-5′), 8.55 (d, 1 H, J = 4.8 Hz, H-6′), 8.64 (d, 1 H, J = 5.5 Hz, H-6), 8.74 (s, 1 H, H-2), 8.81 (s, 1 H, H-2′).

MS (%): m/z = 369 (M^+, 40), 367 (80), 365 (40), 171 (100 %), 169 (99).

3-Bromo-2-cyanomethylpyridine (4):

3-Bromo-2-methylpyridine[7] (**9**; 6 g, 33 mmol), NBS (12.4 g, 69.8 mmol), CCl_4 (50 mL), and AIBN (0.060 g) were refluxed for 5 h. The cooled mixture was filtered and washed with Et_2O (100 mL). The filtrate and the washings were concentrated in vacuo and a mixture of water (10 mL) and EtOH (25 mL) was added to the residue. This solution was then added to a refluxing solution of NaCN (8.5 g, 175 mmol) in water (25 mL) and EtOH (75 mL) and refluxed for 1 h. The cooled reaction mixture was stirred with charcoal (0.5 g), filtered and the solvent removed in vacuo. Water (20 mL) was added and the aqueous phase extracted with EtOAc (3 x 100 mL) which was dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was chromatographed on silica gel (60 g) eluting with light petroleum/Et_2O (10 % to 30 %) to afford **4**; yield: 1.41 g (32 %); mp 64–65 °C (petroleum ether/Et_2O).

$C_7H_5BrN_2$	calc.	C 42.7	H 2.6	Br 40.6	N 14.2
(197.0)	found	42.7	2.8	40.5	14.1

IR (KBr): ν = 2925, 2248 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.09 (s, 2 H, CH_2), 7.40 (dd, 1 H, J = 4.4, 7.8 Hz, H-4), 7.91 (dd, 1 H, J = 1.3, 7.8 Hz, H-5), 8.57 (dd, 1 H, J = 1.3, 4.4 Hz, H-6).

MS (%): m/z = 198 (M^+, 95), 196 (100), 117 (58), 90 (35).

3-Cyano-2-methylthiothieno[2,3-*b*]pyridine (10); Typical Procedure:

CS_2 (0.65 g, 8.6 mmol) was added to a stirred solution of 2-chloro-3-cyanomethylpyridine (**1**; 1.00 g, 8.2 mmol) in DMSO (20 mL) under N_2. NaH (0.35 g, 14 mmol) was added portionwise and the mixture stirred at r. t. for 1 h. It was then warmed to 70 °C for 1 h, allowed to cool to r. t., and MeI (1.86 g, 13.1 mmol) was added. The mixture was stirred for a further 1 h at r. t., poured onto ice (150 g), and the crude product obtained by filtration. This product was dissolved in EtOAc (100 mL), dried ($MgSO_4$), decolourised with charcoal (0.5 g), filtered, and the solvent removed in vacuo. Recrystallization from EtOAc gave **10**; yield: 0.58 g (43 %); mp 143–143.5 °C (Table).

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