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THE PREPARATION OF KETENE DITHIOACETALS AND THIOPHENES FROM CHLOROPYRIDINES CONTAINING AN ACTIVE METHYLENE GROUP

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Abstract – The base catalysed reaction of carbon disulphide with the active methylene groups of chloropyridines **4** and **7**, followed by alkylation with reagents which also contain active methylene groups, lead to ketene dithioacetals. Further reaction with base afforded highly substituted thiophenes.

INTRODUCTION

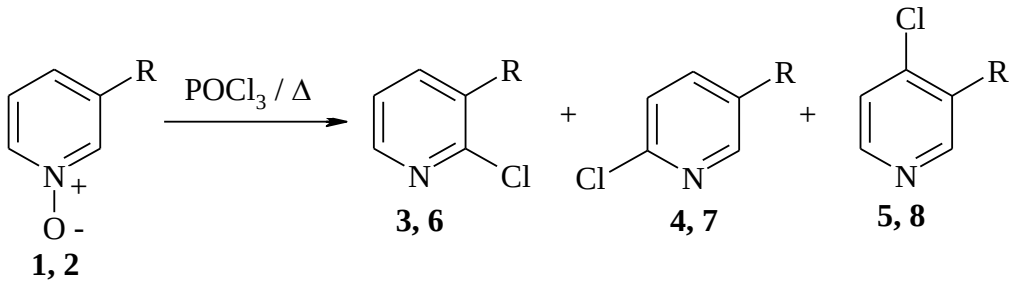
Our work[1-3] on the synthesis of thienopyridines required us to prepare a series of α-halogenated pyridines containing a methylene moiety activated by an electron withdrawing group. We earlier reported[1,2] that reaction of pyridine 3-acetonitrile N-oxide **1** with refluxing $POCl_3$, using the method reported by Okuda and Robison[4] gave the desired chloropyridines **3** and **5** with **4** as a byproduct. Similarly[2] we obtained **6**, **7** and **8** from ethyl 3-pyridylacetate N-oxide **2** (**Equation 1**). The ratio[1,2] of isomers differs for each substituent at the 3-position (**Table 1**). It is well known[5-12] that polyfunctional ketene dithioacetals are available from reaction of carbon disulphide with functionalized carbionic species followed by alkylation of the heteroanions including cyano(3-pyridyl)ketene dimethyldithioacetal[11] from 3-cyanomethylpyridine. Furthermore, it has also been reported[5-10] that treatment of appropriately functionalized ketene dithioacetals with base allows entry into a range of highly substituted heterocycles. In this work, haloalkanes with electron withdrawing groups on the same carbon as the halogen were employed as alkylating agents in the base catalysed nucleophilic addition reaction of **4** and **7** with carbon disulphide. This gave ketene dithioacetals with the required functionality for cyclisation to form thiophenes.

This paper is dedicated to Professor Dr. Albert Eschenmoser on his 85th birthday.

Table 1. Product Ratio by Substituent at C-3

Substitution pattern	R = CH_2CN (%)	R = CH_2CO_2Et (%)
2,3- (**3**, **6**)	37	33
2,5- (**4**, **7**)	21	22
3,4- (**5**, **8**)	5	13

Equation 1



1, **3**, **4**, **5**; R = CH_2CN and **2**, **6**, **7**, **8**; R = CH_2CO_2Et

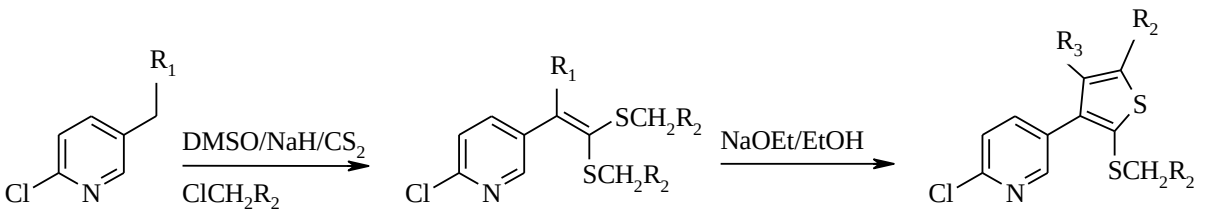
RESULTS AND DISCUSSION

When 2-chloro-5-cyanomethylpyridine **4** and carbon disulphide were treated with a slight excess of sodium hydride in DMSO under anhydrous conditions followed by addition of ethyl chloroacetate, ketene dithioacetal **9** was synthesised in 58% yield. The infrared spectrum showed the molecule to contain a nitrile group (2209 cm^{-1}) and an aliphatic ester (1736 cm^{-1}). The ^1H NMR corroborated the structure, showing signals for two ethyl thioacetate groups and a 2,5 disubstituted pyridine. Further treatment of **9** with sodium ethoxide in ethanol gave thiophene **10** (55%). The infrared spectrum for this compound showed a primary amine (3447 and 3343 cm^{-1}) and two ester groups (1724, 1661 cm^{-1}). The absorbance at 1724 cm^{-1} can be interpreted as being due to the aliphatic ethyl ester. The second, at 1661cm^{-1} can be assigned to the ester directly attached to the thiophene ring, having a similar absorption wavenumber as an anthranilate ester. There will be some hydrogen bonding between the ester carbonyl and the amino hydrogens and this phenomenon is known[13] to move the absorbance to a lower wavenumber. It is thought that the mechanism for the formation of **9** proceeds by base catalysed abstraction of the methylene protons of **4** and subsequent formation, with carbon disulphide, of a ketene dithioacetal dianion. These anions are then alkylated with ethyl chloroacetate. The thiophene **10** is subsequently formed by a Thorpe[14] type cyclisation of the active methylene adjacent to the sulphur onto the nitrile. Ketene ditioacetal **11** was similarly prepared from **4** (54%) using chloroacetonitrile as the alkylating agent and **11** was readily cyclised to the corresponding thiophene **12** (51%) with sodium ethoxide again probably via a Thorpe type reaction.

This methodology was extended to ethyl 2-chloro-5-pyridylacetate **7**, to produce ketene dithioacetal **13**. The infrared spectrum showed a carbonyl stretching absorbance in the expected region for aliphatic esters (1736 cm^{-1}). This was unexpected, as it also contains an α,β-unsaturated ethyl ester group and a second peak should have been observed at a lower wavenumber, typically,[13] 1730-1705 cm^{-1}. The ^1H NMR however supported the structure, showing signals for two ethyl thioacetate groups and an ethyl ester group. Further reaction of **13** with sodium ethoxide in ethanol lead to the production of thiophene **14** in 33% yield. Again two carbonyl stretching absorbances were observed in the IR spectrum, an aliphatic ester (1748 cm^{-1}), and a salicylate type ester at 1666cm^{-1}. It is presumed that formation is by a Dieckmann[15] cyclisation of one of the methylene groups onto the vinyl ester. Reaction of **7** with chloroacetonitrile under the same reaction conditions, gave **15** in 57% yield. The IR spectrum this time showed a carbonyl stretching absorbance typical[13] of an α,β-unsaturated ester group (1720 cm^{-1}). Further reaction of **15** with base afforded **16** in 46% yield, again by a Dieckmann cyclisation.

In conclusion, novel ketene dithioacetals can be conveniently prepared, leading to polyfunctional thiophenes (**Scheme 1**) and we believe this method can be applied in the synthesis of a variety similar highly substituted thiophenes.

Scheme 1



4,7 **9,11,13,15** **10,12,14,16**

4 R_1 = CN
7 R_1 = CO_2Et

9 R_1 = CN, R2 = CO_2Et
11 R_1 = CN, R_2 = CN
13 R_1 = CO_2Et, R_2 = CO_2Et
15 R_1 = CO_2Et, R_2 = CN

10 R_2 = CO_2Et, R_3 = NH_2
12 R_2 = CN, R_3 = NH_2
14 R_1 = CO_2Et, R_3 = OH
16 R_2 = CN, R_3 = OH

EXPERIMENTAL

1.0. General

Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Paragon spectrophotometer. ^1H NMR spectra were recorded on a Jeol PMX 60i spectrometer. Column chromatography was performed using pressurised short path columns with Kieselgel 60, particle size < 0.063 mm (Merck No. 7729) and reactions were

monitored with Merck DC-Alufoilien 60 F_{254} (Merck No. 5554) which were visualised by ultraviolet irradiation.

1.1. Preparation of ketene dithioacetals.

1.1.1. General procedure; **2-chloro-5-(1-cyano-2,2-di(ethyloxycarbonylmethylthio)-1-vinyl)pyridine (9)** as an example.

2-Chloro-5-cyanomethylpyridine **4** (2.0 g, 13.1 mmol) and carbon disulphide (1.1 g, 14.4 mmol) were dissolved in DMSO (40 mL) in a 2-neck round bottom flask fitted with a gas inlet tube under dry nitrogen and sodium hydride (0.66 g, 27.5 mmol) was added in portions with constant stirring and the mixture was stirred for 2 h. Ethyl chloroacetate (3.38 g, 27.5 mmol) was added and stirring continued for another hour, then poured onto ice (100 g) and extracted with EtOAc (3 x 50 mL). The extracts were combined, dried with magnesium sulphate, filtered and the solvent evaporated to give a pale yellow oil (4.46 g) which was chromatographed on silica gel using petroleum ether/EtOAc to give **9** as a colourless oil (58%). Bp (decomp); Anal. Calcd for $C_{16}H_{17}ClN_2O_4S_2$: C, 47.9; H, 4.3; N, 7.0%. Found: C, 48.0; H, 4.4; N, 7.1%; IR ν_{max} (film)/cm^{-1} 2982, 2209, 1736; ^{1}H NMR δ_H ($CDCl_3$) 1.28 (3H, t, J=7.2 Hz, CH_3), 1.32 (3H, t, J=7.2 Hz, CH_3), 3.72 (2H, s, SCH_2), 3.80 (2H, s, SCH_2), 4.16 (2H, q, J=7.2 Hz, CO_2CH_2), 4.20 (2H, q, J=7.2 Hz, CO_2CH_2), 7.33 (1H, d, J=8.4 Hz, H-3), 7.85 (1H, dd, J=8.4 & 2.4 Hz, H-4), 8.52 (1H, d, J=2.4 Hz, H-6).

1.1.2. 2-Chloro-5-(1-cyano-2,2-di(cyanomethylthio)-1-vinyl)pyridine (11)

Off white crystals (61%, EtOAc). Mp 101-102 °C; Anal. Calcd for $C_{11}H_7ClN_4S_2$: C, 47.0; H, 2.4; N, 18.3%. Found: C, 46.9; H, 2.3; N, 18.3%; IR ν_{max}(KBr)/cm^{-1} 2978, 2234; ^{1}H NMR δ_H ($CDCl_3$) 4.48 (4H, s, SCH_2), 7.38 (1H, d, J=8.4 Hz, H-3), 7.66 (1H, dd, J=8.4 & 2.4 Hz, H-4), 8.32 (1H, d, J=2.4 Hz, H-6).

1.1.3. 2-Chloro-5-(1-ethyloxycarbonyl-2,2-di(ethyloxycarbonylmethylthio)-1-vinyl)pyridine (13)

Colourless oil (43%); bp (0.4) 190 °C; Anal. Calcd for $C_{18}H_{22}ClNO_6S_2$: C, 49.3; H, 4.9; N, 3.1%. Found: C, 49.6; H, 4.8; N, 3.3%; IR ν_{max}(film)/cm^{-1} 2982, 2937, 1736; ^{1}H NMR δ_H ($CDCl_3$) 1.24 (3H, t, J=7.2 Hz, CH_3), 1.28 (6H, t, J=7.2 Hz, CH_3), 3.56 (2H, s, SCH_2), 3.68 (2H, s, SCH_2), 4.08 (4H, q, J=7.2 Hz, CO_2CH_2), 4.14 (2H, q, J=7.2 Hz, CO_2CH_2), 7.28 (1H, d, J=8.4 Hz, H-3), 7.72 (1H, dd, J=8.4 & 2.4 Hz, H-4), 8.34 (1H, d, J=2.4 Hz, H-6).

1.1.4. 2-Chloro-5-(1-ethyloxycarbonyl-2,2-di(cyanomethylthio)-1-vinyl)pyridine (15)

Pale yellow needles (57%, EtOH). Mp 98-99 °C; Anal. Calcd for $C_{14}H_{12}ClN_3O_2S_2$: C, 47.5; H, 3.4; N, 11.9%. Found: C, 47.4; H, 3.0; N, 11.7%; IR ν_{max}(KBr)/cm^{-1} 2976, 2246, 1720; ^{1}H NMR δ_H ($CDCl_3$) 1.25

(3H, t, J=7.2 Hz, CH_3), 3.56 (2H, s, SCH_2), 3.68 (2H, s, SCH_2), 4.24 (2H, q, J=7.2 Hz, CO_2CH_2), 7.24 (1H, d, J=8.4 Hz, H-3), 7.58 (1H, dd, J=8.4 & 2.4 Hz, H-4), 8.24 (1H, d, J=2.4 Hz, H-6).

1.2. Preparation of thiophenes

1.2.1. General procedure; **2-chloro-5-(2-ethyloxycarbonyl-5-ethyloxycarbonylmethylthio-3-aminothienyl)pyridine (10)** as an example.

Ketene dithioacetal **9** (0.5 g, 1.1 mmol) was dissolved in EtOH (20 mL) in a 50 mL round bottom flask and sodium ethoxide (0.16 g, 2.4 mmol) added. The mixture was stirred at room temperature for 24 h. The solvent was removed *in vacuo*, the residue flooded with water and extracted with EtOAc (3 x 25 mL). The combined extracts were dried with magnesium sulphate, filtered and the solvent removed to give thiophene **10** (55%) after recrystallisation from EtOAc. Mp 94-95 °C; Anal. Calcd for $C_{16}H_{17}ClN_2O_4S_2$: C, 47.9; H, 4.3; N, 7.0%. Found: C, 48.1; H, 4.2; N, 6.9%; IR ν_{max}(KBr)/cm^{-1} 3447, 3343, 2967, 1724, 1661; ^{1}H NMR δ_H ($CDCl_3$) 1.17 (3H, t, J=7.2 Hz, CH_3), 1.26 (3H, t, J=7.2 Hz, CH_3), 3.46 (2H, s, SCH_2), 4.02 (2H, q, J=7.2 Hz, CO_2CH_2), 4.18 (2H, q, J=7.2 Hz, CO_2CH_2), 5.36 (2H, s, NH_2), 7.30 (1H, d, J=8.4 Hz, H-3), 7.64 (1H, dd, J=8.4 & 2.4 Hz, H-4), 8.26 (1H, d, J=2.4 Hz, H-6).

1.2.2. 2-Chloro-5-(2-cyano-5-cyanomethylthio-3-aminothienyl)pyridine (12)

Pale yellow crystals (51%, EtOAc). Mp 113-114 °C; Anal. Calcd for: $C_{12}H_7ClN_3S_2$: C, 49.2; H, 2.4; N, 14.4%. Found: C, 49.1; H, 2.4; N, 14.2%; IR ν_{max}(KBr)/cm^{-1} 3443, 3339, 2982, 2210; ^{1}H NMR δ_H ($CDCl_3$) 4.38 (2H, s, SCH_2), 5.42 (2H, s, NH_2), 7.32 (1H, d, J=8.4 Hz, H-3), 7.68 (1H, dd, J=8.4 & 2.4 Hz, H-4), 8.36 (1H, d, J=2.4 Hz, H-6).

1.2.3. 2-Chloro-5-(2-ethyloxycarbonyl-5-ethyloxycarbonyl methylthio-3-hydroxythienyl)pyridine (14)

Pale yellow crystals (33%, EtOAc). Mp 74-75 °C; Anal. Calcd for: $C_{16}H_{16}ClNO_5S_2$: C; 47.8; H, 4.0; N, 3.4%. Found: C, 47.8; H, 3.7; N, 3.3%; IR ν_{max}(KBr)/cm^{-1} 3462, 2978, 2914, 1748, 1666; ^{1}H NMR δ_H ($CDCl_3$) 1.20 (3H, t, J=7.2 Hz, CH_3), 1.32 (3H, t, J=7.2 Hz, CH_3), 3.48 (2H, s, SCH_2), 4.02 (2H, q, J=7.2 Hz, CO_2CH_2), 4.24 (2H, q, J=7.2 Hz, CO_2CH_2), 7.22 (1H, d, J=8.4 Hz, H-3), 7.66 (1H, dd, J=8.4 & 2.4 Hz, H-4), 8.34 (1H, d, J=2.4 Hz, H-6), 9.70 (1H, s, OH).

1.2.4. 2-Chloro-5-(2-cyano-5-cyanomethylthio-3-hydroxythienyl)pyridine (16)

Pale yellow prisms (46%, EtOAc). Mp 101-102 °C; Anal. Calcd for $C_{12}H_6ClN_3OS_2$: C, 46.8; H, 1.9; N, 13.6%. Found: C, 46.9; H, 1.7; N, 13.5%; IR ν_{max}(KBr)/cm^{-1} 3452, 2975, 2926, 2211; ^{1}H NMR δ_H

($CDCl_3$) 4.04 (2H, s, SCH_2), 7.58 (1H, d, J=8.4 Hz, H-3), 7.86 (1H, dd, J=8.4 & 2.4 Hz, H-4), 8.42 (1H, d, J=2.4 Hz, H-6).

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