C-Alkylations of Indoles and Pyrroles with α-Chloro Sulfides on an Alumina Surface: A Short Synthesis of Dithyreanitrile

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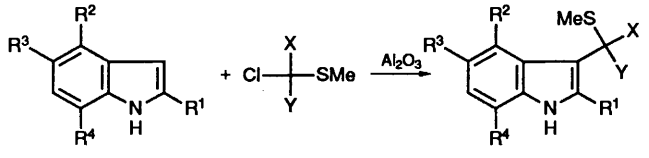
Alumina-mediated *C*-alkylations of indoles and pyrroles with α-chloro sulfides have been examined. Thus, a mixture of indoles **1** and the α-chloro sulfides **2** or **3**, on treatment with neutral alumina, gave the ethyl indol-3-ylacetates **5** and the corresponding acetonitriles **6**, respectively. A similar reaction of the chloride **4** with 7-methoxyindole provided direct access to dithyreanitrile **7h**, which is an insect antifeedant. The pyrrole **10** was also allowed to react with the α-chloro sulfides **2** and **3** to afford the 2-substituted products **11** and **12**, respectively. On the other hand, the reactions of skatole **14** with **2** and **3** gave the 2-alkylation products **15** and **16**, respectively, but in low yields. However, 2,3-dimethylindole **17** reacted smoothly with **2** and **3** to give the indolenines **18** and **19**, respectively. The reaction of 2,5-dimethylpyrrole **25** with **2** afforded the 2,2,5-trisubstituted 2*H*-pyrrole **26** as a major product along with the 2,3,5-trisubstituted 1*H*-pyrrole **27**. Some chemical transformations of the products **5**, **18** and **26** are also described.

It is generally recognized that the Lewis acid-mediated Friedel–Crafts reactions of indole with alkyl halides give a complex mixture of products because of the labile nature of the indole nucleus under the reaction conditions employed. Therefore, the alkylations of indole with alkyl halides have been usually performed *via* the *N*-metallated derivatives of indole (*e.g.*, Grignard reagents).[1] Some modifications of the Friedel–Crafts conditions have also been reported: for example, bis(trimethylsilyl)acetamide was used as an additive to remove hydrogen chloride formed during the course of the reactions.[2] However, probably the most desirable modification is to conduct the reactions under essentially neutral conditions. We found that certain α-chloro sulfides reacted readily with indoles on alumina surface[3,4] to give the expected *C*-alkylation products. Herein we report the results of the reactions of the α-chloro sulfides **2**–**4** with a range of indoles and pyrroles in the presence of alumina. Application of the method to a short synthesis of dithyreanitrile **7h**, a recently isolated indole alkaloid, is also presented.



2,5 X = H, Y = CO_2Et
3,6 X = H, Y = CN
4,7 X = SMe, Y = CN

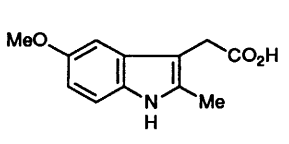
a; $R^1 = R^2 = R^3 = R^4 = H$
b; R^1 = Me, $R^2 = R^3 = R^4 = H$
c; R^1 = Me, $R^2 = R^4 = H$, R^3 = OMe
d; $R^1 = R^3 = R^4 = H$, R^2 = Me
e; $R^1 = R^3 = R^4 = H$, R^2 = Cl
f; $R^1 = R^2 = R^4 = H$, R^3 = Me
g; $R^1 = R^2 = R^4 = H$, R^3 = OMe
h; $R^1 = R^2 = R^3 = H$, R^4 = OMe

Scheme 1

The indole **1a** and ethyl chloro(methylthio)acetate **2** (1.5 mol equiv.)[5a] when mixed thoroughly with an appropriate quantity of neutral chromatographic alumina* gave the alkylation product **5a** in 63% yield, after removal of the alumina by washing with organic solvent, concentration of the extract, and then purification of the crude material by chromatography on alumina (method A). More interestingly, **1a** reacted with **2** simply on passage through a column of the neutral alumina to afford the pure product **5a** in 48% yield (method B). Similarly, chloro(methylthio)acetonitrile **3**[5b] reacted with indoles in the presence of alumina to give the indol-3-ylacetonitriles **6**. The results are summarised in Table 1, which shows that more satisfactory yields are obtained by using method A.

Silica gel† also catalysed the reactions, but the yields were relatively low, *e.g.*, 35 and 26% yields of **5a** were obtained by using methods A and B, respectively. Equimolar mixtures of **1a** and **2** when heated in $CHCl_3$ or treated with $TiCl_4$ in CH_2Cl_2 at 0 °C afforded low yields, 10 or 4%, of the product **5a**, respectively.

Desulfurisation of the product **5c** with zinc dust in hot acetic acid, followed by alkaline hydrolysis of the resultant ester afforded 5-methoxy-2-methylindol-3-ylacetic acid **8**, which has previously been converted into a potent anti-inflammatory agent indomethacin.[7] A similar sequence of the reactions of **5e** provided 4-chloroindol-3-ylacetic acid **9**, one of the most powerful natural auxins.[8]



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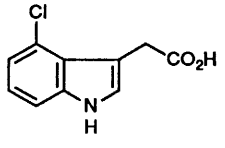

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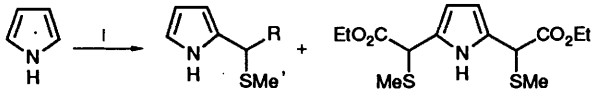
Dithyreanitrile **7h**, a novel sulfur-containing indolic alkaloid isolated recently from the seeds of *Dithyrea wislizenii* (Cruciferae),[9] has been shown to inhibit feeding of fall armyworm and European corn borer larvae. The reaction of chloro[bis(methylthio)]acetonitrile **4** with indoles in the presence of alumina provided a direct access to dithyreanitrile and its derivatives **7** (see Table 1).

* The reaction of **1** with **2** in an organic solvent such as hexane in the presence of alumina gave no alkylation product.
† Silica gel-mediated alkylation of durene and anisole with chloromethyl phenyl sulfide in boiling hexane (28 and 24% yields, respectively) has been reported.[6]

Table 1 Preparation of ethyl indol-3-ylacetates **5** and indol-3-ylacetonitriles **6** and **7**[a]

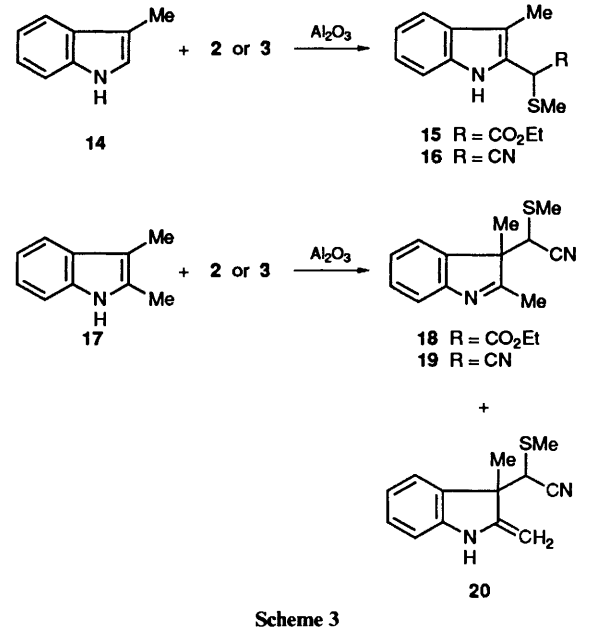
Indole	Chloride	Product (%)
1a	**2**	**5a** 63 (48)
1b	**2**	**5b** 68 (60)
1c	**2**	**5c** 35 (42)
1d	**2**	**5d** 52 (35)
1e	**2**	**5e** 50 (42)
1f	**2**	**5f** 60 (50)
1a	**3**	**6a** 61 (52)
1b	**3**	**6b** 77 (68)
1c	**3**	**6c** 56 (50)
1d	**3**	**6d** 64 (56)
1e	**3**	**6e** 57 (39)
1f	**3**	**6f** 64 (55)
1a	**4**	**7a** 75 (22)
1d	**4**	**7d** 98 (13)
1f	**4**	**7f** 86 (38)
1g	**4**	**7g** 80 (34)
1h	**4**	**7h** 88 (35)

[a] 1.5 mol equiv. of **2**, **3** or **4** were used: yield based on indole **1** by using method A. The yield in parentheses are for method B.



10 **11** R = CO_2Et, **13** R = CN, **12**

Scheme 2 *Reagents:* i, **2** or **3**, Al_2O_3



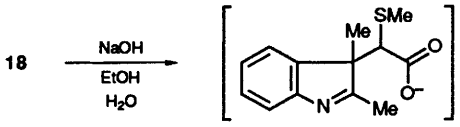
14 **15** R = CO_2Et, **16** R = CN; **17** **18** R = CO_2Et, **19** R = CN; **20**

Scheme 3

Pyrrole **10** reacted with the α-chloro sulfide **2** (1 mol equiv.) in the presence of alumina to give the expected alkylation product **11** in 49% yield (by using method A). In this instance, however, the 2,5-dialkylation product **12** was also obtained in 9% yield. This may be a result of the further alkylation of **11** with **2**. Use of 2 mol equiv. of pyrrole gave the monoalkylated product **11** in good yield (71% based on **2**) together with **12** (8%). A similar reaction of the α-chloro sulfide **3** with **10** afforded **13** in 77% yield (based on **3**).

Our attention was next turned to the behaviour of 3-substituted indoles and 2-substituted pyrroles. When treated with the chloro sulfides **2** or **3** (1.5 mol equiv. each) in the presence of alumina by using method A, skatole **14**, gave the 2-alkylation products **15** (41%) and **16** (10%), together with several unidentified products. 2,3-Dimethylindole **17**, however, reacted cleanly with **2** to afford the indolenine **18** in 85% yield as a mixture of two diastereoisomers in a ratio of *ca.* 1:1. A similar reaction of **17** with **3** gave **19** (73%) together with the 2-methylene compound **20** (4%). Both compounds **19** and **20** were shown to be the mixtures of two diastereoisomers in a ratio of *ca.* 3:1.

Treatment of the indolenine **18** with sodium hydroxide in



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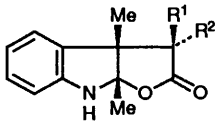


22 R^1 = SMe, R^2 = H
23 R^1 = H, R^2 = SMe
24 R^1 = R^2 = H

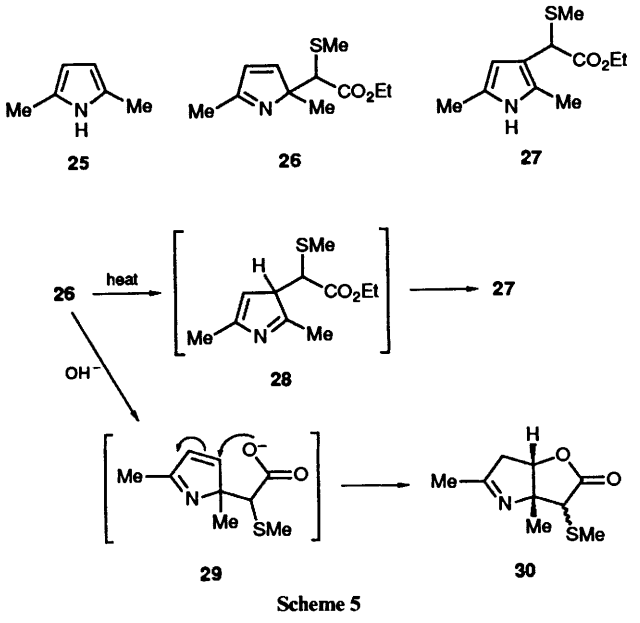
Scheme 4

aqueous ethanol afforded two tricyclic lactones **22** (57%) and **23** (39%) after separation by chromatography on silica gel. Formation of these products from **18** may be explained by a cyclization of the carboxylate anion **21** formed by hydrolysis of the ester **18**.[10] The disagreement between the product ratio (**22**:**23** = 57:39) herein obtained and that (*ca.* 1:1) of starting material **18** may be a result of a partial epimerization at the carbon α to the carbonyl group of **18** or the products **22** and **23** under the basic conditions employed. Accordingly, the major product **22** can be assigned tentatively as an *exo*-methylthio derivative, which is presumed to be thermodynamically more stable than the corresponding *endo*-methylthio isomer **23**.* Desulfurization of **22** and **23** with Bu_3SnH in the presence of azoisobutyronitrile (AIBN) afforded the same lactone **24**.

2,5-Dimethypyrrole **25**, on being treated with **2** in the presence of alumina by using method B, gave the 2,2,5-trisubstituted 2*H*-pyrrole **26** [a mixture of two diastereoisomers (*ca.* 5:1)] and the 3-alkylated product **27** in 71 and 12% yields, respectively. Exposure of **26** to alumina resulted in recovery of unchanged **26**, indicating that the pyrrole **27** was a primary product of the reaction of **25** with **2**. However, when heated in refluxing xylene **26** afforded **27** in 67% yield, a result of a [1,5]sigmatropic rearrangement to give **28**, followed by a 1,3-hydrogen shift.[11] On the other hand, treatment of **26** with sodium hydroxide in aqueous ethanol provided, *via* the carboxylate **29**, a small quantity (11%) of the bicyclic lactone **30** as a single stereoisomer, though the stereochemistry is unknown.

Several explanations might be offered for the role of alumina in effecting the present reactions. One possible mechanism would involve the carbenoid intermediate.[12] The possibility, however, may be ruled out by the fact that the chloro sulfide **4**, bearing no hydrogen atom α to the chlorine atom, functions as an excellent alkylating agent. Furthermore, no cyclopropane derivative was obtained when cyclohexene was subjected to the reaction with **3**. Another possible mechanism would involve the participation of basic and Lewis acid sites of alumina. In order

* The nuclear Overhauser effect (NOE) experiments for **22** and **23** gave unsatisfactory results.



Scheme 5

to test the possibility, *N*-methylindole was subjected to the reaction with **3** according to method A: this gave the alkylation product **31** in good yield (79%). Furthermore, similar

reaction of **3** with *N*-methylpyrrole afforded the pyrrol-2-ylacetonitrile **32** in 49% yield. Thus, no marked difference in yields of the products was observed by the *N*-substitution of indole or pyrrole. However, other π-excessive aromatics such as furan, thiophene and anisole were totally unreactive. Accordingly, we assume that the basic site of alumina plays some role in inducing proton abstraction from indole, in spite of the high yield of formation of **31**, which is probably due to the strong nucleophilicity of the enamine structure of *N*-methylindole.

In conclusion, we have shown that the α-chloro sulfides **2**–**4** react readily with a variety of indoles and pyrroles in the presence of alumina to give *C*-alkylation products. Indol-3-ylacetic acids and the corresponding acetonitriles are important subunits in many natural products and serve as valuable building blocks for complex molecules. The synthesis herein described of this class of compounds has several advantages in terms of mildness, efficiency and convenience.

Experimental

M.p.s are uncorrected. IR spectra were recorded on a JASCO-IR-A-100 spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a JEOL JNM-PMX 60 or Varian XL-300 spectrometer; solutions in $CDCl_3$. δ Values quoted are relative to Me_4Si and *J* values are given in Hz. Exact mass determinations were obtained on a Hitachi M-80 instrument at 20 eV. Column chromatography was performed on aluminium oxide 60 GF_{254} neutral (Type E) for preparative TLC (Merck No. 1092) or on silica gel 60 PF_{254} for preparative TLC (Nacalai Tesque No. 308-36) under pressure.

Chloro[*bis*(*methylthio*)]*acetonitrile* **4**.—*N*-Chlorosuccinimide (5.34 g, 0.04 mol) was added in portions to a solution of bis(methylthio)acetonitrile [13] (5.32 g, 0.04 mol) in CCl_4 (50 cm^3) at 0 °C and the mixture was stirred at room temperature for 15 h. The precipitated succinimide was filtered off and the filtrate was concentrated under reduced pressure to give **4** in quantitative yield; δ_H(60 MHz) 2.56 (6 H, s). This compound, without further purification, was used immediately in the next step or stored in a refrigerator.

General Procedure for the Reaction of 1H-*Indole* **1** *with* α-*Chloro Sulfides* **2**–**4**.—*Method A*. Neutral alumina (Merck No. 1092) (10 g) was added to a solution of indole **1** (1 mmol) and the α-chloro sulfide **2**,[5a] **3**[5b] or **4** (1.5 mmol) in hexane (50 cm^3) and the mixture was stirred for 1 min. The solvent was removed by means of a rotary evaporator under reduced pressure and the residue was allowed to stand at room temperature for 1 h with occasional shaking. Hexane–AcOEt (10:1) was added to the reaction mixture and the alumina was removed by suction. The organic phase was concentrated under reduced pressure and the residue was chromatographed on alumina [hexane–AcOEt (10:1)] to give the products **5**, **6** and **7**.

Method B. A mixture of indole **1** (1 mmol) and the α-chloro sulfide **2**, **3** or **4** (1.5 mmol) in a minimum amount of solvent was placed on a column (40 mm i.d.) of neutral alumina (Merck No. 1092) (40 g) packed in hexane–AcOEt (10:1), and the column was eluted with hexane–AcOEt (10:1) under pressure. The fraction containing product was concentrated under reduced pressure to give the products **5**, **6** and **7**. The following compounds were thus obtained.

Ethyl 1H-*Indol*-3-*yl*(*methylthio*)*acetate* **5a**. An oil (Found: M$^+$, 249.0804. $C_{13}H_{15}NO_2S$ requires *M*, 249.0822); ν_{max}(CHCl$_3$)/cm^{-1} 3490 and 1720; δ_H(60 MHz) 1.25 (3 H, t, *J* 7), 2.05 (3 H, s), 4.20 (2 H, q, *J* 7), 4.84 (1 H, s), 6.9–7.5 (4 H, m), 7.6–7.9 (1 H, m) and 8.1–8.6 (1 H, br).

Ethyl 2-*Methyl*-1H-*indol*-3-*yl*(*methylthio*)*acetate* **5b**. An oil (Found: M$^+$, 263.1004. $C_{14}H_{17}NO_2S$ requires *M*, 263.0979); ν_{max}(CHCl$_3$)/cm^{-1} 3500 and 1725; δ_H(60 MHz) 1.20 (3 H, t, *J* 7), 2.06 (3 H, s), 2.36 (3 H, s), 4.14 (2 H, q, *J* 7), 4.84 (1 H, s), 6.9–7.3 (3 H, m) and 7.5–8.2 (2 H, m).

Ethyl 5-*Methoxy*-2-*methyl*-1H-*indol*-3-*yl*(*methylthio*)*acetate* **5c**. An oil (Found: M$^+$, 293.1074. $C_{15}H_{19}NO_2S$ requires *M*, 293.1083); ν_{max}(CHCl$_3$)/cm^{-1} 3480 and 1725; δ_H(60 MHz) 1.22 (3 H, t, *J* 7), 2.07 (3 H, s), 2.37 (3 H, s), 3.80 (3 H, s), 4.17 (2 H, q, *J* 7), 4.80 (1 H, s), 6.70 (1 H, dd, *J* 9 and 2.5), 7.06 (1 H, d, *J* 9), 7.31 (1 H, d, *J* 2.5) and 7.8–8.2 (1 H, br).

Ethyl 4-*Methyl*-1H-*indol*-3-*yl*(*methylthio*)*acetate* **5d**. An oil (Found: M$^+$, 263.0949. $C_{14}H_{17}NO_2S$ requires *M*, 263.0978); ν_{max}(CHCl$_3$)/cm^{-1} 3500 and 1725; δ_H(60 MHz) 1.28 (3 H, t, *J* 7), 2.10 (3 H, s), 2.78 (3 H, s), 4.23 (2 H, q, *J* 7), 5.14 (1 H, s), 6.7–7.2 (3 H, m), 7.46 (1 H, d, *J* 2.5) and 8.0–8.5 (1 H, br).

Ethyl 4-*Chloro*-1H-*indol*-3-*yl*(*methylthio*)*acetate* **5e**. M.p. 105–107 °C (from hexane–AcOEt) (Found: C, 54.9; H, 5.0; N, 4.9. $C_{13}H_{14}ClNO_2S$ requires C, 55.0; H, 5.0; N, 4.9%); ν_{max}(CHCl$_3$)/cm^{-1} 3495 and 1725; δ_H(60 MHz) 1.30 (3 H, d, *J* 7), 2.18 (3 H, s), 4.25 (2 H, q, *J* 7), 5.52 (1 H, s), 6.9–7.4 (3 H, m), 7.55 (1 H, d, *J* 2.5) and 8.2–8.6 (1 H, br).

Ethyl 5-*Methyl*-1H-*indol*-3-*yl*(*methylthio*)*acetate* **5f**. An oil (Found: M$^+$, 263.0988. $C_{14}H_{17}NO_2S$ requires *M*, 263.0979); ν_{max}(CHCl$_3$)/cm^{-1} 3495 and 1725; δ_H(60 MHz) 1.26 (3 H, t, *J* 7), 2.07 (3 H, s), 2.43 (3 H, s), 4.21 (2 H, q, *J* 7), 4.82 (1 H, s), 6.8–7.2 (2 H, m), 7.26 (1 H, d, *J* 2.5), 7.50 (1 H, br s) and 7.9–8.4 (1 H, br).

1H-*Indol*-3-*yl*(*methylthio*)*acetonitrile* **6a**. M.p. 78–81 °C (from hexane–AcOEt) (Found: C, 65.6; H, 4.9; N, 13.9. $C_{11}H_{10}N_2S$ requires C, 65.3; H, 5.0; N, 13.85%); ν_{max}(CHCl$_3$)/cm^{-1} 3490 and 2240; δ_H(60 MHz) 2.18 (3 H, s), 5.05 (1 H, s), 6.9–7.5 (4 H, m), 7.6–7.9 (1 H, m) and 8.1–8.6 (1 H, br).

2-*Methyl*-1H-*indol*-3-*yl*(*methylthio*)*acetonitrile* **6b**. An oil (Found: M$^+$, 216.0732. $C_{12}H_{12}N_2S$ requires *M*, 216.0720); ν_{max}(CHCl$_3$)/cm^{-1} 3485 and 2240; δ_H(60 MHz) 2.33 (3 H, s), 2.46 (3 H, s), 4.99 (1 H, s), 6.9–7.4 (3 H, m) and 7.5–8.3 (2 H, m).

*5-Methoxy-2-methyl-*1H*-indol-3-yl(methylthio)acetonitrile* **6c**. An oil (Found: M^+, 246.0856. $C_{13}H_{14}N_2OS$ requires *M*, 246.0826); $\nu_{max}(CHCl_3)/cm^{-1}$ 3490 and 2240; δ_H(60 MHz) 2.29 (3 H, s), 2.39 (3 H, s), 3.83 (3 H, s), 4.96 (1 H, s), 6.76 (1 H, dd, *J* 9 and 2), 7.12 (1 H, d, *J* 9), 7.15 (1 H, d, *J* 2) and 7.9–8.3 (1 H, br).

*4-Methyl-*1H*-indol-3-yl(methylthio)acetonitrile* **6d**. M.p. 135–138 °C (from hexane–AcOEt) (Found: C, 66.8; H, 5.6; N, 12.95. $C_{12}H_{12}N_2S$ requires C, 66.6; H, 5.6; N, 12.95%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3490 and 2235; δ_H(60 MHz) 2.22 (3 H, s), 2.73 (3 H, s), 5.23 (1 H, s), 6.7–7.5 (4 H, m) and 8.0–8.6 (1 H, br).

*4-Chloro-*1H*-indol-3-yl(methylthio)acetonitrile* **6e**. M.p. 115–116 °C (from hexane–AcOEt) (Found: C, 55.7; H, 3.8; N, 11.8. $C_{11}H_9ClN_2S$ requires C, 55.8; H, 3.8; N, 11.8%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3480 and 2240; δ_H(60 MHz) 2.23 (3 H, s), 5.65 (1 H, s), 7.0–7.3 (3 H, m), 7.35 (1 H, d, *J* 2.5) and 8.2–9.0 (1 H, br).

*5-Methyl-*1H*-indol-3-yl(methylthio)acetonitrile* **6f**. An oil (Found: C, 66.5; H, 5.6; N, 12.8. $C_{12}H_{12}N_2S$ requires C, 66.6; H, 5.6; N, 12.95%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3490 and 2240; δ_H(60 MHz) 2.17 (3 H, s), 2.43 (3 H, s), 4.97 (1 H, s), 6.9–7.4 (3 H, m), 7.48 (1 H, br s) and 8.0–8.4 (1 H, br).

1H*-Indol-3-yldi(methylthio)acetonitrile* **7a**. M.p. 90.5–92 °C (from hexane–AcOEt) (Found: C, 57.8; H, 4.8; N, 11.0. $C_{12}H_{12}N_2S_2$ requires C, 58.0; H, 4.9; N, 11.3%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3490 and 2230; δ_H(60 MHz) 2.25 (6 H, s), 7.0–7.3 (3 H, s), 7.38 (1 H, d, *J* 2.5), 7.9–8.2 (1 H, m) and 8.2–8.6 (1 H, br).

*4-Methyl-*1H*-indol-3-yldi(methylthio)acetonitrile* **7d**. M.p. 155–156 °C (from hexane–AcOEt) (Found: C, 59.4; H, 5.4; N, 10.6. $C_{13}H_{14}N_2S_2$ requires C, 59.5; H, 5.4; N, 10.7%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3495 and 2230; δ_H(60 MHz) 2.33 (6 H, s), 3.03 (3 H, s), 6.7–7.4 (3 H, m), 7.66 (1 H, d, *J* 2.5) and 8.0–8.6 (1 H, br).

*5-Methyl-*1H*-indol-3-yldi(methylthio)acetonitrile* **7f**. M.p. 135.5–137 °C (from hexane–AcOEt) (Found: C, 59.4; H, 5.3; N, 10.5. $C_{13}H_{14}N_2S_2$ requires C, 59.5; H, 5.4; N, 20.7%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3490 and 2230; δ_H(60 MHz) 2.23 (6 H, s), 2.44 (3 H, s), 6.9–7.25 (2 H, m), 7.30 (1 H, d, *J* 2.5), 7.84 (1 H, br s) and 8.0–8.4 (1 H, br).

*5-Methoxy-*1H*-indol-3-yldi(methylthio)acetonitrile* **7g**. M.p. 106.5–107.5 °C (from hexane–AcOEt) (Found: C, 56.15; H, 5.1; N, 9.8. $C_{13}H_{14}N_2OS_2$ requires C, 56.1; H, 5.1; N, 10.1%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3490 and 2230; δ_H(60 MHz) 2.27 (6 H, s), 3.87 (3 H, s), 6.88 (1 H, dd, *J* 9 and 2), 7.24 (1 H, d, *J* 9), 7.38 (1 H, d, *J* 3), 7.53 (1 H, d, *J* 2) and 8.4–8.8 (1 H, br).

*7-Methoxy-*1H*-indol-3-yldi(methylthio)acetonitrile (dithyreanitrile)* **7h**. M.p. 135–136 °C (from hexane–AcOEt) (lit.,[9] 135 °C) (Found: C, 56.0; H, 5.05; N, 10.1. Calc. for $C_{13}H_{14}N_2OS_2$: C, 56.1; H, 5.1; N, 10.1%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3490 and 2230; δ_H(300 MHz) 2.29 (6 H, s), 3.96 (3 H, s), 6.70 (1 H, d, *J* 7.6), 7.10 (1 H, t, *J* 7.9), 7.45 (1 H, d, *J* 2.7), 7.67 (1 H, d, *J* 8.2) and 8.48 (1 H, br s); δ_C(75.5 MHz) 15.7, 48.2, 55.4, 102.9, 110.3, 113.7, 117.2, 120.8, 124.0, 124.9, 128.0 and 146.2. These spectral data were virtually identical with those reported in the literature.[9]

*5-Methoxy-2-methyl-*1H*-indol-3-ylacetic Acid* **8**.—Zinc dust (1 g) was added to a solution of compound **5c** (293 mg, 1 mmol) in acetic acid (1 cm^3) and the mixture was heated at 100 °C for 2 h. After the reaction mixture had been cooled it was diluted with CH_2Cl_2 (10 cm^3) and the inorganic materials were filtered off. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel [hexane–AcOEt (4:1)] to give ethyl 5-methoxy-2-methyl-1*H*-indol-3-ylacetate[14] (180 mg, 73%). To a solution of this compound (178 mg, 0.72 mmol) in EtOH (10 cm^3) was added NaOH solution (6 mol dm^{-3}; 1 cm^3) and the mixture was stirred at room temperature for 3 h. EtOH was evaporated off, the residue was diluted with water (3 cm^3), and the whole was acidified with HCl (6 mol dm^{-3}). The precipitates were collected and recrystallised from hexane–AcOEt to give the title compound **8** (143 mg, 91%), m.p. 160.5–161.5 °C (lit.,[15] 161–162 °C).

*4-Chloro-*1H*-indol-3-ylacetic Acid* **9**.—According to the procedure for the preparation of compound **8**, compound **5e** (283 mg, 1 mmol) was desulfurised with zinc dust in acetic acid and saponified with NaOH to give the title compound **9** (144 mg, 69% based on **5e**), m.p. 185–187 °C (lit.,[8] 185–187 °C).

Ethyl 1H*-Pyrrol-2-yl(methylthio)acetate* **11** *and Diethyl* 1H*-Pyrrol-2,5-diylbis[(methylthio)acetate]* **12**.—Following method A, the pyrrole **10** (67 mg, 1 mmol) was allowed to react with the α-chloro sulfide **2** (169 mg, 1 mmol) in the presence of alumina, and the crude material was purified by chromatography on silica gel [hexane–AcOEt (10:1)].

The first fraction gave **11** (97 mg, 49%) as an oil (Found: M^+, 199.0679. $C_9H_{13}NO_2S$ requires *M*, 199.0666); $\nu_{max}(CCl_4)/cm^{-1}$ 3475 and 1730; δ_H(60 MHz) 1.26 (3 H, t, *J* 7), 2.04 (3 H, s), 4.20 (2 H, q, *J* 7), 4.55 (1 H, s), 6.0–6.25 (2 H, m), 6.75 (1 H, dd, *J* 3 and 2) and 8.45–9.45 (1 H, br).

The second fraction gave **12** (30 mg, 9%) as an oil (Found: M^+, 331.0886. $C_{14}H_{21}NO_4S_2$ requires *M*, 331.0910); $\nu_{max}(CCl_4)/cm^{-1}$ 3445 and 1735; δ_H(60 MHz) 1.31 (6 H, t, *J* 7), 2.07 (6 H, s), 4.23 (4 H, q, *J* 7), 4.52 (2 H, s), 6.05 (2 H, d, *J* 3) and 9.0–9.6 (1 H, br).

1H*-Pyrrol-2-yl(methylthio)acetonitrile* **13**.—Following method A, the pyrrole **10** (134 mg, 2 mmol) was allowed to react with the α-chloro sulfide **3** (122 mg, 1 mmol) in the presence of alumina, and the crude material was purified by chromatography on silica gel [hexane–AcOEt (10:1)] to give **13** (117 mg, 77%), m.p. 36.0–36.5 °C (from hexane–AcOEt) (Found: C, 55.2; H, 5.3; N, 18.2. $C_7H_8N_2S$ requires C, 55.2; H, 5.3; N, 18.4%); $\nu_{max}(CCl_4)/cm^{-1}$ 3480 and 2245; δ_H(60 MHz) 2.16 (3 H, s), 4.85 (1 H, s), 6.05–6.40 (2 H, m), 6.81 (1 H, dd, *J* 3 and 2) and 7.75–9.0 (1 H, br).

Reactions of 3*-Methyl-*1H*-indoles* **14** *and* **17** *with the α-Chloro Sulfides* **2** *or* **3**.—By using method A, skatole **14** (131 mg, 1 mmol) or 2,3-dimethylindole **17** (145 mg, 1 mmol) was allowed to react with **2** (337 mg, 2 mmol) or **3** (182 mg, 1.5 mmol), and the crude material was purified by chromatography on silica gel [hexane–AcOEt (5:1)] to give the following alkylation products.

*Ethyl 3-Methyl-*1H*-indol-2-yl(methylthio)acetate* **15**. An oil (Found: M^+, 263.0954. $C_{14}H_{17}NO_2S$ requires *M*, 263.0978); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 and 1720; δ_H(60 MHz) 1.27 (3 H, t, *J* 7), 2.05 (3 H, s), 2.29 (3 H, s), 4.22 (2 H, q, *J* 7), 4.82 (1 H, s), 6.75–7.7 (4 H, m) and 8.7–9.1 (1 H, br).

*3-Methyl-*1H*-indol-2-yl(methylthio)acetonitrile* **16**. An oil (Found: C, 66.6; H, 5.75; N, 12.6. $C_{12}H_{12}N_2S$ requires C, 66.6; H, 5.6; N, 12.95%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3460 and 2240; δ_H(60 MHz) 2.23 (3 H, s), 2.32 (3 H, s), 4.97 (1 H, s), 7.0–7.7 (4 H, m) and 8.0–8.5 (1 H, br).

*Ethyl 2,3-Dimethyl-*3H*-indol-3-yl(methylthio)acetate* **18**. An oil (Found: M^+, 277.1137. $C_{15}H_{19}NO_2S$ requires *M*, 277.1136); $\nu_{max}(CHCl_3)/cm^{-1}$ 1725; δ_H(60 MHz) 0.98 and 1.13 (total 3 H, both t, *J* 7), 1.43 and 1.48 (total 3 H, both s), 2.08 and 2.17 (total 3 H, both s), 2.38 (3 H, s), 3.60 (1 H, s), 3.92 and 4.08 (total 2 H, both q, *J* 7) and 6.95–7.7 (4 H, m).

*2,3-Dimethyl-*3H*-indol-3-yl(methylthio)acetonitrile* **19**. An oil (Found: C, 67.5; H, 6.0; N, 11.9. $C_{13}H_{14}N_2S$ requires C, 67.8; H, 6.1; N, 12.2%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2240; δ_H(60 MHz) 1.53 (3 H × 1/4, s), 1.57 (3 H × 3/4, s), 1.93 (3 H × 3/4, s), 2.13 (3 H × 1/4, s), 2.30 (3 H × 3/4, s), 2.43 (3 H × 1/4, s), 3.83 (3/4 H, s), 3.87 (1/4 H, s) and 7.0–7.8 (4 H, m).

*2,3-Dihydro-3-methyl-2-methylene-*1H*-indol-3-yl(methylthio)acetonitrile* **20**. An oil (Found: M^+, 230.0859. $C_{13}H_{14}N_2S$

requires *M*, 230.0876); $\nu_{max}(CHCl_3)/cm^{-1}$ 3480 and 2230; δ_H(60 MHz) 1.53 (3 H × 3/4, s), 1.95 (3 H × 1/4, s), 2.28 (3 H × 1/4, s), 2.35 (3 H × 3/4, s), 3.60 (3/4 H, s), 3.80 (1/4 H, s), 5.13 (1 H, s), 5.57 (1 H, s) and 6.6–7.8 (5 H, m).

8,8a-*Dihydro*-3a,8a-*dimethyl*-3-(*methylthio*)-3a*H*-*furo*[2,3-b]*indol*-2(3*H*)-*ones* **22** *and* **23**.—To a solution of **18** (412 mg, 1.498 mmol) in EtOH (10 cm^3) was added NaOH solution (6 mol dm^{-3}; 2 cm^3) and the mixture was stirred at room temperature for 15 h. After EtOH had been evaporated off, water (5 cm^3) was added to the residue and the whole was acidified with HCl (6 mol dm^{-3}). The aqueous solution was extracted with CH_2Cl_2 and the extract was concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane–AcOEt (2:1)].

The first fraction gave the lactone **23** (145 mg, 39%), m.p. 114.5–115.5 °C (from hexane–AcOEt) (Found: C, 62.5; H, 6.1; N, 5.4. $C_{13}H_{15}NO_2S$ requires C, 62.6; H, 6.1; N, 5.6%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3440 and 1755; δ_H(60 MHz) 1.33 (3 H, s), 1.80 (3 H, s), 2.37 (3 H, s), 3.72 (1 H, s), 4.3–5.1 (1 H, br) and 6.5–7.3 (4 H, m).

The second fraction gave the isomeric lactone **22** (212 mg, 57%), m.p. 131.5–133 °C (from hexane–AcOEt) (Found: C, 62.3; H, 6.0; N, 5.3); $\nu_{max}(CHCl_3)/cm^{-1}$ 3425 and 1755; δ_H(60 MHz) 1.43 (3 H, s), 1.65 (3 H, s), 2.28 (3 H, s), 3.60 (1 H, s), 3.8–4.7 (1 H, br), 6.5–7.3 (3 H, m) and 7.53 (1 H, dd, *J* 7 and 2).

3,3a,8,8a-*Tetrahydro*-3a,8a-*dimethylfuro*[2,3-b]*indol*-2-*one* **24**.—*From* **22**. To a boiling solution of **22** (126 mg, 0.51 mmol) in benzene (8 cm^3) was added a mixture of Bu_3SnH (227 mg, 0.77 mmol) and AIBN (13 mg, 0.77 mmol) in benzene (4 cm^3), and heating was continued for 3 h. After completion of reaction, the solvent was evaporated off and the residue was chromatographed on silica gel [hexane–AcOEt (2:1)] to give **24** (39 mg, 38%), m.p. 102–104 °C (from hexane–AcOEt) (Found: M^+, 203.0970. $C_{12}H_{13}NO_2$ requires *M*, 203.0946); $\nu_{max}(CHCl_3)/cm^{-1}$ 3440; δ_H(60 MHz) 1.33 (3 H, s), 1.69 (3 H, s), 2.75 and 3.00 (1 H each, AB q, *J* 17), 4.85 (1 H, br s) and 6.6–7.3 (4 H, m).

From **23**. In a fashion similar to that described above for the reaction of **22**, compound **23** (50 mg, 0.2 mmol) was treated with Bu_3SnH and AIBN to give **24** (5 mg, 13%) which was identical with that obtained from **22**.

Ethyl 2,5-*Dimethyl*-α-*methylthio*-2H-*pyrrol*-2-*ylacetate* **26** *and Ethyl* 2,5-*Dimethyl*-α-*methylthio*-1H-*pyrrol*-3-*ylacetate* **27**.—Following method B, a mixture of 2,5-dimethylpyrrole **25** (190 mg, 2 mmol) and the α-chloro sulfide **2** (169 mg, 1 mmol) was passed through a column of alumina using hexane–AcOEt (7:1) as eluent.

The first fraction gave **27** (27 mg, 12%) as an oil (Found: M^+, 227.0997. $C_{11}H_{17}NO_2S$ requires *M*, 227.0979); $\nu_{max}(CCl_4)/cm^{-1}$ 3480, 3390 and 1730; δ_H(60 MHz) 1.29 (3 H, t, *J* 7), 2.11 (3 H, s), 2.20 (6 H, s), 4.18 (2 H, q, *J* 7), 4.43 (1 H, s), 5.93 (1 H, d, *J* 3) and 7.3–7.85 (1 H, br).

The second fraction gave **26** (162 mg, 71%) as an oil (Found: M^+, 227.0971); $\nu_{max}(CCl_4)/cm^{-1}$ 1730 and 1620; δ_H(60 MHz) 1.33 (3 H, t, *J* 7), 1.37 and 1.45 (total 3 H, both s), 2.10 (3 H, s), 2.20 and 2.27 (total 3 H, both s), 3.46 and 3.63 (total 1 H, both s), 4.25 (2 H, q, *J* 7), 6.30 (1 H, d, *J* 5) and 7.48 (1 H, d, *J* 5).

Thermolysis of **26**.—A solution of **26** (163 mg, 0.72 mmol) in xylene (5 cm^3) was heated under reflux for 1 h. The solvent was evaporated off and the residue was chromatographed on silica gel [hexane–AcOEt (5:1)] to give **27** (110 mg, 67%), which was identical with that obtained by the reaction of **25** and **2**.

6,6a-*Dihydro*-3a,5-*dimethyl*-3-*methylthio*-3a*H*-*furo*[3,2-b]-*pyrrol*-2-(3*H*)-*one* **30**.—To a solution of **26** (112 mg, 0.49 mmol) in EtOH (2 cm^3) and water (1 cm^3) was added NaOH (59 mg, 1.47 mmol), and the mixture was heated under reflux for 3 h. The reaction mixture was diluted with water (10 cm^3), neutralised with HCl (10%) and then extracted with CH_2Cl_2. The organic phase was concentrated and the residue was chromatographed on silica gel [hexane–AcOEt (1:2)] to give **30** (11 mg, 11%) as an oil (Found: M^+, 199.0646. $C_9H_{13}NO_2S$ requires *M*, 199.0665); $\nu_{max}(CCl_4)/cm^{-1}$ 1785; δ_H(60 MHz) 1.43 (3 H, s), 2.06 (3 H, s), 2.33 (3 H, s), 2.86 (2 H, d, *J* 3), 3.42 (1 H, s) and 4.62 (1 H, t, *J* 3).

1-*Methyl*-1H-*indol*-3-*yl*(*methylthio*)*acetonitrile* **31**.—Following method A, 1-methyl-1*H*-indole (131 mg, 1 mmol) was allowed to react with the α-chloro sulfide **3** (182 mg, 1.5 mmol) and the crude material was purified by chromatography on alumina [hexane–AcOEt (10:1)] to give **31** (171 mg, 79%), m.p. 64–65 °C (from hexane–AcOEt) (Found: C, 66.8; H, 5.7; N, 12.7. $C_{12}H_{12}N_2S$ requires C, 66.6; H, 5.6; N, 12.95%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2240; δ_H(60 MHz) 2.17 (3 H, s), 3.65 (3 H, s), 4.93 (1 H, s), 7.0–7.4 (4 H, m) and 7.5–7.8 (1 H, m).

1-*Methyl*-1H-*pyrrol*-2-*yl*(*methylthio*)*acetonitrile* **32**.—Following method A, 1-methyl-1*H*-pyrrole (162 mg, 2 mmol) was allowed to react with the α-chloro sulfide **3** (169 mg, 1 mmol) and the crude material was purified by chromatography on silica gel [hexane–AcOEt (10:1)] to give **32** (104 mg, 49%), m.p. 56–56.5 °C (from hexane–AcOEt) (Found: C, 57.5; H, 6.0; N, 16.7. $C_8H_{10}N_2S$ requires C, 57.8; H, 6.1; N, 16.85%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2240; δ_H(60 MHz) 2.16 (3 H, s), 3.62 (3 H, s), 4.80 (1 H, s), 6.08 (1 H, dd, *J* 4 and 2), 6.34 (1 H, dd, *J* 4 and 2) and 6.67 (1 H, t, *J* 2).

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