Sythesis of Heteroaromatic Ketene Dithioacetals

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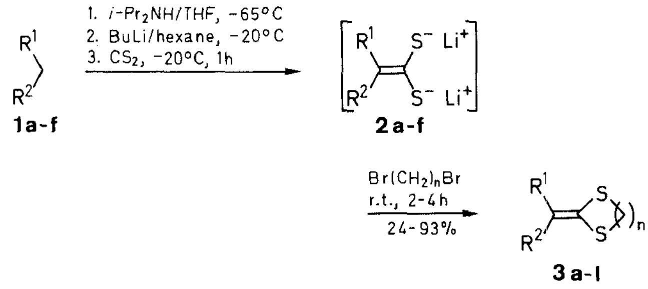
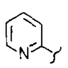
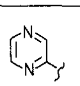
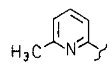
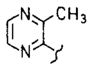
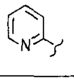
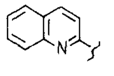
Reaction of 2-methylpyridine with, successively, lithium diisopropylamide, carbon disulphide, and 1,2-dibromoethane or 1,3-dibromopropane, gives 2-(2-pyridylmethylene)dithiolane or 2-(2-pyridylmethylene)dithiane. Analogous reactions of 2-methylpyrazine, 2-methylquinoline, 2,6-dimethylpyridine and 2,3-dimethylpyrazine are reported.

Ketene dithioacetals **3**[1] are very useful in organic synthesis, particularly when one of the substituents, R^1, R^2 is a conjugated multiply bonded group such as acyl[2,3] or cyano.[3] Surprisingly, no compounds **3** in which R^1 is pyridyl or a related heterocyclic group and R^2 is H have been reported. A few analogues where R^1 is pyridyl and R^2 is CN were described after our work was completed.[4] We were interested in such compounds as intermediates for further syntheses and also as ligands possessing both hard and soft donor atoms.

We have prepared several 2-pyridyl, 2-pyrazinyl, and 2-quinolinyl ketene dithioacetals by the route shown in the Scheme.

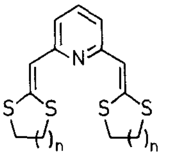


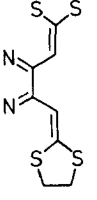
1, 2	R^1	R^2	1, 2	R^1	R^2
a		H	d		H
b		H	e		H
c		Ph	f		H

Scheme

A 2-methylpyridine, -pyrazine, or -quinoline **1** was deprotonated by means of two equivalents of lithium diisopropylamide (LDA). Reaction of the resulting "carbanion" with carbon disulphide gave a dithiolate **2**, which was cycloalkylated by 1,2-dibromoethane, or 1,3-dibromopropane, to give the required compounds **3**. Analogous compounds **3** were also prepared from 2-benzylpyridine.

In the cases of 2,6-dimethylpyridine (**1b**) and 2,3-dimethylpyrazine (**1e**), mixtures of mono- **3** and bis-(ketene dithioacetals), **4** and **6**, were obtained. For the reactions of these starting materials the effect of varying the proportions of the reactants was briefly investigated. In the case of 2,3-dimethylpyrazine (**1e**), reducing the proportions of LDA, carbon disulphide, and 1,2-bromoethane to those given in the general method gave the monosubstituted product **3i** in high yield; the analogous reaction with 1,3-dibromopropane gave a slightly improved yield (37%) of compound **3j**. On the other hand, when a reaction of 2,6-dimethylpyridine (**1b**) was carried out using the proportions of LDA, carbon disulphide and 1,3-dibromopropane given in the general method, a little of the disubstituted compound **5** was still obtained, together with a compound which was not fully characterised but was identified by ^{1}H-NMR [δ = 2.25 (quint, 2H, J = 6.5 Hz, CH_2), 2.54 (s, 3H, CH_3), 3.28 (t, 2H, J = 7 Hz, $5CH_2$), 3.46 (t, 2H, J = 6.5 Hz, CH_2Br), 5.67 (s, 2H, CH_2CS), 7.09 (d, 1H, J = 6 Hz, H-5), 7.16 (d, 1H, J = 6 Hz, H-3), 7.58 (d, 1H, J = 6 Hz, H-4)] and MS (CI, $[M + NH_4]^+$ at m/z = 320 and 322) as the dithioester **7** (16%).


4 n = 1
5 n = 2


6

7

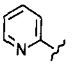
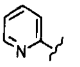
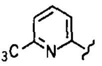
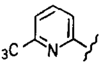
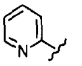
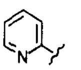
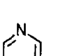
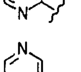
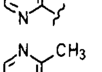
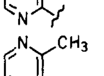
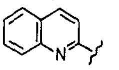
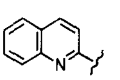
Although most of the products were crystalline solids, they discoloured on standing and were difficult to obtain analytically pure. In the cases of some of the lower-melting compounds, satisfactory elemental analyses could not be obtained, although they appeared to be homogeneous by NMR and TLC; in these cases, accurate mass measurement of their molecular ions confirmed their identities.

All reagents and solvents were of commercial quality. i-Pr_2NH was distilled from KOH and stored over molecular sieves. The methyl heterocycles were redistilled and stored over KOH. THF was distilled from benzophenone ketyl immediately before use. BuLi in hexane was obtained from Lithium Corporation of Europe and standardised by titration with diphenylacetic acid. Elemental analyses were carried out by Butterworth Laboratories Ltd.

Synthesis of Heteroaromatic Ketene Dithioacetals 3; General Procedure:

A dry, 1 L three-necked flask is equipped with a mechanical stirrer, a low-temperature thermometer, and a pressure-equalising dropping funnel, and furnished with an atmosphere of dry Ar. The flask is charged with i-Pr_2NH (189 mmol) and dry THF (300 mL) and the solution is cooled to − 65°C. The temperature is kept below − 20°C as BuLi (ca. 1.5 M in hexane, 189 mmol) is added and the mixture is stirred for 20 min. A methylazine (86 mmol) is added, and the resulting yellow or orange suspension is stirred for 45 min. CS_2 (189 mmol) is added dropwise during 10 min and stirring is continued for 1 h. The appropriate dibromoalkane (189 mmol) is added, and the mixture is stirred at r.t. for 2 to 4 h. Wet Et_2O (50 mL) is added cautiously, and the solvents are removed by rotary evaporator. The residue is dissolved in $CHCl_3$ (100 mL), and the solution is washed successively with 0.5 M

Table. Heteroaromatic Ketene Dithioacetals **3** Prepared

3	R^1	R^2	n	Yield (%)	mp (°C)	Molecular Formula[a]	^{1}H-NMR (300 MHz, $CDCl_3$/TMS) δ, J(Hz)
a		H	2	57	97–98	$C_9H_9NS_2$ (195.2)	3.31 (m, 2H, SCH_2), 3.44 (m, 2H, SCH_2), 6.70 (s, 1H, =CH), 6.96 (m, 1H, H-5), 7.03 (dd, 1H, J = 9, 1, H-3), 7.54 (dt, 1H, J = 8, 2, H-4), 8.60 (dt, J = 5, 1, H-6)
b		H	3	66	45–46	$C_{10}H_{11}NS_2$ (209.2)	2.06 (quint, 2H, J = 6.5, CH_2), 2.86 (t, 2H, J = 6.5, SCH_2), 2.90 (t, 2H, J = 6.5, SCH_2), 6.73 (s, 1H, =CH), 6.90 (ddd, 1H, J = 5, 1, 1, H-5), 7.08 (d, 1H, J = 8, H-3), 7.45 (dt, 1H, J = 8, 2, H-4), 8.49 (d, 1H, J = 5, H-6)
c		H	2	24.5[b]	oil	$C_{10}H_{11}NS_2$ (209.2)	2.55 (s, 3H, CH_3), 3.25 (m, 2H, SCH_2), 3.38 (m, 2H, SCH_2), 6.68 (s, 1H, =CH), 6.72 (d, 1H, J = 8, H-3 or H-5), 6.84 (d, 1H, J = 8, H-5 or H-3), 7.41 (t, 1H, J = 8, H-4)
d		H	3	28[c]	oil	$C_{11}H_{13}NS_2$ (223.2)	2.16 (quint, 2H, J = 7, CH_2), 2.53 (s, 3H, CH_3), 2.94 (t, 2H, J = 7, SCH_2), 2.99 (t, 2H, J = 7, SCH_2), 6.81 (s, 1H, =CH), 6.85 (d, 1H, J = 8, H-3 or H-5), 7.00 (d, 1H, J = 8, H-5 or H-3), 7.44 (t, 1H, J = 8, H-4)
e		Ph	2	93	137–138	$C_{15}H_{13}NS_2$ (271.3)	3.23 (m, 2H, SCH_2), 3.41 (m, 2H, SCH_2), 6.68 (dt, 1H, J = 7, 1, H-$3_{pyridyl}$), 6.98 (ddd, 1H, J = 8.5, 5, 1, H-$5_{pyridyl}$), 7.2–7.5 (m, 6H, $5H_{phenyl}$ + H-$4_{pyridyl}$), 8.65 (ddd, 1H, J = 5, 1, 1, H-$6_{pyridyl}$)
f		Ph	3	88	104–105	$C_{16}H_{15}NS_2$ (285.3)	2.12 (quint, 2H, J = 7, CH_2), 2.93 (t, 2H, J = 7, SCH_2), 2.95 (t, 2H, J = 7, SCH_2), 6.83 (dt, 1H, J = 7, 1, H-$3_{pyridyl}$), 7.06 (ddd, 1H, J = 7, 5, 1, H-$5_{pyridyl}$), 7.2–7.4 (m, 5H, Ph), 7.49 (dt, 1H, J = 8, 2, H-$4_{pyridyl}$), 8.63 (ddd, 1H, J = 5, 2, 1, H-$6_{pyridyl}$)
g		H	2	63	122–123	$C_8H_8N_2S_2$ (196.2)	3.34 (m, 2H, SCH_2), 3.47 (m, 2H, SCH_2), 6.71 (s, 1H, 1H, =CH), 8.18 (d, 1H, J = 2.5, H-6), 8.33 (d, 1H, J = 1.5, H-3), 8.51 (dd, 1H, J = 2.5, 1.5, H-5)
h		H	3	73	62–63	$C_9H_{10}N_2S_2$ (210.2)	2.15 (quint, 2H, J = 7, CH_2), 2.98 (t, 2H, J = 7, SCH_2), 3.02 (t, 2H, J = 7, SCH_2), 6.79 (s, 1H, =CH), 8.22 (d, 1H, J = 2.5, H-6), 8.43 (d, 1H, J = 1.5, H-3), 8.51 (dd, 1H, J = 2.5, 1.5, H-5)
i		H	2	–[d]	80–81	$C_9H_{10}N_2S_2$ (210.2)	2.53 (s, 3H, CH_3), 3.33 (t, 2H, J = 6, SCH_2), 3.43 (m, 2H, J = 6, SCH_2), 6.83 (s, 1H, =CH), 8.08 (d, J = 2, 1H), 8.37 (d, J = 2, 1H)
j		H	3	28	oil	$C_{10}H_{12}N_2S_2$ (224.2)	2.21 (quint, 2H, J = 7, CH_2), 2.54 (s, 3H, CH_3), 2.96 (t, 2H, J = 7, SCH_2), 3.05 (t, 2H, J = 7, SCH_2), 8.15 (d, J = 2.5, 1H), 8.38 (d, J = 2.5, 1H)
k		H	2	69	96–97	$C_{13}H_{11}NS_2$ (245.2)	3.34 (m, 2H, SCH_2), 3.48 (m, 2H, SCH_2), 6.8 (s, 1H, =CH), 7.16 (d, 1H, J = 8.5, H-3), 7.39 (dt, 1H, J = 7, 1, H-6), 7.65 (m, 2H, H-5 and H-7), 7.96 (d, 1H, J = 9, H-8), 8.07 (d, 1H, J = 8.5, H-4)
l		H	3	63	80–81	$C_{14}H_{13}NS_2$ (259.3)	2.15 (quint, 2H, J = 6.5, CH_2), 2.96 (t, 2H, J = 6.5, SCH_2), 2.98 (t, 2H, J = 6.5, SCH_2), 6.96 (s, 1H, =CH), 7.23 (d, 1H, J = 8.5, H-3), 7.38 (dt, 1H, J = 7, 1, H-6), 7.63 (m, 2H, H-5 and H-7), 7.93 (d, 1H, J = 8.5, H-8), 8.06 (d, 1H, J = 8.5, H-4)

[a] Satisfactory microanalyses (C ±0.45, H ±0.10, N ±0.20) or HRMS (m/z ±0.0008) obtained.

[b] Together with compound **4** (36%); mp 105–106°C; ^{1}H-NMR ($CDCl_3$/TMS): δ = 3.31 (m, 4H, SCH_2), 3.47 (m, 4H, SCH_2), 6.77 (s, 2H, =CH), 6.98 (d, 2H, J = 8 Hz, H-3 and H-5), 7.51 (t, 1H, J = 8 Hz, H-4)

[c] Together with compound **5** (7%); oil; ^{1}H-NMR ($CDCl_3$/TMS): δ = 2.13 (quint, 4H, J = 6.5 Hz, CH_2), 2.91 (t, 4H, J = 6.5 Hz, SCH_2), 2.97 (t, 4H, J = 6.5 Hz, SCH_2), 6.86 (s, 1H, =CH), 7.11 (d, 2H, J = 8 Hz, H-3–H-5), 7.49 (t, 1H, J = 8 Hz, H-4).

[d] Compound **6** (42%); mp 189–190°C; ^{1}H-NMR ($CDCl_3$/TMS): δ = 3.33 (m, 4H, SCH_2), 3.41 (m, 4H, SCH_2), 6.92 (s, 2H, =CH), 8.23 (s, 2H, pyrazine H-5 and H-6). For conditions giving compound **3i**, see text.

H_2SO_4 (50 mL), H_2O (50 mL), and brine (50 mL). The aqueous layer is basified with 4 M NaOH and extracted with $CHCl_3$ (50 mL). The combined organic solutions are washed with brine (50 mL), dried ($MgSO_4$) and concentrated by rotary evaporation. The residue is subjected to column chromatography (silica gel, light petroleum/EtOAc) and recrystallised.

For the reactions with 2,6-dimethylpyridine and 2,3-dimethylpyrazine whose results are summarised in the Table the proportion of the heterocyclic starting material to the other reagents is halved. The results of experiments using the proportions of reagents given above are discussed in the main text.

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