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CYCLOCONDENSATION OF OXOKETENE DITHIOACETALS WITH 3-AMINOPYRAZOLES: A FACILE HIGHLY REGIOSELECTIVE GENERAL ROUTE TO SUBSTITUTED AND FUSED PYRAZOLO[a]PYRIMIDINES

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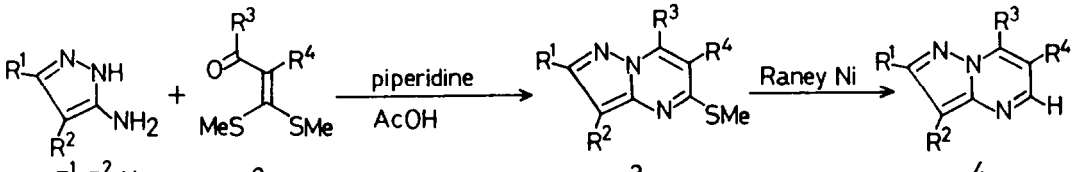
Abstract: Cyclocondensation of 3-aminopyrazole (1a) and 3-amino-5-methylthio-4-phenylpyrazole (1b) with α-oxoketene dithioacetals (2a-j) derived from acyclic active methylene ketones affords 5-methylthio-6,7-substituted pyrazolo[1,5-a]pyrimidines (3a-j) exclusively. The reaction was found to be equally successful for the synthesis of 7-styryl,7-(4-aryl-1,3-butadienyl) and 7-(6-aryl-1,3,5-hexatrienyl)pyrazolopyrimidines (7a-f) from the respective enoylketene dithioacetals (6a-f). Similarly, the reaction of 1a and 1b with cyclic and benzocyclic ketene dithioacetals also afforded the angularly fused 5-methylthiopyrazolo pyrimidines regioselectively in good yields. However the oxoketene dithioacetal from cyclopentanone yielded both angularly and linearly fused regioisomers 10 and 11 respectively in nearly equal amounts. Some of the 5-methylthiopyrazolopyrimidines were dethiomethylated with Raney nickel to afford 5-unsubstituted derivatives in good yields.

Azolo[a]pyrimidines are purine analogs which are shown to be of considerable chemical and pharmacological importance[1,2]. The reported methods for the synthesis of these class of heterocycles usually involve cyclocondensation of aminoazoles with three carbon 1,3-electrophilic fragments such as β-ketoesters, β-diketones, β-ketoaldehydes or their enolethers and acetals[3-5]. However, very often these reactions result in regioisomeric mixtures of azolo[a] pyrimidines[4]. Besides, these methods do not offer much scope for substituent variation and structural modification because of the limited choice of β-dicarbonyl derivatives employed in these reactions. The lack of regioselectivity in these reactions appears to stem from the competitive reactivity of the 1,3-electrophilic centres in the three carbon fragments. In principle, it should, therefore, be possible to suitably modify the electrophilic centres by appropriate functional groups so that the asymmetric binucleophiles attack preferentially only one specific electrophilic carbon atom of 3-carbon components. We recently demonstrated that the ambident binucleophile such as hydroxylamine reacts with α-oxoketene dithioacetals to yield highly regioselective either 5-methylthio or 3-methylthioisoxazoles depending on the pH conditions of the reaction medium[6]. It was therefore considered that the reactivity of α-oxoketene dithioacetals with aminoazoles might result in improved regioselectivity yielding only one regioisomer under a particular reaction condition. We have examined this regioselectivity through the reaction of 3-aminopyrazoles with α-oxoketene dithioacetals,

which yield only one regioisomeric pyrazolo[1,5-a]pyrimidines in high yields. Besides, the easy availability of oxoketene dithioacetals from a variety of acyclic and cyclic active methylene ketones offers much scope for substituent and structural flexibility in azolo[a] pyrimidines. We have successfully realized these goals and the results are described in the present paper[7].

RESULTS AND DISCUSSION

The required oxoketene dithioacetals 2a-j, 6a-f, 9a-c, 15a-d and 19a,b derived from both acyclic and cyclic active methylene ketones were prepared according to the earlier reported procedures[8-10]. In a typical experiment, equimolar quantities of 2a and 3-amino-pyrazole (1a) were refluxed in acetic acid in the presence of catalytic amount of piperidine, the product isolated after work-up was characterized as 7-methyl-5-methylthiopyrazolo[1,5-a] pyrimidine (3a) (Scheme 1). The structure and regiochemistry of 3a was established with the help of spectral and analytical data and by its Raney nickel desulphurization to the known[11] 7-methylpyrazolo[1,5-a]pyrimidine (4a), thus ruling out the regioisomeric 5-methyl-7-methyl-thio structure 5 (R^1, R^2, R^4 = H; R^3 = Me). The physical and spectral data of desulphurized pyrimidine 4a was identical in all respects with that reported in the literature[3]. In the

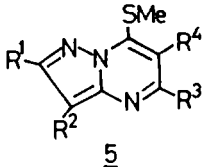


1a R^1=R^2=H 2

b R^1=SMe; R^2=C_6H_5

3 4

2,3	R^1	R^2	R^3	R^4
a,4a	H	H	Me	H
b	H	H	4-ClC_6H_4	H
c	H	H	2-thienyl	H
d,4b	H	H	2-furyl	H
e,4c	H	H	Et	Me
f	H	H	C_6H_5	C_6H_5CO
g	SMe	C_6H_5	Me	H
h	SMe	C_6H_5	4-$MeOC_6H_4$	H
i	SMe	C_6H_5	Me	n-C_4H_9
j	SMe	C_6H_5	C_6H_5	Me
4d	H	C_6H_5	Me	H
4e	H	C_6H_5	4-$MeOC_6H_4$	H

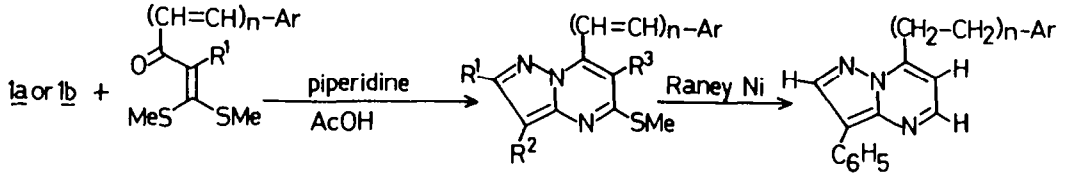


5

Scheme 1

^{1}H n.m.r. spectra of 3a and 4a, the methyl signal was broadened due to allylic coupling with H-6 proton. The ^{13}C n.m.r. spectrum of 3a was also in agreement with the assigned regioisomer. Similarly, the other substituted pyrazolopyrimidines (3b-f) were obtained exclusively in high yields from the corresponding dithioacetals (2b-f) and 1a. A few of the dithioacetals (2g-j) were also reacted with 3-amino-4-phenyl-5-methylthiopyrazoles (1b) to afford the corresponding 2,5-bis(methylthio)-3-phenylpyrazolo[1,5-a]pyrimidines (3g-j) in 78-93% overall yields. In all these cases, only the 5-methylthio regioisomers were obtained which were supported by desulphurization of selected pyrazolopyrimidines (3d, 3e, 3g and 3h) to the respective 4b-e. In the ^{1}H n.m.r. spectra of 4b, 4d and 4e, the observed coupling constant (4.5Hz)between H-5 and H-6 proton was consistent with the reported values[3]. Besides, the signals due to 7-methyl and H-6 protons were found to be broadened in 3g and 4d due to long range coupling[3]. On the otherhand, the H-5 proton signal in 4c appeared as sharp singlet at δ 8.28 which is not expected of H-7 proton in the regioisomeric 5-ethyl-6-methyl-pyrazolopyrimidine.

The reaction was found to be equally facile for the synthesis of 7-styryl-(7a,b), 7-(4-aryl-1,3-butadienyl)-(7c,d) and 7-(6-aryl-1,3,5-hexatrienyl)-(7e-f)pyrazolopyrimidines, when the corresponding enoylketene dithioacetals (6a-f) were reacted either with 1a or 1b under identical conditions. The structures of 7a-f were confirmed by their spectral and analytical data. The regiochemical assignment of 7a-f was supported by the observed coupling constants (4.5Hz) between H-5 and H-6 protons in the ^{1}H n.m.r. spectra of reduced pyrimidines 8a and 8b obtained by Raney nickel treatment of 6a and 6f respectively (Scheme 2).

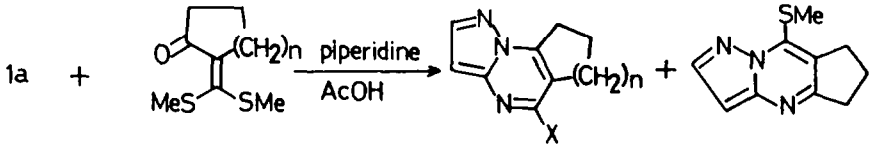


6 7 8a Ar=4-MeOC$_6$H$_4$;n=1 b Ar=C$_6$H$_5$;n=3

6,7	R^1	R^2	R^3	Ar	n
a	SMe	C$_6$H$_5$	H	4-MeOC$_6$H$_4$	1
b	H	H	Me	3,4-CH$_2$O$_2$C$_6$H$_3$	1
c	SMe	C$_6$H$_5$	H	C$_6$H$_5$	2
d	H	H	Me	C$_6$H$_5$	2
e	H	H	H	4-MeOC$_6$H$_4$	3
f	SMe	C$_6$H$_5$	H	C$_6$H$_5$	3

Scheme 2

When 1a was reacted with cyclic ketene dithioacetals 9a–c, the corresponding 9b and 9c afforded the expected 5-methylthio-6,7,8,9-tetrahydropyrazolo[1,5-a]quinazoline (12) and cyclohepta[e]pyrazolopyrimidine (13) respectively, while the dithioacetal (9a) derived from cyclopentanone yielded a mixture of both angular and linearly fused pyrimidines 10 and 11 respectively (Scheme 3). The structure and regiochemistry of 10–13 were confirmed on the basis of their spectral data and also by Raney nickel desulphurization of 12 to 14 which



9a n=1
b n=2
c n=3

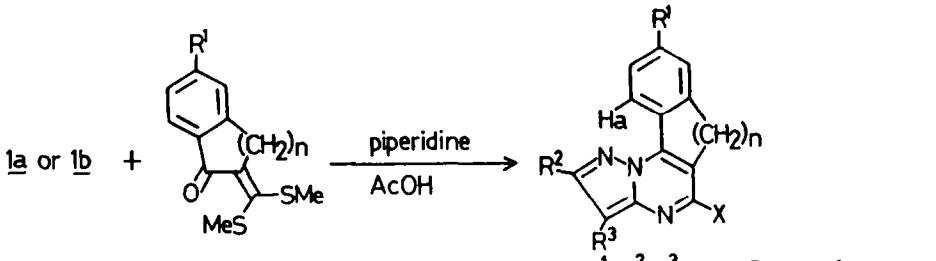
10 X=SMe, n=1
12 X=SMe, n=2
13 X=SMe, n=3
14 X=H, n=2

11

Scheme 3

displayed a sharp singlet at δ 8.28 due to H-5 proton in its ^{1}H n.m.r. spectrum thus showing absence of any long range coupling. The ^{13}C n.m.r. spectra of 10–13 further supported the structure as they showed chemical shifts values very similar to those reported for the corresponding 3-cyano analogs[3]. Also, in the ^{1}H n.m.r. spectrum of 10, the signals due to 6- and 8- methylene protons appeared as broad triplets at δ 2.88 and 3.31 due to long range coupling between methylene protons, while 11 showed signals due to 5 and 7-methylene protons as partially overlapping sharp triplets at δ 2.96 and 3.03.

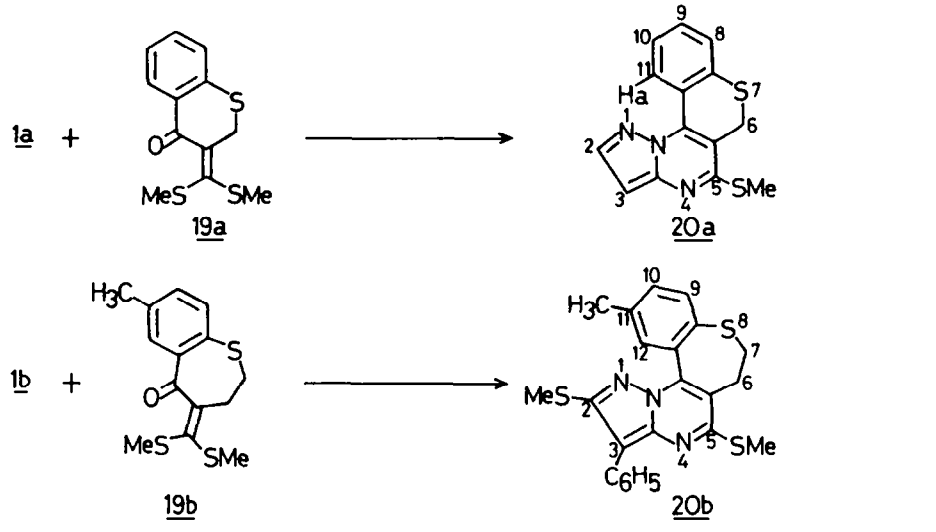
We next investigated the reaction of 1a and 1b with ketene dithioacetals 15a–d and 19a,b derived from benzocyclic ketones. Thus a series of hitherto unknown benzocyclo and benzoheterocyclo pyrazolopyrimidines 16a–e and 20a,b (Scheme 4 and 5) were obtained in high yields through this route. Raney nickel desulphurization of 16b and 16e afforded 17 and 18 respectively, which showed sharp signals at δ 8.37 and 8.56 due to H-5 proton in their ^{1}H n.m.r. spectra thus showing the absence of any long range coupling expected in the linearly fused regioisomers. The regiochemistry in these compounds was further supported by the ^{13}C n.m.r. spectral data of 16a, 16b and 20a which displayed C-5 signal at δ 157.96, 159.25 and 157.76 respectively which are in agreement with the C-5 chemical shift values of 3a and 10. The ^{1}H n.m.r. spectra of pyrazolopyrimidines 16a–c, 17 and 20a exhibited signal due to one of the aromatic protons (Ha) at significantly low field (δ 8.57-9.61) probably due to the deshielding effect[12] of the pyrazole ring nitrogen. However this deshielding effect was not observed in conformationally more flexible pyrazolopyrimidines 16d, e, 18 and 20b.



15a R^1=H, n=1
b R^1=H, n=2
c R^1=MeO, n=2
d R^1=H, n=3

16a R^1=R^2=R^3=H, X=SMe, n=1
b R^1=R^2=R^3=H, X=SMe, n=2
c R^1=MeO, R^2=R^3=H, X=SMe, n=2
d R^1=R^2=R^3=H, X=SMe, n=3
e R^1=H, R^2=X=SMe, R^3=C_6H_5, n=3
17 R^1=R^2=R^3=X=H, n=2
18 R^1=R^2=X=H, R^3=C_6H_5, n=3

Scheme 4



19a 20a
19b 20b

Scheme 5

In conclusion, it is apparent that the reaction of aminopyrazoles 1a and 1b with various α-oxoketene dithioacetals proceeds with high regioselectivity leading to one regioisomer in high yields. Only 9a yielded a mixture of both regioisomers 10 and 11. Our attempts to alter the regioselectivity under different reaction conditions were unsuccessful.

EXPERIMENTAL SECTION

Melting points were determined on a 'Thomas Hoover' capillary melting point apparatus and are uncorrected. I.r. spectra were run as KBr discs on a Perkin Elmer 297 spectrophotometer. ^{1}H n.m.r. spectra were recorded on a Varian EM-390 (90 MHz) spectrometer in deuteriochloroform with tetramethylsilane as internal standard. ^{13}C n.m.r. spectra were recorded on a Brucker WM-400 spectrometer. Mass spectra were obtained using a Jeol JM D-300 spectrometer.

Starting Materials: 3-Aminopyrazole (1a) was prepared according to the reported procedure[13]. 3-Amino-4-phenyl-5-methylthiopyrazole (1b) was prepared by the reaction of equimolar quantities of 3,3-bis(methylthio)-2-phenylacrylonitrile[14] and hydrazine hydrate in refluxing ethanol (monitored by t.l.c.). The reaction mixture was diluted with cold water and the white crystalline solid separated was collected by filteration; yield 90%; m.p. 133-34°C; ν_{max} 3380-3010(br), 1600, 1570 cm^{-1}; δ_H 2.28(3H,s,SCH_3), 6.17(2H,brs,NH_2), 7.20-7.73(6H,m, arom and NH). (Found: C,58.32; H,5.35; N,20.70. $C_{10}H_{11}N_3S$ requires: C,58.51; H,5.40; N, 20.47%).

General Procedure for the Synthesis of Pyrazolopyrimidines 3a-j, 7a-f, 10-13, 16a-e and 20a,b:

A solution of α-oxoketene dithioacetal (5 mmol) and the respective aminopyrazole (5 mmol) in acetic acid (25 ml) and water (7 ml) containing a drop of piperidine was heated at 110-115°C with stirring for 6-12 hr (monitored by t.l.c.). The reaction mixture was cooled, diluted with water (20 ml) and the precipitated pyrazolopyrimidines were collected by filteration, washed free of acetic acid and dried (Method A). In some cases the reaction mixture after dilution with water (50 ml) was extracted with chloroform (3x25 ml) and the combined extracts were washed with water (2x100 ml), dried (Na_2SO_4) and evaporated to give a viscous residue which was purified by silica gel column chromatography (ethylacetate-hexane eluent) to give pure pyrazolopyrimidines (Method B). Analytically pure samples were obtained by recrystallisation from chloroform-hexane.

7-Methyl-5-methylthiopyrazolo[1,5-a]pyrimidine (3a) (Method B); colourless needles (82%); m.p. 88-89°C; ν_{max} 1620, 1545, 1501 cm^{-1}; δ_H 2.57(3H,brs,CH_3), 2.64(3H,s,SCH_3), 6.48(1H,brs, H-6), 6.49(1H,d,J=1.5Hz,H-3), 8.00(1H,d,J=1.5Hz,H-2); δ_C 12.60(SCH_3), 16.73(CH_3), 95.02(C-3), 106.33(C-6), 143.69(C-7), 143.89(C-2), 148.57(C-3a), 159.95(C-5). (Found: C,53.50; H,4.93; N,23.58. $C_8H_9N_3S$ requires: C,53.61; H,5.06; N,23.64%); m/z 179(100%,M^+).

7-(4-Chlorophenyl)-5-methylthiopyrazolo[1,5-a]pyrimidine (3b) (Method A); yellow crystals (93%); m.p. 183-184°C; ν_{max} 1605, 1544 cm^{-1}; δ_H 2.63(3H,s,SCH_3), 6.52(1H,d,J=1.5Hz,H-3), 6.64(1H,s,H-6), 7.47(2H,s,J=8.5Hz,arom), 7.92(2H,d,J=8.5Hz,arom), 8.02(1H,d,J=1.5Hz,H-2). (Found: C,56.49; H,3.52; N,15.29. $C_{13}H_{10}ClN_3S$ requires: C,56.62; H,3.66; N,15.24%); m/z 275 (100%,M^+), 277(35).

5-Methylthio-7-(2-thienyl)pyrazolo[1,5-a]pyrimidine (3c) (Method A); yellow crystals (89%); m.p. 103-104°C; ν_{max} 1597, 1533, 1490 cm^{-1}; δ_H 2.64(3H,s,SCH_3), 6.55(1H,d,J=1.5Hz,H-3), 7.03 (1H,s,H-6), 7.23(1H,distorted t, J=5.0Hz,H-4'), 7.68(1H,d,J=4.5Hz,H-3'), 8.14(1H,d,J=1.5Hz, H-2), 8.25(1H,d,J=4.5Hz,H-5'). (Found: C,53.31; H,3.60; N,17.18. $C_{11}H_9N_3S_2$ requires: C,53.42; H,3.67; N,16.99%); m/z 247(100%,M^+).

7-(2-Furyl)-5-methylthiopyrazolo[1,5-a]pyrimidine (3d) (Method A); yellow needles (88%); m.p. 122-123°C; ν_{max} 1615, 1572, 1528 cm^{-1}; δ_H 2.62(3H,s,SCH_3), 6.36-6.73(2H,m,H-3 and H-4'), 7.12(1H,s,H-6), 7.63(1H,brs,H-3'), 7.93-8.23(2H,m,H-2 and H-5'). (Found: C,57.01; H,3.86; N,18.28. $C_{11}H_9N_3OS$ requires: C,57.12; H,3.92; N,18.17%); m/z 231(100%,M^+).

7-Ethyl-6-methyl-5-methylthiopyrazolo[1,5-a]pyrimidine (3e) (Method B); pale yellow solid (86%); m.p. 95°C; ν_{max} 1616, 1536, 1501 cm^{-1}; δ_H 1.30(3H,t,J=7Hz,CH_2CH_3), 2.23(3H,s,SCH_3),2.58 (3H,s,CH_3), 3.20(2H,q,J=7Hz,CH_2CH_3), 6.46(1H,d,J=1.5Hz,H-3), 7.98(1H,d,J=1.5Hz,H-2). (Found: C,58.03; H,6.33; N,20.40. $C_{10}H_{13}N_3S$ requires: C,57.94; H,6.32; N,20.27%); m/z 207(100%,M^+); 192(37).

6-Benzoyl-5-methylthio-7-phenylpyrazolo[1,5-a]pyrimidine (3f) The reaction was found to be incomplete (t.l.c.) after refluxing for 20 hr. Column chromatography (ethylacetate-hexane 1:20) gave compound 3f as colourless solid (76%) (on the basis of pure recovered starting material); m.p. 149-150°C; ν_{max} 1666,1600,1509 cm^{-1}; δ_H 2.58(3H,s,SCH_3), 6.57(1H,d,J=1.5Hz, H-3), 7.06-7.83(10H,m,arom), 8.04(1H,d,J=1.5Hz,H-2). (Found: C,69.70; H,4.42; N,12.30. $C_{20}H_{15}N_3OS$ requires: C,69.70; H,4.38; N,12.17%): m/z 345(100%,M^+), 312(50).

2,5-Bis(methylthio)-7-methyl-3-phenylpyrazolo[1,5-a]pyrimidine (3g) (Method B); yellow crystals (80%); m.p. 125-126°C; ν_{max} 1616, 1545 cm^{-1}; δ_H 2.57(3H,s,SCH_3), 2.62(3H,s,SCH_3),2.65 (3H,s,CH_3), 6.42(1H,brs,H-6), 7.15-7.50(3H,m,arom), 7.86-8.10(2H,m,arom). (Found: C,59.60; H,5.21; N,14.05. $C_{15}H_{15}N_3S_2$ requires: C,59.77; H,5.02; N,13.94%); m/z 301(100%,M^+),254(73).

2,5-Bis(methylthio)-7-(4-methoxyphenyl)-3-phenylpyrazolo[1,5-a]pyrimidine (3h) (Method A); yellow crystals (93%); m.p. 198-199°C; ν_{max} 1595, 1547, 1496 cm^{-1}; δ_H 2.63(6H,s,SCH_3), 3.86 (3H,s,OCH_3), 6.62(1H,s,H-6), 6.85-7.55(5H,m,arom), 7.82-8.15(4H,m,arom). (Found: C,63.95; H,4.92; N,10.80. $C_{21}H_{19}N_3OS_2$ requires: C,64.09; H,4.87; N,10.68%); m/z 394(100%,MH^+),347(60).

2,5-Bis(methylthio)-6-n-butyl-7-methyl-3-phenylpyrazolo[1,5-a]pyrimidine (3i) (Method B); pale yellow crystals (78%); m.p. 112-113°C; ν_{max} 1602, 1538, 1515 cm^{-1}; δ_H 0.98(3H,t,J=5.6Hz, CH_3), 1.26-1.69(4H,m,CH_2), 2.56(3H,s,SCH_3), 2.64(3H,s,SCH_3), 2.66(3H,s,CH_3), 2.45-2.82(2H, m,CH_2,merged with CH_3), 7.11-7.56(3H,m,arom), 7.95-8.13(2H,m,arom). (Found: C,63.96; H,6.60; N,11.88. $C_{19}H_{23}N_3S_2$ requires: C,63.83; H,6.48; N,11.75%); m/z 358(100%,MH^+),311(42).

2,5-Bis(methylthio)-3,7-diphenyl-6-methylpyrazolo[1,5-a]pyrimidine (3j) (Method A); yellow crystals (81%); m.p. 178-179°C; ν_{max} 1652, 1598, 1567 cm^{-1}; δ_H 2.12(3H,s,CH_3), 2.42(3H,s, SCH_3), 2.62(3H,SCH_3), 7.21-7.63(8H,m,arom), 7.92-8.15(2H,m,arom). (Found: C,66.98; H,5.20; N,11.20. $C_{21}H_{19}N_3S_2$ requires: C,66.81; H,5.07; N,11.13%); m/z 378(100%,MH^+), 330(64).

General Procedure for Reductive Dethiomethylation of 5-methylthio and 2,5-bis(methylthio) pyrazolopyrimidines: Synthesis of 4a-e, 8a, b, 14, 17, 18

A solution of the pyrazolopyrimidine (1 mmol) in methanol (80 ml) was stirred at room temperature with aged (10 days) W2 Raney nickel (ca.15-20 times by weight) for 2-4 hr. (monitored by t.l.c.). Nickel was separated by filteration and the residue was washed with methanol and the combined filterate was evaporated. Extracted with chloroform (30 ml), was washed with water (2x30 ml), dried (Na_2SO_4), evaporated and recrystallised from suitable solvent or purified by passing through short length silica gel column.

7-Methylpyrazolo[1,5-a]pyrimidine (4a); colourless needles (n-pentane), (68%), m.p. 61°C; [lit. m.p. 59-60°C]; ν_{max} 1615, 1540 cm^{-1}; δ_H 2.81(3H,brs,CH_3), 6.70(1H,d,J=4.5Hz,H-6), 6.76 (1H,d,J=1.5Hz,H-3), 8.24(1H,d,J=1.5Hz,H-2), 8.49(1H,d,J=4.5Hz,H-5). (Found: C,62.98; H,5.21; N,31.69. $C_7H_7N_3$ requires: C,63.14; H,5.30; N,31.56%); m/z 133(100%,M^+).

7-(2-Furyl)pyrazolo[1,5-a]pyrimidine (4b); yellow crystals (chloroform-hexane) (75%); m.p. 111-112°C; ν_{max} 1615, 1563 cm^{-1}; δ_H 6.68(1H,dd,J=1.0,1.5Hz,H-4'), 6.75(1H,d,J=1.5Hz,H-3),7.28 (1H,d,J=4.5Hz,H-6), 7.72(1H,d,J=1.9Hz,H-3'), 8.23(1H,d,J=1.5Hz,H-2), 8.28(1H,d,J=1.5Hz,H-5'), 8.56(1H,d,J=4.5Hz,H-5). (Found: C,64.92; H,3.82; N,22.80. $C_{10}H_7N_3O$ requires: C,64.86; H,3.81; N,22.69%); m/z 185(100%,M^+).

7-Ethyl-6-methylpyrazolo[1,5-a]pyrimidine (4c); pale yellow crystals (hexane) (71%); m.p. 74°C; ν_{max} 1609, 1520 cm^{-1}; δ_H 1.33(3H,t,J=7.5Hz,CH_2CH_3), 2.34(3H,s,CH_3), 3.19(2H,q=7.5Hz, CH_2CH_3), 6.63(1H,d,J=1.5Hz,H-3), 8.09(1H,d,J=1.5Hz,H-2), 8.28(1H,s,H-5). (Found: C,67.23; H,7.01; N,26.20. $C_9H_{11}N_3$ requires: C,67.05; H,6.88; N,26.07%); m/z 162(100%,MH^+), 160(74).

7-Methyl-3-phenylpyrazolo[1,5-a]pyrimidine (4d); yellow crystals (chloroform-hexane) (79%); m.p. 224-225°C; ν_{max} 1640, 1575 cm^{-1}; δ_H 2.84(3H,brs,CH_3), 6.80(1H,d,J=4.5Hz,H-6), 8.30(5H, brs,arom), 8.51-8.68(2H,m,H-2 and H-5). (Found: C,74.50; H,5.19; N,20.24. $C_{13}H_{14}N_3$ requires: C,74.62; H,5.30; N,20.80%).

7-(4-methoxyphenyl)-3-phenylpyrazolo[1,5-a]pyrimidine (4e); yellow crystals (chloroform-

hexane); (80%); m.p. 201-202°C; ν_{max} 1503, 1549, 1400 cm^{-1}; δ_H3.82(3H,s,OCH_3), 6.86(1H,d, J=4.5Hz,H-6), 7.09(2H,d,J=8Hz,arom), 7.26-7.60(3H,m,arom), 7.99-8.16(4H,m,arom), 8.43(1H, s,H-2), 8.56(1H,d,J=4.5Hz,H-5). (Found: C,75.62; H,4.96; N,14.08. $C_{19}H_{15}N_3O$ requires: C,75.73; H,5.02; N,13.94%); m/z 301(100%,M^+).

2,5-Bis(methylthio)-7-(4-methoxystyryl)-3-phenylpyrazolo[1,5-a]pyrimidine (7a) (Method A); bright yellow crystals (89%); m.p. 164-165°C; ν_{max} 1604, 1588, 1534 cm^{-1}; δ_H2.60(3H,s,SCH_3), 2.70(3H,s,SCH_3), 3.80(3H,s,OCH_3), 6.68(1H,s,H-6), 6.90(2H,d,J=8.5Hz,arom), 7.24-7.36(6H,m, arom and olefinic), 7.65-8.10(3H,m,arom and olefinic). (Found: C,65.69; H,4.90; N,10.20. $C_{23}H_{21}N_3OS_2$ requires: C,65.84; H,5.03; N,10.02%); m/z 420(100%,MH^+).

6-Methyl-5-methylthio-7-(3,4-methylenedioxystyryl)pyrazolo[1,5-a]pyrimidine (7b) (Method A); yellow crystals (84%); m.p. 181-182°C; ν_{max} 1624, 1580 cm^{-1}; δ_H2.41(3H,s,CH_3), 2.60(3H,s, SCH_3), 5.96(2H,s,CH_2), 6.36(1H,d,J=1.5Hz,H-3), 6.73-7.38(3H,m,arom), 7.24(1H,d,J=16Hz,olefinic), 7.94(1H,d,J=16Hz,olefinic), 7.96(1H,d,J=1.5Hz,H-2). (Found: C,62.60; H,4.66; N,13.02. $C_{17}H_{15}N_3O_2S$ requires: C,62.75; H,4.65; N,12.91%); m/z 325(100%,M^+).

2,5-Bis(methylthio)-3-phenyl-7-(4-phenyl-1,3-butadienyl)pyrazolo[1,5-a]pyrimidine (7c) (Method A); red crystals (86%); m.p. 190-191°C; ν_{max} 1602, 1538 cm^{-1}; δ_H2.56(3H,s,SCH_3), 2.68 (3H,s,SCH_3), 6.56(1H,s,H-6), 6.81-7.01(2H,m,olefinic), 7.20-8.18(12H,m,arom and olefinic). (Found: C,69.48; H,5.26; N,10.27. $C_{24}H_{21}N_3S_2$ requires: C,69.36; H,5.09; N,10.11%); m/z 415 (28%,M^+), 414(93), 300(100).

6-Methyl-5-methylthio-7-(4-phenyl-1,3-butadienyl)pyrazolo[1,5-a]pyrimidine (7d) (Method A); red crystals (87%); m.p. 140-142°C; ν_{max} 1598, 1528 cm^{-1}; δ_H2.38(3H,s,CH_3), 2.60(3H,SCH_3), 6.47(1H,d,J=1.5Hz,H-3), 6.80-7.09(3H,m,olefinic), 7.19-7.60(5H,m,arom and olefinic), 8.02(1H, d,J=1.5Hz,H-2), 7.93-8.22(1H,m,arom). (Found: C,70.41; H,5.43; N,13.80. $C_{18}H_{17}N_3S$ requires: C,70.32; H,5.58; N,13.67%); m/z 307(100%,M^+).

5-Methylthio-7-[6-(4-methoxyphenyl)-1,3,5-hexatrienyl]pyrazolo[1,5-a]pyrimidine (7e) (Method A); red crystals (79%); m.p. 151-152°C; ν_{max} 1585, 1512 cm^{-1}; δ_H2.58(3H,s,SCH_3), 3.76(3H,s, OCH_3), 6.42(1H,d,J=1.5Hz,H-3), 6.60-7.43(11H,m,arom and olefinic), 7.96(1H,d,J=1.5Hz,H-2). (Found: C,68.89; H,5.40; N,12.20. $C_{20}H_{19}N_3OS$ requires: C,68.74; H,5.48; N,12.03%); m/z 349 (27%,M^+), 348(100).

2,5-Bis(methylthio)-3-phenyl-7-(6-phenyl-1,3,5-hexatrienyl)pyrazolo]1,5-a]pyrimidine (7f) (Method A); red crystals (80%); m.p. 181-182°C; ν_{max} 1575, 1530 cm^{-1}; δ_H2.58(3H,s,SCH_3),2.70 (3H,s,SCH_3), 6.43-7.45(15H,m,arom and olefinic), 7.90-8.08(2H,m,arom). (Found: C,70.59; H,5.38; N,9.60. $C_{26}H_{23}N_3S$ requires: C,70.71; H,5.25; N,9.52%); m/z 441(26%,M^+), 440(83).

7-[2-(4-methoxyphenyl)ethyl]-3-phenylpyrazolo[1,5-a]pyrimidine (8a); yellow crystals (chloroform-hexane); (76%); m.p. 151-152°C; ν_{max} 1611, 1562, 1508 cm^{-1}; δ_H3.13(2H,t,J=7Hz,CH_2), 3.45 (2H,t,J=7Hz,CH_2), 3.72(3H,s,OCH_3), 6.58(1H,d,J=4.5Hz,H-6), 6.79(2H,d,J=8Hz,arom), 7.15(2H,d, J=8Hz,arom), 7.29-7.62(3H,m,arom), 8.00-8.16(2H,m,arom), 8.43(1H,d,J=4.5Hz,H-5), 8.48(1H,s, H-2). (Found: C,76.68; H,6.00; N,12.89. $C_{21}H_{19}N_3O$ requires: C,76.57; H,5.81; N,12.76%); m/z 239(36%,M^+); 121(100).

7-(6-phenyl-n-hexyl)-3-phenylpyrazolo[1,5-a]pyrimidine (8b) was purified by silica gel column chromatography using ethylacetate-hexane (1:20) as eluent, pale yellow crystals; (74%); m.p. 91-92°C; ν_{max} 1612, 1600, 1552, 1533 cm^{-1}; δ_H1.31-2.06(8H,m,CH_2), 2.06(2H,t,J=7Hz,CH_2), 3.16 (2H,t,J=7Hz,CH_2), 6.61(1H,d,J=4.5Hz,H-6), 7.10-7.85(8H,m,arom), 8.00-8.19(2H,m,arom), 8.42-8.59(2H,m,H-2 and H-5). (Found: C,81.21; H,7.06; N,11.99. $C_{24}H_{25}N_3$ requires: C,81.09; H,7.09; N,11.82%); m/z 355(68%,M^+), 209(100).

5-Methylthio-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (10) (Method B); ethylacetate hexane 1:30 as eluent; colourless crystals (36%); m.p. 133-134°C; ν_{max} 1620, 1532 cm^{-1}; δ_H2.27(2H,quintet, J=7Hz,CH_2), 2.61(3H,s,SCH_3), 2.88(2H,brt,J=7Hz,CH_2), 3.31(2H,brt,J=7Hz, CH_2), 6.44(1H,d,J=1.5Hz,H-3), 7.93(1H,d,J=1.5Hz,H-2); δ_C 12.13(SCH_3), 21.82, 28.84,29.58(C-6, C-7 and C-8), 94.45(C-3), 120.02(C-5a), 143.97(C-2), 146.81(C-8a), 148.93(C-3a), 157.62(C-5). (Found: C,58.39; H,5.48; N,20.60. $C_{10}H_{11}N_3S$ requires: C,58.51; H,5.40; N,20.47%); m/z 205(99%, M^+), 172(91).

8-Methylthio-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine (11) (EtOAc-hexane 1:20 as eluent); colourless solid (48%); m.p. 103-104°C; ν_{max} 1603, 1500 cm^{-1}; δ_H2.34(2H,quintet, J=7Hz,6-CH_2), 2.73(3H,s,SCH_3), 2.96(2H,t,J=7Hz,CH_2), 3.03(2H,t,J=7Hz,CH_2), 6.47(1H,d,J=1.5Hz,

H-3), 7.97(1H,d,J=1.5Hz,H-2); δ_C15.23(SCH_3), 23.41, 28.93, 34.12(C-5, C-6 and C-7), 95.59 (C-3), 124.40(C-7a), 139.80(C-8), 143.20(C-2), 148.70(C-3a), 166.46(C-4a). (Found: C,58.42; H,5.48; N,20.52. $C_{10}H_{11}N_3S$ requires: C,58.51; H,5.40; N,20.47%); m/z 205(20%,M^+),172(100).

5-Methylthio-6,7,8,9-tetrahydropyrazolo[1,5-*a*]quinazoline (12) (Method B); colourless crystals (81%); m.p. 139-140°C; ν_{max} 1611, 1530 cm^{-1}; δ_H1.62-1.95(4H,m,CH_2), 2.54(3H,s,SCH_3),2.28-2.66(2H,m,CH_2), 2.80-3.16(2H,m,CH_2), 6.35(1H,d,J=1.5Hz,H-3), 7.86(1H,d,J=1.5Hz,H-2); δ_C12.70 (SCH_3), 20.88, 21.74, 23.16(C-6, C-7, C-8 and C-9), 94.46(C-3), 114.65(C-5a), 141.52(C-9a), 143.05(C-2), 147.02(C-3a), 160.54(C-5). (Found: C,60.03;H,6.08; N,19.30. $C_{11}H_{13}N_3S$ requires: C,60.24; H,5.97; N,19.16%); m/z 219(11%,M^+), 218(70), 186(100).

5-Methylthio-7,8,9,10-tetrahydro-6H-cyclohepta[*e*]pyrazolo[1,5-*a*]pyrimidine (13) (Method B); colourless crystals (79%); m.p. 121-122°C; ν_{max} 1617, 1538 cm^{-1}; δ_H1.43-2.03(6H,m,CH_2), 2.56 (3H,s,SCH_3), 2.66-2.96(2H,m,CH_2), 3.31-3.60(2H,m,CH_2), 6.43(1H,d,J=1.5Hz,H-3), 7.96(1H,d, J=1.5Hz,H-2); δ_C13.12(SCH_3), 24.29, 25.75, 26.75, 27.39, 31.37(C-6, C-7, C-8, C-9 and C-10), 94.32(C-3), 119.36(C-5a), 142.76(C-2), 146.97(C-10a), 147.09(C-3a), 159.55(C-5). (Found: C,61.88; H,6.60; N,18.22. $C_{12}H_{15}N_3S$ requires: C,61.77; H,6.48; N,18.01%); m/z 233(100%,M^+).

6,7,8,9-Tetrahydropyrazolo[1,5-*a*]quinazoline (14)! colourless solid (n-hexane), 74%; m.p. 91-92°C; ν_{max} 1618,1517 cm^{-1}; δ_H1.66-2.11(4H,m,CH_2), 2.75(2H,t,J=7Hz,CH_2), 3.10(2H,t,J=7Hz, CH_2), 6.64(1H,d,J=1.5Hz,H-3), 8.08(1H,d,J=1.5Hz,H-2), 8.28(1H,s,H-5). (Found: C,69.52; H, 6.49; N,24.32. $C_{10}H_{11}N_3$ requires: C,69.34; H,6.40; N,24.26%); m/z 174(100%,MH^+), 172(28).

5-Methylthio-6H-indeno[2,1-*e*]pyrazolo[1,5-*a*]pyrimidine (16a) (Method A); yellow crystals (92%); m.p. 150-151°C; ν_{max} 1600, 1532 cm^{-1}; δ_H2.70(3H,s,SCH_3), 3.80(2H,s,CH_2), 6.56(1H,d,J=1.5Hz, H-3), 7.43-7.60(3H,m,arom), 8.12(1H,d,J=1.5Hz,H-2), 8.57-8.73(1H,m,arom); δ_C11.89(SCH_3), 33.36 (CH_2), 94.08(C-3), 118.77(C-5a), 124.33, 127.08, 129.36(CH,ArH), 133.51(C-6a), 142.33(C-10a), 143.05(C-10b), 143.99(C-2), 149.36(C-3a), 157.96(C-5). (Found: C,66.50; H,4.46; N,16.72. $C_{14}H_{11}N_3S$ requires: C,66.38; H,4.38; N,16.59%); m/z 253(100%,M^+), 220(66).

5-Methylthio-6,7-dihydronaphtho[2,1-*e*]pyrazolo[1,5-*a*]pyrimidine (16b) (Method A); yellow crystals (89%); m.p. 118-119°C; ν_{max} 1602, 1492 cm^{-1}; δ_H2.60(3H,s,SCH_3), 2.83(4H,brs,CH_2), 6.50(1H,d,J=1.5Hz,H-3), 7.13-7.54(3H,m,arom), 8.04(1H,d,J=1.5Hz,H-2), 9.23-9.46(1H,m,arom); δ_C12.65(SCH_3), 22.44(CH_2), 28.05(CH_2), 94.43(C-3), 114.89(C-5a), 126.36, 127.11, 128.83, 129.96(CH,ArH), 126.56(C-7a), 137.40(C-11a), 139.09(C-11b), 143.01(C-2), 149.04(C-3a), 159.25 (C-5). (Found: C,67.50; H,5.15; N,15.76. $C_{15}H_{13}N_3S$ requires: C,67.39; H,4.90; N,15.72%); m/z 267(21%,M^+), 266(100), 233(58).

5-Methylthio-9-methoxy-6,7-dihydronaphtho[2,1-*e*]pyrazolo[1,5-*a*]pyrimidine (16c) (Method A); yellow crystals (90%); m.p. 172-173°C; ν_{max} 1605, 1563, 1486 cm^{-1}; δ_H2.62(3H,s,SCH_3), 2.86(4H,brs,CH_2), 3.86(3H,s,OCH_3), 6.47(1H,d,J=1.5Hz,H-3); 6.73-7.01(2H,m,arom), 8.03(1H,d, J=1.5Hz,H-2), 9.36(1H,d,J=8Hz,arom). (Found: C,64.51; H,4.97; N,14.22. $C_{16}H_{15}N_3OS$ requires: C,64.62; H,5.08; N,14.13%); m/z 297(100%,M^+), 264(57).

5-Methylthio-7,8-dihydro-6H-benzocyclohepta[2,1-*e*]pyrazolo[1,5-*a*]pyrimidine (16d) (Method B); pale yellow crystals (73%); m.p. 151-152°C; ν_{max} 1607, 1594 cm^{-1}; δ_H2.03-3.02(6H,m,CH_2), 2.62 (3H,s,SCH_3), 6.52(1H,d,J=1.5Hz,H-3), 7.26-7.57(3H,m,arom), 8.00(1H,d,J=1.5Hz,H-2), 8.01-8.21 (1H,m,arom). (Found: C,68.19; H,5.25; N,15.15. $C_{16}H_{15}N_3S$ requires: C,68.30; H,5.37; N,14.93%); m/z 281(100%,M^+), 248(64).

2,5-Bis(methylthio-3-phenyl-7,8-dihydro-6H-benzocyclohepta[2,1-*e*]pyrazolo[1,5-*a*]pyrimidine (16e) (Method A); yellow needles (75%); m.p. 157-158°C; ν_{max} 1602, 1588, 1500 cm^{-1}; δ_H1.93-2.72(6H,m,CH_2), 2.55(3H,s,SCH_3), 2.62(3H,s,SCH_3), 7.10-7.56(6H,m,arom), 7.96-8.16(3H,m,arom). (Found: C,68.28; H,5.30; N,10.58. $C_{23}H_{21}N_3S_2$ requires: C,68.45; H,5.25; N,10.41%); m/z 404 (100%,MH^+), 357(52).

6,7-Dihydronaphtho[2,1-*e*]pyrazolo[1,5-*a*]pyrimidine (17); yellow crystals (n-hexane), 77%; m.p. 68-69°C; ν_{max} 1604, 1507 cm^{-1}; δ_H2.89(4H,s,CH_2), 6.71(1H,d,J=1.5Hz,H-3), 7.22-7.47(3H,m,arom), 8.17(1H,d,J=1.5Hz,H-2), 8.37(1H,s,H-5), 9.35-9.52(1H,m,arom). (Found: C,75.89; H,5.22; N, 19.15. $C_{14}H_{11}N_3$ requires: C,76.00; H,5.01; N,18.99%); m/z 221(100%,M^+).

3-Phenyl-7,8-dihydro-6H-benzocyclohepta[2,1-*e*]pyrazolo[1,5-*a*]pyrimidine (18); yellow crystals (chloroform-hexane); 79%; m.p. 145-146°C; ν_{max} 1602, 1523 cm^{-1}; δ_H2.13-2.82(6H,m,CH_2), 7.20-7.62(6H,m,arom), 8.02-8.29(3H,m,arom), 8.47(1H,s,H-2), 8.56(1H,s,H-5). (Found: C,81.23; H,5.68; N,13.73. $C_{21}H_{17}N_3$ requires: C,81.00; H,5.50; N,13.50%); m/z 311(100%,M^+).

5-Methylthio-6H[1]benzothiopyrano[3,4-e]pyrazolo[1,5-a]pyrimidine (20a) (Method A); yellow needles (86%); m.p. 154-155°C; ν_{max} 1598, 1495 cm^{-1}; δ_H 2.65(3H,s,SCH_3), 3.86(2H,s,CH_2), 6.52 (1H,d,J=1.5Hz,H-3), 7.14-7.60(3H,m,arom), 8.02(1H,d,J=1.5Hz,H-2), 8.85-9.21(1H,m,arom); δ_C 13.29(SCH_3), 25.40(CH_2), 95.15(C-3), 112.75(C-5a), 126.32(CH,ArH), 126.14(C-11a), 128.31, 130.41, 131.12(CH,ArH), 137.29(C-11b), 137.33(C-7a), 143.58(C-2), 148.84(C-3a), 157.76(C-5). (Found: C,58.80; H,3.99; N,14.94. $C_{14}H_{11}N_3S_2$ requires: C,58.92; H,3.89; N,14.72%); m/z 285 (21%,M^+), 284(84), 269(100).

2,5-Bis(methylthio)-11-methyl-3-phenyl-6,7-dihydro[1]benzothiepino[4,5-e]pyrazolo[1,5-a]pyrimidine (20b) (Method A); yellow crystals (82%); m.p. 232-233°C; ν_{max} 1595, 1518 cm^{-1}; δ_H 2.41 (3H,s,CH_3), 2.53(3H,s,SCH_3), 2.64(3H,s,SCH_3), 2.73-3.72(4H,m,CH_2), 7.24-7.64(5H,m,arom), 7.93-8.15(3H,m,arom). (Found: C,63.20; H,4.75; N,9.72. $C_{23}H_{21}N_3S_3$ requires: C,63.41; H,4.86; N,9.65%); m/z 436(100%,MH^+), 389(39).

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