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AN EFFICIENT SYNTHESIS OF 5–NITROPYRROLES WITH POTENTIAL ANTIAMEBIC PROPERTIES VIA α–OXOKETENE DITHIOACETALS

S. K. SHARMA

Department of Agri. Chemistry and Soil Science,
Nagaland University, SASRD, MEDZIPHEMA – 797 106 (Nagaland) INDIA

ABSTRACT

In the present study, a series of 1–substituted–2–methylthio–3–acyl–5–nitro pyrroles have been synthesized by directly nitrating the correspondingly pyrroles with fuming nitric acid in the presence of acetic anhydride at 20°C. The nitropyrroles thus obtained were characterised by analytical and spectral data. These nitropyrroles were screened against *E. histilitica*. Some of the nitro pyrroles exhibited higher activity than metronidazole *in vitro*.

Key word : Pyrrole, Fuming nitric acid, Acetic anhydride, Antiamoebic

INTRODUCTION

The five membered heterocycles with an appropriately substituted nitro group and side chain substituents have displayed interesting antiamebic properties.[1–4] Among many other five membered heterocycles, 5–nitro–1–substituted pyrroles have also displayed pronounced antiamebic and antihepatic activities.[5,6] In view of these reported activities, it was considered of interest to prepare 1–substituted–2–methylthio–3–acyl–5–nitropyrroles to examine their antiamebic properties. The required pyrroles were conveniently prepared by extending our earlier reported method[7] by reacting various S, N–acetals (**2**) with bromoacetaldehyde diethyl acetal (**3**) to afford corresponding pyrrole (**5**), which were nitrated to yield the corresponding 5–nitro pyrroles (**6**). The chemistry of these pyrroles and their antiamebic properties are presented in this paper.

EXPERIMENTAL

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin Elmer–297 spectrometer and frequencies are expressed in cm^{-1}. The ^1H NMR spectra were recorded on a Varian EM–390 (90 MHz) spectrometer using tetramethylsilane as internal standard and the chemical shifts are expressed as ppm down field from TMS. Elemental analyses were made on Heraus CHN–O rapid analyzer.

The commercial samples of various acetophenones, acetone, amines, ethanol, DMF etc. were purified before use. Commercially available bromoacetaldehyde diethyl acetal (Aldrich) and acetic anhydride were used as such. The α–oxoketene S, N–acetals were prepared by the reported procedure.[8]

General procedure for the synthesis of 1–alkyl/aryl–3–acyl–2–methylthiopyrroles (5a–o). A solution of S, N–acetal (10 mmol) and bromoacetaldehyde diethylacetal (10 mL) in 20 mL DMF was heated to 120°C for 4–8 h. After the completion of the reaction (on the basis of TLC), it was cooled, poured into ice cold water (50 mL), extracted with chloroform (2 x 50 mL), dried (Na_2SO_4) and evaporated to give crude products, which are further purified by column chromatography on silica gel using hexane – ethyl acetate (20 : 1) as eluent. The known pyrroles **(5a–c)** were confirmed by their reported spectral and analytical data[7] and the unknown pyrroles **(5d–o)** were confirmed by their analytical and spectral data given below –

1–Cyclohexyl–3–benzoyl–2–methylthiopyrrole (5d). Colorless solid; mp 71–72°C; Yield 79%; IR (KBr): 1645 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 1.15–2.15 (m, 10H, $(CH_2)_5$), 2.42 (s, 3H, SCH_3), 4.60 (brs, 1H, CH), 6.52 (d, J = 3 Hz, 1H, H–4, ArH), 6.73 (d, J = 3 Hz, 1H, H–5, ArH), 7.36 – 7.66 (m, 3H, ArH), 7.75–8.09 (m, 2H, ArH). Anal Calcd for $C_{18}H_{21}NOS$ (299.4): C, 72.20; H, 7.07; N, 4.67%. Found: C, 72.33; H, 6.91; N, 4.49%.

1–Cetyl–3–benzoyl–2–methylthiopyroole (5e). Colorless solid; mp 41–42°C; Yield 86%; IR (KBr): 1647 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 0.85 (brs, 3H, CH_3), 1.26 (brs, 28H, $(CH_2)_{14}$), 2.46 (s, 3H, SCH_3) 4.09 (t, J = 2 Hz, 2H, CH_2), 6.36 (d, J = 3 Hz, 1H, H–4, ArH), 6.66 (d, J = 3 Hz, 1H, H–5 ArH), 7.36–7.56 (m, 3H, ArH). Anal Calcd for $C_{28}H_{43}NOS$ (441.6): C, 76.13; H, 9.81; N, 3.17%. Found: C, 76.29; H, 9.62; N, 3.02%.

1–Methyl–3–(4–chlorobenzoyl)–2–methylthiopyrrole (5f). Colorless solid; mp 69–70°C; Yield 88%; IR (KBr): 1645 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 2.39 (s, 3H, SCH_3), 3.75 (s, 3H, NCH_3) 6.35 (d, J = 3 Hz, 1H, H–4, ArH), 6.67 (d, J = 3 Hz, 1H, H–5, ArH), 7.35 (d, J = 9 Hz, 2H, ArH), 7.67 (d, J = 9 Hz, 2H, ArH), 7.67 (d, J = 9 Hz, 2H, ArH). Anal Calcd for $C_{13}H_{12}NOSCl$ (265.7): C, 58.75; H, 4.75; N, 5.27%. Found: C, 58.59; H, 4.31; N, 5.41%.

1–Ethyl–3–(4–methoxybenzoyl)–2–methylthiopyrrole (5g). Colorless solid; mp 70–71°C; Yield 71%; IR (KBr): 1629 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 1.46 (t, J = 7 Hz, 3H, CH_3), 2.49 (s, 3H, SCH_3). 3.95 (s, 3H, OCH_3), 4.29 (q, J = 7Hz, 2H, CH_2), 6.59 (d, J = 3Hz, 1H, H–4, ArH), 6.95 (d, J = 3Hz, 1H, H–4, ArH), 6.95 (d, J = 3Hz, 1H, H–5, ArH), 7.01 (d, J = 9Hz, 2H, ArH), 8.06 (d, J = 9 Hz, 2H, ArH). Anal Calcd for $C_{15}H_{17}NO_2S$ (275.3): C, 65.42; H, 6.22; N, 5.08%. Found: C, 65.61; H, 6.38; N, 5.29%.

1–Cyclohexyl–3–(4–methoxybenzoyl)–2–methylthiopyrrole(5h). Colorless solid; mp 90–91°C, Yield 67%; IR (KBr): 1610 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 1.15–2.15 (m, 10H, $(CH_2)_5$), s, 3H, SCH_3), 3.84 (s, OCH_3), 4.66 (brs, 1H, CH), 6.49 (d, J = 3 Hz, 1H, H–4, ArH),

6.82–7.13 (m, 3H, H–5 and 2H, ArH), 7.95 (d, J = 9 Hz, 2H, ArH). Anal Calcd for $C_{19}H_{23}NOS$ (329.4): C, 69.26; H, 7.03; N, 8.50%. Found: C, 69.38; H, 7.16; N, 8.18%.

1–Heptyl–3–(4–methoxybenzoyl)–2–methylthiopyrrole (5i). Viscous liquid; Yield 67% IR (KBr): 1625 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): (brs, 3H, CH_3), 1.09 (brs, 10H, $(CH_2)_5$), 2.23 (s, 3H, SCH_3), 3.95 (s, 3H, OCH_3), 4.06 (t, J = 7 Hz, 2H, CH_2), 6.33 (d, J = 3Hz, 1H, H–4, ArH), 6.72 (d, J = 3Hz, 1H, H–5, ArH), 6.89 (d, J = 9 Hz, 2H, ArH), 7.95 (d, J = 9 Hz, 2H, ArH). Anal Calcd for $C_{20}H_{27}NO_2S$ (345.4): C, 69.52; H, 7.87; N, 4.05%. Found C, 69.67; H, 7.64; N, 3.87%.

1–Butyl–3– (4 – methylbenzoyl)–2– methythiopyrrole (5j). Colorless solid, mp 64 – 65°C, yield 71%, IR (K Br): 1645 cm^{-1}; ^1H NMR (90 MHz, ($CDCl_3$): 0.96 (t, J = 7 Hz, 3H, CH_3), 1.35 (distorted sextet, J = 7 Hz, 2H, CH_2) 1.77 (distorted quintet, J = 7 Hz, 2H, CH_2), 2.43 (s, 3H, SCH_3), 4.16 (t, J = 7 Hz, 2H, CH_2), 6.52 (d, J = 3Hz, 1H, H–4), 6.82 (d, J = 3Hz, 1H, H–5, 7.36 (d, J = 9 Hz, 2H, ArH), 7.89 (d, J = 9Hz, 2H, ArH). Anal Calcd for $C_{17}H_{21}$ NOS (287.4): C, 71.03; H, 7.36; N, 4.87%. Fond: C, 71.28: H, 7.52; N, 4.98%.

4–Benzyl–3–(2,4–dichlorobenzoyl)–2–methylthiopyrrole (5k). Colorless solid; mp 73–74°C; Yield 85%; IR (KBr): 1629 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$); 2.26 (s, 3H, SCH_3), 5.46 (s, 2H, NH_2), 6.56 (d, J = 3 Hz, 1H, H–4, ArH), 6.92 (d, J = 3 Hz, 1H, H–5, ArH), 7.19–7.66 (m, 8H, ArH). Anal Calcd for $C_{19}H_{15}NOSCl_2$ (376.2): C, 60.64: H, 4.01; N, 3.72%. Found: C, 60.82; H, 4.19; N, 3.56%.

1–Cyclohexyl–3–(2,4–dichlorobenzoyl)–2–methylthiopyrrole (5l). Colorless solid; mp 95–96°C; Yield 85%; IR (KBr): 1669 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 1.15–2.15 (m, 10H, $(CH_2)_5$, 2.36 (s, 3H, SCH_3), 3.62 (brs, 1H, CH), 6.39 (d, J = 3 Hz, 1H, H–4, ArH), 6.85 (d, J = 3 Hz, 1H, H–5, ArH), 7.36 (s, 2H, ArH), 7.49 (s, 1H, ArH). Anal Calcd for $C_{18}H_{19}NOSCl_2$ (368.3): C, 58.68; H, 5.19; N, 3.80%. Found: C, 58.79; H, 5.35; N, 3.64%.

1–Benzyl–3–(3,4–dichlorobenzoyl)–2–methylthiopyrrol (5m). Colorless soild; mp 57–58°C; Yield 83%; IR (KBr): 1645 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 2.97 (s, 3H, SCH_3), 5.39 (s, 2H, NCH_2), 6.52 (d, J = 3 Hz, 1H, H–4, ArH), 6.89 (d, J = 3 Hz, 1H, H–5, ArH), 7.16–7.89 (m, 7H, ArH), 8.06 (d, J = 2 Hz, 1H, ArH). Anal Calcd for $C_{19}H_{15}NOSCl_2$ (376.2); C, 60.64; H, 4.01; N, 3.72%. Found: C, 60.79; H, 4.19; N, 3.58%.

1–Cyclohexyl–3–(3,4–dichlorobenzoyl)–2–methylthipyrrole (5n). Colorless solid; mp 112–113°C; Yield 85%; IR (KBr): 1647 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 1.15–2.15 (m, 10H, $(CH_2)_5$) 2.39 (s, 3H SCH_3), 4.66 (brs, 1H, CH), 6.49 (d, J = 3 Hz, 1H, H–4, ArH), 6.89 (d, J = 3 Hz, 1H, H–5, ArH), 7.49–7.82 (m, 2H, ArH), 7.95 (d, J = 2 Hz, 1H, ArH.). Anal Calcd for $C_{18}H_{19}NOSCl_2$ (365.3): C, 59.17; H, 5.24; N, 3.82%. Found: C, 59.28; H, 5.32; N, 3.69%.

1–Cetyl–3–(3,4–dichlorobenzoyl)–2–methylthiopyrrol (5o). Colorless solid; mp 39–40°C; Yield 86%; IR (KBr): 1647 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 0.92 (brs, 3H, CH_3), 1.29 (brs, 28H, $(CH_2)_{14}$), 2.46 (s, 3H, SCH_3), 4.16 (t, J = 7 Hz, 2H, CH_2), 6.36 (d, J = 3 Hz, 1H, H–4,

ArH), 6.72 (d, J = 3 Hz, 1H, H–5, ArH), 7.46–7.79 (m, 2H, ArH), 7.92 (d, J = 2 Hz, 1H, ArH). Anal Calcd for $C_{28}H_{41}NOSCl_2$ (510.5): C, 65.86; H, 8.09; N, 2.74%. Found: C, 65.64; H, 7.87; N, 2.56%.

General procedure for the synthesis of 1–substituted–3–acyl–2–methylthio–5–nitropyrroles (6a–o). To a solution of pyrrole **(5)** (10 mmol) in acetic anhydride (7 mL) at 20°C, a mixture of fuming nitric acid (20 mmol) and acetic anhydride (3 mL) was added drop wise allowing the temperature of the reaction mixture to rise slowly to room temperature. It was stirred at room temperature for 30 min and poured into ice cold water (50 mL), extracted with dichloromethane (3 x 50 mL), washed with water (2 x 50 mL), dried over Na_2SO_4 and evaporated to give the crude products which were further purified by column chromatography using hexane – ethyl acetate (19 : 1) as eleuent. The structures were fully characterized from their spectral and analytical data, which are given below –

1–Ethyl–3–acetyl–2–methylthio–5–nitropyrrole(6a). Colorless solid; mp 120–121°C; Yield 35%; IR (KBr): 1700, 1560, 1325 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 1.56 (t, J = 7 Hz, 3H, CH_3), 2.56 (s, 3H, CH_3) 3.23 (s, 3H, SCH_3), 5.23 (q, J = 7 Hz, 2H, CH_2), 7.46 (s, 1H, H–4, ArH), Anal Calcd for $C_9H_{12}N_2O_3S$ (228.2): C, 47.35; H, 5.29; N, 12.27%. Found: C, 47.52; H, 5.13; N, 12.46%.

1–Butyl–3–benzoyl–2–methylthio–5–nitropyrole (6b). Colorless solid; mp 97–98°C; Yield 43%; IR (KBr); 1660, 1529, 1305 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 1.00 (t, J = 7 Hz, 3H, CH_3), 1.49 (distorted sextet, J = 7 Hz, 2H, CH_2), 1.92 (distorted quintet, J = 7 Hz, 2H, CH_2), 3.33 (s, 3H SCH_3), 5.16 (t, J = 7 Hz, 2H, CH_2), 7.42–7.79 (m, 4H, H–4 and 3H ArH), 7.82–8.31 (m, 2H, ArH). Anal Calcd for $C_{16}H_{18}N_2O_3S$ (318.3): C, 60.53: H, 5.69; N, 8.79%. Found: C, 60.49; H, 5.54; N, 8.96%.

1–Benzyl–3–benzoyl–2–methylthio–5nitropyrrole (6c). Colorless solid; mp 134–135°C; Yield 42%; IR (KBr): 1647, 1545, 1320 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 2.96 (s, 3H, SCH_3), 6.46 (dd, J = 15.9 Hz, 2H, CH_2), 7.06–7.23 (m, 2H, ArH), 7.29–7.46 (m, 3H, ArH), 7.56–7.72 (m, 4H, H–4 and 3H, ArH), 7.25–8.03 (m, 2H, ArH). Anal Calcd for $C_{19}H_{16}N_2O_3S$ (352.4): C, 64.75; H, 4.57; N, 7.94%. Found: C, 64.56; H, 4.41; N, 7.78%.

1–Cyclohexyl–3–benzoyl–2–methylthio–5–nitropyrrole (6d). Colorless solid; mp 129–130°C; Yield 41%; IR (KBr): 1657, 1540, 1304 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 1.19–2.72 (m, 10H, $(CH_2)_5$), 3.33 (s, 3H, SCH_3), 5.69 (brs, 1H, CH), 7.39–7.75 (m, 4H, H–4 and 3H ArH), 7.82–8.00 (m, 2H, ArH). Anal Calcd for $C_{18}H_{20}N_2O_3S$ (344.4): C, 62.76; H, 5.85; N, 8.13%. Found: C, 62.57; H, 5.59; N, 7.92%.

1–Cetyl–3–benzoyl–2–methylthio–5–nitropyrrole (6e). Colorless solid; mp 56–57°C; Yield 55%; IR (KBr); 1657, 1540, 1312 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): brs, 3H, CH_3), 1.29 (brs, 28H, $(CH_2)_{14}$), 3.29 (s, 3H, SCH_3), 5.06 (brs, 2H, CH_2), 7.39–7.66 (m, 4H, H–4 and 3H, ArH),

7.79–8.03 (m, 2H, ArH). Anal Calcd for $C_{28}H_{42}N_2O_3S$ (486.7): C, 69.09; H, 8.69; N. 5.75%. Found: C, 69.21; H, 8.49; N, 5.58%.

1–Ethyl–3–(4–chlorobenzoyl)–2–methylthio–5–nitropyrrole (6f). Colorless solid; mp 155–156°C; Yield 41%; IR (KBr): 1679, 1555, 1325 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 1.56 (t, J = 7 Hz, 3H, CH_3), 3.29 (s, 3H, SCH_3), 5.16 (q, J = 9 Hz, 3H, H–4 and 2H, ArH), 7.89 (d, J = 9 Hz, 2H, ArH). Anal Calcd for $C_{14}H_{13}N_2O_3SCl$ (324.7): C, 51.77; H, 4.03; N, 8.62%. Found: C, 51.96%; H, 4.15; N, 8.49%.

1–Ethyl–3–(4–methoxybenzoyl)–2–methylthio–5–nitropyrrole (6g). Colorless solid; mp 119–120°C; Yield 35%. IR (KBr): 1625, 1500, 1320 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 1.59 (t, J = 7 Hz, 3H, CH_3), 3.36 (s, 3H, SCH_3), 4.33 (s, 3H, OCH_3), 5.19 (brq, J = 3 Hz, 2H, CH_2), 7.13 (d, J = 9 Hz, 2H, ArH), 7.59 (s, 1H, H–4), 8.03 (d, J = 9 Hz, 2H, ArH). Anal Calcd for $C_{15}H_{16}N_2O_4S$ (320.3): C, 56.23; H, 5.03; N, 8.74%. Found: C, 56.42; H, 4.84; N, 8.57%.

1–Benzyl–3–(4–methoxybenzoyl)–2–methylthio–5–nitropyrrole (6h). Colorless solid; mp 118–120°C; Yield 38%; IR (KBr); 1625; 1518, 1300 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 3.00 (s, 3H, SCH_3), 4.00 (s, 3H, OCH_3), 6.52 (dd, J = 15, 9 Hz, 2H, CH_2), 7.06–7.33 (m, 4H, ArH), 7.39–7.56 (m, ArH), 7.69 (s, 1H, H–4), 8.06 (d, J = 9 Hz, 2H, ArH). Anal Calcd for $C_{20}H_{18}N_2O_4S$ (382.4): C, 62.80; H, 4.74; N, 7.32%. Found: C, 62.98; H, 4.57; N, 7.46%.

1–Heptyl–3–(4–methoxybenzoyl)–2–methylthio–5–nitropyrole (6i). Colorless solid; mp 11 5–116°C; Yield 37%; IR (KBr): 1618, 1530, 1305 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 0.56 (t, J = 7 Hz, 3H, CH_3), 1.03 (brs, 10H, $(CH_2)_5$), 3.00 (s, 3H, SCH_3), 3.66 (s, 3H, OCH_3), 4.75 (t, J = 7 Hz, 2H, CH_2), 6.79 (d, J = 9 Hz, 2H ArH), 7.26 (s, 1H, H–4), 7.69 (d, J = 9 Hz, 2H, ArH). Anal Calcd for $C_{20}H_{26}N_2O_4S$ (390.4): C, 61.51; H, 6.71; N, 7.17%. Found: C, 61.77; H, 6.49; N, 6.89%.

1–Butyl–3–(4–methylbenzoyl)–2–methylthio–5–nitropyrrole (6j). Colorless soild, mp 125–126°C; Yield 43%; IR (KBr): 1625, 1520, 1300 cm^{-1}, ^1H NMR (90 MHz, $CDCl_3$): 1.00 (t, J = 7 Hz, 3H, CH_3), 1.19–2.19 (m, 4H, $CH_2)_2$), 2.42 (s, 3H, CH_3), 3.26 (s, 3H, SCH_3), 4.92 (t, J = 7 Hz, 2H, CH_2), 7.06–7.39 (m, 3H, H–4 and 2H, ArH), 7.62 (d, J = 9 Hz, 2H, ArH). Anal Calcd for $C_{17}H_{20}N_2O_3S$ (332.4): C, 61.42; H, 6.06; N, 8.42%. Found: C, 61.27; H, 5.88; N, 8.55%.

1–Benzyl–3–(2,4–dichlorobenzoyl)–2–methylthio–5–nitropyrrole (6k). Colorless solid; mp 94–95°C; Yield 51%; IR (KBr): 1660, 1542, 1318 cm^{-1} ^1H NMR (90 MHz, $CDCl_3$): 2.96 (s, 3H, SCH_3), 6.46 (dd, J = 15.9 Hz, 2H, CH_2), 7.00–7.23 (m, 2H, ArH), 7.29–7.56 (m, 6H, ArH), 7.62 (s, 1H, H–4). Anal Calcd for $C_{19}H_{14}N_2O_3SCl_2$ (421.2): C, 54.16; H, 3.34; N, 6.64%. Found: C, 54.34; H, 3.52; N, 6.48%.

1–Cyclohexyl–3–(2,4–dichlorobenzoyl)–2–methylthio–5–nitropyrrole (6l). Colorless solid; mp 169–170°C; Yield 54%; Ir (KBr): 1605, 1517, 1318 cm^{-1}, ^{1} H NMR (90 MHz, $CDCl_3$): 1.06–2.62 (m, 10H, $(CH_2)_5$), 3.29 (s, 3H, SCH_3), 5.69 (brs, 1H, CH), 7.23 (s, 1H, H–4), 7.46

(brs, 2H, ArH), 7.62 (s, 1H, ArH). Anal Calcd for $C_{18}H_{18}N_2O_3SCl_2$ (413.3): C, 52.30; H, 4.38; N, 6.77%. Found: C, 52.47; H, 4.56; N, 6.98%.

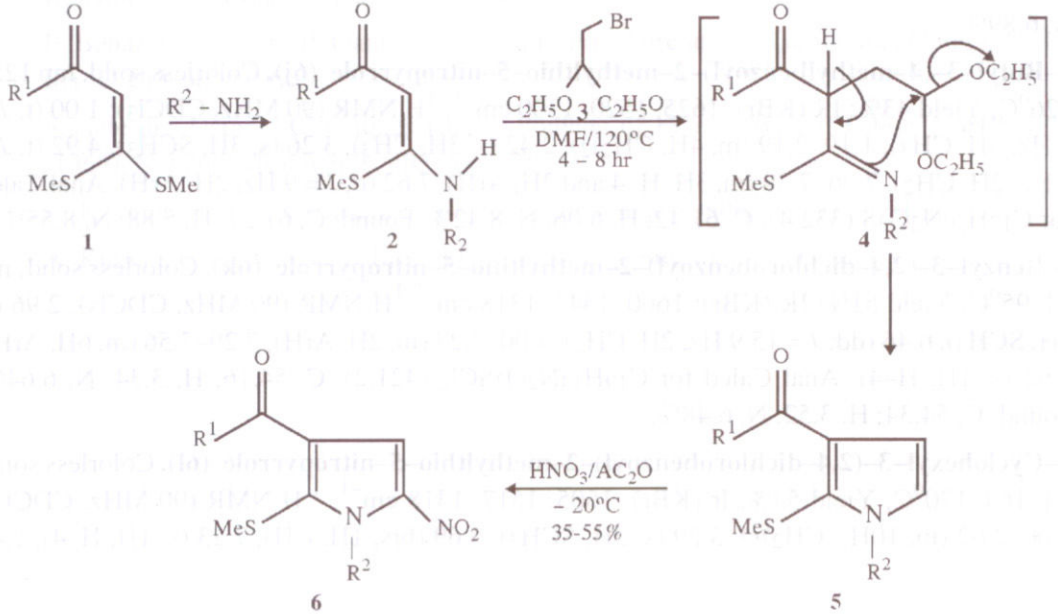
1–Benzyl–3–(3,4–dichlorobenzoyl)–2–methylthio–5–nitropyrrole (6m). Colorless solid; mp 113°C; Yield 51%; IR (KBr): 1657, 1545, 1310 cm^{-1}, ^1H NMR (90 MHz, $CDCl_3$): 2.96 (s, 3H, SCH_3), 6.52 (dd, J = 15, 9 Hz, 2H, CH_2), 7.09–7.26 (m, 2H, ArH), 7.33–7.52 (m, 3H, ArH), 7.62 (s, 1H, H–4, ArH), 7.72–7.95 (m, 2H, ArH), 8.00 (brs, 1H, ArH). Anal Calcd for $C_{19}H_{14}N_2O_3SCl_2$ (421.2): C, 54.16: H, 3.34; N, 6.64%. Found: C, 54.33; H, 3.57; N, 6.49%.

1–Cyclohexyl–3–(3,4–cichlorobenzoyl)–2–methylthio–5–nitropyrrole (6n). Colorless solid; mp 154–155°C; Yield 52%; IR (KBr): 1647, 1536, 1306 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 1.13–1.92 (m, 10H, $(CH_2)_5$), 3.33 (s, 3H, SCH_3), 5.66 (brs, 1H, CH), 7.42 (s, 1H, H–4), 7.69 (brs, 2H, ArH), 8.00 (brs, 1H, ArH). Anal Calcd for $C_{18}H_{18}N_2O_3Cl_2$ (413.3): C, 52.30; H, 4.38; N, 6.77%. Found: C, 52.11; H, 4.56; N, 6.65%.

1–Cetyl–3–(3,4–cichlorobenzoyl)–2–methylthio–5–nitropyrrole (6o). Colorless solid; mp 76–77°C; Yield 55%; IR (KBr): 1641, 1529, 1300 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 0.56 (brs, 3H, CH_3), 1.29 (brs, 28H, $(CH_2)_{14}$), 3.23 (s, 3H, SCH_3), 5.00 (brs, 2H, CH_2), 7.46 (s, 1H, H–4, ArH), 7.69 (brs, 2H, ArH), 7.97 (brs, 1H, ArH). Anal Calcd for $C_{28}H_{40}N_2O_3SCl_2$ (555.5): C, 60.52; H, 7.25; N, 5.04%. Found: C, 60.71; H, 7.49; N, 5.27%.

RESULTS AND DISCUSSION

The hitherto unreported S, N–acetals (**2e–o**) were conveniently prepared by treating the corresponding α–oxoketene dithioacetals with various amines. Thus the α–oxoketene



dithioacetal (**1e**) was reacted with cyclohexylamine in refluxing ethanol to afford the corresponding S,N–acetal in 83% yield. The other S,N–acetals (**2f–t**) were similarly prepared by reacting the dithioacetals with different primary amines in 78–85% overall yield. The S,N–acetals (**2a–d**) were prepared according to the reported procedure.[8]

In a typical experiment, S,N–acetal (**2a**) was reacted with equimolar quantity of bromoacetaldehyde diethylacetal (**3**) in DMF at 120°C to afford after work up the corresponding 1–ethyl–3–acetyl–2–methylthiopyrrole (**4a**) in 71% yield. Similarly, the other S,N–acetals (**2b–o**) were reacted with (**3**) under the above reaction condition to afford 1–substituted 3–aceyl/aryl–2–methylthiopyrroles (**4b–o**) in 67–86% overall yields. The structures of these pyrroles (**5a–o**) were confirmed by spectral and analytical data.

The pyrrole (**5a**) was conveniently nitrated in moderate to good yield by treating with fuming HNO_3 in the presence of acetic anhydride. Thus, a mixture of fuming HNO_3 (20 mmol) and acetic anhydride (3 mL) was added dropwise to a mixture of pyrrole (**5a**) (10 mmol) and acetic anhydride (7 mL) at –20°C and allowed the reaction mixture to rise to room temperature. The reaction mixture after work up and purification by column chromatography on silica gel

Table 1. Synthesis of 1–substituted–3–acyl–2–methylthio–5–nitro pyrroles (6a–o)

1–5,6 R^1	R^2	Yield (%), 6	mp (°C), 6	Antiamebic (*in vitro*) Cydal (Conc. μg/mL)
a Me	Et	35	120–121	Active (25) 24 h
b C_6H_5	n–Bu	43	97–98	Active (12.5) 24 h
c C_6H_5	$C_6H_5CH_2$	42	134–135	Active (12.5) 24 h
d C_6H_5	$CycloC_6H_{11}$	41	129–130	Active (25) 24 h
e C_6H_5	Cetyl	55	56–57	Inactive (100) 72h
f 4–ClC_6H_4	Et	41	155–156	Active (100) 24h
g 4–$MeOC_6H_4$	Et	35	119–120	Active 3.13) 24h
h 4–$MeOC_6H_4$	$C_6H_5CH_2$	38	120–121	Active (3.13) 48h
i 4–$MeOC_6H_4$	heptyl	37	115–116	Active (12.5) 24 h
j 4–$MeOC_6H_4$	n–Bu	43	125–126	Active (25) 24 h
k 2,4–$Cl_2C_6H_3$	$C_6H_5CH_2$	51	94–95	Active (25) 24 h
l 2,4–$Cl_2C_6H_3$	$CycloC_6H_{11}$	54	169–170	Active (25) 24 h
m3,4–$Cl_2C_6H_3$	$C_6H_5CH_2$	51	133–114	Active (3.13) 24 h
n 3,4–$Cl_2C_6H_3$	$CycloC_6H_{11}$	52	154–155	Active (100) 24h
o 3,4–$Cl_2C_6H_3$	Cetyl	55	76–77	Inactive (100) 72h

using hexane–ethyl acetate (19 : 1) as eluent afforded the corresponding 1–ethyl–3–acetyl–2–methylthio–5–nitropyrrole (**6a**) in 35% yield. The compound was confirmed by its spectral and analytical data. The other nitro pyrroles (**6b–o**) were similarly prepared in 35–55% overall yields (Table 1). The spectral and analytical data were in conformity with the assigned structures. The nitropyrroles (**6a–0**) thus prepared were screened for antiamebic activity at Organon Research Centre, Calcutta, India. The biological activity of these pyrroles is given in the Table 1.

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