Novel Synthesis of Thioguanine and Sulfanylpurine Analogues: Reaction of Heterocyclic Ketene Dithioacetals with Nucleophiles†

J. Chem. Research (S), 1998, 162–163†

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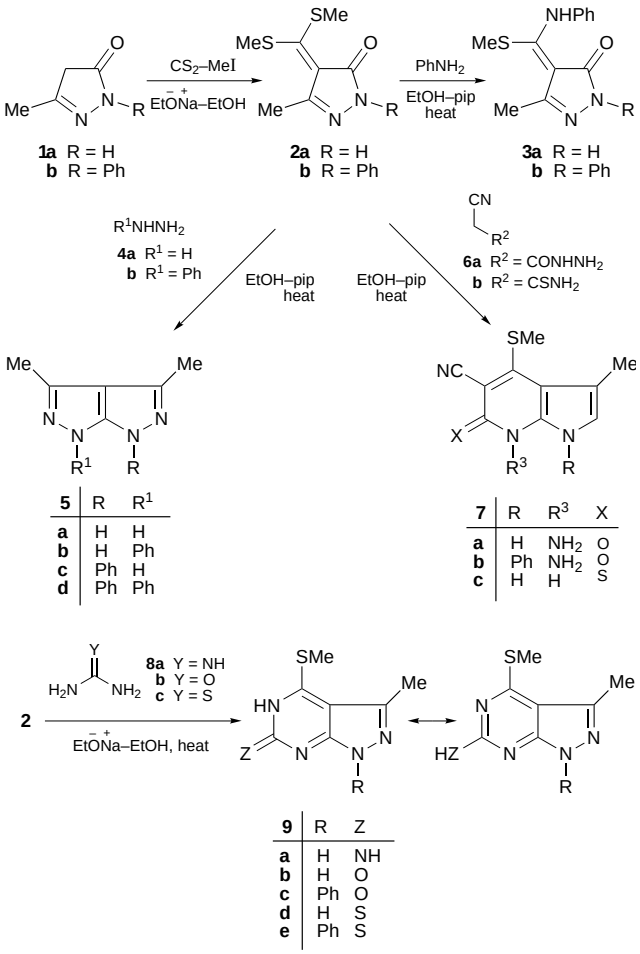
A novel synthesis of thioguanine and sulfanylpurine analogues *via* the reaction of heterocyclic ketone dithioacetals with nucleophiles is reported and the synthetic potential of the method is demonstrated.

Synthetic analogues of purines are widely used in medical science and clinical medicine. The purine analogues of purines are widely used in medical science and clinical medicine. The purine analogue 4-hydroxypyrazolopyrimidine (allopurinol), used in treatment of hyperuricemia and gout, inhibits *de novo* purine biosynthesis and xanthine oxidase activity. Both 6-thioguanine and 6-sulfanylpurine, in which thiol groups replace the hydroxy groups at the 6-position, are widely used clinically. As part of our programme of research on the synthesis of purine analogues and other antimetabolites[1–7] we have recently reported an interesting synthesis of 7-methylsulfanylpyrazolo[1,5-*a*]pyrimidines and 7-methylsulfanylpyrazolo[1,2-*c*]imidazolones *via* the reaction of cyanoketene dithioacetals with 5-aminopyrazoles and 2-sulfanylhydantoins, respectively.[8–10] We report here a novel and convenient method for the synthesis of fused pyrazoles carrying a methysulfanyl group. Derivatives of these ring systems are interesting because they are sulfanylpurine analogues and as such they may have useful properties as antimetabolites in purine biochemical reactions. The heterocyclic ketone dithioacetals **2** were chosen as the key intermediate and were prepared by the reaction of pyrazolin-5-ones **1** with sodium ethoxide and carbon disulfide, followed by methyl iodide treatment in a one-pot reaction (Scheme 1). The structure of **2** was established on the basis of elemental analysis and spectral data. Thus, the mass spectrum of **2a** was compatible with the molecular formula $C_7H_{10}N_2OS_2$ (M^+ 202) and its ^1H NMR spectrum contained two singlets at δ 2.52 and 2.63 ppm, which are assignable to two methylsulfanyl groups, and a broad band at 12.22 ppm assignable to an NH group.

The ^{13}C NMR spectrum was characterized by two signals, at 18.20 and 18.70 ppm corresponding to two SMe carbons. Compounds **2** reacted with aromatic amines in refluxing ethanol containing catalytic amounts of piperidine to afford the corresponding anilino derivates **3**. The structures of compound **3** were established on the basis of elemental analysis and spectral data. Thus, the mass spectrum of **3a** was compatible with the molecular formula $C_{12}H_{13}N_3OS$ (M^+ 247) and its ^1H NMR spectrum contained a band at 2.52 ppm, assigned to the SMe group, and two broad bands at 10.17 and 11.00 ppm assignable to two NH groups. Compounds **2** bearing latent functional substituents were found useful for the synthesis of fused pyrazole derivatives. Thus, it has been found that the reaction of ketone dithioacetals **2** with hydrazine hydrate in refluxing ethanol containing catalytic amounts of piperidine gives the corresponding 4-methylsulfanylpyrazolo[3,4-*c*]pyrazoles (**5**) in good yields. The structures of **5** were established and confirmed for the reaction products on the basis of their elemental analysis and spectral data (MS, IR and ^1H NMR). The analytical data for **5a** indicated a molecular formula $C_6H_8N_4S$ (M^+ 168) and ^1H NMR revealed a band at δ 2.74 ppm, assignable to a SMe group. When compounds **2** were subjected to reaction with cyanoacetohydrazide **6a** or cyanothioacetamide **6b** in refluxing ethanol containing catalytic amounts of piperidine, the corresponding 4-methylsulfanylpyrazolo[3,4-*b*]pyridine derivatives **7** were obtained and their structures were established on the basis of elemental analysis and spectral data. Thus, for **7b** the IR spectrum revealed the presence of a cyano group at 2220 cm^{-1}, and the ^1H NMR spectrum revealed a band at δ 2.56 ppm, assignable to the SMe group, a multiplet at δ 6.91–8.70 ppm, assigned for aromatic protons, and a broad singlet at δ 3.35 ppm assigned to the amino group. The formation



Scheme 1

*To receive any correspondence.
†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

of **7** from the reaction of dithioacetals **2** and cyanoacetohydrazide **6a** is assumed to proceed *via* the intermediacy of Michael adducts, which cyclize to yield the final 4-methylsulfanypyrazolo[3,4-*b*]pyridin-6-one **7**. Direct treatment of **2** with guanidine, urea or thiourea afforded the corresponding 4-methylsulfanylpyrazolo[3,4-*d*]pyrimidine derivatives **9**. The structures of compounds **9** were established on the basis of their elemental analysis and spectral data. The ^{1}H NMR spectrum of **9a** showed a broad band at δ 6.80 ppm assignable to an amino group. The mass spectrum was compatible with the molecular formula $C_7H_9N_5S$ (M^+ 196).

In summary, we have achieved a regiospecific synthesis of interesting non-classical sulfanylpurine and thioguanine analogues and other antimetabolites by the reaction of heterocyclic ketone dithioacetals with hydrazine derivatives and active methylene compounds. The compounds obtained seem promising for further chemical transformations and biological evaluation studies.

Experimental

All mps are uncorrected. The IR spectra were obtained (KBr disk) on a Perkin Elmer/1650 FT-IR instrument. The ^{1}H NMR spectra were measured on a Varian 400 MHz spectrometer for solutions in $(CD_3)_2SO$ using $SiMe_4$ as an internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Center at Cairo University.

4-*Bis*(*methylsulfanyl*)*methylidene*-3-*methylpyrazolin*-5-*ones* (**2a,b**). *General procedure*.—A mixture of 3-methylpyrazolin-5-ones (**1**) (0.01 mol) and a solution of sodium ethoxide (0.02 mol) was boiled under reflux for 20 min, then cooled and carbon disulfide (0.01 mol) was added. The reaction mixture was warmed at 30 °C for 20 min. After cooling, methyl iodide (0.02 mol) was added. The mixture was poured over an ice–water mixture and neutralized with dil. hydrochloric acid. The precipitated product was collected by filtration and recrystallized from ethanol **2a**. Yellow crystals, from EtOH, yield 95%, mp 202 °C; ν_{max}/cm^{-1} (KBr) 1655 (CO), 1525 (C=N); δ_H [$(CD_3)_2SO$] 2.51 (s. 3 H, CH_3), 2.52 (s, 3 H, SCH_3), 2.63 (s, 3 H, SCH_3), 12.22 (s, br, 1 H, NH), δ_C 11.51 (CH_3), 18.22 (SCH_3), 18.70 (SCH_3), 113.10 (C-6), 143.00 (C-4), 160.00 (C-3), 183.00 (C-5); *m*/*z* 202 (Found: C, 41.8; H, 4.5; N, 13.6. $C_7H_{10}N_2OS_2$ requires C, 41.6; H, 4.9; N, 13.8%). **2b**: Yellow crystals, from EtOH, yield 95%, mp 94 °C; ν_{max}/cm^{-1} (KBr) 1655 (CO), 1525 (C=N); *m*/*z* 278 (Found: C, 56.4; H, 5.1; N, 10.3. $C_7H_{10}N_2OS_2$ requires C, 56.1; H, 5.0; N, 10.0%).

4-*Substituted*-3-*methylpyrazolin*-5-*one derivatives* (**3a,b**). *General procedure*.—A mixture of pyrazolinones **2a,b** (0.01 mol) and aniline (0.01 mol) was boiled under reflux in ethanol (30 ml), containing a catalytic amount of piperidine for 3 h. The product was isolated after cooling, and recrystallized from ethanol. **3a**: Yellow crystals, from EtOH, yield 80%, mp 235 °C; ν_{max}/cm^{-1} (KBr) 3426 (NH), 1657 (CO), δ_H [$(CD_3)_2SO$] 2.40 (s, 3 H, CH_3), 2.52 (s, 3 H, SCH_3); 7.1–7.8 (m, 5 H, C_6H_5), 10.17 (s, br, 1 H, NH), 11.00 (s, br, 1 H, NH); *m*/*z* 247 (Found: C, 58.6; H, 4.9; N, 17.2. $C_{12}H_{13}N_3OS$ requires C, 58.3; H, 5.2; N, 17.0). **3b**: Yellow crystals, from EtOH, yield 55%, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3178 (NH), 1668 (CO), 1536 (C=N) (Found: C, 66.5; H, 5.1; N, 13.4. $C_{18}H_{17}N_3OS$ requires C, 66.8; H, 5.3; N, 13.0%).

3-*Methyl*-4-*methylsulfanylpyrazolo*[4,3-*c*]*pyrazoles* (**3a,b**). *General procedure*.—A solution of pyrazolinones **2a,b** (0.01 mol) and hydrazine hydrate or phenylhydrazine (0.01 mol) in ethanol (30 ml) containing a catalytic amount of piperidine was boiled under reflux for 3 h. The solution mixture was left to cool, and the product which separated was collected and recrystallized from the appropriate solvent. **5a**: Buff crystals, from DMF, yield 75%, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3341, 3310, 3270 (NH), 1538 (C=N); δ_H [$(CD_3)_2SO$] 2.51 (s, 3 H, CH_3), 2.74 (s, 3 H, SCH_3), 7.96 (s, br, 1 H, NH), 9.78 (s, br, 1 H, NH); *m*/*z* 168 (Found: C, 42.5; H, 4.5; N, 33.6. $C_6H_8N_4S$ requires C, 42.8; H, 4.7; N, 33.3%). **5b**: Green crystals, from EtOH, yield 60%, mp 190 °C; ν_{max}/cm^{-1} (KBr) 3384, 3182 (NH), 1623 (C=N); (Found: C, 59.4; H, 5.1; N, 23.2. $C_{12}H_{12}N_4S$: requires C, 59.0; H, 4.9; N, 22.9%). **5c**: Buff crystals, from DMF, yield 60%, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3404, 3240, 3035 (NH), 1594 (C=N); δ_H [$(CD_3)_2SO$] 2.36 (s, 3 H, CH_3), 2.53 (s, 3 H, SCH_3), 7.08–8.00 (m, 5 H, C_6H_5), 9.52 (s, br, 1 H, NH) (Found: C, 59.2; H, 5.2; N, 22.7. $C_{12}H_{12}N_4S$ requires C, 59.0; H, 4.9; N, 22.9%). **5d**: Black crystals, from EtOH, yield 75%, mp 203 °C; ν_{max}/cm^{-1} (KBr) 1628 (C=N) (Found: C, 67.1; H, 4.8; N, 17.3. $C_{18}H_{16}N_4S$ requires C, 67.5; H, 5.0; N, 17.5%).

5-*Cyano*-3-*methyl*-4-*methylsulfanylpyrazolo*[3,4-*b*]*pyridines* (**7a–c**). —A mixture of pyrazolinones **2** (0.01 mol) and cyanoacetohydrazide or cyanothioacetamide (0.01 mol) was boiled under reflux in ethanol (20 ml) containing a catalytic amount of piperidine for 6 h. The product was collected and recrystallized from the appropriate solvent. **7a**: Yellow crystals, from EtOH–DMF, yield 55% mp >300 °C; ν_{max}/cm^{-1} (KBr) 3300, 3230 (NH_2, NH), 2201 (CN), 1660 (CO), 1583 (C=N); *m*/*z* 235 (Found: C, 45.5; H, 4.1; N, 29.5. $C_9H_9N_5OS$ requires C, 45.9; H, 3.8; N, 29.8%). **7b**: Yellow crystals, from EtOH, yield 55%, mp 165 °C; ν_{max}/cm^{-1} (KBr) 3204, 3008 (NH_2, NH), 2220 (CN), 1726 (CO), 1569 (C=N); δ_H [$(CD_3)_2SO$] 2.40 (s, 3 H, CH_3), 2.56 (s, 3 H, SCH_3), 3.35 (s, 2 H, N-NH_2), 6.91–8.70 (m, 5 H, C_6H_5) (Found: C, 57.6; H, 4.2; N, 22.8. $C_{15}H_{13}N_5OS$ requires C, 57.9; H, 4.2; N, 22.5%). **7c**: Brown crystals, from EtOH–DMF, yield 50%, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3328, 3140 (NH), 2201 (CN); *m*/*z* 236 (Found: C, 45.4; H, 3.6; N, 23.3. $C_9H_8N_4S_2$ requires C, 45.8; H, 3.4; N, 23.7%).

3-*Methyl*-4-*methylsulfanylpyrazolo*[3,4-*d*]*pyrimidines* (**9a–e**).—*Method (A)*: Guanidine hydrochloride (0.01 mol) was heated in sodium ethoxide (0.01 mol) in EtOH (30 ml) for 30 min, then an equivalent amount of pyrazolinone **2a** (0.01 mol) was added. The reaction mixture was boiled under reflux for 3 h. The product was obtained after treatment with dil. HCl and recrystallized from ethanol. **9a**: Yellow crystals from EtOH, yield 55%, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3637, 3443, 3302 (NH_2, NH), 1553 (C=N); δ_H {$(CD_3)_2SO$] 2.38 (s, 3 H, CH_3), 2.51 (s, 3 H, SCH_3), 6.80 (s, 2 H, NH_2), 10.85 (s, br, 1 H, NH); *m*/*z* 196 (Found: C, 43.4; H, 4.5; N, 35.5. $C_7H_9N_5S$ requires C, 43.0; H, 4.1; N, 35.9%). *Method* (*B*): Equivalent amounts of pyrazolinones **2a,b** (0.01 mol) and thiourea or urea (0.01 mol) were mixed together and heated to 190 °C for 30 min. The solidified product was collected and recrystallized from ethanol. **9b**: Yellow crystals, from EtOH, yield 55%, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3493, 3181 (NH), 1700 (CO) (Found: C, 42.4; H, 4.4; N, 28.1. $C_7H_8N_4OS$ requires C, 42.8; H, 4.0; N, 28.5%). **9c**: Yellow crystals, from EtOH, yield 60%, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3366 (NH), 1734 (CO), 1561 (C=N) (Found: C, 57.1; H, 4.6; N, 20.2. $C_{13}H_{12}N_4OS$ requires C, 57.3; H, 4.4; N, 20.5%). **9d**: Yellow crystals, from EtOH, yield 60%, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3708, 3356 (NH), 1556 (C=N) (Found: C, 39.1; H, 4.2; N, 26.2. $C_7H_8N_4S_2$ requires C, 39.6; H, 3.7; N, 26.4%). **9e**: Yellow crystals, from EtOH yield 55%, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3100 (NH), 1593 (C=N); δ_H [$(CD_3)_2SO$] 2.31 (s, 3 H, CH_3); 2.65 (s, 3 H, SCH_3); 7.38–7.71 (m, 5 H, C_6H_5) (Found: C, 54.4; H, 4.4; N, 19.1. $C_{13}H_{12}N_4S_2$ requires C, 54.1; H, 4.2; N, 19.4%).

Received, 1st July 1997; Accepted, 22nd October 1997
Paper E/7/04612J

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