Novel *N*-Substituted Amino-4-methylsulfanyl-2-pyridones and Deazapurine Analogues from Ketene Dithioacetals†

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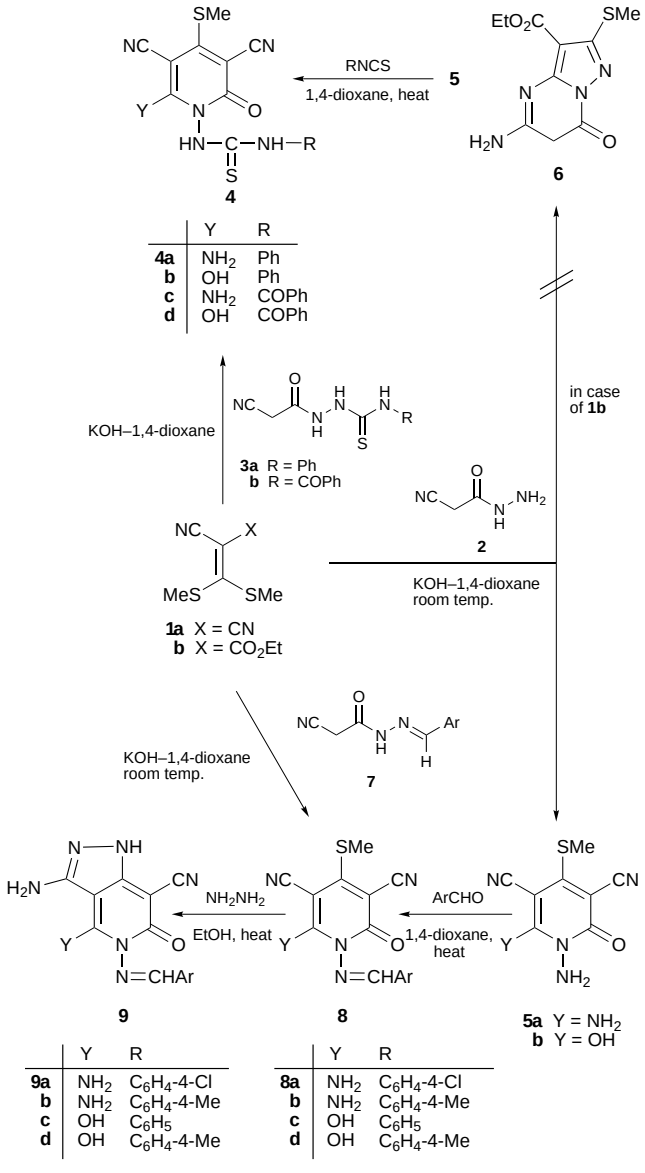
A novel synthesis of *N*-substituted amino-4-methylsulfanyl-2-pyridones and deazapurine analogues *via* the reaction of ketene dithioacetals with substituted semi- and thio-semicarbazide derivatives is reported and the synthetic potential of the method is demonstrated.

Synthetic analogues of purines are widely used in the medical sciences and in clinical medicine. Examples include the 6-sulfanylguanine and 6-sulfanylpurine which are widely used clinically. The purine analogue 4-hydroxypyrazolopyrimidine (allopurine), used in the treatment of hyperuricemia and gout, inhibits *de novo* purine biosynthesis and xanthine oxidase. Azathiopurine, which is catabolized to 6-sulfanylpurine, is employed in organ transplantation to supress events involved in immunologic rejection. As a part of our program directed towards the development of new simple and efficient procedures for the synthesis of antimetabolities,[1] we have recently reported different successful approaches for the synthesis of sulfanylpurine, 5-deazafolic acid and deazapyrimidine nucleosides.[2,3] Derivatives of these ring systems are interesting because they have useful properties as antimetabolites in biochemical reactions.[4] The present research deals with a novel synthesis of *N*-substituted amino-4-methylsulfanyl-2-pyridones and deazapurine analogues using ketene dithioacetals. Thus, it has been found that compounds **1** reacted with 4-substituted 1-cyanoacetylthiosemicarbazide **3a,b** at room temperature in the presence of pulverized potassium hydroxide in 1,4-dioxane to give the corresponding *N*-(4-methylsulfanyl-2-oxo-1-pyridyl)thiourea derivatives **4**. The structures of compounds **4** were established on the basis of their elemental analysis and spectral data (MS, ^{1}H NMR, ^{13}C NMR and IR). Thus, structure **4a** is supported by its mass spectrum which showed a molecular ion corresponding to the formula $C_{15}H_{12}N_6S_2O$ ($M^+ = 356$). The ^{1}H NMR spectrum revealed a band at δ 2.78 assignable to the SCH_3 group, a multiplet at δ 7.21–7.60 assigned to aromatic protons, a broad singlet at δ 8.78 assignable to an amino group and two broad singlets at δ 9.85 and 10.69 assigned to the NH protons. The ^{13}C NMR spectrum was characterized by a signal at δ 19.81 attributed to the SCH_3 carbon and two signals at δ 113.17 and 115.52 attributed to the two CN carbons. Moreover, signals appeared at δ 124.32, 127.56, 146.34, 149.12 and 161.93 corresponding to C-5, C-3, C-4, C-6 and C-2, respectively.

The formation of **4** from the reaction of **1** with **3** is assumed to proceed *via* Michael addition of the active methylene of **3** to the double bond in **1**. The formed Michael adducts then cyclized smoothly *via* MeSH elimination and addition to the cyano group. In a typical experiment, when the ketene dithioacetals **1a,b** reacted with cyanoacetohydrazide **2** at room temperature in the presence of KOH–1,4-dioxane, the *N*-amino-4-methylsulfanyl-2-pyridones **5a,b** were obtained in good yield. In related work, Peseke *et al.*[5] has reported the synthesis of compound **6** by the reaction of **1** with cyanoacetohydrazide **2** in unreported conditions. The structures of **5** were established and confirmed on the basis of their elemental analysis and spectral data (MS, ^{1}H NMR, ^{13}C NMR and IR). The analytical data for **5a** revealed a molecular formula $C_8H_7N_5SO$ ($M^+ = 221$) and ^{1}H NMR spectroscopy was used to confirm



Scheme 1

*To receive any correspondence.
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the structure. Thus, ^{1}H NMR revealed a band at δ 2.68 assignable to the SMe group and two broad singlets at δ 5.52 and 8.42 assignable to two amino groups. The ^{13}C NMR spectrum revealed a signal at δ 18.93 assigned to the SMe group and signals appeared at δ 120.32, 122.90, 147.14, 149.17 and 160.96 corresponding to C-5, C-3, C-4, C-6 and C-2, respectively. The formation of **5** from the reaction of **1** and cyanoacetohydrazide **2** is assumed to proceed *via* the intermediacy of Michael adducts, which cyclized to yield the final *N*-amino-2-pyridones . The reaction of ketene dithioacetals with Schiff bases was also examined. Thus, when **1a,b** were reacted with 1-cyanoacetyl-4-arylmethylidenesemicarbazide **6** in the presence of KOH–1,4-dioxane, the 2-pyridone-*N*-Schiff bases **8** were obtained. The structures of **8** were established on the basis of elemental analysis and spectral data (MS, ^{1}H NMR, ^{13}C NMR and IR). The analytical data for **8c** revealed a molecular formula $C_{16}H_{13}N_5SO$ ($M^+ = 323$). The ^{13}C NMR showed a signal at δ 18.15 due to the SMe carbon and a signal at δ 160.17 attributed to a 2-pyridone carbonyl carbon. Compounds **4** and **8** can also be prepared by the reaction of the corresponding *N*-amino-2-pyridones **5** with substituted isothiocyanates and aldehydes, respectively, in refluxing 1,4-dioxane for 2 h. Compounds **8** reacted with hydrazine in refluxing ethanol to give the corresponding pyrazolo[3,4-*c*]pyridines **9**. The structures of each of the compounds **9** were established on the basis of elemental analysis and spectral data.

In summary, we have achieved a regiospecific synthesis of interesting *N*-substituted amino-4-methylsulfanyl-2-pyridones and deazapurine analogues *via* the reaction of ketene dithioacetals with semi- and thio-semicarbazide-derivatives. The products obtained are currently under biological evaluation studies.

Experimental

All melting points are uncorrected. IR spectra were obtained (KBr) on a Pye Unicam instrument. ^{1}H- and ^{13}C-NMR spectra were measured on a Varian 400 or Wilmad 270 MHz spectrometer for $(CD_3)_2SO$ solutions using $SiMe_4$ as internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Centre at Cairo University.

N-(4-*Methylsulfanyl*-2-*oxo*-1-*pyridyl*)*thiourea Derivatives* **4a,b**. *Method A*.—A mixture of [bis(methylsulfanyl)methylene]malononitriles **1a** or ethyl 2-cyano-3,3-bis(methylsulfanyl)acrylate **1b** (0.01 mol), 4-substituted cyanoacetythiosemicarbazide **3a,b** (0.01 mol), potassium hydroxide (0.012 mol) and dry 1,4-dioxane (50 ml) were stirred at room temperature for 24 h. The reaction mixture was acidified with hydrochloric acid and the formed precipitate was collected by filtration, dried and then crystallized from the appropriate solvent.

Method B.—To a solution of *N*-amino-2-pyridones **5** (0.01 mol) in 1,4-dioxane (50 ml), phenyl isothiocyanate or benzoyl isothiocyanate (0.01 mol) was added. The resulting mixture was refluxed for 2 h and the solid product collected by filtration and crystallized from the appropriate solvent.

4a: yield 52%, mp 280–282 °C (from EtOH); ν_{max} (KBr)/cm^{-1} 3391 (NH, NH_2), 2217 (CN), 1655 (CO) (Found: C, 50.3; H, 3.6; N, 23.5%. $C_{15}H_{12}N_6S_2O$ requires C, 50.7; H, 3.4; N, 23.6%).

4b: yield 52%, mp 242–244 °C (from 1,4-dioxane); ν_{max} (KBr)/cm^{-1} 3600, 3380, 3320–3100 (OH, NH), 2212 (CN), 1655 (CO) (Found: C, 50.7; H, 3.0; N, 19.4%. $C_{15}H_{11}N_5S_2O_2$ requires C, 50.4; H, 3.1; N, 19.6%).

4c: yield 53%, mp > 300 °C (from EtOH); ν_{max} (KBr)/cm^{-1} 3312, 3280 (NH, NH_2, 2211 (CN), 1650 (CO); δ_H (DMSO) 2.69 (s, 3 H, SMe), 6.92 (m, 2 H, NH_2), 7.19–7.77 (m, 5 H, Ph), 9.60 (s, br, 1 H, NH), 10.53 (s, br, 1 H, NH) (Found: C, 49.7; H, 3.2; N, 21.9%. $C_{16}H_{13}N_6S_2O_2$ requires C, 50.0; H, 3.0; N, 21.6%).

4d: yield 55%, mp 290–293 °C (from MeOH); ν_{max} (KBr)/cm^{-1} 3454, 3350 (OH, NH), 2213 (CN), 1634 (CO). 2.82 (s, 3 H, SMe), 7.18–7.81 (m, 5 H, Ph), 11.35 (s, br, 1 H, NH), 13.50 (s, br, 1 H, NH) (Found: C, 49.5; H, 3.0; N, 18.4%. $C_{16}H_{11}N_5S_2O_3$ requires C, 49.9; H, 2.9; N, 18.2%).

N-Amino-4-*methylsulfanyl*-2-*pyridone Derivatives* **5a,b**—*General Procedure*.—A mixture of [bis(methylsulfanyl)methylene]malononitriles **1a** or ethyl 2-cyano-3,3-bis(methylsulfanyl)acrylate **1b** (0.01 mol), cyanoacetohydrazide **2** (0.01 mol), and potassium hydroxide (0.012 mol) in dry 1,4-dioxane (50 ml) was stirred at room temperature for 24 h. The reaction mixture was acidified with hydrochloric acid and the formed precipitate was collected by filtration, dried and then recrystallized from the appropriate solvent.

5a: yield 40%, mp > 300 °C (from MeOH), ν_{max} (KBr)/cm^{-1} 3549, 3292 (NH_2), 2216 (CN), 1734 (CO) (Found: C, 43.6; H, 3.3; N, 31.5%. $C_8H_7N_5SO$ requires C, 43.4; H, 3.2; N, 31.6%).

5b: yield 35%; mp 150–151 °C (from MeOH); ν_{max} (KBr)/cm^{-1} 3609, 3316 (OH, NH_2), 2213 (CN), 1734 (CO) (Found: C, 43.4; H, 2.9; N, 25.0%. $C_8H_6N_4SO_2$ requires C, 43.2; H, 2.7; N, 25.5%).

1-(*N-Substituted*)*arylmethylideneamino*-4-*methylsulfanyl*-2-*pyridone Derivatives* **8a–f**. *Method A*.—A mixture of [bis(methylsulfanyl)-methylene]malononitriles **1a** or ethyl 2-cyano-3,3-bis(methylsulfanyl)acrylate **1b** (0.01 mol), 1-cyanoacetyl-4-arylidenesemicarbazide (0.01 mol), potassium hydroxide (0.012 mol) and 1,4-dioxane (50 ml) were stirred at room temperature for 24 h. The reaction mixture was acidified with hydrochloric acid and the precipitate formed was collected by filtration, dried and then recrystallized from the appropriate solvent.

Method B. To a solution of *N*-amino-2-pyridones **5** (0.01 mol) in 1,4-dioxane (50 ml), aromatic aldehyde (0.01 mol) was added. The resulting mixture was refluxed for 2 h and the solid product collected by filtration and crystallized from the appropriate solvent.

8a: yield 51%; mp > 300 °C (from 1,4-dioxane); ν_{max} (KBr)/cm^{-1} 3425 (NH_2), 2211 (CN), 1634 (CO) (Found: C, 52.7; H, 3.1; N, 20.2%. $C_{15}H_{10}ClN_5SO$ requires C, 52.4; H, 2.9; N, 20.4%).

8b: yield 83%; mp > 300 (from 1,4-dioxane); ν_{max} (KBr)/cm^{-1} 3446 (NH_2), 2220 (CN), 1685 (CO) (Found: C, 59.0; H, 4.2; N, 21.5%. $C_{16}H_{13}N_5SO$ requires C, 59.4; H, 4.0; N, 21.7%).

8c: yield 76%; mp 285–287 °C (from MeOH); ν_{max}(KBr)/cm^{-1} 3506–3345 (OH), 2209 (CN), 1654 (CO) (Found: C, 58.2; H, 3.3; N, 17.8%. $C_{15}H_{10}N_4SO_2$ requires C, 58.0; H, 3.2; N, 18.0%).

8d: yield 62%; mp 210–211 °C (from EtOH); ν_{max}/cm^{-1} 3498, 3381 (NH_2), 2206 (CN), 1687 (CO) (Found: C, 59.0; H, 3.9; N, 17.3%. $C_{16}H_{12}N_4SO_2$ requires C, 59.3; H, 3.7; N, 17.3%).

6-*Amino*-3-*cyanopyrazolo*[3,4-*c*]*pyridin*-2(1H)-*one Derivatives* **9a–d**. *General Procedure*.—A mixture of equivalent amounts of **5b,c,e,f** (0.01 mol) and hydrazine hydrate (0.01 mol) was heated in ethanol (30 ml) for 4 h. The solid product formed was collected by filtration and crystallized from the appropriate solvent.

9a: yield 53%; mp > 300 °C (from DMF); ν_{max} (KBr)/cm^{-1} 3479, 3315 (NH, NH_2), 2210 (CN), 1655 (CO); δ_H (DMSO) 5.68 (s, br, 2 H, NH_2), 6.87–7.89 (m, 4 H, C_6H_4), 8.12 (s, 1 H, ylidic CH), 8.28 (s, br, 2 H, NH_2), 11.85 (s, br, 1 H, NH) (Found: C, 51.5; H, 2.9; N, 30.2%. $C_{14}H_{10}ClN_7O$ requires C, 51.3; H, 3.1; N, 29.9%).

9b: yield 55%; mp > 300 °C (from EtOH); ν_{max} (KBr)/cm^{-1} 3600–3182 (NH, NH_2), 2206 (CN), 1639 (CO) (Found: C, 58.2; H, 4.3; N, 32.2%. $C_{15}H_{13}N_7O$ requires C, 58.6; H, 4.2; N, 31.9%).

9c: yield 54%; mp > 300 °C (from 1,4-dioxane); ν_{max} (KBr)/cm^{-1} 3450, 3350 (OH, NH, NH_2), 2205 (CN), 1702 (CO) (Found: C, 57.4; H, 3.5; N, 28.3%. $C_{14}H_{10}N_6O_2$ requires C, 57.1; H, 3.4; N, 28.6%).

9d: yield 54%; mp > 300 °C (from MeOH); ν_{max} (KBr)/cm^{-1} 3451, 3352 (OH, NH, NH_2), 2205 (CN), 1703 (CO) (Found: C, 58.0; H, 4.0; N, 27.5%. $C_{15}H_{12}N_6O_2$ requires C, 58.4; H, 3.9; N, 27.3%).

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