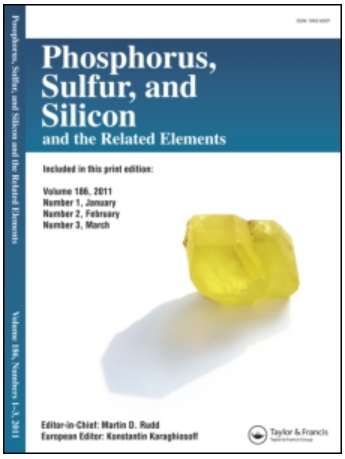

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ANTIMETABOLITES: A CONVENIENT SYNTHESIS OF MERCAPTOPURINE AND THIOGUANINE ANALOGUES

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A novel synthesis of 7-mercaptomethylpyrazolo[1,5-a]pyrimidines and pyrazolo[4,3:6′,7′]pyrazolo[1,5-a]pyrimidines utilizing ketene dithioacetals and 5-aminopyrazoles as starting components is described.

Key words: Ketene dithioacetals, 5-aminopyrazoles, mercaptopurine analogues, antimetabolites, thioguanine analogues.

INTRODUCTION

The heterocyclic bases purines are the parent molecules of nucleosides and nucleotides. Nucleotides are ubiquitous in living cells, where they perform numerous key functions.[1] Synthetic analogues of naturally occurring nucleotides find application in cancer chemotherapy as enzyme inhibitors and can replace the naturally occurring nucleotides in nucleic acids. Therapeutic attempts to inhibit the growth of cancer cells or certain viruses have often employed administration of analogues of bases, nucleosides, or nucleotides that inhibit the synthesis of their DNA or RNA. Such compounds include 6-thioguanine and 6-mercaptopurine.[2,3] Allopurinol, a purine analogue, is widely used in the treatment of gout. As a part of our program directed for development of new simple and efficient procedures for the synthesis of purine analogues and other antimetabolites,[4–7] we have recently reported different successful approaches for the synthesis of pyrazolopyrimidines.[8] Derivatives of this ring system are interesting because they are purine analogues and as such they have useful properties as antimetabolites in purine biochemical reactions.

DISCUSSION

The present paper deals with a novel synthesis of 7-methylthiopyrazolo[1,5-a]pyrimidines by the reaction of ketene dithioacetals with 5-aminopyrazoles. It has

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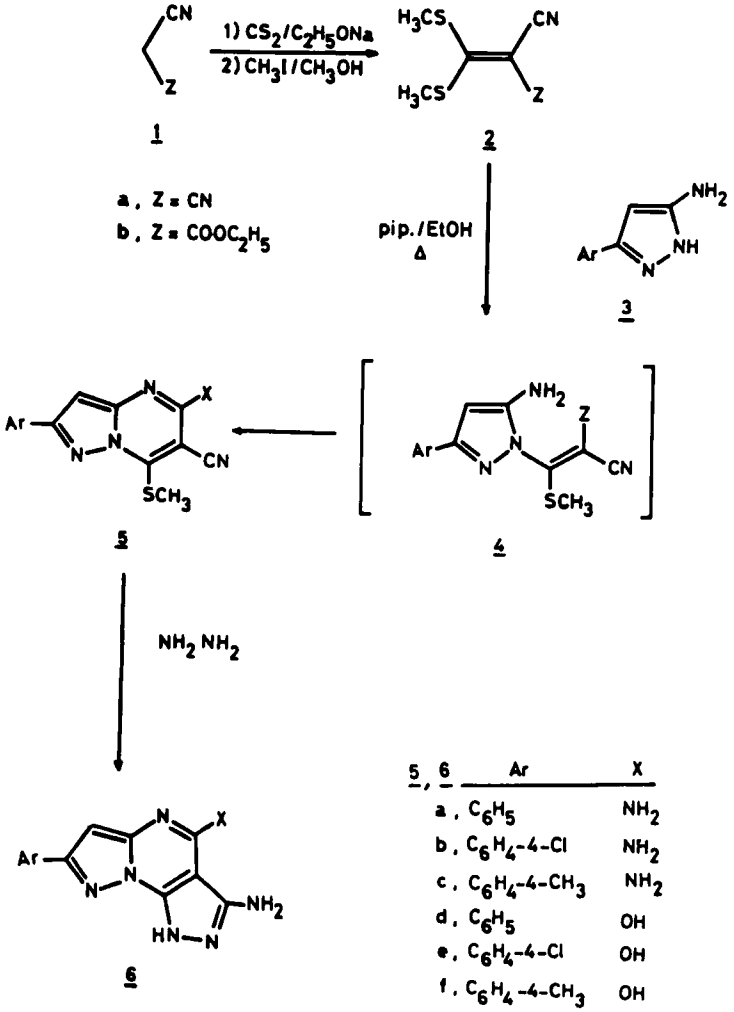
been found that 2-cyano-3,3-bis(methylthio)acrylonitrile **2a** or ethyl 2-cyano-3,3-bis(methylthio)acrylate **2b** reacts with 5-aminopyrazoles **3** in reflexing ethanol containing catalytic amounts of piperidine to give the corresponding 7-methylthiopyrazolo[1,5-a]pyrimidines **5a–f** in good yield. 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 ^{1}H NMR). The analytical data for **5b** revealed a molecular formula $C_{14}H_{10}ClN_5S$ (m^+ 315). ^{1}H NMR spectroscopy was used to confirm this structure for the product. Thus, ^{1}H NMR revealed a band at δ 2.62 ppm assignable to SCH_3 group, a multiplet at δ 7.48–8.16 ppm assigned for aromatic protons and a broad singlet at δ 8.78 ppm assignable for an amino group. The formation of **5** from the reaction of **2** with **3** is assumed to proceed via the intermediate **4**, which cyclised to yield the end products **5**. Although, one may argue that the reaction of **2** with 5-aminopyrazoles **3** may lead to the other possible 7-



5, 6	Ar	X
a	C_6H_5	NH_2
b	C_6H_4-4-Cl	NH_2
c	C_6H_4-4-CH_3	NH_2
d	C_6H_5	OH
e	C_6H_4-4-Cl	OH
f	C_6H_4-4-CH_3	OH

SCHEME 1

amino regioisomers. However, analogues for both of the last two possible isomers were previously synthesized and reported to have different NMR chemical shifts for the amino function.[9] Chemical shifts for amino groups in **5** were in agreement with those of the 5-amino analogues.[9] Compounds **5** bearing latent functional substituents were found useful for the synthesis of fused derivatives. Thus, it has been found that compounds **5** reacted with hydrazine in refluxing ethanol containing catalytic amounts of triethylamine to afford the corresponding pyrazolo[4,3:6',7']pyrazolo[1,5-a]pyrimidine derivatives **6**. The structure of compounds **6** was established on the basis of elemental analysis and spectral data. Thus, the IR spectrum of **6a** revealed the absence of a CN band, the mass spectrum was compatible with the molecular formula $C_{13}H_{11}N_7$ (m^+ 265), and the ^1H NMR spectrum contained two broad bands at δ 7.15 and 7.68 ppm assignable for two amino groups and a broad singlet at δ 8.38 ppm assignable for an NH group.

In summary, we have achieved a regiospecific synthesis of interesting mercaptopurine and pentaaza-as-indacene analogues by the reaction of ketene dithioacetals with 5-aminopyrazoles. The compounds synthesized are being subjected to biological testing.

EXPERIMENTAL

IR spectra were recorded for KBr discs on a Pye Unicam SP-1000 or a Shimadzu IR 200 spectrophotometer. ^1H NMR spectra were run on Wilmad 270 MHz or Bruker 300 MHz spectrometers with hexadeutero-dimethyl sulfoxide as solvent and tetramethylsilane as internal reference; chemical shifts are reported in δ units (ppm). Mass spectra were recorded on an AEI MS 30 mass spectrometer, at 70 ev, in the Institut für Organische Chemie, Universität Darmstadt, Germany. Analytical data were provided by the Microanalytical Center at Cairo University, Egypt.

Compounds **2a,b** were prepared following literature procedures.[10]

7-Methylthiopyrazolo[1,5-a]pyrimidine-6-carbonitriles **5a–f**. A suspension of **2** (0.01 mol) in ethanol (30 ml) was refluxed with 5-aminopyrazoles **3** (0.01 mol) and three drops of piperidine for 4 hours; the mixture was left to cool to room temperature. The crystals separating on cooling were filtered off and crystallized from the appropriate solvent: **5a** (69% yield), m.p. 250°C, ν max/cm^{-1} (KBr) 3425, 3376, 3313 (NH_2), 2211 (CN); δ_H (d_6-DMSO) 2.73 (s, 3H, SCH_3), 6.84 (s, 1H, CH), 7.40–7.76 (m, 5H, C_6H_5), 8.56 (s, br, 2H, NH_2) (Found: C, 59.7, H, 3.6, N 24.5. $C_{14}H_{11}N_5S$ (M^+ 281) requires C, 59.8, H, 3.9, N, 24.9%). **5b** (71% yield), m.p. 248°C, ν max/cm^{-1} (KBr) 3446, 3304 (NH_2), 2223 (CN); δ_H (d_6-DMSO) 2.62 (s, 3H, SCH_3), 6.92 (s, 1H, CH), 7.48–8.16 (m, 4H, C_6H_4), 8.78 (s, br, 2H, NH_2) (Found: C, 52.8, H, 3.5, N, 21.8. $C_{14}H_{10}ClN_5S$ (M^+ 315) requires C, 53.2, H, 3.2, N, 22.2%). **5c** (72% yield), m.p. 240°C, ν max/cm^{-1} (KBr) 3450, 3370 (NH_2), 2220 (CN); δ_H (d_6-DMSO) 2.36 (s, 3H, CH_3), 2.65 (s, 3H, SCH_3), 6.90 (s, 1H, CH), 7.32–7.60 (m, 4H, C_6H_4), 8.42 (s, br, 2H, NH_2) (Found: C, 60.7, H, 4.0, N, 23.3. $C_{15}H_{13}N_5S$ (M^+ 295) requires C, 61.0, H, 4.4, N, 23.7%). **5d** (64% yield), m.p. 315°C, ν max/cm^{-1} (KBr) 3421, 3241 (NH), 2213 (CN), 1665 (CO); δ_H (d_6-DMSO) 2.66 (s, 3H, SCH_3), 4.48 (s, br, 1H, OH), 6.77 (s, 1H, CH), 7.44–7.97 (m, 5H, C_6H_5) (Found: C, 59.2, H, 3.7, N, 19.5. $C_{14}H_{10}N_4SO$ (M^+ 282) requires C, 59.6, H, 3.5, N, 19.9%). **5e** (68% yield), m.p. 310°C, ν max/cm^{-1} (KBr) 3450, 3400 (NH), 2222 (CN), 1685, 1685 (CO); δ_H (d_6-DMSO) 2.63 (s, 3H, SCH_3), 4.52 (s, br, 1H, OH), 6.88 (s, 1H, CH), 7.36–7.90 (m, 4H, C_6H_4) (Found: C, 52.8, H, 3.2, N, 17.3. $C_{14}H_9ClN_4SO$ requires C, 53.1, H, 2.8, N, 17.7%. **5f** (63% yield), m.p. 298–300°C, ν max/cm^{-1} (KBr) 3390, 3350 (NH), 2220 (CN), 1666 (CO); δ_H (d_6-DMSO) 2.41 (s, 3H, CH_3), 2.59 (s, 3H, SCH_3), 4.55 (s, br, 1H, OH), 6.81 (s, 1H, CH), 7.4–7.81 (m, 4H, C_6H_4) (Found: C, 61.1, H, 3.8, N, 18.5. $C_{15}H_{12}N_4SO$ requires C, 60.8, H, 4.1, N, 18.9%).

2H-Pyrazolo[4,3:6',7']pyrazolo[1,5-a]pyrimidines **6a–f**. A solution of **5** (0.01 mol) and hydrazine (0.01 mol) in ethanol (30 ml) and a few drops of triethylamine was refluxed for 5 hours, cooled; the precipitate was filtered off and crystallized from the appropriate solvent. **6a** (75% yield), m.p. > 300°C, ν max/cm^{-1} (KBr) 3560, 3480 (NH_2, NH); δ_H (d_6-DMSO) 6.60 (s, 1H, CH), 7.15 (s, br, 2H, NH_2), 7.28–7.61 (m, 5H, C_6H_5), 7.68 (s, br, 2H, NH_2), 8.38 (s, br, 1H, NH) (Found: C, 58.5, H, 4.5, N, 36.6. $C_{13}H_{11}N_7$ (M^+ 265) requires C, 58.9, H, 4.2, N, 37.0%). **6b** (70% yield), m.p. > 300°C, ν max/

cm^{-1} (KBr) 3520, 3450 (NH_2, NH); δ_H (d_6-DMSO) 6.65 (s, 1H, CH), 7.31 (s, br, 2H, NH_2), 7.33–7.64 (m, 4H, C_6H_4), 7.77 (s, br, 2H, NH_2), 8.70 (s, br, 1H, NH) (Found: C, 51.7, H, 3.6, N, 32.3. $C_{13}H_{10}ClN_7$ (M^+ 299) requires C, 52.1, H, 3.3, N, 32.7%). **6c** (80% yield), m.p. > 300°C, ν max/cm^{-1} (KBr) 3480, 3420, 3360 (NH_2, NH) (Found: C, 59.8, H, 5.0, N, 34.8. $C_{14}H_{13}N_7$ requires C, 60.2, H, 4.7, N, 35.1%). **6d** (70% yield), m.p. 242°C, ν max/cm^{-1} (KBr) 3500, 3450 (NH_2, NH), 1660 (CO); δ_H (d_6-DMSO) 3.47 (s, br, 1H, OH), 6.61 (s, 1H, CH), 7.37 (s, br, 2H, NH_2), 7.48–7.97 (m, 5H, C_6H_5) (Found: C, 58.5, H, 4.1, N, 31.3. $C_{13}H_{10}N_6O$ (M^+ 266) requires C, 58.6, H, 3.8, N, 31.6%). **6e** (65% yield), m.p. 365°C, ν max/cm^{-1} (KBr) 3500, 3430, 3300 (NH_2, NH), 1680 (CO); δ_H (d_6-DMSO) 3.52 (s, br, 1H, OH), 6.63 (s, 1H, CH), 7.21 (s, br, 2H, NH_2), 7.35–7.85 (m, 4H, C_6H_4) (Found: C, 52.1, H, 3.3, N, 27.7. $C_{13}H_9ClN_6O$ requires C, 51.9, H, 3.0, N, 28.0%). **6f** (60% yield), m.p. 255°C, ν max/cm^{-1} (KBr) 3540, 3480 (NH_2, NH), 1690 (CO); δ_H (d_6-DMSO) 2.38 (s, 3H, CH_3), 3.62 (s, br, 1H, OH), 6.58 (s, 1H, CH), 7.20 (s, br, 2H, NH_2), 7.32–7.85 (m, 4H, C_6H_4) (Found: C, 59.7, H, 4.5, N, 29.7. $C_{14}H_{12}N_6O$ requires C, 60.0, H, 4.3, N, 30.0%).

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