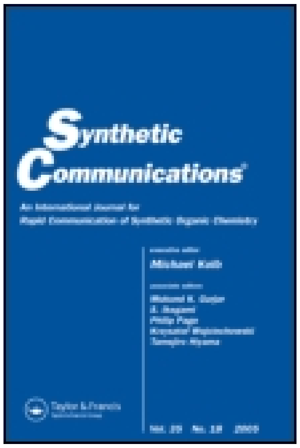

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A Novel Synthesis of N-Aryl-6-methylsulfanyl-4-pyrimidinones and Purine Analogues: The Reaction of Dimethyl N-Cyanodithioiminocarbonate with Cyanoacetanilides

Galal H. Elgemeie [a], Samia R. El-Ezbawy [a] & Soha A. Sood [a]
[a] Chemistry Department, Faculty of Science, Helwan University, Ain-Helwan, Cairo, Egypt
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A Novel Synthesis of *N*-Aryl-6-methylsulfanyl-4-pyrimidinones and Purine Analogues: The Reaction of Dimethyl *N*-Cyanodithioiminocarbonate with Cyanoacetanilides

Galal H. Elgemeie,* Samia R. El-Ezbawy, and Soha A. Sood

Chemistry Department, Faculty of Science, Helwan University, Ain-Helwan, Cairo, Egypt

ABSTRACT

A novel and efficient method for the synthesis of *N*-aryl-6-methylsulfanyl-4-oxopyrimidine-5-carbonitriles via the reaction of dimethyl *N*-cyanodithioiminocarbonate with substituted cyanoacetanilides has been investigated. (3)*N*-Aryl-2,5-diamino-7*H*-pyrazolo[3,4-d]-pyrimidin-4(3*H*)-one have also been prepared from the reaction of 6-sulfanylthio-*N*-aryl-4-pyrimidinones with hydrazines.

*Correspondence: Galal H. Elgemeie, Chemistry Department, Faculty of Science, Helwan University, Ain-Helwan, Cairo, Egypt; E-mail: rughe@rusys.eg.net.

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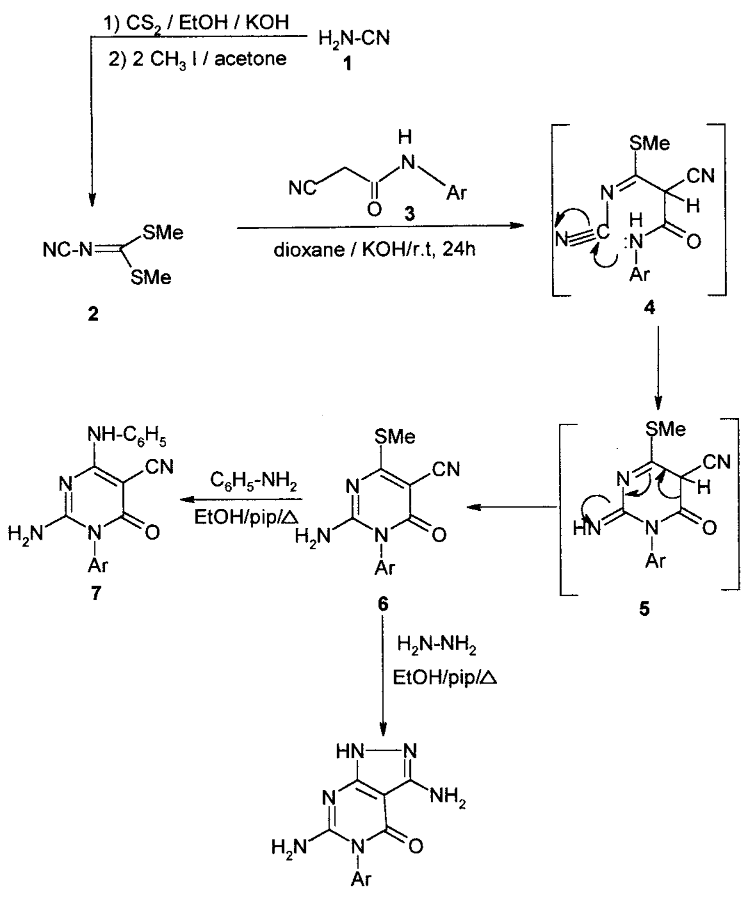
Key Words: Methylsulfanyl-pyridones; Cyanoacetanilides; *N*-Cyanodithioiminocarbonate; Pyrazolo[3,4-*d*]pyrimidines; Antimetabolite agents.

During the course of our studies directed toward exploring the synthetic potential of ketene dithioacetals for synthesizing new classes of novel antimetabolites,[1–3] we have recently reported different successful approaches for synthesis of mercaptopurine and thioguanine analogues by the reaction of ketene dithioacetals with diazoles containing amino and active methylene functions.[4,5] In an extension of this work, the present paper describes a new one-pot synthesis of *N*-aryl-6-methylsulfanyl-4-oxopyrimidine-5-carbonitriles by the reaction of dimethyl *N*-cyanodithioiminocarbonate with cyanoacetanilides. Thus, it has been found that *S*,*S*-dimethyl *N*-cyanodithioimidocarbonate **2** prepared by the reaction of cyanamide **1** with carbon disulfide and methyl iodide in the presence of alkali, was treated with cyanocetanilides **3** in dioxane containing a catalytic amount of potassium hydroxide at room temperature to yield the 4-oxopyrimidine derivatives **6**. The structures of **6** were established on the basis of elemental analysis and spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS). The formation of **6** from the reaction of **2** with **3** is assumed to proceed via Michael addition of active methylene of **3** to the double bond in **2**. The formed Michael adducts then cyclized smoothly via CH_3SH elimination and addition to the cyano group. Compounds **6**, bearing methylthio group and other latent functional substituent, were found to be useful for the synthesis of fused derivatives. Thus, compounds **6** reacted with aromatic amines in fusion to afford the corresponding 6-anilino derivatives **7**. The structure of compounds **7** were established on the basis of elemental analysis and spectral data (IR, ^{1}H NMR and MS). When compounds **6** were subjected to the reaction with hydrazine, the hydrazino derivatives could not be isolated, but cyclized to the pyrazolo[3,4-*d*]pyrimidin-4(3*H*)-one derivatives **8**, whose structure were established by elemental analysis and spectral data (IR, ^{1}H NMR and MS).

In summary, we have achieved a regiospecific synthesis of interesting 6-methylsulfanyl-*N*-aryl-4-oxopyrimidines and their corresponding purine analogues by the reaction of dimethyl *N*-cyanodithioiminocarbonate with cyanoacetanilides. The compounds obtained seems promising as high potential intermediates for synthesizing antimetabolite agents.

EXPERIMENTAL

All melting points were determined in open glass capillaries on Gallenkamp melting point apparatus and are uncorrected. Their spectra were obtioned (KBr disc) on a Perkin Elmer/1650. FT-IR instrument. The ^{1}H NMR and ^{13}C NMR. Spectra were measured in a Varian 400 or



3,6,7,8	Ar
a	C_6H_5
b	$4\text{-}H_3C\text{-}C_6H_4$
c	$4\text{-}H_3CO\text{-}C_6H_4$
d	$4\text{-}Cl\text{-}C_6H_4$
e	$4\text{-}O_2N\text{-}C_6H_4$

Wilmad 270 MHZ spectrometer for $(CD_3)_2$ SO solutions using $SiMe_4$ as internal standard. Mass spectra were recorded in a Varian MAT 112 spectrometer. Analytical data were obtained from the Micro Analytical Data Center at Cairo University.

Compounds **2** and **3** were prepared following literature procedures.[6,7]

2-Amino-(3)*N*-aryl-3,4-dihydro-6-methylthio-4-oxopyrimidine-5-carbonitriles (6a–e)

General Procedure

Dimethyl *N*-cyanodithioiminocarbonate **2** (0.01 mol) was added to a stirred solution of cyanoacetanilides **3** (0.01 mol) in a dry dioxane (50 mL) containing potassium hydroxide (0.01 mol). After stirring under dry conditions at room temperature for 24 h, the reaction mixture was diluted with cold water (50 mL). The resulting solid product was collected by filtration and recrystallized from the appropriate solvent.

6a. Rose, m.p. 225°C (from EtOH), yield (80%). IR (KBr) ν_{max}/cm^{-1} 3446 (NH_2), 2168 (CN) and 1627 (C=O). ^1H NMR (DMSO) δ 2.65 (s, 3H, SCH_3), 7.01–7.49 (m, 5H, C_6H_5), 7.52 (s, br, 2H, NH_2). ^{13}C NMR (DMSO) δ 16.54 (SCH_3), 119.03 (CN), 128.75–129.32 (phenyl carbons), 139.00 (C-5), 157.21 (C-6), 162.60 (C-2), 169.26 (C-4). $C_{12}H_{10}N_4OS$, ($M^+ = 258$), Calcd.: C, 55.81; H, 3.87; N, 21.70; S, 12.40. Found: C, 56.1; H, 3.9; N, 21.8; S, 12.5%.

6b. Buff, m.p. 210°C (from EtOH), yield (79%). IR (KBr) ν_{max}/cm^{-1} 3628 and 3446 (NH_2), 2205 (CN) and 1630 (C=O). ^1H NMR (DMSO) δ 2.24 (s, 3H, CH_3), 2.60 (s, 3H, SCH_3), 7.00–7.52 (m, 4H, C_6H_5), 7.96 (s, br, 2H, NH_2). ^{13}C NMR (DMSO) δ 16.48 (CH_3), 20.73 (SCH_3), 118.98 (CN), 128.14–131.4 (phenyl carbons), 155.41 (C-5), 159.41 (C-6), 162.36 (C-2), 173.83 (C-4). $C_{13}H_{12}N_4OS$, Calcd.: C, 57.35; H, 4.41; N, 20.58; S, 11.76. Found: C, 57.7; H, 4.5; N, 20.8; S, 11.7%.

6c. Colorless, m.p. 225°C (from EtOH), yield (85%). IR (KBr) ν_{max}/cm^{-1} 3394 and 3309 (NH_2), 2205 (CN) and 1677 (C=O). ^1H NMR (DMSO) δ 2.49 (s, 3H, SCH_3), 3.86 (s, 3H, OCH3), 7.05–7.61 (m, 4H, C_6H_5), 7.75 (s, br, 2H, NH_2). ^{13}C NMR (DMSO) δ 12.13 (SCH_3), 55.28 (OCH_3), 115.15 (CN), 126.21–129.58 (phenyl carbons), 152.31 (C-5), 55.63 (C-6), 159.46 (C-2), 173.90 (C-4). $C_{13}H_{12}N_4O_2S$, Calcd.: C, 54.16; H, 4.16; N, 19.44; S, 11.11. Found: C, 54.0; H, 4.1; N, 19.2; S, 11.1%.

6d. Rose, m.p. 240°C (from EtOH), yield (84%). IR (KBr) ν_{max}/cm^{-1} 3487 and 3381 (NH_2), 2215 (CN) and 1671 (C=O). ^1H NMR (DMSO)

δ 2.62 (s, 3H, SCH_3), 7.28–7.58 (m, 4H, C_6H_4), 7.62 (s, br, 2H, NH_2). ^{13}C NMR (DMSO) δ 12.15 (SCH_3), 115.75 (CN), 128.41–136.03 (phenyl carbons), 150.22 (C-5), 154.99 (C-6), 159.11 (C-2), 174.36 (C-4). $C_{12}H_9ClN_4OS$, Calcd.: C, 49.23 ; H, 3.07; N, 19.15; S, 10.94. Found: C, 49.3; H, 3.0; N, 19.2; S, 11.0%.

6e. Yellow, m.p. 125°C (from EtOH), yield (77%). IR (KBr) γ_{max}/cm^{-1} 3418 and 3361 (NH_2), 2171 (CN) and 1631 (C=O). $C_{12}H_9N_5O_3S$, Calcd.: C, 47.52; H, 2.97; N, 23.10; S, 10.56. Found: C, 47.8; H, 3.1; N, 23.2; S, 10.7%.

2-Amino-(3)*N*-aryl-3,4-dihydro-6-anilino-4-oxopyrimidine-5-carbonitriles (7a–e)

General Procedure

A mixture of equivalent amounts (0.01 mol) of **6a–e** and aniline were heated at 150°C, (bath temperature) for 30 min, after cooling, the resulting solid poduct was triturated with water, filtered off and crystallized from the appropriate solvent.

7a. Colorless, m.p. 300°C (from EtOH), yield (76%). IR (KBr) ν_{max}/cm^{-1} 3275 and 3352 (NH_2, NH), 2210 (CN) and 1660 (C=O). $C_{17}H_{13}N_5O$, Calcd.: C, 68.12; H, 4.29; N, 23.10. Found: C, 67.8; H, 4.5; N, 23.3%.

7b. Buff, m.p. 245°C (from EtOH), yield (83%). IR (KBr) ν_{max}/cm^{-1} 3488, 3374 and 3312 (NH_2, NH), 2221 (CN) and 1671 (C=O). $C_{18}H_{15}N_5O$, Calcd.: C, 68.14; H, 4.73; N, 22.08. Found: C, 67.1; H, 4.5; N, 22.2%.

7c. Colorless, m.p. 165°C (from EtOH), yield (85%). IR (KBr) ν_{max}/cm^{-1} 3471, 3361 and 3310 (NH_2, NH), 2213 (CN) and 1668 (C=O). $C_{18}H_{15}N_5O_2$, Calcd.: C, 64.86 ; H, 4.50; N, 21.02. Found: C, 65.0; H, 4.7; N, 21.3%.

7d. Buff, m.p. 220°C (from EtOH), yield (83%). IR (KBr ν_{max}/cm^{-1} 3459 and 3326 (NH_2, NH), 2211 (CN) and 1529 (C=O). $C_{17}H_{12}ClN_5O$, Calcd.: C, 60.04; H, 3.56; N, 20.74. Found: C, 60.0; H, 3.6; N, 20.9%.

7e. Yellow, m.p. 135°C (from EtOH), yield (75%). IR (KBr) ν_{max}/cm^{-1} 3480, 3361 and 3219 (NH_2, NH), 2219 (CN) and 1631 (C=O). ^1H NMR (DMSO) δ 6.59 (s, br, 2H, NH_2), 6.74 (s, br, 1H, NH), 7.84–7.98 (m, 9H, C_6H_4 and C_6H_5). $C_{17}H_{12}N_6O_3$, Calcd.: C, 58.62; H, 3.45; N, 24.14. Found: C, 58.9; H, 3.50; N, 24.4%.

3,6-Diamino-5-aryl-1,5-dihydro-4*H*-pyrazolo-[3,4-*d*]pyrimidin-4-ones (8a–e)

General Procedure

A mixture of **6** (0.01 mol) and hydrazine (0.01 mol) in ethanol (30 mL) containing a catalytic amounts of piperidine was refluxed for 3 h, cooled, the preciptate was filtered off and crystallized from the appropriate solvent.

8a. Colorless, m.p. >300°C (from EtOH), yield (82%). IR (KBr) ν_{max}/cm^{-1} 3511, 3428 and 3313 (NH_2, NH) and 1677 (C=O). $C_{11}H_{10}N_6O$, Calcd.: C, 54.54; H, 4.13; N, 34.71. Found: C, 54.7; H, 4.4; N, 34.9%.

8b. Buff, m.p. 240°C (from EtOH), yield (78%). IR (KBr) ν_{max}/cm^{-1} 3494, 3434 and 3345 (NH_2, NH) and 1680 (C=O). ^1H NMR (DMSO) δ 2.38 (s, 3H, CH_3), 5.07 (s, br, 2H, NH_2), 6.36 (s, br, 2H, NH_2), 7.13–7.37 (m, 4H, C_6H_4), 11.47 (s, br, 1H, NH). $C_{12}H_{12}N_6O$, Calcd.: C, 56.25; H, 4.68; N, 32.81. Found: C, 56.1; H, 4.4; N, 32.6%.

8c. Colorless, m.p. >300°C (from EtOH), yield (70%). IR (KBr) ν_{max}/cm^{-1} 3490, 3430 and 3310 (NH_2, NH) and 1660 (C=O). ^1H NMR (DMSO) δ 3.80 (s, 3H, OCH_3), 5.12 (s, br, 2H, NH_2), 6.23 (s, br, 2H, NH_2), 7.01–7.91 (m, 4H, C_6H_4), 11.34 (s, br, 1H, NH). ^{13}C NMR (DMSO) δ 55.26 (OCH_3), 127.77–130.47 (phenyl carbons), 152.80 (C-9), 154.77 (C-5), 156.31 (C-8), 158.52 (C-2), 159.24 (C-4). $C_{12}H_{12}N_6O_2$, Calcd.: C, 52.94; H, 4.41; N, 30.88. Found: C, 53.0; H, 4.6; N, 31.0%.

8d. Buff, m.p. >350°C (from EtOH), yield (83%). IR (KBr) ν_{max}/cm^{-1} 3313 (NH_2). $C_{11}H_9ClN_6O$, Calcd.: C, 47.74; H, 3.25; N, 30.37. Found: C, 48.0; H, 3.0; N, 30.7%.

8e. Colorless, m.p. >300°C (from EtOH), yield (75%). IR (KBr) ν_{max}/cm^{-1} 3480, 3361 and 3219 (NH_2, NH) and 1631 (C=O). $C_{11}H_9N_7O_3$, Calcd.: C, 45.99; H, 3.13; N, 34.15. Found: C, 46.1; H, 3.3; N, 34.2%.

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