Synthesis of some novel α-cyanoketene *S*,*S*-acetals and their use in heterocyclic synthesis

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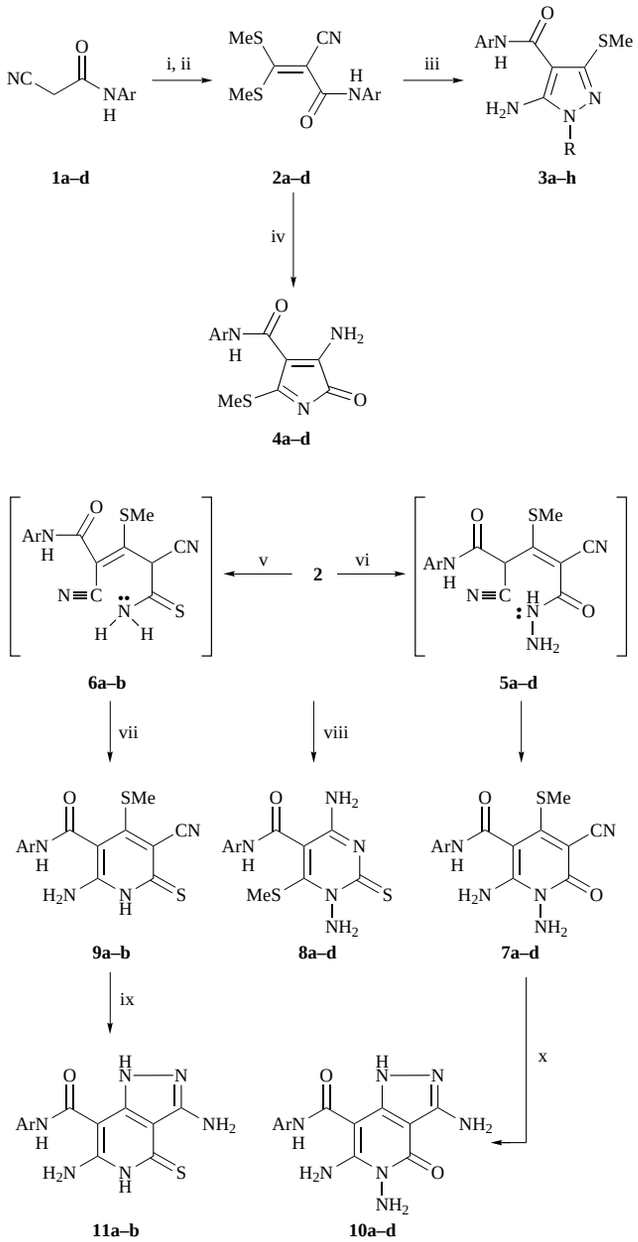
A variety of novel α-cyanoketene *S*,*S*-acetals, readily prepared by the reaction of cyanoacetanilides or cyanothioacetamide with carbon disulfide, followed by alkylation, react smoothly with nucleophiles to afford variously substituted methylthio derivatives of pyrrole, pyrazole, pyridine and pyrimidine.

The synthesis and reactions of ketene *S*,*S*-acetals, versatile starting materials for the synthesis of a wide variety of fused heterocycles,[1] have attracted much attention.[2–4] As a part of our program directed towards the development of new, simple and efficient procedures for the synthesis of mercaptopurine analogues and other antimetabolites[5–9] we have recently reported successful syntheses of mercaptopurine and thioguanine analogues by reactions of ketene dithioacetals with amino- and oxo-substituted azoles.[10] In an extension to this work, we now report a novel synthesis of functionalized pyrimidines, pyridines and other antimetabolite analogues by the reaction of ketene dithioacetals with amidine and active methylene derivatives. Thus, it has been found that reaction of substituted acetanilide derivatives **1** with carbon disulfide in the presence of sodium ethoxide followed by the alkylation with methyl iodide gives the novel ketene dithioacetals **2**, the structures of which have been established on the basis of their elemental analysis and spectral data. Thus, structure **2b** is supported by its mass spectrum which showed a molecular formula $C_{12}H_{12}N_2OS_2$ (M^+ 278) and ^{1}H NMR spectral results: δ_H 2.64 and 2.66 (2 s, 2 × SCH_3), 7.10–7.31 (m, ArH) and 7.94 (br s, NH). The ^{13}C NMR spectrum had signals at δ_C 25.69 and 25.90 (2 × SCH_3). Reaction of compounds **2** with hydrazine in refluxing ethanol containing catalytic amounts of piperidine gave the pyrazole derivatives **3**, the structures of which were established on the basis of spectral evidence: compound **3b** showed the absence of a CN absorption in its IR spectrum whilst its mass spectrum was compatible with the molecular formula $C_{12}H_{14}N_4OS$ (M^+, 262); its ^{1}H NMR spectrum had signals at δ_H 2.51 (SCH_3), 5.98 (br s, NH_2) and 9.31 and 12.61 (both br s, endocyclic and exocyclic NH). The ^{13}C NMR spectrum of **3f** was characterized by signals at δ_C 20.00 (SCH_3) and 162.00 (CO). Compounds **2** reacted with formamide in refluxing ethanol containing catalytic amounts of piperidine to afford the corresponding 5-methylthiopyrrol-2-one derivatives **4**, the structures of which were established on the basis of elemental analysis and spectral data: the mass spectrum of **4a** was compatible with the molecular formula $C_{12}H_{11}N_3O_2S$ (M^+, 262), and its ^{1}H NMR spectrum showed signals at δ_H 2.51 (s, SCH_3) and 5.51 and 9.68 (both br s, NH_2 and NH). Compounds **2** bearing latent functional substituents were used to synthesize pyrimidines, pyridines and their fused-ring derivatives. Thus, compounds **2** reacted with cyanoacetohydrazide in refluxing ethanol containing catalytic amounts of piperidine to give the corresponding 4-methylthio-1-aminopyridones **7** in good yields: structure **7d** was supported by its mass (M^+, 349), which agreed with its molecular formula $C_{14}H_{12}ClN_5O_2S$; its ^{1}H NMR spectrum displayed signals at δ 2.46 (s, SCH_3) and 3.35, 8.30 and 13.21 (three br s, for N–NH_2, NH_2 and NH). The formation of **7** from the reaction of **2** and cyanoacetohydrazide is assumed to proceed *via* intermediacy of the acyclic Michael adducts **5**, which cyclized to yield the final 1-amino-2-pyridone derivatives **7**. Compounds **7** reacted smoothly with hydrazine to yield the pyrazolo[4,3-*c*]pyridin-2-one derivatives **10**, the structures of which were established and confirmed on the basis of their elemental analysis and spectral data (MS, IR and ^{1}H NMR). Thus, a CN absorption was absent from the IR spectrum of **10d**, whilst the mass spectrum was compatible with the molecular formula $C_{13}H_{12}ClN_7O_2$ (M^+, 334); the ^{1}H NMR spectrum showed signals at δ_H 3.49, 6.14 and 9.24 (N–NH_2 and 2 × NH_2) and 9.25 and 12.28 (br s, ring NH and anilide NH). The reaction of ketene dithioacetals **2** with thiosemicarbazide in sodium isopropoxide gave the interesting 6-methylthio-1-aminopyrimidine-2-thione derivatives **8**, the structures of which were established on the basis of mass, IR and ^{1}H NMR spectral evidence. There was no CN absorption in the IR spectrum of compound **8d** and its ^{1}H NMR spectra showed broad signals at δ_H 3.51 and 8.26 (N–NH_2 and NH_2) and 13.21 (br s, NH). Treatment of the ketene dithioacetals **2** with cyanothioacetamide in refluxing ethanol containing catalytic amounts of piperidine gave the 4-methylthiopyridine-2(1*H*)-thione derivatives **9**, a reaction which was assumed to proceed *via* intermediacy of the acyclic Michael adducts **6**. The structures of **9** were established on the basis of their elemental analysis and spectral evidence (MS, IR and ^{1}H NMR). Thus, the IR spectrum for **9b** showed a CN absorption at 2222 cm^{-1}, and its ^{1}H NMR showed signals δ_H 2.47 (SCH_3) and 7.64 and 13.24 (both br s, NH_2 and NH). Compounds **9** reacted with hydrazine to yield the corresponding pyrazolo[4,3-*c*]pyridin-2-one derivatives **11**, the structures of which were established and confirmed on the basis of their elemental analysis and spectral data. Thus, a CN absorption was absent in the IR spectra for **11b** whilst its mass spectrum was compatible with the molecular formula $C_{13}H_{11}ClN_6OS$ (M^+, 334).

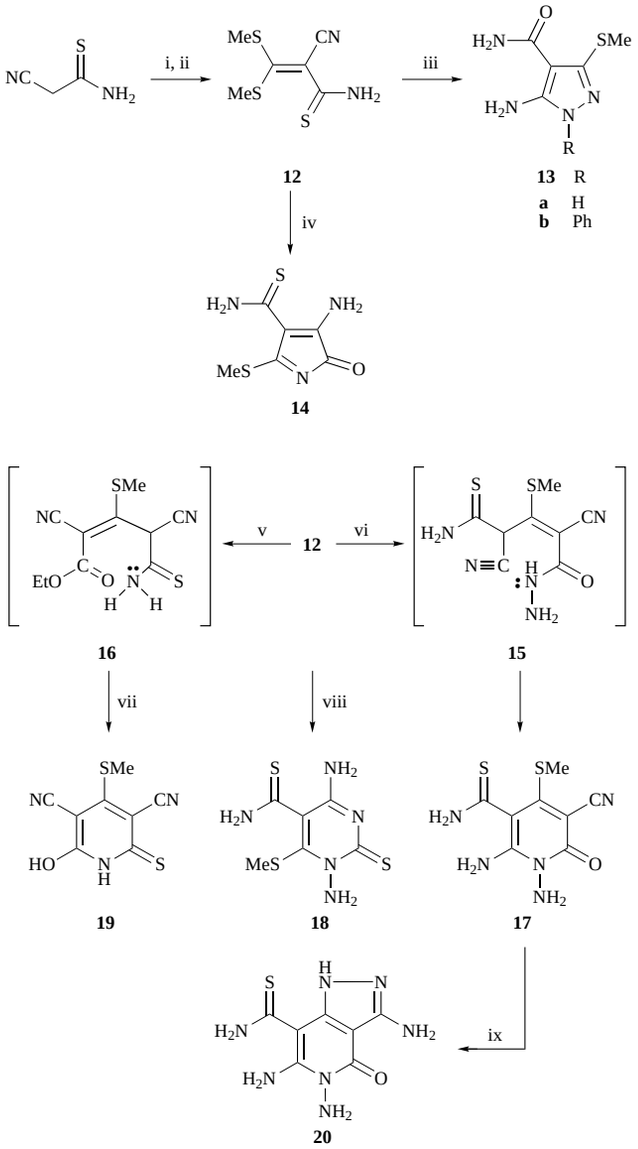
Similarly, it has been found that reaction of cyanothioacetamide with carbon disulfide in the presence of sodium ethoxide followed by alkylation with methyl iodide gave the novel ketene dithioacetals **12**, the structures of which were established on the basis of elemental analysis and spectral evidence. Reaction of compound **12** with hydrazine and formamide gave the 3-methylthiopyrazole **13** and 5-methylthiopyrrol-2-one **14**, respectively. The structure of compound **13** was established on the basis of elemental analysis and spectral evidence. Thus, its mass spectrum was compatible with the molecular formula $C_5H_8N_4S_2$ (M^+, 188). Compound **12** bearing a latent functional substituent was used for the synthesis of pyridine, pyrimidine and their fused-ring compounds. Thus, compound **12** reacted



1,2,4	Ar	3	Ar	R^1	3	Ar	R^1
a	Ph	**a**	Ph	H	**e**	Ph	Ph
b	C_6H_4Me-4	**b**	C_6H_4Me-4	H	**f**	C_6H_4Me-4	Ph
c	C_6H_4Me-4	**c**	C_6H_4Me-4	H	**g**	C_6H_4Me-4	Ph
d	C_6H_4Cl-4	**d**	C_6H_4Cl-4	H	**h**	C_6H_4Cl-4	Ph

Scheme 1 *Reagents and conditions:* i, CS_2, EtONa; ii, MeI, EtONa; iii, $RNHNH_2$, EtOH, PiP, heat; iv, H_2NCHO, EtOH, PiP, heat; v, $NCCH_2C(S)NH_2$, EtOH, PiP, heat; vi, $NCCH_2C(O)NHNH_2$, EtOH, PiP, heat; vii, EtOH, PiP, heat; viii, $H_2NNHC(S)NH_2$, $NaOPr^i$, Pr^iOH, heat; ix, NH_2NH_2, EtOH, PiP, heat; x, NH_2NH_2, EtOH, PiP, heat

with cyanoacetohydrazide and ethyl cyanoacetate in refluxing ethanol containing catalytic amounts of piperidine to give the 4-methylthio-1-aminopyridone **17** and methylthiopyridine-2(1*H*)-thiones **19**, respectively. The structures of **19** were established and confirmed on the basis of elemental analysis and spectral evidence. The reaction of ketene dithioacetal **12** with thiosemicarbazide in sodium isopropoxide gave the 6-methylthio-1-aminopyrimidine-2-thione **18**, the structure of which was established and confirmed on the basis of its elemental analysis and spectral data. Thus, the mass spectrum was compatible with the molecular formula $C_6H_9N_5S_3$ (M^+, 247), whilst its ^{1}H NMR spectrum showed signals at δ_H 2.52 (SCH_3) and 3.37, 5.25 and 8.11 (3 × br s, NH_2).



Scheme 2 *Reagents and conditions:* i, CS_2, EtONa; ii, MeI, EtOH; iii, $RNHNH_2$, EtOH, PiP, heat; iv, H_2NCHO, EtOH, PiP, heat; v, $NCCH_2C(O)OEt$, EtOH, PiP, heat; vi, $NCCH_2C(O)NHNH_2$, EtOH, PiP, heat; vii, EtOH, PiP, heat; viii, $H_2NNHC(S)NH_2$, $NaOPr^i$, Pr^iOH, heat; ix, NH_2NH_2, EtOH, PiP, heat

In summary, by the reaction of ketene dithioacetals with nucleophiles we have achieved a regiospecific synthesis of antimetabolites, compounds which have both chemical and biological potential.

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 $(CD_3)_2SO$ with $SiMe_4$ 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.

N-Substituted bis(methylthiomethylene)(cyano)acetamides 2a–e

A mixture of sodium ethoxide (0.02 mol) and the cyanoacetamide **1a**–**e** (0.01 mol) was heated for 20 min and then cooled and diluted with carbon disulfide (0.01 mol). The reaction mixture was warmed for 20 min after which it was cooled and treated with methyl iodide (0.02 mol). The mixture was poured onto ice–water and neutralized with dilute hydrochloric acid.

The precipitated product was filtered off and recrystallized from ethanol.

Compound 2a. Yellow crystals (80%), mp 145 °C; ν_{max}/cm^{-1} (KBr) 3216 and 3165 (NH), 2200 (CN) and 1652 (CO); δ_H[$(CD_3)_2SO$] 2.64 (s, 3H, SCH_3), 2.66 (s, 3H, SCH_3), 7.00–7.51 (m, 5H, C_6H_5) and 7.89 (s, br, 1H, NH) (Found: C, 54.2; H, 4.3; N, 10.8. Calc. for $C_{12}H_{12}N_2OS_2$: C, 54.5; H, 4.5; N, 10.6%).

Compound 2b. Yellow crystals (85%), mp 170 °C; ν_{max}/cm^{-1} (KBr) 3214 and 3100 (NH), 2200 (CN) and 1659 (CO); δ_H[$(CD_3)_2SO$] 2.37 (s, 3H, CH_3), 2.64 (s, 3H, SCH_3), 2.66 (s, 3H, SCH_3), 7.33 (m, 4H, C_6H_4) and 7.95 (s, br, 1H, NH); δ_C 20.04 (CH_3), 25.69 (SCH_3), 25.90 (SCH_3), 118.17 (CN), 124.81 (aromatic CH), 130.39 (=*C*–CH_3), 134.75 (aromatic CH), 136.91 (=*C*–NH), 142.54 (H_3CS–*C*=C), 168.48 (C=*C*–CN) and 175.66 (C=O); *m*/*z* 278 (Found: C, 56.3; H, 5.2; N, 10.4. Calc. for $C_{12}H_{12}N_2OS_2$: C, 56.1; H, 5.0; N, 10.0%).

Compound 2c. Yellow crystals (75%), mp 160 °C; ν_{max}/cm^{-1} (KBr) 3232 (NH), 2202 (CN) and 1653 (CO) (Found: C, 53.4; H, 4.9; N, 9.2. Calc. for $C_{13}H_{14}N_2O_2S_2$: C, 53.0; H, 4.7; N, 9.5%).

Compound 2d. Yellow crystals (80%), mp 198 °C; ν_{max}/cm^{-1} (KBr) 3243 (NH), 2203 (CN) and 1657 (CO); δ_H[$(CD_3)_2SO$] 2.52 (s, 3H, SCH_3), 2.55 (s, 3H, SCH_3), 7.10–7.61 (m, 4H, C_6H_4) and 13.22 (s, br, 1H, NH) (Found: C, 48.5; H, 3.8; N, 9.5. Calc. for $C_{12}H_{11}ClN_2OS_2$: C, 48.2; H, 3.68; N, 9.38%).

5-Amino-3-methylthiopyrazoles 3a–j

General procedure. A mixture of compounds **2a–e** (0.01 mol) and hydrazine hydrate or phenylhydrazine (0.01 mol) was refluxed in ethanol (20 ml) containing a catalytic amount of piperidine for 6 h. After cooling of the reaction mixture, the solid product was filtered off and recrystallized from ethanol.

Compound 3a. Pale yellow crystals (45%), mp 160 °C, ν_{max}/cm^{-1} (KBr) 3452, 3347 and 3271 (NH_2, NH), 1648 (CO) and 1549 (C=N); *m*/*z* 248 (Found: C, 53.2; H, 4.6; N, 22.9. Calc. for $C_{11}H_{12}N_4OS$: C, 53.4; H, 4.8; N, 22.6%).

Compound 3b. Colourless crystals (50%), mp 165 °C; ν_{max}/cm^{-1} (KBr) 3460, 3340 and 3271 (NH_2, NH), 1652 (CO) and 1608 (C=N); δ_H[$(CD_3)_2SO$] 2.33 (s, 3H, CH_3), 2.51 (s, 3H, SCH_3), 5.89 (s, 2H, NH_2), 7.1–7.4 (m, 4H, C_6H_4), 9.31 (s, br, 1H, ring NH) and 12.61 (s, br, 1H, NH); *m*/*z* 262 (Found: C, 54.6; H, 5.6; N, 21.5. Calc. for $C_{12}H_{14}N_4OS$: C, 54.96; H, 5.3; N, 21.3%).

Compound 3c. Pale yellow crystals (45%), mp 150 °C; ν_{max}/cm^{-1} (KBr) 3444, 3334 and 3295 (NH_2, NH), 1656 (CO) and 1547 (C=N); δ_H[$(CD_3)_2SO$] 2.51 (s, 3H, SCH_3), 3.81 (s, 3H, OCH_3), 6.62 (s, 2H, NH_2), 7.21–7.45 (m, 4H, C_6H_4) and 8.22 (s, br, 1H, ring NH); *m*/*z* 280 (Found: C, 51.6; H, 5.3; N, 20.5. Calc. for $C_{12}H_{14}N_4O_2S$: C, 51.8; H, 5.0; N, 20.1%).

Compound 3d. Colourless crystals (50%), mp 280 °C; ν_{max}/cm^{-1} (KBr) 3458, 3389 and 3349 (NH_2, NH) and 1650 (CO) (Found: C, 46.5; H, 4.1; N, 19.6. Calc. for $C_{11}H_{11}ClN_4OS$: C, 46.7; H, 3.8; N, 19.8%).

Compound 3e. Colourless crystals (60%), mp 200 °C; ν_{max}/cm^{-1} (KBr) 3270, 3207 and 3144 (NH_2, NH), 1669 (CO) and 1561 (C=N) (Found: C, 62.7; H, 4.5; N, 17.1. Calc. for $C_{17}H_{16}N_4OS$: C, 62.9; H, 4.9; N, 17.28%).

Compound 3f. Colourless crystals (65%), mp 145 °C; ν_{max}/cm^{-1} (KBr) 3426, 3376 and 3321 (NH_2, NH), 1661 (CO) and 1536 (C=N); δ_H[$(CD_3)_2SO$] 2.42 (s, 3H, CH_3), 2.61 (s, 3H, SCH_3), 6.61 (s, 2H, NH_2), 7.1–7.5 (m, 9H, C_6H_4 and C_6H_5) and 9.10 (s, br, 1H, NH); δ_C 15.10 (CH_3), 20.00 (SCH_3), 162.00 (C-6), 150.00 (C-5), 145.22 (C-3), 138.12 (C-4) and 120.00–137.11 (2 phenyl C) (Found: C, 63.5; H, 5.6; N, 16.2. Calc. for $C_{18}H_{18}N_4OS$: C, 63.9; H, 5.3; N, 16.56%).

Compound 3g. Pale yellow crystals (55%), mp 168 °C; ν_{max}/cm^{-1} (KBr) 3443, 3340 and 3198 (NH_2, NH) and 1660 (CO) (Found: C, 61.4; H, 5.4; N, 15.5. Calc. for $C_{18}H_{18}N_4O_2S_2$: C, 61.0; H, 5.1; N, 15.8%).

Compound 3h. Colourless crystals (70%), mp 160 °C; ν_{max}/cm^{-1} (KBr) 3427, 3376 and 3321 (NH_2, NH), 1662 (CO) and 1535 (C=N) (Found: C, 56.6; H, 4.4; N, 15.3. Calc. for $C_{17}H_{15}ClN_4OS$: C, 56.9; H, 4.2; N, 15.62%).

3-Amino-5-methylthiopyrrol-2-ones 4a–e

General procedure. A mixture of compounds **2a–e** (0.01 mol) and formamide (0.01 mol) was heated in ethanol (20 ml) containing a catalytic amount of piperidine for 3 h. After this the product was collected and recrystallized from the appropriate solvent.

Compound 4a. Brown crystals (75%), from EtOH–DMF, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3325 and 3161 (NH_2, NH) and 1662 (CO); δ_H[$(CD_3)_2SO$] 2.51 (s, 3H, SCH_3), 5.51 (s, 2H, NH_2), 7.21–7.50 (m, 5H, C_6H_5) and 9.68 (s, br, 1H, NH); *m*/*z* 262 (Found: C, 55.6; H, 4.5; N, 15.8. Calc. for $C_{12}H_{11}N_3O_2S$: C, 55.1; H, 4.2; N, 16.0%).

Compound 4b. Brown crystals (70%), from EtOH–DMF, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3330 and 3154 (NH_2, NH) and 1658 (CO) (Found: C, 56.2; H, 4.5; N, 15.6. Calc. for $C_{13}H_{13}N_3O_2S$: C, 56.7; H, 4.7; N, 15.3%).

Compound 4c. Brown crystals (74%), from EtOH–DMF, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3326 and 3154 (NH_2, NH) and 1656 (CO) (Found: C, 53.4; H, 4.6; N, 14.1. Calc. for $C_{13}H_{13}N_3O_3S$: C, 53.6; H, 4.5; N, 14.4%).

Compound 4d. Brown crystals (65%), from EtOH, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3329 and 3156 (NH_2, NH) and 1660 (CO) (Found: C, 51.41; H, 3.23; N, 15.41. Calc. for $C_{12}H_{10}ClN_3OS$: C, 51.61; H, 3.58; N, 15.05%).

6-Amino-3-cyano-4-methylthiopyridin-2-ones 7a–e

General procedure. A mixture of equivalent amounts (0.01 mol) of compound **2a–e** and cyanoacetohydrazide was refluxed in ethanol containing a catalytic amount of piperidine for 6 h. After cooling of the reaction mixture, the product was filtered off and recrystallized from ethanol.

Compound 7a. Yellow crystals (75%), mp 182 °C; ν_{max}/cm^{-1} (KBr) 3269, 3207 and 3144 (NH_2, NH), 2200 (CN) and 1669 (CO); δ_H[$(CD_3)_2SO$] 2.26 (s, 3H, SCH_3), 3.42 (s, 2H, NH_2), 3.89 (s, 2H, NH_2), 7.10–7.41 (m, 5H, C_6H_5) and 10.25 (s, br, 1H, NH) (Found: C, 53.1; H, 4.5; N, 22.5. Calc. for $C_{14}H_{13}N_5O_2S$: C, 53.3; H, 4.1; N, 22.2%).

Compound 7b. Yellow crystals (70%), mp 148 °C; ν_{max}/cm^{-1} (KBr) 3271 and 3204 (NH_2, NH), 2174 (CN) and 1664 (CO) (Found: C, 54.5; H, 4.2; N, 21.6%. Calc. for $C_{15}H_{15}N_5O_2S$: C, 54.7; H, 4.5; N, 21.3%).

Compound 7c. Yellow crystals (65%), mp 165 °C; ν_{max}/cm^{-1} (KBr) 3250 and 3019 (NH_2, NH), 2188 (CN) and 1708 (CO) (Found: C, 52.4; H, 4.6; N, 20.1. Calc. for $C_{15}H_{15}N_5O_3S$: C, 52.2; H, 4.3; N, 20.3%).

Compound 7d. Yellow crystals (80%), mp 202 °C; ν_{max}/cm^{-1} (KBr) 3240 and 3077 (NH_2, NH), 2200 (CN) and 1660 (CO); δ_H[$(CD_3)_2SO$] 2.46 (s, 3H, SCH_3), 3.35 (s, 2H, NH_2), 7.31–7.6 (m, 4H, C_6H_4), 8.24 (s, 2H, NH_2) and 13.21 (s, br, 1H, NH); *m*/*z* 349 (Found: C, 48.2; H, 3.6; N, 20.2. Calc. for $C_{14}H_{12}ClN_5O_2S$: C, 48.0; H, 3.4; N, 20.0%).

Pyrazolo[4,3-*c*]pyridin-2-ones 10a–d

General procedure. A mixture of equivalent amounts (0.01 mol) of **7a–d** and hydrazine hydrate was heated in ethanol containing a catalytic amount of piperidine for 6 h. The product was filtered off and recrystallized from the appropriate solvent.

Compound 10a. Brown crystals (52%), from EtOH–DMF, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3300, 3245 and 3023 (NH_2, NH) and 1654 (CO); δ_H[$(CD_3)_2SO$] 3.41 (s, 2H, NH_2), 3.41 (s, 2H, NH_2), 6.16 (s, 2H, NH_2), 7.31–7.62 (m, 5H, C_6H_5), 7.78 (s, 2H, NH_2), 9.26 (s, br, 1H, ring NH) and 12.30 (s, br, 1H, NH) (Found: C, 52.5; H, 4.5; N, 32.3. Calc. for $C_{13}H_{13}N_7O_2$: C, 52.2; H, 4.3; N, 32.8%).

Compound 10b. Yellow crystals (55%), from EtOH–DMF, mp >183 °C; ν_{max}/cm^{-1} (KBr) 3404, 3317 and 3200 (NH_2, NH) and 1659 (CO) (Found: C, 53.2; H, 4.5; N, 31.6. Calc. for $C_{14}H_{15}N_7O_2$: C, 53.6; H, 4.8; N, 31.3%).

Compound 10c. Yellow crystals (52%), from EtOH–DMF, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3320 and 3197 (NH_2, NH), 1660 (CO) and 1544 (C=N) (Found: C, 51.5; H, 4.4; N, 29.5. Calc. for $C_{14}H_{15}N_7O_3$: C, 51.1; H, 4.5; N, 29.8%).

Compound 10d. Yellow crystals (60%), from EtOH–DMF, mp 300 °C; ν_{max}/cm^{-1} (KBr) 3409, 3310 and 3112 (NH_2, NH), 1653 (CO) and 1603 (C=N); δ_H[$(CD_3)_2SO$] 3.36 (s, 2H, NH_2), 3.47 (s, 2H, NH_2), 6.14 (2H, NH_2), 7.32–7.56 (m, 4H, C_6H_4), 7.65 (s, 2H, NH_2), 9.24 (s, br, 1H, ring NH) and 12.28 (s, br, 1H, NH) *m*/*z* 334 (Found: C, 46.5; H, 3.9; N, 29.8. Calc. for $C_{13}H_{12}ClN_7O_2$: C, 46.8; H, 3.6; N, 29.4%).

1,4-Diamino-6-methylthiopyrimidine-2-thiones 8a–d

General procedure. To a solution of sodium isopropoxide (0.01 mol), equimolar amounts of compounds **2a–e** (0.01 mol) and thiosemicarbazide (0.01 mol) were added. The reaction mixture was refluxed for 3 h and then neutralized with dilute hydrochloric acid. The resulting precipitate was filtered off and recrystallized from the appropriate solvent.

Compound 8a. Brown crystals (52%), from DMF, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3860 and 3139 (NH_2, NH), 1690 (CO) and 1539 (C=N) (Found: C, 47.4; H, 3.5; N, 22.4. Calc. for $C_{12}H_{12}N_5OS_2$: C, 47.0; H, 3.9; N, 22.9%).

Compound 8b. Brown crystals (51%), from DMF, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3750 and 3220 (NH_2, NH), 1648 (CO) and 1548 (C=N); δ_H[$(CD_3)_2SO$] 2.25 (s, 3H, CH_3), 2.51 (s, 3H, SCH_3), 3.89 (s, 2H, NH_2), 7.15–7.50 (m, 4H, C_6H_4), 8.24 (s, 2H, NH_2) and 13.00 (s, br, 1H, NH) (Found: C, 48.1; H, 4.2; N, 22.1. Calc. for $C_{13}H_{15}N_5OS_2$: C, 48.6; H, 4.8; N, 21.8%).

Compound 8c. Pale yellow crystals (52%), from EtOH–DMF, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3444, 3377 and 3116 (NH_2, NH), 1647 (CO) and 1536 (C=N) (Found: C, 46.5; H, 4.2; N, 20.4. Calc. for $C_{13}H_{15}N_5O_2S_2$: C, 46.29; H, 4.4; N, 20.8%).

Compound 8d. Brown crystals (53%), from EtOH–DMF, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3190 and 3092 (NH_2, NH), 1676 (CO) and 1558 (C=N); δ_H[$(CD_3)_2SO$] 2.51 (s, 3H, SCH_3), 3.51 (s, 2H, NH_2), 7.31–7.62 (m, 4H, C_6H_4), 8.26 (s, 2H, NH_2) and 13.21 (s, br, 1H, NH); *m*/*z* 342 (Found: C, 42.5; H, 3.1; N, 20.1. Calc. for $C_{12}H_{12}ClN_5OS_2$: C, 42.2; H, 3.5; N, 20.5%).

6-Amino-3-cyano-4-methylthiopyridin-2-ones 9a–b

General procedure. A mixture of an equivalent amount (0.01 mol) of compounds **2a–e** and cyanothioacetamide was refluxed in ethanol containing a catalytic amount of piperidine for 6 h. After cooling of the reaction mixture, the product was filtered off and then recrystallized from ethanol.

Compound 9a. Yellow crystals (65%), from EtOH, mp 170 °C; ν_{max}/cm^{-1} (KBr) 3406, 3267 and 3203 (NH_2, NH), 2220 (CN) and 1687 (CO) (Found: C, 54.7; H, 4.5; N, 16.5. Calc. for $C_{15}H_{14}N_4OS_2$: C, 54.5; H, 4.2; N, 16.9%).

Compound 9b. Yellow crystals (70%), from EtOH, mp 165 °C; ν_{max}/cm^{-1} (KBr) 3270, 3187 and 3056 (NH_2, NH), 2222 (CN) and 1669 (CO); δ_H[$(CD_3)_2SO$] 2.47 (s, 3H, SCH_3), 7.31–7.59 (m, 4H, C_6H_4), 7.64 (s, 2H, NH_2), 8.30 (s, br, 1H, ring NH) and 13.24 (s, br, 1H, NH) (Found: C, 48.3; H, 3.5; N, 15.8. Calc. for $C_{14}H_{11}ClN_4OS_2$: C, 48.0; H, 3.1; N, 16.0%).

Pyrazolo[4,3-*c*]pyridin-2-ones 11a–b

General procedure. A mixture of equivalent amounts (0.01 mol) of **9a–b** and hydrazine hydrate was heated in ethanol containing a catalytic amount of piperidine for 6 h. The product was filtered off and recrystallized from EtOH–DMF solvent.

Compound 11a. Brown crystals (54%), mp >300 °C; ν_{max}/cm^{-1} (KBr) 3270, 3207 and 3144 (NH_2, NH), 1688 (CO) and 1560 (C=N) (Found: C, 53.7; H, 4.6; N, 26.5. Calc. for $C_{14}H_{14}N_6OS$: C, 53.5; H, 4.4; N, 26.8%).

Compound 11b. Brown crystals (60%), mp >300 °C; ν_{max}/cm^{-1} (KBr); 3440 and 3196 (NH_2, NH) and 1652 (CO); δ_H[$(CD_3)_2SO$] 7.02 (s, 2H, NH_2), 7.22–7.51 (m, 4H, C_6H_4), 8.86 (s, 2H, NH_2) and 10.6 (s, br, 1H, NH); *m*/*z* 334 (Found: C, 46.2; H, 3.7; N, 24.7. Calc. for $C_{13}H_{11}ClN_6OS$: C, 46.6; H, 3.3; N, 25.0%).

Bis(methylthiomethylene)cyanoacetamide 12

General procedure. A mixture of sodium ethoxide (0.02 mol) and cyanothioacetamide (0.01 mol) was heated for 20 min, after which it was cooled and treated with carbon disulfide (0.01 mol). The reaction mixture was warmed for 20 min and after cooling, was treated with methyl iodide (0.02 mol). It was then poured onto ice–water and neutralized with dilute hydrochloric acid. The precipitated product was filtered off and recrystallized from ethanol.

Compound 12. Brown crystals (70%), mp 185 °C; ν_{max}/cm^{-1} (KBr) 3218, 3215 and 3048 (NH_2, NH) and 2218 (CN); δ_H[$(CD_3)_2SO$] 2.59 (s, 3H, SCH_3), 2.61 (s, 3H, SCH_3), 3.44 (s, 2H, NH_2) and 12.00 (s, br, 1H, NH); *m*/*z* 204 (Found: C, 35.6; H, 3.5; N, 13.4. Calc. for $C_6H_8N_2S_3$: C, 35.3; H, 3.9; N, 13.7%).

5-Amino-3-methylthiopyrazole 13a–b

General procedure. A mixture of compound **12** (0.01 mol) and hydrazine hydrate or phenylhydrazine (0.01 mol) was refluxed in ethanol (20 ml) for 6 h. After cooling of the reaction mixture the solid product was filtered off and recrystallized.

Compound 13a. Red crystals (55%), from EtOH–DMF, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3400, 3296 and 3174 (NH_2, NH) and 1579 (C=N); δ_H[$(CD_3)_2SO$] 2.52 (s, 3H, SCH_3), 5.51 (s, 2H, NH_2) and 7.81 (s, br, 1H, NH); *m*/*z* 188 (Found: C, 31.4; H, 4.6; N, 29.4. Calc. for $C_5H_8N_4S_2$: C, 31.9; H, 4.2; N, 29.7%).

Compound 13b. Brown crystals (70%), from EtOH, mp >300 °C; ν_{max}/cm^{-1} (KBr) 3370 and 3158 (NH_2, NH) (Found: C, 50.3; H, 4.1; N, 21.7. Calc. for $C_{11}H_{12}N_4S_2$: C, 50.0; H, 4.5; N, 21.2%).

3-Amino-5-methylthiopyrrol-2-one 14

A mixture of compound **12** (0.01 mol) and formamide (0.01 mol) was heated in ethanol (20 ml) containing a catalytic amount of piperidine for 3 h. After this the product was collected and recrystallized from EtOH.

Compound 14. Brown crystals (70%), mp 240 °C; ν_{max}/cm^{-1} (KBr) 3330 and 3142 (NH_2, NH) and 1653 (CO) (Found: C, 35.5; H, 3.6; N, 20.6. Calc. for $C_6H_7N_3OS_2$: C, 35.8; H, 3.4; N, 20.9%).

6-Amino-3-cyano-4-methylthiopyridin-2-one 17

A mixture of compound **12** (0.01 mol) and cyanoacetohydrazide (0.01 mol) was refluxed in ethanol containing a catalytic amount of piperidine for 6 h. After cooling of the reaction mixture, the final product was filtered off and recrystallized from EtOH–DMF to give brown crystals (60%), mp >300 °C; ν_{max}/cm^{-1} (KBr) 3385, 3228 and 3082 (NH_2, NH), 2200 (CN) and 1658 (CO); *m*/*z* 256 (Found: C, 54.5; H, 3.7; N, 27.6. Calc. for $C_8H_9N_5OS_2$: C, 37.6; H, 3.5; N, 27.5%).

Pyrazolo[4,3-*c*]pyridin-2-one 20

A mixture of **17** (0.01 mol) and hydrazine hydrate (0.01 mol) was heated in ethanol containing a catalytic amount of piperidine for 6 h. The product was filtered off and recrystallized from EtOH to afford brown crystals (70%), mp >300 °C; ν_{max}/cm^{-1} (KBr) 3132 and 3043 (NH_2, NH), 1680 (CO) and 1591 (C=N) (Found: C, 35.5; H, 3.5; N, 41.3. Calc. for $C_7H_9N_7OS$: C, 35.1; H, 3.8; N, 41.0%).

1,4-Diamino-5-aminothiocarbonyl-6-(methylthio)pyrimidine-2-thione 18

To a solution of sodium isopropoxide (0.01 mol), compound **12** (0.01 mol) and thiosemicarbazide (0.01 mol) were added. The reaction mixture was refluxed for 3 h after which it was neutralized with dilute hydrochloric acid and the product then filtered off and recrystallized from EtOH–DMF to give brown crystals (55%), mp >300 °C; ν_{max}/cm^{-1} (KBr) 3384, 3343, 3228 and 3138 (NH_2, NH) and 1556 (C=N); δ_H[$(CD_3)_2SO$] 2.52 (s, 3H,

SCH_3), 3.21 (s, 2H, NH_2), 3.24 (s, 2H, NH_2) and 3.37 (s, 2H, NH_2); *m*/*z* 247 (Found: C, 29.4; H, 3.4; N, 28.6. Calc. for $C_6H_9N_5S_3$: C, 29.1; H, 3.6; N, 28.3%).

3-Cyano-4-methylthiopyridine-2-ones 19

Equivalent amounts (0.01 mol) of **12** and ethyl cyanoacetate were refluxed in ethanol (20 ml) containing a few drops of piperidine for 6 h. After this the product was filtered off and recrystallized from ethanol to give yellow crystals (70%), mp 190 °C; ν_{max}/cm^{-1} (KBr) 3200 and 3093 (NH_2, NH), 2174 (CN) and 1660 (CO); δ_H[$(CD_3)_2SO$] 2.52 (s, 3H, SCH_3), 9.42 (s, br, H, NH) and 12.89 (s, br, 1H, OH) (Found: C, 60.1; H, 4.3; N, 19.3. Calc. for $C_{15}H_{12}N_4OS$: C, 60.4; H, 4.0; N, 18.9%).

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