Polyfunctional heteroaromatics: a route to dicyanomethylene thiazoles based on the reaction of α-thiocyanatoketones with malononitrile

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Abstract

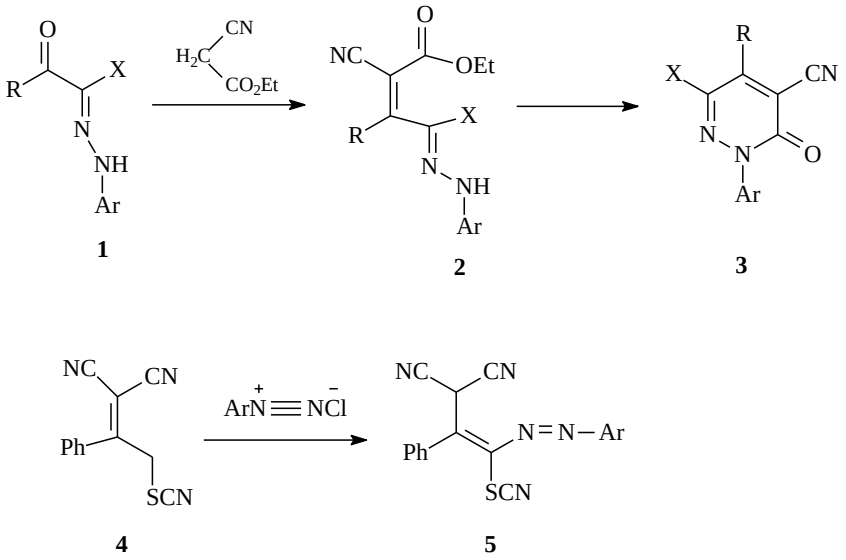
Reactions of α-*S*-cyanothioketones **6a-c** with malononitrile were observed to form 2-(thiazol-2(3*H*)-ylidene)malononitrile derivatives **7a-c**. The thiazole products readily react with aromatic diazonium salts to yield 2-(5-phenylazo-3*H*-thiazol-2-ylidene)-malononitrile derivatives **8a-c**. The malononitrile derivative **8c** undergoes a condensation with DMF/DMA to yield thiazolo[5,4-*c*]pyridazine **12**. Reactions of **7a-c** with hydrazine hydrate leads to the generation of diaminopyrazoles **9a-c**, which react with enaminone **13** to yield the corresponding thiazolylpyrazolo[1,5-*a*]pyrimidines **14**. In addition, reaction of the malononitrile derivative **8a** with benzenediazonium chloride readily affords the coupling product **10**.

Keywords: α-Thiocyanatoketones, malononitrile, thiazoles, thiazolo[5,4-*c*]pyridazine, diaminopyrazoles, thiazolylpyrazolo[1,5-*a*]pyrimidines

Introduction

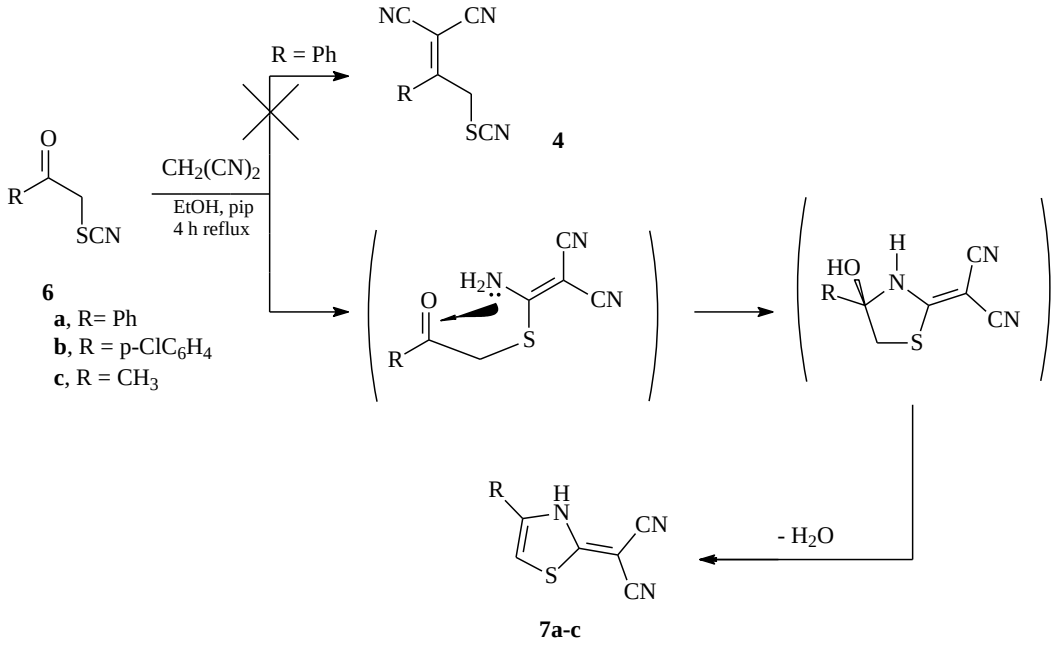
The considerable biological activity observed for pyridazines and condensed pyridazines has stimulated considerable recent interest in the synthesis of these heterocyclic compounds.[1-4] Recent developments in this area have been reviewed by one of us.[5] The results of earlier efforts have shown that condensation reactions of *N*-aryl-α-hydrazonoketones **1** with active methylene nitriles can be employed to prepare *N*-arylsubstituted-pyridazinones and pyridazine-6-imines.[6-8] It is assumed that the pathway for this process involves initial condensation of the α-hydrazonoketones with the active methylene substances to yield conjugated hydrazone-esters **2** that readily cyclize to produce **3**. In contrast, Abdelrazek and Fadda reported that the *S*-cyanothio unsaturated bis-nitrile **4** undergoes coupling with aromatic diazonium salts to yield the diazo compounds **5**, which are reported to be stable substances (Scheme 1).[9] We have already noted

that this observation should be reevaluated since, if correct, it would represent the only reported example of an acyclic diazo compound of this type.[5]



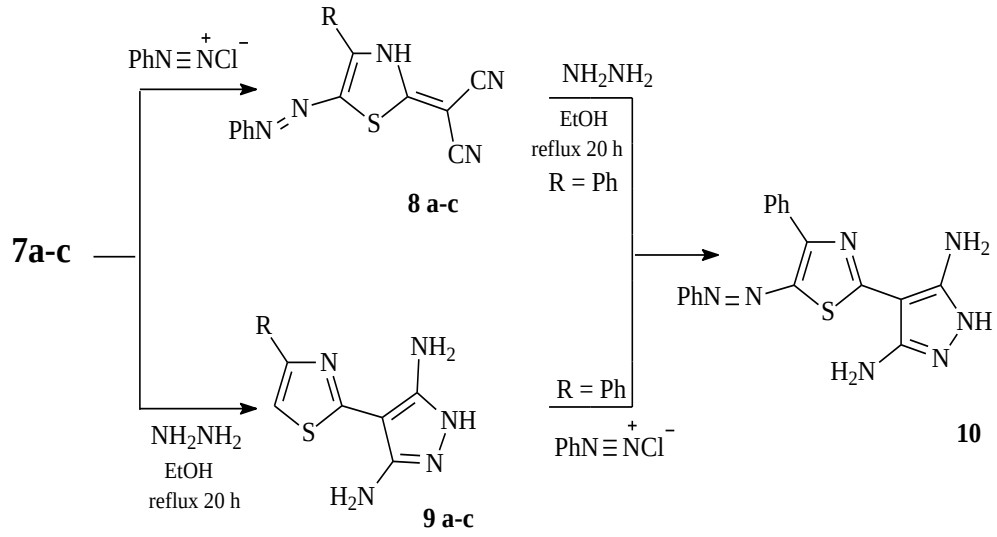
Scheme 1

Herein, we describe the results of an investigation of this process and, which has led to a reassignment of the structure of **5** to that of the thiazolidine derivatives **7a-c**. The recognition of the revised structures led to further work that culminated in the synthesis of a variety of novel condensed thiazolylpyrazolo[1,5-*a*]pyrimidines that are structurally related to zaleplone.[10]



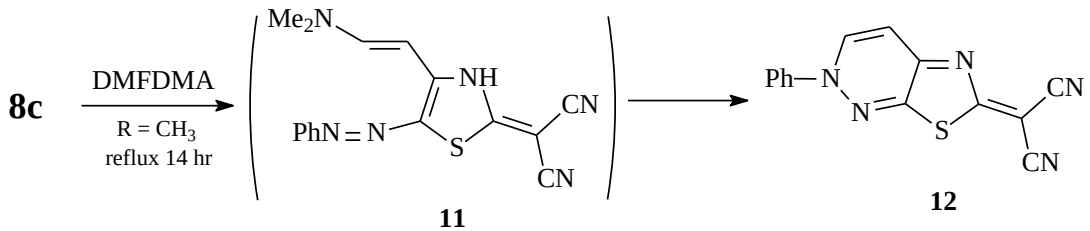
Scheme 2

Initially, we explored the report by Abdelrazek *et al*,[9] which suggested that the *S*-cyanothio unsaturated bis-nitrile **4** is obtained *via* condensation reaction of α-thiocyanatoketones **6a** with malononitrile in presence of piperidine. Indeed, we observed that this reaction affords a product with the same molecular formula of **5,** reported by the authors,[9] However, careful analysis of spectroscopic data indicated that the product of this process has the thiazolidine strucure **7a**. For example, the ^{1}H and ^{13}C NMR spectra of the product contain no resonances that correspond to protons linked to sp^3 hybridized carbons or sp^3 carbons. The obtained data matched to those expected for the thiazolidine structure **7a**. In addition, we observed that reactions of the α-*S*-cyanothioketones **6b,c** with malononitrile afforded dicyanomethylene thiazolidines, whose spectroscopic properties matched those of **7b,c** (cf. Scheme 2).



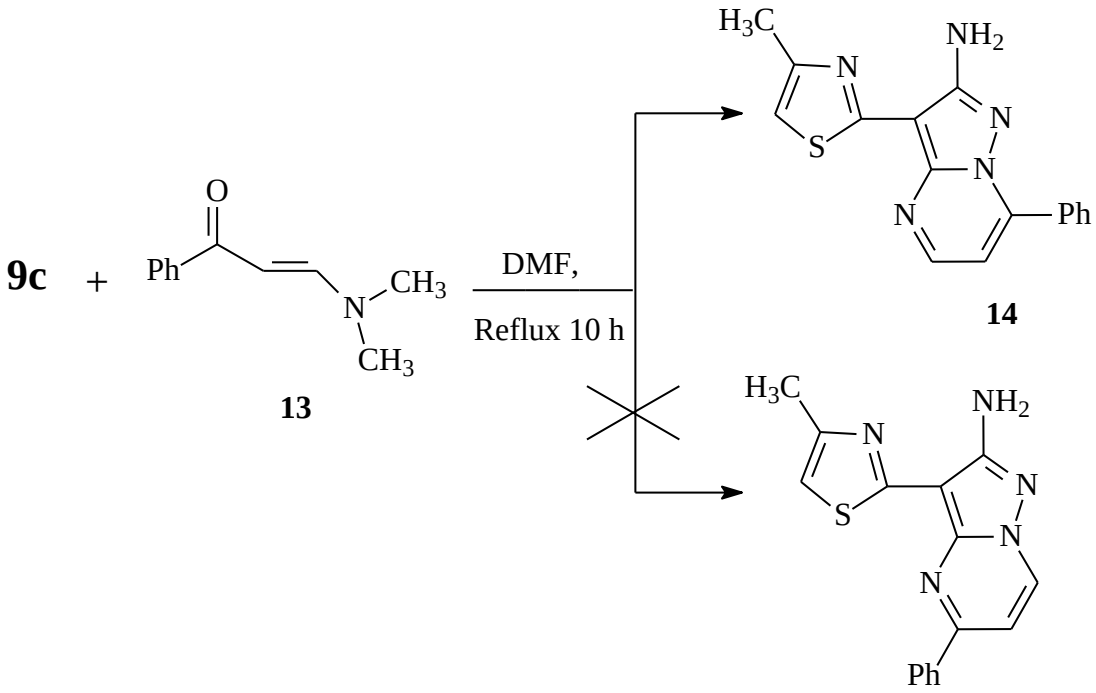
Scheme 3

In further exploratory studies, we observed that **7a-c** react with benzenediazonium chloride to generate the diazo compounds **8a-c** and that **8a** can be transformed to the diaminopyrazoles **10** by reaction with hydrazine hydrate. The pyrazolo-thiazolidines, related to **10**, were also produced by direct reactions of **7a-c** with hydrazine hydrate and subsequent coupling of the diaminopyrazolyl thiazole products **9a-c** with benzenediazonium chloride (cf. Scheme 3).



Scheme 4

In addition, we found that reaction of **8c** with DMF/DMA at reflux for 14 h afforded the thiazolo[5,4-*c*]pyridazine **12** in 80% yield. This process is assumed to follow a route in which **8c** was initially converted to the enamine derivative **11** that then underwent sequential electrocyclization and dimethylamine elimination to form **12** (cf. Scheme 4).



Scheme 5

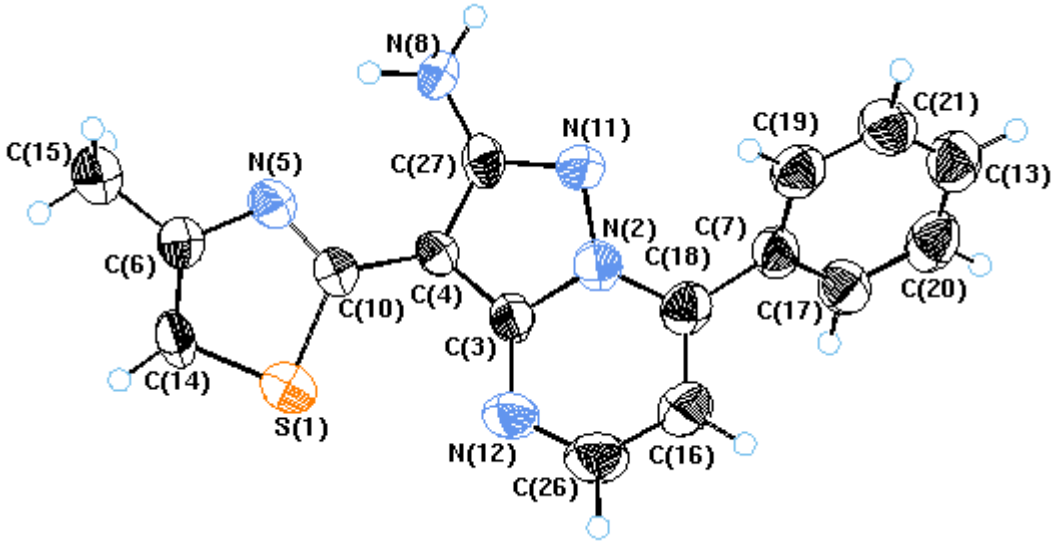


Figure 1. Plot of the x-ray crystallographic data of pyrazolo[1,a]pyrimidine **14**.

Furthermore, diaminopyrazolylthiazoles **9c** participate in an efficient condensation reaction with enaminone **13** to yield thiazolylpyrazolo[1,5-*a*]pyrimidines **14**. X-ray crystallographic analysis of this product showed unambiguously that it has the structure **14** (Figure 1) rather than that of the regioisomer **15** (Scheme 5).[11] It is important to note that **14** exists in a planar conformation, which suggests that the amino group is hydrogen bonded to thiazole ring nitrogen.

Conclusions

In conclusion, the results of this effort have led to the revised assignment of the thiazolidine structures for **7a-c** and a demonstration that these substances serve as versatile precursors to uniquely substituted pyrazolo[1,5-*a*]pyrimidines and thiazolylpyrazolo[1,5-*a*]pyrimidines.

Experimental Section

General. Melting points are reported uncorrected and were determined with a Sanyo (Gallaenkamp) instrument. Infrared spectra were recorded using KBr pellets and a Perkin-Elmer 2000 FT–IR instrument. ^{1}H and ^{13}C NMR spectra were determined by using a Bruker DPX instrument at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR and either $CDCl_3$ or DMSO-d_6 solutions with TMS as internal standards. Chemical shifts are reported in δ (ppm). Mass spectra were measured using VG Autospec Q MS 30 and MS 9 (AEI) spectrometer, with the EI (70 EV) mode. Elemental analyses were carried out by using a LEOCHNS-932 Elemental Analyzer.

General procedure for the syntheses 7a-c

Solutions of malononitrile (0.66 g, 0.01 mol) and α-thiocyanatoketones **5a-c** (0.01 mol) in ethanol (15 mL) containing piperidine (5 drops) were stirred at reflux for 3-4 h (completion assessed by TLC, 1:1 ethyl acetate- petroleum ether). The solid products, produced by pouring the reaction mixtures into ice-water and subsequent separation by filtration, were crystallized from EtOH (green crystals).

2-(4-Phenylthiazol-2(3*H*)-ylidene)malononitrile (7a). Yield 93 %; mp 275-76 ºC; Anal. calcd. for $C_{12}H_7N_3S$ (225.27): C, 63.98; H, 3.13; N, 18.65; S, 14.23. Found: C, 63.94; H, 3.31; N; 18.45; S, 13.92; IR (KBr): υ_{max} = 3147 (NH), 2210 (CN), 2175 (CN); ^{1}H-NMR (DMSO): δ, ppm = 7.33 (s, 1H, CH), 7.45-7.49 (m, 3H, Ar-H), 7.71-7.72 (m, 2H, Ar-H), 13.23 (br, 1H, NH, D_2O exchangeable); ^{13}C-NMR (DMSO): δ, ppm = 172.27, 143.70, 130.01, 129.12(2C), 128.92, 127.51 (2C), 127.64 117.75, 105.93 (2CN). MS: *m/z* (%) 225 (M^+, 100), 180 (20), 134 (45), 108 (10), 102 (15), 89 (15), 77 (10).

2-(4-(4-Chlorophenyl)thiazol-2(3*H*)-ylidene)malononitrile (7b). Yield 95 %; mp 270-72 ºC; Anal. calcd. for $C_{12}H_6ClN_3S$ (259.7): C, 55.50; H, 2.33; N, 16.18; S, 14.34. Found: C, 55.32; H, 2.15; N; 15.95; S, 14.52; IR (KBr): υ_{max} = 3155 (NH), 2219 (CN), 2185 (CN); ^{1}H-NMR

(DMSO): δ, ppm = 7.38 (s, 1H, CH), 7.53-7.55 (d, 2H, Ar-H), 7.75-7.77 (d, 2H, Ar-H), 13.01 (br, 1H, NH, D_2O exchangeable); ^{13}C-NMR (DMSO): δ, ppm = 171.70, 142.49, 133.98, 128.71 (2C), 128.62 (2C) , 127.82, 117.43, 115.75, 106.10 (2CN). MS: *m/z* (%) 261 (M^{+2}, 40), 260 (M^{+1}, 30), 259 (M^+, 100), 224 (10), 168 (30), 159 (10), 133 (15), 89 (15), 75 (5).

2-(4-methylthiazol-2(3*H*)-ylidene)malononitrile (7c). Yield 85 %; mp 290-91 ºC; Anal. calcd. for $C_7H_5N_3S$ (163.2): C, 51.52; H, 3.09; N, 25.75; S, 19.64. Found: C, 51.26; H, 3.12; N; 25.54; S, 19.27; IR (KBr): υ_{max} = 3160 (NH), 2179 (2CN); ^{1}H-NMR (DMSO): δ, ppm = 2.17 (s, 3H, CH_3), 6.71 (s, 1H, CH), 13.1 (br, 1H, NH, D_2O exchangeable); ^{13}C-NMR (DMSO): δ, ppm = 170.10, 142.54, , 105.93 (2CN), 87.68, 16.54. MS: *m/z* (%) 163 (M^+, 100), 136 (20), 118 (30), 98 (10), 71 (50).

General procedure for syntheses of 8a-c

A cold solution of benzenediazonium chloride (0.01 mol) was prepared by adding a solution of sodium nitrite (0.7 g in 10 mL H_2O) to a cold solution of aniline hydrochloride (0.93 g, 0.01 mol of aniline in 5 mL concentrated HC1) with stirring at room temperature. The resulting solution was then added to cold solutions of **7a-c** (0.01 mol) in ethanol (50 mL) containing sodium acetate (2 g). The reaction mixtures was stirred for 1 h and then filtered. The solid products were crystallized from EtOH to give the products as red crystalls.

2-(4-Phenyl-5-phenylazo-3*H*-thiazol-2-ylidene)malononitrile (8a). Yield 85 %; mp 198-200 ºC; Anal. calcd. for $C_{18}H_{11}N_5S$ (329.38): C, 65.64; H, 3.37; N, 21.26; S, 9.73. Found: C, 65.49; H, 3.51; N; 21.15; S, 9.39; IR (KBr): υ_{max} = 3180 (NH), 2216 (2CN); ^{1}H-NMR (DMSO): δ, ppm = 5.03 (br, 1H, NH, D_2O exchangeable), 7.25-7.60 (m, 8H, Ar-H), 8.22-8.24 (m, 2H, Ar-H); ^{13}C-NMR (DMSO): δ, ppm = 175.46, 147.29, 138.67, 131.79, 131.47, 130.73 (2C), 130.70 (2C), 129.59 (2C), 128.63 (2C), 127.05, 118.96, 117.71, 115.70 (2CN). MS: *m/z* (%) 329 (M^+, 100), 301 (20), 237 (15), 225 (25), 153 (5), 103 (20), 92 (25), 77 (65).

2-[4-(4-Chloro-phenyl)-5-phenylazo-3*H*-thiazol-2-ylidene]malononitrile (8b). Yield 88 %; mp 240-42 ºC; Anal. calcd. for $C_{18}H_{10}ClN_5S$ (363.82): C, 59.42; H, 2.77; N, 19.25; S, 8.81. Found: C, 58.99; H, 3.02; N; 18.99; S, 8.60; IR (KBr): υ_{max} = 3183 (NH), 2222 (2CN); ^{1}H-NMR (DMSO): δ, ppm = 5.12 (br, 1H, NH, D_2O exchangeable), 7.28-7.65 (m, 7H, Ar-H), 8.25-8.28 (m, 2H, Ar-H); ^{13}C-NMR (DMSO): δ, ppm = 171.23, 143.49, 135.54, 132.65, 131.98, 130.56 (2C), 130.42 (2C), 128.99 (2C), 128.63 (2C), 127.83, 118.54, 117.06, 115.70 (2CN). MS: *m/z* (%) 365 (M^{+2}, 40), 364 (M^{+1}, 20), 363 (M^+, 100), 335 (10), 259 (20), 168 (10), 137 (15), 105 (10), 92 (35), 77 (50).

2-(4-Methyl-5-phenylazo-3*H*-thiazol-2-ylidene)malononitrile (8c). Yield 92 %; mp 235-36 ºC; Anal. calcd. for $C_{13}H_9N_5S$ (276.31): C, 58.41; H, 3.39; N, 26.20; S, 11.99. Found: C, 57.99; H, 3.63; N; 26.14; S, 11.59; IR (KBr): υ_{max} = 3193 (NH), 2222 (2CN); ^{1}H-NMR (DMSO): δ, ppm = 2.65 (s, 3H, CH_3), 4.22 (br, 1H, NH, D_2O exchangeable), 7.28-7.60 (m, 5H, Ar-H); ^{13}C-NMR (DMSO): δ, ppm = 169.88, 144.89, 134.44, 129.65 (2C), 129.30, 128.77 (2C), 119.77, 116.36, 114.11, 112.82 (2CN). MS: *m/z* (%) 276 (M^+, 100), 239 (40), 176 (25), 162 (30), 98 (10), 71 (50).

General procedure for the syntheses of 9a-c

Mixtures of **7a-c** (0.01 mol) and hydrazine monohydrate (0.50 g, 0.01 mol) in DMF (10 mL) were stirred at rflux for 20 h (completion assessed by TLC analysis using ethyl acetate-petroleum ether 1:1). The mixtures were cooled and poured into ice-water. The solid products, collected by filtration, were crystallized from DMF to give light yellow crystals.

4-(4-Phenylthiazol-2-yl)-1H-pyrazole-3,5-diamine (9a). Yield 78 %; mp 322-23 ºC; Anal. calcd. for $C_{12}H_{11}N_5S$ (257.31): C, 56.01; H, 4.31; N, 27.22; S, 12.41. Found: C, 55.80; H, 4.41; N; 26.88; S, 11.99; IR (KBr): υ_{max} = 3372, 3256 (NH_2), 3176, 3112 (NH_2), 3132 (NH); ^{1}H-NMR (DMSO): δ, ppm = 5.39 (br, 4H, $2NH_2$, D_2O exchangeable), 7.31-7.46 (m, 3H, Ar-H), 7.75 (s, 1H, CH), 7.96-7.98 (m, 2H, Ar-H), 10.73 (br, 1H, NH, D_2O exchangeable); ^{13}C-NMR (DMSO): δ, ppm = 166.29, 162.08, 152.30 (2C), 134.31, 128.69 (2C), 127.69, 125.89 (2C), 107.48, 87.97. MS: *m/z* (%) 257 (M^+, 100), 226 (10), 200 (5), 134 (35), 128 (10), 90 (10).

4-(4-(4-chlorophenyl)thiazol-2-yl)-1*H*-pyrazole-3,5-diamine (9b). Yield 75 %; mp 328-30 ºC; Anal. calcd. for $C_{12}H_{11}ClN_5S$ (291.76): C, 49.40; H, 3.45; N, 24.00; S, 10.96. Found: C, 49.24; H, 3.61; N; 23.67; S, 10.85; IR (KBr): υ_{max} = 3369, 3289 (NH_2), 3248, 3176 (NH_2), 3123 (NH); ^{1}H-NMR (DMSO): δ, ppm = 5.43 (br, 4H, $2NH_2$, D_2O exchangeable), 7.49 (d, 2H, Ar-H), 7.75 (s, 1H, CH), 8.00 (d, 2H, Ar-H), 10.73 (br, 1H, NH, D_2O exchangeable); ^{13}C-NMR (DMSO): δ, ppm = 165.79, 162.31, 151.08 (2C), 133.16, 132.09, 128.68 (2C), 127.61 (2C), 108.24, 87.94. MS: *m/z* (%) 293 (M^{+2}, 45), 292 (M^{+1}, 45), 291 (M^+, 100), 260 (10), 168 (35), 133 (15), 123 (5), 89 (10), 67 (5).

4-(4-Methylthiazol-2-yl)-1*H*-pyrazole-3,5-diamine (9c). Yield 76 %; mp 330-32 ºC; Anal. calcd. for $C_7H_9N_5S$ (195.24): C, 43.06; H, 4.65; N, 35.87; S, 16.42. Found: C, 42.89; H, 4.73; N; 35.60; S, 15.98; IR (KBr): υ_{max} = 3371, 3275 (NH_2), 3255, 3180 (NH_2), 3118 (NH); ^{1}H-NMR (DMSO): δ, ppm = 2.23 (s, 3H, CH_3), 5.62 (br, 4H, $2NH_2$, D_2O exchangeable), 6.86 (s, 1H, CH), 10.67 (br, 1H, NH, D_2O exchangeable); ^{13}C-NMR (DMSO): δ, ppm = 164.33, 161.56, 150.03 (2C), 106.88, 87.68, 16.84. MS: *m/z* (%) 195 (M^+, 100), 164 (20), 138 (10), 123 (15), 112 (5), 72 (15).

Synthesis of 4-(4-phenyl-5-phenylazo-thiazol-2-yl)-1*H*-pyrazole-3,5-diamine (10)

Procedure 1*:* A cold solution of benzenediazonium chloride (0.01 mol) was prepared by adding a solution of sodium nitrite (0.7 g into 10 mL H_2O) to a cold solution of aniline hydrochloride (0.93 g, 0.01 mol of aniline in 5 mL concentrated HC1) with stirring at room temperature. The resulting solution was then added to a cold solution of **9a** (2.57 g, 0.01 mol) in ethanol (50 mL) containing sodium acetate (2 g). The resultingmixture was stirred for 1 h.giving a solid , which was collected by filtration and crystallized from EtOH to give the pure product as yellow crystalls.

Procedure 2: A mixture of **8a** (3.29 g, 0.01 mol) and hydrazine monohydrate (0.50 g, 0.01 mol) in DMF (10 mL) was stirred at reflux for 20 h (completion assessed by TLC analysis using ethyl acetate-petroleum ether 1:1 as eluent). The mixture was cooled and poured into ice-water, giving a solid that was collected by filtration and crystallized from EtOH to give the product as yellow

crystalls in a 75 % yield; mp 295-97 ºC; Anal. calcd. for $C_{18}H_{15}N_7S$ (361.42): C, 59.82; H, 4.18; N, 27.13; S, 8.87. Found: C, 60.10; H, 3.98; N; 27.19; S, 8.93; IR (KBr): υ_{max} = 3398, 3312 (NH_2), 3258, 3137 (NH_2); ^{1}H-NMR (DMSO): δ, ppm = 6.24 (br, 4H, $2NH_2$, D_2O exchangeable), 7.48-8.09 (m, 10H, Ar-H). MS: *m/z* (%) 361 (M^+, 100), 340 (60), 323 (15), 224 (45), 136 (40), 124 (10), 90 (15).

Synthesis of 2-(2-phenylthiazolo[5,4-c]pyridazin-6(2*H*)-ylidene)malononitrile (12)

A mixture of **8c** (2.76 g, 0.01 mol) and *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA, 1.19 g, 0.01 mol) in DMF (10 mL) was stirred at reflux for 14 h. Concentration the mixture in vacuo gave a residue which was crystallized from EtOH to give the product as dark yellow crystalls in a 75 % yiled; mp 298-299 ºC; Anal. calcd. for $C_{14}H_7N_5S$ (277.30): C, 60.64; H, 2.54; N, 25.26; S, 11.56. Found: C, 60.39; H, 2.66; N; 25.19; S, 11.23; IR (KBr): υ_{max} = 2192 (2CN); ^{1}H-NMR (DMSO): δ, ppm = 7.34-7.50 (m, 6H, Ar-H, CH), 7.65 (d, 1H, *J* = 5, CH). MS: *m/z* (%) 277 (M^+, 100), 256 (10), 169 (15), 129 (10), 93 (15), 77 (60), 73 (20).

Synthesis of 3-(4-Methyl-thiazol-2-yl)-7-phenyl-pyrazolo[1,5-a]pyrimidin-2-ylamine (14)

A mixture of **9c** (1.95 g, 0.01 mol) and 3-dimethylamino-1-phenyl-propenone **13** (1.75 g, 0.01 mol) in DMF (10 mL) was stirred at reflux for 10 h (completion assessed by TLC analysis using ethyl acetate-petroleum ether 1:1 as eluent). The reaction mixture was cooled and poured into ice-water giving a solid which was collected by filtration and crystallized from DMF to give a the product as yellow crystalsin a yield of 80 %; mp 285-87 ºC; Anal. calcd. for $C_{16}H_{13}N_5S$ (307.37): C, 62.52; H, 4.26; N, 22.78; S, 10.43. Found: C, 62.35; H, 4.39; N; 22.72; S, 10.18; IR (KBr): υ_{max} = 3380, 3279 (NH_2); ^{1}H-NMR (DMSO): δ, ppm = 2.41 (s, 3H, CH_3), 6.88 (br, 2H, NH_2, D_2O exchangeable), 7.13 (d, 1H, *J* = 5.4, CH), 7.60-8.10 (m, 5H, Ar-H), 8.56 (d, 1H, *J* = 5, CH); ^{13}C-NMR (DMSO): δ, ppm = 195.12, 158.00, 150.33, 149.45, 146.80, 144.65, 130.93, 130.64, 129.39 (2C), 128.41 (2C), 110.30, 106.78, 89.28, 16.79.. MS: *m/z* (%) 307 (M^+, 100), 234 (15), 182 (5), 156 (15), 103 (5), 72 (30).

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11. CCDC 771782 contains the supplementary crystallographic data for compound **14**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk.