Synthesis and reactions of pyrazolo[5,1-c][1,2,4]triazine-3-carbothioamides

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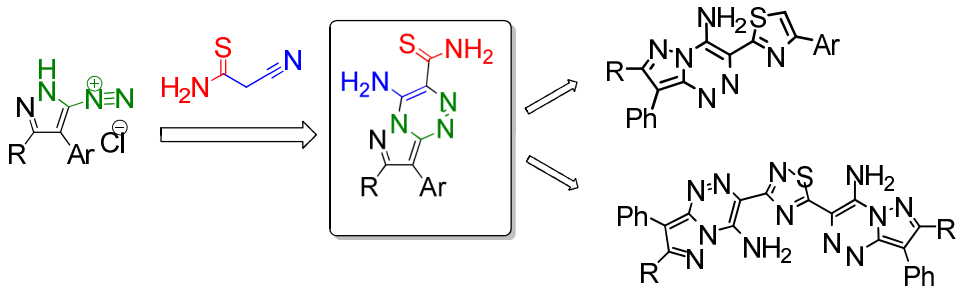
Abstract: Cyanothioacetamide reacts with pyrazole-3(5)-diazonium chlorides under mild conditions to afford pyrazolo[5,1-c][1,2,4]triazine-3-carbothioamides. The latter can be oxidized with H_2O_2 to give either pyrazolo[5,1-c][1,2,4]triazine-3-carboxamides or 1,2,4-thiadiazole derivatives, depending on the reaction conditions. The Hantzsch-type reaction of thioamides **5** with α-bromo ketones leads to 3-(thiazol-2-yl)pyrazolo[5,1-c][1,2,4]triazines.

Keywords: Azo-coupling, Cyanothioacetamide, Hantzsch thiazole synthesis, Heterocyclization, Pyrazole-3(5)-diazonium salts, Pyrazolo[5,1-c][1,2,4]triazines, Oxidation of thioamides



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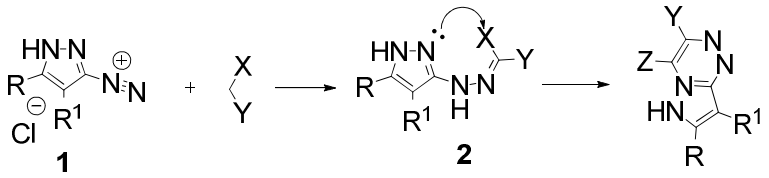
Introduction

Pyrazolo[5,1-*c*][1,2,4]triazines are known to exhibit a broad range of biological activity.[1-5] Due to their structural similarities to nucleic bases, pyrazolo[5,1-*c*][1,2,4]triazines may act as metabolites and therefore useful as antiviral and antitumor agents.[1] Pyrazolotriazines were reported to have remarkable cytotoxic activity against colon, breast and lung carcinoma cells.[6] Some derivatives showed selective cytotoxicity in hypoxic and normoxic conditions.[7] According to the patent data,[8] certain polysubstituted pyrazolo[5,1-*c*][1,2,4]triazines selectively inhibit B-Raf kinase activity and are useful for treating disorders mediated by B-Raf kinase. The most concise approach to the synthesis of pyrazolo[5,1-*c*][1,2,4]triazine scaffolds is based on the azo-coupling of pyrazole-3(5)-diazonium salts **1** with active methylene/methine compounds followed by the intramolecular cyclization of hydrazone intermediates **2**:[1,9,10]



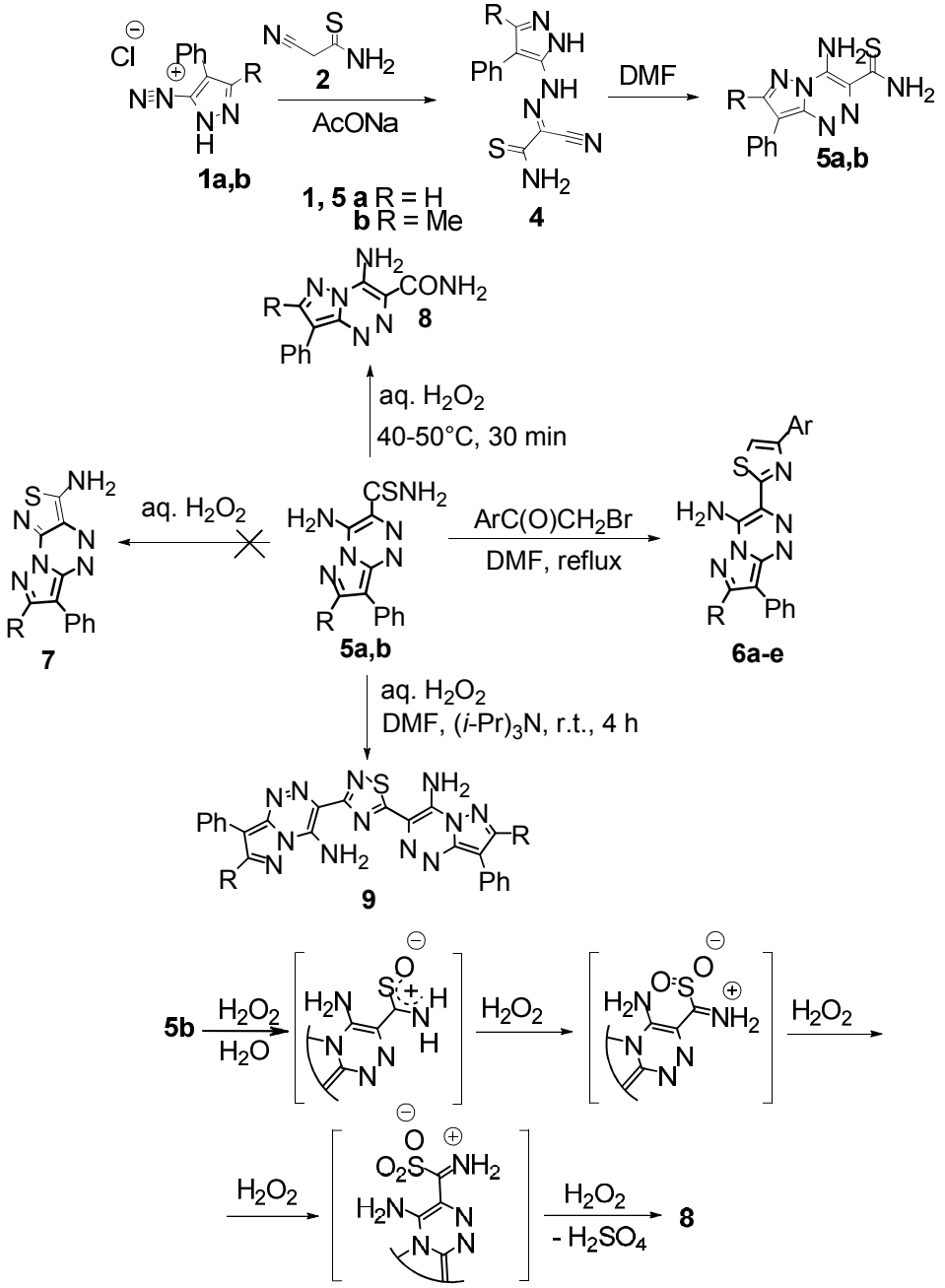
X, Y = CN, C(O)R, CO_2Et, etc.

A number of 4-aminopyrazolo[5,1-*c*][1,2,4]triazines were obtained by reactions of diazonium salts **1** with methylene active nitriles such as malononitrile[11-27], 2-(cyanomethyl)thiazoles,[28,29] 2-(cyanomethyl)benzoxazole,[19] ethyl cyanoacetate,[11,17,20,21,26,30,31] α-cyanoketones,[30,32-35] 2-(cyanomethyl)thiadiazoles,[36,37] cyanoacetamides,[38-42] nitroacetonitrile,[43,44] cyanomethylphosphonates,[45] 2-cyanomethylpyridine,[46] 2-(cyanomethyl)benzimidazole[47,48] etc. In continuation of our studies on the azocoupling reactions,[49-52] we report herein the results of the cyanothioacetamide **3** azo-couplings with diazonium salts **1**. Cyanothioacetamide **3** and its derivatives are widely used for the synthesis of *S*,*N*-heterocyclic compounds (see the reviews[53-59] and some recent examples[60-63]). Cyanothioacetamide can be easily prepared by running hydrogen sulfide through a malononitrile solution in the presence of catalytic amounts of base.[64,65]

Results and Discussion

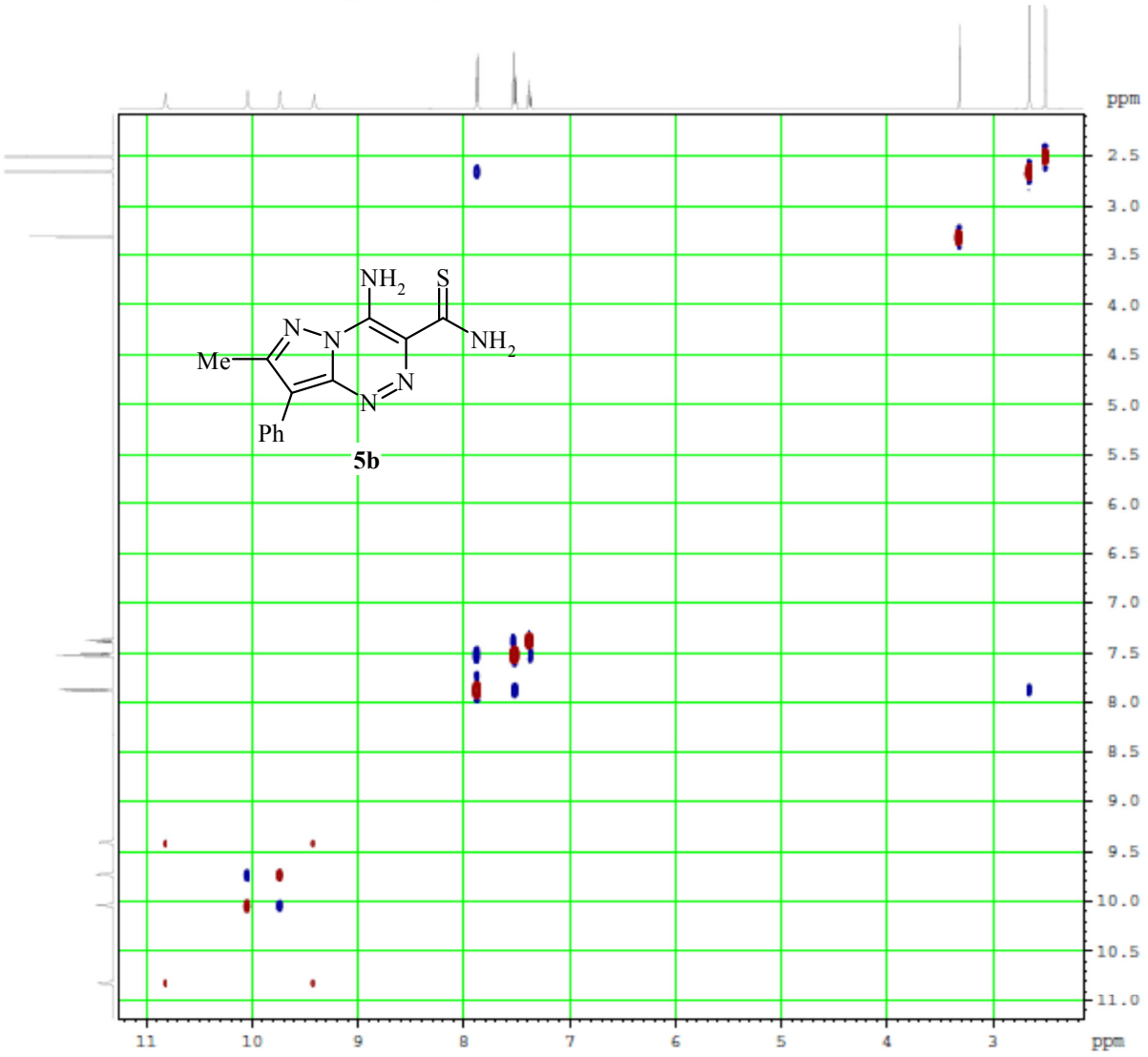
It was found that salts **1** readily react with cyanothioacetamide **3** under mild conditions to compounds of bright color which are presumed to be hydrazones **4**. The resulting hydrazones are quite unstable and undergo fast intramolecular cyclization when purified by column chromatography or recrystallization, or even under moderate heating while trying to determine melting points. The heterocyclization in preparative scale was performed by heating hydrazone

products **4** in DMF and led to the expected pyrazolo[5,1-*c*][1,2,4]triazine-3-carbothioamides **5** in moderate yields.



The structure of thioamides **5** was elucidated on the basis of FTIR, ^{1}H NMR, ^{13}C NMR, 2D NOESY (Fig. 1) and ^{13}C APT NMR spectra. The ^{1}H NMR spectra of **5** showed the presence of the four one-proton signals at δ 9.30-10.92 ppm and the absence of pyrazole NH signal at low field. The 2D NOESY NMR spectrum of **5b** displayed cross peaks between C(S)NH_2 protons (δ 9.73 and 10.03 ppm) and between NH_2 protons (δ 9.41 and 10.80); due to C=S…H–N hydrogen bonding, the signal of one of the NH_2 protons is downshifted by 1.4 ppm compared to the unbound one.

Fig. 1. NOESY 2D spectrum of 4-amino-7-methyl-8-phenylpyrazolo[5,1-*c*][1,2,4]triazine-3-carbothioamide **5b**



When the thioamides **5a,b** were treated with α-halo ketones in hot DMF, the Hantzsch-type thiazoles **6a-e** were obtained in high yields. Therefore pyrazolo[5,1-*c*][1,2,4]triazine-3-carbothioamides **5** serves as a useful synthon to architecture polyheterocyclic ensembles due to the neighboring NH_2 and $C(S)NH_2$ groups.

Then we decided to study the oxidation of compounds **5** under various conditions. In general, oxidation of thioamides is very unpredictable and can take several different courses.[66-68] Depending on the structures of both the oxidant and the substrate, as well as on the reaction conditions, the oxidation process may lead to the formation of amides, thioamide-*S*-oxides, 1,2,4-thiadiazoles, disulfides, benzothiazoles, α-oxothioamides, 1,2-dithiolium salts, 1,2,4-dithiazoles, 1,2,3-thiadiazolium salts, *etc*.[68] However, the oxidation of 3-aminoprop-2-enethioamides and related compounds with neighboring NHR and C=S moieties is known to be one of the most convenient methods for the construction of isothiazole unit.[69-72] It

was expected that the oxidation of 4-aminopyrazolotriazine-3-carbothioamides **5** would give isothiazolo[5,4-*e*]pyrazolo[5,1-*c*][1,2,4]triazines **7**. Surprisingly, only 4-aminopyrazolo[5,1-*c*][1,2,4]triazin-3-carboxamide **8** was isolated in almost quantitative yield when thioamide **5b** was gently heated to 50 °C with aqueous H_2O_2 for 30 min. The plausible mechanism for the formation of amide **8** includes an oxidation of sulfenate fragment followed by hydrolysis[73]. On the other hand, upon the change of conditions, the reaction of thioamide **5b** with hydrogen peroxide took another direction and 3,3'-(1,2,4-thiadiazole-3,5-diyl)*bis*(pyrazolo[5,1-*c*][1,2,4]triazine) **9** was obtained as the major oxidation product.

Table 1. Compounds **5a,b**, **6a-e**, **8** and **9** prepared as shown above.

Compound	R	Ar	Yield %	M.p., °C
5a	H	–	50	277-279
5b	Me	–	54	257-259
6a	Me	Ph	66	>300
6b	H	Ph	75	>300
6c	H	4-ClC_6H_4	78	>300
6d	H	4-MeC_6H_4	80	>300
6e	Me	4-BrC_6H_4	72	276-278
8	Me	–	93	228-230
9	Me	–	55	>300

Conclusion

To summarize, a novel method of azo-coupling has been developed. With this approach 4-aminopyrazolo[5,1-*c*][1,2,4]triazin-3-carbothioamides were generated as convenient building blocks for the construction of heterocyclic ensembles with potential bioactivity.

Experimental

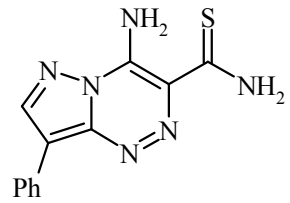
Melting points were measured on a Kofler hot stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker AM300 (300.13 MHz), Bruker DPX400 (400.4 MHz) and Bruker DRX500 (500.07 MHz) instruments in DMSO-d_6 and TFA-d. All chemical shifts are reported in parts per million downfield from TMS. Coupling constants (J) are reported in hertz. Multiplicity in ^{1}H NMR is reported as singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), and multiplet (m). The ^{13}C NMR spectra were recorded on a Bruker DRX-500

instrument (125.76 MHz) in DMSO-d_6 with Me_4Si as the internal standard. IR spectra were recorded on a Specord M82 spectrophotometer in KBr pellets. Elemental analysis was carried out on a Perkin-Elmer C,H,N-analyzer. The mass spectra were measured on a LKB 9000 spectrometer (direct inlet probe, EI, 70 eV). The individuality of the compounds obtained was checked by TLC on Silufol UV-254 plates (sorbent – Silpearl, large-pore silicagel after Pitra with luminiscent indicator for UV 254 on the aluminium foil, binder – starch) in $HCCl_3$–EtOAc (1 : 2); spots were visualized with the iodine vapor or under UV light. For column chromatography Merck silica gel 60 (particle size 0.063–0.200 mm, 70–230 mesh) was used, eluent – EtOAc. The reported yields are given for purified compounds.

Preparation of 4-amino-8-phenylpyrazolo[5,1-c][1,2,4]triazine-3-carbothioamides 5a,b. A suspension of corresponding 3(5)-aminopyrazole[74] (0.03 mol) in water (30 mL) was treated with hydrochloric acid (9.0 mL, d = 1.19 g/mL) and then cooled down to 0 °C. To the solution formed, crystalline $NaNO_2$ (2.07 g, 0.03 mol) was added portionwise over a period of 15 min under vigorous stirring. Once addition was completed, the obtained cold (0…5 °C) solution of pyrazolediazonium chloride **1a,b** was added dropwise to a solution of cyanothioacetamide **2** (3.0 g, 0.03 mol) and excessive AcONa (30 g, 0.37 mol) in AcOH (30 mL). The reaction mixture was stirred at ambient temperature for 1 h and the obtained orange solid of hydrazone **4** was then collected by filtration and washed with a plenty of water, and then heated in DMF (30 mL) for 20 min. The solution was allowed to cool and canary-yellow crystalline products were filtered off, washed with *i*-PrOH and dried to give pyrazolotriazines **5a,b**. Compounds **5a,b** were purified by recrystallization from appropriate solvents.

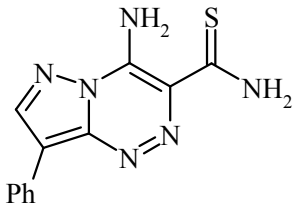
4-Amino-8-phenylpyrazolo[5,1-c][1,2,4]triazine-3-carbothioamide 5a. Yield 56%, yellow crystals, mp 279-281 °C (DMAA); Recrystallization from DMF gave solvate (1:1) with mp 277-279 °C, yield 50%. ν_{max} (KBr): 3470, 3292, 3153, 3088 (N–H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.33-7.49 (1H, m, Ph), 8.25-8.30 (2H, m, Ph), 8.92 (1H, s, H-7), 9.41 (1H, br.s, NH_2), 9.75 (1H, s, $CSNH_2$), 10.06 (1H, s, $CSNH_2$), 10.88 (1H, s, NH_2); ^{13}C NMR (126 MHz, DMSO-d_6): 111.7 (C-3), 121.6 (C-8), 126.2 (C-3, C-5 Ph), 126.9 (C-4 Ph), 128.8 (C-2, C-6 Ph), 130.8 (C-1 Ph), 142.1 (C-4 or C-8a), 144.0 (C-7), 144.8 (C-8a or C-4), 190.4 (C=S). MS (EI, 70 eV): *m*/*z* (%): 270 $[M]^+$ (100), 237 (60), 236 (51), 142 (23), 116 (16), 73 (25), 58 (22), 43 (24), 42 (22). Anal. Calcd for $C_{12}H_{10}N_6S$: C, 53.32; H, 3.73; N, 31.09. M =270.32. Found C, 53.37; H, 3.82; N, 31.33.

^{1}H NMR spectrum of 4-Amino-8-phenylpyrazolo[5,1-*c*][1,2,4]triazine-3-carbothioamide **5a** (DMF solvate 1:1) (DMSO-d_6, 300 MHz)

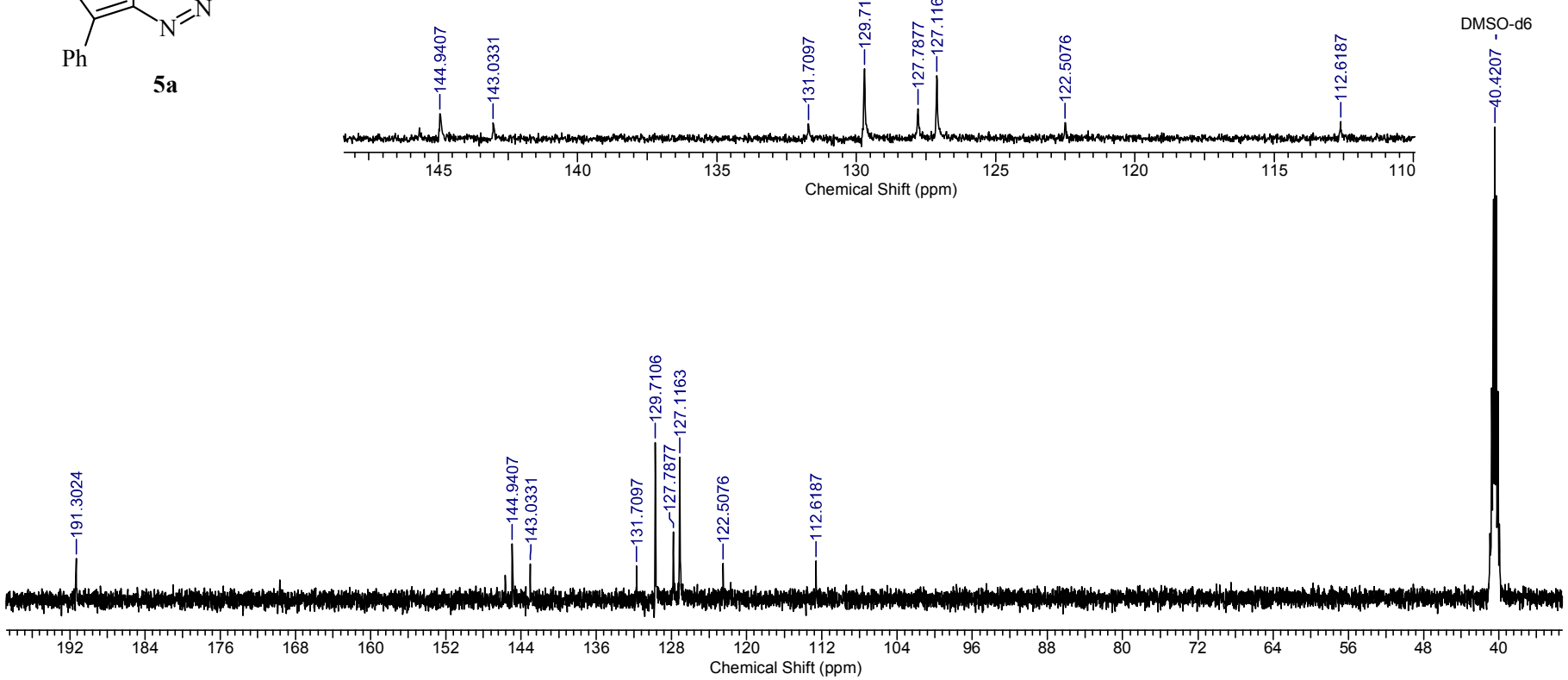


5a

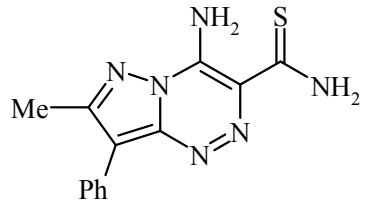
^{13}C NMR spectrum of 4-amino-8-phenylpyrazolo[5,1-*c*][1,2,4]triazine-3-carbothioamide **5a** (DMSO-d$_6$, 125.76 MHz)



5a

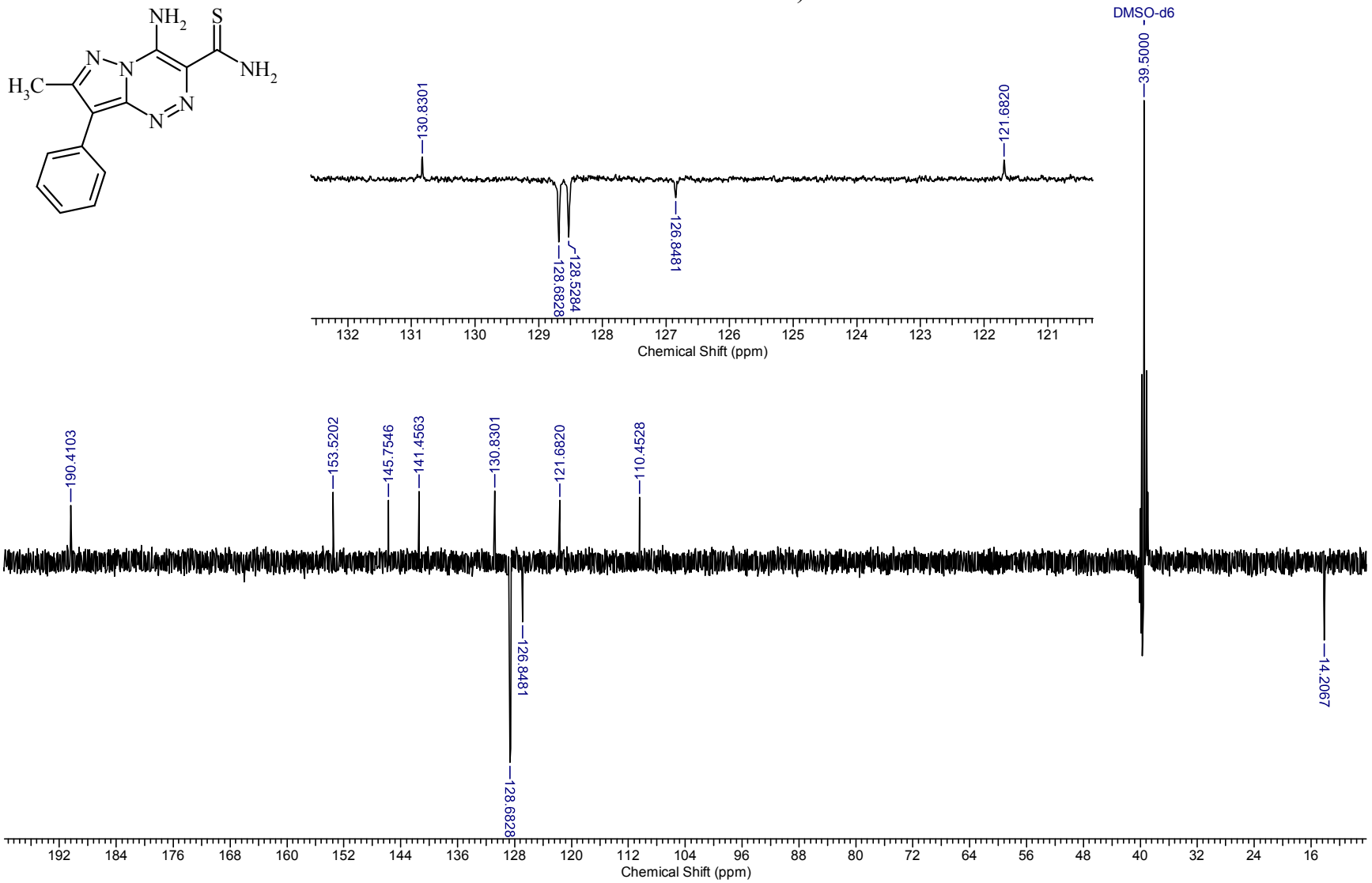


^{1}H NMR spectrum of 4-amino-7-methyl-8-phenylpyrazolo[5,1-*c*][1,2,4]triazine-3-carbothioamide 5b (DMSO-d_6, 500 MHz)



5b

^{13}C APT NMR spectrum of 4-amino-7-methyl-8-phenylpyrazolo[5,1-*c*][1,2,4]triazine-3-carbothioamide 5b (DMSO-d_6, 125.76 MHz)



4-Amino-7-methyl-8-phenylpyrazolo[5,1-c][1,2,4]triazine-3-carbothioamide 5b. Yield 54%, yellow crystals, mp 257-259 °C (DMF); ν_{max} (KBr): 3462, 3447, 3319, 3294 (N–H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.64 (1H, s, CH_3), δ 7.35-7.37 (1H, m, Ph), 7.49-7.52 (2H, m, Ph), 7.86 (2H, d, ^3J = 8.0 Hz, Ph), 9.40 (1H, s, NH_2), 9.73 (1H, s, $CSNH_2$), 10.03 (1H, s, $CSNH_2$), 10.80 (1H, s, NH_2); ^{13}C NMR (126 MHz, DMSO-d_6): 14.2 (Me), 110.5 (C-3), 121.7 (C-8), 126.9 (C-4 Ph), 128.6 (C-3, C-5 Ph), 128.7 (C-2, C-6 Ph), 130.8 (C-1 Ph), 141.5 (C-4), 145.8 (C-7), 153.5 (C-8a), 190.4 (C=S). ^{13}C APT NMR (126 MHz, DMSO-d_6): 14.2* (CH_3), 110.5 (C-3), 121.7 (C-8), 126.9* (C-4 Ph), 128.5* (C-3, C-5 Ph), 128.7* (C-2, C-6 Ph), 130.8 (C-1 Ph), 141.5 (C-4), 145.8 (C-7), 153.5 (C-8a), 190.4 (C=O). *Negative peaks. Anal. Calcd for $C_{13}H_{12}N_6S$: C, 54.91; H, 4.25; N, 29.56. M =284.34. Found C, 54.85; H, 4.37; N, 29.50.

Synthesis of 4-amino-3-(4-arylthiazol-2-yl)-8-phenylpyrazolo[5,1-c][1,2,4]-triazines 6a-e. The solution of pyrazolotriazine-3-carbothioamide **5a,b** (5 mmol) and corresponding α-bromo ketone (5 mmol) in DMF (5 mL) was kept under reflux for 10 min. Upon cooling to room temperature, the solid deposit was separated by filtration and washed with *i*-PrOH. Analytically pure products were obtained by recrystallization from *N*,*N*-dimethylacetamide (DMAA).

Selected spectral data:

4-Amino-7-methyl-8-phenyl-3-(4-phenylthiazol-2-yl)pyrazolo[5,1-c][1,2,4]triazine 6a. Yield 66%, yellow crystals, mp >300 °C (from DMAA); ν_{max} (KBr): 3294, 3136 (NH_2), 1636 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.67 (1H, s, CH_3), 7.40-7.42 (2H, m, Ph), 7.50-7.54 (4H, m, Ph), 7.88 (2H, d, ^3J = 6.8 Hz, Ph), 8.02 (2H, d, ^3J = 7.0 Hz, Ph), 8.16 (1H, s, H-5 thiazolyl), 9.23 (1H, br.s, NH_2), 9.50 (1H, br.s, NH_2); ^{1}H NMR (500 MHz, TFA-d): δ 2.55 (1H, s, CH_3), 7.25-7.47 (8H, m, 2 Ph), 7.65-7.72 (3H, m, Ph, thiazolyl H-5). The signals of NH_2 protons are not observed due to H–D exchange. ^{13}C NMR (126 MHz, TFA-d): 13.8 (CH_3), 110.6 (C-3), 116.7 (C-8), 118.4 (thiazolyl C-5), 125.5 (C-Ar), 128.0 (C-Ar), 128.1 (CH Ph), 131.06 (CH Ph), 131.12 (CH Ph), 131.4 (CH Ph), 131.7 (CH Ph), 132.0 (CH Ph), 134.4 (C-Ar), 138.9 (C-Ar), 144.1 (C-7), 159.2 (thiazolyl C-1), 163.2 (C-8a); MS (EI, 70 eV): m/z (%): 384 $[M]^+$ (39), 209 (5), 200 (13), 187 (27), 172 (11), 156 (22), 142 (55), 134 (100), 130 (13), 115 (60), 102 (46), 89 (53), 77 (28), 63 (14), 51 (17), 42 (26), 29 (5). Anal. Calcd for $C_{21}H_{16}N_6S$: C, 65.61; H, 4.19; N, 21.86. M = 384.47. Found C, 65.70; H, 4.12; N, 21.81.

Preparation of 4-amino-7-methyl-8-phenylpyrazolo[5,1-c][1,2,4]triazine-3-carboxamide 8. Solution of thioamide **5b** (1.42 g, 0.005 mol) in aqueous hydrogen peroxide (30%, 10 mL) was heated at 50 °C during 30 min. Upon cooling to room temperature, the solid was filtered off, washed with water and dried to give **8**, yield 1.25 g (93%), yellow crystals, mp 228-230 °C (from *i*-PrOH); ν_{max} (KBr): 3334 (NH_2), 3483 (NH_2), 1627 (C=N), 1500 (N=N); ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.65 (1H, s, CH_3), 7.37 (1H, t, ^3J = 7.0 Hz, Ph), 7.50-7.53 (2H, m, Ph), 7.69 (1H, br.s, NH_2), 7.86 (2H, d, ^3J = 7.3 Hz, Ph), 8.36 (1H, s, NH_2), 9.09 (1H, s, NH_2), 9.22 (1H, s, NH_2); MS (EI, 70 eV): m/z (%): 268 $[M]^+$ (100), 251 (7), 156 (20), 142 (15), 128 (14), 115 (75), 103 (6); 89 (13), 77 (10), 68 (10), 44 (38), 39 (10). Anal. Calcd for $C_{13}H_{12}N_6O$: C, 58.20; H, 4.51; N, 31.33. M = 268.28. Found C, 58.31; H, 4.44; N, 31.25.

Preparation of 3,3'-(1,2,4-thiadiazole-3,5-diyl)bis(4-amino-7-methyl-8-phenylpyrazolo[5,1-c][1,2,4]triazine) 9. The mixture of thioamide **5b** (1.42 g, 0.005 mol), aq. hydrogen peroxide (30%, 1.0 mL) in DMF (15 mL) was stirred at room temperature for 4 h in the presence of a catalytic amount of *i*-Pr_3N. The solid deposit obtained was collected by filtration, washed with *i*-PrOH and recrystallized from DMF to give thiadiazole **9**, yield 55%, yellow crystals, mp >300 °C (DMF); ν_{max} (KBr): 3439, 3412, 3294 (NH_2), 1624 (C=N); ^{1}H NMR (TFA-d, 500 MHz): δ 2.57 (3H, s, CH_3), 2.60 (3H, s, CH_3), 7.48-7.60 (10H, m, 2Ph). The signals of NH_2 protons are not observed due to H–D exchange; ^{13}C NMR (126 MHz, TFA-d): 13.93, 13.95 (2 CH_3), 112.1, 112.9 (C-3, C-3'), 122.6, 122.8 (C-8, C-8'), 127.6, 127.9 (C-4, C-4'), 131.1, 131.2 (C-3, C-5 Ph), 131.78, 131.82 (C-2, C-6 Ph), 132.2, 132.3 (C-4 Ph), 138.5, 139.1 (C-1 Ph), 143.8, 145.3 (C-7, C-7'), 164.2, 164.7 (C-8a, C-8a'), 168.2 (thiadiazole C-3), 184.6 (thiadiazole C-5); MS (EI, 70 eV): m/z (%): 531 $[M-1]^+$ (53), 251 (23), 157 (24), 142 (55), 115 (65), 89 (10), 77 (14), 36 (40). Anal. Calcd for $C_{24}H_{16}N_{12}S$: C, 57.13; H, 3.20; N, 33.31. M = 532.59. Found C, 57.02; H, 3.34; N, 33.23.

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