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Research paper

Synthesis of some substituted pyrazole-1-carbothioamides and spectral correlations in 3-(3,4-dibromophenyl)-5-(substituted phenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamides

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ABSTRACT

Background: This study aims to synthesise a series of 1-thiocarbomyl pyrazolines, including 3-(3,4-dibromophenyl)-5-(substituted phenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamides, using solvent-free fly-ash:PTS catalyzed cyclization between chalcones and thiosemicarbazide, under microwave irradiation. Then to characterize them using analytical, physical and spectroscopic data.

Methods: Solvent-free microwave assisted cyclization was adopted for the synthesis of 1-thiocarbomyl, including 3-(3,4-dibromophenyl)-5-(substituted phenyl)-4,5-dihydro-1*H*- pyrazole-1-carbothioamides, using fly-ash:PTS as the catalyst. They were characterised by IR, NMR and mass spectroscopic data. The infrared (IR) and nuclear magnetic resonance (NMR) spectral data was correlated with substituent constants, F and R parameters, using Hammett equation, to study the effect of substituents.

Results: The yields of the synthesised chalcones were more than 85%. The spectral data of these 3-(3,4-dibromophenyl)-5-(substituted phenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamides had been correlated, using single and multi-linear regression analysis. These gave a satisfactory or fair degree of correlation with some parameters.

Conclusion: Easy handling, non-hazardous and environmentally benign cyclization method had been adopted for the synthesis of 1-thiocarbomyl pyrazolines using fly-ash:PTS as catalyst, with better yields. Some of the Hammett spectral correlations were found to be satisfactory, with the observed spectroscopic data.

Keywords: 3-(3,4-dibromophenyl)-5-(substituted phenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamides, fly-ash:PTS, solvent-free synthesis, Hammett correlations

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INTRODUCTION

Numerous solvent-free [1,2] green synthetic methods have been applied for the stereospecific, stereoselective and regioselective synthesis of organic compounds. These solvent free reactions, involving the formation of carbon-carbon bond and carbon-heteroatom bond, are important and interesting in green synthesis. Among the five membered nitrogen heterocyclics, the 1-thiocarbomyl pyrazoline derivatives are important compounds and they possess $-CS\text{-}NH_2$ group in N_1 atom of pyrazoline ring.[3,4] These 1-thiocarbomyl pyrazoline derivatives have many important biological activities such as, anti-bacterial,[5] anti-fungal,[5] anti-depressant,[6] anti-convulsant,[7] anti-inflammatory,[8] anti-tumour,[9] anaesthetic,[10] analgesic,[11] anti-cancer,[12] MAO-B inhibitors,[13] steroidal, nitric oxide synthase inhibitor, anti-viral and cannabinoid CBI receptor antagonists,[8] Many solvent-free and conventional synthetic methods are reported in literature for the synthesis of thiocarbomyl pyrazoline derivatives.[3,12,14–17] In these methods, many 1-thiocarbomyl pyrazoline derivatives were synthesised by cyclization of chalcones with hydrazine hydrate,[18] phenylhydrazine[19] or phenyl hydrazine hydrochloride.[20–22] Similarly, 1-thiocarbomyl pyrazoline derivatives were synthesised by cyclization of chalcones with thiosemicarbazide,[3,12,13,23] substituted thiosemicarbazide[3,8,13] or hydrazenidium dithiocyanate.[24] At present, synthetic organic chemists, scientists and researchers prefer greener synthesis, due to easy working procedure, shorter reaction time, higher yields, it is less hazardousness and solvent usage.[25–30] Based on the above advantages, the greener synthetic methods, such as solvent-free microwave irradiation and ultrasonication, were used for the synthesis of thiocarbomyl pyrazoline derivatives.[22,31,32] A number of catalysts were utilized for the synthesis of 1-thiocarbomyl pyrazoline derivatives, such as Lewis acids, bases and their salts,[12,31,32] CH_3COOH/CH_3COONa,[3] NaOH/EtOH,[23,31,33] KOH/EtOH,[19,32] neat reaction in ethanol[3,13] and basic alumina/ K_2CO_3.[34,35] These thiocarbomyl pyrazolines are used as starting materials for the synthesis of thiazole substituted pyrazoles.[17] Chawla et al.[34] have synthesised more than 80% yield of some 3-substituted phenyl-5-substitutedphenyl-4,5-dihydropyrazole-1-carbothioamides by the microwave irradiation method, and evaluated their antimicrobial activities. The same yield of 5-(1,3-benzodioxol-yl)-3-(substituted)phenyl-4,5-dihydro-1H-pyrazol-1-carbothioamides have been synthesised by the microwave method, and their anticarcinogenic activities studied.[12] Ashok co-workers have synthesised 80% yields of some 3-(3-benzoyl-6-hydroxy-3-methylbenzo[b]furon-5-yl)-5-(aryl)-4, 5-dihydro-1H-pyrazole carbothioamides using microwave irradiation technique and studied their antibacterial activities.[14–16] Patel and Desai[35] have synthesised 60–85% yields of 1-thiocarbomyl-2-(2,4-dichloro-5-fluorophenyl)-5-(substitutedphenyl)-pyrazoline derivatives using a microwave, with alumina/K_2CO_3 as the catalyst. Spectroscopic data is useful for predicting the ground state equilibrium of organic compounds. The ultraviolet spectroscopic data, of absorption maxima (λ max, nm), is also applied to predict the effect of substituents.[30] In pyrazoline molecules (^{1}H pyrazoles), the infrared spectra is used for predicting the effects of substituents on the vibrations of C═N, C-H, N-H.[20] From NMR spectroscopy, the spatial arrangements of the protons H_a, H_b and H_c, or H_a, H_b, H_c and H_d of the types shown in Figure 1, were predictable by their frequencies with multiplicities viz., doublet or triplet, or doublet of doublets. Based on the geometry, the chemical shift of the protons of respective pyrazoles has been assigned, and the effects of substituent will be studied. The effects of substituent on the 2-naphthyl based pyrazoline ring protons were first studied by Sakthinathan et al.[20] They assigned infrared νC═N(cm^{-1}), NMR chemical shifts (δ, ppm) of H_a, H_b, H_c, C═N values and correlated with Hammett substituents. In these correlations they observed satisfactory r values. Recently, Thirunarayanan et al.[22] have studied the solvent- free synthesis, spectral correlations of some

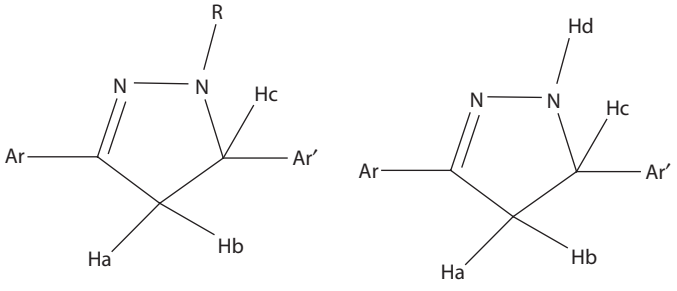


Figure 1. General structure of 1*H*-pyrazoles.

1-phenyl-3-(5-bromothiophen-2-yl)-5-(substituted phenyl)-2-pyrazolines. The literature reveals that there is no information available for solvent-free synthesis of some thiocarbomyl pyrazolines, including 1-thiocarbomyl-2-(3,4-dibromophenyl)-5-(substituted phenyl)-pyrazoline derivatives by cyclization of the respective chalcones and thiosemicarbazide in presence of solid fly-ash: PTS catalyst. Therefore, the authors have taken efforts to synthesize some thiocarbomyl pyrazolines, including 1-thiocarbomyl-2-(3,4-dibromophenyl)-5-(substituted phenyl)-pyrazoline derivatives, by solvent-free microwave assisted cyclization of chalcones and thiosemicarbazide, in presence of fly-ash:PTS. The purities of these pyrazolines were assessed using their physical constants and spectral data, published in earlier literature. The infrared and NMR spectra of these synthesised 3-(3,4-dibromophenyl)-5-(substituted phenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamides were recorded to study the Hammett spectral correlations.

METHODS

General

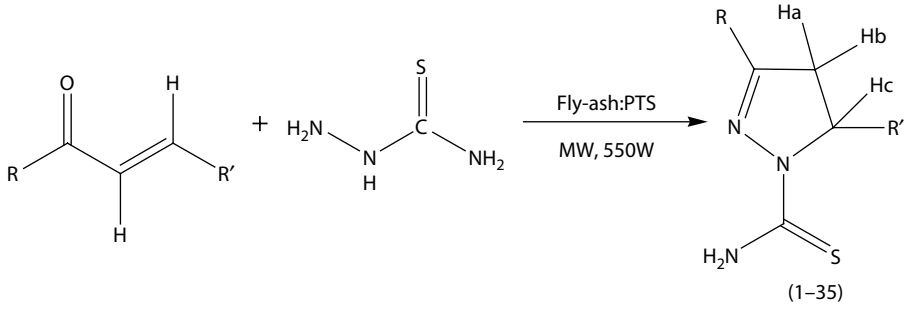
All chemicals used were procured from Sigma-Aldrich and E-Merck. Melting points of all pyrazoles have been determined in open glass capillaries on Mettler FP51 melting point apparatus and are uncorrected. Infrared spectra (KBr, 4000 – 400 cm^{-1}) have been recorded on BRUKER (Thermo Nicolet) Fourier transform spectrophotometer. The NMR spectra of all pyrazolines have been recorded on Bruker AV400 spectrometer, operating at 400 MHz for recording ^{1}H and 100 MHz for ^{13}C spectra in $CDCl_3$ solvent, using TMS as internal standard. Mass spectra have been recorded on SHIMADZU spectrometer, using chemical ionization technique.

Preparation of fly-ash:PTS catalyst

The fly-ash:PTS catalyst was prepared by adopting the method from literature.[36] In a 50 mL Borosil beaker, 1 g of fly-ash and 0.8 mL (0.5 mol) of 4-methylbenzenesulphonic acid were taken and mixed thoroughly with glass rod. This mixture was heated on a hot air oven at 85°C for 1 h, cooled to room temperature, stored in a Borosil bottle and tightly capped. This was characterized by infrared spectra and SEM analysis.

Synthesis of substituted pyrazole-1-carbothioamide derivatives

Appropriate equi-molar quantities of chalcones (2 mmol), thiosemicarbazide (2 mmol) and fly-ash:PTS (0.5 g) were taken in 50 mL borosil glass tubes. The mixture was subjected to microwave irradiation for 4-6 min in a microwave at 550 watts, 2540 MHz frequency, 140°C and atmospheric pressure in a microwave oven (Scheme 1) (Samsung Grill, GW73BD Microwave oven, 230 V A/c, 50 Hz, 2450 Hz, 100-750 W (IEC-705). Depending on the nature of the substituent present in the chalcones, it was assigned various time intervals 4 min, 5.5 min and 6 min, for halogen and nitro substituents,

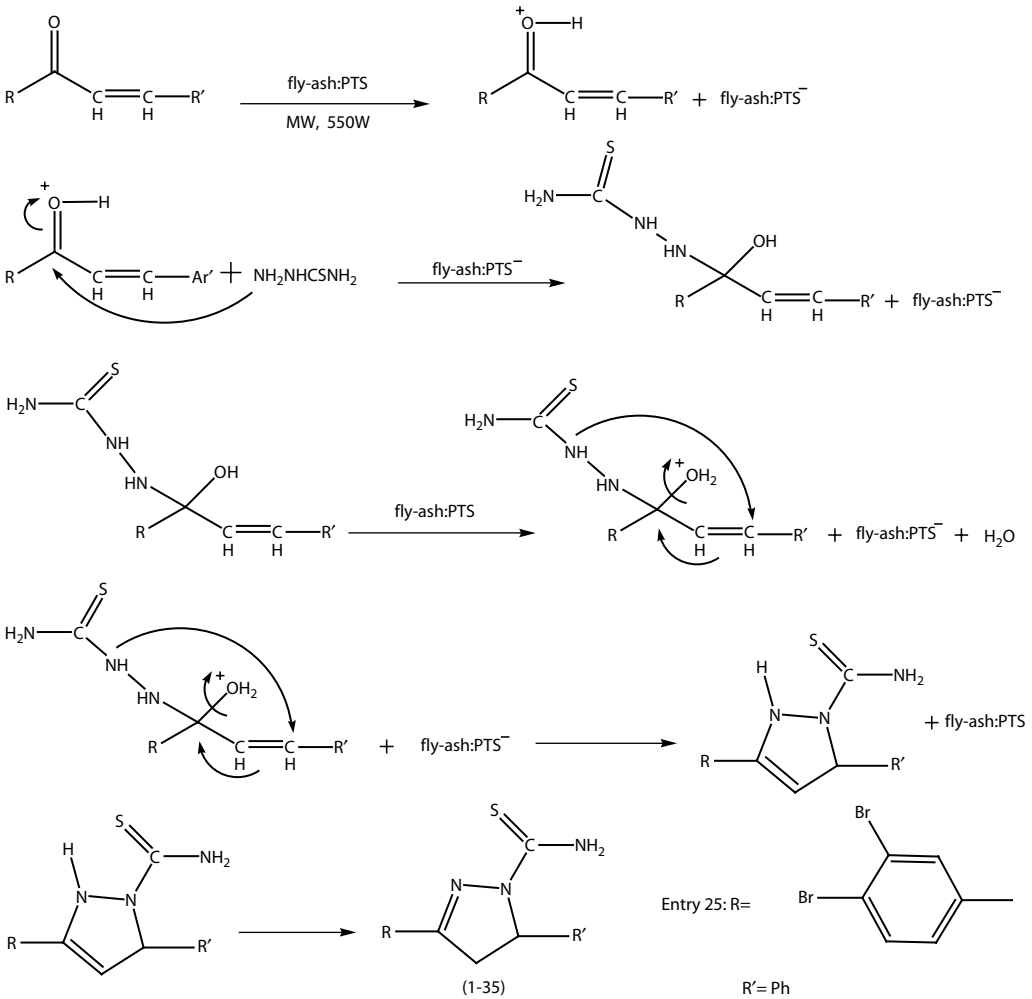


Scheme 1. Synthesis of 1-thiocarbomyl pyrazolines by fly-ash:PTS catalyzed solvent-free cyclization of chalcones and thiosemicarbazide, under microwave irradiation.

respectively. The completion of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature. The product was isolated by adding 10 mL of dichloromethane and evaporation. The solid, on recrystallization from benzene-hexane mixture, afforded the glittering product. The insoluble catalyst has been recycled by washing with ethyl acetate (8 mL), followed by drying in an oven at 100°C for 1 h and reused for further reactions.

RESULTS AND DISCUSSION

Attempts have been made to synthesize substituted pyrazoline carbothioamide derivatives by cyclization of various aryl chalcones and thiosemicarbazide, in the presence of acidic catalyst fly-ash:PTS under microwave irradiation. Hence, we have synthesized the substituted 1-thiocarbomyl pyrazoline derivatives by the cyclization of 2 mmol of chalcone, 2 mmol of thiosemicarbazide, under microwave irradiation, with 0.5 g of fly-ash:PTS catalyst at 550 W, 4-6 min (Samsung Grill, GW73BD Microwave oven, 230 V A/c, 50 Hz, 2450 Hz, 100-750 W (IEC-705), (Scheme 1). During the course of this reaction, fly-ash:PTS catalyses cyclization between chalcones and thiosemicarbazide by the elimination of water, followed by proton transfer, gave the 1-thiocarbomyl pyrazolines. The yields of the pyrazolines in this reaction are more than 85%. The proposed general mechanism of this reaction is shown in (Scheme 2). The chalcones containing electron donating substituent ($-OCH_3$) gave higher yields than electron-withdrawing halogens and $-NO_2$ substituents. Further, we have investigated this cyclization reaction with equimolar quantities of the styryl 3,4-dibromophenyl ketone (entry 25) and thiosemicarbazide, under the same condition as above. In this reaction the obtained yield was 90%. The effect of a catalyst on this reaction was studied by varying the catalyst quantity from 0.1 g to 1 g. As the catalyst quantity is increased from 0.1 g to 1 g, the percentage yield of product is increased from 85% to 90%. Further increase in the catalyst amount beyond 0.4 g, saw no significant increase in the percentage product yield. The effect of catalyst loading is shown in (Figure 2). The optimum quantity of catalyst loading was found to be 0.4 g. The results, analytical and mass spectral data are summarized



Scheme 2. The proposed mechanism for the synthesis of 1-thiocarbomyl pyrazolines by fly-ash:PTS catalyzed solvent-free cyclization of chalcones and thiosemicarbazide, under microwave irradiation.

in Table 1. The reusability of this catalyst was studied for the cyclization of styryl 3,4-dibromophenyl ketone and thiosemicarbazide (entry 25), and is presented in Table 2. From Table 2, the first two runs give 90% product yield. The third, fourth and fifth runs give product yields of 89.5%, 89.5% and 89%, respectively, of 1-thiocarbomyl pyrazolines. No appreciable loss in its catalytic activity were observed, up to the fifth run. The effect of solvents on the yield was also studied with methanol, ethanol, dichloromethane and tetrahydrofuran, from each component of the catalyst (entry 25). Similarly, the effect of microwave irradiation was studied on the each component of the catalyst. The effect of solvents on the yields of 1-thiocarbomyl pyrazolines was presented in Table 3. From the table, the highest yield of 1-thiocarbomyl pyrazolines is obtained from the cyclization of chalcone and thiosemicarbazide, with the catalyst fly-ash:PTS, in microwave irradiation.

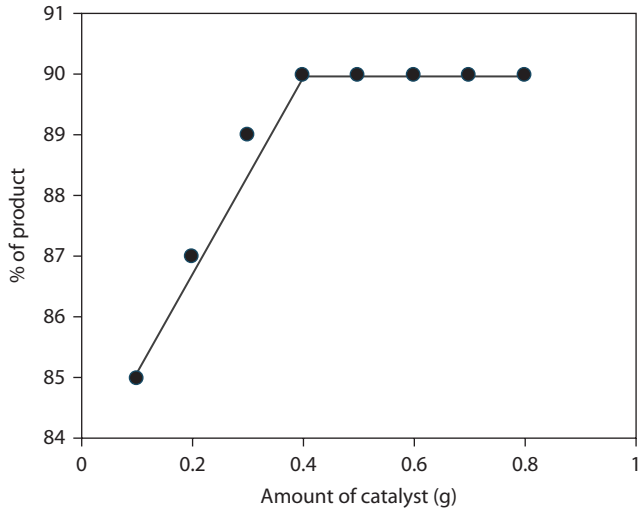


Figure 2. Effect of catalyst loading.

IR spectral study

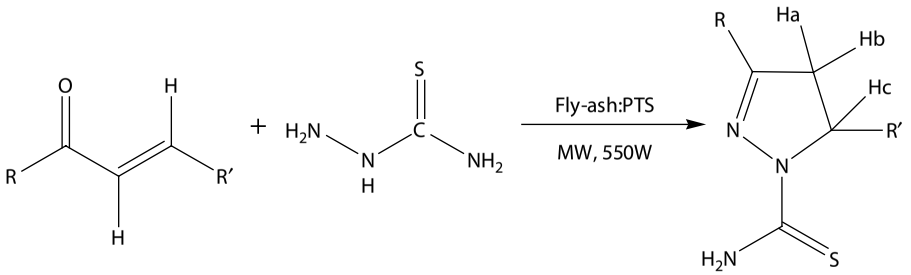
The synthesis of 1-thiocarbomyl pyrazoline derivatives are shown in Scheme 1. In the present study, a series of 1-thiocarbomyl pyrazoline derivatives, namely 3-(3,4-dibromophenyl)-5-(substituted phenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamides (entries 25–35), were chosen to study the effects of substituent on the spectral data. The infrared νC=N, NH and C=S stretching frequencies (cm^{-1}) of these 1-thiocarbomyl pyrazolines (entries 25–35) have been assigned and are presented in Table 4. This data is correlated[20,22,27–30,36,38–42] with Hammett substituent constants and Swain-Lupton's[43] parameters. In this correlation the structure parameter Hammett equation employed is as shown in Equation (1).

$$\nu = \rho\sigma + \nu_0 \quad (1)$$

where ν_0 is the frequency for the parent member of the series.

The observed νC=N stretching frequencies (cm^{-1}) of these 1-thiocarbomyl pyrazolines are correlated with various Hammett substituent constants, and F and R parameters, through single and multi-regression analyses including Swain-Lupton's[43] parameters. The results of statistical analyses of single parameter correlations are shown in Table 5. The correlation of νC=N (cm^{-1}) frequencies of 1-thiocarbomyl pyrazolines with Hammett σ, σ^+ and σ_I constants were satisfactory, excluding H, 4-OH and 4-CH_3 substituents. If these substituents are included in the regression, they reduced the correlation considerably. The σ_R constant, F and R parameters gave poor correlation. A satisfactory correlation was obtained for νC=S (cm^{-1}) frequencies of pyrazolines with Hammett σ_R substituent constants R parameters, excluding 4-F and 4-OH substituents. All correlations gave positive ρ values. This may mean that the normal substituent effect operates in all thiocarbomyl pyrazolines.

Table 1. Analytical, physical constants, yields and mass fragments of 1-thiocarbomyl pyrazolines synthesised by fly-ash:PTS catalyzed solvent-free cyclization of chalcones and thiosemicarbazide reaction of the type under microwave irradiation.

Entry	R	R′	Product	M.W.	Yield	m.p. (°C)	Mass (m/z)
							
1	CH_3	C_6H_5	$C_{11}H_{13}N_3S$	219	85	273–274 273[24]	219[M^+]
2	CH_3	4-$OCH_3C_6H_4$	$C_{12}H_{15}N_3OS$	249	90	182–183 182[24]	249[M^+]
3	CH_3	4-$N(CH_3)_2C_6H_4$	$C_{13}H_{18}N_4S$	263	86	238–239 238[24]	263[M^+]
4	CH_3	C_4H_3O(2-Furyl)	$C_9H_{15}N_3OS$	213	88	221–222 220–222[24]	213[M^+]
5	CH_3	C_4H_3S(2-Thienyl)	$C_9H_{15}N_3S_2$	229	87	119–220 220[24]	213[M^+]
6	C_4H_3S(2-Thienyl)	C_6H_5	$C_{14}H_{17}N_3S_2$	291	86	164–165 160–165[31]	291[M^+]
7	C_4H_3S(2-Thienyl)	4-BrC_6H_4	$C_{14}H_{16}BrN_3S_2$	370	87	254–255 250–255[31]	370[M^+], 372[M^{2+}],

8	C_4H_3S(2-Thienyl)	2,4,5-$(OCH_3)_3C_6H_2$	$C_{17}H_{23}N_3O_3S_2$	381	91	214 – 215 210 – 215[31]	381[M^+],
9	C_4H_3S(2-Thienyl)	4-$N(CH_3)_2C_6H_4$	$C_{16}H_{18}N_4S_2$	330	88	174 – 175 170 – 175[31]	330[M^+],
10	C_6H_5	2,4-Cl_2-C_6H_3	$C_{16}H_{13}Cl_2N_3S$	350	89	220 – 221 217 – 220[32]	350[M^+], 352[M^{2+}]
11	2,4-Cl_2-5-F-C_6H_2	C_6H_5	$C_{16}H_{12}Cl_2FN_3S$	368	94	165 – 166 165[35]	368[M^+], 370[M^{2+}], 372[M^{+4}]
12	2,4-Cl_2-5-F-C_6H_2	2-ClC_6H_4	$C_{16}H_{11}Cl_3FN_3S$	402	90	145 – 146 145[35]	402[M^+], 404[M^{2+}], 408[M^{+4}], 410[M^{+6}]
13	2,4-Cl_2-C_6H_3	4-ClC_6H_4	$C_{16}H_{12}Cl_3N_3S$	323	88	212 – 213 211 – 213[23]	323[M^+], 325[M^{2+}], 327[M^{4+}]
14	2,4-Cl_2-C_6H_3	4-$OCH_3C_6H_4$	$C_{17}H_{17}Cl_2FN_3S$	381	93	210 – 211 209-210[23]	381[M^+], 383[M^{2+}]
15	4-$OCH_3C_6H_4$	C_6H_5	$C_{17}H_{17}N_3OS$	311	86	162 – 163 160 – 162[34]	311[M^+]
16	4-ClC_6H_4	C_6H_5	$C_{16}H_{14}ClN_3S$	315	85	123 – 124 122 – 123[34]	315[M^+], 317[M^{2+}]
17	3-$NO_2C_6H_4$	C_6H_5	$C_{16}H_{14}N_4O_2S$	326	85	129 – 130 128 – 130[34]	326[M^+]
18	4-$OCH_3C_6H_4$	4-ClC_6H_4	$C_{17}H_{16}ClN_3OS$	345	92	127 – 128 125 – 127[34]	360[M^+], 362[M^{2+}],
19	4-ClC_6H_4	4-ClC_6H_4	$C_{16}H_{13}Cl_2N_3S$	350	86	148 – 149 147 – 148[34]	350[M^+], 352[M^{2+}], 354[M^{2+4}],
20	3-$NO_2C_6H_4$	4-ClC_6H_4	$C_{16}H_{13}ClN_4O_3S$	237	87	150 – 151 148 – 150[34]	337[M^+], 396[M^{2+}]
21	2,4-$(CH_3)_2$-C_6H_3	4-FC_6H_4	$C_{18}H_{18}FN_3S$	327	90	225 – 226 223 – 225[23]	327[M^+], 329[M^{2+}]
22	2,4-$(CH_3)_2$-C_6H_3	4-$NO_2C_6H_4$	$C_{18}H_{18}N_4O_2S$	354	89	203-204 202-203[23]	354[M^+]
23	C_4H_3O(2-Furyl)	C_6H_5	$C_{14}H_{13}N_3OS$	271	92	177 – 178 176 – 177[37]	271[M^+]
24	C_4H_3O(2-Furyl)	C_4H_3O(2-Furyl)	$C_{12}H_{11}N_3O_2S$	293	92	164 – 165 163 – 164[37]	293[M^+]
25	3,4-Br_2-C_6H_3	4-C_6H_4	$C_{16}H_{13}Br_2N_3S$	439	90	132 – 133	439[M^+], 441[M^{2+}], 443[M^{4+}]

Table 1. *continued*

Entry	R	R′	Product	M.W.	Yield	m.p. (°C)	Mass (m/z)
26	3,4-Br_2-C_6H_3	2-BrC_6H_4	$C_{16}H_{12}Br_3N_3S$	519	88	217–218 214–216[24]	519[M^+], 521[M^{2+}], 523[M^{4+}]
27	3,4-Br_2-C_6H_3	4-BrC_6H_4	$C_{16}H_{12}Br_3N_3S$	519	88	240–241 239–24[24]	519[M^+], 521[M^{2+}], 523[M^{4+}]
28	3,4-Br_2-C_6H_3	2-ClC_6H_4	$C_{16}H_{12}Br_2ClN_3S$	491	87	221–222 219–221[24]	491[M^+], 493[M^{2+}], 495[M^{4+}]
29	3,4-Br_2-C_6H_3	4-ClC_6H_4	$C_{16}H_{12}Br_2ClN_3S$	491	87	217–218 216–218[24]	491[M^+], 493[M^{2+}], 495[M^{4+}]
30	3,4-Br_2-C_6H_3	2-FC_6H_4	$C_{16}H_{12}Br_2FN_3S$	457	87	237–238 236–237[24]	457[M^+], 459[M^{2+}], 461[M^{4+}]
31	3,4-Br_2-C_6H_3	4-FC_6H_4	$C_{16}H_{12}Br_2FN_3S$	457	87	247–248 246–247[24]	457[M^+], 459[M^{2+}], 461[M^{4+}]
32	3,4-Br_2-C_6H_3	4-OHC_6H_4	$C_{16}H_{13}Br_2N_3OS$	455	87	222–223 221–223[24]	455[M^+], 457[M^{2+}], 459[M^{4+}]
33	3,4-Br_2-C_6H_3	4-$OCH_3C_6H_4$	$C_{17}H_{15}Br_2N_3OS$	469	90	237–238 236–238[24]	469[M^+], 471[M^{2+}], 473[M^{4+}]
34	3,4-Br_2-C_6H_3	4-$CH_3C_6H_4$	$C_{17}H_{15}Br_2N_3S$	453	89	212–213 211–212[24]	453[M^+], 455[M^{2+}], 457[M^{4+}]
35	3,4-Br_2-C_6H_3	4-$NO_2C_6H_4$	$C_{16}H_{12}Br_2N_4O_2S$	485	88	247–248 246–248[24]	361[M^+], 363[M^{2+}], 465[M^{4+}]

Table 2. Reusability of fly-ash:PTS catalyst, on cyclization of styryl 3,4-dibromo phenyl ketone (2 mmol) and thiosemicarbazide (2 mmol), under microwave irradiation (entry 25).

Run	1	2	3	4	5
Yield	90	90	89.5	89.5	89

Table 3. The effect of solvents in conventional heating and without solvent in microwave irradiation, on yield of 1-thiocarbomyl pyrazoline (entry 25).

Solvents													Microwave irradiation		
MeOH			EtOH			DCM			THF						
FA	PTS	FAPTS	FA	PTS	FAPTS	FA	PTS	FAPTS	FA	PTS	FAPTS	FA	PTS	FAPTS
73	47	78	74	45	80	73	40	80	75	41	81	78	66	90

MeOH = Methanol; EtOH = Ethanol; DCM = Dichloromethane; THF = Tetrahydrofuran; FA = fly-ash; PTS = para toluene sulphonic acid; FAPTS = fly-ash:PTS

Table 4. The spectroscopic data of 1- thiocarbomyl pyrazolines (entries 25–35).

		IR(ν, cm − 1)			^{13}C NMR(δ,ppm)				^{13}C NMR(δ,ppm)		
Entry	X	C═N	NH	C═S	Ha (*dd*, 1H)	Hb (*dd*, 1H)	Hc (*dd*, 1H)	X	C═N	C═S	X
25	H	1586	3562	1384	3.071	3.418	5.421	–	163.91	176.47	–
26	2-Br	1582	3559	1381	3.101	3.691	5.314	–	163.94	175.91	–
27	4-Br	1591	3560	1378	3.415	3.891	7.451	–	163.87	175.75	–
28	2-Cl	1597	3537	1378	3.100	3.901	6.344	–	163.79	174.96	–
29	4-Cl	1598	3556	1379	3.235	3.817	6.014	–	162.91	176.29	–
30	2-F	1596	3558	1380	3.106	3.870	5.361	–	163.76	177.94	–
31	4-F	1594	3567	1384	3.247	3.817	5.944	–	161.74	174.17	–
32	4-OH	1592	3559	1382	3.341	3.801	5.967	–	162.65	175.47	–
33	4-OCH_3	1580	3551	1376	3.111	3.765	5.901	2.361	160.76	173.12	58.62
34	4-CH_3	1596	3556	1382	3.141	3.801	5.921	3.654	163.71	176.92	27.98
35	3-NO_2	1598	3559	1396	3.792	3.912	5.981	–	164.17	177.02	–

Hammett σ_R constant, F and R parameters, gave satisfactory correlation for the νNH stretches(cm^{-1}) of these thiocarbomyl pyrazolines. The remaining Hammett substituent constants have shown poor correlation. The failure in correlation was due to the absence of transmittance of inductive, resonance and field effects of the substituent on the spectral group frequencies, νC═N, C═S and NH (cm^{-1}), and is associated with the resonance-conjugative structure shown in Figure 3. Some of the single parameter correlations of νC═N, C═S and NH (cm^{-1}) frequencies, of 1-thiocarbomylpyrazolines with Hammett substituent constants, F and R parameters, failed. Therefore, it is worthwhile to look at the multi-regression analysis of these frequencies with Swain-Lupton's[43] constants. The multi-regressions gave satisfactory correlation with inductive, resonance and field effects of the substituents. The corresponding multi-regression equations are given in (2) – (7).

$$\nu_{CN}(cm^{-1}) = 1589.74(\pm 4.487) + 10.236\sigma_I(\pm 4.589) + 7.087\sigma_R(\pm 1.020) \quad (R = 0.939, P > 90\%, n = 11) \tag{2}$$

$$\nu_{CN}(cm^{-1}) = 1589.48(\pm 4.146) + 10.615F(\pm 2.576) + 6.566R(\pm 1.754) \quad (R = 0.942, P > 90\%, n = 11) \tag{3}$$

Table 5. Results of statistical analysis of infrared $\nu(cm^{-1})$ C═N, C═S, NH, CF, NMR chemical shifts (δ,ppm) of Ha, Hb, Hc, C═N and C═S of 1-thiocarbamyl pyrazolines, with Hammett σ, σ^+, σ_I σ_R constants, and F and R parameters (entries 25–35).

Frequency	Constants	r	I	ρ	s	n	Correlated derivatives
νC═N	σ	0.908	1590.85	8.128	6.18	9	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-NO_2
	σ^+	0.903	1591.54	8.879	6.38	9	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-NO_2
	σ_I	0.903	1588.35	9.444	6.41	9	2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-NO_2
	σ_R	0.813	1593.19	5.787	6.66	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	F	0.833	1588.30	8.584	6.38	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	R	0.815	1592.95	3.713	6.69	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
νNH	σ	0.805	3556.58	1.212	8.04	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	σ^+	0.804	3556.77	-0.656	8.04	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	σ_I	0.791	3556.96	-0.644	8.05	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	σ_R	0.901	3556.88	5.676	8.00	9	H, 2-Br, 4-Br, 4-Cl, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	F	0.901	3554.76	4.719	7.90	9	2-Br, 4-Br, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	R	0.902	3554.12	-1.967	8.03	9	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
νC═S	σ	0.805	1380.76	8.904	4.73	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	σ^+	0.813	1381.58	8.436	5.28	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	σ_I	0.792	1379.75	5.627	5.48	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	σ_R	0.905	1385.45	15.340	4.53	9	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-OCH_3, 4-CH_3, 4-NO_2
	F	0.802	1379.87	4.761	5.49	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	R	0.904	1384.83	9.985	4.88	9	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-OCH_3, 4-CH_3, 4-NO_2
δH_a	σ	0.906	3.193	0406	0.17	10	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 4-NO_2
	σ^+	0.907	3.234	0.106	0.21	10	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 4-NO_2
	σ_I	0.905	3.061	0.494	0.91	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	σ_R	0.814	3.360	0.504	0.19	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	F	0.903	3.106	0.329	0.20	10	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 4-NO_2
	R	0.913	3.325	0.273	0.21	10	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 4-NO_2
δH_b	σ	0.916	3.770	0.157	0.13	10	2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	σ^+	0.903	3.785	0.059	0.14	10	2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	σ_I	0.926	3.673	0.415	0.11	10	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-NO_2
	σ_R	0.817	3.759	-0.217	0.14	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	F	0.906	3.648	0.344	0.11	10	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-NO_2
	R	0.902	3.756	-0.105	0.14	9	4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
δH_c	σ	0.892	5.918	0.400	0.60	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2

	σ^+	0.875	5.961	0.540	0.61	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	σ_I	0.902	5.742	0.608	0.60	10	H, 2-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	σ_R	0.814	6.604	0.400	0.61	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	F	0.805	5.912	0.132	0.61	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	R	0.881	6.024	0.193	0.61	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
δCN	σ	0.905	162.967	1.972	0.92	10	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3
	σ^+	0.907	163.10	1.938	0.80	10	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3
	σ_I	0.903	163.14	0.155	0.92	9	2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-NO_2
	σ_R	0.906	163.98	3.309	0.89	9	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	F	0.805	163.307	-0.759	1.14	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	R	0.907	164.01	2.668	0.86	9	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 4-F, 4-OH, 4-CH_3, 4-NO_2
δCS	σ	0.844	175.59	1.875	1.28	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	σ^+	0.852	175.73	1.284	1.12	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	σ_I	0.813	175.895	− 0.207	1.43	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	σ_R	0.904	176.51	2.901	1.29	10	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	F	0.802	175.76	0.136	1.44	11	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 2-F, 4-F, 4-OH, 4-OCH_3, 4-CH_3, 4-NO_2
	R	0.941	176.46	2.130	1.30	9	H, 2-Br, 4-Br, 2-Cl, 4-Cl, 4-F, 4-OCH_3, 4-CH_3, 4- NO_2

r = correlation co-efficient; ρ = slope; I = intercept; s = standard deviation; n = number of substituents.

$$\nu_{C=S}(cm^{-1}) = 1382.95(\pm 3.026) + 7.455\sigma_I(\pm 1.265) + 16.287\sigma_R(\pm 6.878) \quad (4)$$
$$(R = 0.966, P > 95\%, n = 11)$$

$$\nu_{C=S}(cm^{-1}) = 1382.05(\pm 2.965) + 8.530\,F(\pm 1.134) + 12.136R(\pm 5.703) \quad (5)$$
$$(R = 0.962, P > 95\%, n = 11)$$

$$\nu_{NH}(cm^{-1}) = 3357.08(\pm 5.800) - 0.577\sigma_I(\pm 0.122) + 0.603\sigma_R(\pm 0.032) \quad (6)$$
$$(R = 0.902, P > 90\%, n = 11)$$

$$\nu_{NH}(cm^{-1}) = 3354.63(\pm 5.375) + 4.559F(\pm 1.119) - 0.746R(\pm 0.215) \quad (7)$$
$$(R = 0.915, P > 90\%, n = 11)$$

^{1}H NMR spectral study

The ^{1}H NMR spectra of synthesised 1-thiocarbomyl pyrazoline derivatives (entries 25–35) under investigation, have been recorded in deuteriochloroform solution employing tetramethylsilane (TMS) as the internal standard. The signals of the pyrazoline ring protons have been assigned. They have been calculated as AB or AA' systems, respectively. The chemical shifts (ppm) of H_a are at higher fields than those of H_b and H_c in this series of 1-thiocarbomyl pyrazolines. This is due to the deshielding of H_b and H_c which are in different chemical, as well as magnetic, environments. These H_a protons gave an AB pattern, and the H_b proton doublet of doublet, in most cases, was separated from the signals H_c and the aromatic protons. The assigned chemical shifts (ppm) of the pyrazoline ring H_a, H_b and H_c protons are presented in Table 4.

In nuclear magnetic resonance spectra, the ^{1}H or the ^{13}C chemical shifts (δ, ppm) depend on the electronic environment of the nuclei concerned. These chemical shifts have been correlated with reactivity parameters. Thus the Hammett equation may be used in the form as shown in (8).

$$\text{Log}\,\delta = \text{Log}\,\delta_o + \rho\sigma \quad (8)$$

Where δ_o is the chemical shift of the corresponding parent compound.

The assigned H_a, H_b and H_c proton chemical shifts (ppm) of synthesized 1-thiocarbomyl pyrazolines have been correlated with various Hammett sigma constants. The results of statistical analysis[20,22,27–30,36,38–43] is presented in Table 5. The H_a proton chemical shifts (δ, ppm) with Hammett σ, σ^+, σ_I constants and R parameters gave satisfactory correlation, along with positive ρ values, excluding 4-OH substituent. The resonance and field components failed in correlation. The failure in correlation is associated with the conjugative structure shown in Figure 3.

The results of statistical analysis of H_b proton chemical shifts (δ, ppm) of the synthesised 1-thiocarbomyl pyrazolines with Hammett substituents, F and R parameters, are shown in Table 5. The H_b proton chemical shifts (δ, ppm) with Hammett σ, σ^+, σ_I constants, F and R parameters, gave satisfactory correlation, excluding H, 2-Br and 4-CH_3 substituents. The Hammett σ_R constant produces poor correlation. All correlation gave positive ρ values, excluding Hammett σ_R constant and R parameter. The poor correlation is due to the absence or incapability of transmittance of resonance effect of substituents on the H_b proton chemical shifts (δ, ppm), and the association with a conjugative structure, as shown in Figure 3.

The results of statistical analysis of H_c proton chemical shifts (δ, ppm) with Hammett substituents are presented in Table 5. The H_c proton chemical shifts (δ, ppm) with Hammett σ_I constant, gave satisfactory correlation, excluding 4-Br substituent. The remaining Hammett substituent constants, F and R parameters, showed failing correlation. All correlations produce positive ρ values. This means that the normal substituent effect operates in all systems. The reason for failure in correlation was stated earlier, and associated with a conjugative structure, as shown in Figure 3.

In view of the inability of the Hammett σ constants to produce satisfactory correlation individually, it is worthwhile looking at multiple correlations, involving either σ_I and σ_R constants,

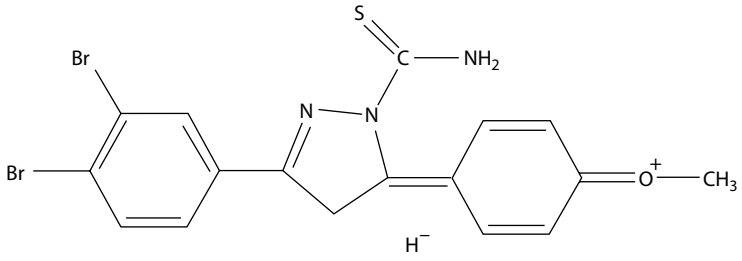


Figure 3. The resonance-conjugative structure (33).

or Swain-Lupton's[43], F and R parameters. The correlation equations for H_{a-c} proton chemical shifts (δ, ppm) are given in (9) – (14).

$$\delta H_a^{(ppm)} = 3.173(\pm 0.108) + 0.557(\pm 0.231)\sigma_I + 0.571\,(\pm 0.210)\sigma_R \quad (9)$$
$$(R = 0.974,\ P > 95\%,\ n = 11)$$

$$\delta H_a^{(ppm)} = 3.177(\pm 0.120) + 0.451(\pm 0.249)\,F + 0.394(\pm 0.131)\,R \quad (10)$$
$$(R = 0.961, P > 95\%,\ n = 11)$$

$$\delta H_b^{(ppm)} = 3.622(\pm 0.079) + 0.407(\pm 0.169)\sigma_I - 0.072(\pm 0.011)\sigma_R \quad (11)$$
$$(R = 0.966, P > 95\%,\ n = 11)$$

$$\delta H_b^{(ppm)} = 3.645(\pm 0.077) + 0.339(\pm 0.161)F - 0.014(\pm 0.001)R \quad (12)$$
$$(R = 0.916, P > 90\%,\ n = 11)$$

$$\delta H_c^{(ppm)} = 5.837(\pm 0.427) + 0.662(\pm 0.092)\sigma_I + 0.484(\pm 0.097)\sigma_R \quad (13)$$
$$(R = 0.926, P > 90\%,\ n = 11)$$

$$\delta H_c^{(ppm)} = 5.955(\pm 0.414) + 0.210(\pm 0.055)F + 0.249(\pm 0.072)R \quad (14)$$
$$(R = 0.912, P > 90\%,\ n = 11)$$

^{13}C NMR spectra

Physical organic chemists and researchers[20,22,27–30,36,38–43] have made extensive study of ^{13}C NMR spectra for a large number of ketones, styrenes and keto-epoxides. The linear correlation of the chemical shifts (ppm) of vinyl and carbonyl carbons with Hammett **σ** constants, F and R parameters, in alkenes, alkynes, acid chlorides and styrenes has been investigated. In the present study, the chemical shifts (δ, ppm) of 1-thiocarbomyl pyrazoline ring C═N and C═S carbon, have been assigned and are presented in Table 4. Attempts have been made to correlate the above assigned carbon chemical shifts (δ, ppm) with Hammett substituent constants, field and resonance parameters, with the help of single and multi-regression analyses, to study the reactivity through the effect of substituents.

The observed C═N and C═S chemical shifts (δ,ppm) of synthesised 1-thiocarbomyl pyrazolines have been correlated with Hammett substituent constants and the results of statistical analysis are presented in Table 5. The C═N chemical shifts (δ, ppm) has shown satisfactory correlation with Hammett substituent constants and R parameters, along with positive **ρ** values, excluding H, 2-F, 4-OCH_3 and 4-CH_3 substituents. The F parameter failed in correlation and gave negative **ρ** values. The failure in the correlation is due to incapability of transmittance of the resonance effect of the substituents on the C═N carbon chemical shifts (δ, ppm). The chemical shifts (δ, ppm) observed for the C═S carbon of the 1-thiocarbomyl pyrazolines, have been correlated satisfactorily with Hammett σ_R constant and R parameters, excluding 2-F and 4-OH substituents. The remaining Hammett

substituent constants and F parameters failed in correlation. All correlation produced positive ρ values, except σ_I constants. This implies that the normal substituent effect operates in all thiocarbomyl pyrazolines. The failure in the correlation was due to the reason stated earlier, and it is associated with the resonance – conjugative structure, as shown in Figure 3.

In view of the inability of some of the σ constants to produce individually satisfactory correlation, multiple correlation, involving either σ_I, σ_R or F and R parameters,[43] were used. The generated correlation equations are given in (15) to (18).

$$\delta_{C=N}^{(ppm)} = 163.80(\pm 0.636) + 0.534(\pm 0.0102)\sigma_I + 3.377(\pm 1.446)\sigma_R \quad (R = 0.963, P > 95\%, n = 11) \tag{15}$$

$$\delta_{C=N}^{(ppm)} = 163.81(\pm 0.571) + 0.618(\pm 0.118)F + 2.833(\pm 0.099)R \quad (R = 0.967, P > 95\%, n = 11) \tag{16}$$

$$\delta_{C=S}^{(ppm)} = 176.46(\pm 1.931) + 0.121(\pm 0.013)\sigma_I + 2.925(\pm 0.1176)\sigma_R \quad (R = 0.943, P > 90\%, n = 11) \tag{17}$$

$$\delta_{C=S}^{(ppm)} = 175.18(\pm 0.472) + 0.863(\pm 0.126)F + 2.347(\pm 1.600)R \quad (R = 0.944, P > 95\%, n = 11) \tag{18}$$

CONCLUSION

A series of 1-thiocarbomyl pyrazolines, including 3-(3,4-dibromophenyl)-5-(substituted phenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamides, have been synthesised by microwave assisted fly-ash:PTS catalyzed solvent-free cyclization of chalcones and thiosemicarbazide. The yields of the synthesized carbothioamides are more than 85%. The correlation study of infrared ν(cm^{-1}) of C=N, C=S frequencies, ^1H and ^{13}C NMR chemical shifts (δ, ppm) of $H_{a\text{-}c}$ and C=N, C=S, of 3-(3,4-dibromophenyl)-5-(substitutedphenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamides, have shown satisfactory correlation co-efficient in both single and multi-regression analyses.

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