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Synthesis of 3,5-disubsituted pyrazolines and their derivatives

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ABSTRACT

2-Acetylthiophene condenses with different aromatic aldehyde in ethanol in the presence of aqueous NaOH to give 1-(2'-thienyl)-3-(substituted phenyl) -2- propen-1-one (Ia-e) which reacts with hydrazine hydrate in ethanol to give pyrazoline (IIa-e). Similarly, 1-(2'-thienyl)-3-(substituted phenyl)-2-propen-1-one (Ia-e) reacts with phenyl hydrazine hydrochloride in the presence of ethanol medium and 1,2 drops of NaOH (2N) to give 1-phenyl pyrazoline (IIIa-e), (Ia-e) Reacts with 2,4-dinitro phenyl hydrazine in presence of ethanol medium to give 1-(2,4-dinitro phenyl) pyrazoline (IVa-e) and also reacts with semicarbazide hydrochloride in presence of ethanol medium and 1,2 drops of NaOH (2N) to give 1- carboxamido pyrazoline (Va-e). Pyrazoline (IIa-e) reacts with acetic acid to give 1–acetyl pyrazoline (VIa-e), as well as it reacts with benzoyl chloride in pyridine medium to give 1-benzoyl pyrazoline (VIIa-e) and also reacts with 1:1 HCl and 10% sodium nitrite to give 1-nitrso pyrazoline (VIIIa-e). Characterization and structural elucidation were done on the basis of melting points determination, analytical and spectral studies.

Key words: Chalcone and pyrazolines, synthesis, structural study.

INTRODUCTION

Pyrazolines are the five membered nitrogen containing heterocyclic compounds. Pyrazolines are known to have fungicidal[1] insecticidal[2] and bacterial[3] properties. Some pyrazolines possess a broad spectrum of biological activity like anaesthetic,[4] antidiabetic,[5] analgesic,[6,7] anti-inflammatory,[7,8] antitumor,[9] anticonvulsant,[10] antidepressant,[11] antimicrobial[12,13] and strong antibacterial[10,14]. Synthesis and characterization of pyrazoline derivatives has been a developing field within the realm of heterocyclic chemistry for the past several years because of their ready accessibility through synthesis and wide range of chemical reactivity. Survey of literature in the recent past reveals that some pyrazoline derivatives possess cerebroprotective[15] effect.

Chalcone reacts with hydrazine hydrate in ethanol to give pyrazoline. Chalcone also reacts with phenyl hydrazine hydrochloride in presence of ethanol medium and 1,2 drops of NaOH (2N) to give 1-phenyl pyrazoline[16-18], reacts with 2,4-dinito phenyl hydrazine in presence of ethanol medium to give 1-(2,4-dinitro phenyl) pyrazoline[18] and also reacts with semicarbazide hydrochloride in presence of ethanol medium and 1,2 drops of NaOH (2N) to give 1-carboxamido pyrazoline[17]. Pyrazoline reacts with acetic acid to give 1-acetyl pyrazoline[16-22] as well as it reacts with benzoyl chloride in pyridine medium to give 1-benzoyl pyrazoline[16-21] and also reacts with 1:1 HCl and 10% sodium nitrite to give 1-nitroso pyrazoline[17]. Literature survey indicates that some pyrazoline[23,24] have been prepared from 1-(2'-thienyl)-3-(substituted phenyl)-2-propen-1-one. Recently, a green synthesis of chalcones and pyrazolines have been reported[25], but their derivatives have not been prepared by sofar. Hence it was thought interesting to prepare pyrazolines and their derivatives from 1-(2'-thienyl)-3-(substituted phenyl)-2- propen-1-one (Scheme 1).

EXPERIMENTAL

2-Aceteylthiophene is of AR grade and was obtained from Sigma Aldrich. Chalcones required for the synthesis of pyrazolines were prepared by earlier known method[23,24]. Melting points were determined in an open capillary tubes and are uncorrected. IR spectra were recorded on Perkin-Elmer-557 spectrophotometer. PMR spectra were recorded in $CDCl_3$ on a Bruker Avance II 400 NMR Spectrometer at 300 MHz using TMS as an internal reference (Chemical shifts in δ ppm down field from TMS). Purity of the compounds was checked by TLC on silica gel – G coated plates.

Synthesis of 1-H-3-(2'-thienyl)-5-(4''-dimethyl amino phenyl)-Δ-pyrazoline (IIa).

The mixture of 1-(2'-thienyl)-3-(4"-dimethyl amino phenyl)-2-propen-1-one (Ia) (0.01 mol) and 99% hydrazine hydrate (0.012 mol) in ethanol (20 ml) was refluxed for 6 hours. The reaction mixture was then concentrated and allowed to cool, the resulting solid was filtered, washed with ethanol and crystallized from ethanol to get 1-H-3-(2'-thienyl)-5-(4"-dimethyl amino phenyl)-Δ-pyrazoline (IIa). Yield 80%, m.p. 80°C, Colour-Reddish.

IR (KBr) cm^{-1}

3336.36 (-NH), 3076 (Ar, C-H), 1614.47 (C=N), 1435.09 (-CH_2- of pyrazoline), 1219.05 (C-N), 1045.45 (C-N-$(CH_3)_2$), 632.67 (C-S).

PMR ($CDCl_3$)

δ: 2.9 (s, 6H, -N$(CH_3)_2$), 3 (dd, 1H, >CHH_A), 3.5 (dd, 1H, >CH_BH), 4.9 (dd,1H,>CH_X-), 5.8 (s, 1H, -NH), 6.7-7.4 (m, 7H, Ar-H and heteroaromatic H).

Synthesis 1-phenyl -3-(2'-thienyl) -5-(4"-dimethyl amino phenyl)-Δ-pyrazoline (IIIa)

The mixture of 1-(2'-thienyl)-3-(4"-dimethyl amino phenyl)-2-propen-1-one (Ia) (0.01 mol) and phenyl hydrazine hydrochloride (0.012 mol) was dissolved in 15 ml ethanol and 1,2 drops of NaOH (2N) refluxed for 3 hours. The reaction mixture was then concentrated and allowed to cool. It was then treated with 1:1 HCl. The resulting solid was filtered, washed with ethanol and crystallized from ethanol to get 1-phenyl-3-(2'-thienyl)-5-(4"-dimethyl amino phenyl)--pyrazoline (IIIa). Yield 68%, m.p. 92°C, Colour-Brown.

IR (KBr) cm^{-1}

3094.4 (Ar, C-H), 1596.3 (C=N), 1497.5 (-CH_2- of pyrazoline), 1351.3 (C-N), 1122.8 (C-N-$(CH_3)_2$), 691.4 (C-S).

PMR ($CDCl_3$)

δ: 2.9 (s, 6H, -N$(CH_3)_2$), 3.1 (dd, 1H, >CHH_A), 3.8 (dd, 1H, >CH_BH), 5.1 (dd, 1H, >CH_X-), 6.4- 7.9 (m, 12H, Ar-H and heteroaromatic H)

Synthesis of 1-(2,4-dinitro phenyl)-3-(2'-thienyl)-5-(4"-dimethyl amino phenyl)-Δ-pyrazoline. (IVa).

The mixture of 1-(2'-thienyl)-3-(4"-dimethyl amino phenyl)-2-propen-1-one (Ia) (0.01 mol) and 2,4-dinitro phenyl hydrazine (0.012 mol) was dissolved in 15 ml ethanol and refluxed for 2 hours. The reaction mixture was then concentrated and allowed to cool. The resulting solid was filtered, washed with ethanol and crystallized from ethanol to get 1-(2,4-dinitro pheyl)-3-(2'-thienyl)-5-(4"-dimethyl amino phenyl)--pyrazoline (IVa). Yield 72%, m.p. 102°C, Colour-Brown.

IR (KBr) cm^{-1}

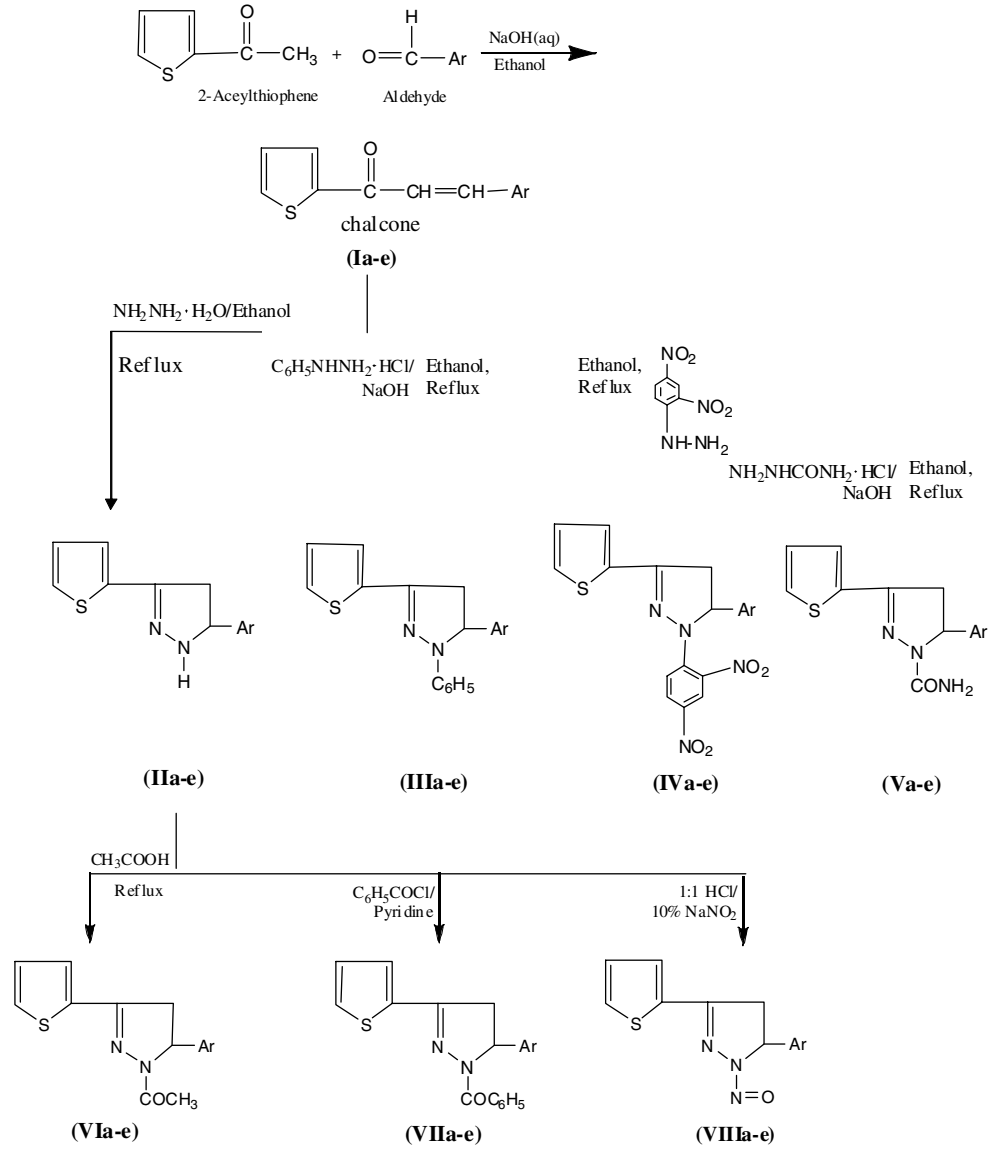
3086.21 (Ar, C-H), 1629.90 (C=N), 1523.82, 1336.71 (-NO_2 Asym. and Sym.), 1415.80 (-CH_2- of pyrazoline), 1230.63 (C-N), 1184.33 (C-N-$(CH_3)_2$), 650.00 (C-S).

PMR ($CDCl_3$)

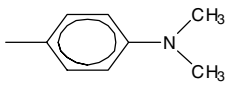
δ: 3.1 (s, 6H, -N$(CH_3)_2$), 3.25 (dd, 1H, >CHH_A), 3.9 (dd, 1H, >CH_BH), 5.42 (dd, 1H, > CH_X-), 6.6 – 7.9 (m, 10H, Ar-H and hetroaromatic H)

Synthesis of 1-carboxamido-3-(2'-thienyl)-5-(4"-dimethyl amino phenyl)-Δ-pyrazoline (Va)

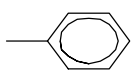
The mixture of 1-(2'-thienyl)-3-(4"-dimethyl amino phenyl)-2-propen-1-one (Ia) (0.01mol) and semicarbazide hydrochloride (0.012 mol) was dissolved in 15 ml ethanol and 1,2 drops of NaOH (2N) refluxed for 3 hours. The reaction mixture was then concentrated and allowed to cool. It was then treated with 1:1 HCl. The resulting solid was filtered, washed with ethanol and crystallized from ethanol to get 1-carboxamido-3-(2'-thienyl)-5-(4"-dimethyl amino phenyl)-Δ-pyrazoline (Va) Yield 70%, m.p. 120°C, Colour-Yellow.



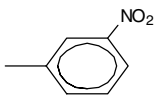
Where : **Ia** to **VIIIa** Ar =



Id to **VIIId** Ar =



Ib to **VIIIb** Ar =



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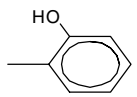
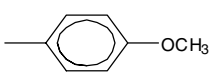


Ic to **VIIIc** Ar =



Scheme 1:

IR (KBr) cm^{-1}

3300.5 (-CO<u>NH</u>$_2$), 3081.6 (Ar, C-H), 1678.1 (C=N), 1631.2 and 1609.1 (-<u>CO</u>NH$_2$), 1434.7 (-CH$_2$- of pyrazoline), 1230.4 (C-N), 1182.1 (C-N-(CH$_3$)$_2$), 697.3 (C-S)

PMR (CDCl3)

δ:3.05 (s, 6H, -N(CH$_3$)$_2$), 3.15 (dd, 1H, >CHH$_A$)), 3.8 (dd, 1H, >CH$_B$H), 5.4 (dd, 1H, >CH$_X$-), 6.6-6.8 (S, 2H, -CONH$_2$), 7.0 -7.9 (m, 7H, Ar-H and heteroaromatic H).

Synthesis of 1-acetyl -3-(2'-thienyl)-5-(4''-dimethyl amino phenyl)--pyrazoline (VIa)

The mixture of 1-H-3-(2'-thienyl)-5-(4''-dimethyl amino phenyl)--pyrazoline (IIa) (0.01 mol) and acetic acid (10 ml) was refluxed for 2 hours. The reaction mixture was then concentrated. On cooling resulting solid was filtered, washed with water and crystallized from ethanol to get 1-acetyl-3-(2'-thienyl)-5-(4''-dimethyl amino phenyl)-Δ-pyrazoline (VIa). Yeild 78%, m.p. 150^{0}C, Colour – Light Yellow.

IR (KBr) cm^{-1}

3098.2 (Ar, C-H), 1661.4, 1614.0 (N-C=O and C=O), 1521.0 (C=N), 1401.2 (-CH$_2$- of pyrazoline), 1226.6 (C-N), 1127.7 (C-N-(CH$_3$)$_2$), 624.3 (C-S)

PMR (CDCl$_3$) δ

2.35 (s, 3H, -COCH$_3$), 2.9 (s, 6H, -N(CH$_3$)$_2$), 3.15 (dd, 1H, >CHH$_A$), 3.7 (dd, 1H, >CH$_B$H), 5.5 (dd, 1H, >CH$_X$-), 6.7-7.4 (m, 7H, Ar-H and heteroaromatic H)

Synthesis of 1-benzoyl-3-(2'-thienyl)-5-(4''-dimethyl amino phenyl)-Δ-pyrazoline (VIIa)

The mixture of 1-H-3-(2'-thienyl) -5-(4''-dimethyl amino phenyl)-Δ-pyrazoline (IIa) (0.01 mol) and benzoyl chloride (0.01mol) was dissolved in pyridine (15ml) and stirred at room temperature for 1 hour. After which the reaction mixture was treated with cold dil HCl (2N). The resulting solid was filtered, washed successively with water, cold 2% NaOH and finally with water. The crude mass was crystallized from acetic acid to get 1-benzoyl- 3-(2'-thienyl)-5-(4''-dimethyl amino phenyl)-Δ-pyrazoline (VIIa). Yield 74%, m. p. 190^{0}C, Colour- Light yellow.

IR(KBr) cm^{-1}

3067.7(Ar, C-H), 1633.7, 1614.5 (N-C=O and C=O), 1523.1 (C=N), 1451.0 (-CH$_2$- of pyrazoline), 1280.2 (C-N), 1167.2 (C-N-(CH$_3$)$_2$), 694.5 (C-S)

PMR (CDCl$_3$)

δ:2.9 (s, 6H, -N(CH$_3$)$_2$), 3.2 (dd, 1H, >CHH$_A$), 3.75 (dd, 1H, >CH$_B$H), 5.75 (dd, 1H. >CH$_X$-), 6.6-8.0 (m, 12H, Ar-H and heteroaromatic H)

Synthesis of 1-nitroso-3-(2'-thienyl)-5-(4''-dimethyl amino phenyl)-Δ-pyrazoline (VIIIa)

1-H-3-(2'-thienyl)-5-(4''-dimethyl amino phenyl)-Δ-pyrazoline (IIa) (0.01 mol) was dissolved in 1:1 HCl (2 ml) and cooled in ice bath. Cold 10 % sodium nitrite (6 ml) was then added dropwise with constant stirring. The reaction mixture was further stirred for 1 hour at room temperature. The solid thus separated was filtered and crystallized from ethanol to get 1-nitroso-3-(2'-thienyl)-5-(4''-dimethyl amino phenyl)-Δ-pyrazoline (VIIIa). Yield 64%, m.p. 180^{0}C, Colour – Blackish Brown.

IR (KBr) cm^{-1}

3063.06 (Ar, C-H) 1649.19 (C=N), 1583.61 (N=O), 1410.01 (-CH$_2$- of pyrazoline), 1348.29 (N-N=O), 1276.92 (C-N), 1190.12 (C-N-(CH$_3$)$_2$), 610.09 (C-S).

PMR (CDCl$_3$) δ

3.1(s, 6H, -N(CH$_3$)$_2$), 3.4 (dd, 1H, >CHH$_A$), 3.9(dd, 1H, >CH$_B$H), 5.8 (dd, 1H, >CH$_X$-), 6.6 – 8.2 (m, 7H, Ar-H and heteroaromatic H)

Similarly, the other members of the series were also prepared in this manner and their characterization data are given in Table 1.

RESULTS AND DISCUSSION

The Structures of synthesized pyrazolines (IIa, IIIa, IVa, and Va) have been established on the basic of analytical data. The IR spectra of IIa showed the presence of band for υ N-H, Ar C-H, C=N, C-N and C-S. The PMR data showed the peaks for –CH$_3$, double doublets for CHH$_A$, CH$_B$H and CH$_X$ as well as peaks for N-H and aromatic protons also. The structure of other derivatives (VIa to VIIIa) were determined in a similar way.

Table 1: Characterization data of pyrazolines and their derivatives

S. No.	Code	Molecular Formula	Molecular Weight	Colour	m.p. °C	Elemental Analysis % Calculated (Found)			
						C	H	N	S
1	Ia	$C_{15}H_{15}NOS$	257	Orange	118 ^{0}C	70.03 (69.60)	5.83 (5.75)	5.44 (5.40)	12.45 (12.21)
2	Ib	$C_{13}H_9NO_3S$	259	Brown	132 ^{0}C	60.23 (59.81)	3.47 (3.40)	5.40 (5.31)	12.35 (12.19)
3	Ic	$C_{14}H_{12}O_2S$	244	Faint Yellow	84 ^{0}C	68.85 (68.36)	4.91 (4.84)	-	13.11 (12.90)
4	Id	$C_{13}H_{10}OS$	214	Off White	70 ^{0}C	72.89 (72.45)	4.67 (4.61)	-	14.95 (14.76)
5	Ie	$C_{13}H_{10}O_2S$	230	Light Green	135 ^{0}C	67.82 (67.31)	4.34 (4.28)	-	13.91 (13.80)
6	IIa	$C_{15}H_{17}N_3S$	271	Reddish	80 ^{0}C	66.42 (65.96)	6.27 (6.20)	15.49 (15.31)	11.80 (11.65)
7	IIb	$C_{13}H_{11}N_3O_2S$	273	Yellowish Brown	130 ^{0}C	57.14 (56.63)	4.02 (3.96)	15.38 (15.24)	11.72 (11.58)
8	IIc	$C_{14}H_{14}N_2OS$	258	Colourless	170 ^{0}C	65.11 (64.67)	5.42 (5.36)	10.85 (10.74)	12.40 (12.19)
9	IId	$C_{13}H_{12}N_2S$	228	Brown	Oily	68.42 (67.98)	5.26 (5.19)	12.28 (12.20)	14.03 (13.84)
10	IIe	$C_{13}H_{12}N_2OS$	244	Light Yellow	115 ^{0}C	63.93 (63.45)	4.91 (4.84)	11.47 (11.36)	13.11 (12.86)
11	IIIa	$C_{21}H_{21}N_3S$	347	Brown	92 ^{0}C	72.62 (72.11)	6.05 (5.91)	12.10 (12.01)	9.22 (9.03)
12	IIIb	$C_{19}H_{15}N_3O_2S$	349	Brown	90 ^{0}C	65.32 (64.86)	4.29 (4.21)	12.03 (11.96)	9.16 (8.97)
13	IIIc	$C_{20}H_{18}N_2OS$	334	Light Brown	170 ^{0}C	71.85 (71.32)	5.38 (5.13)	8.38 (8.27)	9.58 (9.39)
14	IIId	$C_{19}H_{16}N_2S$	304	Faint Brown	145 ^{0}C	75.00 (74.52)	5.26 (5.18)	9.21 (9.14)	10.52 (10.36)
15	IIIe	$C_{19}H_{16}N_2OS$	320	Greenish	280 ^{0}C	71.25 (70.75)	5.00 (4.95)	8.75 (8.67)	10.00 (9.83)
16	IVa	$C_{21}H_{19}N_5O_4S$	437	Brown	102 ^{0}C	57.66 (57.14)	4.34 (4.31)	16.01 (15.99)	7.32 (7.18)
17	IVb	$C_{19}H_{13}N_5O_6S$	439	Light Orange	138 ^{0}C	51.93 (51.47)	2.96 (2.89)	15.94 (15.87)	7.28 (7.11)
18	IVc	$C_{20}H_{16}N_4O_5S$	424	Orange	90 ^{0}C	56.60 (56.13)	3.77 (3.70)	13.20 (13.14)	7.54 (7.38)
19	IVd	$C_{19}H_{14}N_4O_4S$	394	Orange	180 ^{0}C	57.86 (57.37)	3.55 (3.49)	14.21 (14.18)	8.12 (7.94)
20	IVe	$C_{19}H_{14}N_4O_5S$	410	Dark Orange	135 ^{0}C	55.60 (55.16)	3.41 (3.36)	13.65 (13.57)	7.80 (7.62)
21	Va	$C_{16}H_{18}N_4OS$	314	Yellow	120 ^{0}C	61.14 (60.63)	5.73 (5.68)	17.83 (17.74)	10.19 (10.01)

Table 1. Cont..

22	Vb	$C_{14}H_{12}N_4O_3S$	316	Light Grey	158 ^{0}C	53.16 (52.77)	3.79 (3.75)	17.72 (17.65)	10.12 (9.96)
23	Vc	$C_{15}H_{15}N_3O_2S$	301	Light Grey	85 ^{0}C	59.80 (59.54)	4.98 (4.92)	13.95 (13.93)	10.63 (10.48)
24	Vd	$C_{14}H_{13}N_3OS$	271	Off White	124 ^{0}C	61.99 (61.51)	4.79 (4.72)	15.49 (15.46)	11.80 (11.62)
25	Ve	$C_{14}H_{13}N_3O_2S$	287	Light Brown	100 ^{0}C	58.53 (58.07)	4.52 (4.50)	14.63 (14.58)	11.14 (10.97)
26	VI a	$C_{17}H_{19}N_3OS$	313	Light Yellow	150^{0}C	65.17 (64.72)	6.07 (5.95)	13.41 (13.32)	10.22 (10.02)
27	VIb	$C_{15}H_{13}N_3O_3S$	315	Grey White	118^0 C	57.14 (56.68)	4.12 (4.05)	13.33 (13.21)	10.15 (10.01)
28	VIc	$C_{16}H_{16}N_2O_2S$	300	Grey	105 ^{0}C	64.00 (63.57)	5.33 (5.24)	9.33 (9.18)	10.66 (10.48)
29	VId	$C_{15}H_{14}N_2OS$	270	Off White	100 ^{0}C	66.66 (66.14)	5.18 (5.10)	10.37 (10.28)	11.85 (11.68)
30	VIe	$C_{15}H_{14}N_2O_2S$	286	Off White	194 ^{0}C	62.93 (62.44)	4.89 (4.75)	9.79 (9.66)	11.18 (11.04)
31	VIIa	$C_{22}H_{21}N_3OS$	375	Light Yellow	190 ^{0}C	70.40 (69.98)	5.60 (5.54)	11.20 (11.13)	8.53 (8.36)
32	VIIb	$C_{20}H_{15}N_3O_3S$	377	Light Yellow	155 ^{0}C	63.66 (63.11)	3.97 (3.94)	11.14 (11.06)	8.48 (8.32)
33	VIIc	$C_{21}H_{18}N_2O_2S$	362	Off White	240 ^{0}C	69.61 (69.14)	4.97 (4.90)	7.73 (7.69)	8.83 (8.64)
34	VIId	$C_{20}H_{16}N_2OS$	332	Faint Brown	245 ^{0}C	72.28 (71.70)	4.81 (4.73)	8.43 (8.38)	9.63 (9.48)
35	VIIe	$C_{20}H_{16}N_2O_2S$	348	Dark Grey	130 ^{0}C	68.96 (68.43)	4.59 (4.53)	8.04 (7.95)	9.19 (9.01)
36	VIIIa	$C_{15}H_{16}N_4OS$	300	Blackish Brown	180 ^{0}C	60.00 (59.56)	5.33 (5.29)	18.66 (18.58)	10.66 (10.50)
37	VIIIb	$C_{13}H_{10}N_4O_3S$	302	Off White	150 ^{0}C	51.65 (51.18)	3.31 (3.25)	18.54 (18.46)	10.59 (10.40)
38	VIIIc	$C_{14}H_{13}N_3O_2S$	287	Blackish Grey	250 ^{0}C	58.53 (58.06)	4.52 (4.45)	14.63 (14.54)	11.14 (10.99)
39	VIIId	$C_{13}H_{11}N_3OS$	257	Dark Brown	110 ^{0}C	60.70 (60.24)	4.28 (4.20)	16.34 (16.29)	12.45 (12.31)
40	VIIIe	$C_{13}H_{11}N_3O_2S$	273	Dark Grey	100 ^{0}C	57.14 (56.68)	4.02 (3.97)	15.38 (15.29)	11.72 (11.51)

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