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SYNTHESIS OF SOME HETEROCYCLES OF EXPECTED BIOLOGICAL ACTIVITY THROUGH THE ACTION OF ISATIN-3-THIOSEMICARBAZONE ON ACETYLENIC KETONES AND ESTERS

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*Isatin-3-thiosemicarbazone (**1**) reacted with 1-aryl-3-phenylprop-2-yn-1-ones (**2a–c**) in n-butanol to give 4-aryl-6-phenyl-2-[2-oxo-2H,3H-benzo(b) pyrrolidine-3-iminyl]-imino-2H-1,3-thiazines (**3a–c**). Similar treatment of **1** with acetylenic esters (**4a–c**) gave the 6-substituted derivatives of 2-imino-3-[2-oxo-2H,3H-benzo(b)pyrrolidine-3-iminyl]-2,3-dihydro-4-oxo-1,3-thiazine (**5a–c**). Treatment of **1** with **4a–c** in the presence of sodium ethoxide in ethanol gave the 6-substituted derivatives of 3-[2-oxo-2H,3H-benzo(b)pyrrolidine-3-iminyl]-4-oxo-2-thioxo-1,2,4-trihydropyrimidine (**6a–c**). However, when **1** was refluxed with 1-p-chlorophenyl-3-phenylprop-2-yn-1-one (**2b**) in ethanol it gave a mixture of 2,4,6-tris[2-oxo-2H,3H-benzo(b)pyrrolidine-3-iminyl] amino-1,3,5-triazine (**7**) and Z,Z-3,3′-thiodi(1-p-chlorophenyl-3-phenylprop-2-en-1-one) (**8**). The aziridine imine derivative (**9**) and the pyrazole derivatives (**10a** and **b**) were the only isolated products upon treatment of **3c**, **6a**, and **6c** and **3a** and **3b** with hydrazine hydrate, respectively. Structures of all new compounds are evidenced by microanalytical and spectral data.*

Keywords: Acetylenic ketones and esters; diaziridineimine; iminothiazine; isatin-3-thiosemicarbazone; triaminotriazine

INTRODUCTION

Several reports[1–12] have described the addition of nitrogen and sulfur containing compounds to acetylenic ketones and esters. Nonterminal acetylenic esters such as dimethyl acetylenedicarboxylate, methyl methylpropiolate and methyl phenylpropiolate reacted with thioamides

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to give heterocycles or 1:1 addition products.[1–3] Propiolic esters, however, reacted with 1-substituted thiosemicarbazides to give isomeric mixtures of 3,3′-thiodiacrylates[2–4] although in two reports[1,4] a mixture of the thiodiacrylates, 1,3-thiazine-4-ones and thiosemicarbazone derivatives was obtained. The aim of the present work is to prepare new heterocyclic compounds of expected antiinflammatory and poxvirus activities through reaction[13,14] of isatin-3-thiosemicarbazone[13–22] with acetylenic ketones and esters as well as to study the behavior of the reaction course in different media.

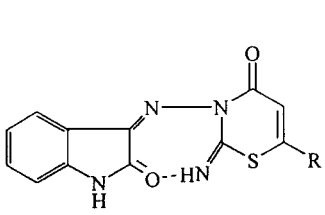
RESULTS AND DISCUSSION

Isatin-3-thiosemicarbazone (**1**) reacted with 1-aryl-3-phenylprop-2-yn-1-ones (**2a–c**) in refluxing n-butanol to give 4-aryl-6-phenyl-2-[2-oxo-2H,3H-benzo(b)pyrrolidine-3-iminyl] imino-2H-1,3-thiazines (**3a–c**).

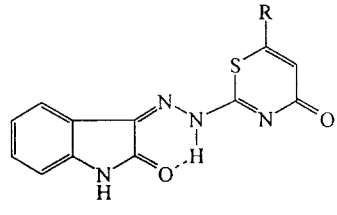
The structure of **3a–c** was elucidated from analytical and spectral data (cf. Experimental section). Thus, the infrared spectra show sharp bands in the region 1710–1700 cm^{-1} characteristic of C=O of cyclic imide. The lack of a band in the region of 1670–1650 cm^{-1} characteristic of carbonyl group of α,β-unsaturated ketones infers the existence of these compounds in the thiazine structure. The IR spectra also show a band in the region 3420–3400 cm^{-1} characteristic of NH. Adequate evidence for the structure was obtained from the ^{1}H-NMR spectra which show only one broad singlet at about δ 10.8 attributable to NH (imide) which collapses rapidly on deuteration. Further support for the assigned structure was gained from mass spectra which show the correct molecular ion beside some of the abundant peaks.

Similar treatment of **1** with acetylenic esters (**4a–c**) yields the 6-substituted derivatives of 2-iminothiazine (**5a–c**) as orange to brown crystalline solids. The structure of **5a–c** was established from their analytical and spectral data. IR spectra show bands of NH and C=O of cyclic imides. The ^{1}H-NMR spectra show signals attributable to olefinic and NH protons, in case of **5c**, signals characteristic of ethyl group are also observed. These data are consistent with two possible six membered ring structures **5a** and **5b** (cf. Scheme 1). The mass spectral data were particularly valuable in assigning one of them.[4] The existence of peaks corresponding to loss of HN≡C (arrow a) and H—N=C=S (arrow b) (cf. Scheme 1), can be explained satisfactorily in terms of their existence as structure **5a** rather than **5b**.

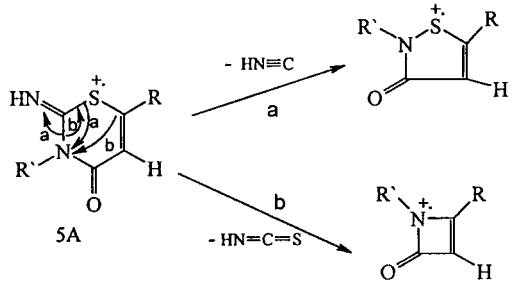
^{1}H-NMR spectra shed further light on the structure **5a** as they showed broad signal at δ 10.8 consistent with (NH) of pyrrolidinone ring and another broad signal corresponding to imino proton in the down field region at δ 12.7. The down field value for this signal



5A



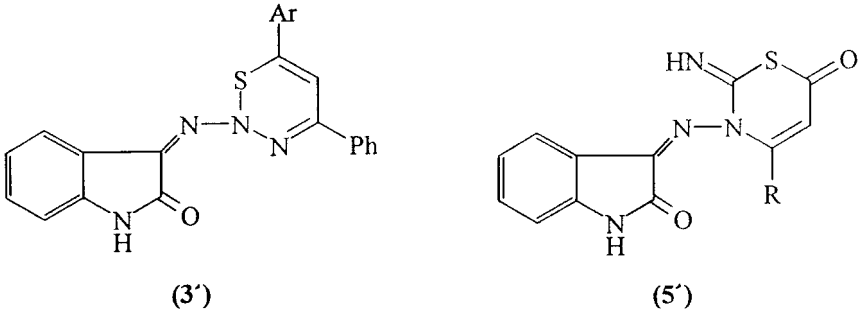
5B



SCHEME 1

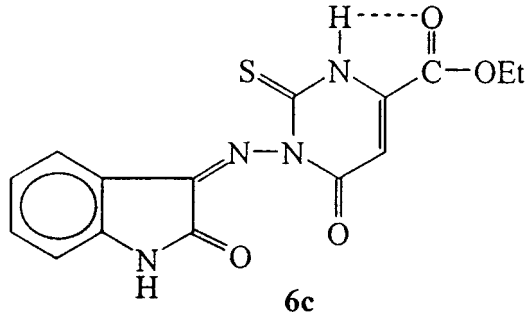
suggests the existence of compound **5** as chelated imino **5a** rather than chelated amino **5b** as shown above.

The reaction of **1** with **2a–c** and with **4a–c** in absence of basic catalyst proceeds initially via nucleophilic attack by the sulfur atom at the β-acetylenic carbon followed by intramolecular cyclocondensation with the carbonyl group as mentioned in previous several reports with thioamides[2,4,5,11,12,19,20] where the susceptibility of the acetylenic bond is further enhanced through conjugation with electron withdrawing carbonyl group. This fact ruled out the formation of the alternative structures **3′** and **5′** (Figure 1).



(3′) (5′)

FIGURE 1



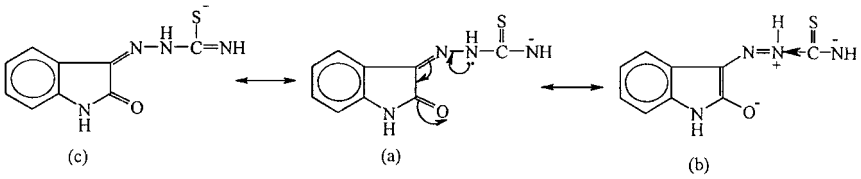
6c

FIGURE 2

The reaction of **1** with acetylenic esters **4a–c** in the presence of sodium ethoxide in ethanol gave the 6-substituted derivatives of 3-[2-oxo-2H,3H-benzo(b)pyrrolidine-3-iminyl]-4-oxo-2-thioxo-1,2,4-trihydropyrimidine (**6a–c**).

The structure of the thione derivatives (**6a–c**) was rigidly established by studying its spectroscopic properties. Thus, their IR spectra are devoid of ν_{S-H} and shows a strong absorption in the region of 1119–1095 cm^{-1} (C=S). This excludes the formation of similar thiazine structure like **5a** but instead a pyrimidinone-2-thione (**6a–c**) is formed. Its existence in the thione form,[21] rather than the thiol form[22] is documented. Further evidence for the pyrimidinone-2-thione structure (**6a–c**) was gained from the ^{1}H-NMR spectra which show a signal at about δ 6.6 (CH=), a broad signal in the region δ 10.79–10.51 corresponding to (NH) of pyrrolidinone ring and another broad signal for (NH) thioimido hidden in the signals of the aromatic ring. It was observed that the signal of NH (thioimido) of diethyl acetylenedicarboxylate adduct (**6c**) was shifted in the down field region at about δ 10.59. This could be explained by its existence in the chelated form which is in consistence with the lower absorption frequency of the carbonyl ester group in its IR spectrum as shown in Figure 2. Mass spectra of **6** support the assigned structure (cf. experimental).

The formation of pyrimidine-2-thione derivatives **6a–c** in the presence of ethanolic sodium ethoxide[23] can be explained on the basis of attack by the anion **11** on the acetylenic ester, which is a strong nucleophile, rather than by the sulfur atom. However, in the absence of a basic catalyst the thiourea attacks the acetylenic bond preferentially by the sulfur atom.[4,5] This is probably due to the fact that the polarized C=S group is more nucleophilic than the amino group, since the latter carries a partial positive charge due to p-π conjugation.[23] The initial attack of the anion **11** to the acetylenic bond followed by cyclization gave the pyrimidine-2-thione derivative **6a–c**. However, when



(11)

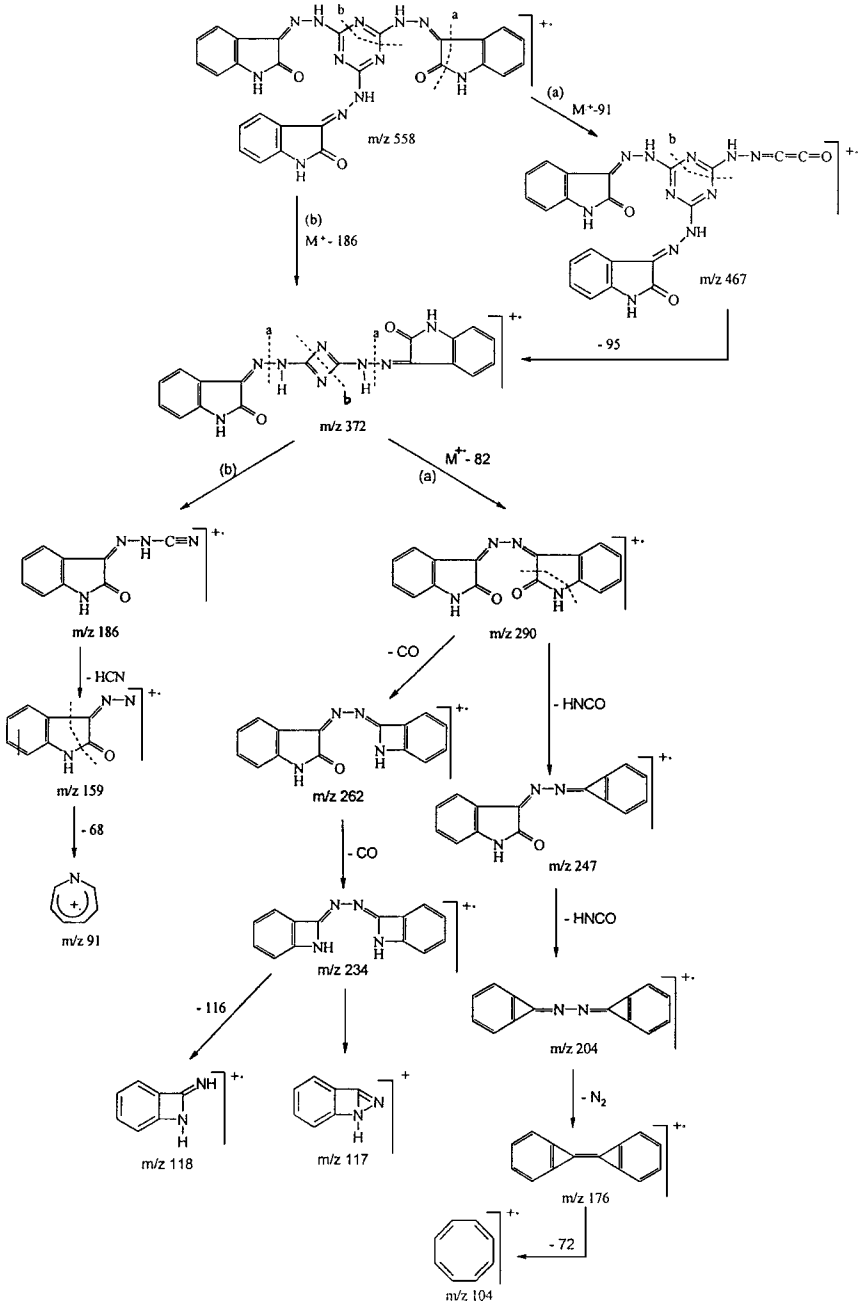
FIGURE 3

1-aryl-3-phenylprop-2-yn-1-ones (**2a–c**) were treated with **1** under similar conditions they gave 1-aroyl-3-benzoyl methanes rather than the pyrimidine-2-thiones as reported with thiourea.[23] The formation of aroylbenzoylmethanes rather than pyrimidine-2-thiones could be interpreted on the basis of the preferential base catalysed addition of water to the acetylenic bond, rather than the addition of anion **11a** because of its weak nucleophilicity as a result of the electron withdrawing effect from the thiocarbonyl carbon by the central nitrogen conjugated with indolinyl moiety as shown in Figure 3.

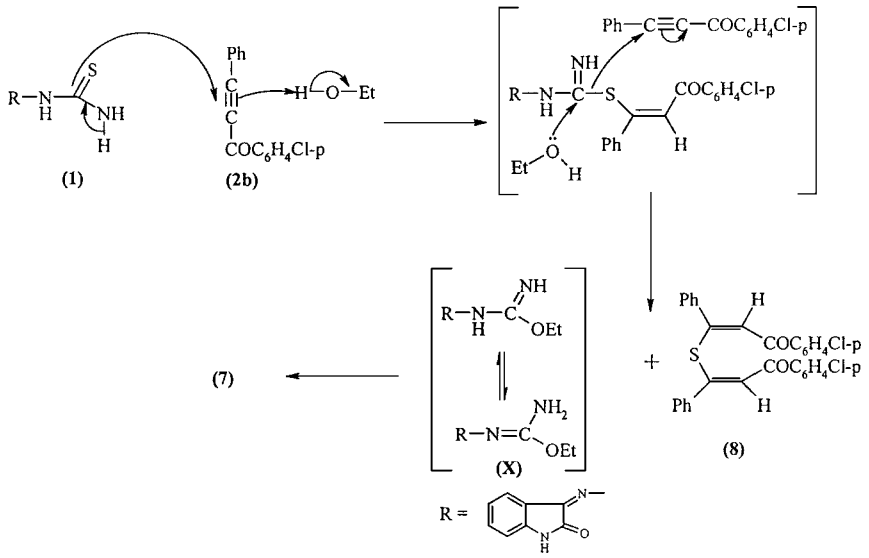
On the other hand 1-p-chlorophenyl-3-phenylprop-2-yn-1-one (**2b**) reacted with **1** in refluxing ethanol to afford the triamino-1,3,5-triazine derivative **7** along with the Z,Z-3,3′-thiodi-(1-p-chlorophenyl-2-phenylprop-2-en-1-one) (**8**).

The structure of triamino-1,3,5-triazine derivative **7** was confirmed on the basis of its spectral data (cf. experimental). Thus IR spectrum devoid of absorptions characteristic of phenyl and p-chlorophenyl groups which infers the absence of these moieties. It shows also one strong band at 1710 (C=O imido) and two bands at 3420, 3250 cm^{-1} (NH). The ^{1}H-NMR spectrum shows signal at δ 11.04 (NH imido), a signal for (NH amino) hidden in the aromatic region and multiplet signals for the four adjacent hydrogens of benzene ring of indolinyl moiety. As the total integration corresponds to the third number of protons in the compound **7**, this means that it has an element of symmetry. Further proof for the proposed structure **7**, was gained from mass spectrum which shows the correct molecular ion beside some of abundant peaks (cf. fragmentation pattern Scheme 2).

The formation[4,5,12] of sulfide **8** could be explained on the basis of initial attack by the sulfur atom of the thiosemicarbazone **1** at the β-carbon of the acetylenic ketone to give a 1:1 addition product (not isolated); a 1:1 addition product was isolated from similar reactions under special conditions.[2] The reaction between the addition product and a second molecule of the acetylenic ketone may give the final product (**8**) and the intermediate (**X**) (not isolated) which undergoes


m/z 558
(a)
M+-91
m/z 467
(b)
M+- 186
- 95
m/z 372
(b)
M+- 82
(a)
m/z 186
m/z 290
- HCN
- CO
- HNCO
m/z 159
m/z 262
m/z 247
- 68
- CO
m/z 91
m/z 234
- HNCO
- 116
m/z 204
- N2
m/z 118
m/z 117
m/z 176
- 72
m/z 104

SCHEME 2



SCHEME 3

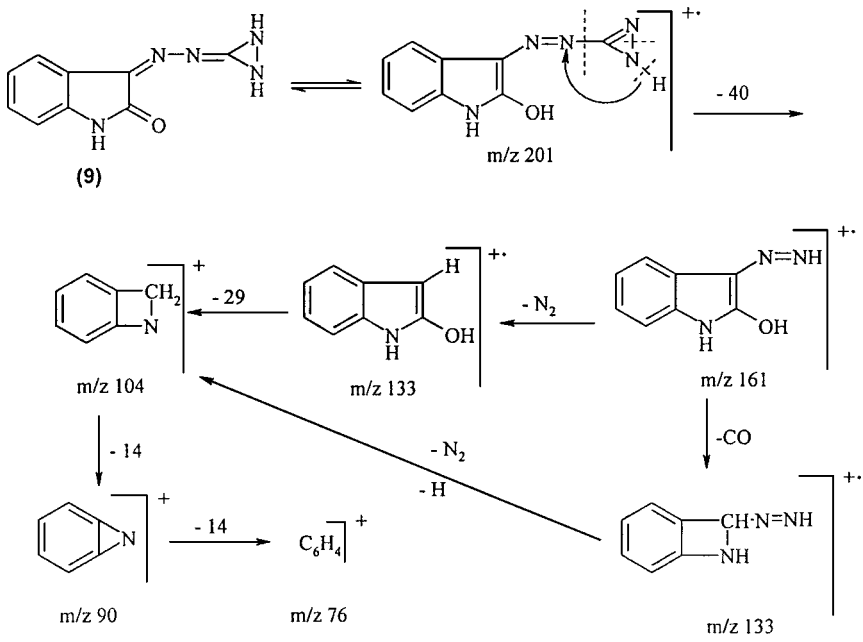
intermolecular trimerisation to give the triamino1,3,5-triazine derivative **7** (cf. Scheme 3). This compound was not isolated in any of the previous reports.[4,5,12]

Treating an ethanolic solution of 1,3-thiazine derivatives **3a–c** or pyrimidine-2-thione derivatives **6a**,**c** with hydrazine hydrate gave only the diaziridine imine derivative **9** together with the pyrazole derivatives **10a–c**. In case of **3c**,**9** was isolated and **10c** was detected by TLC in the reaction mixture, whereas in case of **3a**,**b**; **10a**,**b** were isolated and **9** was detected by TLC in the reaction mixture.

The structure of the diaziridine imine **9** was deduced from spectroscopic data (cf. experimental). Thus, its IR spectrum devoid of bands characteristic of phenyl and substituted phenyl groups which proves the absence of these moieties. It shows absorptions characteristic of C=O and NH groups. A good evidence for the assigned structure was given from its ^{1}H-NMR spectrum as it shows signals at δ 10.71 (NH imido) and two doublet signals centered at δ 10.55, 9.57 for two NH protons ($J = 15.4$ Hz). The appearance of one of the two doublets in the down field region suggests the existence of the compound in its chelated form mentioned in Scheme 6.

Mass spectrum shows a weak molecular ion. Scheme 4 shows the fragmentation pattern of compound **9** and structures of some fragments.

The formation of **9** and **10** from **3a–c** could be explained on the basis of nucleophilic ring fission by hydrazine hydrate through attack at either C_2 or C_6 as shown in Scheme 5. On the other hand, the reaction of



SCHEME 4

hydrazine hydrate with the pyrimidine-2-thione derivatives **6a**,**c** seems to proceed through attack at the thiono carbon followed by ring fission to give **9** as illustrated in Scheme 5.

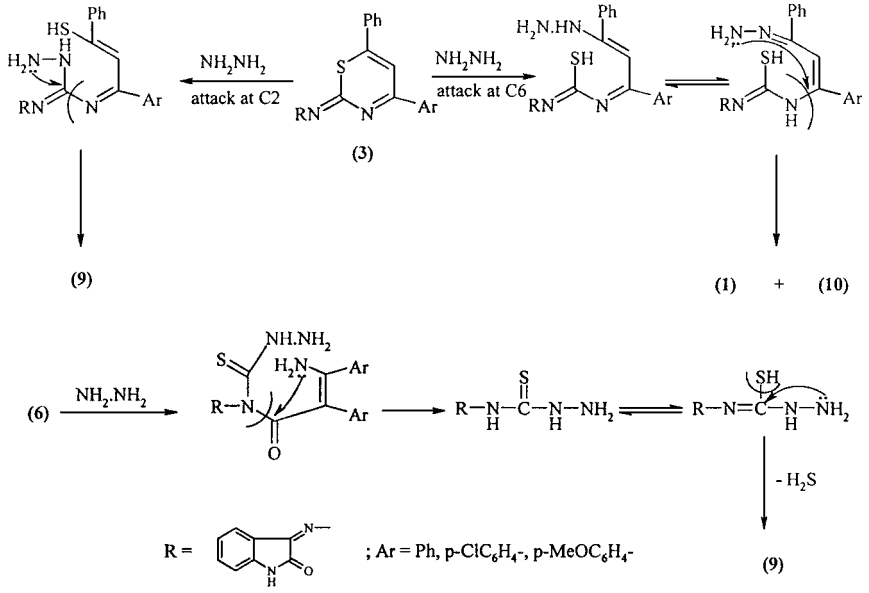
EXPERIMENTAL

All melting points are not corrected. IR spectra were measured on a Unicam SP1200 or FTIR Mattson (Infinity series) spectrometers as KBr discs. Unless otherwise stated the ^{1}H-NMR spectra were measured in DMSO solutions on Varian Gemini 200 MHz or Brucker ES 200 MHz instruments with chemical shift (δ) expressed in ppm downfield from Me_4Si. Mass spectra were recorded on Shimadzu GC-MS-Q_p 1000 Ex or Finnigan GCQ instruments operating at 70 ev. Column chromatography and TLC were runned on silica Gel Voeim, activity 111/30 mm according to Brockmann and Schodder and TLC aluminum sheets Silica Gel 60 F_{254} (Merck, Federal Republic Germany).

Starting Material

Isatin-3-thiosemicarbazone (1)

To a solution of isatin (34 mmol) in ethanol (50 ml) was added thiosemicarbazide (34 mmol) followed by three drops of piperidine. The

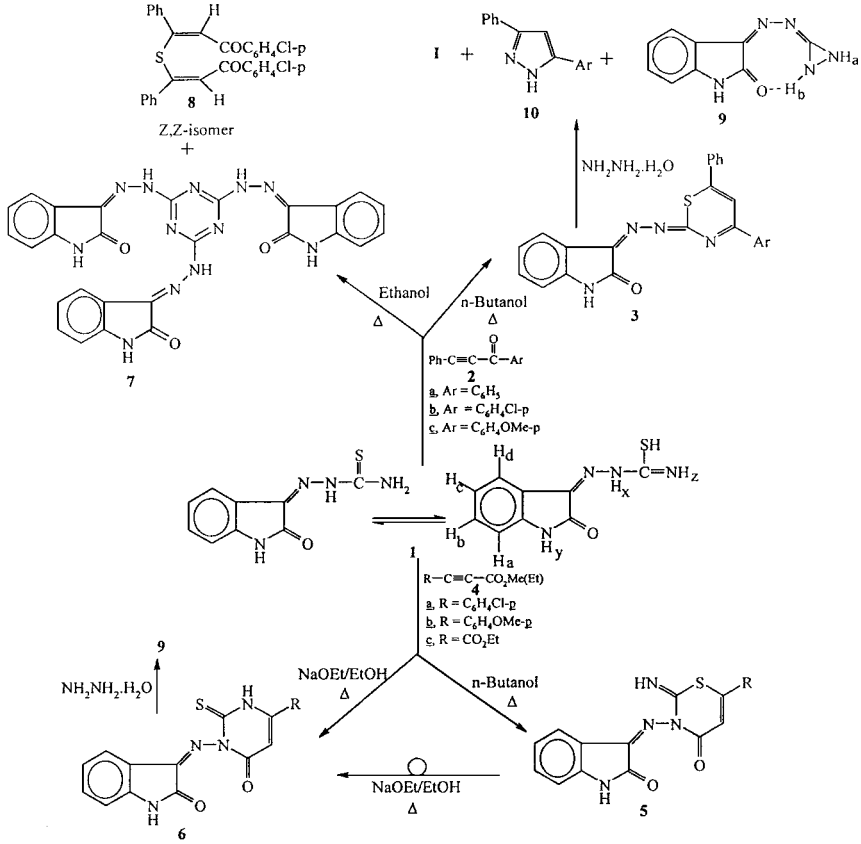


SCHEME 5

reaction mixture was refluxed over water bath for 10 min whereby a yellow cannary solid separates. Crystallization from ethanol gave a yellow crystals (90% yield), m.p. 248–250°C. lit.,[29] m.p. 255°C. IR ν_{max} 3440, 3160 (NH), 1695 (C=O imido). ^{1}H-NMR (DMSO) δ 6.94 (d, H_d, J_{dc} = 7.6 Hz), 7.00 (t, H_b, J_{ab}, J_{bc} = 7.2, 7.6 Hz), 7.37 (t, H_c, J_{cb} = J_{cd} = 7.6 Hz), 7.67 (d, H_a, J_{ab} = 7.0 Hz), 8.72 (s, 1H, 5H exchangeable), 9.07 (s, 1H, NH_x exchangeable), 11.23 (s, 1H, NH_y exchangeable), 12.49 (s, 1H, NH_z exchangeable). ^{1}H-NMR data shows the existence of this compound in solution in the thiol form.

*General procedure for the reaction of Isatin-3-thiosemicarbazone (1) with acetylenic ketones (**2a–c**) or acetylenic esters (**4a–c**) in n-butanol.* A mixture of **1** (4.9 mmol) and **2a–c** or **4a–c** (4.9 mmol) was refluxed in n-butanol (20 ml) for 12 h and the concentrated solution (10 ml), was left to stand at room temperature overnight to precipitate a solid which was recrystallized from a suitable solvent to give **3a–c** or **5a–c** respectively.

*4,6-Diphenyl-2-[2-oxo-2H,3H-benzo(b)pyrrolidine-3-iminyl]imino-2H-1,3-thiazine (**3a**).* (70% yield) dark red crystals, m.p. 241–243°C (from 1,4-dioxane). IR ν_{max} 3400 (NH), 1705 (C=O), 1595, 1560 cm^{-1} (C=N and/or C=C). ^{1}H-NMR (DMSO) δ 6.89–8.42 (m, 15H, ArH+ CH=), 10.82 (s, 1H, NH exchangeable). EIMS m/z (%), 410 (M^++2,0.23), 408



SCHEME 6

(M^+, 1.2), 333 (M^++2-Ph, 0.17), 331 (M^+-Ph, 1), 305 (M^++2-Ph–CO, 0.48) 303 (M^+-Ph–CO, 3.2), 290 (M^++2-Ph–HNCO,0.28), 288 (M^+-Ph–HNCO, 1.5), 263 (9), 248 (10), 191 (13), 144 (14), 78 (Base), 77 (21), 52 (10), 51 (14). Anal. Calcd for $C_{24}H_{16}N_4OS$: C, 70.57; H, 3.95; N, 13.71; S, 7.85. Found: C, 70.42; H, 3.87; N, 13.59; S, 7.76%.

*4-p-Chlorophenyl-6-phenyl-2-[2-oxo-2H,3H-benzo(b)pyrrolidine-3-iminyl] imino-2H-1,3-thiazine (**3b**).* (82% yield), dark red crystals, m.p. 280–282°C (from 1,4-dioxane). IR ν_{max} 3410 (NH), 1700 (C=O), 1590, 1570 cm^{-1} (C=N and/or C=C). ^{1}H-NMR ($CDCl_3$) δ 6.84–8.50 (m, 14H, ArH + CH=), 10.91 (s, 1H, NH exchangeable). EIMS m/z (%) 442 (M^+ + 2,1.4), 440 (M^+, 2.43), 297 (10), 273 (21), 272 (17), 271 (50), 249 (10), 248 (48), 227 (11), 225 (28), 221 (18), 190 (11), 189 (17), 146 (11), 145 (13), 144 (27), 134 (12), 118 (18), 116 (12), 91 (10), 90 (14), 89 (36), 88 (Base), 87 (18), 58 (13), 57 (23). Anal. Calcd for $C_{24}H_{15}N_4OSCl$:

C, 65.08; H, 3.41; N, 12.65; S, 7.24. Found: C, 64.95; H, 3.50; N, 12.71; S, 7.11%.

*4-Methoxyphenyl-6-phenyl-2-[2-oxo-2H,3H-benzo(b)pyrrolidine-3-iminyl] imino-2H-1,3-thiazine (**3c**).* (71% yield), dark red crystals, m.p. 293–295°C (from 1,4-dioxane). IR ν_{max} 3420 (NH), 1710 (C=O), 1590, 1565 cm^{-1} (C=N and/or C=C). ^{1}H-NMR (DMSO) δ 3.89 (s, 3H, OMe), 6.91–8.43 (m, 14H, ArH + CH=), 10.75 (s, 1H, NH exchangeable). EIMS m/z (%) 440 (M^++2, 3.03), 438 (M^+, 22), 363 (M^++2,0.89), 361 (M^+-Ph, 7), 335 (M^++2-Ph–CO, 2.32), 333 (M^+-Ph–CO, 4), 331 (M^+-C_6H_4OMe-*p*, 4), 320 (M^++2-Ph–HNCO, 2.5) 318 (M^+-Ph–HNCO, 20), 319 (M^++2-Ph–NCO, 11.7), 317 (M^+-Ph–NCO, 40), 303, (29), 294 (28), 293 (67), 279 (42), 278 (48), 268 (53), 267 (73), 264 (42), 252 (32), 250 (23), 248 (35), 225 (20), 222 (23), 221 (89), 206 (34), 178 (47), 165 (23), 159 (25), 149 (34), 146 (24), 145 (23), 144 (74), 121 (32), 118 (38), 116 (32), 105 (24), 104 (21), 95 (28), 91 (33), 85 (29), 83 (33), 81 (22), 77 (26), 76 (34), 69 (28), 67 (23), 63 (23), 57 (41), 55 (36), 51 (Base). Anal. Calcld for $C_{25}H_{18}N_4O_2S$: C, 68.48; H, 4.14; N, 12.78; S, 7.31. Found: C, 68.39; H, 4.26; N, 12.85; S, 7.42%.

*6-p-Chlorophenyl-2-imino-3-[2-oxo-2H,3H-benzo(b)pyrrolidine-3-iminyl]-2,3-dihydro-4-oxo-1,3-thiazine (**5a**).* (75% yield), orange crystals, m.p. 277–279°C (from 1,4-dioxane). IR ν_{max} 3450, 3200 (NH), 1705, 1660 (C=O), 1610, 1590 cm^{-1} (C=N and/or C=C). ^{1}H-NMR (DMSO) δ 6.83 (=CH), 6.88 (d, H_d, J_{dc} = 7.8 Hz), 7.02 (t, H_b, J_{bc}, J_{ba} = 7.2, 7.6 Hz), 7.37 (t, H_c, J_{cd}, J_{cb} = 7.8, 7.6 Hz), 7.63 (d, two ortho H's, J_{ortho} = 8.6 Hz), 7.82 (d, two meta H's, J_{ortho} = 8.6 Hz), 8.44 (d, H_a, J_{ab} = 7.8 Hz), 10.75 (s, 1H, NH imido, exchangeable), 12.75 (br.s, 1H, NH imino, exchangeable). EIMS m/z (%) 384 (M^++2,12), 382 (M^+, 26), 357 (M^++2-HNC, 8), 355 (M^+-HNC, 26), 356 (M^++2-CO, 27.3), 354 (M^+-CO, 77), 328 (39), 327 (25), 326 (82), 323 (M^+-HNCS, 12), 197 (30), 196 (25), 171 (29), 170 (47), 168 (Base), 165 (25), 163 (57), 162 (27), 161 (39), 155 (29), 149 (35), 148 (35), 147 (58), 146 (21), 145 (24), 144 (25), 139 (22), 137 (61), 136 (40), 133 (43), 132 (46), 131 (27), 119 (82), 118 (56), 105 (22), 104 (48), 103 (62), 92 (60), 91 (28), 89 (33), 87 (28), 77 (27), 76 (32), 64 (22), 62 (34), 58 (22), 57 (20), 55 (20), 51 (32). Anal. Calcd for $C_{18}H_{11}NO_2SCl$: C, 56.47; H, 2.89; N, 14.63; S, 8.37. Found: C, 56.39; H, 2.91; N, 14.54; S, 8.29%.

*6-p-Methoxyphenyl-2-imino-3-[2-oxo-2H,3H-benzo(b)pyrrolidine-3-iminyl]-2,3-dihydro-4-oxo-1,3-thiazine (**5b**).* (70% yield), brown crystals, m.p. 284–286°C (from 1,4-dioxane). IR ν_{max} 3453, 3130 (NH), 2923, 2853 (alkyl-H), 1710, 1676 (C=O), 1616, 1570 cm^{-1} (C=N and/or C=C). ^{1}H-NMR (DMSO) δ 3.83 (s, 3H, OMe), 6.71 (s, 1H, CH=), 6.86 (d, H_d, J_{cd} = 7.8 Hz), 7.00 (t, H_b, J_{bc}, J_{ab} = 7.2, 7.5 Hz), 7.1 (d, two

meta H's, J_{ortho} = 7.8 Hz), 7.36 (t, H_c, J_{bc}, J_{cd} = 7.71, 7.8 Hz), 7.74 (d, two ortho H's, J_{ortho} = 7.8 Hz), 8.41 (d, H_a, J_{ab} = 7.2 Hz), 10.72 (s, 1H, NH imido, exchangeable), 12.62 (br.s, 1H, NH imino exchangeable). EIMS m/z (%) 380 (M^++2,0.22), 378 (M^+, 1.3), 353 (M^++2-HNC, 0.21), 351 (M^+-HNC, 1.3), 319 (M^+-HNCS, 1), 164 (20), 149 (35), 89 (35), 88 (Base), 57 (31). Anal. Calcd for $C_{19}H_{14}N_4O_3S$: C, 60.31; H, 3.73; N, 14.80; S, 8.47. Found: C, 60.22; H, 3.82; N, 14.91; S, 8.58%.

*6-Ethoxycarbonyl-2-imino-3-[2-oxo-2H,3H-benzo(b)pyrrolidine-3-iminyl]-2,3-dihydro-4-oxo-1,3-thiazine (**5c**).* (85% yield), orange crystals, m.p. 282–284°C (decomp.), (from 1,4-dioxane). IR ν_{max} 3440, 3310 (NH), 1730 (C=O) ester, 1710, 1690 (C=O) amide, 1610, 1570 cm^{-1} (C=N and/or C=C). ^{1}H-NMR (DMSO) δ 1.27 (t, 3H, $COOCH_2C\underline{H}_3$, J = 7.7 Hz), 4.27 (q, 2H, $COOC\underline{H}_2CH_3$, J = 7.7 Hz), 6.71 (s, H, CH=), 6.89 (d, H_d, J_{cd} = 7.0 Hz), 7.03 (t, H_b, J_{ab}, J_{bc} = 7.4, 7.6 Hz), 7.4 (t, H_c, J_{bc}, J_{cd} = 7.6, 7.8 Hz), 8.20 (d, H_a, J_{ab} = 7.4 Hz), 10.83 (s, 1H, NH imido, exchangeable), 13.27 (br.s, 1H, NH imino exchangeable). EIMS m/z (%) 346 (M^++2,0.81), 344 (M^+, 7), 331 (M^++2-Me, 1.2) 329 (M^+-Me, 2), 315 (M^+-Et, 3), 317 (M^+-HNC, 4), 301 (M^+ +2-OEt, 2.8), 299 (M^+-OEt, 5), 273 (M^++2-CO_2Et, 1.5), 271 (M^+-CO_2Et, 7), 174 (35), 149 (37), 147 (20), 146 (71), 145 (29), 144 (74), 131 (54), 121 (24), 119 (37), 118 (Base), 116 (27), 105 (41), 104 (22), 97 (23), 95 (38), 91 (56), 87 (20), 85 (33), 81 (34), 79 (21), 77 (28), 71 (28), 69 (39), 67 (28), 57 (41), 55 (38), 51 (46). Anal. Calcd for $C_{15}H_{12}N_4O_4S$: C, 52.32 ; H, 3.51 ; N, 16.27 ; S, 9.31. Found: C, 52.41; H, 3.59; N, 16.34; S, 9.46%.

*General procedure for the reaction of isatin-3-thiosemicarbazone (1) with acetylenic esters **4a–c** and acetylenic ketones **2a–c** in ethanolic sodium ethoxide.* An alcoholic solution of isatin-3-thiosemicarbazone (**1**) (5 mmol) in 20 ml of ethanol was added to a solution of the acetylenic esters **4a–c** or acetylenic ketones **2a–c** (5 mmol) and sodium ethoxide (0.12 g Na) in ethanol (20 ml) and the mixture was refluxed for 1 h.

In case of **1** with **4a–c**, the reaction mixture was poured into ice cold water to give a precipitate which was recrystallized from a proper solvent to give **6a–c**. The aqueous solution was acidified with conc. HCl to give unreacted **1**.

*6-p-Chlorophenyl-3-[2-oxo-2H,3H-benzo(b)pyrrolidine-3-iminyl]-4-oxo-2-thioxo-1,2,4-trihydropyrimidine (**6a**).* (71% yield), orange crystals, m.p. >320°C (from 1,4-dioxane). IR ν_{max} 3401, 3363 (NH), 1710, 1689 (C=O), 1604, 1535 (C=N and/or C=C), 1119 cm^{-1} (C=S). ^{1}H-NMR (DMSO) δ 6.62 (s, 1H, CH=), 6.79–7.74 (m, 9H, ArH + NH), 10.51 (s, 1H, NH imido, exchangeable). EIMS m/z (%) 384 (M^++2, 0.15), 382

(M^+, 1), 325 (M^++2-HNCS, 0.12), 323 (M^+-HNCS, 0.89), 273 (M^++2-C_6H_4Cl-p, 0.25), 271 (M^+-C_6H_4Cl-p, 0.78), 257 (M^++2-C_6H_4Cl-p–NH, 12.24), 255 (M^+-C_6H_4Cl-p–NH, 39), 248 (M^++2-CH≡C–C_6H_4Cl, 0.32), 246 (M^+-CH≡C–C_6H_4Cl-p, 0.38), 227 (M^+-CH≡C–C_6H_4Cl-p–C=S, 19), 213 (M^+-CH≡C–C_6H_4Cl-p–SH, 16), 141 (28.98), 139 (94.96), 138 (CH≡C–C_6H_4Cl-p, 38.1), 136 (CH≡C–C_6H_4Cl-p, Base), 104 (13), 103 (20), 77 (10), 76 (16), 75 (21), 74 (11). Anal. Calcd for $C_{18}H_{11}N_4O_2SCl$: C, 56.47; H, 2.89; N, 14.63; S, 8.37. Found: C, 56.52; H, 2.92; N, 14.71; S, 8.45%.

*6-p-Methoxyphenyl-3-[2-oxo-2H,3H-benzo(b)pyrrolidine-3-iminyl]-4-oxo-2-thioxo-1,2,4-trihydropyrimidine (**6b**).* (65% yield), brown crystals, m.p. >300°C (from dil. dioxane). IR ν_{max} 3444, 3252 (NH), 1715, 1650 (C=O), 1618, 1586 (C=N and/or C=C), 1135 cm^{-1} (C=S). ^{1}H-NMR ($CDCl_3$)δ3.8 (s, 3H, OMe), 6.69 (s, 1H, CH=), 6.82–8.23 (m, 9H, ArH + NH), 10.79 (br.s, 1H, NH imido, exchangeable). EIMS m/z (%) 380 (M^++2,0.4), 378 (M^+,1), 235 (31), 188 (25), 160 (Base), 159 (37), 145 (19), 133 (14), 132 (66), 117 (13), 104 (65), 77 (41), 76 (13), 75 (15), 51 (22). Anal. Calcd for $C_{19}H_{14}N_4O_3S$: C, 60.31; H, 3.73; N, 14.80; S, 8.47. Found: C, 60.42; H, 3.69; N, 14.86; S, 8.51%.

*6-Ethoxycarbonyl-3-[2-oxo-2H,3H-benzo(b)pyrrolidine-3-iminyl]-4-oxo-2-thioxo-1,2,4-trihydropyrimidine (**6c**).* (80% yield), orange red crystals, m.p. >320°C (from n-butanol). IR ν_{max} 3487, 3228 (NH), 2932, 2854 (alkyl-H), 1722 (C=O), 1627, 1589 (C=N and/or C=C), 1059 cm^{-1} (C=S). ^{1}H-NMR (DMSO) δ 1.35 (t, 3H, $COOCH_2C\underline{H}_3$, J = 7.72 Hz), 4.31 (q, 2H, $COOC\underline{H}_2CH_3$, J = 7.72 Hz), 6.47–8.36 (m, 5H, ArH + CH=), 10.59 (br.s, 1H, NH thioimido, exchangeable), 10.79 (s, 1H, NH imido, exchangeable). EIMS m/z (%) 346 (M^++2, 0.02), 344 (M^+, 0.5), 331 (M^++2-CH_3, 0.18), 329 (M^+-CH^3,1), 285 (M^++HNCS, 0.13), 273 (M^++2-$CO_2C_2H_5$, 0.18), 271 (M^+-$CO_2C_2H_5$, 0.5), 262 (M^++2-CH≡C–$CO_2C_2H_5$, 0.36), 260 (M^+-CH≡C–$CO_2C_2H_5$, 7), 258 (M^++2-$CO_2C_2H_5$–NH, 0.62), 256 (M^++2-$CO_2C_2H_5$–NH, 1.54), 227 (M^+-$CO_2C_2H_5$–C=S, 1.1), 145 (1.7), 144 (67), 118 (Base), 117 (11), 116 (22), 104 (10), 91 (34), 64 (13), 63 (18), 55 (12). Anal. Calcd for $C_{15}H_{12}N_4O_4S$:C, 52.32; H, 3.51; N, 16.27; S, 9.31. Found: C, 52.18; H, 3.62; N, 16.34; S, 9.25%.

In case of **1** with **2a–c**, the reaction mixture was poured into ice cold HCl, extracted with $CHCl_3$ and the combined extract was concentrated and chromatographed over silica gel. Elution with diethyl ether petroleum b.p. 40–60 (1:5 v/v) gave 1-phenyl-3-arylpropan-1,3-diones which were identified by TLC and mixed m.p.'s with authentic specimens[29] prepared by refluxing an alcoholic solution of acetylenic ketones **2a–c** with dil. HCl.

*Conversion of the iminothiazine (**5c**) to the pyrimidine-2-thione (**6c**).* An ethanolic solution of 2-iminothiazine (**5c**) (0.2 g, 0.6 mmol) in 10 ml ethanol was added to solution of sodium ethoxide (0.04 g Na in 5 ml ethanol) and the mixture was refluxed for 1 h. The reaction mixture was poured into ice cold HCl to give a solid. Recrystallization from n-butanol gave an orange crystals which proved to be **6c** by TL, m.p and mixed m.p.

Reaction of Isatin-3-thiosemicarbazone (1) with 1-p-chlorophenyl-3-phenylprop-2-yn-1-one (2b) in ethanol. To a solution of the thiosemicarbazone (**1**) (2.3 mmol) in ethanol (15 ml) was added a solution of the acetylenic ketone (**2b**) (2.3 mmol) in ethanol (10 ml) and the whole mixture was heated over water bath for 15 h. On leaving the reaction mixture to stand at room temperature overnight, it gave a solid which was fractionally crystallized to give **7** and (**8**).

*2,4,6-Tris [2-oxo-2H,3H-benzo(b)pyrrolidine-3-iminyl]amino-1,3,5-triazine (**7**).* (13% yield), red crystals, m.p. 295–297°C (from 1,4-dioxane). IR ν_{max} 3440, 3250 (NH), 1710 (C=O), 1600, 1560 cm^{-1} (C=N and/or C=C). ^{1}H-NMR (DMSO) δ 6.91–7.54 (m, 5H, ArH + NH amino), 11.05 (br.s, 1H, NH imido exchangeable). EIMS m/z (%) 558 (M^+, 0.22), 467 (M^+-91, 1.1), 372 (M^+-186, 1), 371 (M^+-H, 6), 290 (37), 240 (27), 234 (35), 214 (25), 212 (67), 176 (23), 146 (44), 145 (21), 144 (46), 133 (45), 129 (47), 119 (22), 118 (Base), 117 (21), 104 (52), 103 (51), 91 (41), 90 (21), 76 (46), 75 (34), 63 (33), 51 (22). Anal. Calcd for $C_{18}H_{12}N_8O_2$:C, 58.06; H, 3.25; N, 30.09. Found: C, 57.92; H, 3.18; N, 30.19%.

*(Z,Z)-3,3′-Thiodi-(1-p-chlorophenylprop-2-en-1-one) (**8**).* (10% yield), orange crystals, m.p. 199–200°C (lit.5 m.p. 199) (from EtOH), it was identified through TLC and mixed m.p. with authentic specimen prepared from the reaction of 1-p-chlorophenyl-3-phenylprop-2-yn-1-one with thiourea in ethanol at room temperature.

*Reactions of 1,3-thiazine derivatives **3a–c** or pyrimidine-2-thione derivatives **6a**,**c** with hydrazine hydrate.* Hydrazine hydrate (1 ml) was refluxed for 3 h with an ethanolic solution of **3a–c**, **6a**, or **6c** (0.5 g), odor of H_2S gas was smelled during the reaction. The reaction mixture was concentrated (3.0 ml) and chromatographed over silica gel. In case of **3c, 6a**, and **6c**), elution with petroleum ether (b.p. 40–60/ether) (2/1 v/v) gave the diaziridine imine **9**.

However, in the case of **3a** and **3b**, the concentrated reaction mixture gave a solid which was then recrystallized from a suitable solvent to give the pyrazole derivatives **10a** and **10b**.

*(2-Oxo-2H,3H-benzo(b)pyrrolidine-3-iminyl) diaziridineimine (**9**).* (30% yield), yellow crystals, m.p. 210–212°C (from ethanol/benzene). IR ν_{max} 3357, 3156 (NH), 1686 (C=O), 1657, 1586 cm^{-1} (C=N and/or C=C). ^{1}H-NMR (DMSO) δ 6.87 (d, H_d, J_{cd} = 7.8 Hz), 6.98 (t, H_b, J_{bc}, J_{ba} = 7.4, 7.8 Hz), 7.17 (t, H_c, J_{cd}, J_{cb} = 7.6, 7.8 Hz), 7.37 (d, H_a, J = 7.4 Hz), 9.57 (d, 1H, NH_a, J = 15.2 Hz, exchangeable), 10.56 (d, 1H, NH_b, J = 15.0 Hz exchangeable), 10.70 (br.s, 1H, NH imido, exchangeable). EIMS m/z (%) 201 (M^+, 0.5), 161 (M^+-40, 98), 133 (30), 118 (14), 105 (32), 104 (Base), 91 (13), 90 (28), 79 (13), 78 (31), 77 (29), 76 (18), 75 (12), 64 (19), 63 (25), 62 (13), 53 (10), 52 (28), 51 (36), 50 (32). Anal. Calcd for $C_9H_7N_5O$:C, 53.73; H, 3.51; N, 34.81. Found: C, 53.81; H, 3.59; N, 34.79%.

*3,5-Diphenylpyrazole (**10a**).* m.p. 199–200°C, (lit.[30] m.p. 199), undepressed on admixture with an authentic specimen prepared by treating **2a** with hydrazine hydrate.[31,32]

*3(5)-p-Chlorophenyl-5(3)-phenylpyrazole (**10b**).* m.p. 214–215°C (lit,[31] m.p. 214–215°C), undepressed on admixture with an authentic specimen[31] obtained by the reaction of **2a** with hydrazine hydrate.

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