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Synthesis of some new indeno[1,2-e]pyrazolo[5,1-c]-1,2,4-triazin-6-one and indeno[2,1-c]pyridazine-4-carbonitrile derivatives

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ABSTRACT

Diazonium chlorides of 5-amino-3-methypyrazole 1a and 5-amino-4-phenylpyrazole 1b coupled with 1,3-indanedione 2 and led to the formation of acyclic hydrazone 3a and a cyclic product indenopyrazolotriazine 4b respectively. Cyclization of the hydrazone 3a by boiling in acetic acid afforded the corresponding 4a. The hydrazone 3a reacted with malononitrile in boiling ethanol in the presence of piperidine and gave indeno[2,1-c]pyridazine-4-carbonitrile derivatives 5a,b. Also, coupling of 6 with aryl diazonium chlorides gave the corresponding indenopyridazine derivatives 8a-e. Acetylation, benzoylation and hydrolysis of compound 8a afforded the corresponding substitution products 10-12, respectively. The structures of the newly synthesized compounds were established on the basis of chemical and spectral evidences.

Keywords: Diazonium Chlorides; Indenopyrazolotriazine; Indenopyridazine

1. INTRODUCTION

As a part of our program aimed to developing synthesis of functionally substituted heteroaromatics from readily starting materials [1-5], we have previously reported the synthesis of 4,5-dihydrospiropyrazole-indane-1, 3-diones [6] and thiadiazoline derivatives [7] via reaction of hydrazonoyl halides with 2-arylidene indane-1, 3-dione and indane-1,3-dione-2-thiocarboxanilides, respectively. In conjunction of this work we intended here to utilize the known coupling reaction [8] of diazotized heterocyclic amines with active methylene compounds, using 1,3-indanedione as an active methylene compound with unreported heterocyclic amines to synthesize some new derivatives of the title compounds with anticipated biological activities. Our interest in synthesis of some novel indeno[1,2-e]pyrazolo[5,1-c]-1, 2,4-triazines, is owing to the fact that pyrazolo[5,1-c]-1, 2,4-triazines were reported to have remarkable cytotoxic activity against colon, breast and lung carcinoma cells [9], some derivatives show to have selective cytotoxicity in hypoxic and in normoxic conditions [10], hetarylazo derivatives were classified as diazo dyes [11]. Moreover, indeno-fused pyridazines have been reported to show inhibition potency toward monoamine oxidase-B (MAO-B) [12-14] and to display binding affinity for central benzodiazepine receptors [15].

2. EXPERIMENTAL

Melting points were measured on a Gallenkamp electrothermal melting point apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 and Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in DMSO-d_6 on a Varian Mercury VX 200 NMR using TMS as the internal reference. Mass spectra were measured on a GCMS-QP 1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Centre of Cairo University, Giza, Egypt.

2.1. Synthesis of 2-(3-Methylpyrazol-5-yl)Hydrazono-1, 3-Indanedione 3a

To a stirred solution of 2 (1.46 g, 10 mmol) in ethanol (100 ml), sodium acetate trihydrate (1.3 g, 10 mmol) was added. After stirring for 15 min, the mixture was cooled to 0˚C and treated with a cold solution of diazonium salt of aminopyrazole 1a [prepared from 3-methyl-5-aminopyrazole (0.97 g, 10 mmol) and appropriate quantity of hydrochloric acid and sodium nitrite]. The prod-

uct separated on standing, was collected and crystallized from dimethylformamide to give 3a in 70% yield; mp 240˚C; IR (KBr) ν_{max}/cm^{-1} 1654.6 (C = O), 1716.5 (C = O), 3251.8 (NH), 3417.6 (NH); ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3H, CH_3), 6.29 (s, 1H, pyrazole 4-CH), 7.81-8.19 (m, 4H, ArH's), 12.82 (s, 1H, NH), 13.45 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 167.9, 153.7, 145.9, 135.6, 134.8, 130.9, 121.7, 93.8, 15.7; MS m/z 255 (M^+ + 1), 254 (M^+), 213, 186, 158, 102, 76, 67; Anal. Calcd. for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.22; H, 3.79; N, 21.76%.

2.2. Synthesis of 2-Methyl-6H-Indeno[1,2-e]Pyrazolo [5,1-c]-1,2,4-Triazin-6-One 4a

Compound 3a (1.27 g, 5 mmol) was refluxed in boiling acetic acid for 2 h, excess solvent was evaporated under reduced pressure, and the residue was treated with methanol (10 ml). The solid that formed was collected and crystallized from dimethylformamide to give 4a in 85% yield; mp 250˚C; IR (KBr) ν_{max}/cm^{-1} 1728.2 (C = O); ^{1}H NMR (DMSO-d_6) δ 2.71 (s, 3H, CH_3), 7.33 (s, 1H, pyrazole 4-CH), 7.71-8.19 (m, 4H, ArH's); ^{13}C NMR (DMSO-d_6) δ 184.5, 153.6, 151.4, 147.2, 145.8, 139.9, 134.3, 132.6, 128.8, 127.3, 123.6, 96.8, 14.9; MS m/z 237 (M^+ + 1), 236 (M^+), 195, 168, 143, 139, 114, 88, 53; Anal. Calcd. for $C_{13}H_8N_4O$: C, 66.09; H, 3.41; N, 23.72. Found: C, 65.87; H, 3.25; N, 23.54%.

2.3. Synthesis of 3-Phenyl-6H-Indeno[1,2-e]Pyrazolo [5,1-c]-1,2,4-Triazin-6-One 4b

The compound was prepared by the same procedure described for the synthesis of compound 3a using 4-phenyl-3-aminopyrazole 1b in place of 1a. The compound crystallized from dimethylformamide to give 4b in 70% yield; mp. 290˚C; IR (KBr) ν_{max}/cm^{-1} 1726.6 (C = O); ^{1}H NMR (DMSO-d_6) δ 7.32-8.43 (m, 9H, ArH's), 8.82 (s, 1H, pyrazole 2-CH); ^{13}C NMR (DMSO-d_6) δ 184.6, 148.2, 147,3, 139.9, 136.2, 135.7, 132.4, 130.7, 129.7, 129.2, 126.8, 124.7, 123.6, 123.3, 121.6, 97.5; MS m/z 299 (M^++1), 298 (M^+), 214, 168, 130, 88, 51; Anal. Calcd. for $C_{18}H_{10}N_4O$: C, 72.47; H, 3.38; N, 18.78. Found: C, 72.22; H, 3.25; N, 18.49%.

2.4. Synthesis of 2-(Arylpyrazol-5-yl)- and 2-Aryl-3-Imino-9-(1,1-Dicyanomethylene)-2-Hydroindeno[2,1-c]Pyridazine-4-carbonitrile 5a,b and 8a-e

Method A. To a solution of 3a or 7a-e (5 mmol) and malononitrile (6.6 g, 10 mmol) in absolute ethanol (40 ml) was added 3-4 drops of piperidine at room temperature. The reaction mixture was refluxed for 3h. The solvent was evaporated under reduced pressure and the residue was triturated with methanol (10 ml) where it solidified. The crude product was collected and crystallized from dimethylformamide to give 5a and 8a-e respectively.

Method B. To a stirred solution of 6 (2.24 g, 10 mmol) in ethanol (100 ml), sodium acetate trihydrate (1.3 g, 10 mmol) was added. After stirring for 15 min the mixture was cooled to 0˚C and treated with a cold solution of diazonium chloride of aminopyrazoles 1a,b and aromatic amines 9a-e. The product separated on standing was collected by filtration and crystallized from dimethylformamide to give compounds 5a,b and 8a-e respectively.

9-(1,1-*Dicyanomethylene*)-3-*imino*-2-(3-*methylpyrazol*-5-*yl*)-2,3-*dihydro*-9*H*-*indeno*[2,1-*c*]*pyridazine*-4-*carbonitrile* 5*a*, yield 85%; mp 310˚C; IR (KBr) ν_{max}/cm^{-1} 2199.4 (C ≡ N), 2225.6 (C ≡ N), 2299.1 (C ≡ N), 3201.9 (NH), 3425.8 (NH); ^{1}H NMR (DMSO-d_6) δ 2.2 (s, 3H, CH_3), 6.31 (s, 1H, pyrazole 4-CH), 7.91-8.42 (m, 4H), 10.3 (s, 1H, NH), 12.91 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 154.9, 153.6, 150.7, 149.7, 136.8, 136.1, 134.9, 132.4, 131.2, 129.5, 126.6, 126.3, 111.4, 110.6, 98.5, 97.8, 80.6, 15.7; MS m/z 350 (M^+), 349, 309, 214, 202, 152, 100, 67, 53; Anal. Calcd. for $C_{19}H_{10}N_8$: C, 65.14; H, 2.88; N, 31.99. Found: C, 64.98; H, 2.65; N, 31.85%.

9-(1,1-*Dicyanomethylene*)-3-*imino*-2-(4-*phenylpyrazol*-5-*yl*)-2,3-*dihydro*-9*H*-*indeno*[2,1-*c*]*pyridazine*-4-*carbonitrile* 5*b*, yield 85%; mp 322˚C; IR (KBr) ν_{max}/cm^{-1} 2197.2 (C ≡ N), 2223.1 (C ≡ N), 2299.3 (C ≡ N), 3209.1 (NH), 3429.3 (NH); ^{1}H NMR (DMSO-d_6) δ 7.73-8.42 (m, 10H, ArH's), 10.43 (s, 1H, NH), 12.90 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 155.1, 153.8, 151.5, 149.6, 136.7, 136.0, 134.5, 132.6, 131.4, 131.1, 129.3, 129.1, 128.4, 126.1, 126.5, 112.4, 111.6, 110.8, 98.8, 97.9, 80.0; MS m/z 413 (M^+ + 1), 412 (M^+), 387, 348, 329, 214, 202, 152, 103, 64, 50; Anal. Calcd. for $C_{24}H_{12}N_8$: C, 69.89; H, 2.93; N, 27.17. Found: C, 69.87; H, 2.93; N, 27.18%.

2-(4-*Chlorophenyl*)-9-(1,1-*dicyanomethylene*)-3-*imino*-2,3-*dihydro*-9*H*-*indeno*[2,1-*c*]*pyridazine*-4-*carbonitrile* 8*a*, yield 80%; mp 310˚C; IR (KBr) ν_{max}/cm^{-1} 2144.5 (C ≡ N), 2225.3 (C ≡ N), 2275.6 (C ≡ N), 3301.3 (NH); ^{1}H NMR (DMSO-d_6) δ 7.45-8.46 (m, 8H), 10.29 (s, 1H, NH); MS m/z 383 (M^+ + 3), 382 (M^++2), 381 (M^++1), 380 (M^+), 379, 334, 290, 214, 159, 111, 75; Anal. Calcd. for $C_{21}H_9ClN_6$: C, 66.24; H, 2.38; N, 22.07. Found: C, 66.98; H, 2.38; N, 22.08%.

9-(1,1-*Dicyanomethylene*)-3-*imino*-2-(4-*nitrophenyl*)-2,3-*dihydro*-9*H*-*indeno*[2,1-*c*]*pyridazine*-4-*carbonitrile* 8*b*, yield 77%; mp 315˚C; IR (KBr) ν_{max}/cm^{-1} 2167.5 (C ≡

N), 2226.9 (C ≡ N), 2250.6 (C ≡ N), 3283.8 (NH); ^{1}H NMR (DMSO-d_6) δ 7.51-8.46 (m, 8H), 10.28 (s, 1H, NH); MS m/z 391 (M^+), 390, 344, 296, 264, 214, 76; Anal. Calcd. for $C_{21}H_9N_7O_2$: C, 64.45; H, 2.32; N, 25.06. Found: C, 64.38; H, 2.29; N, 24.94%.

2-(4-*Bromophenyl*)-9-(1,1-*dicyanomethylene*)-3-*imino*-2,3-*dihydro*-9*H*-*indeno*[2,1-*c*]*pyridazine*-4-*carbonitrile* 8*c*, yield 83%; mp 280˚C; IR (KBr) ν_{max}/cm^{-1} 2167.4 (C ≡ N), 2227.1 (C ≡ N), 2249.5 (C ≡ N), 3311.2 (NH); ^{1}H NMR (DMSO-d_6) δ 7.42-8.46 (m, 8H), 10.29 (s, 1H, NH); MS m/z 427 (M^+ + 3), 425 (M^+ + 1), 377, 376, 296, 268, 206, 178, 138, 90, 63; Anal. Calcd. for $C_{21}H_9BrN_6$: C, 59.30; H, 2.13; N, 19.76. Found: C, 59.24; H, 2.13; N, 19.72%.

9-(1,1-*Dicyanomethylene*)-3-*imino*-2-(4-*methylphenyl*)-2,3-*dihydro*-9*H*-*indeno*[2,1-*c*]*pyridazine*-4-*carbonitrile* 8*d*, yield 79%; mp 290˚C; IR (KBr) ν_{max}/cm^{-1} 2188.9 (C ≡ N), 2222.9 (C ≡ N), 2249.6 (C ≡ N), 3286.3 (NH); ^{1}H NMR (DMSO-d_6) δ 2.45 (s, 3H, CH_3), 7.45-8.49 (m, 8H), 10.31 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 154.8, 153.6, 149.9, 137.1, 136.9, 136.1, 135.2, 134.5, 132.3, 131.7, 131.1, 126.6, 126.2, 116.8, 111.4, 109.4, 98.4, 80.9, 21.3; MS m/z 361 (M^+ + 1), 360 (M^+), 359, 311, 283, 214, 187, 149, 91, 65; Anal. Calcd. for $C_{22}H_{12}N_6$: C, 73.32; H, 3.36; N, 23.32. Found: C, 73.02; H, 3.32; N, 23.15%.

9-(1,1-*Dicyanomethylene*)-3-*imino*-2-(3-*methylphenyl*)-2,3-*dihydro*-9*H*-*indeno*[2,1-*c*]*pyridazine*-4-*carbonitrile* 8*e*, yield 79%; mp 275˚C; IR (KBr) ν_{max}/cm^{-1} 2182.6 (C ≡ N), 2223.4 (C ≡ N), 2282.7 (C ≡ N), 3276.2 (NH); ^{1}H NMR (DMSO-d_6) δ 2.41 (s, 3H, CH_3), 7.47-8.49 (m, 8H), 10.30 (s, 1H, NH); MS m/z 361 (M^+ + 1), 360 (M^+), 359, 313, 262, 213, 185, 129, 97, 55; Anal. Calcd. for $C_{22}H_{12}N_6$: C, 73.32; H, 3.36; N, 23.32. Found: C, 73.29; H, 3.34; N, 23.31%.

2.5. Synthesis of 3-N-Acetylimino-2-(4-Chlorophenyl)-9-(1,1-Dicyanomethylene)-2,3-Dihydro-9H-Indeno[2,1-c]Pyridazine-4-Carbonitrile 10

A solution of 8a (1.9 g, 5 mmol) in acetic anhydride (25 ml) was refluxed for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The solid formed was collected, washed with water and crystallized from dimethylformamide to give 9, yield 81%, mp. 320˚C; IR (KBr) ν_{max}/cm^{-1} 1674.5 (C = O), 2144.8 (C ≡ N), 2224.4 (C ≡ N), 2275.7 (C ≡ N); ^{1}H NMR (DMSO-d_6) δ 2.37 (s, 3H, CH_3), 7.47-8.49 (m, 8H); MS m/z 425 (M^+ + 3), 424 (M^+ + 2), 423 (M^+ + 1), 422 (M^+), 409, 407, 383, 382, 381, 380, 379, 344, 295, 214, 187, 111, 75; Anal Calcd. for $C_{23}H_{11}ClN_6O$: C, 65.32; H, 2.62; N, 19.87. Found: C, 65.17; H, 2.45; N, 19.69%.

2.6. Synthesis of 3-N-Benzoylimino-2-(4-Chlorophenyl)-9-(1,1-Dicyanomethylene)-2,3-Dihydro-9H-Indeno[2,1-c]Pyridazine-4-Carbonitrile 10

A solution of 8a (1.9 g, 5 mmol) in pyridine (30 ml) and benzoyl chloride (0.58 ml, 5 mmol) was reflux for 30 min. The reaction mixture was left to cool, then treated with dilute hydrochloric acid (50 ml). The crude product was collected and crystallized from dimethylformamide to give N-benzoyl derivative 10, yield 82%, mp. 325˚C; IR (KBr) ν_{max}/cm^{-1} 1674.8 (C = O), 2144.4 (C ≡ N), 2224.9 (C ≡ N), 2275.7 (C ≡ N);); ^{1}H NMR (DMSO-d_6) δ 7.47-8.49 (m, 13H); MS m/z 487 (M^+ + 3), 486 (M^+ + 2), 485 (M^+ + 1), 484 (M^+), 411, 383, 382, 381, 357, 105, 77, 51; Anal Calcd. for $C_{28}H_{13}ClN_6O$: C, 69.35; H, 2.70; N, 17.33. Found: C, 69.28; H, 2.69; N, 17.35%.

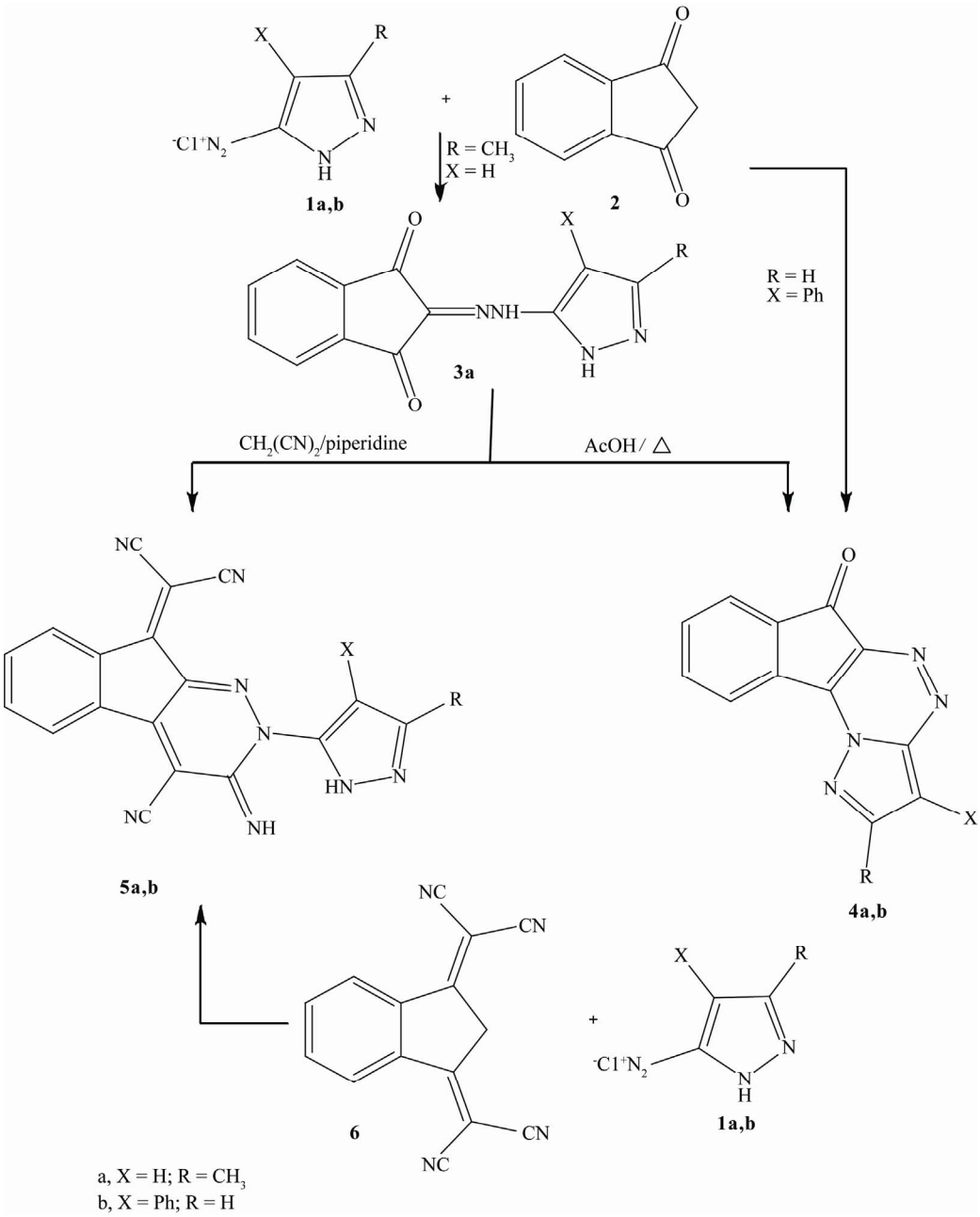
2.7. Synthesis of 2-(4-Chlorophenyl)-9-(1,1-Dicyanomethylene)-3-Oxo-2,3-Dihydro-9H-Indeno[2,1-c] Pyridazine-4-Carbonitrile 11

Compound 8a (1.9 g, 5 mmol) was refluxed in dilute hydrochloric acid (5 ml, 10%) for 3 h. The reaction mixture was cooled and the solid that precipitated was filtered, washed with water and crystallized from dimethylformamide to give 11, yield 82%, mp. 311˚C; IR (KBr) ν_{max}/cm^{-1} 1675.3 (C = O), 2144.9 (C ≡ N), 2224.7 (C ≡ N), 2275.7 (C ≡ N); ^{1}H NMR (DMSO-d_6) δ 7.45-8.47 (m, 8H); MS m/z 384 (M^+ + 3), 383 (M^+ + 2), 382 (M^+ + 1), 381 (M^+), 380, 379, 317, 290, 214, 138, 111, 75; Anal Calcd. for $C_{21}H_8ClN_5O$: C, 66.06; H, 2.11; N, 18.35. Found: C, 66.00; H, 2.09; N, 18.35%.

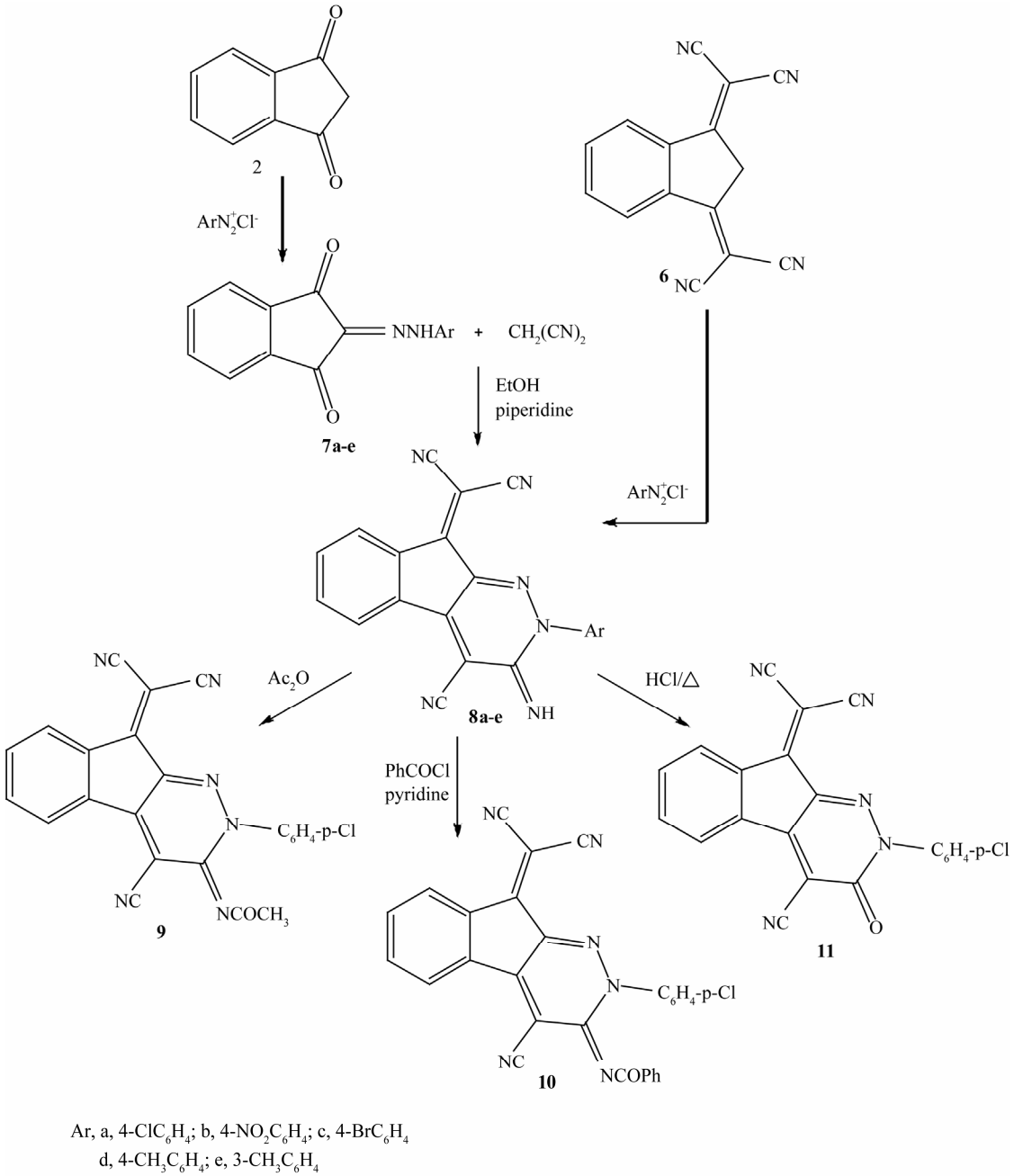
3. RESULTS AND DISCUSSION

Coupling reaction of diazonium chloride of 5-amino-3-methypyrazole 1a with 1,3-indanedione 2 in the presence of sodium acetate led to the formation of one isolable product which analyzed correctly for $C_{13}H_{10}N_4O_2$, although, the coupling reaction of pyrazole-3-diazonium chloride with 1,3-indanedione was reported to give a mixture of opened hydrazone and the cyclized product [16]. The structure of the resulting product was confirmed from its spectroscopic data to be the opened hydrazone 3. IR spectrum revealed absorption bands at ν 3417.6, 3251.8, 1716.5 and 1654.6 corresponding to the two NH and two CO groups, respectively. Its mass spec-

trum showed an intense peak at m/z 254 assignable to molecular ion peak. The ^{1}H NMR spectrum of 3a exhibited singlet signal at δ 2.31 ppm assignable to methyl protons, singlet signal at δ 6.29 ppm for 4-H pyrazole proton and characterized signals at δ 12.82 and at δ 13.45 ppm assignable to the two NH protons which disappeared in shaking with deuterium oxide. From the foregoing data the structure was proved to be 2-(3-methyl-5-pyrazolyl)hydrazono-1,3-indanedione 3a. On refluxing in acetic acid compound 3a cyclized through acid catalyzed nucleophilic addition elimination reaction to give 2-methylindeno[1,2-e]pyrazolo[5,1-c]- 1,2,4-triazin-6-one 4a (**Scheme 1**). The structure of 4a was confirmed on the basis of its elemental analysis and spectral data. ^{1}H NMR spectrum showed significant signals at δ 2.71, 7.33 ppm assignable to methyl protons and 4-H pyrazole proton respectively. The IR spectrum of 4a displayed only one carbonyl band at ν 1728.2 cm^{-1} and showed absence of the bands corresponding to the two NH groups in 3a.



Scheme 1. synthesis of hydrazono-1,3-indanedione 3a, indeno[1,2-e]pyrazolo[5,1-c]triazin-6-one 4a,b and indeno[2,1-c]pyridazines 5a,b.



Scheme 2. Synthesis of iminoindeno[2,1-c]pyridazines 8 and its N-acetyl, N-benzoyl and oxo-derivatives 9-11.

Under similar conditions diazonium chloride of 5-amino-4-phenylpyrazole 1b coupled with 2, but no hydrazone intermediate could be isolated, and instead the cyclized product 4b was isolated. This is could be rationalize if we take into account the presence of more electron releasing phenyl group, compared with methyl one, increase the nucleophilicity of the pyrazole nitrogen to the extent it could complete the cyclization step to give the isolated product 4b. The structure of the new derivative 4b was confirmed by its elemental and spectral analysis data [Experimental part].

Compound 3a reacted with malononitrile in boiling ethanol in the presence of piperidine and afforded the expected product 5a [17,18] (**Scheme 1**).The structure of the product was established on the basis of elemental and spectral analyses. The IR spectrum of 5a revealed presence of three nitrile group bands at ν 2199.4, 2225.6 and 2299.1 cm^{-1}, in addition to bands at ν 3201.9 and 3425.8 cm^{-1} corresponding to imino NH in pyridazine [18] ring and NH of pyrazole ring, respectively. Its mass

spectrum revealed the respective molecular ion peak at m/z 350. Also, the ^{1}H NMR (DMSO-d_6) spectrum of 5a showed characteristic signals at δ 2.26 (s, 3H, CH_3), 6.31 (s, 1H, 4-CH pyrazole), in addition to two singlet signals at δ 10.32 (1H, NH) and at δ 12.91 (1H, NH), which disappeared by shaking with D_2O. Also, the structure of 5a was confirmed by its alternative synthesis by coupling of 1,3-bis-(dicyanomethylene)-2-hydroindene 6 [19], prepared from condensation of 1,3-indanedione with malononitrile, with diazonium salt of 3-methyl-5-aminopyrazole 1a (Scheme 1). Similar treatment of 6 with diazotized 4-phenyl-5-aminopyrazole 1b afforded the respective 5b; whose structure was proved on the basis of its correct analytical and spectral data (MS, IR, ^{1}H- and ^{13}C-NMR).

Also, coupling of 6 with aryl diazonium chlorides 7a-e gave the corresponding [18] indeno[2,1-c]pyridazine 8a-e. The structures of the products 8a-e were confirmed by their spectal (MS, IR, ^{1}H- and ^{13}C-NMR) and elemental analyses data (see Experimental). In the IR spectra of all products 8a-e, the characteristic nitrile absorption bands were at about ν 2144.5-2188.9, 2222.9-2227.1 and 2249.5-2282.7 cm^{-1} as well as imino NH absorption bands near ν 3276.3-3311.2 cm^{-1}. The structures of 8a-e were also confirmed by their alternative synthesis. Thus, reaction of 7a-e [20,21], prepared by coupling of 1,3-indanedione 2 with aryl diazonium chloride, with malononitrile in boiling ethanol in the presence of piperidine gave 8a-e (**Scheme 2**). Boiling compound 8a in acetic anhydride gave the corresponding N-acetylimino derivative 9. Benzoylation of 8a with benzoyl chloride in pyridine afforded the corresponding N-benzoylimino derivative 10. Also, hydrolysis of 8a by refluxing in dilute hydrochloric acid gave the corresponding carbonyl derivative 11 (**Scheme 2**). The elemental analyses and spectral data (MS, IR, ^{1}H- and ^{13}C-NMR) of the products 9-11 were all in agreement with the proposed structures [Experimental part].

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