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Research Article

Hydrolysis and Hydrazinolysis of Isatin-Based Ald- and Ketazines

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The hydrolysis of isatin aldazine **4a–d** afforded the unexpected 3,3′-(hydrazine-1,2-diylidene)bis(indolin-2-one) (**5**) and 1,2-di(arylidene)hydrazines **6a–d** through dual hydrolysis of **4a–d**. A mechanism to explain the formation of **5** and **6a–d** was proposed. In addition, the hydrazinolysis of **4a–d** yielded 3-hydrazonoindolin-2-one (**2**) and 1,2-di(arylidene)hydrazines **6a–d** instead of hydrazones **17a–d**, while hydrazinolysis of isatin ketazine **5** gave the expected 3-hydrazonoindolin-2-one (**2**). These results indicated the ability of the title compounds for unusual hydrolysis and hydrazinolysis reactions.

1. Introduction

Isatin imines including Schiff bases **1b** and isatin hydrazones **2**, which are the product of condensation of amines or hydrazines with isatins **1a**, respectively, are considered as a pharmacophore for diverse spectrum of biological activities [1–5] (Figure 1). They have been reported as anticancer agents where they were found to be inhibitors of tyrosine phosphatase Shp2 [6]. Furthermore, they have been identified as kinase inhibitors and they also have been reported as cytotoxic agents towards U937 lymphoma cells [7]. In addition, hydrazones **2** (R = –COAr) revealed a good cytotoxic activity against K562, MDA-MB-468, and HT-29 cell lines [8].

Isatin-based azines **4** are usually prepared by the condensation of isatin hydrazones **2** (R^1 = H) with aldehydes or ketones **3** to construct the connectivity >C=N–N=CR^2R^3 and then the formation of isatin aldazines (**4**, R^2 or R^3 = H) or isatin ketazines (**4**, R^2 and R^3 ≠ H), respectively (Figure 1). Isatin aldazines **4** showed a significant anticancer activity against human breast cell line MCF-7 [9], whereas a series of symmetrical and asymmetrical isatin ketazines **5** showed a selective activity against multidrug-resistant cancer cells [10]. Moreover, bis-Schiff bases of isatins **4** represent significant antiglycation activity [11].

On the other hand, azines undergo hydrolysis to regenerate the hydrazine and aldehydes or ketones. However, ketazines are important intermediates in the production of hydrazine hydrate when subjected to hydrolysis processes [12]. In addition, the reaction of azines with hydrazine (hydrazinolysis) regenerates the hydrazones [13]. In light of the latter results and in continuation of our interest in the chemistry of isatin-based azines **4** and **5**, we hope to report herein the unexpected results of hydrolysis and hydrazinolysis of isatin aldazines **4a–d** and isatin ketazines **5**.

2. Experimental

2.1. General. Melting points were measured with a Stuart melting point apparatus and were uncorrected. IR spectra (KBr disks) were recorded with a Pye Unicam SP 1000 IR spectrophotometer. The NMR spectra were recorded by Varian Gemini-300BB 300 MHz FT-NMR spectrometers (Varian Inc., Palo Alto, CA). ^{1}H and ^{13}C spectra were run at 300 and 75 MHz, respectively, in deuterated dimethyl sulfoxide (DMSO-d_6). Chemical shifts (δ_H) are reported relative to TMS as internal standard. All coupling constant (J) values are given in Hertz. Chemical shifts (δ_C) are reported relative to

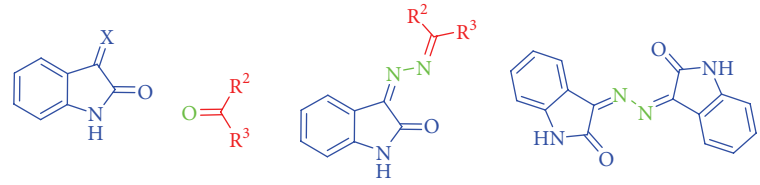


Figure 1: General structure of **1–5**.

DMSO-d_6 as internal standards. The abbreviations used are as follows: s: singlet; d: doublet; and m: multiplet. Mass spectra were recorded on Helwett Packard 5988 spectrometer at 70 eV. Reaction courses and product mixtures were routinely monitored by thin layer chromatography (TLC) on silica gel precoated F_{254} Merck plates. Unless otherwise noted, all solvents and reagents were commercially available and were used without further purification.

*2.2. Synthesis of Isatin Aldazines **4a–d**.* A mixture of 3-hydrazonoindolin-2-one (**2**) (0.161 g, 1 mmol) and aldehyde from **3a–c** (1 mmol) in acetic acid (25 mL) was stirred at room temperature for 12 h. The resulted precipitate was filtered, dried, and finally crystallized from EtOH/DMF to afford hydrazones **4a–c**, respectively. Aldazines **4a–d** were also prepared by the reaction of **2** with **3a–d** in refluxing ethanol, in the presence of catalytic amount of glacial acetic acid for 6 h [10].

*2.2.1. 3-((Benzylidene)hydrazono)indolin-2-one (**4a**).* Yield (62%), mp > 300°C (lit. mp 300°C [14]); IR (KBr) ν 3280 (NH), 1722 (C=O), 1614 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.90 (d, 1H, J = 7.8 Hz, H4 of isatin), 7.04 (t, 1H, J = 7.5 Hz, H5 of isatin), 7.42 (t, 1H, J = 7.5 Hz, H6 of isatin), 7.51 (d, 1H, J = 7.8 Hz, H7 of isatin), 7.57–7.99 (m, 5H, Ar–H), 8.61 (s, 1H, N=CH), 10.97 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 110.95, 111.19, 115.73, 122.39, 122.63, 128.03, 128.25, 134.26, 134.47, 144.70, 145.16, 163.36 (C=O); MS m/z (%) 249 (M$^+$, 30.02), 221 (17.03), 145 (35.41).

*2.2.2. 3-((4-Nitrobenzylidene)hydrazono)indolin-2-one (**4b**) [11].* Yield (66%), mp 254–256°C; IR (KBr) ν 3161 (NH), 1734 (C=O), 1616 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.90 (d, 1H, J = 7.8 Hz, H4 of isatin), 7.01 (t, 1H, J = 7.5 Hz, H5 of isatin), 7.41 (t, 1H, J = 7.5 Hz, H6 of isatin), 7.73 (d, 1H, J = 7.8 Hz, H7 of isatin), 8.20 (d, 2H, J = 8.7 Hz, Ar–H), 8.37 (d, 2H, J = 8.7, Ar–H), 8.66 (s, 1H, N=CH), 10.86 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 110.85, 111.08, 116.01, 122.29, 122.53, 124.23, 128.59, 128.78, 129.64, 133.98, 134.19, 139.06, 145.27, 148.97, 149.67, 156.21, 156.35, 164.10 (C=O); MS m/z (%) 294 (M$^+$, 10.49), 266 (100).

*2.2.3. 3-((4-Chlorobenzylidene)hydrazono)indolin-2-one (**4c**).* Yield (78%), mp = 270–272°C (lit. mp = 200°C [14]); IR (KBr) ν 3248 (NH), 1734 (C=O), 1604 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.90 (d, 1H, J = 7.5 Hz, H4 of isatin), 7.02 (t, 1H, J = 7.8 Hz, H5 of isatin), 7.41 (t, 1H, J = 7.8 Hz, H6 of isatin), 7.63 (d, 2H, J = 8.4 Hz, Ar–H), 7.85 (d, 1H, J = 7.5 Hz, H7 of isatin), 7.98 (d, 2H, J = 8.4, Ar–H), 8.61 (s, 1H, N=CH), 10.86 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 110.73, 110.98, 116.26, 128.82, 129.23, 130.37, 130.45, 132.24, 133.92, 136.65, 141.72, 145.07, 150.29, 158.75, 164.35 (C=O); MS m/z (%) 285 (M$^+$ + 2, 6.78), 283 (M$^+$, 20.10), 255 (89.86), 145 (16.96), 138 (54.66), 111 (95.01).

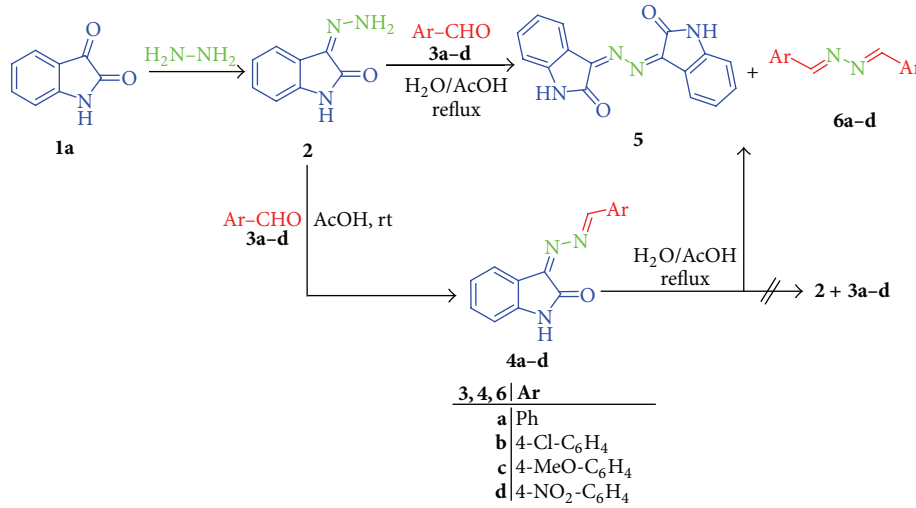
*2.2.4. 3-((4-Methoxybenzylidene)hydrazono)indolin-2-one (**4d**).* Yield (69%), mp = 182-183°C (lit. mp = 182°C [14]); IR (KBr) ν 3194 (NH), 1732 (C=O), 1606 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 6H, 2OCH$_3$), 6.89 (d, 1H, J = 7.5 Hz, H4 of isatin), 7.04 (t, 1H, J = 7.8 Hz, H5 of isatin), 7.12 (d, 2H, J = 8.4, Ar–H), 7.39 (t, 1H, J = 7.5 Hz, H6 of isatin), 7.94 (d, 2H, J = 8.4 Hz, Ar–H), 8.02 (d, 1H, J = 7.8 Hz, H7 of isatin), 8.61 (s, 1H, N=CH), 10.76 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 55.55 (OCH$_3$), 110.58, 110.81, 114.62, 114.87, 116.59, 122.13, 122.36, 126.32, 128.79, 128.86, 130.91, 131.03, 133.29, 133.52, 144.80, 145.15, 150.65, 161.81, 161.93, 162.58, 163.36, 164.69 (C=O); MS m/z (%) 279 (M$^+$, 30.31), 251 (100), 134 (17.79).

*2.3. Hydrolysis of Isatin Aldazines **4a–d***

Method A. A solution of isatin aldazines **4a–d** (1 mmol) in H_2O/AcOH (1 : 3, v : v, 25 mL) was refluxed for 4 h. The given 3,3′-(hydrazine-1,2-diylidene)bis(indolin-2-one) (**5**) was filtered while hot and crystallized from EtOH/DMF. The filtrate of the latter reaction was concentrated. The solid formed was washed with 50% ethanol, dried, and crystallized from EtOH to give 1,2-di(arylidene)hydrazines **6a–d**. The physical constants of **5** and **6a–d** were identical with that reported.

Method B. A mixture of 3-hydrazonoindolin-2-one (**2**) (0.161 g, 1 mmol) and the appropriate aldehyde from **3a–c** (1 mmol) in H_2O/AcOH (1 : 3, v : v, 25 mL) was refluxed for 4 h. Ketazine **5** was filtered while hot and crystallized from EtOH/DMF while aldazines **6a–d** were isolated from the filtrate after evaporation of the solvent.

*2.3.1. 3,3′-(Hydrazine-1,2-diylidene)diindolin-2-one (**5**) [8].* Yield (46%), mp > 300°C; IR (KBr) ν 3276 (2NH), 1722 (2C=O), 1615 (2C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.82 (d,



Scheme 1: The reaction of 3-hydrazonoindolin-2-one (**2**) with aldehydes **3a–d**.

2H, J = 7.8 Hz, H5 of isatin), 6.96 (t, 2H, J = 7.5 Hz, H6 of isatin), 7.14 (t, 2H, J = 7.5 Hz, H7 of isatin), 7.34 (d, 2H, J = 7.8 Hz, H4 of isatin), 10.55 (s, D_2O exchangeable, 2H, 2NH); ^{13}C NMR (DMSO-d_6) δ 111.59, 116.26, 123.03, 128.66, 134.89, 145.22, 145.68, 163.89 (2C=O).

*2.3.2. 1,2-Di(benzylidene)hydrazine (**6a**).* Yield (70%), mp = 95–97°C (Lit. mp = 92–93°C [15]). IR 1615–1620 (2C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.57–7.99 (m, 10H, Ar–H), 8.61 (s, 2H, N=CH); MS m/z (%) 209 (M^+ + 1, 11.68), 208 (M^+, 79.43), 207 (100), 138 (100).

*2.3.3. 1,2-Bis(-4-chlorobenzylidene)hydrazine (**6b**).* Yield (82%), mp = 211–213°C (Lit. mp = 207-208°C [15]) IR 1617–1625 (2C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.56 (d, 4H, J = 8.4 Hz, Ar–H), 7.88 (d, 4H, J = 8.4 Hz, Ar–H), 8.61 (s, 2H, N=CH); ^{13}C NMR (DMSO-d_6) δ 128.93, 129.89, 132.56, 135.791, 160.44 (2C=N); MS m/z (%) 279 (M^+ + 2, 9.68), 277 (M^+, 31.14), 165 (100), 138 (23.01), 111 (34.85).

*2.3.4. 1,2-Bis(4-methoxybenzylidene)hydrazine (**6c**).* Yield (77%), mp = 170–172°C (Lit. mp = 175°C [15]) IR 1615–1622 (2C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 6H, OCH_3), 7.04 (d, 4H, J = 8.4 Hz, Ar–H), 7.79 (d, 4H, J = 8.4 Hz, Ar–H), 8.61 (s, 2H, N=CH); ^{13}C NMR (DMSO-d_6) δ 55.27 ($2OCH_3$), 114.23, 126.53, 129.83, 160.35, 161.62 (2C=N); MS m/z (%) 268 (M^+, 18.37), 161 (31.72), 134 (26.80), 107 (16.07).

*2.3.5. 1,2-Bis(4-nitrobenzylidene)hydrazine (**6d**).* Yield (74%), mp = 223–225°C (Lit. mp = 223.3-223.4°C [16]) IR 1610–1617 (2C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.55 (d, 4H, J = 8.4 Hz, Ar–H), 7.88 (d, 4H, J = 8.4 Hz, Ar–H), 8.60 (s, 2H, N=CH); MS m/z 272 (%) 298 (M^+, 10.03), 252 (100), 176 (50.55).

*2.4. Hydrazinolysis of **4a–d**.* To a solution of hydrazones **4a–d** (1 mmol) in ethanol (25 mL), hydrazine hydrate (0.06 g 0.12 mmol) was added. The reaction was refluxed for 5 h. The formed precipitate was filtered, washed with ethanol, dried, and finally crystallized from EtOH/DMF to give 3-hydrazonoindolin-2-one (**2**) with mp = 217–219°C (Lit. mp = 219–220°C [16]); IR (KBr) ν 3361–3215 (NH, NH_2), 1687 (C=O), 1608 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.87 (d, 1H, J = 7.5; Hz, H5 of isatin), 6.97 (t, 1H, J = 7.8 Hz, H6 of isatin), 7.15 (t, 1H, J = 7.8 Hz, H7 of isatin), 7.37 (d, 1H, J = 7.5 Hz, H4 isatin), 9.55 (d, 1H, J = 14.0 Hz, D_2O exch., amino H), 10.56 (d, 1H, J = 14.0 Hz, D_2O exch., amino H), 10.72 (s, D_2O exch., 1H, NH isatin); MS m/z (%) 161.1 (M^+). The filtrate was evaporated under vacuum. The obtained residue was filtered, washed with 50% ethanol, dried, and crystallized from EtOH to yield 1,2-di(arylidene)hydrazines **6a–d**.

*2.5. Hydrazinolysis of **5**.* To a solution of **5** (0.29 g, 1 mmol) in ethanol (25 mL), hydrazine hydrate (0.06 g 0.12 mmol) was added. The reaction was refluxed for 5 h. The formed precipitate was filtered, washed with ethanol, dried, and finally crystallized from EtOH/DMF to give hydrazonoindolin-2-one (**2**).

3. Results and Discussion

In the reaction of 3-hydrazonoindolin-2-one (**2**) (R = H) with aldehydes **3a–d** in glacial acetic acid for 12 h, at ambient temperature, isatin aldazines **4a–d** were isolated extensively. The targeted aldazines **4a–d** were also prepared by the reaction of 3-hydrazonoindolin-2-one (**2**) with aldehydes **3a–d** in refluxing ethanol, in the presence of catalytic amount of glacial acetic acid for 6 h (Scheme 1) [9].

Hydrolysis of hydrazones **4a–d** by their refluxing in H_2O/AcOH afforded reddish precipitates during reflux in each case. These precipitates showed identical physical and chemical properties and they are not matched with the expected hydrazone **2** (R = H) (Scheme 1).

The ^{1}H NMR spectrum of the isolated precipitate did not show the characteristic signal of NH_2 of **2** and its mass

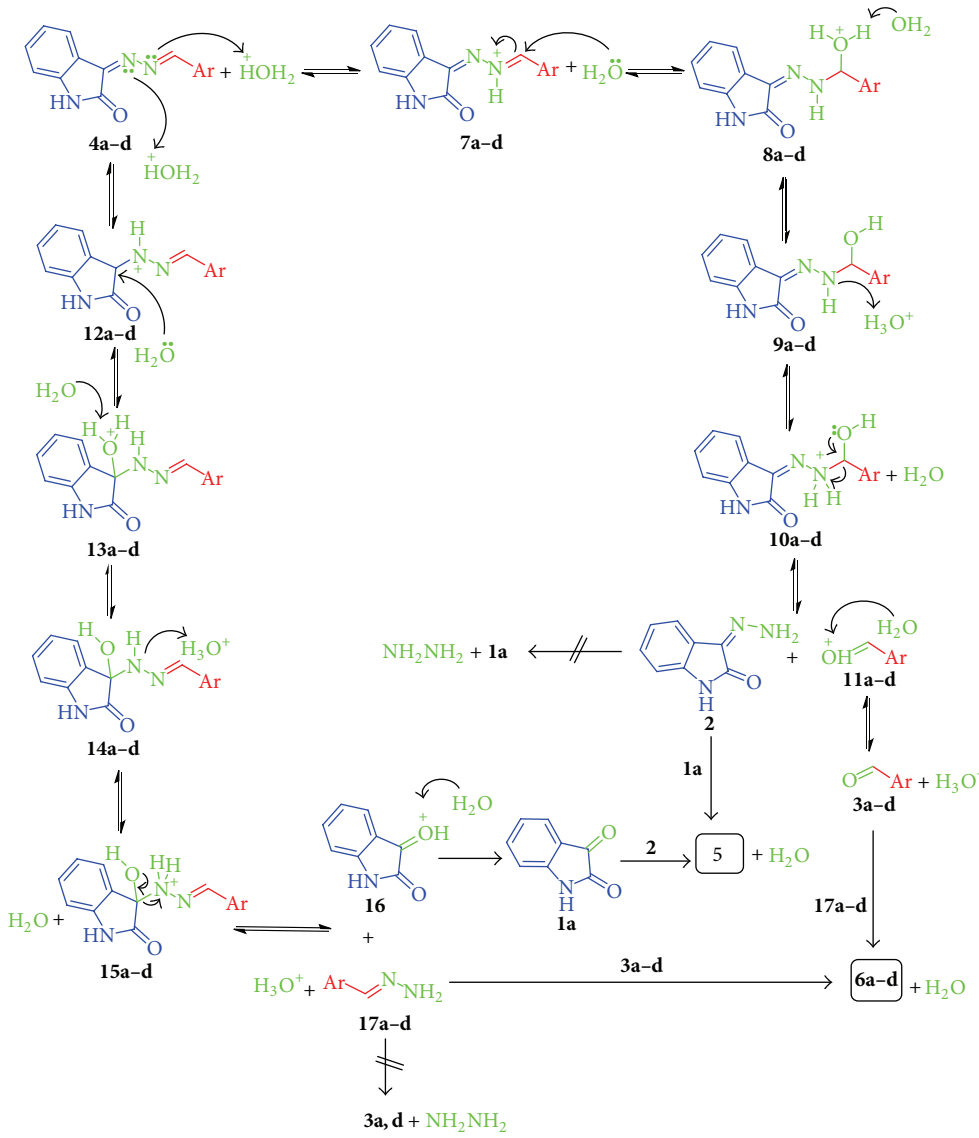
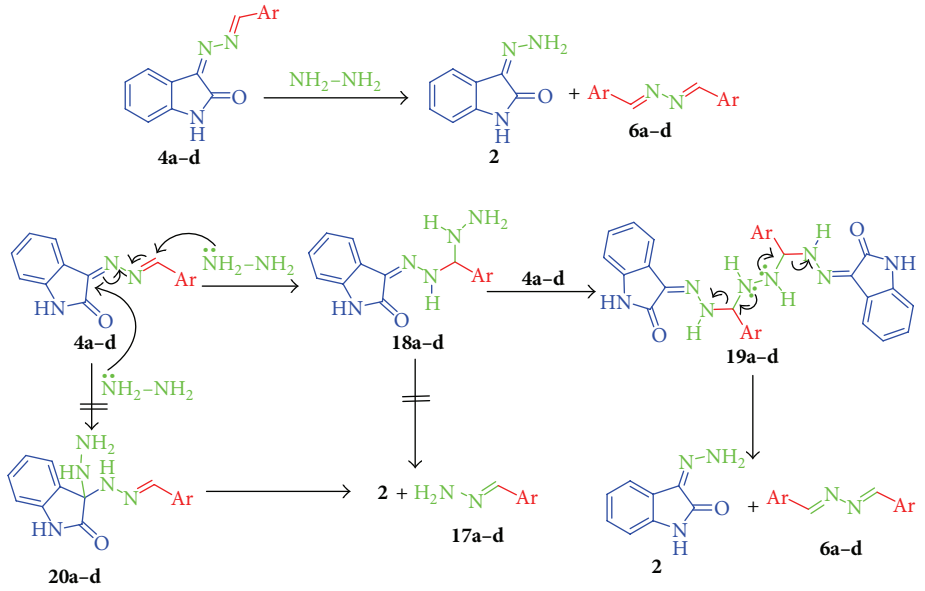


Figure 2: The proposed mechanism for the hydrolysis of isatin aldazines **4a–d** in refluxing H_2O/AcOH.

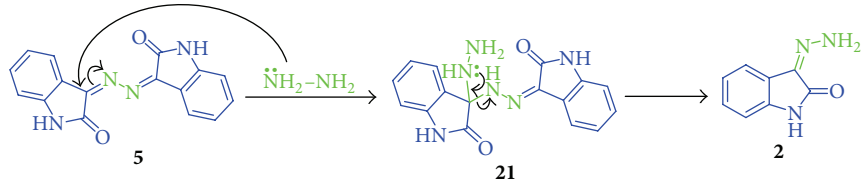
spectrum exhibited molecular ion peak at $m/z = 290$. The latter data proposed the assigned structure 3,3′-(hydrazine-1,2-diylidene)bis(indolin-2-one) (**5**) for the isolated compound. An authentic sample of compound **5** is prepared [10] and it was identical in all respects with the isolated compound in our hands.

After evaporation of the filtrates of the latter reactions, they gave in each case a compound with melting points 97°C (Ar = Ph), 213°C (Ar = 4-Cl-C_6H_4), 172°C (Ar = 4-MeO-C_6H_4), and 225°C (Ar = 4-NO_2-C_6H_4), respectively. These values do not match this reported for **2**, 217–219°C. Our attempts to explore these unknown compounds guided us to assign structure 1,2-di(arylidene)hydrazines **6a–d** for the isolated compounds. We found that the analytical data of authentic samples of isolated compounds is identical with those of **6a–d** [17–20]. Interestingly, refluxing **2** with aldehydes **3a–d** in H_2O/AcOH, 3,3′-(hydrazine-1,2-diylidene)bis(indolin-2-one) (**5**) and aldazines **6a–d** were also isolated.

Keeping in mind the reported data about the mechanism of hydrolysis of –C=N– imines [21], we are interested in proposing a mechanism to explain the formation of 3,3′-(hydrazine-1,2-diylidene)bis(indolin-2-one) (**5**) and 1,2-di(arylidene)hydrazines **6a–d**. In this mechanism, dual acidic hydrolysis of aldazines **4a–d** took place in their two nucleophilic centers which are accessible to attack by two protons from the acidic medium (Figure 2). The first pathway, in which acidic proton attack took place by the nitrogen of –N=C–Ar followed by hydrolysis to give intermediates **7(a–d)–10(a–d)**, respectively, yielded aldehydes **3a–d** and 3-hydrazonoindolin-2-ones (**2**) which would not undergo further hydrolysis. The second pathway, in which the other



Scheme 2: Hydrazinolysis of aldazines **4a–d**.



Scheme 3: Hydrazinolysis of 3,3′-(hydrazine-1,2-diylidene)bis(indolin-2-one) (**5**).

nitrogen of hydrazone function attacked the acidic proton followed by hydrolysis to give intermediates **12(a–d)–15(a–d)**, respectively, yielded indoline-2,3-dione (**1**) and the corresponding hydrazones **17a–d** without further hydrolysis. Finally, the reaction of **1a** with **2** (R = H) and **3a–d** with **17a–d** led to the formation of final products 3,3′-(hydrazine-1,2-diylidene)bis(indolin-2-one) (**5**) and aldazines **6a–d**, respectively. The expected last step is hydrolysis of **2** (R = H) and/or **17a–d**.

According to the previous results and in light of behavior of hydrazine hydrate towards certain –N=N– containing compounds [12], we stimulated to explore the reactivity of hydrazine hydrate towards –N=C– function in aldazines **4a–d**. Thus, the reaction of **4a–d** with hydrazine hydrate in refluxing ethanol afforded 3-hydrazonoindolin-2-one (**2**) and 1,2-di(arylidene)hydrazines **6a–d**, respectively, instead of **2** and **17a–d** (Scheme 2).

Hydrazine, as a nucleophile, attacked the carbon of –N=C– function of two molecules of hydrazones **4a–d** to form the nonisolable intermediates **18a–d** and **19a–d**, respectively (Scheme 3). Finally, the nonisolable intermediate **19a–d** afforded 3-hydrazonoindolin-2-one (**2**) and 1,2-di(arylidene)hydrazines **6a–d** as final isolated compounds.

Consequently, the reaction of hydrazine hydrate with C-3 of 3,3′-(hydrazine-1,2-diylidene)bis(indolin-2-one) (**5**) yielded the corresponding 3-hydrazonoindolin-2-one (**2**) as hydrazinolysis product (Scheme 3). The previous reaction proceeded through the attack of nucleophilic nitrogen of hydrazine on ketazine **5** to form the nonisolable intermediate **21** and then the formation of 3-hydrazonoindolin-2-one (**2**).

4. Conclusion

In conclusion, we reported herein the hydrolysis of isatin aldazines **4a–d** which gave unusual product 3,3′-(hydrazine-1,2-diylidene)bis(indolin-2-one) (**5**) and aldazines **6a–d** were formed through dual acidic hydrolysis. The hydrazinolysis of isatin aldazines **4a–d** yielded 3-hydrazonoindolin-2-one (**2**) and **6a–d** instead of **17a–d**. These results established the ability of the title compounds for unusual hydrolysis and hydrazinolysis reactions.

Conflict of Interests

The authors have declared that there is no conflict of interests.

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