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 (R1 = H) with aldehydes or ketones 3 to construct the connectivity >C=N–N=CR2R3 and then the formation of isatin aldazines (4, R2 or R3 = H) or isatin ketazines (4, R2 and R3 ≠ 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). 1H and 13C spectra were run at 300 and 75 MHz, respectively, in deuterated dimethyl sulfoxide (DMSO-d6). Chemical shifts (δH) are reported relative to TMS as internal standard. All coupling constant (J) values are given in Hertz. Chemical shifts (δC) are reported relative to
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), 7.57–7.79 (m, 5H, Ar–H), 8.61 (s, 1H, N=CH), 10.97 (s, D$_2$O exchangeable, 1H, NH); $^{13}$C NMR (DMSO-$d_6$) δ 111.90, 113.19, 115.73, 122.39, 122.63, 128.03, 128.25, 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-((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$_2$O 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), 7.52 (d, 2H, J = 8.4 Hz, Ar–H), 7.65 (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$_2$O 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, 3H, OCH$_3$), 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$_2$O exchangeable, 1H, NH); $^{13}$C NMR (DMSO-$d_6$) δ 55.55 (OCH$_3$), 110.58, 110.81, 114.62, 114.87, 116.59, 121.13, 122.36, 126.32, 128.79, 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 (1779).

2.3. Hydrolysis of Isatin Aldazines 4a–d

Method A. A solution of isatin aldazines 4a–d (1 mmol) in H$_2$O/AcOH (1:1; v:v, 25 mL) was refluxed for 4 h. The obtained 3,5′-[(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$_2$O/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. 3,5′-(Hydrazine-1,2-diylidene)diindolin-2-one (5) [8]. Yield (46%), mp > 300°C; IR (KBr) ν 3276 (NH), 1722 (C=O), 1615 (C=N) cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) δ 6.82 (d,
Scheme I: The reaction of 3-hydrazonoinolin-2-one (2) with aldehydes 3a–d.

The formed precipitate was filtered, washed with ethanol, dried, and finally crystallized from EtOH/DMF to give 3-hydrazonoinolin-2-one (2) with mp = 217–219°C (Lit. mp = 219–220°C [16]); IR (KBr) ν 3361–3215 (NH, NH₂), 1687 (C=O), 1608 (C=N) cm⁻¹; ¹H NMR (DMSO-d₆) 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, D₂O exch., amino H), 10.56 (d, 1H, J = 14.0 Hz, D₂O exch., amino H), 10.72 (s, D₂O exch., NH, NH isatin); MS m/z (%) 161.1 (M⁺), 116.2 (M⁺−2, 9.68), 277 (M⁺+2, 208 (M⁺, 79.43), 207 (100), 138 (100).

3. Results and Discussion

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

Hydrolisy of hydrazones 4a–d by their refluxing in H₂O/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 I).

The ¹H NMR spectrum of the isolated precipitate did not show the characteristic signal of NH₂ of 2 and its mass spectroscopic data were consistent with the assigned structure.
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 (\( \text{Ar} = \text{Ph} \)), 213°C (\( \text{Ar} = 4-\text{Cl-C}_6\text{H}_4 \)), 172°C (\( \text{Ar} = 4-\text{MeO-C}_6\text{H}_4 \)), and 225°C (\( \text{Ar} = 4-\text{NO}_2-\text{C}_6\text{H}_4 \)), 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 \( \text{H}_2\text{O}/\text{AcOH} \), 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=\text{C}–\text{Ar} followed by hydrolysis to give intermediates 7(a–d)–10(a–d), respectively, yielded aldehydes 3a–d and 3-hydr azonoindolin-2-ones (2) which would not undergo further hydrolysis. The second pathway, in which the other
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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