A comprehensive approach to the photochemical synthesis of bioactive compounds by the reaction of oxazolidine, thiazolidine and pyrazolidine derivatives with indol-2,3-diones

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Abstract. The reactions of indol-2,3-dione derivatives with 3-phenyl-5-isoxazolone, 2-thiazoline-2-thiol, 1-phenyl-3-methyl-5-pyrazolone under photochemical conditions have been described. The UV light-induced irradiation mainly produced benzazepine and quinoline carboxylic acid derivatives. The products have been characterized on the basis of spectral data and elemental analyses.

Keywords. Indol-2,3-dione; 3-phenyl-5-isoxazolone; 2-thiazoline-2-thiol; 1-phenyl-3-methyl-5-pyrazolone; photochemical irradiation; spectral characterization.

1. Introduction

Indol-2,3-dione (isatin) derivatives **1a–c** have been long known for a wide spectrum of biological activities.^{1–3} It is a core constituent of many naturally occurring alkaloids and drugs. We have investigated the photochemical reactions of indol-2,3-dione derivatives with various five-membered heterocycles containing O–C–N, N–C–S and N–C–N linkages. All these nuclei viz. 3-phenyl-5-isoxazolone^{4,5} **2**, 2-thiazoline-2-thiol^{6,7} **3** and 1-phenyl-3-methyl-5-pyrazolone **4** are well recognized for their pharmacological activities. Thus, emergent molecules from the reaction between **1** and **2–4** may be associated with wide spectrum of biological activities. Keeping in view the observation of Haucke *et al*⁸ that under photochemical conditions, indol-2,3-dione decomposes to isatic acid **5** which may react through various intermediates coupled with the fact that reacting five-membered heterocycles may exist in different tautomeric forms and can react *via* multiple pathways, we have investigated the photo-reactions of indol-2,3-diones with oxazolidine, thiazolidine and pyrazolidine derivatives and the results are presented herein.

2. Experimental

Melting points were determined in open glass capillaries and were uncorrected. The IR spectra were recorded on Nicolet Magna IRTM spectrometer Model 550 in KBr pellets. The ¹H NMR and ¹³C NMR spectra were obtained in CDCl₃ and DMSO-*d*₆ on a FX 90Q Jeol spectrometer at 300 MHz and 89.55 MHz, respectively, using TMS as an internal

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standard. Microanalyses were obtained using a Perkin–Elmer series 11 C, H, N, S and O Analyser-2400. Photochemical irradiation was conducted under nitrogen atmosphere by a Hanovia 1 L photochemical reactor equipped with a medium pressure mercury arc lamp (298–310 nm). The solvents were purified by standard procedures.^{11,12}

2.1 Typical method for photochemical reactions

A mixture of 5-bromoisatin **1b** (0.81 g; 3.3 mmol) and 3-phenyl-5-isoxazolone **2** (1.07 g; 6.6 mmol) in the molar ratio of 1:2 in dry THF (190 ml) was subjected to UV irradiation in the photochemical reactor under an inert atmosphere for 48 h. The reaction was monitored till complete consumption of 5-bromoisatin. The mixture was then concentrated under vacuum and subjected to column chromatography over silica gel. Two major fractions were obtained. The first fraction from petroleum ether-chloroform (1:3) gave compound **6b** as a dark violet solid (0.66 g, 35%, mp 180°C) whereas another fraction from ethylacetate-methanol (9:1) afforded **7b** as a light brown solid (0.27 g, 15%, mp 199°C).

3. Results and discussion

The reaction of isatin **1a–b** with 3-phenyl-5-isoxazolone **2** is shown in scheme 1. Two products characterized as 4,5-dioxo-3-phenylisoxazolo[5,4-b]benzazepine **6** and 3-phenylisoxazolo[5,4-b]quinoline-4-carboxylic acid **7** were obtained in 35% and 15% yield (scheme 1).

The formation of compound **6** may be explained by the condensation of isatic acid **5** with enolic form of isoxazolone, while compound **7** may arise by the condensation of the

Scheme 1. Photochemical condensation of isatin with 3-phenyl-5-isoxazolone.

keto group of isatin acid **5** with the active methylene group of isoxazolone, followed by cyclization (scheme 2).

The fact that isatin decomposes to isatin acid under photochemical conditions has been supported by molecular modelling using PC PH4 programme. Results of the calculation of the heat of formation have been summarised in table 1.

The photochemical irradiation of isatin derivatives **1a–c** with 2-thiazoline-2-thiol **3** also produced two products which were characterized as 2,4'-dehydro-2-[2'-mercaptothiazolidine]indol-3-one **8** and 2-mercaptothiazolo[5,4-b]quinoline-4-carboxylic acid **9** in 50% and 20% yield respectively (scheme 3).

Scheme 2. Mechanism for the formation of the photo-products **6** and **7**.

Table 1. Heat of formation of indol-2,3-diones and the corresponding isatin acids.

Compound	5-Bromoisatin	5-Bromoisatin acid	5-Nitroisatin	5-Nitroisatin acid
$H_f(\text{kcal/mol}^{-1})$	+ 9.80	−35.52	+ 31.78	−10.19

The formation of **8** may be explained through the intermediacy of diketone resulting from the condensation of isatic acid **5** with 2-thiazoline-2-thiol. The intramolecular nucleophilic attack of the amino group on the carbonyl carbon and subsequent dehydration results in **8** (scheme 4).

Compound **9** (see scheme 3) may arise by the coupling of keto group of isatic acid **5** with methylene of 2-thiazoline-2-thiol followed by cyclisation. Such functionalized thiazolinoquinolines **9** may serve as useful synthons for the total synthesis of naturally occurring quinoline alkaloids.⁹

When the reaction of isatin **1a** was carried out with pyrazolone **4** under photochemical irradiation, 3-methyl-4,5-dioxo-1-phenylpyrazolo [3,4-b]benzazepine **10** was obtained as

Scheme 3. Photo-condensation of isatin with 2-thiazoline-2-thiol.

Scheme 4. Mechanism for the formation of the product **8**.

a major product in 32% yield (scheme 5). Analogous reaction of **1b** with **4** furnished 3-[2'-(1''-carboxy-2''-oxoethyl)-4'-fluorophenyl]-5-fluoroindol-2-one **11** in 42% yield along with minor products **12** and **13** (scheme 6). The compound **10** is formed in the similar fashion as compound **6** whereas **11** may arise by the condensation of amino group of isatic acid with one of the keto group of isatin.

Scheme 5. Photo-condensation reaction of isatin with pyrazolone.

Scheme 6. Photo-condensation reaction of 5-fluoroisatin with pyrazolone.

4. Spectral studies

In IR spectra of products **6a–b**, **8a–c**, **10** and **11** the characteristic absorption band for the imino group was present at 3230–3190 cm⁻¹. The absorption peak expected from the carbonyl group was observed in all the photo-products at 1760–1690 cm⁻¹. The absorption peak for >C=N in quinoline carboxylic acids **7a–b** and **9a–c** was seen at 1610 cm⁻¹. The peak at 2715 cm⁻¹ corresponding to SH group was found in compounds **8a–c** and **9a–c**.

In ¹H NMR spectra of all the photo-products aromatic protons were seen in the normal range i.e. **d** 6.0–8.5 ppm. A singlet around **d** 9.2–10.5 ppm corresponded to imino protons in all the products. Carboxylic proton in **7a–b** and **9a–c** appeared as broad singlet at **d** 11.0 and 12.2 ppm respectively. The ¹⁹F NMR of compound **11** showed two signals at **d** –118.9 and –119.6 ppm indicating that two F atoms are present in this compound and

Table 2. Physical and analytical data of photo-products.

Compd. no.	Physical state	Molecular formula	MP (°C)	Yield (%)	Elemental analyses calculated (found)		
					C	H	N
6b	Violet solid	C ₁₇ H ₉ N ₂ O ₃ Br	180	35	55.28 (55.26)	2.43 (2.40)	7.58 (7.57)
6c	Brick red solid	C ₁₇ H ₉ N ₃ O ₅	190	28	60.89 (60.85)	2.68 (2.64)	12.53 (12.49)
7b	Brown solid	C ₁₇ H ₉ N ₂ O ₃ Br	199	15	55.28 (55.25)	2.43 (2.40)	7.58 (7.56)
7c	Yellowish solid	C ₁₇ H ₉ N ₃ O ₅	110	18	60.89 (60.87)	2.68 (2.64)	12.53 (12.53)
8a	Orange solid	C ₁₁ H ₈ N ₂ OS ₂	190	50	53.22 (53.18)	3.22 (3.19)	11.29 (11.22)
8b	Red solid	C ₁₁ H ₇ N ₂ OS ₂ Br	230	52	40.36 (40.32)	2.14 (2.11)	8.56 (8.48)
8c	Yellow solid	C ₁₁ H ₇ N ₃ O ₃ S ₂	240	45	45.05 (45.00)	2.38 (2.32)	14.32 (14.26)
9a	Yellow solid	C ₁₁ H ₆ N ₂ O ₂ S ₂	180	18	50.38 (50.32)	2.29 (2.23)	10.68 (10.68)
9b	Red solid	C ₁₁ H ₅ N ₂ O ₂ S ₂ Br	210	15	38.72 (38.70)	1.46 (1.41)	8.21 (8.19)
9c	Yellow solid	C ₁₁ H ₅ N ₃ O ₄ S ₂	235	20	42.99 (42.94)	1.62 (1.57)	13.6 (13.4)
10	Orange crystals	C ₁₈ H ₁₃ N ₃ O ₂	186	32	71.28 (71.35)	4.29 (4.20)	13.86 (13.79)
11	Yellow	C ₁₈ H ₈ N ₂ O ₄ F ₂	206	42	58.18 (58.07)	2.42 (2.33)	8.48 (8.41)
12	White crystals	C ₂₈ H ₂₂ N ₅ O ₃ F	168	13	67.87 (67.78)	4.44 (4.52)	14.14 (14.21)
13	Violet solid	C ₁₈ H ₁₂ N ₃ O ₂ F	234	7	67.29 (67.21)	3.72 (3.67)	13.08 (13.01)

Table 3. Spectral data of photo-condensation products.

Compd. no.	IR (cm ⁻¹)	¹ H NMR (d ppm)
6b	3230 (<i>s</i> , NH), 1760, 1740 (a -diketone)	7.0 (<i>d</i> , <i>J</i> = 6.0 Hz, H-9), 7.3–7.4 (<i>m</i> , 3-C ₆ H ₅), 8.1 (<i>dd</i> , <i>J</i> ₁ = 7.0 Hz, <i>J</i> ₂ = 2.5 Hz, H-8), 8.23 (<i>d</i> , <i>J</i> = 2.5 Hz, H-6), 9.8 (<i>s</i> , NH)
6c	3228 (<i>s</i> , NH), 1758, 1740 (a -diketone)	6.8 (<i>d</i> , <i>J</i> = 6.0 Hz, H-9), 7.4 (<i>m</i> , 3-C ₆ H ₅), 8.15 (<i>dd</i> , <i>J</i> ₁ = 7.0 Hz, <i>J</i> ₂ = 2.5 Hz, H-8), 8.20 (<i>d</i> , <i>J</i> = 2.5 Hz, H-6), 9.9 (<i>s</i> , NH)
7b	3590 (<i>s</i> , <i>br</i> , OH), 1690 (<i>s</i> , >C=O), 1610 (<i>s</i> , C=N)	6.97 (<i>d</i> , <i>J</i> = 7.0 Hz, H-8), 7.44 (<i>m</i> , 3-C ₆ H ₅), 8.11 (<i>dd</i> , <i>J</i> ₁ = 7.0 Hz, <i>J</i> ₂ = 2.0 Hz, H-7), 8.2 (<i>d</i> , <i>J</i> = 2.0 Hz, H-5)), 9.9 (<i>s</i> , NH)
7c	3600 (<i>s</i> , <i>br</i> , OH), 1710 (<i>s</i> , >C=O), 1610 (<i>s</i> , C=N)	6.99 (<i>d</i> , <i>J</i> = 6.5 Hz, H-8), 7.34–7.45 (<i>m</i> , 3-C ₆ H ₅), 8.20 (<i>dd</i> , <i>J</i> ₁ = 6.5 Hz, <i>J</i> ₂ = 2.0 Hz, H-7), 8.25 (<i>d</i> , <i>J</i> = 2.0 Hz, H-5)), 11.35 (<i>s</i> , COOH)
8a	3320 (<i>s</i> , NH), 2910 (<i>sh</i> , CH ₂), 2715 (<i>s</i> , SH), 1690 (<i>s</i> , >C=O)	3.70 (<i>s</i> , CH ₂), 6.97–8.2 (<i>m</i> , Ar-H), 8.50 (<i>s</i> , NH), 11.1 (<i>s</i> , SH)
8b	3290 (<i>s</i> , NH), 2970 (<i>sh</i> , CH ₂), 2735 (<i>s</i> , SH), 1710 (<i>s</i> , >C=O)	3.65 (<i>s</i> , CH ₂), 6.90–8.4 (<i>m</i> , Ar-H), 9.3 (<i>s</i> , NH), 11.0 (<i>s</i> , SH)
8c	3350 (<i>s</i> , NH), 2980 (<i>sh</i> , CH ₂), 2785 (<i>s</i> , SH), 1730 (<i>s</i> , >C=O), 1610 (<i>m</i> , C=N), 1575, 1360 (<i>m</i> , NO ₂)	3.72 (<i>s</i> , CH ₂), 6.83–8.12 (<i>m</i> , Ar-H), 9.25 (<i>s</i> , NH), 11.4 (<i>s</i> , SH)
9a	3560 (<i>s</i> , OH), 2810 (<i>s</i> , SH), 1760 (<i>s</i> , >C=O), 1630 (C=N)	7.3–8.81 (<i>m</i> , Ar-H), 11.2 (<i>s</i> , SH), 12.2 (<i>s</i> , COOH)
9b	3520 (<i>s</i> , OH), 2800 (<i>s</i> , SH), 1740 (<i>s</i> , >C=O), 1610 (C=N)	7.4–8.5 (<i>m</i> , Ar-H), 11.0 (<i>s</i> , SH), 12.5 (<i>s</i> , COOH)
9c	3550 (<i>s</i> , OH), 2790 (<i>s</i> , SH), 1730 (<i>s</i> , >C=O), 1620 (C=N), 1570, 1400 (<i>m</i> , NO ₂)	7.35–8.21 (<i>m</i> , Ar-H), 11.4 (<i>s</i> , SH), 12.25 (<i>s</i> , COOH)
10	3230 (<i>s</i> , NH), 1760, 1740 (<i>s</i> , >C=O), 1630 (<i>m</i> , C=N)	2.1 (<i>s</i> , CH ₃), 6.5–7.2 (<i>m</i> , Ar-H), 9.35 (<i>s</i> , NH)
11	3480 (<i>s</i> , OH), 3180 (<i>s</i> , NH), 1770, 1750, 1720 (<i>s</i> , C=O)	7.15–8.32 (<i>m</i> , Ar-H), 9.4 (<i>s</i> , NH), 11.0 (<i>s</i> , COOH)
12	3350 (<i>s</i> , NH), 1730, 1700, 1690 (<i>s</i> , >C=O), 1630 (<i>m</i> , C=N)	2.1 (<i>s</i> , 2 × CH ₃), 3.8 (<i>m</i> , 2 × CH), 6.8–7.4 (<i>m</i> , Ar-H), 9.3 (<i>s</i> , NH)
13	3260–3220 (<i>s</i> , NH), 1700, 1680 (>C=O), 1615 (C=C)	1.9 (<i>s</i> , CH ₃), 6.8–7.4 (<i>m</i> , Ar-H), 9.3 (<i>s</i> , NH)

are in different environments. A broad hump at **d** 11.1 for SH proton was present in **8a–c** and **9a–c**. In ¹³C NMR of the product **6a**, the carbonyl carbon appeared at **d** 181.9, C-2' appeared at **d** 158.3, benzenoid carbons appeared in the range of **d** 147.85–126.3, olefinic carbons (C-2 and C-5') appeared at **d** 126.3 and methylene carbon appeared at **d** 112.8 ppm. In ¹H NMR of compounds **12** and **13**, signals corresponding to the active methylene protons of pyrazolone **4** were absent in the region of **d** 4.14 whereas methyl, aromatic and imino protons were present in their required region. Additional evidence was obtained from the mass spectra of **10**, **11**, **12** and **13** in which *M*⁺ peaks were seen at 303 (8%), 303

Table 4. Antimicrobial activity of the photo-products **8a–c** and **9a–c**.

Compd. no.	Zone of inhibition in mm (activity index)				
	<i>E. coli</i>	<i>S. facaelus</i>	<i>R. solani</i>	<i>F. oxysporium</i>	<i>F. solani</i>
8a	8.9 (0.88)	9.4 (0.95)	10.2 (1.02)	8.4 (0.84)	7.9 (0.78)
8b	11.2 (1.12)	9.8 (1.02)	12.6 (1.04)	9.8 (0.92)	10.6 (1.06)
8c	13.4 (1.10)	11.6 (1.12)	12.6 (1.02)	13.0 (1.13)	12.2 (1.12)
9a	10.0 (1.00)	9.1 (0.98)	9.8 (1.07)	12.2 (1.05)	11.0 (1.10)
9b	10.5 (1.05)	9.8 (0.98)	10.0 (1.02)	12.0 (1.06)	12.6 (1.08)
9c	11.5 (1.15)	10.5 (1.05)	11.4 (1.12)	12.5 (1.20)	13.5 (1.20)

Activity index = inhibition zone of the sample/inhibition zone of the standard

(20%), 495 (12%) and 321 (52%), respectively. All these assignments are in harmony with the proposed structures (table 3), which structures were further established by elemental analyses (table 2).

5. Antimicrobial activity

Some of the synthesized compounds **8a–c** and **9a–c** were evaluated for their antimicrobial activities at a concentration of 100 μ g/disc in agar media. The method adopted for the estimation of the antimicrobial activity is the paper disc diffusion method of AW Bauer *et al*¹⁰. In this method the compound is allowed to diffuse through a solid medium so that a gradient is established. The test bacterium or fungus is seeded on the medium and its sensitivity to the compound is determined from the inhibition of the growth. *Streptomycin* and *Mycostatin* were used as the reference compounds for antibacterial and antifungal activities. The test organisms were *E. coli*, *S. facaelus* (bacteria), *R. solani*, *F. oxysporium* and *F. solani* (fungi) and the results are summarized in table 4.

6. Conclusions

- On the basis of the calculation of the heat of formation (table 1) it may be concluded that isatic acid is thermodynamically more stable than the corresponding isatin.
- Under photochemical conditions, isatin decomposes to isatic acid (2-amino-phenyl-glyoxalic acid) whereas there is no such decomposition under thermal conditions.
- There is significant enolization of isoxazolone and pyrazolone under photochemical conditions and this fact is supported by the predominant formation of **6a–b** and **10**.
- From table 3, it may be concluded that some of the screened compounds were highly active against the test microorganisms.

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