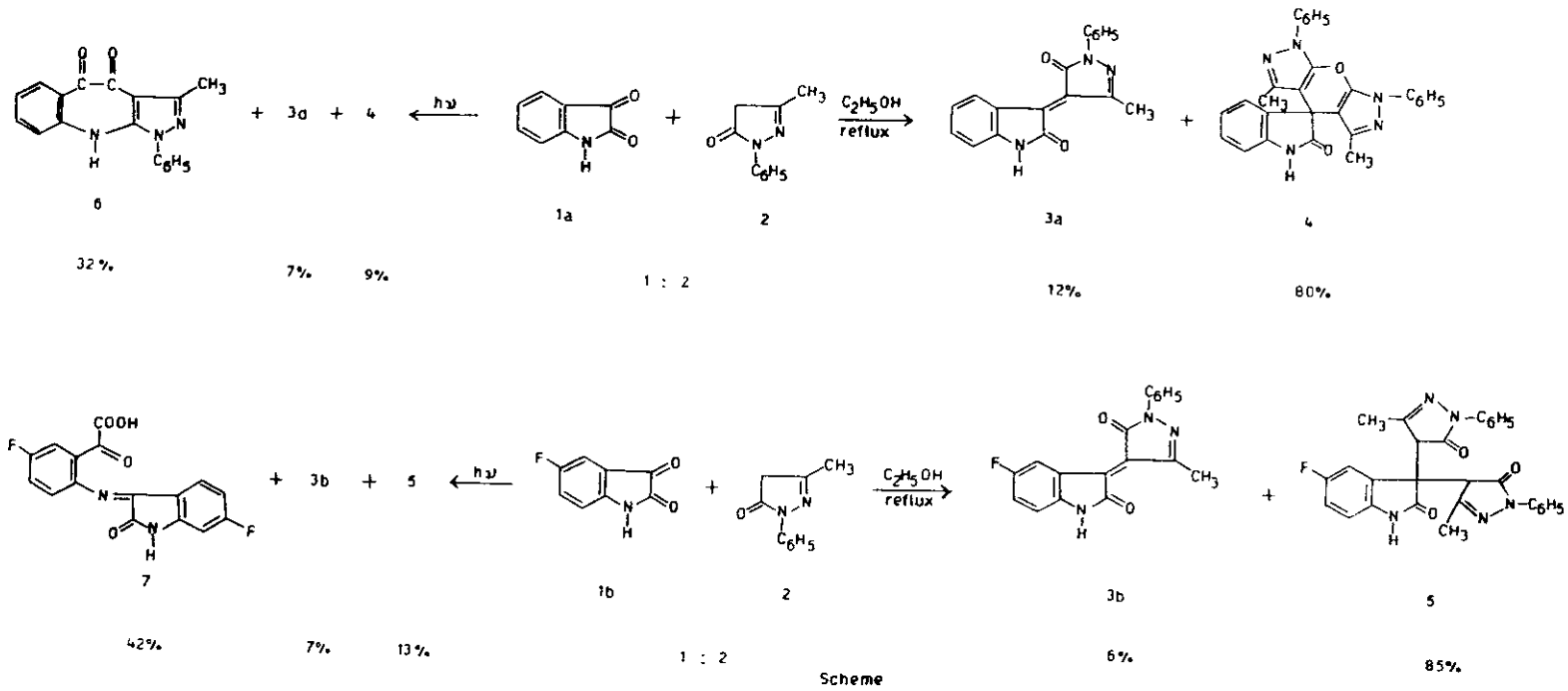
THERMAL AND PHOTOCHEMICAL INVESTIGATION OF THE REACTION OF INDOLE-2,3-DIONE WITH PYRAZOLONE

Krishna C. Joshi, Ramchand T. Pardasani*, Anshu Dandia, and
Sunita Bhagat (nee Baweja)
Department of Chemistry, University of Rajasthan, Jaipur-302004, India

Abstract - Some novel reactions of indole-2,3-dione (1) with pyrazolone (2) under thermal and photochemical conditions have been studied. Under thermal conditions, a variety of novel compounds viz. 1,3-dihydro-3-[(3'-methyl-5'-oxo-1'-phenylpyrazolidene)]-2H-indol-2-one (3), 3,5-dimethyl-1,7-diphenylspiro-[dipyrazolo(3,4-b;4,3-e)pyran-4(4H),3'(3H)indol]-2'[1'H]-one (4), and 5-fluoro-3,3-bis(3'-methyl-5'-oxo-1'-phenylpyrazol-4'-yl)indol-2[1H]-one(5) were obtained. The photochemical irradiation afforded other compounds like 3-methyl-4,5-dioxo-1-phenylpyrazolo[3,4-b]benzapine (6), and 3-[2'-(1"-carboxy-2"-oxoethyl)-4'-fluoro-phenyl]-5-fluoroindol-2-one (7) in addition to thermal products (3) and (4) or (5).

In continuation to our interest in the chemistry of indole-2,3-dione derivatives[1,2] and synthesis of spiroindolines,[3,4] we have recently reported that the reaction of indole-2,3-dione with 1,3-cyclohexanedione affords spiro compounds.[5] We also noted that the reaction of indole-2,3,-dione (1) with pyrazolone (2) has not been explored extensively. There is only one report in the literature[6] concerning this reaction under Pfitzinger conditions and reporting the formation of nonspiro compounds like pyrazoloquinolinecarboxylic acids. We were interested in this reaction as a wide spectrum of biological activities are associated with indole derivatives[7-9] and besides, pyrazole nucleus is also well recognised for its pharmacological properties.[10,11] Thus, a system incorporating these two moieties is likely to result in the formation of some interesting bioactive compounds. Therefore, we have investigated the reaction of indole-2,3-dione (isatin) (1) with pyrazolone (2) under thermal conditions. Besides, keeping in view the observations of Haucke *et al.*[12] that under photochemical conditions, isatin may react through various intermediates, and considering that pyrazolone also exists in different tautomeric forms and may also react in more than one manner, we were prompted to explore this reaction under photochemical conditions as well.

The reaction of isatin (1a and 1b) with pyrazolone (2) was carried out in the molar ratio 1:2 in refluxing ethanol. The reaction of isatin (1a) with pyrazolone (2) afforded compounds 1,3-dihydro-3-[(3'-methyl-5'-oxo-1'-phenylpyrazolidine)]-2H-indol-2-one (3a, 12% yield) and


6
32%
3a
7%
4
9%
hν
1a
2
1 : 2
C2H5OH
reflux
3a
12%
4
80%
7
42%
3b
7%
5
13%
hν
1b
2
1 : 2
C2H5OH
reflux
3b
6%
5
85%

Scheme

spiro compound 3,5-dimethyl-1,7-diphenylspiro[dipyrazolo(3,4-b;4,3-e)pyran-4(4H),3'(3H)indol]-2'[1'H]-one (4, 80%). Isatin (1b) with pyrazolone (2) gave compounds (3b, 6%) and 5-fluoro-3,3-bis(3'-methyl-5'-oxo-1'-phenylpyrazol-4'-yl)indol-2[1H]-one (5, 85%) (Scheme).

The formation of compounds (3) and (5) may be explained by reaction of isatin with active methylene group of pyrazolone in 1:1 or 1:2 equivalents whereas compound (4) may arise by cyclisation of enol form of compound (5). To check the reactivity and enolisation of pyrazolene (2), we have carried out the reactions of isatin (1a and 1b) with pyrazolone (2) in 1:1 molar ratio under neutral conditions and it gave compounds (3a and 3b) exclusively in 80% yield supporting the existence of pyrazolone in the keto form. Thus, it is evident from these observations that under neutral conditions, (i) there is no decomposition of isatin to isatic acid (2-aminophenylglyoxalic acid), and (ii) there is no significant enolisation of pyrazolone as reactive methylene group takes part in the reaction. These observations are in contrast to earlier report by Seshadri *et al.*[6] whereby weak basic conditions (ph 10-11) are to be requird to prevent the enolisation of pyrazolone. Furthermore, these workers have reported the formation of pyrazoloquinolinecarboxylic acids instead of compounds (3)-(5) as observed by us. The structure of compounds (3)-(5) was unambiguously established by their special data. In the ir spectrum of compounds (3), characteristic absorption bands were observed at 1710 and 1680 cm^{-1}, assignable to two conjugated carbonyl groups. The exocyclic C=C absorption band was observed at 1620 cm^{-1}. Regarding the stereochemistry of compounds (3a) and (3b), it appears from making models that both these compounds would be more stable in the *anti* form as shown in the scheme. Compound (4) displayed only one carbonyl absorption at 1680 cm^{-1} (NHCO) along with (NH) absorption in the region 3320-3150 cm^{-1} suggesting the involvement of 3-carbonyl group of isatin in the reaction. The exocyclic C=C absorption band was not observed and instead, pyran-ether linkage was noticed at 1180 cm^{-1}. Compound (5), showed three distinct carbonyl absorptions at 1730, 1700, 1690 cm^{-1} along with (NH) absorption at 3350 cm^{-1} indicating the presence of two pyrazolone units. In the ^1H nmr spectrum of all these products (3-5), signals corresponding to the active methylene protons of pyrazolone (2) were absent in the region δ 4.14, whereas methyl, aromatic, and imino protons were present in the required regions (Table II). The structure of all these products was further established by elemental analyses (Table I) as well as by appearance of molecular ion peak (M^+) of compound (3a) : m/z 303 (100%); compound (4) : m/z 459 (18%); compound (5) : m/z 495 (12%) in their mass spectra.

When the same reaction was carried out under photochemical irradiation using isatin (1a) and pyrazolone (2), the thermal products (3) and (4) were obtained only in small amounts, 7%

Table I

Physical Data of the Various Products Obtained by Reaction of Isatin (1) with Pyrazolone (2)

Compound	Nature	Yield %	mp(°C)	Molecular formula	m/z M^+ (%)	Analysis					
						Calcd			Found		
						C	H	N	C	H	N
Thermal-products											
3a	Violet solid	12	218	$C_{18}H_{13}N_2O_2$	303(100)	71.28	4.29	13.86	71.37	4.26	13.93
3b	Violet solid	6	234	$C_{18}H_{12}N_3O_2F$	321(52)	67.29	3.72	13.08	67.21	3.67	13.01
4	White powder	80	178	$C_{18}H_{21}N_5O_2$	459(18)	73.20	4.57	11.57	73.29	4.49	11.65
5	White crystals	85	168	$C_{28}H_{22}N_5O_3F$	495(12)	67.87	4.44	14.14	67.78	4.52	14.21
Photo-products											
6	Orange crystals	32	186	$C_{18}H_{13}N_3O_2$	303(8)	71.28	4.29	13.86	71.35	4.20	13.79
7	Yellow	42	206	$C_{18}H_8N_2O_4F_2$	303(20)	58.18	2.42	8.48	58.07	2.33	8.41

Table II

Spectral Data of the Various Products Obtained by Reaction of Isatin (1) with Pyrazolone (2)

Compound	Ir(KBr, cm^{-1})			^1H Nmr (δ ppm from TMS)			
	NH	C=O	Others	CH_3	Ar-H	NH	Others
Thermal-products							
3a	3250-3220	1710,1680	1620[a]	1.9(3H,s)	6.7-7.3(9H,m)	9.3(1H,s)	-
3b	3260-3220	1700,1680	1615[a]	1.9(3H,s)	6.8-7.4	9.3(1H,s)	-
4	3220-3150	1680	1180[b]	2.1(6H,s)	6.9-7.6(14H,m)	9.1(1H,s)	-
5	3350	1730,1700, 1690	1630[c]	2.1(6H,s)	6.8-7.4(13H,m)	9.3(1H,s)	3.8 (2XC-H,m)
Photo-products							
6	3230	1760,1740	1630[c]	2.1(3H,s)	7.2(9H,m)	9.35(1H,s)	-
7	3180	1750,1720	1630[c]	-	7.15(6H,m)	9.4(1H,s)	10.3(br,OH)

[a] C=C, [b] pyran-ether linkage, [c] C=N

and 9% respectively; identified by comparison with compounds obtained in thermal reaction. The major product, however, was characterised as 3-methyl-4,5-dioxo-1-phenylpyrazolo[3,4-b]benzapine (6) in 32% yield. The reaction of isatin (1) with pyrazolone (2) on irradiation produced thermal products (3b) and (5) in 7% and 13% respectively whereas the major compound in this case was identified as 3-[2'-(1"-carboxy-2"-oxoethyl)-4'-fluorophenyl]-5-fluoro-indol-2-one (7) in 42% yield. The formation of compound (6) seems to occur from the reaction of isatic acid[12] resulting from the decomposition of isatin (1) and the enolic form of pyrazolone (2) and hence it may be suggested that there is greater enolisation of pyrazolone under photochemical conditions. The structure of all the photo products was also ascertained by their spectral data.

Compound (6) displayed characteristic infrared absorption bands at 3230, 1760, and 1740 cm^{-1} expected from an imino group and carbonyl groups of an α-diketone respectively. In the ^1H nmr spectrum, a singlet was observed at δ 2.1 for the methyl protons and a multiplet at δ 7.2 for aromatic protons. A singlet at δ 9.35 was associated with imino proton. Further, in the mass spectrum, the molecular ion peak was observed at m/z 303 (8%). Compound (7) gave infrared absorption band at 3480 (COOH), 3180 (NH) and 1770, 1750, 1720 (C=O) cm^{-1}. The ^1H nmr spectrum showed only aromatic and imino protons at δ 7.15 and δ 9.4 ppm respectively whereas the region between δ 1.5-2.5 ppm was clear, thereby indicating that methyl protons are absent which means that pyrazolone unit is not involved. Further, in its mass spectrum, the molecular ion peak was observed at m/z 330 (29%) suggesting the presence of even numbered nitrogen atoms. Moreover, the ^{19}F nmr spectrum showed two signals at δ -118.9 and δ — 119.6 ppm indicating that two fluorine atoms are present in this compound and in different environment. Molecular model indicates that this compound also would be more stable in the anti form as depicted in the scheme. All these photoproducts also gave satisfactory elemental analyses (Table I) confirming the assigned structure.

EXPERIMENTAL

Melting points were determined in open glass capillary and are uncorrected. The ir spectra were recorded on Perkin-Elmer model 577 in KBr pellets. The ^1H nmr spectra were recorded on JEOL FX-900 model at 89.55 MHz with TMS as internal standard. Chemical shifts are given in δ ppm. Mass spectra were recorded Kratos 30 and 50 mass spectrometers. Elemental analyses were performed by Coleman C, H, and N analyser-29. Photochemical irradiation was conducted under nitrogen atmosphere by Hanovia 11 Photochemical reactor equipped with medium pressure arc. All compounds were homogeneous on tlc in various solvent systems.

5-Fluoroindole-2,3-dione was prepared by literature method.[13]

General Procedure for the Thermal Reaction of Isatin (1) with Pyrazolone (2) in the Molar Ratio 1:2 - A mixture of isatin (0.01 mol) and pyrazolone (3.48 g, 0.02 mol) in absolute ethanol (100 ml) was refluxed for 6 h. On cooling, a coloured product separated which was filtered. Tlc of the filtrate indicated only the presence of unreacted reactants and hence was rejected, whereas tlc of the crude solid showed two distinct spots. The crude solid was trituated with benzene, and from benzene solution a violet coloured compound was obtained in small amount (6-12% yield) and characterised as 1,3-dihydro-3-[(3'-methyl-5'-oxo-1'-phenyl-pyrazolidine)]-2H-indol-2-one (3a, 3b). The benzene insoluble portion was further recrystallised from ethanol and afforded a white crystalline solid in 80% yield. It was characterised as 3,5-dimethyl-1,7-diphenylspiro[dipyrazolo[3,4-b;4,3-e]pyran-4(4H),3'(3H)indol]-2'[1'H]-one (4) in case of the reaction of isatin (1a) with pyrazolone (2). However, in case of the reaction of isatin (1b) with pyrazolone (2), the ethanol recrystallised product was identified as 5-fluoro-3,3-bis-(3'-methyl-5'-oxo-1'-phenylpyrazol-4'-yl)indol-2[1H]-one (5).

General Procedure for the Photochemical Reaction of Isatin (1) with Pyrazolone (2) in the Molar Ratio 1:2 - A mixture of isatin (0.01 mol) and pyrazolone (3.48 g, 0.02 mol) in dry tetrahydrofuran (150 ml) was irradiated with ultraviolet light of medium pressure arc with constant stirring at room temperature under nitrogen atmosphere for 20 h. The progress of the reaction was monitored through tlc. After completion of the reaction, as indicated by disappearance of isatin spot in tlc, a white solid mass separated which was filtered. Both, the white powder and the filtrate showed several spots on tlc and therefore, were subjected to column chromatography separately. The white powder was subjected to column chromatography over silica gel and eluted with solvents of rising polarity. The first compound was separated from fraction benzene : ethyl acetate (4:1) as an orange crystalline powder identified as 3-methyl-4,5-dioxo-1-phenylpyrazolo[3,4-b]benzapine (6) (32%, mp 186°C) in case of isatin (1a). However, in case of isatin (1b), compound (7) was obtained from the fraction benzene:ethyl acetate (1:4) as yellow brown crystals and characterised as 3-[2'-(1"-carboxy-2"-oxoethyl)-4'fluorophenyl]-5-fluoroindol-2-one (7), in 42% yield, mp 206°C.

The second compound was obtained from the fraction ethyl acetate:methanol (4:1) as white crystalline powder in 10% yield, and identified as thermal product (4) or (5) in case of isatin (1a) or (1b) respectively by comparison with authentic samples and spectral studies. The filtrate, was concentrated under vacuo to afford a yellow-brown gum and subjected to

column chromatography by using solvents of increasing polarity.

The fraction from benzene:ethyl acetate (1:1) was identified as thermal product (3) in 7% yield, mp 218°C, on the basis of mixed mp and spectral studies.

The physical and spectral data of all the above products (3-7) are summarised in Tables I and II.

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