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Microwave induced diastereoselective synthesis of spiro[indole-oxiranes] and their conversion to spiro[indole-pyrazoles]

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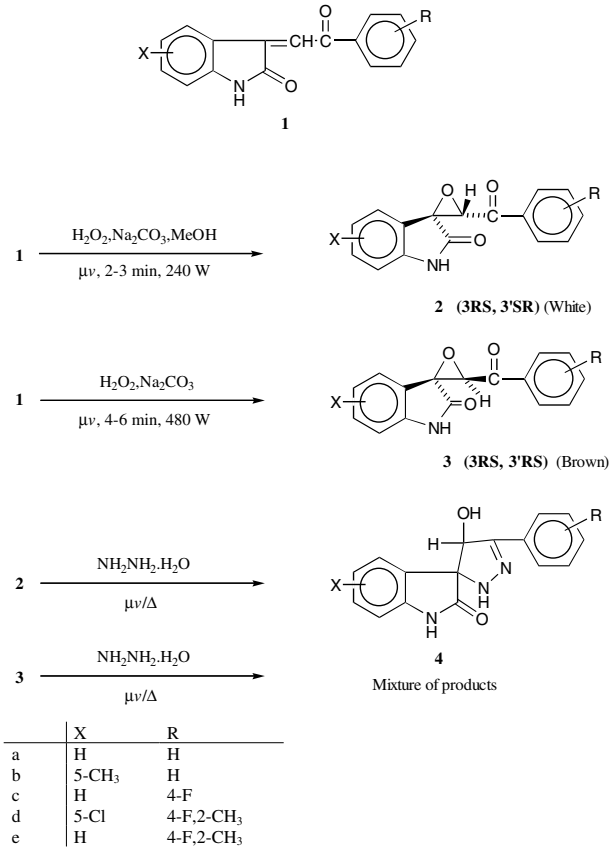
The microwave induced diastereoselective synthesis of spiro[3*H*-indole-3,2′-oxiranes]-3′-benzoyl-2 (1*H*)-one is reported. Epoxidation of 3-aroylmethylene indole-2-one **1** with alkaline H_2O_2 under microwave irradiation in an open vessel under controlled conditions yields a diastereomeric pair of spiro[3*H*-indole-3,2′-oxiranes]-3′-benzoyl-2 (1*H*) ones **2** and **3** in 65–85% yield. The stereoselectivity depends upon the reaction time and power output. The spiro[indole-pyrazoles] **4** have been synthesised by the reaction of **2** with hydrazine hydrate. Under the same condition **3** gave the mixture of products. All synthesised compounds have been screened *in vitro* for their antifungal activity against *Rhizoctonia solani*, *Fusarium oxysporum* and *Collectotrichum capsici* and antitubercular activity against *Mycobacterium tuberculosis*.

1. Introduction

Microwave induced reaction rate enhancement is just a decade old. The use of a domestic microwave oven as a convenient source of energy in organic synthesis is a well established procedure [1, 2]. Rapid heating of reactants can be achieved, resulting in a dramatic reduction in reaction times with improved yield, reactivity and selectivity [3, 4].
Research on spiro indoles is of current interest, due to their exceptional biological activity [5–8]. In continuation of our work on microwave irradiations for the synthesis of bioactive spiro heterocycles containing an indole ring system [9–13], we have now investigated another system with an oxiran ring at the 3-position of the 2-indoline skeleton. A number of spiro[indole-oxiranes] have a wide range of biological activities [14–17]. Optically active epoxides are useful as neoplasm inhibitors, antibiotics, insect pheromones, etc. [18].

Scheme



	X	R
a	H	H
b	5-CH_3	H
c	H	4-F
d	5-Cl	4-F,2-CH_3
e	H	4-F,2-CH_3

2. Investigations, results and discussion

2.1. Synthesis and properties of the compounds

In contrast to earlier reports [19, 20], the reinvestigation of the reaction of 3-aroylmethylene indole-2-one (**1**) with alkaline H_2O_2 under microwave irradiation afforded two diastereomers **2** and **3** of spiro [3*H*-indole-3,2′-oxiran]-3′benzoyl-2(1*H*) one depending upon the reaction time and power output. These reactions reflect kinetic/thermodynamic preferences for diastereoselectivity. Studying oxiran formation in a microwave oven we have noticed that irradiating the reaction mixture for 2 min at 240 W lead to the preferential formation of **2** in 72–80% yield. While irradiation at 480 W for 4–6 min gave compound **3** exclusively in 76–80% yield.
The stereoselectivity has been controlled by simply modifying the microwave power level. At high power levels, isomer **3** is formed, whereas at lower power levels isomer **2** is obtained exclusively. On the basis of these observations, it is suggested that the effect of heating rate on the reaction leads to this selectivity.
The structural identification of compounds **2** and **3** is based on their IR, ^{1}H NMR and MS studies. IR spectrum of compounds **2** and **3** showed characteristic absorption bands at 1200–1250 and 1020–1080 cm^{-1} indicating the presence of an oxirane ring system in both. The two C=O absorption bands appeared at 1700–1725 and 1670–1685 cm^{-1}, while NH stretching was observed at 3190–3320 cm^{-1}. However, they differ in the finger print region. The PMR spectra of these diastereomers were not identical, as different chemical shifts have been observed for the diasterotopic proton. The ^{1}H NMR spectrum of **2c** showed characteristic signals for NH at δ 9.22 and oxirane methine proton at 4.92 ppm, while in case of **3c** signals for NH appeared at δ 8.9 and methine proton at 4.74 ppm. Aromatic protons appeared at δ 7.1–8.27 ppm.

Table 1: Physical and structural characteristics of spiro[3H-indole-3,2′-oxiran]-3′-benzoyl-2(1H)ones (2, 3) and 2′,4′-dihydro-5′-aryl-4′-hydroxy-spiro[3H-indole-3,3′-(3H)-pyrazol]-2(1H)-ones (4)

Compd.	Reaction time (min)	Yield (%)	Mp (°C)	^{1}H NMR (δ, ppm)	IR (cm^{-1})	MS: m/z (% relative intensity)	Molecular Formula
2a	2	82/68*	170/166*	4.95 (s, 1 H, CH) 7.0–8.17 (m, 9 H, Ar-H) 9.17 (br, s, 1 H, NH#)	3200 (NH) 1700–1670 (2 × C=O) 1230 and 1030 (oxirane ring)		$C_{16}H_{11}NO_3$
2b	2	80	163	2.31 (s, 3 H, CH_3), 5.01 (s, 1 H, CH) 7.2–8.25 (m, 8 H, Ar-H) 9.20 (br, s, 1 H, NH#)	3190 (NH) 1715–1685 (2 × C=O) 1225–1035 (oxirane ring)		$C_{17}H_{13}NO_3$
2c	2	79	165	4.92 (s, 1 H, CH) 7.1–8.27 (m, 8 H, Ar-H) 9.22 (br, s, 1 H, NH#)	3200 (NH), 1700–1675 (2 × C=O) 1240–1025 (oxirane ring)	283 (M^+, 196), 225 (78.6), 226 (30), 160 (29), 123 (100), 104 (5), 105 (7), 96 (50.5), 77 (20.6)	$C_{16}H_{10}FNO_3$
2d	2	75	171(d)	2.34 (s, 3 H, CH_3), 4.90 (s, 1 H, CH), 7.0–8.15 (m, 6 H, Ar-H), 9.15 (br, s, 1 H, NH#)	3150 (NH), 1715–1670 (2 × C=O) 1230–1035 (oxirane ring)		$C_{17}H_{11}ClFNO_3$
2e	2	78	174	2.36 (s, 3 H, CH_3), 4.98 (s, 1 H, CH), 7.1–8.17 (m, 7 H, Ar-H), 9.18 (br, s, 1 H, NH#)	3180 (NH), 1710–1675 (2 × C=O) 1240–1030 (oxirane ring)	297 (M^+, 26), 269 (53), 240 (30), 161 (29), 137 (100), 132 (10), 104 (15), 105 (6), 109 (53), 77 (12)	$C_{17}H_{12}FNO_3$
3a	4	76	198*	4.75 (s, 1 H, CH), 7.0–8.0 (m, 9 H, Ar-H) 8.75 (br, s, 1 H, NH)	3200 (NH), 1705–1670 (2 × C=O) 1220–1040 (oxirane ring)		$C_{16}H_{11}NO_3$
3b	5	70	195	2.30 (s, 3 H, CH_3), 4.81 (s, 1 H, CH) 7.4–8.52 (m, 8 H, Ar-H), 8.52 (br, s, 1 H, NH#)	3200 (NH), 1710–1680 (2 × C=O) 1220–1040 (oxirane ring)		$C_{17}H_{13}NO_3$
3c	6	66	186	4.74 (s, 1 H, CH), 7.0–8.2 (m, 8 H, Ar-H) 8.9 (br, s, 1 H, NH#)	3200 (NH), 1720–1680 (2 × C=O) 1230–1050 (oxirane ring)		$C_{16}H_{10}FNO_3$
3d	6	79	240 (d)	2.40 (s, 3 H, CH_3), 4.72 (s, 1 H, CH), 7.2–8.19 (m, 6 H, Ar-H), 8.82 (br, s, 1 H, NH#)	3220 (NH), 1720–1670 (2 × C=O) 1250–1080 (oxirane ring)		$C_{17}H_{11}ClFNO_3$
3e	5	74	202 (d)	2.54 (s, 3 H, CH_3), 4.74 (s, 1 H, CH) 7.3–8.21 (m, 7 H, Ar-H), 8.84 (br, s, 1H NH#)	3210 (NH), 1722–1660 (2 × C=O) 1255–1090 (oxirane ring)		$C_{17}H_{12}FNO_3$
4a	10	77	240	5.6 (s, 1 H, CH), 6.23 (br, 1 H, OH#) 6.8–7.9 (m, 9 H, Ar-H) 8.03 (s, 1 H, NH# pyrazole), 9.20 (s, 1 H, NH# indole)	3410–3390 (OH), 3320–3150 (two NH) 1685 (C=O) 1600 (C=N)	279 (M^+, 53.3), 251 (12.3), 222 (25.9), 204 (17.7), 147 (73.5), 134 (35.5), 104 (65.4), 77 (100), 63 (30.6), 50 (38.5)	$C_{16}H_{13}N_3O_2$
4b	9	80	220	2.24 (s, 3 H, CH_3), 5.54 (s, 1 H, CH) 6.22 (br, 1 H, OH#) 6.7–7.85 (m, 8 H, Ar-H), 8.23 (s, 1 H, NH# pyrazole), 9.28 (s, 1 H, NH# indole)	3405–3395 (OH), 3330–3150 (two NH), 1690 (C=O), 1620 (C=N)		$C_{17}H_{15}N_3O_2$
4c	12	78	280	5.42 (s,1H, CH), 6.21 (br, 1 H, OH) 6.8–7.9 (m, 8 H, Ar-H), 8.1 (s, 1 H, NH# pyrazole), 9.20 (s, 1 H, NH# indole)	3420–3390 (OH) 3320–3145 (two NH) 1690 (C=O), 1610 (C=N)		$C_{16}H_{12}FN_3O_2$
4d	10	73	260	2.34 (s, 3 H, CH_3), 5.44 (s, 1 H, CH), 6.23 (br, 1 H, OH#), 6.7–7.7 (m, 6 H, Ar-H), 8.2 (s, 1 H, NH# pyrazole), 9.31 (s, 1 H, NH#- indole)	3410–3495 (OH), 3320–3140 (two NH), 1700 (C=O), 1610 (C=N)		$C_{17}H_{13}ClFN_3O_2$

Table 1: (contd.)

Compd.	Reaction time (min)	Yield (%)	Mp (°C)	^{1}H NMR (δ, ppm)	IR (cm^{-1})	MS: m/z (% relative intensity)	Molecular Formula
4e	9	76	>360	2.38 (s, 3 H, CH_3), 5.48 (s, 1 H, CH), 6.31 (br, 1 H, OH#), 6.5–7.6 (m, 7 H, Ar-H), 8.4 (s, 1 H, NH# pyrazole), 9.25 (s, 1 H, NH# indole)	3400–3395 (OH), 3325–3130 (two NH), 1705 (C=O), 1615 (C=N)		$C_{17}H_{14}FN_3O_2$

* **2a/3a** – Lit. [19] (Stereochemistry of reported compound not studied); ** **4a** – Lit. [19], m.p. 247 °C; d = decomposed
# Both –NH and –OH are D_2O exchangeable
The microanalysis were in satisfactory agreement with the calculated value : C ± 0.35, N ± 0.25.

The assignment of the NH proton was confirmed by its disappearance on deuteration and the molecular ion peak at m/z 283 in the MS of both **2c** and **3c** established their molecular weights.

The structure of the two isomers has been confirmed on the basis of the fact that in case of **2**, the oxirane proton lies in the deshielding zone of the phenyl ring of indole moiety, hence it would be expected to be more deshielded than that of the 3-isomer. Accordingly the (3*RS*,3′*SR*) configuration was assigned to the **2** isomer, in which the hydrogen atom experienced the greater downfield shift i.e., δ 4.95 ppm, while (3*RS*,3′*RS*) was assigned to the **3** isomer, in which the methine proton was comparatively shielded and appeared at δ 4.82 ppm [21]. On this basis, compounds **2** and **3** have been identified as diastereomeric pair of 3′-benzoyl spiro[3*H*-indole-3,2′-oxiran]-2(1*H*)-ones, each one of which will have its enantiomer however, which could not be separated.

Further, both isomers were subjected to chemical reaction separately under microwave irradiation. It was observed that **2** reacted with hydrazine hydrate to give spiro [indole-pyrazoles] **4**, while compound **3** gave an interactable mixture of products which could not be separated.

The formation of these two diastereomers under microwave irradiation represented an interesting challenge, since the diastereoselectivity of the process was achieved by varying the reaction time and the power output. Furthermore, the possibility of performing the stereocontrolled process in an open vessel using a domestic microwave oven makes it a cheap and efficient alternative to conventional procedures.

2.2. Evaluation of antifungal activity

The antifungal activity of the all synthesized compounds were tested against three pathogenic fungi namely *Rhizoctonia solani*, *Fusarium oxysporum, Collectotrichum capsici* by the poison plate technique [22]. The stock solution of 1000 ppm and 500 ppm of all compounds were prepared in acetone and then incorporated in required quantities to Potato Dextrose Agar medium (PDA) before dispersing into petri-plates. 100 ml of PDA was uniformly distributed into three petri-plates, served as replicates. Three plates containing unamended PDA were maintained as control.

The petri-plates were inoculated with a 4 mm disc cut from a 7 days old fungus culture. The inoculated plates were incubated at 25 ± 1 °C for 5 days. The radial growth of the fungal colonies was measured on 6th day and data were statistically analysed. The fungicidal data (Table 2) indicates that some of the compounds were found significantly superior than control (9.0 cm) in controlling the radial growth (1.25–5.00 cm) of all the three pathogens. The others were similar to control.

Table 2: Effect of the compounds synthesized on the mean radial growth (cm) of fungi *in vitro* (poison plate technique)

Compd.	*Rhizoctonia solani*		*Fusarium oxysporum*		*Colletotrichum capsici*	
	1000 ppm	500 ppm	1000 ppm	500 ppm	1000 ppm	500 ppm
1a	3.92	4.57	4.72	4.50	4.77	5.17
1b	3.42	4.17	3.75	5.17	4.07	5.42
1c	6.42	8.83	1.42	3.50	3.77	4.50
1d	7.25	8.33	2.25	4.17	3.25	5.58
1e	8.50	9.00	4.00	5.17	1.92	2.83
2a	4.25	6.00	3.67	3.67	2.25	2.67
2b	5.00	6.25	3.68	5.28	3.58	6.17
2c	8.17	8.92	2.08	2.83	3.58	4.92
2d	9.00	9.00	2.25	4.17	3.42	4.00
2e	9.00	9.00	1.83	2.75	1.92	3.25
3a	6.08	8.75	1.42	2.67	2.67	3.75
3b	1.42	2.25	3.42	5.37	3.83	6.53
3c	7.08	9.00	3.58	5.58	3.00	3.92
3d	8.08	9.00	3.25	4.33	3.25	4.25
3e	7.50	8.75	3.17	3.58	1.33	2.91
4a	8.25	9.00	3.00	4.00	3.00	3.67
4b	9.00	9.00	3.75	4.25	2.67	3.92
4c	1.83	2.75	2.25	3.33	1.25	2.08
4d	7.33	8.42	2.50	4.25	2.83	4.33
4e	9.00	9.00	3.08	3.75	4.17	4.25
Control	9.00	9.00	8.67	8.67	7.67	7.67
CD 1%	0.74	1.22	0.94	0.92	1.08	1.25

□ min. value
—— min. value

It was found that compound **3b** (X = 5-CH_3, R = H), **4c** (X = H, R = 4-F) was the most effective against *R. solani* (1.42–1.83 cm), compounds **1c** (X = H, R = 4-F), **1d** (X = 5-Cl, R = 4-F, 2-CH_3), **2c** (X = H, R = 4-F), 2d (X = 5-Cl, R = 4-F, 2-CH_3), 2e (X = H, R = 4-F, 2-CH_3), **3a** (X = H, R = H) **4c** (X = H, R = 4-F) were most effective against *F. oxysporum* (1.42–2.25 cm) and **1e, 2e, 3e** (X = H, R = 4-F, 2-CH_3), **4c**, were also found effective against *C. capsici* (1.25–1.92 cm). Compounds **1a, 1b, 2b, 3c, 3d, 4a, 4b** and **4e** have shown moderate activity (2.50–3.92 cm) against these pathogens.

2.3. Evaluation of antitubercular activity

The antitubercular evaluation of the compounds was carried out at the "Tuberculosis Antimicrobial Acquisition and Coordinating Facility" (TAACF) USA. Primary screening of the compounds for antitubercular activity have been conducted at 12.5 μg/ml against *Mycobacterium tuberculosis* H37Rv, in BACTEC 12B medium using BACTEC 460 radiometric system. Antitubercular activity data were compared with the standard drug rifampicin at

Table 3: ***In vitro*** **activity against** ***Mycobacterium tuberculosis***

Compd.	MIC (μg/ml) Vs. $H_{37}R_v$	% Inhibition
1a	<12.5	99(+)
1b	<12.5	96(+)
1c	<12.5	99(+)
2a	>12.5	98(+)
3a	>12.5	72(−)
2b	>12.5	11(−)
3b	>12.5	93(+)
2c	>12.5	13(−)
3c	>12.5	0
2d	>12.5	0
3d	>12.5	0
2e	>12.5	0
3e	>12.5	0

MIC = Minimum inhibitory concentration in μg/ml
MIC rifampicin = 0.25 μg/ml, 98% inhibition vs. *M. tuberculosis*
% Inhibition = Activity of each compound at the 12.5 μg/ml level
(+) = Inhibition greater than 90%,
(−) = Significant activity

0.25 μg/ml concentration which showed 98% inhibition. The results are presented in Table 3. Compounds **1a, 1d, 1c, 2a** and **3b** were most effective against *M. tuberculosis* at a concentration of 12.5 μg/ml.

3. Experimental

Melting points were determined in open glass capillaries and were uncorrected. IR spectra were recorded in KBr on a Perkin Elmer spectrophotometer model 577 (ν_{max} in cm^{-1}). ^1H NMR was recorded on Model Bruker DRX-300, using $CDCl_3$ as solvent and TMS as internal reference at 300.15 MHz. MS was recorded on MS-50 Kratos mass spectrometer at 70ev. Purity of the compounds were checked by TLC using silica gel G (Merck) in various solvent systems (by volume) benzene : ethylacetate (80 : 20), chloroform : ethylacetate (90 : 10).

3.1. Stereoselective synthesis of spiro [3H-indole-3,2′-oxiran]-3′-benzoyl-2(1H)-ones (2, 3) under microwave irradiation

A mixture of **1** (0.01 mol), Na_2CO_3 (500 mg) and H_2O_2 (8 ml, 15%) in absolute ethanol (10 ml; minimum quantity required to form slurry) in open borosil vessel was irradiated inside a microwave oven for 2 min at 240 Watt, when a white compound **2** separated out, which was found to be pure by TLC.
When the reactants were irradiated at 480 Watt for 2 min, the colour of the solution turned brown. After every 2 min, an interval of 1 min was allowed to avoid excessive evaporation of the solvent, until the completion of reaction (4–6 min), (TLC). The reaction mixture was then allowed to stand at room temperature and product **3** separated exclusively was filtered, dried and recrystallized from methanol.

3.2. Synthesis of 2′,4′-dihydro-5′-aryl-4′-hydroxy-spiro[3H-indole-3,3′(3H)-pyrazol]-2 (1H)-one (4)

A mixture of **2** (0.01 mol) and hydrazine hydrate (0.012 mol) in absolute ethanol (10 ml; minimum quantity required to form slurry) was irradiated at 480 Watt until the completion of the reaction (2 min) (TLC). On cooling crystals separated out which were dried and found to be pure by TLC.
In an analogous reaction of the brown isomer spiro[3*H*-indole-3,2′-oxiran]-3′-benzoyl-2(1*H*)-one **3** with hydrazine hydrate under microwave irradiation, a interactable mixture (TLC) was obtained along with **4** which, however, could not be separated.

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References

1 Banik, B. K.; Manhas, M. S.; Robb, E. W.; Bose, A. K.: Heterocycles **44**, 405 (1997)
2 Bose, A. K.; Banik, B. K.; Lavlinskaia, N.; Jayaraman, M.; Manhas, M. S.: Chemtech. **18** (1997)
3 Bose, A. K.; Banik, B. K.; Manhas, M. S.: Tetrahedron Lett. **36**, 213 (1995)
4 Galema, A.: Chem. Soc. Rev. **26**, 223 (1997)
5 Joshi, K. C.; Jain, R., Chand, P.: Heterocycles **23**, 957 (1995)
6 Joshi, K. C., Joshi, R.: J. Indian. Chem. Soc. **76**, 515 (1999)
7 Edmondson, S.; Danishefsky, J. S.; Sepp-Lorenzino, L.; Rosen, N.: J. Am. Chem. Soc. **121**, 2147 (1999)
8 Khan, M. H.; Tewari, S.; Begum, K.; Nizamudin: Indian J. Chem. **37B**, 1075 (1998)
9 Dandia, A.; Saha, M., Rani, B.: J. Chem. Res. (S), 360, (1998), JCR (M), 1425 (1998)
10 Dandia, A.; Paul, S.; Gupta, R.; Loupy, A.; Rani, B.: Synth. Commun. **31**, 711 (2001)
11 Dandia, A.; Taneja, H.; Gupta, R., Paul, S.: Synth. Commun. **29**, 2323 (1999)
12 Dandia, A.; Taneja, H.; Singh, R.: Synth. Commun. **31**, 1879 (2001)
13 Dandia, A.; Taneja, H., Singh, R.: J. Chem. Res. (S), 272 (2000)
14 Upjohn Co: French Patent 1,445,824 (1966): C.A., **66**, 75921x (1967)
15 Upjohn Co: Netherland Appl., 6,505,845 (1966): C.A. **67**, 21850e (1967)
16 Anthony, W. C.: US Patent, 3,413,299 (1968): C.A., **70**, 47294j (1969)
17 Kikugawa, K., Ichino, M.: Chem., Pharm. Bull. **21**, 1151 (1973)
18 Tonaka, Y., Sakuraba, E.: JPN Kakai Tokyokoho JP, 01,249,763 (1989), C.A. **112**, 118629w (1990)
19 Kobayashi, G.; Furukawa S.; Matsuda, Y.: Yakugaku Zasshi. **86**, 1156 (1966) C.A. **67**, 108594u (1967)
20 Joshi, K. C.; Jain R.; Garg, S.: J. Heterocyclic. Chem. **21**, 977 (1984)
21 Baiocchi L.; Giannangeli, M.: J. Heterocyclic. Chem. **25**, 1905 (1988)
22 Carpentor, J. B.: Phytopathology **32**, 845 (1942).

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