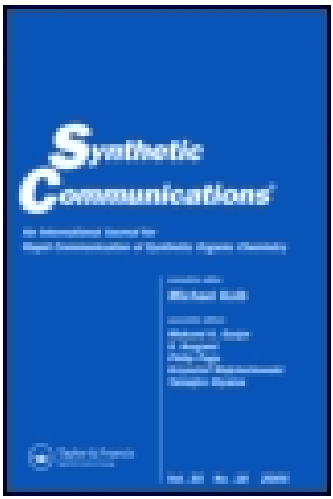

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K. Rajendra Prasad [a] & Malleshwar Darbarwar [a]
[a] Department of Chemistry , Osmania University , Hyderabad, 500 007, India
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SYNTHESIS OF 3-(2H-INDAZOL-2-YL)-2H[1]-BENZOPYRAN-2-ONES

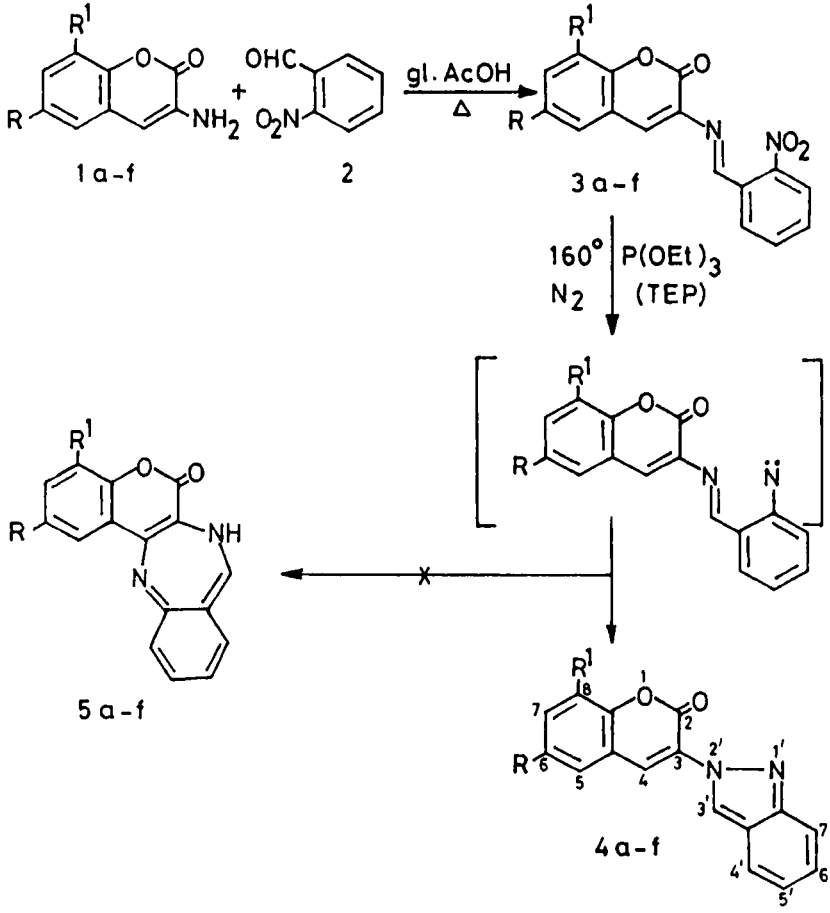
K. Rajendra Prasad and Malleshwar Darbarwar*

Department of Chemistry
Osmania University
Hyderabad 500 007, India

ABSTRACT : Hitherto unknown 3-(2H-Indazol-2-yl)-2H[1]benzopyran-2-ones (**4a-f**) have been synthesized under the triethyl phosphite (TEP) mediated reaction conditions of 3-[[(2-nitrophenyl)-methylene]amino]-2H-1-benzopyran-2-ones (**3a-f**), obtained by the condensation of 3-amino coumarins (**1a-f**) with 2-nitrobenzaldehyde (**2**).

Coumarins are widely distributed in nature[1] and exhibit various physiological effects[2-4]. Many natural and synthetic coumarin derivatives have found wide application in therapy as anticoagulants[5] and antibiotics[6]. Amino coumarins are of interest not only because of their biological activities such as hypotensive[7], spasmolytic[8], antibacterial[9,10] and antiallergic[11], but also because of their use as optical brighteners[12] and laser dyes[13]. Recently interest on these compounds has been revived because of their use as fluorescent markers in fluorogenic substances for the more sensitive biochemical determination of enzymes[14]. On the other hand indazole derivatives have pharmacological

* To whom correspondence should be addressed.



	a	b	c	d	e	f
R	H	H	Br	Br	Br	Cl
R^1	H	OMe	H	OMe	Br	H

SCHEME

importance possessing antiinflammatory, anticonvulsant, antispamodic, sedative, analgesic[15,16] and antibacterial[17] activity and also used as a bronchodilator[18]. It is interesting to evaluate physiological activity when two rings are fused. Therefore, in this communication a facile synthesis of hitherto unknown 3-(2H-indazol-2-yl)-2H-[1]-benzopyran-2-ones from 3-amino coumarins[19,20] (**1a-f**) and 2-nitrobenzaldehyde (**2**) (**Scheme**) has been reported.

In a typical experiment, 8-methoxy-3-amino coumarin (**1b**) and 2-nitrobenzaldehyde (**2**) were heated in glacial acetic acid for 6 hours. A systematic work up gave a crude compound which was chromatographed over a neutral alumina using benzene - ethylacetate (3:7) mixture as an eluent to obtain yellow crystalline compound with a melting point 172-173°C (**3b**).

The UV spectrum (MeOH) of the compound (**3b**) showed λmax 222 nm, 250 nm and 330 nm. The IR spectrum (KBr) of **3b** showed characteristic bands at 1725 cm^{-1}, 1605 cm^{-1}, 1510 cm^{-1} and 1320 cm^{-1}. These absorptions may be assigned to lactonic carbonyl, -C=N and $-NO_2$ functions respectively. Its ^1H NMR spectrum ($CDCl_3$) displayed signals at δ 8.66 (s, 1H) assigned for C_4-H of 2H-1-benzopyran-2-one ring, δ 7.71 (s, 1H, azomethyne, -N=CH), δ6.9-7.5 (m, 7H, aromatic) and at δ 3.1 (s, 3H) due to $-OCH_3$ group. The mass spectrum of the compound revealed the molecular ion at m/z 324. Based on the spectral data and elemental analysis, the compound has been assigned

Table : Physical data of 3-[[(2-nitrophenyl)methylene]amino]-2H-1-benzopyran-2-ones (3a-f) and 3-(2H-indazol-2-yl)-2H-1-benzopyran-2-ones (4a-f)

Product No.	R	R'	Reaction time in h	Yield (%)	M.P[a] °C	Molecular[b] formula (M^+)	IR (KBr) max C=O	C=N	NO_2	^{1}H NMR ($CDCl_3$/TMS) (δ)
3a	H	H	6	75	208-9	$C_{16}H_{10}N_2O_4$ (294)	1720	1600	1520 1320	8.61 (s, 1H, C_4-H), 7.66 (s, 1H, N=CH), 7.0-7.51 (m, 8H, arom)
3b	H	OMe	5	80	172-73	$C_{17}H_{12}N_2O_5$ (324)	1725	1605	1510 1320	8.66 (s, 1H, C_4-H), 7.71 (s, 1H, N=CH), 6.9-7.5 (m, 7H, arom), 3.1 (s, 3H, OMe).
3c	Br	H	6	70	221-22	$C_{16}H_9N_2O_4Br$ (372)	1730	1605	1520 1320	8.57 (s, 1H, C_4-H), 7.9 (s, 1H, N=CH), 7.01-7.7 (m, 7H, arom).
3d	Br	OMe	7	71	254-55	$C_{17}H_{11}N_2O_5Br$ (402)	1720	1605	1520 1315	8.5 (s, 1H, C_4-H), 7.9 (s, 1H, N=CH), 6.9-7.7 (m, 6H, arom), 3.3 (s, 3H, -OMe).
3e	Br	Br	6	61	232-33	$C_{16}H_8N_2O_4Br_2$ (450)	1710	1605	1510 1330	8.48 (s, 1H, C_4-H), 7.73 (s, 1H, N=CH), 6.9-7.6 (m, 6H, arom).
3f	Cl	H	6	68	233-34	$C_{16}H_9N_2O_4Cl$ (328)	1715	1600	1540 1315	8.44 (s, 1H, C_4-H), 7.9 (s, 1H, N=CH), 6.9-7.7 (m, 7H, arom).
4a	H	H	14	60	254-55	$C_{16}H_{10}N_2O_2$ (262)	1720	1605		8.66 (s, 1H, C_4-H), 8.01 (s, C_3'-H), 6.9-7.8 (m, 8H, arom).

4b	H	OMe	14	68	249-50	$C_{17}H_{12}N_2O_3$ (292)	1715	1600	8.5 (s, 1H, C_4-H), 7.9 (s, 1H, C_3'-H), 6.9-7.7 (m, 7H, arom), 3.8 (s, 3H, -OMe).
4c	Br	H	15	58	278-79	$C_{16}H_9N_2O_2Br$ (340)	1715	1595	8.61 (s, 1H, C_4-H), 8.1 (s, 1H, C_3'-H), 7.0-7.8 (m, 7H, arom).
4d	Br	OMe	14	61	274-75	$C_{17}H_{11}N_2O_3Br$ (370)	1715	1605	8.64 (s, 1H, C_4-H), 8.1 (s, C_3'-H), 7.0-7.8 (m, 6H, arom), 3.81 (s, 3H, OMe).
4e	Br	Br	16	54	281-82	$C_{16}H_8N_2O_2Br$ (418)	1705	1600	8.6 (s, 1H, C_4-H), 8.0 (s, 1H, C_3'-H), 7.1-7.9 (m, 6H, arom).
4f	Cl	H	15	59	286-87	$C_{16}H_9N_2O_2Cl$ (296)	1720	1595	8.54 (s, 1H, C_4-H), 8.0 (s, 1H, C_3'-H), 7.1-7.7 (m, 7H, arom).

[a] Melting points are uncorrected.

[b] Satisfactory microanalysis obtained C ± 0.26; H ± 0.22; N, ± 0.28.

8-methoxy-3-[[(2-nitrophenyl)methylene]-amino]-2H-1-benzopyran-2-one (**3b**). The fragmentation pattern of the compound is consistant with the assigned structure.

8-Methoxy-3-[[(2-nitrophenyl)methylene]amino]-2H-1-benzopyran-2-one (**3b**) and triethylphosphite (TEP) were allowed to react in nitrogen atmosphere for 14 hours at 160°C. After the completion of the reaction, the excess of TEP and triethylphosphate formed during the reaction were distilled off under vaccum. The crude product obtained was purified by chromatography over a column of neutral alumina. Elution with benzene-ethyl acetate (1:1) mixture afforded a crystalline colourless compound, m.p. 249-50°C (**4b**).

The UV spectrum (MeOH) of **4b** showed λ max at 267 nm, 285 nm and 320 nm, indicating the presence of indazole and 2H-1-benzopyran-2-one ring systems. The IR spectrum (KBr) of compound showed absorption at 1715 cm^{-1} characteristic of lactonic carbonyl group and at 1600 cm^{-1} which may be assigned to -C=N. ^1H NMR spectrum ($CDCl_3$) exhibited signals at δ 8.5 (s, 1H, C_4-H of 2H-1-benzopyran-2-one), δ 7.9 (s, 1H, N-CH, C_3'-H of indazole ring), δ 6.9-7.7 (m, 7H, aromatic) and at δ3.8 (s, 3H, -OMe). In the mass spectrum the molecular ion was present at m/z 292. Based on the spectral data and elemental analysis, the compound is assigned as 8-methoxy-3-(2H-indazol-2-yl)-2H-1-benzopyran-2-one (**4b**). The fragmentation pattern is in accordance with **4b**. The TEP mediated cyclisation of **3b**

to **4** proceeds through the nitrene intermediate. The other possible structure benzopyran[3,4-b][1,4]benzodiazepinone (**5**) during TEP mediated cyclisation of **3b** has been ruled out by spectroscopic evidences (IR, ^{1}H NMR).

Adopting this procedure five other substituted 3-amino coumarins (**1a, c-f**) and 2-nitrobenzaldehyde (**2**) were reacted to give corresponding **3a, c-f** and **4a, c-f** in good yields. Their physical data is presented in the Table.

EXPERIMENTAL

General procedure for 3-(2H-indazol-2-yl)-2H-1-benzopyran-2-ones (4a-f)

a) **Reaction of 1a-f with 2**

A mixture of appropriate 3-amino coumarin (**1a-f**) (0.002 mol) and 2-nitrobenzaldehyde (**2**, 0.002 mol) were heated in glacial acetic acid (10 ml) on a steam bath. The reaction was monitored by TLC. The solid that separated was filtered, washed with petroleum ether, dried and chromatographed over a column of neutral alumina using benzene-ethylacetate as an eluent to yield corresponding 3-[[(2-nitrophenyl)-methylene]amino]-2H-1-benzopyran-2-ones (**3a-f**). The data is presented in the Table.

b) **Cyclisation of 3a-f to 4a-f**

3-[[(2-nitro phenyl)methylene]amino]-2H-1-benzopyran-2-ones (0.002 mol) and triethylphosphite (6 ml) were refluxed at 160°C on oil

bath under nitrogen atmosphere. Excess of triethylphosphite and triiethylphosphate formed during the reaction were distilled off under vacuum and the resulting residue was subjected to chromatography over a column of neutral alumina. Elution with benzene-ethyl acetate mixture yielded corresponding 3-(2H-indazol-2-yl)-2H-1-benzopyran-2-one as crystalline compound. The data is given in the Table.

Biological activity

Antibacterial properties : Antibacterial efficacy was tested by observing the zone of inhibition on filter discs with compound in dimethyl sulfoxide (DMSO) at different concentrations. The discs were placed on the overnight cultures of Escherichia coli and Staphylococus aureus. Compounds **3c, e, f** showed moderate activity against E.coli. Whereas compounds **4c** and **4f** showed moderate activity against both the organisms. The activity of other compounds was not significant.

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