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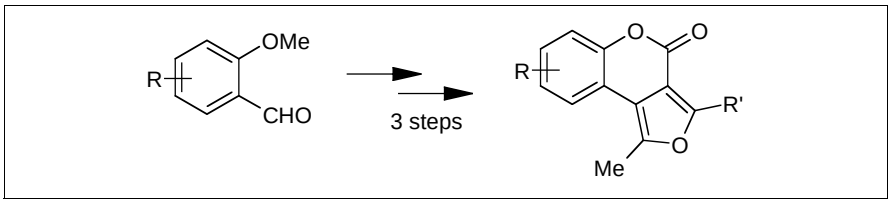
Received January 23, 2006



Various 1,3-dimethyl and 1-methyl-3-phenylfuro[3,4-*c*]coumarins (**5a-h** and **6a-h**) have been synthesized by demethylation cyclization of the respective 3-aryl-4-ethoxycarbonyl furans (**3a-h** and **4a-h**). These ethoxycarbonyl furans were prepared by reacting appropriate 1-aryl-2-nitro-prop-1-ene (**1a-h**) with ethyl acetoacetate or ethyl benzoylacetate under Nef reaction condition.

J. Heterocyclic Chem., **43**, 1699 (2006).

Introduction.

Coumarins (2*H*-1-benzopyran-2-ones) are best known as aromatic lactones isolated from variety of plant sources [1]. Owing to their diverse bioactivities *viz.* anticoagulant [2], antibacterial, and antifungal [3] *etc.* many natural, semi synthetic and synthetic coumarins have become important class of molecules in drug research. In this direction, several biological activities have been claimed for compounds comprising both coumarins and coumarins fused to a heterocyclic ring. Among the heterocyclic fused coumarins, furocoumarins are one of the important derivatives. Numbers of furocoumarins are naturally occurring and show a wide range of biological properties, the most prominent of which is the photobiological effects it that can exert upon irradiation with long-wavelength UV light. Thus many furocoumarins are potent photosensitizers to human skin with valuable application in medicine especially for the treatment of skin diseases [4-6]. Many furocoumarins are recorded to have phototoxic effects to insects, fungi, viruses and bacteria [7-10]. Owing to the natural occurrence and varied biological activities, the synthesis of furocoumarins has remained a subject of an active interest. Very recently, synthesis, natural occurrence and biological activity of furocoumains have been reviewed [11].

As the name suggests, these compounds are based on a skeleton formed by fusion of a furan ring to coumarin unit. Among furocoumarins if one restricts the fusion of furan ring with the lactone ring of coumarin, three structural isomers; furo[2,3-*c*] (**I**), furo[3,2-*c*] (**II**) and furo[3,4-*c*] (**III**) are possible (Figure 1). In literature a large number of reports are documented for the synthesis of furo[2,3-*c*] and furo[3,2-*c*] coumarins [12-20], however the synthesis of furo[3,4-*c*]coumarin to our knowledge has not been reported except for a single report on a saturated skeletal analog of furo[3,4-*c*]coumarin [21]. Hence in continuation of our interest in heterocyclic fused coumarins [20,22-24] it was thought worthwhile to envisage a synthetic route to such novel molecules. Therefore in the present work we report the first synthesis of various 1,3-dimethyl and 1-methyl-3-phenyl-furo[3,4-*c*]coumarins (**5a-h** and **6a-h**).

Results and Discussion.

Our strategy for the synthesis of **5a-h** and **6a-h** was based on the straight-forward disconnection illustrated in Scheme 1.

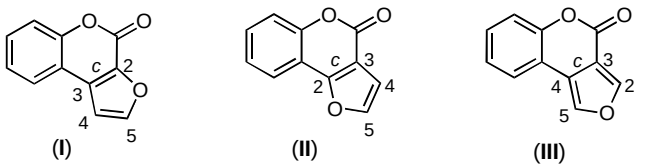
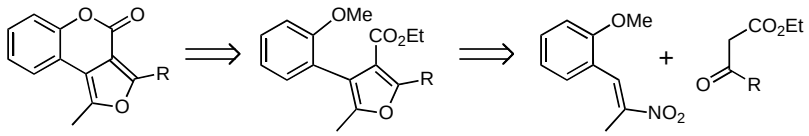
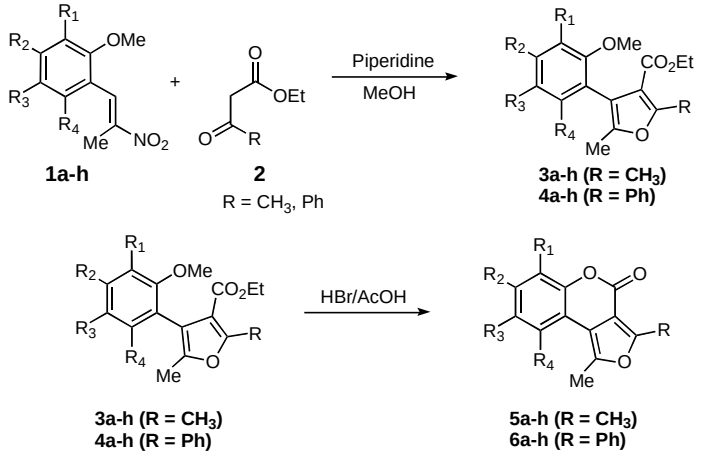


Figure - 1

Scheme - 1



Scheme - 2



a : $R_1 = R_2 = R_3 = R_4 = H$
b : $R_1 = R_3 = R_4 = H$, $R_2 = OCH_3$
c : $R_1 = R_2 = R_4 = H$, $R_3 = CH_3$
d : $R_1 = R_2 = R_4 = H$, $R_3 = Cl$
e : $R_1 = R_2 = R_4 = H$, $R_3 = Br$
f : $R_1 = R_3 = Br$, $R_2 = R_4 = H$
g : $R_1 = R_2 = R_4 = H$, $R_3 = NO_2$
h : $R_1 = R_2 = H$, $R_3 + R_4 =$ Benzo

Table I

Characterization of Compounds **5a-h** and **6a-h**

Compd.*	Mol. Formula	mp	Yield (%)	Found (Cal.) % C	% H	% N	NMR (δ, ppm)
5a	$C_{13}H_{10}O_3$	175	50	72.9 (72.8	4.7 4.6)	-- --	2.61 & 2.65 (6H, 2 x s, 2 x CH3), 7.0-7.6 (4H, m, Ar-H)
5b	$C_{14}H_{12}O_4$	168	50	68.9 (68.8	5.0 4.9)	-- --	2.65 & 2.75 (6H, 2 x s, 2 x CH3), 4.05 (3H, s, OCH3), 6.8-7.5 (3H, m, Ar-H)
5c	$C_{14}H_{12}O_3$	155	60	73.7 (73.6	5.3 5.2)	-- --	2.58 & 2.64 (9H, 2 x s, 2 x CH3), 6.8-7.7 (3H, m, Ar-H)
5d	$C_{13}H_9ClO_3$	183	55	62.8 (62.7	3.7 3.6)	-- --	2.59 & 2.64 (6H, 2 x s, 2 x CH3), 6.9-7.6 (3H, m, Ar-H)
5e	$C_{13}H_9BrO_3$	191	50	53.3 (53.2	3.1 3.0)	-- --	2.6 & 2.64 (6H, 2 x s, 2 x CH3), 6.9-7.8 (3H, m, Ar-H)
5f	$C_{13}H_8Br_2O_3$	246	50	42.0 (41.9	2.2 2.1)	-- --	2.7 & 2.75 (6H, 2 x s, 2 x CH3), 7.67 (2H, m, Ar-H)
5g	$C_{13}H_9NO_5$	208	65	60.3 (60.2	3.5 3.4	5.5 5.4)	2.6 & 2.7 (6H, 2 x s, 2 x CH3), 7.1-8.6 (3H, m, Ar-H)
5h	$C_{17}H_{12}O_3$	225	50	77.3 (77.2	4.6 4.5)	-- --	2.6 & 2.65 (6H, 2 x s, 2 x CH3), 7.1-8.6 (6H, m, Ar-H)
6a	$C_{18}H_{12}O_3$	176	55	78.1 (78.2	4.1 4.3)	-- --	2.7 (3H, s, CH3), 7.1-8.6 (9H, m, Ar-H)

Table I (Continued)

Compd.*	Mol. Formula	mp	Yield (%)	Found (Cal.) % C	% H	% N	NMR (δ, ppm)
6b	$C_{19}H_{14}O_4$	180	53	74.3 (74.5	4.3 4.6)	-- --	2.7 (3H, s, CH3), 3.9 (3H, s, OCH3), 6.9-8.0 (8H, m, Ar-H)
6c	$C_{19}H_{14}O_3$	204	63	78.5 (78.6	4.7 4.8)	-- --	2.4 & 2.7 (6H, 2 x s, 2 x CH3), 7.0-8.6 (8H, m, Ar-H)
6d	$C_{18}H_{11}ClO_3$	195	57	69.6 (69.5	3.4 3.5)	-- --	2.7 (3H, s, CH3), 7.2-8.4 (8H, m, Ar-H)
6e	$C_{18}H_{11}BrO_3$	208	60	60.5 (60.8	3.0 3.1)	-- --	2.7 (3H, s, CH3), 7.1-8.3 (8H, m, Ar-H)
6f	$C_{18}H_{10}Br_2O_3$	195	62	49.6 (49.8	2.4 2.3)	-- --	2.7 (3H, s, CH3), 7.2-8.3 (7H, m, Ar-H)
6g	$C_{18}H_{11}NO_5$	198	52	67.1 (67.3	3.2 3.4	4.2 4.3)	2.7 (3H, s, CH3), 7.1-8.4 (8H, m, Ar-H)
6h	$C_{22}H_{14}O_3$	210	59	80.7 (80.9	4.5 4.3)	-- --	2.7 (3H, s, CH3), 7.1-8.5 (11H, m, Ar-H)

* All compounds exhibit IR frequency bands at ~1735 (δ-lactone carbonyl of coumarin), ~1121 cm^{-1} (furan –C–O–C– stretching).

Thus title compounds (**5a-h** and **6a-h**) have been synthesized by demethylation-cyclization reaction of the intermediates, 3-substituted-4-ethoxycarbonyl furans (**3a-h** and **4a-h**). These furans (**3a-h** and **4a-h**) were obtained by the base catalyzed Nef reaction [25,26] of corresponding 1-aryl-2-nitro-prop-1-ene (**1a-h**) with either ethyl-acetoacetate or ethyl benzoyl acetate in refluxing methanol containing catalytic amount of piperidine (Scheme – 2). The starting materials (**1a-h**) were prepared using literature procedure [27].

For the demethylation and *in situ* lactonization step several reagents where tried, of which, pyridine hydrochloride and HBr in acetic acid were found promising. However, owing to the highly hygroscopic nature of pyridine hydrochloride and elevated reaction temperatures required, HBr in acetic acid was finally chosen as the reagent of choice to afford the title compounds in moderate to good yields (Table – 1). Structures of all the compounds synthesized (**3/4a-h** and **5/6a-h**) have been supported by elemental and spectral data.

EXPERIMENTAL

All Melting points are in degree centigrade and are uncorrected. IR spectra were recorded in KBr on a Nicolet 400D spectrophotometer and ^1H NMR in $CDCl_3$ on Hitachi R-1500, 60 MHz spectrometer using TMS as an internal standard. High resolution NMR ^1H & ^{13}C of selected compounds were recorded on Brucker Avance 300 spectrometer using $CDCl_3$ as solvent and TMS as an internal standard. Mass spectra of selected compounds were scanned on Thermo-Finnigan Polaris Q mass-spectrometer (EI mode).

Synthesis of Ethoxycarbonyl Furan derivatives **(3a-h and 4a-h)**.

General Procedure.

To a well-stirred solution of the appropriate 1-aryl-2-nitro-prop-1-ene (**1**, 0.02 mole) in 40 mL of methanol, 3-4 drops of piperidine were added at room temperature. To this ethyl acetoacetate or ethyl benzoyl acetate (0.02 moles) was added dropwise with stirring. The reaction mixture was then refluxed for 4 hrs. Excess of methanol was then removed and the residue was poured into water. It was then extracted with chloroform (3 x 30 mL). The chloroform extract was washed with dil. HCl and water successively. It was then dried over anhydrous sodium sulphate. Removal of chloroform gave a viscous residue which was subjected to column chromatography using silica gel as an absorbent and hexane-toluene (1:1) as an eluent to afford the furans as thick oils.

All compounds exhibit IR frequency bands at 1720 (C=O stretching of carbethoxy group), 1121 (furan –C–O–C– stretching), 3020 cm^{-1} (aromatic C-H stretching).

Compound 3a: Yield: 40%, Found C 68.9%; H 6.5% $C_{16}H_{18}O_4$ required C 70.1%; H 6.6%.

Compound 3b: Yield: 35%, Found C 67.2%; H 6.5% $C_{17}H_{20}O_5$ required C 67.1%; H 6.6%.

Compound 3c: Yield: 35%, Found C 70.7%; H 6.8% $C_{17}H_{20}O_4$ required C 70.8%; H 6.9%.

Compound 3d: Yield: 40%, Found C 62.1%; H 5.4% $C_{16}H_{17}ClO_4$ required C 62.2%; H 5.5%.

Compound 3e: Yield: 42%, Found C 54.3%; H 4.7% $C_{16}H_{17}BrO_4$ required C 54.4%; H 4.8%.

Compound 3f: Yield: 40%, Found C 44.3%; H 3.6% $C_{16}H_{16}Br_2O_4$ required C 44.4%; H 3.7%.

Compound 3g: Yield: 35%, Found C 60.1%; H 5.2%; N 4.3% $C_{16}H_{17}NO_6$ required C 60.2%; H 5.3%; N 4.4%.

Compound 3h: Yield: 44%, Found C 74.2%; H 6.3% $C_{20}H_{20}O_4$ required C 74.1%; H 6.2%.

Compound 4a: Yield: 60%, Found C 74.7%; H 5.7% $C_{21}H_{20}O_4$ required C 74.9%; H 5.9%.

Compound 4b: Yield: 45%, Found C 72.0%; H 6.3% $C_{22}H_{22}O_5$ required C 72.1%; H 6.0%.

Compound 4c: Yield: 63%, Found C 75.2%; H 6.2% $C_{22}H_{22}O_4$ required C 75.4%; H 6.3%.

Compound 4d: Yield: 55%, Found C 67.8%; H 5.3% $C_{21}H_{19}ClO_4$ required C 68.0%; H 5.1%.

Compound 4e: Yield: 59%, Found C 60.5%; H 4.7% $C_{21}H_{19}BrO_4$ required C 60.7%; H 4.6%.

Compound 4f: Yield: 60%, Found C 51.2%; H 3.5% $C_{21}H_{18}Br_2O_4$ required C 51.0%; H 3.6%.

Compound 4g: Yield: 57%, Found C 66.3%; H 4.9%; N 3.4% $C_{21}H_{19}NO_6$ required C 66.1%; H 5.0%; N 3.6%.

Compound 4h: Yield: 62%, Found C 77.5%; H 5.5% $C_{25}H_{22}O_4$ required C 77.7%; H 5.7%.

Synthesis of Furo[3,4-*c*]coumarins **(5a-h and 6a-h)**.

General Produce.

The ethoxycarbonyl furan derivatives (**3a-h** or **4a-h**, 0.01 mole) and HBr (15 mL) in glacial acetic acid (30 mL) was taken in a 100 mL round bottom flask and heated at 130 ^{O}C for 4 hrs. The reaction mixture was allowed to come to room temperature and poured into crushed ice. The reddish brown solid obtained was extracted with chloroform (3 x 30 mL) and washed with saturated sodium bicarbonate (3 x 30 mL), water (2 x 30 mL) and brine (2 x 30mL) successively. The chloroform layer was then dried over anhydrous sodium sulphate. The solvent was removed by distillation and the crude product was purified by column chromatography using silica gel as an absorbent and toluene as an eluent to give **5a-h** and **6a-h**. In case of compound **5b** and **6b** the reaction initially gave the hydroxyl derivatives (OH group at 8-position) which were converted in to **5b** and **6b** by methylation of hydroxyl group using K_2CO_3 and MeI in acetone.

Compound 5a: White solid (Chloroform-hexane); ^{1}H nmr: ($CDCl_3$ 300MHz) δ 2.61 (s, 3H, -CH_3), 2.66 (s, 3H, -CH_3), 7.18-7.27 & 7.57-7.60 (m, 4H, aromatic protons) ; ^{13}C nmr: δ 13.52 (CH_3), 13.89 (CH_3), 108.01 (C), 114.44 (C), 116.09 (C), 117.74 (CH), 123.52 (CH), 124.42 (CH), 128.21 (CH), 144.30 (C), 151.48 (C), 157.63 (C=O), 158.69 (C); ms: *m/z* 215 (16.6), 214 (76.93), 199 (5.19), 185 (8.41), 171 (8.68), 115 (30.15), 89 (15.63), 74 (8.15), 63 (17.5), 43 (100).

Compound 6a: White solid (Chloroform-hexane); ^{1}H nmr: ($CDCl_3$ 300MHz) δ 2.74 (s, 3H, -CH_3), 7.22-7.31, 7.41-7.49, 7.65-7.68 & 8.31-8.34 (m, 9H, aromatic protons) ; ^{13}C nmr: δ 14.32 (CH_3), 107.42 (C), 115.68 (C), 116.78 (C), 117.57 (CH), 123.44 (CH), 124.53 (CH), 127.84 (2xCH), 128.53 (CH), 128.67 (2xCH), 128.81 (C), 130.04 (CH), 145.25 (C), 151.28 (C), 156.26 (C=O), 158.04 (C); ms: *m/z* 276 (1.2), 219 (5.23), 176 (10.47), 115 (20.0), 105 (100).

Acknowledgement.

The authors are thankful to the Head, Department of Chemistry, Sardar Patel University for providing research facilities.

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