SEARCH FOR PHYSIOLOGICALLY ACTIVE COMPOUNDS

Part XXI. Synthesis of 3-(2-Furyl) and 3-(2-Furyl)-4-Methyl Coumarins

By B. Sreenivasulu, V. Sundaramurthy and N. V. Subba Rao

(*Department of Chemistry, Osmania University, Hyderabad-7*)

Abstract

The synthesis of a number of 3-(2-furyl) coumarins adopting three different methods is described. The comparative merits of the methods are also discussed. The presence of a furyl moiety at the 3-posiiton of the coumarin ring has been shown to be comparatively better than a phenyl moiety in regard to the fish toxicity of the molecule. Among the coumarins tested on fish, 7-bromo-4-methyl-3-(2-furyl) coumarin has the maximum activity and is one-third as active as rotenone. The U.V., I.R. and N.M.R. spectral data of some of the compounds are also presented.

Introduction

In a brief communication from these laboratories, the synthesis of 3-(2-furyl) coumarins[1] by the demethylative cyclisation of β-o-methoxyphenyl-α-(2-furyl) acrylonitriles and also by the condensation of o-hydroxy acetophenones with sodium 2-furyl acetate was reported. In continuation of this work, a number of new 3-(2-furyl) coumarins have now been synthesized adopting different methods. Details of the synthesis, spectral properties and physiological activity of the compounds synthesized have been presented in this paper.

2-Methoxy-1-naphthaldehyde and a few other orthomethoxy benzaldehydes have been condensed with 2-furanacetonitrile under alkaline conditions to give rise to the corresponding acrylonitriles (I). These have also been prepared using piperidine as a condensing agent. However, the yields obtained adopting the latter procedure have been comparatively poor. The acrylonitriles thus prepared have been converted into the respective coumarins by treating them with pyridine hydrochloride. It is interesting to note that during the demethylative cyclisation of β-2, 4-dimethoxyphenyl-α-(2-furyl) acrylonitrile, a mixture of 7-hydroxy and 7-methoxy-3-(2-furyl) coumarins has been formed due to partial demethylation during the

reaction. The 7-hydroxy derivative was formed in major quantity and the relative proportion of 7-hydroxy and 7-methoxy derivatives seems to depend on the time of reflux with pyridine hydrochloride. Longer durations in the refluxing time invariably resulted in the exclusive formation of the 7-hydroxy derivative. From the 1% alkali solubles of the reaction product, the 7-hydroxy-3-(2-furyl) coumarin was separated. The alkali insolubles consisting of 7-methoxy-3-(2-furyl) coumarin was found to be identical with the methylation product of 7-hydroxy-3-(2-furyl) coumarin.

On an analogy with conversion of o-hydroxybenzylidenemalononitrile into 3-cyano coumarin,[2] the formation of 3-(2-furyl) coumarin (III) from the β -o-methoxyphenyl acrylonitrile (I) can also be considered to pass through an intermediate iminolactone stage (II) which in turn can get hydrolysed to give rise to the 3-(2-furyl) coumarin (Fig 1).
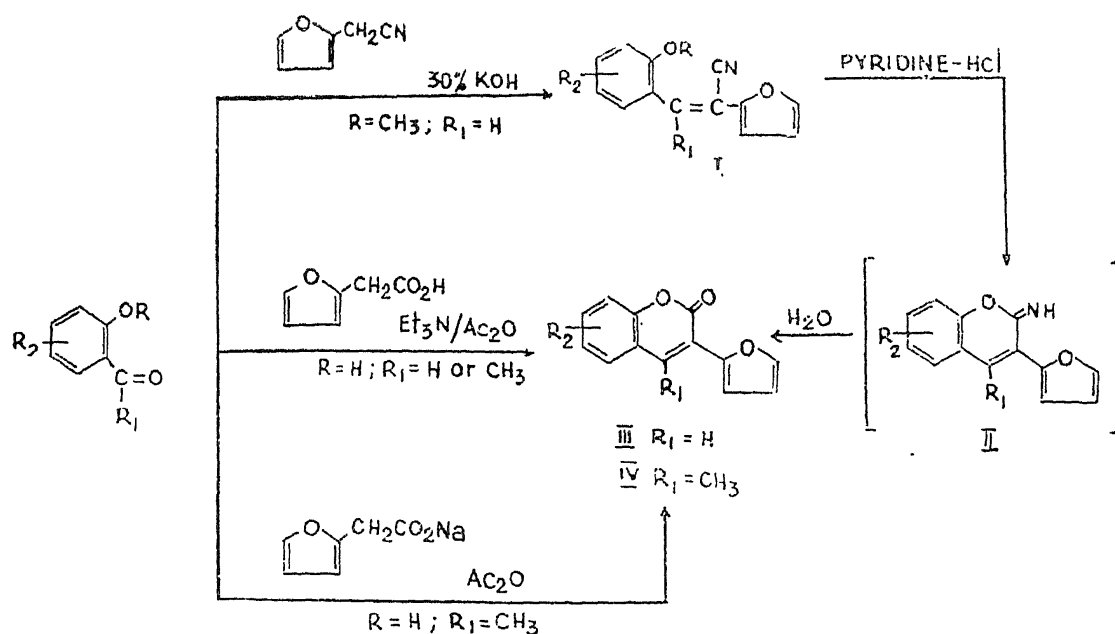

FIG. 1

The synthieis of 3-(2-furyl) and 3-(2-furyl)-4-methyl coumarins (IV) has been carried out adopting the more versatile Bargellini procedure[3] in which o-hydroxybenzaldehydes or o-hydroxyacetophenones were condensed with the sodium 2-furyl acetate and acetic anhydride. Alternatively, the modified Perkin method[4] involving the condensation of the respective salicyl-aldehydes with furan acetic anhydride in the presence of triethylamine has also been used. The required furan acetic anhydride is obtained *in situ* from

furanacetic acid and acetic anhydride. Of the different methods adopted, the acrylonitrile method gave better yields of 3–(2–furyl) coumarins than the other procedures. In the case of 3–(2–furyl)–4–methyl coumarins the Bargellini procedure was the best.

All the intermediate acrylonitriles synthezized are listed in Table I. The 3–(2–furyl) and the 3–(2–furyl)–4–methyl coumarins prepared have been given in Table II.

TABLE I

β-o-Methoxyphenyl α-(2-furyl) acrylonitriles (I)

Sl. No.	–α–(2–furyl) acrylonitriles	M.P. (°C)	Yield (%)	Mol. Formula	Found			Required		
					C	H	N	C	H	N
1.	β–o–methoxyphenyl	89	85	$C_{14}H_{11}NO_2$	74·81	5·01	6·32	74·65	4·92	6·22
2.	β–5–Chloro–2–methoxyphenyl	112	92	$C_{14}H_{10}ClNO_2$	64·57	3·78	5·40	64·62	3·85	5·38
3.	β–5–Bromo–2–methoxyphenyl	118	89	$C_{14}H_{10}BrNO_2$	55·48	3·02	4·71	55·26	3·29	4·61
4.	β–2, 4–dimethoxy-phenyl	116	83	$C_{15}H_{13}NO_3$	70·74	5·15	5·51	70·60	5·13	5·49
5.	β–2, 3–dimethoxy-phenyl	86	86	$C_{15}H_{13}NO_3$	70·48	5·21	5·68	70·60	5·13	5·49
6.	β–3, 5–dichloro–2–methoxyphenyl	118	95	$C_{14}H_9Cl_2NO_2$	57·30	3·21	4·84	56·98	3·15	4·75
7.	β–3, 5–dibromo–2–methoxyphenyl	136	92	$C_{14}H_9Br_2NO_2$	43·61	2·28	3·70	43·86	2·35	3·66
8.	β–2–methoxy–1–naphthyl	108	87	$C_{18}H_{13}NO_2$	78·36	4·73	5·11	78·21	4·77	5·09

The U.V. data presented in Table III indicate that the substitution pattern of the coumarin has a significant effect on the U.V. spectra of 3–(2–furyl) coumarins.

3–(2–furyl) coumarin without any substituent in the benzenoid ring shows three bands at λ_{max} 223 nm (log 4·01), λ_{max} 246 nm (4·18) λ_{max} 350 nm (4·25). While a methoxyl in 7–position brings about a bathochromic shift in the long wavelength band by about 16 nm, a methoxyl in 8–position

Table II

3-(2-furyl) coumarins

Sl. No.	3-(2-furyl) coumarin	Solvent	M.P. (°C)	Yield (%)	Mol. Formula	Found C	Found H	Required C	Required H
1.	.. ..	EtOH	93	85	$C_{13}H_8O_3$	73·51	3·87	73·58	3·77
2.	6-Chloro[a]	EtOH	150	89	$C_{13}H_7ClO_3$	63·02	2·84	63·31	2·83
3.	6-Bromo[a]	EtOH	171	94	$C_{13}H_7BrO_3$	53·92	2·64	53·64	2·42
4.	6-Nitro[b]	HOAc	227	82	$C_{13}H_7NO_5$	60·42	2·75	60·70	2·72
5.	7-Hydroxy[a]	EtOH	212	65	$C_{13}H_8O_4$	68·74	3·50	68·42	3·51
6.	7-Acetoxy[b]	EtOH	168	71	$C_{15}H_{10}O_5$	66·54	3·73	66·67	3·70
7.	7-Methoxy	EtOH	133	89	$C_{14}H_{10}O_4$	69·31	4·16	69·42	4·03
8.	7-Nitro[b]	HOAc	220	80	$C_{13}H_7NO_5$	60·43	2·88	60·70	2·72
9.	8-Hydroxy[a]	EtOH	222	85	$C_{13}H_8O_4$	68·64	3·64	68·42	3·57
10.	8-Methoxy	EtOH	155	83	$C_{14}H_{10}O_4$	69·64	4·10	69·42	4·03
11.	8-Nitro[b]	HOAc	201	54	$C_{13}H_7NO_5$	60·42	2·61	60·70	2·72
12.	8-Methoxy-6-Nitro[b]	EtOH	245	74	$C_{14}H_9NO_6$	58·42	3·24	58·54	3·16
13.	8-Hydroxy-6-nitro	HOAc/MeOH	295	89	$C_{13}H_7NO_6$	57·42	2·71	57·15	2·58
14.	8-Methoxy-6-bromo[b]	–do–	185	76	$C_{14}H_9BrO_4$	52·68	2·68	52·34	2·80
15.	8-Hydroxy-6-bromo	–do–	216	73	$C_{13}H_7BrO_4$	51·11	2·31	50·82	2·27
16.	8-Nitro-6-bromo[b]	–do–	150	68	$C_{13}H_6BNO_5$	46·71	1·8	46·43	1·79
17.	8-Bromo-6-Nitro	–do–	175	70	$C_{13}H_6BrNO_5$	46·22	1·76	46·43	1·79
18.	6, 8-Dichloro[a]	EtOH	174	70	$C_{13}H_6Cl_2O_3$	55·64	2·10	55·55	2·13
19.	6, 8-Dibromo[a]	–do–	187	91	$C_{13}H_6Br_2O_3$	42·21	1·64	42·16	1·62
20.	5, 6-Benzo[a]	–do–	219	89	$C_{17}H_{10}O_3$	77·64	3·71	77·85	3·82
21.	4, 6-Dimethyl[c]	EtOH	150	51	$C_{15}H_{12}O_3$	75·62	5·13	75·31	5·00
22.	6-Nitro-4-methyl[c]	HOAc	155	42	$C_{14}H_9NO_5$	62·31	3·35	62·00	3·32
23.	6-Chloro-4-methyl[c]	EtOH	185	59	$C_{14}H_9ClO_3$	64·77	3·51	64·51	3·45
24.	6-Bromo-4-methyl[c]	EtOH	190	56	$C_{14}H_9BrO_3$	54·82	3·04	55·11	3·00
25.	4, 7-Dimethyl[c]	EtOH	134	50	$C_{15}H_{12}O_3$	75·51	5·21	75·31	5·00
26.	7-Acetoxy-4-methyl[c]	EtOH	185	72	$C_{16}H_{12}O_5$	67·38	4·29	67·61	4·23
27.	7-Hydroxy-4-methyl	EtOH	195	62	$C_{14}H_{10}O_4$	69·53	4·21	69·42	4·13
28.	7-Methoxy-4-methyl	EtOH	160	75	$C_{15}H_{12}O_4$	70·62	4·38	70·33	4·69
29.	7-Acetamino-4-methyl[c]	HOAc	280	71	$C_{16}H_{13}NO_4$	68·01	4·78	67·84	4·63
30.	7-Amino-4-methyl	HOAc	195	64	$C_{11}H_{11}NO_3$	70·02	4·42	69·71	4·60
31.	7-Chloro-4-methyl[c]	EtOH	132	55	$C_{11}H_9ClO_3$	64·42	3·52	64·51	3·45
32.	7-Bromo-4-methyl[c]	EtOH	141	52	$C_{14}H_9BrO_3$	55·38	3·02	55·11	2·97

a:—Prepared by method A
b:—Prepared by method B
c:—Prepared by method C

has an adverse effect causing a hypsochromic shift by 12 nm. Substituents like the halogens in the 6-position however have no marked effect. The introduction of a methyl substituent in the 4-position of 3-(2-furyl) coumarin cause a hypsochromic shift in the long wevelength band. This is probably due to the increase in steric strain which would throw the furyl substituent in the 3-position out of the plane with the plane of the coumarin ring. A similar effect was reported by Seshadri *et al.*[5] in the case of 3-aryl coumarins.

The formation of 3-(2-furyl) coumarins from acrylonitriles is readily distinguished by I.R. Spectra. While the intermediate acrylonitriles show a typical absorption around 2223 cm^{-1} assignable to the $-C \equiv N$, this band was totally absent in the final demethylative cyclised products. Instead, they show a typical coumarin carbonyl absorption around 1740 cm^{-1} (Table III) confirming that the cyclisation has taken place.

The N.M.R. Spectrum of 7-methoxy-3-(2-furyl) coumarin has been taken as the model compound in the series and is presented in Table IV. The effect of a 2-substituted furan in the 3-position of coumarin is similar to the effect of a phenyl substituent in this position on the chemical shifts of the protons in coumarin ring.[6] Further, the chemical shifts of protons in 3, 4 and 5-positions of furan ring are in accordance with those reported in literature for the 2-substituted furans.[7]

Fish toxicity.—The compounds synthesized have been tested against locally available freshwater fish " *Barbus ticto* ". The data are presented in Table V. As far as the effect of the substituent in the benzenoid ring on the fish toxicity is concerned, a 7-methoxy derivative is more toxic than a 7-hydroxy derivative. The contribution of a methoxyl in 8-position seems to be more or less the same as the one in 7-position and a 4-methyl substituent is found to step up the activity. The introduction of a halogen in 7-position confers the maximum effect on the molecule. Of all the compounds tested in this series 7-bromo-4-methyl-3-(2-furyl) coumarin has the maximum activity and is one-third as active as rotenone.

Bacteriostatic Activity

Of all the 3-(2-furyl) coumarins tested (Table V), 6-nitro, 7-nitro-8-nitro and 6-bromo-3-(2-furyl) coumarins have shown appreciable bacteriostatic activity against *Staphylococcus aureus, Bacillus subtilis* and *Bacillus coli* at 100 ppm.

TABLE III

U.V. and I.R. data of 3-(2-furyl) coumarins

Sl. No.	3-(2-furyl) coumarin	U.V. λ_{max} in nm. (log ϵ)	I.R. $\diagdown C = O$ cm^{-2}
1.	.. .. ..	223 (4·01), 246 ((4·18), 350 (4·18)	1,740
2.	6-Chloro	226 (4·32), 247 (4·10), 354 (4·22)	1,740
3.	6-Bromo	224 (4·32), 249 (4·07), 351 (4·24)	1,735
4.	7-Methoxy	251 (4·04), 366 (4·41)	1,740
5.	8-Methoxy	224 (4·00), 254 (4·11) 338 (4·13)	1,730
6.	7-Hydroxy	252 (4·06), 372 (4·34)	1,740
7.	7-Methoxy-4-methyl	285 (3·79), 342 (4·13)	1,735
8.	7-Hydroxy-4-methyl	283 (3·81), 352 (4·50)	1,740
9.	6-Chloro-4-methyl	278 (380), 340 (4·17)	1,735

Experimental procedure.—Melting points were taken in a sulphuric acid bath and are uncorrected. U.V. Spectra were recorded on a Beckmann, D.B. spectrophotometer using methanol as solvent and I.R. on Perkin Elmer–I model 137. N.M.R. was taken on a varian 60 MHz using tetramethyl silane as internal reference and deuterated chloroform as solvent.

General Proceedure for the Synthesis of 3-(2-furyl) Coumarins from Acrylo-nitriles (Method-A)

(*i*) *Preparation of β-o-Methoxyphenyl -α- (2-furyl) Acrylonitriles.*—To a mixture of *o*-methoxybenzaldehyde (0·01 mole) and 2-furan-acetonitrile (0·01 mole) in warm ethanol (5 ml.), a few drops of aqueous potassium hydroxide solution were added with shaking. The acrylonitrile separated immediately either as a solid or as an oil which solidified after a short stay in the refrigerator. It was filtered, washed well with water and recrystallised from alcohol.

TABLE IV

N.M.R. data of 7-methoxy-3-(2-furyl) coumarin

Sl. No.	Assignment		Value (δ)	Multiplicity
1.	Methoxyl in 7–position	(a)	3·88	Singlet
2.	Furyl 4 H	(b)	6·51	Multiplet
3.	Coumarin 8 H	(c)	6·83	Doublet
4.	Coumarin 6 H	(d)	6·91	Doublet
5.	Coumarin 5 H	(e)	7·30	Quartet
6.	Furyl 3 H	(f)	7·45	Multiplet
7.	Furyl 5 H	(g)	7·53	Multiplet
8.	Coumarin 4 H	(h)	8·03	Singlet

(*ii*) *Conversion of acrylonitriles into* 3–(2-*furyl*) *coumarins.*—A mixture of β –o– methoxyphenyl –α– (2–furyl) acrylonitrile (1 g.) and freshly distilled pyridine hydrochloride (5 g.) was refluxed gently in an oil bath till a clear solution formed (*ca* 15 min.). It was cooled, treated with water and filtered. The coumarins thus obtained as solids were recrystallised from suitable solvents.

Method–b

Salicylaldehydes (0·02 mole), 2–furan acetic acid (0·025 mole) acetic anhydride (15 ml.) and triethylamine (3 ml.) were heated in an oil–bath 150–160° C for two hours. Before heating, colourless solid separated out and it slowly disappeared during reaction time. The reaction mixture was then poured in ice–water while stirring. Th furyl coumarins thus settled down as solid were filtered and recrystallised from suitable solvents.

Method–C

2–Hydroxy acetophenones (4 g.), sodium furyl acetate (8 g.) and acetic anhydride (50 ml.) were heated at 170–180° C for 4–6 hours in

TABLE V

Fish toxicity and bacteriostatic activity data of 3-(2-furyl) coumarins

Sl. No.	3-(2-furyl) coumarins	Fish toxicity 20 ppm. Turning time in minutes	S.A. A	S.A. B	B. S. A	B. S. B	B. C. A	B. C. B
1.	..	8·0	+		+		+	
2.	6-Chloro	21·0	±	+	+		±	+
3.	6-Bromo	17·0	—	+	—	+	—	±
4.	6-Nitro	Not active in 24 hours	—	±	—	±	—	±
5.	7-Hydroxy	7·2	±	+	+		—	+
6.	7-Methoxy	3·0	±	+	+		±	+
7.	7-Nitro	Not active in 24 hours	—	+	—	+	—	±
8.	8-Hydroxy	7·5	+		+		±	+
9.	8-Methoxy	2·8	+		+		+	
10.	8-Nitro	Not active in 24 hours	—	+	—	+	—	+
11.	8-Methoxy-6-nitro	Not active in 24 hours	+		+		+	
12.	8-Hydroxy-6-nitro	Not active in 24 hours	±	+	—	±	—	+
13.	8-Methoxy-6-bromo	57·5	+		+			
14.	8-Hydroxy-6-bromo	71·0	+		+		+	
15.	8-Nitro-6-bromo	Not active in 24 hours	±	+	+		+	
16.	8-Bromo-6-nitro	Not active in 24 hours	+		+		±	+
17.	6, 8-Dichloro	42·0	±	+	±	+	±	+
18.	6, 8-Dibromo	38·5	±	+	±	+	+	
19.	5, 6-Benzo	Not active in 24 hours	+		+		+	
20.	4, 6-Dimethyl	28·0	+		±	+	+	
21.	6-Nitro-4-methyl	Not active in 24 hours	—	±	—	+	—	±
22.	6-Chloro-4-methyl	8·0	±	+	±	+	+	
23.	6-Bromo-4-methyl	6·4	±	+	±	+	—	+
24.	4, 7-Dimethyl	27·1	—	+	±	+	+	
25.	7-Hydroxy-4-methyl	6·4	±	+	±	+	±	+
26.	7-Methoxy-4-methyl	2·5	+		+		±	+
27.	7-Acetamino-4-methyl	Not active in 24 hours	±	+	±	+	±	+
28.	7-Amino-4-methyl	3·9	—	+	±	+	—	±
29.	7-Chloro-4-methyl	1·4	±	+	—	±	—	+
30.	7-Bromo-4-methyl	1·2	—	+	±	+	—	±

S.A. = *Staphylococcus aureus.*　　+ = Full growth　　A = 100 ppm.
B.S. = *Bacillus subtilis*　　— = No growth　　B = 10 ppm.
B.C. = *Bacillus coli.*　　± = Partial growth.

an oil bath. The reaction mixture was then poured in ice–water, allowed to stand overnight when a pasty mass separated out. Water was decanted off and the residue was triturated with cold alcohol (5 ml.). The 4–methyl-3–(2–furyl) coumarins that separated were recrystallised from suitable solvents.

General Procedure for Deacetylation of Acetoxy Coumarins (Compound No. 5 and 27 *vide* Table II)

Acetoxy coumarin (1 g.) was dissolved in methanol (60 ml.), 15% hydrochloric acid (75 ml.) was added and refluxed on a water–bath for four hours. Half the quantity of methanol was removed under reduced pressure and the mixture was poured in water. The solid thus separated was recrystallised from a suitable solvent.

Methylation of 7– and 8-Hydroxy-3-(2-Furyl) Coumarins

To 7– or 8–Hydroxy –3– (2–furyl) coumarin (0·75 g.) dissolved in dry acetone (70 ml.), freshly ignited potassium carbonate (6 g.) and dimethyl sulphate (1 ml.) were added. The mixture was refluxed for six hours on a water–bath. Acetone was removed and the residue was treated with water and acidified. The methoxy coumarin thus separated was recrystallised from alcohol.

7–Amino–4–Methyl–3–(2–Furyl) Coumarin

The 7–acetamino–4–methyl–3–(2–furyl) coumarin (2 g.) was heated with alcoholic hydrochloric acid (2:1, 75 ml.) for two hours and allowed to stand overnight. The 7–amino–4–methyl–3–(2–furyl) coumarin that settled down (1·5 g.) was recrystallised from acetic acid.

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