SYNTHESIS OF 4-ARYL-1,4-DIHYDRO- DICOUMARINO[4,3-b;3',4'-e]PYRIDINES

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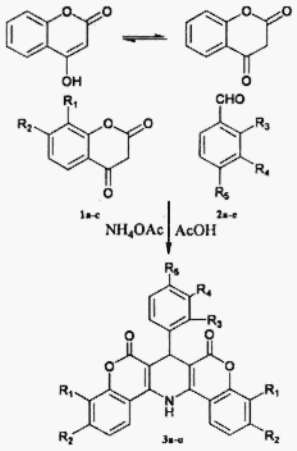
Abstract: Various 4-aryl-1,4-dihydro dicoumarino[4,3-b;3',4'-e]pyridines **3a-o** have been synthesized by reacting 4-hydroxy coumarins **1a-c** with aromatic aldehydes **2a-e** in the presence of ammonium acetate in acetic acid, under Hantzsch reaction conditions.

Introduction: Number of 4-aryl-1,4-dihydro pyridines are marketed as cardiovascular drugs. Nifedipine (1) was the first molecule of this class of compounds used as antihypertensive agent. Since then, synthesis of 4-aryl-1,4-dihydro pyridines has remained the subject of an active interest (2-5). Literature survey reveals that, however though number of 4-aryl-1,4-dihydro pyridines are reported, reports on hetero fused 1,4-dihydro pyridines are rare (6,7). As coumarins (2H-1-benzopyran-2-ones) themselves are known for varied physiological activities, their fusion with 4-aryl-1,4-dihydro pyridines may result in compounds with enhanced physiological activity. Hence, with a view to synthesizing coumarin fused 4-aryl-1,4-dihydro pyridines the present work was undertaken.

Various 4-aryl-1,4-dihydro dicoumarino [4,3-b;3',4'-e]pyridines **3a-o** have been synthesized using Hantzsch reaction. In the Hantzsch reaction (8) an aromatic aldehyde is condensed with two moles of β-keto ester and ammonia to give rise 4-aryl-1,4-dihydro pyridine. In the present work the tautomeric forms of 4-hydroxy coumarins **1a-c** (**Scheme-1**) act as a cyclic β-ketoester and condense with aromatic aldehydes **2a-e** in the presence of ammonium acetate in acetic acid and give rise the expected coumarin fused dihydropyridines **3a-o** in good yields.



3	R_1	R_2	R_3	R_4	R_5
a	H	H	H	H	H
b	H	H	NO_2	H	H
c	H	H	H	H	CH_3
d	H	H	H	H	OCH_3
e	H	H	H	OCH_3	OCH_3
f	CH_3	H	H	H	H
g	CH_3	H	NO_2	H	H
h	CH_3	H	H	H	CH_3
i	CH_3	H	H	H	OCH_3
j	CH_3	H	H	OCH_3	OCH_3
k	---benzo---		H	H	H
l	---benzo---		NO_2	H	H
m	---benzo---		H	H	CH_3
n	---benzo---		H	H	OCH_3
o	---benzo---		H	OCH_3	OCH_3

Scheme-1

Experimental Section

IR spectra were recorded in KBr on a Nicolet 400D spectrophotometer and ^1H NMR in $CDCl_3$ or DMSO-d_6 on Hitachi R-1500, 60 MHz spectrometer using TMS as an internal standard. ^{13}C of selected compounds were scanned on Bruker DPX 200MHz instrument. The required 4-hydroxy coumarins were prepared by the literature method (9).

Synthesis of 4-aryl-1,4-dihydro dicoumarino [4,3-b;3',4'-e]pyridines 3a-o. General proceudre :

In a 100mL round bottom flask, 4-hydroxy coumarin **1a-c** (0.02mole), aromatic aldehyde **2a-e** (0.01mole) and ammonium acetate (2.0g) were taken in 50mL of acetic acid. The reaction mixture was stirred for 10 minutes at room temperature and then refluxed in an oil bath at 130^{0}C for 6 hours. It was allowed to come to room temperature and was left overnight. The reaction mixture was poured into ice-cold water (150mL) and extracted with ethyl acetate (3 × 50mL). The combined organic layer was washed with 5% $NaHCO_3$ solution (3 × 25mL) and then with water (3 × 30mL). It was dried on sodium sulfate and ethyl acetate was distilled under vacuum to afford crude solid. The crude product was purified by column chromatography over silica-gel using hexane-ethylacetate as an eluent to give 4-aryl-1,4-dihydro dicoumarino[4,3-b;3',4'-e]pyridines **3a-o** in good yields (**Table-1**).

Acknowledgements

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

Table I — Characterization data of compounds **3a-o**

Compd*	mp (°C)	Yield (%)	Mol. formula	Found (Calc.) (%)			^{1}HMR (δ, ppm)
				C	H	N	
3a	209	59	$C_{25}H_{15}NO_4$	76.2 (76.3	3.7 3.8	3.5 3.6)	6.10 δ (1H, s, methine -CH), 7.26-8.08 δ (13H, m, aromatic protons), 11.51 δ (1H, broad, -NH, D_2O exchangeable)
3b	216	57	$C_{25}H_{14}N_2O_6$	68.4 (68.5	3.0 3.2	6.2 6.4)	6.63 δ (1H, s, methine -CH), 7.29-8.08 δ (12H, m, aromatic protons), 11.46 δ (1H, broad, -NH, D_2O exchangeable)
3c	257-58	61	$C_{26}H_{17}NO_4$	76.5 (76.7	4.0 4.2	3.5 3.4)	2.32 δ (3H, s, $-CH_3$), 6.06 δ (1H, s, methine -CH), 7.10-8.09 δ (12H, m, aromatic protons), 11.33 δ (1H, broad, -NH, D_2O exchangeable)
3d**	237	60	$C_{26}H_{17}NO_5$	73.6 (73.8	4.1 4.0	3.2 3.3)	3.78 δ (3H, s, $-OCH_3$), 6.40 δ (1H, s, methine -CH), 6.75-8.08 δ (12H, m, aromatic protons), 11.30 δ (1H, broad, -NH, D_2O exchangeable)
3e	239-41	57	$C_{27}H_{19}NO_6$	71.4 (71.5	4.1 4.2	3.0 3.1)	3.73 & 3.90 δ (6H, 2×s, 2×-OCH_3), 6.07 δ (1H, s, methine -CH), 6.79-8.09 δ (11H, m, aromatic protons), 11.40 δ (1H, broad, -NH, D_2O exchangeable)
3f	261	60	$C_{27}H_{19}NO_4$	76.9 (77.0	4.4 4.5	3.2 3.3)	2.49 δ (6H, s, 2×-CH_3), 6.12 δ (1H, s, methine -CH), 7.11-7.93 δ (11H, m, aromatic protons), 11.45 δ (1H, broad, -NH, D_2O exchangeable)
3g	209	59	$C_{27}H_{18}N_2O_6$	69.4 (69.5	3.8 3.9	5.9 6.0)	2.47 δ (6H, s, 2×-CH_3), 6.65 δ (1H, s, methine -CH), 7.12-7.92 δ (10H, m, aromatic protons), 11.38 δ (1H, broad, -NH, D_2O exchangeable)
3h**	286	63	$C_{28}H_{21}NO_4$	77.1 (77.2	4.7 4.8	3.3 3.2)	2.32 & 2.49 δ (9H, 2×s, 3×-CH_3), 6.37 δ (1H, s, methine -CH), 7.10-7.93 δ (10H, m, aromatic protons), 11.43 δ (1H, broad, -NH, D_2O exchangeable)
3i	259	60	$C_{28}H_{21}NO_5$	74.4 (74.5	4.5 4.7	3.0 3.1)	2.48 δ (6H, s, 2×-CH_3), 3.78 δ (3H, s, -OCH_3) 6.05 δ (1H, s, methine -CH), 6.75-7.92 δ (10H, m, aromatic protons), 11.45 δ (1H, broad, -NH, D_2O exchangeable)
3j	248	59	$C_{29}H_{23}NO_6$	72.3 (72.4	4.6 4.8	2.8 2.9)	2.50 δ (6H, s, 2×-CH_3), 3.74 & 3.86 δ (6H, 2×s, 2×-OCH_3) 6.09 δ (1H, s, methine-CH), 6.80-7.93 δ (9H, m, aromatic protons), 11.55 δ (1H, broad, -NH, D_2O exchangeable)

3k	240	58	$C_{33}H_{19}NO_4$	80.2 (80.3	3.7 3.9	2.7 2.8)	6.04 δ (1H, s, methine -CH), 7.32-8.10 δ (17H, m, aromatic protons), 11.40 δ (1H, broad, -NH, D_2O exchangeable)
3l	243	55	$C_{33}H_{18}N_2O_6$	73.5 (73.6	3.5 3.4	5.4 5.2)	6.62 δ (1H, s, methine -CH), 7.50-8.08 δ (16H, m, aromatic protons), 11.42 δ (1H, broad, -NH, D_2O exchangeable)
3m**	255	57	$C_{34}H_{21}NO_4$	80.6 (80.5	4.1 4.2	2.6 2.7)	2.33 δ (3H, s, $-CH_3$), 6.19 δ (1H, s, methine -CH), 7.15-8.56 δ (16H, m, aromatic protons), 11.60 δ (1H, broad, -NH, D_2O exchangeable)
3n	194	60	$C_{34}H_{21}NO_5$	77.9 (78.0	3.9 4.0	2.5 2.7)	3.86 δ (3H, s, $-OCH_3$), 6.23 δ (1H, s, methine -CH), 6.85-8.55 δ (16H, m, aromatic protons), 11.35 δ (1H, broad, -NH, D_2O exchangeable)
3o	222	58	$C_{35}H_{23}NO_6$	76.6 (76.4	4.1 4.2	2.4 2.5)	3.70 & 3.85 δ (6H, 2×s, 2×-OCH_3), 6.20 δ (1H, s, methine -CH), 6.82-8.54 δ (15H, m, aromatic protons), 11.45 δ (1H, broad, -NH, D_2O exchangeable)

*All compounds exhibited the characteristic IR bands at ~3450 (N-H stretching) and ~1697-1700 cm^{-1} (δ-lactone carbonyl of coumarin).

** ^{13}C-NMR data:

Compound 3d: (DMSO-d_6, 200MHz, δ ppm): 34.13 (CH), 53.95 (OCH_3), 103.71 (2xC), 112.67 (2xCH), 115.13 (2xCH), 115.76 (2xC), 122.88 (2xCH), 123.15 (2xCH), 126.70 (2xCH), 128.30 (C), 131.28 (2xCH), 151.11 (2xC), 156.79 (C), 163.00 (2xC), 164.59 (2xCO).

Compound 3h: ($CDCl_3$, 200MHz, δ ppm): 14.43 (2xCH_3), 19.89 (CH_3), 34.65 (CH), 103.56 (2xC), 115.53 (2xC), 120.71 (2xCH), 122.97 (2xCH), 124.47 (2xC), 125.65 (2xCH), 128.12 (2xCH), 132.63 (2xCH), 133.25 (C), 134.55 (C), 149.65 (2xC), 163.51 (2xC), 165.17 (2xCO)

Compound 3m: (DMSO-d_6, 200MHz, δ ppm): 21.64 (CH_3), 36.61 (CH), 106.37 (C), 112.79 (C), 113.25 (C), 120.16 (2xCH), 123.02 (2xCH), 123.39 (2xC), 125.47 (2xCH), 127.09 (2xCH), 127.96 (2xCH), 128.61 (2xCH), 129.68 (2xCH), 130.02 (2xCH), 132.82 (2xC), 136.05 (2xC), 137.13 (2xC), 150.50 (C), 150.79 (C), 166.13 (CO), 167.52 (CO).

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Received on July 13, 2004.