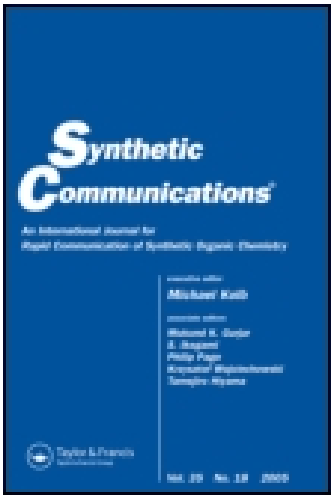

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Synthesis of 2-Methyl-9-oxo-9H-furo[2,3-c]benzopyrans and 2-Methyl-3H,4H[1]benzopyrano[3,4-b]pyrrol-4-ones

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SYNTHESIS OF 2-METHYL-9-OXO-9*H*-FURO[2,3-*c*]BENZO PYRANS AND 2-METHYL-3*H*,4*H*[1]BENZOPYRANO[3,4-*b*] PYRROL-4-ONES

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Abstract: *3:4-Fused furocoumarins and pyrrolocoumarins are synthesised from 3-hydroxy and 3-benzamido- substituted coumarins by a novel two step sequence.*

Many substituted natural coumarins are biologically active and development of new synthetic methodologies for coumarins and fused-ring derivatives has received considerable attention, with numerous routes reported. The relatively few methods available for the synthesis of 3,4-fused coumarins include (i) allylation, migration and cyclisation[1,2,3,4] (ii) acetonylation and cyclisation[1] (iii) phenacylation and cyclisation[1] etc.. These three routes are all multistep and often utilise severe reaction conditions and may lack generality. Coumarins with 3,4-additional heterocyclics, such as furo [3,2-*c*]coumarins are reported in the literature, for which the starting materials are 4-hydroxy-

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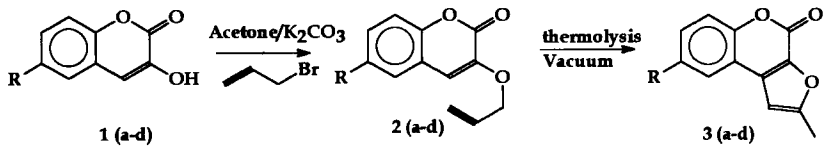
coumarins[5,6,7,8]. However , similar fused heterocyclics starting from 3-hydroxy-coumarins do not seem to have been well studied.

We now report that 3-hydroxycoumarins(1a-d) and 3-benzamido-coumarins(4a-d) react readily with propargyl bromide to form O- and N- propargyl derivatives which on thermal cyclisation form fused five membered rings(3a-d & 6a-d). Thus 6-halo-, 6-alkyl-, and 8-halo- 3,4-fused furo- and pyrrolo- coumarins have been prepared from the respective 3-hydroxy- or 3-benzamidocoumarins.

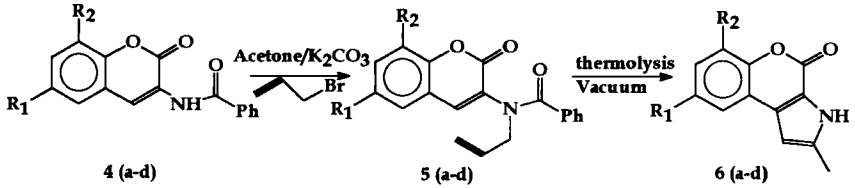
3-Hydroxycoumarins (1a-d) were prepared from salicylaldehydes and acetylglycine[9,10.11]. Compound (1a) reacts with propargyl bromide in the presence of acetone / K_2CO_3 on a steam bath to afford 3-propargyloxycoumarin(2a) (Scheme 1). 3-Propargyloxycoumarin(2a) was subjected to Claisen rearrangement by heating in vacuum at 150^{0}C to yield 2-methyl-9-oxo-9*H*-furo[2,3-*c*]benzopyran (3a). Similarly, starting from 1b,1c and 1d, compounds 3b, 3c and 3d were synthesised. Satisfactory I.R, N.M.R and EIMS spectra were obtained .

3-Benzamidocoumarins (4a-d) were prepared from respective salicylaldehydes and benzoylglycine[12,13]. Thus 3-benzamidocoumarin (4a) was subjected to propargylation in acetone / K_2CO_3 on a steam bath to yield 3-N-propargyl-N-benzoylcoumarin (5a) which on Claisen rearrangement in vacuum at 160^{0}C yielded 2-methyl-3*H*,4*H*[1]benzopyrano[3,4-*b*]pyrrol-4-one[14](6a), m.p. 209^{0}C. Similarly compounds 6b, 6c and 6d were synthesised from 4b, 4c and 4d respectively. We observed that the benzoyl group present on nitrogen atom in 3-N-benzoyl-N-propargylcoumarins was expelled in the thermal reaction conditions. Similar observation was also reported by Makisumi et al.[15] in the synthesis of the

indole ring system from N-benzoyl-N-propargylaniline. The intermediate compounds (2a-d), and (5a-d) are new and gave satisfactory I.R, N.M.R and analytical data. (The antifeedent data for these compounds will be reported elsewhere).



SCHEME-1



SCHEME-2

1. a. R=H	2. a. R=H	3. a. R=H	4. a. R1=H,R2=H	5. a. R1=H,R2=H	6.a. R1=H,R2=H
b.R=CH3	b. R=CH3	b. R=CH3	b. R1=H,R2=Cl	b. R1=H,R2=Cl	b. R1=H,R2=Cl
c. R=Cl	c. R=Cl	c. R=Cl	c. R1=CH3,R2=H	c. R1=CH3,R2=H	c. R1=CH3,R2=H
d.R=Br	d. R=Br	d. R=Br	d. R1=Br,R2=H	d. R1=Br,R2=H	d. R1=Br,R2=H

Experimental

Melting points were taken in open capillary on sulphuric acid bath and are uncorrected. ^{1}H-NMR spectra were obtained on Varian Gemini 200 spectrometer. Chemical shifts are reported in (δ) ppm in $CDCl_3$ with internal TMS. I.R spectra were determined on FT-IR Perkin-Elmer 1710 spectrophotometer. Mass spectra were recorded on UG Micromass 7070 H spectrometer. Purification of compounds was done by silica gel columns.

General procedure for the synthesis of 3-propargyloxycoumarins 2(a-d)

3-Hydroxycoumarins (1a-d) (10mmol) propargyl bromide (10mmol) and K_2CO_3 (5g) in acetone (40ml.) were refluxed on steam bath for 36h. The solution was filtered and distilled. The crude product was chromatographed over silica gel and eluted with benzene to give 3-propargyloxycoumarins (2a-d).

3-Propargyloxycoumarin (2a). mp 160^{0}C (Yield 75%) ^{1}H NMR ($CDCl_3$): δ2.50 (t,1H,$\equiv$CH), 4.8(d, 2H ,OCH_2), 7.00(s,1H,H-4), 7.20-7.40(m, 4H,arom). Anal: calc for $C_{12}H_8O_3$: C 72.00, H 4.03%; Found: C 71.87, H 4.09%.

6-Methyl-3-propargyloxycoumarin (2b). mp 167^{0}C. (Yield 80%)^{1}H NMR ($CDCl_3$): δ 2.4(s, 3H,CH_3), 2.55(t,1H,$\equiv$CH), 4.80(d, 2H ,OCH_2), 7.00(s,1H,H-4), 7.20 (m, 3H,arom). Anal: calc for $C_{13}H_{10}O_3$ C 72.89, H 4.71%; Found: C 72.86, H 4.72%.

6-Chloro-3-propargyloxycoumarin (2c). mp 185^{0}C. (Yield 70%) ^{1}H NMR ($CDCl_3$): δ 2.50(t,1H,$\equiv$CH), 4.80(d, 2H ,OCH_2), 7.00(s,1H,H-4), 7.20(d, J=10Hz, 1H,H-8), 7.35(d,J=10Hz,H-7), 7.45(d,J=2Hz,H-5). Anal: calc for $C_{12}H_7O_3Cl$: C 61.54, H 2.99%; Found: C 61.53, H 3.00%.

6-Bromo-3-propargyloxycoumarin (2d). mp 183^{0}C. (Yield 75%) ^{1}H NMR ($CDCl_3$): δ 2.50(t,1H,$\equiv$CH), 4.75(d, 2H ,OCH_2), 6.85(s,1H,H-4), 7.15(d, J=10Hz, 1H,H-8), 7.4(d,J=10Hz,H-7), 7.50(d,J=2Hz,H-5). Anal: calc for $C_{12}H_7O_3Br$: C 49.82, H 2.42%; Found: C 49.80, H 2.41%.

General procedure for synthesis of 2-methyl-9-oxo-9*H*-furo[2,3-*c*]benzopyrans (3a-d) 3-Propargyloxycoumarins (2a-d) (10mmol) were heated under vacuum at their melting points for 24hrs. The crudes were chromatographed over silica gel

and eluted with benzene to give 2-methyl-9-oxo-9*H*-furo[2,3-*c*]benzopyrans(3a-d).

2-Methyl-9-oxo-9*H*-furo[2,3-*c*]benzopyran (3a) mp.159^{0}C, (Yield 40%) I.R (KBr) cm^{-1} 1723, ^{1}H NMR 7.6(d,1H), 7.4(m,1H),7.25(m,1H), 6.65 (s,1H); 2.5 (s,3H). ^{13}C NMR 162,153,137,135,130,125,124,118,116,103,15.and MS m/z(%) 200(100), 185(20), 144(35). Anal.: calc. for $C_{12}H_8O_3$ C 72.00, H 4.03%; Found: C 71.89, H 4.07%.

2,8-Dimethyl-9-oxo-9*H*-furo[2,3-*c*]benzopyran (3b) mp136^{0}C.(Yield 45%) IR (KBr) cm^{-1}1717, ^{1}H NMR 7.40(s,1H); 7.30(m,2H); 6.60(s,1H); 2.60(s,3H); 2.40 (s,3H), MS m/z(%) 214(100),199(10),158(20). Anal.: calc. for $C_{13}H_{10}O_3$ C 72.89, H 4.71%; Found: C 72.85, H 4.70%.

8-Chloro-2-methyl-9-oxo-9*H*-furo[2,3-*c*]benzopyran (3c) mp.170^{0}C. (Yield 35%) IR (KBr) 1740, ^{1}H NMR 7.62(d,1H);7.58(d,1H),7.4(d,1H); 6.6(s,1H); 2.5(s,3H), MS m/z(%) 234(100),219(10),181(30). Anal.: calc. for $C_{12}H_7ClO_3$ C 61.54, H 2.99%; Found: C 61.52, H 3.01%.

8-Bromo-2-methyl-9-oxo-9*H*-furo[2,3-*c*]benzopyran (3d) mp.222^{0}C ,(Yield 45%) IR (KBr) 1738, ^{1}H NMR 7.65(d,1H);7.45(d,1H);7.25(d,1H); 6.5(s,1H); 2.5(s,3H), MS m/z (%) 278(100),263(20),224(30),209(28). Anal.: calc. for $C_{12}H_7BrO_3$ C 49.82, H 2.42% ; Found: C 49.81, H 2.40%.

General procedure for the synthesis of 3-benzamido-N-propargylcoumarins (5a-d). 3-Benzamidocoumarins (4a-d) (10mmol) propargyl bromide (10mmol) and K_2CO_3 (5g) in acetone (40ml.) were refluxed on steam for 10h. Acetone was filtered and distilled and the crude chromatographed over silica gel and eluted with benzene to give 3-benzamido-N-propargyl coumarins (5a-d).

3-Benzamido-N-propargyloxycoumarin (5a). mp 133^{0}C. (Yield 70%)^{1}H NMR ($CDCl_3$): δ 2.20 (t,1H, $^{\equiv}$CH), 4.70 (d, 2H, N-CH_2), 7.00 (s,1H, H-4), 7.15-7.60 (m, 9H, arom). Anal: calc for $C_{18}H_{13}NO_3$: C 74.22, H 4.50, N 4.81%; Found: C 74.20, H 4.80, N 4.80%.

8-Chloro-3-benzamido-N-propargylcoumarin (5b). mp 138^{0}C. (Yield 60%) ^{1}H NMR ($CDCl_3$): δ 2.30(t,1H, $^{\equiv}$CH), 4.70(d, 2H ,N-CH_2), 6.85 (s,1H, H-4), 7.15-7.70 (m, 8H, arom). Anal: calc for $C_{18}H_{12}ClNO_3$: C 66.46, H 3.69, N 4.31%; Found: C 66.44, H 3.69, N 4.30%.

6-Methyl-3-benzamido-N-propargylcoumarin (5c). mp 150^{0}C. (Yield 55%) ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.60 (t,1H, $^{\equiv}$CH), 4.80 (d, 2H ,N-CH_2), 7.00 (s,1H,H-4), 7.10-7.70 (m, 8H, arom). Anal: calc for $C_{19}H_{15}NO_3$: C 74.74, H 4.95, N 4.59%; Found: C 74.70, H 4.93, N 4.58%.

6-Bromo-3-benzamido-N-propargylcoumarin (5d). mp 187^{0}C. (Yield 60%), ^{1}H NMR ($CDCl_3$): δ 2.40 (t,1H, $^{\equiv}$CH), 4.70(d, 2H ,N-CH_2), 6.90 (s,1H, H-4), 7.10(m, 8H, arom). Anal: calc for $C_{18}H_{12}BrNO_3$: C 58.54, H 3.25, N 3.79%; Found : C 58.52, H 3.26, N 3.79%.

General procedure for synthesis of 2-methyl-3*H*,4*H*[1]benzopyrano[3,4-*b*]pyrrol-4-ones (6a-d) 3-Benzamido-N-propargylcoumarins (5a-d) (10mmol) were heated under vacuum at their melting points for 24h. The crudes were chromatographed over silica gel and eluted with benzene to give 2-methyl-3*H*,4*H*[1]benzopyrano[3,4-*b*]pyrrol-4-ones(6a-d).

2-Methyl-3*H*,4*H*[1]benzopyrano[3,4-*b*]pyrrol-4-one (6a)

mp. 209^{0}C, (Yield 45%) IR (KBr) 3232,1699,^{1}H NMR 7.25(m,4H); 6.45(s,1H);

2.55(s,1H); 2.4 (s,3H) MS m/z(%) 199(100), 170(48), 142(10). Anal.: calc for $C_{12}H_9NO_2$, C 72.35%, H 4.55%, N 7.02%, found : C 72.36%, H 4.54%, N 7.02%.

6-Chloro-2-methyl-3*H*,4*H*[1]benzopyrano[3,4-*b*]pyrrol-4-one (6b) mp.282^{0}C, (Yield 35%) IR (KBr)3245, 1716, ^{1}H NMR 7.68(d,1H); 7.40(d,1H);7.25(d,1H); 6.45(s,1H); 2.60(s,1H); 2.45(s,3H); Ms m/z(%) 235(30), 233(100), 204(20). Anal.: calc for $C_{12}H_8ClNO_2$: C 61.80%, H 3.43%, N 6.01%, found : C 61.82%, H 3.40%, N 6.02%.

2,8-Dimethyl-3*H*,4*H*[1]benzopyrano[3,4-*b*]pyrrol-4-one (6c)

mp138^{0}C (Yield 30%) IR (KBr) cm^{-1} 3246,1719, ^{1}H NMR 7.40(s,1H); 7.25 (m,2H); 6.60(s,1H); 2.60(s,3H); 2.50(s,1H), 2.4(s,3H), MS m/z(%) 213(100), 198(10), 158(20). Anal.: calc. for $C_{13}H_{11}NO_2$: C 73.23%, H 5.20%, N 6.57%, found : C 73.25%, H 5.18%, N 6.56%.

8-Bromo-2-methyl-3*H*,4*H*[1]benzopyrano[3,4-*b*]pyrrol-4-one (6d)

mp.245^{0}C (Yield 30%) IR (KBr) 3229,1716, ^{1}H NMR 7.55(d,1H); 7.25(m,2H); 6.60(s,1H), 2.60(s,1H), 2.50(s,3H), MS m/z (%) 279(100), 277(100), 262(20), 224 (30), 209(28). Anal.: calc. for $C_{12}H_8BrNO_2$: C 51.61%, H 2.87%, N 5.02%, found : C 51.63%, H 2.85%, N 5.03%.

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