FACILE SYNTHESIS OF SUBSTITUTED 4-HYDROXY COUMARINOBENZOTHIOPHENES

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***Abstract**: The Lewis acid in dichloromethane mediated cyclization and demethylation of substituted 2-aryl-2-((2-methoxy phenyl)thio)acetophenones 3a-f at room temperature converting into 7-hydroxy-2,3-diaryl substituted benzothiophenes 4a-f.These were condenced with substituted malonic acids by the same reagent to produce the substituted 4-hydroxy coumarino benzothiophenes (6a-f & 7a-f).*

Introduction:

4-Hydroxy coumarins and their derivatives are reported to possess a wide range of biological activities, predominantly anti-coagulants[1] and HIV Protease inhibitors[2,3]. Some derivatives of 4-hydroxy coumarins having potent anti-coagulant properties[4].In continuation of our studies on the synthesis of 4-hydroxy coumarino benzothiophene derivatives, we carried out studies on the reaction of 7-hydroxy-2,3-diaryl substituted benzothiophenes 4a-f with substituted malonic acids leading to the formation of mono substituted 4-hydroxy coumarino benzothiophenes (6a-f & 7a-f).

Results and discussions:

4-Hydroxy coumarin is normally synthesized from a condensation of phenol with malonic acid in the prosence of $ZnCl_2$,and $POCl_3$[5]. Synthesis of 4-hydroxy coumarin by starting from o-hydroxy acetophenone and condensing with diethyl carbonate[6] and other carbonyl equivalents[7,8] has also been well studied.

In continuation of our interest in the development of efficient and simple procedures for the synthesis of the fused sulfur heterocyclic compounds, as we report in this paper a new synthesis of substituted 4-hydroxy coumarino benzothiphenes 6a-f

and 7a-f by the reaction of 7-hydroxy-2,3-diaryl benzothiophenes 4a-f with substituted malonic acids. Thus it has been found that 2-methoxy thiophenol reacted with substituted desylbromide[9] 2a-f to give 2-aryl-2- ((2-methoxy phenyl) thio-acetophenones 3a-f. Later these were treated with anhydrous $AlCl_3$ in DCM at room temperature, condensation and demethylation takes place yielding the corresponding 7-hydroxy-2,3-diaryl benzothiophenes 4a-f in good yields. Treatment of 4a-f with substituted malonic acids with anhydrous $AlCl_3$ in DCM as a solvent, and by stirring for 12-14 h at room temperature gave the title compounds 6a-f and 7a-f.

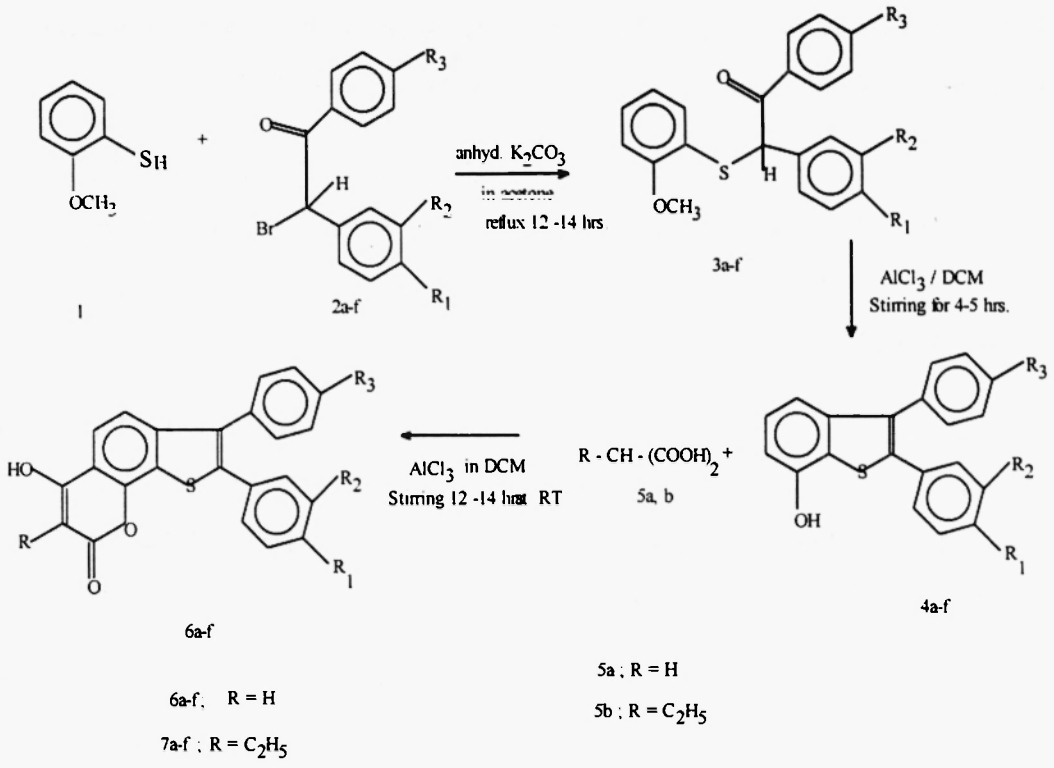
The structures of compounds 6a-f and 7a-f were established on the basis of their elemental and spectral data(IR,MASS,^{1}HNMR).

The I.R. spectra of all the final products exhibit a broad bands in the region of 3430-3450 cm^{-1} due to –OH stretching vibrations, while a sharp peak is observed in the region of 1680-1700cm^{-1} for –CO group and the peak at 750cm^{-1} is for C-S stretching vibrations.

The ^{1}HNMR spectra of all the products 6a-f and 7a-f having hydroxy group at fourth position exhibits a singlet at δ 12.4, and a singlet is observed at δ 5.34-5.42 due to coumarino-3H proton. In mass spectra of all compounds 6a-f and 7a-f, molecular ion peaks are all in accordance with their molecular weights.

Experimental procedure:

All the melting points are uncorrected.The purity was checked by thin layer chromatography and characterized by spetral studies.The IR spectra were recorded on shimadzu FTIR model 8010 Spectrophotometer and are given in cm^{-1} in KBr.The ^{1}HNMR spectra in $CDCl_3$ were record on C17-20-ZM-390 200 MHz NMR Spectrophotometer and are reported in δ units (ppm) relative TMS as an internal standard. The mass spectra of the compounds described are recorded on Jeol TMS-D300 at 70ev.



2a : $R_1 = R_2 = R_3 = H$ 2b : $R_1 = R_2 = H : R_3 = Br$ 2c : $R_1 = R_2 = H : R_3 = CH_3$
2d : $R_1 = R_2 = F : R_3 = H$ 2e : $R_1 = R_2 = F : R_3 = Br$ 2f : $R_1 = R_2 = F : R_3 = CH_3$

7-Hydroxy-2,3-diaryl benzothiophenes(4a-f):

Compound 3c(3.09g,0.01mol)was dissolved in dry DCM(10ml)to obtained a clear solutions.To this was added a solution of aluminium chloride(26.0g) in dry DCM(5ml) and the resulting solution was stirred under N_2 atmosphere for 4-5 h at room temperature and washed with water (20ml) dried with Na_2SO_4 and Concentrated in vaccuo to afforded a light brown oil separated by coloumn chromatography (EtOAc/pet.ether=1:9) provided 1.89g(60%)of the desired compound 4c.^{1}HNMR (200MHz, $CDCl_3$) δ(Ppm) 6.78-6.92 (4H, dd, Ph-CH_3), 7.06-7.35 (5h, m, Ar-H), 7.49-7.92 (3H,m,Ph-OH),10.46 (1H,br,S-OH), 2.42 (3H,s,CH_3) ; Mass(m/z) : 335(M^+);

Substituted 4-hydroxy coumarino benzothiophenes (6a-f and 7a-f):

Mixture of compounds 4a-f (0.01mol) substituted malonic acids(0.01mol)was in dry DCM (10ml) to obtained a clear solution.To this was added solution of $AlCl_3$(26.0g) in dry DCM and the resulting solution was stirred under N_2 atmosphere for 12-14 h at room temperature.The mixture was poured in to crushed ice containig conc.HCl.The organic layer was separated out with DCM and dried over anhydrous

Na_2SO_4.The solvent is removed under reduced pressure to afford a reddish crude which was purified by coloumn chromotography (EtOAc:pet.ether=2:8).

6a : Mol.formula: $C_{23}H_{14}O_3S$:Yield:61%,IR(cm^{-1}) : 3430 (br,-OH), 3100, 2900(C-H), 1720 (C=O),1010 (C-O), 750 (C-S), ^{1}HNMR(200MHz,$CDCl_3$) δ(Ppm) 5.42 (s,1H,Coumarino-H), 6.74-6.83 (m, 5H, Ar-H), 6.95-6.83(m, 5H, Ar-H), 7.40-7.51 (dd, 2H, Ar-H), 12.42 (s,1H,-OH) : Mass;370(M^+).

6b : Mol.formula : $C_{23}H_{13}O_3S$: Yield:59%, IR(cm^{-1}) : 3432 (br,-OH), 3095, 2905 (C-H), 1720 (C=O), 1010 (C-O), 750 (C-S), ^{1}HNMR(200MHz, $CDCl_3$) δ(Ppm) 5.43 (s, 1H, Coumarino-H), 6.76-6.86 (m, 4H, Ar-H), 6.91-7.00 (m, 5H, Ar-H), 7.38-7.49 (dd,2H,Ar-H), 12.43 (s, 1H, -OH) : Mass(m/z) ; 421(M^+),

6c : Mol.formula : $C_{24}H_{16}O_3S$: Yield : 62%, IR(cm^{-1}) : 3430 (br,-OH), 3100, 2900 (C-H), 1720 (C=O), 1000 (C-O), 750 (C-S), ^{1}HNMR(200MHz,$CDCl_3$) δ(Ppm) 2.42 (s, 3H, CH_3), 5.42 (s, 1H, Coumarino-H), 6.78-6.89 (m, 4H, Ar-H), 6.90-7.05 (m, 5H, Ar-H), 7.39-7.47 (dd, 2H, Ar-H), 12.42 (s, 1H, -OH) : Mass(m/z) ; 384 (M^+), 356.

6d : Mol.formula: $C_{23}H_{12}O_3SF_2$: Yield: 60%, IR (cm^{-1}): 3430 (br, -OH), 3105, 2905 (C-H), 1720 (C=O), 1000 (C-O), 750 (C-S), ^{1}HNMR(200MHz,$CDCl_3$) δ(Ppm) 5.42 (s, 1H, Coumarino-H), 6.70-6.89 (m, 5H, Ar-H), 7.43-7.52 (dd, 2H, Ar-H), 7.71-7.82 (s, 1H, Ar-H), 7.82-7.89 (dd, 2H, Ar-H), 12.40 (s, 1H, -OH) : Mass(m/z) ; 406 (M^+), 378.

6e : Mol.formula : $C_{23}H_{13}O_3SF_2Br$: Yield : 58%, IR (cm^{-1}) : 3440 (br,-OH), 3050, 2900 (C-H), 1720 (C=O), 1000 (C-O), 750 (C-S), ^{1}HNMR(200MHz, $CDCl_3$) δ(Ppm) 5.4 (s, 1H, Coumarino-H), 7.12-7.24 (s, 1H, Ar-H), 7.34-7.57 (dd, 2H, Ar-H), 7.62-7.84 (dd, 4H, Ph-Br), 7.91-8.14 (dd, 2H, Ar-H), 12.40(s, 1H, -OH) : Mass(m/z) ; 485 (M^+), 457.

6f : Mol.formula : $C_{24}H_{16}O_3F_2S$: Yield : 61%, IR (cm^{-1}) : 3435 (br, -OH), 3100, 2900 (C-H), 1720 (C=O), 1000 (C-O), 750 (C-S), ^{1}HNMR(200MHz, $CDCl_3$) δ(Ppm) 2.42 (s, 3H, CH_3), 5.42 (s, 1H, Coumarino-H), 6.92-7.1 (s, 1H, Ar-H), 7.23-7.34 (dd, 2H, Ar-H), 7.46-7.74 (dd, 4H, Ph-CH_3), 7.87-7.91 (dd, 2H, Ar-H), 12.40 (s, 1H, -OH) : Mass (m/z) ; 420 (M^+), 392.

7a : Mol.formula: $C_{25}H_{18}O_3S$: Yield: 60%, IR (cm^{-1}): 3430 (br, -OH), 3100, 2900 (C-H), 1720 (C=O), 1010 (C-O), 750 (C-S), ^{1}HNMR(200MHz, $CDCl_3$) δ(Ppm) 2.41 (t, 3H, CH_3), 3.80-4.10 (q, 2H, CH_2), 6.74-6.83 (m, 5H, Ar-H), 6.95-6.83 (m, 5H, Ar-H), 7.40-7.51 (dd, 2H, Ar-H), 12.42 (s, 1H, -OH) : Mass ; 398 (M^+).

7b: Mol.formula: $C_{25}H_{17}O_3S$: Yield: 59%, IR (cm^{-1}): 3432 (br, -OH), 3095, 2905 (C-H), 1720 (C=O), 1010 (C-O), 750 (C-S), ^{1}HNMR(200MHz, $CDCl_3$) δ(Ppm) 2.40 (t, 3H, CH_3), 3.79-4.09 (q, 2H, CH_2), 6.76-6.86(m, 4H, Ar-H), 6.91-7.00 (m, 5H, Ar-H), 7.38-7.49 (dd, 2H, Ar-H), 12.43 (s, 1H, -OH) : Mass (m/z) ; 449 (M^+).

7c: Mol.formula: $C_{26}H_{20}O_3S$: Yield: 61%, IR (cm^{-1}): 3430 (br, -OH), 3100, 2900 (C-H), 1720 (C=O), 1000 (C-O), 750 (C-S), ^{1}HNMR(200MHz, $CDCl_3$) δ(Ppm) 2.38 (t, 3H, CH_3), 3.81-4.08 (q, 2H, CH_2), 6.78-6.89 (m, 4H, Ar-H), 6.90-7.05 (m, 5H, Ar-H), 7.39-7.47 (dd, 2H, Ar-H), 12.42 (s, 1H, -OH) : Mass (m/z) ; 409 (M^+), 384.

7d : Mol.formula : $C_{25}H_{16}O_3SF_2$: Yield : 63%, IR (cm^{-1}) : 3430 (br, -OH), 3105, 2905 (C-H), 1720 (C=O), 1000 (C-O), 750 (C-S), ^{1}HNMR(200MHz, $CDCl_3$) δ(Ppm) 2.40 (t, 3H, CH_3), 3.81-4.09 (q, 2H, CH_2), 6.70-6.89 (m, 5H, Ar-H), 7.43-7.52 (dd, 2H, Ar-H), 7.71-7.82 (s, 1H, Ar-H), 7.82-7.89 (dd, 2H, Ar-H), 12.40 (s,1H, -OH) : Mass (m/z) ; 434 (M^+), 406.

7e: Mol.formula: $C_{25}H_{17}O_3SF_2Br$: Yield: 58%,IR(cm^{-1}): 3440 (br,-OH), 3050, 2900 (C-H),1720 (C=O), 1000 (C-O), 750 (C-S), ^{1}HNMR(200MHz, $CDCl_3$) δ(Ppm) 2.42 (t, 3H, CH_3), 3.80-4.10 (q ,2H, CH_2), 7.12-7.24 (s, 1H, Ar-H), 7.34-7.57 (dd, 2H, Ar-H), 7.62-7.84 (dd, 4H, Ph-Br), 7.91-8.14 (dd, 2H, Ar-H), 12.40 (s, 1H, -OH) : Mass (m/z) ; 513 (M^+), 485.

7f : Mol.formula : $C_{26}H_{20}O_3F_2S$: Yield : 61%, IR (cm^{-1}) : 3435 (br, -OH), 3100, 2900 (C-H), 1720 (C=O), 1000 (C-O), 750 (C-S), ^{1}HNMR(200MHz, $CDCl_3$) δ(Ppm) 2.37 (t, 3H, CH_3), 3.78-4.08 (q, 2H, CH_2) 2.42 (s, 3H, CH_3), 6.92-7.1 (s, 1H, Ar-H), 7.23-7.34 (dd, 2H, Ar-H), 7.46-7.74 (dd, 4H, Ph-CH_3), 7.87-7.91 (dd, 2H, Ar-H), 12.40 (s, 1H, -OH) : Mass (m/z) ; 448 (M^+), 420.

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