

ONE-STEP SYNTHESIS OF,7,7¹-ARYLIDENE BIS- [6-HYDROXY,SUBSTITUTEDTHIENO(3,2-h)COUMARINS]

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ABSTRACT: One step synthesis of 7,7¹-Arylidene bis-[6-hydroxy,substituted thieno(3,2-h)coumarins] (3a-d), (4a-d),(5a-d)&(6a-d) was described by the condensation of 6-hydroxy,substituted thieno(3,2-h)coumarins (1a-d) with substituted aromatic aldehydes (2a-d) in the presence of Iso-propyl alcohol.

Keywords: 6-hydroxy,substitutedthieno(3,2-h)coumarins,7,7¹-Arylidenebis-[6-hydroxy, substituted thieno(3,2-h)coumarins]

INTRODUCTION:

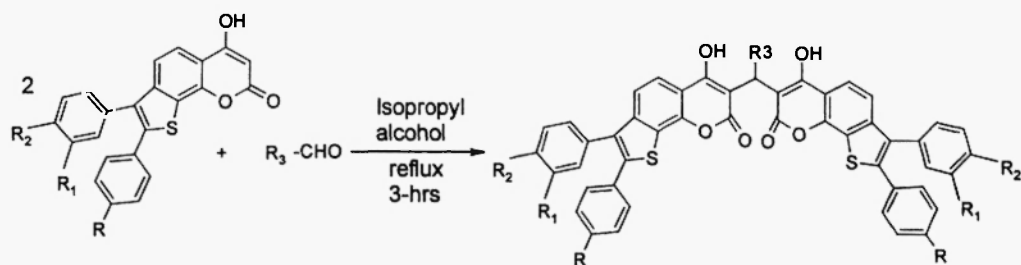
4-Hydroxy coumarins and their derivatives are used as bacteriocides [1-3], fungicides [4], anti-inflammatory [5], anticoagulant [6], and antitumour agents [7, 8]. 4- Hydroxy pyrone ring was proved to be as a pharmacophore based on its crystal structure [9]. The sulfonamide containing 4-hydroxy coumarins and 4- hydroxy-2-pyrones were established as protease inhibitory template [10]. Simultaneously number of dimeric and tetrameric coumarins were explored for their inhibitory potency for another enzyme responsible for HIV i.e. integrase. Many structural modifications explained that two aryl units having a central linker should show high inhibitory potency. The activity of "horizontal" and vertical dimers were compared and studied in detail. The unsubstituted 4- hydroxy coumarin and 4, 7-dihydroxy coumarin were used for formation of dimeric coumarins also for similar series of compounds and to study the inhibition of HIV-1 for both enzymes namely integrase and protease [11-13]. The above results prompted us to undertake synthesis of 7,7¹-Arylidene bis-[6-hydroxy,substituted thieno(3,2-h)coumarins].

RESULTS AND DISCUSSION:

According to the existing literature the most feasible method for producing dicoumarols is by starting from 4-hydroxycoumarin and to reflux the reactants in ethanol for 18hours[14], in which the reported yields are very less[15].

In the present investigation we performed the same reaction in iso-propyl alcohol medium for 3-4hours upon a series of new 6-hydroxy,substitutedthieno(3,2-h)coumarins with aromatic aldehydes. The yields were found to be better and the reaction time got decreased considerably. A series of new 7,7¹-Arylidene bis-[6-hydroxy,substituted thieno(3,2-h)coumarins] (3a-d),(4a-d),(5a-d) & (6a-d) are prepared by reacting two moles of (1a-d) with one mole substituted aromatic aldehydes(2a-d) in the presence of iso-propyl alcohol for three hours. All the compounds are obtained in 80-90% yields and they have been confirmed by their elemental and spectral analysis. The study of biological activity of these compounds are in progress.

The I.R. spectrum of all the final compounds showed absorption peaks at 1680-1720 cm⁻¹ accountable to the coumarin C=O group and 1220-1228 cm⁻¹ assigned to C-O-C group. 3450-3500 cm⁻¹ indicates the presence of - OH group of coumarin. The ¹H NMR spectrum of all the final compounds exhibited a singlet at δ6.20 to δ6.27, which is associated with -CH of arylidene. The fragment peaks and molecular ion peaks in mass spectra were in accordance with their molecular structures.

3a) $R=H$, $R_1=H$, $R_2=H$, $R_3=C_6H_5$ 3c) $R=H$, $R_1=H$, $R_2=H$, $R_3=C_6H_3Cl_2$ (2,3)4a) $R=H$, $R_1=H$, $R_2=CH_3$, $R_3=C_6H_5$ 4c) $R=H$, $R_1=H$, $R_2=CH_3$, $R_3=C_6H_3Cl_2$ (2,3)5a) $R=H$, $R_1=H$, $R_2=Br$, $R_3=C_6H_5$ 5c) $R=H$, $R_1=H$, $R_2=Br$, $R_3=C_6H_3Cl_2$ (2,3)6a) $R=H$, $R_1=Cl$, $R_2=Cl$, $R_3=C_6H_5$ 6c) $R=H$, $R_1=Cl$, $R_2=Cl$, $R_3=C_6H_3Cl_2$ (2,3)

*p=para position

3b) $R=H$, $R_1=H$, $R_2=H$, $R_3=C_6H_3Cl_2$ (3,4)3d) $R=H$, $R_1=H$, $R_2=H$, $R_3=C_6H_5OH$ (p)4b) $R=H$, $R_1=H$, $R_2=H$, $R_3=C_6H_3Cl_2$ (3,4)4d) $R=H$, $R_1=H$, $R_2=H$, $R_3=C_6H_5OH$ (p)5b) $R=H$, $R_1=H$, $R_2=Br$, $R_3=C_6H_3Cl_2$ (3,4)5d) $R=H$, $R_1=H$, $R_2=Br$, $R_3=C_6H_5OH$ (p)6b) $R=H$, $R_1=Cl$, $R_2=Cl$, $R_3=C_6H_3Cl_2$ (3,4)6d) $R=H$, $R_1=Cl$, $R_2=Cl$, $R_3=C_6H_5OH$ (p)

Scheme-I

EXPERIMENTAL PROCEDURE:

All the melting points were determined by an open capillary method and are uncorrected. The IR spectra were recorded on Shimadzu FTIR model 8010 spectrophotometer and given in cm^{-1} in KBr. The $^1\text{H-NMR}$ spectra in CDCl_3 were recorded on a C 17-20-ZM-390-200MHz NMR spectrophotometer using TMS as an internal standard (Chemical shifts in δ units ppm) and mass spectra of compounds described are recorded on Joel TMS-D300 at 70eV. Compounds are obtained in 80-90% yields. Elementary analysis was carried out using Carlo-Erba EA-1108-analyzer. The purity of the compound was monitored and checked by TLC using silica gel during reactions.

General procedure for the preparation of 7,7'-Arylidene bis-[6-hydroxy,substituted thieno(3,2-h)coumarins]:

0.02 mole of 6-hydroxy,substitutedthieno(3,2-h)coumarin, was dissolved in 30ml of iso-propyl alcohol and heated on a water bath just to get a clear solution, 0.01mole substituted benzaldehyde was added to the hot solution and refluxed for three hours the solvent was distilled off and 7,7'-arylidene bis-[6-hydroxy,substituted thieno(3,2-h)coumarin] separated out as crystals. It was recrystallized from ethanol as pale yellow crystals.

3a : Mol. Formula: $\text{C}_{53}\text{H}_{32}\text{O}_6\text{S}_2$: Yield: 78%, IR (cm^{-1}): 750(C-S), 1228(C-O-C), 1680(C=O), 3450(OH), $^1\text{H-NMR}(\text{CDCl}_3)\delta(\text{ppm})$ 6.21(s, 1H, -CH), 6.73-6.80(m, 10H, Ar-H), 6.95-7.02(m, 10H, Ar-H), 7.28-7.30(dd, 4H, Ar-H), 12.42(s, 2H, coumarin-OH): Mass(m/z); 829(M^+)

3b : Mol. Formula: $\text{C}_{53}\text{H}_{30}\text{Cl}_2\text{O}_6\text{S}_2$: Yield : 80%, IR (cm^{-1}): 752(C-S), 1226(C-O-C), 1710(C=O), 3456(OH), 710(C-Cl), $^1\text{H-NMR}(\text{CDCl}_3)\delta(\text{ppm})$ 6.26(s, 1H, -CH), 6.72-6.78(m, 10H, Ar-H), 6.90-6.96(m, 10H, Ar-H), 7.27-7.30(dd, 4H, Ar-H), 7.40(dd, 2H, Ar-H), 7.45(dd, 1H, Ar-H), 12.45(s, 2H, coumarin-OH): Mass(m/z); 897(M^+).

3c : Mol. Formula: $C_{53}H_{30}Cl_2O_6S_2$:Yield : 75%, IR (cm^{-1}): 750(C-S),1220(C-O-C), 1710(C=O),3480(OH),710(C-Cl), 1H NMR($CDCl_3$) δ (ppm) 6.27(s,1H,-CH),6.70-6.76 (m,10H,Ar-H),6.93-6.98(m,10H,Ar-H),7.24-7.28(dd,4H,Ar-H),7.40(dd,1H,Ar-H), 7.42(dd,1H,Ar-H),7.46(dd,1H,Ar-H),12.43(s,2H,coumarin-OH): Mass(m/z);897(M^+).

3d : Mol. Formula: $C_{53}H_{32}O_7S_2$:Yield : 80%, IR (cm^{-1}): 750(C-S),1228(C-O-C), 1680(C=O),3450(OH),1345(b-OH), 1H NMR($CDCl_3$) δ (ppm) 6.21(s,1H,-CH),6.73-6.80 (m,10H,Ar-H),6.94-7.02(m,10H,Ar-H),7.24-7.28(dd,4H,Ar-H),7.40(dd,2H,Ar-H), 7.48(dd,2H,Ar-H),5.42(s,1H,Ar-OH),12.45(s,2H,coumarin-OH): Mass(m/z);844(M^+).

4a : Mol. Formula: $C_{55}H_{36}O_6S_2$:Yield : 76%, IR (cm^{-1}): 752(C-S),1224(C-O-C), 1720(C=O),3500(OH), 1H NMR($CDCl_3$) δ (ppm) 2.42(s,6H,2[CH₃]),6.26(s,1H,-CH), 6.72-6.76(m,8H,Ar-H), 6.98-7.04(m,10H,Ar-H),7.26-7.28(dd,4H,Ar-H),7.30-7.35 (m,5H,Ar-H), 12.40(s,2H,coumarin-OH): Mass(m/z);857(M^+).

4b : Mol. Formula: $C_{55}H_{34}Cl_2O_6S_2$:Yield : 79%, IR (cm^{-1}): 750(C-S),1226(C-O-C), 1710(C=O),3480(OH), 1H NMR($CDCl_3$) δ (ppm) 2.40(s,6H,2[CH₃]),6.24(s,1H,-CH),6.70 - 6.75(m,8H,Ar-H),7.02-7.08(m,10H,Ar-H),7.22-7.26(dd,4H,Ar-H),7.40(dd,2H,Ar-H), 7.48(dd,1H,Ar-H),12.40(s,2H,coumarin-OH): Mass(m/z);925(M^+).

4c : Mol. Formula: $C_{53}H_{34}Cl_2O_6S_2$:Yield : 72%, IR (cm^{-1}): 750(C-S),1228(C-O-C), 1680(C=O),3476(OH), 1H NMR($CDCl_3$) δ (ppm) 2.42(s,6H,2[CH₃]),6.21(s,1H,-CH), 6.73 - 6.78(m,8H,Ar-H),6.93-6.98(m,10H,Ar-H),7.26-7.28(dd,4H,Ar-H),7.39(dd,1H,Ar-H), 7.42(dd,1H,Ar-H),7.46(dd,1H,Ar-H),12.45(s,2H,coumarin-OH): Mass(m/z);925(M^+).

4d : Mol. Formula: $C_{55}H_{36}O_7S_2$:Yield : 70%, IR (cm^{-1}): 750(C-S),1224(C-O-C), 1720(C=O),3450(OH),1340(b-OH), 1H NMR($CDCl_3$) δ (ppm) 2.40(s,6H,2[CH₃]), 6.27(s,1H,-CH),6.75 -6.82(m,8H,Ar-H),7.00-7.06(m,10H,Ar-H),7.20-7.25(dd,4H,Ar-H),7.40(dd,2H,Ar-H),7.48(dd,2H,Ar-H),5.40(s,1H,Ar-OH),12.40(s,2H,coumarin-OH): Mass(m/z);873(M^+).

5a : Mol. Formula: $C_{53}H_{30}Br_2O_6S_2$:Yield : 83%, IR (cm^{-1}): 750(C-S),1226(C-O-C), 1710(C=O),3470(OH), 1H NMR($CDCl_3$) δ (ppm) 6.20(s,1H,-CH),6.80-6.85(m,8H,Ar-H), 6.97-7.02(m,10H,Ar-H),7.23-7.26(dd,4H,Ar-H),7.30-7.35(m,5H,Ar-H),12.42 (s,2H,coumarin-OH): Mass(m/z);986(M^+).

5b : Mol. Formula: $C_{53}H_{28}Br_2Cl_2O_6S_2$:Yield : 75%, IR (cm^{-1}): 750(C-S),1220(C-O-C), 1720(C=O),3468(OH), 1H NMR($CDCl_3$) δ (ppm) 6.27(s,1H,-CH),6.79-6.84(m,8H,Ar-H), 7.01-7.05(m,10H,Ar-H),7.20-7.24(dd,4H,Ar-H),7.40(dd,2H,Ar-H),7.45(dd,1H,Ar-H), 12.45(s,2H,coumarin-OH): Mass(m/z);1055(M^+).

5c : Mol. Formula: $C_{53}H_{28}Br_2Cl_2O_6S_2$:Yield : 80%, IR (cm^{-1}): 750(C-S),1228(C-O-C), 1720(C=O),3460(OH), 1H NMR($CDCl_3$) δ (ppm) 6.21(s,1H,-CH),6.80-6.85(m,8H,Ar-H), 7.03-7.05(m,10H,Ar-H),7.28-7.30(dd,4H,Ar-H),7.40(dd,1H,Ar-H),7.42(dd,1H,Ar-H), 7.46(dd,1H,Ar-H),12.43(s,2H,coumarin-OH): Mass(m/z);1055(M^+).

5d : Mol. Formula: $C_{53}H_{30}Br_2O_7S_2$:Yield : 78%, IR (cm^{-1}): 750(C-S),1222(C-O-C), 1680(C=O),3500(OH),1350(b-OH), 1H NMR($CDCl_3$) δ (ppm) 6.24(s,1H,-CH),6.78-6.84 (m,8H,Ar-H),6.98-7.04(m,10H,Ar-H),7.20-7.24(dd,4H,Ar-H),7.40(dd,2H,Ar-H), 7.48(dd,2H,Ar-H),5.42(s,1H,Ar-OH),12.40(s,2H,coumarin-OH): Mass(m/z);1002(M^+).

6a : Mol. Formula: $C_{53}H_{28}Cl_4O_6S_2$:Yield : 70%, IR (cm^{-1}): 750(C-S),1220(C-O-C), 1710(C=O),3450(OH), 1H NMR($CDCl_3$) δ (ppm) 6.25(s,1H,-CH), 7.02-7.10

(m, 10H, ArH), 7.16-7.20(m, 6H, Ar-H), 7.28-7.30(dd, 4H, Ar-H), 7.34-7.38(m, 5H, Ar-H), 12.40(s, 2H, coumarin-OH) : Mass(m/z); 966(M⁺).

6b : Mol. Formula: C₅₃H₂₆Cl₆O₆S₂ : Yield : 80%, IR (cm⁻¹) : 750(C-S), 1226(C-O-C), 1680(C=O), 3480(OH), ¹HNMR(CDCl₃)δ(ppm) 6.26(s, 1H, -CH), 6.97-7.04 (m, 10H, Ar-H), 7.14-7.18(m, 6H, Ar-H), 7.26-7.28(dd, 4H, Ar-H), 7.40(dd, 2H, Ar-H), 7.45(dd, 1H, Ar-H), 12.40(s, 2H, coumarin-OH) : Mass(m/z); 1035(M⁺).

6c : Mol. Formula: C₅₃H₂₆Cl₆O₆S₂ : Yield : 75%, IR (cm⁻¹) : 750(C-S), 1224(C-O-C), 1720(C=O), 3470(OH), ¹HNMR(CDCl₃)δ(ppm) 6.24(s, 1H, -CH), 7.00-7.06 (m, 10H, Ar-H), 7.14-7.18(m, 6H, Ar-H), 7.26-7.28(dd, 4H, Ar-H), 7.40(dd, 1H, Ar-H), 7.42(dd, 1H, Ar-H), 7.46(dd, 1H, Ar-H), 12.43(s, 2H, coumarin-OH) : Mass(m/z); 1035(M⁺).

6d : Mol. Formula: C₅₃H₂₈Cl₄O₇S₂ : Yield : 80%, IR (cm⁻¹) : 750(C-S), 1220(C-O-C), 1680(C=O), 3460(OH), 1340(b-OH), ¹HNMR(CDCl₃)δ(ppm) 6.27(s, 1H, -CH), 6.98-7.06(m, 10H, ArH), 7.12-7.16(m, 6H, Ar-H), 7.28-7.30(dd, 4H, Ar-H), 7.40(dd, 2H, Ar-H), 7.48(dd, 2H, Ar-H), 5.42(s, 1H, Ar-OH), 12.40(s, 2H, coumarin-OH) : Mass(m/z); 982(M⁺).

References

- 1 El-Sayed, A.M.; Abd-Allah, O.A. Phosphorous, sulfur and silicon. *Relat. Elem.*, **170**, 75-86, (2001).
- 2 Kalluraya, B.; Vishwanatha, p.; Isloor, A.M.; Rai, G.; Kotian, M. *Bull. Cim. Farm.*, **139**, 263-266, (2000).
- 3 Abd-Allah, O.A. *Farmaco.*, **55**, 641-649, (2001).
- 4 El-Agrody, A.H.; Abd.; Dedair, A.H. *Molecules*, **6**, 519-527, (2001).
- 5 Emmanuel-Giota, A.A.; Fylaktakidou, K.C.; Hadjipavlou-litina, D.J.; Litinas, K.E.; Nicolaides, D.N.J. *Heterocyclic. Chem.*, **38**, 717-722, (2001).
- 6 Manolov, I.; Danchev, N.D. *Eur. J. Med. Chem. Chim. Ther.*, **30**, 531-536, (1995).
- 7 Nofal, Z.M.; El-Zahar, M.I.; Abd El-Karim, S.S. *Molecules*, **5**, 99-113, (2000).
- 8 Raev, L.; Voinov, E.; Ivanov, I.; Popov, D. *Pharmazie*, **45**, 696, (1990).
- 9 Romines K.R. and Thaisrivongs. S. *Drugs of the future*, **20**(4), 377, (1995).
- 10 Thaisrivongs, Janakiraman. M.N.; Chong. K. T.; Tomich. P. K.; Dolak. L. A.; turner. S. R.; Stroback. J. W.; Lynn. J. C.; Horng. M. M.; Hinshaw R. R.; and Waten paugh. K. D. **39**, 2400, (1996).
- 11 Durka. T. R.; Fesen. M. R.; Mazunder. A.; Wang. J.; Carothers. A. M.; Grunberger. D.; Driscoll. J.; Kohn. K. and Pommier., **38**, 4171, (1995).
- 12 Zhao. H.; Neamati. N. Hong. H.; Mazumder. A.; Wangs, Sunder. S.; Milne. G. W. A.; Pommier. Y. and Burke (Jr). T. R. *J. Med. Chem.*, **40**(2), 242, (1997).
- 13 Mazumder. A., Wangs, Neamati. N.; Nikolaus. M.; Sunder. S.; Chen. J.; Milne. G. W. A.; Rice. W. G.; Burke (Jr).; T. R. and Pommier. Y., *J. Med. Chem.*, **39**(13), 2472, (1996).
- 14 Shah. A. K.; Bhatt. N. S.; Raval. R. V. & Thakor. V. M., *Sci. & Cul.*, **52**(7), 2289, (1986).
- 15 Sullivan. W. R.; Huenbner. C. F.; Stahmann. M. A. & Link. K. P. *J. Am. Chem. Soc.*, **65**, 2288, (1943).

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