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CONVENIENT SYNTHESIS OF 2-(5-CHLORO-2-HYDROXYPHENYL) -4H-CHROMEN-4-ONE FROM 1-(2-HYDROXY-5-CHLOROPHENYL) ETHENYLDIPHENYLAMINE

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ABSTRACT

The methods of synthesis of flavones mostly by cyclization and condensation of o-hydroxy acetophenone, dehydrogenation of flavanones or using chalcones as starting materials have very limited applicability hence it is need of the time to go for some alternative methods. The present study reports an experiment where a more convenient method is used to synthesize some substituted flavones from the enamines. The bromo and nitro substituted 2-(5-chloro-2-hydroxyphenyl)-4H-chromen-4-ones were synthesized by the reaction of bromo and nitro substituted 1-(2-hydroxy-5-chlorophenyl)ethenyldiphenylamines with heptanedioylchloride followed by the cyclization of intermediate thus obtained in the suitable solvents.

KEYWORDS: **Enamine, heptanedioylchloride, flavone, tetrahydroflavone**

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INTRODUCTION

The flavones, which are also known as "Anthoxanthins" occur in a free state or as glycosides in the nature. They have been isolated from many plants having medicinal value viz. *Cuscuta reflexa*[1], *Tridax procumbens*[2] , *Digitalis thapsi, Ficus gomelleira*[3], *Saponaria officinals* etc. The chemical synthesis was carried out mostly by cyclization and condensation of o-hydroxy acetophenone or by dehydrogenation[4] of flavanones, so also by the cyclization of 1,3-diphenylpropane-1,3-diones or 2-hydroxy chalcones[5]. The main difficulty in the Kostaneecki method, which is conventionally being used for the preparation of flavones from bromochalcones, is the possibility of nuclear bromination and predominant tendency to form benzalcoumaranones instead of flavones. An alternative method in which direct dehydrogenation of chalcones or flavanones is carried out with selenium dioxide seems to be failed when the chalcones contains free hydroxyl groups. The present work deals with a more convenient alternative method for the synthesis of flavone from enamine and heptanedioylchloride. A wide range of biological activities exhibited by flavones such as antiviral[6], antioxidant[7], antibacterial[8], anti-inflammatory[9], anticancer[10] and anti-HIV[11] etc. also became a driving force behind this study.

MATERIALS AND METHODS

Melting points reported were determined in a hot paraffin bath and are uncorrected. The IR spectra were recorded on SHIMADZU FTIR Presige-21 spectrophotometer mode 1310. ^{1}H NMR spectra were recorded on Varian NMR Mercury-300 spectrometer in $CDCl_3$ solvent with TMS as an internal standard.

EXPERIMENTAL SECTION

1. Preparation of acetophenone and substituted acetophenones (Ia,Ib,Ic)

2-Hydroxy-5-chloroacetophenone (Ia) was prepared by refluxing p-chlorophenol with aceticanhydride in presence of fused sodium acetate so as to get p-chloroacetate which on Fries migration gave the compound (Ia).

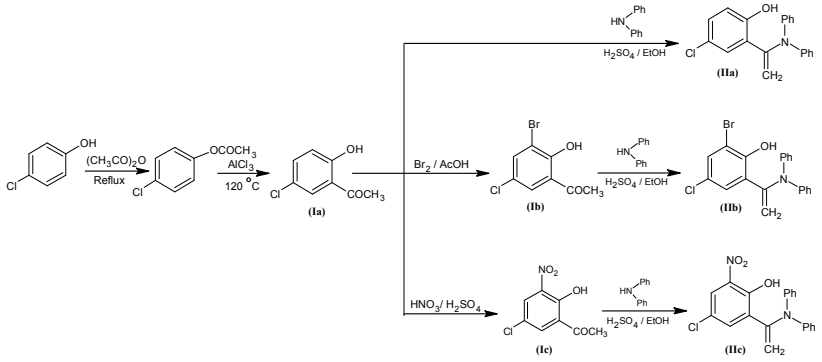
The compound (Ia) on treatment with brominating and nitrating agents separately gives 2-hydroxy-3-bromo-5-chloroacetophenone (Ib) and 2-hydroxy-3-nitro-5-chloroacetophenone (Ic) respectively.

2. Synthesis of 1-(2-hydroxy-5-chlorophenyl)ethenyldiphenylamine (IIa)

2-Hydroxy-5-chloroacetophenpone (Ia) (0.01 mole) was refluxed with diphenylamine (0.01 mole) and few drops of conc. H_2SO_4. The reaction mixture was then cooled, diluted with water and crystallised from ethanol to get 1-(2-hydroxy-5-chlorophenyl)ethenyldiphenylamine (IIa). B.P.: 272 ^{o}c, Yield: 70%. Similarly 1-(2-hydroxy-3-bromo-5-chlorophenyl)ethenyldiphenylamine (IIb) (M.P.: 94^{o}C, Yield: 80 %) and 1-(2-hydroxy-3-nitro-5-chlorophenyl)ethenyldiphenylamine (IIc) (M.P. : 66 ^{o}C, Yield: 80 %) were synthesized from 2-hydroxy-3-bromo-5-chloroacetophenpone (Ib) and 2-hydroxy-3-nitro-5-chloroacetophenpone (Ic) respectively.

The synthetic root for IIa, IIb, and IIc is shown in scheme-I.

SCHEME-I

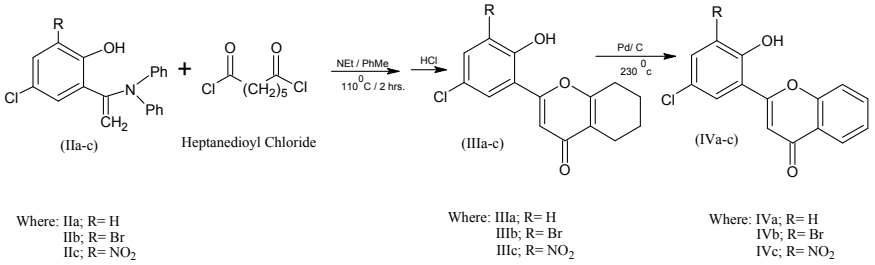


3. Synthesis of 2-(5-chloro-2-hydroxyphenyl)-4H-chromen-4-one (IVa)

1-(2-Hydroxy-5-chlorophenyl)ethenyldiphenylamine (IIa) (1 mole, 3.2 gm.) was refluxed with heptanedioylchloride (1 mole, 1.9 gm.) in toluene and heptanedioylchloride in presence of triethylamine for 2 hours. The product, thus obtained, was then hydrolysised followed by dehydration with Pd/C catalyst in diphenyl ether under the normal pressure at about 230 ^{0}c. to get 2-(5-chloro-2-hydroxyphenyl)-4H-chromen-4-one (IVa). M. P.: 146^{o}c. Yield: 69%

Similarly 2-(3-bromo-5-chloro-2-hydroxyphenyl)-4H-chromen-4-one (IVb) M. P.: 132^{o}c. Yield: 76% and 2-(5-chloro-2-hydroxy-3-nitrophenyl)-4H-chromen-4-one (IVc) M.P.: 152^{o}c. Yield: 71 % were synthesized from 1-(2-hydroxy-3-bromo-5-chlorophenyl)ethenyldiphenylamine (IIb) from 1-(2-hydroxy-3-nitro-5-chlorophenyl)ethenyldiphenylamine (IIc) respectively. The synthetic root for IVa, IVb and IVc is shown in the scheme-II.

SCHEME-II

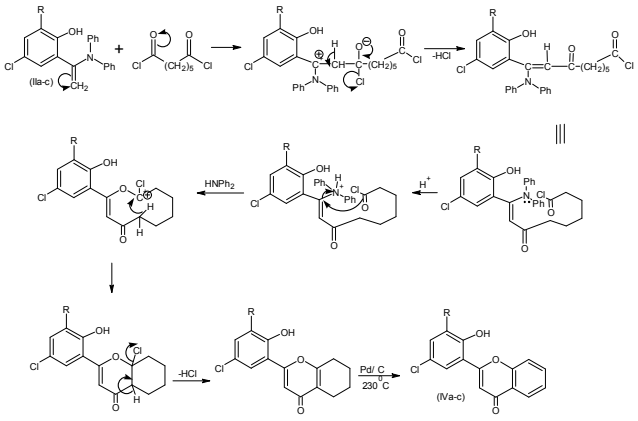


Where: IIa; R= H
IIb; R= Br
IIc; R= NO_2

Where: IIIa; R= H
IIIb; R= Br
IIIc; R= NO_2

Where: IVa; R= H
IVb; R= Br
IVc; R= NO_2

Mechanism



The synthesized compounds were characterized on the basis of elemental analysis and U.V., I.R., N.M.R. spectral data.

1-(2-Hydroxy-5-chlorophenyl)ethenyldiphenylamine (IIa)

B.P. 272 °c, Yield 70%; Elemental analysis for compound: $C_{20}H_{16}ONCl$: (Found: C=75.50, H= 3.90, O= 5.80, N= 3.49 Cl= 12.00, Calculated: C=74.65, H= 4.97, O= 5.87, N= 3.50, Cl= 11.04); UV (nm) λmax= 362,286 π→π* and n→π*; IR (cm^{-1}): 3250-3350 (-OH stret.); 1678 (C=C; Ar-H); 690 (C-Cl stret.); ^{1}HNMR (δ ppm): δ 2.7 (s, 2H, -C=CH_2), δ 6.6-7.9 (m, 13 H, Ar-H), δ 12.75 (s, 1 H, Ar-OH).

1-(2-Hydroxy-3-bromo-5-chlorophenyl)ethenyldiphenylamine (IIb)

M.P. 94°c, Yield 80 %; Elemental analysis for compound: $C_{20}H_{15}ONClBr$: (Found: C=58.80, H= 4.50, O= 4.30, N= 3.00, Cl= 8.37, Br= 19.339: Calculated: C=59.52, H= 3.74, O= 3.99, N= 3.49, Cl= 8.83, Br= 19.79); UV (nm) λmax= 356,264 π→π* and n→π*; IR (cm^{-1}): 3300-3350 (-OH stret.); 1680 (C=C; Ar-H); 690 (C-Cl stret.); 610 (C-Br bond stret.); ^{1}HNMR (δ ppm): δ 2.6 (s, 2H, -C=CH_2), δ 6.8-7.8 (m, 12 H, Ar-H), δ 12.85 (s, 1 H, Ar-OH).

1-(2-Hydroxy-3-nitro-5-chlorophenyl)ethenyldiphenylamine (IIc)

M.P. 66°C, Yield 80 %; Elemental analysis for compound: $C_{20}H_{15}O_3N_2Cl$: (Found: C=66.30, H= 3.90, O= 14.00, N= 6.80, Cl= 10.40, Calculated: C=64.45, H= 4.09, O= 13.09, N= 7.63, Cl= 9.68 ; UV (nm) λmax= 356,286 π→π* and n→π*; IR (cm^{-1}): 3250-3300 (-OH stret.); 1672 (C=C; Ar-H); 680 (C-Cl stret.); ^{1}HNMR (δ ppm): δ 2.6 (s, 2H, -C=CH_2), δ 6.7-7.9 (m, 12 H, Ar-H), δ 12.36 (s, 1 H, Ar-OH).

2-(5-Chloro-2-hydroxyphenyl)-4H-chromen-4-one (IVa)

M. P. 146°c.; Yield 69%; Elemental analysis for compound: $C_{15}H_9ClO_3$: (Found: C=59.93, H= 3.11, Cl= 12.89, O= 17.47. Calculated (%): C=66.07, H= 3.33, Cl= 13.01, O= 17.60; IR (cm^{-1}): 1640 (C=O stret.), 1610 (c=c stret.), 1119 (C-O-C stret.), 717.7 (C-Cl stret.) ^{1}HNMR (δ ppm): δ 1.6 (s, 1H, Ar-H); δ 6.54 (s, 1H, -CO-CH=C<), δ 6.62-7.64 (M, 8h, Ar-H).

2-(5-Chloro-2-hydroxy-3-nitrophenyl)-4H-chromen-4-one (IVc)

M. P. 132°c.; Yield 76%; Elemental analysis for compound: $C_{15}H_9ClO_3$: (Found: C=59.93, H= 3.11, Cl= 12.89, O= 17.47. Calculated: C=66.07, H= 3.33, Cl= 13.01, O= 17.60; IR (cm^{-1}): 1636 (C=O stret.), 1610 (c=c stret.), 1121 (C-O-C stret.), 717.7 (C-Cl stret.), (C-Br stret.) ^{1}HNMR (δ ppm): δ 1.6 (s, 1H, Ar-H); δ 6.54 (s, 1H, -CO-CH=C<), δ 6.62-7.64 (M, 8h, Ar-H).

2-(3-Bromo-5-chloro-2-hydroxyphenyl)-4H-chromen-4-one (IVb)

M. P. 152°c.; Yield 71%; Elemental analysis for compound: $C_{15}H_8ClNO_5$: (Found: C=59.93, H= 3.11, Cl= 12.89, O= 17.47. Calculated: C=56.71, H= 2.74, Cl= 11.16, N=4.41, O= 25.18; IR (cm^{-1}): 1618(C=O stret.), 1622 (C=C stret.), 1119 (C-O-C stret.), 716 (C-Cl stret.), 1345 (C-NO_2 stret.) ^{1}HNMR (δ ppm): δ 1.6 (s, 1H, Ar-H); δ 6.54 (s, 1H, -CO-CH=C<), δ 6.62-7.64 (M, 8h, Ar-H).

RESULTS AND DISCUSSION

In this article, a more convenient method is recommended for the synthesis of substituted 2-(5-chloro-2-hydroxyphenyl)-4H-chromen-4-one (IVa-c). The findings of study demonstrated that the synthetic root mentioned provides satisfactory percentage of product yield.

CONCLUSION

In the present study some substituted flavones have been synthesized by using enamine as a starting material. The synthetic root proposed in this part is more convenient for the synthesis of flavones to overcome the difficulties like nuclear bromination and predominant tendency to form benzalcoumaranones instead of flavones.

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