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SYNTHESIS OF ISOCOUMARINS AND ISOQUINOLONES

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ABSTRACT

5H-furo[2,3-c] [2]benzopyran-1,5(2H)-dione was synthesized accidentally in excellent yield while trying to synthesize 1H-furo[3,4-c][2]benzopyran-1,5(3H)-dione using a different method. The reaction of homophthalic anhydride was carried with chloroacetyl chloride using pyridine as a catalyst, followed by rearrangement of 4-(chloroacetyl)-1H-2-benzopyran-1,3(4H)-dione at high temperature. Further 4-(chloroacetyl)-1H-2-benzopyran-1,3(4H)-dione was converted to 3-(chloromethyl)-1-oxo-1H-2-benzopyran-4-carboxylic acid at room temperature. As an extension to this work 5H-furo[2,3-c] [2]benzopyran-1,5(2H)-dione was derrivatised to its respective Isoquinolones using ammonia and primary amines. Also the chemistry of 3-(chloromethyl)-1-oxo-1H-2-benzopyran-4-carboxylic acid has been studied.

KEYWORDS: Isocoumarin, homophthalic anhydride, chloroacetyl chloride, pyridine, furo compound, isoquinolone.

1. INTRODUCTION

Isocoumarins are available in nature as well they can be prepared synthetically. Natural sources include microbes[1], mold metabolites[2], plants[3-7], and insects. Isoquinolones have been studied and synthesized from quite a long time for its various medicinal properties. Literature study reveals that 8-hydroxy-3-methyl-isocoumarin was the first Natural Isocoumarin known and isolated by Bendz[8] in 1959 from the Fungus Ramealis. There are natural products which are simple isocoumarin derivatives.

These Isocoumarins have assumed importance due to its prevalence in numerous natural products that exhibit a wide range of biological activities[9-12]. Isocoumarins have also found

to be the starting material in the synthesis of isoquinolones which is another class of N-containing compound that has broad spectrum activity over various diseases beginning from fever to cancer. Review articles on Isocoumarins include those by R.D. Barry[13], W.B. Turner[14], M. Yamato[15], R.A. Hill[16], E. Napolitano[17], and I. U. Rehman[18].

2. MATERIAL AND METHOD

2.1. Chemicals

All reagents and solvents were commercially available and used as supplied. All the chemicals used were of AR grade. Indene was bought from lobachem Pvt. Ltd. Indene was used to prepare Homophthalic acid. Whereas chloroacetyl chloride and pyridine used was from S.D. Fine-chem. Ltd. The melting points of the compounds were determined in open capillaries on an electro thermal apparatus and are uncorrected. The purity of the compounds were monitored by thin layer chromatography on silica gel coated aluminium plates (merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on varian 500MHz NMR spectrophotometer using CDCl3/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N, estimation was recorded on Carlo Erba 1108 (CHN) Elemental analyzer.

2.2. General Procedure

Homophthalic acid(2) was prepared by oxidation of indene(1) using potassium dichromate in presence of sulphuric acid. This homophthalic acid was further dehydrated to homophthalic anhydride(3) using acetic anhydride at reflux temperature. Homophthalic anhydride was used as a substrate to prepare 4-(chloroacetyl)-1H-2-benzopyran-1,3(4H)-dione (8) using pyridine and chloroacetyl chloride.

2.3 Synthesis of 3-(chloromethyl)-1-oxo-1H-2-benzopyran-4-carboxylic acid(9)

Step 1. To a round bottom flask, Chloroacetyl chloride (0.037mole, 4.26g) was added followed by addition of Pyridine (0.061mole, 4.89g) drop wise with stirring. Addition was carried in ice bath due to exothermicity of the reaction. After complete addition of Pyridine, Compound **3** (0.012mole, 2g) was added in small portions over 20 minutes. Ice bath was removed after complete addition and the mixture was stirred for 3 hours at R.T. After stirring for 3 hours, reaction mixture was quenched over cold 1:1 HCl and then again it was allowed to stir for another 30 minutes. Liquid was decanted and sticky solid **(** 4-(chloroacetyl)-1H-2-benzopyran-1,3(4H)-dione) was left behind. This intermediate 4-(chloroacetyl)-1H-2-

benzopyran-1,3(4H)-dione (8) was soluble in water at higher temperature. Hence it was washed with cold water.

Step 2. Compound 8 was added to 2 ml of 90% H_2SO_4 and kept overnight in a refrigerator at 0-5^oC. Next day 5ml of ice water was added and stirred by immersing the container in an ice bath. A free flowing residue was obtained which was washed with cold water and filtered. Residue was treated with sodium bicarbonate and filtered. The filtrate obtained was then acidified to get the pure compound 9 and then a final washing of cold water was given to the purified compound. M.P. 175^0C - 177^0C.

- Spectral interpretation of 3-(chloromethyl)-1-oxo-1H-2-benzopyran-4-carboxylic acid:
Anal. Calcd for $C_{11}H_7O_4Cl$: C, 60.00; H, 3.18; Cl, 7.72%. Found C, 60.08; H, 3.15; Cl, 7.75%. ^1H NMR (δ ppm): 4.521(2H, sp^3C, d), 7.5-7.8(3H, Ar-H, m), 8.1 (1H,t) ^{13}C NMR (δ ppm): 173.03(O=C-OH, sp^2C), 161.73(C=O), 155.66(ClH_2C-C-O-, sp^2C), 121.6, 129.35, 125.3, 131.68, 129.81, 132.5, 113.26 , 40.01(-CH_2Cl, sp^3C).

2.4 Synthesis of methyl 3-(chloromethyl)-1-oxo-1H-2-benzopyran-4-carboxylate(10):
Compound 9 was esterified by refluxing it with methanol in presence of H_2SO_4 on a boiling water bath for 48 hours. methyl 3-(chloromethyl)-1-oxo-1H-2-benzopyran-4-carboxylate (10) was obtained as a whit e product. M.P. 55^0C - 57^0C.

- Spectral interpretation of 3-(chloromethyl)-1-oxo-1H-2-benzopyran-4-carboxylate:
Anal. Calcd for $C_{12}H_9O_4Cl$: C, 61.53; H, 3.84; Cl, 7.26%. Found C, 61.51; H, 3.85; Cl, 7.24%. ^1H NMR (δ ppm): 8.2(1H,t), 3.76(3H, O-CH_3, m), 4.51(2H, -CH_2Cl, d), 7.5-7.8(3H, Ar-H, m) ^{13}C NMR (δ ppm): 166.9(H_3C-O-C=O, C=O), 161.73(C=O), 155.66(ClH_2C-C-O-, sp^2C), 131.68, 132.5, 129.81, 129.35, 121.6, 113.26, 125.3, 40.01(-CH_2Cl, sp^3C), 51.91(-CH_3).

2.5 Synthesis of 5H-furo[2,3-c] [2]benzopyran-1,5(2H)-dione(4):
To a 25ml R.B. flask immersed in ice bath, 5ml chloroacetyl chloride was added followed by addition of 2ml Py dropwise with stirring. After complete addition of Py 3 gm of homophthalic anhydride was added in small portions over twenty minutes. Then the entire mix was stirred for 3 hours at boiling water bath. It was expected that we should get compound 6 or compound 7 having M.P. as 131-132 or 117-118 respectively, but surprisingly what we observed is that we got a solid mass whose M.P. was found to be 174-

176. Then with the help of spectral data we found that compound 4 is the compound that was formed. We then tried to establish a possible mechanism and also derrivatised compound 4 to various isoquinolones using ammonia and primary amines.

- Spectral interpretation of 5H-furo[2,3-c] [2]benzopyran-1,5(2H)-dione

Anal. Calcd for $C_{11}H_6O_4$: C, 65.34; H, 2.97%. Found C, 65.37; H, 2.95%. ^{1}H NMR (δ ppm): 5.7 (2H, -CH_2,d), 7.4-7.7(3H, Ar-H, m), 8.23 (1H,d) ^{13}C NMR (δ ppm): 189.5 (-H_2C-C=O, sp^2C), 167.7(-O-C-O-,sp^2C) 165.9 (-O-C=O, sp^2C), 119.8, 129.8, 129.3, 129.2, 124.1, 135.02, 131.6, 74.1 (-O-CH_2, sp^3C).

2.6 Synthesis of isoquinolones(5a-5d)

Compound 4 was treated with Ammonia, Methyl Amine, ethanol amine, and hydroxyl amine. Compound **4**(0.0024 mole, 0.5g), were refluxed with (0.1 mole) ammonia and methyl amine for three hours to yield compound 5a, m.p.- 160-162^{0}C and 5b, m.p.- 138-140^{0}C respectively. The progress of reaction was monitored over tlc. The solution was cooled at R.T., and the solid was separated. This solid was filtered and washed with cold water.

- Spectral interpretation of 5H-furo[2,3-c] [2]benzopyran-1,5(2H)-dione(5a):

Anal. Calcd for $C_{11}H_7O_3N$: C, 65.67; H, 3.48; N, 6.96%. Found C, 65.65; H, 3.45; N, 6.93%. ^{1}H NMR (δ ppm): 5.6 (2H, -CH_2,s), 7.4-7.9(4H, Ar-H, m) ^{13}C NMR (δ ppm): 189.5 (-H_2C-C=O, sp^2C), 175.89(-N-C-O-,sp^2C), 165.9 (-N-C=O, sp^2C), 74.1 (-O-CH_2, sp^3C), 124.1, 129.17, 131.68, 91.7, 135.02, 126.95, 125.5.

- Spectral interpretation of 4-methylfuro[2,3-c]isoquinoline-1,5(2H,4H)-dione(5b):-

Anal. Calcd for $C_{12}H_9O_3N$: C, 66.97; H, 4.18; N, 6.51%. Found C, 66.95; H, 4.15; N, 6.56%. ^{1}H NMR (δ ppm):3.54(3H,-N-CH_3) 5.5 (2H,-CH_2,s), 7.4-7.9(4H, Ar-H, m) ^{13}C NMR (δ ppm): 189.5 (-H_2C-C=O, sp^2C), 154.02(-N-C-O-,sp^2C), 165.1 (-N-C=O, sp^2C), 74.1 (-O-CH_2, sp^3C), 124.8, 129.17, 131.68, 91.7, 135.02, 127.4, 124.1, 37.79(N-CH_3,sp^3C).

- Synthesis of 4-(2-hydroxyethyl)furo[2,3-c]isoquinoline-1,5(2H,4H)-dione(5c)

Compound 4(0.0024 mole, 0.5g) was kept with 8ml 50% ethanol amine on a boiling water bath for about 3 hrs and it was then observed that the solid mass dissolves in it. The solution is then cooled and acidified to obtain our final product 4-(2-hydroxyethyl)furo[2,3-c]isoquinoline-1,5(2H,4H)-dione(5c). After acidifying the solution 5c was extracted in 20ml of diethyl ether twice. Then it was washed with water and dried over sodium sulphate. Later

ether was distilled out and what remained was a sticky mass which was triturated with 40-60 pet ether. Then we obtain pure product 5c. m.p.- 110-112^{0}C.

Spectral interpretation of 4-(2-hydroxyethyl)furo[2,3-c]isoquinoline-1,5(2H,4H)-dione:

Anal. Calcd for $C_{13}H_{11}O_4N$: C, 63.67; H, 4.48; N, 5.71%. Found C, 63.69; H, 4.45; N, 5.75%. ^{1}H NMR (δ ppm): 5.56 (2H, -CH_2,s), 7.4-7.9(4H, Ar-H, m), 3.49(2H,-CH_2-OH,m), 4.33(2H,N-CH_2-,m) ^{13}C NMR (δ ppm): 189.5 (-H_2C-C=O, sp^{2}C), 154.02(-N-C-O-,sp^{2}C), 165.1 (-N-C=O, sp^{2}C), 74.1 (-O-CH_2, sp^{3}C), 124.8, 127.4, 131.68, 91.7, 135.02, 129.17, 124.1, 59.21(-CH_2-OH,sp^{3}C), 49.52(-N-CH_2-,sp^{3}C).

- Synthesis of 4-hydroxyfuro[2,3-c]isoquinoline-1,5(2H,4H)-dione(5d)

Hydroxyl amine HCl (0.12 mole, 4g) was added in 15 ml water to which compound 4 (0.0024 mole, 0.5g) was added and they were heated together on a boiling water bath. Later on to this solution we slowly (drop wise) added sodium carbonate solution, which was prepared by adding 3 g of sodium carbonate in 15 ml water ,and heated further for three hours. Then the solution was kept overnight and acidified next day to obtain the product 4-hydroxyfuro [2,3-c]isoquinoline-1,5(2H,4H)-dione(5d). m.p.- 150-152^{0}C.

Spectral interpretation of 4-hydroxyfuro[2,3-c]isoquinoline-1,5(2H,4H)-dione:

Anal. Calcd for $C_{11}H_7O_4N$: C, 60.82; H, 3.22; N, 6.45%. Found C, 60.85; H, 3.27; N, 6.41%. ^{1}H NMR (δ ppm): 5.6 (2H, -CH_2,s), 7.4-7.6(3H, Ar-H, m), 8.05(1H, Ar-H, d) ^{13}C NMR (δ ppm): 189.5 (-H_2C-C=O, sp^{2}C), 159.32(-N-C-O-,sp^{2}C), 166.13 (-N-C=O, sp^{2}C), 74.1 (-O-CH_2, sp^{3}C), 124.1, 129.17, 128.8, 131.68, 91.7, 135.02, 126.17.

Table 1: Characterisation data of all the compounds

Structure	M.F.	M.P.	Mol. Wt.
1	C_9H_8	181-183^{0}C	116
2	$C_9H_8O_4$	179-181^{0}C	180
3	$C_9H_6O_3$	139-141^{0}C	162
4	$C_{11}H_6O_4$	174-176^{0}C	202
5a, R=NH_2	$C_{11}H_7O_3N$	160-162^{0}C	201
5b, R=NH-CH_3	$C_{12}H_9O_3N$	138-140^{0}C	215
5c, R=NH-$(CH_2)_2$OH	$C_{13}H_{11}O_4N$	110-112^{0}C	245
5d, R=NH-OH	$C_{11}H_7O_4N$	150-152^{0}C	217
9	$C_{11}H_7O_4Cl$	175-177^{0}C	220
10	$C_{12}H_9O_4Cl$	055-057^{0}C	234

3. RESULTS AND DISCUSSION

Condensation of Chloroacetyl chloride with Homophthalic anhydride in presence of Pyridine furnished 4-Chloracetylisochroman-1,3-dione which underwent rearrangement with 90% Sulphuric acid at 25-30^{0}C in 12 hrs and gave 4-Carboxy-3-Chloromethylisocoumarin as expected. Methyl ester was prepared of compound 9.The same condensation reaction of homophthalic anhydride, when carried out at 95-100^{0}C did not give expected 3-Chloromethylisocoumarin or 3H-Furo[3, 4-c] isochromene-1, 5-dione as reported in the literature by Hussain MT, Rama NH, Khan KM as novel unusual isocoumarin derivative[2], M.P. 132^{0}C. They carried out the reaction with homophthalic acid and chloroacetyl chloride at 200^{0}C. We are reporting in this paper the isolation of unexpected 4H-Furo[3,4-c]isochromene-1,5-dione in excellent yield and characterized by the spectral data. Reaction of ammonia and various primary amines furnished respective isoquinolones.

The mechanism for the formation of 4-chloroacetyl-isochroam-dione, 4-carboxy-3-methylisocoumarin and 4H-Furo[3,4-c]isochromene-1,5-dione is outlined below. Initially there is an abstraction of proton of the active methylene group of homophthalic anhydride by pyridine followed by attack of chloroacetyl chloride to form an intermediate product 4-chloroacetyl-1,3-isochroman-1,3dione which undergoes further rearrangement with Sulphuric acid at 25-30^{0}C and forms 4-carboxy-3-chloromethylisocoumarin.

4H-Furo[3,4-c]isochromene-1,5-dione is formed due to cyclisation of 4-chloroacetylisochroan-1,3-dione as shown below before it underwent the rearrangement at high temperature in presence of pyridine which is usually the case as seen in condensation of homophthalic anhydride with acetyl chloride (similar to the sulphuric acid rearrangement).

- GENERAL SCHEME

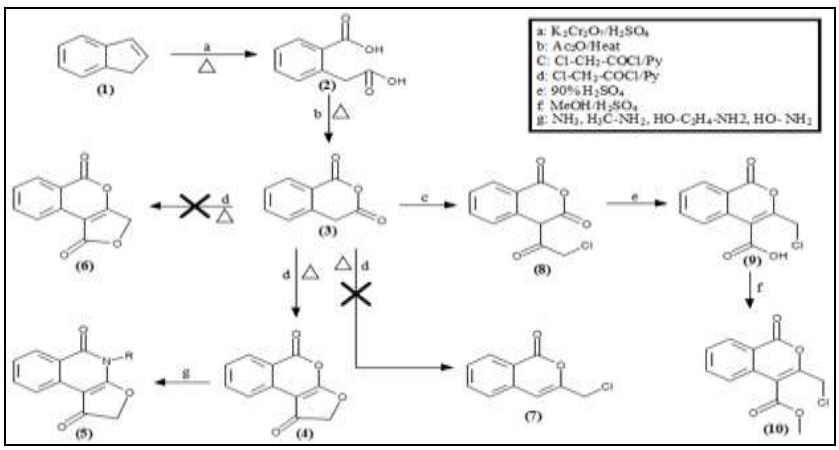

Figure I: General scheme of reactions carried out

4. CONCLUSION

On the basis of above data following, structures and mechanisms have been established.

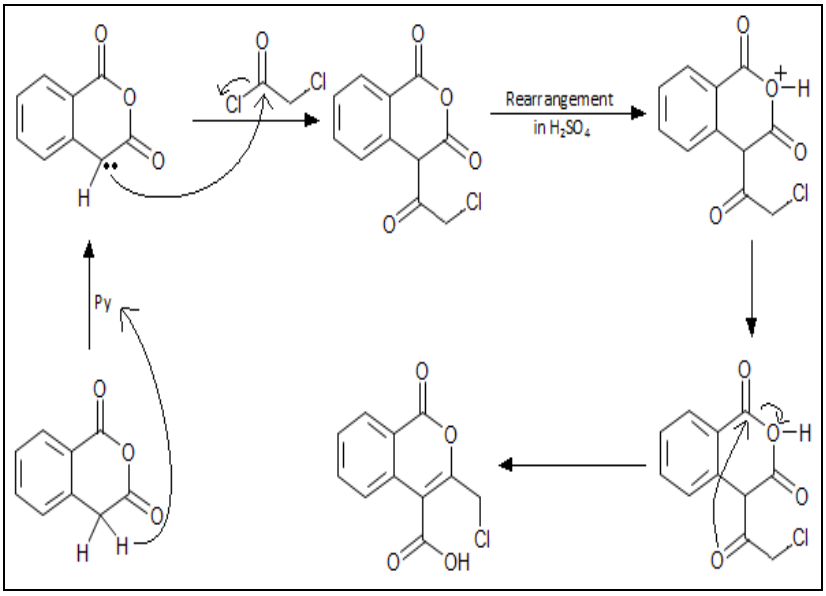

Figure II: Reaction Mechanism for the formation of 3-(chloromethyl)-1-oxo-1H-2-benzopyran-4-carboxylic acid

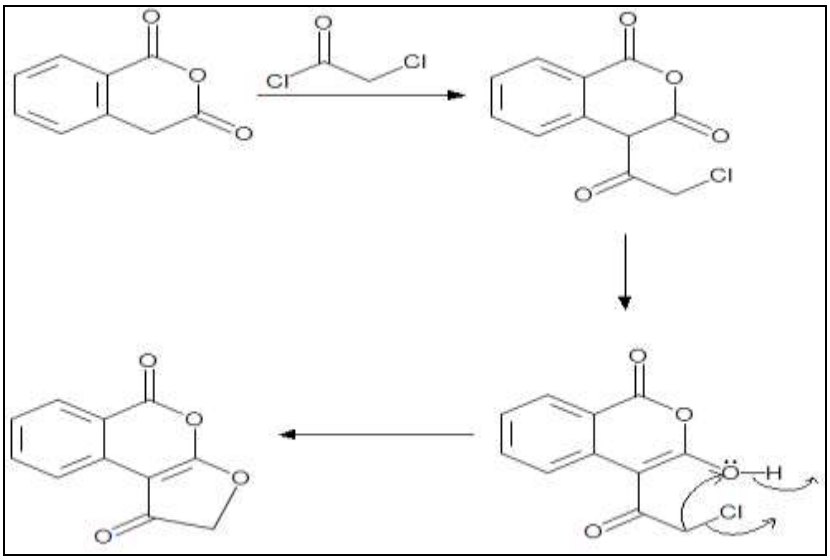

Figure III: Reaction Mechanism for the formation of 5H-furo [2,3-c] [2]benzopyran-1,5(2H)-dione

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