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Synthesis of Isocoumarins and its derivatives

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ABSTRACT

3-methyl-1-oxo-1-H-2-benzopyran-4-carboxylic acid was synthesized in excellent yields by the reaction of homophthalic anhydride with acetyl chloride using pyridine as a catalyst, followed by rearrangement of 4-acetyl-1H-2-benzopyran-1,3(4H)-dione with Conc. Sulphuric acid. Further 3-methyl-1-oxo-1H-2-benzopyran-4-carboxylic acid was derivatised to various isoquinolones using ammonia and respective primary amines. It was also inferred the isoquinolones obtained were same when ammonia and other primary amines were treated with 3-methyl-1-oxo-1-H-2-benzopyran-4-carboxylic acid, 4-acetyl-1H-2-benzopyran-1,3(4H)-dione, or 3-methyl-1H-2-benzopyran-1-one.

Key words: Isocoumarins, homophthalic anhydride, acetyl chloride, pyridine, isoquinolone, benzopyran.

INTRODUCTION

Isocoumarins are obtained naturally as well synthetically. Natural sources include microbes[1], mold metabolites[2], plants[3-7], and insects. Isocoumarins 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 paved way for synthesis of isoquinolones, which are another set of biologically active group of compounds having N as an hetero atom. These isoquinolones have a broad activity spectrum right from fever to cancer.

MATERIALS AND METHODS

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 acetyl 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 and are uncorrected. The purity of the compounds was monitored by thin layer chromatography on silica gel coated aluminium plates (merck) as adsorbent and UV light as visualizing agent. ¹H NMR spectra were recorded on varian 500MHz NMR spectrophotometer using CDCl₃/DMSO-d₆ 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.

General Procedure

Oxidation of indene(1) using potassium dichromate in presence of sulphuric acid yielded Homophthalic acid(2). Compound 2 was further dehydrated to homophthalic anhydride(3) using acetic anhydride at reflux temperature for two hours. Compound 3 was used as a substrate to prepare 4-acetyl-1H-2-benzopyran-1,3(4H)-dione(4) using pyridine and acetyl chloride.

Synthesis of 3-methyl-1-oxo-1-H-2-benzopyran-4-carboxylic acid(5):

Step 1: To a round bottom flask, Acetyl chloride (0.042mole, 3.3g) was added to Pyridine (0.061mole, 4.89g) drop wise with stirring. Addition was carried in ice bath. To facilitate stirring 10 ml diethyl ether was added. After complete addition of Pyridine, Compound 3 (0.012mole, 2g) was added. 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-acetyl-1H-2-benzopyran-1,3(4H)-dione) was left behind. This intermediate 4-acetyl-1H-2-benzopyran-1,3(4H)-dione(4) was soluble in water at higher temperature. Hence it was washed with cold water. Compound 4 was recrystallized in chloroform. m.p. 161-163.

Step 2: Compound 4 was added to 2 ml of 90% H₂SO₄ and kept overnight in a refrigerator at 0-5°C. 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 5 and then a final washing of cold water was given to the purified compound. Recrystallized in ethyl acetate, M.P. 217-219°C.

Spectral interpretation of 3-methyl-1-oxo-1-H-2-benzopyran-4-carboxylic acid:

Anal. Calcd for C₁₀H₈O₄: C, 64.70; H, 3.92%. Found C, 64.73; H, 3.98%. ¹H NMR (δ ppm): 8.17(1H, m), 7.5(1H, m), 7.8(1H, m), 7.6(1H, m), 2.4(3H, s) ¹³C NMR (δ ppm): 165.42(H₃C-C-O), 173.0 (C=O), 169.2 (C=O), 129.3, 129.8, 124.1, 119.8, 113.26, 135.02, 131.68, 19.85(-CH₃, sp³C)

Synthesis of 3-methyl-1H-2-benzopyran-1-one(6)

Compound 4 was added to 2 ml of 90% H₂SO₄ and then heated on a boiling water bath for three hours and kept overnight. Then to this we added 3ml of ice water and stirred by immersing the container in an ice bath. Then a free flowing white coloured residue was obtained which was again washed with cold water and filtered. This residue was treated with sodium bicarbonate and again filtered. The remaining residue obtained was then washed with cold water and then it was recrystallized in pet ether. M.P of 71-72°C.

Spectral interpretation of 3-methyl-1H-2-benzopyran-1-one:

Anal. Calcd for C₁₁H₈O₂: C, 76.74; H, 4.65%. Found C, 76.78; H, 4.61%. ¹H NMR (δ ppm): 8.05(1H,d), 7.49(1H,t), 7.60(1H,t), 7.68(1H,d), 6.66(1H,s), 2.34(3H, s) ¹³C NMR (δ ppm): 161.73(C=O), 155.35(H₃C-C-O-), 129.35, 120.46, 126.7, 135.1, 128.6, 103.93, 130.23, 19.35(-CH₃, sp³C)

Synthesis of isoquinolones(7a-e):

Compound 4(0.0024 mole, 0.5g), Compound 5 (0.0024 mole, 0.5g), and Compound 6(0.0031 mole, 0.5g) were individually refluxed with (0.1 mole) ammonia and primary amines for three hours. 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 to yield compound 7. Similarly compounds 7a-e were synthesized. Compound 4, Compound 5 and Compound 6 gave same isoquinolones.

Spectral interpretation of 3-methylisoquinolin-1(2H)-one (7a)

Anal. Calcd for C₁₀H₉NO: C, 75.47; H, 5.66; N, 8.80%. found C, 75.45; H, 5.68; N, 8.83%. ¹H NMR (δ ppm): 2.314(3H, s), 6.178(1H,s), 7.514(1H, t), 7.507(1H, d), 7.507(1H, d), 8.029(1H, t) ¹³C NMR (δ ppm): 160.2(C=O), 151.51, 135.1, 130.23, 129.17,127.8, 126.85, 126.70, 117.98, 19.61

Spectral interpretation of 2,3-dimethylisoquinolin-1(2H)-one(7b)

Anal. Calcd for C₁₁H₁₁NO: C, 76.30; H, 6.35; N, 8.09%. found C, 76.34; H, 6.32; N, 8.08%. ¹H NMR (δ ppm): 2.343(3H, s), 3.365(3H, s), 6.719(1H, s), 7.516(1H, t), 7.502(1H, t), 7.508(1H, t), 7.887 (1H, t) ¹³C NMR (δ ppm): 165.18(C=O), 145.73, 135.7, 130.23, 129.17, 128.2, 126.8, 125.1, 117.98, 34.63(sp³, H₃C-N), 20.37 (sp³ C)

2-hydroxy-3-methylisoquinolin-1(2H)-one(7c)

Anal. Calcd for C₁₂H₁₃NO₂: C, 70.93; H, 6.35; N, 6.40%. found C, 70.95; H, 6.38; N, 6.45%. ¹H NMR (δ ppm): 3.525(2H, d, J=2.67, 2.67 Hz), 4.134(2H, d), 2.36(3H, s), 6.742(1H, s), 7.5(3H, m), 7.891 (1H, d, J=1.334, 7.9Hz) ¹³C NMR: (δ ppm): 161.8(C=O), 149.73, 135.75, 129.17, 126.8, 117.98, 130.23, 128.2, 125.1, 59.21(sp³ H₂C-O), 49.52(sp³ H₂C-N), 20.37(sp³ C),

2-benzyl-3-methylisoquinolin-1(2H)-one(7d)

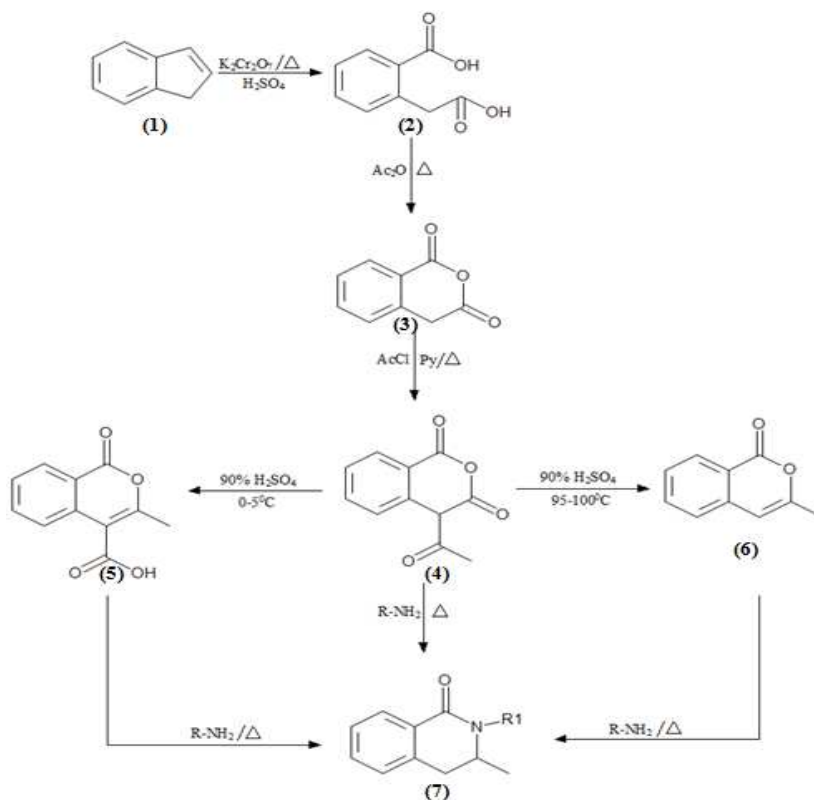
Anal. Calcd for C₁₇H₁₅NO: C, 81.92; H, 6.02 N, 5.62%. found C, 81.93; H, 6.03; N, 5.65%. ¹H NMR (δ ppm): 3.525(2H, d), 4.134(2H, d), 2.36(3H, s), 6.742(1H, s), 7.5(3H, m), 7.891 (1H, d) ¹³C NMR (δ ppm): 161.8(C=O)145.73(sp² C, H₃C-C-N), 130.23, 135.75, 128.2, 128.59(2C, Ar. Ring) 125.1, 132.66, 126.8, 129.17, 128.92, 127.97 (2C, Ar. Ring), 117.986, 48.1(sp³C, H₂C-N) 20.37

2-hydroxy-3-methylisoquinolin-1(2H)-one(7e)

Anal. Calcd for C₁₀H₉NO₂: C, 68.57; H, 5.14 N, 8%. found C, 68.59; H, 5.18; N, 8.02%. ¹H NMR (δ ppm): 2.232(3H, s), 7.1(1H, s), 7.6(1H, d), 7.4(2H, m.), 8.1(1H, d) ¹³C NMR (δ ppm): 166.13(C=O), 137.48(sp²C, H₃C-C-N), 135.75, 130.23, 129.17, 128.2, 128.8, 126.17, 117.98, 15.51(sp³C, Ar-CH₃)

Table 1: Characterization data of all the compounds

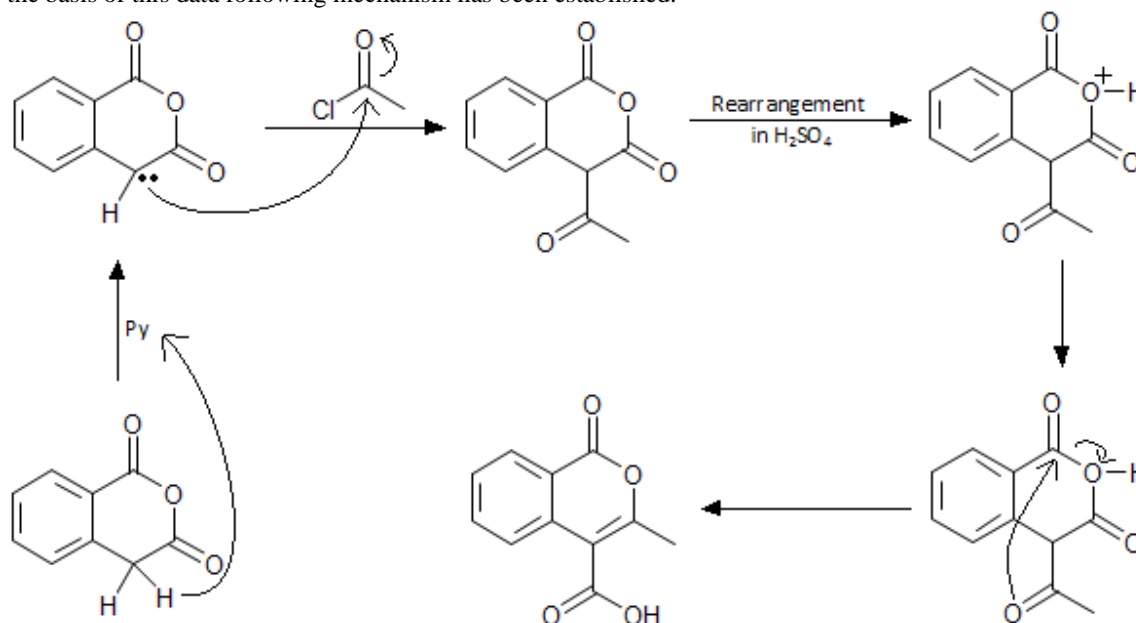
Compound	M.F.	M.P./B.P.	Mol. Wt.
1	C ₉ H ₈	181-183	116
2	C ₉ H ₈ O ₄	179-181	180
3	C ₉ H ₆ O ₃	139-141	162
4	C ₁₁ H ₈ O ₄	161-163	204
5	C ₁₁ H ₈ O ₄	217-219	204
6	C ₁₀ H ₈ O ₂	71-72	160
7a, R1=NH ₂	C ₁₀ H ₉ NO	210-211	159
7b R1=NH-CH ₃	C ₁₁ H ₁₁ NO	103-104	173
7c R1=NH-(CH ₂) ₂ OH	C ₁₂ H ₁₃ NO ₂	097-098	203
7d R1=NH-CH ₂ -Ar	C ₁₇ H ₁₅ NO	108-110	249
7e R1=NH-OH	C ₁₀ H ₉ NO ₂	125-126	175

General Scheme

RESULTS AND DISCUSSION

In the present research it was discovered that isoquinolones(7a-e) obtained from compound **4** were same as the isoquinolones obtained from compound **5** and compound **6**. Thus in this study we could also put forward a mechanism for our research work. It was also found that during purification of compound **5** in step 2, some residue remained in the filter paper after filtration, which gave a similar m.p. with compound **6**. During synthesis of compound **6**, major amount of solid was undissolved in sodium bicarbonate, but still a small amount of solid reprecipitated upon acidification of this filtrate. The m.p. of the precipitate was similar to compound **5**.

On the basis of this data following mechanism has been established.



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