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Synthesis of Isocoumarins and isoquinolones

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ABSTRACT

3-methyl-1H-2-benzopyran-1-one 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 at high temperature.

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

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].

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. This 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. ^{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.

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-acetyl-1H-2-benzopyran-1,3(4H)-dione**(4)** using pyridine and acetyl chloride.

Synthesis of 4-acetyl-1H-2-benzopyran-1,3(4H)-dione(4):
Acetyl chloride (0.042mole, 3.3g) was taken in a round bottom Flask to which Pyridine (0.061mole, 4.89g) was added drop wise with stirring. Addition was carried in ice bath. To facilitate stirring 10 ml diethyl ether was added. After complete addition of Pyridine homophthalic anhydride**(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. Yield- 80%, m.p. 161-163.

Spectral details of 4-acetyl-1H-2-benzopyran-1,3(4H)-dione
Anal. Calcd for $C_{11}H_8O_4$: C, 64.70; H, 3.92%. found C, 64.65; H, 3.95%. ^{1}H NMR (δ ppm): 2.1(3H, s), 4.3(1H,s), 7.08(1H, d), 7.704(1H, t), 7.438(1H, t), 7.969(1H, d) ^{13}C NMR(δ ppm): 207.42(H_3C-C=O), 172.0 (C=O), 165.9 (C=O), 139.24, 130.3, 129.35, 126.8, 124.6, 122.91, 58.1, 29.7

Synthesis of 3-methyl-1*H*-2-benzopyran-1-one(5):
Compound 4was added to 2 ml of 90% H_2SO_4 and then heated on a boiling water bath for three hours and kept overnight. Then to this we added 3ml if 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^{0}C.

Spectral interpretation of 3-methyl-1*H*-2-benzopyran-1-one
Anal. Calcd for $C_{11}H_8O_2$: C, 76.74; H, 4.65%. Found C, 76.78; H, 4.61%. ^{1}H 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) ^{13}C NMR (δ ppm): 161.73(C=O), 155.35(H_3C-C-O-), 129.35, 120.46, 126.7, 135.1, 128.6, 103.93, 130.23, 19.35(-CH_3, sp^3C)

Synthesis of isoquinolones(6a-e):
Compound 5 (0.0031 mole, 0.5g) was 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 6. Similarly compounds 6a-e were synthesized.

3-methylisoquinolin-1(2H)-one (6a)
Anal. Calcd for $C_{10}H_9NO$: C, 75.47; H, 5.66; N, 8.80%. found C, 75.45; H, 5.68; N, 8.83%. ^{1}HNMR (δ ppm): 2.314(3H, s), 6.178(1H,s), 7.514(1H, t), 7.507(1H, d), 7.507(1H, d, J=7.899, 1.659Hz), 8.029(1H, t) ^{13}C 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

2,3-dimethylisoquinolin-1(2H)-one(6b)
Anal. Calcd for $C_{11}H_{11}NO$: C, 76.30; H, 6.35; N, 8.09%. found C, 76.34; H, 6.32; N, 8.08%. ^{1}H 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) ^{13}C 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(sp^3, H_3C-N),20.37 (sp^3 C)

2-hydroxy-3-methylisoquinolin-1(2H)-one(6c)
Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.93; H, 6.35; N, 6.40%. found C, 70.95; H, 6.38; N, 6.45%. ^{1}H 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) ^{13}C 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(sp^3 H_2C-O), 49.52(sp^3 H_2C-N), 20.37(sp^3 C),

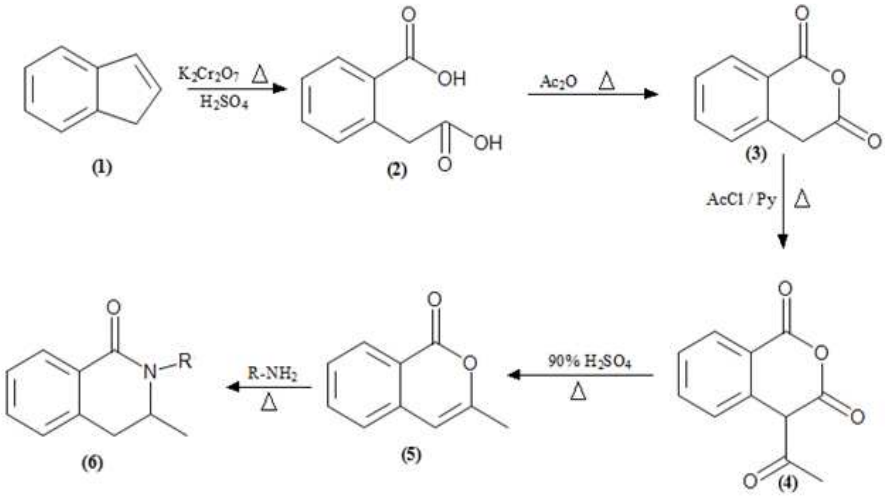
2-benzyl-3-methylisoquinolin-1(2H)-one(6d)
Anal. Calcd for $C_{17}H_{15}NO$: C, 81.92; H, 6.02 N, 5.62%. found C, 81.93; H, 6.03; N, 5.65%. ^{1}H NMR (δ ppm): 3.525(2H, d), 4.134(2H, d), 2.36(3H, s), 6.742(1H, s), 7.5(3H, m), 7.891 (1H, d) ^{13}C NMR (δ ppm): 161.8(C=O)145.73(sp^2 C, H_3C-C-N), 130.23, 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(sp^3C, H_2C-N) 20.37

2-hydroxy-3-methylisoquinolin-1(2H)-one(6e)
Anal. Calcd for $C_{10}H_9NO_2$: C, 68.57; H, 5.14 N, 8%. found C, 68.59; H, 5.18; N, 8.02%. ^{1}H NMR (δ ppm): 2.232(3H, s), 7.1(1H, s), 7.6(1H, d), 7.4(2H, m,), 8.1(1H, d) ^{13}C NMR (δ ppm): 166.13(C=O), 137.48(sp^2C, H_3C-C-N), 135.75, 130.23, 129.17, 128.2, 128.8, 126.17, 117.98, 15.51(sp^3C, Ar-CH_3)

Table 1:Characterisation data of all the compounds

Compound	M.F.	M.P.	Mol. Wt.
4	$C_{11}H_8O_4$	160-161^{0}C	204
5	$C_{10}H_8O_2$	071-072^{0}C	160
6a, R=NH_2	$C_{10}H_9NO$	210-211^{0}C	159
6b R=NH-CH_3	$C_{11}H_{11}NO$	103-104^{0}C	173
6c R=NH-$(CH_2)_2$OH	$C_{12}H_{13}NO_2$	097-098^{0}C	203
6d R=NH-CH_2-Ar	$C_{17}H_{15}NO$	108-110^{0}C	249
6e R=NH-OH	$C_{10}H_9NO_2$	125-126^{0}C	175

General Scheme

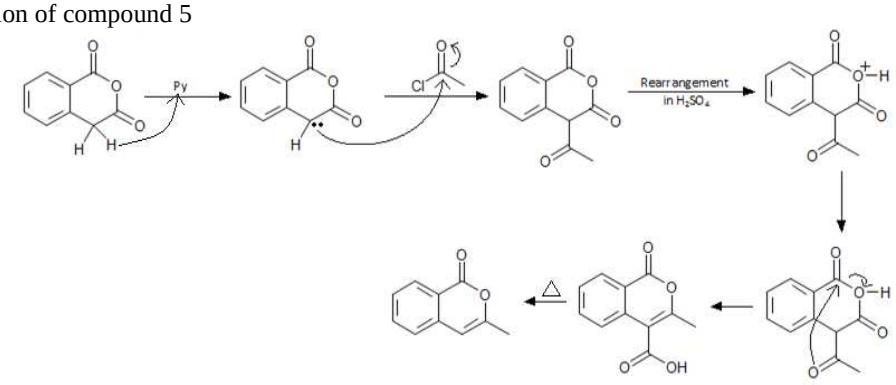


RESULTS AND DISCUSSION

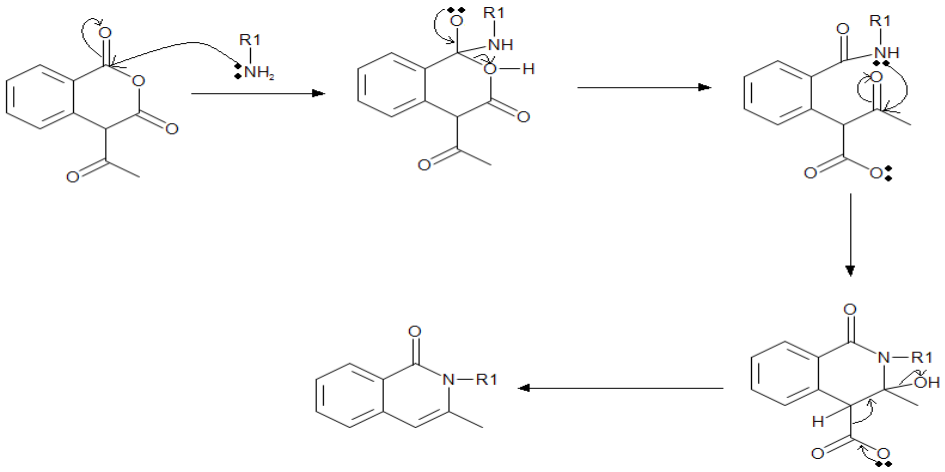
In previous studies compound 5 was directly prepared from compound 2, but the path was unknown. In the present work we tried to establish the path by which compound 5 is formed. Probable mechanisms are also established which shows decarboxylation of compound 4 as well as how oxygen in compound 5 gets replaced by nitrogen in compound 6.

Mechanisms

1. For formation of compound 5



2. For formation of compound 6



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