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NEW SYNTHETIC METHOD OF 4-METHOXY-7H-FURO [3, 2-g][1]BENZOPYRAN-7-ONE

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ABSTRACT

4-Methoxy-7H-Furo[3,2-g][1]benzopyran-7-One is one kind of linear Furanocoumarins, which shows a wide range of biological properties. A simple method for its synthesis was proposed in this paper, which was accomplished from phloroglucinol and ethyl propiolate as original materials by etherification, iodination, Pechmann condensation, coupling reaction, hydrolysis and decarboxylation. Intermediates and the target compound were characterized by ^{1}H NMR, IR and MS. The proper reaction conditions were optimized by experiments and the feasibility of route was also studied. All reactions were preceded under normal pressure with mild condition and relatively simple post-processing, which shows a new route for the preparation of furanocoumarins.

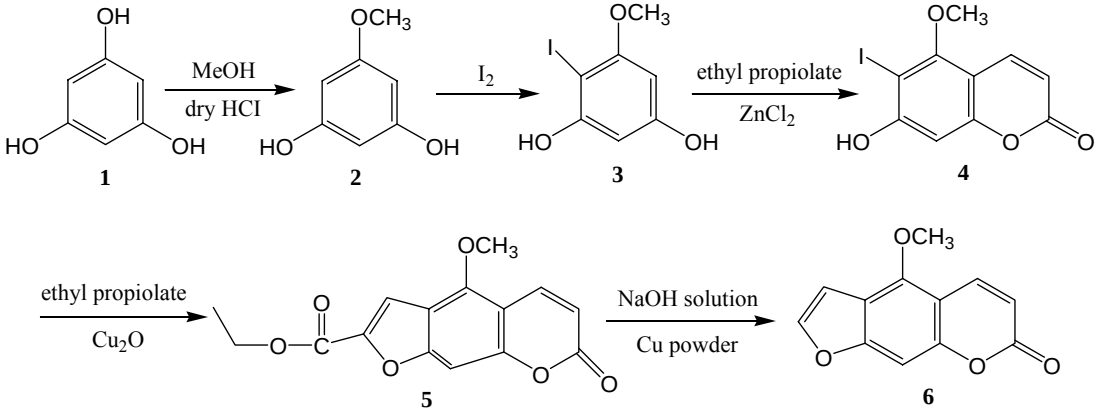
Keywords furanocoumarin, phloroglucinol, o-iodophenol, total synthesis.

INTRODUCTION

Furanocoumarins are natural products attracting a great deal of attention due to their potential biological properties[1-3]. Many of them are effective in inhibitory activity against bacterium, virus, tumor, hyperplasia and HIV[4-8]. Furanocoumarins are also extensively used in photosensitive medicament, photosensitive pesticide and molecular biology[9].

4-Methoxy-7*H*-Furo[3,2-g][1]benzopyran-7-One, which was first isolated from a plant called Bergamia in 1947 and total synthesized by Goupil[10] in 1984, is one kind of linear Furanocoumarins, and have attracted much attention in recent years due to a wide variety of biological features, including cytotoxic, antitumoral, and antimalarial activities[11]. It is also an applicable intermediate for the synthesis of more complex natural products[12,13]. For its content in Bergamia is very low[14] (< 2%), the synthesis of furanocoumarins has been paid considerable attention in the world. Several synthetic methods were reported[15-17]. However, due to the too-long technics and low chemoselectivity, many methods only lead to very low yield[15-20]. Meanwhile, rigorous conditions of the reaction and the use of expensive catalyst make furanocoumarins' synthesis very difficult to industrialization. In this paper, a new synthesis route to

4-Methoxy-7*H*-Furo[3,2-g][1]benzopyran-7-One was designed by etherification, iodination, Pechmann condensation, coupling reaction, hydrolysis and decarboxylation using phloroglucinol and ethyl propiolate as original materials (Scheme **1**). All the reaction conditions are not rigorous, the catalyst is cheap, and the purification is relatively easy. The whole synthesis route provided a practical and economical path for industrialization.



Scheme-1

EXPERIMENTAL

Preparation of 5-Methoxy-1,3-benzenediol 2

Under an atmosphere of gaseous HCl, phloroglucinol (40g, 0.326mol) and methanol (200mL) were placed in a three-neck flask. The mixture was stirred under reflux for 3h. The excessive solvent is evaporated leaving a red dope. The residue was dissolved in a solution composed of ether (50mL) and water (30mL), then ether (2×20mL) was added to the mixture to extract the product. The combined organic layers were successively washed with saturated sodium bicarbonate solution (60mL) and water (60mL), dried over anhydrous calcium chloride, and evaporated under reduced pressure, 18.94g (54.8%) of **2** was obtained by re-crystallization in toluene. mp 78-79□. IR (KBr,σ/cm^{-1}): 1354(OH), 1440(CH_3). ^{1}H NMR ($CDCl_3$): 3.75(s, 3H), 4.72(s, 2H), 5.98(s, 1H), 6,01(s, 2H). MS (%): 139(M^-, 5), 124(80), 96(100), 63(10), 42(24).

4-Iodo-5-Methoxy-1,3-benzenediol 3

A three-neck flask immersing in ice bath was charged with I_2 (10g, 0.039mol), chloroform (30mL). After being stirred for 10min, H_2SO_4 (80mL,1.7mol·l^{-1}), **2** (10g, 0.71mol) and H_2O_2 (30mL, 9.7mol·L^{-1}) were added and reaction was continued for 15min. The resulting mixture was extracted with ether (3×40mL), and the combined extracts were successively washed with saturated sodium bicarbonate solution (100mL) and water (100mL), dried over anhydrous calcium chloride. The solvent was removed under reduced pressure and the residue was washed with chloroform (150mL). 16.6g (81.4%) of **3** was obtained after filtering. mp 116-118□. IR (KBr,σ/cm^{-1}): 1340(OH), 1486(CH_3). ^{1}H NMR ($CDCl_3$): 3.84(s, 3H), 4.84(s, 1H), 5.45 (s, 1H), 6.03(d, 1H, J=2.5, 6.22(d, 1H, J=2.5). MS (%): 265(M^-, 18), 249(3), 122(100).

7-Hydroxy-6-Iodo-5-Methoxy-2H-benzopyran-2-One 4

Under an atmosphere of nitrogen, a there-neck flask containing a condenser and stir bar was charged with **3** (10g, 0.038mol), ethyl propiolate (12ml, 0.122mol) and $ZnCl_2$ (5g, 0.043mol) previously dried. The resulting mixture was heated and stirred at 90□for 1.5h. After cooling to room temperature, ethanol (10mL) was added to dissolve the red thick liquid. The whole was poured to ice water and filtrated. The residue was dissolved by ethyl acetate (10mL), then successively washed with saturated sodium bicarbonate solution (2×50mL) and brine (50mL), dried over anhydrous calcium chloride, The solvent was removed under reduced pressure and the residual mixture underwent a chromatographic process on silica gel G, eluting with ethyl acetate to give 6.9 g (57.7%) of **4**. mp 221-224□. IR (KBr,σ/cm^{-1}): 1119(-$COCH_3$), 1366(OH), 1719(CO-O). ^{1}H NMR ($CDCl_3$): 3.85(s, 3H), 6.03(s, 1H), 6.14(d, 1H, J=9.6), 6.55(s, 1H), 7.82(d, 1H, J=9.6). MS (%): 317(M^-, 62), 302(18), 147(10), 127(100).

4-Methoxy-7-Oxo-7H-Furo[3, 2-g][1]benzopyran-2-Ethyl formate 5

DMF (80mL), **4** (10g, 0.031mol), ethyl propiolate (5mL, 0.050mol) and Cu_2O (3.2g, 0.022mol) were placed in a three-neck flask with a condenser and stir bar. The mixture was heated and stirred at 110□ for 36h under the atmosphere of nitrogen. The solvent was removed under reduced pressure and the residual mixture was dissolved by chloroform (20mL) and then underwent a chromatographic process on silica gel G, eluting with dichloromethane to give 0.56g (61.9%) of **5**. mp 203-205□. IR (KBr,σ/cm^{-1}): 1122(-$COCH_3$), 1728(CO-O). ^{1}H NMR ($CDCl_3$): 1.44(t, 3H), 4.23(s, 3H), 4.46(q, 2H), 6.32(d, 1H, J=9.5), 7.25(s, 1H), 8.00(s, 1H), 8.18(d, 1H, J=9.5). MS (%): 289(M^+,54), 274(9), 261(100), 246(28), 217(9).

4-Methoxy-7H-Furo[3,2-g][1]benzopyran-7-One 6

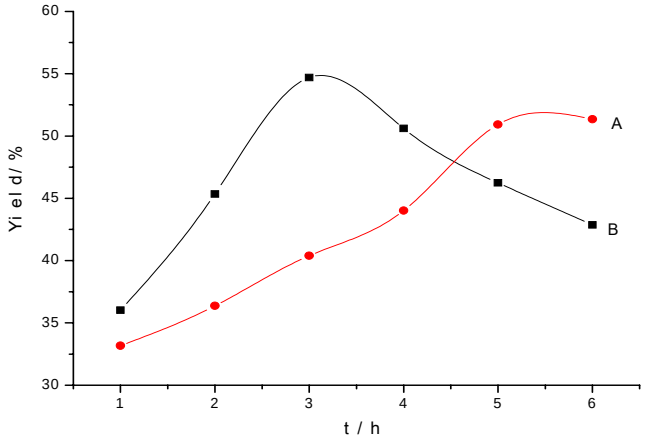
A three-neck flask containing a condenser and stir bar was charged with **5** (5g, 0.017mol) and saturated sodium hydroxide t solution (60mL). The mixture was stirred under reflux for 2h. After cooling to room temperature, hydrochloric acid (100mL,1mol·L^{-1}) was added to make the solution PH **<** 1, and vigorously stirred for 1h. After filtration, the residue was dissolved in quinoline (80mL) and reacted with Cu powder (0.2g, 0.031mol) at 210□for 2h under the atmosphere of nitrogen. Cold hydrochloric acid(100mL, 1mol·L^{-1}) was added and yellow emulsion was formed. Ethyl acetate (3×100mL) was added to the mixture to extract the product. The combined organic layers were successively washed with brine (2×80mL) and water (3×80mL), dried over anhydrous calcium chloride, The solvent was removed under reduced pressure and the residual mixture was dissolved by chloroform (40mL), and then underwent a chromatographic process on silica gel G, eluting with dichloromethane to give 0.28g (74.7%) of **6**. mp 181-183□. IR (KBr,σ/cm^{-1}): 1129(-$COCH_3$),1730(CO-O). ^{1}H NMR ($CDCl_3$): 4.27(s, 3H), 6.28(d, 1H, J=9.7), 7.02(d, 1H J=2.5), 7.14(s, 1H), 7.60(d, 1H, J=2.5), 8.16(d, 1H, J=9.7). MS (%): 217(M^+, 4), 202(100), 174(89), 146(18), 118(22), 90(9).

RESULTS AND DISCUSSION

The choice of Etherification solution in the synthesis of 2

Methanol is not only reactant but also solvent in the reaction. Excessive methanol results in the formation of diether and thiether. In contrast with methanol, 1,4-Dioxane was also chosen as the solution for its

better dissolving capacity of phloroglucinol and almost the same boiling point as methanol. Effects of solvent were studied as follows.



A: methanol (100mL)+1,4-Dioxane(100mL) ; B: methanol (200mL)

Fig.-1: Yield of Compound 2 *vs* reaction time
Reaction condition: phloroglucinol (40g), temperature(80□)

As is shown in Figure1, the addition of solvent lowers the etherification activity of methanol, and prolongs the time of monoetherification. The best reaction time is 3h when using methanol as solvent. If 1,4-Dioxane was used as solvent, the yield of **Compound 2** increased with time, but the process needs much more time and the addition of other solvent was not propitious to the recycle of methanol. So, methanol was chosen as reaction solvent, and the yield of monoetherification product was 54.8%.

The effect of acid strength to the synthesis of 3

In order to gain the 4-iodo-product, the formation of 2-iodo-isomer and diiodo-product should be restrained. Experiments showed the ratio of 4-iodo- and 2-iodo-isomert has direct business with acid strength.

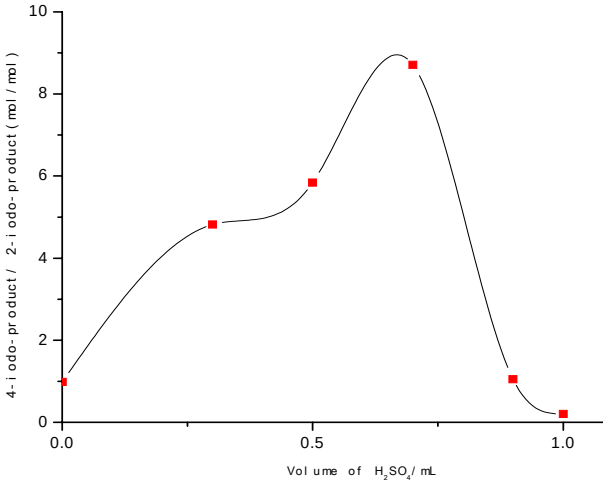


Fig.-2 Effect of acid strength on the yield of Compound 3

Reaction condition: Compound **2** (2.8g, 0.02mol), iodine (2.5g, 0.01mmol), H_2O (7mL), ice-water bath, H_2O_2 solution (10mL, 9.7mol·L^{-1}), reaction time 30 min

The increase of acid strength restrains the formation of 2-iodo-isomer, and enhances the ratio of 4-iodo-idomer. However, reversible rearrangement reaction occurs under strongly acidic condition. Fixing the amount of water, when the addition of H_2SO_4 reaches 0.7mL, the yield of 4-iodo-product is the largest, and the concentration of sulphuric acid solution is 1.7mol·L^{-1}.

CONCLUSION

In conclusion, a simple method for the preparation of 4-Methoxy-7*H*-Furo[3, 2-g][1]benzopyran-7-One from phloroglucinol was accomplished in 5 steps from phloroglucinol and ethyl propiolate as original materials. The proposed route is concise and modular, making it convenient for large scale preparation and rapid synthesis of Furanocoumarins. Meanwhile, the work towards this direction is being pursued in our laboratory.

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