A Facile and Practical Preparation of 5,7-Dihydroxy-3-(4-nitrophenyl)-4*H*-1-benzopyran-4-one

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In spite of the fact that several preparative methods for the synthesis of hydroxylated isoflavones were reported during the past fifty years, none is suitable for the preparation of isoflavones containing 5,7-dihydroxyl functions. This paper reports a simple, large scale preparation of 5,7-dihydroxy-3-(4-nitrophenyl)-4*H*-1-benzopyran-4-one (**2a**) by the condensation of the readily available 4-nitrobenzyl 2,4,6-trihydroxyphenyl ketone (**1a**) and acetic-formic anhydride in high yields. Similar isoflavones, such as 7-hydroxy-3-(4-nitrophenyl)-4*H*-1-benzopyran-4-one (**2b**) can also be obtained in good yields in analogous manner.

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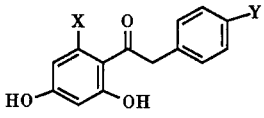
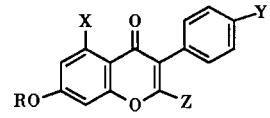
In connection with our continued study on the total design of antineoplastic agents [1], a key intermediate, 5,7-dihydroxy-3-(4-nitrophenyl)-4*H*-1-benzopyran-4-one (5,7-dihydroxy-4'-nitroisoflavone, **2a**), is required in relatively large quantity. One of the existing reports indicated that compound **2a** could be prepared by the condensation of 4-nitrobenzyl 2,4,6-trihydroxylphenyl ketone (**1a**) with triethyl orthoformate in pyridine using piperidine as the catalyst [2], albeit in low yield. It is surprising to note that a similar preparation for the closely related 7-hydroxy analogue **2b** from the corresponding ketone **1b** gave a good (77%) yield of the desired product [2,3] but repeated attempts in our laboratory for the preparation of **2a** could not raise the yields to more than 15%. Its average yield from **1a** was only 10%. A number of modifications of that reaction condition were also conducted, including change of reaction solvent, change of condensation catalyst, change of the molar ratio of reactants and change of *p*H of the reaction medium, but these experiments either failed to secure the product or resulted in isolation of the product in similar or even lower yields.

Treatment of the benzyl phenyl ketone **1a** with ethoxalyl chloride in pyridine, followed by base hydrolysis of the ester **2c** formed, and subsequent decarboxylation of the resulting acid **2d** to the desired compound **2a** was reported in 1953 [4]. Aside from the involvement of the multi-stage operations, the method suffers from the fact that the decarboxylation step can only be carried out in very small quantities (*ca* 50 mg) and the decarboxylation process should be conducted either by heating the material rapidly at 10° above the melting point of the acid (mp 260°) or by sublimation. The yield in the final decaboxylation step was reported as 23%.

A newer preparation of isoflavones by the condensation of *o*-hydroxyacetophenones of type **1** with dimethoxy(dimethylamino)methane (dimethylformamide dimethylacetal) [5] was also reported [6]. These investigators claimed



1a X = OH, Y = NO_2
b X = H, Y = NO_2
c X = H, Y = OCH_3
d X = OH, Y = OCH_3



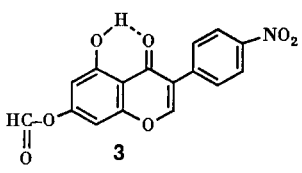
2a R = H, X = OH, Y = NO_2, Z = H
b R = H, X = H, Y = NO_2, Z = H
c R = H, X = H, Y = NO_2, Z = $CO_2C_2H_5$
d R = H, X = H, Y = NO_2, Z = CO_2H
e R = OH, X = H, Y = OCH_3, Z = H
f R = OH, X = OH, Y = OCH_3, Z = H
g R = HCO, X = OH, Y = NO_2, Z = H
h R = HCO, X = H, Y = NO_2, Z = H

that their method could be used for large scale synthesis of a variety of isoflavones. However, a close examination of that paper revealed that the method only worked well for those *o*-hydroxyacetophenones wherein the phenyl moiety is not substituted by hydroxyl groups at both *ortho* positions with respect to the carbonyl function. For example, compound **1c** gave a 87% yield of **2e**. In contrast, with compounds having both *ortho* positions occupied by hydroxy groups, such as **1d**, th yield of the corresponding isoflavones **2f** drastically dropped to only 15%. Treatment of compound **1a** with dimethoxy(dimethylamino)methane under the same reaction condition provided by these authors failed to isolate any desired **2a** in our hands.

It thus appears that, up to the present, none of the existent procedures for the cyclization of *o*-hydroxyacetophenones **with both ortho positions occupied by hydroxyl groups** could afford corresponding isoflavones in acceptable yields. Consequently, search for other agents which could serve as one-carbon components to the desired cyclization reaction was undertaken.

Acetic-formic anhydride, prepared from a mixture of formic acid and acetic anhydride [7,8], has been used for the formylation of alcohols. Attempted formylation of compound **1a** with the mixed anhydride gave, surprisingly, a 70% yield of the cyclized product **2g** directly. Structural assignment for **2g** was based on elemental analysis, mass

spectrum detemination, and the fact that hydrogen bonding formation often existed between a carbonyl oxygen atom and a *peri*-substituted hydroxyl group [9,10], shown as **3**. Thus the possibility of the product to exist as structure **4** was ruled out. Mild base hydrolysis of **2g** readily gave the desired product **2a** in almost quantitative yield.



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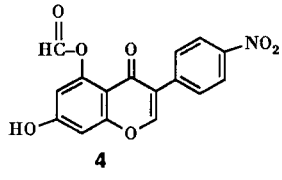

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In order to ensure that the mixed anhydride method is applicable for the synthesis of other related isoflavones, the following experiment for preparing the aforementioned 7-hydroxy-3-(4-nitrophenyl)-4*H*-1-benzopyran-4-one (**2b**) was conducted. Treatment of 2,4-dihydroxyphenyl 4-nitrobenzyl ketone (**1b**) with acetic-formic anhydride under the analogous reaction condition gave the corresponding formyloxy isoflavone **2h** in 76% yield. Subsequent mild hydrolysis of **2h** in dilute base readily gave the expected **2b**. Thus a simple and practical process for the preparation of these isoflavones is realized.

EXPERIMENTAL

7-Formyloxy-5-hydroxy-3-(4-nitrophenyl)-4*H*-1-benzopyran-4-one (**2g**).

To 500 ml of 99% acetic anhydride cooled at 0° was added dropwise 250 ml of 96% formic acid with stirring. After the addition was complete, the solution was stirred continuously at 0° for 30 minutes, then stirred at 50-55° for another 30 minutes. The resulting mixed anhydride was immediately chilled to 0°. To the cold solution was added protionwise, with stirring, 28.9 g (0.1 mole) of 4-nitrobenzyl 2,4,6-trihydroxyphenyl ketone (**1a**) at 0°. The yellow suspension was stirred continuously at 0° for 30 minutes, then stirred at 50-55° until all solids dissolved, which took a total of 10 hours. There was no starting material remaining in the clear brownish yellow solution, as indicated by thin layer chromatography. The solution was evaporated to dryness under reduced pressure. To the residue was added 150 ml of ethyl acetate. The resulting yellow solid was collected by filtration, washed with ethyl acetate and dried to give 23 g (70% yield) of pure **2g**, mp 265-268°; uv: λ max 205 (log ε 4.40) and 286 nm (log ε 4.33); ms: 327 (M^+).

Anal. Calcd. for $C_{16}H_9NO_7 \cdot \frac{1}{2}H_2O$: C, 57.15; H, 3.00; N, 4.17. Found: C, 57.45; H, 2.54; N, 4.01.

5,7-Dihydroxy-3-(4-nitrophenyl)-4*H*-1-benzopyran-4-one (**2a**).

To 120 ml of 2*N* sodium hydroxide was added, at room temperature, 12 g of **2g**. The suspension was stirred for 2 hours at room temperature. The resulting alkaline solution was acidified with 2*N* of hydrochloric acid to *p*H 4. During the acidification the color of the solution gradually changed from brownish red to yellow and, finally, a yellow precipitate was formed. The solid was collected by filtration, washed with water and dried at 50° *in vacuo*. The yield was 10.7 g. The crude product was triturated with 150 ml of butanol and after stirred for 2 hours, the resulting fine particles were collected by filtration and dried to give 10 g (94% yield) of **2a**, mp 292-295°. An analytical sample was prepared by recrystallization from butanol, mp 295-296°; uv: λ max 204 (log ε 4.40), 239 (log ε 4.28) and 285 nm (log ε 4.35); ms: 299 (M^+).

Anal. Calcd. for $C_{15}H_9NO_6$: C, 60.21; H, 3.03; N, 4.68. Found: C, 60.04; H, 3.03; N, 4.62.

7-Formyloxy-3-(4-nitrophenyl)-4*H*-1-benzopyran-4-one (**2h**).

The compound was prepared in a manner similar to that for the preparation of **2g** from 750 ml of freshly prepared acetic-formic anhydride and 26.2 g (0.096 mole) of 2,4-dihydroxyphenyl 4-nitrobenzyl ketone (**1b**), except that 150 ml of ethanol rather than ethyl acetate was added to the evaporated residue. The resulting triturated mixture produced a pale yellow solid, which was collected by filtration, washed with ethanol and dried to give 22.7 g (76% yield) of **2h**, mp 105-110°. An analytical sample was prepared by recrystallization from ethanol, mp 112-114°; uv: λ max 208 (log ε 4.46) and 277 nm (log ε 4.40); ms: 311 (M^+).

Anal. Calcd. for $C_{16}H_9NO_6$: C, 61.74; H, 2.91; N, 4.50. Found: C, 61.66; H, 2.96; N, 4.50.

7-Hydroxy-3-(4-nitrophenyl)-4*H*-1-benzopyran-4-one (**2b**).

The preceding formyloxy isoflavone **2h** was stirred with 200 ml of 1*N* sodium hydroxide at room temperature. A dark purple solution was observed initially, soon a brown suspension was formed. The mixture was stirred for one hour at room temperature, then acidified with 2*N* hydrochloric acid to *p*H 4. The color of the reaction suspension gradually changed from brownish red to pale yellow. The solid was collected by filtration, washed with water and dried at 50° *in vacuo* to give 19.5 g (94% yield), mp 285-290°. An analytical sample was prepared by recrystallization from ethanol; uv: λ max 216 (log ε 4.44), 245 (log ε 4.22) and 293 nm (log ε 4.40). The fine, white needles metled at 290°. The compound was found to be identical with that prepared by the method reported previously [2].

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REFERENCES AND NOTES

[1] C. C. Cheng, *Prog. Med. Chem.*, **25**, 36 (1988).

[2] N. L. Dutta and J. L. Bose, *J. Sci. Ind. Res.*, **10B**, 75 (1951); *ibid*, **11B**, 413 (1952).

[3] R. N. Iyer, K. H. Shah and K. Venkataraman, *Curr. Sci.*, **18**, 404 (1949); *Proc. Indian Acad. Sci.*, **33A**, 116 (1951).

[4] W. Baker, J. Chadderton, J. B. Harborne and W. D. Ollis, *J. Chem. Soc.*, 1852 (1953).

[5] H. Bredereck, G. Simchen, S. Rebsdat, W. Kantlehmer, P. Hern, R. Wahl, H. Hoffman and P. Grieshaber, *Chem. Ber.*, **101**, 41 (1968).

[6] A. Pelter and S. Foot, *Synthesis*, 326 (1976).

[7] V. C. Mehlenbacher, *Org. Anal.*, **1**, 37 (1953).

[8] W. Stevens and A. van Es, *Rec. Trav. Chim.*, **83**, 1287 (1964).

[9] A. C. Mehta and T. R. Seshadri, *J. Sci. Ind. Res.*, **18B**, 24 (1959).

[10] T. Hayashi, S. Kawai and T. Ohno, *Chem. Pharm. Bull.*, **19**, 792 (1971).