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A single-step synthesis of ayapin, limmettin, scoparone, leptodactylone, fraxinol, isoscopoletin, 5,6,7-trimethoxy coumarin and 7-methoxy-8-hydroxy coumarin

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Abstract

A single-step synthesis of eight natural coumarins, namely, ayapin, limmetin, scoparone, leptodactylone, fraxinol, isoscopoletin, 5,6,7-trimethoxy coumarin and 7-methoxy-8-hydroxy coumarin is being reported. The method involves the transfer of C-3 unit of cinnamic acids on to appropriate phenols in the presence of polyphosphoric acid (PPA) to obtain the corresponding coumarins. The ease with which the reaction occurs, the moderately good yields and the ready availability of starting materials are hallmarks of this reaction. The scope of the reaction has been discussed in the present paper.

Key words: Synthesis, coumarins, ayapin, limmetin, scoparone, leptodactylone, fraxinol, isoscopoletin, 5, 6,7-trimethoxy coumarin, 7-methoxy-8-hydroxy coumarin, cinnamic acids, C-3 unit, polyphosphoric acid.

1. Introduction

The pyrone ring in coumarins has been synthesised in many ways. These methods include classical reactions such as Perkin's reaction and Pechmann condensation to modern methods like lithiation and others[1]. In this paper, we wish to report the application of a single-step synthesis of the pyrone ring of coumarins by the transfer of the C-3 unit of cinnamic acids on to appropriate phenols using PPA, to the synthesis of eight natural coumarins.

Our study was prompted by a report of Talapatra *et al*[2] who reported the formation of 7-methoxy coumarin (**1**) during the reaction of *p*-methoxy cinnamic acid (**2**) with resorcinol monomethyl ether (**3**) in the presence of PPA. These authors visualised an oxidative biogenetic-type self-condensation of *p*-methoxy cinnamic acid to 7-methoxy coumarin. They proposed a mechanism (Scheme 1) which bears a close analogy to the biogenesis of (**1**) from (**2**)[3].

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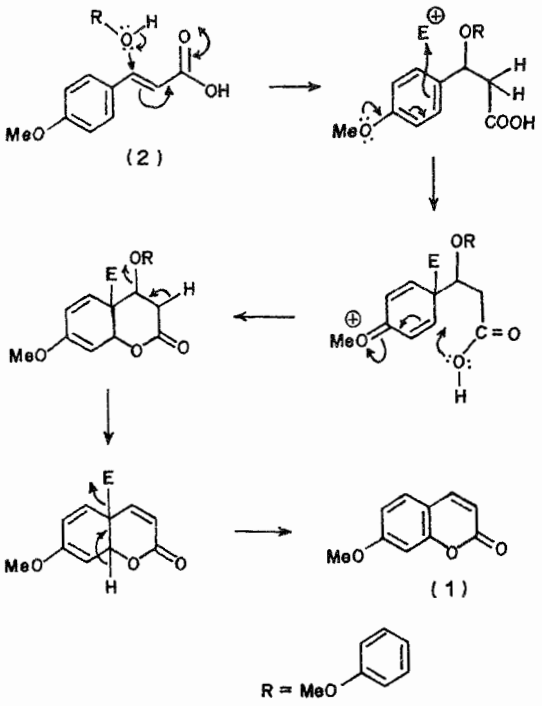


SCHEME 1.

However, some interesting observations were made when we repeated the reaction of *p*-methoxy cinnamic acid with various phenols under the same experimental conditions as that of Talapatra *et al.* From our results, it is evident that the aromatic ring of the cinnamic acid gets eliminated during the reaction leaving the C-3 unit (the carboxyl group and the double-bonded carbons of cinnamic acids) with the phenols used, leading to the formation of coumarins. The preliminary results were reported by us in a communication[4].

Our mechanism for the above reaction which is based on the intermediacy of 4-aryl-

3,4-dihydro coumarins is shown in Scheme 2. From this reaction mechanism it was evident that by using different phenols and *p*-methoxy cinnamic acid, one could obtain different coumarins. We have since then used this method for the synthesis of many natural and synthetic coumarins, the former of which we are now reporting.

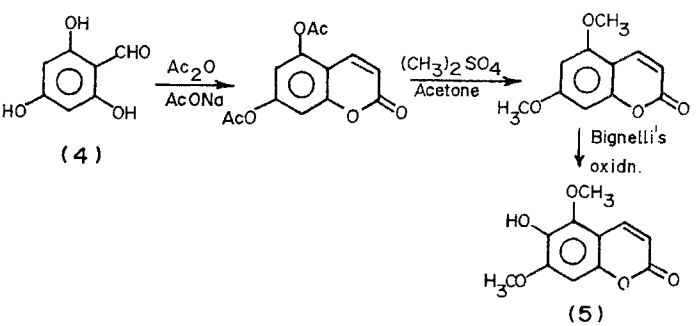
2. Results and discussion

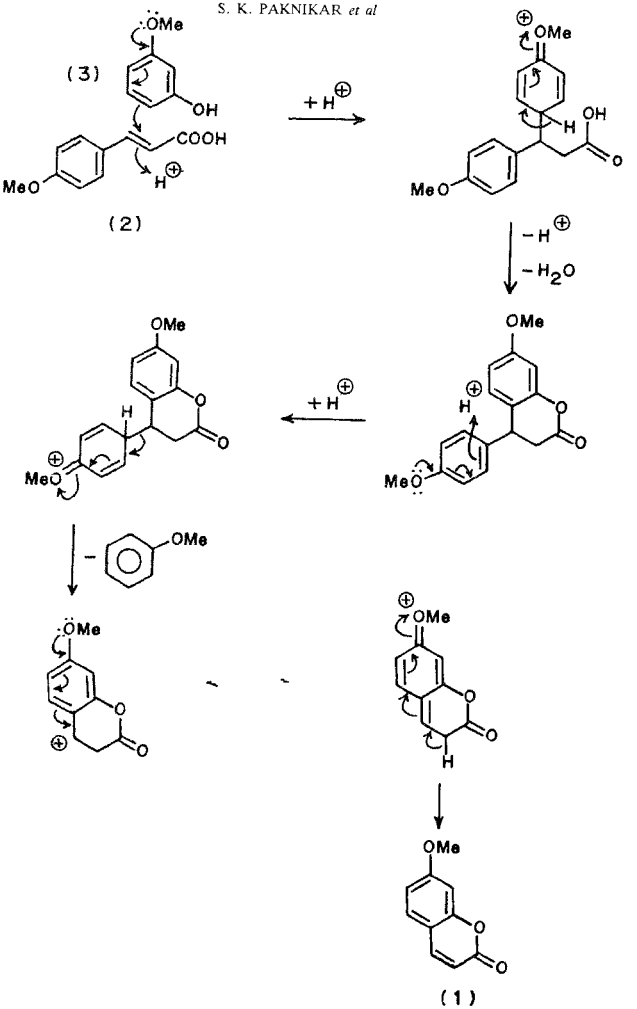
An electron-donating substituent (*e.g.*, methoxyl) at the position meta to the phenolic hydroxyl (*e.g.*, resorcinol mono methyl ether) appears to be beneficial to the course of the reaction. Such a substituent facilitates initial alkylation of the phenol at the *ortho* position to the phenolic hydroxyl and *para* to itself, thus allowing cyclisation of the carboxyl and phenolic hydroxyl to the pyrone ring system. Also, the same group appears at C-7 of the coumarin nucleus and helps in the stabilisation of the intermediate cations during the loss of the aryl group at the 4-position (see Scheme 2).

Most natural coumarins (in fact all but 35) have an oxygen functionality at C-7 of the coumarin nucleus. In the light of what we have said above, this method is most appropriate for the synthesis of natural coumarins. The phenols which are starting materials in the synthesis were either commercially purchased or in some cases obtained by a Baeyer–Villiger or Dakin oxidation of the corresponding aldehydes.

The synthetic utility of the reaction can be gauged when one compares it with the reported syntheses of particular coumarins. For example, the most recent method of synthesis of fraxinol (**5**) by Wagner and Bladt[5] uses phloroglucinaldehyde (**4**) as the starting material. The pyrone ring is first constructed using the Perkin reaction and the 6-hydroxy substituent is introduced using the Bignelli's oxidation method.

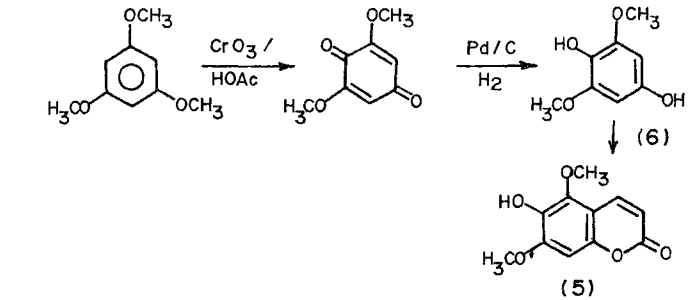
We have synthesised fraxinol (**5**) by the reaction of 2, 6-dimethoxy-*p*-hydroquinone (**6**) with *p*-methoxy cinnamic acid in 51% yield in a single step. The required phenol



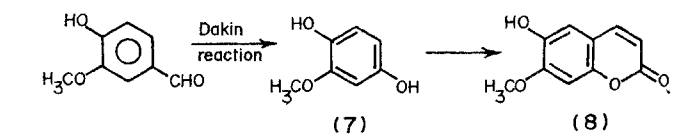


SCHEME 2.

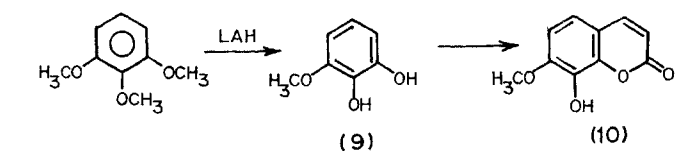
(6) was obtained from 1,3,5-trimethoxy benzene by oxidation with CrO_3/AcOH to furnish the intermediate benzoquinone which was catalytically reduced to the hydroquinone (6) using Pd/C as catalyst.



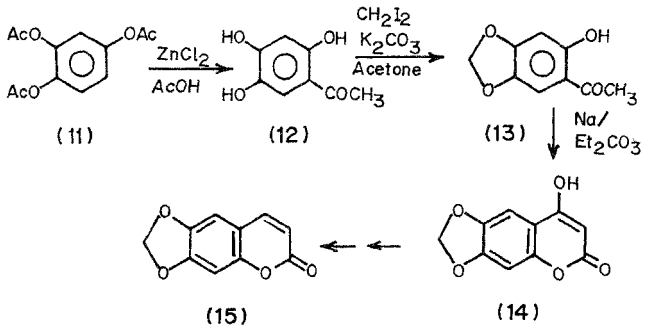
Similarly, isoscopoletin (**8**) was synthesised recently by Ishii and co-workers[6] from vanillin in seven steps. We have obtained the same coumarin from vanillin in two steps. The starting phenol 2-methoxy-*p*-hydroquinone (7) was prepared in good yields by Dakin's reaction on vanillin. Reaction of (7) with *p*-methoxy cinnamic acid afforded isoscopoletin (**8**) in 18% yield.



7-Methoxy-8-hydroxy coumarin (**10**) isolated in 1970 from *Artemisia dracunculoids* by Herz and co-workers[7] was synthesised by us from 2-hydroxy-3-methoxy phenol (**9**). The phenol was obtained from 1,2,3-trimethoxy benzene by selective demethylation with $LiAlH_4$. The coumarin was obtained in 57% yield.

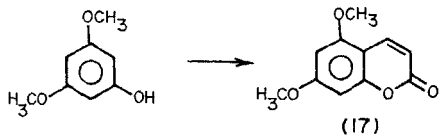


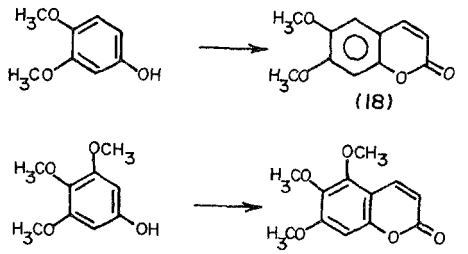
Trivedi *et al*[8] have recently reported a multistep synthesis of ayapin (**15**) starting from 1,2,4-triacetoxy benzene (**11**) which on Hoesch synthesis gave the trihydroxy acetophenone (**12**). This on treatment with methylene iodide and K_2CO_3 in acetone afforded (**13**) which on reaction with sodium and diethyl carbanate furnished the 4-hydroxy derivative of ayapin (**14**). The hydroxyl group at the 4-position was removed *via* the tosylate.



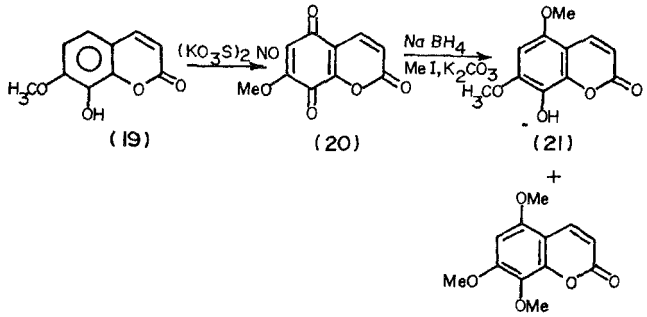
Commercially available sesamol (**16**) was converted to ayapin (**15**) by us in a single step in 45% yield.

Similarly, limmettin (**17**) was obtained from 3,5-dimethoxy phenol in 50% yield. 3, 4-Dimethoxy phenol was converted to scoparone (**18**) in 55% yield and 5,6,7-trimethoxy coumarin was obtained from 3,4,5-trimethoxy phenol in 55% yield by the same method.

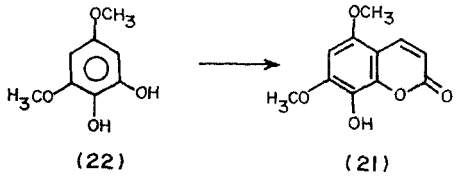




Leptodactylone (**21**) was synthesised by Dean *et al*[9]. They found that 5,8-dihydroxy-7-methoxy coumarin could be prepared from 8-hydroxy-7-methoxycoumarin (**19**) by Fremy's salt (potassium nitrosodisulphonate) oxidation to the quinone (**20**) which was immediately reduced by $NaBH_4$. Methylation of the diphenol gave leptodactylone (**21**) and 5,7,8-trimethoxy coumarin in approximately equal amounts.



Our synthesis of leptodactylone (**21**) is from 2-hydroxy-3,5-dimethoxyphenol (**22**) in 55% yield in a single step.



The coumarins which we have synthesised either have free hydroxyl groups in the aromatic ring, or such a group may be obtained by selective demethylation of the methoxyl groups. Starting from these coumarins, others may be synthesised by O-alkylation followed by Claisen's rearrangement.

Thus, in conclusion, we would like to state that this method of pyrone ring formation is a versatile one. It is most suitable for the synthesis of 7-oxygenated coumarins and can also be used as a starting reaction for many more coumarins by further conversions.

3. Experimental

3.1. General procedure for coumarin synthesis

A solution of PPA was prepared as follows. 10 g of phosphorus pentoxide and 8 ml of *ortho* phosphoric acid were stirred mechanically on a water bath at 90°C till clear. The temperature of the bath was decreased to 70°C. *p*-methoxy cinnamic acid (0.01 mole) was then added to the PPA solution followed immediately by the phenol (0.01 mole). The mixture was stirred at 70°C for 4 h. After cooling to room temperature, the reaction mixture was poured on ice-cold water and extracted with chloroform. Chloroform extracts were washed with both water and brine. Removal of solvent left a gummy solid which was chromatographed on silica gel. Elution with petroleum ether containing increasing amounts of ethyl acetate afforded the coumarins which were finally purified by recrystallisation from chloroform–petroleum ether.

All coumarins were characterised by their spectral data and melting point as compared to standard coumarins.

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References

1. MURRAY, R. D. H., MENDEZ, J. AND BROWN, S. A. — *The natural coumarins. Occurrence, chemistry and biochemistry*, Ch. 7, pp. 131–162, 1982, Wiley Interscience.
2. TALAPATRA, B., DEB, T. AND TALAPATRA, S. K. — *Indian J. Chem. B*, 1986, **25**, 1122–1125.
3. BUNTON, C. A., KENNER, G. W., ROBINSON, M. J. T. AND WEBSTER, B. R. — *Tetrahedron*, 1963, **19**, 1001–1010.
4. BHATTACHARJEE, J. AND PAKNIKAR, S. K. — *Indian J. Chem. B*, 1989, **28**, 205–207.
5. WAGNER, H., BLADT, S., ABRAHAM, D. J. AND LOTTER, H. — *Tetrahedron Lett.*, 1974, 3807–3808.
6. ISHII, H., ISHIKAWA, T., WADA, H., MIYAZAKI, H. KANEKO, Y. AND HARAYAMA, T. — *Chem. Pharmac. Bull.*, 1992, **40**, 2614–2619.

7. HERZ, W., BHAT, S. V. AND SANTHANAM, P. S. *Phytochemistry*, 1970, **9**, 891–894.

8. TRIVEDI, K. N. AND SOMAN, S. S. *Indian J. Chem. B*, 1993, **32**, 372–373.

9. DEAN, F. M., COSTA, A.M.B.R.C.S., HARBORNE, J. B. AND SMITH, D. M. *Phytochemistry*, 1978, **17**, 505–509.