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Convenient Two-step Syntheses of Seselin and Angelicin Derivatives

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Abstract : Convenient two-step approaches are described for the syntheses of seselin (**3a**), seselin and angelicin derivatives (**3b-d** and **5a-d**) from 2,4-dihydroxybenzaldehyde (**1a**) and 2,4-dihydroxyacetophenone (**1b**) using tandem Claisen rearrangement and Wittig reaction.

Several linear and angular pyrano- and furocoumarins have been isolated from natural sources[1]. The parent compounds seselin and angelicin are widespread in nature. These compounds are known to possess useful biological activities. Thus, seselin (**3a**), other pyranocoumarins and furocoumarins are clinically used as photoactive drugs in the photochemotherapy of skin, in the treatment of vitiligo and to prevent sun burning[2]. Seselin also exhibits molluscicidal activity[3] and has been recently used for the synthesis of various naturally occurring coumarins[4,5].

Various methods have been developed for the synthesis of angular pyrano- and furocoumarins[1,5,6-9]. Most make use of preformed 7-hydroxycoumarins. These on allylation followed by Claisen rearrangement and cyclisation provide 8-methylangelicins[1,7,8].The classical method for the synthesis of seselin involves propargylation of 7-hydroxycoumarin followed by cyclisation of the propargyl ether[1,5,9]. It was also synthesised from various naturally occurring coumarins[10]. In this communication, we report a two-step method (**scheme 1**) for the synthesis of seselin (**3a**), seselin and angelicin derivatives (**3b-d** and **5a-d**).

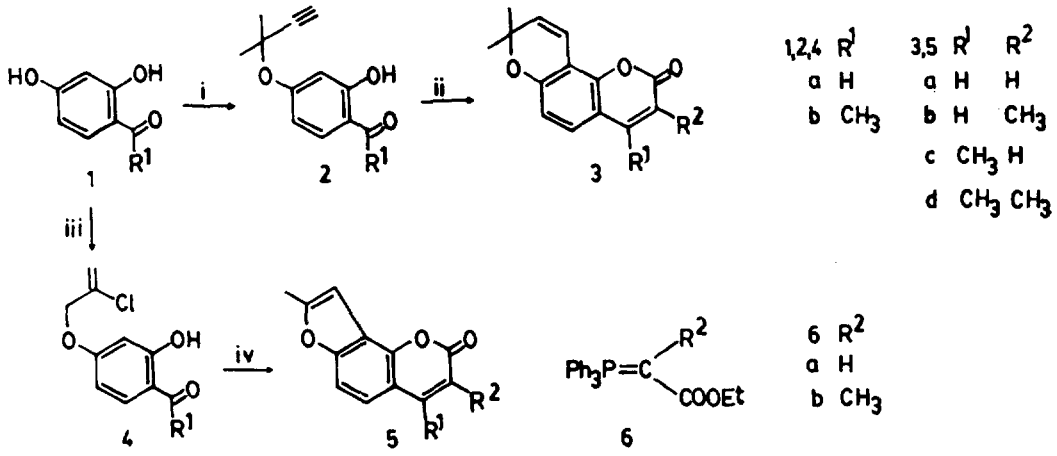
The propargyl ethers[11](**2a** and **2b**) required for the synthesis of seselin (**3a**) and its derivatives **3b-d** were prepared from **1a** and **1b**. Heating a mixture of **2a** and phosphorane **6a** at 180-190°C for 3h provided seselin (**3a**), mp 119°C (lit[5]. mp 117.5°C) in 55% yield. Similarly, reaction of **2a** with **6b** and of **2b** with **6a** and **6b** gave seselin derivatives (**3b-d**) in 50,63, and 40% yields respectively[12].

Reaction of **1a** and **1b** with 2,3-dichloropropene in acetone solution (at 60°C) in presence of potassium carbonate gave the β -chloroallyl ether **4a** (mp 47°C) and **4b** (mp 44°C) in 87 and 95% yield. A solution of allyl ether (**4a**) and phosphorane (**6a**) in N,N-dimethylaniline on heating at 220°C gave 8-methylangelicin (**5a**) mp.152°C (lit[7]. mp 153-154°C) in 59% yield. Similarly reaction of **4a** with **6b** and of **4b** with **6a** and **6b** provided angelicin derivatives (**5b-d**) in 54, 65 and 60% yields respectively[12].

In conversion of **2a** and **2b** into pyranocoumarins (**3a-d**) and of **4a** and **4b** into furocoumarins (**5a-d**) using phosphoranes **6a** and **6b** at high temperature Claisen rearrangement, Wittig reaction and cyclisation occur

in one pot in a tandem manner.The present approach provides a convenient and general route for the synthesis of seselin and angelicin derivatives. The synthesis of more complex naturally occurring pyranocoumarins[13] using this approach is in progress.

Scheme 1



Reagents : (i) $HC{\equiv}CC(Me)_2Cl$, K_2CO_3, acetone, 60°C; (ii) 6, 180 - 190°C;
(iii) $ClCH_2C(Cl){=}CH_2$, K_2CO_3, acetone, 60°C; (iv) 6, $PhNMe_2$, 220°C

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12. Typical Procedure: (a) A mixture of propargyl ether (2a or 2b, 1 mmol) and phosphorane (6a or 6b, 1.2 mmol) was heated at 180-190° C for 3-10 h. The residue was chromatographed on silica gel using AcOEt:n-hexane (1:9) to give pyranocoumarins (3a-d). (b) A solution of β -chloroallyl ether (4a or 4b, 1 mmol) and phosphorane (6a or 6b, 1.2 mmol) in $PhNMe_2$ (10 ml) was heated at 220°C for 20-22 h. The reaction mixture was diluted with 5% HCl and extracted with chloroform. The chloroform layer was dried (Na_2SO_4) and evaporated to give a residue which was chromatographed on silica gel using AcOEt:n-hexane (1:4) to afford furocoumarins (5a-d).
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