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EFFICIENT SYNTHESIS OF PRECOCENES

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Abstract : Precocenes and related intermediates were synthesised in good yields using hydrogen peroxide, selenium dioxide and methylene chloride combination in the key step.

In 1976 oxygenated chromenes obtained from natural source were shown to cause precocious metamorphosis in insects and hence were named as Precocenes[1]. Later on in the structure-activity relationship studies presence of alkoxy substituents particularly at the C_6 and C_7 positions were found to enhance the precocious activity of chromenes[2]. Thus the 2, 2 - dimethyl 6-methoxy 7-ethoxy chromene was found to be the most active system.

Various syntheses of above chromenes have been reported earlier, [3-10] involving a recent one by

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Miranda et.al.[11] based on their photo-Fries rearrangement approach. All these methods suffer from drawbacks like a) critical reaction conditions b) formation of side products c) low yields.

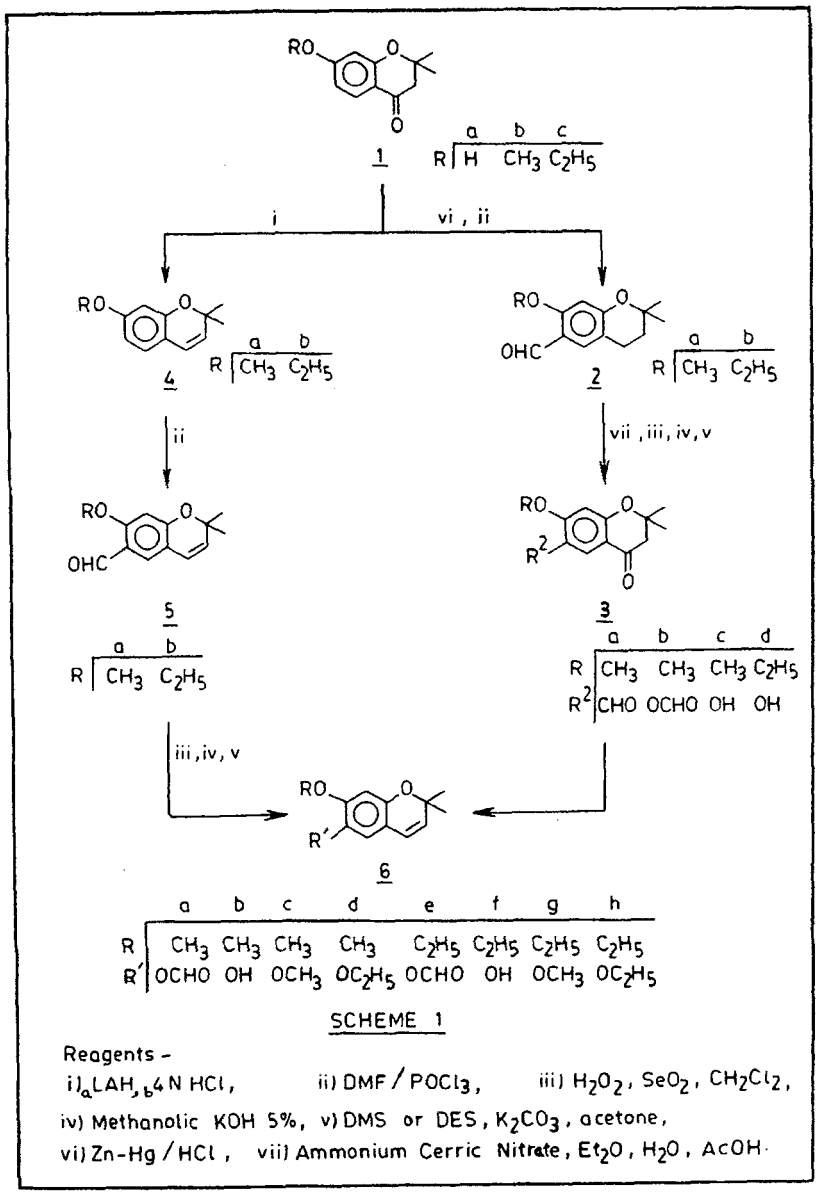
In order to meet our requirement of chromenes having desired alkoxy substitution pattern for their further elaboration, development of a more convenient general method for these compounds was undertaken.

Strategically synthesis of chromenes with required alkoxy substitution pattern at C_6 and C_7 positions could be derived either by building up of a chromene part using a suitably substituted phenol as a starting compound or by introducing the alkoxy substituent on the benzenoid part of the chromene with due regioselectivity. All the earlier reports follow the first route so the second route was thought of and attempted which is presented in this paper.

In our previous communication[12] we reported an efficient method to obtain 2, 2 - dimethyl 6-formyl 7-methoxy chromanone 3a making precise use of CAN (Cerric Ammonium Nitrate). Recently Miranda et.al[13] reported formation of 2, 2-dimethyl 6-hydroxy 7-alkoxy 4-chromanones 3c and 3d using photo - Fries approach followed by nucleophilic substitution . Now in order

to obtain the same key intermediate 3c for the target precocenes, the formyl group at the C_6 position of the compound 3a was decided to be transformed into a hydroxyl function. In order to effect this transformation from the various methods available the one involving a combination of hydrogen peroxide and selenium dioxide[14] in dichloromethane as a solvent furnished desired product in much better yield. Thus the formyl group at C_6 position in the compound 3a underwent smooth conversion to formate ester which was further easily hydrolysed providing a hydroxy function at C_6 position in good yield. This clearly indicated the regioselectivity of the above combination wherein formyl group is attacked keeping the ketone function intact. Conversion of 3c and 3d into target precocenes has already been reported.[11]

At this juncture the above route was then further modified in order to make it shorter. The 2, 2-dimethyl 7-alkoxy 4-chromanones 1b and 1c were reduced and dehydrated to the corresponding chromenes 4a and 4b using standard methods which were then subjected to Vilsmeier reaction which yielded the corresponding 2, 2-dimetyl 6-formyl 7-alkoxy chromenes 5a and 5b. These aldehydes were again transformed into the corresponding 6-formate esters 6a and 6e using the same combination which were hydrolysed in a course of few minutes using



SCHEME 1

Reagents –

i) a LAH, b 4 N HCl, ii) DMF / $POCl_3$, iii) H_2O_2, SeO_2, CH_2Cl_2,
iv) Methanolic KOH 5%, v) DMS or DES, K_2CO_3, acetone,
vi) Zn-Hg / HCl, viii) Ammonium Cerric Nitrate, Et_2O, H_2O, AcOH.

TABLE

Compd.	Yield %	MP° C	PMR $CDCl_3$/TMS ppm
3c	88	136	1.4 s 6H, 2.6 s 2H, 3.9 s 3H, 5.5 bs 1H (exchang. D_2O), 6.4 s 1H, 7.4 s 1H.
6c	61	Liq.	1.4 s 6H, 3.8 s 6H, 5.5. d(J 9Hz) 1H, 6.2 d(J 9Hz) 1H, 6.4 s 1H, 6.5 s 1H.
6d	66	Liq	1.4 bs 9H, 4.0 s 3H, 4.1 q 2H, 5.6 d(J 10.2Hz) 1H, 6.5 m 3H.
6g	68	Liq	1.4 bs 9H, 3.9 s 3H, 4.2 q 2H, 5.6 d(J 10.2 Hz) 1H, 6.5 m 3H.
6h	64	Liq	1.3 bs 12H, 4.1 m 4H, 5.6 d(J 10.2Hz) 1H, 6.3 d(J 10.2 Hz) 1H, 6.5 s 1H, 6.6 s 1H.

All compounds gave satisfactory microanalysis [$\pm$ 0.2 for C and H]

methanolic KOH (5%) giving the expected 2, 2-dimethyl 6-hydroxy 7-alkoxy chromenes 6b and 6f respectively. These phenols were converted to their methyl or ethyl ethers furnishing the desired precocenes in high yields.

This communication thus describes a general method for the obtaination of precocenes and related intermediates in high yield using either 7-methoxy or 7-ethoxy 2, 2-dimethyl 4-chromanone 1b and 1c, easily accessible reagents and milder reaction conditions.

EXPERIMENTAL

Compounds 1a-c, 4a, 4b, 2a, 2b, 5a and 5b were prepared using known standard methods. Compound 3a was prepared according to the method developed by the authors.[12]

General procedure for the conversion of 6-formyl chromanones and 6-formyl chromenes into parent 6-hydroxy systems.

To a mixture of aldehyde (50 mmol), dichloromethane (100 mL), selenium dioxide (4 mmol), hydrogen peroxide (aq.30%, 13 mL) was added at R.T. and the reaction mixture was stirred at R.T. for 36 h. and then filtered. Usual workup of the organic layer furnished the desired products as pale yellow liquids. These formates were hydrolysed in refluxing methanolic KOH (5%) to furnish the required phenols.

Conversion of 6b and 6f into precocenes 6c, 6d, 6g and 6h

6b and 6f were subjected to Williamson reaction using acetone, potassium carbonate and either dimethyl sulphate or diethyl sulphate. Usual workup provided the precocenes in good yields.

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