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Calcium Chloride faciled Intramolecular Oxa addition of 2'-Hydroxychalcone to Flavanone

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Abstract – An efficient cyclization of 2'-hydroxychalcone to flavanone using calcium chloride as a catalyst was developed. The scope of the reaction was studied with substituted 2'-hydroxychalcone and these chalcones was converted into corresponding flavanone in good yield. The merits of this method are inexpensive and easily available catalyst, easy workup procedure, avoid use of toxic solvent.

Keywords: 2'-hydroxy chalcone, flavanone, calcium chloride, intramoleclar, Oxa-michael reaction

Introduction:

Flavanone is heterocyclic compounds which belong to flavonoid flamily. It is abundant in natural products and occurs in the form of glycosylated or aglycon form and pyrano and furano form. Natural and synthetic flavanone shows various biological activities like antitumoral [1], anti-tyrosinase [2], Anti-Sindbis [3], anti-inflammatory [4], antileishmanial and antitrypanosomal [5], antioxidant properties [6], antimalarial [7], anti-atherosclerosis [8], Vasorelaxant agents [9] and oviposition stimulants [10]. Flavanones is a key intermediate for synthesis of other flavonoids compound [11] as shown in figure 1.

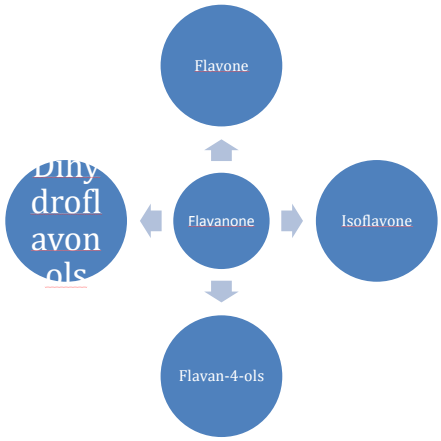


Figure 1: Use of flavanone in synthesis of different flavonoids

Flavanones are generally prepared from the cyclization of 2'-hydroxychalcone using intramlecular OxaMichael addition. The regents used for this cyclization are Methane sulphonic acid [12], amino acid [13], Trifluoroacetic acid [14], Sulfuric acid in methanol [15], polyphosphoric acid [16], Amberlyst A-21 [17], Potassium carbonate [18], N-methylimidazole [19]. Although these notable contributions, further there is scope to develop more competent and convenient catalytic method for synthesis of flaavanones.

$CaCl_2$ is an inexpensive and commercially available reagent and as it has been shown recently to be a very good catalyst in organic reactions like the Aldol reaction of dimethyl silyl(DMS)enolates [20], in the Bigineli reaction [21], in the synthesis of α -aminophosphonic esters[22], in three component Mannich reaction for synthesis of β-amino ketone [23].

Results and Discussion

First we studied cyclization of 2'-hydroxychalcone to flavanone using calcium chloride as a catalyst in ethanol under reflux condition. The progress of the reaction was monitored by TLC using (1:9) ethyl acetate and pet ether. We observed that reaction proceed in the forward direction and formation of a new product that is flavanone (2a). After completion of the reaction, added water to the reaction mixture the product was precipitated out, filter it and purified by recrystallization from ethanol afforded pure flavanone. The structure of the product was confirmed by spectroscopy method and spectral data match with flavanone (2a). The ^{1}H- NMR spectra of 2a shows a triplet at 5.47ppm due to –CH proton at 2-position and doublet at 2.84-

3.13ppm due to CH_2 proton at 3-position which is the characteristic of flavanone and the complete absence of a peak near at 12.35ppm due to an o-hydroxy group is in agreement with cyclization of 2'-hydroxy chalcone to flavnone. Next we explored the scope of reaction with various substituted 2'-hydroxychalcone by varying the substrates on the B ring from electron donating groups to withdrawing groups. The results are presented in Table 1. From table 1, it is clear that, the cyclization of chalcones proceeds well to give flavanones in good yield. As usual electron donating groups present on ring B, cyclization proceeds very smoothly to afford flavanones in good yield while electrondrawing groups and steric effects generate cyclization slow leading to fair yield of flavanone.

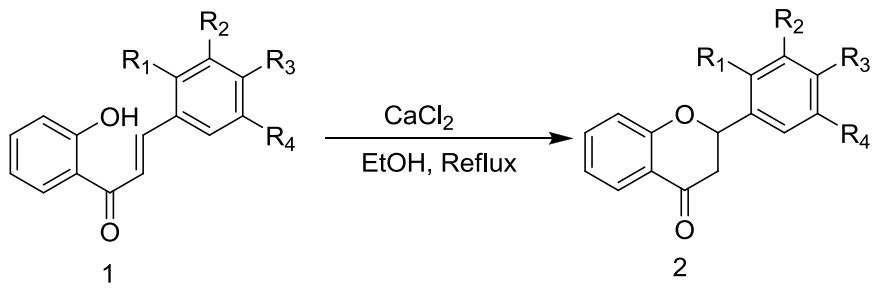
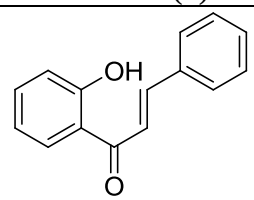
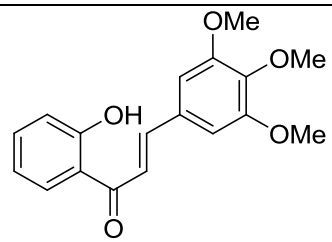
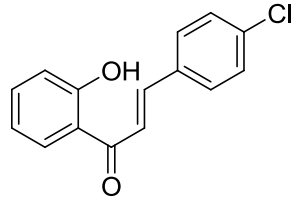
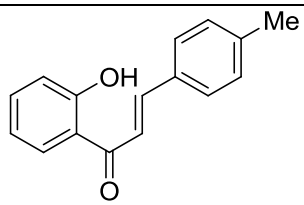
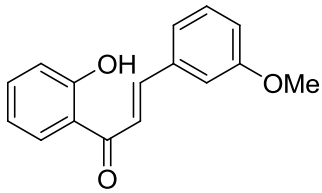
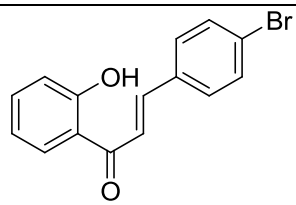
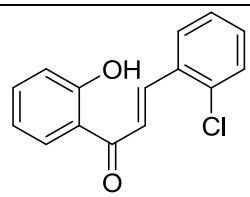
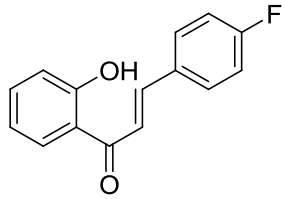
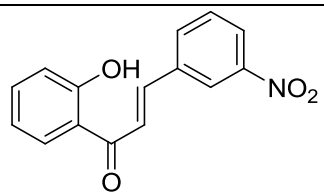
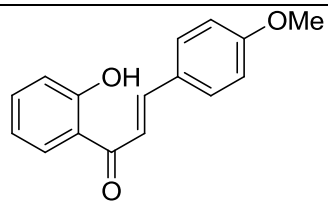
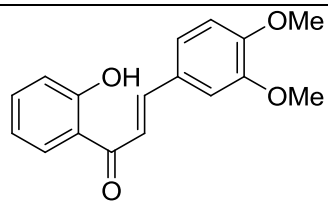
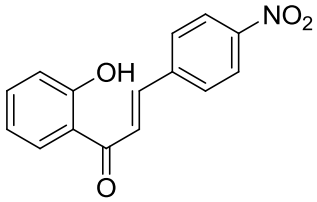
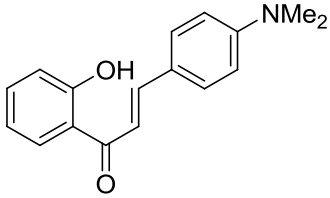


Figure 2: Cyclization of 2'-hydroxychalcone to Flavanone using Calcium Chloride

Table 1: Cyclization of 2'-hydroxychalcone to Flavanone using $CaCl_2$ [a]

Entry	Chalcone(1)	Flavanone(2)	%Yield[b]	Melting Point °C
1		**2a**	92	75-76
2		**2b**	87	132-133
3		**2c**	74	93-94

4		**2d**	85	65-66
5		**2e**	77	76-78
6		**2f**	73	117-118
7		**2g**	69	83-85
8		**2h**	81	78-79
9		**2i**	78	143-144
10		**2j**	84	88-89
11		**2k**	80	125

12		**2l**	62	161-162
13		**2m**	75	122-124

Reaction condition: a 5mmol of 2'-hydroxychalcone, 5mmol of $CaCl_2$ dissolved in 5mL of EtOH b: isolated yield

CONCLUSION

In conclusion, here in we report an inexpensive, eco-friendly synthesis of flavanones using calcium chloride as a catalyst. This method has merits over other reported methods like inexpensive and easily available catalyst, high yield and short reaction time, avoid use of toxic solvent.

Experimental

General:

All reagents, chemicals and solvents were purchased from Loba, Merck and Sigma Aldrich. TLC (pre-coated silica gel 60 F254, Merck) was used to monitor the progress of the reaction. Melting points were recorded by open capillary method and are uncorrected. IR spectra were recorded as KBr pellets using shizmude FTIR. The 1H NMR spectra were obtained on a Bruker DRX-300 Avance instrument using CDCl3 as solvent and TMS as internal standard at 300MHz. All products are known and their authenticity was ensured on the basis of spectroscopic data and on comparison with authentic samples.

General procedure for Cyclization of 2'-Hydroxychalcone to Flavanone using $CaCl_2$:

2'-hydroxychalcone 1(5mmol) were dissolved in 5mL ethanol. To this solution calcium chloride (5mmol) was added and refluxed for 1 hour. . The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled, added water (10mL) and the soild was precipitated out and filter on suction pump, wash with (2×10 mL) water and then with 5mL ice cold ethanol to yield flavanone (2). A pure sample was obtained by recrystallization from ethanol.

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