Asian Journal of Chemistry Vol. 19, No. 4 (2007), 2885-2890

Synthesis of Chalcones and Flavanones in The Absence of Metal Ion

N. JAGANNADHA REDDY*, M. NARENDRA KUMAR, M. MURALI and
P.V.V. SATYANARAYANA†
Department of Chemistry, RVR & JC College of Engineering, Chandramoulipuram
Chowdavaram, Guntur-522 019, India
E-mail: njreddy_6@yahoo.co.in

2'-Hydroxychalcones were synthesized in alkaline medium after trapping the metal ion of the hydroxide and sodium ethoxide with the crown ether. Synthesis of chalcone with bases like tetramethyl-ammonium hydroxide, and tetra-*n*-butyl ammonium hydroxide met with failure. But, flavanones were formed from the corresponding 2'-hydroxychalcone using alkaline medium without the metal ion, using tetramethyl ammonium hydroxide and tetra-*n*-butyl ammonium hydroxide.

Key Words: Synthesis, Chalcones, Flavanones.

INTRODUCTION

Chalcone, the important intermediate in the synthesis of flavonoids, is obtained in the acid or base catalyzed aldol condensation of 2-hydroxyacetophenone with aromatic aldehydes. Since the cyclization of chalcones to flavanones is favoured by acid or alkali[1,2], the acid catalyzed reaction results in the formation of pairs of chalcone-flavanone isomers or even flavanone alone. The more frequently used base-catalyzed condensation is carried out with 50-60% sodium or potassium hydroxide at 0 to 20ºC for 15 to 28 h or even in extreme cases[3,4] for 1 to 3 d. Hydroxylamine hydrochloride was used in highly basic medium for the cyclization of chalcone which was a failure[5,6]. Poonia *et al.*[7] reported that synthesis of chalcone is increased by increase in charge density and concentration of metal. They claimed that metal coordinates with carbonyl oxygen of aldehyde without proper evidence and clear explanation. The condensation of acetophenone with aldehyde depends on strength of aldehyde and metal bond[7] but not on the concentration of hydroxyl ion and the concentration of the substrate. These authors also did not explain the importance of nitrogen atmosphere which is actually not required. It is not essential to dehydrate the medium. Hence, the present investigation was carried out to investigate the role of

---

†Department of Chemistry, Acharaya Nagarjuna University, Guntur, India.

metal ion and hydroxyl ion as well as the concentration of acetophenone in the synthesis of chalcone and its cyclization to flavanone which are important in the flavonoid inter-conversions.

EXPERIMENTAL

All melting points are uncorrected. Hydroxychalcones were prepared by following the reported procedure in the literature.

Synthesis of 2'-hydroxy chalcone using 18-crown-6: To 2.6 g of 18-crown-6 in 15 mL ethanol was added 1.4 g of KOH slowly in 0.5 h. To this add *o*-hydroxy acetophenone (1 mL) and benzaldehyde (1 mL) and stir the mixture for 4 h at room temperature. Acidify the mixture with 10% HCl in ice. The yellow solid separated was filtered, washed with water and recrystallized from ethanol to furnish the 2'-hydroxy chalcone **1a** (0.86 g, 52%): m.p. 89ºC (lit[8]. m.p. 89-90ºC).

Similar procedure was carried out to synthesize the various hydroxyl chalcones and the yields were reported as shown in Table-1. All the compounds were identified by using the authentic samples with TLC, melting point and mixture melting point. Similar results were obtained by using 15-crown-5 and sodium ethoxide.

Synthesis of flavanones: To 20 mL of ethyl alcohol add 2.5 g of 18-crown-6 and then 0.5 g of KOH slowly with shaking. Now add 1 g of the chalcone to the reaction mixture and the reaction mixture was kept for 3 d. The mixture was diluted, the solid separated was filtered and recrystallized from alcohol to give colourless crystals of flavanone **2a** (0.58 g, 58%): m.p. 76ºC (lit[9]. m.p. 76ºC). Similar synthesis was carried out with 15-crown-5 and sodium ethoxide and the results are almost the same as shown in Table-1.

TABLE-1
m.p., YIELD (%) OF 2´-HYDROXYCHALCONES AND FLAVANONES SYNTHESIZED

Compd.	m.p. (ºC) (lit.m.p. ºC)	Yield (%)	Compd.	m.p. (ºC) (lit.m.p. ºC)	Yield (%)
1b	92 (92-93)[10]	64	**2b**	90 (90-91)[15]	68
1c	108-109 (111)[11]	42	**2c**	105 (105)[16]	52
1d	99 (98-99)[12]	48	**2d**	109-110 (110)[17]	62
1e	150 (150)[13]	65	**2e**	116	59
1f	151-152 (152-153)[14]	68	**2f**	120	72

Synthesis of chalcones with tetra-*n*-butyl ammonium hydroxide did not occur but the cyclization of chalcone to flavanone occurred as sited in the literature using NaOH. But the synthesis of **2e** and **2f** required longer duration (10 d).

RESULTS AND DISCUSSION

When variedly substituted 2-hydroxy acetophenone was condensed with aromatic aldehyde in basic medium, chalcone was obtained. The basic medium was maintained using LiOH, NaOH, KOH or sodium ethoxide. The reaction did not occur with tetramethyl ammonium hydroxide or even in dilute alkali. Cyclization of chalcone to flavanone is achieved either by using acid or alkali. Even tetramethyl ammonium hydroxide which failed to condense the acetophenone, cyclizes the chalcone to give flavanone in good yield.

Poonia *et al*[7]. claimed the formation of chalcone and flavanone is mainly due to the presence of metal ion. When metal ion was trapped with dicyclohexyl 18-crown-6, hydroxy acetophenone did not condense with aldehyde. Similarly cyclization of chalcone to flavanone was failed in presence of crown ether. The formation of chalcone and its cyclization to give flavanone was considered as a function of the nature and concentration of alkali which the author failed to explain in the mechanism. The present investigation was carried out to find the role of metal ion in the synthesis of chalcone and its conversion to flavanone.

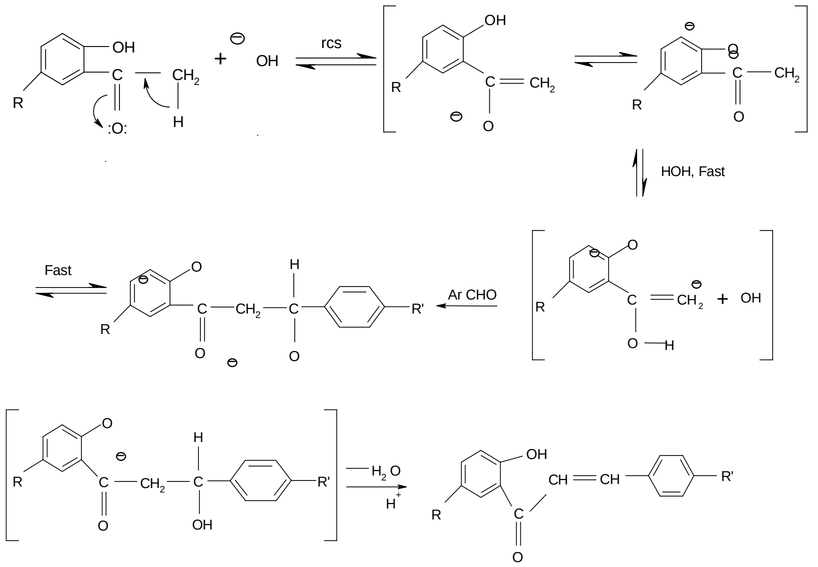
The present work does not agree with the result obtained in previous work[7]. Condensation of 2-hydroxy acetophenone and benzaldehyde does not occur in presence of tetramethyl ammonium hydroxide, tetra-*n*-butyl ammonium hydroxide and also in sodium acetate which are less basic than the alkali or ethoxide media. When the experiment was conducted using LiOH, NaOH, KOH or NaOEt, chalcone and its cyclization product-flavanone were obtained. It is concluded that strong basic medium was essential for the condensation of acetophenone with aromatic aldehyde. Formation of flavanone from chalcone in dilute alkali or in presence of tetramethyl ammonium hydroxide and tetra-*n*-butyl ammonium hydroxide proved that the metal ion is not essential.

The interconversion of carbonyl and enol forms is catalyzed by both acid and base. In basic medium, abstraction of α-hydrogen atom is the initial rate controlling step. Proton abstraction from the solvent then competes the enolization process. The proton that accounts for the acidity of the carbonyl compounds containing a carbonyl group is located on the carbon atom α to the carbonyl group. Acidity is attributed to the ability of carbonyl group to delocalize the negative charge of the conjugate base. The conjugate base of a carbonyl group is the resonance stabilized enolate anion, a species that is also involved in the base catalyzed enolization process. Rate controlling step involves both base and substrate which is bimolecular.

$$\text{Rate} = K[>C=O][OH]$$

Chalcone was cyclized to flavanone in NaOH medium. When chalcone dissolved in alcohol was kept for 12 h after adding tetramethyl ammonium hydroxide (10 %), the conversion was complete.

But Poonia *et al.*[7] proposed during the cyclization of chalcone, the formation of metal bond with (C=C) which is against the basic principle due to lack of available *d*-orbitals. Cyclization of chalcone in presence of H_2SO_4 etc. was already reported. Deprotonation of $HClO_4$ by chalcone results in the formation of carbonium ion at the β carbon as per the earlier report is baseless. Hence, a new mechanism of cyclization of chalcone is given in **Scheme-1** which differs from Poonia *et al*[7].

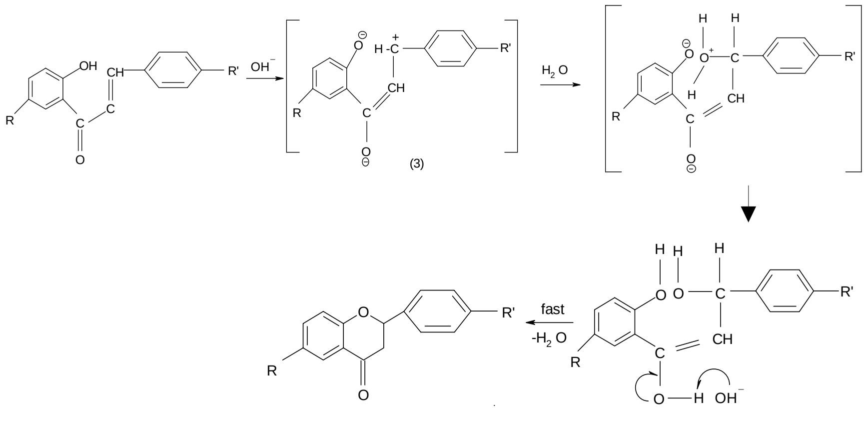


1 a	R = R' = H
b	R = H; R' = OCH_3
c	R = CH_3; R' = H
d	R = CH_3; R' = OCH_3
e	R = H; R' = Cl
f	R = CH_3; R' = Cl

Scheme-1 Synthesis of 2'-hydroxy chalcone in the absence of metal ion

α,β-Unsaturated carbonyl compounds contain two electrophilic sites- the carbonyl carbon and the carbon atom that is β to it. With the nucleophiles, the addition takes place at the carbon-carbon double bond rather than at the carbonyl group. Such reactions proceed *via* enol intermediate. The nucleophile becomes bonded to the β carbon. Loss of water results in the cyclization to give flavanone as shown in **Scheme-2**.

Poonia *et al.*[7] reported that metal ion charge density plays a major role in the synthesis of chalcone. It is found that the chalcone was converted to flavanone using tetra-*n*-butyl ammonium hydroxide and tetra methyl ammonium hydroxide. The chalcones were synthesized by trapping the metal with the crown ethers. This shows that metal ion may polarize carbonyl carbon, but it is not essential either for the cyclization of chalcone or for the condensation of acetophenone and benzaldehyde to give chalcone. The results obtained in the reactions are *at par* with the reactions carried by using the metal hydroxide like LiOH, NaOH and KOH. When the MOH was used chalconate salt is formed. But, when the metal ions were trapped, the solid was not much separated but on acidification the product was obtained. Keeping these in view, the suggested mechanism without the involvement of the metal ion was as shown in **Schemes 1** and **2**. In the synthesis of chalcones, more basic medium is essential for the formation of carbanion. But in the cyclization of chalcone to flavanone, slight alkaline medium is favourable for the reaction. Due to this reason we failed to synthesise chalcone by using tetra-*n*-butyl ammonium hydroxide and tetra methyl ammonium hydroxide. In the synthesis of flavanone, alkali metal cation due to lack of vacant *d*-orbitals will not interact with the π bond of the chalcone, but it can form a metal coordinate bond with -OH group of chalcone[18].



2 a R = R' = H
b R = H; R' = OCH_3
c R = CH_3; R' = H
d R = CH_3; R' = OCH_3
e R = H; R' = Cl
f R = CH_3; R' = Cl

Scheme-2 Synthesis of Flavanone in the absence of metal ion

As the chalcone is α,β-unsaturated ketone, enolization takes place in the alkali medium before the formation of carbocation at the β-position with which the -OH group interacts to give the intermediate (**3**) which looses water molecule resulting in the cyclization process.

Metal ion does not play role in the condensation of 2-hydroxyacetophene with different asymmetric aldehydes. Like aldol condensation, in basic medium chalcone was formed from the corresponding hydroxyl acetophenone and aldehyde.

The synthesis of flavanones from 2'-hydroxychalcone require weak alkaline medium. So, the chalcone was cyclized to flavanone by using tetramethyl ammonium hydroxide, tetra-*n*-butylammonium hydroxide and also KOH, NaOH, LiOH, NaOEt, after trapping the metal ion with the crown ether. The metal ion may polarize the (C=O), but it is not essential either for the synthesis of chalcone or flavanone.

ACKNOWLEDGEMENTS

The authors are grateful to Dr. M. Gopalkrishna, Secretary & Correspondent, Dr. K. Basavapunnaiah, President and Prof. P.S. Sankara Rao, Principal of the college for providing facilities and their encouragement. Thanks are also due to UGC, New Delhi, for the award of major research project to one of the authors NJR.

REFERENCES

1. S.C. Datta, V.V.S. Murthy and T.R. Seshadri, *Indian J. Chem.*, **9**, 614 (1971).
2. T.A. Geissman and R.O. Clinton, *J. Am. Chem. Soc.*, **68**, 697 (1946).
3. Y. Kinura, S. Takahashi and J. Yoshida, *Yakugukuzasshi*, **88**, 239 (1968).
4. S.C. Datta and P.K. Roy, *Indian J.Chem.*, **13**, 425 (1975).
5. M.B. Bagade, A.V. Thool and P.D. Ghiya, *Indian J. Chem.*, **30B**, 973 (1991).
6. D. Dhawan and S.K. Grover, *Indian J. Chem.*, **36B**, 73 (1997).
7. N.S. Poonia, K. Chabra, C. Kumar and V.B. Bhagawat, *J. Org. Chem.*, **42**, 20 (1977).
8. T. Oyamada, *J. Chem. Soc. (Japan)*, **55**, 1256 (1934).
9. K. Freudenberg and L. Orthner, *Chem. Ber.*, **55**, 1748 (1922).
10. P. Karrer, Y. Yen and I. Reichstein, *Helv. Chim. Acta*, **13**, 1308 (1930).
11. K.V. Anwers and R. Doll, *Ann.*, **421**, 86 (1920).
12. K.V. Anwers and L. Anschutz, *Ber*, **54B**, 1543 (1921).
13. P.L. Cheng, P. Fournari and J. Tirouflet, *Bull. Soc. Chim. (France)*, **10**, 2248 (1963).
14. C.-H. Lin; C. Tsudin and C.-L. Yeh, *J. Chim. Chem. Soc. (Taipei)*, **14**, 9 (1967).
15. T. Oyamada, *J. Chem. Soc. (Japan)*, **64**, 331 (1943).
16. O. Dann and G. Mylius, *Ann.*, **587**, 1 (1964).
17. J.W. Clark-Lewis, L.M. Tackman and L.R. Williams, *J. Chem. Soc.*, 3858 (1962).
18. J.D. Lee, Concise Inorganic Chemistry, edn. 5, p. 307 (1996).

(*Received*: 5 May 2006; *Accepted*: 23 January 2007) AJC-5338