An Improved and Eco-Friendly Method for the Synthesis of Flavanone by the Cyclization of 2'-Hydroxy Chalcone using Methane Sulphonic Acid as Catalyst

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Abstract

Flavanones are important biosynthetic precursors for the synthesis of flavones, isoflavones, flavonols and dihydroflavonols. The flavanone skeleton is present in a wide range of synthetic and naturally occurring products exhibiting various interesting pharmacological activities. The present paper describes the use of methane sulphonic acid as an efficient organocatalyst for the synthesis of substituted flavanones from 2'-Hydroxy Chalcones in good yields and in short reaction time. The catalytic efficiency of methane sulphonic acid in cyclization of chalcones to flavanones has been demonstrated with a variety of substrates bearing electron–deficient to electron rich groups on chalcones and the yields obtained are higher than the reported methods with trifluoroacetic acid / mineral acids. Methane sulphonic acid is an inexpensive, safe, eco-friendly acid catalyst with low LD₅₀. The present protocol could find wide spread application in the synthesis of flavanones bearing free hydroxyl groups on the aromatic moiety. At the same time the methodology would be useful for the synthesis of naturally occurring bioactive flavanones.

Keywords: Methane Sulphonic Acid, 2'-Hydroxy Chalcone, Flavanone, Cyclization, Acetic acid

1. Introduction

Flavanones (2,3-dihydro-2-phenyl-4H-1-benzo-pyran-4-one derivatives) are the main biosynthetic precursors for major flavonoids such as flavones or isoflavones and for two important flavonoid intermediates: the flavan-4-ols (biosynthetic precursors for the formation of 3-deoxyanthocyanins) and the dihydroflavonols (biosynthetic intermediates in the formation of catechins, flavonols, anthocyanins and proanthocyanidins) (Heller & Forkmann, 1988; Haslam, 1993 and Mann, 1994). The flavanone skeleton is present in a wide range of synthetic or naturally occurring products exhibiting various interesting pharmacological activities (Bertram, 1989; Pathak et al, 1991; Spilkova & Hubik, 1992 and Manach et al, 1996). Flavanones widely distributed in nature, continue to attract attention due to their ample range of biological activities (like hypotensive, antibacterial, antitumoral) (Middleton & Kandaswami, 1994; Harborne & Williams, 2001; Nijveldt et al, 2001; Wang et al, 2001 and Heim et al, 2002).

obtained yields are often moderate and sometimes poor. The acid catalyzed cyclization can be carried out by refluxing the chalcone in acetic acid or also in ethanol or other suitable solvent in the presence of an acid catalyst such as H$_3$PO$_4$ (Sagara et al., 1998). Flavanones can also be obtained from precursors other than chalcones, namely by (i) reacting 3-chloro-2,3-dihydro-3-nitro-2-phenyl-4H-1-benzopyran-4-ones with tributyl tin hydride and 2,2'-azobisisobutyronitrile (Dauzonne & Monneret, 1997) (ii) treating 3-bromo-1-phenyl prop-2-ynyl aryl ethers with mercury (II) trifluorooacetate (Subramanian & Balasubramanian, 1990) (iii) oxidizing flavan-4-ols (Bhatia et al, 1968) (iv) treating 1-(2-hydroxyphenyl)-3-phenyl-propane-1,3-diones with benzaldehydes (Joglekar & Samant, 1988).

Methane sulphonic acid is a clear colourless liquid available as a 70% solution in water and anhydrous form. The structure of methane sulphonic acid lends itself to many catalytic reactions, due to its high acid strength ($pK_a = -1.9$) and low molecular weight (96.0 g/mol). Further it is easy to handle methane sulphonic acid as liquid and can be recycled. The other attributes includes low LD$_{50}$ and it is biodegradable forming sulphate and CO$_2$. Methane sulphanic acid is considered to be natural product and is part of the natural sulfur cycle (Commarieua et al, 2002). Also as a Bronsted acid it has been widely used to catalyze wide variety of reaction and as solvent for condensation and rearrangement reaction (Sharhqi, 1998; Kaboudin, 1999 and Leleti et al, 2007).

Therefore, there is scope to develop a new method for the synthesis of flavanone by using an inexpensive, safe, simple and eco-friendly catalyst i.e. methane sulphonic acid. To, the best of our knowledge, there is no report on the use of methane sulphonic acid as catalyst for the cyclization of 2'-hydroxy chalcone into flavanone.

2. Experimental

All purchased chemicals were of analytical grade and used without further purification. Melting point is determined by open capillary method and uncorrected. The 1H NMR spectra were obtained on a Bruker DRX-300 Avance instrument using CDCl$_3$ as solvent and TMS as internal standard at 300MHz.

2.1. General Procedure for Cyclization of 2'-Hydroxychalcone to Flavanone

A mixture of 2'-hydroxy chalcones (1.0 mM), catalytic amount of methane sulphonic acid (10 mol %) in acetic acid was subjected to reflux for 2 hours. Workup with water afforded flavanone as solid which was filtered off and purified by column chromatography using ethyl acetate: petroleum ether (9:1) as eluent to get pure product. The hydroxy flavanone was purified by column chromatography using MeOH: CHCl$_3$.

3. Results and Discussion

When refluxed in acetic acid in the presence of methane sulphonlic acid, chalcones (I) were transformed into equilibrium mixture containing (I a) and isomeric flavanone (II a), in 2 hours, the latter being the predominant component ( Scheme 1). To study the effect of solvent on equilibrium ratio, the reaction was performed in various solvents such as acetic acid, ethanol, DMF and DMSO. The reaction proceeds well in acetic acid compared to other solvents. The results are shown in Table 1.

![Scheme 1. Synthesis of Flavanone by using Methane Sulphonic Acid Catalyst](image)

**Table 1. Effect of Solvent on Cyclization of 2'-Hydroxychalcone to Flavanone Catalyzed by Methane Sulphonic Acid**

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Solvent</th>
<th>Temperature</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetic acid</td>
<td>110</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>140</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>DMSO</td>
<td>140</td>
<td>No Reaction</td>
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</table>

*Reaction Condition: 2'-hydroxychalcone (1mmole), Methane Sulphonic Acid

Further the scope of the reaction was studied with substituted chalcones prepared by varying the substrates on B ring from electron donating groups to withdrawing groups. The results are presented in Table 2. As obvious from the results, the Cyclization of chalcones proceeds well to afford flavanones in good yield. As expected electron donating groups facilitate the cyclization to afford the corresponding flavanone in good yield while electron withdrawing groups and steric effects render the cyclization slow leading to moderate yield of flavanone. In next step the scope of reaction was examined by subjecting substituted ring A chalcon with 5-hydroxy, 7-hydroxy, 5,7-dihydroxy which undergo cyclization easily, giving good yields of corresponding flavanones. By using this
methodology we have synthesised 5-hydroxyflavanone, 4'-chloro-7-hydroxyflavanone, 4'-methoxy-7-hydroxyflavanone, 5,7-dihydroxyflavanone, and 4-methoxy-5,7-hydroxyflavanone.

A possible reaction mechanism for the intramolecular oxo-Michael addition in 1a, promoted by Bronsted acid, as given by Johnson’s group, is outlined in Scheme 2 (Ellis et al., 1982 and 1983). The carbonyl oxygen of 1a accepts

### Table 2. Cyclization of 2'-Hydroxy Chalcone to Flavanone Catalyzed by Methane Sulphonic Acid

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chalcone (1)</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>Flavanone (2)</th>
<th>Time (hrs)</th>
<th>% Yield</th>
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<td>72</td>
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</tbody>
</table>

* Reaction Condition : 2'-Hydroxychalcone (1 mmole), Methane Sulphonic Acid (10% v/v) in Solvent b : Isolated Yield

Available online at [www.scientific-journals.co.uk](http://www.scientific-journals.co.uk)
proton from the Brønsted acid to give the protonated form of I and canonical form II undergoes ring closure to give the enol form III of 2a.

4. Conclusion

In conclusion, here in we report simple and an efficient method for the synthesis of flavanone from 2'-hydroxychalcone by the use of methane sulphonic acid an inexpensive and safe acid catalyst. This protocol will be a good addition to the most recent environmentally friendly methods reported for the synthesis of flavanones. This protocol is also useful for the synthesis of phloroglucinol type flavanone. Other advantages of this method are high yield and shorter reaction time compared to other reaction conditions. Merits of this method over trifluoroacetic acid and mineral acid are that 1) this acid is biodegradable and can be recycled while trifluoroacetic acid is not biodegradable 2) example reported with trifluoroacetic acid includes only methoxy group while this method is applicable to all types of functional groups.

References


Highly selective methanesulfonic acid-catalyzed 1,3-isomerization of allylic alcohols. Tetrahedron Letters, 48, pp. 8505-8507


