

Green Synthesis of Bioactive Flavanone Using Environmental Friendly Catalyst

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Introduction:

Flavanones are important naturally occurring organic compounds possessing a wide range of biological activities¹ used in the treatment of various diseases². Different methods are used for the synthesis of flavones, includes Allan- Robinson synthesis³, synthesis from chalcones⁴ and via intramolecular witting reaction⁵. The most common method used involves Baker- Venkatramn arrangement. In this method 2- hydroxy acetophenone are converted to benzoyl ester, which in presence of base (pyridine/KOH) form 1,3 diketones. The diketones are further cyclized under strong acidic condition to afford the flavones⁶. In recent development of such dehydrative cyclization it includes the use of Amberlyst15⁷, Co^{III}(sulpr)OH⁸, FeCl₃⁹, Br₂/CHCl₃¹⁰, EtOH/HCl¹¹, clay¹², NaOAc/AcOH¹³ and H₂SO₄ under microwave irradiation¹⁴. Prenylated flavanone is a unique class of naturally occurring flavonoids characterized by the presence of a Prenylated side chain in the flavonoid skeleton. It was reported that one phenolic group and certain degree of lipophilicity are required for the activity of the flavonoids.¹⁰ Substitution of the flavonoid ring system with phenyl groups would increase their lipophilicity and consequently enhance their interaction with cellular membranes¹⁵.

4',5,7-Trihydroxy-3'-prenylflavanone (1) has been isolated for the first time in 1989 from the chloroform extract of the stem bark of *Erythrina eriotriocho*¹⁶.

The chemical and pharmaceutical industries are always under the pressure to find out environmental friendly organic reaction methodologies. Microwave irradiation is used for a variety of organic reactions due to their use in a rapid and cleaner synthesis of organic compounds¹⁷⁻¹⁸.

Ionic liquids are possible green catalyst acts as alternatives for several catalytic reactions. Ionic liquids attracted attention of researchers due to their mild reaction conditions, short reaction times and better yield, solvating ability and easy recyclibility¹⁹. Various reactions have been reported recently using ionic liquids as an catalyst, reaction media²⁰ and as rate enhancers²¹.

Result and Discussion:

Herein we wish to report for the first time a novel synthesis of flavanone (2) promoted by ionic liquid catalyst, **H[bimBF₄]** at room temperature irradiation in excellent yield with shorter reaction time (Scheme 1). The ionic liquid can be recycled and reused several times. The ionic liquid H[bimBF₄] was prepared as per literature method²².

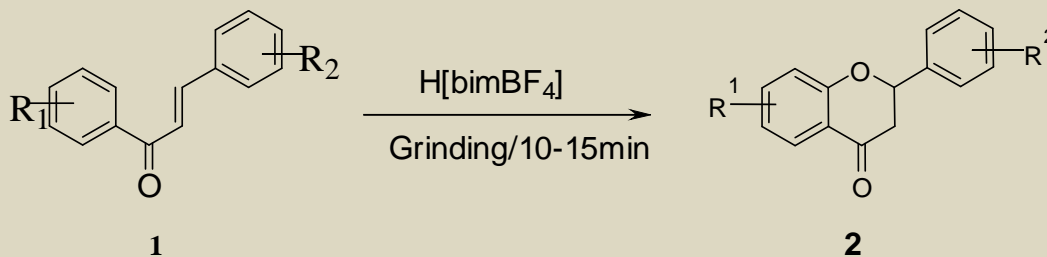
In a typical reaction, the α - β -unsaturated carbonyl compounds (1) in ionic liquid H[bimBF₄] was grind into motor in a specified time. The progress of the reaction was monitor by TLC. After completion of the reaction, reaction mixture was directly extracted with 50% ethyl acetate in petroleum ether. Compound comes in organic layer, was washed with water, brine & dried over

MgSO₄. Organic solvent is evaporated to afford pure flavanones (2). Ionic liquid was dried under reduced pressure & re used for another reaction gives same yield..

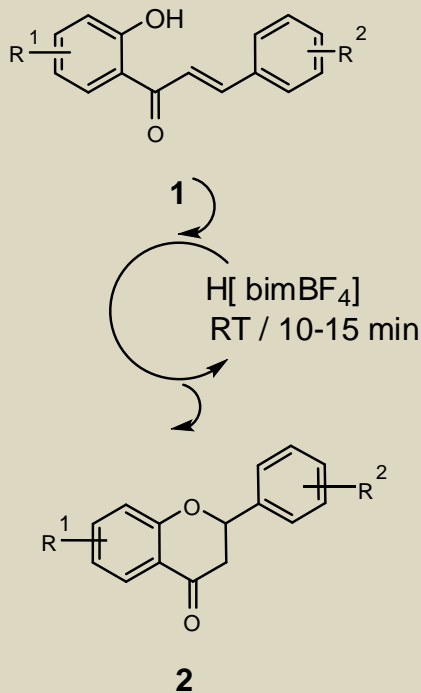
To evaluate the synthetic utility of the process, various substituted chalcones were prepared by the established procedure⁶ and subjected to the reaction under rt grinding. The results are shown in Table-1.

The reaction proceeds cleanly without formation of any side product except water. The protocol of the process offers advantages in terms of simple procedure and work up, mild reaction conditions and excellent yields.

The reactions are also carried out in presence of [bbim]Br ionic liquid catalyst for comparison. The resulting flavanones are forms with same yield. The ionic liquid used for reaction was recovered and reused with identical results. Thus, the recyclibility was confirmed as listed in a **Table-2**.



Scheme-1



Scheme-2

Fig: Possible mechanism of (2) flavanone

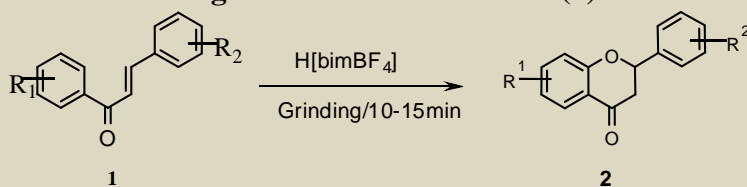


Table1: Synthesis of Flavones (2 a-h) using ionic liquid H[bimBF₄] grinding at room temperature

Entry	unsaturated carbonyl compounds 1(a-h)	Product 2(a-h)	Time(min.)	Yield(%) ^a	M.P.(°C) ^b
a			10	81	97
b			12	90	185-187
c			10	83	155-156
d			14	88	277
e			12	89	154
f			10	80	240-241
g			13	87	118
h			15	90	128-129

^a : Isolated yields.

^b:Melting points of compounds are uncorrected and compared with reported compounds.

Table 2 :Synthesis of flavavanones **2(a-b)** with recovered ionic liquid H[bimBF₄]

Entry	unsaturated carbonyl compounds	product	Time(Sec)	Yield(%)		
				Cycle 1	Recycle 1	Recycle 2
1	1a	2a	10	93	91	91
2	1b	2b	12	90	88	88

Spectral Data:

Melting points were determined in open glass capillaries and uncorrected. ¹H NMR and ¹³C NMR spectra were recorded at room temperature on a varian Inova Spectrometer in CDCl₃ using TMS as internal standard.

The spectral data of some selected compounds:

Compound 2b: ¹H NMR (300 MHz, CDCl₃) δ 2.44 (s, 3H), 7.22 (s, 1H), 7.69 (dd, 1H, J = 8.9, 2.1 Hz), 7.74 (d, 1H, J = 8.6 Hz), 7.85 (m, 1H), 8.38 (s, 4H); ¹³CNMR (125 MHz, CDCl₃) 21.5, 109.9, 119.6, 125.1, 125.3, 128.8, 136.5, 136.8, 138.3, 149.7, 154.8, 160.6, 177.2.

Compound 2e: ¹H NMR (300 MHz, CDCl₃) δ 3.95 (s, 3H), 3.98 (s, 3H), 6.72 (s, 1H), 6.96 (d, 1H, J = 8.1Hz), 7.36 (d, 1H, J=1.8 Hz), 7.40 (dd, 1H, J = 7.2 Hz, J = 7.5 Hz), 7.51 (dd, 1H, J = 1.8 Hz, J = 8.1 Hz), 7.53 (d, 1H, J = 7.5 Hz), 7.67 (ddd, 1H, J = 1.5 Hz, J = 7.2, J = 7.8 Hz) 8.20 (dd, 1H, J = 1.5 Hz, J = 7.8 Hz); ¹³CNMR (125 MHz, CDCl₃) 56.1, 106.4, 108.8, 111.2, 118.0, 120.0, 123.9, 124.2, 125.6, 133.6, 149.3, 152.1, 156.1, 163.3, 178.3.

Compound 2f: ¹H NMR (300 MHz, CDCl₃) δ 6.91 (s, 1H), 7.95 (dd, 1H, J = 1.8, J = 9.0 Hz), 7.02 (d, 1H, J = 1.8 Hz), 7.57-7.29 (m, 3H), 7.91 (d, 4H, J = 9.0 Hz), 8.05-8.08 (m, 2H); 10.8 (s, 1H); ¹³CNMR (125 MHz, CDCl₃) 102.6, 106.6, 115.1, 116.2, 126.2, 126.5, 129.1, 131.3, 131.5, 157.5, 161.2, 162.8, 176.4.

Conclusion:

In summary we have demonstrated an efficient and mild protocol for the dehydrative cyclization of α-β-unsaturated carbonyl compounds to flavanones in presence of ionic liquids H [bimBF₄] catalyst by grinding. Shorter reaction time, simple reaction conditions and higher yield render this grinding method superior. The method is clean and simple, which can be used as an alternative to the existing methods.

Experimental:

The α-β-unsaturated carbonyl compounds **1** (1 mmol) was added in ionic liquid H[bimBF₄] (2 mmol) and grind into mortar for 10-15 min. The reaction was monitored on TLC. After completion on the reaction, the mixture was extracted 5 X 20 ml. of ethyl acetate: petroleum ether (50%+50%). Compound comes in organic layer, was again treated with water, brine & dried over MgSO₄. Organic solvent is evaporated to afford pure flavones **2**. Further, Ionic liquid was dried under reduced pressure & re used for another reaction gives same yield.

The recovery percentage of ionic liquid is given in a Table-2.The obtained products **2a-h** were identified by comparison with authentic samples ¹H NMR and their melting points.

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