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Methane Sulphonic Acid Catalyzed Efficient Protocol for Synthesis of 2-Hydroxy Chalcones

Ramesh G[1], Sunil J[2] and Pramod K[3*]

[1]Department of Chemistry, Yashavantrao Chavan Institute of Science, Satara, MH 415001, India

[2]Department of Chemistry, Mahatma Phule College, Panvel, MH 410206, India

[3]Department of Chemistry, Hutatma Rajguru Mahavidyalaya, Rajgurunagar, MH 410505, India

[*]**Corresponding author:** Pramod Kulkarni, Department of Chemistry, Hutatma Rajguru Mahavidyalaya, Rajgurunagar, MH 410505, India, E-mail: pramodskulkarni3@gmail.com

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Abstract

Methane sulphonic acid was found an efficient catalyst for synthesis of 2'-hydroxy chalcone via aldol condensation of 2-hydroxy acetophenone and substituted benzaldehyde. The merits of this protocol are efficient, eco-friendly, and inexpensive catalyst, short reaction time, high yield, and easy workup procedure. The catalyst is also well work with electron donating as well as electron with drawing group present aromatic ring. The structures of products were confirmed by melting point, IR, and 1H NMR.

Keywords: ***2-hydroxy acetophenone; Substituted benzaldehyde; Chalcone; Claisen-Schmidt condensation***

Introduction

Chalcones are found in natural products which belong to the class of open chain flavonoids in which two aromatic rings are linked by a three carbon α, β-unsaturated carbonyl skeleton. The chalcones are main chemical intermediates for synthesis of flavonoids like flavanone, flavones, isoflavones and synthesis of bioactive heterocyclic [1,2] as well as these compounds are main synthons for the preparation of five and six member ring systems [3] and use for the synthesis of medicinal intermediates [4,5].

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Chalcones shows broad spectrum of medicinal properties due to the presence of α, β-unsaturated carbonyl skeleton. The chalcone exhibits biological activities like antimalarials [6], anti-inflammatory, antioxidant and antiulcer [7], anti HIV [8], antiviral [9], antibacterial [10], antituberculosis [11], anticancer [12], and antileishmanials activity [13].

Due to its importance medicines and key intermediate for the synthesis of bioactive molecules, chalcone attracted many researchers for their synthesis. Numerous methods are reported for the synthesis of chalcones, the widely used method is the base catalysed Clasien-Schmidt reaction in which the condensation of aromatic ketone with an aldehyde is carried out in the presence of catalyst like KOH [14], Basic Al_2O_3 [15], $ZnCl_2$ [16], $AlCl_3/CS_2$ [17], BF_3 [18], KOH/TEBA/EtOH [19], Mg-Al-O^{t}Bu [20], $NaNO_3$/EtOH , using ultrasound [21], NaOH/EtOH [22], $Ba(OH)_2$ grinding [23], CaO /microwave [24]. However, some of these reported methods suffer from drawbacks like use of toxic and hazardous solvent, longer reaction time, low yield, not applicable to acid and base sensitive functional group, the addition of reactant and catalyst in cooling condition. Due to these limitations, hence, there is a scope to develop new methods.

Methane sulphonic acid is a clear colourless liquid available as a 70% solution in water and anhydrous form. Its pKa value is -1.9 and low molecular weight. Due to low pKa value, methane sulphonic acid is strong acid. Methane sulphonic acid is easily available, inexpensive, and biodegradable forming sulphate and carbon dioxide. Due to this all properties methane sulphonic acid attracts many chemists to use as catalyst in many organic transformations [25]. In this paper, we report methane sulphonic acid catalyzed Claisen-Schmidt condensation reaction between 2'-hydroxy acetophenone and substituted benzaldehyde to afford corresponding 2'-hydroxychalcone in good yield.

Experimental

General

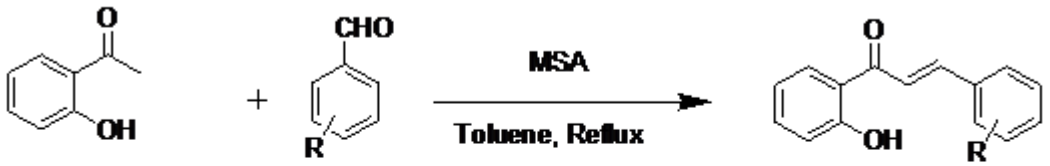
All purchased chemicals were of analytical grade and used without further purification. The ^{1}HNMR spectra were obtained on a Bruker DRX-300 Avance instrument using $CDCl_3$ as solvent and TMS as internal standard at 300 MHz. All products are known compounds; their physical and spectroscopic data were compared with those reported in the literature and found to be identical.

Procedure for synthesis of 2'-hydroxychalcone

In a 50 mL round bottom flask, substituted benzaldehyde (1 mmol), 2-hydroxyacetophenone (1 mmol) dissolved in 10 mL toluene, 0.1 mmol of methane sulphonic acid dissolved in 1 mL of ethanol added to the reaction mixture and the resulting reaction mixture was refluxed for 4 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure and oily product was separate out. The oily product was dissolved in ethanol and added crushed ice to separate out solid product. The crude product was filtered on suction pump, followed by washing with water and ice cold ethanol. The resulting product was purified by recrystallisation from ethanol. The physical constant and spectral data IR, ^{1}HNMR, ^{13}CNMR for 2'-hydroxy chalcone (TABLE. 1), were identified with those of authentic samples.

Results and Discussion

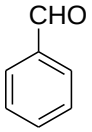
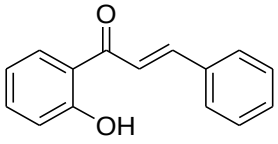
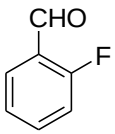
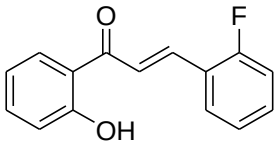
The present protocol describes a new efficient and environmentally benign procedure for the synthesis of 2'-hydroxy chalcone using strong Brønsted –Lowry acid that is methane sulphonic acid. The reaction of benzaldehyde (1 mmol), 2-hydroxy acetophenone (1 mmol), was carried out in the presence of methane sulphonic acid (0.1 mmol in 1 mL of ethanol) in toluene (10 mL) at reflux temperature. The reaction proceeded smoothly to afford the corresponding 2'-hydroxy chalcone in 87% yield within 4 hours. After completion of the reaction, reaction mixture was cooled and toluene was removed under reduced pressure. The oily product was separated from reaction mixture. Oily product was dissolved in ethanol and added crushed ice to separate out crude solid product. The solid was filtered on suction pump, followed by washing with water and ice cold to give the desired product. Also reaction of aromatic aldehydes bearing electron donating and withdrawing groups on aromatic ring underwent smooth conversion to afford the corresponding 2'-hydroxy chalcones in good to moderate yield without affecting the functional group (TABLE. 2). The obtained products were characterized by spectroscopic methods (IR, ^{1}HNMR, ^{13}CNMR) and by comparison of physical constant with authentic samples (FIG. 1).

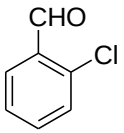
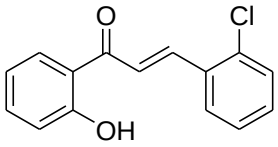
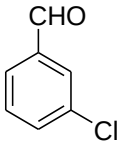
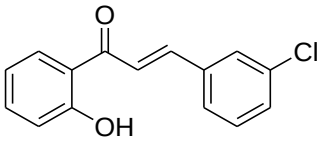
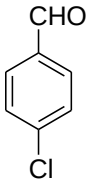
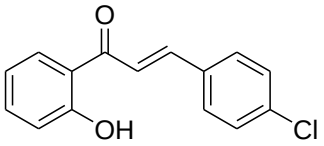
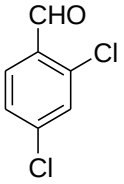
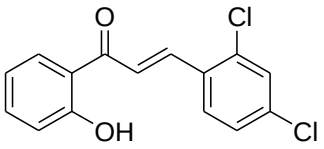
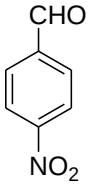
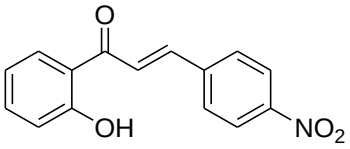
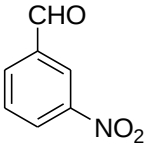
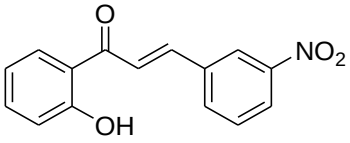
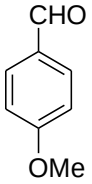
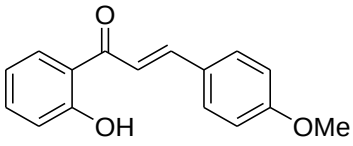
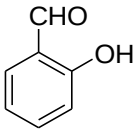
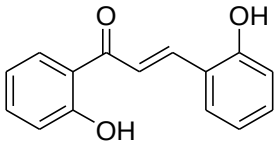


R= H, o-F, o-Cl, m-Cl, p-Cl, 2,4-Cl, p-NO_2 , 3-NO_2 , p-OMe, 2-OH

FIG. 1. **Synthesis of 2'-hydroxy chalcone using methane sulphonic acid is catalyst**.

TABLE. 1. **Synthesis of substituted 2'-hydroxy chalcone using methane sulphonic acid as a catalysis[a]**.

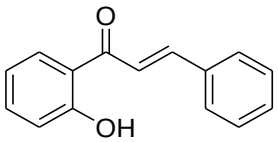
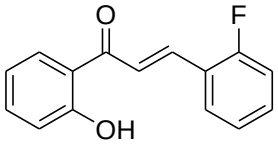
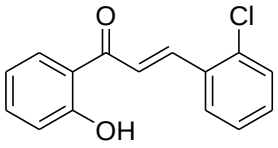
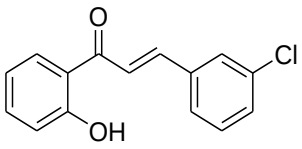
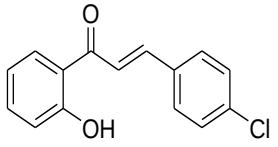
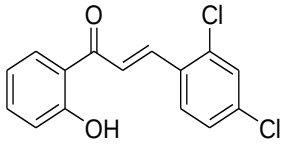
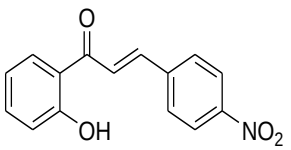
Entry	Aldehyde	Product	% Yield[b]	M.P. °C [Ref]
1			87	78 [26]
2			80	57 [27]

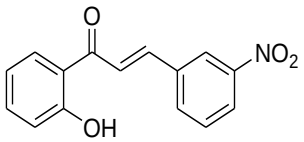
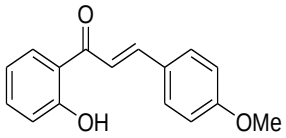
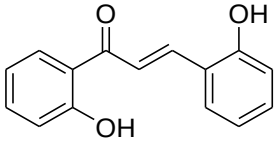
3			82	80 [28]
4			86	61 [29]
5			81	47 [26]
6			85	150-153 [26]
7			87	205 [24]
8			90	172-174 [30]
9			83	91-92 [25]
10			72	161-163 [25]

[a]Reaction condition: 2-hydroxy acetophenone (1 mmol), substituted benzaldehyde (1 mmol), dissolved in 10 mL toluene in 50 mL RB, 0.1 mmol methane sulphonic acid dissolved in 1 mL EtOH added to this solution, and reflux the reaction mixture for 4 hr b: isolated yield after purification.

TABLE. 2. **Spectral data of chalcone.**

S.N.	**Structure**	**Spectral analysis**

1		IR: (KBr) ν/cm^{-1} 3531 (-OH), 1650 (C=O), 1613 (C=C), 13555 (O-C), 683 (Ar-H); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.75 (s, 1H, -OH), 7.92 (d, 1H, J=8.06) 7.89 (d 1H *J*=7.85 Hz) 7.85 (d 1H *J*=14.89 Hz) 7.80 (d, 1H, *J*=14.88 Hz), 7.34-7.81 (m 5 H), 7.00-7.09 (m 2H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 194.22, 164.52, 160.70, 142.47, 135.52, 134.94, 129.93, 129.88, 128.21, 127.24, 115.78, 112.13, 111.58, 110.6
2		IR: (KBr) ν/cm^{-1} 3453 (-OH), 1651 (C=O), 1617 (C=C), 1354 (O-C), 688 (Ar-H); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.94 (s, -OH), 8.23 (d, 1H, *J*=15.56 Hz) 7.93 (dd, 1H, *J*=8.06 Hz, *J*=1.46 Hz), 7.79 (d 1H, J=15.58 Hz) 7.66 (dd 1H *J*=7.79 Hz *J*=1.45 Hz) 7.49 (m 1H) 7.4 (m 1H) 7.09-6.8 (m 4H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 192.91, 164.22, 159.09, 141.19, 136.12, 133.50, 129.42, 129.32, 124.65, 120.91, 120.30, 117.48, 117.32, 112.29
3		IR: **(**KBr) ν/cm^{-1} 3468 (-OH), 1653 (C=O), 1615 (C=C), 1322 (O-C), 680 (Ar-H); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.89 (s, -OH),8.21 (d, 1H *J*=15.54 Hz), 7.90 (dd, 1H *J*=8.07 Hz, *J*=1.47 Hz) 7.78 (d 1H *J*=15.19 Hz), 7.68 (dd 1H *J*=7.72 Hz, *J*=1.42 Hz) 7.45 (m 1H),7.40 (m, 1H), 7.10-6.85 (m, 4H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ193.12, 163.98, 159.04, 140.37, 138.05, 132.18, 129.24, 129.11, 122.32, 120.52, 118.9, 118.56, 111.31
4		IR: **(**KBr) ν/cm^{-1} 3538 (-OH),1665 (C=O), 1613 (C=C), 1328 (C-O), 676 (Ar C-H); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.81 (s –OH) 7.91 (dd 1H *J*=8.06 Hz, *J*=1.44 Hz), 7.89 (d 1H *J*=15.50 Hz) 7.65 (d 1H *J*=15.51 Hz) 7.55 (m,1H), 7.36 (d 1H *J*=8.05) 7.25 (d, 1H *J*=7.85 Hz) 7.15 (m 1H) 7.02 (d 1H *J*=8.1 Hz) 7.01-6.93 (m 2H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 194.73, 162.75,163.01, 148.38,135.02, 137.02, 129.95, 128, 122.02, 121.08, 120.19, 119.07, 118.08, 110.68, 114.15
5		IR: **(**KBr) ν/cm^{-1} 3351 **(**-OH), 1635 (C=O), 1552 (C=C), 1204 (C-O), 642 (Ar C-H); ^{1}H NMR **(**$CDCl_3$, 300 MHz): δ 12.74 (s 1H, -OH), 7.90 (d 1H *J*=8.06 Hz), 7.86 (d 1H *J*=15.60 Hz), 7.64 (d 1H *J*=15.61 Hz), 7.61 (d 2H *J*=8.40 Hz),7.51 (m 1H) 7.40 (d 2H *J*=8.41 Hz), 7.04 (d1H *J*=8.43 Hz),6.90 (m 1H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 190.92, 164.56, 144.01, 137, 136.02,133,130.19, 129.85, 129, 120.50, 119.80, 118.19, 117.95.
6		IR: **(**KBr) ν/cm^{-1} 3432 **(**-OH), 1635 (C=O), 1598 (C=C), 1337 (C-O), 686 (Ar C-H); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.95 (s, 1H -OH) 8.24 (d 1H *J*=15.60 Hz), 7.95 (m 1H), 7.80 (d 1H *J*=15.61 Hz), 7.65 (m 1H), 7.51 (m 1H) 7.42 (m 1H) 7.04-6.9 (m 3H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 119.2, 120.4, 120.9, 123.3, 128.1, 128.9, 129.7,130.2,136, 139.29, 136.9,140,163.7,193.2
7		IR: **(**KBr) ν/cm^{-1} 3505 **(**-OH), 1697 (C=O), 1529 (C=C), 1345 (C-O), 671 (Ar C-H); ^{1}H NMR **(**$CDCl_3$, 300 MHz): δ 12.92 (s 1H –OH), 7.94 (d 1H *J*= 8.01 Hz) 7.89 (d 1H *J*=14.9 Hz), 7.65 (d 1H *J*=14.8 Hz);7.63 (d 2H *J*=8.2 Hz),7.53 (m 1H), 7.44 (d 2H *J*=8.1 Hz), 7.03 (d 1H *J*= 8.4 Hz) 6.92 (m1H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ196.14, 165.78, 145.96, 136, 136.91,133.25, 130.19, 129.12, 124, 121, 120.17, 118.85, 118.11

8		IR: **(**KBr) ν/cm^{-1} 3428 **(**-OH), 1688 (C=O), 1593 (C=C), 1294 (C-O), 693 (Ar C-H); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.85 (s 1H –OH), 7.95 (d 1H *J*= 8.02 Hz), 7.90 (d 1H *J*=15.5 Hz), 7.66 (d 1H *J*=15.4 Hz), 7.52 (m 1H), 7.35 (d 1H *J*=8.05 Hz), 7.27 (d 1H *J*=7.78 Hz), 7.21 (m 1H), 7.04 (d 1H 7.98), 7.01-6.93 (m 2H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 196.12, 163.78, 160.02, 145.18, 136.91, 136.03, 130.05, 129.68, 121.12, 120.57, 118.85, 117.11, 116.61, 115.72
9		IR**: (**KBr) ν/cm^{-1} 3542 (-OH), 1645 (C=O), 1608 (C=C), 1338 (O-C), 675 (Ar-H); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.61 (s 1H, -OH), 7.74 (d 1H *J*=8.1 Hz), 7.71 (d 1H *J*=15.62 Hz), 7.61 (d 1H *J*=15.62 Hz), 7.52 (d 2H *J*=8.14 Hz),7.44 (m 1H) 7.32 (d 2H *J*=8.14 Hz), 7.02 (d,1H *J*=8.1 Hz),6.86 (m 1H), 3.84 (s, 3H); ^{13}CNMR ($CDCl_3$, 5 MHz): δ190.23, 164.51,163.3 143.94, 137.11, 136.22,133.42,130.12, 129.20, 128.9, 120.45, 119.32, 118.10, 117.53, 55.33
10		IR: **(**KBr) ν/cm^{-1} 3462 (-OH), 1648 (C=O), 1610 (C=C), 1327 (O-C), 670 (Ar-H); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.72 (s, -OH), 11.15 (s, OH), 7.95 (d, 1H *J*=15.41 Hz), 7.86 (dd, 1H *J*=8.37 Hz, *J*=1.45 Hz) 7.72 (d 1H *J*=15.41 Hz), 7.56 (dd 1H *J*=8.3 Hz, *J*=1.45 Hz) 7.34 (m, 1H),7.29 (m 1H), 7.03-6.82 (m, 4H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ193.16, 163.85, 162.97, 140.36, 137.97, 132.13, 128.93, 128.5, 121.93, 120.42, 118.67, 118.10, 111.21

Conclusion

In conclusion here we report, an efficient synthesis of 2'-hydroxy acetophenone using methane sulphonic acid is catalysis. The merits of this protocol is high yield, easily available and inexpensive, biodegradable acid catalysis, simple reaction condition, easy work procedure, high yield, short reaction time (TABLE. 3).

TABLE. 3. **Comparison of this method with other reported methods.**

Entry	Catalyst	Time	Temperature	% yield	Ref.
1	KOH	24 h to 47 h	Room Temp.	41-50	[14]
2	Basic Al_2O_3	2.5 h	Room Temp.	72-83	[15]
3	$ZnCl_2$	5 min.	M. W.	75-90	[16]
4	$AlCl_3/CS_2$	6 h	Room Temp.	91	[17]
5	BF_3	3 h	Room Temp.	61	[18]
6	$KOH/TEBA/C_2H_5OH$	24 h	30°C	71-92	[19]
7	Mg-Al-O^{t}Bu	18 h	Reflux	77-93	[20]
8	$NaNO_3/CH_3OH$	16 h to 48 h	Room Temp.	40-98	[20]
9	KOH/C_2H_5OH	4 min to 300 min	U. Sonication	52-97	[21]
10	KF/Al_2O_3	4 min to 900 min	U. Sonication	83-98	[22]

11	$NaOH/C_2H_5OH$	2 min	M.W.	85-96	[23]
12	$Ba(OH)_2$ grinding	2 min to 5 min	Room Temp.	83-92	[24]
13	Methane sulphonic acid	4 h	Reflux	72-90	In this Paper

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