



CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Environmentally Benign Protocol for the Synthesis of 1,2-dihydro-1-aryl naphtho [1,2-e] [1,3] oxazine-3-one Derivatives.

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Received 22 November 2014; Accepted 26 December 2014

Abstract: 1,2-dihydro-1-aryl naphtho [1,2-e] [1,3] oxazine-3-one derivatives have been synthesized *via* one-pot condensation of aromatic aldehyde, β -naphthol and urea using cellulose sulfuric acid (CSA) as catalyst in solvent free condition under microwave irradiation. CSA has efficiently catalyzed the cyclocondensation and enhanced the product yields by reducing reaction time. The uniqueness of CSA is that it is isolable after the reaction and reusable.

Keywords: Cellulose sulfuric acid (CSA); 1,2-dihydro-1-aryl naphtho [1,2-e] [1,3] oxazine-3-one; solvent free condition; microwave irradiation.

Introduction

Oxazinone derivatives are one of the most important heterocycles in the field of medicinal chemistry due to their potent biological activities [1,2]. Naphthalene condensed 1,3-oxazine-3-one derivatives have shown a broad spectrum of antibacterial, anti-inflammatory, analgesics, and muscle relaxant activities [3,6]. Considering these paramount importance of naphthoxazinone derivatives considerable attention has been paid towards the synthesis of naphthoxazinone derivatives *via* multicomponent reaction (MCR) due to their convergence and high yields of the

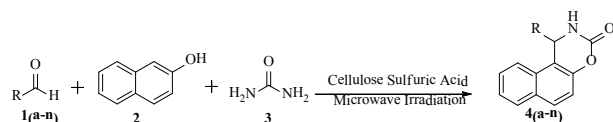
products [7].

Synthesis of naphthoxazinone derivatives includes condensation of aromatic aldehydes, β -naphthol and urea. Several methods have been reported in the literature for the synthesis of naphthoxazinone derivatives, which includes acidic catalyst [8, 9], pyridinium-based ionic liquid [10], pyridinium-based ionic liquid [11], wet cyanuric chloride [12], ZnO nanoparticles [13] and using TiCl_4 [14]. However, these reported methods suffer from many disadvantages such as longer reaction time, low yield, harsh reaction conditions and

tedious work up procedure.

In recent years more attention has been paid towards the use of environmentally benign and readily available, cost effective and heterogeneous catalysts. Biopolymer supported catalysts deserve as a heterogeneous catalysts. Several biopolymer supported catalysts have been reported which includes Alginate [15], gelatin [16, 17], starch [18] and chitosan [19]. One of the efficient biopolymer derivative cellulose sulfuric acid has also been reported for accelerating the condensation reactions [20]. Cellulose sulfuric acid is an efficient heterogeneous catalyst [21] which shown unique properties such as having high thermal stability [22] ready availability and environmentally benign.

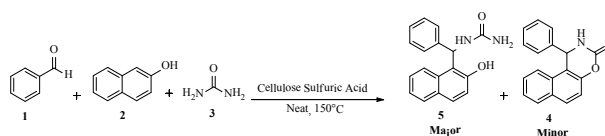
The CSA has been used to accelerate rate of various organic transformation leading imidazoazines, azides [23,24] and phthalazine-triones [25]. Microwave irradiation has excellent heating source for organic reaction [26] Microwave heating has important contribution for enhancing green synthesis [27,28]. Organic synthesis under microwave irradiation has advantage of shorter reaction time of using only small amount of energy [26-29]. Considering the above reported potential catalytic activity of CSA and importance of microwave irradiation in organic synthesis and in the continuation of research group in the development of green synthetic approach [30]. Herein, we wish to report the convenient synthesis of 1,2-dihydro-1-aryl naphtho [1,2-e] [1,3] oxazine-3-one derivatives using CSA as catalyst under microwave irradiation and solvent free condition (Scheme 1)



Scheme 1. Synthesis of 1,2-dihydro-1-aryl naphtho [1,2-e] [1,3] oxazine-3-one derivatives.

Results and Discussion

In the search of an efficient catalyst for the synthesis of 1,2-dihydro-1-aryl naphtho [1,2-e] [1,3] oxazine-3-one derivatives, a cyclocondensation of benzaldehyde **1a**, β -naphthol **2** and Urea **3** was considered as a model reaction. Initially, we carried out the model reaction in the absence of CSA under neat condition at 120°C. We observed that After 3.5 h desire product i.e. **4a** was not formed. Then, we employed CSA as catalyst for model reaction under neat condition at 120°C after 3.5 h, we found that the intermediate **5** was formed as major product and the desire product **4a** was formed as minor product (Scheme 2). The intermediate **5** was confirmed by TLC and melting point. In next step, we performed model reaction under microwave irradiation in absence of CSA. We observed that it did not give satisfactory yield even with 15 minute microwave irradiation under solvent free condition. Then attempt has been made to carry out model reaction in presence of cellulose sulfuric acid under microwave irradiation. Surprisingly, we found that within 4 minute the product **4a** was formed with 90% yield (Table 1, entry 9).



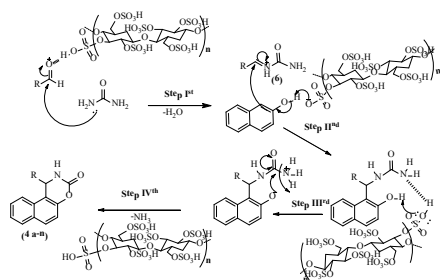
Scheme 2 Synthesis of 1,2-dihydro-1-aryl naphtho [1,2-e] [1,3] oxazine-3-one derivatives under neat condition.

Table 1 Screening of the different catalysts for the model reaction^a

Entry	Catalyst	Time (min)	Yield ^b (%)
1	Without catalyst	15	60
2	Citric acid	15	85
3	Sulfamic acid	15	86
4	Boric acid	15	83
5	K ₂ CO ₃	15	68
6	NaOH	15	58
7	Polyethylene glycol-400	15	70
8	CSA	4	90

^aReaction conditions: benzaldehyde (1 mmol), β -naphthol (1 mmol), urea (1.5 mmol) and 0.05 g CSA, under microwave irradiation at 700 W and temp. 120°C, ^bIsolated yields.

We conceived that, the mechanism of this reaction in presence of cellulose sulfuric acid under microwave irradiation may be proceed through, firstly, the cellulose sulfuric acid act as Bronsted acid which increases electrophilicity of carbonyl carbon of aromatic aldehyde that lead to the formation of acyliimine intermediate (**6**) which was formed in situ by condensation of aromatic aldehyde and urea [31]. In next step, conjugate base cellulose sulfuric acid enhances the nucleophilicity of β -naphthol that may be lead to the addition on acyliimine intermediate (**6**). Further cellulose sulfuric acid increase the rate of cyclisation by protonation of nitrogen atom of -NH₂ group to eliminate the -NH₃ and gives corresponding products (**4a-n**) (Scheme 3).

**Scheme 3** Proposed mechanism for the synthesis

of 1,2-dihydro-1-aryl naphtho [1,2-e] oxazine-3-one derivatives using CSA.

Moreover, we have been studied the effect of microwave irradiation powers such as, 500, 550, 600, 650, 700, 750, 800 and 850 W on model reaction, out of which best result was obtained at 700 W (Table 2. Entry 5), above this power that is at 750, 800 and 850 W yield was less as compared to product obtained at 700 W. We therefore concluded that high temperature causes the decomposition of the product. (Table 2).

Table 2 Effect of different microwave irradiation powers on model reaction^a.

Entry	Power (W)	Time (min)	Yield ^b (%)
1	500	4	85
2	550	4	85
3	600	4	87
4	650	4	87
5	700	4	90
6	750	4	88
7	800	4	88
8	850	4	85

^aReaction conditions: benzaldehyde (1 mmol), β -naphthol (1 mmol), urea (1.5 mmol) and 0.05 g CSA, under microwave irradiation at 700 W and temp. 120°C, ^bIsolated yields.

To evaluate the effect of solvent, different solvents have been screened for the model reaction with CSA under microwave irradiation *viz* ethanol, DMF, water and CH₃CN but best result was obtained in solvent free condition (Table 3, Entry 5).

Table 3. Effect of solvents on model reaction on model reaction^a.

Entry	Solvent	Time (min)	Yield ^b (%)
1	Ethanol	15	67
2	DMF	15	55
3	Water	15	58
4	CH ₃ CN	15	58
5	Solvent free	4	90

^aReaction conditions: benzaldehyde (1 mmol), β -naphthol (1 mmol), urea (1.5 mmol) and 0.05 g CSA, under microwave irradiation at 700 W and temp. 120°C, ^bIsolated yields.

We further studied the effect of different aromatic aldehydes on model reaction in various aspects like time and yield, we observed that benzaldehyde gives 90% yield and electron donating and withdrawing group on the aldehydes was not shown any considerable change in the yield of the products even enhancing reaction time (Table 4).

One of the most important aspect of CSA as catalyst is that it can be recyclable. It can be recycled after washing with DCM and drying for subsequent reaction. We have been screening out the reusability of said catalyst for the model

Table 4 Synthesized derivatives of 1,2-dihydro-1-aryl naphto [1,2-e] [1,3] oxazine-3-one derivatives^a

Product	Aldehyde R	Time (Min)	Yield ^b %	Melting Point (°C)	
				Found	Reported
4a	C ₆ H ₅	4.00	90	164-166	164-165 [14]
4b	4-MeOC ₆ H ₅	5.00	81	190-192	188-190 [14]
4c	4-ClC ₆ H ₅	5.30	83	211-213	210-212 [14]
4d	2-thiophen	6.00	87	209-211	208-210 [11]
4e	4-HOC ₆ H ₅	4.30	71	182 dec.	180 dec.[14]
4f	3-MeOC ₆ H ₅	5.30	73	203-205	202-204 [11]
4g	2-ClC ₆ H ₅	6.00	88	250-252	249-251 [12]
4h	4-BrC ₆ H ₅	5.00	87	217-219	216-218 [12]
4i	Pipernal	5.00	78	218-220	232-234 [14]
4j	4-CH ₃ C ₆ H ₅	5.00	81	168-170	166-168 [14]
4k	3- ClC ₆ H ₅	4.50	79	194-196	194-196 [14]
4l	4-FC ₆ H ₅	4.00	80	203-205	202-204 [14]
4m	4-NO ₂ C ₆ H ₅	4.50	85	188-190	188-190 [14]
4n	2- NO ₂ C ₆ H ₅	5.00	75	196-198	195-197 [14]

^aReaction conditions: benzaldehyde (1 mmol), β -naphthol (1 mmol), urea (1.5 mmol) and 0.05 g CSA, under microwave irradiation at 700 W and temp. 120°C, ^bIsolated yields.

reaction. We found that recycled cellulose sulfuric acid has been accelerating rate of at least four successive similar condensations with variable yields (Table 5).

Table 5 Reusability of cellulose sulfuric acid in model reaction^a.

cycle	Time (min)	Yield ^b (%)
1	4	90
2	4	90
3	4	89
4	4	88

^aReaction conditions: benzaldehyde (1 mmol), β -naphthol (1 mmol), urea (1.5 mmol) and 0.05 g CSA, under microwave irradiation at 700 W and temp. 120°C, ^bIsolated yields.

Experimental

Microwave synthesizer (STARSYNTH Microwave having maximum out-put power of 1200 W) has been used for microwave irradiation. ¹H NMR spectra were recorded on Bruker Advance 400, in DMSO in presence TMS as an internal standard. ¹³C NMR spectra recorded on Bruker DRX-300 in DMSO as solvent. Mass spectra were recorded on water UPLC TQD Mass spectrometer, showing M⁺ peak. Melting points were recorded in open capillary method and uncorrected.

General experimental procedure.

The catalyst cellulose sulfuric acid was prepared according to the literature procedure [23]. A mixture of aromatic aldehyde (1 mmol), β -naphthol (1 mmol), urea (1.5 mmol) and 0.05 g cellulose sulfuric acid was taken in 50 dm³ two necked round bottom flask. Then the reaction mixture was subjected to microwave irradiation at 700 W for the indicated time to

afford the corresponding 1,2-dihydro-1-aryl naphtho [1,2-e] [1,3] oxazine-3-one derivatives (Table 1). The progress of the reaction was monitored by TLC, the products were extracted by dichloromethane (2X25 ml). Undissolved residue in dichloromethane *i.e.* CSA which was dried, recycled and reused. The Products were obtained by removing solvent from extract under reduced pressure. The obtained products were crystallized from ethanol.

The spectral data of representative compounds *i.e.* **4a** and **4i** are given here.

1-phenyl-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-one (4a)

White crystals; **M. P.** 164-166 °C; ¹H NMR (DMSO-d₆, δ ppm): 6.19-6.19 (s, 1H, CH), 7.23-7.35 (m, 1H, Ar-H), 7.29-7.35 (q, 4H, Ar-H), 7.37-7.44 (d, 1H, Ar-H), 7.46-7.50 (q, 2H, Ar-H), 7.80-7.82 (d, 1H, Ar-H), 7.93-7.95 (d, 1H, Ar-H), 7.97-8.0 (d, 1H, Ar-H), 8.87 (s^{bs}, 1H, NH); ¹³C NMR (75 MHz, DMSO): δ 53.45, 114.07, 116.89, 123.12, 125.09, 127.00, 128.04, 128.64, 128.97, 130.25, 130.44, 142.90, 147.40, 149.38; **Mass** EI-MS *m/z* cal. 275.1, *m/z* obs. [M⁺+H] = 276.1.

1-(benzo[d][1,3]dioxol-5-yl)-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-one (4i)

White crystals; **M.P.** 218-220 °C; ¹H NMR (DMSO-d₆, δ ppm): 5.95-5.97 (d, 2H, CH₂), 6.12 (s, 1H, CH), 6.7 (d, 1H, Ar-H), 6.84-6.85 (d, 2H, Ar-H), 7.35-7.37 (d, 1H, Ar-H), 7.43-7.51 (m, 2H, Ar-H), 7.795-7.518 (d, 1H, Ar-H), 7.94-7.99 (dd, 2H, Ar-H), 8.79 (s^{bs}, 1H, NH); ¹³C NMR (75 MHz, DMSO): 53.45, 101.22, 107.37, 108.48, 114.01, 116.86, 120.36, 123.17, 125.09, 127.37, 128.62, 128.91, 130.22, 130.41, 136.85, 146.92, 147.40, 147.60, 149.29; **Mass** EI-MS *m/z* cal. 319, *m/z* obs. [M⁺+H] = 320.

Conclusion:

The cellulose sulfuric acid (CSA) act as the most

efficient catalyst which gives desire product under the microwave irradiation while using other catalysts gives intermediate **5** as major product. This most important in the synthesis of 1,2-dihydro-1-aryl naphtho [1,2-e] [1,3] oxazine-3-one derivatives because most of time we got intermediate **5** rather than desire product (**4a**) for model reaction. So rate of cyclisation of intermediate **5** and covert in to **4a** is enhanced by CSA. We also observed that the cellulose sulfuric acid has reusability and easy work up procedure.

With optimized condition in hand, we have furnished the scope and generated the newer methodology for the condensation of aromatic aldehydes with β -naphthol and urea for obtains respective naphthoxazinone derivatives with excellent yields within shorter reaction time.

Acknowledgements

The Emeritus Scientist Scheme awarded to MSS by the Council of Scientific and Industrial Research, New Delhi is gratefully acknowledge. The Authors are thanks to Head, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad for providing laboratory facilities and SAIF, CDIR, Lukhnow for providing spectral data.

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