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Environmentally Benign Synthesis of 1-Amidoalkyl-2-Naphthols by Using *Citrus limon* Juice

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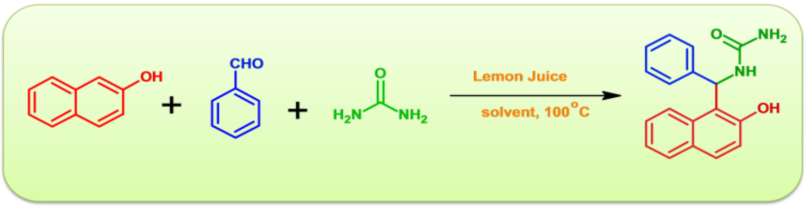
ABSTRACT

Fruit juice of Citrus limon (lemon juice) has been utilized as a natural, green and eco-friendly reagent for the synthesis of 1-amidoalkyl-2-naphthols by one-pot multicomponent reaction of 2-naphthol with a variety of aryl aldehydes and urea/amides. The beneficial features of this new synthetic approach include short reaction time, cleaner reaction profile and easy work up procedure.

Graphical Abstract



Keywords: *Citrus lemon*, One-pot, MCRs, 1-amidoalkyl-2-naphthols

INTRODUCTION

In the perspective of green chemistry, multi-component reactions (MCRs) is found to be growing technique in organic synthesis as it shows remarkable significance in construction of diverse and complex organic molecules in a single event which includes all essential parts of the starting materials [1,2]. Furthermore, MCRs also have additional merits such as simple experimental procedures, high atom-economy, building up complex molecules and the formation of vital carbon-carbon and carbon-heteroatom bonds by one-pot method [3,4].

In the last decades over the environmental protection, great attentions have been paid for the synthetic utility of natural catalyst in organic transformations. Natural catalysts are environmentally acceptable; eco-friendly hence minimizes problems of waste disposal [5]. Previously several natural catalysts such as aqueous fruit extract of *Tamarindus indica* [6] pineapple [7], coconut [8], *Acacia concinna* [9], and *Sapindus trifolistus* [10] are used in many organic transformations. Among the all-natural catalysts, lemon juice is one of the attractive candidates for the organic synthesis which efficiently catalyzes various organic transformations [11-15]. Still there is scope to exploit its catalytic potential in synthesis of large number of medicinally important scaffolds. Lemon fruits are widely grown in all tropical and subtropical countries which belongs to *Citrus aurantium, C. indica* and *C. limonium* class of citrus family having highly acidic nature (pH=2-3). Moreover, owing to high solubility of lemon juice in water, it can be effortlessly removed by simple filtration.

1-amidoalkyl-2-naphthols and their derivatives bearing 1,3-amino oxygenated functional groups are the key intermediate in number of natural products and synthetic pharmaceuticals and act as potential drugs in number of nucleoside antibiotics and HIV protease inhibitors [16]. In addition, they also shows potential biological activities, such as antibiotic, anticonvulsant, antimalarial, antihypertensive, antitumor, anti-rheumatic, analgesic, antipsychotic, antianginal [17-25]. Owing to their unique biological profile, synthesis of 1-Amidoalkyl-2-naphthols and their derivatives is of prime task for the organic chemist. The synthesis of 1-amidoalkyl-2-naphthols has been carried out by multi-component condensation reaction of 2-naphthol, aromatic aldehydes, and acetonitrile or various amides in the presence of different catalysts.

Several catalysts have been applied to achieve this reaction, including LSA [26], $RuCl_2(PPh_3)_3$ [27], Cp_2ZrCl_2 [28], tannic acid [29], $Bi(OTf)_3$ [30], phosphotungstic acid encapsulated montmorillonite clay [31], $BF_3.SiO_2$ [32], aluminatesulfonic acid [33], CBSA [34], β-cyclodextrin-butane sulfonic acid [35], melamine-Br_3 [36], etc.

Though, the existing procedures have certain advantages they also have many drawbacks such low yield, prolonged reaction time, tedious work-up, harsh reaction conditions, toxic and corrosive solvent, strongly acidic media, expensive catalysts and high temperature reaction condition. Therefore, syntheses of amidoalkyl naphthols via clean, mild and eco-friendly catalyst are consequently become a popular area to develop a safe alternative method [37,38].

Based on the above facts, herein we report lemon juice as a new biodegradable and renewable natural catalyst for the synthesis of 1-amidoalkyl-2-naphthols from the one-pot condensation of 2-naphthol with a variety of aryl aldehydes and urea/amides in ethanol.

MATERIALS AND METHODS

General

All chemicals were purchased from local sources and were of used analytical grade. All reactions were carried out under air atmosphere in dried glassware. Melting points were measured by an open capillary method under open atmosphere and are uncorrected. The products were in good agreements with those of known compounds by their spectral data. IR spectra were measured with a Perkin-Elmer Spectrum one FT-IR spectrometer. NMR spectra were recorded on a Bruker AC (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) spectrometer using DMSO-d_6 as the solvent and TMS as an internal standard. The δ-values are expressed in parts per million (ppm) with TMS as an internal standard. A mass spectrum was recorded on a Shimadzu QP2010 gas chromatograph mass spectrometer.

General procedure for extraction of lemon juice

Fresh fruits of *Citrus limon* was purchased from the local market and authenticated by the botany department. The pieces were pressed in a fruit juicer to obtain the extract. Then the juice was filtered through cotton and finally through filter paper to remove solid material and to get the clear portion of juice which was used as a catalyst. The pH of the extracted lemon juice was in between 2-3.

General procedure for the synthesis of 1-amidoalkyl-2-naphthols

In typical procedure, 2-naphthol (1 mmol), aryl aldehyde (1 mmol), benzamide or acetamide or urea (1.5 mmol) and lemon juice: ethanol (3 ml, 1:1, v/v) was added in the reaction vessel. The materials were mixed and stirred at room temperature for a specified time. After reaction completion (indicated by TLC), the cold water was added to quench the reaction and mixture was stirred continuously until free flowing solid was obtained. The resulting solid was filtered, air dried followed by recrystallization from ethanol to get pure product which was subsequently characterized by spectroscopic techniques.

Spectral data of representative compound

N-[(2-Hydroxynaphthalen-1-yl)phenylmethyl] urea

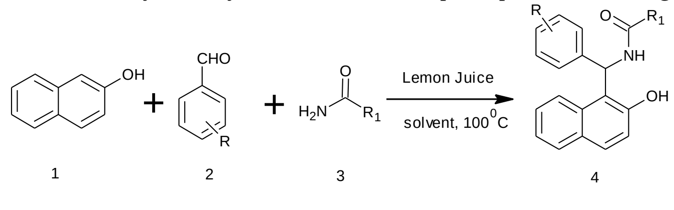
White Solid, Mp: 177°C, ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 9.85 (bs, ^{1}H, OH), 7.88 (s, ^{1}H, NH), 7.76 (s, ^{2}H, NH_2), 7.59-7.73 (m, ^{3}H Ar-H), 7.19-7.28 (m, ^{5}H Ar-H) 7.06-7.15 (m, ^{2}H, Ar-H), 6.99-6.94 (m, ^{1}H, Ar-H), 5.57 (s, ^{1}H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 48.3, 119.2, 121.4, 123.1, 126.5, 126.9, 128.4, 130.1, 130.5, 131.4, 132.7, 145.3, 154.2, 159.3; IR (KBr) (cm^{-1}): 3443 (OH), 3399 (NH), 3358 (NH_2), 3058 (C-H), 1642 (C=O); MS(EI): m/z 292 [M^+].

N-[(2-Hydroxynaphthalen-1-yl)phenylmethyl]benzamide

White solid, Mp: 236°C, ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 10.3 (s, ^{1}H),8.16-8.12 (m, ^{6}H), 7.90-7.86 (m, ^{5}H), 7.41 (s, ^{1}H),7.20-7.15 (m, ^{5}H), 6.06 (s, ^{1}H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 169,153, 148, 145, 135, 133, 132, 131, 130, 128, 127, 124, 122, 119, 118, 50; IR (KBr) (cm^{-1}): 3422 (OH), 3343 (NH), 3016 (C-H), 1667 (C=O); MS(EI): m/z 353 [M^+].

RESULTS AND DISCUSSION

Herein we chose ethanol as a reaction media for condensation of 2-naphthol with a variety of aryl aldehydes and urea/amides using Lemon juice, because ethanol is considerably safe, environmentally-friendly, non-toxic, and cheap compared to other organic solvents (Scheme 1).



Scheme 1: Lemon juice catalyzed multi-component synthesis of 1-amidoalkyl-2-naphthol

To optimize the reaction conditions 2-naphthol (1 mmol), benzaldehyde (1 mmol) and urea (1.5 mmol) were chosen as a model reaction partners. In pilot experiment, only trace amount of corresponding product was formed when model reaction was carried out in lemon extract (1 ml) at room temperature for 5 h (Table 1, Entry 1). On increasing the amount of catalyst from 2 to 4 ml, no profound influence on the yield of the product was observed (Table 1, Entries 2-4). Surprisingly, significant improvement in the yield (75%) was obtained when model reaction carried out at 100°C in 3 ml lemon juice (Table 1, Entry 5). Finally, excellent yield (89%) was achieved in mixed solvent system of lemon juice: ethanol (3 m, 1:1, v/v) at 100°C indicating that the role solvent is decisive for the completion of reaction (Table 1, Entry 8). Also, variations in the amount of ethanol (1, 2 and 4 ml) gave 78, 80, and 85% yields of the desired product respectively (Table 1, Entries 6, 7 and 9). In order to check the effect of other solvents on the yield of the product, the model reaction was performed in water, methanol (Table 1, Entries 10 and 11) which afforded product in moderate yields. In a control experiment, when the model reaction was performed in the absence of lemon juice, low yield of product was observed (Table 1, Entry 12).

Table 1: Optimization of amount of catalyst for the synthesis of 1-amidoalkyl-2-naphthol[a]

Entry	Amount of catalyst (ml)	Solvent (ml)	Temp (°C)	Time (min)	Yield[b] (%)
1	1	-	RT	180	Trace
2	2	-	RT	180	20
3	3	-	RT	180	40
4	4	-	RT	180	40
5	3	-	100	60	75
6	3	Ethanol (1)	100	60	78
7	3	Ethanol (2)	100	60	80
8	3	Ethanol (3)	100	60	89
9	3	Ethanol (4)	100	60	85
10	3	Water (3)	100	80	73
11	3	Methanol (3)	100	80	76
12	-	Ethanol	100	180	Trace

[a]**Reaction conditions:** 2-Naphthol (1 mmol), benzaldehyde (1 mmol), urea (1.5 mmol) and Lemon Juice:ethanol (3 mL, 1:1, v/v) at 100°C
[b]Isolated yields

We then compared our results with the previously used catalysts for synthesis of 1-amidoalkyl-2-naphthol, and the results are shown in Table 2. It observed that our reported is best fitted with the previous results in terms of reaction time and product yields.

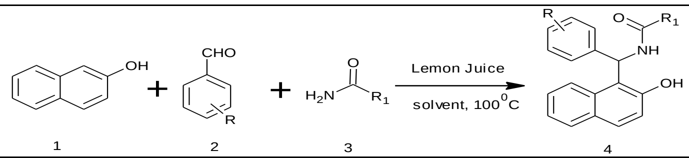
Table 2: Comparison of different catalysts for the reaction of 1-amidoalkyl-2-naphthol

S. No.	Catalyst used	Reaction condition	Time (min)	Yield (%)	References
1	Iodine (5 mol %)	125°C	270	97	[39]
2	Montmorillonite K10(0.1 g)	125°C	90	86	[40]
3	$K_5CoW_{12}O_{40}.3H_2O$ (1 mol %)	125°C	180	80	[41]
4	Sulphamic acid (10 mol %)	EDC, RT	720	81	[42]
5	Cp_2ZrCl_2 (20 mol %)	EDC, RT	420	91	[28]
6	MNPs–$PhSO_3H$ (0.02 g)	120°C	25	91	[43]
7	Lemon Juice	100°C	60	89	This work

After optimization of reaction conditions, we further explored the scope and limitation of this protocol for synthesis of variety of 1-amidoalkyl-2-naphthols by reacting 2-naphthol and urea/acetamide/benzamide with structurally dissimilar aryl aldehydes (Table 3). The nature of substituents on the aryl aldehydes had an intense effect on the yield of the desired product. It was observed that aryl aldehydes with electron-withdrawing substituents activates the aldehydes and reacted faster than those with electron releasing substituents while sterically hindered aldehydes required longer reaction times for completion of reaction.

The aromatic aldehydes bearing both activating and deactivating groups, such as halogens, nitro, methyl, and methoxy proceeded efficiently with 2-naphthol and urea, to furnish the corresponding products in excellent yields (Table 3, Entries 1-6) [44-45].

Table 3: Lemon juice catalyzed synthesis of 1-amidoalkyl-2-naphthols

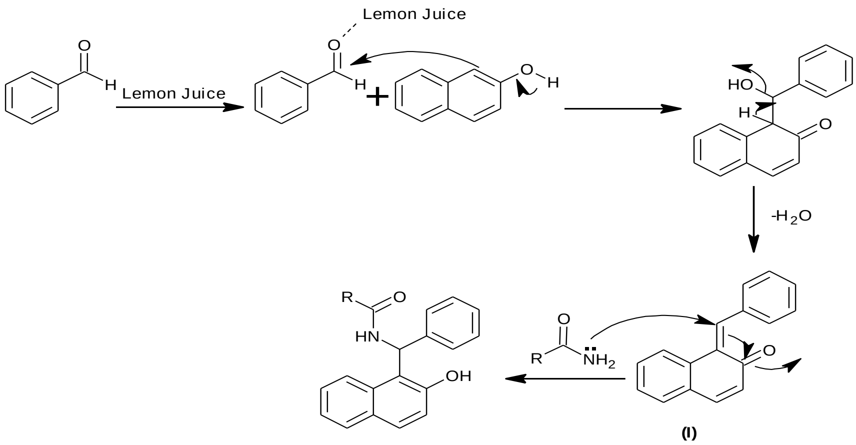


Entry	R	R_1	Product	Time (min)	Yield (%)	Physical const. (°C)
1	H	NH_2	4a	60	89	177 [177-178][44]
2	4-Cl	NH_2	4b	60	86	168 [167][28]
3	4-Br	NH_2	4c	50	90	172 [171][44]
4	3-NO_2	NH_2	4d	80	83	179 [179][28]
5	4-OCH_3	NH_2	4e	90	81	185 [186][28]
6	4-CH_3	NH_2	4f	80	52	118 [117][28]
7	H	CH_3	4g	80	87	244 [242-244][44]
8	4-Cl	CH_3	4h	60	86	225 [225][28]
9	3-NO_2	CH_3	4i	50	87	254 [253-254][44]
10	4-CH_3	CH_3	4j	90	72	223 [223-224][44]
11	4-OCH_3	CH_3	4k	90	79	186 [184-186][44]
12	3,4,5-OCH_3	CH_3	4l	110	68	190 [191][28]
13	H	C_6H_5	4m	80	87	236 [235-237][45]
14	4-Cl	C_6H_5	4n	60	84	175 [175-176][45]
15	4-NO_2	C_6H_5	4o	50	87	238 [237-238][45]
16	4-CH_3	C_6H_5	4p	90	73	174 [175][28]
17	4-OCH_3	C_6H_5	4q	110	71	196 [196][28]
18	3,4,5-OCH_3	C_6H_5	4r	90	65	233 [233][28]

Reaction conditions: 2-Naphthol (1 mmol), benzaldehyde (1 mmol), urea (1.5 mmol) and Lemon Juice in ethanol at 100°C

In addition, acetamide and benzamide was able to undergo the condensation reaction smoothly with substituted aldehydes and 2-naphthol, and gave excellent yields of desired products (Table 3, Entries 7-18). In all cases, the corresponding 1-amidoalkyl-2-naphthols were the sole product and no side products were observed.

A plausible mechanism of formation of 1-amidoalkyl-2-naphthols catalyzed by Lemon juice is depicted in Scheme 2. The reaction of 2-naphthol with aldehydes in the presence of acid catalyst is known to give *ortho*-quinonemethides (I) as an extremely reactive and ephemeral intermediate which further underwent nucleophilic addition of amides to give the expected 1-amidoalkyl-2-naphthols. It was conclude that aryl aldehydes with electron-poor groups reacted at faster rate in *o*-QMs intermediate than electron-rich groups.



Scheme 2: Proposed mechanism for the synthesis of 1-amidoalkyl-2-naphthol

CONCLUSION

In summary, we have described the fruit juice of citrus lemon as eco-friendly catalysts for multi-component synthesis of 1-amidoalkyl-2-naphthols in ethanol media. Present greener protocol offers several significant advantages such as a high yield, shorter reaction times, and simple experimental and work-up procedure.

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