

# Lactic acid as an efficient catalyst for the one-pot three-component synthesis of 1-amidoalkyl-2-naphthols under thermal solvent-free conditions

Arezo Motamedi-Asl, Khatereh Khandan-Barani\*

Department of Chemistry, Islamic Azad University, Zahedan Branch, P.O. Box 98135-978, Zahedan, Iran.

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## ABSTRACT

For the first time lactic acid was applied as an efficient and green catalyst for the one-pot three-component synthesis of amidoalkyl naphthols via the condensation between arylaldehydes, 2-naphthol and amides or urea under thermal solvent-free conditions in good to excellent yields. We have demonstrated a mild and efficient eco-friendly tandem synthesis of amidoalkyl naphthols using lactic acid as a novel organoacid green promoter, which uses neither harsh conditions nor the use of hazardous or toxicant catalysts and reagents. This methodology has a number of advantages including: short reaction times, high yield, use of non-toxic and inexpensive catalyst, elimination of solvent and easy work-up.

**Keywords:** Lactic acid; Amidoalkyl naphthol; Solvent-free; Thermal conditions.

## 1. Introduction

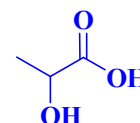
Multi-component reactions (MCRs) are a promising and vital field of chemistry because the synthesis of complicated molecules can be achieved in a very fast, efficient and time saving manner without the isolation of any intermediate [1,2]. There has been tremendous development in three or four-component reactions specially the Bigenilli, Ugi, Passerini and Mannich reactions which have further led to renaissance of MCRs [3-8].

1-amidoalkyl-2-naphthols can be converted to useful and important biological building blocks, since this compounds exhibit depressor and bradycardia effects in humans [9,10]. Moreover, this 1-aminoalkyl alcohol-type ligand has been used for asymmetric synthesis and as catalyst [11,12].

The preparation of 1-amidoalkyl-2-naphthols can be carried out by three-component condensation of 2-naphthol, aldehydes, and acetonitrile or different amides in the presence of homogeneous or heterogeneous catalysts such as p-toluenesulfonic acid [13], H<sub>2</sub>NSO<sub>3</sub>H [14], oxalic acid [15], Fe(HSO<sub>4</sub>)<sub>3</sub> [16], Sr(OTf)<sub>2</sub> [17], I<sub>2</sub> [18], K<sub>5</sub>CoW<sub>12</sub>O<sub>40</sub>·3H<sub>2</sub>O [19], HPMo

[20], Yb(OTf)<sub>3</sub> in ionic liquid [21], Indion-130 [22], montmorillonite K10 [23], TMSCl/NaI [24], InCl<sub>3</sub> [25], 2,4,6-trichloro-1,3,5-triazine [26]. However, some of the reported methods suffer from disadvantages such as long reaction time, toxic and corrosive solvent, and the use of additional microwave or ultrasonic irradiation. Furthermore, the yields of the corresponding amidoalkyl naphthols are not always satisfactory.

Lactic acid is an  $\alpha$ -hydroxy acid containing a hydroxyl group adjacent to the carboxylic acid functional group. Generally, it can be produced through chemical synthesis or through the fermentation of some carbohydrates, such as glucose, maltose, sucrose, or lactose [27]. With increasing demand for sustainable materials, lactic acid has become an important chemical platform for the bio-renewable economy (Scheme 1). Lactic acid shows environmentally friendly characters. Compared to acetic acid, its pK<sub>a</sub> is 1 unit smaller, meaning lactic acid loses its proton ten times as easily as acetic acid does.



**Scheme 1.** The structure of lactic acid.

\*Corresponding author email: kh\_khandan\_barani@yahoo.com

Tel: +98 54 3344 3600; Fax: +98 54 3344 1099

Because of the importance of these compounds, the introduction of a milder, faster, and more ecofriendly method accompanied with higher yields is needed.

In continuation of our work under the framework of MCRs [28-31], we have developed an environmentally benign solvent-free approach for the synthesis of amidoalkyl naphthols from the condensation between arylaldehydes, 2-naphthol and amides or urea using lactic acid as catalyst under solvent-free and thermal conditions (Scheme 2).

## 2. Experimental

### 2.1. General

Melting points and infrared (IR) spectra of all compounds were measured on an Electrothermal 9100 apparatus and a JASCO FT/IR 460 Plus spectrometer, respectively. The <sup>1</sup>H NMR spectra were recorded on a BRUKER DRX-400 AVANCE instrument with DMSO-*d*<sub>6</sub> as solvent at 400.1 MHz. All reagents and solvents obtained from Aldrich and Merck were used without further purification.

### 2.2. Typical procedure for synthesis of 1-amidoalkyl-2-naphthols

Lactic acid (10 mol%, 0.012 g) was added into a mixture of benzaldehyde (1 mmol), 2-naphthol (1 mmol), and acetamide (1.1 mmol), then the reaction mixture was heated to 115°C and maintained for the appropriate time. After completion of the reaction as monitored TLC, the reaction mixture was washed with H<sub>2</sub>O (3 × 10 mL). The catalyst is solvable in water and was removed from the reaction mixture. Then, the

residue was recrystallized from EtOH. The structures of the synthesized compounds were characterized by their IR, melting points and <sup>1</sup>H NMR spectra and were found to be identical with data described in the literature [37-44].

### Selected spectral data

*N*-((2-hydroxynaphthalen-1-yl) (phenyl) methyl) benzamide (**Table 2, entry 1**):

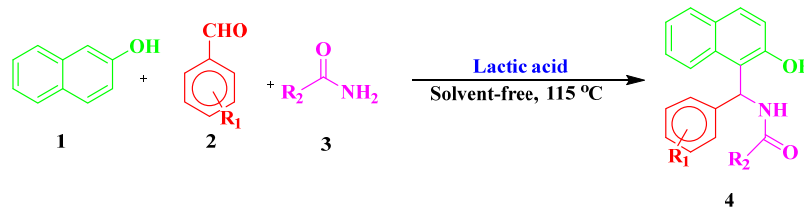
White solid. m.p.= 232-234°C. FT-IR (KBr):  $\bar{\nu}$  = 3421 (NH), 3170 (OH), 1629 (C=O) cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz):  $\delta$ = 10.32 (br, 1H, OH), 9.05 (br, 1H, NH), 7.08-8.06 (m, 17H, Ar and CH) ppm.

*N*-((2-hydroxynaphthalen-1-yl) (phenyl) methyl) acetamide (**Table 2, entry 8**):

White solid. m.p.= 240-242°C. FT-IR (KBr):  $\bar{\nu}$  = 3407 (NH), 3166 (br, OH), 1635 (C=O) cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz):  $\delta$ = 9.63 (br, 1H, OH), 8.04 (d, 1H, *J* = 8.40Hz, NH), 7.05-7.96 (m, 12H), 2.00 (s, 3H, CH<sub>3</sub>).

## 3. Results and Discussion

We performed a set of preliminary experiments on 2-naphthol, acetamide, and benzaldehyde in the presence of catalyst as a model reaction. In the initial work, different amount of catalyst were screened in the model reaction. The reaction did not progress even after 24 h in the absence of catalyst. However, 10 mol% of catalyst proved to be an efficient amount (Table 1, entry 3). As shown in Table 1, the shortest time and best yield were achieved at 115°C.



**Scheme 2.** Synthesis of 1-amidoalkyl-2-naphthols under solvent-free and thermal conditions.

**Table 1.** Optimization for the synthesis of 1-amidoalkyl-2-naphthols

Entry	Catalyst (mol%)	Temp. (°C)	Time (min)	Isolated Yield (%)
1	10	80	40	60
2	10	100	30	75
<b>3</b>	<b>10</b>	<b>115</b>	<b>10</b>	<b>93</b>
4	10	120	10	93
5	10	130	10	93
6	5	115	35	80
7	15	115	35	93
8	20	115	35	93
9	-	115	120	-

With the optimized conditions in hand, we proceeded to evaluate the scope and generality of the method using various substrates (Table 2). The reactions of 2-naphthol with various aromatic aldehydes and amides or urea were carried out in the presence of lactic acid (10 mol %) at 115 °C. In all the reactions, good to excellent yields were obtained in short reaction times. Clean and complete conversions leading to the corresponding amidoalkyl naphthols were observed, and no side products such as dibenzoxanthenes were formed. Aromatic aldehydes carrying either electron-withdrawing or electron-donating groups were all suitable for the reaction. On the other hand, the scope of different amide components was studied. Both amides and urea participated well in the reactions. As compared with the amides, urea afforded the corresponding amidoalkyl naphthol in longer reaction time (Table 2).

The results obtained with benzaldehyde, acetamide and 2-naphthol under the optimized conditions were compared with the best ones published so far for this reaction using inorganic or organic catalysts, the data

listed in Table 3. It showed that the lactic acid was fairly a good reagent for this reaction.

A plausible mechanism for this transformation is proposed in Scheme 3. As reported in the literature [37], reaction of 2-naphthol with aldehydes in the presence of catalyst is known to give ortho-quinone methides (o-QMs). The same o-QMs, generated in situ, have been reacted with amides via conjugate addition to form 1-amidoalkyl-2-naphthol derivatives.

#### 4. Conclusions

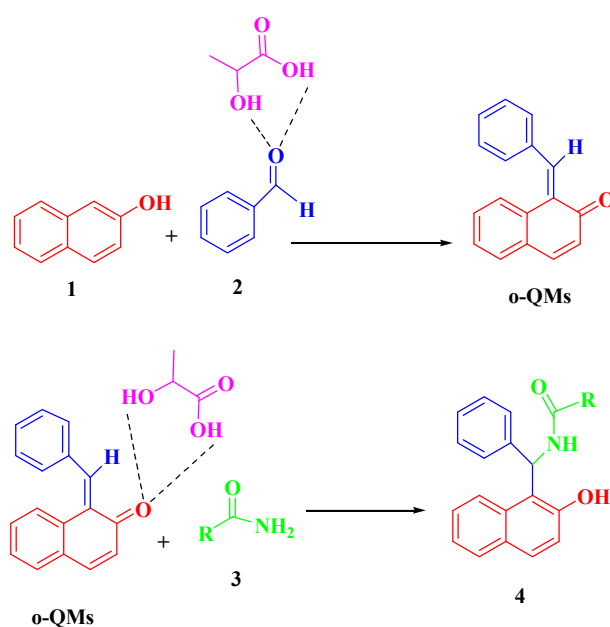
We have developed a new method for preparation of 1-amidoalkyl-2-naphthol derivatives via one-pot three-component reaction of 2-naphthol with aromatic aldehydes and different amides/urea using lactic acid as a neutral organic catalyst at 115 °C under solvent-free conditions. The catalyst shows environmentally friendly characters. Namely, it is inexpensive, clean, safe, nontoxic, and easily obtained, which makes it a useful and attractive process for synthesis of a wide variety of biologically active compounds.

**Table 2.** Synthesis of 1-amidoalkyl-2-naphthols in the presence of lactic acid under thermal solvent-free conditions

Entry	R <sub>1</sub>	R <sub>2</sub>	Time (min)	Yield (%)	m.p. (°C)		Ref.
					Found	Reported	
1	H	Ph	10	93	232-234	234-236	[32]
2	NO <sub>2</sub> -4	Ph	6	95	240-241	237-239	[33]
3	4-Cl	Ph	6	98	266-268	265-267	[33]
4	4-Br	Ph	8	89	179-181	182-184	[34]
5	2,4-di-Cl	Ph	5	95	235-237	238-239	[33]
6	3-OMe	Ph	20	85	213-215	214-216	[19]
7	2,5-di-OMe	Ph	25	80	236-238	238-240	[34]
8	H	CH <sub>3</sub>	10	95	240-242	241-243	[35]
9	NO <sub>2</sub> -2	CH <sub>3</sub>	15	85	179-181	180-182	[35]
10	NO <sub>2</sub> -4	CH <sub>3</sub>	13	98	250-252	248-250	[16]
11	4-Cl	CH <sub>3</sub>	10	95	234-236	235-236	[36]
12	4-Br	CH <sub>3</sub>	15	94	230-231	229-231	[34]
13	3,4-(OMe) <sub>2</sub>	CH <sub>3</sub>	20	88	233-235	235-236	[36]
14	2,5-(OMe) <sub>2</sub>	CH <sub>3</sub>	25	95	218-220	220-221	[37]
15	3-OMe	CH <sub>3</sub>	14	92	200-202	203-205	[39]
16	4-(Me) <sub>2</sub> N	CH <sub>3</sub>	17	90	250-252	251-253	[37]
17	2,4-(Cl) <sub>2</sub>	CH <sub>3</sub>	13	80	201-203	198-199	[35]
18	H	NH <sub>2</sub>	45	90	178-180	176-178	[38]
19	NO <sub>2</sub> -4	NH <sub>2</sub>	20	85	162-164	163-165	[40]
20	4-Cl	NH <sub>2</sub>	25	82	169-171	168-169	[41]

**Table 3.** Different catalysts for reaction of benzaldehyde, acetamide and 2-naphthol.

Entry	Catalyst	Conditions	Time	Isolated Yield (%)	Ref.
1	KHSO <sub>4</sub>	Solvent-free, 100°C	1 h	90	[42]
2	Succinic acid	Solvent-free, 120°C	25 min	95	[43]
3	MgSO <sub>4</sub> .7H <sub>2</sub> O	Solvent-free, 100°C	1 h	91	[44]
4	I <sub>2</sub>	Solvent-free, 125°C	5.5 h	85	[18]
5	K <sub>3</sub> CoW <sub>12</sub> O <sub>40</sub> .3H <sub>2</sub> O	Solvent-free, 125°C	2 h	86	[19]
6	Sulphamic acid	Solvent-free, 30°C	15 min	89	[14]
7	Fe(HSO <sub>4</sub> ) <sub>3</sub>	Solvent-free, 85°C	20 h	56	[16]
8	Lactic acid	Solvent-free, 115°C	10 min	95	This work

**Scheme 3.** The plausible mechanism for the synthesis of 1-amidoalkyl-2-naphthol derivatives in the presence of lactic acid.

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