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Glutamic acid catalyzed multicomponent synthesis of 1-amidoalkyl-2-naphthols from amides, aromatic aldehydes and 2-naphthol in solvent-free conditions

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Abstract: An efficient and direct protocol for the preparation of amidoalkyl naphthols employing a multi-component, one-pot condensation reaction of 2-naphthol, aromatic aldehydes and amides in the presence of glutamic acid under solvent-free and green conditions is described. The thermal solvent-free and green catalyst offer advantages such as shorter reaction times, simple work-up, and excellent yield. It is noteworthy that 1-amidomethyl-2-naphthols can be converted into important biological 'drug like' active 1-aminomethyl-2-naphthols derivatives by amide hydrolysis.

Keywords: One-pot reaction, 1-Aamidoalkyl 2-naphthols, Solvent-free, Green catalyst.

Introduction

One-pot catalytic conversion of organic reactions with readily available, non-toxic, and inexpensive reagents has attracted significant research interest in recent years [1]. Multicomponent reactions with atom-economy under catalytic solvent-free conditions are ideal protocols for the development of environment-friendly and cost-advantageous chemical processes [2, 3]. Compounds bearing 1,3-amino-oxygenated functional groups are ubiquitous to a variety of biologically important natural products and potent drugs including a number of nucleoside antibiotics and HIV protease inhibitors, such as ritonavir and lipinavir [4,5]. Amidoalkyl naphthol derivatives are of significant importance because of their promising biological and pharmaceutical activities [6,7]. With the aim to improve the reaction's efficiency, several methods have been developed using different catalysts such as montmorillonite K10 clay [8], $Ce(SO_4)_2$ [9,10], iodine [11], $K_5CoW_{12}O_{40}\cdot 3H_2O$ [12], p-TSA [13], sulfamic acid [14], cation-exchanged resins [15], silica-sodium hydrogen sulphate [16], silica-perchloric acid [17,18], acidic ionic liquid [19], and phosphorus pentaoxide [20] for synthesis of 1-amidoalkyl 2-naphthol derivatives by condensation of aryl aldehydes, 2-naphthol, and amide. Although these methods are quite useful, many of these methods suffer from limitations such as the requirement for a large excess of reagents, long reaction times, harsh reaction conditions and also involvement of toxic solvents.

In continuation of our research on multi-component reactions, [21-24] in the present work, we report a new, simple, mild and effective procedure for the one-pot synthesis of 1-amidoalkyl 2-naphthol derivatives via a multi-component condensation reaction between aryl aldehydes, 2-naphthol and amides in the presence of glutamic acid as a natural catalyst under solvent-free and thermally conditions (Scheme **1**).

Glutamic acid is one of the most common non-essential amino acids. Glutamic acid as a recyclable solid Broństed acid catalyst is safe, easy to handle,

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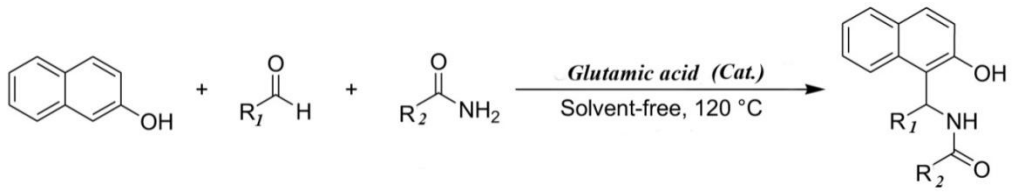
environmentally benign and presents fewer disposal problems (Figure **1**).



Scheme 1: Synthesis of 1-amidoalkyl-2-naphthols under solvent-free and thermal conditions in the presence of glutamic acid as catalyst.

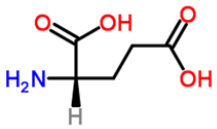


Figure 1: Structure of glutamic acid.

Results and discussion

We conducted the reaction of 2-naphthol, aromatic aldehydes and amides in the presence of glutamic acid as a green catalyst under solvent-free and thermally conditions (Scheme **1**). The experimental procedure is remarkably simple and requires no toxic organic solvent.

To find out the optimum quantity of glutamic acid, the reaction of 2-naphthol, benzaldehyde and acetamide was carried out under thermally solvent-free conditions using different quantities of glutamic acid (Table **1**). Five mole percent of glutamic acid gave excellent yield in 15 min as can be seen from Table **1**. Thus, we prepared a range of amidoalkyl naphthols under the optimized reaction conditions in excellent yields (Table **2**).

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

Entry	Catalyst (mol%)	Temprature (°C)	Time (min)	Isolated Yield (%)
1	5	80	45	60
2	5	100	35	70
3	5	115	20	95
4	**5**	**120**	**15**	**95**
5	5	130	15	95
6	10	120	25	85
7	15	120	35	75
8	20	120	35	65
9	-	120	120	-

As shown in Table **2**, 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**).

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

Entry	R_1	R_2	Time(min)	Yield(%)	Obs.m.p (lit.reported) [**Ref**]
1	H	Ph	15	95	**233-235 (234-236) [13]**
2	4-NO_2	Ph	10	95	**236-238 (237-239) [25]**
3	4-Cl	Ph	15	90	**266-268 (265-267) [25]**
4	4-Br	Ph	10	90	**183-185 (182-184) [19]**
5	4-OMe	Ph	25	80	**210-211 (208-210) [26]**
6	3-OMe	Ph	20	85	**213-215 (214-216) [12]**
7	H	CH_3	15	95	**240-242 (241-243) [9]**
8	4-NO_2	CH_3	10	95	**250-252 (248-250) [18]**
9	4-Cl	CH_3	10	95	**234-236(235-236) [20]**
10	4-Br	CH_3	15	90	**230-231 (229-231) [19]**
11	3-NO_2	CH_3	15	85	**184-186 (182-184) [27]**
12	4-OMe	CH_3	20	90	**182-184 (185-187) [26]**
13	3-OMe	CH_3	14	80	**200-202 (203-205) [28]**
14	H	NH_2	40	90	**176-178 (178-180) [18]**
15	4-NO_2	NH_2	25	85	**163-165 (162-164) [29]**
16	3-NO_2	NH_2	35	80	**194-196 (192-194) [25]**

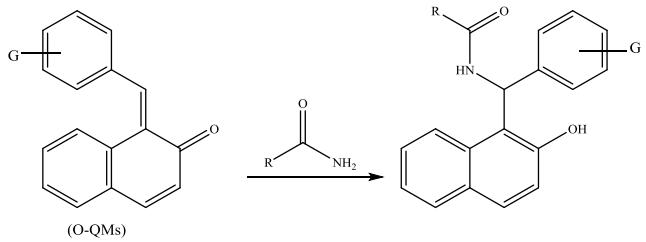
The results obtained with benzaldehyde, acetamide and 2-naphthol under the optimized conditions were compared with the best ones published so far for this reaction using inorganic or organic catalysts, the data listed in Table **3**. It showed that the glutamic acid was fairly a good reagent for this reaction.

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

Entry	Catalyst	Condition	Time	Yield (%)	[Ref]
1	$KHSO_4$	Solvent-free,100°C	1h	90	[30]
2	Succinic acid	Solvent-free,120°C	25min	95	[31]
3	$MgSO_4.7H_2O$	Solvent-free,100°C	1h	91	[32]
4	$NaHSO_4.SiO_2$	Solvent-free,125°C	9min	95	[33]

5	Montmorillonite k_{10} clay	Solvent-free,125°C	1.5h	89	[8]
6	Copper p-toluenesulfonate	Solvent-free,80°C	1.5h	94	[34]
7	$K_5CoW_{12}O_{40}.3H_2O$	Solvent-free,125°C	2h	86	[12]
8	Sulfamic acid	Solvent-free,30°C	15min	89	[14]
9	$Fe(HSO_4)_3$	Solvent-free,85°C	20h	56	[28]
10	p-TSA	Solvent-free,125°C	5h	98	[13]
11	Glutamic acid	Solvent-free,120°C	15min	95	This work

As reported in the literature [8], reaction of 2-naphthol with aldehydes in the presence of catalyst is known to give ortho-quinone methides (o-QMs) (Scheme **2**). o-Quinone methides (o-QMs) have emerged as interesting molecules due to their toxicological properties against both normal and cancerous cells and also proposed intermediary in the formation of many biologically important polymers [35]. o-QMs also act as intermediates for the synthesis of antitumor agents [36]. One of the tandem reactions which involves the in situ generation of o-QMs and its reaction with acetamide or benzamide gives amidoalkyl naphthols [37].



Scheme 2: Amides reaction with o-QMs via conjugate addition to form 1-amidoalkyl-2-naphthol derivatives.

Conclusion

In summary, we have developed a new, general and efficient procedure for one-pot synthesis of amidoalkyl naphthols by coupling various aromatic aldehydes with amides or urea and 2-naphthol using glutamic acid as a green catalyst under thermally solvent-free conditions. The advantageous of this environmentally safe and benign protocol include a simple reaction set-up, high products yields, short reaction times and elimination of solvents and toxic catalysts.

Experimental

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 ^{1}HNMR spectra were recorded on a BRUKER DRX–400 AVANCE instrument with DMSO-d_6 as solvent at 400.1 MHz. All reagents and solvents obtained from Aldrich and Merck were used without further purification.

Typical procedure for synthesis of 1-amidoalkyl-2-naphthols:

Glutamic acid (5 mol%) 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 120°C and maintained for the appropriate time (Table **2**). After completion of the reaction as monitored by thin-layer chromatography (TLC), the reaction mixture was washed with H_2O (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 ^{1}H NMR spectra and were found to be identical with data described in the literature (Table **2**).

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

FT-IR (KBr) (ν_{max}, cm^{-1}): 3421 (NH), 3170 (OH), 1629 (C=O). ^{1}HNMR (DMSO-d_6, 400 MHz) δ: 9.02 (br, 1H, OH), 8.06 (br, 1H, NH), 7.23-8.06 (m, 17H).

N-((2-hydroxynaphthalen-1-yl)(phenyl)methyl) acetamide (Table 2, entry 7):

FT-IR (KBr) (ν_{max}, cm^{-1}): 3407 (NH), 3166 (br, OH), 1635 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.01 (br, 1H, OH), 8.45 (d, 1H, *J* = 8.4Hz, NH), 7.10-7.80 (m, 12H), 1.96 (s, 3H, CH_3) ppm.

N-((2-hydroxynaphthalen-1-yl)(3-nitrophenyl)methyl) acetamide (Table 2, entry 11):

IR (KBr) (ν_{max}, cm^{-1}): 3363 (NH), 3185 (br, OH), 1645 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.24 (br, 1H, OH), 8.10 (br, 1H, NH), 7.85–6.95 (m, 10H), 6.60 (br. s, 1H), 2.10 (s, 3H, CH_3) ppm.

N-((2-hydroxynaphthalen-1-yl)(4-methoxyphenyl) methyl) acetamide (Table 2, entry 12):

FT-IR (KBr) (ν_{max}, cm^{-1}): 3374 (NH), 3178 (br, OH), 1646 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.90 (br, 1H, OH), 8.36 (d, 1H, *J* = 8.1Hz, NH), 7.24-7.82 (m, 11H), 3.88 (s, 3H, CH_3), 1.96 (s, 3H, CH_3) ppm.

N-((2-hydroxynaphthalen-1-yl)(3-Nitrophenyl) methyl)urea (Table 2, entry 16):

FT-IR (KBr) (ν_{max}, cm^{-1}): 3374 (NH), 3178 (br, OH), 1646 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.21 (s, 1H, OH), 8.25-7.55 (m, 11H), 6.75 (br s, 2H, NH_2), 5.80 (br. s, 1H) ppm.

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