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Three-component synthesis of amidoalkyl naphthols catalyzed by bismuth(III) nitrate pentahydrate

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Abstract

Bismuth(III) nitrate pentahydrate catalyzed the three-component condensation of β-naphthol, aldehydes and amines/urea under solvent-free conditions to afford the corresponding amidoalkyl naphthols in excellent yields.

Keywords: Amidoalkyl naphthols; Bismuth(III) nitrate; One-pot synthesis; Solvent-free conditions

Compounds bearing 1,3-amido 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, lipinavir, and the hypotensive [1]. In addition, the bradycardiac effects of these compounds have been evaluated [2]. The importance of amidoalkyl naphthols for their synthesis has attracted renewed attention and various improved procedures have been reported. These reported methods mainly include the one-pot three-component condensation of β-naphthol, aldehydes and amine/CH_3CN, which employs catalysts such as *p*-toluene sulfonic acid [3], H_2NSO_3H [4], $Al(H_2PO_4)_3$ [5], $Yb(OTf)_3$ [6], $Sr(OTf)_2$ [7], I_2 [8], Brønsted acidic ionic liquid [9], $K_5CoW_{12}O_{40}{\cdot}3H_2O$ [10], Indion-130 [11], Al_2O_3–$HClO_4$ [12], montmorillonite K10 [13], and silica sulfuric acid [14]. Most of these methods suffer from drawbacks including long reaction time, expensive reagent, toxic and corrosive solvent, high reaction temperature (>100 °C), high catalyst loading, strongly acidic conditions, and the use of additional microwave or ultrasonic irradiation. Moreover, aliphatic aldehydes did not give satisfactory yields in earlier reports. Therefore, the development of less expensive and high yielding catalytic method is desired.

Recently, the use of bismuth(III) nitrate as a catalyst or as a stoichiometric reagent in organic synthesis has increased considerably [15–18]. The main reasons for this are their low cost, nontoxicity, commercial availability, ease handling and resistant to air/moisture. That is why bismuth(III) compounds are termed as ''green'' reagents in organic synthesis [19–21]. In continuation of our work on the development of useful synthetic methodologies, we herein disclose the catalytic activity of bismuth(III) nitrate pentahydrate for the efficient three-component synthesis of amidoalkyl naphthols **4** under solvent-free conditions (Scheme 1).

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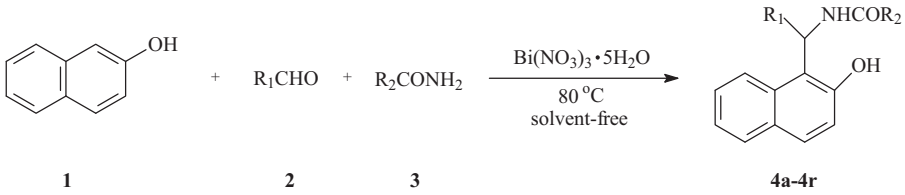


Scheme 1. One-pot three-component synthesis of amidoalkyl naphthols.

1. Experimental

General procedure for the synthesis of amidoalkyl naphthols (**4**): To a mixture of *β*-naphthol (10 mmol), an aldehyde (10 mmol), and an amide (11 mmol), $Bi(NO_3)_3{\cdot}5H_2O$ (0.2 mmol) was added. The reaction mixture was magnetically stirred on a preheated water bath at 80 °C. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to r.t., washed with H_2O/EtOH (v/v = 1/1), and the residue was recrystallized from EtOH. The products were characterized by comparing their mp, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis with those reported for the authentic samples. Spectral data for some representative compounds.

N-(1-(2-hydroxynaphthalen-1-yl)propyl)benzamide (**4j**). White solid. IR (KBr, cm^{-1}): 3405, 3184, 1635, 1532, 1514, 1344, 1073, 816, 747, 707. ^{1}H NMR (500 MHz, DMSO-d_6): *δ* 10.10 (s, 1H, OH), 8.62 (d, 1H, *J* = 8.0 Hz, NH), 8.23 (d, 1H, *J* = 8.8 Hz, ArH), 7.82 (t, 3H, *J* = 7.2 Hz, ArH), 7.70 (d, 1H, *J* = 8.8 Hz, ArH), 7.53–7.44 (m, 4H, ArH), 7.30 (t, 1H, *J* = 7.2 Hz, ArH), 7.20 (d, 1H, *J* = 8.8 Hz, ArH), 5.92 (q, 1H, *J* = 7.5 Hz, CH), 2.18–1.96 (m, 2H, CH_2), 0.93 (t, 3H, *J* = 7.3 Hz, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): *δ* 165.4, 152.9, 134.7, 132.1, 131.0, 128.5, 128.4, 128.3, 128.2, 126.9, 126.2, 122.5, 119.5, 118.6, 48.5, 26.9, 11.3. Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.58. Found: C, 78.54; H, 6.33; N, 4.52%.

N-(1-(2-hydroxynaphthalen-1-yl)propyl)acetamide (**4p**). White solid. IR (KBr, cm^{-1}): 3430, 3236, 2963, 1644, 1583, 1517, 1333, 1079, 814, 746, 709. ^{1}H NMR (500 MHz, DMSO-d_6): *δ* 9.94 (s, 1H, OH), 8.08 (d, 1H, *J* = 8.6 Hz, NH), 8.03 (s, 1H, ArH), 7.72 (d, 1H, *J* = 8.0 Hz, ArH), 7.64 (d, 1H, *J* = 8.8 Hz, ArH), 7.39 (t, 1H, *J* = 7.4 Hz, ArH), 7.21 (t, 1H, *J* = 7.4 Hz, ArH), 7.13 (d, 1H, *J* = 9.1 Hz, ArH), 5.63 (q, 1H, *J* = 7.8 Hz, CH), 1.89–1.84 (m, 2H, CH_2), 1.81 (s, 3H, CH_3), 0.77 (t, 3H, *J* = 7.4 Hz, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): *δ* 169.1, 153.5, 132.9, 129.0, 128.9, 128.7, 126.6, 123.1, 122.7, 120.0, 119.1, 48.0, 27.2, 23.2, 11.9. Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.75. Found: C, 74.17; H, 6.98; N, 5.68%.

N-(1-(2-hydroxynaphthalen-1-yl)butyl)acetamide (**4q**). White solid. IR (KBr, cm^{-1}): 3409, 3220, 2956, 1642, 1583, 1531, 1515, 1336, 1076, 816, 749, 705. ^{1}H NMR (500 MHz, DMSO-d_6): *δ* 9.86 (s, 1H, OH), 8.13 (d, 1H, *J* = 8.6 Hz, NH), 8.02 (s, 1H, ArH), 7.78 (d, 1H, *J* = 7.7 Hz, ArH), 7.68 (d, 1H, *J* = 8.8 Hz, ArH), 7.46 (t, 1H, *J* = 7.2 Hz, ArH), 7.28 (t, 1H, *J* = 7.4 Hz, ArH), 7.18 (d, 1H, *J* = 8.8 Hz, ArH), 5.83 (q, 1H, *J* = 7.6 Hz, CH), 2.05–1.97 (m, 1H, CH_2), 1.88–1.80 (m, 4H, CH_2 and CH_3), 1.40–1.30 (m, 1H, CH_2), 1.22–1.13 (m, 1H, CH_2), 0.88 (t, 3H, *J* = 7.4 Hz, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): *δ* 168.4, 152.9, 132.2, 128.4, 128.2, 128.1, 126.0, 122.1, 119.8, 118.5, 45.5, 35.9, 22.7, 19.5, 13.7. Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.79; H, 7.37; N, 5.36%.

1-((2-Hydroxynaphthalen-1-yl)(phenyl)methyl)urea (**4r**). White solid. IR (KBr, cm^{-1}): 3447, 3212, 2932, 1651, 1535, 1438, 1354, 1063, 814, 751, 698. ^{1}H NMR (500 MHz, DMSO-d_6): *δ* 9.97 (s, 1H, OH), 7.83–7.75 (m, 3H, ArH), 7.40 (s, 1H, NH), 7.29–7.11 (m, 7H, ArH), 6.94 (s, 2H), 5.86 (s, 2H, NH_2). ^{13}C NMR (125 MHz, DMSO-d_6): *δ* 158.5, 152.9, 144.2, 128.9, 128.6, 127.8, 126.4, 125.8, 122.4, 120.2, 118.5, 48.1. Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.51; N, 9.58. Found: C, 74.08; H, 5.59; N, 9.46%.

2. Results and discussion

First, in order to optimize the reaction conditions, various reaction media were screened using the model reaction of *β*-naphthol, benzaldehyde and benzamide in Table 1. It was found that the best results were obtained with 2 mol% $Bi(NO_3)_3{\cdot}5H_2O$ under solvent-free conditions (Table 1, entry 9). The reaction was completed within 12 min and the expected product was obtained in a 96% yield, while diminish the amount of catalyst would decrease the product yield (Table 1, entry 10).

Table 1
Amidoalkylation reaction of β-naphthol, benzaldehyde and benzamide catalyzed by $Bi(NO_3)_3{\cdot}5H_2O$ under various conditions.[a]

Entry	Solvent	Amount of catalyst (mol%)	Time (h)	Yield (%)
1	CH_2Cl_2	2	2	11
2	$CH_3COOC_2H_5$	2	2	25
3	Toluene	2	2	36
4	THF	2	2	49
5	H_2O	2	2	64
6	EtOH	2	2	64
7	CH_3CN	2	2	77
8	Cyclohexane	2	2	86
9	None	2	0.2	96
10	None	1	0.3	75

[a] Reaction conditions: β-naphthol 10 mmol, benzaldehyde 10 mmol, benzamide 11 mmol, the amount of solvent used for entries 1–8 was 3 mL.

Having established the reaction conditions, we extended the reaction to substituted aromatic aldehydes and aliphatic aldehydes, which reacted with amides/urea and β-naphthol in Table 2. In all cases, amidoalkyl naphthols were the sole products and no by-product was observed. Aromatic aldehydes carrying either electron-withdrawing or electron-donating groups reacted successfully and gave the desired products in high yields. Aliphatic aldehydes also underwent the transformation conveniently. However, the reactions of aliphatic aldehydes in most reported literatures were sluggish and isolated no desired products [3–5,8,10–12]. In addition, urea and different amines such as benzamide and acetamide worked equally, whereas the reaction was unsuccessful with thiourea.

In order to show the merit of $Bi(NO_3)_3{\cdot}5H_2O$ in comparison with other reported catalysts, we summarized some of the results for the preparation of *N*-(1-(2-hydroxynaphthalen-1-yl)benzyl)benzamide (**4a**) in Table 3. The results showed that $Bi(NO_3)_3{\cdot}5H_2O$ is a more efficient catalyst with respect to reaction temperature, catalyst load, reaction time and yield than those reported ones.

We propose a reaction mechanism of the $Bi(NO_3)_3{\cdot}5H_2O$-catalyzed condensation as shown in Scheme 2. $Bi(NO_3)_3{\cdot}5H_2O$ act as a Lewis acid catalyst that facilitates the formation of *o*-QMs, which further react with a nucleophile (amide/urea) to form the desired amidoalkyl naphthols [3,8].

From the results of the above study it can be concluded that the synthesis of amidoalkyl naphthols catalyzed by $Bi(NO_3)_3{\cdot}5H_2O$ offers several significant advantages such as short reaction time (0.1–2.5 h), mild reaction condition, simple work-up, excellent yields (79–97%), and extensive applicability.

Table 2
Synthesis of amidoalkyl naphthols in the presence of $Bi(NO_3)_3{\cdot}5H_2O$ without solvent.[a]

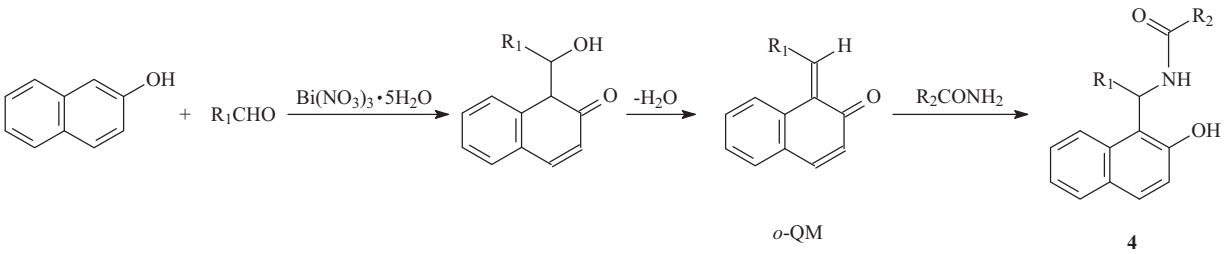
Entry	R_1	R_2	Time (h)	Product	Yield (%)	Mp (°C)
1	C_6H_5	C_6H_5	0.2	**4a**	96	237–238 [9]
2	2-$NO_2C_6H_4$	C_6H_5	0.5	**4b**	81	264–266 [22]
3	3-$NO_2C_6H_4$	C_6H_5	0.3	**4c**	89	232–234 [9]
4	4-$NO_2C_6H_4$	C_6H_5	1.0	**4d**	81	237–239 [23]
5	2-ClC_6H_4	C_6H_5	0.5	**4e**	96	265–267 [24]
6	4-ClC_6H_4	C_6H_5	1.5	**4f**	92	187–189 [7]
7	2,4-$Cl_2C_6H_3$	C_6H_5	0.2	**4g**	92	238–239 [24]
8	4-$CH_3C_6H_4$	C_6H_5	1.0	**4h**	80	207–09 [9]
9	4-$CH_3OC_6H_4$	C_6H_5	1.5	**4i**	79	208–210 [22]
10	CH_3CH_2	C_6H_5	0.1	**4j**	92	246–248 [7]
11	$CH_3CH_2CH_2$	C_6H_5	0.1	**4k**	95	240–242 [24]
12	C_6H_5	CH_3	0.3	**4l**	95	239–240 [10]
13	3-$NO_2C_6H_4$	CH_3	0.2	**4m**	81	255–257 [7]
14	2-ClC_6H_4	CH_3	0.5	**4n**	92	208–210 [22]
15	4-$CH_3C_6H_4$	CH_3	0.5	**4o**	85	218–220 [25]
16	CH_3CH_2	CH_3	0.3	**4p**	81	179–180 [26]
17	$CH_3CH_2CH_2$	CH_3	0.3	**4q**	97	224–226
18	C_6H_5	NH_2	2.5	**4r**	91	177–179 [4]

[a] Reaction conditions: β-naphthol 10 mmol, aldehyde 10 mmol, amide 11 mmol, $Bi(NO_3)_3{\cdot}5H_2O$ 0.2 mmol, 80 °C.

Table 3
Comparison of $Bi(NO_3)_3{\cdot}5H_2O$ with reported catalysts for synthesis of *N*-(1-(2-hydroxynaphthalen-1-yl)benzyl)benzamide.[a]

Entry	Catalyst	Solvent/temp. (°C)	Catalyst load	Time (h)	Yield (%)	Ref.
1	*p*-TSA	Solvent-free/125	10 mol%	6.0	86	[3]
2	H_2NSO_3H	Solvent-free/28–30	50 mol%	0.4	92	[4]
3	$Al(H_2PO_4)_3$	Solvent-free/125	24 mol%	0.4	91	[5]
4	$Sr(OTf)_2$	$CHCl_3$/reflux	10 mol%	9.0	93	[7]
5	[TEBSA][HSO_4]	Solvent-free/120	5 mol%	0.2	86	[9]
6	$K_5CoW_{12}O_{40}{\cdot}3H_2O$	Solvent-free/125	1 mol%	2.0	80	[10]
7	Indion-130	Solvent-free/110	50 g/mol	0.2	94	[11]
8	Al_2O_3–$HClO_4$	Solvent-free/125	100 g/mol	0.3	90	[12]
9	Montmorillonite K10	Solvent-free/125	100 g/mol	1.5	78	[13]
10	$Bi(NO_3)_3{\cdot}5H_2O$	Solvent-free/80	2 mol%	0.2	96	This work

[a] Reaction conditions: molar ratio of β-naphthol/benzaldehyde/benzamide = 1:1:1.1–1.3.



Scheme 2. Proposed mechanism.

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