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SYNTHESIS OF 1-AMIDOALKYL-2-NAPHTHOLS VIA THREE-COMPONENT CONDENSATION OF 2-NAPHTHOL, ALDEHYDES, AND AMIDES/UREA

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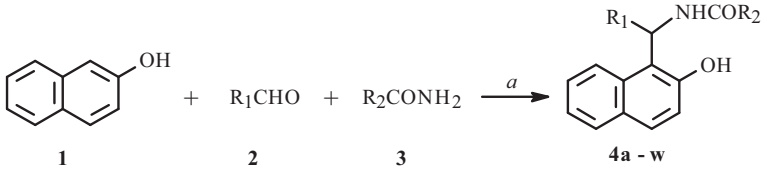
An efficient three-component one-pot synthesis of 1-amidoalkyl-2-naphthols from 2-naphthol, aldehydes, and amides/urea using tin tetrachloride as catalyst at 80°C without solvent is described. The structures of the new compounds were characterized by IR, ^1H NMR, and ^{13}C NMR spectra and by elemental analysis. The advantages of the new method were good yields (45–97%), short reaction times (0.1–4 h), simple work-up, inexpensive catalyst, and the diversity of the method.

Keywords: amidoalkyl naphthols, multicomponent synthesis, tin tetrachloride, solvent-free conditions.

In recent years, multicomponent reactions (MCRs) have gained much attention in organic synthesis as they furnish the desired products in a single operation without isolating the intermediates. Thus, reaction times are reduced and energy and raw materials saved. Therefore, researchers have made great efforts to find and develop new MCRs.

Compounds containing 1,3-amino-oxygenated functional groups are frequently found in biologically active natural products and potent drugs such as nucleoside antibiotics and HIV protease inhibitors [1–3]. Furthermore, 1-amidoalkyl-2-naphthols can be converted to useful and important biological building blocks and to 1-aminomethyl-2-naphthols by an amide hydrolysis reaction, since these compounds exhibit antibacterial, hypotensive, and bradycardiac effects, etc. [4, 5]. 1-Amidoalkyl-2-naphthols can be prepared by three-component condensation of 2-naphthol, aldehydes, and acetonitrile or different amides in the presence of Bronsted or Lewis acids such as *p*-toluene sulfonic acid [6], H_2NSO_3H [7], $Fe(HSO_4)_3$ [8], $Sr(OTf)_2$ [9], I_2 [10], $Al(H_2PO_4)_3$ [11], and other types of catalysts such as heteropoly acid $K_5CoW_{12}O_{40}\cdot 3H_2O$ [12] and HPMo [13], Bronsted acidic ionic liquid [14], and cation-exchange resin catalysts like Indion-130 [15], montmorillonite K10 [16], Al_2O_3–$HClO_4$ [17], and $HClO_4$–SiO_2 [18, 19]. However, some of the reported methods suffer from disadvantages such as prolonged reaction time, low product yields, toxic and corrosive reagents, and the use of additional microwave or ultrasonic irradiation. Therefore, it was of interest to develop a more universal method for the synthesis of these products.



1 **2** **3** **4a - w**

a, l, w: $R_1 = C_6H_5$; **b, m:** $R_1 = 2\text{-}NO_2C_6H_4$; **c, n:** $R_1 = 3\text{-}NO_2C_6H_4$
d, o: $R_1 = 4\text{-}NO_2C_6H_4$; **e, p:** $R_1 = 2\text{-}ClC_6H_4$; **f, q:** $R_1 = 4\text{-}ClC_6H_4$
g, r: $R_1 = 2,4\text{-}Cl_2C_6H_3$; **h, s:** $R_1 = 4\text{-}CH_3C_6H_4$
i, t: $R_1 = 4\text{-}CH_3OC_6H_4$; **j, u:** $R_1 = CH_3CH_2$; **k, v:** $R_1 = CH_3CH_2CH_2$
a – k: $R_2 = C_6H_5$, **l – v:** $R_2 = CH_3$, **w:** $R_2 = NH_2$

a. $SnCl_4\cdot 5H_2O$, 80°C, Neat

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TABLE 1. Effect of Solvent Conditions in the Synthesis of **4** ($SnCl_4 \cdot 5H_2O$[a], 2 h)

Entry	Solvent	Yield, %	Entry	Solvent	Yield, %
1	THF	33	6	CH_3CN	66
2	CH_2Cl_2	38	7	H_2O	71
3	$CH_3COOC_2H_5$	45	8	Cyclohexane	88
4	Toluene	51	9	None*	97
5	EtOH	56			

[a]$SnCl_4 \cdot 5H_2O$ was 2 mol%, the amount of solvent used in entries 1–8 was 3 mL.
*Time reaction was 0.3 h.

TABLE 2. Catalyst Screening in the Reaction for the Synthesis of **4**

Entry	Catalyst*	Time, h	Yield, %	Entry	Catalyst*	Time, h	Yield, %
1	$ZnCl_2$	2	5	6	$La(CH_3SO_3)_3 \cdot 2H_2O$	1.5	67
2	$MnSO_4 \cdot H_2O$	2	14	7	$KAl(SO_4)_2 \cdot 12H_2O$	1	84
3	$FeSO_4(NH_4)_2SO_4 \cdot 6H_2O$	2	42	8	$SnCl_4 \cdot 5H_2O$	0.3	97
4	$SrCl_2 \cdot 6H_2O$	1.5	45	9	$SnCl_4 \cdot 5H_2O$**	0.3	91
5	$Pr(CH_3SO_3)_3 \cdot 2H_2O$	1.5	55				

*Amount of catalyst was 2 mol%; ** amount of catalyst, 1 mol%.

Recently, tin tetrachloride has emerged as an efficient Lewis acid in promoting various organic transformations, such as aromatization [20], heterocycloadditions [21], coupling reactions [22], rearrangement of epoxides [23], oxidation [24], and ring opening reactions [25]. The versatility of this reagent encourages us to study its utility for the three-component amidoalkylation reaction. To our knowledge, amidoalkylation of arenes and the extension of Mannich-type reactions catalyzed by $SnCl_4 \cdot 5H_2O$ have not been reported. In this communication, we report a facile and efficient synthetic strategy for preparing 1-amidoalkyl-2-naphthols **4** from 2-naphthol (**1**), aldehydes **2**, and amides/urea **3** at short reaction times and with excellent yields using $SnCl_4 \cdot 5H_2O$ as a catalyst.

At the onset of the research, we investigated the model reaction of 2-naphthol, benzaldehyde, and benzamide in different reaction media at 80°C. The results are summarized in Table 1. After screening a variety of reaction media, solvent-free conditions were determined to be the best. Compared with reactions carried out in organic solvent, condensation without solvent required only 0.3 h to furnish excellent yields (Table 1, entry 9). Indeed in many cases, solid organic reactions occur efficiently and more selectively than those of their solution counterparts [8, 18, 19]. Moreover, solvent-free conditions for organic transformations offer several environmental benefits. So for the synthesis of our target compounds, solvent-free conditions were selected.

Next, the catalytic activity of several Lewis acids was compared with $SnCl_4 \cdot 5H_2O$ in the same model reaction at 80°C; the results are shown in Table 2. After several trials, it could be noted that $SnCl_4 \cdot 5H_2O$ was the most efficient catalyst for this transformation, since it results in the highest conversion to the desired product in the shortest reaction time (Table 2, entry 8). It should be mentioned that 2 mol% of $SnCl_4 \cdot 5H_2O$ was suitable to catalyze the reaction, and reducing the amount of catalyst would decrease the yields to a certain extent (Table 2, entry 9).

In order to evaluate the generality of the process, several examples illustrating the present method for the synthesis of 1-amidoalkyl-2-naphthols **4** were studied (Table 3). The reactions of 2-naphthol with various aromatic or aliphatic aldehydes and amides or urea were carried out in the presence of $SnCl_4 \cdot 5H_2O$ at 80°C. In all the reactions, good to excellent yields were obtained at short reaction times (0.1–4 h). Clean and complete conversions leading to the corresponding amidoalkyl naphthols were observed. No side products such as dibenzoxanthenes were formed, which are normally observed under the influence of strong acids. Aromatic aldehydes carrying either electron-withdrawing (nitro) or electron-donating (halide, alkyl, alkoxyl) groups were all suitable for the reactions. It is worth mentioning that the yields of products from aliphatic aldehydes were as high as those of products from aromatic aldehydes, whereas the reactions of aliphatic aldehydes in most of the reported literature were sluggish and no desired products were isolated [6, 7, 11–13, 15, 17]. On the other hand, the scope of different amide components was studied. Both amides (benzamide and acetamide) and urea participated well in the reactions. As compared to the amides, urea afforded the corresponding amidoalkyl naphthol at longer reaction times (Table 3, entry 23).

TABLE 3. Preparation of 1-Amidoalkyl-2-naphthols Catalyzed by $SnCl_4 \cdot 5H_2O$

Product	Time, h	Yield, %	Mp (°C) [ref.]	Product	Time, h	Yield, %	Mp (°C) [ref.]
4a	0.3	97	236–238 [14]	**4m**	0.2	81	218–220 [26]
4b	0.2	93	261–263 [26]	**4n**	0.2	78	253–255 [9]
4c	0.2	96	233–235 [14]	**4o**	0.3	84	245–247 [11]
4d	0.2	82	237–239 [27]	**4p**	1	68	208–210 [26]
4e	0.2	92	266–268	**4q**	1	63	236–238 [26]
4f	0.3	85	187–189 [9]	**4r**	1.2	75	226–228 [28]
4g	0.15	95	238–239	**4s**	1	87	217–219 [8]
4h	0.4	90	207–209 [14]	**4t**	4	45	185–187 [8]
4i	0.8	70	208–210 [26]	**4u**	1	69	176–178 [29]
4j	0.1	90	246–248 [9]	**4v**	0.1	92	221–223
4k	0.1	93	240–242	**4w**	4	85	178–180 [7]
4l	0.3	91	241–243 [12]				

In conclusion, a very simple and efficient method for the synthesis of 1-amidoalkyl-2-naphthol derivatives has been developed. Several derivatives of the title compounds with different substituents were synthesized, which shows the diversity of the method. The catalyst showed good efficiency for this transformation under solvent-free conditions at 80°C. Work-up procedure was simple, which only includes washing the mixture with H_2O–EtOH and recrystallization from EtOH. Therefore, we believe this method could be an attractive alternative to existing methods for the synthesis of 1-amidoalkyl-2-naphthols.

EXPERIMENTAL

General Methods. Melting points were determined using an RY-1 micromelting point apparatus. Infrared spectra were recorded on a Scimitar 2000 series Fourier transform instrument (Varian). ^{1}H NMR spectra were recorded on a Bruker AV-500 spectrometer in DMSO-d_6 using TMS as an internal standard. ^{13}C NMR spectra were performed on a Bruker AV-500 spectrometer at 125 MHz in DMSO-d_6 using TMS as an internal standard. Elemental analyses were carried out on EA 2400II elemental analyzer (Perkin–Elmer) and agreed favorably with the calculated values.

General Procedure for the Synthesis of 1-Amidoalkyl-2-naphthols. To a mixture of 2-naphthol (10 mmol), an aldehyde (10 mmol), and an amide (11 mmol), $SnCl_4 \cdot 5H_2O$ (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 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 authentic samples and with spectral data for some representative compounds.

***N*-((2-Chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl)benzamide (4e)**. White solid. IR spectrum (KBr, ν, cm^{-1}): 3426, 3067, 1632, 1573, 1538, 1346, 1075, 822, 753, 711. ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 9.90 (1H, s, OH), 8.98 (1H, d, J = 6.2, NH), 8.08 (1H, d, J = 8.6, ArH), 7.89 (2H, d, J = 7.3, ArH), 7.82 (1H, d, J = 7.7, ArH), 7.78 (1H, d, J = 8.8, ArH), 7.52 (1H, t, J = 7.3, ArH), 7.44–7.40 (5H, m, ArH), 7.36 (1H, d, J = 5.0, CH), 7.30–7.22 (3H, m, ArH), 7.19 (1H, d, J = 8.8, ArH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ): 165.3, 153.6, 138.7, 134.2, 132.9, 132.7, 131.1, 130.1, 129.4, 128.6, 128.5, 128.3, 128.1, 127.4, 126.6, 126.3, 122.8, 122.3, 118.6, 116.8, 48.6. $C_{24}H_{18}NO_2Cl$ (387.8).

***N*-((2,4-Dichlorophenyl)(2-hydroxynaphthalen-1-yl) methyl)benzamide (4g)**. White solid. IR spectrum (KBr, ν, cm^{-1}): 3423, 3069, 1633, 1574, 1537, 1344, 1074, 819, 749, 709. ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 9.96 (1H, s, OH), 9.17 (1H, d, J = 6.3, NH), 8.05 (1H, d, J = 8.6, ArH), 7.89 (2H, d, J = 7.2, ArH), 7.82 (1H, d, J = 7.5, ArH), 7.78 (1H, d, J = 8.8, ArH), 7.57 (1H, d, J = 2.1, ArH), 7.52–7.42 (5H, m, ArH), 7.37 (1H, dd, J = 2.1, 6.3, CH), 7.30–7.27 (2H, m, ArH), 7.18 (1H, d, J = 8.8, ArH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ): 165.5, 153.7, 138.2, 134.1, 133.6, 132.7, 132.1, 131.4, 131.2, 129.6, 128.6, 128.3, 128.1, 127.5, 126.7, 126.5, 122.6, 122.3, 118.6, 116.1, 48.3. $C_{24}H_{17}NO_2Cl_2$ (422.3).

***N*-(1-(2-Hydroxynaphthalen-1-yl)butyl)benzamide (4k)**. White solid. IR spectrum (KBr, ν, cm^{-1}): 3415, 3221, 3204, 1633, 1575, 1529, 1342, 1075, 815, 747, 715. ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 10.08 (1H, s, OH), 8.60 (1H, d, J = 6.3, NH), 8.23 (1H, d, J = 7.6, ArH), 7.81 (3H, t, J = 7.2, ArH), 7.70 (1H, d, J = 8.8, ArH), 7.53–7.44 (4H, m, ArH), 7.31 (1H, t, J = 7.3, ArH), 7.20 (1H, d, J = 8.8 ArH), 6.04 (1H, q, J = 7.1, CH), 2.19–2.11 (1H, m, CH_2), 1.92–1.85 (1H,

m, CH_2), 1.51–1.41 (1H, m, CH_2), 1.33–1.23 (1H, m, CH_2), 0.93 (3H, t, J = 7.3, CH_3). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ): 165.2, 152.8, 134.7, 132.0, 131.0, 128.5, 128.4, 128.3, 128.2, 126.9, 126.2, 122.3, 119.8, 118.6, 118.5, 46.6, 36.0, 19.6, 13.8. $C_{21}H_{21}NO_2$ (319.4).

***N*-(1-(2-Hydroxynaphthalen-1-yl)butyl)acetamide (4v)**. White solid. IR spectrum (KBr, ν, cm^{-1}): 3409, 3220, 2956, 1642, 1583, 1531, 1515, 1337, 1076, 815, 749, 705. ^1H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 9.86 (1H, s, OH), 8.14 (1H, d, J = 8.6, NH), 8.02 (1H, s, ArH), 7.77 (1H, d, J = 7.7, ArH), 7.68 (1H, d, J = 8.8, ArH), 7.46 (1H, t, J = 7.2, ArH), 7.28 (1H, t, J = 7.4, ArH), 7.18 (1H, d, J = 8.8, ArH), 5.83 (1H, q, J = 7.6, CH), 2.05–1.97 (1H, m, CH_2), 1.88–1.80 (4H, m, CH_2 and CH_3), 1.40–1.30 (1H, m, CH_2), 1.22–1.13 (1H, m, CH_2), 0.88 (3H, t, J = 7.4, CH_3). ^{13}C NMR spectrum (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; $C_{16}H_{19}NO_2$ (257.3).

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