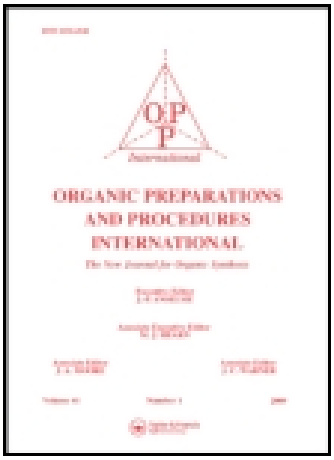

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One-pot Synthesis of 1-Amidoalkyl-2-naphthols from 2-Naphthol, Aldehydes, and Amides under Solvent-free Conditions

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Amidoalkylnaphthols are important precursors for the synthesis of 1,3-amino oxygenated compounds frequently found in biologically important natural products and potent drugs including a number of nucleoside antibiotics and HIV protease inhibitors.[1–3] Furthermore, 1-amidoalkyl-2-naphthols have been reported to show cardiovascular activity.[4] To the best of our knowledge, there have been reports on the synthesis of amidoalkylnaphthols catalyzed by *p*-toluenesulfonic acid,[5] H_2NSO_3H,[6] $Fe(HSO_4)_3$,[7] $Sr(OTf)_2$,[8] I_2,[9] $Al(H_2PO_4)_3$,[10] heteropoly acid $K_5CoW_{12}O_{40}\cdot 3H_2O$,[11] Brønsted acidic ionic liquid,[12] and heterogeneous catalysts like Indion-130,[13] montmorillonite K10,[14] Al_2O_3-SO_3H,[15] and Al_2O_3-$HClO_4$[16] *via* a one-pot MCR.[17,18] However, some of the reported methods suffer from disadvantages such as long reaction times, toxic and corrosive solvent, high reaction temperature ($>100^\circ$C), and the need to use microwave or ultrasonic irradiation in some cases. Therefore, it seemed desirable to develop greener and milder methods for the synthesis of amidoalkylnaphthols. During the course of our study on Lewis acid–catalyzed organic reactions, we found stannous chloride to be an inexpensive and commercially available catalyst to efficiently catalyze the one-pot three-component Mannich-type reaction[19] and now report a one-pot MCR of 2-naphthol (**1**), aldehydes (**2**) and primary amides (**3**) in the presence of 2 mol% $SnCl_2\cdot 2H_2O$ at 80°C without solvent (*Scheme 1*).

Most products were formed within short reaction times and in excellent yields. The results showed that $SnCl_2\cdot 2H_2O$ is an excellent catalyst for this conversion. Compared with the reported procedure employing $Sr(OTf)_2$ as a catalyst,[8] the new protocol has many advantages such as use of small amounts of catalyst, and of no toxic solvent. Although *Table 1* shows that the scope of the reaction is wide, no product was obtained with urea and thiourea as a reaction partner. A possible mechanism for this transformation involves the initial condensation of 2-naphthol with the aldehyde catalyzed by $SnCl_2\cdot 2H_2O$ to generate an

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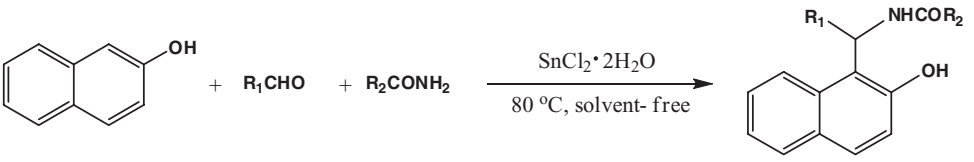

1 **2** **3** **4a-4v**

Scheme 1

ortho-methylidenequinone (*o*-MQ) intermediate,[5,20] this would then followed by Michael addition of the amide to *o*-MQ generated *in situ* to give the desired amidoalkylnaphthols **4**.

In conclusion, the mild and solvent-free conditions, short reaction times (0.2–7 h), excellent yields (except for *p*-anisaldehyde), inexpensive, non-toxic, and commercially available catalyst, and simple work-up make this procedure a useful process for the synthesis of a variety of amidoalkylnaphthols.

Table 1
Preparation of Amidoalkylnaphthols Catalyzed by $SnCl_2{\cdot}2H_2O$

Product	R_1	R_2	Time (h)	Yield (%)	mp (°C)	lit. (°C)
4a	C_6H_5	C_6H_5	0.3	96	236–238	233–235[16]
4b	2-$NO_2C_6H_4$	C_6H_5	1	94	262–264	266–267[20]
4c	3-$NO_2C_6H_4$	C_6H_5	1	93	234–236	233–235[12]
4d	4-$NO_2C_6H_4$	C_6H_5	1	86	238–240	239–241[21]
4e	2-ClC_6H_4	C_6H_5	0.2	94	266–268	—
4f	4-ClC_6H_4	C_6H_5	1	93	185–186	187–188[8]
4g	2,4-$Cl_2C_6H_3$	C_6H_5	0.5	91	237–239	—
4h	4-$CH_3C_6H_4$	C_6H_5	2	92	208–210	209–211[12]
4i	4-$CH_3OC_6H_4$	C_6H_5	2	66	205–208	206–208[20]
4j	CH_3CH_2	C_6H_5	0.3	85	244–246	244–245[8]
4k	$CH_3CH_2CH_2$	C_6H_5	0.2	90	239–241	—
4l	C_6H_5	CH_3	3	83	243–245	241–243[11]
4m	2-$NO_2C_6H_4$	CH_3	1	82	218–220	218–219[20]
4n	3-$NO_2C_6H_4$	CH_3	1.5	89	256–258	255–256[8]
4o	4-$NO_2C_6H_4$	CH_3	1	85	244–246	245–246[10]
4p	2-ClC_6H_4	CH_3	1	83	204–206	206–207[20]
4q	4-ClC_6H_4	CH_3	1.5	88	235–237	237–238[20]
4r	2,4-$Cl_2C_6H_3$	CH_3	1.5	84	227–229	225–228[22]
4s	4-$CH_3C_6H_4$	CH_3	2	77	219–220	222–223[7]
4t	4-$CH_3OC_6H_4$	CH_3	7	30	185–187	183–185[7]
4u	CH_3CH_2	CH_3	1.5	80	176–179	173–175[23]
4v	$CH_3CH_2CH_2$	CH_3	1	77	224–226	—

Experimental Section

Melting points were determined using an RY-1 micromelting point apparatus. Infrared spectra were recorded on a Scimitar 2000 series Fourier Transform instrument from VARIAN. ^{1}H NMR spectra were obtained 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 an EA 2400II elemental analyzer (Perkin Elmer).

General Procedure

To a mixture of 2-naphthol (1.44 g, 10 mmol), the aldehyde (10 mmol) and the amide (11 mol) with a stir bar was added $SnCl_2{\cdot}2H_2O$ (0.2 mmol), the reaction mixture was stirred on a pre-heated water bath at 80°C. After completion of the reaction (monitored by TLC, v(ethyl acetate)/v(petroleum ether) = 1/3), the reaction mixture was cooled to R.T., where upon it solidified. The solid mixture was tritwashed with 15 mL H_2O/EtOH (v/v = 1/1), and the collected solid was recrystallized from EtOH. The products were characterized by comparison of their mp, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis with those reported for the authentic samples. Combustion analysis and spectral data for new compounds are given below:

N-[(2-Chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl]benzamide (4e), white solid, IR (KBr): 3426, 3067, 1633 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.92 (s, 1H, OH), 9.01 (d, J = 6.2 Hz, 1H, NH), 8.08 (d, J = 8.6 Hz, 1H, ArH), 7.89 (d, J = 7.3 Hz, 2H, ArH), 7.82 (d, J = 7.5 Hz, 1H, ArH), 7.78 (d, J = 8.8 Hz, 1H, ArH), 7.52 (t, J = 7.3 Hz, 1H, ArH), 7.44-7.40 (m, 5H, ArH), 7.36 (d, J = 5.0 Hz, 1H, CH), 7.30-7.22 (m, 3H, ArH), 7.19 (d, J = 8.8 Hz, 1H, CH); ^{13}C NMR (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.

Anal. Calcd. for $C_{24}H_{18}ClNO_2$: C, 74.32; H, 4.68; N, 3.61. Found: C, 74.25; H, 4.61; N, 3.67.

N-[(2,4-Dichlorophenyl)(2-hydroxynaphthalen-1-yl)methyl]benzamide (4g), white solid, IR (KBr): 3423, 3069, 1634 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.97 (s, 1H, OH), 9.18 (d, J = 6.3 Hz, 1H, NH), 8.05 (d, J = 8.6 Hz, 1H, ArH), 7.89 (d, J = 7.2 Hz, 2H, ArH), 7.82 (d, J = 7.4 Hz, 1H, ArH), 7.78 (d, J = 8.8 Hz, 1H, ArH), 7.57 (d, J = 2.1 Hz, 1H, ArH), 7.52-7.42 (m, 5H, ArH), 7.37 (dd, J = 2.1, 6.3 Hz, 1H, CH), 7.30-7.27 (m, 2H, ArH), 7.18 (d, J = 8.8 Hz, 1H, ArH); ^{13}C NMR (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.

Anal. Calcd. for $C_{24}H_{17}Cl_2NO_2$: C, 68.26; H, 4.06; N, 3.32. Found: C, 68.35; H, 4.02; N, 3.28.

N-[1-(2-Hydroxynaphthalen-1-yl)butyl]benzamide (4k), white solid. IR (KBr): 3416, 3222, 3204, 1632 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.08 (s, 1H, OH), 8.60 (d, J = 6.3 Hz, 1H, NH), 8.22 (d, J = 7.6 Hz, 1H, ArH), 7.81 (t, J = 7.2 Hz, 3H, ArH), 7.71 (d, J = 8.8 Hz, 1H, ArH), 7.53-7.44 (m, 4H, ArH), 7.31 (t, J = 7.3 Hz, 1H, ArH), 7.20 (d, J = 8.8 Hz, 1H, ArH), 6.04 (q, J = 7.1 Hz, 1H, CH), 2.19-2.11 (m, 1H, CH_2), 1.92-1.85 (m, 1H, CH_2), 1.51-1.41 (m, 1H, CH_2), 1.33-1.23 (m, 1H, CH_2), 0.93 (t, J = 7.3 Hz, 3H,

CH_3); ^{13}C NMR (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.

Anal. Calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.87; H, 6.58; N, 4.43.

N-[1-(2-Hydroxynaphthalen-1-yl)butyl]acetamide (4v), white solid. IR (KBr): 3409, 3220, 2956, 1642 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 9.86 (s, 1H, OH), 8.13 (d, $J = 8.6$ Hz, 1H, NH), 8.02 (s, 1H, ArH), 7.77 (d, $J = 7.7$ Hz, 1H, ArH), 7.68 (d, $J = 8.8$ Hz, 1H, ArH), 7.46 (t, $J = 7.2$ Hz, 1H, ArH), 7.28 (t, $J = 7.3$ Hz, 1H, ArH), 7.18 (d, $J = 8.8$ Hz, 1H, ArH), 5.82 (q, $J = 7.6$ Hz, 1H, 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, $J =$ 7.4 Hz, 3H, 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, 74.77; H, 7.38; N, 5.36.

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