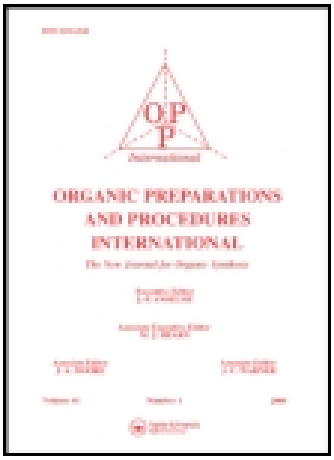

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One-pot Solvent-free Sonochemical Synthesis of 1-Amidoalkyl-2-naphthols

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In recent years, organic synthesis involving greener processes, including solvent-free conditions, has been explored due to stringent environmental and economic regulations.[1] Homogeneous, liquid acid catalysts, such as H_2SO_4, HCl and complexes of BF_3 are inherently associated with problems such as high toxicity, corrosion, catalyst waste, difficulty in separation and recovery. Replacement of these conventional acids by solid catalysts is desirable to achieve effective catalyst handling and product purification.

Multicomponent reactions (MCRs) have elicited increased interest since they are performed without the need to isolate any intermediate, thus reducing time and saving energy and raw materials.[2] One of these MCRs is the synthesis of amidoalkyl naphthols, which are ubiquitous to a variety of biologically important natural products and potent drugs, including a number of nucleoside antibiotics and HIV protease inhibitor, such as *ritonavir* and *lipinavir*.[3,4] Furthermore, amidoalkyl naphathols can be converted to useful synthetic building blocks for drugs exhibiting depressor and bradycardiac activities.[5,6] The preparation of amidoalkyl naphthols **(1)** can be carried out by the condensation of aromatic aldehydes, 2-naphthol and urea or amides in the presence of Lewis or Brønsted acid catalysts such as montmorillonite K10 clay,[7] $HClO_4$-SiO_2,[8] iodine,[9] $K_5CoW_{12}O_{40}{\cdot}3H_2O$,[10] *p*-TSA,[11] sulfamic acid,[12] cation-exchange resins[13] and ionic liquids.[14,15] One of the major drawbacks of these reactions is that in some cases when a solid aldehyde or high amounts of catalyst is used, an organic solvent such as dichloroethane is needed. Many of the reported methods suffer from long reaction times, poor yields, and harsh reaction conditions. These shortcomings suggest that a safe, eco–friendly and efficient method be devised.

Ultrasound-assisted organic synthesis (UAOS) is a powerful and green approach[16,17] which is increasingly used to accelerate the rates and improve the yields of reactions.[18–23] In continuation of our work on the study of new catalysts[24–27] for organic functional group transformations, we now report a general, efficient and eco-friendly solvent-free procedure

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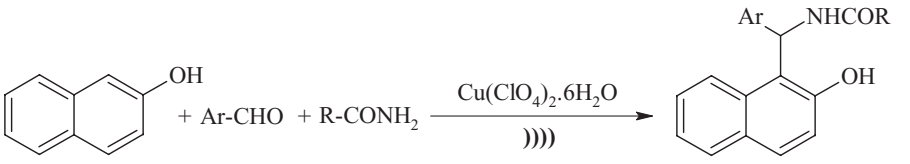

(1a-l)

a) R = CH_3 , Ar = C_6H_5 b) R = CH_3 , Ar = 3-$NO_2C_6H_4$ c) R = CH_3 , Ar = 4-FC_6H_4

d) R = CH_3 , Ar = 4-ClC_6H_4 e) R = CH_3 , Ar = 3-BrC_6H_4 f) R = CH_3 , Ar = 2-$NO_2C_6H_4$

g) R = NH_2 , Ar = C_6H_5 h) R = NH_2 , Ar = 3-$NO_2C_6H_4$ i) R = NH_2 , Ar = 4-ClC_6H_4

j) R = C_6H_5 , Ar = 4-FC_6H_4 k) R = C_6H_5 , Ar = 4-ClC_6H_4 l) R = C_6H_5 , Ar = C_6H_5

Scheme 1

for the synthesis of 1-amidoalkyl-2-naphthols **(1a-l)** by condensation of 2-naphthol, urea/amides and aromatic aldehydes catalyzed by 20 mole% of copper perchlorate hexahydrate at 35 kHz under ultrasonic irradiation (*Scheme 1*).

In initial experimentations to determine the optimum amount of catalyst, 2-naphthol was first treated with benzaldehyde and urea for 30 minutes under ultrasound irradiation in presence of varying mol% of copper perchlorate hexahydrate. The best results were obtained using 20 mol% of catalyst. Using lower amounts of catalyst resulted in lower yields, while higher amounts of catalyst did not affect reaction time and yield. In absence of the catalyst, the yield was very low. To verify the effect of ultrasound irradiation, the synthesis of **1g** was performed with and without ultrasound irradiation; in this case, the use of ultrasound irradiation led to a faster reaction and higher yield. However, in terms of the scope of the reaction, yields were very poor with aliphatic aldehydes, phenols and 1-naphthols. Only 2-naphthol was used as reactant as 1-amidoalkyl-2-naphthols can be converted to important drug like 1-aminomethyl-2-naphthols derivatives by amide hydrolysis reaction. Unlike previously reported methods, the present procedure does not require toxic organic solvents. A wide range of aromatic aldehydes were used and gave excellent yields of 1-amidoalkyl-2-naphthols. All the products were characterized by elemental analysis, NMR and by comparison of melting points with authentic samples (*Table 1*).

Experimental Section

All mps are uncorrected and were determined in open capillaries. ^{1}H NMR spectra were measured on a AL-300F (Bruker) FT NMR spectrophotometer using tetramethylsilane (TMS) as internal standard. Sonication was performed using an ELMA Transsonic T 310/H Ultrasonic cleaner with a frequency of 35 KHz (Hans Schmidbauer GmbH & Co., Germany). Copper perchlorate hexahydrate was prepared by a standard procedure[28] and perchlorates are safe and stable under ordinary conditions of use and storage, but their contact with heat and reducing agents must be avoided as Lithium and magnesium perchlorates are dangerous if heated over their decomposition temperatures (300–500°C).[29]

Table 1
Yields, mps and ^{1}H NMR Spectral Data of **1a-l**

Cmpd	Yield (%)	mp.(°C) (lit. mp.)	Time (min.)	^{1}H NMR[a] (δ)
1a	90	229–231 (229–230)[12]	30	9.98 (1H, s, OH), 8.44 (1H, d, J = 8.4 Hz, NH), 7.84–7.75 (3H, m, ArH), 7.36 (1H, t, J = 7.6 Hz, ArH), 7.27–7.20 (4H, m, ArH), 7.17–7.12 (4H, m, ArH), 1.98 (3H, s, CH_3)
1b	88	236–238 (236–237) [12]	80	10.13 (1H, s, OH), 8.63 (1H, d, J = 8.0 Hz, NH), 8.06–8.01 (2H, m, ArH), 7.88–7.80 (3H, m, ArH), 7.59–7.53 (2H, m, ArH), 7.42 (1H, t, J = 7.6 Hz, ArH), 7.30 (1H, t, J = 7.6 Hz, ArH), 7.23–7.17 (2H, m, ArH), 2.02 (3H, s, CH_3).
1c	86	203–204 (203–205) [12]	30	9.62 (1H, s), 8.05 (1H, d, j = 6Hz), 7.77–7.41 (3H, m), 7.32–6.86 (7H,m), 2.07 (3H, s).
1d	89	233–234 (232–233) [12]	75	9.68 (1H, brs), 8.12–7.98 (2H, m), 7.78–7.59 (2H, m), 7.30 (1H, m), 7.28–7.06 (7H, m), 2.02 (3H, s).
1e	90	245–247 (250–252)[30]	60	1.97 (s, 3H), 7.08 (d, J = 7.2 Hz, 1H), 7.19 (t, J = 7.2 Hz, 2H), 7.26 (t, J = 7.6 Hz, 1H), 7.31–7.40 (m, 4H), 7.76–7.81 (m, 3H), 8.59 (d, J = 8.4 Hz, 1H), 10.00 (s, 1H).
1f	88	211–213 (210–212)[30]	75	10.02 (1H, s, OH), 8.51 (1H, d, J = 8.0 Hz, NH), 8.10–8.00 (2H, m, ArH), 7.80–7.74 (2H, m, ArH), 7.59–7.53 (3H, m, ArH), 7.30–7.15 (3H, t, ArH), 2.02 (3H, s, CH_3)
1g	90	173–174 (172–174)[12]	35	9.97 (1H, s, OH), 7.83–7.75 (3H, m, ArH), 7.40 (1H, s, NH), 7.29–7.11 (7H, m, ArH), 6.94 (2H, s), 5.86 (2H, s, NH_2).
1h	85	184–185 (184–186)[12]	40	10.13 (1H, s, OH), 8.09–7.99 (2H, m), 7.87–7.46 (7H, m), 7.33–7.21 (2H, m), 7.12 (1H, d, J = 8.4 Hz), 7.06–6.99 (1H, m), 5.96 (1H, s).
1i	90	169–170 (168–169)[12]	60	10.00 (1H, s, OH), 7.83–7.76 (3H, m, ArH), 7.43 (1H, s, NH), 7.31–7.14 (6H, m, ArH), 6.90 (2H, s), 5.86 (2H, s, NH_2).
1j	86	198–199 (193–194)[12]	55	10.37(1H, s, OH), 9.35 (1H, d, J = 9 Hz, NH), 8.08-7.06 (16H, m, ArH).
1k	84	178–180 (177–178)[12]	75	10.36 (1H, s, OH), 9.02 (1H, d, J = 8.5 Hz, NH), 8.06 (1H, d, J = 8.5 Hz, ArH), 7.88–7.80 (4H, m, ArH), 7.57–7.45 (4H, m, ArH), 7.35–7.23 (7H, m, ArH).
1l	89	235–236 (234–236)[12]	45	10.34 (1H, s, OH), 9.03 (1H, d, J = 8.4 Hz, NH), 8.09 (1H, d, J = 8.8 Hz, ArH), 7.88–7.79 (4H, m, ArH), 7.57–7.45 (4H, m, ArH), 7.33–7.19 (8H, m, ArH).

a) in DMSO –d_6.

Typical Procedure

To a mixture of 2-naphthol (0.144 g; 1 mmol), benzaldehyde (0.106 g; 1 mmol) and urea (0.066 g; 1.1 mmol) was added copper perchlorate hexahydrate (0.287 g; 20 mol%) in a 50 mL beaker and the reaction mixture was subjected to ultrasound irradiation at room temperature for 30–80 min. The progress of reaction was followed by TLC (silica gel using methanol: chloroform (1 : 9) as solvent). After completion of the reaction, the reaction mixture was quenched by addition of water (15–20 mL) and stirred for 5 min to dissolve the copper perchlorate. The insoluble solid was collected and recrystallized from ethanol to afford the pure product **(1a-l).**

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