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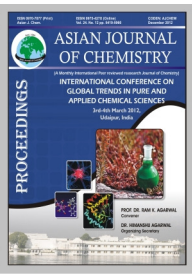

Microwave Assisted Synthesis of 1-Amidoalkyl-2-naphthols Catalyzed by Anhydrous Zinc Chloride†

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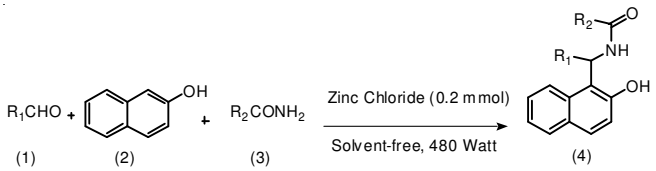
A new, facile and cost-effect process involving the solvent-free synthesis of amidoalkyl naphthols using a three-component, one-pot condensation reaction of β-naphthol, aromatic aldehyde and amides in the presence of anhydrous zinc chloride as heterogeneous catalyst under microwave irradiation has been described. The results obtained clearly showed that the catalyst was recyclable and highly efficient.

Key Words: 1-Amidoalkyl-2-naphthols, One-pot synthesis, Anhydrous Zinc chloride.

INTRODUCTION

One-pot multicomponent reactions by virtue of their convergence, productivity, facile execution and high yield have attracted considerable attention in recent years. Multicomponent reactions involve three or more compounds reacting in a single operation without isolating the intermediates. 1-Amidoalkyl-2-naphthol derivatives are of importance because they can be easily converted to the important biologically active compounds, 1-aminoalkyl-2-naphthols, by amide hydrolysis reaction. The hypotensive and bradycardiac properties have been reported for this class of compounds[1,2]. 1-Amidoalkyl-2-naphthols can be also converted to 1,3-oxazine derivatives[3] which have potentially different biological activities including antibiotic[4], antitumor[5], analgesic[6], anticonvulsant[7], antipsychotic[8], antimalarial[9], antianginal[10], antihypertensive[11] and antirheumatic properties[12]. The preparation of 1-amidoalkyl-2-naphthols can be carried out by multi-component condensation of aryl aldehydes, 2-naphthol and amide derivatives in the presence of Lewis or Bronsted acid catalysts such as $Ce(SO_4)_2$[13], montmorillonite K10[14], iodine[15], cation-exchanged resins[16], $NaHSO_4.H_2O$[17], $Fe(HSO_4)_3$[18], sulfamic acid/ultrasound[19], $HClO_4/SiO_2$[20], cyanuric chloride[21] and $K_5CoW_{12}O_{40}\cdot 3H_2O$[22]. However, some of these catalysts suffer from the drawback of green chemistry such as prolonged reaction times, low yields, toxicity and recovery and reusability of the catalyst. Therefore, introducing clean processes and utilizing eco-friendly and green catalysts, which can be simply recycled at the end of reactions, have been under permanent attention. The demand for environmentally benign procedure with heterogeneous and reusable catalysts promoted us to develop a safe alternate method for the synthesis of amidoalkyl naphthols. Zinc chloride is a Lewis acid and therefore electrophilic in character. Zinc chloride is particularly effective in catalyzing reactions that eliminate molecules of water, ammonia or mercaptans. It absorbs readily on charcoal or silica for catalyzing acylations and alkylations by Friedel-Crafts synthesis. In esterifications and condensation reactions, it facilitates the elimination of water or ammonia molecules from the reactants.



Scheme-I

EXPERIMENTAL

All compounds were identified by comparison of their spectral data and physical properties with those of the authentic samples. All chemicals were purchased from commercial suppliers. The melting points were determined on Veego-programmable melting point apparatus (microprocessor based) and are uncorrected. Proton (^1H) nuclear magnetic resonance spectra were obtained using Brucker AC-400 F, 400 MHz spectrometer and are reported in parts per million (ppm), downfield from tetramethylsilane as internal standard. Infrared spectra were obtained with Perkin Elmer 882 spectrum and RXI, FT-IR model using potassium bromide pellets (cm^{-1}). Elemental analyses for C, H and N were performed on Perkin-Elmer 2400

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CHN elemental analyzer. Reactions were monitored and the homogeneity of the products was checked by TLC which were prepared with silica gel G and activated at 110 ºC for 0.5 h. The plates were developed by exposure to iodine vapours. Anhydrous sodium sulphate was used as drying agent.

Synthesis of amidoalkyl naphthols: To a mixture of aromatic aldehyde (1 mmol), 2-naphthol (1 mmol), amide/urea (1.2 mmol) and zinc chloride (0.2 mmol, 20 mol %) as catalyst was irradiated in microwave oven (LG model MS1927C) at 480 w for the appropriate time (10-15 min). After completion of the reaction, the reaction mixture was cooled and ethyl acetate was added to it. The resulting solution was filtered off to separate catalyst. The filtrate was washed with aqueous $Na_2S_2O_3$. The organic layer was dried on anhydrous Na_2SO_4, which was concentrated to get the required product. The products were further recrystallized from ethanol.

Spectral data

***N*-[(2-Hydroxynaphthalen-1-yl)-phenyl-methyl)]urea (4a):** Light brown solid, m.p. 171-173 ºC; IR (KBr, ν_{max}, cm^{-1}): 3320, 3067, 3026, 1695, 1594, 1337, 1077, 831, 745; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.76 (s, 1H, -CONH), 7.21-7.89 (m, 11H, ArH), 6.09 (bs, 1H, -OH), 5.62 (s, 2H); Anal. calcd. for $C_{18}H_{16}N_2O_2$: C 73.95, H 5.52, N 9.58 %; Found C 73.90, H 5.49, N 9.59 %.

***N*-[(2-Hydroxynaphthalen-1-yl)-phenyl-methyl]-acetamide(4b):** Light yellow solid, m.p. 242-245 ºC; IR (KBr, ν_{max}, cm^{-1}): 3420, 3061, 3021, 1629, 1538, 1254, 1076, 822, 759; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.85 (s, 1H, -CONH), 8.29 (bs,1H, -OH), 7.9 (s, 1H), 7.75 (d, 1H), 7.60 (d, 1H), 7.30 (t, 1H), 7.12-7.99 (m, 8H, ArH), 2.04 (s, 3H, $-CH_3$); Calcd. for $C_{19}H_{17}NO_2$: C 78.33, H 5.87, N 4.81 %; Found C 77.47, H 5.79, N 4.76 %.

N-[(2-Hydroxynaphthalen-1-yl)-phenyl-methyl)]-benzamide (4c): Light brown solid, m.p. 235-237 ºC; IR (KBr, ν_{max}, cm^{-1}): 3420, 3061, 1802, 1629, 1538, 1347, 1026, 825, 750; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.1 (bs, 1H, -CONH), 8.91 (bs, 1H, -OH), 7.38-7.87 (m, 16H, ArH); Anal. calcd. for $C_{24}H_{19}NO_2$: C 81.56, H5.42, N 3.96 %; C 81.49, H 5.38, N 3.89 %.

***N*-[(4-Chlorophenyl)-(2-hydroxy-naphthalen-1-yl)-methyl)]urea (4d):** Light yellow solid, m.p. 168-170 ºC; IR (KBr, ν_{max}, cm^{-1}): 3450, 3321, 3076, 3022, 1694, 1592,1515, 1337, 1222, 831; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.75 (s,1H, -CONH), 7.27-7.89 (m, 10H, ArH),), 6.09 (bs, 2H); Anal. calcd. for $C_{18}H_{15}N_2O_2Cl$: C 66.16, H4.63, N 8.57 %; Found: C 66.20, H 4.57, N 8.63 %.

***N*-[(4-Chlorophenyl)-(2-hydroxynaphthalen-1-yl)-methyl)]acetamide (4e):** White solid, m.p. 225-227 ºC; IR (KBr, ν_{max}, cm^{-1}): 3450, 3392, 3056, 2701, 2612, 1624, 1515, 1332, 1277, 1013, 817, 746, 586; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.86 (s, 1H, -CONH), 8.27 (bs, 1H, -OH), 7.72 (d, 1H), 7.21-7.77 (m, 10H, ArH), 3.50 (s, 1H, -CH), 2.04 (s, 3H, $-CH_3$); Anal. calcd. for $C_{19}H_{16}NO_2Cl$: C 70.3, H 4.95, N 4.30 %; Found: C 69.97, H 4.91, N 4.38 %.

***N*-[(4-Chlorophenyl)-(2-hydroxy-naphthalen-1-yl)-methyl)]benzamide (4f):** Light yellow solid, m.p. 185-186 ºC; IR (KBr, ν_{max}, cm^{-1}): 3419, 3179, 1629, 1513, 1340, 1012, 812, 723, ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.14 (s, 1H, -CONH), 8.91 (d, 1H, -OH), 8.12 (d, 1H), 7.81 (d, 2H), 7.78 (d, 1H), 7.73 (d, 1H), 7.20-7.52 (m, 11H, ArH); Anal. calcd. for $C_{24}H_{18}NO_2Cl$: C 74.32, H 4.68, N 3.61 %; Found: C 73.78, H 4.76, N 3.56 %.

***N*-[(4-Methyphenyl)-(2-hydroxy-naphthalen-1-yl)-methyl)]urea (4g):** Light orange solid, m.p. 115-117 ºC; IR (KBr, ν_{max}, cm^{-1}): 3350, 3241, 3073, 3022, 2804, 1946, 1694, 1592, 1223, 1140, 931, 840, 713; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.52 (s, 1H, -CONH), 8.72 (d, 1H, CH), 8.13 (s, 2H, NH_2), 7.18-7.48 (m, 12H, ArH), 2.25 (s, 3H); Anal. calcd. for $C_{19}H_{18}N_2O_2$: C 74.49, H 5.92, N 9.14 %; Found: C 74.39, H 5.97, N 9.20 %.

***N*-[(4-Methyphenyl)-(2-hydroxy-naphthalen-1-yl)-methyl)]acetamide (4h):** Light orange solid, m.p. 223-225 ºC; IR (KBr, ν_{max}, cm^{-1}): 3402, 3320, 3076, 3022, 1645, 1592, 1512, 1436, 1320, 1280, 1114, 831, 785, 712; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.86 (s, 1H, -CONH), 8.32 (d, 1H, CH), 7.82 (br d, 1H), 7.75 (d, 1H), 7.61 (d, 1H), 7.33 (t, 1H), 6.98-7.24 (m, 7H, ArH), 2.23 (s, 3H), 1.99 (s, 3H); Anal. calcd. for $C_{20}H_{19}NO_2$: C 78.66, H 6.27, N 4.95 %; Found: C 78.52, H 6.31, N 4.53 %.

***N*-[(4-Methyphenyl)-(2-hydroxy-naphthalen-1-yl)-methyl)]benzamide (4i):** Light orange solid. m.p. 216-218 ºC; IR (KBr, ν_{max}, cm^{-1}): 3320, 3261, 3052,1982, 1694, 1570, 1450, 1351, 1210, 790; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.2 (s, 1H, -CONH), 8.95 (d, 1H, CH), 8.81 (d, 1H), 7.81-7.84 (m, 4H, ArH), 7.78 (d, 1H), 7.72 (d, 1H), 7.16-7.51 (m, 9H, ArH), 7.03 (d, 2H), 2.23 (s, 3H); Anal. calcd. for $C_{25}H_{21}NO_2$: C 81.72, H 5.76, N 3.81 %; Found: C 81.65, H 5.69, N 3.87 %.

N-[(4-Dimethylaminophenyl)-(2-hydroxynaphthalen-1-yl)-methyl)]acetamide (4j): Pale yellow solid, m.p. 122-124 ºC; IR (KBr, ν_{max}, cm^{-1}): 3350, 3238, 3150, 1895, 1738, 1518, 1447, 1240, 1062, 741; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.86 (s, 1H, CONH), 7.9 (d, 1H), 7.85 (d, 1H), 7.60-7.68 (m, 5H, ArH), 7.06-7.31 (m, 4H, ArH), 6.73 (d, 2H), 3.10 (s, 6H, CH_3), 2.14 (s, 3H, CH_3); Anal. calcd. for $C_{18}H_{22}N_2O_2$: C 72.63, H 5.56, N 8.78 %; Found: C 72.57, H 5.48, N 8.65 %.

***N*-[(3-Nitrophenyl)-(2-hydroxynaphthalen-1-yl)-methyl)]-urea (4k):** Light brown solid, m.p. 178-179 ºC; IR (KBr, ν_{max}, cm^{-1}): 3450, 3394, 3056, 1624, 1516, 1332, 1012, 818, 746; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.86 (s, 1H, -CONH), 8.13-8.26 (m, 2H, ArH), 7.23-7.58 (m, 10H, ArH), 6.37 (s, 1H, -CH), 5.87 (s, 1H); Anal. calcd. for $C_{18}H_{15}N_3O_4$: C 64.09, H 4.48, N 12.46 %; Found: C 64.15, H 4.55, N 12.39 %.

***N*-[(2,5-Dimethoxyphenyl)-(2-hydroxynaphthalen-1-yl-)-methyl)]acetamide (4l):** White solid, m.p. 251-252 ºC; IR (KBr, ν_{max}, cm^{-1}): 3392, 3156, 3001, 2930, 1625, 1545, 1430, 1375, 1250, 1081, 817, 790; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.72 (s, 1H, -CONH), 8.45 (d, 1H), 7.71-7.82 (m, 2H), 7.70-7.93 (m, 9H, ArH), 3.60 (s, 3H, $-OCH_3$), 3.45 (s, 3H, $-OCH_3$), 2.02 (s, 3H, CH_3); Anal. calcd. for $C_{21}H_{21}NO_4$: C 71.78, H 6.02, N 3.99 %; Found: C 71.52, H 6.48, N 3.91 %.

RESULTS AND DISCUSSION

Initially to optimize the amount of catalyst, the reaction of 2-naphthol (1 mmol), benzaldehyde (1 mmol) and acetamide (1.2 mmol) was performed under solvent-free conditions at

480 w in the presence of different quantities of zinc chloride. As the catalyst concentration increases there is an increase in the product yield and decrease in the time required with maximum yield at 20 mol % of catalyst. Further increase in the concentration of catalyst did not have any significant effect on the product yield. Therefore, 0.2 mmol (20 mol %) of catalyst was chosen as the optimal quantity of anhydrous zinc chloride. It is also important to note that, no products were afforded when the reactions were carried out in the absence of zinc chloride. The results are summarized in Table-1.

TABLE-1
AMOUNTS OF CATALYST OPTIMIZATION FOR THE SYNTHESIS OF AMIDOALKYL NAPHTHOLS UNDER SOLVENT-FREE MICROWAVE IRRADIATION*

Entry	Catalyst (mol %)	Time (min)	Yield (%) **
1	10	14	72
2	15	11	78
3	20	8	87
4	25	9	85
5	30	8	87

*Reaction conditions: 2-naphthol (1 mmol), aldehyde (1 mmol) and acetamide (1.2 mmol); 480 w
**Yields refer to the pure isolated products

Thus, we prepared a range of 1-amidoalkyl-2-naphthols under the optimized reaction conditions to investigate its scope and generality of reactions. Aromatic aldehydes bearing electron donating substituents such as 3-methoxybenzaldehyde and electron withdrawing group such as 3-nitrobenzaldehyde gave good yields. It was shown that the aromatic aldehydes with electron withdrawing groups reacted faster than the aromatic aldehydes with electron releasing group as would be expected. The results are summarized in Table-2.

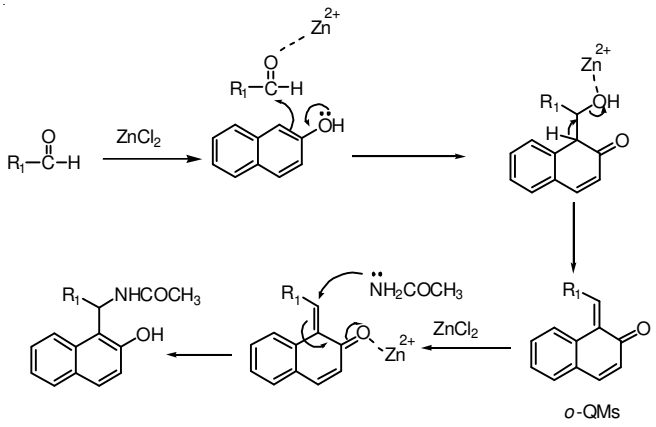
Reusability of catalyst: After completion of the reaction, anhydrous zinc chloride was separated by simple filtration. The separated catalyst was washed with ethyl acetate and dried at 100 ºC. This was reused further for four times without loss in its activity (Table-3).

A role of $ZnCl_2$ has been proposed to activate the aldehyde by binding of Zn^{2+} with the oxygen atom which ultimately enhances the electrophile of the aldehyde and leads to reduction in reaction time. The condensation of 2-naphthol with the activated aldehyde give *ortho*-quinone methides. The same *ortho*-quinone methides, generated in-situ, have been reacted with acetamide to form 1-amidoalkyl-2-naphthol derivatives. A reasonable explanation for this result can be given by considering the nucleophilic addition to *ortho*-quinone methide intermediate favourable *via* conjugate addition on the α,β-unsaturated carbonyl group and finally this intermediate will aromatize to produce the final aromatic compound. A mechanistic portraying the probable sequence of events is given in **Scheme-II**.

TABLE-3
EFFECT OF RECYCLABILITY OF ZINC CHLORIDE CATALYST ON AMIDOALKYL NAPHTHOLS*

Cycles	Yield (%)**
Initial	87
1	87
2	85
3	78
4	75

*Reaction conditions: 2-naphthol (1 mmol), aldehyde (1 mmol) and acetamide (1.2 mmol); 480 w; ** Isolated yield



Scheme-II: Plausible mechanism of action of $ZnCl_2$ in the synthesis of amidoalkyl naphthols

Conclusion

In conclusion, we have reported a new catalytic method for the synthesis of 1-amidoalkyl-2- naphthols derivatives by using anhydrous zinc chloride as efficient, inexpensive, reusable and eco-friendly heterogeneous catalysts. The microwave solvent free green chemistry approach offer advantages such as shorter reaction times, simple work up and excellent yield.

TABLE-2
SYNTHESIS OF 1-AMIDOALKYL 2-NAPHTHOLS CATALYZED BY ZINC CHLORIDE UNDER MICROWAVE IRRADIATION*

Entry	Aldehyde (R_1)	Urea/Amide (R_2)	Product	Time (min)	Yield (%)	m.p (°C)
1.	C_6H_5	NH_2	4a	9	89	171-173 (174-175)[23]
2.	C_6H_5	CH_3	4b	8	87	242-245 (241-243)[13]
3.	C_6H_5	C_6H_5	4c	10	86	235-237 (234-236)[23]
4.	4-ClC_6H_4	NH_2	4d	8	88	168-170 (168-169)[23]
5.	4-ClC_6H_4	CH_3	4e	11	85	225-227 (224-227)[13]
6.	4-ClC_6H_4	C_6H_5	4f	12	87	185-186 (187-188)[23]
7.	4-MeC_6H_4	NH_2	4g	15	84	115-117 (117-118)[25]
8.	4-MeC_6H_4	CH_3	4h	14	83	223-225 (222-223)[17]
9.	4-MeC_6H_4	C_6H_5	4i	10	86	216-218 (216-217)[25]
10.	4-$Me_2NC_6H_4$	CH_3	4j	9	82	112-124 (78-79)[13]
11.	3-$NO_2C_6H_4$	NH_2	4k	12	84	178-179 (179-180)[19]
12.	(2,5-$MeO)_2C_6H_3$	CH_3	4l	9	87	251-252 (251-253)[24]

*Reaction conditions: 2-naphthol (1 mmol), aldehyde (1 mmol) and amide/urea (1.2 mmol); 480 w; ** Isolated yield

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