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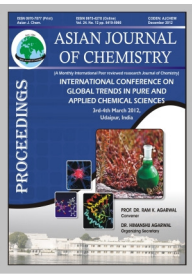

Environment Friendly, Efficient Chloroacetic Acid Promoted Synthesis of 1-Amidoalkyl-2-naphthols Under Neat Condition†

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An environment friendly synthesis of 1-amidoalkyl-2-naphthols was developed by one-pot reaction of 2-naphthol with various aldehydes and urea or amides catalyzed by chloroacetic acid in the absence of solvent media under thermal and microwave irradiation conditions. This greener protocol offer many advantages such as shorter reaction times, simple work-up and excellent yield.

Key Words: Chloroacetic acid, 1-Amidoalkyl-2-naphthol, One-pot reaction, Solvent-free media, Green chemistry.

INTRODUCTION

Among the various approaches for the synthesis of organic compounds, one pot multi-component reactions appeared as a powerful tool for construction of small drug like molecules with several levels of structural diversity[1,2]. One of the multi-component reactions of current interest is 1-amidoalkyl-2-naphthols syntheses, which have potentially different biological activities[3-5]. The preparation of 1-amidoalkyl-2-naphthols can be carried out in the presence of several Lewis or Bronsted acid catalysts such as $H_3PMo_{12}O_{40}.xH_2O/SiO_2$[6], montmorillonite K10 clay[7], iodine[8], cation-exchanged resins[9], oxalic acid[10], sulfamic acid[11], silica sulphuric acid[12], silico tungstic acid[13], $NaHSO_4.H_2O$[14], $Fe(HSO_4)_3$[15], zirconyl chloride[16], Zeolite H-Beta(IV)[17] and 1,3-dibromo 5,5-dimethylhydantoin[18]. However, many of the above reported protocols suffer from several drawbacks of green chemistry[19] such as long reaction time, low product yield, toxicity, the use of expensive and corrosive reagents, high catalyst loading, strongly acidic and vigorous conditions. Therefore, the search for a novel green procedure and easily available catalyst with high catalytic activity promoted us to develop a safe alternate method for the synthesis of amidoalkyl naphthols. Herein, we describe practical and inexpensive methods for the synthesis of 1-amidoalkyl-2-naphthol derivatives *via* multi-component reactions in the presence of chloroacetic acid as economical, easily available catalyst by two methods (Method A and B) (**Scheme-I**).

EXPERIMENTAL

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 CHN elemental analyzer.

Chloroacetic acid catalyzed preparation of amidoalkyl naphthols

Method A-(Microwave irradiation method): To a mixture of 2-naphthol (1 mmol), aldehydes (1 mmol) and amide (1.2 mmol), effective amount of chloroacetic acid (0.2 mmol, 20 mol %) was added. The mixture was inserted in a microwave oven (LG model MS1927C) at 480 W for the appropriate time and each pulse was of 30s with intermittent time to avoid overheating. The reaction was followed by TLC. After completion of reaction, mass was cooled to 25 ºC, then the solid residue was purified by recrystallization in EtOH.

Method B-(Oil bath method): To a mixture of 2-naphthol (1 mmol), aldehydes (1 mmol) and amide (1.2 mmol), effective amount of chloroacetic acid (0.2 mmol) was added. The mixture

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was stirred under thermal solvent-free condition at 125°C in oil bath for the appropriate time and the reaction was followed by TLC. After completion of reaction, mass was cooled to 25°C, then the solid residue was purified by recrystallization in EtOH.

The spectral data of the new amidoalkyl naphthols are given below:

***N*-[(2-Hydroxynaphthalen-1-yl)-phenyl-methyl)]urea (4a):** Light brown solid. m.p. 172-173 ºC; IR (KBr, ν_{max}, cm^{-1}): 3319, 3067, 3025, 1694, 1594, 1336, 1076, 830, 745; ^{1}H NMR (400 MHz,DMSO-d_6): δ 8.76 (s, 1H, CONH), 7.20-7.89 (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 73.88, H 5.47, N 9.58 %.

***N*-[(4-Chlorophenyl)-(2-hydroxynaphthalen-1-yl)-methyl)]acetamide (4b):** White solid m.p. 225-227 ºC; IR (KBr, ν_{max}, cm^{-1}): 3450, 3392, 3056, 2700, 2521, 1624, 1515, 1332, 1275, 1012, 817, 746, 555; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.86 (s, 1H, CONH), 8.27 (d, =12H, 1H), 7.72(d, *J* = 8Hz, 1H), 7.2-7.7 (m, 10H, ArH), 3.46 (s, 1H), 2.04 (s, 3H, CH_3); anal. calcd. for $C_{19}H_{16}NO_2Cl$: C 70.03, H 4.95, N 4.30 %; Found: C 69.95, H 4.89, N 4.39 %.

***N*-[(3-Nitrophenyl)-(2-hydroxynaphthalen-1-yl)-methyl)]urea (4c):** Light brown solid. m.p. 178-179 ºC; IR (KBr, ν_{max}, cm^{-1}): 3450, 3392, 3056, 1624, 1515, 1332, 1012, 817, 746; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.86 (s, 1H, CONH), 8.11-8.26 (m, 2H, ArH), 7.23-7.58 (m, 8H, ArH), 6.37 (s, 1H), 5.89 (brs, 2H); Anal. calcd. for $C_{18}H_{15}N_3O_4$: C 64.09, H 4.48, N 12.46; Found: C 64.16, H 4.56, N 12.38.

***N*-[(2-Hydroxynaphthalen-1-yl)-phenyl-methyl]-acetamide (4d):** Light yellow solid. m.p. 241-243 ºC; IR (KBr, ν_{max}, cm^{-1}): 3441, 3177, 3057, 1685, 1555, 1243, 1080, 802, 770, 746; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.85 (s, 1H, CONH), 8.27 (d, *J* = 12, 1H) 7.9 (s, 1H), 7.75 (d, *J* = 8 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.30 (t, *J* = 8 Hz, 1H), 7.12-7.27 (m, 8H, ArH), 2.04 (s, 3H, CH_3); Anal. calcd. for $C_{19}H_{17}NO_2$: C 78.33, H 5.87, N 4.81 % ; Found: C 77.50, H 5.79, N 4.75 %.

***N*-[(4-Methyphenyl)-(2-hydroxy-naphthalen-1-yl)-methyl)]acetamide (4e):** Light orange solid. m.p. 220-223 ºC; IR (KBr, ν_{max}, cm^{-1}): 3400, 3320, 3075, 3022, 1645,1592, 1512, 1435, 1320, 1280, 1114, 830, 785, 711; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.86 (s, 1H, CONH), 8.32 (d, *J* = 8 Hz, 1H) 7.81 (br d, 1H), 7.75 (d, *J* = 8 Hz, 1H), 7.61 (d, *J* = 8Hz, 1H), 7.33 (t, *J* = 8.2 Hz, 1H), 6.98-7.24 (m, 7H, ArH), 2.22 (s, 3H), 1.98 (s, 3H); Anal. calcd. for $C_{20}H_{19}NO_2$: C 78.66, H 6.27, N 4.95 % ; Found: C 78.50, H 6.32, N 4.51 %.

***N*-[(4-Dimethylaminophenyl)-(2-Hydroxynaphthalen-1-yl)-methyl)]acetamide (4f). Green solid:** m.p. 125-127 ºC; IR (KBr, ν_{max}, cm^{-1}): 3350, 3237, 3150, 1895, 1736, 1518, 1445, 1240, 1062, 741; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.68 (s, 1H, CONH), 7.9 (d, *J* = 8 Hz, 1H), 7.85 (d, J = 8 Hz, 1H), 7.60-7.69 (m, 5H, ArH), 7.06-7.32 (m, 4H, ArH), 6.73 (d, *J* = 8 Hz, 2H), 3.10 (s, 6H, CH_3), 2.13 (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 72.56, H 5.47, N 8.63 %.

***N*-[(4-Chlorophenyl)-(2-hydroxy-naphthalen-1-yl)-methyl)]amide (4g):** Light yellow solid. m.p. 167-168 ºC; IR (KBr, ν_{max}, cm^{-1}): 3450, 3350, 3320, 3075, 3022, 1694, 1592, 1512, 1322, 1222, 830; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.75 (s,1H, CONH), 7.27-7.89 (m, 10H, ArH) 6.09 (bs, 2H); Anal. calcd. for $C_{18}H_{15}ClN_2O_2$: C 66.16, H 4.63, N 8.57 %; Found: C 66.28, H 4.54, N 8.64 %.

***N*-[(2-Hydroxynaphthalen-1-yl)-phenyl-methyl)]-benzamide (4h):** Light brown solid. m.p. 238-240 ºC; IR (KBr, ν_{max}, cm^{-1}): 3420, 3061, 1800, 1629, 1538, 1348, 1026, 822, 750; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.09 (bs, 1H, CONH), 8.91 (bs, 1H), 7.40-7.91 (m, 16H, ArH); Anal. calcd. for $C_{24}H_{19}NO_2$: C 73.95, H 5.52, N 9.58 % ; Found: C 73.88, H 5.47, N 9.63 %.

***N*-[(4-Methyphenyl)-(2-hydroxy-naphthalen-1-yl)-methyl)]benzamide (4i):** Light orange solid. m.p. 216-217 ºC; IR (KBr, ν_{max}, cm^{-1}): 3320, 3260, 3052,1980, 1694, 1570, 1450, 1350, 1210, 790; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.2 (s, 1H, CONH), 8.95 (d, *J* = 8 Hz,1H), 8.80 (d, *J* = 8.1 Hz, 1H), 7.81-7.84 (m, 4H, ArH), 7.77 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.16-7.51 (m, 9H, ArH), 7.02(d, *J* = 8 Hz, 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 81.63, H 5.68, N 3.88 %.

***N*-[(4-Chlorophenyl)-(2-hydroxy-naphthalen-1-yl)-methyl)]benzamide (4j):** Light yellow solid. m.p.188-189 ºC; IR (KBr, ν_{max}, cm^{-1}): 3419, 3179, 1629, 1513, 1339, 1012, 811, 723, ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.14 (s, 1H, CONH), 8.90 (d, *J* = 8 Hz, 1H), 8.12 (d, *J* = 8 Hz, 1H), 7.81 (d, *J* = 8 Hz, 2H), 7.78 (d, *J* = 8 Hz, 1H), 7.73 (d, *J* = 12 Hz, 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 73.80, H 4.76, N 3.55 %.

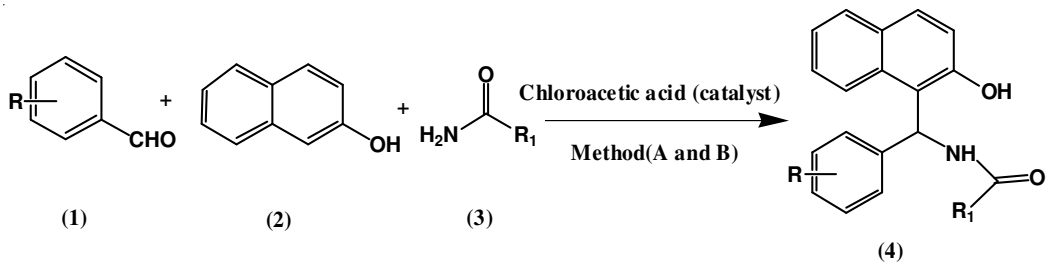
***N*-[(4-Methyphenyl)-(2-hydroxy-naphthalen-1-yl)-methyl)]urea (4k):** Light orange solid. m.p. 117-119 ºC; IR (KBr, ν_{max}, cm^{-1}): 3350, 3240, 3075, 3022, 2804, 1694, 1592,1944, 1222, 1140, 930, 840, 713; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.51 (s, 1H, CONH), 8.72 (d, *J* = 4 Hz, 1H), 8.12 (s, 2H), 7.18-7.50 (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 74.38, H 5.96, N 9.21 %.

***N*-[(2,5-Dimethoxyphenyl)-(2-hydroxynaphthalen-1-yl)-methyl)]acetamide (4l):** White solid. m.p. 250-252 ºC; IR (KBr, ν_{max}, cm^{-1}): 3392, 3156, 3000, 2930, 1624, 1545, 1430, 1375, 1250, 1080, 817, 790; 1H NMR (400 MHz, DMSO-d_6): δ 9.72 (s, 1H, CONH), 8.45 (d, *J* = 8 Hz, 1H), 7.71-7.81 (m, 2H), 7.70-6.90 (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 71.50, H 6.50, N 3.90 %.

RESULTS AND DISCUSSION

In order to optimize the reaction conditions, we carry out the synthesis of *N*-[phenyl-(2-hydroxynapthalene-1-yl)methyl] acetamide as a model reaction (**Scheme-I**). We studied the reaction by using 2-naphthol, benzaldehyde and acetamide in the ratio (1:1:1.2 mmol) with different quantities of chloroacetic acid as catalyst under solvent free conditions (Fig. 1). It was found that the best result was obtained when the reaction was carried in the presence of 0.2 mmol (20 mol %) chloroacetic acid. The fewer amounts gave a low yield and the more amounts could not cause the obvious increase for the yield of product.

After optimization of the reaction conditions, we studied the generality of this method. Using this procedure, different kinds of aromatic aldehydes (1 mmol) and urea (1.2 mmol) or



Scheme-I: Method A: Microwave irradiation; Method B: Oil bath

TABLE-1
CHLOROACETIC ACID CATALYZED ONE-POT SYNTHESIS OF 1-AMIDOALKYL-2-NAPHTHOLS*

Entry	Aldehyde (R)	Amide (R_1)	Product	Method A Time (min)/Yield (%)**	Method B Time (min)/Yield (%)**	m.p. (ºC) (lit. m.p)[ref]
1.	H	NH_2	4a	7/86	15/82	172-173 (175-176)[15]
2.	4-Cl	CH_3	4b	11/88	25/87	225-227 (224-227)[15]
3.	3-NO_2	NH_2	4c	7/87	25/82	178-179 (178-180)[15]
4.	H	CH_3	4d	6/85	15/92	241-243 (239-240)[10]
5.	4-CH_3	CH_3	4e	5/86	14/82	220-223 (222-223)[19]
6.	4-$N(CH_3)_2$	CH_3	4f	13/80	35/78	125-127 (123-125)[19]
7.	4-Cl	NH_2	4g	9/83	16/79	167-168 (169-170)[15]
8.	H	C_6H_5	4h	9/83	18/80	238-240 (237-239)[10]
9.	4-CH_3	C_6H_5	4i	6/86	14/82	216-217 (215-216)[15]
10.	4-Cl	C_6H_5	4j	11/84	17/77	188-189 (187-189)[15]
11.	4-CH_3	NH_2	4k	10/88	15/84	117-119 (118-120)[15]
12.	2,5-$(OCH_3)_2$	CH_3	4l	12/83	20/80	250-252 (251-253)[19]

*Yields refer to pure products were characterized by comparison of their physical and spectral data with that of authentic samples.
**All the compounds are known, structure of the products were confirmed from their spectral IR, ^{1}H NMR and CHN data;
Method A: Microwave irradiation; Method B: Oil bath.

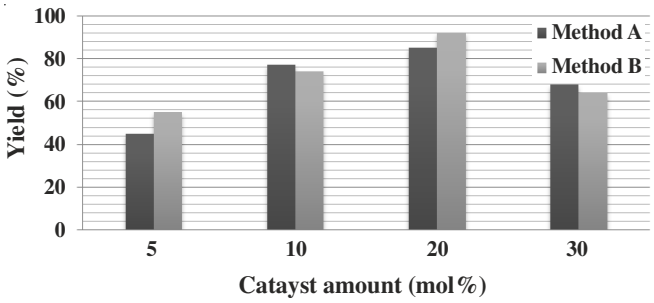
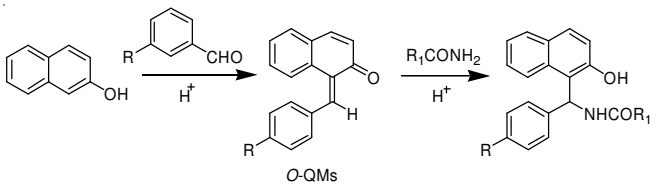


Fig. 1. Amount of the catalyst optimization for the synthesis of 1-amidoalkyl-2-naphthols

amide were treated with 2-naphthol to produce a range of amidoalkyl naphthols (Table-1). In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the products in high yields. It was observed that the microwave method was found to have beneficial and superior effect on the reaction as compared to the oil bath method.

The proposed mechanism for the chloroacetic acid catalyzed preparation of amidoalkyl naphthols is shown in **Scheme-II**. The condensation of 2-naphthol with aromatic aldehyde under acid catalyst gave *ortho*-quinone methides. The generated *ortho*-quinone methides reacted with amide *via* the conjugated addition to afford 1-amidoalkyl-2-naphthols. Electron-withdrawing groups on the benzaldehydes in the *ortho*-quinone methides increase the rate of the 1,4-nucleophilic addition reaction because the alkene LUMO is at lower energy in the presence of electron-withdrawing groups as compared to electron donating groups.



Scheme-II: Mechanism of choloroacetic acid catalyzed reaction

To show the merit of the present work in comparison with reported results in the literature for the synthesis of amidoalkyl naphthols, we have tabulated turn-over frequency {TOF = yield (%)/[reaction time (min) × mol % of catalyst]} of these catalysts. As Table-2 indicates, chloroacetic acid is superior to the previously reported catalysts in term of TOF.

Conclusion

Microwave assisted synthesis of amidoalkyl naphthols using chloroacetic acid is superior and fast over the oil bath method. The advantages of presented green protocol are shorter reaction time, clean reaction profile, simple work up, reliable, environmentally benign, safe, non-toxic and moreover, under solvent-free conditions. Thus, we have elaborated a novel, highly efficient and green approach for the synthesis of amidoalkyl naphthols.

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TABLE-2
COMPARISON OF THE TOF RESULTS OF CHLOROACETIC ACID WITH THOSE OBTAINED BY THE RECENTLY REPORTED CATALYSTS

Catalyst (d)	Catalyst, (mol %)	Time (min)	Yield (%)	TOF (c), (min^{-1})	Ref.
Chloroacetic acid	20	(a) 6; (b) 15	85; 92	0.7083; 0.3066	Present work
$H_3PMo_{12}O_{40}.xH_2O/SiO_2$	3.17	15	91	1.91	10
MontmorilloniteK10 Clay	0.1 g	90	89	0.00033	11
$KHSO_4$	15	60	90	0.1	12
Iodine	5	330	85	0.051	13
Sulfamic acid	51.5	15	89	0.115	16
$Fe(HSO_4)_3$	5	65	83	0.255	20
Cyanuric chloride	10	10	91	0.91	21

(a) Method A (b) Method B. (c) Turn-over frequency (d) Reaction condition: 2-naphthol:benzaldehyde: acetamide in the ratio (1:1:1.2 mmol)

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