Asian Journal of Chemistry; Vol. 26, No. 24 (2014), 8380-8382

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.17618

Magnesium Sulfate Promoted Efficient and Green Synthesis of Aminoalkyl, Amidoalkyl and Diarylmethane Derivatives

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Received: 18 March 2014; *Accepted*: 31 May 2014; *Published online*: 1 December 2014; AJC-16365

Under solvent-free condition, magnesium sulfate promoted the synthesis of substituted aminoalkyl naphthols, amidoalkyl naphthols and diarylmethane derivatives in excellent yield. Robust dehydrating nature and mild Lewis acidity of magnesium sulfate was exploited to carry out all the transformations.

Keywords: Green synthesis, Magnesium sulfate, One-pot synthesis, Solvent-free synthesis, Substituted naphthol.

INTRODUCTION

Substituted naphthol derivatives are interesting class of compounds exhibit wide spectrum of biological activity such as anticancer[1], antiviral[2], antitubercular[3], antihypertensive[4], anti-HIV[5], *etc.* (Fig. 1). Assorted varieties of catalysts/reagents are reported in literature for substituted amidoalkyl and aminoalkyl naphthol synthesis[6-9]. However, several methods have limitations such as tedious preparation procedure of catalysts, corrosive and/or toxic nature of reagents, use of organic solvents, difficult product isolation processes, *etc.*

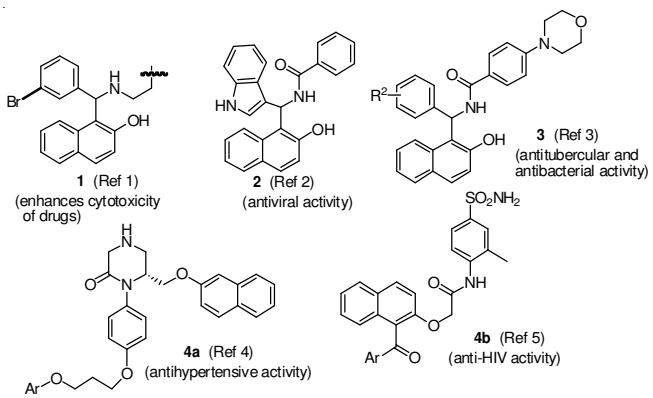


Fig. 1. Bioactive aminoalkyl and amidoalkyl naphthols

Anhydrous $MgSO_4$ is commercially available, safe, non-toxic dehydrating agent with mild Lewis acidity. $MgSO_4$ mediated dihydropyrimidin-2(1*H*)-ones[10], phenazine and quinoxaline[11], β-nitroalkanols[12], urea/acetamide derived substituted naphthol synthesis[13] have been previously reported in literature. Multicomponent reactions offer a convenient way to synthesize highly functionalized molecules. Recently, several modern variants of multicomponent reaction have been reported in literature[14a-b]. Solvent-free multicomponent reactions are known for their rapid conversion, energy efficient and environmentally benign nature[14c]. In continuation of our efforts to devise efficient multicomponent reaction[15a-b], herein we report $MgSO_4$ mediated solvent-free substituted naphthol synthesis.

EXPERIMENTAL

Anhydrous $MgSO_4$ was purchased from HIMEDIA. Except benzaldehyde, all other reagents were used as such without further purification. Freshly distilled benzaldehyde was used for the reaction.

General procedure for the magnesium sulfate promoted substituted naphthol synthesis

Representative procedure for the synthesis of aminoalkyl naphthol: To a stirred mixture of β-naphthol (1 mmol, 144 mg), anhydrous $MgSO_4$ (0.5 mmol, 60 mg) and 1.5 mmol of amine in a 5 mL round bottom flask, 1.5 mmol of aldehyde was added and the mixture was further stirred in an oil bath at RT or 60 °C for required time. After completion of reaction, the reaction mixture was quenched with 5 mL of water, stirred and the aqueous layer was decanted and for **7** and **8**, after quenching with 5 mL water, the reaction mixture was extracted with ethyl acetate (2 × 5 mL). The organic layer was washed with water, brine and dried over anhydrous sodium sulfate.

1-(Morpholinomethyl)naphthalen-2-ol (6): Yield = 240 mg (98 %); White solid; m.p. 114-115 °C (Lit.[16] 113-115 °C);

FT- IR (KBr, ν_{max}, cm^{-1}): 3046, 2975, 2898, 1621, 1478, 1265, 815 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.65 (br s, 4 H), 3.78 (s, 4 H), 4.15 (s, 2 H), 7.09 (d, *J* = 8.7 Hz, 1H), 7.25-7.32 (m, 1H), 7.42-7.47 (m, 1H), 7.68-7.83 (m, 3H).

General procedure for the synthesis of amidoalkyl naphthol: To a stirred mixture of β-naphthol (1 mmol, 144 mg), anhydrous $MgSO_4$ (2 mmol, 241 mg) and benzamide (1.5 mmol, 181 mg) in a 5 mL round bottom flask, 1.2 mmol of aldehyde was added and the mixture was further stirred and heated in an oil bath at 90 °C for 5 h. After completion of the reaction, the reaction mixture was quenched with 5 mL of water, stirred and the aqueous layer was decanted. The gummy residue was stirred with ethanol:water mixture (1:3 v/v, 20 mL), filtered, washed with 5 mL of cold ethanol and dried.

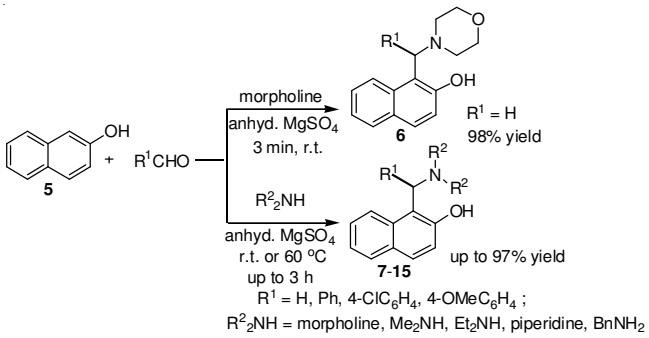
***N*-[(2-Hydroxynaphthalen-1-yl)(4-nitrophenyl)methyl]-benzamide (16):** Yield = 342 mg (86 %); Yellowish white crystals; m.p. 236-238 °C (Lit.[17] 233-235 °C); FT-IR (KBr, ν_{max}, cm^{-1}): 3408, 3260, 1643, 1517, 1347, 1057, 865, 810, 706 ; ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 7.24 (d, *J* = 9.0 Hz, 1 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 7.39 (d, *J* = 7.8 Hz, 1 H), 7.45-7.58 (m, 6 H), 7.82-7.91 (m, 4 H), 8.06 (d, *J* = 8.4 Hz, 1 H), 8.16 (d, *J* = 8.4 Hz, 2 H), 9.08 (d, *J* = 7.8 Hz, 1 H), 10.41 (br s, 1 H).

General procedure for the synthesis of diarylmethanes: To a stirred mixture of β-naphthol (1 mmol, 144 mg), anhydrous $MgSO_4$ (1 mmol, 120 mg) in a 5 mL round bottom flask, 2 mmol of formaldehyde (37 % soln.) and 1.2 mmol of *N,N*-dialkylaniline were subsequently added and the mixture was further stirred at room temperature for 15 min. After completion, the reaction mixture was quenched with 5 mL of water, stirred and the aqueous layer was decanted. To the gummy solid, hexane (2 × 5 mL) was added and the product was filtered and dried.

1-{[4-(Dimethylamino)phenyl]methyl}naphthalen-2-ol (17): Yield = 247 mg (89 %); Brown solid; m.p. 129-131 °C (Lit.[18] 127-130 °C); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.87 (s, 6 H), 4.34 (s, 2 H), 5.10 (br s, 1 H), 6.64 (d, *J* = 9.0 Hz, 2H), 7.06-7.25 (m, 3H), 7.29-7.35 (m, 1H), 7.41-7.47 (m, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H).

RESULTS AND DISCUSSION

Initially, anhydrous $MgSO_4$ mediated representative 1-(morpholin-4-ylmethyl)naphthalen-2-ol **6** synthesis was carried out under solvent-free condition. To our delight, with 0.5 equivalents of anhydrous $MgSO_4$ itself the transformation was completed within 3 min in 98 % yield (**Scheme-I**).



Scheme-I: Anhydrous $MgSO_4$ mediated aminoalkyl naphthol synthesis

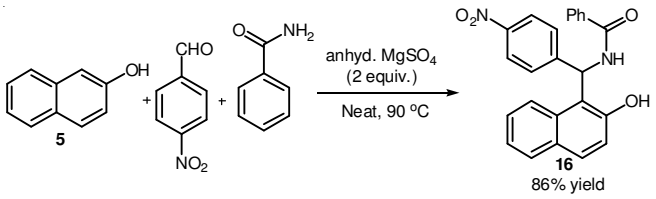
With 0.2 equivalents of anhydrous $MgSO_4$, the reaction took 15 min to complete with a marginal decrease in the product yield to 95 %. Increasing the quantity of anhydrous $MgSO_4$ to one equivalent reduced the reaction time to one minute with 98 % yield. Half equivalent of anhydrous $MgSO_4$ was chosen to carry out further transformations (**Scheme-I**, Table-1).

The aminoalkyl naphthols **6-8** synthesis in excellent yield at room temperature could be attributed to the high reactivity of formaldehyde (**Scheme-I**, Table-1, Entries **1**, **2**). With two equivalents of anhydrous $MgSO_4$, both **7** and **8** were obtained within 1 h. This reaction was found to be general for aldehydes with electron withdrawing (Table-1, Entries **3**, **8**) and electron donating substituents (Table-1, Entry **9**). Aromatic aldehydes with electron withdrawing substituent gave better yield than aldehydes with electron donating substituent (Table-1, Entry **8** *vs* **9**). Anhydrous $MgSO_4$ mediated aminoalkyl naphthol synthesis was screened with various aliphatic cyclic and acyclic amines (Table-1, Entries **1-9**). Secondary amines gave relatively better yield than that of primary amine (Table-1, Entry **1-4** *vs* 5). Both cyclic and acyclic amines gave the corresponding aminonaphthols in excellent yield (Table-1, Entry **2**, **6**). It is of interest to extend this methodology to the amidoalkyl naphthol and diarylmethane synthesis. After screening several conditions, it was found that reaction carried out at 90 °C gave the expected product in good yield (**Scheme-II**). Interestingly, reactions carried out in solvents such as ethanol, toluene and glycerol at 90 °C did not give expected product.

TABLE-1
ANHYDROUS $MgSO_4$ MEDIATED AMINOALKYL NAPHTHOL SYNTHESIS[a]

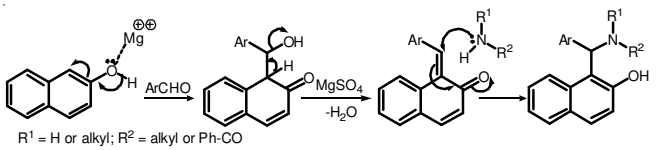
Entry	R^1	R^2_2NH	Product	Temp (°C)	Time (h)	Yield[b] (%)	m.p. (°C)	Reported m.p. (°C)
1[c]	H	Et_2NH	7	r.t.	3	96	-	-
2[c]	H	Me_2NH	8	r.t.	3	97	57-59	74-75[19]
3	4-ClC_6H_4	Me_2NH	9	60	3	75	128-130	128-130[9]
4	C_6H_5	Me_2NH	10	60	3	85	162-164	161-162[20]
5	C_6H_5	$BnNH_2$	11	r.t.	3	66 (51)[d]	141-142	143[21]
6	C_6H_5	Morpholine	12	60	1.5	91	174-176	175-177[15b]
7	C_6H_5	Piperidine	13	60	1.5	85	197-199	195-196[20]
8	4-ClC_6H_4	Morpholine	14	60	3	87	127-129	130-132[22]
9	4-$MeOC_6H_4$	Morpholine	15	60	3	69	124-125	126[23]

[a]To a finely ground mixture of anhydrous $MgSO_4$ (0.5 mmol) and β-naphthol (1 mmol), aldehyde (1.5 mmol) and amine (1.5 mmol) were added and stirred. In entries **3** and **8**, aldehyde was ground along with anhydrous $MgSO_4$ and β-naphthol. [b]Yields are for the isolated products. [c]With 2 mmol of anhydrous $MgSO_4$ the reaction completes within 1 h. [d]Reaction was carried out at 60 °C for 3 h



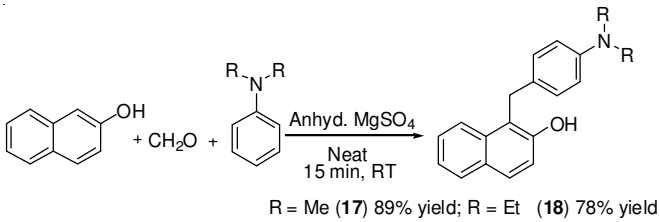
Scheme-II: Anhydrous $MgSO_4$ mediated amidoalkyl naphthol synthesis

The formation of both amino/amidoalkyl naphthols can be explained based on the following mechanism (**Scheme-III**).



Scheme-III: Mechanism for the formation of substituted naphthols

We have also screened Friedel-Crafts reaction of β-naphthol with formaldehyde and *N,N*-dialkylaniline with one mmol of anhydrous $MgSO_4$. To our delight, the reaction completed within 15 min at room temperature itself and the product **17** was obtained in 89 % yield (**Scheme-IV**).



Scheme-IV: Anhydrous $MgSO_4$ mediated diarylmethane synthesis

Moreover, the product can be isolated from the reaction medium by simple aqueous work-up. Previously available methods for diarylmethane synthesis use longer reaction time[18]. Anhydrous $MgSO_4$ was identified as suitable reagent to carry out diarylmethane synthesis under mild condition. Investigations on synthetic utility of the magnesium sulfate in Mannich-type reactions are underway in our laboratory.

Conclusion

In summary, the mild, environmentally benign, non-toxic, readily available nature of anhydrous $MgSO_4$ makes it a viable reagent for substituted naphthol synthesis. All the reactions were carried out under neat condition followed by simple isolation of the product from the reaction medium. In all transformations, products were obtained in good to excellent yield.

ACKNOWLEDGEMENTS

One of the authors, S. Selva Ganesan thanks DST for DST-Fast Track grant (No: SR/FT/CS-09/2011). Thanks are also due to SASTRA University for providing lab space and NMR facility.

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