



Aluminium Sulphate in PEG as a Green Recyclable Homogeneous Catalytic System to Synthesis of Amidoalkyl Naphthol

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ABSTRACT

Aluminium sulphate as a catalyst in PEG as a reaction solvent is found to be an attractive, environmentally benign and highly efficient catalytic system for the one-pot multicomponent reaction of aromatic aldehyde, β -naphthol and amide to form the corresponding amidoalkyl naphthol. The procedure is simple, rapid and high yielding. Moreover, the catalyst exhibited a remarkable reactivity and is reusable in PEG-400 as a solvent. The Aluminium sulphate in PEG-400 can be reused upto four times without significant loss in yields and selectivity of the product. The remarkable features of this new one pot C-C and C-N bond forming reaction procedure are high conversions, operationally simple and eco-friendly and economically inexpensive method.

Keywords: Multicomponent reaction; Amidoalkyl naphthol; β -Naphthol; Aldehyde; Aluminium sulphate; PEG-400

INTRODUCTION

One-pot multicomponent reactions have attracted considerable attention in recent years. MCRs are furnished the desired product in a single operation without need to isolate any intermediates during the processes. This reaction reduces the reaction time considerably increase the yield of the products than ordinary multistep methods, save an energy input [1-3]. They have merits over two components reaction in several aspects including the simplicity of a one pot procedures, good yield, possible structural variation and building up complex molecules. Biginelli [4,5], Ugi [6], Passerini [7,8] and Mannich [9,10] are some examples of MCRs. In addition the implementation of several transformations in a single manipulation is highly compatible with the goals of sustainable and green chemistry.

Compounds having 1,3-amino-oxygenated functional groups are widely used in many biologically important natural products, potent drugs including a number of nucleoside antibiotics and HIV protease inhibitors such as ritonavir and lipinavir [11,12]. It is noteworthy that 1-amidoalkyl-2-naphthol can be easily hydrolyzed to important biologically active 1-aminoalkyl-2-naphthol derivatives. These compounds show biological activities like hypotensive and bradycardic effects [13-15].

Traditionally, these compounds have been synthesized by one-pot multicomponent condensation reaction of β -naphthol, aryl-aldehyde and amide in presence of different catalysts such as *p*-toulene sulphonic acid [16], $\text{Ce}(\text{SO}_4)_2$ [17], Iodine [18,19], P_2O_5 [20], $\text{Fe}(\text{HSO}_4)_3$ [21], $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ in 1,2-dichloroethane [22], Montmorillonite K-10 [23], $\text{Yb}(\text{OTf})_3$ [24], $\text{Sr}(\text{OTf})_2$ [25], InCl_3 [26], TMSCl/NaI [27], 2,4,6-trichloro-1,3,5-triazine [28], polyphosphate ester [29], $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ [30], $\text{Bi}(\text{OTf})_3$ [31]. However these procedures have some drawbacks of green chemistry such as high reaction temperature, prolonged reaction time, low yield, recovery and reusability of catalysts etc. The recovery and reusability of the catalyst is also a major problem. Therefore the demand for green and eco-friendly procedure that uses reusable catalyst necessitated us to develop an alternative method for the synthesis of amidoalkyl naphthol.

Recyclable catalysts have gained much importance in recent years due to economic and environmental considerations [32,33]. These catalysts are generally cheap, very reactive, environmentally benign, easy to handle, diminish reaction times, uncomplicated work up and reusability of the catalyst.

On the other hand, the development of green and clean synthetic methods, those involving solvent-free or the use of different solvents, like as water, ionic liquids and polyethylene glycol (PEG), has increased in recent years [34-38]. Solvent play a critical role in mixing of the reaction components to allow molecular interaction. Despite several advantages, the solvent-free methods are restricted to systems where at least one of the reagent is liquid at room temperature, whereas the use of ionic liquids, especially imidazolium systems with PF₆ and BF₄ anions have some drawbacks such as the high cost and liberation of hazardous HF during recycling and ionic liquids safety is still debated and the reactions in water do not give good yields because of the hydrophobic nature of the organic reactants. Thus, the use of PEG and other alternative non-volatile solvents has been shown as an attractive way to cleaner organic synthesis. Recently polyethylene glycol is found to be an interesting recyclable and eco-friendly solvent system in synthetic chemistry for various organic transformations with unique properties such as thermal stability, commercial availability and immiscibility with a number of organic solvents. In general PEG is cheap, non-toxic and fully non-halogenated. Green synthetic methods are the main concern of the present century and current synthetic efforts are focussed to achieve this goal. Certainly there is an increasing pressure on chemist to replace toxic catalyst and volatile solvents. Now a days PEG is finding widely used in organic synthesis as it is a well-known green solvent. [39-42]

Due to the low cost and easy handling of Aluminium sulphate (Al₂(SO₄)₃.18H₂O) and the green nature of recyclable PEG encouraged us to combine them together and used their utility for the synthesis of amidoalkyl naphthol.

In continuation of our work on the development of useful synthetic methodologies for the C-C and C-N bond formation [43-44] by using an efficient and environmental benign catalyst. Herein, we are reporting the multicomponent reaction of β-naphthol, aromatic aldehyde and amide using aluminium sulphate in PEG-400 as catalyst for the preparation of amidoalkyl naphthol in good to excellent yield (**Scheme 1**). However, literature survey reveals that, no such recyclable aluminium sulphate in PEG as a homogeneous catalytic system has been explored for the amidoalkyl naphthol synthesis. It has various advantages such as low toxicity, low price, experimental simplicity and ease of handling.

EXPERIMENTAL SECTION

All the chemicals were used without any additional purification. Some selected products were characterized using ¹H-NMR on 300MHz spectrophotometer and ¹³C-NMR on 75MHz spectrophotometer in DMSO-d₆ as solvent and recorded in ppm relative to the TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer spectrum on FTIR spectrophotometer using KBr pellets. TLC was performed on 0.25mm. E. Merck precoated silica gel plates (60 F254). All compounds are already well known in the literature. Melting points were determined in open capillary tubes and are uncorrected.

General reaction procedure

A mixture of aromatics aldehyde (1 mmol), β-naphthol (1 mmol), amide (1.1 mmol) and aluminium sulphate (10 mol%) in PEG-400 (4 ml) at rt was stirred for the 16h. The progress of the reaction was monitored by TLC. On completion of the reaction was diluted with ethyl acetate (20 ml). Then separate the above ethyl acetate layer, concentrated and poured in chilled water, solid obtained was filtered and purified by recrystallisation by using EtOH-H₂O (1:1) and the pure products were obtained (82- 92% yields). The lower layer of the PEG and catalyst was recovered and recycled without affecting the yield of the products.

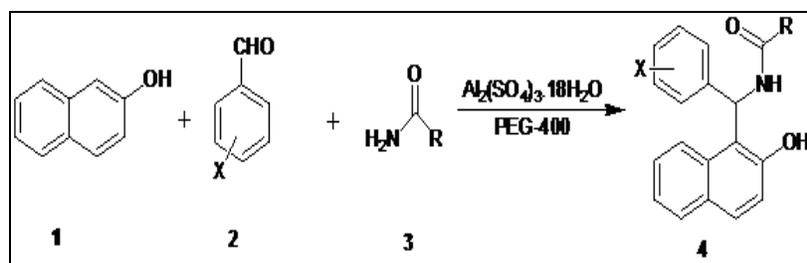
The NMR spectral data of some selected compounds are summarized below.

[(2-Hydroxy naphthalene-1-yl)-phenyl-methyl]acetamide; (Table 2, entry 1) :

¹H-NMR (300 MHz, DMSO-d₆) :- δ 10.06 (s, 1H), 8.62 (d, 2H), 7.82 (s, 1H), 7.77 (d, 2H), 7.36-7.22 (m, 4H), 7.19-7.11 (m, 4H), 1.98 (s, 1H). ¹³C-NMR (75 MHz, DMSO-d₆):- δ 169.84, 153.58, 143.00, 132.76, 129.72, 129.01, 128.90, 128.46, 126.80, 126.57, 126.47, 123.70, 122.88, 119.25, 118.89, 48.26, 23.09.

[(2-Hydroxy naphthalene-1-yl)-phenyl-methyl]benzamide; (Table 2, entry 8) :

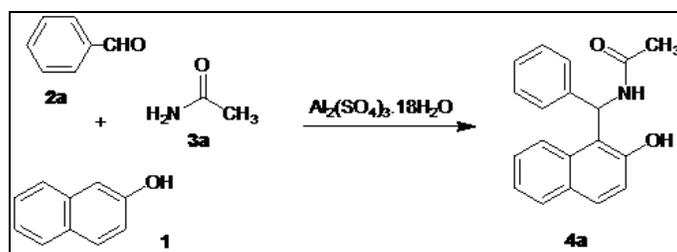
¹H-NMR (300 MHz, DMSO-d₆) :- δ 10.39 (s, 1H), 9.04 (d, *J* = 8.4 Hz, 2H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.885- 7.793 (m, 4H), 7.577-7.446 (m, 5H), 7.34-7.21 (m, 7H). ¹³C-NMR (75 MHz, DMSO-d₆):- δ 166.24, 153.64, 142.45, 134.77, 132.77, 131.92, 129.85, 129.09, 128.99, 128.84, 128.67, 127.59, 127.25, 127.03, 126.89, 123.17, 119.13, 118.78, 49.69.



Scheme 1: Synthesis of 1-amidoalkyl-2-naphthols

RESULTS AND DISCUSSIONS

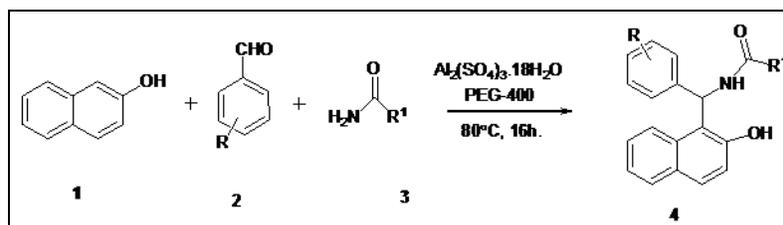
At the onset of the research, we made a conscious effort to develop a catalytic system that would address the limitations of the previously reported 1-amidoalkyl-2-naphthols synthesis reaction. During preliminary studies, benzaldehyde and acetamide was chosen as a model system for the reaction with β -naphthol. Benzaldehyde was treated with equimolar amount of β -naphthol and acetamide in the presence of aluminium sulphate in various solvent to afford amidoalkyl naphthol. A series of experiments were performed to optimize various reaction parameters such as the catalyst loading, solvent, temperature and time (Tables 1).

Table 1: Optimization of reaction parameters^a

Entry	Mol % of catalyst	Solvent	Temp. (°C)	Time (h.)	Yield (%) ^b
1	--	PEG	80	20	8
2	5	PEG	80	16	78
3	10	PEG	80	16	92
4	15	PEG	80	16	92
5	10	1,2-dichloroethane	80	16	64
6	10	Ethanol	80	16	58
7	10	Methanol	80	16	52
8	10	Acetonitrile	80	16	66
9	10	Water	80	16	26
10	10	--	80	20	16
11	10	PEG	rt	16	36
12	10	PEG	60	16	64
13	10	PEG	70	16	82
14	10	PEG	90	16	88
15	10	PEG	80	14	76
16	10	PEG	80	18	92

^aReaction conditions: β -naphthol (1 mmol), Benzaldehyde (1 mmol), acetamide (1.1 mmol), aluminium sulphate (catalyst), solvent (4 mL).

^bIsolated yield.

Table 2: Aluminium sulphate in PEG-400 catalysed one-pot multicomponent synthesis of substituted amidoalkyl naphthols.^a

Entry	R	R ¹	Product	Yield (%) ^b	M.P. (°C),(Reported) ^(ref.)
1	H	0	4a	92	238-240 (241-243) ¹⁷
2	2-Cl	0	4b	76	210-212 (213-215) ²¹
3	4-Cl	0	4c	92	232-234 (237-238) ²⁰
4	4-O CH ₃	0	4d	84	182-184 (183-185) ²¹
5	4- CH ₃	0	4e	90	222-224 (224-225) ²⁰
6	3-NO ₂	0	4f	86	240-242 (256-258) ²⁰
7	4-NO ₂	0	4g	90	242-244 (237-238) ²⁰
8	H	- C ₆ H ₅	4h	91	234-236 (238-240) ²⁰
9	4-Cl	- C ₆ H ₅	4i	88	168-170 (168-170) ²⁰
10	4-O CH ₃	- C ₆ H ₅	4j	82	202-204 (206-208) ²⁰
11	4- CH ₃	- C ₆ H ₅	4k	90	214-216 (214-215) ²⁰
12	3-NO ₂	- C ₆ H ₅	4l	84	240-242 (242-243) ²⁰
13	4-NO ₂	- C ₆ H ₅	4m	88	228-230 (228-229) ²⁰

^aReaction condition: β -naphthol (1 mmol), aldehyde (1 mmol), amide (1.1 mmol), aluminium sulphate (10 mol%) and PEG-400 (4 ml) at 80°C for 16 hr. ^bIsolated yield.

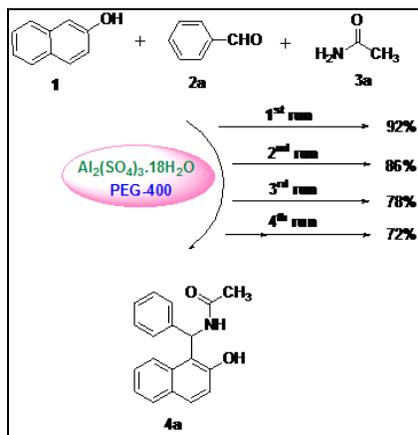
A study of the effects of the temperature (Table 1, entries 3, 11-14) showed that the yield of 4a increased with increasing reaction temperature from 60 to 80°C. But there was the slight decreased in yield when the temperature was further increased to 90°C (Table 1, entries 14). Thus 80°C is the optimum temperature. The reaction time was optimised at 16 hours (Table 1, entries 3, 15 and 16). In these reactions no corrosive substances were used and no waste formation was observed. The experimental procedure for these reactions was remarkably simple and required no toxic organic solvent or inert atmosphere. We found that the transformations could be accomplished by exposing a mixture of β -naphthol (1 mmol), benzaldehyde (1 mmol), acetamide (1 mmol) and aluminium sulphate (10 mol%) in 4 mL PEG-400 at 80°C for 16h.

Having optimized reaction conditions in hand, we explored the substrate scope of the aluminium sulphate in PEG-400 catalyzed various aryl aldehydes containing different functional groups were investigated (Table 2). Products containing electron-donating as well as electron withdrawing groups were obtained. Gratifyingly a variety of common functional groups such as alkyl, ether, halo, nitro and amino were tolerated regardless of the *meta*- or *para*-position. However *ortho* substituted aryl aldehyde gave lower yields of product, possibly due to steric hindrance.

Additionally, a reuse study of the aluminium sulphate in PEG-400 system was carried out for the reaction of 1a, 2 with 3a to obtain 4a. After stirring at 80°C for 16 hours, the reaction mixture was extracted with ethyl acetate (3 x 10 mL). The upper organic phase was removed, the solvent evaporated and the product 4a was isolated. The remaining inferior phase containing a mixture of aluminium sulphate in PEG-400 was dried under vacuum and directly reused for further reactions simply by adding more reagents 1a, 2 and 3a. Product 4a was obtained in 92%, 86%, 78% and 72% yields after successive cycles showing a good level of efficiency (Scheme 2).

Initially we screened catalyst loadings ranging from 0 to 15 mol%; the yield improved as the amount of aluminium sulphate catalyst increased from 0 to 10 mol% and became almost steady when the amount of catalyst was further increased beyond this (Table 1, entries 1-4). Only trace product was detected in absence of catalyst. We further studied various solvents such as 1,2-dichloroethane, ethanol, methanol, acetonitrile, water and poly-ethylene glycol

(PEG-400)(Table 1, entries 3, 5-9). Among the solvents examined, PEG-400 was found to be the best, providing excellent yields of the desired product 4a. On the other hand, the yields of these reactions did not exceed more than 16%, in absence of solvent, even after long reactions times (Table 1, entry 10).



Scheme 2: Recycle study of the catalytic system

CONCLUSIONS

In conclusion we have developed an efficient $\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$ catalysed, green method for the synthesis of amidoalkyl naphthol by using PEG-400 as the solvent. The mild reaction conditions, operational simplicity, volatile-solvent free conversion, application of a nontoxic and recyclable catalytic system, high yields and rapid formation of the products are the notable advantages of this method. These remarkable characteristics made this new protocol economically and eco-friendly attractive, inexpensive and offering the possibility of perform the reaction in the absence of toxic and volatile organic solvents.

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