



Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

MgSO₄ catalyzed one-pot multi-component reaction: Synthesis of amidoalkyl naphthols

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ABSTRACT

The development of highly efficient multicomponent reaction for the preparation of 1-amidoalkyl-2-naphthols using inexpensive and readily available MgSO₄ as an efficient Lewis acid catalyst is reported.

Key Words: Amidoalkyl naphthols, Multicomponent reaction, Magnesium sulphate, Solvent-free conditions

INTRODUCTION

A multicomponent reaction (MCR) is a convergent reaction, in which three or more starting materials react to form a single product, where essentially all or most of the atoms contribute to the newly formed product [1]. In recent years multicomponent reactions have gained much importance in organic syntheses, since they produce the desired products in a single operation without isolating the intermediates [2]. The advantages of MCRs are one pot reactions, consumes very less amount of solvents or no solvents (solvent free or neat reaction), superior atom economy [3a-c], generally take less time compare to divergent reactions, lower costs, simpler procedures and environmentally friendly [4a-c].

Amidoalkyl naphthols have interesting structural units with wide utility for the synthesis of various biologically active natural products and potent drugs including nucleoside antibiotics and HIV protease inhibitors such as ritonavir and lipinavir [5a,b]. It is noteworthy to remember that 1-amidoalkyl-2-naphthols can be converted to important biologically active 1-aminomethyl-2-naphthol derivatives by amide hydrolysis reaction. Since these compounds evaluated for depressor and bradycardia effects in humans [6,7]. 1-amidoalkyl-2-naphthols can also be converted to 1,3 oxazine derivatives [8]. 1,3-oxazines have potentially different biological activities including antibiotic [9], antitumor [10], analgesic [11], antipsychotic [12], antimalarial [13], antianginal [14], antihypertensive [15] and antirheumatic [16] properties.

Amidoalkyl naphthols can be prepared by multicomponent condensation of aldehydes, β -naphthol and different amides in the presence of various Lewis or Bronsted acids and also other catalysts such as Iodine [17], FeCl₃·SiO₂ [18], K₅CoW₁₂O₄₀·3H₂O [19], HClO₄-SiO₂ [20], ionic liquid [21a,b], P₂O₅ [22], cyanuric chloride [23], montmorillonite K10 [24a,b], sulfamic acid [25a,b], Thiamine hydrochloride [26], Sr(OTf)₂ [27], silica sulfuric acid [28], Yb(OTf)₂ [29], Ce(SO₄)₂ [30], *p*-TSA [31], Fe(HSO₄)₃ [32], molybdophosphoric acid [33], cation-exchange resins [34a] and Pentafluorophenylammonium Triflate (PFPAT) [34b]. However some of the reported methods suffer from certain disadvantages such as prolonged reaction time, use of carcinogenic solvents, use of toxic, highly acidic and expensive catalysts, unsatisfactory yield, high temperature and the use of additional microwave [35] or ultrasonic irradiation [25]. In view of these problems, development of an efficient and versatile method for the

preparation of 1-amidoalkyl-2-naphthols is an important aspect. Therefore, it is noteworthy to find a clean procedure using eco-friendly catalysts with high catalytic activity and short reaction time for the preparation of 1-amidoalkyl-2-naphthols.

Anhydrous magnesium sulfate is commonly used as a desiccant in organic synthesis due to its affinity for water. During work-up, an organic phase is saturated with magnesium sulfate until it no longer forms clumps. It is inexpensive and readily available. In our investigation towards the development of highly efficient multicomponent reaction for the preparation of 1-amidoalkyl-2-naphthols we found that MgSO_4 acts as an efficient Lewis acid catalyst for this transformation (Figure-1).

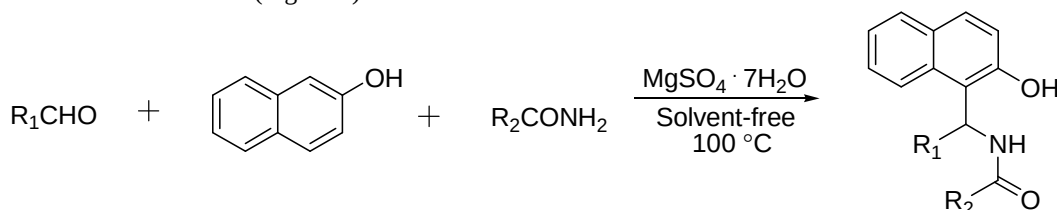


Figure1. Synthesis of amidoalkyl naphthols using $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ catalyst under solvent-free condition

EXPERIMENTAL SECTION

Procedure for the preparation of amidoalkyl naphthols

To a mixture of 2-naphthol (1 mmol), aldehydes (1 mmol) and acetamide/urea (1.1 mmol), $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ (15 mol%) was added. The mixture was stirred at 100 °C and the reaction was monitored by TLC. After completion of the reaction, crude product was cooled to 25 °C, then the solid residue was dissolved in boiling methanol and stirred it for 5 min. Then the solution was cooled to 25 °C, the solid so obtained was filtered and recrystallized from aqueous methanol (30% MeOH/ H_2O). Melting points and R_f values of TLCs of all the products were matching with reported compounds.

RESULTS AND DISCUSSION

Different aldehydes and amides were subjected to 15 mol% $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ mediated one pot multicomponent condensation with 2-naphthol to obtain the amidoalkyl naphthols. All reactions proceeded smoothly within 0.5 – 1 h (entries 1-10, Table-1) producing excellent yields.

Table 1. Synthesis of amidoalkyl naphthols with magnesium sulphate as a catalyst under solvent free condition

Entry	R ₁	R ₂	Time (h)	% of Yield	mp °C
1	C ₆ H ₅	CH ₃	1.0	91	224
2	C ₆ H ₅	NH ₂	1.0	92	170
3	4-Cl C ₆ H ₅	CH ₃	0.5	92	223
4	4-Cl C ₆ H ₅	NH ₂	0.5	94	167
5	3-NO ₂ C ₆ H ₅	CH ₃	0.5	92	234
6	3-NO ₂ C ₆ H ₅	NH ₂	1.0	93	182
7	4- NO ₂ C ₆ H ₅	CH ₃	0.5	94	231
8	4- NO ₂ C ₆ H ₅	NH ₂	0.5	93	176
9	4-Br C ₆ H ₅	CH ₃	0.5	72	260
10	4-Br C ₆ H ₅	NH ₂	0.5	88	166

Benzaldehyde was selected as a representative aldehyde along with 2-naphthol, acetamide or urea and $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ were reacted under solvent-free conditions at 100 °C in order to optimize the reaction conditions. The condensation of mixture of benzaldehyde (1 mmol) with 2-naphthol (1 mmol) and acetamide or urea (1.1 mmol) in the presence of $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ (0.15 mmol) was carried out at 100 °C for 1 hour under solvent-free conditions. Water was added to the reaction mixture and by simply filtering the mixture gave the crude product, which was purified by recrystallization from 30% methanol/water to obtain the amidoalkyl naphthols as solid compounds.

A plausible mechanism for the formation of 1-amidoalkyl-2-naphthols in presence of Lewis acid catalyst MgSO_4 is shown in Figure 2. The reaction of 2-naphthol with aromatic aldehydes in the presence of acid catalyst is known to

give *ortho*-quinone methides (*o*-QMs) [36a]. The nucleophilic addition of amides (acetamide or urea) to *o*-QMs intermediate is favourable *via* conjugate addition on the α,β -unsaturated carbonyl group that aromatizes to give the expected 1-amidoalkyl-2-naphthols (Figure 2) [36b].

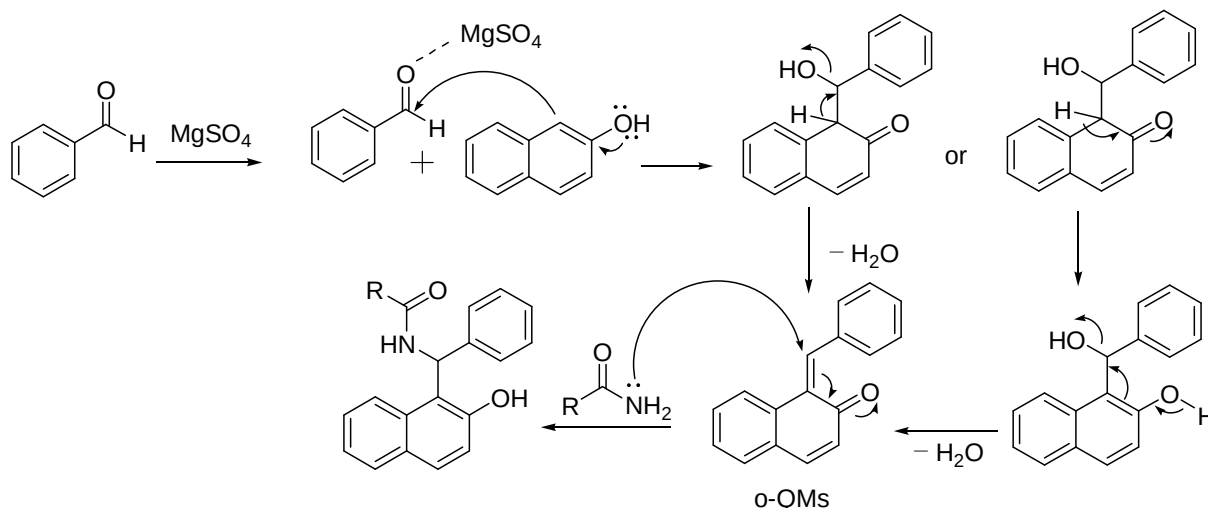


Figure 2. Possible mechanism for the synthesis of amidoalkyl naphthols by MgSO_4

The aromatic aldehydes with electron-withdrawing groups in *o*-QMs intermediate may react faster than the aromatic aldehydes with electron-donating groups. The rate of conjugate addition is higher to *o*-QMs as the LUMO of alkene in *o*-QMs is at lower energy in the presence of electron-withdrawing groups compared with electron-donating groups [36a].

CONCLUSION

In conclusion, an efficient, simple, novel and eco-friendly method for the synthesis of amidoalkyl naphthols is reported. By employing Magnesium sulphate catalyzed one-pot, MCR (three-component reaction) up on condensation reaction of 2-naphthol, aromatic aldehydes, and amide or urea under solvent-free conditions.

Acknowledgements

The authors thank Prof. G.V.P. Chandramouli, Prof. K. Laxma Reddy, former heads of the department and Prof. B. Rajitha present head of the department of chemistry, National Institute of Technology, Warangal for their constant encouragement.

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