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Citric Acid Catalyzed Synthesis of Amidoalkyl Naphthols under Solvent-free Condition: An Eco-friendly Protocol

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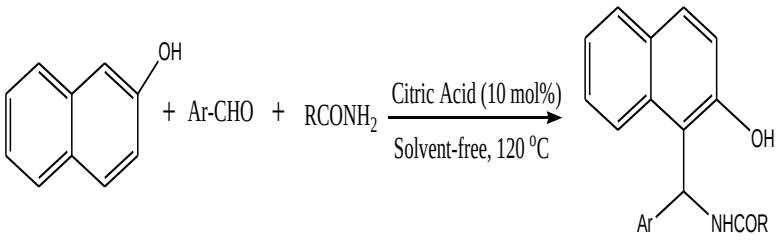
Abstract: *An efficient synthesis of amidoalkyl naphthols using Citric acid as a biodegradable catalyst is described. It involves the three-component reaction of 2-naphthol, aldehydes and amides/urea in the presence of catalytic amount of Citric acid under thermal solvent-free conditions.*
Keywords: *One-pot synthesis, Amidoalkyl npththols, Citric acid, Solvent-free conditions.*

I. Introduction

One-pot multi-component reactions have attracted a considerable attention in organic synthesis as they can produce the target products in a single operation without isolating the intermediates and thus reducing the reaction time and energy [1, 2]. Multi-component contribute to the requirements of an environment friendly process by reducing number of synthetic steps, energy consumption, less amount of solvents or no solvents and waste material production. One such example is the synthesis of amidoalkyl naphthols. Compounds bearing 1, 3-amino oxygenated functional groups are ubiquitous to a variety of biologically important natural products and potent drugs including a number of nucleoside antibiotics and HIV protease inhibitors, such as ritonavir and lipinavir. [3] Aminoalkyl naphthols have attracted strong interest to their useful biological and pharmacological properties such as adrenoceptor blocking, antihypertensive, and Ca2+ channel blocking activities [4-8]. Amidoalkyl naphthols are also important synthetic building blocks and are used as precursors for the synthesis of 1-aminomethyl-2-naphthol derivatives, which exhibit important cardiovascular activity [9]. The hypotensive and bradycardiac affects of these compounds have been evaluated [10].

Synthesis of amidoalkyl naphthols can be carried out by the multi-component condensation of aldehydes, 2-naphthols and amide/urea in the presence of Lewis or Bronsted acid catalysts such as chlorosulphonic acid [11], p-toluene sulphonic acid [12], $NaHSO_4.H_2O$ [13], $Fe(HSO_4)_3$ [14], $Sr(OTf)_2$ [15], Iodine [16], hetropoly acid $K5CoW12O40.3H_2O$ [17], and hetropoly acid catalysts like cation-exchange resins [18], silica supported perchloric acid [19,20], $FeCl_3.SiO_2$ [21], montmorillonite K10 clay [22], silica sulfuric acid [23], sulfamic acid [24,25], N,N,N',N'-tetrabromobenzene-1,3-disulfonamide [26]. Moreover, very recently P_2O_5/SiO_2 [27] magnetic nanoparticle-supported sulfuric acid [28] and MCM-41-N-propylsulfamic acid [29] has been used to carry out the synthesis. However some of the above reported methods suffer from disadvantages such as long reaction times [17], the use of expensive reagents [15], low yields of products [24, 25], high catalyst loading [23], corrosive reagents [11], strongly acidic conditions [19,20] and the use of an additional microwave oven [14], or ultrasonic irradiation [23].



Scheme 1: Citric acid catalyzed synthesis of 1-amidoalkyl-2-naphthols.

Therefore, to overcome these limitations, the discovery of a new, eco-friendly and easily available catalyst with high catalytic activity and short reaction time for the preparation of amidoalkyl naphthols is still desirable. The demand of eco-friendly benign procedure, promoted us to develop a safe alternative method for the synthesis of amidoalkyl naphthols.

Use of naturally as well as easily available and biodegradable catalyst for organic transformation is achieving enormous significance in the last few years as a result of both the novelty of the concept and, more importantly, the fact that the efficiency and selectivity of these reactions meet the standards of established organic reactions. In this regard, Citric acid keeps the potential of performing the role of ideal catalyst. It is a

relatively strong organic acid. Citric acid and its salts are widely used because they are nontoxic, relatively non-corrosive, safe to handle, and easily biodegradable. There are reports in the literature on the use of Citric acid as catalyst in organic synthesis [30-33]. Therefore, in continuation of our studies to develop neat methodologies in synthetic chemistry [33, 34], attempt has been made to carry out the synthesis of amidoalkyl naphthols using Citric acid as a biodegradable catalyst.

II. Results And Discussion

For our initial study, reaction of benzaldehyde, 2-naphthol, acetamide and Citric acid as catalyst was considered as a standard model reaction (Scheme 1). Model reaction in the absence of catalyst did not lead to product formation. It means intervention of catalyst was must for initiation of the reaction. So, the catalytic activity of Citric acid as an organopromoter was investigated on the model reaction under solvent-free condition.

To evaluate the temperature effect on reaction rate, the model reaction was performed at different temperature, 90 ^{o}C, 100 ^{o}C, 110 ^{o}C and 125 ^{o}C temperature. Temperature of 120 ^{o}C found to carry out the reaction efficiently in 90 % yield. Any further increase in temperature failed to enhance the reaction rate substantially, while lowering the temperature below 120 ^{o}C, slow down the reaction rate (**Table 1).**

To know the exact requirement of catalyst for the transformation, we investigated the model reaction using different concentrations of citric acid such as 5, 10, 15 and 20 mo l%. 10 mol % catalyst was found to be optimum (**Table 1)**. Increasing the amount further did not improve the yield.

Table 1. Optimization of Catalysts concentration for Entry (1) at various temperatures (under solvent-free condition)

Entry	Conc. (mol %)	Time((min.	Temp. ^{o}C	Yield[a] (%)
1	5	60	90	60
2	10	45	90	68
3	10	30	100	76
4	10	15	110	83
5	**10**	**15**	**120**	**87**
6	15	15	120	87
7	20	15	120	88

[a] Isolated yield.

Table 2. Synthesis of amidoalkyl naphthols catalyzed by Citric acid:

Entry	Ar	R	Time (Min.)	Product	Yield, (%)[a]	M.P. °C	Lit. mp , °C [Ref],[b]
1	C_6H_5	CH_3	40	4a	87	241-243	241-243[15]
2	4-Cl-C_6H_4	CH_3	18	4b	91	234-237	237-238[22]
3	4-MeO-C_6H_4	CH_3	22	4c	87	183-185	184-186[15]
4	4-NO_2-C_6H_4	CH_3	12	4d	93	235-236	237–238[22]
5	2-NO_2-C_6H_4	CH_3	43	4e	90	183-185	180-182[15]
6	2-Cl-C_6H_4	CH_3	18	4f	92	207-210	206-207[22]
7	C_6H_5	C6H_5	10	4g	90	234-235	234-236[17]
8	4-Cl-C_6H_4	C6H_5	15	4h	92	186-187	187-188[21]
9	4-MeO-C_6H_4	C6H_5	13	4i	88	206-207	206-208[22]
10	4-NO_2-C_6H_4	C6H_5	12	4j	93	236-238	237-239[26]
11	2-NO_2-C_6H_4	C6H_5	07	4k	92	266-268	266-267[22]
12	2-Cl-C_6H_4	C6H_5	10	4l	94	262-264	265-267[26]
13	C_6H_5	NH_2	35	4m	90	171-172	170–173[24]
14	4-Me-C_6H_4	NH_2	18	4n	91	115-118	117-118[21]
15	4-Cl-C_6H_4	NH_2	15	4o	93	166-168	168-169[24]

a= Isolated Yield.
b= Ref. No.

III. Experimental

Chemicals were purchased from S.D. fine chemicals [India] and used as such without further purification. Melting points were determined by an open capillary method and are uncorrected. IR spectra were recorded on Schimadzu FT-IR spectrophotometer. Samples were recorded on potassium bromide (KBr) discs. ^{1}H spectra were recorded in DMSO-d_6 as solvent on Brucker 200 MHz spectrophotometer. All the compounds are known compounds; their physical and spectroscopic data were compared with those reported in literature and found to be identical.

3.1 General procedure for the synthesis of amidoalkyl naphthols:

To a mixture of 2-naphthol (1 mmol), aromatic aldehyde (1 mmol) and amide (1.2 mmol), Citric acid (10 mol %) was added. The mixture was stirred at 120 ^{0}C in an oil bath. After completion of reaction (TLC check), the crude product was cooled to room temperature and washed with ice-cold water and stirred well. The catalyst is soluble in water and was removed from the reaction mixture. The pure product was obtained by recrystallization using ethyl alcohol.

3.2 Selected Characterization Data:

Entry 6: **IR** (KBr): 3426, 3057, 1647, 752. **^{1}H NMR** (200 MHz, DMSO-d6**)** δ10.41 (s, 1H), 9.17 (d, J =8.6Hz, 1H), 7.88 (m, 3H), 7.34 (t, J = 7.6Hz, 1H), 7.20 (m, 3H), 7.18 (d, J = 8.7Hz), 7.08 (d, J =8.7 Hz, 2H), 7.04 (d, J = 8.1 Hz), 1.64 (s, 3H).

Entry 10: IR (KBr): 3410, 2924, 1637, 820. **^{1}H NMR** (200 MHz, DMSO-d6**)** δ 10.38 (s, 1H), 9.09 (d, 1H, J = 8.4 Hz), 8.17 (d, 2H, J = 8.6 Hz), 8.04 (d, 1H, J = 8.4 Hz), 7.50-7.92 (m, 4H), 7.23-7.61 (m, 9H).

IV. Conclusion

In summary, we have developed an efficient, mild and clean synthetic protocol for the synthesis of amidoalkyl naphthols. In this protocol, attempt has been made to exploit catalytic activity of Citric acid in organic synthesis. Citric acid catalyzed the reaction efficiently without using any other harmful organic reagents/solvents. Moreover this method have the advantages of shorter reaction time, solvent-free condition, easy work up.

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