One-Pot Synthesis of Amidoalkyl Naphthols Using POCl₃/Na₂B₄O₇ as a Heterogeneous Catalyst

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Abstract: A convenient and efficient procedure for the synthesis of 1-amidoalkyl-2-naphthols by condensation of β -naphthol, aldehydes and amid/urea in the presence of POCl₃/Na₂B₄O₇ is described. This method offers several advantages including low cost and easy availability of the catalyst, environmentally friendly procedure and easy work-up under solvent-free conditions.

Keywords: 1-Amidoalkyl-2-naphthols, borax, multicomponent reactions, POCl₃

INTRODUCTION

The multicomponent reactions (MCRs) [1] are attracting the interest of organic chemists and other researchers due to their significant potential for converting more than two adducts directly into respective products in quantitative yields in a one-pot reaction as compared to conventional strategies used in multi-step synthesis of various biologically active organic compounds. MCRs are particularly useful to generate diverse chemical libraries of 'druglike' molecules for biological screening [2, 3]. One of these MCRs is the preparation of amidoalkyl naphthols. 1-amidoalkyl-2naphthols and their derivatives have attracted considerable interest in recent years due to biologically important antibacterial, natural products and potent drugs including a number of nucleoside antibiotics and HIV protease inhibitors, such as ritonavir and lipinavir [4, 5].

The preparation of 1-amidoalkyl-2-naphthols can be carried out by multi-component condensation of aryl aldehydes, 2-naphthol amide/urea in the presence of catalysts such as PPA-SiO₂, Iodine, $K_5COW_{12}O_{40}.3H_2O$, cation-exchange resins, HClO₄-SiO₂, Ce(SO₄)₂, Yb(OTF)₃ and Indium(III) Chloride [6-8]. However, many of these methodologies suffer from the drawback of green chemistry and have been associated with several shortcomings such as long reaction times, expensive reagents and low product yields. Therefore, to overcome these limitations, the search for a new, easily available catalyst with high catalytic activity for the preparation of amidoalkyl naphthols is strongly desirable.

The use of catalysts and reagents on solid supports has been developed because such reagents not only simplify purification processes but also help to prevent the release of reaction residue into the environment [9]. In continuation of our interest in the use of POCl₃/Na₂B₄O₇ (BPO) [10, 11] as a supported catalyst, we wish to report the synthesis of 1-amidoalkyl-2-naphthols **4** by condensation of aryl aldehydes,2-naphthol and amide/urea in the presence of $POCl_3/Na_2B_4O_7$ at 120 °C under solvent-free conditions (Scheme **1**).

RESULTS AND DISCUSSION

To study the feasibility of the BPO catalyzed in this reaction, the reaction of benzaldehyde (10 mmol) 2, β - naphthol (10 mmol) 1 and acetamide (12 mmol) 3 was selected as a model under solvent-free conditions. We first studied the model reaction catalyzed by 0.1 g BPO at different temperatures. The reaction rate was increased as the reaction temperature was raised. When it was carried out at 120 °C, the maximum yield was obtained in a short reaction period. Next, to evaluate the effect of catalyst concentration, the model reaction was carried out in the presence of different amounts of catalyst (0.05, 0.08, 0.1 and 0.12 g) at 120 °C. The result showed, that for the model reaction 0.1 g of catalyst was sufficient to achieve a fairly high yield (Table 1).

With the optimized condition established above, we then attempted to extend the process to β -naphthol, various types of aromatic aldehydes and different amides including acetamide, urea and benzamide under solvent-free conditions at 120 °C. The results have been summarized in Table 2. In all cases, 1-amidoalkyl-2-naphthols 4 were obtained in high to excellent yields without formation of any side products such as di-benzoxanthenes, which are normally observed under the influence of strong acids. Although as it can be seen from the results of Table 2, this reaction is affected by electronic and steric factors. Aldehydes with electronwithdrawing groups, give higher yields than aldehydes with electron-donating Aliphatic groups. aldehyde like propionaldehyde was also examined, but the yields were low as compared to aromatic aldehyde (Table 2, entry 15).

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Scheme 1.

 Table 1.
 Different Reaction Conditions for the Condensation of β-naphthol (10 mmol), Benzaldehyde (10 mmol) and Acetamide (12 mmol) in the Presence of BPO

Entry	BPO (gr)	Time (h)	Temperature (° C)	Yield (%) ^a
1	0.1	5	r.t	15
2	0.1	5	60	48
3	0.1	5	90	65
4	0.1	0.5	120	92
5	0.1	0.5	130	94
6	0.05	0.5	120	65
7	0.08	0.5	120	78
8	0.12	0.5	120	93

^aIsolated yield.

Table 2. Preparation of 1-amidoalkyl-2-naphthols

Entry	\mathbf{R}^{1}	R ²	Yield (%) ^a	Product	M.p (° C)	
					Found	Reported
1	Ph	CH ₃	92	4a	240-242	242-244 [6]
2	4-MePh	CH ₃	88	4b	220-223	220-222 [6]
3	4-ClPh	CH ₃	92	4c	227-229	228-229 [6]
4	2-ClPh	CH ₃	89	4d	193-195	194-196 [7]
5	4-MeOPh	CH ₃	85	4e	183-186	184-186 [6]
6	3-NO ₂ Ph	CH ₃	94	4f	213-215	212-215 [6]
7	Ph	NH ₂	86	4g	171-172	171-173 [6]
8	4-ClPh	NH_2	92	4h	211-213	210-212 [6]
9	2-ClPh	NH ₂	85	4i	150-152	150-153 [8]
10	3-NO ₂ Ph	NH ₂	92	4j	185-188	186-188 [6]
11	Ph	Ph	90	4k	232-235	234-236 [7]
12	4-MePh	Ph	82	41	191-193	192-193 [7]
13	4-ClPh	Ph	94	4m	176-179	177-178 [7]
14	3-NO ₂ Ph	Ph	93	4n	215-218	216-217 [7]
15	CH ₃ CH ₂	CH ₃	-	40	-	-

^aIsolated yield.

CONCLUSION

POCl₃/Borax is an inexpensive, easily available, noncorrosive and environmentally benign compound. A convenient and efficient procedure for the preparation of 1amidoalkyl-2-naphthols under solvent-free conditions was reported in this work. This thermal solvent-free green procedure not only affords the products in high to excellent yields but also avoids the problems associated with catalyst cost, handling and work-up procedure. Furthermore, the easy removal of the catalyst makes this method a better choice for chemical industries.

EXPERIMENTAL SECTION

POCl₃/Borax (BPO) was prepared according to the previous work [10]. All the products were known compounds, which were characterized by IR and ¹H-NMR spectral data and their m.p's compared with literature reports.

General Procedure for the Synthesis of 1-amidoalkyl-2-naphthols

To a mixture of β -naphthol (10 mmol), aldehydes (10 mmol), and amid or urea (12 mmol), BPO (0.1 g) was added and the reaction mixture was heated at 120 °C for 0.5 h. Then the mixture was washed thoroughly with water to remove the catalyst. The resulting precipitate was recrystalylied from ethanol:water (1:3) to afford pure amidoalkyls.

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