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Solvent Free Multi-component Synthesis of Amidoalkylnaphthols Using Phenylphosphinic Acid as an Organocatalyst

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Abstract: One pot solvent less synthesis of amidoalkylnaphthol derivatives via reaction of aldehydes, 2-naphthol and acetamide/urea in the presence of phenylphosphinic acid is described. This methodology provides a simple synthetic route to amidoalkylnaphthols in good to high yields.

Key words: Amidoalkylnaphthol; Aldehyde; Naphthol; Amide/Urea; Phenylphosphinic acid.

1.Introduction

Amidoalkylnaphthol derivatives have attracted the organic chemists interest due to their biological, medicinal and pharmacological activities [1]. It is noteworthy that 1-amidoalkyl-2-naphthols can be converted to hypertensive and bradycardia active 1-aminoalkyl-2-naphthol derivatives by amide hydrolysis reaction [2].

The preparation of 1-amidoalkyl-2-naphthols can be carried out by multi-component condensation of aldehydes, 2-naphthol and urea or amide in the presence of Lewis or Brønsted acid catalysts such as montmorillonite K10-clay [3], silica-sodium hydrogen sulphate [4], Iodine [5], $K_5CoW_{12}O_{40}.3H_2O$ [6],*p*-TSA [7], sulfamic acid [8], proticpyridinium ionic liquid [9],poly(4-vinylpyridinium butane sulfonic acid) hydrogen sulfate [10], and cation-exchange resins [11].However, some of these methods suffer from some drawbacks such as prolonged reaction times, low yields and using toxic catalyst.

Organocatalysts are usually inexpensive, available, and non-toxic. Due to their inertness towards oxygen and moisture, demanding reaction conditions, for example inert atmosphere, low temperatures and absolute solvents, are in many instances, not required [12].

Here in, we report a simple and convenient procedure for the preparation of 1-amidoalkyl-2-naphthols in high yields using 2-naphthol, aldehydes and acetamide or urea in the presence of phenylphosphinic acid as an organocatalyst (Scheme 1).

2. Experimental Section

2.1. Materials and methods

Materials were purchased from Fluka and Merck companies. Products were characterized by comparison of their spectroscopic data (^{1}H NMR and ^{13}C NMR).

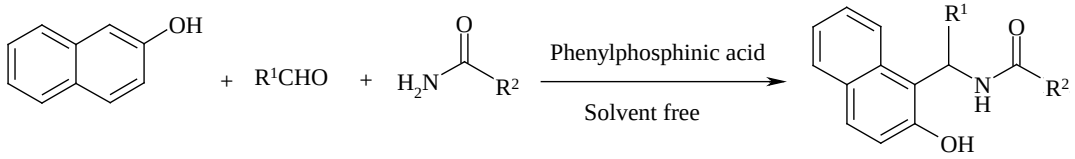
2.2. General procedure for the synthesis of 1-amidoalkyl-2- naphtols

A mixture of aldehyde (1 mmol), 2-naphthol (1 mmol), urea/acetamide (2mmol), phenylphosphinic acid (10 mol%) was heated in an oil bath at 120 °C under solvent free conditions for the appropriate time according to Table 3. (The progress of reaction was monitored by TLC). After completion of the reaction, the mixture was washed with water to remove the catalyst. The resulting precipitate was recrystalyzed from Ethanol:Water (1:3) to afford pure 1-amidoalkyl 2-naphthol. If necessary the products were further purified by column chromatography on silica gel with suitable eluents.

3. Results and discussion

In this work, we initially treated benzaldehyde (1 mmol) with 2-naphthol (1 mmol) and urea (2 mmol) in the presence of phenylphosphinic acid (10 mol%) for the preparation of 1-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)urea in various temperatures under solvent-free conditions (Table 1). As it is clear from this Table, the highest yield of 1-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)urea was obtained at 120 °C in shorter reaction time (Table 1, entry 4).

To evaluate the quantity of catalyst, different amounts of phenylphosphinic acid was used and the products were obtained in 30–80% yields (Table 2). It was observed that this reaction proceed well in the presence of 10 mol% of catalyst (Table 2 entry3).



R^1= Aryl

R^2= NH_2, Me

Scheme 1

Table 1. Optimization of Preparation of 1-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)urea at different temperatures.

Entry	Temperature (°C)	Time (min)	Yield (%)[a]
1	25	180	_
2	80	120	80
3	100	180	50
4	120	20	80
5	150	20	50

[a]Yields refer to the isolated pure products.

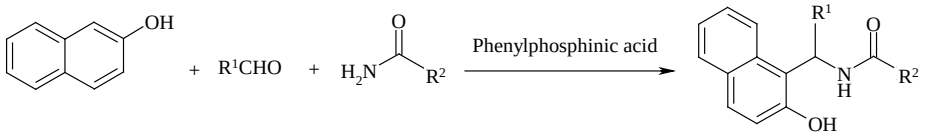
Table2. Screening of catalyst concentration on model reaction

Entry	Catalyst (mol%)	Time (min)	Yield (%)[a]
1	2	180	60
2	5	30	50
3	10	20	80
4	20	120	30

[a] Isolated yield.

In order to show the generality of this reaction we synthesized different substituted amidoalkyl-2-naphthol using multi-component reaction of 2-naphthol, various aldehydes and amides or urea in the presence of phenylphosphinic acid as an organocatalyst under solvent free conditions (Table 3).

Table 3. Preparation of 1-amidoalkyl-2-naphthol derivatives.[a]



Entry	R^1	R^2	Time(min)	(%)Yield[b]	Mp (lit. m.p.)/°C[ref.]
1	C_6H_5	NH_2	20	80	176-178(177-178)[13]
2	4-BrC_6H_4	NH_2	25	98	169-170(170-172)[8]
3	4-ClC_6H_4	NH_2	20	95	166-168(160-168)[11]
4	2-ClC_6H_4	NH_2	20	85	150-152(149-151)[6]
5	3- $O_2NC_6H_4$	NH_2	25	87	190-192(191-193)[13]
6	4-$O_2NC_6H_4$	NH_2	20	95	164-166(164-166)[14]
7	4-MeC_6H_4	NH_2	35	85	116-117(117-118)[15]
8	4-$MeOC_6H_4$	NH_2	25	78	169-171(168-170)[4]
9	C_6H_5	CH_3	30	80	240-242(240-242)[4]
10	4-BrC_6H_4	CH_3	35	85	229-230(226-228)[3]
11	4-ClC_6H_4	CH_3	35	83	226-228(225-227)[4]
12	4- $O_2NC_6H_4$	CH_3	25	80	246-248(248-249)[16]
13	4-$MeOC_6H_4$	CH_3	50	60	183-185(182-184)[4]
14	4-MeC_6H_4	CH_3	50	80	213-215(215-216)[13]

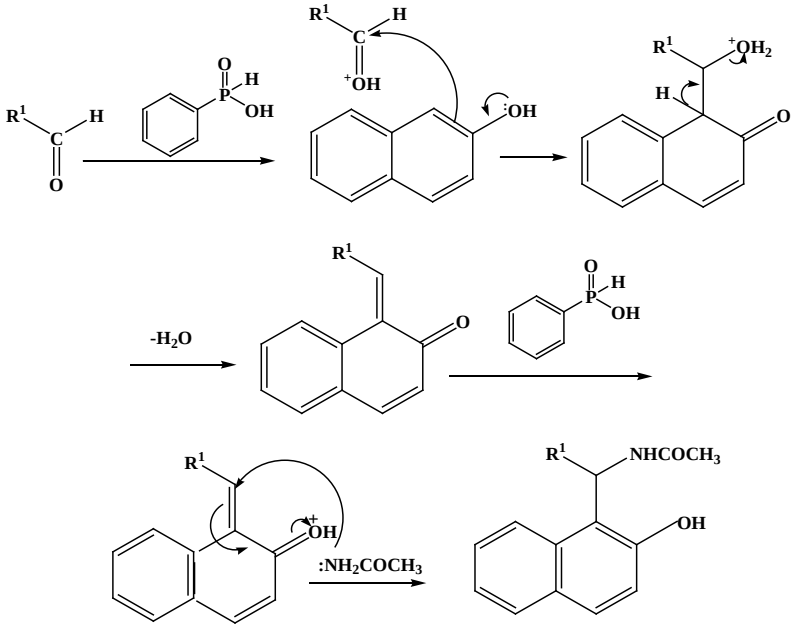
[a] Reactions were performed using 2-naphthol (1 mmol), aldehydes (1 mmol) and urea/acetamide (2 mmol) at 120°C under solvent free conditions.
[b]Isolated yield.

As shown in Table 3, various aromatic aldehydes bearing electron-withdrawing groups and electron-donating groups reacted with urea in the presence of phenylphosphinic acid under optimal reaction conditions to give desired 1-amidoalkyl-2-naphthols in high yields at short time (Table 3, entries 1-8).

Attempts to bring aliphatic aldehyde such as isobutyraldehyde into the reaction with naphthol and urea under the mild conditions were mostly unsuccessful. This reaction was also successfully performed with amide in high yield.

For example, when acetamide, 2-naphthol and benzaldehyde were used, the reaction was complete under solvent free conditions and desired amidoalkylnaphthol was obtained in 80% yield (Table 3, entry 9).

An investigation of this method indicated that the reaction of acetamide with electron-withdrawing or electron-donating substituted benzaldehyd afforded amidoalkylnaphthols under optimal reaction conditions (Table 3, entries 10-14).A plausible mechanism for the formation of amidoalkylnaphthol is shown in scheme 2 [17].



Scheme 2

3.1. Spectral data for the selected compound

N-[(4-Nitro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (Table 3, entry 12).

^{1}H NMR (DMSO-d_6): δ (ppm)= 2.02 (s, 3H), 7.16 (d, J = 8.0Hz, 1H), 7.22 (d, J = 8.8, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.39 (t, J = 8.8, 1H), 7.79–7.86 (m, 3H), 7.81 (d, J = 8.8 Hz, 2H) 8.58 (d, J=8.0 1H), 10.11(s, 1H).

^{13}C NMR (DMSO-d_6): δ (ppm)=22.9 , 48.3, 118.3, 118.7, 118.8, 123.0, 123.7, 127.2, 127.6, 128.7, 128.9, 129.1,130.3, 132.6,143.9, 151.7,170.2.

4. Conclusion

We have developed an efficient and versatile method for the synthesis of 1-amidoalkyl-2-naphtols viabenzaldehydes, *β*-naphthol and urea/acetamide in the presence of phenylphosphinic

acid as an organocatalyst under solvent free conditions. The simple experimental procedure and using catalytic amount of catalyst are notable advantages of this method.

5. References

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