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Zwitterionic-type molten salt: An efficient mild organocatalyst for synthesis of 2-amidoalkyl and 2-carbamatoalkyl naphthols

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ABSTRACT

A green, general, and efficient method has been developed for the synthesis of 2-amidoalkyl and 2-carbamatoalkyl naphthol derivatives through a one-pot three-component condensation of 2-naphthol, aldehydes and amide or carbamates in the presence of zwitterionic-type molten salt as mild organocatalyst under solvent-free conditions.

1. Introduction

One-pot catalytic conversion of organic reactions with readily available, non-toxic, and inexpensive reagents has attracted significant research interest in recent years [1]. Multicomponent reactions with atom-economy under catalytic solvent-free conditions are ideal protocols for the development of environment-friendly and cost-advantageous chemical processes [2,3]. 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 [4,5]. 2-Amidoalkyl and 2-carbamatoalkyl naphthol derivatives are of significant importance because of their promising biological and pharmaceutical activities [6,7]. With the aim to improve the reaction's efficiency, several methods have been developed using different catalysts such as montmorillonite K10 clay [8], $Ce(SO_4)_2$ [9,10], iodine [11], $K_5CoW_{12}O_{40}\cdot 3H_2O$ [12], p-TSA [13], sulfamic acid [14], cation-exchanged resins [15], silica-sodium hydrogen sulphate [16], silica-perchloric acid [17,18], acidic ionic liquid [19], and phosphorus pentaoxide [20] for synthesis of 2-amidoalkyl naphthol derivatives by condensation of aryl aldehydes, 2-naphthol, and amide. Although these methods are quite useful, many of these methods suffer from limitations such as the requirement for a large excess of reagents, long reaction times, harsh reaction conditions and also involvement of toxic solvents. The recovery and reusability of the catalyst are also a problem. By contrast with 2-amidoalkyl naphthols, a few reports was found describing the synthesis of 2-carbamatoalkyl naphthols [16,21]. In addition, most of these reactions were limited to only aromatic aldehydes. Thus, there is a need for a simple, environment-friendly efficient and more general method for the synthesis of these useful derivatives. Recently, we reported the reaction of 2-naphthol and aldehyde (2:1) to form dibenzoxanthenes [22] and the condensation of 2-naphthol, aldehydes and urea (1:1:1.5) to form naphthoxazinones [23]. Our goal is to develop a tandem process that would allow *in situ* trapping of *ortho*-quinone methides [24–26] with nitrogen nucleophiles to provide a rapid access to amidoalkyl naphthol derivatives.

As a part of our continuing programme to explore molten salt promoted novel reactions [27,28], we have observed that an imidazole-based zwitterionic-type molten salt, 4-(1-imidazolium) butane sulfonate (IBS) promotes the condensation of 2-naphthol, aldehyde and carbamate or amide to produce 2-amidoalkyl and 2-carbamatoalkyl naphthol derivatives under solvent-free conditions (Scheme 1).

2. Results and discussions

In a typical experimental procedure, a mixture of 2-naphthol, aldehyde and amide in presence of 10 mol% molten salt was heated at 80 °C for a certain period of time as required to complete the reaction. A wide range of structurally diverse aldehydes underwent condensation by this reaction to provide 2-amidoalkyl naphthol derivatives in excellent yields. The results are summarized in Table 1. As evident from the results, this procedure is uniformly effective for both aliphatic and aromatic aldehydes. The aliphatic aldehydes such as *n*-butyraldehyde, *iso*-butyraldehyde, and valeraldehyde were subjected under the reaction conditions and corresponding desired products were isolated

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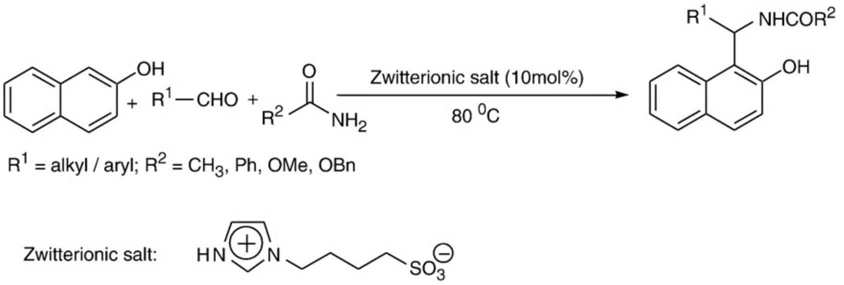


Scheme 1. Three-component synthesis of 2-amidoalkyl and 2-carbamatoalkyl naphthols.

in excellent yields. Aromatic aldehydes with both activating and deactivating groups such as such as Me, OMe, Cl, Br, F and NO_2 reacted to afford the corresponding products almost equally in high yields. Both acetamide and benzamide underwent smooth transformation under the reaction conditions.

In addition, the scope and efficiency of the reaction were explored for the synthesis of 2-carbamatoalkyl naphthols using carbamate, 2-naphthol and aldehydes. The desired products were obtained in good yields without formation of any side products (Table 2). The condensation reaction proceeded very well with aliphatic aldehydes such as propionaldehyde, *n*-butyraldehyde, *iso*-butyraldehyde, and cyclohehaxecarboxaldehyde under the reaction conditions. The efficiency and generality of present protocol can be realized by direct comparing the entry 1 presented here with a recently reported method [16] where same reaction did not proceed. However, heteroaromatic aldehydes do not produce the corresponding 2-carbamatoalkyl naphthols, instead leads to multiple products.

A mechanistic rationale portraying the probable sequence of events is given in Scheme 2. The reaction is believed to proceed through the formation *o*-quinone methide (*o*-QM) intermediate [24–26]. Further, nucleophilic conjugate addition of amide or carbamate on *o*-QM intermediate leads to the formation of amidoalkyl naphthol as a product in excellent yields. In this reaction, the zwitterionic-type molten salt may act a bifunctional organocatalyst [28–30]. It could activate both aldehydic carbonyl oxygen and acidic hydrogen of 2-naphthol [31].

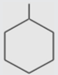
Our attention was then turned to the possibility of recycling the catalyst from the reaction media since the recovery and reuse of the catalyst are highly preferable for a greener process. At the completion of the reaction, the reaction mixture was poured into crushed ice and stirred for 5–10 min. The solid separated was filtered under suction. The catalyst was recovered from the aqueous layer after evaporation under reduced pressure, and reused for subsequent reactions. The reusability of the catalyst was investigated by using 2-naphthol, benzaldehyde and benzamide as model substrates. After five recycles, the catalyst still had a high activity and gave the corresponding product in good yield (77% for entry 11, Table 1).

Table 1
Preparation of amidoalkyl naphthols.

Entry	Aldehyde R^1	Amide R^2	Time h/(min)	Yield[a](%)
1	n-C_3H_7	Me	(20)	75
2	n-C_4H_9	Me	(25)	74
3	Me_2CH	Ph	(20)	75
4	Ph	Me	2	80
5	4-OMe-C_6H_4	Me	3	75
6	4-F-C_6H_4	Me	2	85
7	4-Br-C_6H_4	Me	2	84
8	4-Cl-C_6H_4	Me	2	85
9	3-NO_2-C_6H_4	Me	1.5	88
10	4-NO_2-C_6H_4	Me	1.5	90
11	Ph	Ph	2	80
12	4-Me-C_6H_4	Ph	2	78
13	4-Cl-C_6H_4	Ph	2	84
14	3-NO_2-C_6H_4	Ph	2	90

[a] Isolated yield.

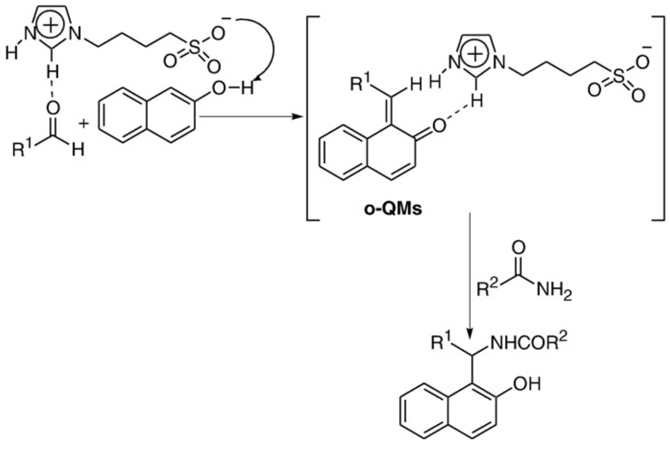
Table 2
Preparation of carbamatoalkyl naphthols.

Entry	Aldehyde R^1	Carbamate R^2	Time h/(min)	Yield[a](%)
1	C_2H_5	OMe	(15)	72[b]
2	n-C_3H_7	OMe	(20)	77
3	Me_2CH	OMe	(20)	76
4		OMe	(25)	74
5	Ph	OMe	2	78
6	4-Cl-C_6H_4	OMe	2	82
7	3-NO_2-C_6H_4	OMe	1.5	85
8	4-NO_2-C_6H_4	OMe	1.5	88
9	Ph	OBn	2	75
10	2-Cl-C_6H_4	OBn	3.5	72

[a]Isolated yield. [b]Propionaldehyde was taken 1.5 equiv. w.r.t. 2-naphthol.

3. Experimental

Typical procedure for the synthesis of Methyl [1-(2-Hydroxynaphthalen-1-yl)-butyl] carbamate (entry 2, Table 2): A mixture of 2-naphthol (288 mg, 2 mmol), *n*-butyraldehyde (179 µl, 144 mg, 2 mmol), and methylcarbamate (165 mg, 2.4 mmol) was taken in a round-bottom flask with glass stopper in presence of molten 4-(1-imidazolium) butane sulfonate (41 mg, 10 mol%) and the whole mixture was stirred at 80 °C (oil bath) for 20 min as indicated by TLC for a complete reaction. The reaction mixture, being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5–10 min. The solid separated was filtered under suction. The aqueous layer consisting of zwitterionic salt was extracted with ethyl acetate (5 mL) to remove the organic impurities. The catalyst was recovered from aqueous layer after evaporation under reduced pressure and used for subsequent reaction. The analytical pure sample was prepared by recrystallization



Scheme 2. A plausible reaction mechanism.

from ethanol (420 mg, 77% as white powder). mp 160–161 °C; IR (KBr) 3305, 2954, 1685, 1525, 1340 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 9.97$ (s, 1H), 8.10 (d, $J = 8.1$ Hz, 1H), 7.76 (d, $J = 8.1$ Hz, 1H), 7.67 (d, $J = 8.7$ Hz, 1H), 7.44 (t, $J = 7.5$ Hz, 1H), 7.26 (t, $J = 7.5$ Hz, 1H), 7.17 (d, $J = 9.0$ Hz, 2H), 5.53 (q, $J = 7.2$ Hz, 1H), 3.48 (s, 3H), 2.02–1.96 (m, 1H), 1.81–1.74 (m, 1H), 1.37–1.33 (m, 1H), 1.25–1.14 (m, 1H), 0.87 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 156.2$, 152.8, 132.1, 128.6, 128.5, 128.3, 126.3, 122.4 (2 °C), 119.9, 118.5, 51.3, 48.0, 36.4, 19.6, 13.8; Anal. Cald. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.18; H, 6.92; N 4.94.

4. Conclusion

In summary, we have demonstrated herein that imidazole-based zwitterionic-type molten salt is a new class of bifunctional organocatalyst for the synthesis of 2-amidoalkyl and 2-carbamatoakyl naphthol derivatives through a three-component condensation reaction under solvent-free conditions. The present procedure is equally effective to aliphatic and aryl aldehydes. The non-hazardous experimental conditions, reusable catalyst, ease of reaction, short reaction times, high yields, and metal-free catalyst are the notable advantages of this procedure. Thus, it provides a better and more practical alternative to the existing methodologies.

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