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Original article

Caffeine catalyzed green synthesis of novel benzo[*a*][1,3]oxazino[6,5-*c*] phenazines *via* a one-pot multi-component sequential protocol in a basic ionic liquid

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ABSTRACT

Caffeine was applied as a green and natural catalyst for the one-pot, four-component sequential condensation between 2-hydroxy-1,4-naphthoquinone, aromatic 1,2-diamines, ammonium thiocyanate and acid chlorides in the presence of a basic ionic liquid (1-butyl-3-methylimidazolium hydroxide) to afford the corresponding benzo[*a*][1,3]oxazino[6,5-*c*]phenazine derivatives. In this one-pot transformation, five bonds and two new rings are efficiently formed. This protocol has the advantages of operational simplicity, high yields, easy workup, avoidance of hazardous or toxic catalysts and organic solvents and high chemo- and regioselectivities.

1. Introduction

In recent years, interest in green chemistry [1–3] has developed, and a major challenge to organic chemists is to identify facile, efficient, and nonpolluting synthetic procedures that reduce the use of organic solvents and toxic reagents. In this area, use of natural materials as promising catalysts in organic reactions has received a considerable amount of attention due to their green credentials [4,5] and also ionic liquids (ILs) have become increasingly popular over the last few years in the field of green organic synthesis [6] owing to several advantages such as their catalytic role, ability to dissolve a wide range of materials and mild reaction conditions, non-inflammability, high isolation and purification yields, reusability and high thermal stability [7,8].

In order to achieve economic savings and pollution prevention, multi-component reactions [9–12] (MCRs) have considerable ecological interest as a powerful strategy in the synthesis of complex heterocyclic molecules, drug design and drug discovery, arising from minimization of time, waste, energy, and cost.

Functionalized nitrogen- and oxygen-containing heterocyclic molecules play key roles in medicinal chemistry [13]. Among them, oxazines and their derivatives have been recognized as an important class of heterocyclic compounds due to a diversity of biological functions [14–16]. Both natural and synthetic oxazine compounds exhibit a wide range of biological activities, including anticoagulant [17], fungicidal [18], AMPA receptors modulation [19], analgesic, antispasmodic [20], antidiabetic and hypolipidaemic activities [21].

Also, phenazine-based compounds are nitrogen-containing heterocycles that have been illustrated to possess numerous biological functions including antimicrobial [22], antimycobacterial [23], antifungal [24] and antitumour [25] activities. For example, pyridophenazinediones and pyridazinophenazinedione derivatives are antitumor agents [26,27].

Considering the significance of oxazine and phenazine derivatives and as part of our continuing interest in the development of new synthetic methods for heterocyclic compounds [28–32] herein, we report a green and efficient method for the synthesis of novel benzo[*a*][1,3]oxazino[6,5-*c*]phenazine derivatives through a sequential, one-pot, four-component condensation reaction between 2-hydroxy-1,4-naphthoquinone **1**, 1,2-diamines **2**, ammonium thiocyanate **4** and acid chlorides **5** catalyzed by caffeine as a green and natural catalyst in 1-butyl-3-methylimidazolium

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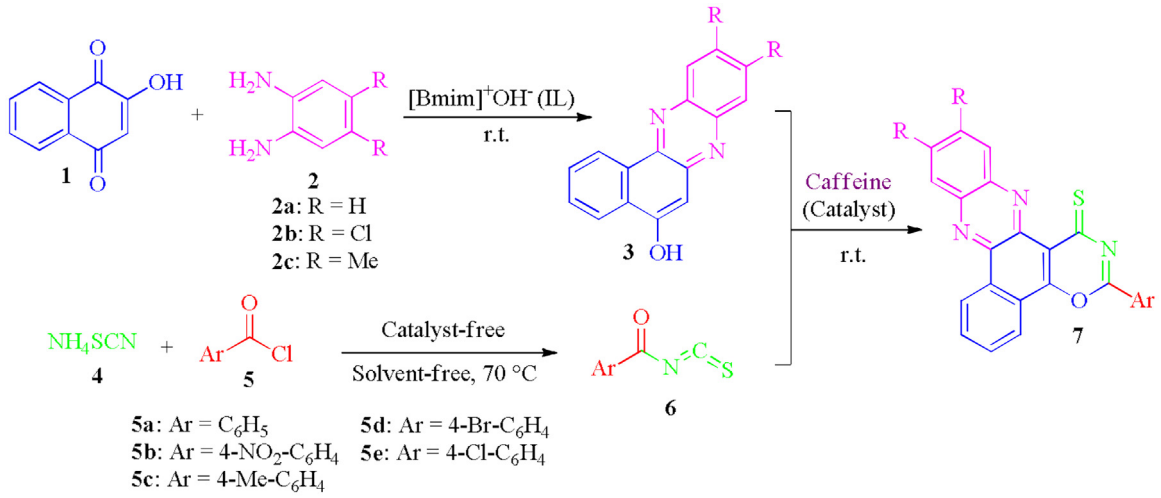

Scheme 1. One-pot, four-component synthesis of novel benzo[*a*][1,3]oxazino[6,5-*c*]phenazine derivatives in the presence of caffeine as a natural and solid base catalyst.

hydroxide (ionic liquid), which acts as reaction medium as well as a basic catalyst and is easily prepared (Scheme 1).

2. Results and discussion

Benzo[*a*][1,3]oxazino[6,5-*c*]phenazine derivatives can be synthesized *via* a three-step procedure: in the first step, 2-hydroxy-1,4-naphthoquinone **1** (1 mmol) and 1,2-diamines **2** (1 mmol) were mixed at room temperature until benzo[*a*]phenazines **3** was formed (<30 min) in $[bmim]^+OH^-$ (ionic liquid). Then, ammonium thiocyanate **4** (1 mmol) and acid chlorides **5** (1 mmol) were mixed at 70 °C (solvent-free) to produce a solid of aroyl isothiocyanate derivatives **6**. The final step involves the reaction between the products of the first step **3** with aroyl isothiocyanate derivatives **6** in the presence of caffeine in $[bmim]^+OH^-$ to form the corresponding products **7**.

To further appraise the activity of the catalyst, the one-pot four-component reaction of 2-hydroxy-1,4-naphthoquinone **1** (1 mmol), benzene-1,2-diamine **2a** (1 mmol), ammonium thiocyanate **4** (1 mmol) and benzoyl chloride **5a** (1 mmol) in $[bmim]^+OH^-$ (IL) was selected as a model reaction and the yield and reaction time were monitored in different molar ratios of caffeine. The obtained results have been summarized in Table 1. As shown in Table 1, higher yield and shorter reaction time were obtained when the reaction was carried out in the presence of 20 mol% of the catalyst (Table 1, entry 4).

With the optimized conditions in hand, the scope and efficiency of the reaction were explored for the synthesis of benzo[*a*][1,3]oxazino[6,5-*c*]phenazine derivatives. Thus, 2-hydroxy-1,4-naphthoquinone **1** was condensed with various aromatic 1,2-diamines **2**, ammonium thiocyanate **4**, and different acid chlorides **5** in the presence of caffeine (20 mol%) in ionic liquids at room temperature. The results are shown in Table 2.

Table 1
Condensation reaction between **1** (1 mmol), **2a** (1 mmol), **4** (1 mmol), and **5a** (1 mmol) in the presence of different amounts of caffeine in $[bmim]^+OH^-$ (IL) at room temperature.

Entry	Catalyst (mol %)	Time (h)	Yield (%)[a]
1	–	8	46
2	10	6	77
3	15	5	85
4	20	2	91
5	30	2	90

[a] Isolated yield.

Table 2
Synthesis of novel benzo[*a*][1,3]oxazino[6,5-*c*]phenazine derivatives **7** from the reaction of **1**, **2**, **4** and **5** in the presence of caffeine (20 mol%) as catalyst in $[bmim]^+OH^-$ (IL) at room temperature.

Entry	R	Ar	Product	Time (h)	Yield (%)[a]
1	H	C_6H_5	**7a**	2	91
2	H	4-NO_2-C_6H_4	**7b**	2	92
3	H	4-Me-C_6H_4	**7c**	4	86
4	H	4-Br-C_6H_4	**7d**	3	90
5	H	4-Cl-C_6H_4	**7e**	3	88
6	Cl	C_6H_5	**7f**	3	88
7	Cl	4-NO_2-C_6H_4	**7g**	3	90
8	Cl	4-Me-C_6H_4	**7h**	4	86
9	Me	C_6H_5	**7i**	4	87
10	Me	4-NO_2-C_6H_4	**7j**	4	90

[a] Isolated yields.

In the first step of this one-pot sequential reaction, different aromatic 1,2-diamines containing benzene-1,2-diamine, 4,5-dichlorobenzene-1,2-diamine and 4,5-dimethylbenzene-1,2-diamine were condensed with 2-hydroxy-1,4-naphthoquinone to form the corresponding benzo[*a*]phenazines. Using benzene-1,2-diamine, higher yields of the products were obtained in shorter reaction times in comparison with 4,5-dichlorobenzene-1,2-diamine and 4,5-dimethylbenzene-1,2-diamine (Table 2, entries 1, 6, and 9).

In the next step of this sequential protocol, various acid chlorides containing electron-withdrawing groups and electron-donating groups were used. In all cases the products were obtained in good to high yields (Table 2, entries 1–10).

The structures of all the newly synthesized compounds were characterized by IR, ^1H NMR, and ^{13}C NMR spectroscopy and by elemental analysis. The mass spectra of these compounds displayed molecular ion peaks with the appropriate *m/z* values.

We also studied the recycling of the ionic liquid using a selected model reaction of 2-hydroxy-1,4-naphthoquinone, benzene-1,2-diamine, ammonium thiocyanate and benzoyl chloride in the presence of caffeine (20 mol%) in $[bmim]^+OH^-$ (0.5 mL) at room temperature (Table 2, entry 1). After the completion of the reaction, 5 mL of water was added and the precipitate was filtered off for the separation of crude products. After washing the solid products with water completely, the water containing ionic liquid (ionic liquid is soluble in water) was evaporated under reduced pressure and ionic liquid was recovered and reused. As shown in Fig. 1, the reaction media could be successfully recycled for up to