Synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e] [1,3]oxazine-3-one catalyzed by pyridinium-based ionic liquid

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Abstract Some pyridinium-based functionalized ionic liquids have been used as novel catalysts for the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-one derivatives via the one-pot multi-component condensation of β -naphthol, aromatic aldehydes, and urea under solvent-free conditions, to afford good to excellent yields ranging from 76 to 91 % within 60 min. A possible mechanism to account for the reaction is proposed.

Keywords Naphthoxazinone · Synthesis · Pyridinium-based ionic liquid · Solvent-free · Multi-component reaction

Introduction

One-pot multi-component reactions (MCRs) have gained wide applicability in the field of synthetic organic chemistry, as they increase the efficiency of the reaction and decrease the number of laboratory operations, along with quantities of solvents and chemicals used. Since they are performed without the need to isolate any intermediate, the process reduces the reaction time and saves both energy and raw materials. Therefore, the design of novel MCRs has attracted a great deal of attention from research groups working in the field of medicinal chemistry, drug discovery, and materials science [1-5].

Aromatic-condensed oxazinone derivatives are an important class of heterocyclic compounds studied, because many of these heterocyclic systems exhibit biological activities as potential antimicrobial agents, anti-inflammatory, acetylcholinesterase inhibitor, analgesics, bactericides, and muscle relaxants [6–8].

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Several synthetic methods for benzoxazinones have been reported in the literature; however, very few were concerned with the synthesis of naphthalene-condensed oxazinone derivatives reported in the literature. Szatmari et al. [9] reported the syntheses of naphthalene-condensed 1,3-oxazin-3-ones derivatives by condensation of amino alkylnaphthols as precursors with phosgene in the presence of triethylamine, Cimarelli et al. [10] synthesized these compounds using carbonyl diimidazole instead of phosgene. Bazgir and co-workers [11] reported a one-pot synthesis of naphthoxazinone derivatives with the same reactants under the irradiation of MW. Recently, Mahdavinia and co-authors [12] reported the solvent-free synthesis of similar naphthoxazinone in the presence of perchloric acid supported on silica. Therefore, the development of novel, simple, and green methods for the synthesis of naphthoxazinone derivatives are of great importance.

In recent years, ionic liquids have attracted increasing attention due to their particular properties, such as negligible vapor pressure, wide liquid range, high thermal stability, and making them a greener alternative to volatile organic solvents. In addition, Brønsted acidic task-specific ionic liquids (TSILs) have a dual role (solvent and catalyst) in multi-component reactions [13–18] to afford higher yields and selectivity against traditional acid catalysts. In fact, the use of Brønsted acidic TSILs as catalysts is an area of ongoing activity, and it is currently a hot area for the development and exploration of TSILs in multi-component.

In continuation of our work on clean MCRs, and considering the importance of ionic liquid catalytic systems [19, 20], we synthesized some pyridinium-based functionalized ionic liquids (Py-FILs) including *N*-propanesulfonic acid pyridinium-hydrogen sulfate ([PSPy][HSO₄]), *N*-propanesulfonic acid hexafluorophosphate ([PyPS][PF₆]), *N*-propanesulfonic acid tetrafluoroborate ([PyPS][BF₄]), *N*-propanesulfonic acid dihydrogen phosphate ([PyPS][H₂PO₄]) (Fig. 1). These ionic liquids were investigated to catalyze for the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine.

Results and discussion

In the initial study, the reaction of 2-naphthol, benzaldehyde and urea was selected as the model. We screened some pyridinium-based ionic liquids with different anions for their ability to catalyze the model reaction under different thermal conditions. A variety of them, such as [PSPy][HSO₄], [PyPS][H₂PO₄], [PyPS]p-TSA, [PyPS][BF₄], and [PyPS][PF₆], were investigated for comparison.

We found that $[PyPS][H_2PO_4]$ and [PyPS]p-TSA have relatively lower catalytic activity for this model reaction, while $[PyPS][HSO_4]$, $[PyPS][BF_4]$, and $[PyPS][PF_6]$ have relatively higher yields. But $[PyPS][BF_4]$ and $[PyPS][PF_6]$ began to decompose at high temperature for a long time. Furthermore, the procedures for the preparation of $[PyPS][HSO_4]$ are easier than for $[PyPS][BF_4]$ and $[PyPS][PF_6]$. Additionally, $[PyPS][HSO_4]$ is a halogen-free ionic liquid, which might be more eco-friendly and less expensive. As the precursor of $[PyPS][HSO_4]$, PPS is commercially available as a relatively inexpensive brightening agent for bath electroplating. The material of $[PyPS][HSO_4]$ is less expensive than imidazolium-based



Fig. 1 Structures of the Py-FILs

ionic liquids. Herein, [PyPS][HSO₄] was selected and the results are summarized in Table 1. It worth noting that the reaction temperature for synthesis of naphthoxazinone should be above 150 °C, as only amidoalkyl naphthols were isolated and detected when the reaction temperature was lower than 120 °C (Table 1, entry 8).

After the selection of catalyst, the optimal amount of [PyPS][HSO₄] for the model reaction was subsequently explored, and the results are summarized in Table 2. In the absence of catalysts, no product was obtained even after 5 h. Good or excellent yields could be obtained with 10 mol% catalyst (entry 4). No significant impact was found on the yields when the amount of catalyst increased from 10 to 20 % mol. Thus, 10 mol% was chosen as the optimal dosage of [PyPS][HSO₄].

To optimize the reaction conditions, different polar solvents were then selected as the reaction medium. The results are summarized in Table 3. Among the six reaction conditions, all were accomplished successfully, but only a solvent-free condition could be considered the optimal procedure. Considering the reaction rate and yield, solvent-free condition was confirmed to be the best, especially because, in addition, it is an eco-friendly and economic procedure under solvent-free conditions.

With the experiment data above to hand, a Ritter-type reaction with various aldehydes was then explored under the above optimized reaction conditions (Scheme 1), and the results are presented in Table 4. It can be easily seen that this

Table 1 Catalytic performance in the model reaction of naphthol, benzaldehyde and urea reaction	Entry	Catalytic system	T (°C)	Time (min)	Isolated yield (%)
	1	[PyPS][H ₂ PO ₄]	150	60	56
	2	[PyPS]p-TSA	150	60	60
	3	[PyPS][PF ₆]	150	60	68
Reaction conditions: naphthol (2.5 mmol), benzaldehyde (2.5 mmol), urea (3.5 mmol), ionic liquids (0.25 mmol)	4	[PyPS][BF ₄]	150	60	73
	5	[PyPS][HSO ₄]	150	60	85
	6	[PyPS][HSO ₄]	160	60	85
	7	[PyPS][HSO ₄]	150	90	85
^a Amidoalkyl naphthols were produced	8	[PyPS][HSO ₄]	120	20	95 ^a

Table 2 Influence of the catalytic amounts of [PyPS][HSO4] on the model reaction	Entry	Catalytic system	Catalytic amounts (mol%)	Time (min)	Isolated yield (%)
	1	[PyPS][HSO4]	3	60	62
	2	[PyPS][HSO4]	5	60	68
	3	[PyPS][HSO4]	8	60	77
Reaction conditions: naphthol (2.5 mmol), benzaldehyde (2.5 mmol), urea (3.5 mmol), $150 \degree$ C	4	[PyPS][HSO4]	10	60	85
	5	[PyPS][HSO4]	15	60	86
	6	[PyPS][HSO ₄]	20	60	86

Table 3[PyPS][HSO4]-catalyzed model reaction indifferent solvents at reflux	Entry	Solvent	Time (min)	Isolated yield (%)
conditions	1	Solvent-free	60	85 ^a
	2	DMF	120	16
	3	Ethanol	120	0
Reaction conditions: naphthol (2.5 mmol), benzaldehyde (2.5 mmol), urea (3.5 mmol) ^a 150 °C	4	Acetonitrile	120	0
	5	Dichloromethane	120	0
	6	Water	120	0

one-pot, three-component condensation reaction was completed successfully. In the case of optimal conditions, aromatic aldehydes with electron-donation or weak electron-withdrawing substituents could afford reasonable or good yields of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine; however, almost no product 4 could be detected for strong electron-withdrawing substituents such as m-, or p-NO₂. The reason was not very clear. Meanwhile, amidoalkyl naphthols were also prepared just for comparison under a relatively lower temperature of 120 °C (Table 5).

Lastly, we found that product 4a could be obtained from product 5a under thermal conditions (Scheme 2) in the presence of [PyPS][HSO₄]. Intermolecular cyclo-condensation was accomplished when a molecular of NH₃ was eliminated.

Therefore, we propose the following possible mechanism to account for the reaction (Fig. 2). The reaction could be mechanistically considered to proceed through the acylimine intermediate or *ortho*-quinone methides (*O*-QMs) intermediate. The subsequent addition of the β -naphthol to the acylimine or addition of the urea to the *O*-QMs, followed by cyclization affords the corresponding products naphthoxazinone **4**.

Conclusions

In summary, the readily available pyridinium-based functionalized ionic liquid [PSPy][HSO₄] was prepared and it behaved as a novel, re-usable and efficient catalyst for the preparation of a variety of amidoalkyl naphthol or naphthoxazinone by one-pot three-component Ritter-type reaction under solvent-free thermal



Scheme 1 Synthesis of naphthoxazinone catalyzed by [PSPy][HSO₄]

Entry	Ar	Product	Time (min)	m.p. (°C) $[Ref.]^a$	Isolated yields (%)
1	C ₆ H ₅	4a	60	216–218 [11]	85
2	3-CH ₃ OC ₆ H ₄	4b	60	200-202 [12]	85
3	4-CH ₃ OC ₆ H ₄	4c	60	189–191 [<mark>1</mark> 1]	86
4	$4-CH_3C_6H_4$	4d	60	167–169 [<mark>1</mark> 1]	87
5	4-OHC ₆ H ₄	4e	60	181 dec. [11]	76
6	$4-FC_6H_4$	4f	60	203–205 [11]	91
7	4-ClC ₆ H ₄	4g	60	210–212 [11]	90
8	2-ClC ₆ H ₄	4h	60	249–251 [12]	85
9	$4-BrC_6H_4$	4i	60	216–218 [11]	89
10	3-NO ₂ C ₆ H ₄	4j	120	-	≤ 5
11	$4-NO_2C_6H_4$	4k	120	-	≤5

Table 4 [PyPS][HSO₄] catalyzed three-component reaction for naphthoxazinone

Reaction conditions: naphthol (2.5 mmol), benzaldehyde (2.5 mmol), urea (3.5 mmol), [PyPS][HSO₄] (0.25 mmol), 150 $^{\circ}\text{C}$

 $^{\rm a}$ The products were identified by $^1{\rm H}$ NMR, and physical data (m.p.) with those reported in the References

Isolated yields (%) Time (min) m.p. (°C) Entry Ar Product 1 C_6H_5 20 175-176 95 5a 2 3-CH₃OC₆H₄ 5b 30 166-168 90 3 4-CH₃OC₆H₄ 5c 30 99-100 92 4 4-CH₃C₆H₄ 5d 30 118-120 95 5 4-OHC₆H₄ 93 5e 30 146-148 6 $4-ClC_6H_4$ 5f 30 169-170 94 7 2-ClC₆H₄ 5g 25 152-154 90 8 4-BrC₆H₄ 5h 20 167-169 90 9 $3-NO_2C_6H_4$ 5i 20 177-179 91 10 4-NO₂C₆H₄ 5j 15 163-165 90

Table 5 [PyPS][HSO₄] catalyzed three-component for amidoalkyl naphthols

Reaction conditions: naphthol (2.5 mmol), benzaldehyde (2.5 mmol), urea (3.5 mmol), [PyPS][HSO₄] (0.25 mmol), 120 °C



Scheme 2 Convert 5a into 4a catalyzed by [PyPS][HSO₄]



Fig. 2 Possible mechanism to account for the condensation reaction

conditions. This procedure offers several advantages including short reaction time, good yields, operational simplicity, and being environmentally benign.

Experimental section

Melting points were determined on an X_{-6} data microscope melting apparatus. ¹H NMR spectra were recorded on a Bruker DRX300 (300 MHz) and ¹³C NMR spectra on Bruker DRX300 (75.5 MHz) spectrometer. Mass spectra were obtained with an automated Finnigan Trace Ultra-Trace DSQ LC–MS spectrometer. All chemicals (AR grade) were commercially available and used directly without further purification.

Synthesis of pyridinium-based functionalized ionic liquids (Py-FIL)

The pyridinium-based functionalized ionic liquids was prepared according to reported methods [20] with some changes and the structure was analyzed by 1 H NMR and 13 C NMR (Fig. 1).

To a solution of 20.13 g (0.10 mol) of PPS in 10 mL of water was added 10.0 g of sulfuric acid solution (98 %) (0.10 mol). The mixture was then stirred for 2 h at 80 °C. The combined solution was then dried under vacuum at 100 °C to remove the water. The [PSPy][HSO₄] produced was washed repeatedly with diethyl ether to remove unreacted material and again dried under vacuum. Then, [PSPy][HSO₄] was obtained quantitatively as a colorless oil. The selected spectral data for pyridinium-based functionalized halogen-free [PSPy][HSO₄] are given below.

¹HNMR (300 MHz, D2O): δ 8.62 (d, J = 6.9 Hz, 2H, H-2, H-6), 8.30 (t, J = 7.8 Hz, 1H, H-4), 7.84 (t, J = 6.9 Hz, 2H, H-3, H-5), 4.51 (t, J = 7.5 Hz, 2H, N–CH₂–C–C–SO₃), 2.73 (t, J = 7.2 Hz, 2H, N–C–C–C–CH2–SO₃), 2.18–2.23 (m, 2H, N–C–CH₂–C–SO₃). ¹³CNMR (75.5 MHz, D2O): δ 146.35, 144.70, 128.82, 60.28, 47.48, 26.47.

General procedure for the synthesis of 1,2-dihydro-1-arylnaphtho [1,2-e][1,3]oxazine (Product 4)

A mixture of β -naphthol (2.5 mmol), aldehyde (2.5 mmol), and urea (3.5 mmol), and [PSPy][HSO₄] (0.25 mmol) was stirred at 150 °C for 60 min (Scheme 2). On completion (monitored by TLC), the mixture was cooled to 50 °C, then ethanol (10 mL) was added to dilute the reaction mixture, which was stirred continually for 5 min at 80 °C. The catalyst was separated by filtration. The residue was kept at room temperature for a while and the solid product was collected by filtration. The product **5** was found to be pure and no further purification was necessary.

The selected data for naphthoxazinone:

1,2-Dihydro-1-(4-chlorophenyl)naphtho[1,2-e][1,3]oxazine-3-one (product 4 g $C_{18}H_{12}NO_2Cl$). White solid; m.p. 210–212 °C; ¹H NMR (300 MHz, DMSO-d6): δ , 8.91 (s, 1 H, NH), 8.01–7.31 (m, 10 H, Ar–H), 6.24 (s, 1 H, CH).

General procedure for the synthesis of amidoalkyl naphthols (Product 5)

A mixture of β -naphthol (2.5 mmol), aldehyde (2.5 mmol), and urea (2.5 mmol), and [PSPy][HSO₄] (0.25 mmol) was stirred at 120 °C for 15–30 min (Scheme 2). On completion (monitored by TLC), water (2 mL) was added to the reaction mixture, which was stirred continually for 5 min and then filtered. The solid crude product was recrystallized from 95 % ethanol to afford pure product **4**, which was identified by ¹H NMR and physical data (m.p.), and compared with those reported in the literature.

1-((4-Chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl)urea (product 5f, $C_{18}H_{15}N_2$ O_2Cl). White solid; m.p. 169–170 °C; ¹H NMR (300 MHz, DMSO-d6): δ 10.32 (s, 1H), 7.95–7.75 (m, 3H, Ar–H), 7.50–7.10 (m, 7H, Ar–H), 6.80 (s, 2H), 5.80 (s, 2H).

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