Research Article

A Facile One-Pot Solvent-Free Synthesis of 1,2-Dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones Catalyzed by Wet Cyanuric Chloride

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A novel one-pot synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones by condensation of a variety of aldehydes with β -naphthol and urea or thiourea in the presence of wet cyanuric chloride under solvent-free condition has been described. High yields, simple procedure, easy workup, short reaction times, and avoiding the use of organic solvent are the advantages of this green methodology.

1. Introduction

The construction of new analogs of bioactive heterocyclic compounds represents a major challenge in synthetic organic and medicinal chemistry [8]. Due to their broad spectrum of biological activities, naphthalene-condensed 1,3-oxazine-3-ones have been reported to act as antibacterial agents, such as HIV-1 reverse-transcriptase inhibitors [9]. They have been used as precursors in the preparation of phosphine ligands for asymmetric catalysis [10]. Recently, a few methods for the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones have been reported. Generally they are synthesized by three-component condensation of urea or thiourea with an aldehyde and β -naphthol, which entails the use of *P*-TSA [3], perchloric acid supported on silica [1], montmorillonite K10 [5], phosphomolybdic acid [6], iodine [2], and nano-copper in PEG-400 [4]. However, in spite of their potential utility, some difficulties still exist, such as expensive or toxic reagents. Therefore, the development of new, simple, and cheap methods for the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones is of main importance.

TCT is a solid, nonvolatile, inexpensive, commercially available, and easy-to-handle reagent [11]. It has been utilized

for various synthetic transformations [12–14]. It is extremely soluble in organic solvents, which makes it an ideal catalyst for organic synthesis.

In continuation of our investigation of using TCT in organic transformation [15–18], herein we want to report the convenient synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-one derivatives *via* the one-pot multicomponent condensation reaction of aromatic aldehydes, β -naphthol, and urea or thiourea. The reaction was realised in the presence of a catalytic amount of wet TCT under solvent-free condition (Scheme 1).

Our preliminary experiments focused on the optimization of the most appropriate reaction conditions. So a model study was carried out on the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-one by the condensation of benzaldehyde with β -naphthol and urea. The best result was obtained in the presence of 10 mol% of TCT and 1–2 drops of H₂O at 150°C under solvent-free condition. The reaction was completed in 12 minutes and the corresponding 1,2-dihydro-1-phenylnaphtho[1,2-e][1,3]oxazine-3-one was isolated in 80% yield. A higher amount of the catalyst scale did not improve the yield (Table 1).

SCHEME 1: Condensation of β -naphthol, aldehydes, and urea or thiourea in the presence of wet CT.TABLE 1: Optimization of the reaction conditions in synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-one^a.

Entry	TCT (mol%)	Reaction conditions	Time (min)	Yield (%)
1	10	EtOH/reflux	120	0
2	10	H ₂ O/reflux	120	0
3	10	CH ₃ CN/reflux	120	0
4	5	Solvent free/120°C	60	54
5	5	Solvent free/150°C	30	81
6	10	Solvent free/120°C	60	86
7	10	Solvent free/150°C	12	87
8	15	Solvent free/150°C	12	85

^a Reaction condition: β -naphthol (1 mmol), benzaldehyde (1 mmol), urea (1 mmol), TCT (10 mol%, 0.1 mmol) and, water (1-2 drops) in solvent-free condition at 150°C.

TABLE 2: Synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-one derivatives.

Entry ^a	ArCHO	Urea/thiourea	Time (min)	Yield (%) ^a	Mp (Lit.)°C
1	C ₆ H ₅	Urea	12	87	219–222 [1]
2	4-Br-C ₆ H ₄	Urea	5	89	221–223 [2]
3	3-Br-C ₆ H ₄	Urea	9	93	230–232 [1]
4	4-MeO-C ₆ H ₄	Urea	8	71	185–188 [3]
5	4-NO ₂ -C ₆ H ₄	Urea	3	97	206–207 [4]
6	3-NO ₂ -C ₆ H ₄	Urea	2	91	226–227 [2]
7	4-Me-C ₆ H ₄	Urea	9	82	171–173 [1]
8	4-Cl-C ₆ H ₄	Urea	4	77	213–215 [1]
9	2-Cl-C ₆ H ₄	Urea	5	79	249–251 [1]
10	4-F-C ₆ H ₄	Urea	5	94	197–200 [5]
11	Cinnamaldehyde	Urea	14	87	173–175
12	C ₆ H ₅	Thiourea	15	75	179–181

^a Isolated yields.

SCHEME 2: Plausible mechanism.

TABLE 3: Comparison of efficiency of various catalysts in synthesis of 1,2-dihydro-1-phenylnaphtho[1,2-e][1,3]oxazin-3-one.

Entry	Condition	T°C	Time/min.	Yield%	Reference
1	Montmorillonite K10 clay/neat	160	30	89	[5]
2	HClO ₄ /SiO ₂ /neat	150	60	85	[1]
3	Phosphomolybdic acid/DMF	100	180	87	[6]
4	I ₂ /Hot plate	80	5	96	[2]
5	P-TSA ^a /neat	160	90	58	[3]
6	[bmim]Br/P-TSA	160	180	76	[7]
7	Nano Cu/PEG-400	rt	45	93	[4]
8	TCT	150	12	87	This work

^a *p*-Toluenesulfonic acid.

Results in Table 2 show the generality of this new protocol. The results indicated that the reaction of β -naphthol with various aromatic aldehydes bearing electron-withdrawing groups (entries 2, 3, 6, 7, 9, 10, and 11), electron-releasing groups (entries 4, 5, and 8), non-aromatic aldehyde (entry 12), and urea or thiourea was afforded in high yields (71%–97%) and short reaction times (2–15 minutes) (Table 2).

On the basis of the literature reports [3, 5], we have proposed the following plausible mechanism for the formation of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-one in the presence of wet TCT (Scheme 2). The TCT reacted with incipient moisture and released 3 moles of HCl and cyanuric acid as a byproduct [14]. The *in situ* generated HCl as a protic acid activated the aldehyde (as indicated in Table 1, the aldehydes bearing electron withdrawing group needed shorter reaction times as compared to the others). Then an *N*-acylimine intermediate was formed by the reaction of protonated aldehyde with urea or thiourea. The subsequent addition of the β -naphthol to the *N*-acylimine, followed by the cyclization produces the corresponding products and ammonia. Replacement of β -naphthol with α -naphthol or naphthalene-2-thiol prevented the reaction to proceed.

In Table 3, the efficiency of our method for the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-one is compared with some other published works in the literature. Each of these methods have their own advantages, but they often suffer from some troubles inclusive of use of organic solvent, high load of catalyst, long reaction time, and employing of expensive catalyst.

In summary, the simplicity of the methodology, ease of the product isolation, very fast and low cost of procedure, high yields, and avoidance of organic solvents could make this process available on an industrial scale.

2. Experimental

Chemicals were purchased from the Fluka, Merck, and Aldrich chemical companies. Melting points were determined by an Electrothermal 9100 and are not corrected. TLC on commercial aluminum-backed plates of silica gel 60 F254 was used to monitor the progress of reactions.

¹H NMR spectra were recorded on Bruker Avance3 400 MHz spectrometers in the presence of tetramethyl silan as an internal standard. Elemental analyses were performed by Perkin Elmer CHN analyzer, 2400 series II.

2.1. Typical Procedure for the Synthesis of 1,2-Dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones. A mixture of β -naphthol (1 mmol), aldehyde (1 mmol), urea or thiourea (1 mmol), TCT (0.1 mmol, 0.0184 g), and water (1–2 drops) was mixed well and was heated at 150°C for an appropriate time (Table 1). After the completion of the reaction (monitored by TLC), the reaction mixture was diluted with H₂O (5 mL) and was stirred for 5 minutes. The solid product was filtered and the crude product was crystallized with ethanol to afford the pure product.

2.2. The Spectral (IR, ¹H NMR, ¹³C NMR) and Analytical Data for

1,2-Dihydro-1-styrylnaphtho[1,2-e][1,3]oxazin-3-one (Entry-11, Table 2). mp 173–175°C. IR (KBr, cm⁻¹): 3055, 2831, 1674, 1596, 1496, 1396. ¹H NMR (400 MHz, DMSO-d₆): δ 7.94 (1H, d, *J* = 8 Hz), 7.88–7.80 (4H, m), 7.62 (1H, t, *J* = 7.2 Hz), 7.52–7.45 (3H, m), 7.42–7.34 (2H, m), 5.98 (1H, t, *J* = 4 Hz), 3.87 (2H, d, *J* = 3.6 Hz); ¹³CNMR (100 MHz, DMSO-d₆): δ 148.71, 147.64, 133.93, 131.94, 130.55, 129.00, 128.75, 128.69, 127.37, 124.93, 124.55, 123.21, 116.24, 11.57, 97.47, 21.88; Calcd. for C₂₀H₁₅NO₂ C, 79.73; H, 4.98; N, 4.65; Found: C, 79.81; H, 4.91; N, 4.53.

1,2-Dihydro-1-phenylnaphtho[1,2-e][1,3]pxazine-3-thione (Entry12, Table 2). mp 179–181°C. IR (KBr, cm⁻¹): 3386, 3163, 1627, 1596, 1404, 1172. ¹H NMR (400 MHz, DMSO-d₆): δ 8.70 (1H, d, *J* = 8.8 Hz), 7.94 (3H, d, *J* = 8.8 Hz), 7.56–7.62 (3H, m), 7.57 (1H, d, *J* = 8.8 Hz), 7.47 (2H, t, *J* = 7.6 Hz), 7.15 (2H, t, *J* = 7.6 Hz), 6.98 (1H, t, *J* = 7.6 Hz), 6.73 (1H, s). ¹³CNMR (100 MHz, DMSO-d₆): δ 148.42, 146.04, 131.35, 131.10, 129.48, 129.07, 128.85, 128.42, 127.42, 126.72, 125.02, 123.90, 118.16, 117.90, 36.93; Calcd. for C₁₈H₁₃NOS C, 74.22; H, 4.46; N, 4.81; Found: C, 74.31; H, 4.32; N, 4.75.

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