An Efficient One-Pot Synthesis of Naphthoxazinones by a Three-Component Coupling of Naphthol, Aldehydes, and Urea Catalyzed by Zinc Triflate

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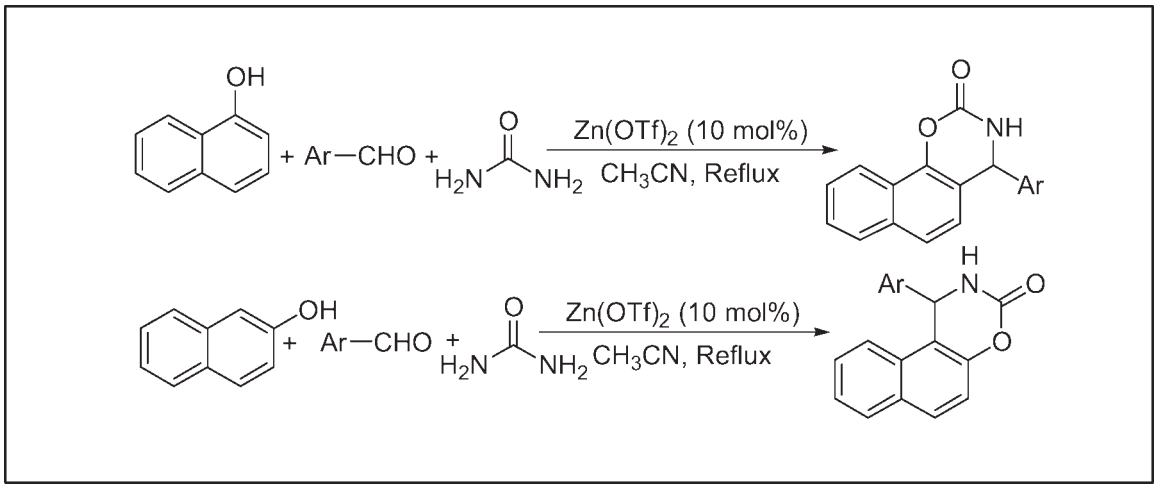

A simple and efficient method has been developed for the synthesis of 4-aryl-3,4-dihydronaphtho[2,1-*e*][1,3]oxazin-2-one and 1-aryl-1,2-dihydronaphtho[1,2-*e*][1,3]oxazin-3-one derivatives through a one-pot three-component coupling of α or β-naphthol, aromatic aldehydes and urea using a catalytic amount of zinc triflate in refluxing acetonitrile.

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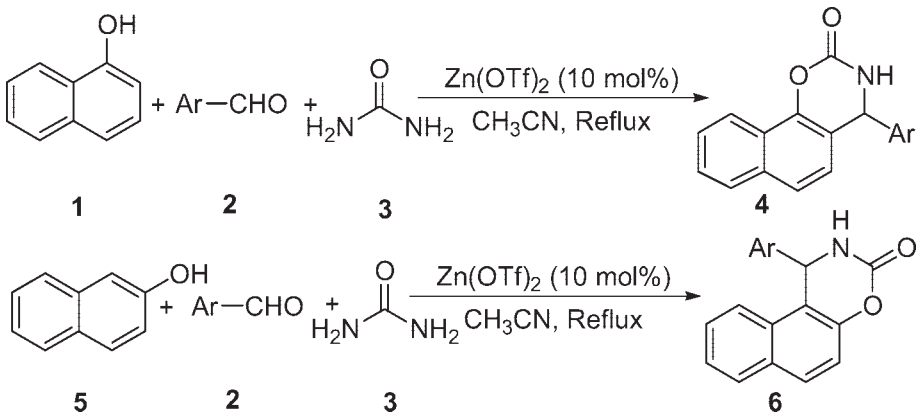
INTRODUCTION

Aromatic-condensed oxazinone derivatives are of significant importance because of their promising biological activities [1]. In addition, these heterocyclic compounds represent an important class of functionalized building blocks. For example, they have been used as valuable precursors in the preparation of phosphinic ligands for asymmetric catalysis and in the synthesis of biologically active heterocyclic derivatives [2]. The general method for the preparation of 2-aminomethyl phenol derivatives is *via* the Mannich-type reaction [3]. To the best of our knowledge, there is only one report for the synthesis of 4-aryl-3,4-dihydronaphtho[2,1-*e*][1,3]oxazin-2-one derivatives in the literature [4]. However, only few methods are available for the preparation of 1-aryl-1,2-dihydronaphtho[1,2-*e*][1,3]oxazin-3-one derivatives [1,4,5]. All of these methods suffer from the same drawbacks, specially in the use of toxic solvents (benzene) or expensive and hazardous reagents (carbamyl chlorides, isocyanates, and phosgene). In addition, they involve multistep synthetic operations which lower the overall yields. Recently, Bazgir *et al.* reported a one-pot synthesis of 1-aryl-1,2-dihydronaphtho[1,2-*e*][1,3]oxaxine-3-one derivatives by three component coupling of β-naphthol, aromatic aldehydes, and urea in moderate to high yields [6]. However, this approach is satisfactory for the condensation with β-naphthol, but α-naphthol produced no product under the reaction conditions. Therefore, it is desirable to develop a more efficient and general method for the synthesis of naphthoxazinone derivatives from both naphthol isomers.

Multicomponent reactions are finding increasing interest in the synthesis of biologically important compounds, as they possess one of the aforementioned qualities namely the possibility of building up complex molecules with simplicity and brevity. The modern synthesis is the one in which the target components are produced in one step, in quantitative yield from readily available and inexpensive starting materials in a resource-effective and environmentally benign process [7]. As a part of our program to synthesize biologically active heterocyclic derivatives using multicomponent coupling reactions [8,9], we wish to report here an efficient zinc triflate catalyzed one-pot synthesis of

Scheme 1



naphthoxazinone derivatives by coupling of α or β-naphthol, an aromatic aldehyde, and urea (Scheme 1).

RESULTS AND DISCUSSION

In our initial investigation, the coupling reaction of β-naphthol (1 mmol), benzaldehyde (1 mmol), and urea (1.5 mmol) was carried out in different solvents in the presence of $Zn(OTf)_2$ (10 mol%) under reflux. Comparing with other organic solvents, CH_3CN was the most effective reaction media (Table 1, entry 1). The coupling reaction was also performed in the presence of different catalysts (10 mol%), such as $La(OTf)_3$, $In(OTf)_3$, $ZnCl_2$, and $Zn(ClO_4)_2$. But, we observed $Zn(OTf)_2$ was the most effective catalyst in the terms of yields (82%).

On the basis of the earlier results, this process was then extended to other aromatic aldehydes to investigate its scope and generality. The results are summarized in Table 2. Aromatic aldehydes with both activating and weekly deactivating groups, such as F, Br, Cl, Me, OMe, and OH, reacted to afford the corresponding products in high yields. Piperonal also afforded high yields without any difficulty.

Table 1

Reaction of β-Naphthol with benzaldehyde and urea under reflux in different reaction conditions.

Entry	Catalyst (10 mol %)	Solvent	Time (h)	Yield (%)[a]
1	$Zn(OTf)_2$	CH_3CN	5	82
2	$Zn(OTf)_2$	$ClCH_2CH_2Cl$	5	70
3	$Zn(OTf)_2$	$HOCH_2CH_2OMe$	5	65
4	$ZnCl_2$	CH_3CN	5	36
5	$Zn(ClO_4)_2$	CH_3CN	5	68
6	$ln(OTf)_3$	CH_3CN	5	60
7	$La(OTf)_3$	CH_3CN	5	55

[a] Isolated yields.

Our attention was then turned to the possibility of reaction with α-naphthol. It was found that the replacement of β-naphthol with α-naphthol produced the naphthoxazine-2-one derivatives in good yields under the similar conditions. On the basis of the earlier results, this process was then extended to other substituted aromatic aldehydes. The results are listed in Table 3. It is cleared that under these similar conditions, benzaldehydes containing methyl or methoxy groups easily undergo condensation with α-naphthol and urea to produce 4-aryl-3,4-dihydronaphtho[2,1-*e*][1,3]oxazin-2-ones in good yields. However, under the present reaction conditions aliphatic aldehydes and thiourea did not afford the corresponding naphthoxazinone derivatives, instead leaded to multiple products whose identities are yet to be established.

Based on the experimental results, a plausible mechanism was proposed in Scheme 2. In this hypothesis, $Zn(OTf)_2$ serves as the Lewis-acid catalyst for several stages. The intermediates **7** were isolated in a couple of reactions and properly characterized. These intermediates were subsequently cyclized to naphthoxazinone

Table 2

$Zn(OTf)_2$-catalyzed reaction of β-naphthol with aromatic aldehydes and urea.

Product **4**	Ar	Time (h)	Yield (%)[a]	Ref.
a	Ph	5	82	6a
b	$4\text{-}MeC_6H_4$	6	77	6a
c	$4\text{-}MeOC_6H_4$	6	72	6a
d		7	74	
e	$4\text{-}HOC_6H_4$	6	70	6a
f	$4\text{-}FC_6H_4$	7	80	6a
g	$2\text{-}ClC_6H_4$	7	78	6b
h	$4\text{-}ClC_6H_4$	6	84	6a
i	$4\text{-}BrC_6H_4$	6	80	6a

[a] Yields refer to isolated pure product.

Table 3

$Zn(OTf)_2$-catalyzed reaction of α-naphthol with aromatic aldehydes and urea.

Product 6	Ar	Time (h)	Yield (%)[a]	Ref.
a	Ph	5	64	4
b	4-MeC_6H_4	6	67	
c		7	69	

[a] Yields refer to isolated pure product.

derivatives by further heating. It should be pointed out that 4-nitrobenzaldehyde and 3-nitrobenzaldehyde reacted with urea and β-naphthol but the reaction stopped at intermediate stage **7** [10]. The reaction did not proceed further on long time heating.

CONCLUSIONS

In conclusion, the work presented here demonstrates a straightforward and general procedure for the efficient one-pot synthesis of naphthoxazinones by a three-component coupling of naphthols, aromatic aldehydes, and urea. The reaction possesses the following synthetic features: (a) mild conditions, (b) simple operation, (c) good yields, (d) nontoxic and cheap metal catalyst, (e) the compatibility with various functional groups, and (f) applicability for an easy synthesis of 1-aryl-1,2-dihydronaphtho[1,2-*e*][1,3]oxazin-3-ones and 4-aryl-3,4-dihydronaphtho[2,1-*e*][1,3]oxazin-2-ones.We believe that this procedure will provide a better and more practical alternative to the existing methodologies for the synthesis of naphthoxazinone derivatives. Further investigations to broaden the scope of this methodology toward pharmaceuticals and chiral products are in progress.

EXPERIMENTAL

Melting points were determined on a glass disk with an electrical bath and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were run in DMSO-d_6 solutions. IR spectra were taken as KBr plates. Elemental analyses were done by Perkin-Elmer autoanalyzer. $Zn(OTf)_2$ was purchased from Aldrich. All liquid reagents were distilled before use.

Typical procedure for the synthesis of 1-phenyl-1,2-dihydronaphtho[1,2-*e*][1,3]oxazin-3 one (Table 2, 4a). A solution of benzaldehyde (212 mg, 2 mmol, 203 μL), β-naphthol (288 mg, 2 mmol), and urea (180 mg, 3 mmol) in CH_3CN (4 mL) was heated under reflux (90–95°C) in the presence of zinc triflate (73 mg, 10 mol%) for 5 h (TLC). At completion, the reaction mixture was distilled under vacuum to remove the solvent and then diluted with cold water (10 mL). After extraction with ethyl acetate (20 mL × 3), the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The residue was concentrated and recrystallized from EtOAc-hexane to afford the pure product as a white powder (451 mg, 82%), mp 216–218°C (reported 218–220°C) [6a].

Typical procedure for the synthesis of 4-phenyl-3,4-dihydronaphtho[1,2-*e*][1,3]oxazin-2-one (Table 3, 6a). The procedure reported in the previous experiment was followed using α-naphthol in place of β-naphthol. The corresponding pure product was obtained as a white powder (352 mg, 64%), mp 195–197°C (reported 196–198°C) [4].

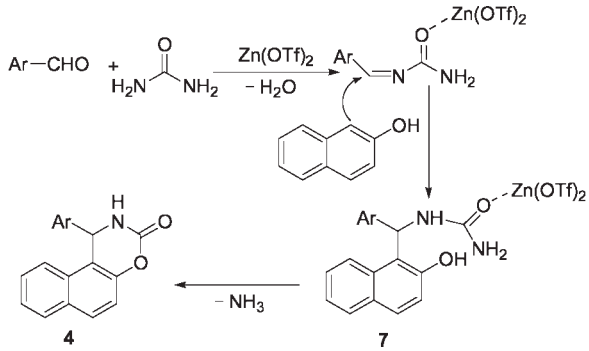
The spectral (IR, ^{1}H, and ^{13}C NMR) data and elemental analyses of the compounds which are not readily found are provided later.

1-Benzo[1,3]dioxol-5-yl-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one (Table 2, 4d). This compound was obtained according to the above procedure as white powder, mp 164–166°C; IR (KBr): 3321, 1701, 1447 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 8.42 (br s, 1H), 7.89–7.84 (m, 2H), 7.64–7.60 (m, 2H), 7.46–7.41 (m, 2H), 7.32–7.27 (m, 1H), 6.83–6.71 (m, 3H), 6.01 (d, J = 4.0 Hz, 1H), 5.91 (d, J = 4.0 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ = 149.5, 147.8, 147.6, 147.1, 137.0, 130.6, 130.4, 129.1, 128.8, 127.6, 125.3, 123.4, 120.6, 117.1, 114.2, 108.6, 107.5, 101.4, 53.6; *Anal*. Calcd for $C_{19}H_{13}NO_4$: C 71.47, H 4.10, N 4.39. Found: C 71.31, H 3.98, N 4.21.

4-p-Tolyl-3,4-dihydronaphtho[2,1-e][1,3]oxazin-2-one (Table 3, 6b). This compound was obtained according to the above procedure as white powder, mp 214–216°C; IR (KBr): 3244, 1723, 1371 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 8.71 (s, 1H), 8.15 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.65–7.55 (m, 3H), 7.16–7.23 (m, 2H), 7.18–7.13 (m, 3H), 5.78 (s, 1H), 2.25 (s, 3H); ^{13}C NMR (DMSO-d_6): δ = 149.2, 143.3, 140.3, 137.3, 133.0, 129.4 (2C), 127.8, 127.0, 126.9, 126.8 (2C), 124.0, 123.7, 122.5, 120.5, 116.3, 56.0, 20.6; *Anal*. Calcd for $C_{19}H_{15}NO_2$: C 78.87, H 5.23, N 4.84. Found: C 78.53, H 5.02, N 4.65.

4-(3,4,5-Trimethoxyphenyl)-3,4-dihydronaphtho[2,1-e][1,3]oxazin-2-one (Table 3, 6c). This compound was obtained according to the above procedure as white powder, mp 228–230°C ; IR (KBr): 2926, 1754, 1592, 1376 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 8.68 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.67–7.57 (m, 3H), 7.23 (d, J = 8.5 Hz, 1H), 6.70 (s, 2H), 5.79 (s, 1H), 3.73 (s, 6H), 3.63 (s, 3H); ^{13}C NMR (DMSO-d_6): δ = 153.1 (2C), 149.1, 143.2, 138.7, 137.1, 133.1, 127.8, 127.0, 126.9, 124.0, 123.6, 122.4, 120.5, 115.8, 104.2 (2C), 60.0, 56.4, 55.9 (2C); *Anal*. Calcd for $C_{21}H_{19}NO_5$: C 69.03, H 5.24, N 3.83. Found: C 68.89, H 5.06, N 3.67.

Scheme 2



[(2-Hydroxynaphthalen-1-yl)-(4-nitrophenyl)-methyl]urea (intermediate 7 from 4-nitrobenzaldehyde). This compound was obtained according as white powder, mp >250°C; IR (KBr): 3480, 3164, 2923, 1714, 1654, 1596, 1347 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 10.08 (s, 1H), 8.14 (d, J = 8.8 Hz, 2H), 7.84 – 7.77 (m, 3H), 7.39 (d, J = 8.8 Hz, 2H), 7.37 – 7.18 (m, 3H), 6.98 (s, 2H), 5.91 (s, 2H); ^{13}C NMR (DMSO-d_6): δ = 158.9, 153.4, 153.3, 146.2, 132.5, 130.0, 129.1, 128.8 (2C), 127.3 (2C), 123.6 (2C), 123.0 (2C), 119.6, 118.8, 48.6; *Anal*. Calcd for $C_{18}H_{15}N_3O_4$: C 64.09, H 4.48, N 12.46. Found: 63.86, H 4.21, N 12.26.

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