A Novel Three-Component, One-Pot Synthesis of 1,2-Dihydro-1-aryl-naphtho[1,2-*e*][1,3]oxazine-3-one Derivatives under Microwave-Assisted and Thermal Solvent-Free Conditions

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Received 11 September 2006

Abstract: 1,2-Dihydro-1-arylnaphtho[1,2-*e*][1,3]oxazine-3-one derivatives were synthesized in moderate to high yields using a novel, facile, and one-pot condensation of β-naphthol, aromatic aldehydes and urea under microwave-assisted and thermal solvent-free conditions.

Key words: naphthoxazinone, microwave, solvent-free, naphthol, multi-component

Aromatic-condensed oxazinone derivatives are an important class of heterocyclic compounds, since many of these heterocyclic systems exhibit biological activities.[1] For example, naphthalene-condensed 1,3-oxazin-3-ones have been reported to act as antibacterial agents.[2] This class of compound has also been used as precursors in the preparation of phosphinic ligands for asymmetric catalysis.[3] However, to the best of our knowledge, there have only been a few reports of the synthesis of naphthalene-condensed oxazinone derivatives in the literature.[2,4] Recently, Fulop et al. disclosed that the condensation of amino alkylnaphthols as precursors with phosgene in the presence of triethylamine, gives naphthalene-condensed 1,3-oxazin-3-one derivatives in moderate yields.[5] Cimarelli and co-workers used carbonyl diimidazole instead of phosgene for the synthesis of these compounds.[6]

In all these methods either expensive reagents or solvents are required or the reagents used are toxic and hazardous. Furthermore, for the preparation of starting materials such as amino alkylnaphthol, a multi-step reaction using harsh conditions is needed.[7] Therefore, discovery of new, simple, green and one-pot methods for the synthesis of naphthoxazinone derivatives is of prime interest.

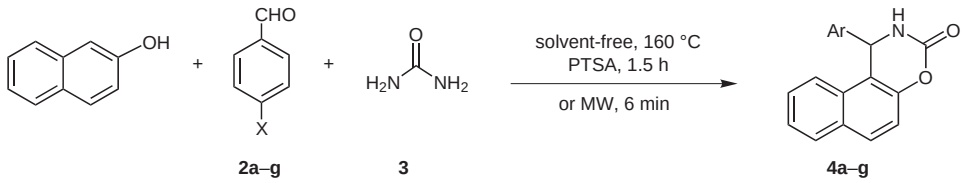
Multicomponent reactions (MCRs) constitute an especially attractive synthetic strategy due to the fact that the products are formed in a single step and diversity can be achieved simply by varying the reacting components.[8]

In continuation of our previous work on the synthesis of heterocyclic compounds[9] and MCRs,[10] we wish to report a novel, efficient, one-pot, three-component method for the preparation of 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3]oxazin-3-one derivatives under thermal as well as microwave-assisted, solvent-free conditions.

After preliminary experimentation, it was found that a mixture of β-naphthol (**1**), benzaldehyde (**2a**) and urea **3** in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA) at 160 °C for 1.5 hours under solvent-free conditions afforded 1,2-dihydro-1-phenylnaphtho[1,2-*e*][1,3]oxazine-3-one (**4a**) in 58% yield (Scheme 1).[11]

In order to find the best catalyst for the synthesis of the naphthalene-condensed oxazinone derivatives, the reaction of β-naphthol, benzaldehyde and urea was carried out either in the absence of catalyst or in the presence of various protic or Lewis acids under similar conditions (Table 1). As shown, the best yield was achieved when PTSA was used (Table 1, entry 2).

Encouraged by this success, we attempted the reaction of β-naphthol with a range of other aromatic aldehydes **2b**–**g** and urea under similar conditions (using PTSA), furnishing the respective naphthoxazinone **4b**–**g** in good yields. The optimized results are summarized in Table 2. The thermal solvent-free conditions are well suited for either electron-donating or electron-withdrawing substituents on the aromatic aldehydes.



Scheme 1

SYNLETT 2007, No. 5, pp 0821–0823
Advanced online publication: 08.03.2007
DOI: 10.1055/s-2007-970763; Art ID: D27006ST

Table 1 Catalyst Effect on Reaction[a]

Entry	Catalyst	Yields (%)[b]
1	AcOH	45
2	PTSA	58
3	LiCl	38
4	$CuCl_2$	30
5	$NiCl_2$	–
6	–	35

[a] Benzaldehyde (1 mmol), urea (1.5 mmol), β-naphthol (1 mmol), catalyst (0.3 mmol).
[b] Isolated yields.

Table 2 Reaction of β-Naphthol with Aldehydes and Urea under Solvent-Free (I) and Microwave-Assisted[a] (II) Conditions

Product **4**	Ar	Yield (%)[b]		Mp (°C)
		I	II	
a	Ph	58	81	218–220
b	4-MeC_6H_4	60	79	166–168
c	4-$MeOC_6H_4$	59	73	185–188
d	4-HOC_6H_4	63	69	180 (dec.)
e	4-FC_6H_4	61	77	202–204
f	4-ClC_6H_4	63	80	208–210
g	4-BrC_6H_4	64	82	220–223

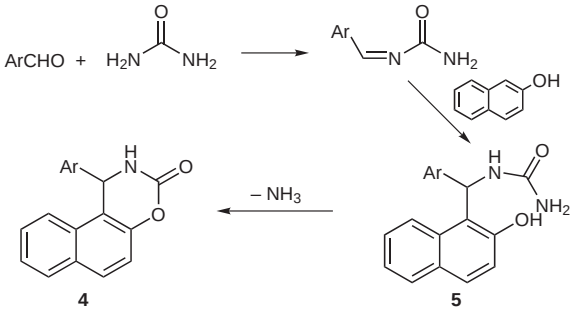
[a] With a power of 900 W.
[b] Isolated yields.

In order to decrease the reaction time, microwave irradiation under solvent-free conditions was used.[12] The reaction time decreased from 1.5 hours to 6 minutes. Moreover, the yields of products increased in all cases that were examined (Table 2). Interestingly, all reactions under microwave-assisted conditions proceeded without the use of any acidic catalyst, which is another advantage of this method in the synthesis of this class of compound.

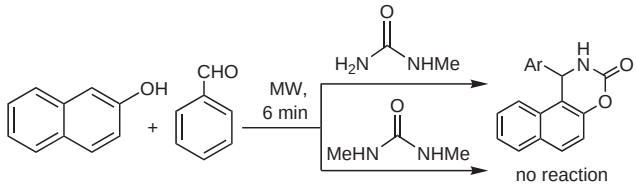
On investigating the reaction mechanism, it was noticed that when β-naphthol, benzaldehyde and urea were irradiated for one minute, the reaction led to the formation of the intermediate **5**. This intermediate was isolated and characterized by spectroscopic methods. However, extension of reaction time to three minutes led to a mixture of **4a** and intermediate **5** (monitored by TLC and ^{1}H NMR). After six minutes, only compound **4a** was detected by TLC and ^{1}H NMR. Furthermore, when intermediate **5** was isolated and exposed to microwave irradiation, the product **4a** was obtained in good yield (Scheme 2).

Scheme 2

According to these results, the reaction can be mechanistically considered to proceed through the acylimine intermediate (formed in situ by reaction of the aldehyde with urea).[13] The subsequent addition of the β-naphthol to the acylimine, followed by cyclization affords the corresponding products **4a**–**g** and ammonia (Scheme 3). The structures of the products were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS spectra.[14] Replacement of urea with *N*-methyl urea also afforded product **4a** in high yield. However, replacement of urea with *N*,*N*′-dimethyl urea gave no product (Scheme 4). All starting materials were recovered indicating that the presence of an unsubstituted amino group is necessary for production of the key acylimine intermediate.



Scheme 3



Scheme 4

In addition, replacement of β-naphthol with α-naphthol under both conditions produced no product.

In conclusion, we have described a novel, efficient and one-pot synthesis for the preparation of naphthoxazine-3-one derivatives in three-component cyclo-condensation reactions of β-naphthol, aromatic aldehydes and urea under thermal solvent-free conditions or microwave irradiation. The novelty and synthetic utility of this methodology was demonstrated in the efficient synthesis of naphthoxazinone derivatives.

Acknowledgment

We gratefully acknowledge the financial support from the Research Council of Shahid Beheshti University.

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(11) **Typical procedure for the preparation of 1,2-dihydro-1-phenylnaphtho[1,2-*e*][1,3]oxazine-3-one (4a) under thermal solvent-free conditions**: A mixture of β-naphthol (1 mmol), benzaldehyde (1 mmol), urea (1.5 mmol) and PTSA (0.3 mmol) was finely mixed together. The reaction mixture was placed in a screw-capped vial and heated at 160 °C for 1.5 h. After cooling, the reaction mixture was washed with H_2O and then recrystallized from EtOAc–hexane (1:3) to afford the pure product **4a** as a white powder (58%).

(12) **Typical procedure under microwave-assisted conditions**: A mixture of β-naphthol (1 mmol), benzaldehyde (1 mmol) and urea (1.5 mmol) were finely mixed together. The reaction mixture was placed in a screw-capped vial and irradiated for 6 min with a power of 900 W. After cooling, the reaction mixture was washed with H_2O and then recrystallized from EtOAc–hexane (1:3) to afford the pure product **4a** (81%); mp 218–220 °C; IR (KBr): 3295, 1730, 1517 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 6.19 (d, *J* = 2.1 Hz, 1 H, CH), 7.24–8.00 (m, 11 H, Ar–H), 8.87 (br s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 54.20, 114.50, 117.32, 123.57, 125.54, 127.42, 127.81, 128.47, 129.08, 129.32, 129.41, 130.68, 130.86, 143.34, 147.85, 149.77; MS (ESI): *m*/*z* (%) = 275 (7) [M^+], 231 (100), 202 (35), 51 (24).

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(14) **Selected characterization data**:
1,2-Dihydro-1-(4-methylphenyl)naphtho[1,2-*e*][1,3]oxazine-3-one (4b): mp 166–16 °C; IR (KBr): 3230, 3139, 1717 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.21 (s, 3 H, CH_3), 6.13 (d, *J* = 2.4 Hz, 1 H, CH), 7.10–7.99 (m, 10 H, Ar–H), 8.81 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.06, 53.98, 114.61, 117.29, 123.56, 125.49, 127.32, 127.76, 129.05, 129.33, 129.89, 130.59, 130.85, 137.78, 140.43, 147.80, 149.81; MS (ESI): *m*/*z* (%) = 290 (10) [M^+ + H], 231 (100), 202 (20).
1,2-Dihydro-1-(4-chlorophenyl)naphtho[1,2-*e*][1,3]oxazine-3-one (4f): mp 208–210 °C; IR (KBr): 3224, 3146, 1734 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 6.24 (s, 1 H, CH), 7.31–8.01 (m, 10 H, Ar–H), 8.91 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 53.42, 114.02, 117.34, 123.50, 125.62, 127.91, 128.06, 129.13, 129.23, 129.37, 129.42, 130.87, 133.06, 142.22, 147.90, 149.61; MS (ESI): *m*/*z* (%) = 309 (5) [M^+], 265 (60), 231 (100), 202 (27), 115 (15).
1-{[2-Hydroxynaphthalen-1-yl](phenyl) methyl} urea (intermediate 5): mp 190–192 °C; IR (KBr): 3463, 3406, 3347, 3219, 1664 cm^{-1}; ^1H NMR (300 MHz, CD_3SOCD_3): δ = 5.82 (s, 2 H, NH_2, exchanges with D_2O), 6.91–7.81 (m, 13 H), 9.94 (br s, 1 H, OH); ^{13}C NMR (75 MHz, CD_3SOCD_3): δ = 48.56, 119.05, 120.58, 122.72, 123.27, 126.22, 126.81, 128.26, 128.69, 129.0, 129.33, 132.71, 144.77, 153.51, 159.01; MS (ESI): *m*/*z* (%): 275 (5) [M^+ – NH_3], 231 (100), 202 (15), 144 (100).