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A clean synthesis of oxazino[5,6-*f*]quinolinone and naphtho[1,2-*e*]oxazinone derivatives

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Abstract A clean, simple, one-pot, and efficient synthesis of 1,2-dihydro-1-aryl[1,3]oxazino[5,6-*f*]quinolin-3-one and 1,2-dihydro-1-arylnaphtho[1,2-*e*]-[1,3]oxazine-3-one derivatives was accomplished in good yields *via* reaction between 6-quinolinol or 2-naphthol, aromatic aldehydes, and methyl carbamate in aqueous medium catalyzed by *TEBA* (triethylbenzylammonium chloride).

Keywords Quinoline; Oxazinoquinolinone; Naphthoxazinone; Triethylbenzylammonium chloride (*TEBA*).

Introduction

Quinolines and their derivatives have received great attention because of their wide range of therapeutic and biological properties [1]. They have emerged as antimalarial, antiasthmatic, antiinflammatory, antibacterial, antihypertensive, and tyrosine kinase PDGF-RTK inhibiting agents [2, 3]. Moreover, quinolines are valuable synthons, used for assembling nano and meso structures with enhanced electronic and photonic properties [4].

One-pot multi-component reactions (MCRs) by virtue of their convergence, productivity, facile execution, and generally high yield of products have attracted considerable attention from the point of view of ideal synthesis [5]. MCRs are perfectly suitable for combinatorial library synthesis, and therefore finding increasing use in the discovery process of new drugs and agrochemicals [6].

In this context, *ortho*-quinone methides (*o-QM*s) are highly reactive intermediates, and have been used in many tandem processes [7, 8]. However, despite general knowledge of *o-QM*s for over a century, these intermediates still lie outside the synthetic mainstream [9], and only limited work has appeared regarding their reaction with nucleophiles [10].

Considering the above reports, we wish to report an efficient, one-pot, and three-component method for the preparation of 1,2-dihydro-1-aryl[1,3]oxazino-[5,6-*f*]quinolin-3-one and 1,2-dihydro-1-arylnaphtho-[1,2-*e*][1,3]oxazine-3-one derivatives in aqueous medium.

Results and discussion

First, it was found that a mixture of 6-quinolinol (**1a**), aromatic aldehyde **2a**–**2f**, and methyl carbamate (**3**) in the presence of a catalytic amount of *TEBA* (triethylbenzylammonium chloride) at 80°C in water afforded 1,2-dihydro-1-aryl-[1,3]oxazino[5,6-*f*]quinolin-3-ones **4a**–**4f** in 78–85% yield (Scheme 1).

The optimized results are summarized in Table 1. Good yields were obtained using aromatic aldehydes carrying electron-donating or electron-with-

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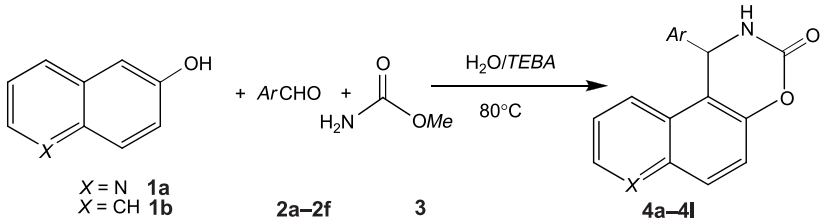


Scheme 1

Table 1 Synthesis of products **4a**–**4l**

Entry	Compound **1**	Compound **2**	Product **4**	Yield[a]/%	Time/h
1	**1a**	benzaldehyde (**2a**)	**4a**	78	4
2	**1a**	4-chlorobenzaldehyde (**2b**)	**4b**	85	4
3	**1a**	4-fluorobenzaldehyde (**2c**)	**4c**	82	4.5
4	**1a**	4-bromobenzaldehyde (**2d**)	**4d**	79	5
5	**1a**	4-methoxybenzaldehyde (**2e**)	**4e**	81	6
6	**1a**	4-methylbenzaldehyde (**2f**)	**4f**	80	5
7	**1b**	**2a**	**4g**	78	4.5
8	**1b**	**2b**	**4h**	79	3.8
9	**1b**	**2c**	**4i**	81	3.5
10	**1b**	**2d**	**4j**	83	4
11	**1b**	**2e**	**4k**	77	5
12	**1b**	**2f**	**4l**	81	5.5

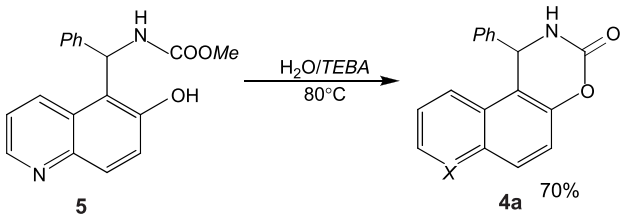
[a] Isolated yields

drawing substituents and problems associated with toxic solvent use (cost, safety, and pollution) were avoided.

Under the same conditions, this reaction almost could not be observed when the aliphatic aldehyde was used as a starting material. In the absence of *TEBA*, the products **4** were obtained in low yields (<20%) when the reactions were carried out in water at 80°C. This indicates that a catalyst is requiring for this reaction.

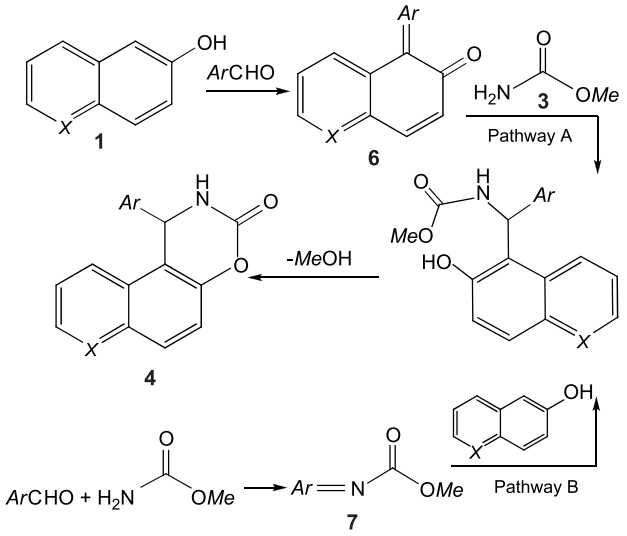
Encouraged by these results, we carried out the reaction between 2-naphthol (**1b**) instead of 6-quinolinol (**1a**) with aromatic aldehydes **2a**–**2f** and methyl carbamate (**3**) in the presence of a catalytic amount of *TEBA* at 80°C in water, which also afforded 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3]oxazine-3-ones **4g**–**4l** in good yields (Table 1).

Regarding the mechanism of this reaction, it is noticeable that the reaction of 6-quinolinol (**1a**), benzaldehyde (**2a**), and methyl carbamate (**3**) under the same conditions (H_2O/*TEBA*/80°C) after 1 h led to the formation of the intermediate **5**, which was isolated and characterized by spectroscopic methods (Experimental section). After 4 h, only compound **4a** was detected by TLC and ^{1}H NMR. Furthermore, intermediate **5** in the presence of a catalytic amount of *TEBA* at 80°C in water afforded 1,2-dihydro-1-phenyl[1,3]oxazino[5,6-*f*]quinolin-3-one (**4a**) in 70% yield (Scheme 2).



Scheme 2

We have not established an exact mechanism for the formation of product **4**, however, two reasonable pathways are proposed in Scheme 3. 6-Quinolinol (**1a**) or 2-naphthol (**1b**) first condenses with an aldehyde to afford *o-QM*s **6** [10a]. Then methyl carbamate (**3**) adds to the *o-QM*s **6**, followed by cyclization affording the corresponding products **4** and methanol (Pathway A, Scheme 3). Alternatively, addition of methyl carbamate (**3**) to aldehyde **2** leads to a highly reactive



Scheme 3

N-acylimine species **7** [11]. Interception of **7** by quinolinol (**1a**) or 2-naphthol (**1b**) and subsequent cyclization affords the corresponding products **4** (Pathway B, Scheme 3). The *TEBA* surfactant acts as a phase transfer agent. It has unique capabilities to enhance the reaction rate in two-phase reactions [12].

In conclusion, we have described an efficient, clean, and one-pot synthesis for the preparation of 1,2-dihydro-1-aryl[1,3]oxazino[5,6-*f*]quinolin-3-one and 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3]oxazine-3-one derivatives in three-component cyclo-condensation reaction of 6-quinolinol or 2-naphtol, aromatic aldehydes, and methyl carbamate in aqueous media.

Experimental

Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on a FT-IR 102MB BOMEM apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. ^{1}H and ^{13}C NMR spectra were obtained on solutions in *DMSO*-d_6 using *TMS*.

General procedure

A mixture of 1 mmol 6-quinolinol or 2-naphtol (**1a**–**1b**), 1 mmol aldehyde **2a**–**2f**, 1.5 mmol methyl carbamate (**3**), and 0.15 g *TEBA* was suspended in 10 cm^3 water, and stirred at 80°C. The reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to room temperature. The solid was collected by filtration and washed with 10 cm^3 water. Recrystallization from *Et*OAc:*n*-hexane (1:3) afforded the pure product.

1,2-Dihydro-1-phenyl[1,3]oxazino[5,6-f]quinolin-3-one (**4a**, $C_{17}H_{12}N_2O_2$)

Colorless powder (0.22 g, 78%), mp 243°C (dec); IR (KBr): $\bar{\nu} = 3417$, 3129, 1743 cm^{-1}; MS: m/z (%) = 276 (M$^+$, 58), 232 (100); ^{1}H NMR (*DMSO*-d_6): $\delta = 6.27$ (s, CH), 7.30–8.80 (m, arom), 8.95 (s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 53.8$, 114.9, 120.9, 122.5, 124.6, 127.3, 128.6, 129.5, 131.6, 132.0, 143.1, 145.6, 147.7, 149.4, 149.8 ppm.

1,2-Dihydro-1-(4-chlorophenyl)[1,3]oxazino[5,6-f]quinolin-3-one (**4b**, $C_{17}H_{11}ClN_2O_2$)

Colorless powder (0.26 g, 85%), mp 209°C (dec); IR (KBr): $\bar{\nu} = 3413$, 3129, 1741 cm^{-1}; MS: m/z (%) = 310 (M$^+$, 15), 266 (100), 232 (96); ^{1}H NMR (*DMSO*-d_6): $\delta = 6.32$ (s, CH), 7.31–8.83 (m, arom), 8.97 (s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 53.0$, 114.4, 120.9, 122.6, 124.5, 129.3, 129.5, 131.8, 131.9, 133.2, 141.9, 145.6, 147.7, 149.3, 149.9 ppm.

1,2-Dihydro-1-(4-flourophenyl)[1,3]oxazino[5,6-f]quinolin-3-one (**4c**, $C_{17}H_{11}FN_2O_2$)

Colorless powder (0.24 g, 82%), mp 205°C (dec); IR (KBr): $\bar{\nu} = 3412$, 1736 cm^{-1}; MS: m/z (%) = 294 (M$^+$, 42), 250 (100), 232 (100); ^{1}H NMR (*DMSO*-d_6): $\delta = 6.31$ (s, CH), 7.15–8.82 (m, arom), 8.95 (s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 53.0$, 114.6, 116.2, 120.9, 122.6, 124.5, 129.5, 131.4, 131.9, 139.3, 145.6, 147.7, 149.3, 149.9, 163.2 ppm.

1,2-Dihydro-1-(4-bromophenyl)[1,3]oxazino[5,6-f]quinolin-3-one (**4d**, $C_{17}H_{11}BrN_2O_2$)

Colorless powder (0.28 g, 79%), mp 224°C (dec); IR (KBr): $\bar{\nu} = 3410$, 3134, 1740 cm^{-1}; MS: m/z (%) = 354 (M$^+$, 32), 310 (100), 232 (100); ^{1}H NMR (*DMSO*-d_6): $\delta = 6.27$ (s, CH), 7.22–8.80 (m, arom), 8.96 (s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 52.6$, 113.84, 120.4, 121.3, 122.1, 123.9, 129.1, 131.3, 131.4, 131.9, 141.8, 145.1, 147.2, 148.8, 149.4 ppm.

1,2-Dihydro-1-(4-methoxyphenyl)[1,3]oxazino[5,6-f]-quinolin-3-one (**4e**, $C_{18}H_{14}N_2O_3$)

Colorless powder (0.25 g, 81%), mp 246°C (dec); IR (KBr): $\bar{\nu} = 3415$, 3128, 1738 cm^{-1}; MS: m/z (%) = 306 (M$^+$, 37), 262 (100), 232 (100); ^{1}H NMR (*DMSO*-d_6): $\delta = 3.66$ (s, OCH_3), 6.20 (s, CH), 6.85–8.80 (m, arom), 8.89 (s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 53.3$, 53.5, 114.7, 115.1, 120.9, 122.5, 124.5, 128.6, 131.5, 132.0, 135.2, 145.6, 147.6, 149.4, 149.8, 159.3 ppm.

1,2-Dihydro-1-(4-methylphenyl)[1,3]oxazino[5,6-f]quinolin-3-one (**4f**, $C_{18}H_{14}N_2O_2$)

Colorless powder (0.23 g, 80%), mp 272°C (dec); IR (KBr): $\bar{\nu} = 3445$, 3139, 1736 cm^{-1}; MS: m/z (%) = 290 (M$^+$, 35), 232 (100), 202 (20); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.21$ (s, CH_3), 6.22 (s, CH), 7.10-8.79 (m, arom), 8.91 (s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 21.0$, 53.5, 115.0, 120.9, 122.5, 124.5, 127.3, 129.9, 131.5, 132.0, 137.9, 140.2, 145.6, 147.6, 149.5, 149.8 ppm.

All the products **4g**–**4l** are known compounds and were characterized by IR, NMR, and mass spectroscopic data and their melting points were compared with reported values [13].

1,2-Dihydro-1-phenylnaphtho[1,2-e][1,3]oxazine-3-one (**4g**, $C_{18}H_{13}NO_2$)
Colorless powder (0.21 g, 78%), 217–219°C; IR (KBr): $\bar{\nu} = 3220$, 3145, 1730 cm^{-1}; MS: m/z (%) = 275 (M^+, 7), 231 (100) ^{1}H NMR (*DMSO*-d_6): $\delta = 6.20$ (s, CH), 7.30–7.96 (m, arom), 8.90 (s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 54.2$, 114.5, 117.3, 123.5, 125.5, 127.4, 127.8, 128.4, 129.1, 129.3, 129.4, 130.7, 130.8, 143.3, 147.8, 149.7 ppm.

1,2-Dihydro-1-(4-chlorophenyl)naphtho[1,2-e][1,3]oxazine-3-one (**4h**, $C_{18}H_{12}ClNO_2$)
Colorless powder (0.24 g, 79%), mp 206–209°C; IR (KBr): $\bar{\nu} = 3225$, 3146, 1736 cm^{-1}; MS: m/z (%) = 309 (M^+, 9), 231 (100), 202 (27); ^{1}H NMR (*DMSO*-d_6): $\delta =$ 6.23 (s, CH), 7.31–8.03 (m, arom), 8.89 (s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 53.4$, 114.1, 117.3, 123.5, 125.6, 127.8, 128.1, 129.1, 129.2, 129.4, 129.4, 130.8, 133.1, 142.2, 147.9, 149.6 ppm.

Methyl (6-hydroxquinoline-5-yl)(phenyl)methylcarbamate (**5**, $C_{18}H_{16}N_2O_3$)
Colorless powder, mp 218°C (dec); IR (KBr): $\bar{\nu} = 3405$, 3198, 1671 cm^{-1}; MS: m/z (%) = 308 (M^+, 5), 250 (45), 77 (100); ^{1}H NMR (*DMSO*-d_6): $\delta = 3.35$ (s, OCH_3), 6.86 (d, $J = 8.3$ Hz, CH), 7.13–8.11 (m, arom), 7.93 (d, $J = 8.1$ Hz, NH), 10.05 (s, OH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 50.5$, 52.2, 117.9, 119.3, 121.8, 123.4, 126.8, 126.8, 127.5, 128.6, 129.1, 129.5, 131.9, 142.9, 153.8, 157.1 ppm.

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References

1. (a) Larsen RD, Corley EG, King AO, Carrol JD, Davis P, Verhoeven TR, Reider PJ, Labelle M, Gauthier JY, Xiang YB, Zamboni RJ (1996) J Org Chem 61:3398; (b) Chen YL, Fang KC, Shen JY, Hsu SL, Tzeng CC (2001) J Med Chem 44:2374; (c) Roma G, Braccio MD, Grossi G, Mattioli F, Ghia M (2000) J Med Chem 35:1021
2. (a) Kalluraya B, Sreenivasa S (1998) Farmaco 53:399; (b) Doube D, Blouin M, Brideau C, Chan C, Desmarais S, Eithier D, Falgueyret JP, Friesen RW, Girrard M, Girard Y, Guay J, Tagari P, Young RN (1998) Bioorg Med Chem Lett 8:1255
3. Maguire MP, Sheets KR, McVety K, Spada AP, Zilberstein A (1994) J Med Chem 37:2129
4. (a) Agrawal AK, Jenekhe SA (1991) Macromolcules 24:6806; (b) Zhang X, Shetty AS, Jenekhe SA (2000) Mocromolecules 33:2064
5. (a) Armstrong RW, Combs AP, Tempest PA, Brown SD, Keating TA (1996) Acc Chem Rev 29:123; (b) Domling A (2006) Chem Rev 106:7
6. Domling A, Ugi I (2000) Angew Chem Int Ed 39:3168
7. Van De Water RW, Pettus TRR (2002) Tetrahedron 58:5367
8. Wan P, Backer B, Diao L, Fischer M, Shi Y, Yang C (1975) Can J Chem 74:465
9. Desimoni G, Tacconi G (1975) Chem Rev 75:651
10. (a) Shaabani A, Rahmati A, Farhangi E (2007) Tetrahedron Lett 48:7291; (b) Angle SR, Rainer JD, Woytowiez Z (1997) J Org Chem 62:5884; (c) Khodaei MM, Khosropour AR, Moghanian H (2006) Synlett 916
11. (a) Kappe CO (1997) J Org Chem 62:7201; (b) Huang S, Pan Y, Zhu Y, Wu A (2005) Org Lett 7:3797; (c) Cristau P, Vors J, Zhu JP (2003) Tetrahedron Lett 44:5575
12. (a) Jang DO (1996) Tetrahedron Lett 37:5367; (b) Yorimitsu H, Shinokubo H, Oshima K (2000) Chem Lett 104; (c) Khan TA, Tripoli R, Crawford JJ, Martin CG, Murphy JA (2003) Org Lett 5:2971
13. (a) Dabiri M, Delbari AS, Bazgir A (2007) Synlett 821; (b) Dabiri M, Delbari AS, Bazgir A (2007) Heterocycles 71:543