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A SIMPLE AND ENVIRONMENTALLY BENIGN METHOD FOR THE SYNTHESIS OF NAPHTHOXAZIN-3-ONE DERIVATIVES

Minoo Dabiri, Akram Sadat Delbari, and Ayoob Bazgir*

Department of Chemistry, Faculty of Science, Shahid Beheshti University, P. O. Box 19396-4716, Postal Code 1983963113, Tehran, Iran, *E-mail:* a_bazgir@sbu.ac.ir

Abstract – Carbamatoalkylnaphthol derivatives have been synthesized in good yields in a one-pot, and efficient process by condensation of β-naphtol, aromatic aldehydes and methyl carbamate in ionic liquid media. Ring closure of carbamatoalkylnaphthol derivatives occurred in ionic liquid media at 160 ^{o}C to give 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3]oxazin-3-one derivatives.

Aromatic-condensed oxazinone derivatives are a very important class of heterocyclic compounds since many of this heterocyclic system exhibit biological activities.[1] For example, naphthalene-condensed 1,3-oxazin-3-ones have been reported as anti-bacterial agents.[2] This class has also been used as precursors in the preparation of phosphinic ligands for asymmetric catalysis.[3] However, to the best of our knowledge, there was only very few reports of the synthesis of naphthalene-condensed oxazinone derivatives in the literature.[2,4] Recently, Fulop and co-workers, disclosed that the condensation of amino alkylnaphthols as precursors with phosgene in the presence of Et_3N, gave naphthalene-condensed 1,3-oxazin-3-one derivatives in moderate yields.[5] Cimarelli et al. used carbonyl diimidazole instead of phosgene.[6] All methods have used either expensive, toxic and hazardous reagents and solvents or starting material such as amino alkylnaphthol which was prepared in a multi-step reaction using harsh reaction conditions.[7] Therefore, the discovery of new, simple and green methods for synthesis of naphthoxazinone derivatives is of prime importance.

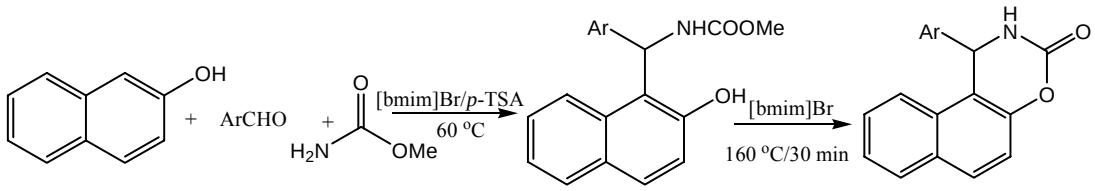
Carbamates have attracted considerable interest in the recent years. Its derivatives widely used as intermediate for the synthesis of pesticides, herbicides and medical drugs.[8] Furthermore, carbamates are found as protecting groups for the amino function, especially in the chemistry of peptides and peptidomimetics.[9] Initially these compounds were almost prepared from phosgene,[10a] phosgene derivatives[10b] or isocyanates[10c] in reaction with alcohols. This procedure had several drawbacks, among which the extreme toxicity of phosgene and generation of by-products.

The past few years have witnessed a growing interest in ionic liquids as solvent systems for organic

synthesis.[11] Reaction carried out in ionic liquids often exhibit different thermodynamic and kinetic behaviors than those run in conventional solvents. Their lack of vapor pressure is most notable and their use in a wide variety of environmentally friendly organic transformations (green chemistry) has been widely reported.[12]

Considering the above reports, we wish to report an efficient, fast and green method for the preparation of methyl (2-hydroxynaphthalen-1-yl)(aryl)methylcarbamate and 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3]-oxazin-3-one derivatives in ionic liquid, 1-buthyl-3-methylimidazolium bromide ([bmim]Br).

First, it was found that a mixture of β-naphthol (**1**), benzaldehyde (**2a**) and methyl carbamate (**3**) in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) in [bmim]Br media at 60 °C for 55 min afforded methyl (2-hydroxynaphthalen-1-yl)(phenyl)methylcarbamate (**4a**) in 76 % yield (**Scheme 1**).



1 **2a-e** **3** **4a-f** **5a-f**

Scheme 1

To explore the scope and limitations of this reaction, we extended the procedure to various aromatic aldehydes (**2b-h**). We found that the reaction proceeds efficiently with the aldehydes (**2b-f**) having electron-withdrawing substituent, but it did not proceed when the aldehyde (**2g**,**h**) having electron-releasing substituent benzaldehydes were used (**Table 1**). A reaction similar to our method has been previously reported by Betti which involved a multi-step reaction of β-naphthol, aromatic aldehydes and ammonia in a harsh reaction conditions.[7] Nevertheless**,** our method is green, efficient, simple and most importantly is one-step synthesis.

Table 1. Reaction of β-naphthol (**1**), aldehydes (**2**) and methyl carbamate (**3**)

Entry	ArCHO **2**		Product **4**	Time(min)	Yield(%)	MP(°C)
1	C_6H_5	**a**	**a**	55	76	213 dec.
2	4-Cl-C_6H_4	**b**	**b**	40	88	206 dec
3	4-F-C_6H_4	**c**	**c**	35	83	202-204
4	4-Br-C_6H_4	**d**	**d**	45	77	195-197
5	2-Cl-C_6H_4	**e**	**e**	50	78	182-184
6	3-Br-C_6H_4	**f**	**f**	60	75	193-195
7	4-MeO-C_6H_4	**g**	-	180	0	-
8	Me-C_6H_4	**h**	-	180	0	-

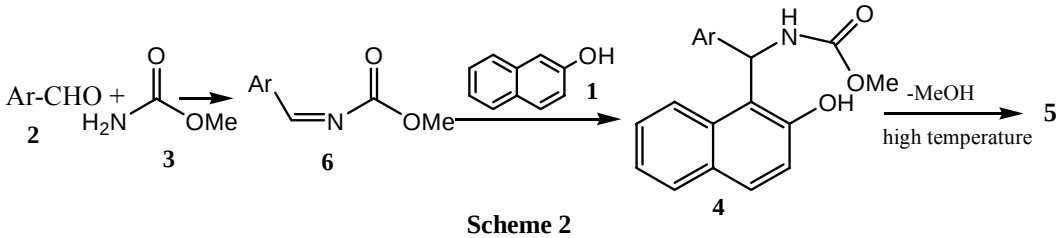
Then, after some preliminary experimentation, it was found that carbamatoalkylnaphthol derivatives (**4a-f)** were converted into 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3]oxazine-3-one derivatives **(5a-f)** by heating in [bmim]Br in the absence of any catalyst at 160 °C for 30 min (**Scheme 1**). The optimized results are summarized in **Table 2**. As can be seen from **Table 2**, naphthoxazinone derivatives **(5a-f)** were obtained in good yields.

Table 2. Synthesis of naphthoxazinones (**5**)[a]

Product **5**	ArCHO **2**	Yield(%)[b]	MP(°C)
a	C_6H_5 **a**	76	217-219
b	4-Cl-C_6H_4 **b**	58	208-210
c	4-F-C_6H_4 **c**	65	202-203
d	4-Br-C_6H_4 **d**	79	219-221
e	2-Cl-C_6H_4 **e**	73	251-253
f	3-Br-C_6H_4 **f**	69	226-228

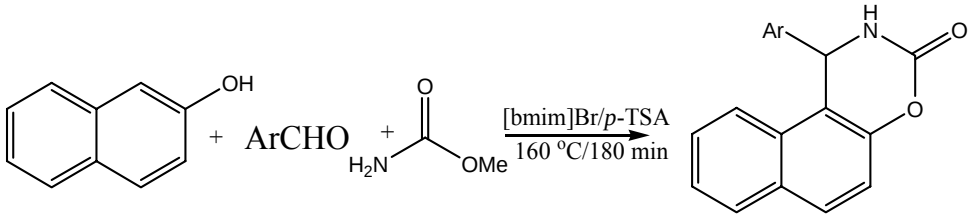
[a]reaction time= 30 min. [b]isolated yield

According to the results, and as in numerous classical multi-component reaction,[13] the reaction can be mechanistically considered to proceed through the acylimine intermediate (**6**) (formed in situ by reaction of the aldehyde (**2**) with methyl carbamate (**3**)) and the subsequent addition of the β-naphthol (**1**) to the acylimine (**6**), thus affording the corresponding products (**4**). In high temperature, products (**4**) followed by cyclization to afford the corresponding products (**5a-f**) (**Scheme 2**).



Scheme 2

For investigation of one-step synthesis of naphthoxazine-3-one derivatives (**5**), we examined reaction of β-naphthol (**1**), aldehyde (**2a-f**) and methyl carbamate (**3**) in different conditions. The best results were obtained in [bmim]Br at 160 °C for 180 min in absence of any catalyst to produce product (**5a-f**) in 30-35 % yields (**Scheme3**).



Scheme 3

In conclusion, an efficient and green methodology for the synthesis of carbamatoalkylnaphthol derivatives and naphthoxazine-3-one derivatives in ionic liquid media is reported. The simplicity and speed of the reactions are other merits.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on FT-IR 102MB BOMEM apparatus. ^{1}H NMR and ^{13}C NMR spectra were determined on a BRUKER DRX-300

AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Typical procedure for the preparation of methyl (2-hydroxynaphthalen-1-yl)(phenyl)methyl carbamate (4a): A mixture of β-naphthol (**1**) (0.14 g, 1 mmol), benzaldehyde (**2a**) (0.10 mL, 1 mmol), methyl carbamate (**3**) (0.11 g, 1.5 mmol), *p*-TSA (0.10 g) and [bmim]Br (0.30 g) was heated with stirring at 60 ^{o}C for 55 min. After cooling, the reaction mixture was washed with water (15 mL) and then recrystallized from EtOAc/ hexane (1:3) to afford the pure product.

Typical procedure for the preparation of 1,2-dihydro-1-phenylnaphtho[1,2-*e*][1,3]oxazin-3-one (5a): A mixture of methyl (2-hydroxynaphthalen-1-yl)(phenyl)methyl carbamate (**4a**) (0.31 g, 1 mmol) and [bmim]Br (0.30 g) was heated with stirring at 160 ^{o}C for 30 min. After cooling, the reaction mixture was washed with water (10 mL) and then recrystallized from EtOAc/ hexane (1:3) to afford the pure product.

Spectral data for products:

4a: mp 213 ^{o}C (decomp.), IR (KBr) (ν_{max}, cm^{-1}): 3415, 3190, 1673; ^{1}H NMR (DMSO-*d*$_6$) δ_H: 3.38 (3H, s, OMe), 6.86 (1H, d, J = 9 Hz, CH), 7.15-7.81 (11H, m, Arom.), 7.91 (1H, d, J = 8.8 Hz, NH), 10.11 (1H, s, OH); ^{13}C NMR (DMSO-*d*$_6$) δ_C: 50.84, 52.10, 118.91, 119.31, 122.98, 123.51, 126.48, 126.82, 126.98, 128.56, 128.84, 129.02, 129.76, 132.52, 142.81, 153.36, 157.06. MS (m/z, %): 307 (M$^+$, 7), 231 (100), 202 (35), 77 (24). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.24; H, 5.57; N, 4.57.

4b: mp 206 ^{o}C (decomp.), IR (KBr) (ν_{max}, cm^{-1}): 3410, 3220,1680; ^{1}H NMR (DMSO-*d*$_6$) δ_H: 3.56 (3H, s, OMe), 6.84 (1H, d, J= 8.6 Hz, CH), 7.20-7.81 (10H, m, Arom.), 7.89 (1H, d, J = 8.1 Hz, NH), 10.16 (1H, s, OH); ^{13}C NMR (DMSO-*d*$_6$) δ_C: 50.37, 52.15, 118.86, 123.03, 123.39, 127.09, 128.37, 128.50, 128.83, 129.07, 129.98, 131.39, 132.41, 141.92, 153.41, 157.07; MS (m/z, %): 341 (M$^+$, 6), 265 (12), 231 (24), 213 (100). Anal. Calcd for $C_{19}H_{16}NO_3Cl$: C, 66.77; H, 4.72; N, 4.10. Found: C, 66.75; H, 4.73; N, 4.08.

4c: 202-204 ^{o}C, IR (KBr) (ν_{max}, cm^{-1}): 3410, 3225,1677; ^{1}H NMR (DMSO-*d*$_6$) δ_H: 3.57 (3H, s, OMe), 6.84 (1H, d, J = 8.1 Hz, CH), 7.05-7.82 (10H, m, Arom.), 7.91 (1H, d, J = 7.6 Hz, NH), 10.16 (1H, s, OH); ^{13}C NMR (DMSO-*d*$_6$) δ_C: 49.93, 51.62, 114.75, 118.45, 118.59, 122.52, 122.85, 126.57, 127.92, 128.35, 128.56, 129.39, 131.93, 138.41, 152.87, 156.53, 161.46; MS (m/z, %): 325 (M$^+$, 5), 294 (6), 249 (100), 144 (78). Anal. Calcd for $C_{19}H_{16}NO_3F$: C, 70.14; H, 4.96; N, 4.31. Found: C, 70.12; H, 4.95; N, 4.30.

4d: mp 195-197 ˚C, IR (KBr) (ν_{max}, cm^{-1}): 3420, 1683; ^{1}H NMR (DMSO-*d*$_6$) δ_H: 3.57 (3H, s, OMe), 6.81 (1H, d, J = 7.4 Hz, CH), 7.14-7.86 (10H, m, Arom.), 7.89 (1H, d, J = 7.5 Hz, NH), 10.16 (s, OH); ^{13}C NMR (DMSO-*d*$_6$) δ_C: 50.38, 52.16, 118.81, 118.86, 119.87, 123.03, 123.42, 127.08, 128.76, 128.78, 129.07, 129.99, 131.42, 132.40, 142.38, 153.42, 157.08; MS (m/z, %): 386 (M$^+$, 11), 355 (6), 313 (100),

144 (63). Anal. Calcd for $C_{19}H_{16}BrNO_3$: C, 59.08; H, 4.18; N, 3.63. Found: C, 59.09; H, 4.17; N, 3.64.

4e: mp 182-184 °C, IR (KBr) (ν_{max}, cm^{-1}): 3415, 3223,1687; ^{1}H NMR (DMSO-d_6) δ_H: 3.53 (3H, s, OMe), 6.89 (1H, d, J= 6.8 Hz, CH), 7.18-7.81 (10H, m, Arom.), 8.08 (1H, d, J = 7.1 Hz, NH), 9.95 (1H, s, OH); ^{13}C NMR (DMSO-d_6) δ_C: 50.16, 51.98, 117.42, 119.03, 125.96, 126.79, 126.99, 128.56, 128.72, 128.92, 129.06, 129.77, 129.96, 130.36, 132.93, 133.05, 139.81, 153.96, 156.59; MS (m/z, %): 341 (M^+, 12), 310 (9), 282 (25), 231 (27), 213 (100). Anal. Calcd for $C_{19}H_{16}NO_3Cl$: C, 66.77; H, 4.72; N, 4.10. Found: C, 66.73; H, 4.76; N, 4.07.

4f: mp 193-195 °C, IR (KBr) (ν_{max}, cm^{-1}): 3415, 1685; ^{1}H NMR (DMSO-d_6) δ_H: 3.28 (3H, s, OMe), 6.87 (1H, d, J = 6.4 Hz, CH), 7.12-7.92 (10H, m, Arom.), 8.14 (1H, d, J = 6.5 Hz, NH), 10.80 (s, OH); ^{13}C NMR (DMSO-d_6) δ_C: 50.93, 52.12, 118.91, 122.15, 123.66, 125.96, 126.79, 128.01, 128.57, 129.33, 130.25, 131.17, 131.42, 131.54, 132.27, 138.22, 140.57, 145.95, 154.04; MS (m/z, %): 385 (M^+-1, 15), 355 (24), 313 (100), 231 (56).. Anal. Calcd for $C_{19}H_{16}NO_3Br$: C, 59.08; H, 4.18; N, 3.63. Found: C, 59.06; H, 4.19; N, 3.65.

5a: mp 217-219 °C, IR (KBr) (ν_{max}, cm^{-1}): 3295, 1730, 1517; ^{1}H NMR (DMSO-d_6) δ_H: 6.19 (1H, d, J = 2.1 Hz, CH), 7.24-8.00 (11H, m, Arom.), 8.87 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 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 (m/z, %): 275 (M^+, 7), 231 (100), 202 (35). Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.52; H, 4.75; N, 5.11.

5b: mp 208-210 °C, IR (KBr) (ν_{max}, cm^{-1}): 3224, 3146, 1734; ^{1}H NMR (DMSO-d_6) δ_H: 6.24 (1H, s, CH), 7.31-8.01 (10H, m, Arom.), 8.91 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 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 (m/z, %): 309 (M^+, 5), 265(60), 231(100), 202(27). Anal. Calcd for $C_{18}H_{12}NO_2Cl$: C, 69.80; H, 3.90; N, 4.52. Found: C, 69.82; H, 3.89; N, 4.51.

5c: mp 202-203 °C, IR (KBr) (ν_{max}, cm^{-1}): 3135, 2954, 1758; ^{1}H NMR (DMSO-d_6) δ_H: 5.98 (1H, d, J = 3 Hz, CH), 6.88-7.76(10H, m, Arom.), 8.63 (1H, d, J = 2.7 Hz, NH); ^{13}C NMR (DMSO-d_6) δ_C: 53.39, 114.29, 116.07, 116.35, 117.33, 123.51, 125.58, 127.87, 129.11, 129.56, 130.84, 139.58, 147.84, 149.68, 160.41, 163.65; MS (m/z, %): 294 (M^++1, 15), 249 (100), 231(10), 220 (25). Anal. Calcd for $C_{18}H_{12}FNO_2$: C, 73.71; H, 4.12; N, 4.78. Found: C, 73.70; H, 4.10; N, 4.76.

5d: mp 219-221 °C, IR (KBr) (ν_{max}, cm^{-1}): 3146, 1732; ^{1}H NMR (DMSO-d_6) δ_H: 6.22 (1H, s, CH), 7.25-8.01(10H, m, Arom.), 8.90 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 53.53, 113.94, 117.33, 121.65, 123.46, 125.61, 127.91, 129.12, 129.22, 129.68, 130.87, 132.34, 142.59, 147.91, 149.60; MS (m/z, %): 353 (M^+, 25), 309 (100), 230 (100), 200 (100). Anal. Calcd for $C_{18}H_{12}NO_2Br$: C, 61.04; H, 3.41; N, 3.95. Found: C, 61.03; H, 3.42; N, 3.93.

5e: mp 251-253 °C, IR (KBr) (ν_{max}, cm^{-1}): 3218, 3141, 1728; ^{1}H NMR (DMSO-d_6) δ_H: 6.50 (1H, s, CH),

7.19-8.02 (10H, m, Arom.), 8.90 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 52.17, 112.94, 117.32, 122.73, 125.59, 128.09, 128.81, 129.25, 129.31, 130.28, 130.52, 130.87, 131.10, 132.15, 139.96, 148.27, 149.13; MS (m/z, %): 309 (M^+, 9), 283(17), 231(100). Anal. Calcd for $C_{18}H_{12}NO_2Cl$: C, 69.80; H, 3.90; N, 4.52. Found: C, 69.78; H, 3.87; N, 4.50.

5f: mp 226-228 ^{o}C, IR (KBr) (ν_{max}, cm^{-1}): 3142, 1730; ^{1}H NMR (DMSO-d_6) δ_H: 6.26 (1H, s, CH), 7.19-7.99 (10H, m, Arom.), 8.95 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 53.49, 113.74, 117.35, 122.48, 123.49, 125.68, 126.32, 128.01, 129.16, 129.24, 130.39, 130.87, 131.01, 131.43, 131.77, 145.79, 148.01, 149.62; MS (m/z, %): 353 (M^+, 18), 310 (63), 231 (100). Anal. Calcd for $C_{18}H_{12}NO_2Br$: C, 61.04; H, 3.41; N, 3.95. Found: C, 61.06; H, 3.44; N, 3.97.

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