Synthesis of 2-aryl-1,2-dihydronaphtho[1,2-f][1,4]oxazepin-3(4H)-ones. Part I

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Abstract

Oxazepines, which were synthesized in literature by means a variety of methods, are of great importance in heterocyclic chemistry along with biology and pharmacology. In this work we tried to synthesize naphthoxazepines by using a number of Schiff bases, which were synthesized from 2-hydroxy-1-napthaldehyde and anilines. The obtained imines were reduced to amines, acylated with chloroacetyl chloride and cyclised to give naphthoxazepinones in an overall yield of 20-49%. The identifications of the isolated and purified compounds were determined by IR, UV, ^{1}H-NMR, ^{13}C-NMR, mass spectra and elemental analysis.

Keywords: Schiff bases, chloroacetyl chloride, naphthoxazepines, ring closure

Introduction

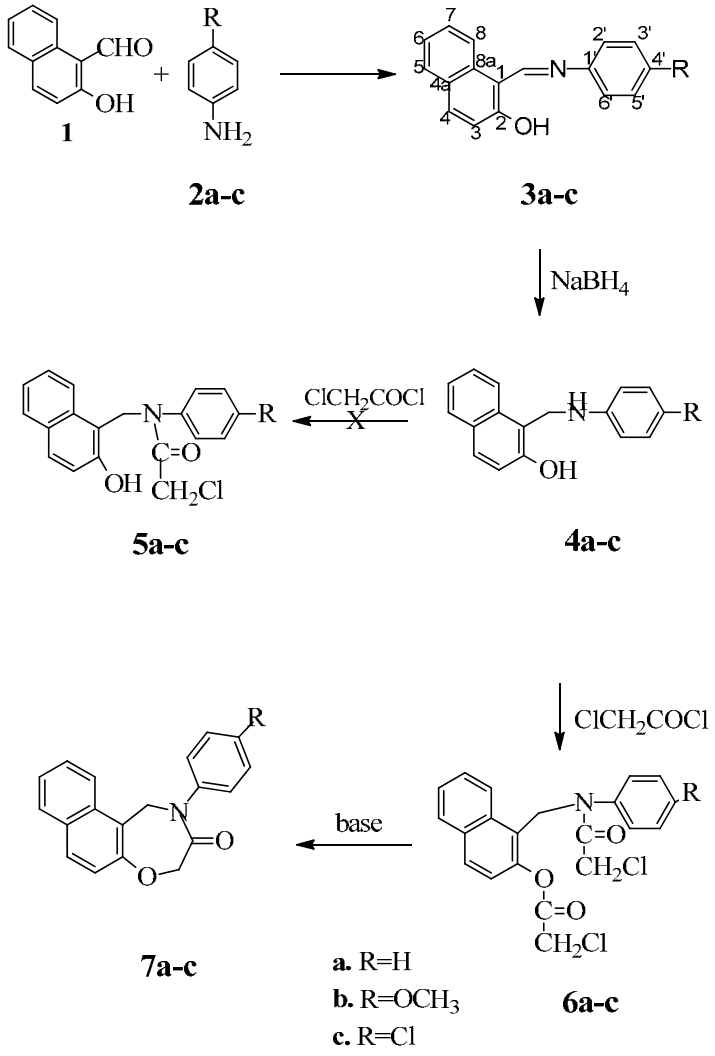
Benzoxazepines, naphthoxazepines and their derivatives have some important biological[1] and pharmacological activities[2] such as on the central nervous system as enzyme inhibitors,[3] analgesic,[2] antipsychotics[4] and antidepressant.[5,6] Additionally, benzo[1,4]oxazepines are crucial moieties in many psychoactive drugs.[7,8] It was found that dibenzo[*b,f*][1,4]oxazepin-11(10*H*)-ones to be selective inhibitors of human immunodefiency virus (HIV) type 1 reverse transcriptase.[9] Known synthesis of benzoxazepines includes condensations of 2-aryloxyethylamines with 2-formylbenzoic acid,[10] rearrangement of methyl 2-(8-methoxy-2,3-dihydro-1,4-benzoxazepin-5-yl)benzoate using Bischler-Napieralski conditions[11] and scandium or copper triflate catalyzed acylaminoalkylation of α-methoxyisoindolones with the formation of 1,4-benzoxazepines in moderate yields.[12] Some oxazepines and benzoxazepines were synthesized from amides,[13-15] aminoacids,[16-19] esters,[20] acid chlorides,[21] flavones,[22,23] amines[24] and Mannich base.[25]

Working on Schiff bases **3a-c** for a long time and biological interest of naphthoxazepines impelled us to synthesize different naphthoxazepines **7a-c** in our laboratory.

Results and Discussion

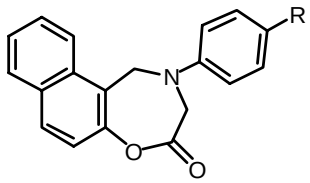
Naphtholic Schiff bases **3a-c** were obtained from 2-hydroxy-1-naphthaldehyde **1** and substituted anilines **2** in ethyl alcohol according to the method of Sawich and his coworkers.[26] The synthesized Schiff bases were reduced[27,28] in a mixture of dioxane-methyl alcohol (1:1) with $NaBH_4$ until no CH=N group was seen in IR spectra at 1625 cm^{-1}. 1-N-arylaminomethyl-2-naphthols **4a-c** were obtained in good yields. The isolated and purified amines **4a-c** were refluxed in dry benzene with chloroacetyl chloride to give 1-(2-chloro-*N*-arylacetamido)methylnapthalen-2-yl-2-chloroacetates **6a-c** instead of 2-chloro-*N*-((2-hydroxynapthalen-1-yl)methyl)-*N*-arylacetamides **5a-c** in our reaction conditions. ^{1}H-NMR spectra of diacetylated products gave three singlets at 5.35, 4.22 and 3.65 ppm. The singlets at 5.35, 4.22 and 3.65 ppm were assigned to (Ar-CH_2-N-Ar), O-acyl (CH_2-Cl) and N-acyl (CH_2-Cl) methylene protons respectively. Since we saw three methylene protons in ^{1}H-NMR we thought that the acetylation occurred on both phenolic oxygen and amines nitrogen atoms. The peaks that were observed in IR at 1804 and 1651 cm^{-1} were due to the absorption of ester and amide carbonyl absorptions, respectively. The diacyl derivatives structures **6a-c** were confirmed by ^{13}C-NMR spectra. Then we warmed the diacetyl derivatives **6a-c** in 10 % NaOH solution by controlling with IR spectra until the two peaks at 1804 and 1651 cm^{-1} were not observed in IR spectra. The IR spectra of crude products showed typical peaks at 1656 cm^{-1} for amide carbonyl and at 1242 cm^{-1} for ethers. These peaks confirmed us that oxazepine rings were formed. The presence of two singlets at 5.24 and 4.83 ppm in ^{1}H-NMR spectra of isolated and purified oxazepines also confirmed the oxazepines formation. ^{13}C-NMR spectra of the products also confirmed oxazepines formation. After four steps we obtained the 2-(phenyl)-1,2-dihydronaptho[1,2-*f*][1,4]oxazepin-3(1*H*)-ones **7a-c**.

The schematic diagram for oxazepines synthesize is given in Scheme 1.



Scheme 1. Synthesis of naphthoxazepines **7a-c**.

In our reaction conditions we isolated only the naphthoxazepin-3-ones **7a-c**, which were formed from the oxygen attack. The other regioisomer 2-aryl-2,3-dihydronaphto[1,2-f][1,4]oxazepin-4(1H)-ones **8a-c**, which could be formed from the nitrogen attack, were not isolated.



8a-c

Experimental Section

General. All melting points were taken in open capillaries and uncorrected. IR spectra in KBr were recorded on Mattson 1000 FTR spectrometer and JASCO ST / IR-420 machine and UV spectra were recorded on Unicam UV2-100/Visible spectrometer and 150-20 Hitachi spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were determined at Bruker AC 200L and Bruker 400 MHz spectrometer using $CDCl_3$. Mass spectra were obtained in a (LS/MS-APCl) Agilent 1100 MSD Instrument. Elemental analyses were obtained LECO CHNS 932 Machine. Merck Kieselgel HF_{254} type-60 and Kieselgel 40-60 μm type were used for TLC. For analytical work 0.25 mm, for preparative work 0.75 mm plates were used. All solvents and reagents used were analytical reagent grade.

Synthesis of Schiff bases 3a-c

Schiff bases **3a-c** were synthesized according to the method of Sawich and his coworkers.[26] The structures of the Schiff bases **3a-c** substrates prepared were determined by IR, UV, ^{1}H-NMR, ^{13}C-NMR and mass spectra and compared with literature data.

Reductions of Schiff bases with $NaBH_4$

Schiff base **3a-c** (4mmol) were dissolved in methanol-dioxane (1:1) (20 ml) and then 0.76 g (20 mmol) $NaBH_4$ was added slowly until the evolution of H_2 gase ceases and yellow color disappears. Ice water was added to the reaction mixture. Crude product was crystallized after preparative TLC (SiO_2/toluene) purification.

Reactions of reduced Schiff bases 4a-c with chloroacetyl chloride

Chloroacetyl chloride (1.58 ml, 0.02 mole) was added to a vigorously stirred solution of **4a-c** (0.01 mole) in dry benzene (50 ml). The reaction mixture was refluxed for 2 hours. The solvent was removed *in vacuo* and the gummy residue was crystallized from dry ethyl alcohol yielding white crystals **6a-c**.

Ring closure reactions of of diacetyl derivatives 6a-c

Compound **6a-c** (0.001 mole) was added to 5% NaOH solution (15 ml) and the mixture was stirred on water bath for 1 hour. The white solid obtained on cooling was filtered, washed with water and crystallized from alcohol to give the compounds **7a-c**.

1-((Phenylamino)methyl)naphthalen-2-ol 4a. Yield: 85%. mp: 122 °C. IR (KBr) ν_{max}: 3387, 3285, 1600-1446, 1242 cm^{-1}. UV (EtOH) λ_{max}(log ε): 334.8 (0.536), 324.4 (0.321), 290.0 (0.563) nm. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.78 (2H, s, -CH_2-NH-), 6.79 (2H, d, *J*=7.8 Hz, 2′-H and 6′-H), 6.86 (1H, t, *J*=7.3 Hz, 4′-H), 7.05 (1H, d, *J*=8.8 Hz, 3-H), 7.18 (2H, t, *J*=8.0 Hz, 3′-H and 5′-H), 7.27 (1H, t, *J*=8.8 Hz, 6-H), 7.39 (1H, t, *J*=7.6 Hz, 7-H), 7.65 (1H, d, *J*=8.8 Hz, 4-H), 7.73 (1H, d, *J*=8.0 Hz, 5-H), 7.82 (1H, d, *J*=8.5 Hz, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.5 (-CH_2-NH-), 112.8 (2′-C), 116.3 (1-C), 119.6 (3-C), 121.5 (8-C), 121.7 (4′-C), 123.4 (6-C), 127.1 (7-

C), 129.4 (5-C), 129.8 (4-C), 129.9 (8a-C), 131.1 (3′-C), 132.1 (4a-C), 147.4 (1′-C), 155.3 (2-C). MS: m/z 249 (M^+). Anal. Calcd. for $C_{17}H_{15}NO$ (249.31): C, 81.90; H, 6.06; N, 5.62. Found: C, 81.33; H, 5.70; N, 5.15.

1-((4-Methoxyphenylamino)methyl)naphthalen-2-ol 4b. Yield: 87%. mp: 125 °C. IR (KBr) ν_{max}: 3400, 3250, 1600-1500, 1250 cm^{-1}. UV (MeOH) λ_{max}(log ε): 335.0 (0.187), 325.0 (0.170), 294.0 (0.230), 274.0 (0.302), 231.0 (0.250) nm. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.67 (3H, s, -OCH_3), 4.77 (2H, s, -CH_2-NH), 6.71 (2H, d, *J*=8.1 Hz, 3′-H and 5′-H), 6.78 (2H, d, *J*=8.2 Hz, 2′-H), 7.08 (1H, d, *J*=8.5 Hz, 3-H), 7.26 (1H, t, *J*=6.5 Hz, *J*=6.8 Hz, 6-H), 7.39 (1H, t, *J*=7.0 Hz, 7-H), 7.64 (1H, d, *J*=8.0 Hz, 4-H), 7.71 (1H, d, *J*=8.0 Hz, 5-H), 7.78 (1H, d, *J*=8.6 Hz, 8-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 46.2 (-CH_2-NH), 55.9 (-OCH_3), 112.6 (2′-C), 114.9 (1-C), 115.2 (3-C), 118.6 (8-C), 119.7 (6-C), 121.5 (7-C), 123.2 (5-C), 127.1 (4-C), 129.2 (8a-C), 129.3 (3′-C), 129.9 (4a-C), 132.5 (1′-C), 155.4 (2-C), 156.2 (4′-C). MS: m/z 279 (M^+). Anal. Calcd. for $C_{18}H_{17}NO_2$ (279.33): C, 77.40; H, 6.13; N, 5.01. Found: C, 77.78; H, 7.01; N, 4.96.

1-((4-Chlorophenylamino)methyl)naphthalen-2-ol 4c. Yield: 70%. mp: 135 °C. IR (KBr) ν_{max}: 3480, 3250, 1580-1510, 1240 cm^{-1}. UV (MeOH) λ_{max}(log ε): 331.6 (0.093), 321.2 (0.101), 289.6 (0.138), 254.8 (0.326), 217.2 (0.646) nm. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.78 (2H, s, -CH_2-NH), 6.70 (2H, dd, *J*=2.0 Hz, *J*=7.0 Hz, 3′-H), 7.04 (1H, d, *J*=9.0 Hz, 3-H), 7.10 (2H, dd, *J*=2.0 Hz, 2′-H), 7.28 (1H, t, *J*=7.7 Hz, 6-H), 7.42 (1H, m, 7-H), 7.65 (1H, d, *J*=8.8 Hz, 5-H), 7.72 (1H, d, *J*=8.0 Hz, 4-H), 7.81 (1H, d, *J*=7.7 Hz, 8-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 44.1 (-CH_2-NH), 112.9 (2′-C), 117.2 (8-C), 119.4 (1-C), 121.7 (6-C), 126.1 (4′-C), 127.3 (7-C), 129.4 (5-C), 129.4 (4-C), 129.7 (8a-C), 130.2 (3′-C), 132.5 (4a-C), 146.4 (1′-C), 155.3 (2-C). MS: m/z 283, 285 (M^+). Anal. Calcd. for $C_{17}H_{14}ClNO$ (283.75): C, 71.96; H, 4.97; N, 4.94. Found: C, 71.89; H, 4.92; N, 4.62.

1-((2-Chloro-*N*-phenylacetamido)methyl)napthalen-2-yl-2-chloroacetate 6a. White crystals. Yield: 78%. mp: 108 ºC. IR (KBr) ν_{max}: 1704, 1651, 1600-1421, 578 cm^{-1}. UV (EtOH) λ_{max}(log ε): 349.2 (0.061), 288.8 (0.713), 230.0 (0.116) nm. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.65 (2H, s, N(CO)CH_2Cl), 4.22 (2H, s, O(CO)CH_2Cl), 5.35 (2H, s, Ar-CH_2-N-Ar), 6.73 (1H, d, *J*=7.5 Hz, 3′-H), 7.03 (1H, t, *J*=4.0 Hz, 2′-H), 7.04 (1H, t, *J*=4.0 Hz, 4′-H), 7.10 (1H, t, *J*=7.3 Hz, 6-H), 7.30 (1H, t, *J*=7.4 Hz, 7-H), 7.31 (1H, d, *J*=6.0 Hz, 3-H), 7.67 (1H, d, *J*=9.0 Hz, 4-H), 7.68 (1H, d, *J*=9.2 Hz, 5-H), 7.74 (1H, dd, *J*=6.5 Hz, *J*=3.0 Hz, 8-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 40.8 (Ar-<u>C</u>H_2-N-Ar), 41.9 (N(CO)-<u>C</u>H_2Cl), 42.3 (O(CO)-<u>C</u>H_2Cl), 120.9 (8-C), 122.1 (3-C), 124.2 (1-C), 126.2 (6-C), 127.7 (7-C), 128.9 (2′-C), 128.9 (4-C), 129.5 (8a-C), 130.6 (5-C), 131.5 (3′-C), 132.7 (4a-C), 138.9 (1′-C), 147.5 (2-C), 165.8 (N(<u>C</u>O)-CH_2Cl), 165.8 (O(<u>C</u>O)-CH_2Cl). MS: m/z 401 (M^+). Anal. Calcd. for $C_{21}H_{17}Cl_2NO_3$ (402.27): C, 62.70; H, 4.26; N, 3.48. Found: C, 62.97; H, 4.21; N, 3.79.

1-((2-Chloro-*N*-4-methoxyphenylacetamido)methylnapthalen-2-yl-2-chloroacetate 6b. White crystals. Yield: 72%. mp: 116 °C. IR (KBr) ν_{max}: 1700, 1660, 1560-1500, 570 cm^{-1}. UV (EtOH) λ_{max}(log ε): 335.0 (0.359), 307.0 (0.197), 279.6 (0.302), 255.4 (0.254), 232.0 (0.250). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.61 (3H, s, -OCH_3), 3.69 (2H, s, N(CO)CH_2Cl), 4.24 (2H, s, O(CO)CH_2Cl), 5.33 (2H, s, Ar-CH_2-N-Ar), 6.56 (2H, d, *J*=9.0 Hz, 3′-H), 6.65 (2H, d, *J*=9.0 Hz,

2′-H), 7.07 (1H, d, *J*=8.9 Hz, 3-H), 7.34-7.36 (2H, m, *J*=6.4 Hz, 6-H and 7-H), 7.72 (2H, d, *J*=8.0 Hz, 4-H and 5-H), 7.76 (1H, d, 1H, *J*=6.0 Hz, 8-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 41.4 (Ar-$\underline{C}H_2$-N-Ar), 42.5 (N(CO)-$\underline{C}H_2$-CI), 42.6 (O(CO)-$\underline{C}H_2$-Cl), 55.8 (O-CH_3), 115.2 (3′-C), 121.1 (8-C), 122.8 (3-C), 124.3 (2′-C), 126.2 (1-C), 127.7 (6-C), 128.9 (7-C), 130.0 (4-C), 130.6 (8a-C), 132.0 (5-C), 132.1 (4a-C), 133.3 (1′-C), 148.0 (2-C), 160.2 (4′-C), 166.3 (N($\underline{C}$O)-CH_2-Cl), 166.8 (O($\underline{C}$O)-CH_2-Cl). MS: m/z 432 (M^+). Anal. Calcd. for $C_{22}H_{19}Cl_2NO_4$ (432.30): C, 61.12; H, 4.43; N, 3.24. Found: C, 61.18; H, 4.19; N, 3.66.

1-((2-Chloro-*N*-4-chlorophenylacetamido)methylnapthalen-2-yl-2-chloroacetate 6c. White crystals. Yield: 40%. mp: 118 °C. IR (KBr) ν_{max}: 1706, 1670, 1515-1400, 588 cm^{-1}. UV (EtOH) λ_{max}(log ε): 335.2 (0.106), 320.0 (0.108), 287.6 (0.367), 255.6 (0.299) nm. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.66 (2H, s, N(CO)CH_2Cl), 4.25 (2H, s, O(CO)CH_2Cl), 5.35 (2H, s, Ar-CH_2-N-Ar), 6.65 (2H, d, *J*=9.0 Hz, 2′-H), 6.70 (2H, d, *J*=8.0 Hz, 3′-H), 7.07 (1H, d, *J*=8.9 Hz, 3-H), 7.34-7.36 (2H, m, *J*=6.4 Hz, 6-H and 7-H), 7.72 (2H, d, *J*=8.0 Hz, 4-H and 5-H), 7.76 (1H, d, *J*=6.0 Hz, 8-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 41.3 (Ar-$\underline{C}H_2$-N-Ar), 42.2 (N(CO)-$\underline{C}H_2$Cl), 42.4 (O(CO)-$\underline{C}H_2$Cl), 121.1 (8-C), 122.4 (1-C), 123.9 (6-C), 127.8 (2′-C), 129.0 (7-C), 130.2 (4-C), 130.4 (8a-C), 130.8 (5-C), 131.4 (3′-C), 132.1 (4′-C), 133.1 (4a-C), 139.4 (1′-C), 148.0 (2-C), 166.3 (N($\underline{C}$O)-CH_2Cl), 166.4 (O($\underline{C}$O)-CH_2Cl). MS: m/z 435 (M^+); Anal. Calcd. for $C_{21}H_{16}Cl_3NO_3$ (436.72): C, 57.75; H, 3.69; N, 3.21. Found: C, 57.55; H; 3.80; N, 3.46.

2-Phenyl-1,2-dihydronaphtho[1,2-*f*][1,4]oxazepin-3(4*H*)-one 7a. Yield: 65%. mp: 91 °C. IR (KBr) ν_{max}: 1656, 1523-1395, 1242 cm^{-1}. UV (EtOH) λ_{max}(log ε): 329.6 (0.295), 321.6 (0.480), 315.2 (0.349), 291.2 (0.707), 277.2 (0.101). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.83 (2H, s, -CH_2-O-), 5.24 (2H, s, -CH_2-N-), 7.17 (2H, d, *J*=8.0 Hz, 3′-H), 7.18 (2H, d, *J*=7.3 Hz, 2′-H), 7.39 (1H, t, *J*=7.0 Hz, 6-H), 7.42 (1H, t, *J*=8.4 Hz, 7-H), 7.70 (1H, d, *J*=8.4 Hz, 4-H), 7.78 (1H, d, *J*=8.7 Hz, 5-H), 7.81 (1H, d, *J*=8.4 Hz, 8-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 47.2 (Ar-CH_2-N), 73.4 (O-$\underline{C}H_2$), 120.8 (1-C), 122.4 (3-C), 124.3 (8-C), 125.3 (6-C), 126.9 (7-C), 127.6 (2′-C), 127.8 (4-C), 129.4 (4′-C), 129.9 (5-C), 131.0 (4a-C), 131.4 (3′-C), 134.4 (8a-C), 144.5 (1′-C), 156.5 (2-C), 169.4 (C=O). MS: m/z 290 (M^+). Anal. Calcd. for $C_{19}H_{15}NO_2$ (289.33): C, 78.87; H, 5.23; N, 4.84. Found: C, 78.91; H, 5.22; N, 4.35.

2-(4-Methoxyphenyl)-1,2-dihydronaphtho[1,2-*f*][1,4]oxazepin-3(4*H*)-one 7b. Yield: 78%. mp: 96 °C. IR (KBr) ν_{max}: 1656, 1500, 1250 cm^{-1}. UV (MeOH) λ_{max}(log ε): 406.0 (0.287), 322.0 (0.446), 318.0 (0.397), 225.5 (0.148) nm. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.74 (3H, s, -OCH_3), 4.81 (2H, s, -CH_2-O), 5.19 (2H, s, Ar-CH_2-N), 6.85 (2H, d, *J*=8.0 Hz, 2′-H), 7.07 (2H, d, *J* =8.0 Hz, 3′-H), 7.26 (1H, d, *J*=8.0 Hz, 3-H), 7.37 (1H, t, *J*=8.0 Hz, 6-H), 7.44 (1H, t, *J*=8.0 Hz, 7-H), 7.69 (1H, d, *J*=8.0 Hz, 4-H), 7.78 (1H, d, *J*=9.0 Hz, 5-H), 7.80 (1H, d, *J*=8.0 Hz, 8-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 47.4 (Ar-CH_2-N), 55.9 (-OCH_3), 73.4 (O-CH_2), 115.2 (3′-C), 120.8 (1-C), 122.4 (3-C), 124.6 (8-C), 125.3 (2′-C), 127.7 (6-C), 128.0 (7-C), 129.4 (4-C), 130.9 (5-C), 131.2 (4a-C), 131.4 (8a-C), 137.4 (1′-C), 156.5 (2-C), 158.9 (4′-C), 169.6 (C=O). MS: m/z 319 (M^+). Anal. Calcd. for $C_{20}H_{17}NO_3$ (319.35): C, 75.22; H, 5.37; N, 4.39. Found: C, 75.03; H, 5.17; N, 4.51.

2-(4-Chlorophenyl)-1,2-dihydronaptho[1,2-*f*][1,4]oxazepin-3(4*H*)-one 7c. Yield: 72%. mp: 133 °C. IR (KBr) ν_{max}: 1656, 1615-1495, 1242 cm^{-1}. UV (EtOH) λ_{max}(log ε): 388.0 (0.017), 314.4 (0.065), 278.8 (0.202), 259.2 (0.997) nm. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.82 (2H, s, -CH_2-O), 5.20 (2H, s, -CH_2-N), 7.12 (2H, d, *J*=8.0 Hz, 3′-H), 7.30 (1H, d, *J*=8.8 Hz, 3-H), 7.31 (2H, d, *J*=8.0 Hz, 2′-H), 7.37 (1H, t, *J*=8.4 Hz, 6-H), 7.48 (1H, t, *J*=6.8 Hz, 7-H), 7.70 (1H, d, *J*=8.4 Hz, 4-H), 7.79 (1H, d, *J*=8.4 Hz, 5-H), 7.81 (1H, d, *J*=7.1 Hz, 8-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 47.1 (Ar-CH_2-N), 73.3 (O-CH_2), 120.4 (3-C), 122.2 (8-C), 122.5 (2′-C), 125.4 (6-C), 127.9 (7-C), 130.1 (4-C), 130.1 (5-C), 130.8 (4a-C), 131.2 (8a-C), 131.4 (3′-C), 133.5 (4′-C), 142.9 (1′-C), 156.5 (2-C), 169.5 (C=O). MS: m/z 323 (M^+). Anal. Calcd. for $C_{19}H_{14}ClNO_2$ (323.77): C, 70.48; H, 4.36; N, 4.33. Found: C, 70.31; H, 4.69; N, 4.34.

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