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, 1H-NMR, 13C-NMR, mass spectra and elemental analysis.

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

Introduction

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

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. The synthesized Schiff bases were reduced in a mixture of dioxane-methyl alcohol (1:1) with NaBH₄ 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 chloroaacetyl chloride to give 1-(2-chloro-N-arylacetamido)methylnaphthalen-2-yl-2-chloroacetates 6a-c instead of 2-chloro-N-((2-hydroxynaphthalen-1-yl)methyl)-N-arylacetamides 5a-c in our reaction conditions. ¹H-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-CH₂-N-Ar), O-acyl (CH₂-Cl) and N-acyl (CH₂-Cl) methylene protons respectively. Since we saw three methylene protons in ¹H-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 ¹³C-NMR spectra. Then we warmed the diacyl 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 ¹H-NMR spectra of isolated and purified oxazepines also confirmed the oxazepines formation. ¹³C-NMR spectra of the products also confirmed oxazepines formation. After four steps we obtained the 2-(phenyl)-1,2-dihydropatho[1,2-][1,4]oxazepin-3(1H)-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-dihydrnaphto[1,2-f][1,4]oxazepin-4(1H)-ones 8a-c, which could be formed from the nitrogen attack, were not isolated.
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-APCI) 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. 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$_2$ gas 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 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.
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). \(^1\)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). \(^1\)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\(_{18}\)H\(_{14}\)Cl\(_2\)NO (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)naphthalen-2-yl-2-chloroacetate 6a.** White crystals. Yield: 78%. mp: 108 °C. 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\(_2\)-Cl), 4.22 (2H, s, O(CO)CH\(_2\)-Cl), 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). \(^1\)C-NMR (100 MHz, CDCl\(_3\)): δ: 40.8 (Ar-CH\(_2\)-N-Ar), 41.9 (N(CO)-CH\(_2\)-Cl), 42.3 (O(CO)-CH\(_2\)-Cl), 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(CO)-CH\(_2\)-Cl), 165.8 (O(CO)-CH\(_2\)-Cl). MS: m/z 401 (M'). Anal. Calcd. for C\(_{21}\)H\(_{17}\)Cl\(_2\)NO\(_3\) (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-methoxyacetamido)methyl)naphthalen-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\(_2\)-Cl), 4.24 (2H, s, O(CO)CH\(_2\)-Cl), 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). \(^1^3\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 41.4 (Ar-CH\(_2\)-N-Ar), 42.5 (N(CO)-CH\(_2\)-Cl), 42.6 (O(CO)-CH\(_2\)-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(CO)-CH\(_2\)-Cl), 166.8 (O(CO)-CH\(_2\)-Cl). MS: m/z 432 (M\(^+\)). Anal. Calcd. for C\(_{22}\)H\(_{19}\)Cl\(_2\)NO\(_4\) (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)methyl)napthalen-2-yl-2-chloroacetate 6c. White crystals. Yield: 40%. mp: 118 °C. IR (KBr) \(\nu_{\text{max}}\): 1706, 1670, 1515-1400, 588 cm\(^{-1}\). UV (EtOH) \(\lambda_{\text{max}}\) (log \(\varepsilon\)): 335.2 (0.106), 320.0 (0.108), 287.6 (0.367), 255.6 (0.299) nm. \(^1^H\)-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 3.66 (2H, s, N(CO)CH\(_2\)Cl), 4.25 (2H, s, O(CO)CH\(_2\)Cl), 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). \(^1^3\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 41.3 (Ar-CH\(_2\)-N-Ar), 42.2 (N(CO)-CH\(_2\)-Cl), 42.4 (O(CO)-CH\(_2\)-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(CO)-CH\(_2\)-Cl), 166.4 (O(CO)-CH\(_2\)-Cl). MS: m/z 435 (M\(^+\)). Anal. Calcd. for C\(_{21}\)H\(_{18}\)Cl\(_3\)NO\(_3\) (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-dihydonaphtho[1,2-\(f\)]1,4]oxazepin-3(4\(H\))-one 7a. Yield: 65%. mp: 91 °C. IR (KBr) \(\nu_{\text{max}}\): 1655, 1523-1395, 1242 cm\(^{-1}\). UV (EtOH) \(\lambda_{\text{max}}\) (log \(\varepsilon\)): 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\(_3\)): \(\delta\) 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). \(^1^3\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 47.2 (Ar-Ch \(_{2}\)-N), 73.4 (O-CH\(_2\)), 120.8 (1-C), 122.4 (3-C), 124.3 (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), 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-dihydonaphtho[1,2-\(f\)]1,4]oxazepin-3(4\(H\))-one 7b. Yield: 78%. mp: 96 °C. IR (KBr) \(\nu_{\text{max}}\): 1655, 1500, 1250 cm\(^{-1}\). UV (MeOH) \(\lambda_{\text{max}}\) (log \(\varepsilon\)): 406.0 (0.287), 322.0 (0.446), 318.0 (0.397), 225.5 (0.148) nm. \(^1^H\)-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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). \(^1^3\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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-dihydronaphtho[1,2-f][1,4]oxazepin-3(4H)-one 7c. Yield: 72%. mp: 133 °C. IR (KBr) \( \nu_{\text{max}} \): 1656, 1615-1495, 1242 cm\(^{-1}\). UV (EtOH) \( \lambda_{\text{max}}(\log \varepsilon) \): 388.0 (0.017), 314.4 (0.065), 278.8 (0.202), 259.2 (0.997) nm. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \( \delta \): 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). \(^1^3\)C-NMR (100 MHz, CDCl\(_3\)) \( \delta \): 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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References