One-Pot Synthesis of 2-Substituted 4-Aryl-4,5-dihydro-3,1-benzoxazepines from 2-(2-Aminophenyl)-1-arylethanols *via* Dehydration of the Corresponding Amides

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An efficient method for the preparation of 2-substituted 4-aryl-4,5-dihydro-3,1-benzoxazepine derivatives under mild conditions has been developed. The reaction of 2-(2-aminophenyl)ethanols **1** with acid chlorides in the presence of excess Et_3N in THF at room temperature gave the corresponding *N*-acylated intermediates **2**, which were dehydrated by treatment with $POCl_3$ to give 2-substituted 4-aryl-4,5-dihydro-3,1-benzoxazepines **3** in a one-pot reaction.

Introduction. – The 4*H*-3,1-benzoxazine skeleton is found in many biologically active compounds [1]. Therefore, compounds with the 4,5-dihydro-3,1-benzoxazepine structure, a homolog of 4*H*-3,1-benzoxazine, are also of potential biological importance. However, few general methods for the preparation of 4,5-dihydro-3,1-benzoxazepine derivatives have been elaborated, though *Ito et al.* have reported a synthesis of 2-unsubstituted 4,5-dihydro-3,1-benzoxazepine derivatives by the treatment of 2-(2-isocyanophenyl)ethanols, available from 2-methylphenyl isocyanides, with Cu_2O [2a]. In this article, we describe a facile one-pot procedure for the synthesis of 2-substituted 4-aryl-4,5-dihydro-3,1-benzoxazepines from 2-(2-aminophenyl)-1-arylethanols, easily prepared from 2-nitrotoluene and its derivatives by a conventional two-step sequence, *via* dehydration of the corresponding amides. This is the first report on the general preparation of 2-substituted 4-aryl-4,5-dihydro-3,1-benzoxazepines. Although the formation of 4,5-dihydro-4-[(methylsulfanyl)methyl]-2-phenyl-3,1-benzoxazepine [2b] and 4,5-dihydro-2-phenyl-3,1-benzoxazepine [2c] have been reported by *Capozzi et al.*, and *Ganton* and *Kerr*, respectively, their methods suffer from limited generality.

Results and Discussion. – The one-pot synthesis of 2-substituted 4-aryl-4,5-dihydro-3,1-benzoxazepine derivatives **3** from 2-(2-aminophenyl)ethanols **1** was conducted by the process depicted in *Scheme 1*. The amino alcohols **1** were prepared by the treatment of *ortho*-nitrotoluene and its derivatives with aryl aldehydes in the presence of MeONa, followed by hydrogenation of the resulting 1-aryl-2-(2-nitrophenyl)ethanols with Pd on activated C under reported condition [3]. Compounds **1** were treated with acid chlorides in the presence of excess Et_3N in THF at room temperature to give the corresponding *N*-acylated intermediates **2**, which were then dehydrated with 2 mol-equiv. of $POCl_3$ at the same temperature. The usual aqueous workup and subsequent

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purification by column chromatography on neutral alumina afforded the desired products **3**. The results are compiled in the *Table*; the yields are generally moderate-to-fair. While isolation of the products by column chromatography on silica gel caused considerable decreases of their yields owing to hydrolysis of the imino-ether moiety, little hydrolysis seemed to take place during purification with neutral alumina in general. However, the yields of the products with Me or Et groups at C(2) of the 4,5-dihydro-3,1-benzoxazepine **3d**, **3e**, and **3k** were rather low compared to the other products (*cf. Entries 4*, *5*, and *11*). 4-Aryl-4,5-dihydro-3,1-benzoxazepines with cinnamyl (*Entry 6*), heteraryl (*Entries 7* and *14*), trichloromethyl (*Entry 8*), or *t*-Bu (*Entry 13*) substituent at C(2) could also be obtained. We also examined the reaction using chloroacetyl chloride in order to obtain the product with a $ClCH_2$ substituent, which might be elaborated to structurally more complex molecules. Unfortunately, however, the corresponding 4,5-dihydro-3,1-benzoxazepine derivative could not be obtained due to its instability during the purification by column chromatography.

Scheme 1

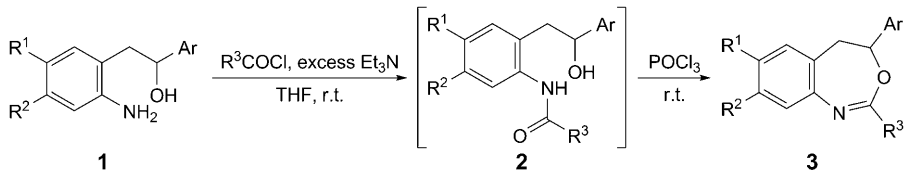


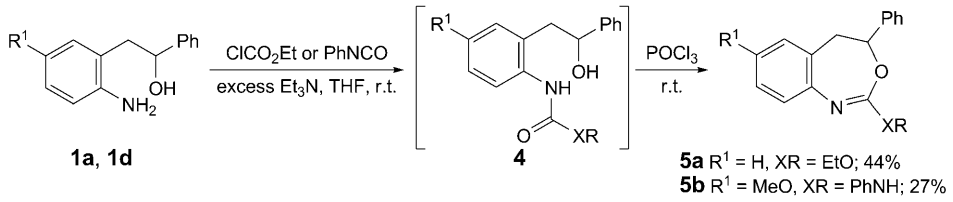
Table. *Preparation of 2-Substituted 4-Aryl-4,5-dihydro-3,1-benzoxazepine Derivatives* **3**

Entry	**1**	R^3	**3**	Yield[a]) [%]
1	**1a** ($R^1 = R^2 = H$, Ar = Ph)	Ph	**3a**	52
2	**1a**	4-Cl–C_6H_4	**3b**	55
3	**1a**	4-MeO–C_6H_4	**3c**	57
4	**1a**	Me	**3d**	34
5	**1a**	Et	**3e**	43
6	**1a**	(*E*)-PhCH=CH	**3f**	56
7	**1a**	3-Py	**3g**	62
8	**1a**	CCl_3	**3h**	62
9	**1b** ($R^1 = R^2 = H$, Ar = 3-MeO–C_6H_4)	Ph	**3i**	35
10	**1c** ($R^1 = H$, $R^2 = Cl$, Ar = 4-Cl–C_6H_4)	Ph	**3j**	68
11	**1c**	Et	**3k**	56
12	**1d** ($R^1 = MeO$, $R^2 = H$, $Ar^3 = Ph$)	i-Pr	**3l**	74
13	**1d**	*t*-Bu	**3m**	54
14	**1d**	Thiophen-2-yl	**3n**	72

[a]) Yields of isolated products.

Ethyl chloroformate (ClCOOEt) or phenyl isocyanate (PhNCO) proved to be usable in the present reaction in place of acid chlorides, and 4-aryl-4,5-dihydro-3,1-benzoxazepines with EtO or PhNH substituent at C(2) **5a** or **5b**, respectively, were obtained, *via* the respective intermediates **4**, as illustrated in *Scheme 2*.

Scheme 2



In conclusion, we have developed a facile method for the synthesis of 2-substituted 4-aryl-4,5-dihydro-3,1-benzoxazepines **3** from 2-(2-aminophenyl)ethanols **1**, *via* the corresponding amides **2**. Notable advantages of the present synthesis are: *i*) simplicity of the procedure, *ii*) mild reaction conditions, and *iii*) easy availability of the starting materials.

Experimental Part

General. All solvents used were dried over the appropriate drying agents and distilled under Ar prior to use. 2-(2-Nitrophenyl)-1-phenylethanol and *2-(2-aminophenyl)-1-phenylethanol* (**1a**) were prepared according to the procedure in [3]. All other chemicals used were commercially available. TLC: *Merck Alumina 60 Neutral F_{254}*, or *Merck Kieselgel 60 PF_{254}*. Column chromatography (CC): *Merck Alumina*, activated neutral, activity I. M.p.: *Laboratory Devices MEL-TEMP II* melting-point apparatus; uncorrected. IR Spectra: *Shimadzu FTIR-8300* spectrometer. ^{1}H-NMR Spectra: Me_4Si as an internal reference; in $CDCl_3$; *JEOL ECP 500 FT NMR* spectrometer; at 500 MHz. ^{13}C-NMR Spectra: Me_4Si as an internal reference; in $CDCl_3$; *JEOL ECP 500 FT NMR* spectrometer; at 125 MHz. Low-resolution (LR) MS spectra (EI, 70 eV): *JEOL JMS AX 505 HA* spectrometer.

1-Aryl-2-(2-nitrophenyl)ethanols were prepared by the treatment of *ortho*-nitrotoluene and its derivatives with aryl aldehydes in the presence of a cat. amount of MeONa under conditions reported for the preparation of 2-(2-nitrophenyl)-1-phenylethanol [3].

1-(3-Methoxyphenyl)-2-(2-nitrophenyl)ethanol. Yield: 58%. Yellow oil. R_f (SiO_2; THF/hexane 1:4) 0.22. IR (neat): 3453, 1603, 1524, 1348. ^{1}H-NMR: 1.92–2.33 (br., 1 H); 3.22 (*dd*, *J* = 13.7, 9.2, 1 H); 3.38 (*dd*, *J* = 13.7, 4.1, 1 H); 3.82 (*s*, 3 H); 5.02 (*dd*, *J* = 9.2, 4.1, 1 H); 6.84 (*ddd*, *J* = 8.2, 2.7, 1.4, 1 H); 6.96 (*d*, *J* = 2.7, 1 H); 6.98 (*dd*, *J* = 7.8, 1.4, 1 H); 7.27 (*t*, *J* = 8.2, 1 H); 7.34 (*dd*, *J* = 8.2, 1.4, 1 H); 7.40 (*td*, *J* = 7.8, 1.4, 1 H); 7.52 (*td*, *J* = 7.8, 1.4, 1 H); 7.95 (*dd*, *J* = 7.8, 1.4, 1 H). Anal. calc. for $C_{15}H_{15}NO_4$ (273.28): C 65.92, H 5.53, N 5.13; found: C 65.73, H 5.64, N, 5.03.

2-(4-Chloro-2-nitrophenyl)-1-(4-chlorophenyl)ethanol. Yield: 52%. Yellow oil. R_f (SiO_2; THF/hexane 1:5) 0.27. IR (neat): 3383, 1537, 1348. ^{1}H-NMR: 2.08 (*d*, *J* = 3.7, 1 H); 3.15 (*dd*, *J* = 13.7, 8.7, 1 H); 3.21 (*dd*, *J* = 13.7, 3.7, 1 H); 4.99–5.02 (*m*, 1 H); 7.25 (*d*, *J* = 8.2, 1 H); 7.30–7.35 (*m*, 4 H); 7.49 (*dd*, *J* = 8.2, 1.8, 1 H); 7.96 (*d*, *J* = 1.8, 1 H). Anal. calc. for $C_{14}H_{11}Cl_2NO_3$ (312.15): C 53.87, H 3.55, N 4.49; found: C 53.89, H 3.64, N 4.42.

2-(5-Methoxy-2-nitrophenyl)-1-phenylethanol. Yield: 54%. Pale-yellow solid. M.p. 62–64° (hexane/Et_2O). IR (KBr): 3440, 1512, 1337. ^{1}H-NMR: 2.08–2.42 (br., 1 H); 3.21 (*dd*, *J* = 13.2, 8.7, 1 H); 3.46 (*dd*, *J* = 13.2, 4.1, 1 H); 3.81 (*s*, 3 H); 5.06 (*dd*, *J* = 8.7, 4.1, 1 H); 6.71 (*d*, *J* = 2.7, 1 H); 6.84 (*dd*, *J* = 9.2, 2.7, 1 H); 7.30 (*t*, *J* = 7.3, 1 H); 7.36 (*t*, *J* = 7.3, 2 H); 7.42 (*d*, *J* = 7.3, 2 H); 8.07 (*d*, *J* = 9.2, 1 H). Anal. calc. for $C_{15}H_{15}NO_4$ (273.28): C 65.92, H 5.53, N 5.13; found: C 65.72, H 5.59, N 5.03.

2-(2-Aminophenyl)-1-arylethanol derivatives **1** were prepared by the hydrogenation of the respective 1-aryl-2-(2-nitrophenyl)ethanol derivatives on Pd/C under the conditions reported for the preparation of **1a** [3].

2-(2-Aminophenyl)-1-(3-methoxyphenyl)ethanol (**1b**). Yield: 82%. Pale-yellow oil. R_f (SiO_2; THF/hexane 2:5) 0.47. IR (neat): 3426, 3374, 1603. ^{1}H-NMR: 1.38–1.82 (br., 1 H); 2.89 (*dd*, *J* = 14.1, 3.7, 1 H);

3.01 (*dd*, *J* = 14.1, 8.7, 1 H); 3.20–3.70 (br., 2 H); 3.80 (*s*, 3 H); 4.96 (*dd*, *J* = 8.7, 3.7, 1 H); 6.72 (*dd*, *J* = 7.8, 1.4, 1 H); 6.75 (*td*, *J* = 7.8, 1.4, 1 H); 6.83 (*dd*, *J* = 8.2, 2.7, 1 H); 6.93 (*d*, *J* = 2.7, 1 H); 6.97 (*d*, *J* = 8.2, 1 H); 7.01 (*dd*, *J* = 7.8, 1.4, 1 H); 7.07 (*td*, *J* = 7.8, 1.4, 1 H); 7.28 (*t*, *J* = 8.2, 1 H). Anal. calc. for $C_{15}H_{17}NO_2$ (243.30): C 74.05, H 7.04, N 5.76; found: C 73.91, H 7.13, N 5.51.

2-(2-Amino-4-chlorophenyl)-1-(4-chlorophenyl)ethanol (**1c**). Yield: 83%. Pale-yellow solid. M.p. 97–99° (hexane/Et_2O). IR (KBr): 3395, 3296. ^{1}H-NMR: 2.36 (*s*, 1 H); 2.83 (*dd*, *J* = 14.6, 4.1, 1 H); 2.91 (*dd*, *J* = 14.6, 8.2, 1 H); 3.98 (*s*, 2 H); 4.93–4.96 (*m*, 1 H); 6.67 (*d*, *J* = 7.8, 1 H); 6.69 (*s*, 1 H); 6.81 (*d*, *J* = 7.8, 1 H); 7.26 (*d*, *J* = 8.2, 2 H); 7.32 (*d*, *J* = 8.2, 2 H). Anal. calc. for $C_{14}H_{13}Cl_2NO$ (282.17): C 59.59, H 4.64, N 4.96; found: C 59.41, H 4.82, N, 4.64.

2-(2-Amino-5-methoxyphenyl)-1-phenylethanol (**1d**). Yield: 94%. Pale-yellow crystal. M.p. 64–66° (hexane/Et_2O). IR (KBr): 3356, 3277. ^{1}H-NMR: 2.70–3.75 (br., 3 H); 2.88 (*dd*, *J* = 14.2, 4.1, 1 H); 3.01 (*dd*, *J* = 14.2, 8.7, 1 H); 3.70 (*s*, 3 H); 4.98 (*dd*, *J* = 8.7, 4.1, 1 H); 6.57 (*d*, *J* = 2.3, 1 H); 6.64–6.68 (*m*, 2 H); 7.29 (*tt*, *J* = 7.3, 1.8, 1 H); 7.34–7.39 (*m*, 4 H). Anal. calc. for $C_{15}H_{17}NO_2$ (243.30): C 74.05, H 7.04, N 5.76; found: C 73.96, H 7.01, N 5.66.

4,5-Dihydro-2,4-diphenyl-3,1-benzoxazepine (**3a**; *Representative Procedure*). To a stirred soln. of **1a** (0.21 g, 1.0 mmol) and Et_3N (1.32 g, 13 mmol) in THF (5 ml) at r.t. was added BzCl (0.14 g, 1.0 mmol) dropwise. After 5 min, the resulting mixture was treated with $POCl_3$ (0.31 g, 2.0 mmol), and stirring was continued overnight at the same temp. before sat. aq. $NaHCO_3$ (10 ml) was added. The org. materials were extracted with AcOEt (3 × 10 ml), and the combined extracts were washed with brine (10 ml), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by CC (Al_2O_3; Et_2O/hexane 1:5) to afford **3a** (0.16 g, 52%). White solid. M.p. 86–88° (hexane/Et_2O). IR (KBr): 1647. ^{1}H-NMR: 3.22 (*d*, *J* = 15.6, 1 H); 3.54 (*dd*, *J* = 15.6, 8.2, 1 H); 5.60 (*d*, *J* = 8.2, 1 H); 6.75–7.09 (*m*, 2 H); 7.29 (*td*, *J* = 7.8, 2.7, 1 H); 7.35–7.47 (*m*, 9 H); 8.15 (*dd*, *J* = 8.2, 1.8, 2 H). ^{13}C-NMR: 44.52; 84.17; 124.94; 125.85; 127.61; 128.03; 128.18; 128.56; 128.74; 128.86; 129.32; 130.51; 133.40; 135.38; 141.07; 143.26; 151.51. MS: 299 (24, M^+), 106 (100). Anal. calc. for $C_{21}H_{17}NO$ (299.37): C 84.25, H 5.72, N 4.68; found: C 84.22, H 5.79, N 4.69.

2-(4-Chlorophenyl)-4,5-dihydro-4-phenyl-3,1-benzoxazepine (**3b**). Pale-yellow viscous oil. R_f (Al_2O_3; Et_2O/hexane 1:5) 0.85. IR (neat): 1651. ^{1}H-NMR: 3.21 (*d*, *J* = 16.0, 1 H), 3.53 (*dd*, *J* = 16.0, 8.2, 1 H); 5.57 (*d*, *J* = 8.2, 1 H); 7.07 (*td*, *J* = 7.8, 2.3, 1 H); 7.09 (*td*, *J* = 7.8, 2.3, 1 H); 7.29 (*td*, *J* = 7.8, 2.3, 1 H); 7.35 (*d*, *J* = 8.7, 2 H); 7.36–7.45 (*m*, 6 H); 8.07 (*d*, *J* = 8.7, 2 H). ^{13}C-NMR: 44.45; 84.20; 125.17; 125.83; 127.68; 128.21; 128.29; 128.79; 128.93; 129.37; 129.94; 133.39; 133.89; 136.66; 140.88; 142.97; 150.50. MS: 333 (25, M^+), 106 (100). Anal. calc. for $C_{21}H_{16}ClNO$ (333.81): C 75.56, H 6.82, N 5.57; found: C 75.50, H 6.80, N, 5.30.

4,5-Dihydro-2-(4-methoxyphenyl)-4-phenyl-3,1-benzoxazepine (**3c**). Colorless crystals. M.p. 104–106° (hexane/Et_2O). IR (KBr): 1643. ^{1}H-NMR: 3.20 (*d*, *J* = 16.0, 1 H); 3.52 (*dd*, *J* = 16.0, 8.7, 1 H); 3.84 (*s*, 3 H); 5.58 (*d*, *J* = 8.7, 1 H); 6.89 (*d*, *J* = 9.1, 2 H); 7.04–7.06 (*m*, 2 H); 7.26–7.44 (*m*, 7 H); 8.80 (*d*, *J* = 9.1, 2 H). ^{13}C-NMR: 44.43; 55.33; 84.20; 113.31; 124.58; 125.85; 127.57; 127.87; 128.13; 128.71; 128.82; 129.07; 130.28; 133.18; 141.20; 143.51; 151.59; 161.63. MS: 329 (21, M^+), 106 (100). Anal. calc. for $C_{22}H_{19}NO_2$ (329.39): C 80.22, H 5.81, N 4.25; found: C 80.05, H 5.93, N 4.14.

4,5-Dihydro-2-methyl-4-phenyl-3,1-benzoxazepine (**3d**). Colorless oil. R_f (Al_2O_3; Et_2O/hexane 1:5) 0.83. IR (neat): 1668, 1599. ^{1}H-NMR: 2.26 (*s*, 3 H); 3.12 (*d*, *J* = 16.0, 1 H); 3.44 (*dd*, *J* = 16.0, 8.2, 1 H); 5.40 (*d*, *J* = 8.2, 1 H); 7.00 (*d*, *J* = 7.3, 1 H); 7.03 (*td*, *J* = 7.3, 1.4, 1 H); 7.21–7.26 (*m*, 2 H); 7.31–7.41 (*m*, 5 H). ^{13}C-NMR: 24.61; 44.25; 84.20; 99.90; 124.59; 125.71; 127.56; 128.16; 128.25; 128.71; 133.25; 140.98; 143.17; 154.91. MS: 237 (19, M^+), 106 (100). Anal. calc. for $C_{16}H_{15}NO$ (237.30): C 80.98, H 6.37, N 5.90; found: C 80.95, H 6.43, N 5.75.

2-Ethyl-4,5-dihydro-4-phenyl-3,1-benzoxazepine (**3e**). Pale-yellow oil. R_f (Al_2O_3; Et_2O/hexane 1:5) 0.89. IR (neat): 1667. ^{1}H-NMR: 1.28 (*t*, *J* = 7.3, 3 H); 2.47–2.52 (*m*, 2 H); 3.12 (*d*, *J* = 15.6, 1 H); 3.41 (*dd*, *J* = 15.6, 8.2, 1 H); 5.40 (*d*, *J* = 8.2, 1 H); 7.00 (*d*, *J* = 7.3, 1 H); 7.03 (*td*, *J* = 7.3, 1.4, 1 H); 7.23 (*td*, *J* = 7.3, 1.4, 1 H); 7.26–7.41 (*m*, 6 H). ^{13}C-NMR: 11.77; 31.17; 44.33; 84.15; 124.47; 125.66; 127.52; 128.08; 128.30; 128.63; 128.64; 133.23; 141.15; 143.29; 158.63. MS: 251 (17, M^+), 106 (100). Anal. calc. for $C_{17}H_{17}NO$ (251.32): C 81.24, H 6.82, N 5.57; found: C 81.23, H 6.77, N 5.54.

*4,5-Dihydro-4-phenyl-2-[(*E*)-2-phenylethenyl]-3,1-benzoxazepine* (**3f**). Pale-yellow solid. M.p. 116–118° (hexane/Et_2O). IR (KBr): 1632, 1620. ^{1}H-NMR: 3.18 (*d*, *J* = 15.6, 1 H); 3.47 (*dd*, *J* = 15.6, 8.2, 1 H); 5.55 (*d*, *J* = 8.2, 1 H); 6.75 (*d*, *J* = 16.0, 1 H); 7.05 (*td*, *J* = 7.8, 1.8, 1 H); 7.07 (*td*, *J* = 7.8, 1.4, 1 H);

7.26–7.45 (*m*, 11 H); 7.49 (*dd*, *J* = 7.3, 1.4, 2 H). ^{13}C-NMR: 44.09; 84.83; 125.06; 125.42; 125.85; 127.50; 127.70 (two overlapped Cs); 128.21; 128.71 (two overlapped Cs); 128.92; 128.96; 132.96; 135.75; 138.12; 141.07; 143.67; 153.02. MS: 325 (14, M^+), 106 (100). Anal. calc. for $C_{23}H_{19}NO$ (325.40): C 84.89, H 5.89, N 4.30; found: C 84.70, H 5.93, N, 4.29.

4,5-Dihydro-4-phenyl-2-(pyridin-3-yl)-3,1-benzoxazepine (**3g**). Yellow oil. R_f (Al_2O_3; Et_2O/hexane 1:5) 0.34. IR (neat): 1651. ^{1}H-NMR: 3.24 (*d*, *J* = 16.0, 1 H); 3.55 (*dd*, *J* = 16.0, 8.2, 1 H); 6.75 (*d*, *J* = 8.2, 1 H); 7.08 (*t*, *J* = 7.3, 1 H); 7.11 (*t*, *J* = 7.3, 1 H); 7.29–7.33 (*m*, 2 H); 7.36–7.44 (*m*, 5 H); 7.47 (*d*, *J* = 7.3, 1 H); 8.39 (*d*, *J* = 7.3, 1 H); 8.66 (*d*, *J* = 4.6, 1 H); 9.33 (*s*, 1 H). ^{13}C-NMR: 44.49; 84.13; 122.81; 125.45; 125.74; 127.71; 128.32; 128.79; 128.95; 129.50; 131.03; 133.44; 135.86; 140.59; 142.65; 149.34; 150.01; 151.03. MS: 300 (17, M^+), 106 (100). Anal. calc. for $C_{20}H_{16}N_2O$ (300.35): C 79.98, H 5.37, N 9.33; found: C 79.98, H 5.56, N 9.28.

4,5-Dihydro-4-phenyl-2-(trichloromethyl)-3,1-benzoxazepine (**3h**). Pale-yellow oil. R_f (Al_2O_3; Et_2O/hexane 1:5) 0.55. IR (neat): 1684. ^{1}H-NMR: 2.99 (*d*, *J* = 15.1, 1 H); 3.80 (*dd*, *J* = 15.1, 8.2, 1 H); 6.22 (*d*, *J* = 8.2, 1 H); 7.09 (*d*, *J* = 7.3, 2 H); 7.12–7.19 (*m*, 3 H); 7.23 (*t*, *J* = 7.3, 2 H); 7.34 (*td*, *J* = 8.2, 2.7, 1 H); 8.23 (*d*, *J* = 8.2; 1 H). ^{13}C-NMR: 39.36; 65.33; 93.28; 118.83; 124.87; 125.33; 125.96; 127.24; 127.84; 128.58; 130.07; 142.36; 143.33; 158.61. MS: 339 (19, M^+), 106 (100). Anal. calc. for $C_{16}H_{12}ClNO$ (340.63): C 56.42, H 3.55, N 4.11; found: C 56.36, H 3.64, N 3.87.

4,5-Dihydro-4-(3-methoxyphenyl)-2-phenyl-3,1-benzoxazepine (**3i**). Pale-yellow oil. R_f (Al_2O_3; Et_2O/hexane 1:5) 0.82. IR (neat): 1651. ^{1}H-NMR: 3.22 (*d*, *J* = 16.0, 1 H); 3.52 (*dd*, *J* = 16.0, 8.2, 1 H); 3.83 (*s*, 3 H); 5.57 (*d*, *J* = 8.2, 1 H); 6.91 (*dd*, *J* = 8.2, 2.7, 1 H); 6.98 (*d*, *J* = 2.7, 1 H); 7.02 (*d*, *J* = 7.8, 1 H); 7.06–7.10 (*m*, 2 H); 7.29 (*td*, *J* = 8.2, 2.7, 1 H); 7.34 (*t*, *J* = 7.8, 1 H); 7.38–7.47 (*m*, 4 H); 8.15 (*dd*, *J* = 7.8, 1.4, 2 H). ^{13}C-NMR: 44.52; 55.28; 84.09; 111.57; 113.49; 118.14; 124.95; 127.61; 128.03; 128.57; 128.86; 129.30; 129.81; 130.51; 133.34; 135.35; 142.63; 143.24; 151.47; 159.88. MS: 329 (27, M^+), 136 (100). Anal. calc. for $C_{22}H_{19}NO_2$ (329.39): C 80.22, H 5.81, N 4.25; found: C 80.25, H 5.85, N 4.06.

8-Chloro-4-(4-chlorophenyl)-4,5-dihydro-2-phenyl-3,1-benzoxazepine (**3j**). Colorless needles. M.p. 146–148° (hexane/Et_2O). IR (KBr): 1643. ^{1}H-NMR: 3.18 (*d*, *J* = 15.6, 1 H); 3.44 (*dd*, *J* = 15.6, 7.8, 1 H); 5.56 (*d*, *J* = 7.8, 1 H); 6.95 (*d*, *J* = 8.2, 1 H); 7.04 (*dd*, *J* = 8.2, 2.3, 1 H); 7.33 (*d*, *J* = 8.7, 2 H); 7.38–7.41 (*m*, 4 H); 7.44 (*d*, *J* = 2.3, 1 H); 7.46 (*tt*, *J* = 8.7, 1.4, 1 H); 8.10 (*dd*, *J* = 8.7, 1.4, 2 H). ^{13}C-NMR: 43.57; 83.55; 124.81; 127.21; 128.15; 128.59; 129.00; 129.05; 129.83; 130.95; 131.35; 133.10; 134.16; 134.78; 139.06; 144.47; 152.28. MS: 367 (28, M^+), 140 (100). Anal. calc. for $C_{21}H_{15}ClNO$ (368.26): C 68.49, H 4.11, N 3.80; found: C 68.49, H 4.29, N 3.77.

8-Chloro-4-(4-chlorophenyl)-2-ethyl-4,5-dihydro-3,1-benzoxazepine (**3k**). Pale-yellow solid. M.p. 80–82° (hexane/Et_2O). IR (KBr): 1667. ^{1}H-NMR: 1.25 (*t*, *J* = 7.3, 3 H); 2.47 (*q*, *J* = 7.3, 2 H); 3.08 (*d*, *J* = 15.6, 1 H); 3.31 (*dd*, *J* = 15.6, 7.8, 1 H); 5.36 (*d*, *J* = 7.8, 1 H); 6.89 (*d*, *J* = 7.8, 1 H); 6.98 (*dd*, *J* = 7.8, 2.3, 1 H); 7.24 (*d*, *J* = 8.2, 2 H); 7.26 (*d*, *J* = 2.3, 1 H); 7.35 (*d*, *J* = 8.2, 2 H); ^{13}C-NMR: 11.57; 30.96; 43.48; 83.39; 124.39; 127.02; 128.25; 128.87; 129.62; 131.24; 133.02; 134.02; 139.16; 144.49; 159.40. MS: 319 (30, M^+), 140 (100). Anal. calc. for $C_{17}H_{15}ClNO$ (320.21): C 63.76, H 4.72, N 4.37; found: C 63.68, H 4.79, N 4.38.

4,5-Dihydro-7-methoxy-2-(1-methylethyl)-4-phenyl-3,1-benzoxazepine (**3l**). Pale-yellow oil. R_f (Al_2O_3; Et_2O/hexane 1:5) 0.57. IR (neat): 1668. ^{1}H-NMR: 1.15 (*d*, *J* = 7.3, 3 H); 1.18 (*d*, *J* = 7.3, 3 H); 2.58–2.62 (*m*, 1 H); 2.97 (*d*, *J* = 15.6, 1 H); 3.25 (*dd*, *J* = 15.6, 8.2, 1 H); 3.67 (*s*, 3 H); 5.26 (*d*, *J* = 8.2, 1 H); 6.45 (*d*, *J* = 2.7, 1 H); 6.67 (*dd*, *J* = 8.7, 2.7, 1 H); 7.13 (*d*, *J* = 8.7, 1 H); 7.21–7.31 (*m*, 5 H). ^{13}C-NMR: 20.79; 20.85; 36.65; 44.71; 55.37; 83.00; 112.35; 114.03; 125.61; 127.97; 128.60; 129.77; 134.35; 136.75; 141.37; 156.50; 159.70. MS: 295 (30, M^+), 106 (100). Anal. calc. for $C_{19}H_{21}NO_2$ (295.38): C 77.26, H 7.17, N 4.74; found: C 76.98, H 7.23, N 4.44.

*2-(*tert*-Butyl)-4,5-dihydro-7-methoxy-4-phenyl-3,1-benzoxazepine* (**3m**). Colorless oil. R_f (Al_2O_3; Et_2O/hexane 1:5) 0.71. IR (neat): 1667. ^{1}H-NMR: 1.21 (*s*, 9 H), 2.97 (*d*, *J* = 16.0, 1 H); 3.22 (*dd*, *J* = 16.0, 7.8, 1 H); 3.67 (*s*, 3 H); 5.25 (*d*, *J* = 7.8, 1 H); 6.45 (*d*, *J* = 2.7, 1 H); 6.67 (*dd*, *J* = 8.2, 2.7, 1 H); 7.13 (*d*, *J* = 8.2, 1 H); 7.21–7.31 (*m*, 5 H). ^{13}C-NMR: 28.82; 39.24; 44.79; 55.37; 82.68; 112.31; 113.92; 125.56; 127.82; 128.53; 130.06; 134.29; 136.82; 141.53; 156.41; 160.90. MS: 309 (32, M^+), 106 (100). Anal. calc. for $C_{20}H_{23}NO_2$ (309.40): C 77.64, H 7.49, N 4.53; found: C 77.60, H 7.62, N 4.40.

4,5-Dihydro-7-methoxy-4-phenyl-2-(thiophen-2-yl)-3,1-benzoxazepine (**3n**). Yellow solid. M.p. 122–124° (hexane/Et_2O). IR (KBr): 1641. ^{1}H-NMR: 3.16 (*d*, *J* = 16.0, 1 H); 3.51 (*dd*, *J* = 16.0, 8.2, 1 H); 3.79

(*s*, 3 H); 5.56 (*d*, *J* = 8.2, 1 H); 6.61 (*d*, *J* = 2.3, 1 H); 6.81 (*dd*, *J* = 8.7, 2.3, 1 H); 7.01 (*dd*, *J* = 5.0, 3.2, 1 H); 7.33 – 7.42 (*m*, 7 H); 7.55 (*d*, *J* = 3.2, 1 H). ^{13}C-NMR: 44.48; 55.41; 83.19; 112.54; 114.35; 125.72; 127.45; 128.13; 128.68 (two overlapped Cs); 128.92; 129.17; 130.64; 134.34; 136.32; 140.95; 147.00; 156.97. MS: 335 (32, M^+), 106 (100). Anal. calc. for $C_{20}H_{17}NO_2S$ (335.42): C 71.62, H 5.11, N 4.18; found: C 71.56, H 5.13, N 3.93.

2-Ethoxy-4,5-dihydro-4-phenyl-3,1-benzoxazepine (**5a**). Colorless oil. R_f (Al_2O_3; Et_2O/hexane 1:5) 0.45. IR (neat): 1667. ^{1}H-NMR: 1.37 (*t*, *J* = 7.3, 3 H); 3.12 (*dd*, *J* = 16.0, 1.4, 1 H); 3.44 (*dd*, *J* = 16.0, 8.2, 1 H); 4.24 – 4.38 (*m*, 2 H); 5.49 (*dd*, *J* = 8.2, 1.4, 1 H); 6.95 – 6.99 (*m*, 2 H); 7.16 (*d*, *J* = 7.8, 1 H); 7.19 – 7.23 (*m*, 1 H); 7.29 – 7.38 (*m*, 5 H). ^{13}C-NMR: 14.28; 42.83; 64.42; 84.44; 123.43; 125.83; 127.00; 127.74; 128.26; 128.62; 128.97; 131.83; 140.26; 142.20; 149.97. MS: 267 (49, M^+), 238 (100). Anal. calc. for $C_{17}H_{17}NO_2$ (267.32): C 76.38, H 6.41, N 5.24; found: C 76.33, H 6.49, N 4.94.

4,5-Dihydro-7-methoxy-N,*4-diphenyl-3,1-benzoxazepin-2-amine* (**5b**). White solid. M.p. 125 – 127° (hexane/CH_2Cl_2). IR (KBr): 3404, 1672. ^{1}H-NMR: 2.99 (*dd*, *J* = 16.5, 4.1, 1 H); 3.76 (*s*, 3 H); 3.77 (*dd*, *J* = 16.5, 6.4, 1 H); 5.34 (*dd*, *J* = 6.4, 4.1, 1 H); 6.31 (*s*, 1 H); 6.71 (*d*, *J* = 2.7, 1 H); 6.79 (*dd*, *J* = 8.7, 2.7, 1 H); 6.97 (*ddd*, *J* = 8.7, 7.3, 1.4, 1 H); 7.10 (*dd*, *J* = 7.3, 1.4, 2 H); 7.19 (*t*, *J* = 8.7, 2 H); 7.32 – 7.41 (*m*, 5 H); 7.96 (*d*, *J* = 8.7, 1 H). ^{13}C-NMR: 39.26; 55.62; 63.00; 111.07; 112.34; 115.99; 119.72; 123.20; 125.46; 128.63; 128.76; 129.67; 129.96; 137.34; 138.27; 142.27; 152.52; 155.79. MS: 344 (69, M^+), 225 (100). Anal. calc. for $C_{22}H_{20}N_2O_2$ (344.41): C 76.72, H 5.85, N 8.13; found: C 76.66, H 5.81, N 8.05.

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REFERENCES

[1] E. R. Kurbatov, A. V. Kurochkin, L. M. Korkodinova, B. Y. Syropyatov, L. N. Markova, *Pharm. Chem. J.* **2008**, *42*, 674; K. R. Shreder, J. Cajica, L. Du, A. Fraser, Y. Hu, Y. Kohno, E. C. K. Lin, S. J. Liu, E. Okerberg, L. Pham, J. Wu, J. W. Kozarich, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4743; B. D. Sanders, B. Jackson, M. Brent, A. M. Taylor, W. Dang, S. L. Berger, S. L. Schreiber, K. Howitz, R. Marmorstein, *Bioorg. Med. Chem.* **2009**, *17*, 7031; J. R. Miller, V. Thanabal, M. M. Melnick, M. Lall, C. Donovan, R. W. Sarver, D.-Y. Lee, J. Ohren, D. Emerson, *Chem. Biol. Drug Des.* **2010**, *75*, 444; P.-W. Hsieh, H.-P. Yu, Y.-J. Chang, T.-L. Hwang, *Eur. J. Med. Chem.* **2010**, *45*, 3111.

[2] a) Y. Ito, K. Kobayashi, T. Saegusa, *Tetrahedron Lett.* **1978**, *19*, 2087; b) G. Capozzi, R. Ottana, G. Romeo, *Heterocycles* **1987**, *26*, 39; c) M. D. Ganton, M. A. Kerr, *Org. Lett.* **2005**, *7*, 4777.

[3] T. Izumi, T. Yokota, *J. Heterocyclic Chem.* **1992**, *29*, 1085.

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