Efficient Synthesis of 2,3-Disubstituted-1,3-benzoxazines by Chlorotrimethylsilane-Mediated Aza-Acetalizations of Aromatic Aldehydes

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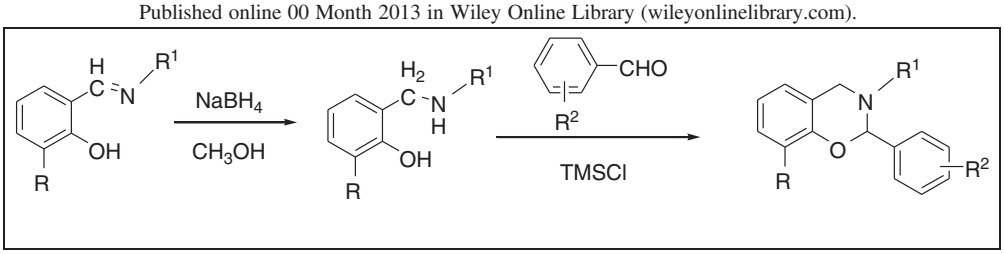

A series of novel substituted 3,4-dihydro-2*H*-1,3-benzoxazines were prepared in moderate to good yields by aza-acetalizations of aromatic aldehydes with 2-(*N*-substituted aminomethyl)phenols in the presence of chlorotrimethylsilane or $SnCl_4$. It was found that chlorotrimethylsilane was more effective for the reaction, especially for the reaction of fluorobenzaldehyde, and thereby, an efficient method for the preparation of 3,4-dihydro-2*H*-1,3-benzoxazines was developed. The structures of the compounds were determined by FT-IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis.

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INTRODUCTION

3,4-Dihydro-2*H*-1,3-benzoxazine and its derivatives have been recognized to exhibit different antimicrobial properties [1] such as bactericidal, fungicidal and many pharmacological features such as antitumour, antituberculosis, and anthelmintic activity [2]. Along this line, *N*-substituted 3,4-dihydro-2*H*-1,3-benzoxazines are potential intermediates for the preparation of high performance polymers [3]. Therefore, the synthesis of these compounds containing special functional group has attracted great interest. Several elegant methods for the preparation of these compounds have been documented in the literature [4]. For example, Burke and co-workers disclosed a Mannich-type condensation of phenols with primary amines and two equivalents of formaldehyde to provide 2-unsubstituted 3,4-dihydro-2*H*-1,3-benzoxazines [4a–d]. In addition, condensations of 2-aminomethylphenol with aliphatic aldehydes or ketones provided another route to 3,4-dihydro-2*H*-1,3-benzoxazines [4a–g]. It was noted that the condensations could be operated without catalyst, but sometimes, catalysts such as TsOH or triethylamines were necessary. Despite these advances, the synthesis of novel 3,4-dihydro-2*H*-1,3-benzoxazines and the search for more efficient routes to this type of compounds are still highly desirable for drug discovery and medicinal chemistry. In our previous report [5], we described a new route to prepare aryl-substituted 3,4-dihydro-2*H*-1,3-benzoxazines by using $SnCl_4$-mediated aza-acetalization reactions of aromatic aldehydes with 2-arylaminomethylphenols. Although the reactions gave the desired products in good yields under mild conditions, the yields decreased with benzaldehyde or fluorobenzaldehydes as reactants. In addition, the toxicity of $SnCl_4$ will limit its application in this kind of reactions. In these regards, we planned to develop green and more efficient catalysts and, hence, will present herein our results of the synthesis of substituted 3,4-dihydro-2*H*-1,3-benzoxazines by using chlorotrimethylsilane (TMSCl) [6] as catalyst (Scheme 1).

RESULTS AND DISCUSSION

For the purpose of finding new type of fungicides, we planned to prepare fluorine-containing 3,4-dihydro-2*H*-1,3-benzoxazines because of the fluorine atom's special structure and biological character. The synthetic route to the target compound **1** is shown in Scheme 1. 2-(*N*-substituted aminomethyl)phenols **4a–f** were easily prepared in high yields according to the literature [5,7]. Then, the reaction of **4a** with 4-fluorobenzaldehyde **5d** was initially performed in the presence of TsOH (20 mol%) [2e] in mixed solvent of chloroform and cyclohexane (v/v 1:2) under reflux by removing the water of condensation azeotropically; however, the desired product **1a** was obtained in only 9% yield (Table 1, entry 1). Also, compound **1e** was obatined in merely 12% yield under the same conditions (entry 4). However, to our surprise, the yield of compound **1e** dramatically decreased to 0% with $AlCl_3$ (20 mol%) as catalyst (entry 5). We next used $SnCl_4$ (20 mol%) to promote the reaction, the yield of **1e** was enhanced to 48% (entry 6) but still low. Similarly, a relatively low yield of 43% was obtained for compound **1a** by reaction of **4a** with **5d** (entry 2). To further improve the yield, TMSCl (20 mol%) was finally chosen as catalyst for the reaction of **4a** with **5d**, and as expected, the reaction gave the corresponding product **1a** in higher yield of 57%

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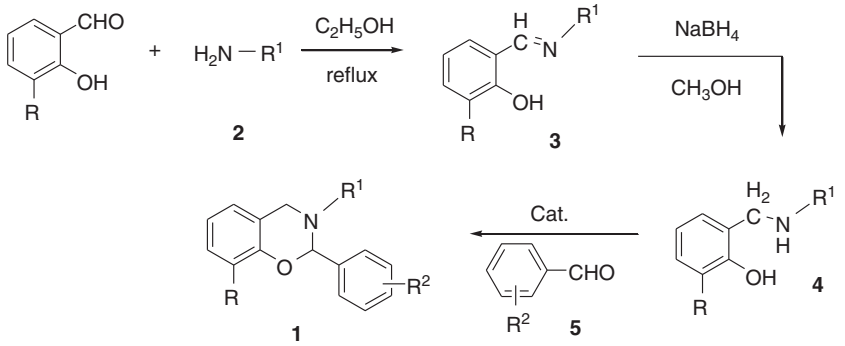
Scheme 1. Synthesis of disubstituted 3,4-dihydro-2*H*-1,3-benzoxazines **1**.



4a: R = H, R^1 = 4-$CH_3C_6H_4$; **4b**: R = H, R^1 = C_6H_5; **4c**: R = H, R^1 = 4-$CH_3OC_6H_4$

4d: R = H, R^1 = 4-ClC_6H_4; **4e**: R = H, R^1 = CH_2COOCH_3; **4f**: R = CH_3, R^1 = 4-$CH_3C_6H_4$

5a: R^2 = 2-NO_2; **5b**: R^2 = 4-NO_2; **5c**: R^2 = 3-NO_2; **5d**: R^2 = 4-F; **5e**: R^2 = H

Table 1

Searching catalyst for the preparation of compound **1**.

Entry	*R*	R^1	R^2	Conditions[a]	Product	Yield (%)[b]
1	H	4-$CH_3C_6H_4$	4-F	TsOH	**1a**	9
2	H	4-$CH_3C_6H_4$	4-F	$SnCl_4$	**1a**	43
3	H	4-$CH_3C_6H_4$	4-F	TMSCl	**1a**	57
4	H	CH_2COOCH_3	4-F	TsOH	**1e**	12
5	H	CH_2COOCH_3	4-F	$AlCl_3$	**1e**	0
6	H	CH_2COOCH_3	4-F	$SnCl_4$	**1e**	48
7	H	CH_2COOCH_3	4-F	TMSCl	**1e**	62

[a]The mole ratio of *n* (aldehyde **5**) : *n* (aminomethyl phenol **4**) = 1.3:1 for all reactions. The amount of catalyst is 20 mol% based on aminomethyl phenol. $CHCl_3/C_6H_{12}$ = 1:2 (v: v). Reaction time: 5 h. Temperature: 85°C.
[b]Isolated yield.

(entries 3). Also, a higher yield of 62% was obtained for compound **1e** (entry 7). Consequently, we synthesized compounds **1b–l** by reactions of aromatic aldehydes **5** with 2-(*N*-substituted aminomethyl)phenols **4a–f** in the presence of TMSCl. Moreover, to compare the catalytic activity of the two catalysts, $SnCl_4$-mediated reactions of **4** with **5** were also performed. All the experimental results are depicted in Table 2. It can be seen clearly from the table that all reactions produced the desired products **1b–l** in moderate to good yields for both catalysts but in higher yields with TMSCl as catalysts. Particularly, the reactions of *p*-fluorobenzaldehyde **5d** or benzaldehyde **5e** gave much higher yields in the presence of TMSCl (Table 2, entries 1–3 and 5). In the meantime, we observed for both catalysts that reactions of 2-aminomethylphenols with nitrobenzaldehydes afforded the products in higher yields than those with fluorobenzaldehyde or benzaldehyde. In all cases, the reactions of 2-(*N*-alkylaminomethyl)phenols gave higher yields than those of *N*-aryl-substituted aminomethylphenols. The lower nucleophilicity of the latter can be attributed to the conjugation effect between the electron pair on the nitrogen atom and the aryl group. All these results clearly indicated TMSCl was the most efficient catalyst compared with $SnCl_4$, $AlCl_3$, and TsOH, and to the best of our knowledge, this is the first time to adopt TMSCl as catalyst for aza-acetalizations of aromatic aldehydes with 2-(*N*-substituted aminomethyl)phenols to prepare substituted 3,4-dihydro-2*H*-1,3-benzoxazines.

The structures of the products were established on the basis of their spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, MS) and elemental analysis [5a]. All compounds exhibited characteristic signals appropriately (see the Experimental section). Typically, in IR spectrum of compound **1k**, the strong absorption at 1731 cm^{-1} is for the C═O group, 1524 and 1365 cm^{-1} are for the NO_2 group, and 1585 and 1607 cm^{-1} for the C═C group. A singlet at 6.57 observed in ^{1}H NMR corresponded to OCHN proton of benzoxazine ring. The downfield shift of OCHN proton was due to the strong electron negative of nitrogen and oxygen atoms. Particularly, the NCH_2 group absorbed as two doublets at 3.77 and 4.14 instead of a singlet. The ^{13}C NMR spectrum showed 17 signals, which are in agreement with the proposed structure.

Table 2

The results of the preparation of compound **1**.[a]

Entry	R	R^1	R^2	Product	Yield[b] (%)	
					$SnCl_4$	TMSCl
1	H	C_6H_5	4-F	**1b**	39	55
2	H	4-$CH_3OC_6H_4$	4-F	**1c**	39	53
3	H	4-ClC_6H_4	4-F	**1d**	45	59
4	H	4-ClC_6H_4	3-NO_2	**1f**	61	67
5	H	4-ClC_6H_4	H	**1g**	42	57
6	CH_3	4-$CH_3C_6H_4$	2-NO_2	**1h**	72	75
7	CH_3	4-$CH_3C_6H_4$	3-NO_2	**1i**	73	78
8	H	C_6H_5	4-NO_2	**1j**	72	73
9	H	CH_2COOCH_3	2-NO_2	**1k**	84	88
10	H	CH_2COOCH_3	4-NO_2	**1l**	85	91

[a]The mole ratio of n (aldehyde **5**) : n (aminomethyl phenol **4**) = 1.3: 1 for all reactions. The amount of TMSCl: 20 mol% or $SnCl_4$: 20 mol% based on aminomethyl phenol. $CHCl_3/C_6H_{12}$ = 1:2. (v/v) Reaction time: 5 h. Temperature: 85°C.
[b]Isolated yield.

CONCLUSIONS

In summary, we have prepared a series of novel 2,3-disubstituted 3,4-dihydro-2*H*-1,3-benzoxazines **1a–l** in moderate to good yields in the presence of TMSCl or $SnCl_4$. TMSCl was shown to be a more effective Lewis acid catalyst for the aza-acetalizations of aromatic aldehydes with 2-(*N*-substituted aminomethyl)phenols, especially for the reaction of fluorobenzaldehyde, and thereby, a green and efficient method for the preparation of substituted 3,4-dihydro-2*H*-1,3-benzoxazines was developed.

EXPERIMENTAL

All solvents were dried by standard procedure. Aromatic aldehydes and substituted anilines were commercially available. IR spectra were recorded on a PE-2000 FT-IR. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance-500 MHz spectrometer. Chemical shifts (δ) were given relative to Me_4Si (0, ^1H) or $CDCl_3$ (77.0, ^{13}C). Mass spectra were obtained with Thermo Finnigan LCQ Advantage spectrometer. Elemental analysis was measured on a PE 2400 II CHNS instrument. Melting points were determined on a WRS-1B digital melting point instrument. Thin-layer chromatography was run on precoated silica gel plates (Merck $60F_{254}$). Column chromatography was carried out using flash silica gel.

Synthesis of 2-(*N*-substituted aminomethyl)phenols 4a–f

[5,7]2-((4-Methylphenylamino)methyl)phenol (**4a**). Yield 91%, white solid, mp 120.5–121.2°C; IR (KBr): 3435, 3260, 3032, 3011, 2977, 2861, 2734, 1614, 1592, 1512, 1467, 1456, 1402, 1291, 1249, 1232, 1187, 1110, 1057, 976, 911, 863, 834, 820, 801, 788, 753, 742, 719, 706 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.30 (s, 3H, CH_3), 4.42 (s, 2H, CH_2), 6.79 (d, J = 8.5 Hz, 2H), 6.88–6.93 (m, 2H), 7.08 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.5 Hz, 1H), 7.23 (t, J = 7.45 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.60, 49.34, 116.25 (2C), 116.67, 119.98, 122.98, 128.67, 129.19, 129.91 (2C), 130.46, 144.64, 157.00.

2-((Phenylamino)methyl)phenol (4b). Yield 85%, white solid, mp 129.4–130.8°C; IR (KBr): 3445, 3264, 30652, 2854, 1594, 1499, 1459, 1436, 1389, 1358, 1316, 1301, 1266, 1251, 1237, 1184, 1166, 1114, 1088, 1056, 1040, 1025, 971, 903, 841, 796, 754, 727, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 4.45 (s, 2H, CH_2), 6.87–6.97 (m, 5H), 7.18 (d, J = 7.5 Hz, 1H), 7.24–7.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 48.71, 115.93 (2C), 116.66, 120.13, 120.85, 122.99, 128.78, 129.26, 129.43 (2C), 147.22, 156.76.

2-((4-Methoxyphenylamino)methyl)phenol (4c). Yield 85%, purple solid, mp 132.1–133.8°C; IR (KBr): 3444, 3253, 3000, 2956, 2862, 1714, 1637, 1593, 1510, 1468, 1457, 1409, 1358, 1289, 1249, 1225, 1177, 1112, 1058, 1033, 979, 909, 864, 830, 788, 759, 742, 717 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.78 (s, 3H, OCH_3), 4.40 (s, 2H, CH_2), 6.83–6.87 (m, 4H), 6.88–6.93 (m, 2H), 7.14 (d, J = 7 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 50.24, 55.66, 114.77 (2C), 116.67, 117.85 (2C), 119.87, 122.78, 128.58, 129.18, 140.39, 154.61, 157.17.

2-((4-Chlorophenylamino)methyl)phenol (4d). Yield 89%, white solid, mp 121.7–122.4°C; IR (KBr): 3435, 3257, 3013, 2969, 2938, 2729, 2626, 1594, 1492, 1462, 1454, 1403, 1392, 1357, 1314, 1285, 1250, 1232, 1181, 1120, 1109, 1097, 1060, 1008, 974, 907, 866, 844, 829, 815, 796, 770, 758, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 4.40 (s, 2H, CH_2), 6.77 (d, J = 9 Hz, 2H), 6.90 (t, J = 6.5 Hz, 2H), 7.17–7.28 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 48.42, 116.62, 116.89 (2C), 120.31, 122.66, 125.52, 128.86, 129.28 (2C), 129.38, 145.77, 156.39.

2-((3-Methoxycarbonylmethylamino)methyl)phenol (4e). Yield 74%, white solid, mp 84.9–85.9°C; IR (KBr): 3 451, 3 352, 2 894, 2 857, 2 118, 1 898, 1 735, 1 616, 1 587, 1 484, 1 429, 1 369, 1 302, 1 260, 1 224, 1 206, 1 185, 1 136, 1 104, 1 037, 988, 929, 899, 866, 847, 756, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.46 (s, 2H), 3.76 (s, 3H), 4.00 (s, 2H), 6.77–6.80 (m, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.9 8(d, J = 7.0 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ/ppm: 48.57, 51.99, 52.07, 116.44, 119.19, 121.72, 128.66, 129.00, 157.81, 171.83.

2-((4-Methylphenylamino)methyl)-6-methyl phenol (4f). Yield 85%, white solid, mp 81.0–81.7°C; IR (KBr): 3421, 3335, 2919, 2853, 2731, 1714, 1615, 1592, 1517, 1471, 1446, 1432, 1314, 1259, 1237, 1217, 1123, 1085, 1051, 1012, 930, 883, 822, 812, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.24 (s, 3H), 2.28 (s, 3H), 4.37 (s, 2H), 6.77 (t, J = 7.5 Hz, 3H), 6.98 (d, J = 7.5 Hz,

1H), 7.05 (dd, $J = 8.0$ Hz, $J = 7.5$ Hz, 3H), 8.93 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ/ppm: 15.73, 20.51, 49.34, 116.14 (2C), 119.32, 122.08, 125.47, 126.13, 129.77 (2C), 130.29, 130.33, 144.54, 155.07.

General procedure for the synthesis of 3,4-dihydro-2*H*-1, 3-benzoxazines 1a–l.

Method A: Under nitrogen, into a 250-mL three-necked flask equipped with a Dean-stark, 2-(phenylaminomethyl)phenol **4b** (0.99 g, 5 mmol), 4-nitrobenzaldehyde **5b** (0.98 g, 6.5 mmol), mixed solvent of chloroform and cyclohexane (150 mL, v/v 1:2), and TMSCl (0.11 g, 20 mol%) were added with stirring. The solution was heated at 85°C for 5 h (checked by thin-layer chromatography), and the water of condensation was removed by azeotropic distillation of most of solvent. Then, triethyl amine was added to make solution at pH = 8 followed by ethyl acetate (100 mL) and washed sequentially with water (2 × 100 mL) and saturated brine (2 × 100 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The obtained yellow oil was purified by recrystallization from ethyl acetate-petroleum ether to give the product **1j** (73% yield) as a yellow solid. *Method B*: See Method A for the procedure, but $SnCl_4$ (0.26 g, 20 mol%) was used as catalyst.

2-(4-Fluorophenyl)-3-p-tolyl-3,4-dihydro-2H-1,3-benzoxazine (1a). Yield 57% (Method A), 43% (Method B); white solid, mp 66.5–66.9°C; IR (KBr): 3427, 2922, 2869, 2339, 1612, 1585, 1514, 1505, 1456, 1382, 1339, 1232, 1217, 1194, 1154, 1128, 1034, 975, 949, 898, 819, 753, 714 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.27 (s, 3H, CH_3), 4.29 (s, 2H), 6.54 (s, 1H), 6.82–6.88 (m, 2H), 6.95 (d, $J = 8.5$ Hz, 1H), 7.00 (t, $J = 8.5$ Hz, 2H), 7.07 (s, 4H), 7.13 (t, $J = 7.0$ Hz, 1H), 7.50 (t, $J = 6.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.67, 46.59, 88.17, 115.39, 115.56, 116.90, 120.47, 120.60 (2C), 120.70, 126.61, 128.08, 128.55, 128.61, 129.82, 131.95, 135.02 (d, $J_{CF} = 3.0$ Hz), 147.30, 152.83, 161.55, 163.51; MS (ESI): 320 $[M + H]^+$. *Anal*. Calcd for $C_{21}H_{18}FNO$: C, 78.98; H, 5.68; N, 4.39. Found: C, 78.46; H, 5.64; N, 4.42.

2-(4-Fluorophenyl)-3-phenyl-3,4-dihydro-2H-1,3-benzoxazine (1b). Yield 55% (Method A), 39% (Method B); white solid, mp 85.0–86.2°C; IR (KBr): 3040, 2959, 2853, 2369, 1942, 1899, 1601, 1581, 1509, 1495, 1451, 1394, 1346, 1293, 1226, 1158, 1125, 1110, 1033, 1014, 976, 952, 937, 822, 764, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.33 (d, $J = 4.5$ Hz, 2H), 6.61 (s, 1H), 6.83–6.89 (m, 2H), 6.97–7.04 (m, 4H), 7.14–7.19 (m, 3H), 7.26–7.29 (m, 2H), 7.50–7.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 46.14, 87.59, 115.37, 115.54, 116.86, 120.09, 120.29, 120.68, 122.18, 126.51, 128.06, 128.43, 128.49, 129.24, 134.78 (d, $J_{CF} = 3.0$ Hz), 149.58, 152.61, 156.67, 161.47, 163.43, *Anal*. Calcd for $C_{20}H_{16}FNO$: C, 78.67; H, 5.28; N, 4.59. Found: C, 78.24; H, 5.31; N, 4.56.

2-(4-Fluorophenyl)-3-(4-methoxyphenyl)-3,4-dihydro-2H-1, 3-benzoxazine (1c). Yield 53% (Method A), 39% (Method B); white solid, mp 76.9–77.4°C; IR (KBr): 3256, 2954, 2911, 1839, 2052, 1908, 1870, 1605, 1581, 1509, 1490, 1456, 1437, 1379, 1346, 1240, 1230, 1153, 1105, 1038, 1019, 980, 956, 894, 836, 759 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.74 (s, 3H, OCH_3), 4.27 (d, $J = 4.0$ Hz, 2H), 6.42 (s, 1H), 6.78 (d, $J = 9.0$ Hz, 2H), 6.85–6.88 (m, 2H), 6.96–7.03 (m, 3H), 7.10–7.16 (m, 3H), 7.51–7.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 47.37, 55.40, 88.83, 114.25, 114.63, 115.25, 115.42, 116.78, 117.93, 120.66, 122.92, 126.54, 127.98, 128.52, 128.58, 129.16, 134.86 (d, $J_{CF} = 3.1$ Hz), 143.08, 152.89, 161.43, 163.39. *Anal*. Calcd for $C_{21}H_{18}FNO_2$: C, 75.21; H, 5.41; N, 4.18. Found: C, 75.53; H, 5.39; N, 4.20.

2-(4-Fluorophenyl)-3-(4-chlorophenyl)-3,4-dihydro-2H-1, 3-benzoxazine (1d). Yield 59% (Method A), 45% (Method B); white solid, m.p 80.7–81.3°C; IR (KBr): 3436, 3059, 2955, 1894, 1710, 1605, 1584, 1507, 1488, 1457, 1381, 1342, 1224, 1158, 1022, 1006, 982, 959, 952, 838, 830, 763, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.29 (s, 2H), 6.51 (s, 1H), 6.83–6.87 (m, 2H), 6.95 (d, $J = 8.0$ Hz, 1H), 6.99 (t, $J = 8.5$ Hz, 2H), 7.08 (d, $J = 8.5$ Hz, 2H), 7.14 (t, $J = 7.0$ Hz, 1H), 7.19 (d, $J = 8.5$ Hz, 2H), 7.46–7.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 46.65, 87.58, 115.44, 115.61, 116.89, 119.89, 120.88, 121.68, 126.53, 127.33, 128.24, 128.38, 128.44, 129.15 (2C), 134.35 (d, $J_{CF} = 3.1$ Hz), 148.09, 152.47, 161.52, 163.48. *Anal*. Calcd for $C_{20}H_{15}ClFNO$: C, 70.69; H, 4.45; N, 4.12. Found: C, 70.37; H, 4.47; N, 4.09.

Methyl 2-(2-(4-fluorophenyl)-2H-1,3-benzoxazin-3(4H)-yl) acetate (1e). Yield 62% (Method A), 48% (Method B); white solid, mp 119.8–120.3°C; IR (KBr): 3472, 3084, 3061, 2956, 2909, 1909, 1747, 1607, 1582, 1510, 1487, 1450, 1389, 1341, 1310, 1248, 1219, 1157, 1138, 1107, 1032, 1000, 992, 948, 903, 861, 827, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.42 (s, 2H), 3.68 (s, 3H, CH_3), 3.94 (d, $J = 17.0$ Hz, 1H), 4.25 (d, $J = 1 \times 7.0$ Hz, 1H), 5.95 (s, 1H), 6.89–6.98 (m, 3H), 7.05–7.08 (m, 2H), 7.16–7.20 (m, 1H), 7.59–7.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 49.47, 49.91, 51.84, 89.87, 115.23, 115.42, 116.63, 119.07, 121.06, 127.66, 128.02, 128.59, 128.66, 133.46 (d, $J_{CF} = 3.0$ Hz), 133.48, 153.30, 171.36; MS (ESI): 319 $[M + NH_4]^+$. *Anal*. Calcd for $C_{17}H_{16}FNO_3$: C, 67.76; H, 5.35; N, 4.65. Found: C, 67.42; H, 5.32; N, 4.63.

2-(3-Nitrophenyl)-3-(4-chlorophenyl)-3,4-dihydro-2H-1, 3-benzoxazine (1f). Yield 67% (Method A), 61% (Method B); yellow solid, mp 145.1–145.8°C; IR (KBr): 3444, 3074, 3040, 2973, 2873, 1884, 1732, 1594, 1583, 1521, 1495, 1455, 1386, 1348, 1231, 1198, 1131, 1095, 1034, 990, 954, 893, 824, 808, 757, 725, 706 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.26 (d, $J = 17.0$ Hz, 1H), 4.36 (d, $J = 17.0$ Hz, 1H), 6.55 (s, 1H), 6.87 (d, $J = 4.5$ Hz, 2H), 7.02 (d, $J = 8.0$ Hz, 1H), 7.13 (d, $J = 8.5$ Hz, 2H), 7.17 (q, $J = 4.5$ Hz, 1H), 7.21 (d, $J = 8.5$ Hz, 2H), 7.52 (t, $J = 8.0$ Hz, 1H), 7.88 (d, $J = 8.0$ Hz, 1H), 8.16 (d, $J = 8.5$ Hz, 1H), 8.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 47.25, 87.02, 117.08, 119.54, 121.34, 122.11 (3C), 123.34, 126.59, 127.98, 128.53, 129.26 (2C), 129.76, 132.91, 140.99, 147.78, 148.59, 152.00. *Anal*. Calcd for $C_{20}H_{15}ClN_2O_3$: C, 66.49; H, 4.12; N, 7.64. Found: C, 66.68; H, 4.14; N, 7.61.

3-(4-Chlorophenyl)-2-phenyl-3,4-dihydro-2H-1,3-benzoxazine (1g). Yield 57% (Method A), 42% (Method B); white solid, mp 108.6–108.8°C; IR (KBr): 3432, 3044, 2980, 1887, 1711, 1609, 1575, 1500, 1479, 1368, 1346, 1220, 1141, 1036, 1001, 968, 854, 836, 831, 768, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.27 (d, $J = 16.5$ Hz, 1H), 4.32 (d, $J = 16.5$ Hz, 1H), 6.57 (s, 1H), 6.83–6.88 (m, 2H), 6.98 (d, $J = 8.0$ Hz, 1H), 7.11 (d, $J = 7.0$ Hz, 2H), 7.14 (t, $J = 8.5$ Hz, 1H), 7.20 (d, $J = 9.0$ Hz, 2H), 7.28–7.36 (m, 3H), 7.51 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 46.55, 88.02, 116.58, 116.87, 120.06, 120.19, 120.71, 121.48, 126.52, 127.10, 128.16, 128.59, 128.96, 129.12, 129.33, 129.72, 134.44, 138.69, 148.29, 152.75. *Anal*. Calcd for $C_{20}H_{16}ClNO$: C, 74.65; H, 5.01; N, 4.35. Found: C, 75.98; H, 4.98; N, 4.33.

8-Methyl-2-(2-nitrophenyl)-3-p-tolyl-3,4-dihydro-2H-1, 3-benzoxazine (1h). Yield 75% (Method A), 72% (Method B); yellow solid, mp 138.3–139.3°C; IR (KBr): 3433, 3082, 2981, 2918, 1611, 1594, 1531, 1514, 1468, 1439, 1389, 1365, 1224, 1200, 1144, 968, 820,766, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.24 (s, 3H, CH_3), 2.32 (s, 3H,CH_3), 3.98 (d, $J = 17.0$ Hz, 1H), 4.19 (d, $J = 17.0$ Hz, 1H), 6.68 (d, $J = 7.5$ Hz,

1H), 6.75 (t, $J = 7.0$ Hz, 1H), 7.03 (t, $J = 9.0$ Hz, 6H), 7.43–7.46 (m, 2H), 7.49–7.51 (m, 1H), 7.72–7.73 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 15.81, 20.65, 47.04, 85.43, 119.65, 120.29, 120.70 (2C), 124.05, 124.35, 125.60, 128.28, 129.08, 129.34, 129.64 (2C), 131.79, 132.49, 132.99, 146.69, 148.92, 150.36. *Anal.* Calcd for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.59; H, 5.56; N, 7.73.

8-Methyl-2-(3-nitrophenyl)-3-p-tolyl-3,4-dihydro-2H-1,3-benzoxazine (1i). Yield 78% (Method A), 73% (Method B); yellow solid, mp 118.4–118.7°C; IR (KBr): 3434, 3090, 3026, 2917, 2856, 1714, 1612, 1595, 1579, 1528, 1514, 1472, 1451, 1378, 1345, 1222, 1194, 1127, 1079, 998, 967, 940, 811, 767, 730, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.28 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.25 (d, $J = 17.0$ Hz, 1H), 4.35 (d, $J = 17.0$ Hz, 1H), 6.61 (s, 1H), 6.71 (d, $J = 7.0$ Hz, 1H), 6.75 (t, $J = 7.0$ Hz, 1H), 7.03 (d, $J = 7.0$ Hz, 1H), 7.07–7.12 (m, 4H), 7.51 (t, $J = 8.0$ Hz, 1H), 7.86 (d, $J = 7.5$ Hz, 1H), 8.15–8.17 (m, 1H), 8.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 15.86, 20.62, 46.98, 87.55, 119.39, 120.41, 120.77 (2C), 122.01, 123.16, 124.02, 125.99, 129.31, 129.65, 129.80 (2C), 132.29, 132.75, 141.66, 146.99, 148.59, 150.19. *Anal.* Calcd for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.64; H, 5.56; N, 7.74.

2-(4-Nitrophenyl)-3-phenyl-3,4-dihydro-2H-1,3-benzoxazine (1j). Yield 73%, (Method A), 72% (Method B); yellow solid, mp 117.2–118.8°C; IR (KBr): 3444, 3087, 3056, 3038, 3007, 2970, 2912, 1707, 1596, 1581, 1522, 1492, 1453, 1388, 1346, 1230, 1208, 1144, 1109, 1034, 978, 958, 888, 853, 828, 759, 741 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.25 (d, $J = 17.0$ Hz, 1H), 4.40 (d, $J = 17.0$ Hz, 1H), 6.64 (s, 1H), 6.87 (d, $J = 7.5$ Hz, 2H), 7.00–7.03 (m, 2H), 7.17–7.21 (m, 3H), 7.26–7.31 (m, 2H), 7.74 (d, $J = 8.5$ Hz, 2H), 8.19 (d, $J = 7.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 46.72, 87.22, 116.51, 116.95, 119.96, 120.28, 121.15, 122.68, 123.84, 124.26, 126.60, 127.86, 128.31, 129.34 (2C), 130.46, 146.28, 147.68, 149.21, 152.21. *Anal.* Calcd for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.59; H, 4.83; N, 8.39.

Methyl 2-(2-(2-nitrophenyl)-2H-1,3-benzoxazin-3(4H)-yl)acetate (1k). Yield 88% (Method A), 84% (Method B); white solid, mp 108.6–109.0°C; IR (KBr): 3446, 3010, 2958, 2881, 1953, 1912, 1731, 1607, 1585, 1524, 1488, 1461, 1444, 1424, 1365, 1275, 1263, 1222, 1122, 1109, 1034, 1002, 963, 780, 761, 742 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.38 (s, 2H), 3.66 (s, 3H, CH_3), 3.78 (d, $J = 17.0$ Hz, 1H), 4.14 (d, $J = 17.0$ Hz, 1H), 6.57 (s, 1H), 6.94–7.00 (m, 3H), 7.21–7.24 (m, 1H), 7.49–7.53 (m, 1H), 7.57–7.60 (m, 1H), 7.81–7.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 48.99, 51.33, 51.92, 87.19, 116.58, 119.18, 121.39, 124.71, 127.86, 128.20, 128.26, 129.41, 131.95, 132.16, 148.86, 152.95, 170.57; MS (ESI): 346 $[M + NH_4]^+$. *Anal.* Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.47; H, 4.88; N, 8.49.

Methyl 2-(2-(4-nitrophenyl)-2H-1,3-benzoxazin-3(4H)-yl)acetate (1l). Yield 91% (Method A), 85% (Method B); white solid, mp 137.2–138.9°C; IR (KBr): 3468, 3079, 3038, 2854, 1745, 1609, 1580, 1523, 1488, 1447, 1420, 1384, 1346, 1313, 1221, 1134, 1109, 992, 952, 904, 826, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.37 (s, 2H), 3.71 (s, 3H, CH_3), 3.94 (d, $J = 17.0$ Hz, 1H), 4.21 (d, $J = 17.0$ Hz, 1H), 6.03 (s, 1H), 6.92–7.00 (m, 3H), 7.20 (t, $J = 7.0$ Hz, 1H), 7.84 (d, $J = 8.5$ Hz, 2H), 8.24 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 49.11, 50.41, 51.97, 89.34, 116.68, 118.80, 121.45, 123.68 (2C), 127.72, 127.92 (2C), 128.26, 144.90, 147.82, 152.70, 171.04. *Anal.* Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.50; H, 4.89; N, 8.57.

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REFERENCES AND NOTES

[1] (a) Mireya, E. R.; Carrajal, M.A.; Rincon, J. M. Rev Colomb Cienc Quim Farm 1980, 3, 63; (b) Gomez, P. G.; Pabon, H. P.; Carvajal, M. A.; Rincon, J. M. Rev Colomb Cienc Quim Farm 1985, 4, 15; (c) Waisser, K.; Gregor, K.; Kubicova, L.; Klimesova, V.; Kunes, J.; Machacek, M.; Kaustova, J. Eur J Med Chem 2000, 35, 733; (d) Waisser, K.; Gregor, K.; Dostal, H.; Kunes, J.; Kubicova, L.; Klimesova, V.; Kaustova, J. Il Farmaco 2001, 56, 803; (e) Mathiew, B.P.; Kumar, A.; Sharma, S.; Shula, P. K.; Nath, M. Eur J Med Chem 2010, 45, 1502.

[2] (a) Chylinska, J. B.; Urbanski, T.; Mordarski, M. J. Med Chem 1963, 6, 484; (b) Bouaziz, Z.; Riondel, J.; Mey, A.; Berlion, M.; Villard, J.; Filliond, H. Eur J Med Chem 1991, 26, 469; (c) Benameur, L.; Bouaziz, Z.; Nebois, P.; Bartoli, M-H.; Boitard, M.; Fillion, H. Chem Pharm Bull 1996, 44, 605; (d) Wang, S.; Li, Y.; You, Q.; Liu, Y.; Lu, A. Bioorg Med Chem Lett, 2008, 18, 4095; (e) Pasternak, A.; Goble, S. D.; Struthers, M.; Vicario, P. P.; Ayala, J. M.; Salvo, J. D.; Kilburn, R.; Wisniewski, T.; DeMartino J. A; Mills, S. G.; Yang, L. ACS Med Chem Lett 2010, 1, 14; (f) Eva Petrlikova, E.; Waisser, K.; Divišova, H.; Husakova, P.; Vrabcova, P.; Kuneš, J.; Kolar, K.; Stolarikova, J. Bioorg Med Chem 2010, 18, 8178.

[3] (a) Wang, Y-X.; Ishida, H. Macromolecules 2000, 33, 2839; (b) Agag, T.; Arza, C. R.; Maurer, F. H. J.; Ishida, H. Macromolecules 2010, 43, 2748; (c) Lin, J.; Tarek, A.; Yusuf, Y.; Hatsuo, I. Macromolecules 2011, 44, 767.

[4] (a) Burke, W. J. J Am Chem Soc 1949, 71, 609; (b) Burke, W. J.; Ec, K. C.; Murdock, G. J Am Chem Soc 1954, 76, 1677; (c) Rivera, A.; Ospina, E.; Sanchez, A.; Joseph-Nathan, P. Heterocycles 1986, 24, 2507; (d) Mathew, B. P.; Kumar, A.; Sharma, S.; Shukla, P. K.; Nath, M. Eur J Med Chem 2010, 45, 1502; (e) McDonagh, A. F.; Smith, H. E. J Org Chem 1968, 33, 1; (f) Neuvonen, K.; Pihlaja, K. J Chem Soc Perkin Trans. II, 1988, 461; (g) Szatmari, I.; Martinek, T. A.; Lazar, L.; Fulop, F. Eur J Org Chem 2004, 2231; (h) Colin, J. L.; Loubinoux, B. Tetrahedron Lett 1982, 23, 4245; (i) Campi, E. M.; Jackson, W. R.; McCubbin, Q. J.; Trnacek, A. E. J Chem Soc Chem Commun 1994, 2763; (j) Campi, E. M.; Jackson, W. R.; McCubbin, Q. J.; Trnacek, A. E. Aust J Chem 1996, 49, 219.

[5] (a) Tang, Z.; Chen, W.; Zhu, Z.; Liu, H. J. Heterocyclic Chem 2011, 48, 255; (b) Tang, Z.; Chen, W.; Zhu, Z.; Liu, H. Synth Commun 2012, 42, 1372.

[6] (a) Xu, L. W.; Zhou, W.; Yang, L.; Xia, C. G. Synth Commun 2007, 37, 3095; (b) Xu, L. W.; Xia, C. G. Tetrahedron Lett 2004, 45, 4507; (c) Xu, L. W.; Xia, C. G.; Hu, X. X. Chem Commun 2003, 2570; (d) Tang, Z. Chin J Org Chem 2006, 26, 1059.

[7] (a) Palmieri, G. Eur J Org Chem 1999, 805; (b) Cimarelli, C.; Palmieri, G.; Volpini, E. Tetrahedron 2001, 57, 6089.