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Synthesis of 3,4-Dihydro-2H-1,3-benzoxazines by Condensation of 2-Hydroxyaldehydes and Primary Amines: Application to the Synthesis of Hydroxy-Substituted and Deuterium-Labeled Compounds

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Abstract: We report the synthesis of several substituted 3,4-dihydro-2H-1,3-benzoxazines by simple ring closure of 2-hydroxybenzylamines with paraformaldehyde. The facile synthesis of the benzylamine precursors from commercially available salicylaldehyde derivatives affords a powerful general synthetic way to prepare a variety of substituted benzoxazines, avoiding the formation of undesirable oligomeric species, thus leading to a simple workup and improving the yield and purity of the final product. This straightforward method allows synthesis of hydroxy-substituted and deuterium-labeled 1,3-benzoxazines that are not attainable using other synthetic ways.

Keywords: Benzoxazine monomers; Deuterium labeling

INTRODUCTION

3,4-Dihydro-2H-1,3-benzoxazines are bicyclic heterocycles that are of significant interest in the polymeric and pharmacological fields. 1,3-Benzoxazines have long been recognized for their wide range of biological activity with uses as herbicides and agricultural microbiocides, as well

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as bactericide, fungicide, antidepressive, anti-inflammatory, and antitumor agents.[1–4] Moreover, 1,3-benzoxazine monomers were recently used to develop a new type of phenolic resin, namely polybenzoxazines, by the ring-opening polymerization on thermal curing.[5–8] The resulting materials possess typical characteristics of the traditional phenolic resins such as heat resistance, good flame retardance, and electronic properties. In addition, they provide unique characteristics such as low water absortion and excellent dimensional stability, due to near-zero volumetric shrinkage upon curing.[9–12] Other applications of these compounds are in supramolecular chemistry.[13,14] or the synthesis of metallic complexes with catalytic activity.[15]

Synthetic approaches for 3,4-dihydro-2H-1,3-benzoxazines include Mannich condensation of phenol and a primary amine with formaldehyde,[16,17] condensation of o-hydroxybenzylamine with an aldehyde,[18–20] rearrangement reactions of 2-(allyloxy)benzylamine with H_2/CO in the presence of rhodium catalyst,[21] condensation of 4-substituted phenols with 1,3,5-trimethyl-hexahydro-s-triazine in the presence of oxalyl chloride,[22] reaction of 1-(bromomethyl)-2-(chloromethoxy)benzene with primary amines,[23] dehydratation of N-(2-hydroxybenzyl)-3-aminopropanoic acid with H_2SO_4,[24] and reaction of ortho-lithiated phenol dianions with N,N-bis[(benzotriazol-1-yl)methyl]amines.[25]

By far the most extended method for the synthesis of these compounds was described by Burke et al.[16] and consists of the reaction of a phenol, a primary amine, and formaldehyde in 1:1:2 molar ratio. This reaction involves the C-C formation by attack of the *ortho* phenol position on the amine Mannich adduct. Many authors tested different modifications of this basic method to optimize results. Solventless conditions reduce reaction times and improve the yields.[26] The presence of water induces the benzoxazine ring opening and leads to the formation of olygomeric species, so the use of paraformaldehyde instead of aqueous formaldehyde and solvents of low polarity also increase benzoxazine yields.[27,28]. Alternatively, water produced during the condensation can be reduced by using the corresponding 1,3,5-triazine instead of the aromatic amine and formaldehyde. Unfortunately, this approach is limited to the case of stable aromatic triazines.[29]

In any case, the main drawback of this synthetic route is the extensive formation of oligomers, which reduce the benzoxazine yield and make its purification difficult. Moreover, the presence of some functional groups in the benzoxazine is incompatible with the use of this direct synthetic methodology. This is the case of the phenolic groups that are desirable to prepare new polymeric materials with well-defined properties. This fact and the aim to prepare deuterium-labeled benzoxazine monomers for mechanistic studies led us to explore the utility of alternative synthetic routes.

From all these synthetic methods, the condensation of substituted 2-hydroxybenzylamines with formaldehyde seemed the most reliable for

our purposes. The necessary 2-hydroxybenzylamines can be conveniently synthesized by in situ reduction of the imines generated by condensation of the readily available 2-hydroxybenzaldehydes and primary amines.

In this article, we report the application of this method to the synthesis of high-purity 3,4-dihydro-2H-1,3-benzoxazines and a family of their deuterated derivatives.

EXPERIMENTAL

Materials

Salicylaldehyde (Aldrich), 2,5-dihydroxybenzaldehyde (Aldrich), $NaBH_4$ (Aldrich), paraformaldehyde (Probus), methylamine 40% (Probus), benzylamine (Probus), aniline (Aldrich), 4-aminophenol (Fluka), phenol (Probus), NaOD 40% in D_2O (Aldrich), paraformaldehyde-d_2 (Aldrich), aniline-d_5 (Aldrich), phenol-d_6(Aldrich), $NaBD_4$ (Aldrich), and $CDCl_3$ (SDS) were used as received. Solvents were purified by standard procedures.

Instrumentation

Melting points were determined on an electrothermal Büchi 510 melting-point apparatus. ^1H and ^{13}C NMR spectra were registered on a Varian Mercury-400 using TMS as an internal standard. Elemental analysis was carried out on a Carlo Erba EA 1108 microanalyzer.

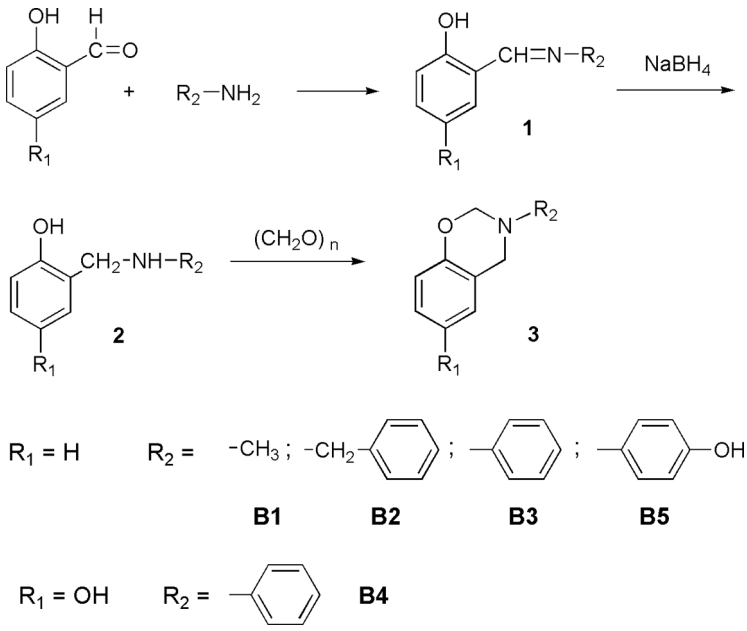
Synthesis of 2-Hydroxybenzylamines (2 in Scheme 1)

Salicylaldehyde or 2,5-hydroxybenzaldehyde (40 mmol) was added slowly to a solution of amine (40 mmol) in EtOH (50 mL), and the mixture was stirred at 60 °C for 4–8 h. The resulting solution was cooled to room temperature, and $NaBH_4$ (0.76 g, 20 mmol) was added in small portions while stirring. When the reduction was complete, 100 mL of water was added, and the resulting product was extracted with diethyl ether, washed with water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The resulting 2-hydroxybenzylamines were colorless oils or white solids.

Data

2-Hydroxy-N-methylbenzylamine

Yield 90%, mp = 39–41 °C. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ_H 7.20–6.70 (4H, Ar-H), 6.35 (2H, OH and NH, broad), 3.91 (2H, Ar-CH_2-N), 2.43 (3H, N-CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$, ppm): δ_C 158.6



Scheme 1. Synthetic pathway used in the preparation of benzoxazines B1 to B5.

(C-O), 128.9 (CH), 128.7 (CH), 122.6 (C), 119.3 (CH), 116.6 (CH), 54.9 (Ar-CH_2-N), 35.5 (N-CH_3).

2-Hydroxy-N-(benzyl)benzylamine

Yield 92%, viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ_H 7.30–6.70 (11H, Ar-H, OH and NH), 3.88 (2H, Ar-CH_2), 3.70 (2H, Ar-CH_2). ^{13}C NMR (100.5 MHz, $CDCl_3$, ppm): δ_C 158.0 (C-O), 138.1 (C-N), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.3 (CH), 122.1 (C), 118.9 (CH), 116.1 (CH), 52.2 (Ar-CH_2), 51.5 (Ar-CH_2).

2-Hydroxy-N-phenylbenzylamine

Yield 95%, mp = 113–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 8.42 (1H, OH), 7.30–6.80 (9H, Ar-H), 4.40 (2H, Ar-CH_2-N), 3.95 (1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm): δ_C 156.7 (C-O), 147.2 (C-N), 129.3 (CH), 129.2 (CH), 128.6 (CH), 122.8 (C), 120.8 (CH), 120.0 (CH), 116.6 (CH), 115.8 (CH), 48.7 (Ar-CH_2-N).

2-Hydroxy-N-(4-hydroxyphenyl)benzylamine

Yield 86%, mp = 123–125 °C. ^{1}H NMR (400 MHz, DMSO, ppm): δ_H 9.50 (1H, OH), 8.40 (1H, OH), 7.20–6.40 (8H, Ar-H), 5.33 (1H, NH), 4.11 (2H, Ar-CH_2-N). ^{13}C NMR (100.5 MHz, DMSO, ppm): δ_C 155.1 (C-O), 148.4 (C-O), 141.7 (C-N), 128.4 (CH), 127.4 (CH), 126.2 (C), 118.8 (CH), 115.6 (CH), 114.8 (CH), 113.7 (CH), 42.7 (Ar-CH_2-N).

2,5-Dihydroxy-N-phenylbenzylamine

Yield 88%, mp = 117–119 °C. ^{1}H NMR (400 MHz, DMSO, ppm): δ_H 8.80 (1H, OH), 8.59 (1H, OH), 7.03 (2H, Ar-H), 6.65–6.40 (6H, Ar-H), 6.00 (1H, NH), 4.12 (2H, Ar-CH_2-N). ^{13}C NMR (100.5 MHz, DMSO, ppm): δ_C 149.9 (C-O), 148.9 (C-N), 147.3 (C-O), 128.9 (CH), 126.6 (C), 115.6 (CH), 115.5 (CH), 114.7 (CH), 113.6 (CH), 112.2 (CH), 41.4 (Ar-CH_2-N).

Synthesis of Benzoxazines (3 in Scheme 1)

The necessary amounts of the corresponding 2-hydroxybenzylamine derivative (in all cases 30 mmol) and paraformaldehyde (0.9 g, 32 mmol) were added to 50 mL of 1,4-dioxane, and the reaction mixture was stirred at 100 °C for 18–24 h. The solvent was evapored, and the residue was dissolved in diethyl ether and washed with 2 M NaOH solution (except **B4** and **B5**). The organic layer was dried over anhydrous $MgSO_4$ and concentrated to dryness. The obtained products were purified as described Table 1.

3-Methyl-3,4-dihydro-2H-1,3-benzoxazine (B1)

Yield 87%, liquid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ_H 7.15–6.70 (4H, Ar-H), 4.76 (2H, O-CH_2-N), 3.92 (2H, Ar-CH_2-N), 2.56 (3H, N-CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$, 25 °C, ppm): δ_C 153.6 (C-O), 127.5 (CH), 127.4 (CH), 120.4 (CH), 119.8 (C), 116.2 (CH), 83.6 (O-CH_2-N), 52.0 (Ar-CH_2-N), 39.5 (N-CH_3). Elemental analysis: $C_9H_{11}NO$ (149.19). Calculated (%): C, 72.46; H, 7.43; N; 9.39. Experimental (%): C, 72.38; H, 7.40; N, 9.35.

3-Benzyl-3,4-dihydro-2H-1,3-benzoxazine (B2)

Yield 92%, mp = 71–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ_H 7.35–6.80 (9H, Ar-H), 4.85 (2H, O-CH_2-N), 3.94 (2H, Ar-CH_2), 3.90 (2H,

Table 1. Experimental conditions and yields used in the synthesis of benzoxazines

Number	Aldehyde	Amine	Reaction time (h)[a]	Yield %[b]	Reaction time (h)[c]	Yield %[d]	Purification
B1	o-HOPhCHO	$MeNH_2$	4	90	24	87	Distillation (42–43 °C, 0.4 mm Hg)
B2	o-HOPhCHO	$BnNH_2$	4	92	24	92	Cryst. in ethanol
B3	o-HOPhCHO	$PhNH_2$	4	95	24	94	Cryst. in diethyl ether
B3a	o-HOPhCHO	$PhNH_2$	4	95	18	90	C. chrom. hexane/CH_2Cl_2 (3:1)
B3b	o-HOPhCHO-d_1	$PhNH_2$	4	92	18	88	C. chrom. hexane/CH_2Cl_2 (3:1)
B3c	o-HOPhCHO	$PhNH_2$-d_5	4	94	18	87	C. chrom. hexane/CH_2Cl_2 (3:1)
B3d	o-HOPhCHO-d_5	$PhNH_2$	4	95	18	88	C. chrom. hexane/CH_2Cl_2 (3:1)
B4	o-HOPhCHO	4-$HOPhNH_2$	8	86	18	92	C. chrom. CH_2Cl_2
B5	2,5-$(HO)_2$PhCHO	$PhNH_2$	8	88	18	95	C. chrom. CH_2Cl_2

[a]Synthesis of the imines (step 1).
[b]Yield of 2-hydroxybenzylamines (combined steps 1 and 2).
[c]Synthesis of benzoxazines (step 3).
[d]Yield of benzoxazines (step 3).

Ar-CH_2). ^{13}C NMR (100.5 MHz, $CDCl_3$, ppm): δ_C 153.8 (C-O), 137.9 (C-N), 128.7 (CH), 128.2 (CH), 127.5 (CH), 127.4 (CH), 127.1 (CH), 120.4 (CH), 119.8 (C), 116.2 (CH), 82.1 (O-CH_2-N), 55.5 (CH_2-Ar), 49.5 (Ar-CH_2-N). Elemental analysis: $C_{15}H_{15}NO$ (225.29). Calculated (%): C, 79.97; H, 6.71; N, 6.22. Experimental (%): C, 79.88; H, 6.93; N, 6.19.

3-Phenyl-3,4-dihydro-2H-1,3-benzoxazine (B3)

Yield 94%, mp = 55–57 °C. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ_H 7.30–6.70 (9H, Ar-H), 5.33 (2H, O-CH_2-N), 4.61 (2H, Ar-CH_2-N). ^{13}C NMR (100.5 MHz, $CDCl_3$, ppm): δ_C 154.3 (C-O), 148.3 (C-N), 129.2 (CH), 127.8 (CH), 126.7 (CH), 121.4 (CH), 120.8 (C), 120.7 (CH), 118.2 (CH), 116.9 (CH), 79.4 (O-CH_2-N), 50.4 (Ar-CH_2-N). Elemental analysis: $C_{14}H_{13}NO$ (211.26). Calculated (%): C, 79.59; H, 6.20; N, 6.63. Experimental (%): C, 79.87; H, 6.55; N, 6.64.

3-(4-Hydroxyphenyl)-3,4-dihydro-2H-1,3-benzoxazine (B4)

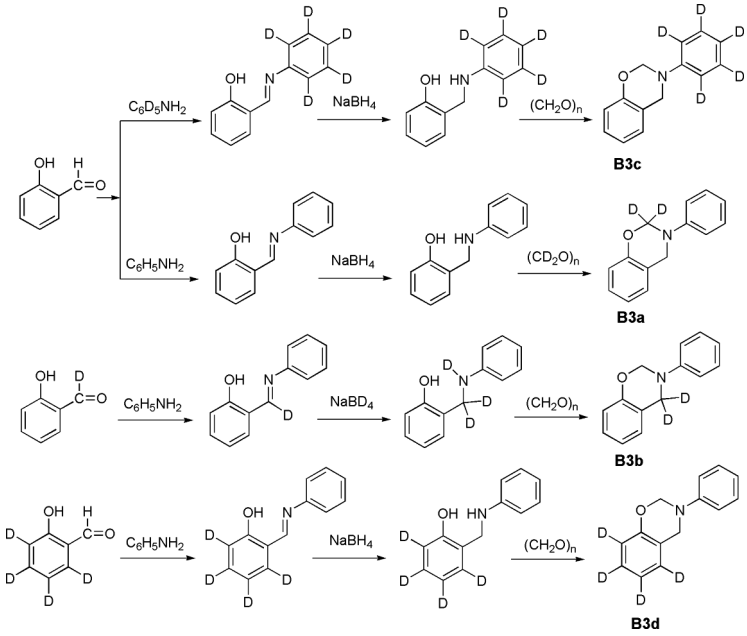
Yield 92%, mp = 70–72 °C. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ_H 7.15–6.70 (8H, Ar-H), 5.27 (2H, O-CH_2-N), 4.54 (2H, Ar-CH_2-N), 4.49 (1H, OH). ^{13}C NMR (100.5 MHz, $CDCl_3$, ppm): δ_C 154.1 (C-O), 150.8 (C-O), 142.0 (C-N), 127.8 (CH), 126.7 (CH), 121.0 (CH), 120.8 (CH), 120.7 (C), 116.8 (CH), 116.0 (CH), 80.8 (O-CH_2-N), 50.9 (Ar-CH_2-N). Elemental analysis: $C_{14}H_{13}NO_2$ (227.26). Calculated (%): C, 73.99; H, 5.77; N, 6.16. Experimental (%): C, 73.79; H, 5.63; N, 6.31.

6-Hydroxy-3-phenyl-3,4-dihydro-2H-1,3-benzoxazine (B5)

Yield 95%, mp = 102–103 °C. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ_H 7.25–6.40 (8H, Ar-H), 6.22 (1H, OH), 5.23 (2H, O-CH_2-N), 4.44 (2H, Ar-CH_2-N). ^{13}C NMR (100.5 MHz, $CDCl_3$, ppm): δ_C 149.5 (C-O), 148.1 (C-O), 147.8 (C-N), 129.1 (CH), 121.5 (C), 121.4 (CH), 118.1 (CH), 117.5 (CH), 114.9 (CH), 112.8 (CH), 79.4 (O-CH_2-N), 50.1 (Ar-CH_2-N). Elemental analysis: $C_{14}H_{13}NO_2$ (227.26). Calculated (%): C, 73.99; H, 5.77; N, 6.16. Experimental (%): C, 74.46; H, 6.22; N, 6.09.

Synthesis of the Deuterated Benzoxazines (B3a, B3b, B3c, B3d in Scheme 2)

Deuterium-labeled compounds were synthesized according the synthetic sequence shown in Scheme 2.



Scheme 2. Synthetic pathway used in the preparation of deuterated benzoxazines B3a, B3b, B3c, and B3d.

2,2-Dideutero-3-phenyl-3,4-dihydro-2H-1,3-benzoxazine (B3a)

2-Hydroxy-N-phenylbenzylamine (2.0 g, 10.1 mmol) and paraformaldehyde-d_2 (0.34 g, 10.1 mmol) were added to 50 mL of 1,4-dioxane and heated at 100 °C for 18 h. The residue obtained after concentration was dissolved in diethyl ether and washed with 2 M NaOH solution. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to dryness, and the resulting product was purified by flash-chromatography using hexane/dichloromethane 3:1 as eluant.

Yield 90%, mp 56–58 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, ppm): δ_H 7.26–6.78 (9H, Ar-H), 4.60 (2H, Ar-CH_2-N). ^{13}C NMR (100.5 MHz, $CDCl_3$, 25 °C, ppm): δ_C 154.3 (C-O), 148.3 (C-N), 129.2 (CH), 127.8 (CH), 126.7 (CH), 121.3 (CH), 120.8 (C), 120.7 (CH), 118.1 (CH), 116.8 (CH), 79.3 (O-CD_2-N, low-intensity multiplet), 50.2 (Ar-CH_2-N). Anal. calcd. for $C_{14}H_{11}D_2NO$ (213.27): C, 78.84; H + D, 7.09; N, 6.57. Found: C, 79.45; H, 7.38; N, 6.58. Deuteration degree by ^{1}H NMR 98%.

4,4-Dideutero-3-phenyl-3,4-dihydro-2H-1,3-benzoxazine (B3b)

Salicyladehyde-d_1. Phenol (5.0 g, 53 mmol) was added to 20 mL of a 40% solution of NaOD in D_2O. The mixture was stirred for 30 min and heated

up to 65–70 °C. After the addition of a solution of benzyltrimethylammonium chloride (61 mg, 0.21 mmol) in 8 ml of 1,4-dioxane, deuterated chloroform (8.2 g, 70 mmol) was added dropwise, and the mixture was stirred vigorously at 70 °C for 1 h. The excess chloroform and the dioxane were eliminated by distillation, and the aqueous layer was neutralized with diluted hydrochloric acid. o-Hydroxybenzaldehyde and some unreacted phenol were separated from the para isomer by steam distillation. The crude product was purified by flash chromatography using a mixture hexane/CH_2Cl_2 2:1 to give 2.6 g (40%) of a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, ppm): δ_H 11.05 (1H, OH), 7.55–7.00 (4H, Ar-H). ^{13}C NMR (100.5 MHz, $CDCl_3$, 25 °C, ppm): δ_C 196.2 (CDO), 161.6 (C-OH), 136.9 (CH), 133.6 (CH), 120.5 (C), 119.8 (CH), 117.5 (CH). Deuteration degree by ^{1}H NMR: 94%.

α,α-Dideutero-2-hydroxybenzylamine. A mixture of salicylaldehyde-d_1 (1.0 g, 8.12 mmol) and aniline (0.78 g, 8.37 mmol) in 5 mL of ethanol was stirred for 1 h at room temperature. $NaBD_4$ (0.1 g, 4.05 mmol) in 5 mL of ethanol was added in small portions, and the reaction was monitored by thin-layer chromatography (TLC) until complete disappearance of intermediate imine. After pouring the mixture onto 150 mL of water, the obtained solid product was separated by filtration and dried.

Yield 92%, mp 112–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, ppm): δ_H 8.41 (1H, OH), 7.23–6.80 (9H, Ar-H), 3.95 (1H, NH). ^{13}C NMR (100.5 MHz, $CDCl_3$, 25 °C, ppm): δ_C 156.6 (C-O), 147.1 (C-N), 129.3 (CH), 129.1 (CH), 128.6 (CH), 122.8 (C), 120.6 (CH), 120.0 (CH), 116.4 (CH), 115.7 (CH), 48.0 (Ar-CD_2-N, low-intensity multiplet). Deuteration grade by ^{1}H NMR: 97%.

B3b. A mixture of α,α-dideutero-2-hydroxybenzylamine (0.95 g, 4.70 mmol) and paraformaldehyde (0.13 g, 4.70 mmol) in 30 mL of 1,4-dioxane was stirred at 100 °C for 16 h. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography using a mixture of hexane/dichloromethane 3:1.

Yield 1.6 g (88%), mp 55–57 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, ppm): δ_H 7.40–6.80 (9H, Ar-H), 5.33 (2H, O-CH_2-N). ^{13}C NMR (100.5 MHz, $CDCl_3$, 25 °C, ppm): δ_C 154.3 (C-O), 148.3 (C-N), 129.2 (CH), 127.8 (CH), 126.7 (CH), 121.3 (CH), 120.8 (C), 120.7 (CH), 118.1 (CH), 116.8 (CH), 79.3 (O-CH_2-N), 50.2 (Ar-CD_2-N, low-intensity multiplet). Anal. calcd. for $C_{14}H_{11}D_2NO$ (213.27): C, 78.84; H + D, 7.09; N, 6.57. Found: C, 79.24; H, 7.21; N, 6.43. Deuteration degre by ^{1}H NMR: 97%.

3-(Pentadeuterophenyl)-3,4-dihydro-2H-1,3-benzoxazine (B3c)

2-Hydroxy-N-pentadeuterophenylbenzylamine. A mixture of salicylaldehyde (1.2 g, 10.2 mmol) and aniline-d_5 (1.0 g, 10.1 mmol) in 10 mL of ethanol was stirred for 1 h at room temperature. Then, $NaBH_4$ (0.1 g,

4.05 mmol) in 10 mL of ethanol was added in small portions, and the reaction was monitored by TLC until complete disappearance of the intermediate imine. After the addition of 250 mL of water, the resulting white crystalline solid was collected by filtration washed and dried.

Yield (94%), mp 112–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, ppm): δ_H 8.41 (1H, OH), 7.26–6.80 (4H, Ar-H), 4.42 (2H, Ar-CH_2-N), 3.95 (1H, NH). ^{13}C NMR (100.5 MHz, $CDCl_3$, 25 °C, ppm): δ_C 156.6 (C-O), 147.0 (C-N), 129.1 (CH), 128.8 (CD, triplet), 128.6 (CH), 122.9 (C), 120.2 (CD, triplet), 120.0 (CH), 116.5 (CH), 115.2 (CD, triplet), 48.5 (Ar-CH_2-N). Deuteration degree by ^{1}H NMR: 98%.

B3c. 2-Hydroxy-N-pentadeuterophenylbenzylamine (1.5 g, 7.3 mmol), paraformaldehyde (0.23 g, 7.3 mmol), and 30 mL of 1,4-dioxane were heated at 100 °C for 18 h following the same procedure described for product **B3a** to give a white crystalline.

Yield 87%, mp 55–57 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, ppm): δ_H 7.10–6.78 (4H, Ar-H), 5.33 (2H, O-CH_2-N), 4.60 (2H, Ar-CH_2-N). ^{13}C NMR (100.5 MHz, $CDCl_3$, 25 °C, ppm): δ_C 154.3 (C-O), 148.2 (C-N), 128.7 (CD, triplet), 127.8 (CH), 126.7 (CH), 120.8 (CD, triplet), 120.8 (C), 120.7 (CH), 117.8 (CD, triplet), 116.8 (CH), 79.4 (O-CH_2-N), 50.3 (Ar-CH_2-N). Anal. calcd. for $C_{14}H_8D_5NO$ (216.29); C, 77.74; H + D, 8.38; N, 6.48. Found: C, 78.34; H, 7.40; N, 6.35. Deuteration degree by ^{1}H NMR: 98%.

5,6,7,8-Tetradeuterophenyl-3,4-dihydro-2H-1,3-benzoxazine (B3d)

Salicyladehyde-d_4. Starting from phenol-d_6 (2.5 g, 25 mmol) and chloroform (4.1 g, 35 mmol) and proceeding as for salicylaldehyde-d_1, the resulting brown oil was purified by flash chromatography using a mixture hexane/CH_2Cl_2 2:1 to give a pale yellow liquid.

Yield 38%. Deuteration degree by ^{1}H NMR: 98%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, ppm): δ_H 11.05 (1H, OH), 9.82 (1H, CHO). ^{13}C NMR (100.5 MHz, $CDCl_3$, 25 °C, ppm): δ_C 196.4 (CHO), 161.5 (C-OH), 136.7 (CD, triplet), 133.5 (CD, triplet), 120.5 (C), 119.6 (CD, triplet), 117.3 (CD, triplet).

2-Hydroxy-3,4,5,6-tetradeutero-N-Phenylbenzylamine. A mixture of salicylaldehyde-d_4 (1.0 g, 7.92 mmol) and aniline (0.75 g, 8.05 mmol) in 5 mL of ethanol was stirred for 1 h at room temperature. The resulting imine was reduced using $NaBH_4$ (0.1 g, 4.05 mmol) in 5 mL of ethanol. After pouring the mixture onto 100 mL of water, the obtained solid product was separated by filtration and dried.

Yield 92%, mp 111–113 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 8.40 (1H, OH), 7.30–6.80 (5H, Ar-H), 4.41 (2H, Ar-CH_2-N), 3.95 (1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm): δ_C 156.7 (C-O), 147.2 (C-

N), 129.0 (CD, triplet), 129.2 (CH), 128.4 (CD, triplet), 122.8 (C), 120.8 (CH), 119.8 (CD, triplet), 116.4 (CD, triplet), 115.8 (CH), 48.7 (Ar-CH_2-N). Deuteration degree by ^{1}H NMR:98%.

B3d. 2-Hydroxy-3,4,5,6-tetradeutero-N-phenylbenzylamine(1.5 g, 7.3 mmol), paraformaldehyde (0.23 g, 7.3 mmol), and 30 mL of 1,4-dioxane were heated at 100 °C for 18 h. Following the same procedure described for product **B3a**, a white solid was obtained.

Yield 80%, mp 56–58 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, ppm): δ_H 7.30–6.80 (5H, Ar-H), 5.26 (2H, O-CH_2-N), 4.53 (2H, Ar-CH_2-N). ^{13}C NMR (100.5 MHz, $CDCl_3$, 25 °C, ppm): δ_C 154.3 (C-O), 148.3 (C-N), 129.2 (CH), 127.3 (CD, triplet), 126.2 (CD, triplet), 121.3 (CH), 120.7 (C), 120.3 (CD, triplet), 118.2 (CH), 116.4 (CD, triplet), 79.4 (O-CH_2-N), 50.3 (Ar-CH_2-N). Anal. calcd. for $C_{14}H_9D_4NO$ (215.28): C; 78.11; H + D, 7.96; N, 6.51. Found: C, 78.54; H, 6.82: N, 6.72.

RESULTS AND DISCUSSION

The synthetic pathway checked in this work is depicted in Scheme 1. Condensation of salicylaldehyde or 2,5-dihydroxybenzaldehyde with different amines was performed in ethanol at 60 °C in absence of catalyst. After 4 to 8 h, the formation of the imine was complete and could be isolated upon cooling if necessary. The reduction of the imine (**1**) was performed in the same flask by the addition of an excess of $NaBH_4$ to the warm ethanolic solution. The crude product was isolated as a white powder by precipitation with water and dried under vacuum. In all cases, the corresponding 2-hydroxybenzylamines (**2**) were obtained in good to excellent yields and were pure enough by ^{1}H NMR to be used in the following step without further purification. The benzoxazine ring formation was achieved by reacting the corresponding 2-hydroxybenzylamine with 1 equivalent of paraformaldehyde in refluxing dioxane for 18 to 24 h. The pure 3,4-dihydro-2H-1,3-benzoxazines (**3**) were isolated simply by dissolving the dry crude in ethyl ether, washing with 2 M NaOH to remove traces of unreacted phenol, and crystallizing the obtained product after concentration in the appropriate solvent. In the case of hydroxyl-substituted benzoxazines, the treatment with aqueous NaOH was obviously omitted. This synthetic procedure and simple workup yield the desired benzoxazines with high purity and yields ranging from 87 to 95%, which are higher than those reported using conventional methods. Moreover, under the assayed conditions, no significant amounts of oligomeric species or by-products were detected by TLC, indicating the selectivity of this three-step pathway. It must be pointed out that this methodology allows synthesis of the hydroxy-substituted derivatives 4-[2H-1,3-benzoxazin-

3(4H)-il]phenol **B4** and 3-phenyl-3,4-dihydro-2H-1,3-benzoxazin-6-ol **B5**, which were described for the first time and are not attainable using other synthetic methods.

The sequential incorporation of the aromatics and the benzoxazine ring methylene units used in this synthetic approach is the key to obtain deuterium-labeled benzoxazine derivatives and gives the possibility of preparing other labeled target compounds, with ^{13}C or ^{15}N for instance.

We used this methodology to prepare different 3-phenyl-3,4-dihydro-2H-1,3-benzoxazines deuterated selectively in both methylene carbons and in both aromatic rings. As shown in Scheme 2, the appropriate use of deuterated paraformaldehyde or sodium borodeuteride allow labeling easily the methylene positions. To obtain the other compounds, readily available deuterated aniline-d_5 or phenol-d_5 were used. The necessary intermediates salicylaldehyde-d_1 and salicylaldehyde-d_4 were conveniently prepared by the Riemer–Tiemann reaction[30] from deuterated phenol and chloroform or deuterated chloroform as reported in the experimental section. These deuterated salicylaldehyde derivatives are obtained with moderate yields by this single-step procedure, but obtained products are pure and their deuterium content is very high (94 to 98%).

The procedure used to prepare these compounds was the same as that for the nondeuterated equivalents, but a smaller scale was used and the final purification was performed by column chromatography. Yields and purity were also satisfactory in all cases.

Table 1 summarizes the experimental conditions and yields for all the synthesized benzoxazines. It must be pointed out that the procedure has been scaled up to 100 g of compound with reproducible results. Moreover, we have also synthesized 3-phenyl-3,4-dihydro-2H-1,3-benzoxazines with different substituents (CH_3, Cl, OCH_3, NO_2) in the 6 or 8 positions or in the para position of the N-phenyl group, with the same satisfactory results, thus proving that this methodology is of general application.

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