A Straightforward Route to 4*H*-1,4-Benzoxazine-2-carbaldehydes by Swern Oxidation

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Swern oxidation of saturated (1,4-benzoxazine-2-yl)-methanols **2** furnished 4*H*-1,4-benzoxazine-2-carbaldehydes **3**, which possess an α,β ethylenic bond. The reactivity of these compounds was examined.

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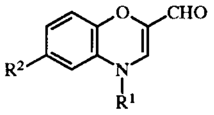
Among the numerous oxidation methods of alcohols, the Swern method [1,2] has gained an increasing popularity, due to its selectivity and mild conditions.

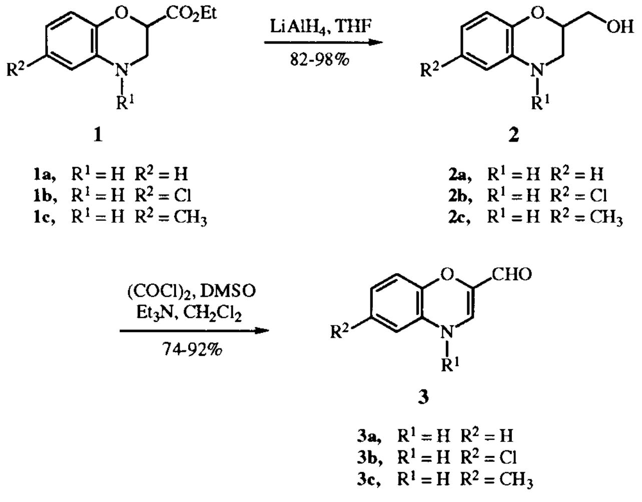
Our laboratory has developed different strategies for the synthesis of 1,4-benzoxazines [3,4] and 1,4-benzodioxines [5,6,7]. In the pursuit of these studies, we report, in this paper, the use of Swern oxidation as a ready synthetic route to 4*H*-1,4-benzoxazine-2-carbaldehydes of type **3**, used as intermediates in a program devoted to cardiovascular drugs.



3

Precursors of compounds **3** were the alcohols **2**, which were submitted to Swern oxidation. As shown in Scheme 1, the Swern oxidation at -78° of alcohols **2a-c**, obtained by reduction with lithium aluminium hydride of the corresponding esters **1a-c** (formed by the reaction of the appropriate aminophenols with ethyl 2,3-dibromopropionate [12]) furnished in high yields (74-92%) the α,β ethylenic aldehydes **3a-c**, which were relatively unstable compounds.

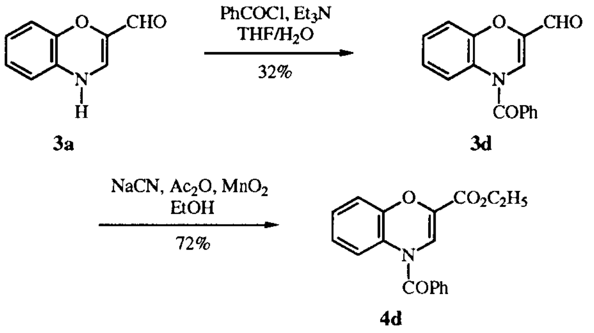
Scheme 1



The structure of the aldehydes **3a-c** was confirmed by two independent syntheses. First, we have synthesized the compound **4d**, which we have precedently obtained by another synthetic route [3]. As shown in Scheme 2, compound **4d** was prepared from the aldehyde **3a** in two steps.

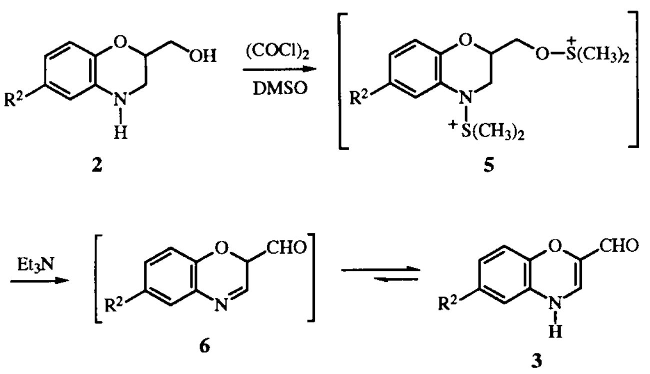
N-Benzoylation of aldehyde **3a** in tetrahydrofuran/water resulted in the formation of the benzoyl compound **3d**, which was then oxidized to the unsaturated ester **4d** in 72% yield, following a procedure reported by Corey [8] using sodium cyanide, acetic acid and manganese dioxide in ethanol. The structure of **4d** was in agreement with our preceding works [3].

Scheme 2



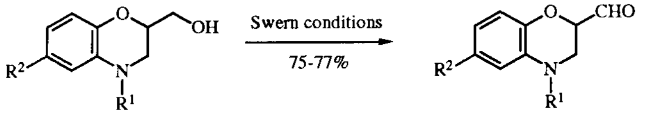
Secondly, compound **3e** (R^1 = CH_3, R^2 = H) was obtained from the aldehyde **3a** by *N*-methylation according to standard procedure (iodomethane, potassium carbonate, *N*,*N*-dimethylformamide). Bartsch [9] has described the formation of this *N*-methylaldehyde **3e**, in low yield, according to a variation of the Polonovski reaction; the structures of these two compounds were identical. Formation of **3** can be rationalized according to Scheme 3, as the result of electrophilic attacks by the acyloxysulfonium reagent on both the OH and the NH groups of **2**, affording the intermediate **5**. Double proton-elimination from **5** can lead to the formation of the iminoaldehyde **6**, which isomerizes to the more stable structure of α,β ethylenic aldehyde **3**.

Scheme 3



Moreover, Simay [10] has reported that Swern oxidation of aryloxyaminoalcohols ($ArOCH_2CHOHCH_2NHR$) led to ketoimine, which is in agreement with our postulated mechanism. If the oxidation of the aminoalcohols **2a-c** led almost exclusively to the aldehydes **3a-c**, oxidation in the same manner, of the *N*-alkyl substituted alcohols **2e** and **2f** furnished the expected aldehydes **7e** and **7f**, respectively in 75% and 77% yield, as the result of a single electrophilic attack of the reagent on the OH group (Scheme 4). Alcohols **2e** and **2f** were obtained by *N*-alkylation of the ester **1a**, according to standard procedure (iodomethane, potassium carbonate, *N,N*-dimethylformamide or benzyl chloride, potassium carbonate, *N,N*-dimethylformamide) and followed by the reduction of the ester group into alcohol with lithium aluminium hydride in tetrahydrofuran.

Scheme 4



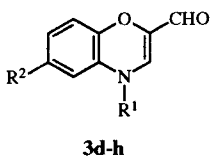
2e, $R^1 = CH_3$ $R^2 = H$
2f, $R^1 = CH_2Ph$ $R^2 = H$

7e, $R^1 = CH_3$ $R^2 = H$
7f, $R^1 = CH_2Ph$ $R^2 = H$

In order to increase the stability of the unsaturated aldehydes **3**, different substitutions of the nitrogen atom were accomplished from compound **3a**. Compounds **3d-h** were obtained in relatively good yields, as shown in Table 1. As reported *vide supra* the *N*-benzoyl **3d** and *N*-methyl **3e** aldehydes were also isolated. Compound **3f** was obtained by benzylation of **3a** in *N,N*-dimethylformamide at 60° with benzyl chloride and potassium carbonate. Acetylation of **3a** was performed in dichloromethane at 0°, in presence of triethylamine to lead to **3g**. Reaction of di-*tert*-butyl dicarbonate with **3a** in dichloromethane at 0°, in the presence of 4-dimethylaminopyridine and triethylamine, furnished **3h** in 87% yield.

Table 1

Compounds **3d-h** Prepared

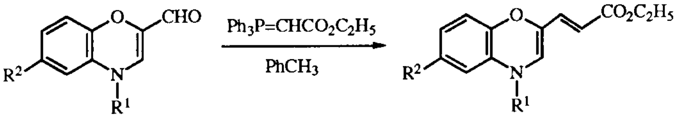


3d-h

3	R¹	R²	Yield
d	COPh	H	32%
e	CH_3	H	85%
f	CH_2Ph	H	75%
g	$COCH_3$	H	70%
h	CO_2-*t*-Bu	H	87%

The reactivity of the carbonyl function was also examined. We have recently reported [11] inverse electron demand Diels-Alder reactions with 1-ethoxyethene of aldehydes **3g** and **3h**, which led to the expected [4+2] cycloadducts and, more surprisingly to vinyl compounds (resulting from a formal methylenation of the aldehyde group). On the other hand, aldehydes **3f** and **3h** were submitted to a Wittig reaction with carbethoxymethylenetriphenylphosphorane and gave, in good yields (respectively 75% and 87%), the expected unsaturated esters **8f** and **8h**, as *E* isomers, which are valuable synthons for Diels-Alder reactions.

Scheme 5

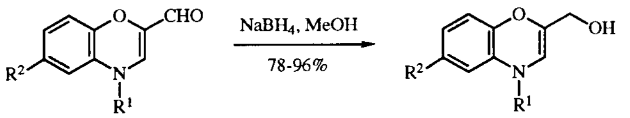


3f, $R^1 = CH_2Ph$ $R^2 = H$
3h, $R^1 = CO_2$-*t*-Bu $R^2 = H$

8f, $R^1 = CH_2Ph$ $R^2 = H$
8h, $R^1 = CO_2$-*t*-Bu $R^2 = H$

We have also studied, in the same way, the behavior of the aldehydes **3** towards reduction conditions. Indifferently, the use of sodium borohydride in methanol or lithium aluminium hydride in tetrahydrofuran with the aldehydes **3a** and **3e** led to the regeneration of the saturated alcohols **2a** and **2e** in good yields. But, otherwise the aldehydes **3g** and **3h** were reduced into their corresponding unsaturated alcohols **9g** and **9h** by the action of sodium borohydride in methanol, respectively in 78% and 96% yield, as shown in Scheme 6.

Scheme 6



3g, $R^1 = COCH_3$ $R^2 = H$
3h, $R^1 = CO_2$-*t*-Bu $R^2 = H$

9g, $R^1 = COCH_3$ $R^2 = H$
9h, $R^1 = CO_2$-*t*-Bu $R^2 = H$

In conclusion, the Swern oxidation of (1,4-benzoxazin-2-yl)methanols **2** gave a new and easy route to 4*H*-1,4-benzoxazine-2-carbaldehydes **3** in good yields, which were potentially useful synthons.

EXPERIMENTAL

Analytical thin layer chromatography (tlc) was performed on silica gel (Merck 60F_{254}). Column chromatography used silica gel Kieselgel (230-400 mesh). The ^{1}H nmr spectra were recorded on a Bruker AM 300WB spectrometer. The chemical shifts were reported per million (δ, ppm) downfield from tetramethylsilane (TMS) which was used as internal standard. Melting points, determined on a Kofler hot-stage apparatus, were uncorrected. Infrared spectra were obtained with a Perkin Elmer 1310 spectrophotometer. Mass spectra were recorded on a R-10-10-C Nermag apparatus.

General Procedure for the Preparation of Esters **1a-c**.

To a solution of the appropriate *o*-aminophenol (30 mmoles) in dry acetone (40 ml), was added potassium carbonate (20 mmoles). The mixture was heated at 40° and ethyl 2,3-dibromopropionate (9.80 mmoles) was added dropwise. Then, in boiling acetone, potassium carbonate (70 mmoles) and ethyl 2,3-dibromopropanoate (30 mmoles) were added slowly in three times and the mixture was refluxed 18 hours. After cooling, potassium carbonate was filtered; the solvent was evaporated and the solution hydrolyzed. The product was extracted with ether, the organic layers were washed, dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica gel column.

3,4-Dihydro-2*H*-1,4-benzoxazine-2-carboxylic Acid, Ethyl Ester (**1a**).

The ester **1a** was prepared according to the literature procedure [12].

6-Chloro-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic Acid, Ethyl Ester (**1b**) [13].

The crude product was purified by column chromatography (eluent: dichloromethane) to furnish **1b** as a solid (72% yield), mp 86-88° (ethanol); ir (potassium bromide): 3360 (NH), 1720 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.21 (t, 3H, J = 7.3 Hz, CH_3), 3.49-3.54 (m, 2H, NCH_2), 3.75 (br s, 1H, N*H*), 4.18 (qd, 2H, J = 2.2, 7.3 Hz, OCH_2), 4.69-4.74 (m, 1H, OC*H*), 6.52 (d, 1H, J = 2.9 Hz, *H*-5), 6.59 (dd, 1H, J = 2.9, 8.1 Hz, *H*-7), 6.77 (d, 1H, J = 8.1, *H*-8).

Anal. Calcd. for $C_{11}H_{12}ClNO_3$: C, 54.67; H, 5.00; N, 5.80. Found: C, 54.58; H, 4.93; N, 5.74.

6-Methyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic Acid, Ethyl Ester (**1c**).

Purification by column chromatography (eluent: dichloromethane) gave the ester **1c** as a solid (72% yield), mp 46-48° (ethanol); ir (potassium bromide): 3370 (NH), 1730 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform + deuterium oxide): δ 1.18 (t, 3H, J = 7.3 Hz, CH_3), 2.15 (s, 3H, CH_3), 3.44-3.57 (m, 2H, NCH_2), 4.19 (q, 2H, J = 7.3 Hz, OCH_2), 4.67-4.74 (m, 1H, OC*H*), 6.36 (d, 1H, J = 1.5 Hz, *H*-5), 6.46 (dd, 1H, J = 1.5, 8.1 Hz, *H*-7), 6.76 (d, 1H, J = 8.1, *H*-8).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.00; H, 6.90; N, 6.39.

General Procedure for the Preparation of Alcohols **2a-c** by Reduction of Esters **1a-c**.

A solution of the appropriate ester **1** (10 mmoles) in dry tetrahydrofuran (20 ml) was added slowly, under argon atmosphere at 0°, to a suspension of lithium aluminium hydride (30 mmoles) in dry tetrahydrofuran (10 ml). The mixture was stirred at 0° for 0.5 hour then it was allowed to warm to room temperature for 3 hours. The solvent was evaporated and the residue was slowly quenched with cold water at 0°. After filtration, the alcohol was extracted with dichloromethane. The organic layers were washed, dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on a silica gel column.

(3,4-Dihydro-2*H*-1,4-benzoxazine-2-yl)methanol (**2a**).

Purification by column chromatography (eluent: dichloromethane/methanol 99:1) gave alcohol **2a** as an oil (98% yield); ir (film): 3350 (OH and NH) cm^{-1}; ^{1}H nmr (deuteriochloroform + deuterium oxide): δ 3.28 (dd, 1H, J = 7.3, 11.8 Hz, NC*H*), 3.35 (dd, 1H, J = 2.9, 11.8 Hz, NC*H*), 3.77 (dd, 1H, J = 5.9, 11.8 Hz, OC*H*), 3.83 (dd, 1H, J = 4.4, 11.8 Hz, OC*H*), 4.17-4.25 (m, 1H, OC*H*), 6.58 (d, 1H, J = 8.1 Hz, H_{arom}), 6.64 (t, 1H, J = 8.1 Hz, H_{arom}), 6.74 (t, 1H, J = 8.1 Hz, H_{arom}), 6.79 (d, 1H, J = 8.1 Hz, H_{arom}).

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.23; H, 6.81; N, 8.69.

(6-Chloro-3,4-dihydro-2*H*-1,4-benzoxazine-2-yl)methanol (**2b**).

Column chromatography (eluent: dichloromethane/methanol 99:1) led to alcohol **2b** as a powder (82% yield), mp 67-69° (ethanol); ir (potassium bromide): 3330 (OH and NH) cm^{-1}; ^{1}H nmr (deuteriochloroform + deuterium oxide): δ 3.24 (dd, 1H, J = 7.4, 11.8 Hz, NC*H*), 3.32 (dd, 1H, J = 2.9, 11.8 Hz, NC*H*), 3.69-3.83 (m, 2H, CH_2O), 4.10-4.18 (m, 1H, OC*H*), 6.52 (d, 1H, J = 2.2 Hz, *H*-5), 6.53 (dd, 1H, J = 2.2, 8.1 Hz, *H*-7), 6.66 (d, 1H, J = 8.1 Hz, *H*-8).

Anal. Calcd. for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05; N, 7.02. Found: C, 54.37; H, 4.99; N, 6.90.

(6-Methyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-yl)methanol (**2c**).

Purification by column chromatography (eluent: dichloromethane/methanol 99:1) gave **2c** as an oil (96% yield); ir (film): 3380 (NH and OH) cm^{-1}; ^{1}H nmr (deuteriochloroform + deuterium oxide): δ 2.15 (s, 3H, CH_3), 3.24 (dd, 1H, J = 7.3, 11.8 Hz, NC*H*), 3.31 (dd, 1H, J = 2.9, 11.8 Hz, NC*H*), 3.73-3.80 (m, 2H, OCH_2), 4.11-4.20 (m, 1H, OC*H*), 6.36 (s, 1H, *H*-5), 6.41 (d, 1H, J = 8.1 Hz, *H*-7), 6.65 (d, 1H, J = 8.1 Hz, *H*-8).

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.75; H, 7.43; N, 7.99.

General Procedure for the Preparation of Aldehydes **3a-c** by Oxidation of Alcohols **1a-c**.

A solution of oxalyl chloride (19.60 mmoles) in dichloromethane (40 ml) was cooled to -78°, under argon atmosphere. Dimethyl sulfoxide (39.20 mmoles) was then added dropwise while stirring and cooling to maintain the temperature below -60°, and stirring was continued for 5 minutes. A solution of the appropriate alcohol **1** (9.00 mmoles) in dichloromethane (10 ml) was then added and the mixture was stirred for 1 hour at

-78°. Triethylamine (62.30 mmoles) was finally added and the temperature was allowed to warm to -40°. After stirring for 15 minutes, the resulting solution was warmed to room temperature and evaporated *in vacuo*. The residue was purified by flash chromatography.

4*H*-1,4-Benzoxazine-2-carbaldehyde (**3a**).

Flash chromatography on silica gel (eluent: dichloromethane/methanol 99:1) led to the unsaturated aldehyde **3a** as a highly yellow colored solid (92% yield), mp 206-208° (ethanol); ir (potassium bromide): 3210 (NH), 1660 (C=O), 1620 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 5.50 (br s, 1H, N*H*), 6.19-6.28 (m, 2H, H_{arom}), 6.24 (s, 1H, =C*H*), 6.58-6.73 (m, 2H, H_{arom}), 8.52 (s, 1H, C*H*O); ms: (CI/ammonia) m/z 162 (M$^+$).

Anal. Calcd. for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 66.79; H, 4.47; N, 8.83.

6-Chloro-4*H*-1,4-benzoxazine-2-carbaldehyde (**3b**).

Flash chromatography (eluent: dichloromethane/methanol 98:2) led to **3b** as a yellow solid (87% yield), mp 218-220° (ethanol); ir (potassium bromide): 3210 (NH), 1670 (C=O), 1620 (C=C) cm^{-1}; ^{1}H nmr (perdeuteriomethanol + deuterium oxide): δ 6.39 (d, 1H, J = 2.2 Hz, *H*-5), 6.45 (d, 1H, J = 8.8 Hz, H-8), 6.66 (dd, 1H, J = 2.2, 8.8 Hz, *H*-7), 6.72 (s, 1H, =C*H*), 8.36 (s, 1H, C*H*O).

Anal. Calcd. for $C_9H_6ClNO_2$: C, 55.26; H, 3.09; N, 7.16. Found: C, 55.53; H, 3.01; N, 7.02.

6-Methyl-4*H*-1,4-benzoxazine-2-carbaldehyde (**3c**).

Flash chromatography (eluent: dichloromethane/methanol 98:2) gave **3c** as a yellow solid (74% yield), mp 216-218° (ethanol); ir (potassium bromide): 3350 (NH), 1670 (C=O), 1640 (C=C) cm^{-1}; ^{1}H nmr (perdeuteriomethanol + deuterium oxide): δ 2.14 (s, 3H, C*H*$_3$), 6.28 (s, 1H, *H*-5), 6.43 (d, 1H, J = 8.1 Hz, *H*-8), 6.55 (d, 1H, J = 8.1 Hz, *H*-7), 6.76 (s, 1H, =C*H*), 8.34 (s, 1H, C*H*O).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.33; H, 5.24; N, 8.06.

4-Benzoyl-4*H*-1,4-benzoxazine-2-carbaldehyde (**3d**).

Triethylamine (0.20 ml, 1.39 mmoles) and benzoyl chloride (0.15 ml, 1.24 mmoles) were added dropwise, at 0°, to a solution of aldehyde **3a** (0.250 g, 1.55 mmoles) in tetrahydrofuran/water (5 ml/0.5 ml). The solution was stirred at 0° for 0.5 hour, then it was allowed to warm to room temperature for 8 hours. The solvent was evaporated and the residue was quenched with water. After extraction with dichloromethane, organic layers were washed, dried (magnesium sulfate) and evaporated. The crude product was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate 8:2) to give **3d** as an oil (0.131 g, 32% yield); ir (film): 1680, 1670 (C=O), 1640 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 6.80-6.87 (m, 1H, H_{arom}), 6.92-7.06 (m, 2H, H_{arom}), 7.07 (s, 1H, =C*H*), 7.38-7.63 (m, 6H, H_{arom}), 8.92 (s, 1H, C*H*O).

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.73; H, 4.15; N, 5.22.

4-Methyl-4*H*-1,4-benzoxazine-2-carbaldehyde (**3e**).

Potassium carbonate (0.257 g, 1.86 mmoles) and iodomethane (0.15 ml, 2.48 mmoles) were added to a solution of aldehyde **3a** (0.100 g, 0.62 mmole) in dry dimethylformamide (5 ml). The mixture was stirred at 60° for 4 hours. After evaporation of the solvent, hydrolysis and extraction with dichloromethane, organic layers were washed, dried (magnesium sulfate) and evaporated. The crude product was purified by silica gel column chromatography (eluent: dichloromethane) to give **3e** as a yellow solid (0.092 g, 85% yield), mp 140-142° (ethanol) (lit [9] mp 142-144°); ir (potassium bromide): 1670 (C=O), 1640 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.00 (s, 3H, NC*H*$_3$), 6.06 (s, 1H, =C*H*), 6.32-6.38 (m, 1H, H_{arom}), 6.58-6.80 (m, 3H, H_{arom}), 8.45 (s, 1H, C*H*O).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.26; H, 5.20; N, 8.12.

4-Benzyl-4*H*-1,4-benzoxazine-2-carbaldehyde (**3f**).

Potassium carbonate (0.128 g, 0.93 mmole), sodium iodide (catalytic amount) and benzyl chloride (0.05 ml, 0.46 mmole) were added to a solution of aldehyde **3a** (0.050 g, 0.31 mmole) in dry dimethylformamide (10 ml). The solution was stirred at 30° for 18 hours. After evaporation of the solvent and hydrolysis of the solution, the compound was extracted with dichloromethane and purified on silica gel (eluent: dichloromethane) to give **3f** as an oil (0.058 g, 75% yield); ir (film): 1680 (C=O), 1640 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.49 (s, 2H, NC*H*$_2$Ph), 6.16 (s, 1H, =C*H*), 6.28-6.34 (m, 1H, H_{arom}), 6.58-6.76 (m, 3H, H_{arom}), 7.24-7.44 (m, 5H, H_{arom}), 8.52 (s, 1H, C*H*O).

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.81; H, 5.27; N, 5.63.

4-Acetyl-4*H*-1,4-benzoxazine-2-carbaldehyde (**3g**).

Triethylamine (0.35 ml, 2.73 mmoles) and acetyl chloride (0.18 ml, 2.73 mmoles) were added at 0° to a solution of the aldehyde **3a** (0.400 g, 2.48 mmoles) in dichloromethane (10 ml) under argon atmosphere. The mixture was stirred at 0° for 0.5 hour and then hydrolyzed. The crude product, which was extracted with dichloromethane, was purified by silica gel column chromatography (eluent: dichloromethane) to give **3g** as an oil (0.352 g, 70% yield); ir (film): 1700, 1650 (C=O), 1630 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.42 (s, 3H, COC*H*$_3$), 6.96-7.14 (m, 3H, H_{arom}), 7.02 (s, 1H, =C*H*), 7.84 (d, 1H, J = 8.1 Hz, H_{arom}), 9.14 (s, 1H, C*H*O).

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.32; H, 4.52; N, 7.01.

2-Formyl-4*H*-1,4-benzoxazine-4-carboxylic Acid, *t*-Butyl Ester (**3h**).

Triethylamine (0.07 ml, 0.50 mmole), 4-dimethylaminopyridine (0.061 g, 0.50 mmole) and di-*tert*-butyl dicarbonate (0.130 g, 0.60 mmole) were added at 0° to a solution of aldehyde **3a** (0.080 g, 0.50 mmole) in dichloromethane (10 ml). The mixture was stirred for 4 hours at 0°, then for 24 hours at room temperature. After hydrolysis and extraction with dichloromethane, a column chromatography (eluent: dichloromethane) led to the expected compound **3h** as a yellow solid (0.113 g, 87% yield), mp 116-118° (ethanol); ir (potassium bromide): 1720, 1670 (C=O), 1650 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.54 (s, 9H, 3 x C*H*$_3$), 6.82-6.99 (m, 3H, H_{arom}), 7.04 (s, 1H, =C*H*), 7.87 (dd, 1H, J = 1.5, 8.1 Hz, H_{arom}), 8.95 (s, 1H, C*H*O).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.09; H, 5.90; N, 5.43.

4-Benzoyl-4*H*-1,4-benzoxazine-2-carboxylic Acid, Ethyl Ester (**4d**).

A solution of the aldehyde **3d** (0.040 g, 0.15 mmole) in absolute ethanol (5 ml) was stirred with sodium cyanide (0.040 g, 0.80 mmole), acetic acid (0.014 g, 0.24 mmole) and manganese dioxide (0.275 g, 3.14 mmoles) for 24 hours at 20-25°. The solvent was evaporated and the mixture diluted in dichloromethane. After filtration on celite to eliminate the excess of manganese dioxide and hydrolysis, the crude product was extracted with dichloromethane, and purified on silica gel column chromatography (eluent: cyclohexane/ethyl acetate 8:2) to give **4d** as a yellow solid (0.033 g, 72% yield), mp 116-118° (ethanol) (lit [3] mp 117-118°); ir (potassium bromide): 1710, 1680 (C=O), 1650 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.23 (t, 3H, J = 7.3 Hz, CH_3), 4.21 (q, 2H, J = 7.3 Hz, OCH_2), 6.80-7.04 (m, 3H, H_{arom}), 7.20 (s, 1H, =C*H*), 7.36-7.59 (m, 6H, H_{arom}).

Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 70.04; H, 4.98; N, 4.57.

General Procedure for the Preparation of the Aldehydes **7e,f** by Oxidation of Alcohols **1e,f**.

A solution of oxalyl chloride (1.55 mmoles) in dichloromethane (8 ml) was cooled to -60°, under argon atmosphere. Dimethyl sulfoxide (3.10 mmoles) was added dropwise while stirring and cooling to maintain the temperature below -60°, and stirring was continued for 5 minutes. A solution of the appropriate alcohol **1** (1.40 mmoles) in dichloromethane (5 ml) was then added and the mixture was stirred for 1 hour at -60°. Triethylamine (7.05 mmoles) was finally added and the temperature was allowed to warm to room temperature. After hydrolysis (10 ml), the corresponding aldehyde **7** was extracted with dichloromethane and purified on a silica gel column.

4-Methyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carbaldehyde (**7e**).

Column chromatography (eluent: dichloromethane) gave **7e** as an oil (75% yield), ir (film): 1730 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.86 (s, 3H, NCH_3), 3.38 (d, 2H, J = 4.4 Hz, NCH_2), 4.60 (t, 1H, J = 4.4 Hz, OC*H*), 6.54-6.90 (m, 4H, H_{arom}), 9.72 (s, 1H, C*H*O).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.51; H, 6.24; N, 7.85.

4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carbaldehyde (**7f**).

Column chromatography (eluent: dichloromethane) led to **7f** as an oil (77% yield); ir (film): 1730 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.47 (d, 2H, J = 4.4 Hz, NCH_2), 4.39 (d, 1H, J = 15.4 Hz, NC*H*Ph), 4.46 (d, 1H, J = 15.4 Hz, NC*H*Ph), 4.64 (t, 1H, J = 4.4 Hz, OC*H*), 6.71-6.79 (m, 1H, H_{arom}), 6.82-6.89 (m, 1H, H_{arom}), 7.00-7.04 (m, 3H, H_{arom}), 7.23-7.39 (m, 4H, H_{arom}), 9.79 (s, 1H, C*H*O).

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.12; H, 6.04; N, 5.61.

General Procedure for the Wittig Reactions with Aldehydes **3**.

A solution of the appropriate aldehyde **3** (2.87 mmoles) in dry toluene (15 ml) was stirred with carbethoxymethylenetriphenylphosphorane (4.30 mmoles) at 90° for 3 hours. After evaporation of the solvent, the crude product **8** was purified on a silica gel column.

(*E*)-3-(4-Benzyl-4*H*-1,4-benzoxazine-2-yl)acrylic Acid, Ethyl Ester (**8f**).

Flash chromatography (eluent: petroleum ether/dichloromethane 1:1) led to **8f** as an oil (75% yield); ir (film): 1720 (C=O), 1650 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.22 (t, 3H, J = 7.3 Hz, CH_3), 4.13 (q, 2H, J = 7.3 Hz, OCH_2), 4.35 (s, 2H, NCH_2Ph), 5.66 (s, 1H, =C*H*), 5.78 (d, 1H, J = 14.7 Hz, =C*H*), 6.20 (dd, 1H, J = 2.2, 7.3 Hz, H_{arom}), 6.47-6.64 (m, 4H, H_{arom}), 6.70 (d, 1H, J = 14.7 Hz, =C*H*), 7.21-7.32 (m, 4H, H_{arom}).

Anal. Calcd. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.63; H, 5.81; N, 4.25.

(*E*)-4-*t*-Butyloxycarbonyl-4*H*-1,4-benzoxazine-2-acrylic Acid, Ethyl Ester (**8h**).

Column chromatography (eluent: dichloromethane) led to **8h** as an oil (87% yield); ir (film): 1720, 1700 (C=O), 1650 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.25 (t, 3H, J = 7.3 Hz, CH_3), 1.51 (s, 9H, 3 x CH_3), 4.17 (q, 2H, J = 7.3 Hz, OCH_2), 6.12 (d, 1H, J = 15.4 Hz, =C*H*), 6.52 (s, 1H, =C*H*), 6.77 (dd, 1H, J = 2.2, 15.4 Hz, =C*H*), 6.84-6.98 (m, 3H, H_{arom}), 7.84 (d, 1H, J = 8.1 Hz, H_{arom}).

Anal. Calcd. for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.53; H, 6.57; N, 4.30.

General Procedure for the Reduction of Aldehydes **3**.

Sodium borohydride (0.115 mmole) was added to a solution of the corresponding aldehyde **3** (0.231 mmole) in methanol (5 ml) at 0°. After decoloration of the solution (10-15 minutes), the solvent was evaporated, and the residue quenched with water. The crude product **9** was extracted with dichloromethane and purified on a silica gel column.

(4-Acetyl-4*H*-1,4-benzoxazine-2-yl)methanol (**9g**).

Column chromatography (eluent: cyclohexane/ethyl acetate 3:7) gave **9g** as an oil (78% yield); ir (film): 3410 (OH), 1650 (C=O), 1630 (C=C) cm^{-1}; ^{1}H nmr (DMSO-d$_6$ + deuterium oxide): δ 2.14 (s, 3H, COCH_3), 3.88 (s, 2H, OCH_2), 6.36 (s, 1H, =C*H*), 6.82-6.85 (m, 1H, H_{arom}), 6.89-7.07 (m, 3H, H_{arom}); ms: (CI/ammonia) m/z 206 (M$^+$+1).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.12; H, 5.29; N, 6.69.

2-Hydroxymethyl-1,4-benzoxazine-4-carboxylic Acid, *t*-Butyl Ester (**9h**).

Column chromatography (eluent: dichloromethane/methanol 99:1) led to **9h** as an oil (96% yield); ir (film): 3410 (OH), 1690 (C=O), 1650 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform + deuterium oxide): δ 1.48 (s, 9H, 3 x CH_3), 4.02 (s, 2H, OCH_2), 6.21 (s, 1H, =C*H*), 6.70-6.75 (m, 1H, H_{arom}), 6.83-6.93 (m, 2H, H_{arom}), 7.73 (br s, 1H, H_{arom}).

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.08; H, 6.67; N, 5.41.

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