New synthesis of methylfuro[3,4-\textit{b}][1,4]benzoxazine as an intermediate in the preparation of polycyclic compounds

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Abstract
A new multi-step procedure for the preparation of 2,3-disubstituted-1,4-benzoxazines has been developed from readily available precursors. The tricyclic lactone 10 can be considered a key intermediate in the synthesis of polycyclic heterocyclic systems. The new pathway involves a DoM (directed ortho-metalation) reaction of the 1,4-benzoxazine nucleus 5 followed by an intramolecular ring closure of the corresponding hydroxy acid.

Keywords: 2,3-Disubstituted-1,4-benzoxazines, DoM reaction, polycyclic heterocyclic systems

Introduction
The 1,4-benzoxazine structure has attracted considerable interest due to its wide range of biological and therapeutic properties. The 1,4-benzoxazine nucleus is present in a large number of pharmacologically active molecules such as calcium channel antagonists,\textsuperscript{1} central nervous system drugs,\textsuperscript{2} analgesic\textsuperscript{3} and others.\textsuperscript{4} Moreover, the 2,3-disubstituted-1,4-benzoxazines constitute an interesting group, which could find important application as key intermediates in several synthetic pathways directed towards the preparation of bioactive polycyclic heterocyclic systems.\textsuperscript{5} Unfortunately, these applications have not been rigorously studied and only a few synthetic methods are available for their preparation.\textsuperscript{6} In the course of research directed towards the synthesis of new therapeutic agents related to natural products, several polycyclic compounds containing the 1,4-benzodioxine substructure have been prepared,\textsuperscript{7} but the analogous 2,3-disubstituted-1,4-benzoxazine has not yet been described. As part of this research, we investigated the preparation of 2,3-disubstituted-1,4-benzoxazines which could be used as key intermediates in the synthesis of other polycyclic heterocyclic compounds, in particular the bioisostere of 1,4-benzodioxine derivatives.
Results and Discussion

For the synthesis of 2,3-disubstituted-1,4-benzoxazines we required the ester 2, which has been prepared according to the described method\(^8\) by condensation of ethyl 2,3-dibromopropionate with 2-aminophenol in the presence of anhydrous sodium carbonate (Scheme 1).

\[
\begin{align*}
\text{1} & \xrightarrow{i} \text{2} \xrightarrow{ii} \text{3} \\
\text{5} & \xleftarrow{iv} \text{4}
\end{align*}
\]

Scheme 1. (i) BrCH\(_2\)BrCHCOOEt, K\(_2\)CO\(_3\), acetone, reflux, (ii) CI\(_2\)COOEt, K\(_2\)CO\(_3\), CH\(_2\)Cl\(_2\), rt. (iii) (a) NBS, CCl\(_4\), reflux. (b) NaI, Acetone, rt. (iv) 2N KOH / ethanol, rt.

In order to obtain the unsaturated 1,4-benzoxazine\(^9\) analogue of 1,4-benzodioxine\(^10\) it was found necessary to protect the nitrogen under mild conditions, with an electron-withdrawing group, otherwise, the yield of halogenation / dehalogenation decreased. The \(N\)-substituent is important, thus the bromination / debromination of \(N\)-acetyl analogues under various radical conditions reported by Bartsch et al.\(^11\) were unsuccessful. Treatment of the 1,4-benzoxazine ester 2 with ethyl chloroformate in basic media, which upon reaction with the heterocyclic nitrogen smoothly, produced the carbamate 3 in good yield. The bromination of the carbamate 3 using NBS in CCl\(_4\) under the same conditions used by Bartsch (addition of AIBN (2,2’-azo-bis-isobutironitrile) and heated at reflux temperature with a bulb lamp),\(^9\) followed by debromination with NaI in acetone provides, in acceptable yield, the 2-substituted-1,4-benzoxazine 4. The structure of the ester 3 and 4 has been confirmed on the basis of the spectroscopic data and mechanistic considerations.
Hydrolysis of 4 gives regioselectively the carboxylic acid 5. The carbamate group was resistant to attack at C=O, and can be ortho-lithiated without difficulty with LDA in THF at -78 °C. The lithiated compound reacts with acetaldehyde giving 3-alkylated benzoxazine 6 or 7 (Scheme 2).

Carboxylic acids and carbamates, considered directed ortho-metalation groups\textsuperscript{12} (DoMs), favor the deprotonation process. But the great majority of studies have been carried out on the benzene ring, while heterocyclic nuclei have received comparatively less attention. According to the previous related experiences in our laboratory related to 1,4-benzodioxine, here we applied the same synthetic route with modifications.\textsuperscript{13} In this case the carboxylic acid 5 reacts with an excess of LDA (2.2 equiv) at -78 °C to give the hydroxy acid 6 in good yield (73%), following treatment with acetaldehyde, suggesting that a dianion might have been generated under these conditions. It is interesting to note that the reaction using an excess of LDA (4-5 equiv) afforded the hydroxy acid 7 (71%) instead of 6; the acid 5 undergo hydrolysis of the carbamate after alkylation at C-3 in this step (Scheme 2).

Attempts to obtain the lactone 8 by intramolecular ring closure of the hydroxy acid 6 under the usual conditions were unsatisfactory only the treatment with ZnCl\textsubscript{2} gives the corresponding lactone in acceptable yields. It was found that treatment of 6 with p-toluenesulfonic acid\textsuperscript{14,15} in dry toluene at reflux temperature furnished the ketone 9. All the attempts were carried out under an inert atmosphere for avoiding the formation of the keto-acid 9; however, the oxidation could occur during the work up of the reaction. These results are demonstrative of the greater ease of oxidation with an unknown mechanism of this hydroxy acid in the same way that the hydroxy amides reported before.\textsuperscript{13} As an alternative, the hydroxy acid 6 was treated with acid resin Amberlyst 15\textsuperscript{®} in dry CH\textsubscript{2}Cl\textsubscript{2}\textsuperscript{16}, first at room temperature and later at reflux temperature, and only the unaltered starting material was recovered in both attempts. Conditions such as the solvent, the temperature or the stirring process (magnetic or ultrasonic agitation) were considered and modified to arrive at the expected lactone but all the attempts were unsuccessful. However,
dehydration of hydroxy acid 7 to the corresponding lactone was accomplished with ZnCl$_2$ and molecular sieves 4 Å in dry THF$^{17}$ at room temperature (Scheme 3).

Scheme 3. (i) See Table I. (ii) ZnCl$_2$, molecular sieves 4 Å, THF, rt.

This method was found to be the most satisfactory for the preparation of the 2,3-disubstituted-1,4-benzoxazines, and the lactone 10 obtained with a 63 % of yield exhibited analytical data in agreement with the expected results. The ketone 9 and the lactone 10 could serve as building blocks in various syntheses.

Conclusions

We report the formation of 1,4-benzoxazine derivatives which indicate that the new approach enables the efficient synthesis of 2,3-disubstituted-1,4-benzoxazines as the lactone 10, considered a useful intermediate for the preparation of new polycyclic systems. Directed ortho-lithiation of protected benzoxazines allows facile generation of 2,3-disubstituted 1,4-benzoxazines. Moreover, the removal of the N-protecting group in the alkylation process provides the unprotected 1,4-benzoxazines as central scaffolds for designed pharmaceutical compounds.
Experimental Section

General Procedures. Melting points were determined on an MFB 595010 M Gallenkamp melting point apparatus and are uncorrected. The $^1$H and $^{13}$C-NMR spectra were recorded on a Varian Gemini 200 with tetramethylsilane as internal standard and using CDCl$_3$. Chemical shifts were expressed in ppm downfield from internal TMS. IR spectra were recorded on a FTIR Perkin Elmer 1600 spectrophotometer. Mass spectra were recorded with a Hewlett-Packard HP-quadropol 5988A. The chromatography was carried out on SiO$_2$ (silica gel 60, SDS, 60-200 µm). Microanalyses were determined on a Carlo Erba 1106 Analyzer by Serveis Científico-Tècnics, Universitat de Barcelona, and analytical values obtained were within ± 0.3 % of the calculated values. All reagents were of commercial quality or were purified before use and the organic solvents were of analytical grade or purified by standard procedures.

$N$-Ethoxycarbonyl-2,3-dihydro-1,4-benzoxazine-2-ethyl carboxylate (3). A mixture of the ester 2 (1.1 g, 5.3 mmol) and anhydrous K$_2$CO$_3$ (2.19 g, 15.9 mmol) in 30 mL of CH$_2$Cl$_2$ was cooled at 0 ºC and ethyl chloroformate (0.76 mL, 7.8 mmol) was added. The mixture was heated at reflux temperature for 8 h. Then, the cooled suspension was extracted with CH$_2$Cl$_2$ (3 x 20 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated. The carbamate 3 was obtained as brown oil (1.4 g, 93% yield) after purification of the mixture by silica gel column chromatography (hexane / ethyl acetate 60 / 40). IR (KBr) ν (cm$^{-1}$): 2982, 1756, 1690, 1588, 1496, 1261, 1215, 1089. $^1$H-NMR (CDCl$_3$, 200 MHz) δ (ppm): 1.27 (t, J = 7.4 Hz, 3H, CH$_3$); 1.31 (t, J = 7.4 Hz, 3H, CH$_3$); 3.95 (dd, J$_1$ = 3.5 Hz, J$_2$ = 12 Hz, 2H, CH$_2$N); 4.25 (q, J = 7.4 Hz, 4H, CH$_2$O); 4.85 (t, J = 4.4 Hz, 1H, H-2); 7.02 (m, 3H, H-6, H-7, H-8); 7.72 (bs, 1H, H-5). $^{13}$C-NMR (CDCl$_3$, 50.3 MHz) δ (ppm): 14.3 and 14.5 (CH$_3$); 43.2 (CH$_2$, C-3); 61.9 and 62.5 (CH$_2$-O); 73.0 (CH, C-2); 117.0 (CH, C-5); 120.8 (CH, C-8); 123.3 (CH, C-7); 125.0 (CH, C-6); 125.3 (C, C-4a); 144.9 (C, C-8a); 153.5 (C, NCOOEt); 168.3 (C, COOEt). Anal. calcd. for C$_{14}$H$_{17}$NO$_5$: C 60.20 %; H 6.13 %; N 5.01 %. Found: C 60.42 %; H 6.32 %; N 4.99 %.

$N$-Ethoxycarbonyl-(4H)-1,4-benzoxazine-2-ethyl carboxylate (4). To a solution of the carbamate 3 (500 mg, 1.8 mmol) in 20 mL of CCl$_4$, NBS (800 mg, 4.5 mmol) and a catalytic amount of AIBN (2,2’-azo-bis-isobutirionitrile) were added. The mixture was heated at reflux temperature with a bulb lamp (100 w) for 6 h. The crude product was filtered and the solvent was removed. Then, the residue obtained was dissolved in acetone (20 mL), and NaI (670 mg, 4.46 mmol) was added. The mixture was stirred at room temperature for 15 h. After removing the acetone, the solid obtained was treated with Na$_2$S$_2$O$_3$ and extracted with ether (3 x 30 mL), dried over Na$_2$SO$_4$ and the solvent was evaporated. The expected compound 4 (330 mg, 66 % yield) was obtained after purification by silica gel column chromatography of the crude product (hexane / ethyl acetate 95 / 5). Mp (hexane): 73-75 ºC. IR (NaCl) ν (cm$^{-1}$): 2982, 1724, 1588, 1496, 1227, 1035. $^1$H-NMR (CDCl$_3$, 200 MHz) δ (ppm): 1.35 (t, J = 7.2 Hz, 6H, CH$_3$); 4.33 (q, J = 7.2 Hz, 4H, CH$_2$O); 7.00 (m, 3H, H-6, H-7, H-8); 7.37 (s, 1H, H-3); 7.95 (dd, J$_1$ = 7 Hz, J$_2$ = 1.5 Hz, 1H, H-5). $^{13}$C-NMR (CDCl$_3$, 50.3 MHz) δ (ppm): 14.3 and 14.5 (CH$_3$); 61.4 and 63.2 (CH$_2$); 117.0
(CH, C-5); 118.5 (CH, C-3); 120.6 (CH, C-8); 124.1 (CH, C-7); 126.5 (CH, C-6); 131.5 (C, C-2); 146.5 (C, C-4a); 150.5 (C, C-8a); 160.9 (C, CO). Anal. calcd. for C$_{14}$H$_{15}$NO$_{5}$: C 60.64 %; H 5.45 %; N 5.05 %. Found: C 60.40 %; H 5.23 %; N 5.32 %.

N-Ethoxycarbonyl-(4H)-1,4-benzoxazine-2-carboxylic acid (5). To a solution of KOH (800 mg, 1.4 mmol) in 10 mL of water was added a solution of the ester 4 (230 mg, 0.8 mmol) in 10 mL of ethanol. The mixture was stirred at room temperature for 24 h. Then, a solution of 1N HCl was slowly added until an acidic pH. After removing the ethanol, the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 20 mL), dried over Na$_2$SO$_4$ and concentrated. The crude of reaction was purified by silica gel column chromatography (hexane / ethyl acetate 90 / 10) giving the expected carboxylic acid 5 as a brown solid (154 mg, 74 % yield). Mp (hexane): 169-171 ºC. IR (NaCl) ν (cm$^{-1}$): 3470, 2923, 1684, 1495, 1338, 1232, 1185. $^1$H-NMR (CDCl$_3$ + CD$_3$OD, 200 MHz) δ (ppm): 1.39 (t, J = 7 Hz, 3H, CH$_3$); 4.35 (q, J = 7 Hz, 2H, CH$_2$); 7.00 (m, 3H, H-6, H-7, H-8); 7.51 (s, 1H, H-3); 7.97 (dd, J$_1$ = 7.2 Hz, J$_2$ = 1.8 Hz, 1H, H-5).

13C-NMR (CDCl$_3$, 50.3 MHz) δ (ppm): 14.4 (CH$_3$); 63.4 (CH$_2$); 117.0 (CH, C-5); 120.6 (CH, C-3, C-8); 124.3 (CH, C-7); 125.6 (C, C-2); 126.7 (CH, C-6); 146.1 (C, C-4a); 150.3 (C, C-8a); 165.3 (C, COOH, COOEt). Anal. calcd. for C$_{12}$H$_{11}$NO$_5$: C 57.83 %; H 4.45 %; N 5.62 %. Found: C 57.79 %; H 4.29 %; N 5.84 %.

3-(1-Hydroxyethyl)-N-ethoxycarbonyl-1,4-benzoxazine-2-carboxylic acid (6) and 3-(1-hydroxyethyl)-1,4-benzoxazine-2-carboxylic acid (7). A solution of the acid 5 (84 mg, 0.3 mmol) in dry THF (2 mL) under an argon atmosphere was prepared. The mixture was cooled at -78 ºC and a solution of 2M LDA (heptane / THF) was added (0.4 mL, 0.8 mmol) and stirred at -78 ºC for 2.5 h. Following, acetaldehyde (0.075 mL, 1.3 mmol) was added and the suspension obtained was stirred and allowed to warm to room temperature. Then, the mixture was treated with a solution of 1N HCl, extracted with CH$_2$Cl$_2$ (3 x 20 mL), dried over Na$_2$SO$_4$ and the solvent was evaporated. The crude of reaction was purified by silica gel column chromatography (ethyl acetate / methanol 90 / 10). The N-ethoxycarbonyl derivative 6 was obtained as a brown oil (70 mg, 73 % yield). IR (NaCl) ν (cm$^{-1}$): 3448, 2970, 1734, 1501, 1372, 1262, 1149, 1057. $^1$H-NMR (CDCl$_3$ + CD$_3$OD, 200 MHz) δ (ppm): 1.25 (m, 3H, CH$_3$); 1.52 (d, J = 6.4 Hz, 3H, CH$_3$); 4.14 (q, J = 7.4 Hz, 2H, CH$_2$O); 5.51 (q, J = 5.6 Hz, 1H, CHOH); 6.82 (m, 3H, H-6, H-7, H-8); 7.62 (bs, 1H, OH); 7.79 (dd, J$_1$ = 7.2, J$_2$ = 1.6 Hz, 1H, H-5). $^{13}$C-NMR (CDCl$_3$, 50.3 MHz) δ (ppm): 19.4 (CH$_3$); 23.0 (CH$_3$); 61.7 (CH$_3$); 74.3 (CH, CHOH); 116.1 and 116.2 (CH, C-5, C-8); 123.0 (C, C-2); 124.1 (CH, C-7); 127.3 (CH, C-6); 133.0 (C, C-3); 144.0 (C, C-4a); 150.5 (C, C-8a); 161.8 (C, COOEt); 171.5 (C, COOH). Anal. calcd. for C$_{14}$H$_{15}$NO$_6$: C 57.33 %; H 4.45 %; N 5.62 %. Found: C 57.79 %; H 4.29 %; N 5.84 %.

Starting from the acid 5 (89 mg, 0.35 mmol) and a large excess of 2M LDA (heptane-THF) (0.8 mL, 1.61 mmol) and following the same procedure as described before the N-deprotected derivative 7 was obtained as a brown oil, which was used for the next reaction without further purification (55 mg, 71 % yield). Because of its high polarity and instability we were not able to purify compound 7, however it was detected by $^1$H-NMR spectrum of the crude product. $^1$H-NMR (CDCl$_3$ + CD$_3$OD, 50.3 MHz) δ (ppm): 1.57 (d, J = 5.4 Hz, 3H, CH$_3$); 5.52 (q, J = 5.4 Hz,
1H, CH); 6.85 (m, 3H, H-6, H-7, H-8); 7.82 (dd, J₁ = 7.0, J₂ = 1.8 Hz, 1H, H-5). EI-MS (m/z, %): 221 (M⁺, 12); 204 (M⁺-OH, 10); 134 (100); 106 (23); 28 (46).

3-Acetyl-1,4-benzoxazine-2-carboxylic acid (9). To a solution of the hydroxy acid 7 (107 mg, 0.37 mmol) in 45 mL of dry toluene, prepared under an argon atmosphere, p-toluenesulfonic acid and molecular sieves (4 Å) were added. The mixture was stirred at reflux temperature for 22 h. Then, the mixture was washed with a 2 N NaOH solution (3 x 20 mL), the organic layer was dried over Na₂SO₄, filtered off, and the solvent removed. The crude product was purified by silica gel column chromatography (hexane / ethyl acetate 80 / 20) affording 66 mg of the ketone 9 as brown oil (80 % yield). IR (NaCl) ν (cm⁻¹): 3440, 1728, 1670, 1432, 1173. ¹H-NMR (CDCl₃, 200 MHz) δ (ppm): 2.15 (s, 3H, CH₃); 4.25 (bs, 1H, NH); 7.06 (m, 3H, H-6, H-7, H-8); 8.19 (dd, J₁ = 7.1, J₂ = 1.8 Hz, 1H, H-5). ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm): 14.1 (CH₃); 113.7 (C, C-2); 117.2 and 117.4 (CH, C-5, C-8); 122.9 (CH, C-7); 123.4 (C, C-3); 125.4 (CH, C-6); 130.6 (C, C-4a); 145.0 (C, C₈₅); 167.2 (C, COOH); 198.1 (C, CO). Anal. calcd. for C₁₁H₉NO₄: C 60.37 %; H 4.14 %; N 6.39 %. Found: C 60.62 %; H 4.29 %; N 6.12 %.

3-Methyl-1-oxo-(3H)-furo[3,4-b][1,4]benzoxazine (10). To a solution of the hydroxy acid 7 (104 mg, 0.46 mmol) in 20 mL of dry THF, prepared under an argon atmosphere, ZnCl₂ (128 mg, 0.94 mmol) and molecular sieves (4 Å) were added. The mixture was stirred at room temperature for 48 h. Then, the mixture was filtered and the solvent removed. The crude product was purified by silica gel column chromatography (hexane / ethyl acetate 50 / 50) affording 60 mg of the desired lactone 10 as yellow oil (63% yield). IR (NaCl) ν (cm⁻¹): 3514, 2927, 1705, 1610, 1420, 1263. ¹H-NMR (CDCl₃ + CD₃OD, 200 MHz) δ (ppm): 1.60 (d, J = 5.6 Hz, 3H, CH₃); 3.05 (bs, 1H, NH); 5.41 (q, J = 5.6 Hz, 1H, H-3); 6.98 (m, 3H, H-6, H-7, H-8); 7.95 (dd, J₁ = 7.0, J₂ = 1.7 Hz, 1H, H-5). ¹³C NMR (CDCl₃ + CD₃OD, 50.3 MHz) δ (ppm): 19.7 (CH₃); 74.6 (CH, C-3); 116.3 and 116.4 (CH, C-5, C-8); 122.7 (C, C-9a); 124.3 (CH, C-7); 127.2 (CH, C-6); 132.2 (C, C-3a); 143.8 (C, C₅α); 152.2 (C, C₈α); 168.0 (C, CO). EI-MS (m/z, %): 203 (M⁺, 22); 188 (M⁺-CH₃, 34); 108 (12); 106 (100); 76 (67). Anal. calcd. for C₁₁H₉NO₃: C 65.02 %; H 4.46 %; N 6.89 %. Found: C 64.72 %; H 4.26 %; N 6.47 %.

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References and Footnotes