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A Convenient Synthesis of Pyrrolo[2,1-*c*][1,4] benzoxazines

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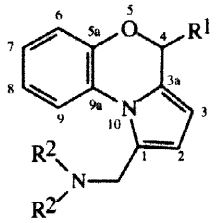
Abstract: The pyrrolo[2,1-*c*][1,4]benzoxazine system was synthesized from 2-fluoroaniline involving an intramolecular nucleophilic displacement of the fluoride atom. The intermediate alcohols **7a** and **10** were treated in basic media under strictly controlled conditions which led to the desired tricyclic structure. The unsubstituted alcohol **10** was more stable than the substituted one. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: polycyclic heterocyclic compounds, benzoxazines, cyclization

1. Introduction

The 2-substituted-1,4-benzoxazine heterocyclic system has served as a rich source for a variety of pharmaceutical agents such as central nervous system depressants [1], analgesics [2], calcium antagonists [3], antibiotic compounds [4] and others [5].

As a part of a program aimed at the discovery of novel polycyclic systems with therapeutic potential, here we detail the synthesis of pyrrolo[2,1-*c*][1,4]benzoxazines (**1-3**) with variation of the substituents in the pyrrole ring and introduction of a substituent at position 4 of the condensed heterocycle.



1. $R^1 = p\text{-}MeOC_6H_4$ $R^2 = Me$
2. $R^1 = p\text{-}MeOC_6H_4$ $R^2, R^2 = CH_2CH_2OCH_2CH_2$
3. $R^1 = H$ $R^2, R^2 = CH_2CH_2OCH_2CH_2$

2. Results

The starting N-(2-fluorophenyl)pyrrole **5** was prepared by condensation of 2-fluoroaniline with 2,5-dimethoxytetrahydrofuran in glacial acetic acid by a modified Paal-Knorr procedure [6][7]. As shown in Scheme 1, the introduction of a formyl group at C1 of the condensed heterocyclic system, in Vilsmeier-Haak conditions, gave the aldehyde **6** in excellent yield. Treatment of the aldehyde **6** with the appropriate lithium derivative (prepared *in situ* from 4-methoxybromobenzene with *n*-butyllithium at -78 °C in dry THF) gave the carbinol **7a** in reasonable yield. In related studies the corresponding alcohol was generated from the appropriate carbonyl compound with Grignard reagents. When a large amount of *n*-butyl lithium was used, a mixture of **7a** and **7b** was isolated.

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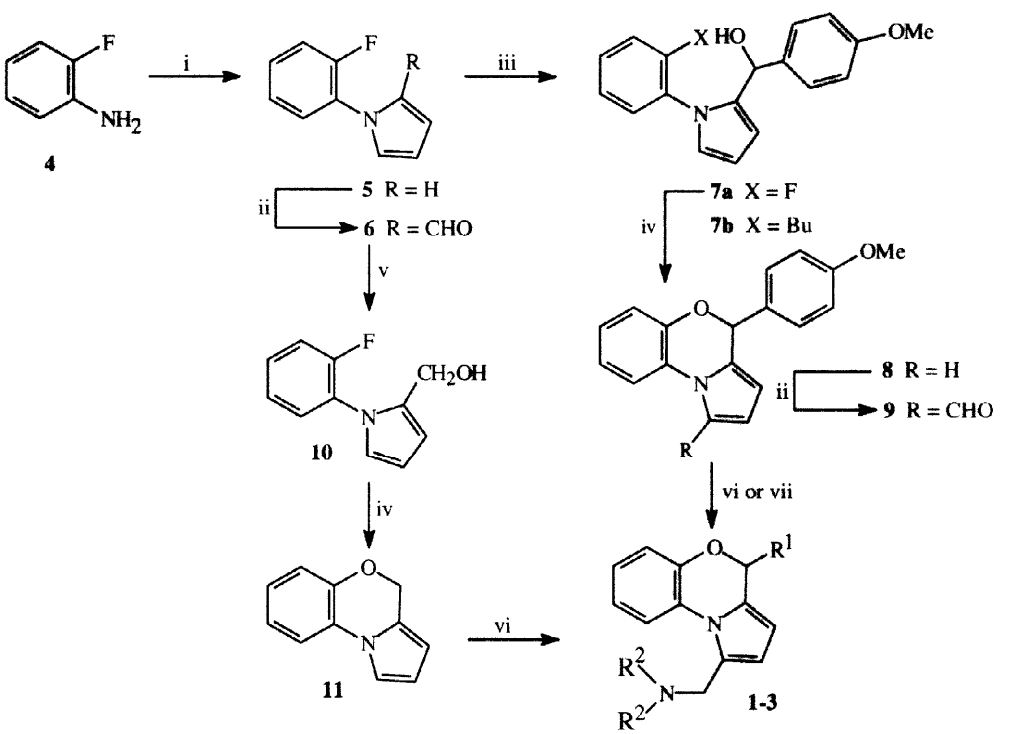
After a conventional work up (extractions with ether) the mixture was separated, with difficulty, by column chromatography. The ^{1}H and ^{13}C NMR spectra of **7a** showed the presence of the fluorine atom and those of **7b** the incorporation of the butyl group and the absence of fluorine. Compound **7b** was analyzed by GC-MS in the EI mode and the molecular peak at *m/z* 335.4 suggested a molecular formula of $C_{22}H_{25}NO_2$, which was consistent with NMR and IR data. The formation of **7b** from **6** can be explained by the nucleophilic attack of the *p*-methoxyphenyllithium on the aldehyde function, followed by the nucleophilic attack of the butyllithium excess on the aromatic ring, with fluorine displacement. These results suggest a broad spectrum of utilities in synthesis for alkylating aryl systems from fluoroaryl derivatives with the corresponding alkyl lithium. It is noteworthy that the alcohol **7a** was an unstable intermediate, which was immediately converted into the cyclic ether by an efficient intramolecular fluorine displacement reaction [8][9].



Reagents:
i. 2,5-dimethoxytetrahydrofuran / AcOH **ii.** DMF / $POCl_3$ **iii.** *p*-$MeOC_6H_4Br$ / BuLi / THF / -78 °C **iv.** NaH / DMF **v.** $NaBH_4$ / MeOH **vi.** H_2CO / HNR^2R^2 / AcOH **vii.** 1. Me_2NH 2. $NaBH_4$

Scheme 1

The nucleophilic alkoxide was generated *in situ* with sodium hydride in dimethylformamide or dimethoxyethane. Several attempts were made to optimize this cyclization, but changing the base or using other solvents gave similar results. The low yields found in this cyclization reaction (26-30%) could be attributed to an oxidation process from alcohol **7a** to the corresponding ketone. This ketone was only stable at low temperature but undergone the *p*-metoxibenzoic acid at room temperature. Similarly, the analogue **11** was obtained from **6** by reduction of the aldehyde function with $NaBH_4$ followed by intramolecular cyclization of the alcohol obtained **10**, as described above. Unfortunately, extensive decomposition of alcohol **7a** was observed; the primary alcohol was more stable than the secondary, under both acidic and

basic conditions. This lack of stability was confirmed in the cyclization step (**7a** to **8** 26% and **10** to **11** 78%). We hypothesize that the doubly benzylic alcohol **7a** is easily oxidized, whereas the primary alcohol **10** was more stable. The benzoxazine **8** was alkylated, either by treatment with formaldehyde and the respective amine in the Mannich reaction conditions, or by formylation (compound **9**) and subsequent treatment with the appropriate amine, followed by reduction of the intermediate imine with $NaBH_4$. In all cases, the corresponding amines **1** and **2** were obtained in moderate yield. In the same way, compound **11**, a tricyclic non substituted system, was treated in the Mannich reaction conditions, providing amine **3** in good yield. Compounds **5** and **6** are previously described as reaction intermediates [10].

3. Experimental

Melting points were determined in capillary tubes on a MFB-595010M Gallenkamp melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian-200 instrument at 200 (^{1}H) or 50.3 (^{13}C) MHz or Varian XL-300 at 300 (^{1}H) or 75.5 (^{13}C) MHz spectrometer, in $CDCl_3$ using tetramethylsilane as an internal standard. The assignments of ^{13}C NMR signals were made with the aid of DEPT sequence. Standard abbreviations are used. COSY ^{1}H / ^{1}H experiments were performed using standart procedures and COSY ^{1}H / ^{13}C experiments were performed using HMQC sequence with an indirect detection probe. Chemical shifts are in δ (ppm) and coupling constants (J) are measured in Hz. ^{13}C NMR assignments marked *, #, ⊕, • are interchangeable. IR spectra were recorded on a Perkin Elmer 1600 series FTIR; only noteworthy IR absortions are listed (cm^{-1}). Elemental microanalyses were performed by Serveis Científico-Tècnics, Universitat de Barcelona; results obtained for C, H and N were within ± 0.4 % of the values calculated for the formula shown. Merck 60 (40-60 microns) and Merck 60 F_{254} silica gel were used for column chromatography and thin layer chromatography respectively. The organic extracts were dried over Na_2SO_4. Organic solvents were purified by standard procedures. All reagents were of commercial quality or were purified before use.

General procedure of formylation

Dimethylformamide freshly distilled (2.9 mL, 34 mmol) was cooled at 0 °C and $POCl_3$ (3.2 mL, 34 mmol) was added dropwise. The solution obtained was stirred at room temperature for 15 min. Following, a solution of the corresponding pyrrole (5 g, 31 mmol) in distilled DMF (15 mL) was added. The reaction mixture was stirred at 50 °C for 3 h and basified with a saturated solution of Na_2CO_3. The precipitate was filtered, washed with water and dried under reduced pressure (P_2O_5). The crude product obtained was purified by silica gel column chromatography (hexane / ethyl acetate in the ratio 70:30).

General method of cyclization

The corresponding hydroxy derivative (1 mmol) was slowly added to a suspension of NaH (2 mmol; 60% dispersion in oil) in distilled DMF (10 mL). The reaction mixture was stirred at 60 °C for 12 h and hydrolyzed with small amounts of water. The excess of DMF was removed and the residue obtained was extracted with ether (3 x 25 mL). The organic layers were dried and filtered. After removing the solvent under reduced pressure the crude product was purified by silica gel column chromatography (hexane / ethyl acetate in the ratio 70:30).

General procedure of Mannich reaction [11]

The solution obtained by mixing the corresponding amine (10 mmol), formaldehyde (10 mmol) and acetic glacial acid (2 mL) was cooled at 0 °C and stirred for 1 h. The corresponding

pyrrole (1 mmol) and acetic glacial acid (1 mL) were then added and the mixture was stirred at room temperature for 5 h. The suspension was poured into ice and small amounts of K_2CO_3 were added until basic pH was obtained. The suspension was extracted with ether (3 x 10 mL), dried, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane / ethyl acetate in the ratio 70:30).

***N*-(2-Fluorophenyl)pyrrole (5)**

2-Fluoroaniline (5 g, 45 mmol) and 2,5-dimethoxytetrahydrofuran (6 g, 45 mmol) were dissolved in acetic glacial acid (25 mL) and stirred at reflux temperature for 1 h. The excess of acetic acid was removed under reduced pressure and the crude product obtained was purified by silica gel column chromatography (hexane / ethyl acetate in the ratio 70:30). Compound **5** (85% yield) was obtained as a colorless oil. ^{1}H NMR (300 MHz) δ: 6.35 (t, J = 2, 2H, H-3, H-4); 7.03 (t, J = 2, H-2, H-5); 7.20 (m, 3H, H-3', H-4', H-5'); 7.40 (m, 1H, H-6'). ^{13}C NMR (75.5 MHz) δ: 109.9 (CH, C3, C4); 117.8 (CH, J = 21, C3'); 121.2 (CH, C2, C5); 124.5 (CH, J = 8, C6'); 124.7 (CH, C5'); 126.8 (CH, J = 8, C4'); 128.7 (C, J = 10, C1'); 154.7 (C, J = 249, C2').

***N*-(2-Fluorophenyl)pyrrole-2-carbaldehyde (6)**

The aldehyde **6** was obtained as a white solid (5 g, 85% yield) starting from pyrrole **5** and following the general procedure of formylation. Mp.118-119 °C (recrystallized from a mixture of hexane / ethyl acetate in the ratio 1:1). IR ($CHCl_3$): 1665, 1206, 1100. ^{1}H NMR (300 MHz) δ: 6.45 (dd, J = 4, J = 2.6, 1H, H-4); 7.02 (dd, J = 2.6, J = 1.6, 1H, H-3); 7.14 (dd, J = 4, J = 1.6, 1H, H-5); 7.27 (m, 2H, H-3', H-6'); 7.38 (m, 2H, H-4', H-5'). ^{13}C NMR (75.5 MHz) δ: 110.9 (CH, C4); 116.3 (CH, J = 20, C3'); 122.8 (CH, C3); 124.2 (CH, J = 8, C6'); 127.2 (C, C2); 128.2 (CH, C5'); 129.9 (CH, J = 8, C4'); 131.2 (CH, C5); 132.7 (C, J = 10, C1'); 156.9 (C, J = 251, C2'); 178.5 (CH, CHO).

***N*-(2-Fluorophenyl)-2-[(*p*-methoxyphenyl)hydroxymethyl]pyrrole (7a)**

A solution of 4-bromomethoxybenzene (591 mg, 3.16 mmol) in anhydrous THF (3 mL) was prepared under an argon atmosphere and cooled at -78 °C. Next, *n*-BuLi (1.6 M in hexane, 2 mL, 3.16 mmol) was added and the mixture reaction was stirred at -78 °C for 1 h. A solution of the aldehyde **6** (300 mg, 1.58 mmol) in 3 mL of dry THF was added. After warming to room temperature the mixture was hydrolyzed with a saturated solution of NH_4Cl and extracted with ether (3 x 10 mL). The organic layers were dried, filtered and concentrated. The hydroxy derivative **7a** was obtained as an unstable, orange oil (759 mg, 79% yield). ^{1}H NMR (300 MHz) δ: 3.78 (s, 3H, CH_3O); 5.59 (s, 1H, CH-OH); 6.10 (dd, J = 4, J = 2, 1H, H-4); 6.24 (t, J = 4, 1H, H-3); 6.72 (dd, J = 2, J = 1.3, 1H, H-5); 6.79 (m, 2H, H-3", H-5"); 7.16 (m, 2H, H-2", H-6"); 7.30 (m, 4H, H-3', H-4', H-5', H-6'). ^{13}C NMR (75.5 MHz) δ: 55.2 (CH_3, CH_3O); 68.5 (CH, CH-OH); 108.4* (CH, C3); 108.7* (CH, C4); 113.4 (CH, C3", C5"); 116.4 (CH, J = 20, C3'); 123.8 (CH, C5); 124.2 (CH, J = 8, C6'); 127.5 (CH, C2", C6"); 128.3 (C, J = 8, C1'); 129.7 (CH, C4', C5'); 134.4 (C, C1"); 136.6 (C, C2); 157.2 (C, J = 250, C2'); 158.8 (C, C4"). Compound **7b** was obtained as a colorless oil (108 mg; 11% yield). IR ($CHCl_3$): 3500, 1550, 1247, 1199. EIMS m / z 335.4. ^{1}H NMR (300 MHz) δ: 0.96 (q, J = 8, 3H, CH_3); 1.48 (m, 2H, CH_2); 1.70 (m, 2H, CH_2); 2.58 (t, J = 8, 2H, CH_2); 3.81 (s, 3H, CH_3O); 5.09 (ba, 1H, OH); 5.31 (s, 1H, CH); 6.04 (m, 1H, H-4); 6.33 (m, 1H, H-3); 6.82 (m, 1H, H-5); 6.83 (d, J = 8.8, 2H, H-3", H-5"); 7.09 (m, 4H, Ar); 7.13 (d, J = 8.8, 2H, H-2", H-6"). ^{13}C NMR (75.5 MHz) δ: 13.9 (CH_3); 22.6 (CH_2); 27.3 (CH_2); 34.7 (CH_2); 55.2 (CH_3, CH_3O); 73.9 (CH, CHOH); 103.9 (CH, C3); 110.4 (CH, C4); 113.6 (CH, C3", C5"); 114.6* (CH, C3'); 114.8* (CH, C4'); 117.9 (CH, C5');

122.9 (CH, C5); 124.8 (CH, C6'); 127.1 (C, C1'); 129.2 (CH, C2", C6"); 135.1 (C, C1", C2); 146.1 (C, C2'); 157.2 (C, C4").

4-(*p*-Methoxyphenyl)-4H-pyrrolo[2,1-*c*][1,4]-benzoxazine (8)

Compound **8** was obtained as a yellow oil (210 mg, 26% yield) from the carbinol **7a** following the general procedure of cyclization. IR ($CHCl_3$): 1500, 1240, 1180. ^1H NMR (300 MHz) δ: 3.81 (s, 3H, CH_3O); 5.71 (m, 1H, H-2); 6.02 (s, 1H, H-4); 6.30 (t, J = 3, 1H, H-3); 6.92 (d, J = 8.8, 2H, H-3', H-5'); 7.04 (m, 4H, H-6, H-7, H-8, H-9); 7.20 (m, 1H, H-1); 7.42 (d, J = 8.8, 2H, H-2', H-6'). ^{13}C NMR (75.5 MHz) δ: 55.3 (CH_3, CH_3O); 76.2 (CH, C4); 106.6* (CH, C2); 110.5* (CH, C3); 114.5 (CH, C3', C5'); 115.3 (CH, C9); 118.3 (CH, C6); 122.2 and 124.9 (CH, C1, C7, C8); 126.7# (C, C3a); 127.8 # (C, C1'); 130.0 (C, C9a); 146.0 (C, C5a); 160.1 (C, C4').

1-Formyl-4-(*p*-methoxyphenyl)-4H-pyrrolo[2,1-*c*][1,4]-benzoxazine (9)

Compound **9** (78% yield) was obtained starting from compound **8** and following the general procedure of formylation. IR ($CHCl_3$): 1670, 1200, 1137. ^1H NMR (200 MHz) δ: 3.84 (s, 3H, CH_3O); 5.90 (m, 2H, H-3, H-4); 6.95 (d, J = 9, 2H, H-3', H-5'); 7.15 (m, 4H, H-2, H-6, H-7, H-8); 7.39 (d, J = 9, 2H, H-2', H-6'); 8.20 (m, 1H, H-9); 9.71 (s, 1H, CHO). ^{13}C NMR (50.3 MHz) δ: 55.2 (CH_3, CH_3O); 76.9 (CH, C4); 108.1 (CH, C3); 114.1 (CH, C3', C5'); 118.1* (CH, C6); 120.9* (CH, C9); 122.6# (CH, C7); 126.8# (CH, C8); 125.5 (C, C1); 127.8 (CH, C2); 128.3 (C, C3a); 129.5 (CH, C2', C6'); 130.5 (C, C1'); 140.0 (C, C5a); 147.0 (C, C9a); 160.5 (C, C-OCH_3); 178.1 (CH, CHO).

***N*-(2-Fluorophenyl)-2-hydroxymethylpyrrole (10)**

$NaBH_4$ (100 mg, 2.64 mmol) was added to a solution of pyrrole aldehyde **6** (250 mg, 1.32 mmol) in methanol. The reaction mixture was stirred at room temperature for 30 min. The excess of hydride was hydrolyzed with water, then extracted with ether (3 x 20 mL). Compound **10** was obtained as a yellow oil (96 mg, 100% yield). IR ($CHCl_3$): 3500, 1218, 1110. ^1H NMR (200 MHz) δ: 4.44 (s, 2H, CH_2OH); 6.28 (m, 2H, H, H-3, H-4); 6.78 (m, 1H, H-5); 7.30 (m, 4H, H-3', H-4', H-5', H-6'). ^{13}C NMR (50.3 MHz) δ: 56.3 (CH_2, CH_2OH); 108.6* (CH, C3) 109.9* (CH, C4); 116.5 (CH, J = 20, C3'); 124.0 (CH, C5); 124.4 (CH, J = 8, C1', C6'); 129.2# (CH, C4') 129.4# (CH, C5'; 157.9 (C, J = 267, C2'); 159.0 (C, C2).

4H-Pyrrolo[2,1-*c*][1,4]benzoxazine (11)

The corresponding tricyclic compound was obtained as a yellow oil (70 mg, 78% yield) starting from compound **10** (100 mg, 0.52 mmol) and *via* the general procedure of cyclization. ^1H NMR (200 MHz) δ: 5.12 (s, 2H, CH_2O); 6.05 (m, 1H, H-2); 6.32 (m, 1H, H-3); 7.03 (m, 3H, H-6, H-7, H-8); 7.15 (m, 1H, H-1); 7.35 (m, 1H, H-9). ^{13}C NMR (50.3 MHz) δ: 63.7 (CH_2, CH_2O); 104.4* (CH, C2); 110.4* (CH, C3); 114.6 (CH, C9); 117.8 (CH, C6); 122.2 and 124.8 (CH, C1, C7, C8); 124.2 (C, C3a); 127.0 (C, C9a); 146.0 (C, C5a).

1-Dimethylaminomethyl-4-(*p*-methoxyphenyl)-4H-pyrrolo[2,1-*c*][1,4]-benzoxazine (1)

The amine **1** (170 mg, 71% yield) was obtained from dimethylamine (40% solution in water, 0.9 ml, 7.2 mmol); formaldehyde (37% solution in water, 0.6 mL, 7.2 mmol) and compound **8** (200 mg, 0.72 mmol) following the general procedure of Mannich reaction (71% yield). ^1H NMR (300 MHz) δ: 2.34 (s, 6H, CH_3N); 3.21 (d, J = 14, 1H, CH_2N); 3.61 (d, J = 14, 1H, CH_2N); 3.82 (s, 3H, CH_3O); 5.57* (d, J = 4, 1H, H-2); 5.87 (s, 1H, H-4); 6.14* (d, 1H, J = 4, H-3); 6.92 (d, J = 9, 2H, H-3', H-5'); 7.07 (m, 3H, H-6, H-7, H-8); 7.42 (d, J = 9, 2H, H-2', H-6'). 8.24 (m, 1H, H-9). ^{13}C NMR (75.5 MHz) δ: 44.8 (CH_3, CH_3N); 55.3 (CH_3, CH_3O); 56.1

(CH_2, CH_2N); 76.5 (CH, C4); 105.0* (CH, C2); 112.8* (CH, C3); 113.8 (CH, C3', C5'); 117.9# (CH, C6); 119.3# (CH, C9); 122.5⊕ (CH, C7); 124.9⊕ (CH, C8); 127.8• (C, C1); 129.1• (C, C3a); 129.6 (CH, C2', C6'); 130.0 (C, C9a); 146.0 (C, C5a); 160.1 (C, C4'). Anal. Calcd. for $C_{21}H_{22}N_2O_2$: C, 75.42% H, 6.63% N, 8.37%. Found: C, 75.39% H, 6.60% N, 8.40%.

1-Morpholinomethyl-4-(*p*-methoxyphenyl)-4H-pyrrolo[2,1-*c*][1,4]-benzoxazine (2)

The amine **2** (30 mg, 54% yield) was obtained from morpholine (0.037 mL, 1.48 mmol); formaldehyde (37% solution in water, 0.11 mL, 1.48 mmol) and compound **8** (41 mg, 0.148 mmol) following the general procedure of Mannich reaction. ^{1}H NMR (300 MHz) δ: 2.62 (m, 4H, CH_2N); 3.70 (m, 4H, CH_2O); 3.84 (s, 3H, CH_3O); 5.58* (m, 1H, H-2); 5.87 (s, 1H, H-4); 6.19* (m, 1H, H-3); 6.93 (d, J = 9, 2H, H-3', H-5'); 6.97 (m, 3H, H-6, H-7, H-8); 7.43 (d, J = 9, 2H, H-2', H-6'); 8.24 (m, 1H, H-9). ^{13}C NMR (75.5 MHz) δ: 52.8 (CH_2, CH_2N); 55.1 (CH_2, CH_2N); 55.3 (CH_3, CH_3O); 66.9 (CH_2, CH_2O); 76.5 (CH, C4); 105.1* (CH, C2); 113.6* (CH, C3); 113.8 (CH, C3', C5'); 118.0 # (CH, C6); 119.2# (CH, C9); 122.3⊕ (CH, C7); 125.1⊕ (CH, C8); 127.7 and 130.8 (C, C1', C3a, C1); 129.5 (CH, C2', C6'); 130.8 (C, C5a); 147.6 (C, C9a); 160.0 (C, C4'). Anal. Calcd. for $C_{23}H_{24}N_2O_3$: C, 73.37% H, 6.43% N, 7.44%. Found: C, 73.22% H, 6.73% N, 7.40%.

1-Morpholinomethyl-4H-pyrrolo[2,1-*c*][1,4]-benzoxazine (3)

Compound **3** was obtained starting from morpholine (0.3 mL, 4 mmol), formaldehyde (37% solution in water, 0.3 mL, 4 mmol), and compound **11** (70 mg, 0.4 mmol) *via* the general procedure of Mannich reaction. ^{1}H NMR (200 MHz) δ: 2.56 (t, J = 4, CH_2N); 3.49 (s, 2H, CH_2N); 3.75 (t, J = 4, 4H, CH_2); 5.02 (s, 2H, CH_2O); 5.98* (d, J = 3, 1H, H-2); 6.20* (d, J = 3, H-2; 6.20* (d, J = 3, 1H, H-3); 7.07 (m, 3H, H-6, H-7, H-8); 8.30 (m, 1H, H-9). ^{13}C NMR (50.3 MHz) δ: 52.9 (CH_2, C2', C6'); 55.0 (CH_2, CH_2Ar); 64.2 (CH_2, C4); 66.9 (CH_2, C3', C5'); 103.3 (CH, C2); 113.5 (CH, C3); 117.7* (CH, C9); 119.4* (CH, C6); 122.4# (CH,C8); 125.1# (CH, C7); 126.1 (C, C1); 127.1 (C, C3a); 141.9 (C, C5a); 147.6 (C, C9a). Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.08%, H 6.72% N, 10.37%. Found: C, 71.08% H, 6.39% N, 10.27%.

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