Synthesis of 2-[2-hydroxy-2-phenyl-2*H*-1,4-benzoxazin-3(4*H*)-ylidene]-1-phenyl-1-ethanones

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The reaction of 2-aminophenols with dibenzoylacetylene leads to 2-[2-hydroxy-2-phenyl-2*H*-1,4-benzoxazin-3(4*H*)-ylidene]-1-phenyl-1-ethanones in 78–90% yields.

Keywords: 1,4-benzoxazines, 2-aminophenols, dibenzoylacetylene

1,4-Benzoxazines have attracted considerable interest because of their potential therapeutic properties as intracellular calcium antagonists, serotonin receptors antagonists, and antibacterial agents.[1,2] The 1,4-benzoxazine skeleton has usually been constructed through cyclocondensation of *o*-aminophenols with suitable dibromoalkanes[3] or a-halogeno-acyl bromides followed by carbonyl reduction with diborane[4] or through alkylation of *o*-nitrophenols[5] followed by reductive cyclisation. However, the scale-up of these procedures is hampered by the use of toxic and lachrymatory bromo compounds and dimethylformamide as a solvent, which is difficult to remove efficiently. The reaction between dialkyl acetylenedicarboxylates and 2-aminophenols has been reported to produce 1,4-benzoxazin-2-ones.[6-8]

Results and discussion

As part of our study on the development of new routes to heterocyclic systems,[9-15] we now report a simple one-pot synthesis of 2-[2-hydroxy-2-phenyl-2*H*-1,4-benzoxazin-3(4*H*)-ylidene]-1-phenyl-1-ethanones **1** (Scheme 1).

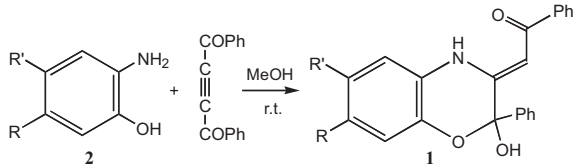
Thus, the reaction of dibenzoylacetylene (DBA) with 2-aminophenols (**2**) leads to **1** in good yields. ^{1}H and ^{13}C NMR spectra of the crude reaction mixture clearly indicated the formation of 1,4-benzoxazines **1**. No product other than **1** could be detected by NMR spectroscopy. The structures of compounds **1a–1e** were deduced from their elemental analyses and their IR, ^{1}H NMR and ^{13}C NMR spectroscopic data. For example, in the ^{1}H NMR spectrum of **1a** exhibits three singlets at δ 3.77, 5.78 and 12.91 ppm, for the OH, vinylic, and NH protons. The protons of the aromatic moieties appear as a multiplet. The ^{13}C NMR spectrum of **1a** showed 18 distinct resonances in agreement with the proposed structure.

A possible explanation for the formation of **1** is proposed in Scheme 2, although there is no experimental verification of this. The first step may involve addition of the amino group of **2** to the acetylenic compound and formation[16] of the 1 : 1 adduct **3**. Then, the carbonyl group of the closer benzoyl moiety is attacked by the oxygen atom of the hydroxyl group to produce compound **1** (Scheme 2).

These 2-[2-hydroxy-2-phenyl-2*H*-1,4-benzoxazin-3(4*H*)-ylidene]-1-phenyl-1-ethanones (**1**) may be considered as potentially useful synthetic intermediates because they possess atoms in different oxidation states. The present method possesses the advantages that the reactions can be performed under neutral conditions and the starting materials and reagents can be mixed without any modifications.

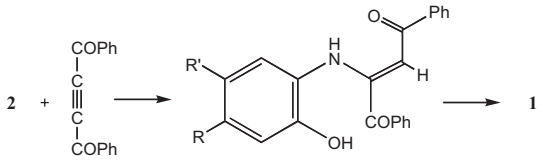
Experimental

2-Aminophenols **2a–2e**, were obtained from Fluka and were used without further purification. Dibenzoylacetylene (DBA) was prepared according to the literature procedure.[17] Melting points were measured using an Electrothermal-9100 apparatus. IR spectra were taken with a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were



1,2	R	R'	yield of **1** (%)
a	H	H	90
b	Me	H	86
c	H	Me	78
d	Cl	H	80
e	H	Cl	84

Scheme 1



Scheme 2

recorded with a Bruker DRX-500 Avance instrument, in $CDCl_3$, at 500.1 and 125.7 MHz, respectively; chemical shifts (δ) are reported in ppm, coupling constants (J) in Hz. For EI-MS (70 eV) a Finnigan-MAT-8430 mass spectrometer was used. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyser.

Preparation of the 1,4-benzoxazinols 1: general procedure

To a stirred solution of the 2-aminophenol (2 mmol) in methanol (10 ml), was added dropwise a mixture of DBA (0.46 g, 2 mmol) in methanol, and the reaction mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure and the residual solid was recrystallised from EtOAc to afford the adducts 1.

2-[2-Hydroxy-2-phenyl-2H-1,4-benzoxazin-3(4H)-ylidene]-1-phenyl-1-ethanone (**1a**): Yellow powder (0.30 g, 90%), m.p. 182–184°C. IR (KBr): 3235 (OH), 3100 (NH). 1592 (C=O). 1570, 1200, 754 cm^{-1}. ^{1}H NMR: δ 3.77 (1 H, s, OH), 5.78 (1 H, s, CH), 6.95–7.04 (4 H, m, 4 CH), 7.37 (2 H, *t*, ^3J = 7.5, 2 CH), 7.44–7.45 (4 H, m, 4 CH), 7.72 (4 H, d, ^3J = 7.0, 4 CH), 12.91 (1 H, s, NH). ^{13}C NMR: δ 91.2 (CH), 96.8 (C-OH), 116.3 (CH), 117.9 (CH), 123.2 (CH), 124.0 (CH), 126.0 (C), 126.7 (2 CH), 127.2 (2 CH), 128.4 (2 CH), 128.5 (2 CH), 129.7 (CH), 131.7 (CH), 138.5 (C), 139.1 (C), 142.6(C), 153.2 (C), 191.4 (C=O). EI MS: *m/z* 343 (M$^+$, 5), 239 (10), 238 (68), 220 (30), 160 (10), 105 (100), 77 (90), 65 (10), 39 (8). Anal. Calcd for $C_{22}H_{17}NO_3$ (343.39): C, 79.95; H, 4.99; N, 4.08. Found: C, 79.81; H, 4.87; N, 4.13%.

2-[2-Hydroxy-7-methyl-2-phenyl-2H-1,4-benzoxazin-3(4H)-ylidene]-1-phenyl-1-ethanone (**1b**): Yellow powder, (0.31 g, 89%, m.p. 195–197°C. IR (KBr): 3200 (OH), 3115 (NH), 1594 (C=O), 1569, 1275, 746 cm^{-1}. ^{1}H NMR: δ 2.23 (3 H, s, Me), 4.80 (1 H, s, OH), 5.71 (1 H, s, CH), 6.65 (1 H, d, ^3J = 7.2, CH) 6.75 (1 H, d, ^3J = 7.5, CH), 6.79 (1 H, s, CH), 7.30 (2 H, *t*, ^3J = 6.4, 2 CH), 7.41 (4 H, m, 4 CH), 7.63 (2 H, d, ^3J = 7.1, 2 CH), 7.69–7.70 (2 H, m, 2 CH), 12.91 (1 H, s, NH). ^{13}C NMR: δ 21.0 (CH_3), 90.8 (CH), 96.8 (C–OH), 116.1 (CH), 118.4 (CH), 123.3 (C), 123.6 (CH), 126.8 (2 CH), 127.2 (2 CH), 128.3 (2 CH), 128.4 (2 CH), 129.6 (CH), 131.6 (CH), 134.3 (CH), 138.7 (C), 139.0 (C), 142.6 (C), 153.8 (C), 191.0 (C=O). EI MS: *m/z* 357 (M$^+$, 5), 253 (12), 252 (60), 118 (6), 105 (100), 77 (80). Anal. Calcd for $C_{23}H_{19}NO_3$ (357.41): C, 77.29; H, 5.36; N, 3.92. Found: C, 77.11; H, 5.27; N, 4.03%.

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2-[2-Hydroxy-6-methyl-2-phenyl-2H-1,4-benzoxazin-3(4H)-ylidene]-1-phenyl-1-ethanone (**1c**): Yellow powder (0.27 g, 78%), m.p. 166–168°C. IR (KBr): 3215 (OH), 3055 (NH), 1594 (C=O), 1570, 1265, 751 cm^{-1}. ^1H NMR: δ 2.20 (3 H, s, Me), 4.73 (1 H, s, OH), 5.73 (1 H, s, CH), 6.68 (1 H, s, CH), 6.71 (1 H, d, ^3J = 8.4, CH), 6.87 (1 H, d, ^3J = 7.5, CH), 7.32 (2 H, *t*, ^3J = 6.5, 2 CH), 7.42 (4 H, m, 4 CH), 7.64 (2 H, d, ^3J = 6.7, 2 CH), 7.69–7.70 (2 H, m, 2 CH), 12.81 (1 H, s, NH). ^{13}C NMR: δ 20.8 (CH_3), 91.2 (CH), 96.8 (C–OH), 116.7 (CH), 117.5 (CH), 124.6 (CH), 125.5 (CH), 126.8 (2 CH), 127.3 (2 CH), 128.3 (2 CH), 128.4 (2 CH), 129.6 (CH), 131.7 (CH), 132.8 (CH), 138.7 (C), 139.0 (C), 140.5 (C), 153.9 (C), 191.3 (C=O). EI MS: *m/z* 357 (M^+, 9), 253 (23), 252 (65), 118 (31), 105 (100), 77 (84). Anal. Calcd for $C_{23}H_{19}NO_3$ (357.41): C, 77.29; H, 5.36; N, 3.92. Found: C, 77.45; H, 5.49; N, 4.08%.

2-[7-Chloro-2-hydroxy-2-phenyl-2H-1,4-benzoxazin-3(4H)-ylidene]-1-phenyl-1-ethanone (**1d**): Yellow powder (0.30 g, 80%), m.p. 184–187°C. IR (KBr): 3315 (OH), 3058 (NH), 1602 (C=O), 1577, 1268, 758 cm^{-1}. ^1H NMR: δ 4.89 (1 H, s, OH), 5.77 (1 H, s, CH), 6.74 (1 H, d, ^3J = 7.5, CH), 6.81 (1 H, d, ^3J = 7.5, CH), 6.95 (1 H, s, CH), 7.31 (2 H, *t*, ^3J = 6.5, 2 CH), 7.42–7.43 (4 H, m, 4 CH), 7.62 (2 H, d, ^3J = 6.7, 2 CH), 7.66–7.67 (2 H, m, 2 CH), 12.84 (1 H, s, NH). ^{13}C NMR: δ 91.6 (CH). 97.1 (C-OH), 116.9 (CH), 118.3 (CH), 123.2 (CH), 124.7 (C), 126.7 (2 CH), 127.3 (2 CH), 128.4 (2 CH), 128.5 (C), 128.6 (2 CH), 129.9 (CH), 132.0 (CH), 138.1 (C), 138.6 (C), 143.3(C), 153.2 (C), 191.7 (C=O). EI MS: *m/z* 377 (M^+, 11), 274 (60), 272 (100), 254 (44), 105 (32), 77 (42). Anal. Calcd for $C_{22}H_{16}ClNO_3$ (377.83): C, 69.94; H, 4.27; N, 3.71. Found: C, 70.81; H, 4.32; N, 3.78%.

2-[6-Chloro-2-hydroxy-2-phenyl-2H-1,4-benzoxazin-3(4H)-ylidene]-1-phenyl-1-ethanone (**1e**): Yellow powder (0.31 g, 78%), m.p. 187–189°C. IR (KBr): 3222 (OH), 3060 (NH), 1589 (C=O), 1568, 1273, 753 cm^{-1}. ^1H NMR: δ 3.77 (1 H, s, OH), 5.84 (1 H, s, CH), 6.91 (1 H, d, ^3J = 8.6, CH), 6.94 (1 H, *d* ^3J = 8.5, CH), 6.98 (1 H, s, CH), 7.38 (2 H, *t*, ^3J = 7.5, 2 CH), 7.45–7.46 (4 H, m, 4 CH), 7.68–7.70 (2 H, m, 2 CH), 7.72 (2 H, *d* ^3J = 7.5, 2 CH), 12.82 (1 H, s, NH). ^{13}C NMR: 91.9 (CH), 96.9 (C-OH), 116.0 (CH), 118.8 (CH), 123.5 (CH), 126.6 (2 CH), 127.2 (C), 127.3 (2 CH), 128.1 (C), 128.5 (2 CH), 129.6 (2 CH), 129.9 (CH), 132.0 (CH), 138.2 (C), 138.9 (C), 143.3(C), 153.2 (C), 191.7 (C=O). EI MS: *m/z* 377 (M^+, 15), 274 (64), 272 (100), 254 (38), 105 (62), 77 (54). Anal. Calcd for $C_{22}H_{16}ClNO_3$ (377.83): C, 69.94; H, 4.27; N, 3.71. Found: C, 70.12; H, 4.31; N, 3.79%.

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