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Note

Solventless synthesis of 2,4,10a-triaryl-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3] benzoxazole

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A solventless synthesis of 2,4,10a-triaryl-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3] benzoxazole has been achieved in good yield by the reaction of 2-[(2-oxo-2-arylethyl) anilino]-1-aryl-1-ethanones with 2-aminophenol in *p*-toluenesulfonic acid. The products have been characterized by ^{1}H and ^{13}C NMR spectroscopy.

Keywords: Pyrazine, *p*-toluenesulfonic acid, benzoxazole, ^{1}H NMR, ^{13}C NMR, microwave irradiation

Benzfused azoles are an important class of molecules and are a common heterocyclic scaffold in biologically active and medicinally significant compounds. Benzoxazoles are found in a variety of natural products[1] and are important targets in drug discovery[2]. Also, much attention has been paid to benzoxazoles because they have a number of optical applications such as photoluminescents[3], whitening agents[4] and in dye lasers[5]. They are also used as intermediates for several therapeutic materials[6,7]. Normally benzoxazoles are synthesized by the condensation of 2-aminophenols with benzaldehyde[8] or benzoic acid derivatives[9] followed by intramolecular cyclization. Pyrazines are found in the luminescent chromophores of certain marine organisms[10], in cephalostatins isolated from *Cephalodiscus gilehrist*, which are powerful anti-cancer agents[11], in the fungal metabolite aspergillic acid[12] and in foods in the form of potent flavour compounds[13].

As a heterocyclic system in which both benzoxazole and pyrazine fused together may assume much biological significance, it has been planned to synthesize 2,4,10a-triaryl-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3]benzoxazoles from 2-[(2-oxo-2-arylethyl)anilino]-1-aryl-1-ethanone.

Results and Discussion

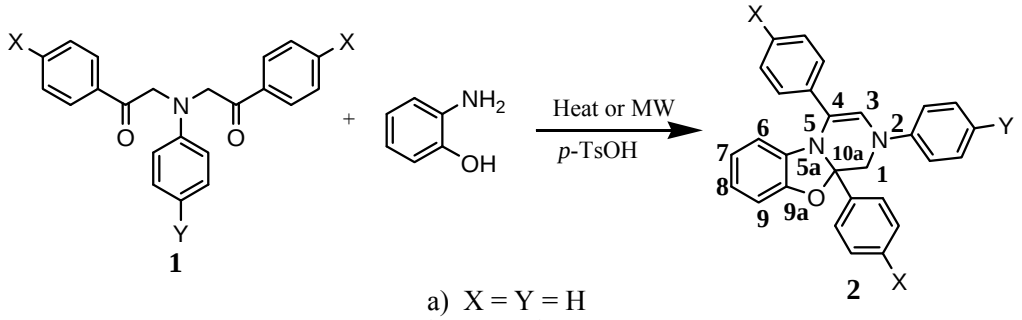
2-[(2-Oxo-2-arylethyl)anilino]-1-aryl-1-ethanones **1**, the precursor for the present investigation were prepared in good yield by simple mixing of phenacyl bromide, aniline and potassium carbonate in the ratio 2:1:1 and leaving the mixture for 3 hr at RT[14]. A finely ground mixture of 2-[(2-oxo-2-arylethyl)anilino]-1-aryl-1-ethanone and 2-aminophenol with a catalytic amount of *p*-toluenesulfonic acid was heated on a water bath for 30 min without any solvent. Quantitative conversion has occurred as indicated by the thin layer chromatographic analysis of the reaction mixture giving a single product. The product has been identified to be 2,4,10a-triaryl-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3]benzoxazole, **2** (**Scheme I**) by NMR spectral analysis. All the products are hitherto unreported. The role played by microwave irradiation on the course of the reaction has also been investigated and it is found that the reaction occurs faster getting completed in just 7 min with almost the same yield.

The diastereotopic methylenic protons of the pyrazine ring give signals around δ 3.7 and 4.4 as doublets along with a singlet integrating for one proton around δ 6.55. The latter signal can be assigned to the alkenic proton. There is an upfield doublet around δ 6.2 attributed to the *peri* hydrogen *ortho* to the nitrogen in the benzoxazole unit. The shielding of this hydrogen is due to the anisotropic effect of the nearby aryl ring, which arrangement is supported by a modelling calculation also. The mechanism of the formation of the product is formulated in **Scheme II**. Formation of fused heterocycles of the type **2** has been recently reported from a different 1,5-diketone and 1,2-diamine.

The semi-empirical PM3 computations were performed with Hyperchem (Version 7.5) at the RHF level. It was found that the total energy of **2a** was E = –98510.5717 Kcal/mole with Gradient 0.0068. The theoretically optimized geometry of **2a** is shown in **Figure 1**.

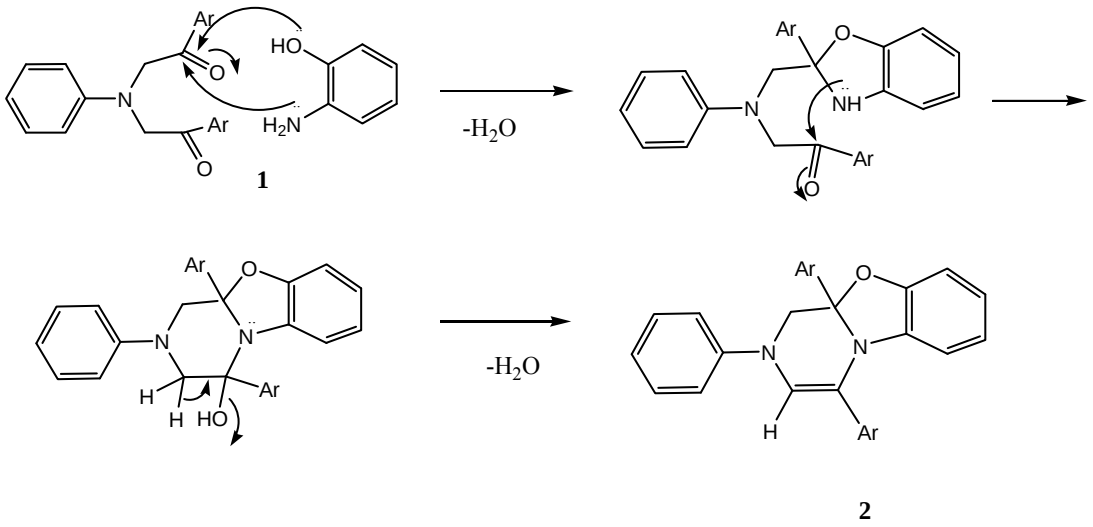
Experimental Section

All chemicals were of reagent grade quality and used as received, without further purification. Melting



a) X = Y = H
b) X = Cl; Y = H
c) X = Me; Y = H
d) X = OMe; Y = H
e) X = H; Y = Me
f) X = Cl; Y = Me
g) X = Y = Me

Scheme I



Scheme II

points were measured on a melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker 300 MHz (Ultrashield) spectrometer. Chemical shifts are reported in δ, ppm relative to tetramethylsilane as an internal standard. The progress of reactions was routinely monitored by thin layer chromatography (TLC) on silica gel plates.

General procedure for the preparation of 2,4,10a-triaryl-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3]benzoxazole

An intimate mixture of 2-[(2-oxo-2-phenyl-ethyl)anilino]-1-phenyl-1-ethanone **1** (0.5 g, 0.0015 mole), 2-aminophenol (0.2 g, 0.0015 mole) and catalytic amount of *p*-toluenesulfonic acid was heated on a water bath for 30 min. The reaction mixture was diluted with water and then extracted with dichloromethane. The organic layer was washed with water repeatedly (3×30 mL) and dried over anhydrous calcium chloride and concentrated under reduced pressure to give the crude product. Purification of the product was performed by column chromatography over silica gel using petroleum ether-ethyl acetate [97:3(v/v)] mixture as eluent.

Irradiation of the above reaction mixture under microwave (600 W) reduces the reaction time to 7 min with almost same yield.

2,4,10a-Triphenyl-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3]benzoxazole, 2a. Yield 80%, m.p.186°C. Anal.

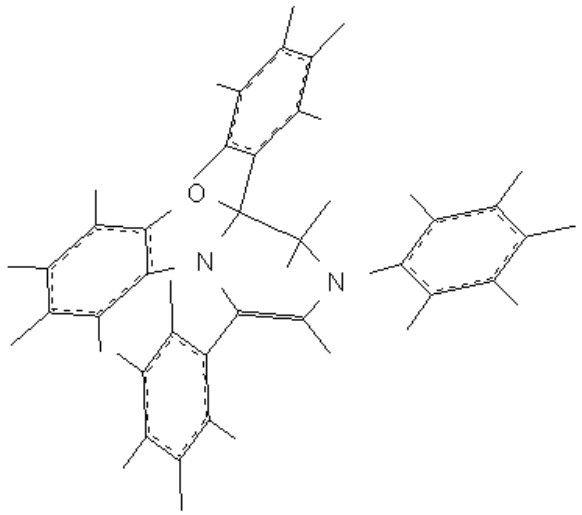


Figure 1 — Theoretically optimised geometry of **2a**

Calcd. for $C_{28}H_{22}N_2O$: C, 83.56; H, 5.51; N, 6.96. Found: C, 83.51; H, 5.55; N, 6.92; ^{1}H NMR ($CDCl_3$): δ 3.7 (d, 1H, *J* = 11.2 Hz), 4.4 (d, 1H, *J* = 11.2 Hz), 6.20 (d, 1H, *J* = 6.6 Hz), 6.6 (s, 1H), 6.60 (td, 1H, *J* = 7.8 Hz and 0.9 Hz), 6.74 (td, 1H, *J* = 7.8 Hz and 0.9 Hz), 6.80-6.95 (m, 5H), 7.20-7.25 (m, 2H), 7.27-7.31 (m, 3H), 7.38-7.44 (m, 2H), 7.58-7.65 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 49.3, 97.0, 109.4, 111.8, 117.2, 117.4, 121.1, 121.7, 121.8, 122.2, 125.3, 126.7, 126.9, 128.7, 129.2, 129.5, 129.7, 135.5, 136.5, 138.5, 145.9, 148.8.

4,10a-bis(4-Chlorophenyl)-2-phenyl-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3] benzoxazole, 2b. Yield 83%, m.p. 182°C. Anal. Calcd. for $C_{28}H_{20}Cl_2N_2O$: C, 71.34; H, 4.28; N, 5.94. Found: C, 71.30; H, 4.30; N, 5.91; ^{1}H NMR ($CDCl_3$): δ 3.65 (d, 1H, *J* = 11.7 Hz), 4.34 (d, 1H, *J* = 11.7 Hz), 6.20 (d, 1H, *J* = 7.0 Hz), 6.57 (s, 1H), 6.62 (td, 1H, *J* = 7.8 Hz and 0.9 Hz), 6.72 (td, 1H, *J* = 7.8 Hz and 0.9 Hz), 6.80-6.82 (m, 3H), 6.95 (m, 1H), 7.20-7.29 (m, 4H), 7.33-7.38 (m, 2H), 7.43-7.51 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 49.1, 96.4, 109.6, 111.8, 117.4, 117.6, 118.1, 121.5, 122.0, 122.3, 126.3, 128.2, 129.0, 129.4, 130.0, 132.5, 134.9, 135.5, 136.6, 138.5, 145.6, 148.6.

4,10a-bis(4-Methylphenyl)-2-phenyl-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3] benzoxazole, 2c. Yield 85%, m.p. 178°C. Anal. Calcd. for $C_{30}H_{26}N_2O$: C, 83.69; H, 6.09; N, 6.51. Found: C, 83.65; H, 6.10; N, 6.49; ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3H), 2.37 (s, 3H), 3.61 (d, 1H, *J* = 11.4 Hz), 4.38 (d, 1H, *J* = 11.4 Hz), 6.21 (d, 1H, *J* = 7.8 Hz), 6.51 (s, 1H), 6.58 (m, 1H), 6.69 (m, 1H), 6.76-6.79 (m, 3H), 6.86 (m, 1H), 7.02-7.05 (m, 2H), 7.16-7.19 (m, 4H), 7.43-7.50 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 21.60, 21.68, 49.0, 97.2, 109.4, 111.8, 116.3, 117.0, 118.6, 119.4, 121.1, 121.7, 125.4, 126.8, 129.5, 129.8, 129.9, 133.8, 135.3, 136.7, 139.1, 139.3, 146.0, 149.0.

4,10a-bis(4-Methoxyphenyl)-2-phenyl-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3]benzoxazole, 2d. Yield 82%, m.p. 180°C. Anal. Calcd. for $C_{30}H_{26}N_2O_3$: C, 77.90; H, 5.67; N, 6.06. Found: C, 77.94; H, 5.69; N, 6.02; ^{1}H NMR ($CDCl_3$): δ 3.61 (d, 1H, *J* = 11.7 Hz), 3.72 (s, 3H), 3.85 (s, 3H), 4.40 (d, 1H, *J* = 11.7 Hz), 6.18 (d, 1H, *J* = 7.6 Hz), 6.43 (s, 1H), 6.58-6.64 (m, 2H), 6.71-6.83 (m, 5H), 6.91-6.98 (m, 3H), 7.20-7.28 (m, 3H), 7.45-7.53 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 48.4, 55.2, 55.4, 96.7, 108.9, 111.2, 112.2, 113.6, 114.2, 114.9, 116.5, 118.7, 120.6, 120.8, 121.0, 121.2, 126.3, 127.8, 128.8, 129.4, 129.8, 138.5, 145.5, 148.5.

2-(4-Methylphenyl)-4,10a-diphenyl-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3] benzoxazole, 2e. Yield 84%, m.p. 174°C. Anal. Calcd. for $C_{29}H_{24}N_2O$: C, 83.63; H, 5.81; N, 6.73. Found: C, 83.61; H, 5.79; N, 6.71; ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H), 3.59 (d, 1H, *J* = 11.4 Hz), 4.31 (d, 1H, *J* = 11.4 Hz), 6.12 (d, 1H, *J* = 7.5 Hz), 6.48 (s, 1H), 6.51-6.73 (m, 3H), 6.89-6.96 (m, 2H), 7.13-7.21 (m, 3H), 7.24-7.30 (m, 2H), 7.41-7.52 (m, 5H), 7.70 (m, 1H), 8.17 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 20.9, 49.4, 96.9, 109.3, 111.0, 117.4, 120.4, 121.0, 121.7, 125.0,125.2, 125.5, 126.7, 128.0, 128.7, 129.2, 129.3, 130.2, 131.9, 136.7, 139.0, 143.7, 148.8.

4,10a-bis(4-Chlorophenyl)-2-(4-methylphenyl)-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3]benzoxazole, 2f. Yield 87%, m.p. 176°C. Anal. Calcd. for $C_{29}H_{22}Cl_2N_2O$: C, 71.76; H, 4.57; N, 5.77. Found: C, 71.78; H, 4.61; N, 5.75; ^{1}H NMR ($CDCl_3$): δ 2.24 (s, 3H), 3.61 (d, 1H, *J* = 11.4 Hz), 4.28 (d, 1H, *J* = 11.4 Hz), 6.20 (d, 1H, *J* = 6.6 Hz), 6.54 (s, 1H), 6.63 (td, 1H, *J* = 7.8 Hz and 0.9 Hz), 6.68-6.73 (m, 3H),6.79 (td, 1H, *J* = 7.8 Hz and 0.9 Hz), 7.02-7.08 (m, 2H), 7.19-7.23 (m, 2H), 7.29-7.34 (m, 2H), 7.41-7.49 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 21.0, 49.3, 96.3, 109.6, 111.8, 117.5, 117.6, 118.1, 121.5, 122.0, 126.2, 128.3, 129.1, 129.4, 130.5, 132.0, 132.3, 135.0, 135.5, 136.7, 138.7, 143.5, 148.7.

2,4,10a-tris(4-Methylphenyl)-1,10a-dihydro-2*H*-pyrazino[2,1-*b*][1,3]benzoxazole, 2g. Yield 87%, m.p. 180°C. Anal. Calcd. for $C_{31}H_{28}N_2O$: C, 83.75; H, 6.35; N, 6.30. Found: C, 83.72; H, 6.38; N, 6.33; ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 6H), 2.39 (s, 3H), 3.63 (d,

1H, *J* = 11.0 Hz), 4.35 (d, 1H, *J* = 11.0 Hz), 6.20 (d, 1H, *J* = 7.0 Hz), 6.51 (s, 1H), 6.59-6.81 (m, 5H), 7.01-7.10 (m, 4H), 7.20 (m, 1H), 7.34 (m, 1H), 7.43-7.52 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 20.5, 21.2, 22.7, 48.7, 96.6, 108.8, 111.2, 116.4, 116.8, 118.2, 120.4, 121.2, 124.7, 126.3, 129.0, 129.4, 129.8, 130.7, 133.4, 134.8, 136.1, 138.7, 138.8, 143.4, 148.5.

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