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## Microwave assisted synthesis of 2-(7-(3-hydroxydiphenylamino)-9,9-diethyl-2-fluorenyl)benzothiazole and 2-(7-(3-hydroxydiphenylamino)-9,9-diethyl-2-fluorenyl)benzoxazoles

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### ABSTRACT

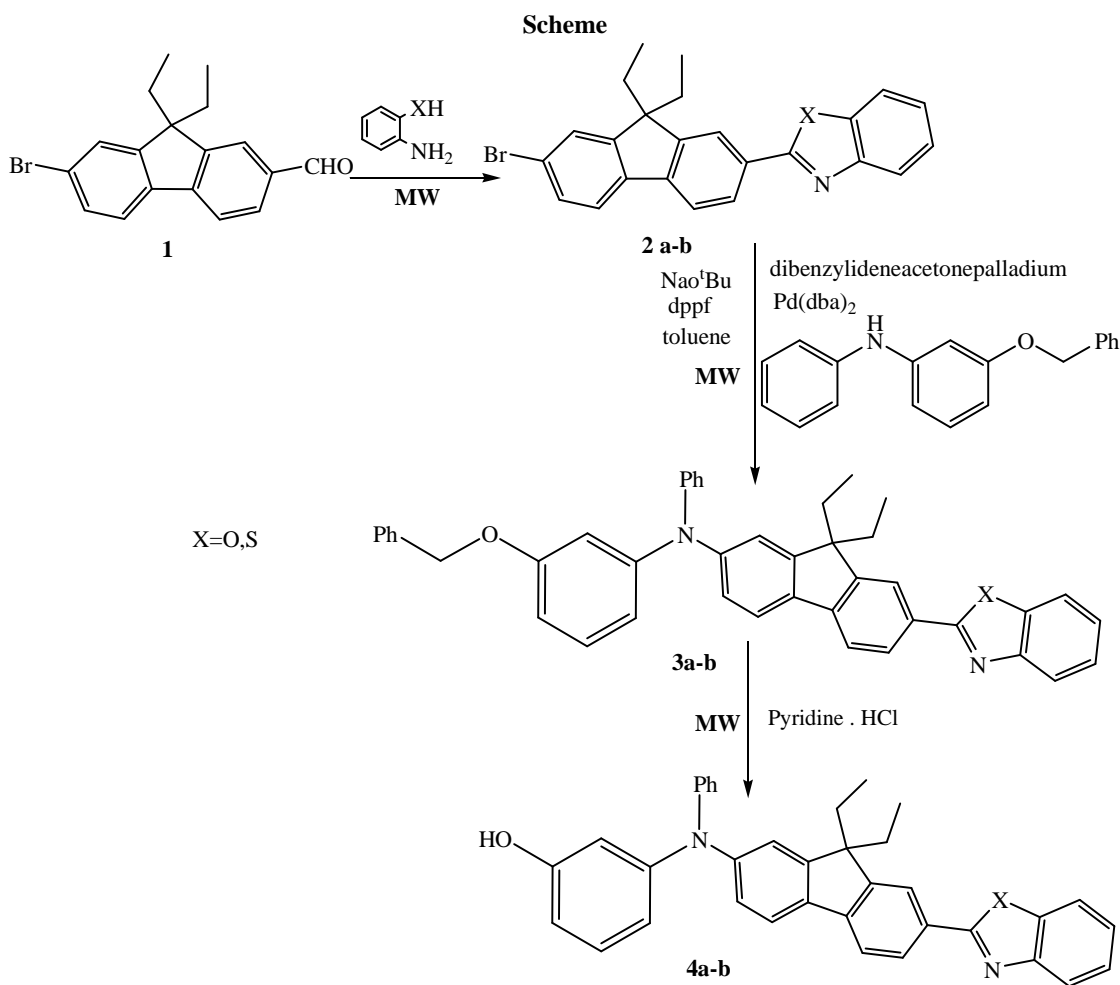
2-Bromo-7-formyl-9,9-diethylfluorene and 2-aminothiophenol / 2-aminophenol were condensed to form 2-(7-Bromo-9,9-diethyl-2-fluorenyl)benzothiazole/benzoxazole (**2a-b**). 2-(7-bromo-9,9-diethyl-2-fluorenyl)benzothiazole/benzoxazole reacted with 3-hydroxydiphenylamine, in presence of Pd(dba)<sub>3</sub> and diphenylphosphinoferrrocene to form 2-(7-(3-benzyloxydiphenylamino)-9,9-diethyl-2-fluorenyl)benzothiazole/benzoxazole (**3a-b**) then the compound was debenzylated to give 2-(7-(3-hydroxydiphenylamino)-9,9-diethyl-2-fluorenyl)benzothiazole/benzoxazole (**4a-b**).

### INTRODUCTION

The small and simple benzothiazole nucleus is present in compounds involved in research aimed at evaluating new products that possess interesting biological activities like- antitumour<sup>1,4</sup>, antimicrobial<sup>5-7</sup>, antitubercular<sup>8</sup>, antimalarial<sup>9</sup>, anticonvulsant<sup>10,11</sup>, anthelmintic<sup>12</sup>, analgesic and anti-inflammatory activity.<sup>13,14</sup> The benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological activities. Heterocycles containing the thiazole moiety are present in many natural products such as bleomycin, epothilone A, lyngbyabellin A & dolastatin.<sup>10,15</sup> Benzothiazole is a privileged bicyclic ring system. Due to their important pharmaceutical utilities, the synthesis of these compounds is of considerable interests.

The benzoxazoles are also a large chemical family used as antimicrobial agents against a wide spectrum of microorganisms. The high therapeutic activity of the related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. The incorporation of the benzoxazole nucleus is an important synthetic strategy in drug discovery. This class of molecules have broaden the scope in remedying various dispositions in clinical medicine. This heterocyclic system has different activities as it can act as bacteriostat or bactericide, as well as fungicide and it is present in numerous antiviral drugs.<sup>16-20</sup>

Hence, we undertook the synthesis of 2-(7-(3-hydroxydiphenylamino)-9,9-diethyl-2-fluorenyl)benzothiazole and 2-(7-(3-hydroxydiphenylamino)-9,9-diethyl-2-fluorenyl)benzoxazoles

**Experimental:**

Chemicals and solvents were reagent grade and used without further purification. Melting points were determined on a capillary melting point apparatus and are uncorrected. The  $^1\text{H}$  NMR was recorded in the indicated solvent on a Jeol 300 MHz spectrometer with TMS as internal standard. All chemical shifts ( $\delta$ ) were reported in ppm from internal TMS. Mass spectra were measured on a Jeol JMS D-300 spectrometer. Infrared spectra were recorded in KBr on Bruker-IFS-66 FTIR spectrophotometer.

**2-(7-Bromo-9,9-diethyl-2-fluorenyl)benzothiazole (2a)**

A mixture of 2-bromo-7-formyl-9,9-diethylfluorene (0.122 mol) and 2-aminothiophenol / 2-aminophenol (18 mL) in DMSO (61 mL) was irradiated in microwave oven at 400 Watts for 2-3 min. The reaction mixture was poured onto crushed ice resulting in a precipitate. The solution was stirred overnight and filtered. The crude product was slurred in ethanol (400 mL), filtered and recrystallized from heptane:

IR (KBr)  $\text{cm}^{-1}$  3059 (C-H), 1283 (C-N);  $^1\text{H}$  NMR in  $\text{CDCl}_3$  0.34 (t, 6H), 2.05 (m, 4H), 7.37-8.1 (m, 10H);  $^{13}\text{C}$  NMR in  $\text{CDCl}_3$  ppm 8.53, 8.64, 8.72, 8.79, 32.88, 57.04, 69.26, 69.33, 121.77, 126.57, 130.43, 132.57, 134.87, 139.60, 143.71, 150.58, 152.99, 153.90, 168.63. ; Mass spectrum,  $m/z$  (relative intensity) 435, 433 ( $\text{M}^+$ , 94.4, 100), 406, 404 (65.9, 66.3), 325 (97.6), 310 (21.4), 162.5 (39.3). ; Anal. Calcd for  $\text{C}_{18}\text{H}_{17}\text{BrO}$  : C, 65.5; H, 5.3. Found C, 63.1; H, 5.1.

**2-(7-Bromo-9,9-diethyl-2-fluorenyl) benzoxazole (2b)**

<sup>1</sup>H NMR in CDCl<sub>3</sub> 0.33 (t, 6H), 2.10 (m, 4H), 7.31-8.3 (m, 10H); Mass spectrum, *m/z* (relative intensity) ; 19(M+), 417, 418, 420, 421

**2-(7-(3-benzyloxydiphenylamino)-9,9-diethyl-2-fluorenyl)benzothiazole (3a)**

A mixture of 3-hydroxydiphenylamine (0.045 mol), 2-(7-bromo-9,9-diethyl-2-fluorenyl)benzothiazole/ benzoxazole (0.038 mol) and toluene (300mL) was distilled and cooled to room temperature. A combination of Pd(dba)<sub>2</sub> (0.4304 g), dppf (diphenylphosphinoferrocene) (0.3938 g) and sodium t-butoxide (5.39 g) were added to the solution and it was irradiated in microwave oven at 400 Watts for 3-4 min. Toluene was added, the organic layer was separated and washed with a saturated solution of sodium chloride and recrystallized from 1:5 toluene:heptane solution to afford product.

IR (KBr) cm<sup>-1</sup> 3031, 2961 and 2918 (C-H), 1592 and 1487 (C=C), 1275 (C-N), 1218 (C-O); <sup>1</sup>H NMR in CDCl<sub>3</sub> 0.38 (t, 6H), 1.85-2.21 (m, 4H), 4.94 (s, 1H), 6.63-8.19 (m, 24H); <sup>13</sup>C NMR in CDCl<sub>3</sub> 32.87, 56.67, 70.10, 110.57, 116.68, 119.16, 119.34, 119.41, 119.56, 25 121.27, 121.41, 121.52, 121.74, 122.87, 123.09, 123.23, 123.41, 123.67, 124.65, 125.31, 126.62, 127.63, 128.07, 128.36, 128.69, 129.42, 130.00, 131.02, 134.59, 139.50, 136.95, 194.96, 147.72, 148.20, 149.18, 150.93, 152.27, 153.51, 159.77, 169.20; Mass spectrum, *m/z* (relative intensity) 628 (M+), 537 (4.0), 508 (3.9), 493 (7.6), 479 (4.4). Anal. Calcd for C<sub>43</sub>H<sub>36</sub>N<sub>2</sub>OS: C, 81.2; H, 4.9; N, 4.1; S, 4.1. Found: C, 80.1; H, 4.8; N, 3.7; S, 4.8.

**2-(7-(3-benzyloxydiphenylamino)-9,9-diethyl-2-fluorenyl)benzoxazole (3b)**

<sup>1</sup>H NMR in CDCl<sub>3</sub> 0.36 (t, 6H), 1.81-2.20 (m, 4H), 4.92 (s, 1H), 6.62-8.20 (m, 24H); Mass spectrum, *m/z* (relative intensity) 612 (M+), 613, 614, 615

**2-(7-(3-hydroxydiphenylamino)-9,9-diethyl-2-fluorenyl)benzothiazole (4a)**

A mixture of 2-(7-(3-benzyloxydiphenylamino)-9,9-diethyl-2-fluorenyl)benzothiazole/ benzoxazole (0.19 mol) and pyridine hydrochloride (0.74 mol) was irradiated in microwave oven for 3-4 sec. The solution was poured into warm water, stirred for 30 min and filtered. A slurry of the red precipitate and a dilute ammonium hydroxide solution (5 %) was stirred overnight (20 h), filtered, and the residue was recrystallized from toluene.

IR cm<sup>-1</sup> 3434 (OH), 3026 (C-H), 2921 (C-H); <sup>1</sup>H NMR in CDCl<sub>3</sub> 0.38 (t, 6H), 1.92-2.25 (m, 4H), 4.95 (s, 1H), 6.65-8.22 (m, 19H), 10.52 (brs, 1H); Mass spectrum, *m/z* 538 (M+, 100), 509 (3.7), 494 (4.4), 269 (0.3). Anal. Calcd for C<sub>36</sub>H<sub>30</sub>N<sub>2</sub>OS: C, 80.2; H, 5.5; N, 5.2; S, 5.9. Found: C, 80.7; H, 5.8; S, 6.1.

**2-(7-(3-hydroxydiphenylamino)-9,9-diethyl-2-fluorenyl)benzoxazole (4a)**

<sup>1</sup>H NMR in CDCl<sub>3</sub> 0.37 (t, 6H), 1.89-2.22 (m, 4H), 4.92 (s, 1H), 6.58-8.25 (m, 19H), 10.82 (brs, 1H)

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