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Facile and environmentally friendly halogenation of BODIPYs in deep eutectic solvent

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A deep eutectic solvent based on choline chloride and 1,1,1,3,3,3-hexafluoro-2-propanol was prepared. This deep eutectic solvent was used as the reaction medium for halogenation of boron dipyrromethene in the presence of *N*-halosuccinimide, which delivered the corresponding products in good to excellent yields (79–94%) in short reaction time (usually within 30 min). Moreover, this deep eutectic solvent could be easily prepared, recovered and reused for several runs without significant loss in the yields.

1. Introduction

4,4-Difluoro-4-bora-3a,4a-diaza-s-indacenes (BODIPYs) have received much attention due to their unique properties including high fluorescence quantum yields (Φ_f), large molar absorption coefficients (ε), excellent thermal and photochemical stabilities [1–3]. Recently, much effort has been spent on the decoration of the BODIPY scaffold with functional groups to modify their photophysical properties, making them excellent fluorophores in various fields [4–6]. Among them, halogenated BODIPYs are of great interest since they are useful precursors for further functionalization. For examples, 3,5-dihalogenated BODIPYs (Fig. 1A) are generally modified via S_NAr reactions and metal-catalyzed cross-coupling reactions to provide more complex BODIPY derivatives [7–10]. The 2,6-halogenated BODIPYs (Fig. 1B) are also effective sensitizers for photodynamic therapy (PDT) [11,12] and photocatalysts [13–15].

Direct electrophilic halogenation of BODIPYs is well-documented in literature. Using bromination as example, a series of reaction systems including *N*-bromosuccinimide (NBS) [16], bromine [17], NBS-AIBN [12] and $CuBr_2$ [18] has been developed. However, prolonged reaction time, relatively lower yields as well as toxic reagents or solvents are still the issues to be addressed.

More recently, deep eutectic solvents (DESs) have invoked great interest as green solvents or catalysts in organic reactions [19–22]. They are mainly prepared by combining a quaternary ammonium salt with a hydrogen-bond donor. The unique properties such as ready available, biodegradable, non-toxic, inexpensive and reusable make them more advantageous than the conventional solvents. On the other hand, it is well known that 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) exhibits high hydrogen bonding donor ability, low nucleophilicity and high ionizing power. Its utilization in organic transformations has also been well-documented [23–26]. We believe that HFIP can be used to form a deep eutectic solvent with a quaternary ammonium salt. Also, HFIP also can activate the *N*-halosuccinimide via hydrogen bonding. Herein, we report the preparation of a new DES (ChCl/HFIP) and halogenation reaction of BODIPYs in such DES (Scheme 1).

2. Experimental

2.1. Method and apparatus

All reagents were obtained from local commercial suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance III 500-MHz spectrometer.

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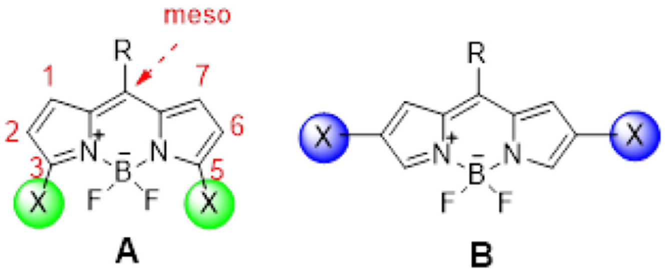


Fig. 1. 3,5- and 2,6-dihalogenated BODIPYs.

NMR experiments are reported in δ units, parts per million (ppm), and were referenced to $CDCl_3$ (δ 7.26 or 77.0 ppm) as the internal standard. The coupling constants J are given in Hz. Melting points (m.p.) are determined with a MPA 100 apparatus and are not corrected. Mass spectra (EI) were measured with Jeol JMS-DX300 and Thermo Fisher LCQ instruments. Elemental analyses were obtained using a Perkin–Elmer EA2400II analyzer.

2.2. Preparation of ChCl/HFIP

Choline chloride (139.6 g, 100 mmol) and 1,1,1,3,3,3-hexafluoro-2-propanol (25.2 g, 150 mmol) were placed in a round bottom flask and stirred at 50 °C. After 3 h, a homogenous colorless liquid formed, which was used directly for the reactions without purification.

2.3. General procedures for halogenation of BODIPYs

A mixture of the BODIPY **1** (0.2 mmol) and either NBS or NIS (0.48 mmol) in ChCl/HFIP (2 mL) was stirred at room temperature for a certain time (usually < 30 min) according to the TLC (EtOAc/petroleum, 1:5). After reaction, the mixture was extracted with CH_2Cl_2, washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was further purified using column chromatography (EtOAc/petroleum ether or CH_2Cl_2/hexane) to afford either the bromo-products **2** or the iodo-products **3**. The ChCl/HFIP, which was insoluble in CH_2Cl_2, was readily recovered by evaporation of the water and reused for the next run. All the products were known compounds and were characterized by comparison with authentic samples.

2,6-Dibromo-4,4-difluoro-1,3,5,7-tetramethyl-8-phenyl-4-bora-3a,4a-diaza-s-indacene (2a): red solid; m.p. 228–232 °C (229–231 °C) [18]; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.36$ (s, 6H, CH_3), 2.61 (s, 6H, CH_3), 7.52–7.53 (m, 5H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 153.9$, 142.1, 140.6, 134.4, 130.4, 129.5, 129.4, 127.8, 111.8, 13.6.

2,6-Dibromo-4,4-difluoro-8-(4-methoxyphenyl)-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (2b): red solid; m.p. 238–240 °C (236–238 °C) [18]; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.47$ (s, 6H, CH_3), 2.62 (s, 6H, CH_3), 3.91 (s, 3H, OCH_3), 7.06 (d, $J = 8.65$ Hz, 2H, ArH), 7.16 (d, $J = 8.65$ Hz, 2H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 160.6$, 153.7, 142.3, 140.6, 130.9, 130.8, 129.1, 128.8, 126.3, 114.8, 111.7, 55.4, 13.9, 13.7.

2,6-Dibromo-4,4-difluoro-8-(4-chlorophenyl)-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (2c): red solid; m.p. 208–210 °C (212–214 °C) [18]; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.41$ (s, 6H, CH_3), 2.61 (s, 6H, CH_3), 7.21–7.23 (d, $J = 10.0$ Hz, 2H, ArH), 7.52–7.54 (d, $J = 10.0$ Hz, 2H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 154.4$, 140.4, 140.3, 135.9, 132.8, 130.3, 129.8, 129.4, 128.6, 112.1, 13.9, 13.7.

2,6-Dibromo-4,4-difluoro-8-(4-nitrophenyl)-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (2d): red solid; m.p. > 250 °C (>300 °C) [18]; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.38$ (s, 6H, CH_3), 2.64 (s, 6H, CH_3), 7.55 (d, $J = 8.6$ Hz, 2H, ArH), 8.44 (d, $J = 8.6$ Hz, 2H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 155.3$, 148.7, 141.2, 140.0, 138.6, 129.6, 124.6, 112.5, 14.0, 13.8.

2,6-Dibromo-4,4-difluoro-8-(3,5-dinitrophenyl)-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (2e): red solid; m.p. > 250 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.37$ (s, 6H, CH_3), 2.64 (s, 6H, CH_3), 8.56 (s, 2H, ArH), 9.23 (s, 1H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 158.0$, 149.0, 141.8, 138.8, 134.5, 130.7, 129.2, 122.6, 119.4, 15.4, 14.8. EI-MS: $m/z = 572$ $[M]^+$. Anal. Calcd for $C_{19}H_{15}BBr_2F_2N_4O_4$: C, 39.90; H, 2.64; N, 9.80. Found: C, 39.87; H, 2.70; N, 9.76.

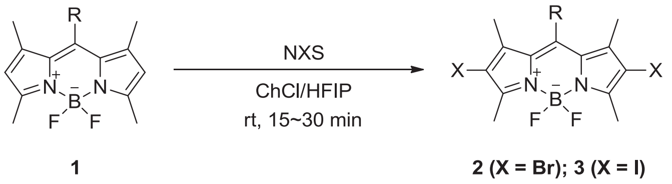
2,6-Dibromo-4,4-difluoro-1,3,5,7-tetramethyl-8-methyl-4-bora-3a,4a-diaza-s-indacene (2f): red solid; m.p. 221–223 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.44$ (s, 6H, CH_3), 2.57 (s, 6H, CH_3), 2.62 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 152.2$, 141.9, 138.4, 29.7, 17.4, 16.4, 13.6. EI-MS: $m/z = 420$ $[M]^+$. Anal. Calcd for $C_{14}H_{15}BBr_2F_2N_2$: C, 40.05; H, 3.60; N, 6.67. Found: C, 40.11; H, 3.52; N, 6.70.

2,6-Diiodo-4,4-difluoro-1,3,5,7-tetramethyl-8-pentyl-4-bora-3a,4a-diaza-s-indacene (2g): red solid; m.p. 216–218 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.93$ (t, 3H, CH_3), 1.36–1.66 (m, 8H), 2.44 (s, 6H, CH_3), 2.57 (s, 6H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 152.3$, 147.3, 137.7, 130.5, 112.0, 32.5, 31.5, 29.0, 22.5, 15.5, 14.0, 13.7. EI-MS: $m/z = 476$ $[M]^+$. Anal. Calcd for $C_{18}H_{23}BBr_2F_2N_2$: C, 45.42; H, 4.87; N, 5.89. Found: C, 45.40; H, 4.91; N, 5.87.

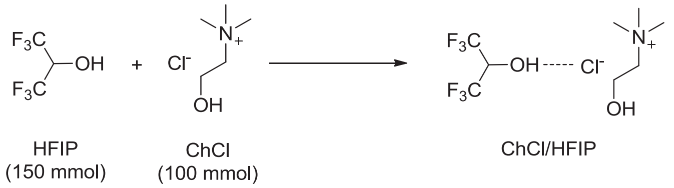
2,6-Dibromo-4,4-difluoro-1,3,5,7-tetramethyl-8-undecyl-4-bora-3a,4a-diaza-s-indacene (2h): red solid; m.p. 202–205 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.88$–0.91 (t, 3H, CH_3), 1.22–1.65 (m, 18H, CH_2), 2.44 (s, 6H, CH_3), 2.57 (s, 6H, CH_3), 3.70–3.74 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 152.3$, 147.3, 137.7, 130.5, 112.0, 31.8, 31.7, 30.3, 29.0, 22.6, 18.4, 15.5, 14.1, 13.7. EI-MS: $m/z = 560$ $[M]^+$. Anal. Calcd for $C_{24}H_{35}BBr_2F_2N_2$: C, 51.46; H, 6.30; N, 5.00. Found: C, 51.47; H, 6.25; N, 5.02.

2,6-Dibromo-4,4-difluoro-1,3,5,7-tetramethyl-8-ethoxycarbonyl-4-bora-3a,4a-diaza-s-indacene (2i): red solid; m.p. > 250 °C; ^{1}H NMR(500 MHz, $CDCl_3$): $\delta = 1.42$–1.45(t, 3H), 2.13(s, 6H), 2.56 (s, 6H), δ4.43–4.48 (q, 2H); ^{13}C NMR(125 MHz, $CDCl_3$): $\delta = 164.5$, 154.6, 135.9, 129.8, 126.9, 122.8, 63.2, 13.8, 12.7, 10.5. EI-MS: $m/z = 478$ $[M]^+$. Anal. Calcd for $C_{16}H_{17}BBr_2F_2N_2O_2$: C, 40.21; H, 3.59; N, 5.86. Found: C, 40.16; H, 3.62; N, 5.80.

2,6-Dibromo-4,4-difluoro-8-(morpholinomethyl)-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (2j): red solid; m.p. 228–231 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.32$ (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.74 (t, 4H, CH_2), 3.76



Scheme 1. 2,6-dihalogenation of BODIPYs in ChCl/HFIP.



Scheme 2. Preparation of ChCl/HFIP.