Section A-Research paper
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Synthesis of a Precursor 1,2-Bis(1*H*-pyrrol-2-yl)ethane Towards Novel PyrroleMacrocycles in Ionic Liquids as a Green Approach

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Abstract

Porphyrin undoubtedly represents one of the most widely studied of all known macrocyclic ring systems. Porphyrin with its multiple biological functions as well as its ability to function as an excellent metal-complexing ligand has inspired the study of a whole range of porphyrin analogs in recent years. The synthesis of a precursor 1,2-bis(1H-pyrrol-2-yl)ethane **1**, leading to novel pyrrolemacrocycles in ionic liquids (ILs) as a reaction media is described herein. The first approach involving six steps provided a low yield (overall 11%) of **1**, whereas the one-pot approach involving bromotriflate**8** as a substrate provided 28% of **1**. This modified version of pyrrolemacrocycles is expected to have a specific ion-binding ability.

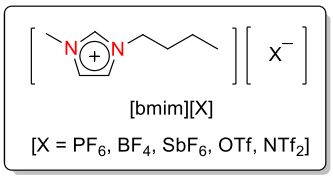
Introduction

Organic chemistry is by tradition, chemistry in solution and for very good reasons. However, for ecological reasons using a solvent has an obvious downside because after the reaction, the products have to be separated from the reaction solution and the solvent has to be either recycled or discarded. The realization that pollution prevention is frequently more cost-effective than remediation has catalyzed tremendous effort in the development of environmentally benign solvents and processes.

Room-temperature ILs are one such class of solvents.[1] They are organic molten salts that in their pure state are liquids at temperatures around ambient. They are ‘designer solvents’, as their physical properties such as melting point, viscosity, density, and hydrophobicity can be modified according to the nature of the desired reactions by altering the nature of their cations and

anions.[2]Recent independent reports and many reviews have highlighted ILs as representing a state-of-the-art, innovative approach to green chemistry.[1,3]

Figure 1. Second GenerationILs



Porphyrin (**I**) undoubtedly represents one of the most widely studied of all known macrocyclic ring systems.[4]Porphyrin with its multiple biological functions and the ability to function as an excellent metal-complexing ligand has inspired the study of a whole range of porphyrin analogs in recent years.[5,6]

On a different level, the electronic structure of various larger, or "expanded" porphyrin systems, in particular their similarities and differences to porphyrins, have made an object of intense study.[7] Another factor driving the study of conjugated expanded porphyrins is that they often display absorbance bands that are considerably red-shifted relative to those of porphyrin, resulting in their application as therapeutics for photodynamic therapy, including anion sensing and transport (for example, drug delivery), as well as chromatography-based purification of anions.[8]

The discovery of sapphyrin, a pentapyrrolicmacrocycle (for example, **II**) in 1966 by Woodward and his research group was the first report of expanded porphyrin chemistry.[9] Later, there were reports of uranyl super phthalocyanine (**III**) by Day, Marks, and Wachter;[10]pentaphyrin (**IV**) by Rexhansen and Gossauer;[11]platyrins (**V**) by Berger and LeGoff,[12] and the generation of a whole series of "Stretched" systems (for example, **VI**) by Franck and co-workers.[13]

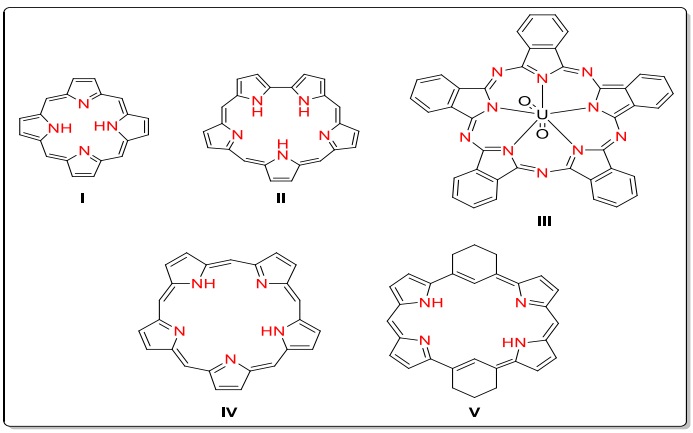


Figure 2. PyrroleMacrocycles (**I-V**)

However, the non-conjugated fully meso-substituted porphyrinogen-like macrocycle (**VIII**) has witnessed a great deal of interest over the past decade.[14,15] After lying virtually dormant in the literature for nearly a century, interest in these macrocycles was renewed in the 1990s by the extensive work of Floriani and co-workers[16-18] on the metallation and attendant synthetic chemistry of deprotonated calixpyrroles. Calix[n]phyrins, hybrid macrocycles (**IX**) at the structural crossroads containing a mixture of sp^2- and sp^3-hybridized meso carbon bridges gained tremendous potential due to their interesting anion and cation recognition properties.[19]

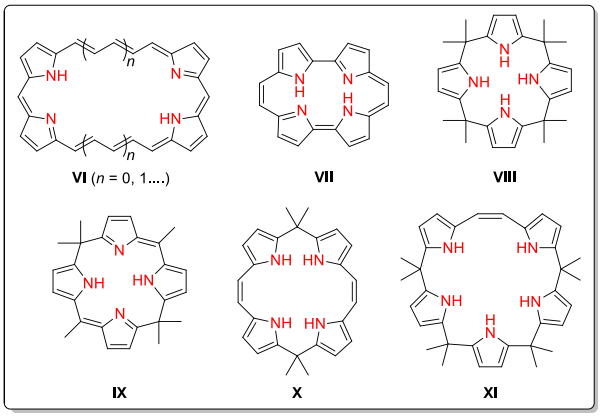
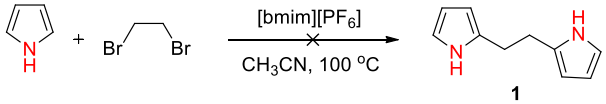


Figure 3. PyrroleMacrocycles (**VI-XI**)

The development of ion-pair of receptors,[20–22] to achieve a higher level of control over recognition than that obtainable from simple ion binding, has intrigued researchers in supramolecular chemistry over the past decade. Pyrrolemacrocycles exhibit exceptional chemical and physical properties that have suggested a vast number of potential applications in host-guest chemistry.

The synthesis of precursor 1,2-bis(1*H*-pyrrol-2-yl)ethane begins with our recently reported protocol. Pyrrole C2-alkylation on 1,2-dibromoethane was performed in [bmim][PF_6] IL and CH_3CN as the mixture solvent system at 100 °C to achieve bis(pyrrolyl)ethane **1** via a one-pot approach. However, the reaction did not occur even after 48 h, presumably due to the substrate with predominant α-effect.

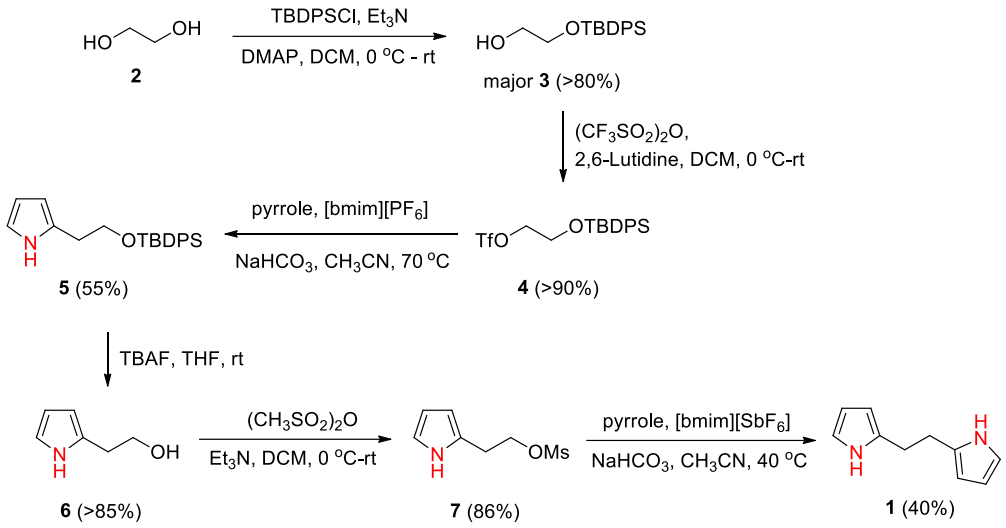
Scheme 1.



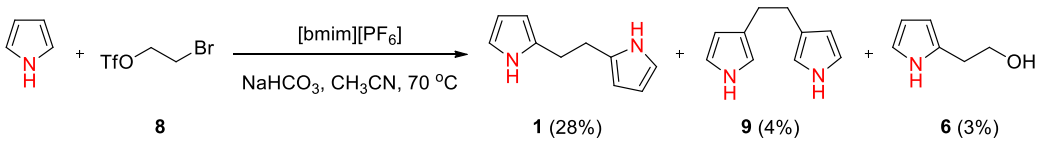
To synthesize precursor 1, we proceeded further with the six-steps approach. Selective protection of

ethylene glycol with tert-butyldiphenylsilyl chloride was achieved with high yield using the procedure reported by Nemotoet al.[23]

Scheme 2. Method A



Scheme 3. Method B



The mono protected silyl compound **3** was treated with trifluoromethanesulfonic anhydride under the condition reported by Chi et al.[24] to give a white solid 2-(*tert*-butyldiphenylsilyloxy)-1-(trifluorosulfonyloxy)ethane**4** with excellent yield (>90%). We next performed pyrrole C2-alkylation on triflate**4** in [bmim][PF_6] and CH_3CN as mixture solvent system at 70 °C. Unfortunately, along with C2-alkylated pyrrole**5** (yield 55%), reaction provided the C3-alkylated pyrrole (yield 30-35%). The deprotection of *tert*-butyldiphenylsilyl group in compound **5**with TBAF in THF provided 85% of 2-(2-hydroxyethyl)-1*H*-pyrrole**6** as a stable colorless liquid. The reaction of alcohol **6** with mesyl anhydride gave 86% of unstable light yellow liquid. However, the final step of pyrrole*C*–alkylation with mesylate**7** in [bmim][SbF_6] and CH_3CN as mixture solvent system at 40 °C afforded 1,2-bis(1*H*-dipyrrol-1-yl)ethane **1** with only 40% yield. Overall, our effort to provide a higher yielding route gave limited success.

EXPERIMENTAL

Chemicals and apparatus

The ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer at room temperature, and the chemical shifts are reported in δ units (ppm) relative to tetramethylsilane (TMS). TLC analysis was performed on 0.25 mm silica gel 60 aluminium sheets containing F254. Column chromatography was performed using 100–200 mesh silica gel. All other known compounds including the IL, [bmim][Cl] were commercially available.

1,2-Bis(1*H*-pyrrol-2-yl)ethane Synthesis: Precursor to PyrroleMacrocycles

2-(tert-Butyldiphenylsilyloxy)-1-(trifluorosulfonyloxy)ethane (**4**). To a stirred solution of 2-(tert-butyldiphenylsilyloxy)ethanol (**3**, 500 mg, 1.67 mmol) in CH_2Cl_2 (10 mL), 2,6-lutidine (0.36 mL, 3.1 mmol) diluted with CH_2Cl_2 (10 mL) was added and cooled to 0 °C. Trifluoromethanesulfonic anhydride (0.42 mL, 2.5 mmol) was added dropwise. After stirring for 1 h, the reaction mixture was quenched with 10% EtOAc/hexanes and passed through a short flash column chromatography to yield **4** (648 mg, 90%) as a white solid.

2-[2-(tert-Butyldiphenylsilyloxy)ethyl]-1*H*-pyrrole (**5**). 2-(tert-butyldiphenylsilyloxy)-1-(trifluorosulfonyloxy)ethane (**4**, 433 mg, 1.0 mmol) was dissolved in anhydrous acetonitrile (2.0 mL), pyrrole (1.0 mL, 15 mmol), $NaHCO_3$ (210 mg, 2.5 mmol), and 1-n-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6] (250 mg, 0.67 mmol). The mixture was stirred over 48 h at 70 °C. The reaction was monitored by thin layer chromatography (TLC). The reaction mixture was extracted from ionic liquid phase with ethyl ether (10 mL x 5). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by short flash column chromatography (silica gel) (10% EtOAc/hexanes) to obtain 192 mg of **5** (55%) as a colorless liquid.

2-(2-Hydroxyethyl)-1*H*-pyrrole (**6**). Tetra-n-butylammonium fluoride (523 mg, 2.0 mmol) was added to (**5**, 350 mg, 1.0 mmol) in THF (5.0 mL). The reaction mixture was stirred over 2 h at rt. The reaction was monitored by TLC. THF was evaporated under reduced pressure and the residue was extracted with EtOAc (15 mL x 3). The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo to give crude 16, which was passed through short flash column chromatography (silica gel) (50% EtOAc/hexanes) to obtain 141 mg of **6** (85%) as a colorless liquid.

2-(2-Methanesulfonyloxyethyl)-1*H*-pyrrole (**7**). To the stirred solution of **6** (500 mg, 4.5 mmol) in dry dichloromethane (30 mL), triethylamine (1.5 mL, 4.5 mmol) was added. The reaction mixture was maintained at 0 °C. Methanesulfonic anhydride (1.02 g, 5.85 mmol) was added to the reaction mixture and was stirred at 0 °C for 1 h. Dichloromethane was evaporated in vacuo and residue obtained was passed through short flash column chromatography (silica gel) (50% EtOAc/hexanes) to obtain mesylate (**7**, 732 mg, 86%): colorless liquid; unstable and decomposes to light brown gel on standing at room temperature.

1,2-Bis(1*H*-pyrrol-2-yl)ethane (**1**, Method A). Mesylate (**7**, 100 mg, 0.529 mmol) was dissolved in anhydrous acetonitrile (2.0 mL), pyrrole (0.67 g, 10 mmol), $NaHCO_3$ (126 mg, 1.5 mmol), and [bmim][SbF_6] (250 mg, 0.67 mmol). The mixture was stirred over 24 h at 40 °C and was monitored by TLC. The reaction mixture was extracted from ionic liquid phase with ethyl ether (10 mL x 5). The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by short flash column chromatography (silica gel) (20% EtOAc/Hexanes) to obtain 34 mg (40%) of 1,2-Bis(1*H*-pyrrol-2-yl)ethane (**1**) as white crystals.

Method B. Prepared according to procedure using compound **4** except that 1-bromo-2-(trifluoromethanesulfonyloxy)ethane (**8**, 257 mg, 1.0 mmol) was used to obtain 45 mg (28%) of 1,2-Bis(*1H*-pyrrol-2-yl)ethane (**1**) and 6 mg (4%) of 20 as white crystals.

2-(*tert*-Butyldiphenylsilyloxy)ethanol (3). colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 9H), 2.13 (bs, OH), 3.66-3.78 (m, 4H), 7.37-7.46 (m, 6H), 7.65-7.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 26.8, 63.7, 64.9, 127.8, 129.8, 133.2, 135.5. Registry No. 138499-16-8.

Bis(*tert*-Butyldiphenylsilyloxy)ethane. white solid; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 26.6, 61.3, 127.9, 130.0, 132.5, 135.5. Registry No. 362494-93-7.

2-(*tert*-Butyldiphenylsilyloxy)-1-(trifluorosulfonyloxy)ethane (4). white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 3.90 (t, *J* = 4.4 Hz, 2H), 4.56 (t, *J* = 4.4 Hz, 2H), 7.38-7.48 (m, 6H), 7.65-7.68 (m, 4H).

2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-1*H*-pyrrole (5). colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 2.86 (t, *J* = 5.6 Hz, 2H), 3.89 (t, *J* = 5.6 Hz, 2H), 5.92 (d, *J* = 0.8 Hz, 1H), 6.13-6.15 (m, 1H), 6.70-6.71 (m, 1H), 7.36-7.44 (m, 6H), 7.63-7.65 (m, 4H), 8.57 (s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 26.9, 30.5, 64.4, 105.7, 107.9, 116.5, 127.7, 129.7, 130.4, 133.3, 135.5.

3-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-1*H*-pyrrole. colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 2.79 (t, *J* = 7.2 Hz, 2H), 3.83 (t, *J* = 7.2 Hz, 2H), 6.05-6.07 (m, 1H), 6.57-6.58 (m, 1H), 6.68-6.70 (m, 1H), 7.35-7.47 (m, 6H), 7.61-7.74 (m, 4H), 8.0 (s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 26.8, 30.5, 65.4, 109.1, 115.7, 117.4, 120.3, 127.5, 129.4, 134.1, 135.6.

2-(2-Hydroxyethyl)-1*H*-pyrrole (6).colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (s, OH), 2.85 (t, *J* = 5.0 Hz, 2H), 3.85 (t, *J* = 5.8 Hz, 2H), 5.96-5.98 (m, 1H), 6.14-6.15 (m, 1H), 6.69-6.71 (m, 1H), 8.48 (s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.6, 62.6, 105.8, 108.2, 116.9, 129.5. Registry No. 22186-60-3.

1,2-Bis(1*H*-pyrrol-2-yl)ethane (1, Method A). white crystals; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93 (s, 4H), 5.98-5.99 (m, 2H), 6.11-6.15 (m, 2H), 6.60-6.64 (m, 2H), 7.80 (s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 105.3, 108.3, 116.5, 131.8; MS (EI) 160 (M^+), 80 (100).

1-Bromo-2-(trifluoromethanesulfonyloxy)ethane (8). colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (t, *J* = 6.4 Hz, 2H), 4.74 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 74.2, 113.8, 116.9, 120.1, 123.3. Registry No. 103935-47-3.

1,2-Bis(1*H*-pyrrol-3-yl)ethane (9). white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (s, 4H), 6.13-6.16 (m, 2H), 6.60-6.61 (m, 2H), 6.72-6.74 (m, 2H), 7.97 (s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6, 108.5, 114.9, 117.5, 124.4.

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CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

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