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Highly efficient synthesis of N-confused *meso*-tetraspirocyclohexyl calix[4]pyrrole using Brønsted acidic ionic liquids as catalysts

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An efficient, green and novel protocol is described for high yield synthesis of N-confused *meso*-tetraspirocyclohexyl calix[4]pyrrole. In aqueous solution, the condensation of pyrrole and cyclohexanone in the presence of Brønsted acidic ionic liquid catalysts afforded N-confused calix[4]pyrrole in up to 62.5% yield which represents a ~threefold yield improvement over existing protocol and makes significant quantity of N-confused calix[4]pyrrole readily available.

Introduction

Many organic ligands used by nature in important biological processes[1] are formed by the condensation of simple starting materials.[2,3] Calix[4]pyrroles (CPs), structurally related to porphyrins and conformationally similar to calixarenes, are usually synthesized by acid catalysed condensation between pyrrole and a ketone in the so called modified Rothemund procedure.[4] Since Sessler's milestone work,[5] the chemistry of CPs blossomed only recently and has become an indispensable part of supramolecular chemistry.[6–15] Consequently, extensive efforts have been devoted in recent years to synthesize CPs under a variety of conditions.[16–20]

On another front, the chemistry of N-confused calix[4]pyrrole (NCCP), the intriguing isomer having one pyrrole NH at the exterior of the macrocycle, has not been well exploited from the synthetic view point except one and the only report by Dehaen and co-workers.[21] Indeed, the NCCP type materials are formed in each CP synthesis in a significantly lower amount, presumably, due to low thermodynamic stability. Nonetheless, the presence of a free α-pyrrolic position in NCCP provides much more latitude in favour of competent functionalization over regular CP and can be well exploited for signalling anion recognition.[22] It is therefore of considerable interest to search for alternative methods for the synthesis of NCCP in high yields.

It is an undeniable fact that the product distribution in the synthesis of porphyrinogens and related compounds can be switched from one to another, depending on the type of acid catalysts and their way of implementing in the reaction. In this context, the literature reports by Dehaen,[21] Radha Kishan,[23] Lee[24] and Lindsey[25,26] are particularly attractive. However, the use of excess and even stoichiometric amount of acids with chlorinated solvents makes such processes environmentally questionable.

In recent years, Brønsted acidic ionic liquids (AILs) have emerged as revolutionary candidates in the replacement of conventional homogeneous and heterogeneous acid catalysts because of their outstanding flexibility, heat resistance, non-volatility, non-corrosiveness, negligible vapour pressure and tunable polarity with common organic solvents.[27–31] In addition, these advantages turn out to be more attractive using ILs in aqueous media.

Inspired by the early report[21] and the critical role of AILs in organic synthesis provoked us to examine the catalytic scope of AILs in the synthesis of NCCP. Further motivation to take this initiative came from our recent observation,[32] where by changing the *meso*-substituent from methyl to cyclohexyl in chromogenic CPs, the selectivity in visual sensing can be fine tuned. Herein, we report the high yield synthesis of NCCP (**2**) in the condensation of pyrrole (**3**) and cyclohexanone (**4**) by making use of AILs as catalysts (Table 1).

Results and discussion

For this study, a diverse range of Brønsted AILs, **I–IV** (Fig. 1) and authentic samples of different macrocycles were synthesized by modification of known procedures (See Supplementary data). The identity of **I–IV** and others was unambiguously confirmed by ^{1}H

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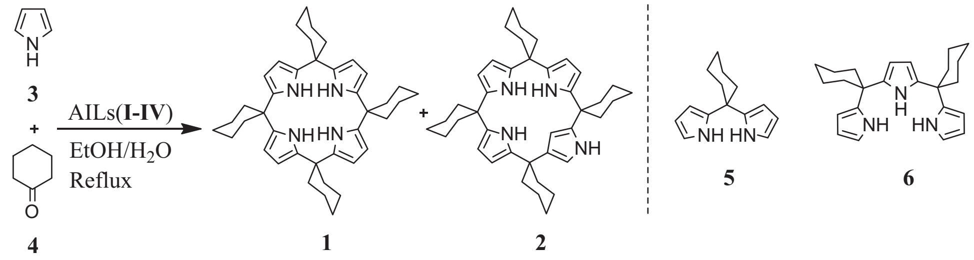
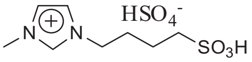
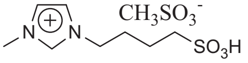
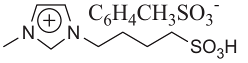
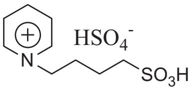
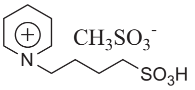
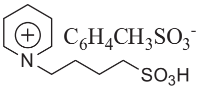
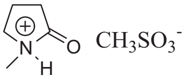
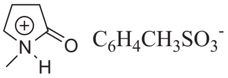
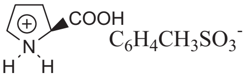
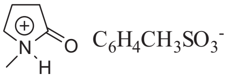
Table 1
The condensation of cyclohexanone[a] and pyrrole[a] at reflux in aq EtOH[b] under the catalytic influence of different Brønsted AILs[c]



Entry	Catalyst	Time (h)	% Conversion of pyrrole[d]	Yield (%)[e]	
				CP	NCCP
1		7	90.1	51.4	31.7 (7.0)[f]
2		7	81.5	43.5	38.0
3		7	85.2	44.0	41.2
4		7	93.8	60.6	33.2
5		7	91.3	45.3	46.0
6		7	94.2	45.5	48.7
7		6	93.9	38.2	55.7
8		6	96.3	33.8	62.5
9		7	91.4	49.9	37.5 (4.0)[f]
10		6	89.3	40.3	49.0
11[g]		6	n.d.[h]	15.8	–

[a] Substrate concentration: 28 mmol.
[b] Ethanol/water (1:1, v/v).
[c] Catalyst concentration: 1.5 mmol; for detailed experimental procedure, see Supplementary data.
[d,e] Based on isolated yields.
[f] Yields in parenthesis represent doubly N-confused calix[4]pyrroles.
[g] Condensation of acetone and pyrrole: linear oligomers were predominantly formed under experimental conditions.
[h] Not detected.

and ^{13}C NMR Spectroscopy. 1-methyl-3-(4-sulfobutyl)imidazolium hydrogen sulfate, **Ia**, was primarily screened under a variety of experimental conditions to optimize the product distribution at room temperature.

Initially, an equimolar amount (28 mmol) of **3** and **4** was mixed together with (50 mL) or without EtOH. A catalytic amount of **Ia** (1 mmol) was added to this stirred solution. Unfortunately, in either case, the rapid formation of sticky material hampered the reaction progress just after 5 min. The TLC (SiO_2, DCM/Hexane; 1:1, v/v) of crude along with authentic samples indicated the predominant formation of linear oligomers, **5** and **6,** which was further assisted by ^1H NMR spectroscopy.

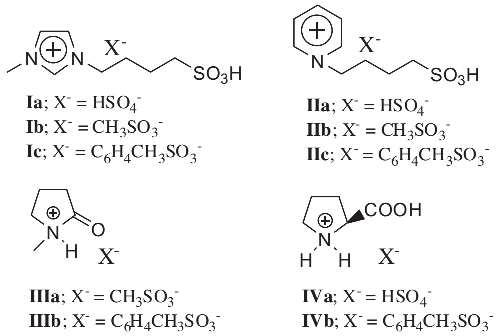


Figure 1. Structures of different Brønsted acidic ionic liquids (AILs).

Using different approach, **Ia** (1 mmol) was added to a well stirred solution of **4** (28 mmol) followed by quick addition of **3** (28 mmol) at room temperature. This protocol of switching the sequence of adding reactants is found ineffective here though it has proved quite useful in the product conversion from dipyrrane to tripyrrane.[24] We observed that stirring became difficult due to immediate precipitation of products. The qualitative TLC (SiO_2, DCM/Hexane; 1:1, v/v) analysis indicated the formation of **1** and **5** (ca. 70%) only and was further confirmed by recording ^1H NMR spectrum of crude (See Supplementary data Fig. S26).

The variation of reactants molar ratio was implemented as another tactic in this study. Nevertheless, the mixing of **3** (28 mmol) and **4** (84 mmol) followed by the addition of **Ia** (1 mmol) afforded almost identical product distribution (**5**+**1**) as mentioned above. Interestingly, this finding was in sharp contrast to that where a declining trend, favouring the formation of cyclic tetramer, is reported using a high stoichiometric ratio of pyrrole and acetone with Al-MCM-41.[33] Presumably, it is due to the strong acidity of **Ia** over Al-MCM-41 which may significantly affect the formation of porphyrinogens.

From this view point, we decided to examine the reaction in biphasic condition using DCM and **Ia** as two distinct phases. The protocol is well known and has been used successfully in the synthesis of porphyrins.[34] Mixing **Ia** and DCM (1:25, v/v) provided almost a single phase. To this well stirred solution, equimolar amounts of **3** and **4** (28 mmol) were added sequentially. After 1 h, the TLC of crude reaction mixture indicated the complete consumption of starting material with the formation of **1**+**5**. Prolonging the reaction time did not offer any noteworthy advantages. The only advantage of using biphasic system, here, was the predominant formation of **1**, consistent with other porphyrinogen synthesis.[34] It is worth mentioning here that the formation of **2** was not recognized in all cases as described above and still we were far away to achieve this challenging target.

After several initial trials in screening experimental conditions, we decided to perform the reaction at reflux. In this way, **Ia** was replaced by **Ib** and an $EtOH/H_2O$ mixture was employed in the reaction. Typically, equimolar amounts of **3** and **4** (28 mmol) were mixed with a well stirred mixture of $EtOH/H_2O$ (1:1, v/v). **Ia** (1.5 mmol) was added to this stirred solution and allowed to reflux. The progress of the reaction was scrutinized after each 30 min. To our delight, after 7 h, an excellent concentration of **2** was recognized on TLC. The reaction was worked-up to this point. Importantly, no dimer formation was observed at refluxing conditions rendering the extraction procedure more facile. Following aqueous-organic extraction and column chromatography, **2** was isolated in ~38% yield.

With this intriguing result in hand, we were encouraged to investigate the feasibility of AILs, **I**–**IV**, in the aforementioned synthesis and the results are summarized in Table 1. The results indicate that the use of AIL catalysts directs the reaction process towards the efficient formation of **2**. The **2** was isolated typically in between 31–62% yields under virtually identical conditions. This yield enhancement in the presence of **I**–**IV** may be attributed to the template effect between pyrrole rings, forcing the reacting groups to the correct position, for NCCP formation. However, in the presence of *N*-methyl-2-pyrrolidonium p-toluene sulfonate, **IIIb**, scrambling occurred and the condensation of pyrrole and acetone (Table 1, entry 11) afforded primarily linear oligomers and little of *meso*-octamethyl calix[4]pyrrole which was isolated in 15% yield. This may be ascribed to the substituent effect on cyclic and acyclic ketones.

The data presented in Table 1 clearly reveal that the cationic and anionic counterparts of ILs have large impact in this specific reaction. In particular, the pyrrolidonium based ILs, **IIIa** and **IIIb** (entry 7 and 8) exhibited very high activity for NCCP synthesis. The activity trends of cationic counterparts in NCCP synthesis were determined to be pyrrolidonium > prolinium > pyridinium > imidazolium. On the other hand, the p-toluenesulfonate counter anion (entry 3, 6, 8 and 10) was found quite efficient over others. The activity trends of anionic counterparts were determined to be p-toluene sulfonate > methane sulfonate > hydrogen sulfate. Although the working action of Brønsted AILs, leading to NCCP in high yields, is not very clear at this stage, the preliminary experimental results dictate that high yield synthesis of NCCP is not only possible but also quite acceptable.

Conclusions

In summary, we have developed and implemented a simple, green, efficient and highly productive methodology in the one-flask reaction of pyrrole and cyclohexanone leading to NCCP. To the best of our knowledge, the Brønsted AILs have been used for the first time as catalysts in calixpyrrole synthesis. The isolated yield of 62.5% represents a ~threefold improvement over previously reported catalytic conditions (22%). It is quite reasonable to expect that the present work will enable the rapid development of the NCCP building blocks, valuable in supramolecular chemistry and stimulate continued investigation of methods for one-flask NCCP synthesis. Further, investigations to broaden the scope of chiral AILs in the synthesis of asymmetric calixpyrroles are currently underway in our laboratory and will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (general procedures, spectroscopic data and copies of ^1H and ^{13}C NMR spectra (**I**–**IV**, **1** and **2**)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.047.

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