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Amit Kumar Rawat, S.M.S. Chauhan

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#### **Graphical Abstract**



#### Efficient ZnCl<sub>2</sub> assisted synthesis of calix[4]pyrroles catalyzed by Brønsted acidic ionic liquids

Amit Kumar Rawat and S.M.S. Chauhan\*

Bio-organic Research Laboratory, Department of Chemistry, University of Delhi, Delhi-110007, India;

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ABSTRACT

\* correspondence Author Tel.: +; Fax : +91-11-27666845

E-Mail: smschauhan@chemistry.du.ac.in

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A facile and efficient protocol is reported for the synthesis of calix[4]pyrroles and *N*-confused calix[4]pyrroles in moderate to excellent yields by one-pot condensation of ketones and pyrrole in the presence of catalytic amount of non-toxic acidic ionic liquids. In this reaction the products were obtained in short reaction time with selectivity of regular calix[4]pyrroles.

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Calix<sup>[4]</sup> pyrroles or meso-substituted porphyrinogens are an important class of neutral macrocycles receptor capable of binding anions,<sup>1</sup> transition metals<sup>2</sup> and neutral molecules<sup>3</sup> in both solution and solid states.<sup>4</sup> Although calix[4]pyrroles have been synthesized 100 years ago by the acid catalyzed condensation of ketones and pyrrole,<sup>5</sup> after that a number of strategies have been employed to synthesize and characterize various functionalized calix[4]pyrroles by using a wide varieties of catalyst including HCl,<sup>6,7</sup> Lewis acids,<sup>8,9</sup> chlorzinc,<sup>10</sup> p-toluenesulfonic acid or organic acid<sup>11,12</sup> to improve the yield of specific calix[4]pyrroles. However, the use of excess and stoichiometric amount of acids with even

chlorinated solvents makes such processes environmentally questionable.

It is therefore of considerable interest to search for alternative methods for the synthesis of calix[4]pyrroles in high yields along with trace amount of N-confused calix[4]pyrroles. The product distribution synthesis of in the porphyrinogens and related compounds can be switched from one to another, depending on the type of acid catalysts and their way of implementation in the reaction. In this context, the literature reports by Dehaen,<sup>13</sup> Radha Kishan,<sup>14</sup> and Chavasiri<sup>15</sup> are particularly attractive. Although all the reported methods for the synthesis of calix[4]pyrroles have been examined in the presence of strong acids such as BF<sub>3</sub>O(Et)<sub>2</sub>, TFA,

and methylsulfuric acid. In order to avoid the use of corrosive acid and to minimize the amount of harmful organic solvents, the development of a new method for the synthesis of calix[4]pyrroles catalyzed by Brønsted acidic ionic liquids assist by zinc chloride would be highly desirable.

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, noncorrosiveness, negligible vapour pressure and tunable polarity with common organic solvents.<sup>16-20</sup> In addition, these advantages turn out to be more attractive using ILs in dichloromethane. Inspired by the early report<sup>21</sup> and the critical role of AILs in organic synthesis encouraged us to examine the catalytic scope of AILs in the synthesis of calix[4]pyrroles and N-confused calix[4]pyrroles assist by zinc chloride (Scheme 1, Figure 1).

For this study various Brønsted acidic ionic liquids (**1a-1h**) were prepared by known literature procedure<sup>22</sup> with minor modification. The different acidic ionic liquids were used for the synthesis of calix[4]pyrroles and better yields were obtained in the presence of acidic ionic liquid **1a** with respect to longer alkyl chains in dichloromethane (Table 1). Due to the short chain length of methylene groups, there is decrease in hydrophobicity and +I effect of ionic liquid leading to an increase in acidic character. Primarily **1a** was screened under a variety of experimental conditions to optimize the product distribution at room temperature.

Initially, equimolar amounts of pyrrole (14 mmol) and acetone (14 mmol) were taken up in dichloromethane (10 mL). A catalytic amount of 1a (0.14 mmol) was added to this stirred solution. After 40 min, the TLC of crude reaction mixture indicated the complete consumption of starting material with the formation of compound 3+4. Prolonging the reaction time did not offer any noteworthy advantages. The yields of products were calculated by HPLC using methanol and water (v/v 1:1) as eluent. The HPLC yield of calix[4]pyrrole and N-confused calix[4]pyrrole was reported 80 and 20 % respectively with retention time 3.4 and 3.8 minute (See Supplementary material, Figure S1). Nonetheless, equimolar amounts of pyrrole (14 mmol) and acetone (14 mmol) were taken up in dichloromethane (10 mL) containing a catalytic amount of zinc chloride. A catalytic amount of 1a (0.14 mmol) was added to this stirred solution and observed the formation of products in 94.67 and 5.33 % HPLC yield of calix[4]pyrrole and N-confused calix[4]pyrrole with retention time 3.4 and 3.8 minute Scheme 1

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(See Supplementary material, Figure S2). Moreover, the same reaction was performed in the presence of (1d) ionic liquid in dichloromethane. After 40 min, the TLC of crude reaction mixture indicated the complete consumption of starting material with the formation of compound 3+4 in 60

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and 10 % yields along with the side products e.g. dipyrromethane and tripyromethane. Apart from this, a black tarry product was also observed, but due to less sample availability and poor solubility in organic solvents a detailed structural characterization was not possible.

Scheme 1: Synthesis of calix[4]pyrroles and N-confused calix[4]pyrroles



The use of ([HSO<sub>3</sub>-pmim][CF<sub>3</sub>COO<sup>-</sup>]) (**1a**) as a catalyst showed a higher catalytic activity as compared to [HSO<sub>3</sub>-pmim][ HSO<sub>4</sub><sup>-</sup>]) (**1d**) and the yields improved further, when catalytic amount of

ZnCl<sub>2</sub> was added (Table 1, Entry 3). The reaction performed without acid catalyst with prolonged reaction time gave calix[4]pyrrole along with other linear products. This type of conversion has been

4

reported in the litrature<sup>23</sup> (Table 1, Entry 2). Typically, equimolar amounts of pyrrole and acetone (14 mmol) were taken up in stirred solution of dichloromethane (10 ml). Ia (0.14 mmol) and catalytic amount of zinc chloride was added to this stirred solution and allowed to reflux. The progress of the reaction was monitored after each 10 min. To our delight, after 40min, an excellent concentration of 3 was recognized on TLC. The reaction was worked-up to this point. Importantly, no dimer formation was observed at refluxing conditions. On the other hand reaction at refluxing temperature did not offer any noteworthy advantages in the yield of N-confused calix[4]pyrrole.

Prompted by above reports and in continuation of our interest in synthesis of various meso substituted calix[4]pyrroles and N-confused calix[4]pyrroles, we report herein a high yielding and time efficient synthesis of calix[4]pyrroles, which would be a new practical alternative to the existing procedures for this useful ring system. The results are summarized in Table 1. The results indicate that the use of AILs catalysts directs the reaction process towards the efficient formation of **3**. Compound **3** was isolated typically in between 80-93 % yields by column chromatography over neutral alumina under virtually identical conditions. This yield enhancement in the presence of **Ia–Ih** assisted by zinc chloride may be attributed to be template effect of chloride anion between pyrrole rings, forcing the reacting groups to the correct position, for regular calix[4]pyrrole formation (Figure 2).



# Figure 2: Plausible geometry of calix[4]pyrrole with chloride anion

Interestingly, when the reaction was performed with various organic solvents the best results were obtained in dichloromethane; where chloride ion act as a template to assist the formation and selectivity of regular calix[4]pyrroles. This finding was in sharp contrast to the report, 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<sup>24</sup>. Presumably, it is due to the strong acidity of **1a** over Al-MCM-41 which may significantly affect the formation of porphyrinogens.

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Table	1: Synthe	sis of c	alix[4]p	yrrole a	nd N-	Ent	
confused calix[4]pyrrole in presence of different							
Brønsted acidic ionic liquids <b>Ia-1h</b> <sup>a</sup>							
Entry	ZnCl <sub>2</sub>	ketone	Time	Yield <sup>c</sup> (%)		2	
	/AILs		(min)	3	4	3	
1	-/1a	2a	120	79.60	20.40	4	
2	ZnCl <sub>2</sub> /-	2a	360	60 <sup>b</sup>	-	5	
3	ZnCl <sub>2</sub> /1a	2a	40	94.76	5.33	6	
4	ZnCl <sub>2</sub> /1b	2a	45	80	5%	<sup>a</sup> Re	
5	ZnCl <sub>2</sub> /1c	2a	45	80	-	pyr	
6	ZnCl <sub>2</sub> /1d	2a	45	49.49 <sup>b</sup>	6.13	(10	
7	ZnCl <sub>2</sub> /1e	2a	50	80	4		

50

50

50

80

75

50<sup>b</sup>

5

7

<sup>a</sup>Reaction conditions: reaction temperature 25 °C, pyrrole (14.4 mmol), acetone (14.4 mmol); solvent (10 mL) dichloromethane; <sup>b</sup>other linear products were observed; <sup>c</sup>HPLC yields

2a

2a

2a

ZnCl<sub>2</sub>/1f

 $ZnCl_2/1g$ 

ZnCl<sub>2</sub>/1h

8

9

10

Thus high yield of compound **3a** in the presence of Brønsted acidic ionic liquids prompted us to examine the reaction in dichloromethane of other ketones **2b-2f** with pyrrole. The reaction products and yields are summarized in Table 2.

Table 2: Reaction of different ketones 2a-2f withpyrrole in presence of (1a)

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Entry	ZnCl <sub>2</sub> /AILs	ketone	Time	Yield $(\%)^{b}$				
			(min)	3	4			
1	ZnCl <sub>2</sub> /1a	2a	40	92%	3%			
2	ZnCl <sub>2</sub> /1a	2b	60	80%	-			
3	ZnCl <sub>2</sub> /1a	2c	40	80%	2%			
4	ZnCl <sub>2</sub> /1a	2d	45	85%	3%			
5	ZnCl <sub>2</sub> /1a	2e	40	93	6			
6	ZnCl <sub>2</sub> /1a	<b>2</b> f	60	90	-			
<sup>a</sup> Reaction conditions: reaction temperature 25 °C,								

pyrrole (14.4 mmol), ketones (14.4 mmol); solvent (10 mL) dichloromethane; <sup>b</sup>Isolated yields.

The structures of **3a-3f** and **4a**, **4c**, **4d** and **4e** were confirmed by IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and HRMS spectroscopic data and compared with reported literature.<sup>25</sup>

The rapid development in the synthesis of calix[4]pyrroles and N-confused calix[4]pyrroles building blocks used in the supramolecular chemistry, stimulate continued investigation of methods for one-flask synthesis.

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