

## A facile synthesis of calix[4]pyrroles using heteropolyacids as green, eco-friendly, reusable and recyclable catalyst

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A catalytic method was proposed for the synthesis of calix[4]pyrroles and *N*-confused calix[4]pyrroles by reaction of dialkyl or cycloalkyl ketones with pyrrole using heteropolyacids as acidic catalysts with good yields under mild and environmentally friendly conditions.

**Keywords:** Calix[4]pyrrole; Heteropolyacid; Preyssler; Catalysis; *N*-confused calix[4]pyrrole

### 1. INTRODUCTION

Heteropolyacids are classified according to their structures. Two classes, the Keggin and the Wells–Dawson structures, have been investigated more extensively than the others [1,2]. The use of heteropolyacids, HPAs, has recently received considerable attention as nontoxic and environmentally benign catalysts for various organic transformations to afford the corresponding products in good yield. Due to the numerous advantages associated with these ecofriendly (green) catalysts, HPAs and their salts have been explored as powerful, efficient and ecofriendly catalysts in organic reactions [3]. An important area of supramolecular chemistry is the design and synthesis of receptors to recognize, sense and bind the anions [4]. Calixarenes are a very important class of macrocyclic compounds which are widely used as ligands in supramolecular chemistry. Modification of the upper rim of calix[4]phenols by means of  $S_N^H$  coupling with electron-deficient triazinones is a new approach to change the molecular cavities of these compounds, which opens new possibilities for construction of highly selective ligands [5]. The research and development have been made under milder methods for the synthesis of porphyrins [6], N-C isomerization [7] and higher homologues of porphyrins [8]. The meso-octamethylcalix[4]pyrrole **3a** has been prepared by condensation of pyrrole with acetone in the presence of aqueous hydrochloric acid or methanesulfonic acid in methanol [9]. Calix

[4]pyrroles are conformationally flexible macrocycles [10] of significant importance due to their binding under different conditions with anions [11], neutral substrates [9] and metal ions [12]. The complexation behavior of calix[4]pyrroles with anions and cations has been widely studied using fluorescence [13], colorimetric [14] and electrochemical signaling [15] devices. They find interesting applications as raw materials for transformation into novel calix[4]pyridines and calix[4]pyridinopyrroles [16], as new solid supports capable of separating anion mixtures [17], in optical recognition of organic vapors [18] and as biologically active species [19]. Porphyrinogens, bearing hydrogen atoms at meso positions, are key intermediates in biological and chemical synthesis of porphyrins [20].

Synthesis of meso-octamethylcalix[4]pyrrole (**3a**) and *N*-confused octamethylcalix[4]pyrrole (**4b**) has been performed using pyrrole and acetone in the presence of trifluoroacetic acid [21]. The reactions of pyrrole with dialkyl ketones in the presence of protic acids (HCl, H<sub>2</sub>SO<sub>4</sub>), organic acids (CH<sub>3</sub>SO<sub>3</sub>H) and Lewis acids (BBr<sub>3</sub> and BF<sub>3</sub>) have also been used in the synthesis of calix[4]pyrroles [22]. The reaction of excess of pyrrole with dialkylketones in the presence of acid gave 5,5-dialkyldipyrromethanes which on subsequent reaction with dialkylketones in the presence of borontrifluoride-etherate formed strapped calix[4]pyrroles [23]. These acids are considered hazardous and corrosive and their removal from the reaction mixtures is difficult. Recently, condensations in dichloromethane of pyrrole with dialkyl ketones in the presence of the molecular sieve Al-MCM-41 and the zeolite HY

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afforded dipyrromethane, calix[4]pyrroles and other linear products, but not the *N*-confused calix[4]pyrroles [24]. Heteropolyacids (HPAs) are inexpensive and non-hazardous solid acids, useful as catalysts.

## 2. EXPERIMENTAL SECTION

### Chemicals and apparatus

All chemical compounds were obtained from commercial sources and used as received.

IR spectra were recorded on a Bruker 500 scientific spectrometer. <sup>1</sup>H NMR spectra were recorded in CDCl<sub>3</sub> with TMS as internal standard on a FT NMR Bruker 100 MHz Aspect 3000 spectrometer. The mass spectra were scanned on a Varian Mat. CH-7 at 70 eV. Melting points were recorded on an Electrothermal type 9100 melting point apparatus and were uncorrected.

### Preparation of Catalysts

**Preyssler catalyst, H<sub>14</sub>[NaP<sub>5</sub>W<sub>30</sub>O<sub>110</sub>] (H<sub>14</sub>-P<sub>5</sub>).** H<sub>14</sub>-P<sub>5</sub> was prepared by passage of an aqueous solution of the potassium salt through a column (50 cm×1 cm) of Dowex50W×8 in the H<sup>+</sup> form and evaporation of the eluate to dryness under vacuum [25].

**Wells-Dawson species H<sub>6</sub>[P<sub>2</sub>W<sub>18</sub>O<sub>62</sub>].** The Wells-Dawson species H<sub>6</sub>[P<sub>2</sub>W<sub>18</sub>O<sub>62</sub>] was prepared as described elsewhere [26] from an aqueous solution of the α/β K<sub>6</sub>P<sub>2</sub>W<sub>18</sub>O<sub>62</sub>·10H<sub>2</sub>O salt, which was treated with ether and concentrated (37%) HCl solution.

### General procedure

**Preparation of calix[4]pyrroles (3a-g) and *N*-confused calix[4]pyrroles (4a-4e).** Synthesis of

meso-octamethylcalix[4]pyrrole (**3a**) and *N*-confused octamethyl calix[4]-pyrrole (**4a**):

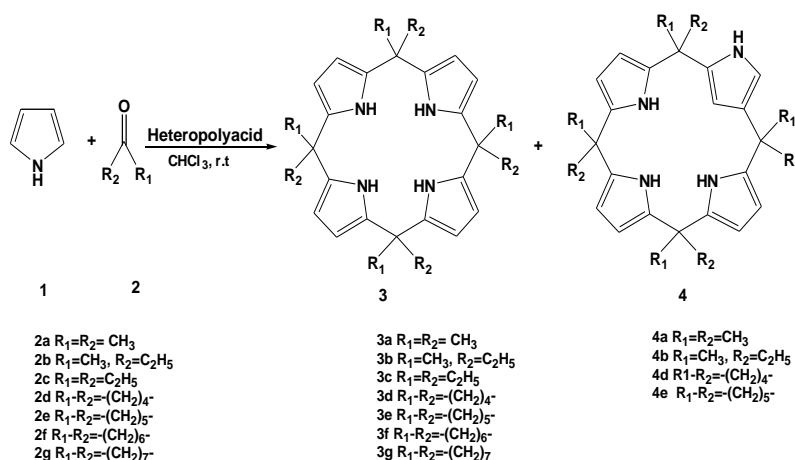
A mixture of pyrrole (8 mmol), acetone (8 mmol), CHCl<sub>3</sub> (10 mL) and heteropolyacid catalyst (0.04 mmol) was added to the bottom flask and the mixture was stirred for 6 hours at room temperature. The reaction progress was monitored by thin layer chromatography (TLC). After completion of the reaction, the catalyst was removed by filtration and washed thoroughly with CHCl<sub>3</sub> to dissolve all contents. The filtrate was pre-concentrated to give the crude product, which was subjected to column chromatography to afford pure meso-octamethylcalix[4]pyrrole (**3a**). The further elution of the column with petroleum ether-chloroform (2:3, v/v) gave the *N*-confused isomer of octamethylcalix[4]pyrrole (**4a**). The above-described general method was used for the synthesis of different calix[4]pyrroles (**3b-3g**) and *N*-confused calix[4]pyrroles (**4b, 4d** and **4e**).

### Reusability of catalyst

The recycled catalyst could be washed with dichloromethane and subjected to a second run of the reaction process with the same substrate. The results of the first and subsequent experiments were almost consistent in yields (83, 82.5 after three runs).

## 3. RESULTS AND DISCUSSION

We wish to report the synthesis of calix[4]pyrrole (**3a**) and the *N*-confused calix[4]pyrrole (**4a**) by using heteropolyacids as acid catalysts, and we performed this synthesis in a chloroform solution of pyrrole (**1**) with acetone for 6 hrs in the presence of Preyssler catalyst (Scheme 1, Table 1).



**Scheme 1.** Synthesis of calix[4]pyrroles using Preyssler and Wells-Dawson heteropolyacids

**Table 1.** Reaction of different ketones (2a-2g) with pyrrole in CHCl<sub>3</sub>, catalyzed by a Preyssler heteropolyacid catalyst H<sub>14</sub>-P<sub>5</sub>.

Compound	Time (h)	% Conversion of Pyrrole	<sup>a</sup> Yield(%) / mp°C, (3)	(lit. mp°C, [ref.]) (3)	<sup>a</sup> Yield(%) / mp°C, (4)	(lit. mp °C, [ref.]) (4)
2a	6	95	84.5/295	(296 [27])	11.5/185	(184-185 [41])
2b	8	88	80/144	(146 [42])	10/121	-
2c	18	71.5	74.5/222	-	-	-
2d	5	93	83/235	(236 [42])	11.5/198	-
2e	5	96	85/273	(271-272 [43])	12/224	(223.2-223.6[43])
2f	24	37	32/163	-	-	-
2g	48	25.5	21.5/223	-	-	-

<sup>a</sup> Isolated yields.**Table 2.** Preyssler catalyzed condensation of pyrrole and acetone in different solvents.

Entry	Solvent	<sup>a</sup> Yield (%) 3a	<sup>a</sup> Yield (%) 4a
1	CHCl <sub>3</sub>	84.5(83, 82.5) <sup>b</sup>	11.5 (11, 10.5) <sup>b</sup>
2	CCl <sub>4</sub>	56	-
3	Benzene	45	-
4	Toluene	44	-
5	DMF	39	-
6	DMSO	36	-
7	Ethanol	71.5	9.5
8	THF	51	-
9	Acetonitril	68	8

<sup>a</sup> Isolated yields. <sup>b</sup> Catalyst was reused over three runs.**Table 3.** Reaction of different ketones (2a-2g) with pyrrole in CHCl<sub>3</sub>, catalyzed by Wells-Dawson and Keggin (12-tungstophosphoric acid).

Compound	Reaction time (min)	<sup>a</sup> Yield (%) using H <sub>6</sub> P <sub>2</sub> W <sub>18</sub> O <sub>62</sub> (3)	<sup>a</sup> Yield (%) using H <sub>3</sub> PW <sub>12</sub> O <sub>40</sub> (3)	<sup>a</sup> Yield (%) using H <sub>6</sub> P <sub>2</sub> W <sub>18</sub> O <sub>62</sub> (4)	<sup>a</sup> Yield (%) using H <sub>3</sub> PW <sub>12</sub> O <sub>40</sub> (4)
2a	6	81	77	8.5	7
2b	8	76.5	75	8	-
2c	18	70	68	-	-
2d	5	79	74.5	8	-
2e	5	82.5	79	7.5	-
2f	24	26	20	-	-
2g	48	16.5	11.5	-	-

<sup>a</sup> Isolated yields.

We carried out the synthesis of calix[4]pyrrole (**3a**) using various heteropolyacids (Table 2). The results showed that the yield of this synthesis is excellent using Preyssler and Wells–Dawson type tungstophosphoric heteropolyacid, H<sub>6</sub>P<sub>2</sub>W<sub>18</sub>O<sub>62</sub>, catalysts. The synthesis reaction (Scheme 1) was tested using different solvents and the best yields were obtained in chloroform (Table 2).

We performed this synthesis with other ketones (**3b–3g**) and pyrrole in chloroform as a solvent and used the Preyssler and Wells–Dawson type tungstophosphoric heteropolyacid, H<sub>6</sub>P<sub>2</sub>W<sub>18</sub>O<sub>62</sub>, catalyst (Table 3).

The reactions of cycloheptanone (**2f**) and cyclooctanone (**2g**) with pyrrole in presence of the Preyssler catalyst gave the corresponding calix[4]pyrroles (**3f**) and (**3g**) in 32% and 21.5% yields at ambient temperature, but the time required for the conversions was considered too long. In the reactions of pyrrole with **2c**, **2f** and **2g**, the corresponding *N*-confused calix[4]pyrroles could not be isolated. This could be attributed to the steric hindrance encountered with these higher acyclic and cyclic ketones. The atoms at C-2 and C-5 positions in pyrrole are more reactive than those at C-3 and C-4 positions, hence the electrophilic reaction at the C-2 and C-5 positions of pyrrole

**Table 4.** <sup>1</sup>HNMR spectral data for meso-octaalkyl and cycloalkyl calix[4]pyrroles (3a-3g).

Compound	<sup>1</sup> HNMR δ (ppm) <sup>a</sup>
<b>3a</b>	7.01 (4H, br s, NH), 5.89 (8H, d, J=2.5 Hz, β-pyrrole), 1.50 (24 H, s)
<b>3b</b>	6.97 (4H, br s, NH), 5.80 (8H, d, J=2.5 Hz, β-pyrrole), 1.79-1.76 (8H, q, -CH <sub>2</sub> ), 1.45-1.18 (12H, br s, CH <sub>3</sub> ), 0.80-0.63 (12 H, t, CH <sub>3</sub> )
<b>3c</b>	7.05 (4H, br s, NH), 5.89 (8H, d, J=2.3 Hz, β-pyrrole), 1.79-1.57 (16H, q, -CH <sub>2</sub> ), 0.71-0.58 (24 H, t, CH <sub>3</sub> )
<b>3d</b>	7.03 (4H, br s, NH), 5.85 (8H, d, J=2.3 Hz, β-pyrrole), 2.21-2.00 (16H, m), 1.68-1.44 (16H, m)
<b>3e</b>	7.25 (4H, br s, NH), 5.89 (8H, d, J=2.5 Hz, β-pyrrole), 1.91-1.90 (16H, m), 1.50-1.41 (24H, m)
<b>3f</b>	6.88 (4H, br s, NH), 5.83 (8H, d, J=2.5 Hz, β-pyrrole), 2.01-1.94 (16H, m), 1.72-1.52 (32H, m)
<b>3g</b>	6.99 (4H, br s, NH), 5.93 (8H, d, J=2.4 Hz, β-pyrrole), 1.97-1.95 (16H, m), 1.52-1.34 (32H, m), 1.23-1.21 (8H, m)

<sup>a</sup>All products are known, characterized by <sup>1</sup>H-NMR and compared with authentic samples [24].

**Table 5.** <sup>1</sup>HNMR spectral data for meso-octaalkyl and cycloalkyl *N*-confused calix[4]pyrroles (4a, 4b, 4d, 4e).

Compound	<sup>1</sup> HNMR δ (ppm)
<sup>a</sup> 4a	NH: 7.75 (1H, br), 7.41 (1H, br), 7.26 (2H, br); α-pyrrole: 6.30 (1H, d, J= 2 Hz); β-pyrrole: 6.04 (2H, br), 5.97 (2H, br), 5.93 (2H, m), 5.50 (1H, br); 1.56-1.48 (24H, m)
4b	NH: 7.63 (1H, br), 7.53 (1H, br), 7.35 (2H, br); α-pyrrole: 6.40 (1H, d, J= 2 Hz); β-pyrrole: 6.03 (2H, br), 5.88 (2H, br), 5.78 (2H, m), 5.53 (1H, br); 1.92 (3H, s, CH <sub>3</sub> ), 1.83-1.12 (29H, m)
4d	NH: 7.48 (1H, br), 7.29 (1H, br), 7.00 (2H, br); α-pyrrole: 6.42 (1H, d, J=1.97 Hz); β-pyrrole: 6.00 (2H, br), 5.90 (2H, br), 5.88 (2H, m), 5.58 (1H, br); 2.25-1.98 (16H, m), 1.50-1.20 (16H, m)
<sup>a</sup> 4e	NH: 7.63 (1H, br), 7.44 (1H, br), 7.10 (2H, br); α-pyrrole: 6.42 (1H, d, J= 1.98 Hz); β-pyrrole: 6.03 (2H, br), 5.97 (2H, br), 5.82 (2H, m), 5.50 (1H, br); 2.70-2.10 (16H, m), 1.60-1.20 (24H, m)

<sup>a</sup>Products *N*-confused calix[4]pyrroles (4a, 4e) are known, characterized by <sup>1</sup>H-NMR and compared with authentic samples [27].

with acetone in the presence of acid gave calix[4]pyrrole in preference to *N*-confused calix[4]pyrrole [27]. The recovered catalyst was recycled twice with a modest loss in product yield (Table 1). The catalytic activity of the heteropolyacid catalysts is remarkable. Heteropolyacid catalysts are environmentally benign and commercially available. The spectral data for the compounds (**3a-3g** and **4a, 4b, 4d, 4e**) are shown in Tables 4, 5.

#### 4. CONCLUSIONS

We reported a catalytic method for the synthesis of calix[4]pyrrole using a Preyssler heteropolyacid catalyst as an efficient, reusable and ecofriendly heterogeneous inorganic catalyst. It is noteworthy that the catalyst is reusable. Even after three runs for the calix[4]pyrrole reaction, the catalytic activity of H<sub>14</sub>[NaP<sub>5</sub>W<sub>30</sub>O<sub>110</sub>] was almost the same as that of a fresh catalyst. H<sub>14</sub>[NaP<sub>5</sub>W<sub>30</sub>O<sub>110</sub>] is non-corrosive, environmentally benign and presents fewer disposal problems. Furthermore it was confirmed that a heteropolyacid with Preyssler structure displays higher activity and leads to higher yields due to the higher number of acidic protons.

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#### REFERENCES

1. I. V. Kozhevnikov, *Chem. Rev.*, **98**, 171 (1998).
2. Y. Izumi, K. Urabe, M. Onaka, *Zeolite, Clay and Heteropoly Acid in Organic Reactions*, Kodansha/VCH, Tokyo, 1992.
3. T. Okuhara, N. Mizuno, M. Misono, *Advances in Catalysis, Catalytic Chemistry of Heteropoly compounds*, 113 (1996).
4. P. A. Gale, J. L. Sessler, V. Král, *Chem. Commun.*, 1 (1998).
5. O. N. Chupakhin, G. L. Rusinov, N. A. Itsikson, D. N. Beresnev, M. I. Kodess. *Abstracts of the First World Congress on Synthetic Receptors*, Lisbon., p. 2.01 (2003).
6. S. M. S. Chauhan, B. B. Sahoo, K. A. Srinivas, *Synth. Commun.*, **31**, 33 (2001).
7. G. R. Geier, D. M. Haynes, J. S. Lindsey, *Org. Lett.*, 1455 (1999).

8. T. K. Chandrashekar, S. Venkatraman, *Acc. Chem. Res.*, **36**, 676 (2003).
9. P. Rothenmund, C. L. Gage, *J. Am. Chem. Soc.*, **77**, 3340 (1955).
10. J. L. Sessler, S. Camiolo, P. A. Gale, *Coord. Chem. Rev.*, **240**, 17 (2003).
11. P. A. Gale, J. L. Sessler, V. Král, V. J. Lynch, *J. Am. Chem. Soc.*, **118**, 5140 (1996).
12. J. Bachmann, D. G. Nocera, *J. Am. Chem. Soc.*, **127**, 4730 (2005).
13. H. Miyaji, P. Anzenbacher, J. L. Sessler, E. R. Bleasdale, P. A. Gale, *Chem. Commun.*, 1723 (1999).
14. P. A. Gale, L. J. Twyman, C. I. Handlin, J. L. Sessler, *Chem. Commun.*, 1851 (1999).
15. P. A. Gale, M. B. Hursthouse, M. E. Light, J. L. Sessler, C. N. Warriner, R. S. Zimmerman, *Tetrahedron Lett.*, **42**, 6759 (2001).
16. V. Král, P. A. Gale, Jr. Anzenbacher, K. Jursíková, V. Lynch, J. L. Sessler, *Chem. Commun.*, 9 (1998).
17. L. J. He, Q. S. Cai, S. J. Shao, S. X. Jiang, *Chin. Chem. Lett.*, **12**, 511 (1998).
18. S. Conoci, M. Palumbo, B. Pignataro, R. Rella, L. Valli, G. Vasapollo, *Eng. Asp.*, **198**, 869 (2002).
19. J. L. Sessler, W. E. Allen, *Chemtech.*, **29**, 16 (1999).
20. C. Floriani, *Chem. Commun.*, 1257 (1996).
21. S. Depraetere, M. Smet, W. Dehaen, *Angew. Chem. Int. Ed.*, **38**, 3359 (1999).
22. Jr. P. Anzenbacher, K. Jursíková, V. M. Lynch, P. A. Gale, J. L. Sessler, *J. Am. Chem. Soc.*, **121**, 11020 (1999).
23. H. Miyaji, S. Hong, D. Jeong, D. Yoon, H. Na, J. Hong, S. Ham, J. L. Sessler, C. A. Lee, *Angew. Chem. Int. Ed.*, **46**, 2508 (2007).
24. M. Radha Kishan, N. Srinivas, K. V. Raghavan, S. J. Kulkarni, J. A. R. P. Sarma, *Chem. Commun.*, 2226 (2001).
25. F. F. Bamoharram, M. M. Heravi, M. Roshani, M. Jahangir, A. Gharib, *Applied Catalysis A: General.*, **302**, 42 (2006).
26. G. Romanelli, J. C. Autino, G. Baronetti, H. Thomas, *Molecules.*, **6**, 1006 (2001).
27. Jr. P. Anzenbacher, R. Nishibayyu, M. A. Palacios, *Coord. Chem. Rev.*, **250**, 2929 (2006).

## ЛЕСНА СИНТЕЗА НА КАЛИКС[4]ПИРОЛИ, ИЗПОЛЗВАЙКИ “ЗЕЛЕНИ”, ЕКОЛОГИЧНО СЪВМЕСТИМИ И РЕЦИКЛИРУЕМИ КАТАЛИЗАТОРИ

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(Резюме)

Предложен е каталитичен метод за синтезата на каликс[4]пироли и техни конформационни изомери с високи добиви чрез реакции на диалкил- и циклоалкил-кетони с пирол използвайки хетеро-поли-киселини като киселинни катализатори при меки и екологично съвместими условия.