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A NOVEL PROTOCOL FOR THE SYNTHESIS CALIX[4]PYRROLES AND *N*-CONFUSED CALIX[4]PYRROLES

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ABSTRACT

Inorganic solid acid have been used for the synthesis of calix[4]pyrroles and *N*-confused calix[4]pyrroles by the one-pot condensation of ketones and pyrrole in methanol at room temperature.

KEYWORDS: Calix[4]Pyrrole, Catalysis, *N*-Confused Calix[4]Pyrrole, Novel Inorganic Acid

INTRODUCTION

Porphyrinogens or meso-substituted calix[4]pyrroles are important tetrapyrrolic macrocycles used in biosynthesis of porphyrinoids[1] and supramolecular chemistry[2]. Calixpyrrole, offer a cup-shaped skeleton, in which four pyrrole hydrogen bond donors are perfectly pre-organized for anions,[3-5] neutral substrates[6] and metal ions[7]. Due to their significant importance a number of strategies have been synthesized and characterized various functionalized calix[4]pyrroles by using strong acids such as Lewis acid,[8,9] HCl[6,7] and organic acid.[11,12] In order to avoid the use of corrosive acid, the development of a new method for the synthesis of calix[4]pyrroles and N-confused calix[4]pyrroles catalysed by inorganic acid would be highly desirable. In recent year, novel acid has gained special attention as a catalyst in organic synthesis because many advantages such as excellent solubility in methanol/ethanol and water, non-toxic, easy to handle, inexpensive, eco-friendly nature, readily available and high reactivity. Lately, synthetically useful organic transformation using inorganic novel acid as a catalyst has been reported in the literature[13].

Inspired by the early report and the critical role of solid acid in organic synthesis[14] motivated us to examine the catalytic scope of novel inorganic acid in the synthesis of calix[4]pyrroles and N-confused calix[4]pyrroles. Herein, we report the high yield synthesis of calix[4]pyrroles and especially N-confused calix[4]pyrroles in the condensation of pyrrole (**1**) and various ketones (**2**) by making use of novel acid as catalysts under stirring at room temperature reaction condition in a very short time <0.5-1.5hrs (**Scheme 1 Table 2**). However, the reported catalysts require longer reaction time giving acceptable yields of products for this conversion. The present procedure is superior in comparison with TFA, CH_3SO_3H and $BF_3O(Et)_2$ catalyzed reactions of ketones with pyrrole which generated several unexpected products[15]. Whereas expensive, TFA, CH_3SO_3H and $BF_3O\ (Et)_2$ catalyzed reactions took a very long reaction time (4h)[16].

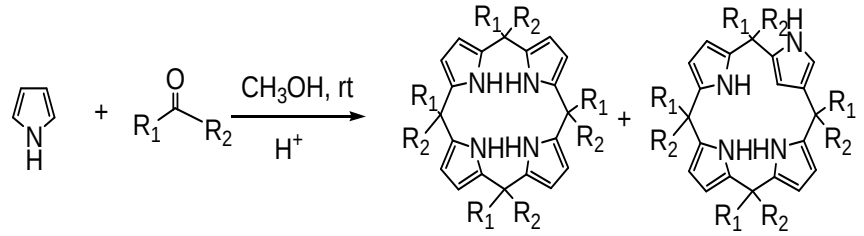
RESULTS AND DISCUSSIONS

The novel inorganic acid was synthesized by known procedures[13] with minor modification (**See Supplementary data**). The reaction of equimolar amount of pyrrole (**1**) with acetone (**2a**) in the presence of novel acid in methanol shows the completion of reaction in 1.5hr at 25˚C forms the octamethylcalix[4]pyrrole (**3a**) and *N*-confused octamethylcalix[4]pyrrole (4a) in 73.52% and 26.48% HPLC yield respectively scheme 1 (**See Supplementary data Figure S3**) while the same reaction was performed in presence of methane sulfonic acid in methanol at 25˚C for 4 hrs gave

octamethylcalix[4]pyrrole (**3a**) and *N*-confused octamethylcalix[4]pyrrole (**4a**) in 85.17, 14.83 % HPLC yields respectively (**See supplementary data Figure S4**). Further the reaction of equimolar amount of pyrrole with acetone in presence of silica sulfuric acid in methanol at room temperature for 6hrs gave octamethylcalix[4]pyrrole (**3a**), *N*-confused octamethylcalix[4]pyrrole (**4a**) and 5,5-dimethyl dipyrromethane in 82.39, 11.39 and 6.13 % HPLC yields and required prolonged reaction time, separation of compounds were difficult due to the solid materials mixed with silica and settled down in bottom resulted hampered the reaction. On the other hand reaction of pyrrole with acetone in presence of Amberlyst-15 in dry dichloromethane at ambient temperature for 8hrs gave calix[4]pyrrole (**3a**) and *N*-confused calix[4]pyrrole (**4a**) in 82.17 and 17.83 % HPLC yield with retention time 3.4 and 3.9 minute (**See Supplementary data Figure S6**). The structure of **3a** and **4a** were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and ESI-MS spectroscopic data and comparison of HPLC retention time with authentic sample (**See supplementary data).** The above reaction was performed in other solvents and results were summarized in Table 1. The moderate to excellent yields of calix[4]pyrrole (**3a**) and *N*-confused calix[4]pyrrole (**4a**) were obtained when the reaction was performed in methanol (**Table 2, Entry 8**).

The formation of compound **3a** and **4a** in the presence of novel acid prompted us to examine the cyclization of other ketones **2b-2e** with pyrrole (**Table 2**) and characterized by different spectroscopic data match with reported in literature[17]

The reaction of cyclohexanone with pyrrole in the presence of novel acid in methanol gave solid precipitate within 30 min indicating two product formations on TLC with R_f values 0.85 and 0.42 respectively.



2a. R_1=R_2 = CH_3 3a. R_1=R_2 = CH_3 4a. R_1=R_2 = CH_3

2b. R_1=R_2 = C_2H_5 3b. R_1=R_2 = C_2H_5

2c. R_1= CH_3, R_2 = C_2H_5 3c. R_1= CH_3, R_2 = C_2H_5 4c. R_1= CH_3, R_2 = C_2H_5

2d. R_1-R_2 = $(CH_2)_4$ 3d. R_1-R_2 = $(CH_2)_4$ 4d. R_1-R_2 = $(CH_5)_4$

2e. R_1-R_2 = $(CH_2)_5$ 3e. R_1-R_2 = $(CH_2)_5$ 4e. R_1-R_2 = $(CH_2)_5$

Scheme 1

The reactions of different di-substituted ketones with pyrrole in presence of novel acid in different solvents were performed and results summarized in **table 1**.

Table 1: Various Solid Acid Catalyzed Condensations of Pyrrole and Acetone in Different Solvents[a]

Entry	Solvents	Conversion of Pyrrole (%)	HPLC Yield (%)		
			3	4	Other[c]
1	CH_2CL_2(GO)	99			
2	CH_2CL_2(zeoliteHY)	87.9			16.2
3	HZSM-5	69.6	10.7		5.9
4	A1-mcm-41	92.4	67.4		21.8
5	DCM(Am berlystTM-15)	99	82.17	17.83b	
6	CH_3OH(MSA)	97	85.17	14.83b	
7	Silica-SO3H	98	82.38	11.48b	6.13b
8	CH_3OH/C_2H_5OH(Novel acid)	99	73.52	26.48b	
9	CH CL_3(Novel acid)	65	55	8	2
10	CH_2CL2(Novel acid)	80	68	10	4
11	EtOAc(Novel acid)	35	35		
12	THF(Novel acid)	50	50		
13	C_6H_6(Novel acid)	42	42		
14	Toluene(Novel acid)	40	40		

[a]**Reaction conditions:** pyrrole (10.0 mmol) and acetone (10.0 mmol); solvent (10 mL); novel acid (100 mg); r.t.; [b]yield were calculated by HPLC. [c]other products: linear trimer and tetramer, respectively could not characterized

This high yield formation of **3a** and **4a** in the presence of novel solid acid encouraged us to examine the reaction in methanol of other ketones **2b-2e** with pyrrole. The reaction products and yields are given in **Table 2**. Further the novel acid catalyzed condensation of different aliphatic ketones with pyrrole in methanol gave the calix[4]pyrrole and improved yield of *N*-confused calix[4]pyrrole were monitored by HPLC data.

Table 2: HPLC Yields by the Reaction of Different Ketones (2a-2e) with Pyrrole in Methanol, Catalyzed by Novel Solid Acid[a]

Entry	Ketones	Time(hrs)	Conversion of Pyrrole (%)	HPLC Yield (%)[b]	
				3	4
1	2a	1.5	99	73.52	26.48
2	2b	4	80	100	
3	2c	1	85	87.45	12.55
4	2d	2	89	81.73	18.27
5	2e	0.5	95	81.50	18.50

[a]Novel acid was dried before use; [b]yield were calculated by HPLC

The products were characterized by m.p. and comparison of HPLC retention time with authentic samples.

EXPERIMENTAL

The melting points were recorded on Thomas Hoover Unimelt capillary melting point apparatus. All m.p. are uncorrected and expressed in degree centigrade. The infrared spectra were recorded on Perkin-Elmer FT-2000 spectrometer and ν_{max} are expressed in cm^{-1}. ^1H NMR was recorded on Jeol-delta-400 spectrometer using tetramethylsilane (TMS) as an internal standard and chemical shifts (δ) are expressed in ppm. HRMS (ESI) were recorded by LC-TOF (KC-455) mass spectrometer of Waters. HPLC analysis was performed on Waters 2998 Photodiode Array Detector on a Waters PAH C18 HPLC column (4.6×250 mm) using methanol as the eluent. The starting materials were purchased from Spectrochem Chemicals India and Aldrich.

Synthesis of *meso*-5, 5, 10, 10, 15, 15, 20, 20-octamethyl calix[4]pyrrole (**3a**)

Equimolar amount of pyrrole (10.0 mmol) and acetone (10.0 mmol) were taken up in methanol (10 mL). Solid acid (100 mg) was added to the reaction mixture, which was stirred at 25˚C for 1.5 h. The progress of reaction was monitored by thin layer chromatography (TLC). After the completion of reaction, the precipitate was filtered and washed with water, dry under vacuum to give the crude product, which was subjected to column chromatography over neutral alumina eluting with petroleum ether-chloroform (9:1, v/v) to afford pure *meso* octamethylcalix[4]pyrrole (**3a**). The above general method is used for the synthesis of different calix[4]pyrroles **3b**-**3e** and *N*-confused calix[4]pyrroles **4c**, **4d** and **4e**.

mp 295° C; R_f = 0.8 (SiO_2, 1:1 petroleum ether/chloroform); IR (KBr) v/cm^{-1} 3444, 2973, 2932, 2870, 1578, 1448, 1414, 1279, 1233, 1044, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (*s*, 24H, CH_3), 5.90 (d, *J* 2.92 Hz, 8H, CH), 7.08 (*bs*, 4H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.08, 35.15, 102.67, 138.55.

Further elution of the column with petroleum ether-chloroform (3:2, v/v) gave the *N*-confused isomer of *meso*-octametylcalix[4]pyrrole (**4a**): mp 185° C; R_f = 0.45 (SiO_2, 1:1 petroleum ether/chloroform); IR (KBr) v/cm^{-1} 3430, 2910, 2845, 1521, 1616, 1179, 749. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48-1.54 (m, 24H, CH_3), 5.07 (brs, 1H, *β*-pyrrole CH), 5.87 (m, 2H, CH), 5.89 (brs, 2H, CH), 5.90 (brs, 2H, CH), 6.51 (*s*, 1H, CH), 6.97 (brs, 1H, NH), 7.13 (br, 1H, NH), 7.48 (brs, 1H, NH),7.76 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.0, 29.4, 29.6, 30.3, 34.6, 35.3, 35.8, 35.9, 101.6, 101.8, 102.1, 102.8, 103.3, 103.9, 104.2, 111.6, 133.2, 137.5, 137.8, 138.2, 138.7, 138.8, 139.4, 141.1.

meso-5,5,10,10,15,15,20,20-Octaethyl calix[4]pyrrole **(3b)**: white solid. mp 224° C. R_f = 0.76 SiO_2, 1:1 petroleum ether/chloroform). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.64-0.68 (24 H, t, CH_3-), 1.79-1.57 (16H, q, -CH_2-), 5.89 (8H, d, *J*=2.80 Hz, *β*-pyrrole), 7.09 (4H, brs, NH). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 8.05(CH_3), 29.1(-CH_2), 42.9(*meso* C), 104.8 (*β*-pyrrole CH), 135.9(*α*-pyrrole C).

meso-5,10,15,20-Tetraethyl-*meso*-5,10,15,20-tetramethyl-calix[4]pyrrole **(3c)**: white solid. mp 144° C. R_f = 0.76 SiO_2, 1:1 petroleum ether/chloroform). IR (KBr pellet, cm^{-1}): 3435 (*br*, pyrrole NH), 2968, 2931, 2876, 1413, 1297, 1211, 1040, 761, 706. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.68-0.71 (12H, t, CH_3-), 1.36-1.40 (8H, q,-CH_2-), 1.85 (12H, brs, CH_3), 5.88 (8H, d, *J* = 1.44 Hz, *β*-pyrrole), 7.08 (4H, brs, NH). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 8.6 (-CH_3), 29.9 (CH_3-), 33.1(-CH_2), 39.1(*meso*-C), 103.7(*β*-pyrrole CH), 137.2(*α*-pyrrole C).

meso-5,10,15,20-Tetraethyl-*meso*-5,10,15,20-tetramethyl N-confused calix[4]pyrrole **(4c)**: white solid. mp 120° C. R_f = 0.4 SiO_2, 1:1 petroleum ether/chloroform). IR (KBr pellet, cm^{-1}): 3435 (*br*, pyrrole NH), 2968, 2931, 2876, 1413, 1297, 1211, 1040, 761, 706. ^{1}H NMR (400 MHz, $CDCl_3$) δ= 1.85-1.21 (9H, m), 1.90 (3H, s, CH_3), 5.49 (1H, br), 5.71 (2H, m), 5.98 (2H, br), 6.04 (2H, br, *β*-pyrrole), 6.42 (1H, d, *J*= 2 Hz, *α*-pyrrole), NH: 7.34 (2H, br), 7.50 (1H, br), 7.52 (1H, br).

meso-5,5,10,10,15,15,20,20-Tetraspirocyclopentyl calix[4]pyrrole **(3d)**: white solid. mp 235° C. R_f = 0.83 SiO_2, 1:1 petroleum ether/chloroform). IR (KBr pellet, cm^{-1}): 3496 (*br*, pyrrole NH), 2959, 2870, 1630, 1580, 1414, 1254, 1042, 765. ^{1}H NMR (400 MHz, $CDCl_3$) δ= 1.71-1.69 (16H, m, -CH_2), 2.03-2.00 (16H, m, -CH_2), 5.86 (8H, d, *J* = 2.8 Hz, *β*-pyrrole), 7.10 (4H, br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ= 23.76, 38.89 (cyclopentyl C), 46.79 (*meso* C), 102.89 (pyrrole *β*-CH), 137.14 (pyrroles *α*-CH).

meso-5,5,10,10,15,15,20,20-Tetraspirocyclopentyl *N*-confused calix[4]pyrrole **(4d)**: white solid. mp 199° C. R_f = 0.42 SiO_2, 1:1 petroleum ether/chloroform). IR (KBr pellet, cm^{-1}): 3496 (*br*, pyrrole NH), 2959, 2870, 1630, 1580, 1414,

1254, 1042, 765. ^{1}H NMR (400 MHz, $CDCl_3$) δ= 1. 65-1.46 (16H, m, -CH_2). 2.05-2.00 (16H, m, -CH_2), 5.49 (s, 1H,), 5.89-5.83 (m, 6H, *β*-pyrrole), 6.41 (1H, d, *J*=2.2 Hz, *α*-pyrrole), NH: 7.39 (2H, br), 7.52 (1H, br), 7.6 (1H, br).

meso-5,5,10,10,15,15,20,20-tetraspirocyclohexyl calix[4]pyrrole **(3e):** white solid. Mp 273° C. R_f = 0.85 SiO_2, 1:1 petroleum ether/chloroform). IR (KBr pellet, cm^{-1}): 3445 (*br*, pyrrole NH), 2924, 2849, 1577, 1413, 1184, 752. ^{1}H NMR (400 MHz, $CDCl_3$) δ= 1.40-1.47 (24H, m), 1.89-1.92 (16H, m), 5.88 (8H, d, *J* = 2.7 Hz, *β*-pyrrole), 7.04 (4H, br s, NH)**;** ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 22.69, 25.96, 37.13, 39.55 (hexyl C), 103.41 (pyrrole *β*-CH), 136.39 (pyrroles *α*-CH).

meso-5,5,10,10,15,15,20,20-tetraspirocyclohexyl N-confused calix[4]pyrrole **(4e):** white solid. mp 223° C. R_f = 0.42 SiO_2, 1:1 petroleum ether/chloroform). IR (KBr pellet, cm^{-1}): 3400 (*br*, pyrrole NH), 2977, 2872, 1579, 1491, 1182 772, 700. ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.20 ± 1.60 (m, 24H, cyclohexyl), 1.70-2.10 (m, 16H, cyclohexyl), 5.50 (br, 1H; pyrrole *β*-H), 5.82 (m, 2H; pyrrole *β*-H), 5.97 (br, 2H; pyrrole *β*-H), 6.03 (br, 2H; pyrrole *β*-H), 6.42 (d, *J*=1.97 Hz, 1H; pyrrole *α*-H), 7.10 (br, 2H; pyrrole NH), 7.44 (br, 1H; pyrrole NH), 7.63 (br, 1H, pyrrole NH). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ.22.77, 25.91, 25.99, 26.36, 36.51, 37.0, 37.4, 37.67, 38.36, 39.31, 39.70, 39.72, (hexyl C), 101.3, 102.2, 103.9 (3× pyrrole *β*-CH), 112.8 (pyrrole *α*-CH), 130.1 (pyrrole *β*-C), 133.7, 134.6, 136.5, 137.8, 139.1, 140.3 (pyrrole *α*-C).

CONCLUSIONS

The calyx[4]pyrroles and specially improved the yield of *N*-confused calix[4]pyrroles were achieved by the facile and efficient cyclocondensation of various ketones and pyrrole in presence of novel inorganic acid in methanol at room temperature. The cheap availability of the reagent, easy procedure and work-up make this method attractive for the large scale operations.

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