# Ytterbium(III) triflate catalyzed synthesis of calix[4]pyrroles in ionic liquids

**Anil Kumar, Israr Ahmad, and M. Sudershan Rao**

**Abstract:** Ytterbium(III) triflate has been utilized as a mild Lewis-acid catalyst for the synthesis of various calix[4]pyrroles by the condensation of pyrrole with different ketones in ionic liquids. The calix[4]pyrroles were obtained in high yield under ecofriendly, economical, and noncorrosive conditions, and the catalyst was recovered and recycled.

*Key words:* calix[4]pyrrole, ionic liquid, ytterbium triflate.

**Résumé :** On a utilisé le triflate d’ytterbium(III) comme catalyseur acide de Lewis doux pour la synthèse de divers calix[4]pyrolles par condensation du pyrrole avec diverses cétones dans des liquides ioniques. Les calix[4]pyrolles ont été obtenus avec des rendements élevés dans des conditions économiques, non corrosives et respectueuses de l’environnement alors que le catalyseur peut être récupéré et recyclé.

*Mots-clés :* calix[4]pyrolle, liquide ionique, triflate d’ytterbium.

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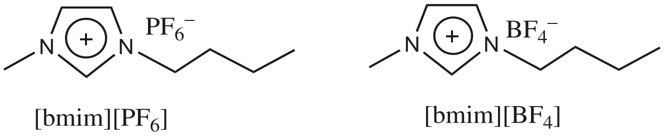
## Introduction

Calix[4]pyrroles, a class of tetrapyrrolic macrocyclic molecules, have been known for a long time but recently have become the subject of intensive research because of their properties for binding with anions, transition metals, and neutral molecules (1). Their anion-binding properties has been extensively studied as a result of their potential biological applications (2). Calix[4]pyrroles were first synthesized over a century before by the condensation of acetone and pyrrole in the presence of hydrochloric acid (3). Since then various methods have been developed to increase the yield and selectivity of the products (4–6). The disadvantages of these methods are that the acid catalysts are corrosive in nature and the workup procedure is tedious and it involves neutralization. Moreover, the yields of calix[4]pyrrole are low and they are accompanied by a mixture of linear oligomers. There is a need to develop a method for the synthesis of calix[4]pyrroles that is ecofriendly, economic, and noncorrosive.

To meet the increasing demands of environmental legislation for the development of organic reactions in environmentally friendly media, synthetic manipulations have to be made to minimize the use of hazardous chemicals, such as replacing the traditional organic solvents in reactions and their subsequent workup with nontoxic solvents. In this regard, ionic liquids, especially those based on 1,3-dialkylimidazolium cations (Fig. 1), have gained considerable interest as a green alternative to volatile organic solvents (VOS) in recent years (7). Their nonvolatile nature and lack of any detectable vapour pressure gives them a significant advantage in minimizing solvent consumption and also addresses the problem of the emission of VOS into the atmosphere, thus making these solvents an environmentally attractive alternative to classical organic solvents (8). The recoverability and reusability of the catalysts immobilized in ionic liquids are key features required to develop economical, efficient, and green chemical processes (9).

**Fig. 1.** Imidazolium ionic liquid.



Lanthanide(III) trifluromethanesulfonates, $Ln(OTf)_3$, have enjoyed extensive applications in a variety of Lewis acid catalyzed organic reactions (10). The growing interest in the use of these salts is due to their ease of handling, noncorrosiveness, reusability, and unique reactivity and selectivity. Ytterbium(III) *tris*-trifluromethanesulfonate, $Yb(OTf)_3$ (commonly called ytterbium triflate), is known to be a useful mild Lewis acid and has gained importance in organic synthesis in recent years (11). It was first used by Forsberg et al. (12) and since then it has found a wide utility in organic synthesis (13). Lanthanide triflates immobilized in ionic liquids have been used as efficient and recyclable catalysts for different organic reactions. The chemistry of lanthanides and actinides in ionic liquids was recently reviewed by K. Binnemans (14).

As a part of our ongoing research, we became interested in ionic liquids as an alternative reaction media for various organic transformations (15). We also reported $Yb(OTf)_3$ catalyzed synthesis of 1,3-oxathiolanes in ionic liquids (16). Herein, we report for the first time the synthesis of calix[4]pyrroles catalyzed by $Yb(OTf)_3$ in ionic liquids

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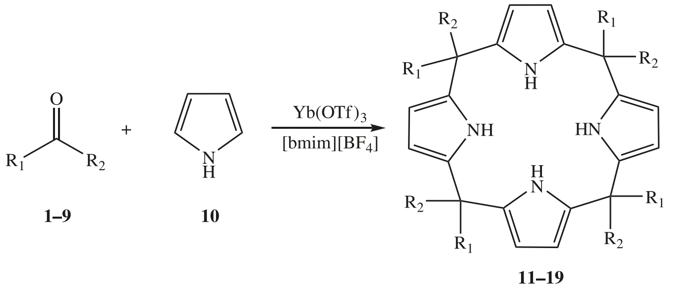
**Scheme 1.** Synthesis of calix[4]pyrroles in ionic liquid.



(Scheme 1), which is superior to previous Brønsted and Lewis acid catalyzed methods and overcomes the problems encountered with classical Lewis acids.

## Results and discussion

The cyclocondensation of acetone (**1**) and pyrrole (**10**) at room temperature in ionic liquid [bmim][$BF_4$] containing 20 mol% Yb(OTf)$_3$ gave 100% conversion of acetone after 10 h as monitored by GC analysis. After completion of the reaction, the product was extracted with an ethyl acetate – hexane mixture and purified by column chromatography to give pure *meso*-octamethyl calix[4]pyrrole (**11**) in 92% yield (Table 1, entry 1). The $^1$H NMR spectrum of **11** showed a broad singlet at $\delta$ 9.23 for NH protons and a singlet at $\delta$ 5.67 and $\delta$ 1.50 for 8 $\beta$-pyrrolic protons and 24 *meso*-methyl protons, respectively. It showed a $[M + H]^+$ ion peak at *m/z* 429.2360 in the positive ion mode HRMS (ESI-MS) spectrum. In the IR spectra of **11**, a peak appeared at 3438 cm$^{-1}$ for N–H stretching.

The reaction was also carried out in a more hydrophobic ionic liquid, [bmim][$PF_6$], and an almost equal yield of calix[4]pyrrole (**11**) was obtained under these conditions. Therefore, we chose [bmim][$BF_4$] as the solvent of choice for further reactions. After the success of this reaction, the synthesis of *meso*-substituted calix[4]pyrroles (**12–19**) was also studied by the condensation of different cyclic and acyclic ketones with pyrrole catalyzed by Yb(OTf)$_3$ in ionic liquid and the results are shown in Table 1. The products were characterized by IR, HR-MS, and $^1$H NMR spectroscopy. Higher cyclic ketones and substituted acyclic ketones produced slightly less yields as compared with acetone (Table 1). The reaction of unsymmetrical ketones produced a mixture of isomers, but $\alpha\alpha\alpha\alpha$-isomer was in the majority. We did not observe the formation of N-confused calix[4]pyrroles under these conditions, which are reported to be accompanied in minor amounts, along with calix[4]pyrrole in a recently reported amberlyst 15 catalyzed synthesis of calix[4]pyrroles (6*d*).

To study the reusability, the recovered ionic liquid containing Yb(OTf)$_3$ was reused for the synthesis of **16**. After extraction of calix[4]pyrrole from the ionic liquid with an ethyl acetate – hexane mixture, the ionic liquid containing Yb(OTf)$_3$ was dried under vacuum for 30 min. To this dried ionic liquid containing Yb(OTf)$_3$, pyrrole and acetophenone (**6**) were added and stirred at room temperature for 12 h. The reaction mixture was extracted by the ethyl acetate – hexane mixture and the combined organic layer was evaporated to give **16**. This cycle was repeated five times. The catalysts showed good reactivity and yield even after five cycles with little deterioration in catalytic activity as shown in Table 2. The slight deterioration in catalytic activity may be due to a slight decomposition of the ionic liquids because of the release of water in the reaction. Generally, ionic liquids based on imidazolium cation with either tetrafluoroborate or hexafluorophosphate as anions are water insensitive; however, the exposure to moisture for a long time can cause some changes in their physical and chemical properties (17). The products obtained were of the same purity as in the first reaction.

## Conclusion

In conclusion, we have developed an efficient, simple, economical, noncorrosive, and ecofriendly method for the synthesis of various calix[4]pyrroles catalyzed by ytterbium(III) triflate in ionic liquids. This method provides several advantages such as easy synthesis, simple workup, and satisfactory recovery and reuse of the ionic liquid immobilized ytterbium triflate with no diminution of product yields.

## Experimental section

All the chemicals and reagents were of analytical grade. Ketones and pyrrole were purchased form S.D. Fine and Spectrochem, India. Sodium tetrafluoroborate and 1-methylimidazole were purchased from Sigma-Aldrich. Ionic liquid [bmim][$BF_4$] was prepared according to an earlier reported procedure (15*a*, 15*b*). The $^1$H NMR spectra were recorded on a Bruker Avance II 400 (400 MHz) spectrophotometer using TMS as internal standard and $CDCl_3$ as solvent, and the chemical shifts were expressed in ppm. The IR spectra were recorded using KBr pellets on a Shimadzu Prestige-21 FTIR spectrophotometer and $\nu_{max}$ was expressed in cm$^{-1}$. Mass spectra were recorded on a KC455 Waters TOF MS spectrometer. TLC was run on silica gel coated aluminium sheets (silica gel 60 $F_{254}$, E. Merck, Germany) and visualized in UV light at 254 nm.

### General procedure for the synthesis of calix[4]pyrrole in ionic liquid catalyzed by Yb(OTf)$_3$

To a 10 mL round bottom flask containing ionic liquid [bmim][$BF_4$] (3.0 mL) was added acetone (110 µL, 1.49 mmol), freshly distilled pyrrole (103 µL, 1.49 mmol), and Yb(OTf)$_3$ (20 mol%, 46.2 mg). The reaction mixture was stirred at room temperature for 10 h. Twenty microlitres of the reaction mixture were removed after every 1 h interval and analyzed by TLC and GC. After completion of the reaction, the reaction mixture was extracted with hexane – ethyl acetate (2 × 5 mL, 1:1 *v*/*v*). Ionic liquid containing ytterbium triflate was recovered and dried under vacuum. The combined organic layer was evaporated under reduced pressure. The residue was column chromatographed over silica gel 60–120 mesh using hexane – ethyl acetate as eluent to give pure **11** (146 mg, 92%). The calix[4]pyrrole obtained was characterized by IR, $^1$H NMR, $^{13}$C NMR, and HRMS spectroscopic data.

**Table 1.** Synthesis of calix[4]pyrroles from different ketones catalyzed by 20 mol% Yb(OTf)$_3$ in ionic liquids

| Entry | Ketone | Product | Time (h) | Conversion (%)[a,b] |
|---|---|---|---|---|
| **1** | $R_1 = R_2 = CH_3$ | **11** | 10 | 100 (92) |
| **2** | $R_1 = C(CH_3)_3$, $R_2 = CH_3$ | **12** | 10 | 98 (84) |
| **3** | $R_1$-$R_2$ = -$(CH_2)_4$- | **13** | 10 | 99 (88) |
| **4** | $R_1$-$R_2$ = -$(CH_2)_5$- | **14** | 10 | 95 (85) |
| **5** | $R_1$-$R_2$ = -$(CH_2)_7$- | **15** | 12 | 93 (79) |
| **6** | $R_1$ = Ph, $R_2 = CH_3$ | **16** | 12 | 97 (85) |
| **7** | $R_1$ = 4-Me-Ph, $R_2 = CH_3$ | **17** | 12 | 98 (84) |
| **8** | $R_1$ = 4-Cl-Ph, $R_2 = CH_3$ | **18** | 15 | 95 (78) |
| **9** | $R_1$ = 3-$NO_2$-Ph, $R_2 = CH_3$ | **19** | 15 | 96 (75) |

[a]The isolated yield provided by column chromatography on silca gel is in parentheses.
[b]All products were characterized by IR, ESI-MS, $^1H$ NMR, and $^{13}C$ NMR spectra.

**Table 2.** Reusability of recovered Yb(OTf)$_3$ in ionic liquid for the synthesis of *meso*-tetramethyl tetraphenyl calix[4]pyrrole (**16**).

| Run | Conversion (%) | Product yield (%) |
|---|---|---|
| 1 | 98 | 85 |
| 2 | 95 | 81 |
| 3 | 90 | 80 |
| 4 | 88 | 75 |
| 5 | 84 | 72 |

### Spectroscopic data of selected calix[4]pyrroles

***meso-Octamethyl calix[4]pyrrole (11)***

$^1H$ NMR ($Me_4Si$; 400 MHz, DMSO-$d_6$) $\delta$: 9.23 (s, 4H), 5.67 (s, 8H), 1.5 (s, 24H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$: 35.4, 41.2, 111.3, 132.6. HRMS *m/z* calcd. for $C_{28}H_{36}N_4$: 428.2940; found: 429.2360 $[M + H]^+$.

***meso-Tetrakis(spirocyclopentane) calix[4]pyrrole (13)***

$^1H$ NMR ($Me_4Si$; 400 MHz, DMSO-$d_6$) $\delta$: 9.16 (s, 4H), 5.72 (s, 8H), 2.14 (t, *J* = 7.6 Hz, 16H), 1.59 (t, *J* = 7.6 Hz, 16H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$: 21.5, 26.5, 36.1, 40.3, 111.3, 132.6. HRMS calcd. for $C_{36}H_{44}N_4$: 532.3566; found: 533.1338 $[M + H]^+$.

***meso-Tetramethyl-tetrakis(3′-nitrophenyl) calix[4]pyrrole (19)***

$^1H$ NMR ($Me_4Si$; 400 MHz, DMSO-$d_6$) $\delta$: 10.47 (s, 4H), 8.09 (m, 4H), 7.72 (m, 4H), 7.58 (m, 4H), 7.48 (m, 4H), 5.92 (s, 8H), 1.99 (s, 12H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$: 32.8, 39.8, 111.6, 118.3, 121.4, 128.5, 131.7, 132.1, 136.3, 143.2. HRMS calcd. for $C_{48}H_{40}N_8O_8$: 856.2969; found: 857.1823 $[M + H]^+$.

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