

## Yb(OTf)<sub>3</sub> Catalyzed Nucleophilic Conjugate Addition of Pyrrole to $\alpha$ , $\beta$ -Unsaturated Ketones and Nitro-compounds

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**Abstract:** Under the catalysis of Yb(OTf)<sub>3</sub>, nucleophilic conjugate addition of pyrrole to electron deficient olefins in CH<sub>2</sub>Cl<sub>2</sub> at ambient temperature gives corresponding 2-alkylated pyrrole derivatives in good yields with high selectivity.

**Keywords:** Ytterbium triflate, catalysis, nucleophilic conjugate addition, pyrrole derivative.

Over recent years, the use of lanthanide (III) compounds as catalysts or promoters in organic synthesis have aroused much attention<sup>1, 2</sup>. Among these works, lanthanide triflate mediated Lewis acid catalysis has attracted tremendous interest throughout scientific communities<sup>3, 4</sup>. Their low toxicity, ease of handling, recyclable nature and low cost make lanthanide derived species attractive alternatives to their classical competitors such as TiCl<sub>4</sub>, particularly in large-scale industrial processes.

Pyrrole containing compounds such as haemin, vitamin B<sub>12</sub>, indigo and bile pigments are widely distributed in nature<sup>5</sup>. Since the 2-position of pyrrole is the preferred site for electrophilic substitution, 2-alkyl and 2-acyl pyrroles are versatile intermediates for the synthesis of a wide range of pyrrole derivatives<sup>6</sup>. There are some traditional methods for the synthesis of these types of compounds, such as Vilsmeier-Haack method<sup>7</sup>, or the thermal rearrangement of N-alkyl pyrroles at high temperature<sup>8</sup>. But these methods usually have to suffer from side reactions and rigorous conditions. So it is very important to look for a simple and effective method to prepare 2-alkyl pyrroles. In our research to the application of rare earth metal reagent in organic synthesis, we have found that under the catalysis of Yb(OTf)<sub>3</sub>, the nucleophilic conjugate addition of pyrrole to electron deficient olefins gives corresponding 2-alkylated pyrrole derivatives in good yields (**Scheme 1**)

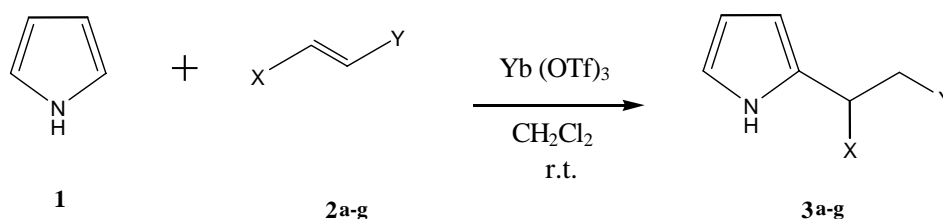
It is a new application of lanthanide compounds in the reaction of heterocyclic compounds. The reaction conditions and the results are showed in **Table 1**. The products were characterised by <sup>1</sup>H NMR, IR, some also further confirmed by MS. Lewis acids such as LaCl<sub>3</sub>, YbCl<sub>3</sub>, YCl<sub>3</sub> and Yb(OTf)<sub>3</sub> were tested to catalyze this reaction, among these Yb(OTf)<sub>3</sub> was found to be the most effective in the same reaction time (Entry b). When 5 mol% of Yb(OTf)<sub>3</sub> were used, the reaction gave the product with lower yield (To the reaction of Entry b, the yield was 50%). The appropriate

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amount of the catalyst is 10 mol%, and using 20 mol% of catalyst could not enhance the yield evidently. Dichloromethane was selected as solvent. At ambient temperature, the reaction proceeds smoothly. To  $\alpha$ ,  $\beta$ -unsaturated ketones and nitro-compounds, it gives 2-substituted products with higher yields and regio-selectivity. Under the present reaction conditions, only trace bis-alkylated products (less than 10% to the main products) were generated. Further more, the reaction conditions are very mild, it does not require any other acidic promoters and activators, so that no side products such as polymerization or decomposition products were observed. Dichloromethane can be used as commercially supplied and no need to be further dried. The catalyst was recovered from the aqueous layer during work-up and recycled in subsequent reactions without loss of activity.

### Scheme 1



**Table 1** The nucleophilic conjugate addition of pyrrole to electron deficient olefins<sup>a)</sup>

Entry	X	Y	Time/hr	Yield/%
a	H	COCH <sub>3</sub>	2	82
b	H	COPh	2	85 (46, 60, 55) <sup>b)</sup>
c	Ph	COCH <sub>3</sub>	2.5	72
d	Ph	COPh	3	65
e	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	COCH <sub>3</sub>	2.5	70
f	Ph	NO <sub>2</sub>	2.5	76
g	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	NO <sub>2</sub>	2.5	75

a) All products were confirmed by <sup>1</sup>H NMR and IR.

b) Catalyzed by 10 mol% LaCl<sub>3</sub>, YbCl<sub>3</sub>, YCl<sub>3</sub>, respectively, for the same reaction time.

### Typical procedure

Under nitrogen atmosphere, 0.1 mmol Yb(OTf)<sub>3</sub> and 1 mmol  $\alpha$ ,  $\beta$ -unsaturated ketone or  $\alpha$ ,  $\beta$ -unsaturated nitro-compound were added in 3 mL CH<sub>2</sub>Cl<sub>2</sub>, then 1 mmol pyrrole was added. The mixture was stirred at room temperature for an appropriate time. After the conversion completed (monitored by GC or TLC), 10 mL water was added and the mixture was extracted with diethyl ether for three times. The extracts were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The pure product was then obtained through column chromatography on silica gel (1: 8 ethyl acetate/petroleum ether). All of the products are known compounds, except compound **3c**. Compound **3c**: IR 3380, 3056, 1710 cm<sup>-1</sup>. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>):  $\delta$ ppm 2.05(s, 3H), 3.15(m, 2H), 4.46(t, 1H, J=6.8Hz), 5.85(m, 1H), 5.98(d, 1H, J=1.6Hz), 6.40(d, 1H, J=1.6Hz),

7.07 (m, 2H), 7.19 (m, 3H), 8.30 (brs, 1H). MS:  $m/z$  213 ( $M^+$ ). Anal. Calcd. for C<sub>14</sub>H<sub>15</sub>NO: C, 78.84; H, 7.09; N, 6.57. Found C, 78.76; H, 7.02; N, 6.50.

In summary, the present work provides a new reaction of pyrrole catalyzed by Yb(OTf)<sub>3</sub>, it is also a new application of lanthanide Lewis acid in organic synthesis. The notable advantages of this method are mild conditions, simple operation, high yields with good selectivity, compatibility with acid sensitive substrates and recoverability of the catalyst. So it is a useful method for the synthesis of 2-alkylated pyrrole derivatives.

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