



# Addition of pyrroles to electron deficient olefins employing $\text{InCl}_3$

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Received 25 June 2001; revised 31 August 2001; accepted 7 September 2001

**Abstract**—Pyrroles undergo conjugate addition with electron deficient olefins in the presence of a catalytic amount of indium trichloride at ambient temperature to afford the corresponding Michael adducts in excellent yields with high selectivity without polymerisation. © 2001 Elsevier Science Ltd. All rights reserved.

The syntheses and reactions of pyrroles have attracted much research interest for over a century because a number of pyrrole containing compounds such as chlorophyll, haemin, vitamin  $\text{B}_{12}$ , indigo and bile pigments are widely distributed in nature.<sup>1</sup> Since the 2-position of pyrrole is the preferred site for electrophilic substitution, 2-alkyl or 2-acyl pyrroles are versatile intermediates for the synthesis of a wide range of pyrrole derivatives.<sup>2</sup> Generally *C*-alkyl pyrroles are synthesised<sup>3</sup> by Wolff–Kishner reduction of 2-formyl or 2-acetyl pyrroles that are obtained by the Vilsmeier–Haack method.<sup>4</sup> Other methods for *C*-alkylation of pyrroles involve the isomerisation of *N*-alkyl pyrroles<sup>5</sup> by thermal rearrangement at high temperature, resulting in the 2- and 3-alkyl pyrroles. Alternatively, 2- and 3-alkyl pyrroles are prepared<sup>6</sup> using pyrrolylmagnesium halides. These indirect methods are used to obtain *C*-alkylated pyrroles as they tend to polymerise under most reaction conditions.

To date, the direct synthesis of 2-alkyl pyrroles remains a challenge for synthetic chemists because of their sensitivity to air and acids. Acid-catalysed reactions of pyrrole are limited and require careful control of acidity to prevent side reactions. As such, there is no report on the conjugate addition of pyrrole with electron deficient olefins to give 2-alkylated derivatives. Following the recent surge in activity on the use of  $\text{InCl}_3$ <sup>7</sup> as a mild Lewis acid, we report herein a simple and direct method for the synthesis of 2-alkyl pyrroles using  $\text{InCl}_3$ .

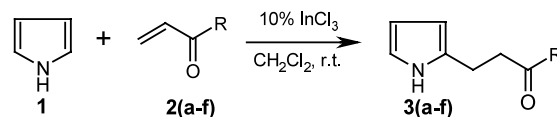
Treatment of pyrrole with methyl vinyl ketone in the presence of a catalytic amount of  $\text{InCl}_3$  in

dichloromethane gave 4-(2'-pyrrolyl)butan-1-one in 85% yield. Similarly, various  $\alpha,\beta$ -unsaturated compounds reacted well with pyrrole to give the corresponding 2-alkylated products in high yields (Scheme 1, Table 1).<sup>8</sup>

The reactions proceeded smoothly at ambient temperature with high selectivity. Other electron deficient olefins like phenyl vinyl ketone, benzyl vinyl ketone, 2-benzylidenemalononitrile and bis(benzylidene) ketone afforded the products in good yields. In the case of bis(benzylidene) ketone, no bis-alkylated product was observed under the reaction conditions (Table 1, entry f). Furthermore, treatment of  $\beta$ -nitrostyrene with pyrrole in the presence of 10 mol%  $\text{InCl}_3$  produced the corresponding 2-alkylated pyrrole in 78% yield (Scheme 2).

The reactions are clean and the products are obtained in high yields without the formation of any side products such as dimers or trimers that are normally observed under the influence of strong acids. In addition, the reaction conditions are very mild so that no side products or decomposition of the products are observed.

The procedure does not require any acidic promoters or activators or anhydrous conditions. The reaction of pyrrole with  $\alpha,\beta$ -unsaturated ketones probably pro-


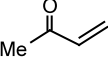
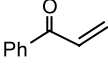
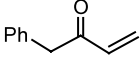
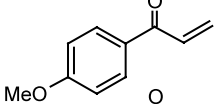
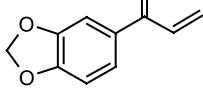
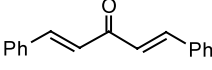
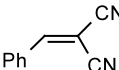
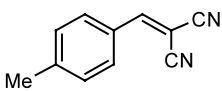
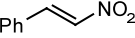
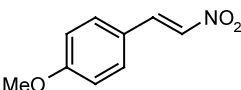
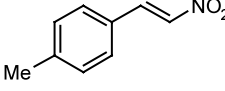
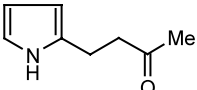
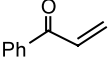
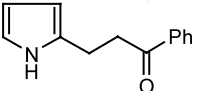
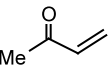
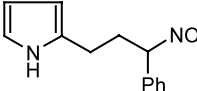
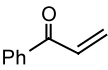


R = aryl, benzyl, anisyl, piperonyl, cinnamoyl and methyl

**Scheme 1.**

**Keywords:** indium trichloride; pyrrole;  $\alpha,\beta$ -unsaturated compounds.  
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**Table 1.** InCl<sub>3</sub>-catalysed alkylation of pyrroles with  $\alpha,\beta$ -unsaturated compounds

Entry	nucleophile(1)	electrophile(2)	2-dialkyl pyrrole(3) <sup>a</sup>		2,5-dialkyl pyrrole(4) <sup>b,c</sup>	
			time (hr)	yield	time (hr)	yield (%)
a			2.0	85	5.0	77
b	"		1.0	79	3.0	76
c	"		1.5	74	4.5	72
d	"		1.5	75	4.0	71
e	"		1.5	73	3.5	68
f	"		2.0	65	—	—
g	"		12	70	—	—
h	"		14	69	—	—
i	"		3.5	78	—	—
j	"		3.0	77	—	—
k	"		3.5	80	—	—
l			—	—	2.5	73
m			—	—	3.0	75
n			—	—	4.5	70

a : Isolated and unoptimised yields of monoalkylated pyrroles

b : Isolated and unoptimised yields of dialkylated pyrroles

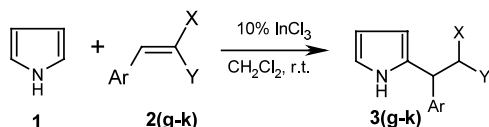
c : 2.4 moles of electron deficient olefins are used

ceeds through an intermediate  $\sigma$ -complex, as shown in Scheme 3.

It should be noted that the reaction of  $\alpha,\beta$ -unsaturated ketones with pyrroles afforded 2,5-dialkylated products

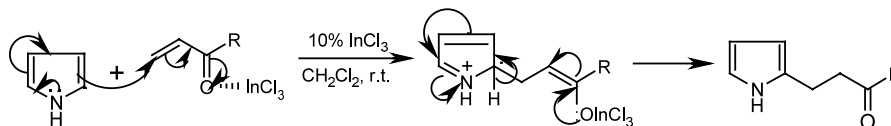
in high yields by increasing the reaction time and changing the molar ratio of reactants (Scheme 4).

In general,  $\alpha,\beta$ -unsaturated ketones,  $\beta$ -nitrostyrenes and benzylidene malononitrile worked well under the



3g, Ar=Phenyl, X=CN, Y=CN  
 3h, Ar=Tolyl, X=CN, Y=CN  
 3i, Ar=Phenyl, X=NO<sub>2</sub>, Y=H  
 3j, Ar=Anisyl, X=NO<sub>2</sub>, Y=H  
 3k, Ar=Tolyl, X=NO<sub>2</sub>, Y=H

Scheme 2.



Scheme 3.

influence of InCl<sub>3</sub> at ambient temperature. Some Michael acceptors such as methyl acrylate and acrylonitrile, failed to react with pyrroles under the present reaction conditions. Among various Lewis acids such as YbCl<sub>3</sub>, YCl<sub>3</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O and TaCl<sub>5</sub> used for this transformation, InCl<sub>3</sub> was found to be the most effective in terms of yield and reaction times. The catalyst was recovered from the aqueous layer during work-up and recycled in subsequent reactions without loss of activity.

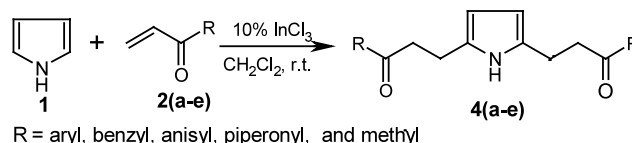
In summary, we have demonstrated that indium chloride is a superior Lewis acid for the alkylation of pyrroles with electron deficient olefins. The procedure has the advantages of mild reaction conditions, high yields of products, cleaner reactions with greater selectivity, short reaction times, operational simplicity, compatibility with acid sensitive substrates, recoverability of the catalyst and simple experimental/product isolation procedures which makes it a useful and attractive process for the synthesis of alkylated pyrrole derivatives.

### Acknowledgements

Authors S.A. and B.V.S.R. thank CSIR for the award of the fellowship.

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R = aryl, benzyl, anisyl, piperonyl, and methyl

Scheme 4.

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- General experimental procedures:** (a) *Monoalkylation of pyrroles*: To a stirred solution of vinyl ketone (5 mmol) or  $\beta$ -nitrostyrene or benzylidene malononitrile and indium trichloride (10 mol%) in dichloromethane (10 mL), a solution of pyrrole was added at 0°C and stirred at ambient temperature for an appropriate time (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (2×15 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9.) to afford the pure product.

(b) *Dialkylation of pyrroles*: To a stirred solution of vinyl ketone (5 mmol) and indium trichloride (10 mol%) in dichloromethane (10 mL), a solution of pyrrole was added at 0°C and stirred at ambient temperature for an appropriate time (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (3×15 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2:8) to afford the pure product.

<sup>1</sup>H NMR of compound **3d** (200 MHz, CDCl<sub>3</sub>):  $\delta$  3.05 (t,  $J=6.7$  Hz, 2H), 3.25 (t,  $J=6.7$  Hz, 2H), 3.85 (s, 3H), 5.85 (m, 1H), 6.05 (m, 1H), 6.60 (d,  $J=1.7$  Hz, 1H), 6.95 (d,  $J=7.8$  Hz, 2H), 7.95 (d,  $J=7.8$  Hz, 2H), 8.70 (brs, NH).  
<sup>1</sup>H NMR of compound **4d** (200 MHz, CDCl<sub>3</sub>):  $\delta$  2.98 (t,  $J=6.5$  Hz, 4H), 3.10 (t,  $J=6.5$  Hz, 4H), 3.87 (s, 6H), 5.70 (d,  $J=1.7$  Hz, 2H), 6.90 (d,  $J=7.7$  Hz, 4H), 7.95 (d,  $J=7.7$  Hz, 4H), 8.65 (brs, NH).