

## The Michael Addition of Indoles to α,β-Unsaturated Ketones Catalyzed by CeCl<sub>3</sub>·7H<sub>2</sub>O-NaI Combination Supported on Silica Gel<sup>1</sup>

Giuseppe Bartoli,<sup>‡</sup> Massimo Bartolacci,<sup>†</sup> Marcella Bosco,<sup>‡</sup> Gioia Foglia,<sup>†</sup> Arianna Giuliani,<sup>†</sup> Enrico Marcantoni,<sup>\*,†</sup> Letizia Sambri,<sup>‡</sup> and Elisabetta Torregiani<sup>†</sup>

Dipartimento di Scienze Chimiche, Università di Camerino, via S. Agostino 1, I-62032 Camerino (MC), Italy, and Dipartimento di Chimica Organica "A. Mangini", Università di Bologna, viale Risorgimento 4, I-40136 Bologna, Italy

enrico.marcantoni@unicam.it

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Abstract: Alkylation of indoles by means of the Michael addition has been the subject of a number of investigation. It is well established that regioselectivity in the additions of indoles to electron-deficient alkenes is strongly controlled by the reaction medium. In a continuation of the work on developing greener and cleaner technologies, the cerium(III) chloride heptahydrate and sodium iodide combination supported on silica gel catalyzes the alkylation of various indoles with  $\alpha,\beta$ -unsaturated ketones giving 3-(3-oxoalkyl)indole derivatives in good yields. The substitution on the indole nucleus occurred exclusively at the 3-position, and Nalkylation products have not been observed.

Michael reactions promoted by Lewis acids have attracted much attention as one of the most important carbon-carbon bond-forming reactions in organic synthesis.<sup>2</sup> In particular, they are totally atom-efficient procedures<sup>3</sup> and thus are inherently green transformations.<sup>4</sup> There are several different metal-based Lewis acid catalysts available for these Michael reactions and the use of lanthanide triflates<sup>5</sup> represents an attractive alternative to their classical competitors such as AlCl<sub>3</sub>, TiCl<sub>4</sub>, and SnCl<sub>4</sub>. Unfortunately, lanthanide triflates are rather expensive and their use in large-scale synthetic methodology is very limited. For this reason cheaper Lewis acid catalysts that secure catalytic activity, low toxicity, moisture, and air tolerance are desirable. In this direction, the use of a cerium(III) chloride heptahydrate and sodium iodide combination, which is relatively nontoxic and inexpensive, is the center of our study. The CeCl<sub>3</sub>·7H<sub>2</sub>O-NaI system offers some advantages over

existing methods with InCl<sub>3</sub><sup>6</sup> and FeCl<sub>3</sub>.<sup>7</sup> Indium salts produce lower Lewis acidity than cerium trichloride while ferric chloride is very hygroscopic. However, this CeCl<sub>3</sub>. 7H<sub>2</sub>O–NaI system provides a powerful tool for organic transformations but stoichiometric amounts of cerium salt are generally necessary.8 Therefore, development of cerium-mediated reactions with a catalytic amount of a cerium source is a challenging subject in organic chemistry.9

In the course of our research on application of CeCl<sub>3</sub> in organic reactions, we have found that the CeCl<sub>3</sub>. 7H<sub>2</sub>O-NaI combination was an effective promoter in the Michael additions of nucleophiles to  $\alpha,\beta$ -unsaturated ketones without using any organic solvents.<sup>10</sup> The methodology, which is desirable from an environmental point of view, prompted us to apply it to the Friedel-Craftstype conjugate addition of aromatic compounds in solventfree conditions.<sup>11</sup> Among the aromatic compounds, we selected indoles as substrates because (i) a number of indole derivatives occur in many pharmacologically and biologically active compounds,<sup>12</sup> (ii) there is high reactivity in the 3-position of indole moiety toward the electrophilic substitution reaction,<sup>13</sup> and (iii) over several years some of us have been involved in developing newer methodologies allowing the synthesis of indoles.<sup>14</sup>

It is well established that regioselectivity in the additions of indoles to electron-deficient alkenes is strongly controlled by the reaction medium. Indoles are N-alkyl-

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<sup>\*</sup> To whom correspondence should be addressed. Phone: +39 0737 402255. Fax: +39 0737 637345.

University of Camerino.

<sup>&</sup>lt;sup>‡</sup> University of Bologna.

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## **SCHEME 1**



ated by conjugate addition under alkaline conditions. On the other hand, the formation of C-3 substituted indoles is usually achieved in the acid-catalyzed additions. Thus, in the last few years numerous methodologies have been reported in the which the C-3 Michael additions of indoles to  $\alpha,\beta$ -unsaturated carbonyl compounds in the presence of Lewis acids are involved.<sup>15</sup> Even if several Lewis acids are deactivated by the nitrogen of the indole moieties, it is interesting to note catalytic asymmetric Lewis acid mediated addition reactions with indoles reported by Jørgensen<sup>16</sup> and Umani–Ronchi.<sup>17</sup> For all these reasons, we wanted to apply the CeCl<sub>3</sub>·7H<sub>2</sub>O–NaI combination to catalyze 3-alkylation of indoles by Michael-type reaction with  $\alpha,\beta$ -unsaturated ketones on a silica gel surface<sup>18</sup> under solvent-free conditions (Scheme 1).

The reaction of indole (1a) with methyl vinyl ketone (2a) in the presence of a stoichiometric amount of the CeCl<sub>3</sub>·7H<sub>2</sub>O-NaI system adsorbed on silica gel<sup>19</sup> proceeds well giving the 3-oxoalkylation adduct **3aa** in good yield (85%) without dimerization and polymerization side reactions.<sup>20</sup> The fact that the reaction can be accomplished without solvent allowed us to adopt the best experimental conditions to reduce the large amounts of organic solvents.<sup>21</sup> In general, an equimolar ratio of cerium trichloride and NaI was found to give the best results, and in optimizing the reaction conditions, we tested several equimolar ratios of CeCl<sub>3</sub>·7H<sub>2</sub>O/NaI. Our results in Figure 1 indicate that 0.3 equiv of cerium salt and 0.3 equiv of sodium iodide supported on  $SiO_2$  (0.5 g/mmol indole) were the most appropriate for this type of reaction. The scope and efficiency of our method are summarized in Table 1, and in all cases the yields of 3-(3oxoalkyl)indoles are satisfactory.

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(21) The reaction mixture was treated with an organic solvent (dichloromethane) able to dissolve the organic material while the CeCl<sub>3</sub>·  $7H_2O-NaI-SiO_2$  system could be easily removed by filtration.

TABLE 1. Michael Addition of Indoles to  $\alpha,\beta$ -Unsaturated Ketones Catalyzed by CeCl<sub>3</sub>·7H<sub>2</sub>O-NaI Combination Supported on SiO<sub>2</sub><sup>*a*</sup>

Entry	Indole	α,β-Enone	Time/h	Product <sup>b</sup>	Yield (%) <sup>c</sup>
1	H Ia	2a	2.0	O H H Saa O	96
2	1a	2Ь	2.5	H 3ab	88
3	1a	2c	3.0	N 3ac	91
4	1a	2d	48	N H Bad	82
5	1a	2e	48		89
6	1a	2f	48	OMe O N H 3af	10 <sup>d</sup>
7	Br	2a	48	Br	79
8	1b Br CH <sub>3</sub> 1c	2a	7.5	Br H CH <sub>3</sub> CH <sub>3</sub>	85
9	$O_2N$	2a	72	O <sub>2</sub> N V CH <sub>3</sub> 3da	89
10	N H	2a	20	O N H 3ea	98 <sup>e</sup>
11	1e MeO If	2a	1.5	MeO H H 3fa	89
12		2a	144		9 <sup>f</sup>

<sup>*a*</sup> Reactions performed in the presence of 30 mol % of CeCl<sub>3</sub>·7H<sub>2</sub>O and 30 mol % of NaI supported on silica gel. <sup>*b*</sup> All products were identified by their IR, NMR, and GC/MS spectra. <sup>*c*</sup> Yields of products isolated by column chromatography. <sup>*d*</sup> No selectivity was obtained, and double-conjugate addition also occurred. <sup>*e*</sup> The chromatographic purification was not necessary. <sup>*f*</sup> Yield by GC/MS analysis.

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## JOC Note

It has been observed that the substitution on the indole nucleus occurred exclusively at the 3-position. In accordance with this finding, 3-methylindole gave (Table 1, entry 12) only 9% of 1,4-adduct (3ga) after the mixture was mechanically stirred at an external temperature of 50 °C for 4 days, together with other uncharacterized products.<sup>22</sup> This important result provides a remarkable contrast to similar reactions under palladium catalysis, where *N*-alkylation is predominat.<sup>23</sup> Furthermore, the indole nitrogen did not require prior protection and the avoidance of strong bases for deprotection permitted compatibility with a wide range of functional groups. Under our conditions we have observed that substituted indole moieties are reactive substrates. The electronic properties of the aromatic ring have an effect on the rate of the Michael reaction. The rate was accelerated if an electron-donating group is present on the indole nucleus (Table 1, entries 8, 10, and 11). Even indolyl rings bearing electron-withdrawing groups such as 5-bromoindole (1b) and 1-methyl-5-nitroindole (1d) afforded the corresponding ketones 3ba and 3da, respectively, in satisfactory yields (Table 1, entries 7 and 9), but the presence of these latter groups on the aromatic ring decelerated the desired transformation.

The reaction also has been accomplished on the CeCl<sub>3</sub>. 7H<sub>2</sub>O–NaI combination, i.e., without silica gel support, but the Michael adduct was obtained in lower yield. In fact, the treatment of indole 1a with enone 2a in the presence of the CeCl<sub>3</sub>·7H<sub>2</sub>O-NaI system gave, under the same condition, the desired adduct 3aa in only 38% after 4 days. Then, although the mechanism of this reaction is not clear, silica gel has an important role, and its presence was found to be essential for the high efficacy of the reaction. Undoubtely the presence of NaI is essential too for the reaction, because when the same additions were performed without NaI, no alkylation took place. In considering the mechanistic role of NaI, it is intriguing and complex since the exact nature of the intermediates obtained by the reaction of reagents with the CeCl<sub>3</sub>·7H<sub>2</sub>O-NaI system on SiO<sub>2</sub> is not yet known. The characterization of all these components is being carried out in our laboratories, but unfortunately, the results are too complicated and many kinds seem to be present.

The fact that the reaction of our C-3 alkylation of indoles can be carried out without solvent allowed us to adopt a very simple workup procedure for the recovery of the promoter system. The reaction mixture was treated with a minimal amount of organic solvent (Et<sub>2</sub>O) able to dissolve the organic material and not the catalyst, which could be easily removed by filtration and regenerated in an oven at 60 °C for 2 h. We have found that the CeCl<sub>3</sub>· 7H<sub>2</sub>O–NaI combination supported on SiO<sub>2</sub> can be filtered, washed, dried under vacuum, and reused for five cycles without noting any appreciable decrease in activity.



FIGURE 1. Improvement of the reaction conditions.



**FIGURE 2.**  $\alpha,\beta$ -Unsaturated ketones used as Michael acceptors.

With regard to Michael acceptors (Figure 2), cyclic enones and  $\alpha,\beta$ -disubstituted enones afforded the corresponding 3-oxoalkylindole adducts in good yields. In all cases the reaction proceeds at room temperature with high selectivity, and no 1,2-adduct was obtained under these reaction conditions. Further, the reaction proceeds smoothly with good yields even in the case of sterically hindered and less reactive enones,24 such as cyclohexenone (2d) and cyclopentenone (2e), although longer reaction times are required (Table 1, entries 4 and 5). It should be noted that the reaction is poorly efficient for enone 2f (Table 1, entry 6), only 10% of expected 3-(3oxoalkyl)indole 3af being isolated. In this case, besides the **3af** product, we observed the formation of a double conjugate adduct. In a similar manner, this Michael addition reaction of indoles does not work for  $\alpha,\beta$ unsaturated esters and nitriles and, in the case of  $\alpha,\beta$ unsaturated aldehydes such as acrolein, the reaction suffers from regiochemical restriction caused by competing 1,2- versus 1,4-addition.

In summary, we have developed a simple procedure for the direct formation of 3-(3-oxoalkyl)indoles in good yields from indoles and  $\alpha,\beta$ -unsaturated ketones with the use of silica gel. Its promoting role, although not well understood, could be explained through the adsorption of the reactants that come into closer contact with each

<sup>(22)</sup> It is known (Iqbal, Z.; Kackson, A. H.; Nagaraja Rao, K. R. *Tetrahedron Lett.* **1988**, *29*, 2577) that Michael addition of 3-methylindole involves attack at the indole 3-position to form 3,3-disubstituted derivative, which undergoes migration to the 2-position of 3-oxoalkyl moiety.

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other on the silica surface. The efficiency of our CeCl<sub>3</sub>· 7H<sub>2</sub>O–NaI combination supported on silica gel, in contrast to the existing methods with many acidic catalysts, is very general, simple, high yielding, and oxygen and moisture tolerant. Then the mildness of the reaction conditions and low cost of reagents should make the present methodology synthetically useful. Further applications of this Michael reaction protocol to alkaloid total synthesis will be reported in due course.

## **Experimental Section**

NMR spectra were recorded in  $CDCl_3$  solutions at 300 (<sup>1</sup>H) and 75.5 MHz (<sup>13</sup>C). Mass spectra were determined by means of the EI technique (70 eV). IR absorption spectra were recorded with thin films on NaCl plates, and only noteworthy absorptions (cm<sup>-1</sup>) are listed. The indoles used as starting materials were obtained from commercial sources or were synthesized according to reported methods in the literature.<sup>25</sup> All solvents were dried and distilled according to standard procedures.

**Representative Procedure for the Synthesis of 3-(3-Oxoalkyl)indoles (Table 1, entry 2).** Silica gel (0.276 g) was added to a mixture of CeCl<sub>3</sub>·7H<sub>2</sub>O (0.067 g, 0.18 mmol) and NaI (0.027 g, 0.18 mmol) in acetonitrile (4 mL), and the mixture was stirred overnight at room temperature. The acetonitrile was removed by rotary evaporation and to the resulting mixture was added indole (**1a**) (0.070 g, 0.60 mmol) and 2-ethylhept-1-en-3one (**2b**) (0.042 g, 0.60 mmol). The mixture reaction was then stirred at room temperature until the disappearance of the starting indole (2.5 h, checked by TLC and GC analyses). After addition of dichloromethane the mixture was passed through a short pad of Celite and the filtrate was concentrate under reduced pressure. The crude was purified by flash chromatography on a silica gel column (eluent, hexanes-ethyl acetate, 60: 40) to give 0.136 g (88% yield) of the corresponding Michael adduct **3ab**.

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**Supporting Information Available:** Experimental procedures, <sup>1</sup>H and <sup>13</sup>C NMR spectra, MS spectra, and other characterization data for new compounds, not reported previously, designated by their entries in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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