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# $I_2$-catalyzed Michael addition of indole and pyrrole to nitroolefins

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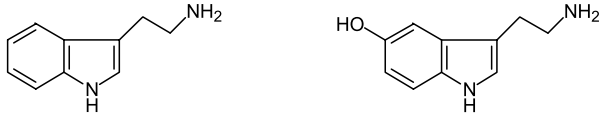
**Abstract**—An easy and efficient method to generate indolyl nitroalkane **5** and pyrrolyl nitroalkane **7** in high yields using β-nitrostyrene and indole/pyrrole at room temperature in the presence of catalytic amount of iodine is reported. The short reaction times and high yields of product are noteworthy. Molecular iodine promoted Michael addition is operationally simple and efficient method compared to the known Lewis acids or rare earth metal catalysts to generate different indolyl/pyrrolyl nitroalkanes in high yield.


## 1. Introduction

Indole and many of its derivatives are most important units in many naturally occurring compounds, because of a wide variety of their pharmacological and biological properties.[1] The hapalindole alkaloids, which exhibit significant antibacterial and antimycotic activity, and several indole alkaloids such as uleine, aspidospermidine, ibophyllidine alkaloids, and numerous tryptamine derivatives are also associated with important biological activity.[2] Likewise, important pyrrole derivatives also present in compounds such as bile pigments, vitamin $B_{12}$, haemin, chlorophyll, and related natural products.[3] In addition, several pyrrole derivatives are important intermediates not only for the synthesis of drugs, pigments and pharmaceuticals but also for the development of organic functional groups.[4] Therefore, development of new synthetic methods of indole and pyrrole derivatives have been widely studied using various Lewis acids as well as Bronsted acids.[5] Since the 3-position of the indole is the ideal site for electrophilic attack, 3-substituted indoles are versatile intermediates for the synthesis of a wide variety of indole derivatives. Conversely, C-2 position of pyrrole is indeed the electron-rich site for Michael addition. Michael addition of indoles and pyrroles to various nucleophiles has been well documented in the literature using either protic or Lewis acids.[6–9] However, Lewis acid-catalyzed Michael addition of indole and pyrrole necessitate careful control over the acidity to avoid the undesirable side reactions such as dimerization and polymerization.[10] Incidentally, the polymerized products of indole and pyrrole derivatives involves troublesome isolation procedures to obtain the desired product with some of the Lewis acids. Furthermore, many procedures require longer reaction times, expensive and toxic reagents in stoichiometric amounts, air sensitive conditions, difficult workup procedures.

The use of molecular iodine in organic synthesis has been known for a long time. In recent years molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations under mild and convenient conditions to afford the corresponding products in excellent yields with high selectivity.[11] Another advantage in using iodine as catalyst, will not influence the nitro group, which is very significant for β-nitrostyrene **3**. Herein, some important pharmaceutical compounds, tryptamine **1** and serotonin **2**, which can be obtained as a result of Michael addition between indole and nitroalkene (Fig. 1). Especially serotonin, a simple derivative of indole is a major neurotransmitter and many indole derivatives also mimic the binding of neurotransmitter to its receptors also have been synthesized.[12] In continuation of our work in exploring the methods using β-nitrostyrene, we had the opportunity to focus on the iodine catalyzed Michael addition of




1 (tryptamine) 2 (serotonin)

**Figure 1.**

*Keywords*: β-Nitrostyrene; Indole; Pyrrole; Iodine; Michael addition.
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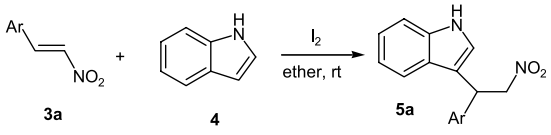
β-nitrostyrene **3** with indole, because the resultant products are analogs of **1** and **2** after reducing the nitro group (Fig. 1).

In this paper, we wish to report that elemental iodine can be used as a mild and efficient catalyst for the Michael addition of β-nitrostyrene **3** with indole **4** and pyrrole **6** at room temperature to afford products 2-indolyl-2-phenyl-1-nitroalkane **5** and 2-pyrrolyl-2-phenyl-1-nitroalkane **7** in high to excellent yields.

## 2. Results and discussion

In the beginning, Michael reaction between indole and β-nitrostyrene **3** was carried out using iodine (30 mol%) in chloroform (0.5 mL) led to the formation of 2-indolyl-2-phenyl-1-nitroalkane **5** in 95% yield. With this encouraging result, next we investigated the fate of reaction in different solvents. Conducting the reaction in DMSO did not proceed and DMF as a solvent afforded only 10% of the product with several unwanted side products. After substantial experimentation with different solvents ($CH_2Cl_2$, 82% yield; $CHCl_3$, 95% yield; EtOAc, 91% yield), diethylether came out as a solvent of choice. The iodine catalyzed reaction in ether not only improved the product yields, but also reduced the reaction times. We next, investigated the amount of iodine required to catalyze the transformation. As less as 10 mol% of iodine afforded the products in 43% yield, after 18 h. By means of 20 mol% of iodine though product yields were improved to 72%, but the reaction time is almost same as that of 10 mol%. On the other hand, using 30 mol% of iodine as a catalyst afforded the products in 99% yield in 2 h (Scheme 1).

To check the versatility of iodine catalyzed Michael reaction, various substituted β-nitrostyrenes (**3a**–**c**) were reacted with indole **4** using iodine (30 mol%) in ether (0.5 mL) solution and the results were summarized




**a**: Ar = $C_6H_5$

| Serial no. | amount of $I_2$(mol%) | solvent | 5a[a] |
|---|---|---|---|
| 1 | 30 | $CHCl_3$ (0.5ml) | 95% |
| 2 | 30 | DMSO (0.5ml) | 10% |
| 3 | 30 | DMF (0.5ml) | 10% |
| 4 | 30 | $CH_2Cl_2$ (0.5ml) | 82% |
| 5 | 30 | EtOAc (0.5ml) | 91% |
| 6 | 30 | ethyl ether (0.5ml) | 99%[b] |
| 7 | 10 | ethyl ether (0.5ml) | 43%[b] |
| 8 | 20 | ethyl ether (0.5ml) | 72%[b] |

a) NMR yields of the crude products
b) The reaction of serial no. 6 was 2h but were over 18h in serial no. 7 and 8

**Scheme 1.**

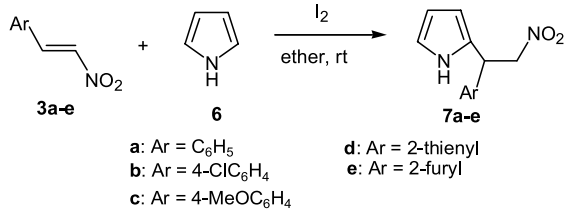
**Table 1**. Iodine catalyzed Michael addition between nitroolefins and indole

| Serial no. | Entry[a] | Time (h) | Product[b] | Yield (%)[c] |
|---|---|---|---|---|
| 1 | **3a** | 2 | **5a** | 99 |
| 2 | **3b** | 2.5 | **5b** | 99 |
| 3 | **3c** | 18 | **5c** | 99 |
| 4 | **3d** | 2 | **5d** | 89 |
| 5 | **3e** | 6 | **5e** | 94 |

[a] All reactions were performed at 1 mmol scale using 30 mol% of iodine in 0.5 mL of ether.
[b] All products were well characterized by $^1H$ NMR, $^{13}C$ NMR, and mass spectroscopy.
[c] NMR yields of the crude products.

(Table 1). Although all Michael adducts were obtained in excellent yields, but the reaction times varied according to the nature of the substitution pattern on the phenyl ring. The electron donating groups substituted in the phenyl ring of the nitrostyrene led to the formation of products with longer reaction times. The heterocyclic nitroolefins (**3d**–**3e**) also afforded the adducts in high yield. The lower yield of **5d** over **5e** can be explained on the basis of the product stability.

In order to extend the scope of this methodology, pyrrole **6** was subjected as a nucleophile in Michael addition with differnet β-nitrostyrenes, to generate 2-pyrrolyl-2-phenyl-1-nitroalkanes **7a**–**e** in good yields (Scheme 2).




**Scheme 2.**

The reasons for the lower product yields in case of pyrrole, when compared to indole may be ascribed due to polymerization of products in some cases. This is due to high nucleophilicity of pyrroles, which facilitates to react rapidly than indole. Using molecular iodine in catalytic amount to generate 2-alkyl pyrroles in excellent yields is noteworthy (Table 2).

**Table 2**. Iodine catalyzed Michael addition between nitroolefins and pyrrole

| Serial no. | Entry[a] | Time (h) | Product[b] | Yield (%)[c] |
|---|---|---|---|---|
| 1 | **3a** | 1 | **7a** | 86 |
| 2 | **3b** | 1 | **7b** | 76 |
| 3 | **3c** | 1.5 | **7c** | 79 |
| 4 | **3d** | 1.3 | **7d** | 85 |
| 5 | **3e** | 1.2 | **7e** | 81 |

[a] All reactions were performed at 1 mmol scale using 30 mol% of iodine in 0.5 mL of ether.
[b] All products were well characterized by $^1H$ NMR, $^{13}C$ NMR, and mass spectroscopy.
[c] NMR yields of the crude products.

So as to utilize this extensively effective protocol, we examined by taking various other indole and pyrrole derivatives with β-nitrostyrene **3**. *N*-methylpyrrole **8**