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ELECTROPHILIC SUBSTITUTION OF 7-AZA INDOLE WITH  
ACTIVATED CARBONYL COMPOUND UNDER SOLVENT-FREE  
CONDITIONS**

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SUBSTITUTION OF 7-AZA INDOLE WITH ACTIVATED CARBONYL COMPOUND  
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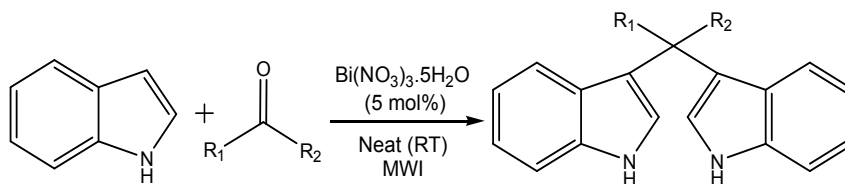
**Sonya Rivera, Debasish Bandyopadhyay and Bimal K. Banik\***

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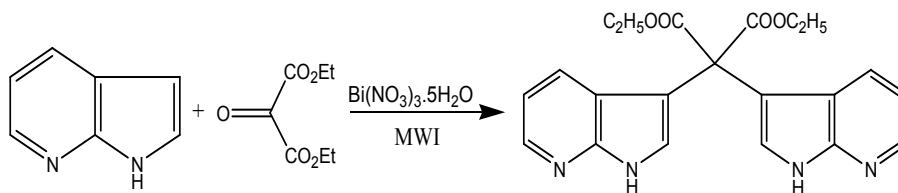
**Abstract:** An expeditious microwave-induced synthetic method for the preparation of bis(azaindollyl)methane derivative has been developed through a bismuth nitrate-catalyzed reaction of 7-azaindole with diethylketomalonate under solvent-free conditions.

**Introduction:** The use of indoles as medicinally active agents is very significant.<sup>1</sup> Bis(indolyl)alkanes are also very crucial as the bioactive metabolites of terrestrial and marine origin. Many studies have been performed toward the synthesis of these types of compounds.<sup>2,3</sup> Excess protic acids and Lewis acids are used to accomplish this goal. The acid-catalyzed electrophilic substitution reaction of indoles with carbonyl compounds is the most attractive method for the synthesis of bis(indolyl)methanes. For example, InCl<sub>3</sub>, In(OTf)<sub>3</sub>, Dy(OTf)<sub>3</sub>, InF<sub>3</sub>, Ln(OTf)<sub>3</sub>, acetic acid, LiClO<sub>4</sub>, TBATB, CuBr<sub>2</sub>, FeCl<sub>3</sub>, N-bromosuccinimide, KHSO<sub>4</sub>, NaHSO<sub>4</sub>.SiO<sub>2</sub>, CAN clay, sulfamic acid, zeolites, H<sub>3</sub>PMo<sub>12</sub>O<sub>40</sub>.xH<sub>2</sub>O and trichloro-1,3,5-triazine were found to be suitable for this reaction (**Scheme 1**).<sup>3</sup> In contrast, a similar reaction with 7-aza indole is very complicated. Despite several attempts, successful realization of a similar reaction with azaindole is not reported. The nitrogen atom present in azaindole molecule makes the system less electron rich and therefore, reaction with carbonyl compounds become problematic. We report a microwave-induced method for the preparation of bis(azaindollyl)alkanes under solvent-free conditions by mixing 7-azaindole with diethylketomalonate in the presence of catalytic amounts of bismuth nitrate (**Scheme 2**).

**Scheme 1:** Bismuth nitrate-catalyzed one-pot synthesis of diindolylmethanes



**Scheme 2:**

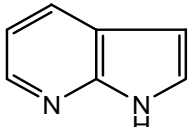
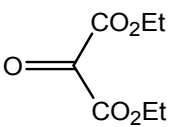
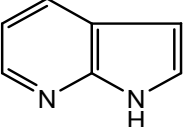
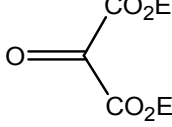
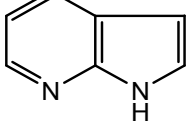
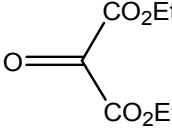
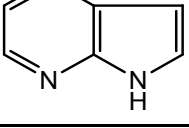
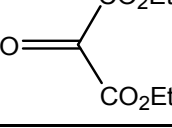
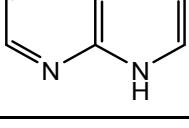
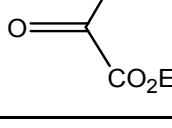


**Results and Discussion:** Trivalent bismuth nitrate pentahydrate has been proved to be very useful in our research.<sup>4</sup> We have developed various methods that include nitration of aromatic systems, protection of carbonyl compounds, deprotection of oximes and hydrazones, Michael reaction and Paal-Knoor reaction using bismuth nitrate. It has been conceived that bis azaindole derivatives can be easily prepared using bismuth nitrate as the catalyst, provided an activated carbonyl compound is used as one of the components. Our success in the bismuth nitrate-induced reaction has revealed that this reagent acts as a Lewis acid. Diethylketomalonate is an oil and this can be mixed with 7-azaindole in the presence of bismuth nitrate as a paste in a reaction flask or an Erlenmeyer flask or even in a sample vial. For better mixing of these reactants, the use of mortar pastel proves can be used. The reactants (7-azaindole: diethylketomalonate= 2:1) were mixed in the presence of catalytic amounts of bismuth nitrate pentahydrate and various methods have been attempted (**Scheme 2** and **Table 1**).

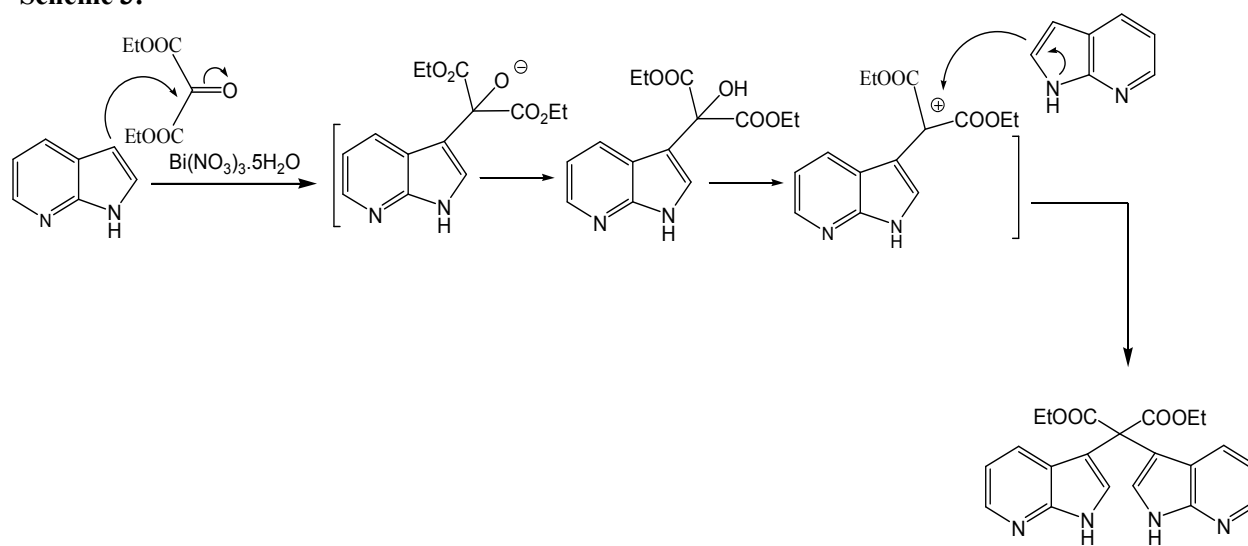
The results indicate that microwave conditions work well. After the reaction, dichloromethane was added to the reaction mixtures and the organic layer was filtered and evaporated. The crude residue was purified through a column using silica gel and ethyl acetate-hexane (1:4) as the solvent.

The reaction follows an electrophilic reaction pathway as described earlier. For example, the C<sub>3</sub> position of 7-azaindole attacks diethylketomalonate in the presence of bismuth nitrate and generates a carbonium ion. This carbonium ion then reacts with another azaindole molecule and produces the bis systems (**Scheme 3**). It is clear that the reaction requires a relatively drastic condition compared to indole as it has produced low yield of the product at room temperature.

**Table 1:**

7 Aza-Indole	Diethyl Ketomalonate	Rxn Conditions	Yield
		Room Temperature 1 h, grinding $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ , 20mg	50
		MWI, 300m, 60°C, 15min, $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ , 20mg	70
		MWI, 300m, 50°C, 25min, $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ , 20mg	70
		Domestic Microwave Power-10, 10min $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ , 20mg	50
		Room Temperature 48 h $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ , 20mg	30

**Scheme 3:**



**Scheme 3:** Plausible mechanism for the synthesis of diindolylmethanes from 7-azaindole.

**Conclusion:** In conclusion, this method produces bis-azaindolylmethanes from 7-azaindole in reasonably good yield. A similar reaction with indole is very fast and high yielding. The presence of the nitrogen in azaindole makes the molecule much less reactive and therefore, electrophilic reaction is difficult to achieve. Nevertheless, our method using microwave-irradiation with catalytic amounts of bismuth nitrate is attractive for the synthesis of this novel type of molecule.

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