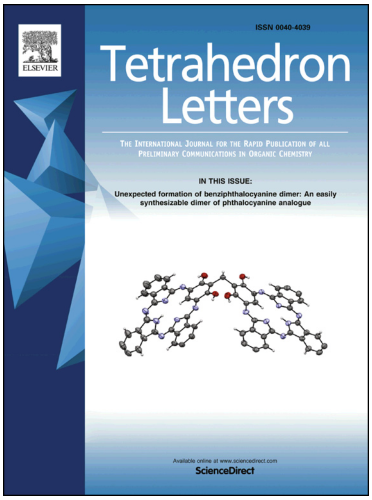

A rapid and highly efficient Michael addition of methoxybenzenes and indoles to α,β-unsaturated ketones using $BF_3.OEt_2$ as a catalyst

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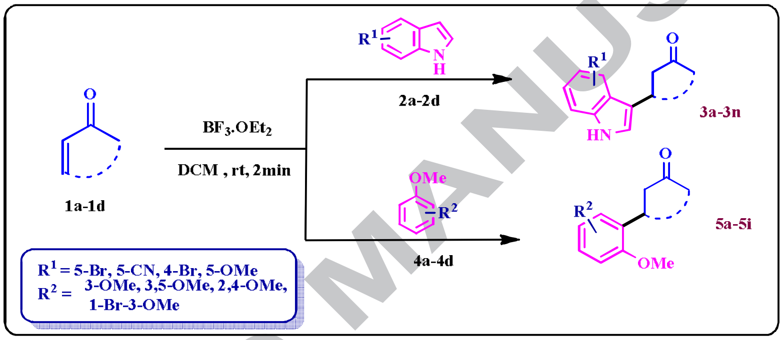

A rapid and highly efficient Michael addition of methoxybenzenes and indoles to α,β-unsaturated ketones using $BF_3.OEt_2$ as a catalyst

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Abstract— An efficient and general protocol is described for the Michael addition of α, β-unsaturated ketones with electron-rich arenes/indoles to give alkylated arenes/indoles under mild reaction condition at room temperature. Shorter reaction time, convenient and good isolated yields are the significant features of this protocol. Moreover, the procedure is environmentally benign in nature and applicable to variety of arenes/indoles as well as α, β-unsaturated ketones.

Keywords: Michael reaction, Methoxybenzenes, Indole, α, β-unsaturated ketones, $BF_3.OEt_2$.

The Lewis acid catalyzed Friedel-Crafts-type alkylation and Michael-type addition reactions are among the most important synthetic tools available for C/C-bond forming reactions and has wide synthetic applications in organic synthesis.[1] Among them the addition reactions of electron-rich arenes/indoles to electron-deficient carbonyl compounds has attracted much attention over the past few years. [2] In addition, these reactions are involved in the total synthesis of a class of biologically active indole alkaloids.[3] Moreover, 3-substituted indoles are important structural motifs that occur in nature and in many natural and synthetic molecules with significant biological activity such as antibacterial, antialgal and antimycotic(Fig. 1).[4] Due to distinct properties of 3-substituted indoles, there is research interest to develop convenient and efficient method for the synthesis of 3-substituted indoles.

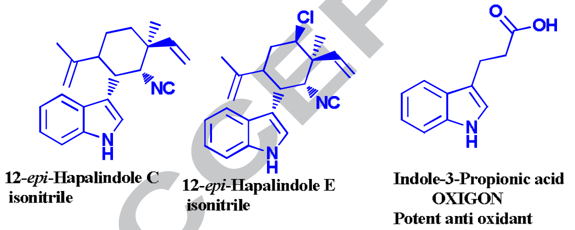
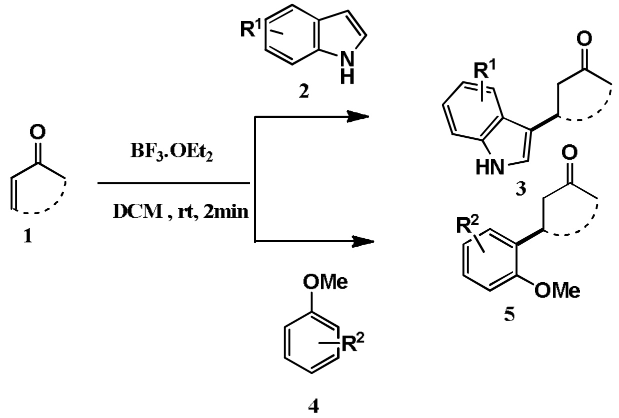


Fig. 1: Representative examples of natural products and biologically active 3-substituted indole derivatives.

There are numerous methods for the Michael reaction of indoles with various α, β-unsaturated carbonyl compounds in the presence of either Lewis acids or protic acids such as $Sc(DS)_3$,[5] clay-supported nickel bromide,[6] $Fe(BF_4)_2.6H_2O$,[7] $InBr_3$,[8] $InCl_3$,[9] Gold(III) Chloride,[10] GaI_3,[11] $Bi(NO_3)_3$,[12] bismuthyl perchlorate,[13] $Bi(OTf)_3$,[14] $Os(NH_3)_5(OTf)_3$,[15] zirconium triflate,[16] $Hf(OTf)_4$,[17] triflic acid,[18] Al_2O_3,[19] rhodium complex,[20] ruthenium complex,[21] I_2,[22] $HClO_4/SiO_2$,[23] PTSA,[24] sulfamic acid,[25] modified silica sulfuric acid (MSSA).[26] However, a plethora of synthetic strategies have been developed, the use of excess amount of reagents,[26] expensive catalysts,[10,14-18] tedious preparation of catalysts,[5,6,26] longer reaction times (48h),[5,16] harsh reaction conditions (*e.g.* ultrasonic irradiation, high temperatures),[13] poor yields of the desired product[5] and cumbersome work-up procedures[19] made the various existing methodologies undesirable under the aspect of sustainable synthesis. Although some of the protocols are satisfactory, still there is a scope to develop rapid, convenient and general protocols for the Michael reaction of indoles with various α, β-unsaturated carbonyl compounds under mild reaction condition.



Scheme 1: Optimization of the reaction conditions.

Recently, $BF_3.OEt_2$ has emerged as a powerful Lewis acid catalyst and has been used for organic transformations effectively under mild reaction conditions.[27] To the best of our knowledge, there is no report for the Micheal addition of indoles and α, β-unsaturated ketone using $BF_3.OEt_2$ as a catalyst. Hence, as a part of our[28] ongoing research in the applications of $BF_3.OEt_2$, herein we wish to report rapid, highly efficient and operationally simple protocol for Micheal addition of indoles and α, β-unsaturated ketones using $BF_3.OEt_2$ under mild reaction condition.

In a preliminary experiment, we performed the reaction of methyl vinyl ketone (**1a**, 1 mmol) and indole (**2a**, 1 mmol) in the presence of $BF_3.OEt_2$ (1 equiv) in DCM (5 mL) at room temperature (Scheme 1). The progress of the reaction was moniterd by TLC. After completion of the reaction, the reaction mixture was quenched with solid $NaHCO_3$.Then silica gel is added to the rection mixture, solvent is evaporated and directly loaded on column chromatography by avoiding aqueous work up-extraction step. After purification **3a** was obtained as a sole product, which was confirmed by ^1H NMR, ^{13}C NMR, IR and Mass spectrometry analysis (Table 2, entry 1).

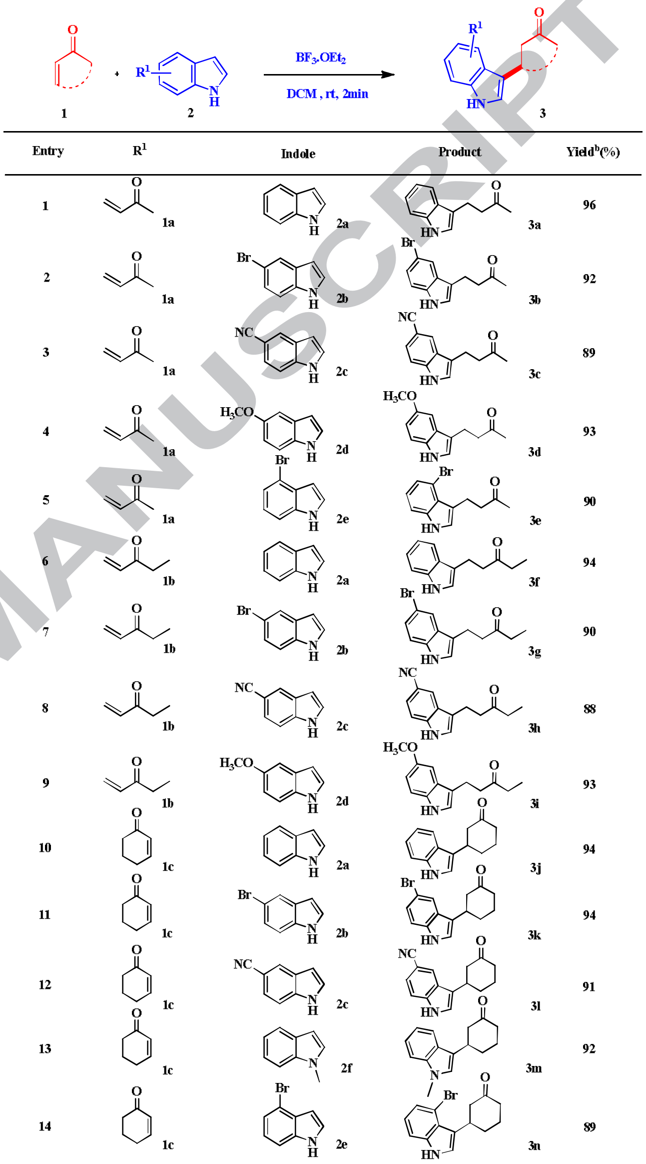
Table 1: Optimization of the reaction conditions.[a]

Entry	Lewis acid (equiv)	Solvent	Time	Yield[b] (%)
1.	**$BF_3.OEt_2$ (1.0)**	**DCM**	**2 min**	**96**
2.	$BF_3.OEt_2$ (3.0)	THF	2 min	94
3.	$BF_3.OEt_2$ (1.0)	MeCN	15 min	85
4.	$BF_3.OEt_2$ (1.0)	Toluene	10 min	81
5.	$BF_3.OEt_2$ (1.0)	THF	10 min	68
6.	$Sc(OTf)_3$ (1.0)	EtOH	60 min	38
7.	$Ti(OTf)_3$ (1.0)	DCE	80 min	51
8.	$Yb(OTf)_3$ (1.0)	DCE	50 min	39
9.	$FeCl_3$ (1.0)	DCM	5 min	18
10.	$AlCl_3$ (1.0)	MeCN	3 min	82
11.	TMSCl (1.0)	MeCN	6 min	56
12.	$TiCl_4$ (1.0)	DCM	8 min	67
13.	$SnCl_4$ (1.0)	DCM	10 min	-

[a] All the reactions were conducted with Methyl vinyl ketone **1a** (1 equiv), indole **2a** (1 equiv) in the presence of $BF_3.OEt_2$ in 5 mL solvent at room temperature. [b] Isolated yield.

The effect of other acid catalysts such as $Bi(OTf)_3$, $Sc(OTf)_3$, $Ti(OTf)_3$, $Yb(OTf)_3$, $FeCl_3$, $AlCl_3$, TMSCl, $TiCl_4$, $SnCl_4$ (Table 1, entries 1-13) were also studied for this conversion. However, the best results were achieved using $BF_3.OEt_2$. The control experiment without $BF_3.OEt_2$ was also performed, but the formation of the product **3a** was not observed even after stretching the reaction time upto 24h.The reaction was also carried out using different amounts of the reagent ranging from a catalytic to stoichiometric. $BF_3.OEt_2$ (1 equiv) was found suitable for optimum conversion. We further examined the effect of solvent for this reaction using various solvents such as THF, MeCN and toluene.

Table 2: Synthesis of new 3-substituted indoles.[a]

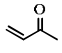
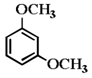
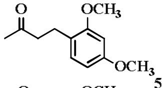
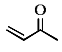
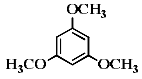
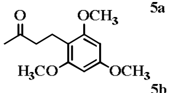
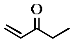
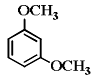
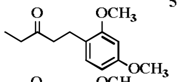
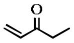
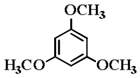
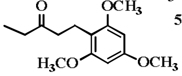
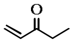
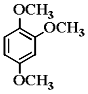
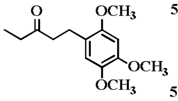
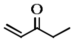
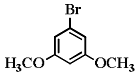
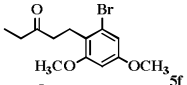
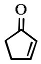
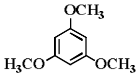
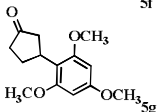
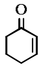
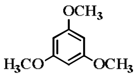
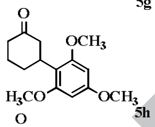
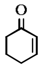
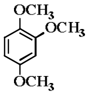
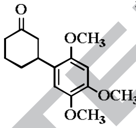


Entry	R¹	Indole	Product	Yield[b](%)
1	1a	2a	3a	96
2	1a	Br 2b	Br 3b	92
3	1a	NC 2c	NC 3c	89
4	1a	H_3CO 2d	H_3CO 3d	93
5	1a	Br 2e	Br 3e	90
6	1b	2a	3f	94
7	1b	Br 2b	Br 3g	90
8	1b	NC 2c	NC 3h	88
9	1b	H_3CO 2d	H_3CO 3i	93
10	1c	2a	3j	94
11	1c	Br 2b	Br 3k	94
12	1c	NC 2c	NC 3l	91
13	1c	2f	3m	92
14	1c	Br 2e	Br 3n	89

[a] All products exhibited physical and spectral (NMR, Mass and IR) properties in accordance with the assigned structure. [b] Isolated Yield

After extensive screening we found DCM as most suitable solvent for maximum conversion interms of reaction time and isolated yield.

Table 3: Synthesis of new 3-substituted arenes.[a]

Entry	1	Methoxybenzene	Product	Yield[b](%)
1	 1a	 4a	 5a	96
2	 1a	 4b	 5b	93
3	 1b	 4a	 5c	92
4	 1b	 4b	 5d	90
5	 1b	 4c	 5e	90
6	 1b	 4d	 5f	88
7	 1d	 4b	 5g	74
8	 1c	 4b	 5h	69
9	 1c	 4c	 5i	78

[a] All products exhibited physical and spectral (NMR, Mass and IR) properties in accordance with the assigned structure. [b] Isolated Yield.

For the general validity of the reaction, the optimized reaction[29] was tested on several α, β-unsaturated ketones as well as indoles and the results are summarized in Table 2 (Scheme 2). The substituents on indoles either electron withdrawing (cyano, bromo) or electron donating (methoxy, methyl) has no substantial effect on the reaction (Table 2, entries 2-5, 7-9 and 11-14). The reaction of indoles such as indole **2a**, 5-bromoindole **2b**, 5-cyano indole **2c,** 5-methoxy indole **2d** and 4-bromoindole **2e** with methyl vinyl ketone **1a** underwent smoothly in optimised reaction condition and furnished the desired products **3a-3e** in a high yield (Table 2, entries 1-5). Similarly, ethyl vinyl ketone **1b** is also reacted with indole **2a**, 5-bromoindole **2b**, 5-cyanoindole **2c** and 5-methoxyindole **2d** to afford the corresponding products **3f-3i** in good yield (Table 2, entries 6-9). It is worthy to mention that the developed protocol is also applicable for cyclic α, β-unsaturated ketone like cyclohex-2-enone **1c** (Table 2, entries 10-14). For example cyclohex-2-enone **1c** with 1-methyl indole **2f** reacted analogously and gave 3-substituted indole **3m** in good yield (Table 2, entry 13).

The efficiency of the reaction was further strengthened by the participation of α, β-unsaturated ketones **1** with methoxy benzenes **4** and the results are summarized in Table 3. The reaction of 1,3-dimethoxybenzene **4a** and 1,3,5-trimethoxybenzene **4b** reacted rapidly with methyl vinyl ketone **1a** to afford the corresponding products **5a** and **5b** respectively in excellent yields (Table 3, entries 1-2). Similarly, ethyl vinyl ketone **1b** and arenes like 1,3-dimethoxybenzene **4a**, 1,2,4-trimethoxybenzene **4c**, 1,3,5-trimethoxybenzene **4b** and 1-bromo-3,5-dimethoxybenzene **4d** also underwent smoothly in the standard reaction condition to furnish the desired product in a high yield (Table 3, entries 3-6). It was found that even cyclopent-2-enone **1d** as fairly sterically demanding precursors reacted with corresponding arenes **4b** in a similar fashion to afford the respective product in acceptable yields (Table 3, entry 7). It is worthy to mention that the method is also applicable for cyclohex-2-enone **1c**. For example the reaction of cyclohex-2-enone **1c** with 1,3,5-trimethoxybenzene **4b** and 1,2,4-trimethoxybenzene **4c** also proceeded same way and afforded corresponding product **5h** and **5i** in good yield (Table 3, entries 8 and 9).

In conclusion, we have proven a rapid, highly efficient and an operationally facile method for the synthesis of 3-substituted indoles and arenes. Moreover, the method is applicable for a variety of acyclic and cyclic α, β-unsaturated ketones as well as substituted indoles and methoxybenzenes. The developed protocol is general, mild and offers easy access for the Michael reaction of indoles and arenes with various α, β-unsaturated ketone.

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