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Gallium(III) triiodide catalyzed conjugate addition of indoles with α,β-unsaturated ketones

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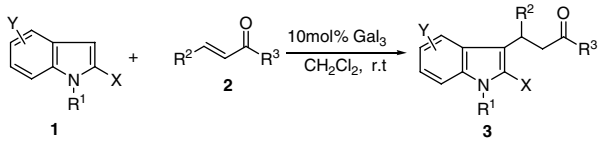
Abstract—Reactions of indoles and α,β-unsaturated ketones could be effectively catalyzed by using 10 mol % gallium triiodide to give the corresponding Michael adducts in good to excellent yields.

Indole is a privilege heterocyclic ring.[1,2] Many biologically active compounds and natural products are found to be 3-substituted indoles.[3] Michael addition of indoles and α,β-unsaturated ketones is an important approach to this class of molecules.[4,5] Lewis acids such as $CeCl_3 \cdot 7H_2O$–NaI,[6] $Bi(OTf)_3$,[7] SmI_3,[8] I_2,[9] $InCl_3$,[10] and $Cu(OTf)_3$[11] have been used to promote Michael addition reactions.

Gallium triiodide (GaI_3) can be easily prepared by the reaction of metal gallium with iodine.[12] It has been used as a Lewis acid catalyst for Sakurai reaction, tetrahydropyranylation of alcohols and phenols, and the coupling reaction of carbonyl compounds, amines and diethyl phosphate.[13] Compared to other Lewis acids, the synthetic application of GaI_3 has not been fully explored. Herein, we report a new application of GaI_3 as a Lewis acid catalyst in the synthesis of 3-substituted indoles (Scheme 1).[14]



Scheme 1. GaI_3-catalyzed Michael addition of indoles.

The initial reaction of indole **1a** and 3-buten-2-one **2a** at an ambient temperature in CH_2Cl_2 did not give any product until GaI_3 was added into the reaction mixture and stirred for 1 h. After the reaction was completed, the mixture was purified by flash column chromatography to give pure product 4-(3-indolyl)butanone-2 **3a**, whose structure was characterized by ^1H NMR, ^{13}C NMR, and HRMS analyses.

The reaction of **1a** and **2a** was optimized by screening the solvent such as CH_3CN, THF, and CH_2Cl_2 (Table 1, entries 1, 2 and 4), changing the amount of GaI_3 and the ratio of indole **1a**/3-buten-2-one **2a**. It was found that the reaction best proceeded with 10 mol % GaI_3, ratio of indole/3-buten-2-one 1:1 to give **3a** in a 95% yield (Table 1, entry 4). Increasing the amount of GaI_3 to 20 mol %, the yield of **3a** was not further improved (Table 1, entry 6). However, if GaI_3 was used

Table 1. Effect of reaction conditions on the GaI_3 catalyzed Michael addition of indole **1a** and 3-buten-2-one **2a**

Entry[a]	Solvent	Time (h)	Amount of GaI_3 (mol %)	Yield (%)
1	CH_3CN	3	10	32
2	THF	3	10	n.r.[b]
3	CH_2Cl_2	3	5	47
4	CH_2Cl_2	3	10	95
5	CH_2Cl_2	1	10	90
6	CH_2Cl_2	3	20	94

[a] Typical reaction condition: indole:3-buten-2-one = 1:1, 10 mol % GaI_3.
[b] n.r. = No reaction.

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Table 2. GaI_3 catalyzed reaction of indoles and α,β-unsaturated ketones

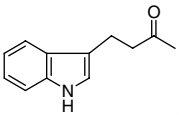
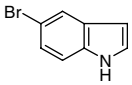
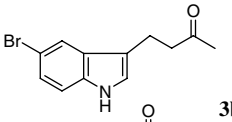
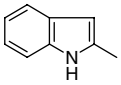
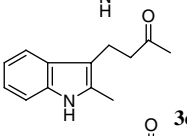
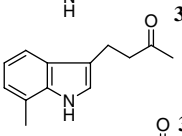
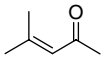
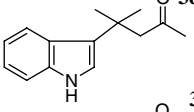
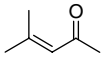
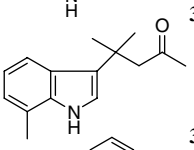
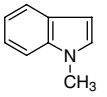
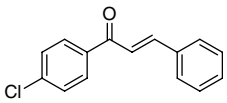
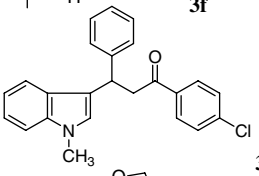
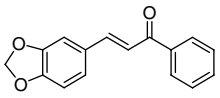
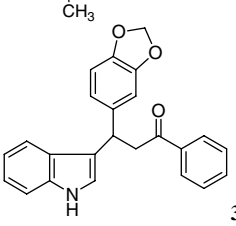
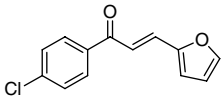
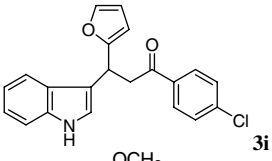
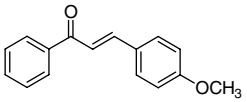
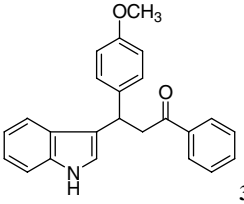
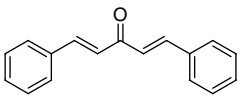
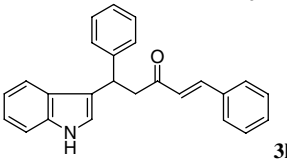
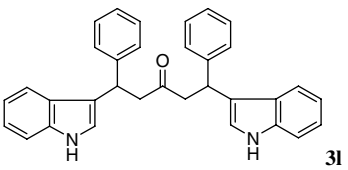
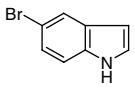
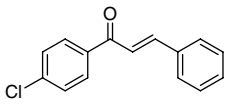
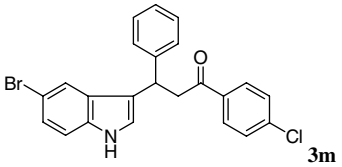
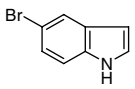
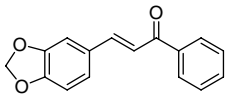
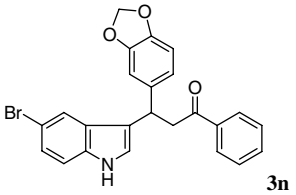
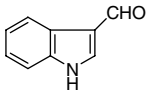
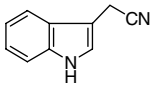
Entry	Indoles	α,β-Unsaturated ketones	Time (h)	Yield[a] (%)	Product[b]
1	 **1a**	 **2a**	1	90	 **3a**
2		 **2a**	1	86	 **3b**
3		 **2a**	1.5	84	 **3c**
4		 **2a**	1.5	85	 **3d**
5		 **2b**	2	85	 **3e**
6		 **2b**	2	87	 **3f**
7		 **2c**	2	85	 **3g**
8		 **2d**	2.5	80	 **3h**
9		 **2e**	3	81	 **3i**
10		 **2f**	2	88	 **3j**
11		 **2g**	2.5	72	 **3k**
				18	 **3l**

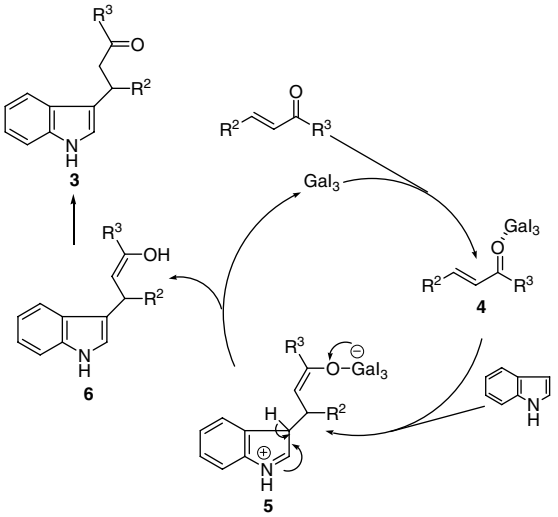
Table 2 (*continued*)

Entry	Indoles	α,β-Unsaturated ketones	Time (h)	Yield[a] (%)	Product[b]
12		 **2c**	1	90	 **3m**
13		 **2d**	1	89	 **3n**
14		 **2a**	24	—	n.r.[c]
15		 **2a**	24	—	n.r.[c]

[a] All products were purified by flash column chromatography.
[b] All products were characterized by ^{1}H and ^{13}C NMR and HRMS spectra.
[c] n.r. = No reaction.

in less than 5 mol %, the yield of **3a** was significantly reduced to 47% (Table 1, entry 3).

Under the optimized conditions described above, a series of substituted indoles and α,β-unsaturated ketones were used to evaluate the scope of GaI_3 catalyzed Michael addition. A steric hindered 4-methyl-3-penten-2-one **2b** reacted with indole **1a** to afford product **1b** in 85% (Table 2, entry 5). The reactions of 1,3-diaryl-α,β-unsaturated ketones with indole **1a** gave products in 80–88% yields (Table 2, entries 7–10). Compound **2g** has two conjugated double bonds; interestingly, both monoaddition product **3k** and diaddition product **3l** were obtained; the former was the major one in a 72% yield (Table 2, entry 11). Indoles with monosubstitution at 1-, 2-, 5-, or 7-position were studied, and the desired products were obtained in good yields (84–90%) (Table 2, entries 2–4, 6, 7, 12, and 13). 3-Substituted indoles did not produce any product since the reactive site was blocked (Table 2, entries 14 and 15). Attempted reactions of α,β-unsaturated aldehydes and α,β-unsaturated esters, such as acrylaldehyde, cinnamaldehyde, methyl acrylate, and ethyl acrylate, failed to give products.



Scheme 2. Proposed mechanism for GaI_3 catalyzed reaction of indole and α,β-unsaturated ketones.

A possible mechanism for the conjugate addition is proposed in Scheme 2.[15,16] GaI_3 coordinating with O atom of α,β-unsaturated ketone to form intermediate **4**; then, electron-rich β-position of indole attacking the conjugated C=C double bond of **4** to afford **5**, followed by a H-transformation to yield **6** and GaI_3, finally, **6** rearranged to target compound **3** and GaI_3 participated the next cycle catalytic reaction.

In conclusion, 10 mol % GaI_3 can effectively catalyze the Michael addition of indoles and α,β-unsaturated ketones to give 3-substituted indoles in good to excellent yields. However, under the same conditions, α,β-unsaturated aldehydes and esters cannot afford the corresponding Michael addition products.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.108.

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14. *Typical experimental procedure for preparation of 3-(5-bromo-1H-indol-3-yl)-1-(4-chlorophenyl)-3-phenylpropan-1-one* (**3m**): GaI_3 was synthesized by stirring a mixture of Ga metal (0.1 mmol) and I_2 (0.15 mmol) in 2 mL CH_2Cl_2 (dried with P_2O_5) in flame-dried glassware. After stirring the mixture of Ga and I_2 for several hours, the red color disappeared and the mixture became a transparent liquid. To this solution were added indoles (1.0 mmol) and α,β-unsaturated ketones (1.0 mmol), stirred at an ambient temperature. After the reaction was completed (TLC analysis), the resultant mixture was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (15 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated, the residue was purified by column chromatography on silica gel (eluted with ethyl acetate: petroleum ether = 1:6) to give **3m** in 90% yield, mp 189–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H, NH), 7.87–7.19 (m, 12H, ArH), 7.01 (s, 1H, indole ring), 4.97 (t, 1H, $J = 7.2$ Hz, CH), 3.77–3.63 (m, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.1, 44.5, 100.8, 107.9, 108.4, 111.1, 113.5, 118.2, 120.8, 121.1, 123.6, 128.2, 128.4, 128.8, 133.3, 135.1, 137.0, 139.2, 145.4, 147.2, 198.4; HRMS: *m*/*z* (%), calcd for $C_{23}H_{17}NOClBr$ (M^+) 437.0182, found 437.0180 (M^+, 9.06).
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