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Catalytic Conjugate Addition of Indoles to 4-Aryl-4-oxobut-2-enoates by $FeCl_3$

Xiaoxia Wang,* Yaohong Zhang, Xiaohui Xiao, and Xinsheng Li
Zhejiang Key Laboratory for Reactive Chemistry on Solid Surfaces, College of Chemistry and Life Sciences,
Zhejiang Normal University, Jinhua, Zhejiang, 321004, P. R. China

(Received October 6, 2008; CL-080963; E-mail: wangxiaoxia@zjnu.cn)

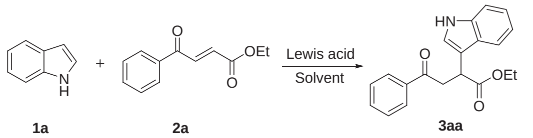
The conjugate addition of indoles to 4-aryl-4-oxobut-2-enoates was achieved with $FeCl_3$ as a catalyst under mild conditions. The reaction was highly regioselective and afforded a variety of new 3-substituted indoles in good to excellent yields.

The synthesis of indole derivatives continues to be an intriguing subject in organic synthesis since the indole nucleus has been found in a number of biologically active natural and unnatural compounds.[1] Among a variety of reactions for the derivation of indole, the conjugate addition (the Michael addition) of indole to electron-deficient olefins provides a straightforward approach to introduce functionalized substituents at its 3-position and has received a great deal of recent attention. Simple enones or nitroalkenes have been frequently employed[2,3] in most investigation as Michael addition templates for indoles. Besides developing more efficient, milder, or greener reaction conditions,[2] chiral catalysts are continually being sought so as to promote the reaction in a highly enatioselective way.[3]

Recently, more and more research focusing on the development of alternative Michael acceptors such as acrylate,[2f,2h] acrylonitrile,[2f] alkylidene malonates,[4] α,β-unsaturated aldehydes,[5] α,β-unsaturated acylbenzotriazoles,[6] and N-acetylated α,β-dehydroalanine methyl ester,[7] together with more functionalized 4-substituted 2-oxo-3-butenoate esters,[8] α,β-unsaturated acyl phosphates,[9] α'-hydroxy enones,[10] α,β-unsaturated 2-acylimidazoles,[11] α'-phosphoric enones,[12] and ethyl 3-nitro-2-alkenoates,[13] has been conducted thus providing a number of methods for the synthesis of diverse 3-substituted indole derivatives (although some of the aforementioned Michael acceptors were designed for chiral metal-catalyzed purposes). In this paper, we wish to report the first efficient regioselective addition of indoles to 4-aryl-4-oxobut-2-enoates, which afforded a new kind of 3-functionalized indole.

4-Oxobut-2-enoates (or γ-oxo-α,β-(*E*)-alkenoic acid esters), particularly those substituted with 4-aryl, are biologically and medicinally important small molecules.[14] The ketonic carbonyl and the esteric carbonyl group present therein activate both termini of the carbon–carbon double bond and make them potential Michael acceptors. The superior electron-withdrawing aptitude exerted by the ketonic carbonyl group can lead to the attack of N-nucleophiles at their 2-position. For example, addition of various amino acids to ethyl β-benzoylacrylate affords ethyl α-amino-γ-oxo-γ-phenylbutyrate derivatives, which are important intermediates for ACE (I) inhibitor.[15] In 2007, Han reported the conjugate addition reaction of a wide variety of NH-containing heterocyclic compounds to these compounds with DBU as a catalyst in constructing a C–N bond.[16] However, the conjugate addition of indoles to 4-aryl-4-oxobut-2-enoates forming a C–C bond was not explored to provide the corresponding 3-functionalized indoles. Herein, catalyzed with Lewis acid, indoles were found to undergo conjugate addition to 4-aryl-4-oxobut-2-enoates smoothly to form a C–C bond exclusively in a highly regioselective way, allowing facile access to a broad range of 2-(3-indolyl)-substituted 4-aryl-4-oxobutanoates in good to excellent yields.

Table 1. The Michael addition of indole **1a** to ethyl (*E*)-4-oxo-4-phenylbut-2-enoate **2a** catalyzed by Lewis acids in various solvents



1a **2a** **3aa**

Entry	Catalyst[a]	Solvent[b]	Time/h	Yields[c]/%
1	SmI_3	THF	14	60
2	$AlCl_3$	THF	14	57
3	$ZnCl_2$	THF	14	35
4	$CuCl_2$	THF	14	55
5	$Zn(OTf)_2$	THF	14	55
6	$Cu(OTf)_2$	THF	14	62
7	$FeCl_3$	THF	14	70
8	$FeCl_3$	CH_2Cl_2	5	90
9	$FeCl_3$	CH_3CN	10	45
10	$FeCl_3$	Toluene	10	85
11	$FeCl_3$	C_2H_5OH	10	16
12	$FeCl_3$	Et_2O	10	32

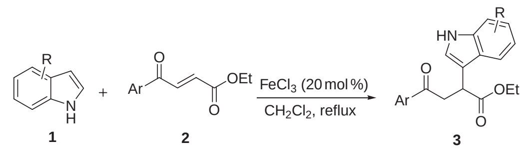
[a]Catalyst load: 20 mol %. [b]The runs were carried out under reflux conditions; at room temperature, lower efficiency was observed. [c]Isolated yields.

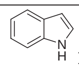
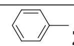
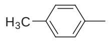
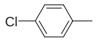
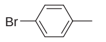
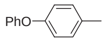
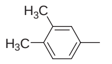
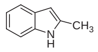
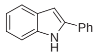
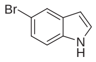
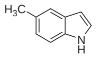
To search for highly efficient reaction conditions, a variety of catalysts and solvents were screened with ester **1a** and indole **2a** as substrates. It was found that anhydrous $FeCl_3$[17] in refluxing CH_2Cl_2 gave the best result in terms of yield and reaction time (Table 1, Entry 8).

Subsequently, a variety of indoles and ethyl (*E*)-4-aryl-4-oxobut-2-enoates were applied as substrates under the optimal conditions to examine the generality of the reaction, and the results are listed in Table 2.

Generally, both indole and the substituted indoles underwent the Michael-addition reaction smoothly to give the corresponding 2-(3-indolyl)-substituted 4-aryl-4-oxobutanoates in good to excellent yields. The attack of indoles with their 3-position on the other termini of the carbon–carbon double bond in ethyl (*E*)-4-aryl-4-oxobut-2-enoates was not observed at all, showing high regioselectivity. Besides indole, the indoles substituted with 2-methyl, 5-methyl, and 5-bromo all worked well. However, the presence of a phenyl on the 2-position of indole required relatively longer time for the reaction to afford comparable yields (Table 2, Entry 10), which may be ascribed to the

Table 2. FeCl$_3$-catalyzed conjugate addition of indoles **1** to ethyl (*E*)-4-aryl-4-oxobut-2-enoates **2**



Entry	Indoles **1**	Ar of **2**	Poducts	Time/h	Yields^{a}/%
1	 **1a**	 **2a**	**3aa**	5	90
2	**1a**	 **2b**	**3ab**	5	85
3	**1a**	 **2c**	**3ac**	3	82
4	**1a**	 **2d**	**3ad**	4	83
5	**1a**	 **2e**	**3ae**	4.5	88
6	**1a**	 **2f**	**3af**	5	87
7	 **1b**	**2a**	**3ba**	5	89
8	**1b**	**2e**	**3be**	3.5	84
9	**1b**	**2f**	**3bf**	4.5	81
10	 **1c**	**2a**	**3ca**	8.5	73
11	 **1d**	**2b**	**3db**	5	92
12	**1d**	**2c**	**3dc**	3.5	89
13	**1d**	**2d**	**3dd**	4	83
14	**1d**	**2f**	**3df**	5	82
15	 **1e**	**2a**	**3ea**	5	83
16	**1e**	**2e**	**3ee**	5	89

^{a}Isolated yields.

steric hindrance resulting from the phenyl. With regard to the substituents on the aryl in ethyl (*E*)-4-aryl-4-oxobut-2-enoates **2**, neither electron-donating groups nor electron-withdrawing groups on the aromatic ring affected the efficiency of the reaction.

It should be mentioned that **2a** in its Z configuration, when reacted with indole **1a**, afforded **3aa** in 63% yield in 5 h, showing lower efficiency than its E isomer (Table 2, Entry 1). Conversion of (*Z*)-**2a** to (*E*)-**2a** was observed under the conditions. Besides, benzyl (*E*)-4-(4-chlorophenyl)-4-oxobut-2-enoate **4** was found to react with 5-bromoindole **1d** giving 2-(3-indolyl)-substituted 4-aryl-4-oxobutanoate **5** (see Supporting Information[18]) in 88% yield in 0.5 h, indicating that benzyl ester could be well tolerated and was more reactive than the corresponding ethyl ester (Table 2, Entry 12).

In conclusion, we have developed for the first time an efficient C–C bond forming Michael addition reaction between indoles and 4-aryl-4-oxobut-2-enoates. The reaction proceeded efficiently and regioselectively with FeCl$_3$ as a catalyst under mild conditions and can tolerate a variety of substituents, thus providing a practical method for the synthesis of multi-functionalized indole derivatives.

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