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Efficient Lewis acid-assisted Brønsted acid (LBA) catalysis in the iron-catalyzed Friedel-Crafts alkylation reaction of indoles

Research Article

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Abstract: Lewis acid-assisted Brønsted acid (LBA) catalysis was proposed for the iron-catalyzed Friedel-Crafts alkylation of indoles with chalcones. This proposal was supported by the ESI-MS and cyclic voltammetry. The addition of acac to the iron-catalyzed Friedel-Crafts alkylation of indoles with chalcones created a powerful catalytic system, which makes the alkylation reactions occur easily under mild conditions.

Keywords: *Iron catalysis • Friedel-Crafts • Lewis acid • Brønsted acid*

1. Introduction

The Friedel-Crafts alkylation reaction of indoles is a very important process because it is involved in the total synthesis of bioactive indole alkaloids such as hapalindoles and other 3-substituted indoles, which are important substructures and building blocks for the synthesis of natural products and therapeutic agents [1]. For example, NVP-LAQ824, currently undergoing human clinical trials, is a potent HDAI and antitumor agent against both solid and leukemia [2]. The preparation of functional indoles is therefore an important research field. The selective akylation at the C-2 or C-3 position will be complementary to the known N-alkylation methodology and holds significant synthetic potential. In particular, functionalization at the C-3 position of the indole skeleton is of great importance for the total synthesis of indole derivatives with potential biological activities [3,4].

During past years, a variety of transition metal salts or metal-free organic molecules are catalyzed Friedel-Crafts alkylation between indoles and an electrophile (for example, enone). This well-established method for the functionalization at the 3-position of the indole nucleus [5-15]. However, some drawbacks still exits in previous synthetic methods, e.g., the necessity to utilize expensive stoichiometric amounts of Lewis acidic catalysts and toxic heavy metals, which does not meet the contemporary requirement for green chemistry. Among transition metal salts, iron(III) chloride is a very cheap and efficient Lewis acid catalyst, and has attracted much attention in a great deal of useful organic transformations [16-18]. With our continuous research in iron catalysis, herein, we wish to report some findings in the iron-catalyzed Friedel-Crafts alkylation of indoles.

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In this reaction, Lewis acid-assisted Brønsted acid (LBA) catalysis was established by the combinational utilities of ESI-MS and cyclic voltammetry.

2. Experiment Procedure

2.1. General considerations

All reaction flask and solvent were dried according to standard methodology prior to use. Flash column chromatography was performed over silica (100-200 mesh). NMR spectra were recorded on a 400-MHz spectrometer. 13C NMR spectra were obtained with broadband proton decoupling. For spectra recorded in $CDCl_3$, unless noted, chemical shifts were recorded relative to the internal TMS (tetramethylsilane) reference signal. IR spectra were recorded using a FTIR apparatus. Thin layer chromatography was performed using Silica. To gain insight into the the mechanism of iron catalyzed Friedel-Crafts alkylation of indoles with chalcones, Cyclic voltammetry (cv) and ESI-MS were performed.

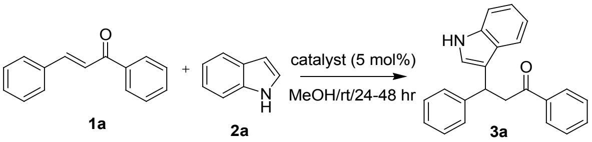
2.1.1. Representative Procedure for Friedel-Crafts Alkylation Reaction of indoles and Chalcones

$FeCl_3$ (0.05 mmol) and acac (0.1 mmol) was added into a solution of chalcone (1.0 mmol) and indole (1.1 mmol) in freshly distilled CH_3OH (2 mL). After stirring at room temperature for 12-24 h, the mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3×15 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography on silica gel (EtOAc-petro ether, 1:5) to gain the pure product. All the products are known compounds [9-15] and confirmed by MS, NMR, and IR. For the 3a:^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (bs, 1 H), 7.93 (d, J = 7.2 Hz, 2 H), 7.53 (t, J = 7.4 Hz, 1 H), 7.40-7.44 (m, 3 H), 7.35 (d, J = 7.2 Hz, 2 H), 7.23-7.31 (m, 3 H), 7.14 (q, J = 7.2, 7.2 Hz, 2 H), 7.01 (t, J = 7.4 Hz, 1 H), 6.96 (s, 1 H), 5.07 (t, J = 7.2Hz, 1 H), 3.81 (dd, J = 6.8, 6.8 Hz, 1 H), 3.72 (dd, J = 7.6, 7.6 Hz, 1 H); ^{13}C NMR (100 MHz,$CDCl_3$): δ = 198.6, 144.2, 137.0, 136.6, 133.0, 128.6, 128.4, 128.1, 127.8, 126.6, 126.3, 122.1, 121.4, 119.5, 119.4, 119.2, 111.1, 45.2, 38.1; IR (KBr): 3462, 3078, 3056, 3024, 1669, 1597, 1580, 1490, 758, 746, 703, 692 cm^{-1}; MS (EI): m/z = 325.

2.1.2. CV analysis

Electrochemical measurements for cyclic voltammetry were performed using a IM-60 electrochemical work station (CH Instruments, Austin, TX). The working electrode is a glass carbon electrode (3-mm-diameter), the auxiliary electrode is a platinum wire, and the reference electrode is a saturated calomel electrode (SCE). The reaction solution has been purged with N_2 for 10 min to remove O_2 from the reaction mixture.

Table 1. $FeCl_3$ catalyzed Friedel-Crafts alkylation reaction of indole with chalcone[a].



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

no ligand or additive: trace
with acac (10 mol%): 75% yield

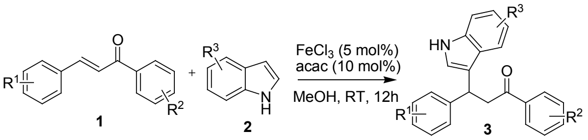
Entry	Catalyst	Solvent	Time (h)	Yield(%)[b]
1	$Mg(ClO_4)_2$	CH_2Cl_2	48	NR[c]
2	$Fe(ClO_4)_3$	CH_2Cl_2	48	Trace[d]
3	$FeCl_3$	CH_2Cl_2	48	Trace
4	$PdCl_2(CH_3CN)_2$	CH_2Cl_2	48	NR
5	$Cu(OTf)_2$	CH_2Cl_2	48	NR
6	$ZnCl_2$	CH_2Cl_2	48	Trace
7	$Ni(ClO_4)_2$	CH_2Cl_2	48	NR
8	$Fe(acac)_3$	CH_2Cl_2	24	NR
9	$FeCl_3$	MeOH	24	Trace
10	$FeCl_3$+acac[e]	CH_2Cl_2	24	50
11	$FeCl_3$+acac[e]	MeOH	24	75

[a] Reactions conditions: 5 mol% of transition metal salt, indole/chalcone = 0.55 mmol/0.5 mmol, 2 mL of solvent, at room temperature; [b] Isolated yield; [c] No reaction; [d] <10% yield; [e] 5 mol% of $FeCl_3$ and 10 mol% of acetylacetone (acac).

3. Results and Discussion

In an initial attempt, we examine the Friedel-Crafts alkylation of indole and chalcone in dichloromethane with several cheap or important Lewis acid catalysts at room temperature. We screened a series of cheap Lewis acidic metal salts as catalyst (5 mol%) such as $PdCl_2(CH_3CN)_2$, $Mg(ClO_4)_2$, $MgCl_2$, $FeCl_3$, $ZnCl_2$, $Cu(OTf)_2$, *etc.* (Entries 1-8). Unfortunately, no addition product was detected with these transition metal salts at room temperature even in different solvents; we then evacuated this reaction with the addition of diketones or others as ligands. Interestingly, with acetylacetone (acac) as an additive, we obtained the C-3 alkylation product of indole in 50% yield. In an effort to improve the yield of the reaction, we next screened the solvent and found methanol is the better solvent (Entry 11). It is important to note that the by-product of Michael addition of acetylacetone to chalcones was not observed in this reaction. We also examined other diketones as ligands under the same conditions. When dibenzoylmethane and 2-acetylcyclohexanone were used, the alkylation product was obtained in 80% and 69% yields, respectively. This clearly showed the combination of $FeCl_3$ and 1,3-diketones was suitable catalytic system to promote the Friedel-Crafts alkylation reaction.

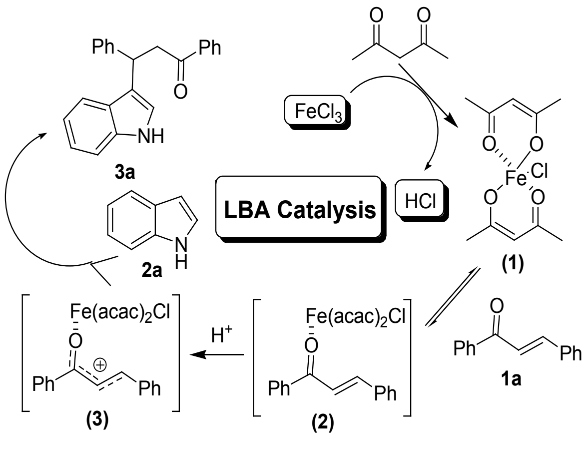
Table 2. $FeCl_3$ catalyzed Friedel-Crafts alkylation reaction of various chalcones and indoles [a].



Entry	R¹	R²	R³	Yield (%)[b]
1	H	H	H	70
2	*p*-Cl	H	H	72
3	*p*-CH_3	H	H	84
4	*p*-OMe	H	2-Me	75
5	*p*-CH_3	*p*-OMe	2-Me	75
6	*p*-OMe	*p*-Cl	5-Br	84
7	*p*-CH_3	H	5-Br	90

Note: [a] Reactions conditions: 5 mol% of FeCl3 and 10 mol% of acetylacetone, indole/chalcone = 0.55 mmol/0.5 mmol, 2 mL of MeOH, at room temperature for 12 h; [b] Isolated yield.

A variety of indoles and chalcones were next examined to generate the desired C-3 Friedel-Crafts alkylation coupling products under the established reaction conditions. As shown in Table 2, the isolated yields of reaction are generally good to excellent. Nearly all reactions are clean and the target compounds are obtained in good yields with no formation of side products like dimmers or trimers, which are normally observed by the influence of strong acids [19,20].



Scheme 1. Proposed LBAs Mechanism for the Iron-catalyzed Friedel-Crafts alkylation of indoles with chalcones

Based on our experimental results, a suggested and more practical mechanism of Lewis acid-assisted Brønsted acid (LBA) catalysis [21-22], is proposed in Scheme 1. The reasons for this proposal of LBA are given as follows: a) Only $FeCl_3$ or other iron salts catalyzed Friedel-Crafts alkylation of indoles with chalcones gave no desired product. However, the addition of acac resulted in good yield, which indicates that the alkylation proceeded with in-situ formed Brønsted acidic HCl as synergistic promoter. b) Without the iron catalyst, no reaction occurred. Only HCl is not good for the alkylation reaction of indole and chalcone, in which acid catalyzed electrophilic substitution of indoles requires careful control of acidity to prevent side reactions such as dimerisation and polymerization. Therefore, the major role of the iron catalyst lies in the possible formation of iron-dicarbonyl complex (1) and (2) for the improvement of selectivity. c) With the combination of a catalytic amount of HCl or TsOH and $Fe(acac)_3$ as a catalytic system, the desired products were also formed with good yields, which supported the proposed mechanism of Lewis acid-assisted Brønsted acid (LBA) catalysis. The proposed process of LBA catalysis makes us easy to understand that the catalytic activity of iron in organic transformation is increased dramatically in the presence of readily available acetylacetone (acac).

Direct evidence for this hypothesis of LBA catalysis was attained by ESI-MS and cyclic voltammetry (CV) analysis of the $FeCl_3$-acac catalytic system (Figs. 1 and 2). In the cation ESI spectra of $FeCl_3$ and the acetyl acetone (acac) dissolved in MeOH, the mass spectra are dominated by $[Fe(acac)_2]^+$ signals (Fig. 1a). As expected, the complex $[Fe(acac)_2\text{-chalcone}]^+$ (Fig. 1b) is also observed in a significant amount in the mixture of $FeCl_3$, acac, and chalcone, in MeOH. However, it remains to be mentioned that no complexes of iron with indole are observed. Therefore it is worthy to note that the intermediates (1) and (2) in Scheme 1 is existed to support the LBA catalysis mechanism

Cyclic voltammetry (cv) is a simple and direct method for measuring the formal potential of a half reaction when both oxidized and reduced forms are stable during the time required to obtain the voltammogram (current-potential curve) [23,24]. However, there are few reports on the analysis of metal ion intermediates in homogeneous catalysis by cv [25]. To further examine the hypothesis that the iron-dicarbonyl complex (1) is generated in MeOH, cyclic voltammetry experiments of $FeCl_3$ and $FeCl_3$-acac in MeOH have shown that a new iron complex is formed and it is greatly different to $FeCl_3$ and $Fe(acac)_3$. The voltammogram of $FeCl_3$ in MeOH is reversible, and the

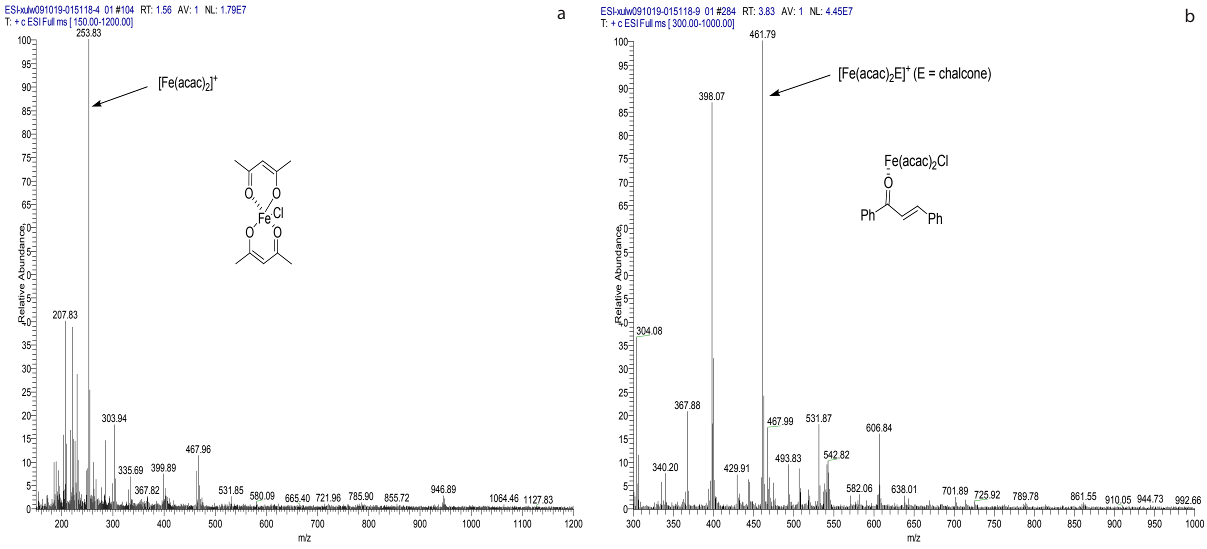


Figure 1. (a) The cation ESI spectrum of the solution of $FeCl_3$ and acac in MeOH; (b) The cation ESI spectrum of the solution of $FeCl_3$, acac, and chalcone, in MeOH.

addition of acac (0.5 equiv.) to a solution of $FeCl_3$ in MeOH generated an irreveible cyclic voltammogram (Fig. 2). Further addition of acac (1 equiv. to 4 equiv.) resulted in no obvious difference with oxidation peak potentials. The cv experiments lead to the conclusion that addition of acac to $FeCl_3$ in MeOH creates a stable iron-dicarbonyl complex. These data in combination with the previous described ESI-MS studies show it is reasonable that $FeCl_3$-acac is a more powerful catalytic system than $FeCl_3$ alone. The mechanistic complexity of the $FeCl_3$-acac system is driven by the high affinity of acac for iron(III) and these results suggest that simple empirical models describing the Lewis acid-assisted Brønsted acid (LBA) catalysis in more complex systems is more likely to be the correct mechanism.

Cyclic voltammetry was performed using platinum wire auxiliary electrodes, glassy carbon working electrodes, and the reference electrode is a saturated calomel electrode (SCE).

4. Conclusions

We have demonstrated that $FeCl_3$ is a superior catalyst for the alkylation of indoles in the presence of acetylacetone. Lewis acid-assisted Brønsted acid (LBA) catalysis is exhibited in the iron-catalyzed Friedel-Crafts alkylation of indoles with chalcones, which has the advantages of mild reaction conditions, convenient operation, and structural diversity of the desired products. The ESI-MS and cyclic voltammogram described herein collectively show that the combination of $FeCl_3$ with acac creates a powerful catalytic system, which makes the alkylation reactions occur easily under mild conditions.

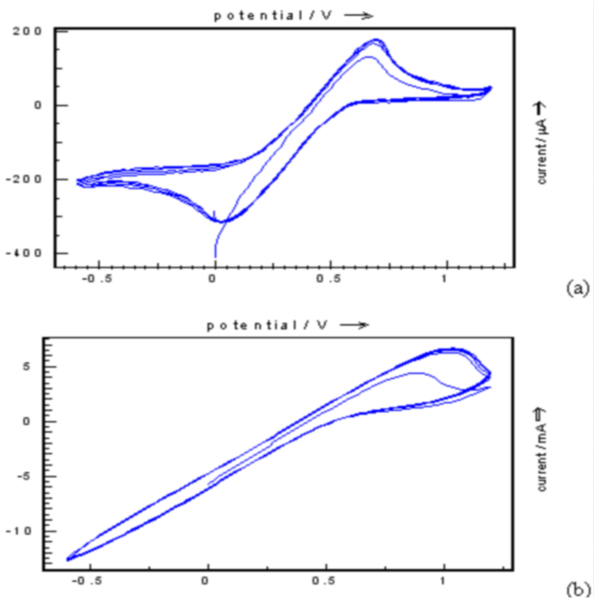


Figure 2. (a) Cyclic voltammogram of FeCl3 in MeOH (0.1 M); (b) Cyclic voltammogram of FeCl3 in MeOH (0.1M) containing 0.05M acetyl acetone (acac).

Acknowledgements

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