

A novel, convenient access to acylferrocenes: acylation of ferrocene with acyl chlorides in the presence of zinc oxide

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Abstract

A convenient access to acylferrocenes was reported. In the presence of ZnO, ferrocene reacted with carboxylic acid chlorides in ethylene chloride or under solvent-free condition to furnish acylferrocenes in up to 96% isolated yield. Mechanism for the acylation has also been suggested based on the React IR and ES-MS observation.

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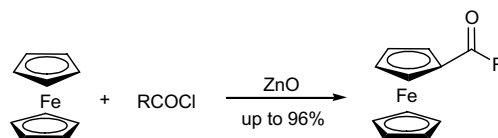
Ferrocene and its derivatives are paid much attention on account of their fascinating sandwich structure and unusual properties.¹ They have shown a broad variety of application prospects in material,² medicine,³ organic synthesis,⁴ etc.

Acylferrocene is one of the most important motifs among the ferrocene derivatives. This class of compounds is traditionally synthesized from ferrocene via Friedel–Crafts acylation in the presence of Lewis acid or Brønsted acid catalysts.⁵ However, in these acylations monoacylferrocenes used to be obtained in low yield due to the formation of di- or polyacylation products or ferricenium salt. In the cases of BF₃–OEt₂, AlCl₃, phosphorus oxochloride, *ortho*-phosphoric acid, or poly-phosphoric acid as catalysts, tremendous acidic waste was produced and caused serious environmental problems. Therefore, to search for new, convenient routes to acylferrocenes is of great practical importance.

Recently, we examined the application of zinc oxide, an inexpensive, nonpoisonous metal oxide, to acylation of ferrocene, and found that it was a highly efficient promoter for the preparation of acylferrocenes. In this Letter, we will

report Friedel–Crafts acylation of ferrocene with acyl chloride in the presence of ZnO (Scheme 1).

As a model reaction, acylation of ferrocene with isobutyric acid chloride was tested employing ZnO as the promoter. It is observed that the acylation is in close relationship with the acyl chloride loading. Influences of the ZnO loading, medium, temperature, and reaction time as well as additive on the reaction were also examined, and the results are summarized in Table 1. As shown in Table 1, the reactions in CH₂Cl₂ have the best chemoselectivity and furnish the monoacylferrocene **A** in the highest yield (entries 1–5 and 7–9). Extension of reaction time leads to a slight decrease in the yield of product **A**, while the diacylation product **B** was increased (entries 7–9). On the other hand, almost no **B** was isolated in similar experiments at ambient temperature. Higher reaction temperature is only favorable for diacylation of ferrocene. With regard to the



Scheme 1. ZnO-promoted Friedel–Crafts acylation of ferrocene with acyl chloride.

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Table 1
Reaction of ferrocene with isobutyryl chloride in the presence of zinc oxide^a

Entry	FcH/ZnO (molar ratio)	Solvent	Time (min)	Yield of A (%)	Yield of B ^c (%)
1	1.0:0.8	CH ₂ Cl ₂	5	95	Trace
2	1.0:1.0	CH ₂ Cl ₂	5	96	Trace
3	1.0:1.2	CH ₂ Cl ₂	5	96	Trace
4	1.0:1.5	CH ₂ Cl ₂	5	96	Trace
5	1.0:1.8	CH ₂ Cl ₂	5	95	Trace
6	1.0:1.2	No	5	92	Trace
7	1.0:1.2	CH ₂ Cl ₂	15	94	1
8	1.0:1.2	CH ₂ Cl ₂	30	92	1.5
9	1.0:1.2	CH ₂ Cl ₂	60	90	5
10	1.0:1.2	CHCl ₃ ^b	15	84	8
11	1.0:1.2	CH ₃ CN ^b	15	82	Trace
12	1.0:1.2	CH ₃ NO ₂ ^b	15	64	31
13	1.0:1.2	CH ₃ NO ₂ ^b	60	43	48

^a All the reactions were performed in a 1:3 molar ratio of ferrocene and the acyl chloride in CH₂Cl₂ under reflux except special indication. A represents isobutyrylferrocene, and B represents 1,1'-diisobutyrylferrocene.

^b Reacted at ca. 70 °C.

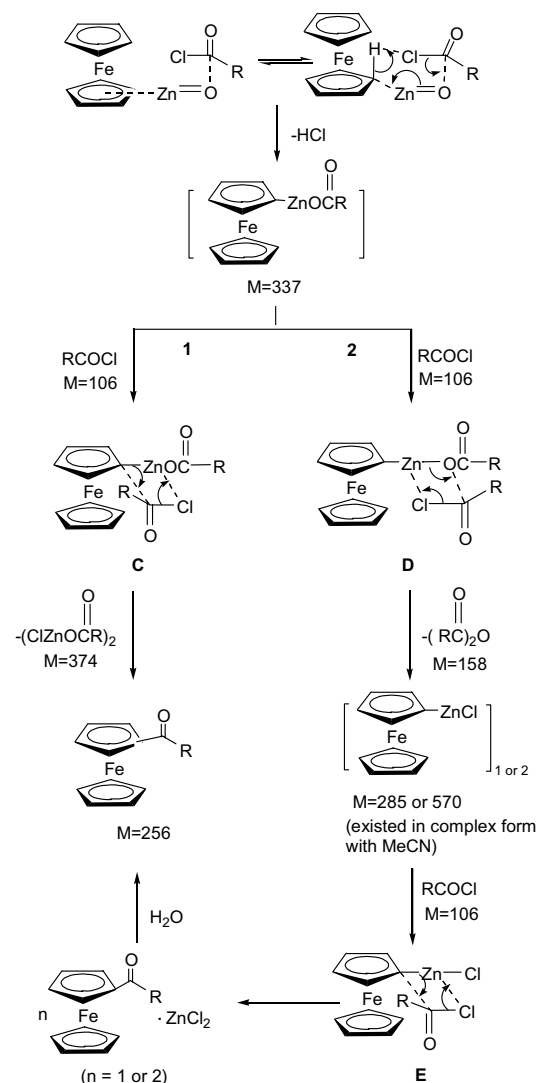
^c Isolated yield.

influence of reaction medium on the acylation, it has been observed that the selectivity of the reaction and the yield of the desired product dropped obviously in the order of CH₂Cl₂, CHCl₃, and CH₃NO₂ (entries 7, 10–12). It appears that the best choice is that in the presence of 1.2 equiv of ZnO, ferrocene is acylated by 3 equiv of the acyl chloride in CH₂Cl₂ for several minutes under reflux or longer time at ambient temperature.

To understand the formation mechanism of the acylferrocenes, we tried to monitor the reaction via in situ IR (React IR 4000) and ES-MS technologies. To a 1:1 mixture of ferrocene and ZnO in CH₂Cl₂ was added 1 equiv of the isobutyryl chloride, ZnO merely was partially consumed, and the React IR spectra of the solution clearly showed that the absorption of the acyl chloride (1810, 1770 cm⁻¹) disappeared within several minutes; meanwhile, two new, strong absorptions corresponding to a ketone carbonyl and carboxylic radical at near 1680 and 1580 cm⁻¹ appear, respectively, meaning that isobutyrylferrocene and zinc salt containing isobutyryl formed in the reaction. However, the TLC analysis of the solution shows that a large amount of ferrocene remains. With the increase of the acyl chloride loading from 1 to 2 equiv, most of ZnO dissolved, but there still was unchanged ferrocene, and the yield of the desired product was not satisfactory. A further increase of the acyl chloride to 3 equiv led to complete transformation of ferrocene and the color of the reaction mixture changed from brown-reddish to purple-reddish. In the ES mass spectra

of the above three kinds of reaction solutions (MeCN as carrier), the molecular ions 326 and 611 corresponding to the acetonitrile complexes of ferrocenyl zinc chloride (FcZnCl, 285) and its dimer [(FcZnCl)₂, 570] and their fragment ions were observed. In addition, there also are some fragment ions derived from the 2:1 complex (648) and 1:1 complex (392) formed from isobutyrylferrocene (256) and byproduct ZnCl₂ (136). For the more concentrated solution resulting from the equimolar reaction, the ion 339 derived from ferrocenyl zinc isobutyrate (M⁺, 337) was observed, but it disappeared with the increase of the acyl chloride.

It can be deduced based on the aforementioned facts that the C–H bond of ferrocene is first activated by π coordination of cyclopentadienyl of ferrocene to the zinc in the mixture of ferrocene and ZnO. When isobutyryl chloride is added to the system, ferrocenyl zinc isobutyrate is formed via a six-center transition state, which reacts further with the second isobutyryl chloride to furnish directly the



Scheme 2. Possible formation mechanism of acylferrocenes in the ZnO-promoted acylation of ferrocene with RCOCl.

Table 2
Acylation of ferrocene with acyl chlorides in the presence of ZnO^a

Entry	R of acyl	Acylferrocene	Mp ^b (°C)	Yield ^c (%)
1	Me	Acetylferrocene	87 (86) ^{5f}	94
2	Et	Propionylferrocene	35 (35) ^{5f}	96
3	<i>n</i> -Pr	<i>n</i> -Butyrylferrocene	36 (34) ⁷	96
4	<i>n</i> -C ₇ H ₁₅	<i>n</i> -Octadecylferrocene	36	91
5	<i>n</i> -C ₁₅ H ₃₁	<i>n</i> -Hexadecylferrocene	63 (61) ⁸	87
6	<i>i</i> -Pr	<i>i</i> -Butyrylferrocene	/	96
7	<i>t</i> -Bu	2,2-Dimethylpropionylferrocene	92 (93) ⁹	88
8	Cyclohexyl	Cyclohexylcarbonylferrocene	83 (80) ¹⁰	90
9	ClCH ₂ CH ₂	3-Chloropropionylferrocene	58 (59) ¹¹	89
10	EtOCO(CH ₂) ₂	3-Ethoxycarbonylpropionylferrocene	37	92
11	PhCH ₂	2-Phenylacetylferrocene	131 (130) ⁷	78
12	PhCH ₂ CH ₂	3-Phenylpropionylferrocene	85 (80) ^{5f}	82
13	1-(3-PhCOC ₆ H ₄)CHCH ₃	2-(3-Benzophenyl)propionylferrocene	123	68
14	1-(4-Bu ^t C ₆ H ₄)CHCH ₃	2-(4-Isobutylphenyl)propionylferrocene	106	72
15	Ph	Benzoylferrocene	111 (107) ^{5f}	48
16	4-CH ₃ C ₆ H ₄	4-Methylbenzoylferrocene	118	45

^a All the reactions were carried out in a 1:1:3 molar ratio of ferrocene, ZnO and acyl chloride in CH₂Cl₂ under reflux for 5–30 min. Entries 13 and 14 were performed with in situ prepared, unpurified acid chlorides.

^b Uncorrected; those in brackets are the literature values.

^c Isolated yield.

desired isobutyrylferrocene and byproduct chlorozinc isobutyrate through a four-center transition state (**C**, route **1**). On the other hand, ferrocenyl zinc isobutyrate can also react with the acyl chloride via the transition state **D** to form ferrocenyl zinc chloride, which further reacts with the acyl chloride in the system via the transition state **E** to give the desired product. It looks as if there are two possible accesses to the acylferrocene in this acylation, and route **2** (via **D** and **E**) is dominative. Thus, the ZnO-promoted acylation of ferrocene with acyl chloride can be summarized in Scheme 2.

It is obvious that in the formation mechanism, it is quite different not only from catalytic acylation by the other Lewis acid (BF₃·OEt₂, AlCl₃, ZnCl₂, etc.), but also from the acylation of aromatic compounds in the presence of ZnO.⁶

The above optimized condition was applied to the reaction of ferrocene and other acyl chlorides. The results are summarized in Table 2. It can be seen in Table 2, in the presence of ZnO, ferrocene was acylated by most of normal or substituted (halo, phenyl, substituted phenyl, alkyl-oxycarbonyl, etc.) aliphatic carboxylic acid chloride and cycloalkylcarboxylic acid chloride to furnish monoacylferrocenes in very high yield, except aromatic acid chlorides or 2-aryl substituted carboxylic acid chlorides (entries 13–16). For the acyl chlorides formed from aliphatic acids, the increase of the chain and substituent does not influence remarkably on the selectivity of the acylation and the yield of the desired product. In regard to the entries 13 and 14, 2-aryl substituted aliphatic carboxylic acid chlorides are prepared in situ and directly employed as the reagent without further purification. In the cases of aromatic acid chlorides (entries 15 and 16), the yield is only at moderate level. It can be rationalized by the conjugation between the aryl

and the carbonyl groups, which results in an increase of the electronic density at the carbonylic carbon; as a result, the nucleophilic attack of the ferrocenyl is inhibited.

All the acylferrocenes prepared¹² were characterized by IR, ¹H, and ¹³C NMR spectroscopy and MS.

It should be indicated that the acylation under solvent-free condition has been attempted. However, the monoacylferrocene was obtained in lower yield compared to those in CH₂Cl₂ (Table 1, entry 6). Additionally, the ZnO-promoted reactions of ferrocene with the lower aliphatic carboxylic acid chlorides are vehement; as a result, the acylation is difficult to be controlled.

It should be also pointed out that all the acylations described herein were performed under conventional conditions without special protection technology, and all solvents used are commercial without special treatment.

In conclusion, an inexpensive, nonpoisonous, and highly effective promoter for the monoacylation of ferrocene has been discovered. In the presence of ZnO, ferrocene is acylated in CH₂Cl₂ by aliphatic carboxylic acid chlorides, 2-aryl substituted aliphatic carboxylic acid chlorides, cycloalkylcarboxylic acid chloride, and aromatic acid chlorides to furnish highly chemoselectively monoacylferrocenes. This acylation procedure is simple, open, and broad spectral. Probably it is one of the most convenient accesses to monoacylferrocenes for the time being.

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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.2007.11.119](https://doi.org/10.1016/j.tetlet.2007.11.119).

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- General procedure for the preparation of acylferrocenes: A mixture of 5 mmol (0.93 g) of ferrocene and 6 mmol (0.49 g) of ZnO in 10 mL dichloromethane was stirred and refluxed. The corresponding acyl chloride (15 mmol) was added and reacted for 5–30 min (controlled by TLC). The resulting solution was cooled, and then poured to the stirred ice water. The organic layer was separated, and the water phase was extracted with petroleum ether. The combined organic phase was neutralized with the solution of NaHCO₃, and followed by washing with water and dried over anhydrous Na₂SO₄. Thereafter, the solvents were removed in vacuo to offer a crude product, which was purified by column chromatography, using 20:1 petroleum ether/ethyl acetate as an eluent. The first fraction is unchanged ferrocene, the second, monoacyl derivative, and the third, diacylferrocene. To obtain a good crystal, the products can be recrystallized in a mixture of CH₂Cl₂ and petroleum ether. All the acylferrocenes showed satisfactory spectroscopy (see Supplementary data).