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The direct alkylation of ferrocene (FC) can be achieved via a Friedel–Craft reaction using an alkyl halide and AlCl$_3$; however, this invariably leads to mixtures of mono- and poly-alkylated complexes. Here, we describe the synthesis of mono-substituted benzyl FC derivatives by a Friedel–Craft reaction utilizing environmentally benign substrates such as benzyl and allyl alcohol and a catalytic amount of Lewis acid in the absence of organic solvents. The use of molten FC, which plays the role of a solvent, proved a robust way to produce excellent yields of the mono-substituted FC derivatives. Furthermore, this novel synthetic method is very simple and offers great potential for the industrial-scale synthesis of FC derivatives.

Introduction

Ferrocene (FC) has attracted the attention of the scientific and technical community on account of its fascinating chemistry.[1] The remarkable and versatile properties of FC have led to its use in homogeneous asymmetric catalysis, molecular electronics, and medicinal chemistry and bio-analysis, as well as in the development of chemical sensors and bioconjugates.[2] The synthesis of mono-substituted FC allows the incorporation of a stereogenic plane, with the added potential for the introduction of stereo centers. Planar stereogenicity and stereo centers of FC derivatives often act cooperatively in a variety of stereoselective transformations in many organic reactions. Furthermore, some mono-substituted benzyl FC derivatives have been shown to possess efficient cytotoxicity.[3,4]

Despite this, the synthesis of mono-substituted FC derivatives is not trivial because of the lack of suitable synthetic routes and difficulties associated with the separation of the desired products from poly-substituted analogs.[5] The direct alkylation of FC can be achieved through a Friedel–Crafts reaction using an alkyl halide and AlCl$_3$; however, this invariably leads to a complex mixture of mono- and poly-alkylated products.[6] In particular, the benzylation of FC produces mono-benzyl FC in <20% yield in the presence of benzyl chloride and AlCl$_3$.[7] In this conventional method, there are additional disadvantages, including the use of an alkyl halide, which is toxic, the presence of stoichiometric amounts of AlCl$_3$, and the requirement of anhydrous conditions. A few direct syntheses of substituted benzyl FC have been reported, including the reaction of ferrocene carboxaldehyde with aryl lithium, followed by reduction of the resulting carbinols.[3] The maximum yields reported for the synthesis of mono-substituted benzyl FC derivatives by direct substitution are <60%.[6]

Therefore, there is an urgent need to develop a novel method for the synthesis of mono-substituted FC derivatives in high yield. In particular, the development of an environmentally friendly process is attractive for industrial-scale application. The development of efficient Friedel–Crafts alkylations of arenes and heteroarenes using only catalytic amounts of Lewis acid has gained much attention over the last decade.[8] This prompted us to develop an efficient synthetic route to mono-substituted FC using allyl and benzyl alcohols in the presence of a Lewis acid catalyst.

Here, we describe the synthesis of mono-substituted benzyl and allyl FC derivatives by the Friedel–Crafts reaction under solvent-free conditions, using environmentally benign benzyl and allyl alcohols and catalytic amounts of Lewis acid. FC was used in excess, and it acted as a solvent in its molten state. To the best of our knowledge, this is the first report on the use of FC as a solvent.

Experimental

Materials and Methods. FC, alcohols (benzyl alcohol, 4-methoxy benzyl alcohol, 4-chlorobenzyl alcohol, 1-phenylethyl alcohol, cinnamyl alcohol, and diphenylmethyl alcohol) and catalysts [indium (III) chloride, scandium (III) triflate, ytterbium (III) trifluoro-methanesulfonate, and aluminum chloride] were purchased from Sigma Aldrich. Acid clay catalyst (DC-260H 30–70 mesh) was purchased from Donghae Chemical (Korea). Solvents (*n*-hexane, *n*-heptane, *n*-octane, and *n*-decane) were purchased from Samchun Chemicals (Korea) and used without further purification. The R_f values on thin-layer chromatography (TLC) were determined by employing precoated silica gel aluminum plates (Kiesel gel 60 F254, Merck, Germany) using *n*-hexane:dichloromethane as eluent. Proton and carbon nuclear magnetic resonance

(^{1}H NMR and ^{13}C NMR) spectra were recorded on a Varian Unity Plus 400 MHz NMR spectrometer (Varian, Palo Alto, CA, USA) with TMS as internal standard. Gas chromatography-mass spectrometry (GC-MS) data were recorded on (Technologies, Santa Clara, CA, USA) Agilent 6890N gas chromatograph/Leco PEGASUS III ToF mass spectrometer.

Screening of Lewis Acid Catalysts. FC (1.00 g, 5.37 mmol), benzyl alcohol (0.11 mL, 1.07 mmol or 0.055 mL, 0.53 mmol), and catalyst (20 mol% with respect to benzyl alcohol) were mixed together and heated at 176 °C for 1 h. Then, the product was isolated by following a typical procedure. The reaction mixture was cooled to room temperature. Excess FC and the product were isolated by silica gel column chromatography (eluent: from 100% hexane to 5% dichloromethane). The yield of mono-benzyl FC was calculated based on the added benzyl alcohol.

Reaction Temperature and Solvent Effect. FC (1.00 g, 5.37 mmol), benzyl alcohol (0.055 mL, 0.53 mmol), and InCl$_3$ (0.023 g, 0.106 mmol) were mixed in 5 mL of each solvent and heated to reflux for 1 h. Then, the product was isolated by a typical procedure as described above.

Molar Ratio of FC to Benzyl Alcohol. FC (0.100 g, 0.53 mmol; 0.200 g, 1.07 mmol; 0.500 g, 2.65 mmol; 1.00 g, 5.37 mmol; 2.00 g, 10.74 mmol), benzyl alcohol (0.11 mL, 1.07 mmol), and InCl$_3$ (0.046 g, 0.21 mmol) were mixed together without solvent and heated at 176 °C for 1 h. Then, the product was isolated by a typical procedure as described above.

Catalyst Loading. FC (1.00 g, 5.37 mmol), benzyl alcohol (0.055 mL, 0.53 mmol), and InCl$_3$ (0.003 g, 0.026 mmol; 0.011 g, 0.053 mmol; 0.023 g, 0.106 mmol; 0.058 g, 0.265 mmol) were mixed together and heated at 176 °C for 1 h. Then, the product was isolated by a typical procedure as described above.

Optimized General Reaction. FC (1.00 g, 5.37 mmol), alcohol (0.53 mmol), and InCl$_3$ (0.024 g, 0.107 mmol) were mixed together and heated at 176 °C for 10 min. The reaction mixture was cooled to room temperature. Excess FC and the product were isolated by silica gel column chromatography (eluent: from 100% hexane to 5% dichloromethane). The yield of mono-benzyl FC was calculated based on the added benzyl alcohol.

Benzyl ferrocene (3a): Yellow solid; yield: 90%; mp 74–76 °C; R_f: 0.35 (hexane); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.17–7.26 (m, 5H), 4.08–4.12 (m, 9H), 3.69 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 141.6, 128.4, 128.2, 125.9, 88.2, 68.9, 68.9, 67.7, 36.1; GC-MS (*m/z*): calcd. 270.06, found 270.1 (M$^+$).

4-Methoxy benzyl ferrocene (3b): Yellow solid; yield: 91%; mp 72–74 °C; R_f 0.20 (hexane); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.08 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 7.6 Hz), 4.08–4.12 (m, 9H), 3.76 (s, 3H), 3.61 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 157.8, 133.8, 129.3, 113.6, 88.8, 70.7, 68.8, 68.7, 67.6, 55.3, 35.1; GC-MS (*m/z*): calcd. 306.07, found 306.1 (M$^+$).

4-Chlorobenzyl ferrocene (3c): Yellow solid; yield: 76%; mp 79−81 °C; R_f 0.45 (hexane); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.49 (d, J = 7.6 Hz, 2H), 7.37 (d, J = 7.2 Hz, 2H), 4.35−4.40 (m, 9H), 3.92 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 140.2, 131.8, 129.9, 128.5, 87.8, 69.0, 68.9, 68.0, 35.6; GC-MS (*m/z*): calcd. 310.02, found 310.1 (M$^+$).

Phenylethyl ferrocene (3d): Brown oil; yield: 91%; R_f 0.40 (hexane); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.13–7.25 (m, 5H), 4.03−4.25 (m, 9H), 3.82 (q, 1H, J = 7.2 Hz), 1.58 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 147.5, 128.2, 127.1, 125.9, 94.8, 69.0, 68.2, 67.9, 67.2, 66.7, 39.8, 22.6; GC-MS (*m/z*): calcd. 290.08, found 290.1 (M$^+$).

Cinnamyl ferrocene (3e): Yellow solid; yield: 81%; R_f 0.40 (hexane); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.18–7.37 (m, 5H), 6.36–6.42 (m, 2H), 4.10–4.16 (m, 9H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 137.6, 130.3, 129.4, 128.5, 127.0, 126.1, 87.6, 68.7, 68.3, 67.6, 32.9; GC-MS (*m/z*): calcd. 302.08, found 302.1 (M$^+$).

Diphenylmethyl ferrocene (3f): Reddish brown oil; yield: 92%; R_f 0.25 (hexane); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.16−7.28 (m, 10H), 5.13 (s, 1H), 4.02−4.17 (m, 9H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 145.0, 128.8, 128.1, 126.1, 91.7, 68.9, 68.9, 67.8, 51.9; GC-MS (*m/z*): calcd. 352.09, found 352.2 (M$^+$).

Results and Discussion

Initially, several Lewis catalysts, including InCl$_3$, Sc(OTf)$_3$, Yb(OTf)$_3$, and AlCl$_3$, as well as acid clay, were screened to optimize the yield of the mono-substituted benzyl FC derivative, as shown in Scheme 1.[4] The reactions were carried out in the absence of a solvent by using an excess of FC with respect to benzyl alcohol and 20 mol% of different Lewis acid catalysts. The reaction temperature was fixed at 176 °C, at which FC melts and plays a dual role as solvent and reagent. The isolated yields of mono-benzyl FC are shown in Table 1. Two different molar ratios (5:1 and 10:1) of FC to alcohol were investigated. All the catalysts produced the desired mono-substituted FC derivative, but, InCl$_3$ produced relatively high yields of mono-benzyl FC (Table 1). Furthermore, it is known that InCl$_3$ is an efficient catalyst in organic synthesis because of its low toxicity, high air/moisture stability, and recyclability.[9] Therefore, InCl$_3$ was chosen as the catalyst for further optimization.
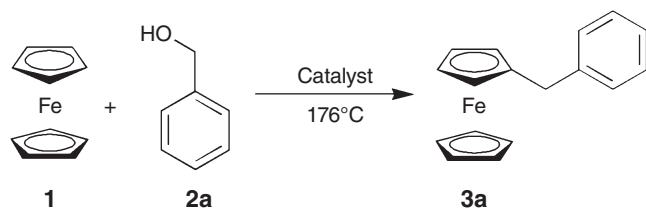
In the initial catalyst screening, the reaction temperature was fixed at the melting temperature of FC; however, this might not be optimal for the reaction. Therefore, four different hydrocarbon solvents were selected for the optimization of the reaction temperature (Table 2). With the exception of the case with FC, all reactions were carried out by heating to reflux in the organic solvent, and the reaction temperature was recorded as the boiling point of the solvent. As the reaction temperature in the organic solvent increased, the yields of mono-benzyl FC gradually increased and reached a maximum 65% in *n*-decane. Even though the boiling point of *n*-decane is comparable to that of FC, the yield of the desired product was significantly better when using the latter as the solvent, probably because of the effective molar concentration of FC as a reagent. The requirement for high temperature in this reaction can be explained by the endothermic nature of the carbon–oxygen dissociative process for generating the reactive benzyl cation.

By considering the obtained yields and cost of solvents, the most economical result giving the best yield of product was the reaction in the absence of an organic solvent, with only FC.

Next, the effect of the molar ratio of FC to benzyl alcohol on the yield of mono-benzyl FC was examined using the previously optimized conditions. The results are shown in Table 3. By increasing the ratio of FC to benzyl alcohol, the yield of mono-benzyl FC increased and reached 90% at a molar ratio 20:1. In all cases, the benzyl alcohol was fully consumed during the course of the reaction. At equimolar ratios (1:1) or less (0.5:1), very low yields of mono-benzyl FC were obtained because of the formation of the poly-alkylated FC.

These poly-benzylated FC derivatives were confirmed by GC-MS, which showed peaks for mono-, di-, and tri-benzylated FC. However, at higher ratios of FC to benzyl alcohol, there is higher availability of FC for the reactive benzyl cation, and, hence, the mono-substituted product was obtained in excellent yield. This result demonstrates the high reactivity of alkyl-substituted FC compared to the parent FC.

Next, the loading of InCl$_3$ catalyst for the formation of mono-alkylated FC was investigated. For this purpose, a 10:1 molar ratio of FC to benzyl alcohol was used for

convenient isolation and characterization of the product. As shown in Table 4, the highest yield (79%) of the mono-alkylated product was achieved using 20 mol% of the catalyst, while the reactions were incomplete when using lower catalyst loadings. At lower catalyst loading (<20 mol%), the added benzyl alcohol was not fully consumed despite using extended reaction times (6 h). This may be due to the partial decomposition of the catalyst at elevated temperatures. To confirm whether the catalyst was decomposing, FC and 20 mol% of InCl$_3$ were mixed together prior to the addition of benzyl alcohol and the mixture was slowly heated up to 176 °C. After the addition of benzyl alcohol, the reaction was stirred for 1 h and the product was monitored by TLC. As expected, there was no product in this reaction mixture. This shows that the catalytic activity of InCl$_3$ was destroyed during prolonged exposure to elevated temperatures, but the actual decomposition mechanism of InCl$_3$ at high temperature remains unclear. It is important to note that FC, benzyl alcohol, and InCl$_3$ should be first mixed together, followed by heating the reaction mixture in a preheated (176 °C) oil bath. During the first 10 min of the reaction, complete consumption of benzyl alcohol and product formation was observed, irrespective of the partial decomposition of the catalyst.

Finally, the optimized reaction conditions were applied to different substrates for the synthesis of mono-substituted FC derivatives. A number of benzyl and allyl alcohols are available for direct incorporation onto FC by this method, and six examples (five benzyl alcohols and one allyl alcohol) for the Friedel–Craft alkylation were chosen (Table 5). The previously optimized conditions of catalyst loading (20 mol%) and molar ratio of FC to alcohol were utilized; all the reagents were premixed together, followed by heating in a preheated oil bath for 10 min (Scheme 2). The isolated yields of mono-substituted FC derivatives are shown in Table 5.

Scheme 1. Synthesis of mono-substituted benzyl ferrocene (FC) from excess FC and benzyl alcohol.

Table 1. Screening of Lewis acid catalysts in excess molar ratio of ferrocene: benzyl alcohol.

Catalyst[a]	1:2a	Yield (%)[b]	1:2a	Yield (%)[b]
InCl$_3$	5:1	59	10:1	79
Sc(OTf)$_3$	5:1	57	10:1	60
Yb(OTf)$_3$	5:1	20	10:1	23
AlCl$_3$	5:1	46	10:1	60
Acid clay	5:1	51	10:1	53

[a] Catalyst (20 mol% with respect to benzyl alcohol).
[b] Isolated yields of mono-benzyl ferrocene.

Table 2. Effect on the yield of mono-benzyl ferrocene at different reaction temperatures.

Solvent	Temperature (°C)	Yield (%)[a]
n-Hexane	69	ND[b]
n-Heptane	98	23
n-Octane	126	48
n-Decane	175	65
Ferrocene	176	79

[a] Isolated yields of mono-benzyl ferrocene.
[b] Negligible amount was detected by TLC.

Table 3. Effect on the molar ratios of ferrocene to benzyl alcohol on the yield of the desired product.[a]

Entry	1:2a	Yield (%)[b]
1	0.5:1	10
2	1:1	35
3	5:1	59
4	10:1	79
5	20:1	90

[a] 20 mol% of InCl$_3$, neat, 176 °C for 1 h.
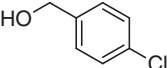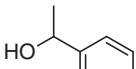[b] Isolated yields of mono-benzyl ferrocene.
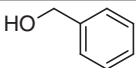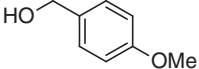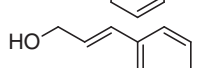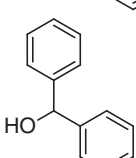
Table 4. Effect of catalyst loading on the yield of the product.[a]

Entry	InCl$_3$ (mol%)	Yield (%)[b]
1	5	65
2	10	68
3	20	79
4	50	79

[a] 10:1 ratio of ferrocene to benzyl alcohol, neat, 176 °C for 1 h.
[b] Isolated yields of mono-benzyl ferrocene.

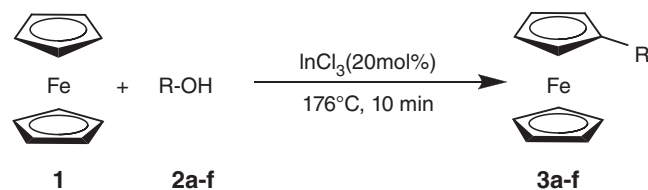**Table 5.** Effect of catalyst loading on the yield of the product.

Entry	Substrate		Yield (%)[a]
1	**2a**	HO—CH₂—C₆H₅	90
2	**2b**	HO—CH₂—C₆H₄—OMe	91
3	**2c**	HO—CH₂—C₆H₄—Cl	76
4	**2d**	HO—CH(CH₃)—C₆H₅	91
5	**2e**	HO—CH₂—CH=CH—C₆H₅	81
6	**2f**	(C₆H₅)₂CH—OH	92

[a] Isolated yields of mono-ferrocene derivatives.

Scheme 2. Synthesis of benzyl and allyl alcohol-substituted ferrocene derivatives in the optimized reaction condition.

These results revealed that mono-benzylation or allylation of FC proceeded efficiently under the optimized reaction conditions. It was observed that the yield of the desired products depended on the stability of the carbocations generated by the catalyst. The isolated yields of the mono-substituted product obtained when using 4-methoxybenzyl alcohol (entry 2) and diphenylmethyl alcohol (entry 6), which can generate relatively stable carbocations, were higher than that obtained when using 4-chlorobenzyl alcohol (entry 3), which contains an electron-withdrawing substituent on the phenyl ring. Notably, 4-nitrobenzyl alcohol was also tested as a substrate for this reaction, but only a small amount of the desired product was formed and its isolation was not possible. This may be due to the greater electron-withdrawing ability of the nitro group as compared to the chloro substituent and the consequent formation of a less stable carbocation. Subsequently, this method was attempted for the synthesis of mono-alkyl FC derivatives using simple alkyl alcohols (primary, secondary, and tertiary) as substrates.

However, no significant mono- or poly-alkylated FCs were formed in any of the cases. This shows that the formation of a stable carbocation from the alcohol is critical for the success of the reaction. The stability of the allyl carbocation is comparable to that of the benzyl carbocation. Indeed, the yield of mono-allyl FC when using a cinnamyl alcohol (entry 5) was comparable to those of benzyl FC (entry 1) and 1-phenylethyl FC (entry 4). Therefore, this method can be broadly applied to the synthesis of a variety of mono-benzyl or mono-allyl FC derivatives. Furthermore, this novel method can be considered as a green process because environmentally benign substrates are used and the by-product is water. Additionally, the reaction is carried out in the absence of a solvent, and the excess FC can be easily recovered by column chromatography in a small-scale reaction or by sublimation in an industrial scale. Typically, in our lab scale, excess FC was recovered by a rotary evaporator (oil bath temperature 120 °C) on the basis of the sublimation process of FC.

Conclusion

In conclusion, a novel and efficient method has been developed for the synthesis of mono-substituted FCs from benzyl and allyl alcohols, catalyzed by InCl₃. In addition, this is the first reported use of FC as a solvent. This method is reliable for the synthesis of bioactive mono-substituted FCs by direct substitution and can be used for the synthesis of chiral molecules and auxiliaries. The present novel approach, in which a molten FC plays the role of a solvent, proved to be a robust way to produce excellent yield of mono-substituted FC derivatives. Furthermore, the adapted method is very simple, affording the desired product in high yield (up to 92%), and offers great potential for the industrial-scale synthesis of FC derivatives.

Supporting Information. Additional supporting information is available in the online version of this article.

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