Effect of the Ferrocene Nucleus on the Microwave-Accelerated Esterification Reaction

Yutaka Okada[1], Masashi Tachi[1]

[1]Department of Applied Chemistry, Ritsumeikan University, 1-1-1 Nojihigashi, Kusattsu, Shiga 525-8577, Japan

Correspondence: Yutaka Okada, Department of Applied Chemistry, Ritsumeikan University, 1-1-1 Nojihigashi, Kusattsu, Shiga 525-8577, Japan.

Abstract

Microwave irradiation has been utilized in the syntheses of a wide variety of organic compounds due to its shorter reaction times and improved selectivities. Since ferrocene is an organometallic compound consisting of an iron center sandwiched between two cyclopentadienyl rings, the iron moiety was expected to efficiently absorb microwave irradiation, thereby resulting in the ferrocene molecules exhibiting an antenna effect. Thus, we herein confirmed this antenna effect by employing an esterification reaction as a model reaction, using both ferrocene and benzene derivatives under microwave irradiation and conventional heating conditions for comparison purposes. It was also found that the reaction could be carried out at lower temperature using ferrocene derivatives.

Keywords: l ferrocene, microwave irradiation, antenna effect, esterification

1. Introduction

In recent years, various global environmental issues have led to the development of environmentally-friendly catalysts and synthetic strategies for organic chemical synthesis to reduce the environmental impact (Sanghi & Singh, 2011). In this context, the use of microwave irradiation has received growing attention since its first report in 1986 (Gedye et al., 1986) due to the high yields and reaction rates achieved. Furthermore, different product profiles are often obtained compared to those under conventional heating conditions, and the reactions tend to proceed in a highly selective manner (Dhanush et al., 2022) (Kappe, 2004).

Ferrocene, which is an organometallic complex having a unique structure in which an iron atom is sandwiched between two cyclopentadienyl rings, was first synthesized by two independent research groups using different protocols in the early 1950s (Kealy & Pauson, 1951). Since then, ferrocene has been subjected to a range of transformations. For example, the Friedel-Crafts acylation reaction produces a acylferrocenes that can be employed as starting materials for the preparation of various ferrocene derivatives (Duan et al., 2017) (Lin et al., 2007) (Stepnicka, 2008). In the acylation reaction, the ferrocene nucleus exhibits a significantly higher reactivity than the benzene nucleus, which was attributed to the presence of the intramolecular iron atom resulting in a particularly high π electron density. It was therefore assumed that ferrocene would efficiently absorb microwave irradiation.

Thus, we herein report the effect of the ferrocene nucleus in a model esterification reaction under microwave irradiation. For comparison, the same process will be carried out using the corresponding benzene derivative, and also under conventional heating conditions (Scheme 1).

R=CH₃-, C₂H₅-, CH(CH₃)₂-, (CH₃)₃CCH₂-
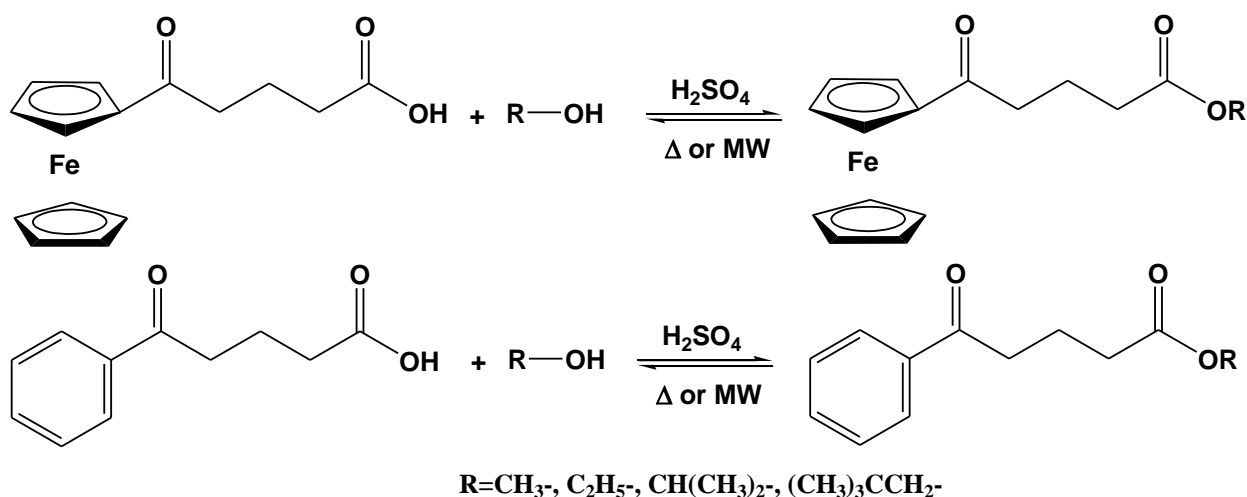
Scheme 1. The esterification reactions in this study

2. Method

2.1 Synthesis

The substrates, 4-benzoylbutanoic acid and 4-(4-methoxybenzoyl)butanoic acid, were purchased from Tokyo Chemical Industry Ltd. and Fluorochem Ltd., respectively.

2.1.1 Synthesis of 5-oxo-5-ferrocenylpentanoic Acid

In a 300 mL three-necked flask, ferrocene (15.5 g, 0.083 mol), aluminum chloride (12.3 g, 0.092 mol), and dichloromethane were stirred until all solids had completely dissolved. A dichloromethane solution containing glutaric anhydride (10.5 g, 0.092 mol) was then added slowly using a dropping funnel and allowed to react at room temperature for 2 h under an argon atmosphere. After this time, the solution was poured into iced water (300 mL), a small volume of 1 M hydrochloric acid was added, and the mixture was allowed to stir for ~10 min. The organic layer was then extracted using a 5% aqueous sodium hydrogen carbonate solution. To this solution, 1 M hydrochloric acid was added to precipitate orange crystals, and the solid was collected by filtration. The product was characterized by ^{1}H NMR spectroscopy and LC-MS.

5-oxo-5-ferrocenylpntanoic acid: ^{1}H NMR (400 MHz, CDCl₃) δ 7.79 (2H, t), 4.51 (2H, t), 4.20 (5H, s), 2.82 (2H, t), 2.51 (2H, t), 2.06 (2H, quin). LC-ESI-MS (positive mode) m/z: 301 (M+1). LC-ESI-MS (negative mode) *m/z*: 299 (M-1).

2.1.2 Synthesis of 5-oxo-5-ferrocenylpentanoic Acid Ester

In a 100-mL three-necked flask, 5-oxo-5-ferrocenylpentanoate (0.25 g, 0.83 mmol), methanol (30 mL), and sulfuric acid (1.2 mL) were mixed, and the esterification reaction was performed under an argon atmosphere at 60 °C. The reaction solution was then extracted using hexane, washed with a 5% aqueous sodium hydrogen carbonate solution, and washed three times with water. After removal of the hexane by distillation, the product was characterized by ^{1}H NMR spectroscopy and GC-MS.

The esterification reaction was also repeated using ethanol, 2-propanol and 2,2-dimethyl-2-propanol under the above conditions.

methyl 5-oxo-5-ferrocenylpntanate: ^{1}H NMR (400 MHz, CDCl₃) δ 4.79 (2H, t), 4.50 (2H, t), 4.20 (5H, s), 3.70 (3H, s), 2.82 (2H, t), 2.51 (2H, t), 2.06 (2H, quin). GC-EI-MS (positive mode) *m/z*: 314 (M).

ethyl 5-oxo-5-ferrocenylpntanate: ^{1}H NMR (400 MHz, CDCl₃) δ 4.79 (2H, t), 4.50 (2H, t), 4.20 (5H, s), 4.16 (2H, q), 2.77 (2H, t), 2.43 (2H, t), 2.03 (2H, quin), 1.27 (3H, t). GC-EI-MS (positive mode) *m/z*: 328 (M).

(1-methylethyl) 5-oxo-5-ferrocenylpntanate: ^{1}H NMR (400 MHz, CDCl₃) δ 5.03 (1H, sep), 4.79 (2H, t), 4.50 (2H, t), 4.19 (5H, s), 4.28 (6H, d), 2.80 (2H, t), 2.40 (2H, t), 2.03 (2H, quin). GC-EI-MS (positive mode) *m/z*: 342 (M).

(2,2-dimethylpropyl) 5-oxo-5-ferrocenylpntanate: ^{1}H NMR (400 MHz, CDCl₃) δ 4.78 (2H, t), 4.50 (2H, t), 4.19 (5H, s), 3.80 (2H, s), 2.80 (2H, t), 2.47 (2H, t), 2.05 (2H, quin), 0.94 (9H, s). GC-EI-MS (positive mode) *m/z*: 370 (M).

2.1.3 Synthesis of 4-benzoylbutanoic acid ester and 4-(4-methoxybenzoyl)butanoic Acid Ester

In a 100 mL three-necked flask, 4-benzoylbutanoic acid (0.18 g, 0.83 mmol), methanol (30 mL), and sulfuric acid (1.2 mL) were mixed, and the esterification reaction was performed under an argon atmosphere at 60 °C. The reaction solution was then extracted using hexane, washed with a 5% aqueous sodium hydrogen carbonate solution, and washed three times with water. The organic layer was removed by distillation.

The esterification reaction was reported using 4-(4-methoxybenzoyl)butanoic acid, and ethanol, 2-propanol and 2,2-dimethyl-2-propanol under the above conditions, and all products were characterized using ^{1}H NMR spectroscopy and GC-MS.

methyl 4-benzoylbutanate: ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (2H, d), 7.63 (1H, t), 7.52 (2H, t), 3.62 (3H, s), 3.12 (2H, t), 2.44 (2H, t), 1.98 (2H, quin). GC-EI-MS (positive mode) *m/z*: 206 (M).

ethyl 4-benzoylbutanate: ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (2H, d), 7.64 (1H, t), 7.52 (2H, t), 4.10 (2H, q), 3.12 (2H, t), 2.42 (2H, t), 1.99 (2H, quin), 1.21 (3H, t). GC-EI-MS (positive mode) *m/z*: 220 (M).

(1-methylethyl) 4-benzoylbutanate: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (2H, d), 7.55 (1H, t), 7.46 (2H, t), 4.99 (2H, sep), 3.01 (2H, t), 2.33 (2H, t), 2.06 (2H, quin), 1.19 (6H, d). GC-EI-MS (positive mode) *m/z*: 234 (M).

(2,2-dimethylpropyl) 4-benzoylbutanate: ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (2H, d), 7.60 (1H, t), 7.52 (2H, t), 3.77 (2H, s), 3.14(2H, t), 2.47 (2H, t), 1.99 (2H, quin), 0.92 (9H, s). GC-EI-MS (positive mode) *m/z*: 262 (M).

(1-methylethyl) 4-(4-methoxybenzoyl)butanate: ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.00 (2H, d), 7.04 (2H, d), 4.97 (2H, sep), 3.88 (3H, s), 3.04 (2H, t), 2.37 (2H, t), 1.96 (2H, quin), 1.19 (6H, d). GC-EI-MS (positive mode) *m/z*: 264 (M).

(2,2-dimethylpropyl) 4-(4-methoxybenzoyl)butanate: ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (2H, d), 7.02 (2H, d), 3.88 (3H, s), 3.70 (2H, s), 3.04(2H, t), 2.46 (2H, t), 1.95 (2H, quin), 0.92 (9H, s). GC-EI-MS (positive mode) *m/z*: 292 (M).

2.2 The Esterification Reaction

2.2.1 Under Microwave Irradiation

Microwave irradiation was performed using a Green Motif II instrument (J Science Lab). In a test tube (length: 130 mm, inner diameter: 15.0 mm), 5-oxo-5-ferrocenylpentanoate (0.056 g, 0.19 mmol), the desired alcohol (6 mL), and sulfuric acid (240 μL) were added and reacted under microwave irradiation at a power of 150 W. The reaction solution was then extracted using hexane, washed with a 5% aqueous sodium hydrogen carbonate solution, and washed three times with water. The organic layer was removed by distillation. In the esterification reaction using 2,2-dimethyl-1-propanol as the alcohol, the reaction was performed using 0.708 g (8.0 mmol) of the alcohol and 5 mL of toluene as the solvent under a microwave output of 300 W. All yields were determined from the areas under the HPLC signals.

The esterification reactions using 4-benzoylbutanoic acid and 4-(4-methoxybenzoyl)butanoic acid were also performed under the above conditions.

For the reactions carried out at lower temperatures, the reaction vessel was covered with dry ice to give an internal temperature of −55 to −8 °C. In this case, a μ-Reactor (Shikoku Measurements) was used for microwave irradiation.

2.2 Under Conventional Heating

In a test tube (length: 130 mm, inner diameter: 15.0 mm), 5-oxo-5-ferrocenylpentanoate (0.056 g, 0.19 mmol), the desired alcohol (6 mL), and sulfuric acid (240 μL) were mixed. The reaction was carried out at the highest temperature achieved under microwave irradiation.

The esterification reactions using 4-benzoylbutanoic acid and 4-(4-methoxybenzoyl)butanoic acid were also performed under the above conditions.

For the reactions carried out at lower temperatures, a sodium chloride/ice-water bath (−8 °C) was employed.

2.3 Apparatus

he instruments and measurement methods employed for analysis by ^{1}H NMR spectroscopy, LC-MS and GC-MS were as those described in a previous paper (Pramesti & Okada, 2017) (Okada & Tuchida, 2019).

3. Results and Discussion

We herein examined the effects of microwave irradiation and the ferrocene moiety on a range of esterification reactions, where the microwave effect was defined as the difference between the yields obtained under microwave irradiation and under conventional heating (MWy−CHy). Benzene derivatives were employed to determine the effect of the ferrocene moiety.

3.1 Reaction of the Benzene Derivative

Table 1 presents the yields of the esterification reaction using 4-benzoylbutanoic acid under microwave irradiation and

conventional heating conditions. It should be noted that for the various results presented, "temp." indicates the maximum temperature reached inside the test tube during microwave irradiation, and this temperature was employed as the oil bath temperature for conventional heating. For entries 1 and 2, a reaction time of 30 s was employed after reaching 60 °C, while for entries 3 and 4, this was 10 s upon reaching 60 °C, for entries 5 and 6, this was 30 s upon reaching 70 °C, for entries 7 and 8, the reaction time was 30 s after reaching 80 °C, and for entries 9 and 10, this was 45 s after reaching 25 °C. In addition, with the exception of entry 9, which was carried out at 300 W, all reactions carried out under microwave irradiation were performed at a microwave output of 150 W.

For entries 1 and 2, the reactions were performed using methanol as the solvent using both heating techniques, but no differences in yield were observed. For entries 3–6, ethanol was employed, and again no differences in yield were observed. However, when the esterification reaction was carried out using 2-propanol as the solvent (entries 7 and 8), yields of 30 and 42% were obtained under conventional heating and microwave irradiation, respectively. In addition, using 2,9-dimethyl-2-propanol (entries 9 and 10), where toluene was employed as the solvent, yields of 12 and 32% were obtained under conventional heating and microwave irradiation, respectively.

### 3.2 Reaction of the Ferrocene Derivative

Table 2 presents the yields of the 5-oxo-5-ferrocenylpentanoic acid esterification reaction under microwave irradiation and conventional heating conditions, where the conditions employed were as those outlined in Table 1.

For entries 1 and 2, the reaction was performed using methanol under both microwave irradiation and conventional heating, while for entries 3 and 4, ethanol was employed. In both pairs of comparisons, no differences in yield were observed. In contrast, comparison of entries 5 and 6 (also using ethanol) gave a 90% yield under microwave irradiation and a 61% yield under conventional heating. In addition, when 2-propanol was employed (entries 7 and 8), a 20% greater yield was obtained under microwave irradiation. In the reactions using 2,2-dimethyl-2-propanol (entries 9 and 10), toluene was employed as the solvent at 300 W, to give yields of 60 and 21% under microwave irradiation and conventional heating conditions, respectively.

3.3 Comparison of the Reactions of the Benzene and Ferrocene Derivatives

Upon comparison of the results presented in Tables 1 and 2, it was apparent that under the conditions outlined for entries 5 and 6, no microwave effect was observed for the benzene derivative, while a 29% microwave effect was confirmed for the ferrocene derivative. Furthermore, under the conditions of entries 7 and 8 and entries 9 and 10, the microwave effect was observed for both derivatives, but a larger effect was confirmed for the ferrocene derivative. This was attributed to the fact microwaves have a greater effect on the ferrocene nuclei compared to the benzene nuclei.

Table 1. Esterification reaction of the benzene derivative under microwave irradiation and conventional heating conditions.

$R=CH_3-, C_2H_5-, CH(CH_3)_2-, (CH_3)_3CCH_2-$
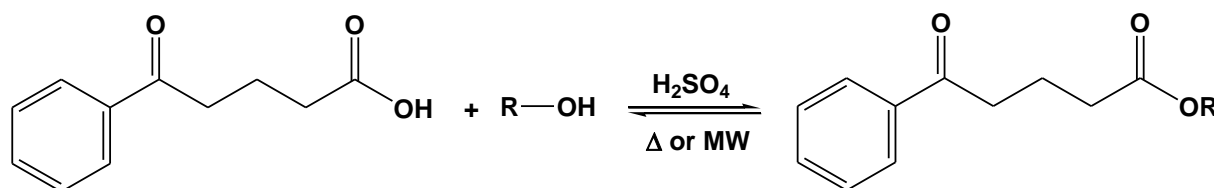
Entry	R-	Condition	Time (s)	Temperature (°C)	Yield (%)
1	CH_3-	microwave (150 W)	30	64	82[a]
2	CH_3-	conventional	30	70	91[a]
3	CH_3CH_2-	microwave (150 W)	10	80	49[a]
4	CH_3CH_2-	conventional	10	90	46[a]
5	CH_3CH_2-	microwave (150 W)	30	80	84[a]
6	CH_3CH_2-	conventional	30	90	81[a]
7	$(CH_3)_2CH-$	microwave (150 W)	30	85	42[a]
8	$(CH_3)_2CH-$	conventional	30	90	30[a]
9	$(CH_3)_3CCH_2-$	microwave (300 W)	30	67	32[b]
10	$(CH_3)_3CCH_2-$	conventional	30	90	12[b]
a: isolated yield, b: determined by HPLC					

Table 2. Esterification reaction of the ferrocene derivative under microwave irradiation and conventional heating conditions

$R=CH_3-, C_2H_5-, CH(CH_3)_2-, (CH_3)_3CCH_2-$
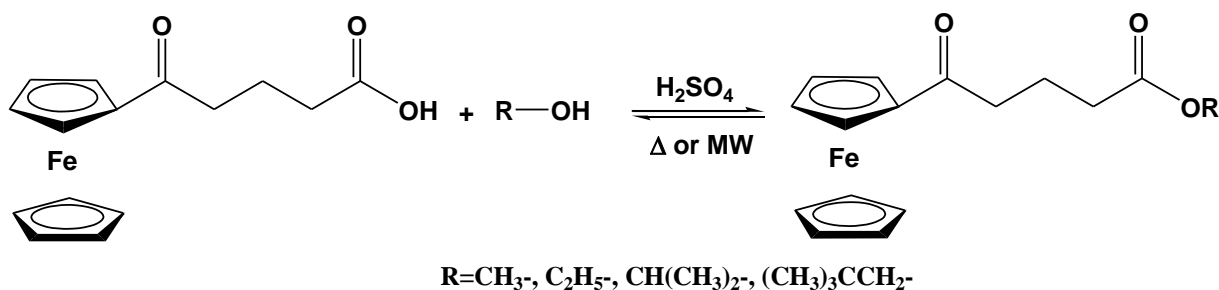
Entry	R-	Condition	Time (s)	Temperature (°C)	Yield (%)
1	CH_3-	microwave (150 W)	30	64	84[a]
2	CH_3-	conventional	30	70	90[a]
3	CH_3CH_2-	microwave (150 W)	10	80	47[a]
4	CH_3CH_2-	conventional	10	90	49[a]
5	CH_3CH_2-	microwave (150 W)	30	80	90[a]
6	CH_3CH_2-	conventional	30	90	61[a]
7	$(CH_3)_2CH-$	microwave (150 W)	30	85	53[a]
8	$(CH_3)_2CH-$	conventional	30	90	33[a]
9	$(CH_3)_3CCH_2-$	microwave (300 W)	30	67	60[b]
10	$(CH_3)_3CCH_2-$	conventional	30	90	21[b]
a: isolated yield, b: determined by HPLC					

3.4 Reaction of Benzene Derivatives Bearing Polar Group

As mentioned above, the ferrocene derivatives were more strongly affected by microwaves than the benzene derivatives, which was attributed to the magnitudes of their dielectric constants (i.e., 2.3 for benzene, and 2.8–3.0 for ferrocene (Gaffar & Hussien, 2001)). We therefore decided to carry out 2-propylation and 2,2-dimethyl-1-propylation reactions using 4-(4-methoxybenzoyl)butanoic acid, which bears a substituent with a higher dielectric constant (dielectric constant of anisole = 4.3 (Jaworski ei al., 2005)). The yields obtained under microwave irradiation and conventional heating are presented in Table 3.

The reaction times for entries 1 and 2 are 30 s after reaching 80 °C, and for entries 3 and 4, the reactions times were 45 s after reaching 25 °C. The microwave output was 150 W for entry 1 and 300 W for entry 3.

For entries 1 and 2, where 2-propanol was employed, a 10% greater yield was obtained under microwave irradiation. Similarly, when 2,3-dimethyl-1-propanol was employed (entries 3 and 4), the yield was 19% higher under microwave irradiation. Upon comparison with entries 7 to 10 in Table 1 for the 2-propylation and 2,2-dimethyl-1-propylation processes, no significant difference in yield was obtained based on the presence or absence of a methoxy group, and so the microwave effect was similar. However, upon comparison with the results presented in Table 2, it was apparent that the ferrocene derivative exhibited a 10% higher microwave effect for 2-propylation and a 20% higher effect for 2,2-dimethyl-1-propylation. It therefore cannot simply be considered that the difference in dielectric constants determines the magnitude of the microwave effect, and so it was proposed that the iron center of the ferrocene nucleus may promote microwave absorption via the antenna effect.

Table 3. Esterification reaction of the benzene derivative with methoxy group under microwave irradiation and conventional heating conditions

Entry	R-	Condition	Time (s)	Temperature (°C)	Yield (%)
1	$(CH_3)_2CH-$	microwave (150 W)	30	85	28[a]
2	$(CH_3)_2CH-$	conventional	30	90	18[a]
3	$(CH_3)_3CCH_2-$	microwave (300 W)	45	67	31[b]
4	$(CH_3)_3CCH_2-$	conventional	45	90	12[b]

a: isolated yield, b: determined by HPLC
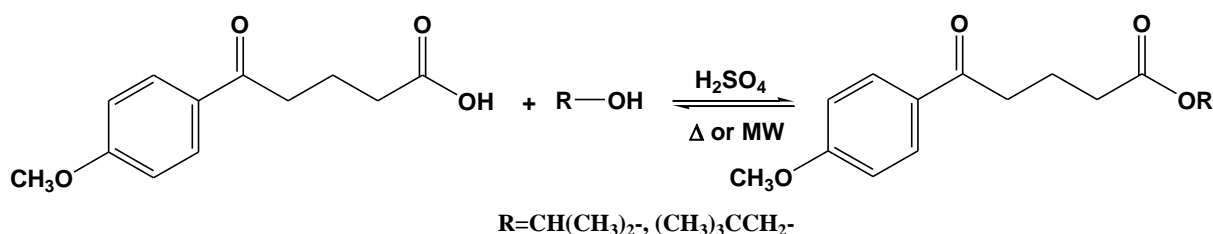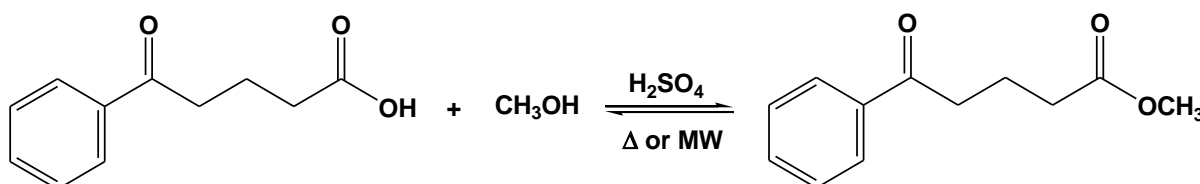

$R=CH(CH_3)_2-, (CH_3)_3CCH_2-$

Table 4. Esterification reaction of the benzene derivative under cooling conditions

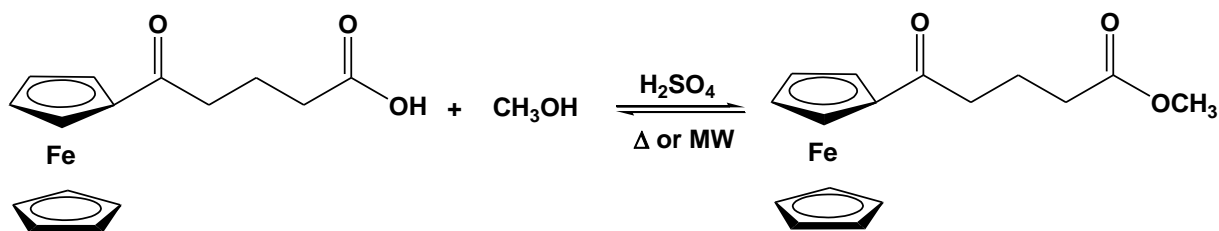| Entry	R-	Condition	Time (s)	Temperature (°C)	Yield (%)[a]
1	CH_3-	microwave (130 W)	90	-55 ~ -8	6
2	CH_3-	microwave (130 W)	360	-55 ~ -8	6
3	CH_3-	microwave (330 W)	90	-55 ~ -8	12
4	CH_3-	microwave (330 W)	30	-55 ~ -8	31
5	CH_3-	conventional	90	-8	0
6	CH_3-	conventional	30	-8	0

a: determined by HPLC

3.5 Reaction Under Low Temperature Conditions

The esterification reaction was then attempted under low temperature conditions by covering the reaction vessel with dry ice, as we expected that the microwave effect would be more pronounced upon lowering the reaction temperature. Thus, Tables 4 and 5 show the yields obtained under these low temperature conditions with microwave irradiation using the ferrocene and benzene derivatives, respectively.

In these experiments, microwave irradiation was performed at internal temperatures ranging from −55 to −8 °C (entries 1–4), while for entries 5 and 6, the reaction was carried out using a sodium chloride/ice-water bath (−8 °C). As shown in Table 5, the reaction failed to take place under any of the conditions presented in entries 1–6 for the benzene derivative. However, for the ferrocene derivative, yields of 12 and 31% were obtained for the reactions presented in entries 3 and 4, respectively, thereby indicating that ferrocene derivatives are more susceptible to microwave irradiation than benzene derivatives. As such, using the ferrocene derivatives, the esterification reaction can be carried out under milder conditions when microwave irradiation is employed.

Table 5. Esterification reaction of the ferrocene derivative under cooling conditions

Entry	R-	Condition	Time (s)	Temperature (°C)	Yield (%)[a]
1	CH_3-	microwave (130 W)	90	-55 ~ -8	5
2	CH_3-	microwave (130 W)	360	-55 ~ -8	7
3	CH_3-	microwave (330 W)	90	-55 ~ -8	2
4	CH_3-	microwave (330 W)	30	-55 ~ -8	6
5	CH_3-	conventional	90	-8	0
6	CH_3-	conventional	30	-8	0

a: determined by HPLC

4. Conclusions

Microwave irradiation is of particular interest in synthetic organic chemistry due to its shorter reaction times and improved selectivities. Thus, we herein reported our investigation of the antenna effect of ferrocene derivatives in the esterification reaction, using benzene derivatives for comparison, and employing both microwave irradiation and conventional heating conditions. Indeed, this antenna effect was confirmed, thereby indicating that ferrocene derivatives are more susceptible to microwaves than benzene derivatives. This therefore allows the esterification reaction could to be carried out at lower temperatures when ferrocene derivatives are employed. and so such a system could be useful in the reaction of thermally unstable compounds.

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