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Highly selective acylation of ferrocene using microfluidic chip reactor

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Abstract—A rapid and highly selective acylation of ferrocene with various acid anhydrides using microfluidic chip as the reactor is described. The pressure driven glass microreactor was fabricated by standard photolithography and wet etching techniques. High conversions of ferrocene to the corresponding acylferrocenes were achieved at 25 °C and no diacylferrocene was observed in any case.

Since ferrocene was reported in 1951, the number of ferrocene derivatives has rapidly increased due to their importance in catalysis and material sciences.[1] Acylation is one of the most important synthetic methods in ferrocene chemistry. It opens access to ferrocenyl ketones, which are valuable intermediates for further transformations. The classical Friedel–Crafts acetylation of ferrocene may be performed using acetyl chlorides as the acetylation reagents and aluminum chloride as the catalyst,[2] or using acetic anhydrides as the acetylation reagents and hydrogen fluoride,[3] stannic chloride,[4] boron fluoride,[2] or polyphosphoric acid as the catalysts.[5] However, most of these methods suffer from the formation of diacetylferrocene by-product.

Microfluidic reactors have attracted great interest in the last decade.[6] In comparison with the classical batch systems, microfluidic chip reactors need less space, energy and reagents, and give better yields and improved reaction selectivity in short reaction time but produce less wastes because of its short diffusion distance, large specific surface area, and increased thermal transfer. A large number of synthetic reactions have been carried out in microreactors since Harrison successfully used the microfabricated reactor chip to synthesize azo dyes in 1997.[7] As part of our ongoing research to develop new synthetic methods based on microfluidic reactor,[8] we herein report a highly selective acylation of ferrocene performed in a microfluidic chip.

Our reactor is a microfluidic chip fabricated in soda-lime glass with channels produced by photolithography and wet etching.[9] The internal geometry of our microfluidic chip is 500 μm × 100 μm × 1000 mm. The structure of the chip is illustrated in Figure 1. PTFE tubing (inner diameter ID = 0.9 mm) was fitted to the inlet and outlet hole directly. The end of inlet tube was connected to a Harvard 22 syringe pump and the end of outlet tube was connected to a sample vial, which was used to collect the final solution. The final solution containing ferrocene and products was neutralized by saturated sodium bicarbonate solution and extracted with hexane. The conversions of ferrocene were determined by HPLC.[10]

We first examined the acetylation of ferrocene with acetic anhydride in the presence of H_3PO_4 at different flow

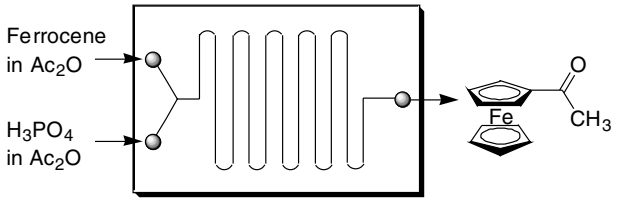

Figure 1. Schematic structure of the microfluidic chip.

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rates and temperatures. The reactions were performed at 15 and 25 °C, respectively. The acetic anhydride solution containing ferrocene (0.15 M) and the acetic anhydride solution containing phosphoric acid (1.5 M) were introduced through two syringe pumps, respectively. The results are summarized in Table 1. When the reactions were performed at 15 °C, the HPLC conversions of ferrocene increased from 78% to 98% with the increase of flow rate and reached a peak at 35 μL/min flow rate (Table 1, entries 1–9). While further increasing the flow rate led to a decrease of conversions (Table 1, entries 10–14). On the other hand, the conversions in all cases were excellent (96–99%) when the reactions were carried out at 25 °C. The by-product diacetylferrocene was not detected by HPLC in any case. Therefore, our microchip procedure gave excellent selectivity.

In comparison, we used the standard batch system with vigorous stirring to perform the acetylation of ferrocene at 55–60 °C for 15 min and the conversions were only 60–70%. It was found that lower temperature slowed the reaction while higher temperature led to the formation of by-product diacetylferrocene. Thus, temperature control was the key operation in this reaction.

Table 1. Acetylation of ferrocene using microfluidic chip at different flow rates and temperature

Entry	Flow rate[a] (μL/min)	Average reaction time[b] (s)	Conversion[c] (%)	
			At 15 °C	At 25 °C
1	5	440	78	96
2	7.5	300	82	98
3	10	220	79	99
4	12.5	176	84	98
5	15	150	93	97
6	20	110	93	96
7	25	88	95	97
8	30	75	96	97
9	35	67	98	98
10	40	55	97	97
11	45	49	96	96
12	50	44	91	98
13	55	40	90	99
14	60	37	86	98

[a] Flow rates of two syringes are same.
[b] Average time for three reaction runs, measured by stopwatch.
[c] Conversions were determined by HPLC.[10]

The high heat exchange efficiency of microfluidic chips allows fast heating and cooling, making the accurate temperature control possible. The dramatic increase in conversions at low flow rates depends on the improved mixing efficiency. The high surface-to-volume ratio of microfluidic chips implies that viscose force is more important than other factors. This property of microfluidics is well represented by the Reynolds number *Re*:[11]

$$Re = \rho v l/\mu \quad (1)$$

where ρ (kg/m^3) is the mass density, v (m/s) is the velocity, l (m) is the length, and μ (Ns/m^2) is the dynamic viscosity. Contrary to the conventional batch equipment, where mixing is provided by turbulence, typical microfluidic chips including our chips are operating at much lower *Re*, typically in the range of 2–200. Low Reynolds number flows are referred to as laminar and are characterized by a high degree of symmetry.[12] In our microchip reactors, mixing is accomplished through random molecular motion along the concentration gradient, and this diffusion depends on the nature of the solutions to be mixed and on the microchannel geometry, as described below:[11]

$$t_d = L^2/D \quad (2)$$

$$D = kT/6\pi\eta r \quad (3)$$

where t_d is the diffusion time, L (m) is the distance over which diffusion must take place, D (m^2/s) is the diffusion coefficient, k is the Boltzmann constant (1.38×10^{-23} J/K), T (K) is the absolute temperature, η (kg/m s) is the absolute viscosity, and r is the hydrodynamic radius (m). In our reaction, η and T are variables affecting the diffusion time t_d, and η is a function of T when the composition of solution is determined. Rising temperature from 15 to 25 °C led to a fall of viscosity, thus the diffusion time was shortened greatly and the conversion was increased. In one microfluidic chip, reaction time was determined by flow rate. When the flow rate increased, the reaction time became shorter. At certain temperature, the conversion of ferrocene improved with the increase of the flow rate.

Subsequently, the selective acylations of ferrocene with several other acid anhydrides were investigated using the established microfluidic chip procedure. As shown

Table 2. Selective acylation of ferrocene with various acid anhydrides using microfluidic chip[a]

Entry	Acid anhydride	Flow rate[b] (μL/min)	Average reaction time[c] (s)	Product	Conversion[d] (%)
1	Propionic anhydride	30	75	Propionylferrocene	95
2	Propionic anhydride	40	55	Propionylferrocene	95
3	*n*-Butyric anhydride	30	75	*n*-Butyrylferrocene	93
4	*n*-Butyric anhydride	40	55	*n*-Butyrylferrocene	95
5	*n*-Hexanoic anhydride	20	110	*n*-Hexanoylferrocene	93
6	*n*-Hexanoic anhydride	30	75	*n*-Hexanoylferrocene	90
7	*n*-Octanoic anhydride	10	220	*n*-Octanolyferrocene	92
8	*n*-Octanoic anhydride	30	75	*n*-Octanolyferrocene	88

[a] Performed at 25 °C.
[b] Flow rates of two syringes are same.
[c] Average time for three reaction runs, measured by stopwatch.
[d] Determined by HPLC.

in Table 2, the corresponding acylation products were obtained in high conversions (88–97%) and characterized by ^{1}H NMR, ^{13}C NMR, IR, and MS spectrum.[13–16] For the long chain fatty acid anhydrides, lower flow rate was necessary to obtain the high conversions (Table 2, entries 5–8). It is noteworthy that the diacylferrocene by-product was not observed in any case.

In conclusion, we demonstrated an efficient acylation of ferrocene with various acid anhydrides using microfluidic chips as the reactors. Compared with the classical batch systems, the present method is rapid and highly selective due to the accurate temperature control and efficient mixing.

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10. Conversions were determined by HPLC and calculated by area normalizing method. HPLC conditions: *i*-propanol/*n*-hexane (20:80), 1.5 mL/min, detection wavelength 254 nm. Retention time: 10.5–10.6 min for ferrocene, 12.8–13.0 min for acetylferrocene.
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13. *Spectral data for propionylferrocene*: dark red oil; IR (neat): 3096, 2975, 2936, 1669, 1455, 1378, 1248 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12 (br s, 3H), 2.66 (br s, 2H), 4.08–4.18 (m, 5H), 4.39–4.48 (m, 2H), 4.70–4.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 8.65, 35.60, 69.15, 69.54, 71.89, 79.12, 200.65; MS (ESI): *m*/*z* 242 ($[M-H]^-$).
14. *Spectral data for butyrylferrocene*: dark red oil; IR (neat): 3096, 2962, 1669, 1454, 1379, 1245 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (br s, 3H), 1.66 (br s, 2H), 2.60 (br s, 2H), 4.05–4.18 (m, 5H), 4.37–4.45 (m, 2H), 4.68–4.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.95, 17.79, 41.46, 69.13, 69.53, 71.93, 79.05, 204.38; MS (ESI): *m*/*z* 256 ($[M-H]^-$).
15. *Spectral data for hexanoylferrocene*: dark red oil; IR (neat): 3096, 2958, 1669, 1458, 1376, 1242 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (br s, 3H), 1.16–1.29 (m, 4H), 1.62–1.65 (m, 2H), 2.70 (t, $J = 7.4$ Hz, 2H), 4.08–4.18 (m, 5H), 4.38–4.41 (m, 2H), 4.68–4.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.15, 22.04, 23.93, 31.52, 41.28, 69.17, 69.56, 71.75, 79.32, 205.56; MS (ESI): *m*/*z* 284 ($[M-H]^-$).
16. *Spectral data for octanolyferrocene*: dark red oil; IR (neat): 3095, 2952, 1669, 1455, 1376, 1243 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.81 (br s, 3H), 1.28–1.33 (m, 8H), 1.49–1.53 (m, 2H), 2.93 (t, $J = 7.5$ Hz, 2H), 4.05–4.18 (m, 5H), 4.37–4.45 (m, 2H), 4.68–4.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.34, 22.71, 24.05, 28.89, 29.05, 31.78, 41.87, 69.12, 69.45, 71.90, 79.05, 204.67; MS (ESI): *m*/*z* 312 ($[M-H]^-$).