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Synthesis in the ferrocenyl series

I. Preparation of ω-haloalkanoylferrocenes

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Abstract

Synthesis of 4-chlorobutyrylferrocene by $AlCl_3$-catalyzed Friedel–Crafts condensation can be improved by addition of a catalytic amount of $CeCl_3$.

ω-Haloalkanoylferrocenes are valuable synthetic intermediates [1,2] which may be obtained by Friedel–Crafts condensation of ω-haloalkanoyl halides to ferrocene. As part of a programme to prepare new ferrocene derivatives, we were interested in the synthesis of 4-chlorobutyroyl ferrocene on a large scale (Scheme 1). From the large amount of data in the literature [1–4], it appears that experimental conditions described in two patents [2] could be the most appropriate. Preliminary study showed that addition of solutions of ferrocene to the acylating reagent **2**-$AlCl_3$ did not give reproducible results. Moreover, large amounts of **4** were formed. In contrast, when the acylating reagent **2**-$AlCl_3$ was added to a ferrocene solution at 15°C [2], **3** was obtained in 88–90% yield accompanied by 3% of **1** and 4–5% of **4**. This was not appropriate to large scale (grams to kilograms) preparation of pure **3** which would necessitate a difficult purification. Removal of **1** is particularly troublesome since ferrocene sublimes easily. Therefore, we undertook a more careful study of the synthesis of **3** and we report our results here.

We chose to add the acylating reagent to a solution of ferrocene, and first undertook a systematic study of the influence of temperature and on the ratio of reagents. The results are reported in Table 1.

Small variations of the experimental conditions led to large variations in the overall yields, as well as in the selectivity of the condensation. We concluded that the best conditions were when the acylating agent, precooled to -10°C, was added to the ferrocene solution maintained at 0°C, the best reagent ratio being **1**/**2**/$AlCl_3$ of 1 : 1 : 1.1

Under these conditions, **3** was obtained in 93.8% yield accompanied by 3.1% of **1** and 1.5% of **4**. Consequently, we had improved the yield and the selectivity, but we had not solved the problem of the recovered **1**.

We then turned our attention towards the solvent [5] and the catalyst [6]. A systematic study (not reported here) showed the following trend of efficiency as far as overall yields and selectivity were concerned:

$$CH_2Cl_2 > Cl(CH_2)_2Cl \gg C_7H_{16} \ggg PhNO_2$$

$$AlCl_3 \gg SnCl_4 > FeCl_3 > CeCl_3 \ggg ZnCl_2$$

During the reactions with $CeCl_3$, we observed an anomalously fast disappearance of **1** although the acylating reagent **2**-$CeCl_3$ was not easily formed. We

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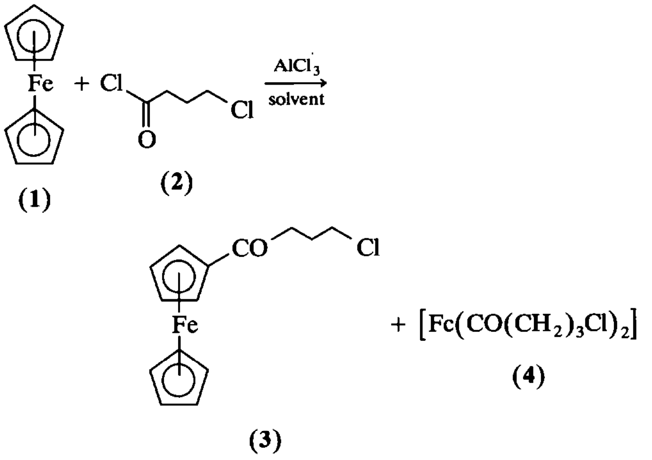

Scheme 1.

thought that this could be used to improve the selectivity of the acylations. From a short systematic study, it appeared that under the conditions of run 4, addition of 0.1 equiv. of $CeCl_3$ to the ferrocene solution just before adding the acylating reagent led to the formation of **3** in 93.5% yield accompanied by only 0.6% of **1** and 1.3% of **4**. Such a crude product may be much more easily purified and **3** is obtained with 99.9% purity after flash chromatography. Note that other salts such as $[NH_4]_2[Ce(NO_3)_6]$ and $[La(OOCH_3)_3]$ are much less efficient as catalysts.

Finally, acylation of **1** with $ClCO(CH_2)_3Br$ was performed under the conditions defined above. The corresponding rather unstable ketone was obtained in 80% yield, accompanied by 1.0% of **1** and 3.0% of diketone.

In conclusion, we have shown that under well-defined conditions, ferrocene may be very selectively acylated with acid chlorides in the presence of $AlCl_3$–$CeCl_3$ catalyst. These experimental conditions may be used on a small as well as a large scale, and the pure ferrocenyl ketones are obtained in good yields.

1. Experimental details

All reactions were carried out under an atmosphere of dry N_2. Infrared spectra were recorded on a Perkin-Elmer IR spectrometer model 841 with polystyrene as reference. ^1H NMR spectra were recorded on a Jeol PMX 60 SI spectrometer with carbon tetrachoride as a solvent and $SiMe_4$ as reference ($\delta = 0$ ppm). ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer with chloroform-*d* as solvent. Melting points were taken on a Tottoli apparatus and are uncorrected. Microanalyses were performed by CNRS Strasbourg.

Ferrocene (Veba) and anhydrous aluminium chloride ($AlCl_3$, 99.99% Aldrich) were used as received. 4-Chlorobutyryl chloride (99%, Aldrich) was distilled before use under reduced pressure (20 mmHg). Methylene chloride was distilled over P_2O_5. The products were isolated by flash chromatography on Kieselgel 60 (230–400 mesh) with methylene choride or hexaneethyl acetate mixtures.

1.1. Synthesis of 4-chlorobutyroylferrocene

A dry methylene chloride (20 ml) solution of 4-chlorobutyroyl chloride (7.05 g, 50 mmol) was added dropwise (over 0.5 h) at room temperature to a suspension of $AlCl_3$ (7.37 g, 55 mmol) in dry CH_2Cl_2 (20 ml). After 2 h stirring at room temperature, the homogeneous yellow-green solution was cooled to −10°C and then added dropwise (using a canula, over 2.5 h) to a

TABLE 1

Run [a]	Relative ratio FcH/RCOCl/AlCl3	Acylating complex temperature (°C) [b]	Reaction temperature (°C) [c]	Crude product isolated yield (%) [d]	Yield (% by weight) [e]		
					3	1	4
1	1:1:1.1	25	25	84.3	90.0	3.0	7.0
2	1:1:1.1	12	12	85.1	90.0	4.0	6.1
3	1:1:1.1	0	0	86.1	92.0	4.0	4.0
4	1:1:1.1	−10	0	93.8	96.0	2.0	2.0
5	1:1:1.1	−25	0	85.1	93.0	7.1	0.0
6	1:1:1.05	−10	0	91.0	95.3	2.5	2.2
7	1:1:1.08	−10	0	89.0	94.0	3.4	2.7
8	1:1:1.12	−10	0	85.4	91.0	4.3	4.6
9	1:1:1.15	−10	0	84.1	88.5	4.6	6.8
10	1:0.9:1.1	−10	0	93.6	90.3	8.4	1.3
11	1:0.95:1.045	−10	0	87.6	92.5	6.1	1.4
12	1:1.1:1.2	−10	0	77.9	85.0	0.8	14.1

[a] All reactions were performed on a 50 mmol scale. [b] Temperature of the precooled acylating complex (see Experimental section). [c] Temperature of the ferrocene solution (see Experimental section). [d] Crude product was a mixture of **3**, **1**, **4** obtained directly after extraction and filtration (see Experimental section). [e] Yields (in weight) of products isolated by flash chromatography.

dry CH_2Cl_2 (120 ml) solution of ferrocene (9.3 g, 50 mmol) precooled to 0°C. The red solution was then slowly allowed to warm to room temperature. After 16 h stirring, the reaction mixture was poured into ice and extracted with CH_2Cl_2 (2 × 150 ml), washed with a saturated $NaHCO_3$ solution and dried over $MgSO_4$. All the organic fractions were filtered over celite. The crude product was obtained after removal of the solvent under reduced pressure. 4-Chlorobutyroylferrocene was separated by flash chromatography (using CH_2Cl_2 as eluant).

1.2. *4-Chlorobutyroylferrocene*

IR spectrum (CCl_4): 1675 (C=O), 1555, 1460, 1380, 1300, 1255, 1110, 1090, 1060, 1030 and 1005 cm^{-1}. ^1H NMR spectrum (CCl_4, $SiMe_4$): 2.07 (q, 6 Hz, 2H); 2.9 (t, 6 Hz, 2H); 3.7 (t, 6Hz, 2H); 4.1 (s, 5H); 4.35 (t, 2 Hz, 2H); 4.65 (t, 2 Hz, 2H) ppm. ^{13}C NMR spectrum ($CDCl_3$): 26.55, 35.75, 44.67, 69.09, 69.69, 72.17, 78.69 and 202.97 ppm. Anal. Found: C, 57.64; H, 5.24; Cl, 13.00; Fe, 19.07. $C_{14}H_{15}ClOFe$ calcd.: C, 57.84, H. 5.20; Cl, 12.20; Fe, 19.21%.

1.3. *1,1'-bis(4-chlorobutyroyl)ferrocene*

^1H NMR spectrum (CCl_4, $SiMe_4$): 2.1 (q, 6 Hz, 4H); 2.8 (t, 6 Hz, 4H); 3.65 (t, 6 Hz, 4H); 4.3–4.5 (m, 4H); 4.65–4.8 (m, 4H) ppm. IR spectrum (CCl_4): 1675 (C=O), 1555, 1460, 1380, 1300, 1255, 1110, 1090, 1060, 1030 and 1005 cm^{-1}. Anal. Found: C, 54.88; H, 5.23; Cl, 18.24; Fe, 14.17. $C_{18}H_{20}Cl_2FeO_2$ calcd.: C, 54.71; H, 5.10; Cl, 17.94; Fe, 14.13%.

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