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# FACILE ONE-STEP SYNTHESIS OF PYRROLIDINYLMETHYLFERROCENE

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## Summary

A convenient one-step method for the preparation of pyrrolidinylmethylferrocene has been developed. By treatment of ferrocene with formaldehyde, pyrrolidine, and phosphoric acid in acetic acid, pyrrolidinylmethylferrocene was obtained in 50% overall yield. The formation of pyrrolidinylmethylferrocene is mainly by the reaction of ferrocene with an iminium ion.

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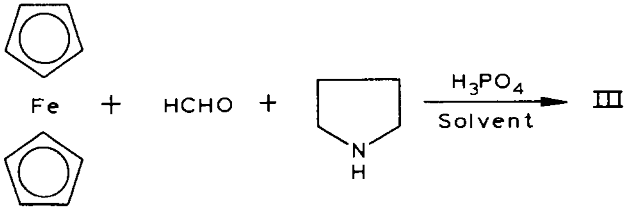
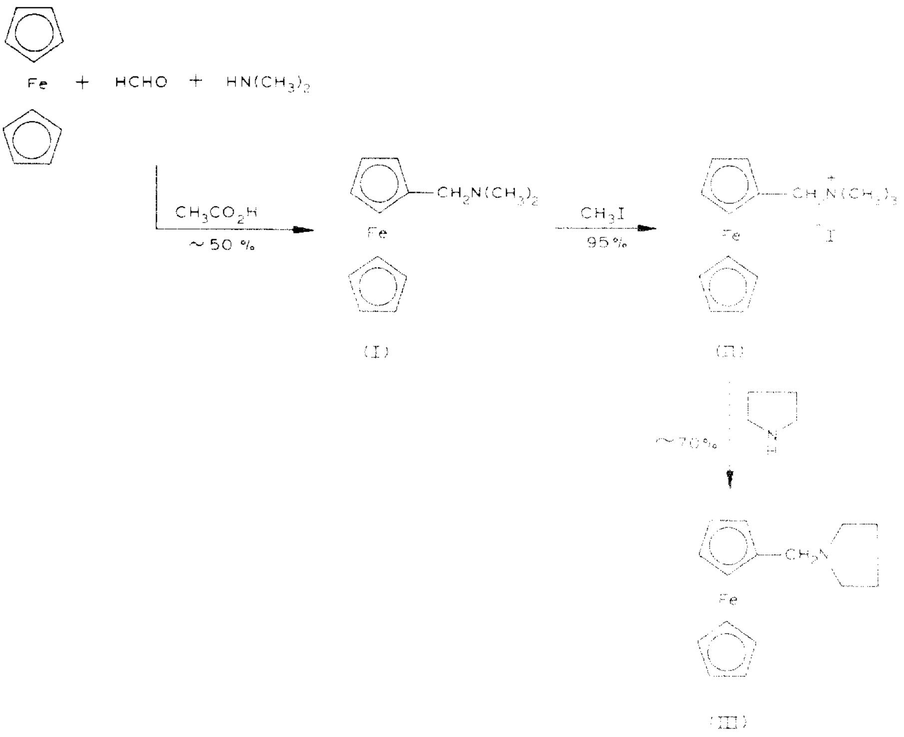
## Introduction

Although there has been considerable interest in the substitution reactions of ferrocene such as acetylation [1] and metalation [2] in the past three decades, aminomethylation of ferrocene has been less intensively investigated. The only example of aminomethylation [4,5] previously reported is the preparation of *N*,*N*-dimethylaminomethylferrocene (I), which is an important intermediate for the preparation of hydroxymethylferrocene and formylferrocene [5]. Compound I can be synthesized by the reaction of ferrocene with formaldehyde and dimethylamine in glacial acetic acid. Nevertheless, this procedure has never been applied to the synthesis of pyrrolidinylmethylferrocene (III). The previous routes [3–6] (see Scheme 1) to compound III included the formation of *N*,*N*-dimethylaminomethylferrocene (I) by mixing ferrocene, formaldehyde, and dimethylamine, followed by methylation with methyliodide to give compound II, which reacted with pyrrolidine to give pyrrolidinylmethylferrocene (III). The overall yield was about 35%.

In this paper a facile one-step (eq. 1) synthesis for pyrrolidinylmethylferrocene with higher yields is reported and the proposed reaction mechanism is discussed.



(1)

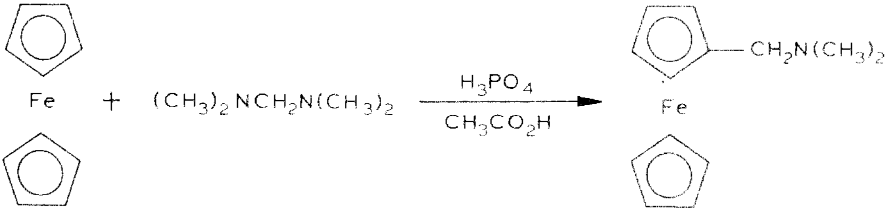


SCHEME 1

## Results and discussion

The one-step synthesis of pyrrolidinylmethylferrocene under several reaction conditions is summarized in Table 1. In runs 1 to 4, the reactions were carried out by addition of formaldehyde, pyrrolidine, ferrocene, and acid simultaneously in various solvents. Pyrrolidinylmethylferrocene was formed only when the reaction was run in glacial acetic acid with phosphoric acid (run 4); 16% of the title compound and a small amount of dipyrrolidinylmethane were isolated.

It was previously reported [3] that *N*,*N*-dimethylaminomethylferrocene can be made by the reaction of ferrocene with bis(dimethylamino)methane (eq. 2).



(2)

Therefore, pyrrolidinylmethylferrocene might be generated from the reaction of a similar intermediate, i.e. dipyrrolidinylmethane, with ferrocene. However, when dipyrrolidinylmethane was treated with ferrocene under the same reaction conditions as in run 4, only 6% of compound III was isolated. In addition, the yield of

TABLE 1

SYNTHESIS OF PYRROLIDINYLMETHYLFERROCENE

| run | HCHO (mol) | Pyrrolidine (mol) | $F_cH$ [a] (mol) | Solvent | $\overline{FcCH_2N(CH_2)_3CH_2}$ Yield(%) [b] |
|---|---|---|---|---|---|
| 1 | 0.5 | 0.5 | 0.3 | none | 0 |
| 2 | 0.12 | 0.12 | 0.08 | dioxane | 0 |
| 3 | 0.12 | 0.12 | 0.08 | THF | 0 |
| 4 [c] | 0.12 | 0.12 | 0.08 | HOAc | 16 |
| 5 [d] | 0.3 | 0.65 | 0.08 | HOAc | 7 |
| 6 | 0.15 | 0.1 | 0.08 | HOAc | 50 |

[a] FcH = ferrocene. [b] Yields are based on added FcH. [c] A mixture of 14.9 g (0.08 mol) of ferrocene, 8.64 g of a 37% aqueous solution of formaldehyde (0.12 mol), 8.5 g (0.12 mol) of pyrrolidine, 10 g (0.087 mol) of 85% phosphoric acid, and 80 ml of glacial acetic acid in a 200 ml round-bottomed flask was stirred and refluxed at 100°C for 5.5 h. Following the same procedure described in the Experimental, 3.44 g (16% yield) of III were obtained. [d] A mixture or 12.6 g of a 37% aqueous solution of formaldehyde (0.3 mol) and 46.15 g (0.65 mol) of pyrrolidine was placed in a 500 ml round-bottomed flask equipped with a magnetic stirrer and cooled in an ice bath (the reaction temperature was kept below 15°C). After 40 min, 14.9 g (0.08 mol) of ferrocene, 17.3 g (0.15 mol) of phosphoric acid and 160 ml of glacial acetic acid were added and the mixture was refluxed at 100°C for 5.5 h. Following the same procedure described in the Experimental, 1.5 g (7%) of III were obtained.

compound III decreased to 7% (run 5) when the reaction was carried out by mixing formaldehyde and pyrrolidine for 40 min below 15°C upon which glacial acetic acid, ferrocene and phosphoric acid were added. In this case the formation of dipyrrolidinylmethane is promoted.

According to these experimental results, the mechanism shown in Scheme 2 is proposed to account for the formation of pyrrolidinylmethylferrocene.

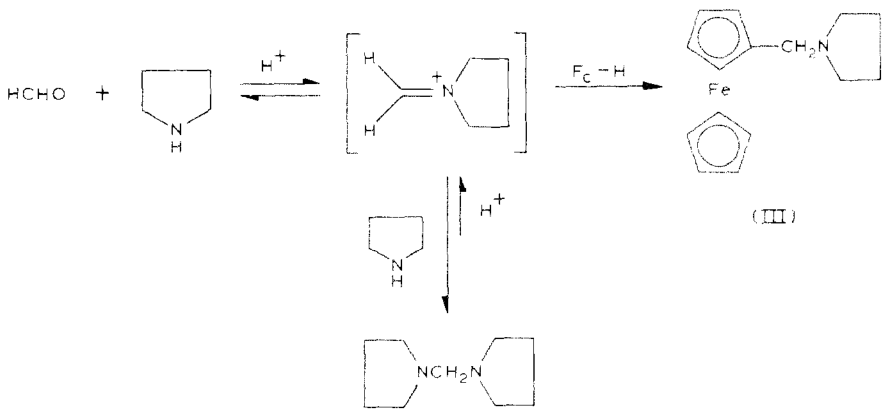
The above experimental results strongly support the mechanism shown in Scheme 2 and that there is indeed competition between the formation of dipyrrolidinylmethane and pyrrolidinylmethylferrocene. The reverse reaction forming dipyrrolidinylmethane is slow. Scheme 2 can also explain the solvent effect in acetic acid because the iminium ion might be stabilized by the acetate anion, making the reaction more efficient.

## Experimental

All solvents were reagent grade and were used without further purification. Ferrocene (Syntex Chemical Inc.), formaldehyde (Fluka 37% aqueous solution), pyrrolidine (Fluka), acetic acid (Union Chemical Works LTD), and phosphoric acid (Union Chemical Works LTD) were used as received. $^1H$ NMR spectra were recorded on a JEOL Model FX 900 in $CDCl_3$ with tetramethylsilane as internal standard, and mass spectra were recorded on Finnigan-4000 and AEI-Kratos-MS30 apparatus.

### *Preparation of pyrrolidinylmethylferrocene*

*(a) Run 6.* In a 200 ml round-bottomed flask, 7.1 g (0.1 mol) of pyrrolidine were added dropwise into a mixture of 10.8 g of a 37% aqueous solution of formaldehyde (0.15 mol) and 10 g (0.087 mol) of 85% phosphoric acid. The addition was completed



SCHEME 2

in 40 min and subsequently 80 ml of glacial acetic acid and 14.9 g (0.08 mol) of ferrocene were added. The resulting solution was stirred and refluxed at 100°C. After 5.5 h, the reaction mixture was diluted with 100 ml of water and the unreacted ferrocene was extracted with diethyl ether. The aqueous layer was neutralized with sodium hydroxide solution and extracted with diethyl ether. The organic layers were combined, washed with water, dried over sodium sulfate, and evaporated to 13.4 g of a deep brown liquid. This liquid was distilled under reduced pressure to give a small amount of a light yellow oil, which was identified as dipyrrolidinylmethane. $^1H$ NMR, $\delta$ 3.2(s, 2H), 2.55(m, 8H), 1.75(m, 8H) ppm. Anal. Found: C, 70.20; H, 11.48; N, 18.04. $C_9H_{18}N_2$ calcd.: C, 70.13; H, 11.69; N, 18.18%. The residue, a dark amber liquid, solidified after 4 h standing at room temperature and was identified as pyrrolidinylmethylferrocene (10.7 g, 50% yield from ferrocene). $^1H$ NMR, $\delta$ 4.1 (m, 9H), 3.4 (s, 2H), 2.4 (m, 4H), 1.7 (m, 4H) ppm. Anal. Found: C, 66.73; H, 7.24; N, 5.24. $C_{15}H_{19}NFe$ calcd.: C, 66.93; H, 7.11; N, 5.20%. Mass, $M^+$ (269).

*(b) Reaction of ferrocene with dipyrrolidinylmethane.* 2.5 g (0.015 mol) of dipyrrolidinylmethane, 1 g (0.009 mol) of 85% phosphoric acid, 1.1 g (0.006 mol) of ferrocene, and 10 ml of glacial acetic acid were mixed, stirred, and heated at 100°C for 5.5 h. By the same procedure as described above, 0.1 g of compound III was isolated (6% yield).

In this reaction sequence an iminium ion is formed readily from the reaction of formaldehyde and pyrrolidine in acidic solution [8], subsequently, the resulting iminium ion is allowed to react with ferrocene via electrophilic aromatic substitution [2a,7] to give product III or it is attacked by a molecule of pyrrolidine to form dipyrrolidinylmethane. Under acidic condition, dipyrrolidinylmethane will regenerate an iminium ion but the rate is very low according to the experimental results.

It is obvious that the yield of product III will increase if the formation of dipyrrolidinylmethane is inhibited. In order to confirm whether there is indeed competition between the formation of compound III and that of dipyrrolidinylmethane, run 6 was carried out. In this reaction, the formation of dipyrrolidinylmethane is decreased by increasing the amount of formaldehyde (the relative molar ratio of formaldehyde to pyrrolidine is 1.5/1). Meanwhile, pyrrolidine was added dropwise to a solution of formaldehyde and phosphoric acid in a round-bottomed flask, followed by addition of ferrocene and glacial acetic acid, and refluxed at 100°C for 5.5 h. After separation and purification, product III was isolated in 50% yield.

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