

## Synthesis, Characterization and Antioxidant Activity of Ferrocenylhydrazones

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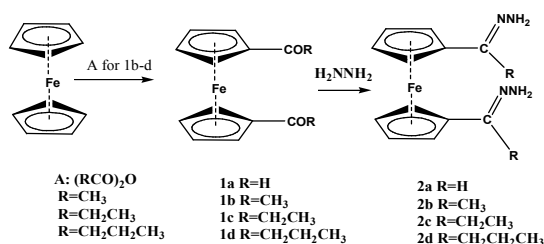
**Summary:** Condensation reactions of 1, 1'-diacylferrocenes with hydrazine hydrate afford a series of 1, 1'-bishydrazonoalkylferrocenes. Characterizations were carried out by using IR, <sup>1</sup>HNMR, electronic absorption and elemental analysis. Antioxidant activity of the compounds and their precursors was investigated with DPPH. The result indicated that diacylferrocene derivatives (hydrazones) had certain antioxidant activity, which were enhanced by the increase of compounds concentration, but reduced as the bulkiness of the  $\alpha$ -substituent hydrozone group increased. The antioxidant activity of diacylferrocenediones was much higher than that of precursors (diacylferrocenes) □

### Introduction

The chemistry of ferrocene and its derivatives attracted a considerable interest in the last decades [1-10], because ferrocenyl compounds have wide applications in areas of the synthesis of mononuclear and binuclear complexes [11-15] and electrochemistry [16-18]. Additionally, they possess potential usage as biosensors [19-20] and catalysts [21-24]. But, to the best of our knowledge, there has been no report on hydrazonoalkylferrocene which had free-radical scavenging capacity and antioxidant activity [25-27]. In this present work, 4 of 1,1'-bishydrazonoalkylferrocenes were synthesized from ferrocene and their antioxidant properties were evaluated. Additionally some literatures had reported that 1,1'-Disubstituted ferrocene (1,1'-diacylferrocene) was synthesized from ferrocene, but its post-processing was actually cumbersome, because the reaction mixture has to be purified by flash column chromatograph over silica gel to be separated [28-31]. The post-processing for 1,1'-diacylferrocene has been greatly simplified in our work.

In the first method, trichloromethane was used as solvent and then acetic anhydride reacted with ferrocene [15], the yield was low, only about 47%~58% [28, 29]; In the other method, dichloromethane was used as solvent and acetyl chloride reacted with ferrocene, the yield was 76-80% [30, 31]. Moreover the post-processing in these two methods above was cumbersome because of the reaction mixture has to be purified by flash column chromatograph over silica gel and 2-5 h reaction time. The post-processing for 1,1'-diacetyl ferrocene was highly simplified in our method as following sequence. The reaction mixture was decomposed with ice the organic phase was washed in the order of water, 5% sodium bicarbonate solution and water. The deep red organic solution was dried under vacuum and finally Cyclohexane-chloroform (1:1) mixture as recrystallized solvent was used. Not only the yield was greatly improved to 90%, but also obviously the post-processing was extremely convenient and the reaction time was shortened to 1 h.

NMR spectra were similar to 2b.



Scheme 1: Preparation of the 1, 1'-bishydrazonoalkylferrocenes.

### Results and Discussion

#### Synthesis of 1,1'-diacetylferrocene

Two methods to obtain 1,1'-diacetylferrocene from ferrocene have been reported.

#### Antioxidant Property

The stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH·) is a useful reagent for investigating scavenger properties of phenols, catechols and aromatic amines, which usually contains O-H and N-H [32, 33]. Based on this, the antioxidant activity of 1,1'-bis(1-hydrazonoalkyl)ferrocene was studied. Standard solutions of the ferrocene hydrozone antioxidants were prepared in methanol and rapidly mixed with a methanolic solution of DPPH. The process of the reaction was followed by determining the decrease of DPPH· absorbance at 517 nm. The amount of decrease was plotted against time (Fig. 1).

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The following calibration curve, made with DPPH· between  $1.0 \times 10^{-5}$  mol and  $1.0 \times 10^{-4}$  mol was used to calculate the DPPH· concentration ( $\text{mol L}^{-1}$ ) in the reaction medium:

$$A_{517\text{ nm}} = 1.1401 \times 10^4 [\text{DPPH}\cdot] - 2.12 \times 10^{-3}, r = 0.9997$$

The percentage of remaining DPPH·  $[\% \text{DPPH}\cdot]_{\text{rem}}$  was calculated as follows:

$$[\% \text{DPPH}\cdot]_{\text{rem}} = \frac{[\text{DPPH}\cdot]}{[\text{DPPH}\cdot]_{t=0}} \times 100,$$

where  $[\text{DPPH}\cdot]_{t=0}$  was the initial concentration of DPPH·;  $[\% \text{DPPH}\cdot]_{\text{rem}}$  was the concentration of DPPH· at the steady state.

The remaining DPPH·  $[\% \text{DPPH}\cdot]_{\text{rem}}$  is negatively correlated to the concentration of the antioxidant compound (Fig. 1) and well follows a general linear regression:  $[\% \text{DPPH}\cdot]_{\text{rem}} = aC + b$ , C representing the concentration of the antioxidant compound. Moreover, for sample 2a-d, antioxidant activity was reduced as the bulkiness of the  $\alpha$ -substituent hydrozones group (the alkyl carbon chain length) increased (Fig. 2). This indicates that there is a correlation between the stereochemistry and the antioxidant activity of the 1,1'-bishydrazono-alkylferrocenes. It has been found that diacylferrocene dihydrazones' precursors (1b as an example that more than 97% of DPPH· remained in 30 min) have almost no antioxidant activity  $\square$

## Experimental

All chemicals and solvents were obtained by Sinopharm Chemical Reagent Co. Ltd. (Shanghai, People's Republic of China). 1,1'-diacylferrocenes were prepared from ferrocene except 1,1'-diformylferrocene (1a). The yields referred to analytically pure compounds and were not optimized. Melting points were taken on a capillary melting-point apparatus and were uncorrected. <sup>1</sup>H NMR spectra were recorded with a Mercury VX-300 MHz NMR spectrometer in  $\text{CDCl}_3$  as a solvent. IR spectra were recorded on a NEXUS-470 spectrometer IR spectrometer, using KBr pellets. Elemental analyses were performed in a FLASH-1112 instrument. Electronic absorptions were measured on a PERKIN ELMER UV/VIS LAMBOA-35 automatic spectrophotometer in  $\text{CHCl}_3$ .

### 1,1'-Diacylferrocene (1b)

Ferrocene (10.0 g, 0.05 mol), dissolved in 30 ml of dry chloroform, was added over a period of 30 minutes to a stirred mixture of aluminum chloride (26.0 g, 0.20 mole) and acetic anhydride (15 ml, 0.15 mol) in 100 ml of dry chloroform at 4-6 °C. After

which, the reaction was carried out at 40 °C with immediate evolution of hydrogen chloride and the formation of an intensely violet solution. The mixture was stirred at 40 °C for 1 h and then cooled, decomposed with ice. Organic layers were washed with water, 5% sodium bicarbonate solution and water. The separated aqueous phase was extracted several times with chloroform and combined with the main body of organic solution. The deep red organic solution was dried under vacuum and the crude product was purified by recrystallization from 50 ml cyclohexane-chloroform (1:1) solvent and large red-brown rectangular plates of 1,1'-diacetylferrocene deposited (13.0 g). The second crop after one recrystallization weighed 12.1 g (90%), m.p. 127-128 °C (lit.<sup>27</sup> mp 127.5-128.5 °C). Anal. Calcd. for  $\text{C}_{14}\text{H}_{14}\text{O}_2\text{Fe}$ : C, 62.25; H, 5.22. Found: C, 62.28; H, 5.10. IR (KBr),  $\text{v}/\text{cm}^{-1}$ : 1656 (C=O), 3103 ( $\text{C}_{\text{sp}^3}\text{-H}$ ), 1114, 2921, 2850 (C-C). Compound 1,1'-Diformylferrocene (1a) was purchased. Compounds 1c-d were prepared using the same procedure as 1b. After the usual workup, the crude products were purified by recrystallization from cyclohexane-chloroform, ratio: (1:1 for 1a; 2:1 for 1c-d) to afford 1,1'-Dipropionylferrocene (1c) and 1,1'-Dibutyrylpropionyl ferrocene (1d). 1c: yield 87%, mp 52-54 °C; mp 52-53 °C [34]. 1d: yield 84%, mp 73-74 °C; mp 73-74.5 °C [35].

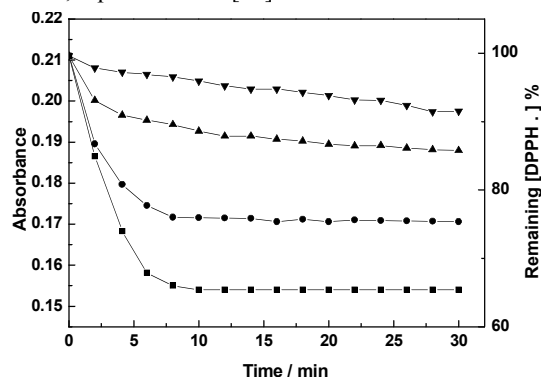


Fig. 1: Reaction of 2b with DPPH·, monitored at 517 nm.

Curves corresponding to different starting concentrations of 2b are reported (▼: 0.044 equiv; ▲: 0.30 equiv; ●: 0.50 equiv; ■: 0.90 equiv).

### 1,1'-bis(1-hydrazonoalkyl)ferrocene (2a-2d)

1.8 ml (0.03 mol) 85% of hydrazine hydrate was added to a flask containing 2.70 g (0.01 mol) of carbonyl component 1a-d in 100 ml anhydrous ethanol, stirred at room temperature for a while to the full mixing, and 1.6 g of sodium carbonate anhydrous was added. The mixture was stirred at reflux temperature. Reaction times: 2 h (for 1a to give 2a, for 1b to give 2b); 3 h (for 1c to give 2c); 4 h (for 1d to give 2d). The sodium carbonate was removed by filtration when solution was cooled

down to the room temperature. The solvent ethanol was removed under reduced pressure. The brown-violet crude products were purified by recrystallization from benzene - petroleum ether (1:3).

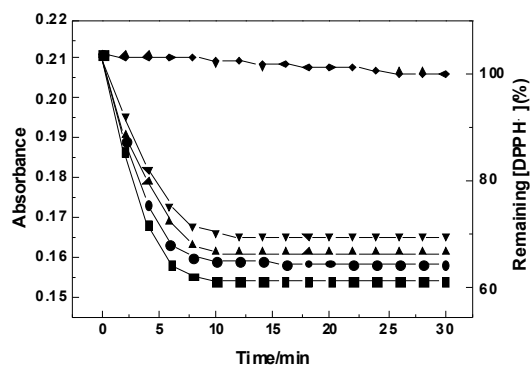


Fig. 2: Reaction of bis-hydrazonealkylferrocenes with DPPH, monitored at 517nm. Curves corresponding to different

compounds (□:1b; ▼:2d; ▲:2c; ●: 2b; ■:2a.)  
Concentration: [DPPH·]:  $2.0 \times 10^{-5}$  mol;  
bis-hydrazonealkylferrocenes:  $5.0 \times 10^{-5}$  mol

1,1'-bis(1-hydrazoneomethyl)ferrocene(2a):

Orange powder. Yield 2.48g (92%). M.p. 190-191 °C.  $C_{12}H_{14}FeN_4$  (270.16): calcd. C 62.22, H 5.19, N 20.74; found C 63.14, H 5.48, N 20.20. IR (KBr)  $\nu/cm^{-1}$ : 3364, 3218(-NH<sub>2</sub>); 1628 ( $\nu C = N$ ), 1080(N-N)  $^1H$ NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$ : 7.79 (s, 2H, H-C=N), 4.50(m, 4H,  $\beta$ H-Cp ring), 4.65(m, 4H,  $\alpha$ H-Cp ring), 5.38 (br-s, 4H, -NH<sub>2</sub>).UV-Vis (MeOH): 445 nm.

1,1'-bis(1-hydrazoneethyl)ferrocene (2b):

Orange powder. Yield 2.62g (88%). M.p. 184-185 °C.  $C_{14}H_{18}FeN_4$  (298.16): Calc.: C, 56.40; H, 6.10; N, 18.83%. Found: C 56.31; H 6.01; N 18.72. IR (KBr)  $\nu/cm^{-1}$ : 3360, 3228(-NH<sub>2</sub>); 1630(-C=N), 1090(N-N).  $^1H$  NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$ : 1.80 (s, 6H, -2CH<sub>3</sub>), 4.57 (m, 4H, Cp ring), 4.68 (m, 4H, Cp ring), 5.09 (br-s, 4H, -NH<sub>2</sub>).UV-Vis (MeOH): 448 nm.

1,1'-bis(1-hydrazonepropionyl)ferrocene (2c):

orange-red powder. Yield 2.74g (84%). M.p. 161-162 °C.  $C_{16}H_{22}FeN_4$  (326.19): calcd. 58.90; H, 6.75; N, 17.18; found C, 58.91; H, 6.09; N, 18.62. IR (KBr)  $\nu/cm^{-1}$ : 3363; 3230(-NH<sub>2</sub>); 1634(-C=N), 1093(N-N).  $^1H$ NMR (CDCl<sub>3</sub>,300 MHz)  $\delta$ : 1.82 (s, 4H, -CH<sub>2</sub>), 1.11 (s, 6H, -CH<sub>3</sub>), 4.58 (m,4H,  $\beta$ H-Cp ring), 4.70(m,4H,  $\alpha$ H-Cp ring), 5.12 (br-s, 4H, -NH<sub>2</sub>).UV-Vis (MeOH): 442 nm.

1,1'-bis(1-hydrazonebutyryl)ferrocene (2d):

orange-red powder. Yield 2.83g (80%). M.p. 149-150 °C.  $C_{18}H_{26}FeN_4$  (354.23): calcd. 61.02; H, 7.34; N, 15.82; found C, 61.91; H, 7.09; N, 15.62. IR (KBr)

$\nu/cm^{-1}$ : 3367; 3234(-NH<sub>2</sub>); 1631(-C=N), 1091(N-N).  $^1H$ NMR (CDCl<sub>3</sub>,300MHz)  $\delta$ : 1.83 (s, 4H, -2CH<sub>2</sub>), 1.42 (s, 4H, -CH<sub>2</sub>), 1.12 (s, 6H, -CH<sub>3</sub>), 4.48(m, 4H,  $\beta$ H-Cp ring), 4.63(m,4H,  $\alpha$ H-Cp ring), 5.16 (br-s, 4H, -NH<sub>2</sub>).UV-Vis (MeOH): 449 nm.

#### Evaluation of the Antioxidant Activity

All spectrophotometric measurements were performed with a UV/VIS LAMBOA-35 automatic spectrophotometer, under room temperature (30 °C). Standard solutions of antioxidants were prepared in methanol and rapidly mixed (volumes from 0.015 mL to 0.2 mL) with a methanol solution (final volume 3 mL) with initial concentrations of DPPH· between  $2.0 \times 10^{-5}$  mol and  $2.2 \times 10^{-5}$  mol were used. The decrease in absorbance at 517 nm was recorded at different time intervals until the reaction reached the plateau (the steady state). Measurements per potential antioxidant were recorded with [antioxidant]/[DPPH·] ratios in the range of 0.044 to 0.90. Simultaneously, a blank solution of DPPH· was screened to estimate DPPH· decomposition during the time of measurement.

#### Conclusion

In summary, 4 of 1,1'-bis(1-hydrazonealkyl)ferrocenes with antioxidant activity from 1,1'-diacylferrocene were successfully prepared and characterized. Post-processing of 1,1'-diacylferrocene was conveniently and efficiently improved, by which the yield was greatly increased and the reaction time shortened. The result also indicates that bishydrazonealkylferrocenes have antioxidant properties which are related to the stereochemistry of the  $\alpha$ -substituent hydrozone group.

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