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A Concise Synthesis of *N*-Methyl-2,3-diferrocenyl-4,4-dicyanopyrrolidine through [3 + 2] Cycloaddition of Azomethine Ylides

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Abstract—Microwave-assisted synthesis of *N*-methyl-2,3-diferrocenyl-4,4-dicyanopyrrolidine has been accomplished in moderate yields via a facile 1,3-dipolar cycloaddition and its crystal structure was determined by single-crystal X-ray diffraction (CCDC no. 1583719). It crystallizes: $C_{27}H_{25}Fe_2N_3$, $Mr = 503.20$, orthorhombic, $P2_12_12_1$, $a = 10.4873(9)$, $b = 10.5251(10)$, $c = 20.8587(19)$ Å, $V = 2302.4(4)$ Å^3, $\rho = 1.452$ g cm^{-3}, $Z = 4$, $T = 298(2)$ K.

Keyword: ferrocene, pyrrolidine, azomethine ylide, 1,3-dipole, microwave irradiation

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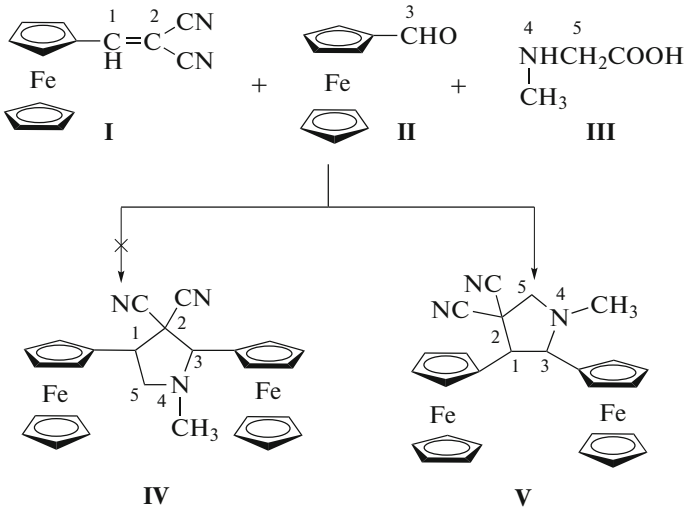
INTRODUCTION

Currently, nitrogen-containing heterocyclic compounds have long attracted synthetic interest due to their relatively simple structural features and wide range of pharmacologic activities [1, 2]. Ferrocene is a good pharmacophore for use in drug design due to its high stability, low toxicity, redox activity and chemical versatility, and favorable electrochemical properties that predispose these compounds for biomedical applications [3]. Presently, some researchers have designed nitrogen heterocycles compounds containing ferrocene with several biological activities [4–6]. Many ferrocene-based heterocycles are known to exhibit anti-bacterial and anti-fungal properties [7, 8]. Ferrocene derivatives have been used for the treatment of malaria and cancer [9, 10]. Studies have shown that the biological activity of N-heterocyclic compounds modified by using ferrocene as a substituent in their core structure is usually retained or enhanced [11, 12]. In our previous work [13, 14], we reported the preparation of a family of ferrocene derivatives of bearing saturated five-membered N-heterocycles. Recently, these compounds were selected for the study to test the anti-tumor activity. The results showed that these complexes have selective inhibition on human gastric cancer cell line. Encouraged by this success, here we are devoted to the study of synthesis of new diferrocenyl pyrrolidines through [3 + 2] cycloaddition of azomethine yields under microwave irradiation which has been widely used in organic synthesis. Compared with normal heating, the microwave irradiation is an environment-friendly method by which organic reactions can be accelerated with shorter reaction time and a higher yield, and the product is easier to be separated. The compound, *N*-methyl-2,3-diferrocenyl-4,4-dicyanopyrrolidine (**V**) was prepared according to Scheme 1.

EXPERIMENTAL

All reactions were monitored by TLC. Melting points (uncorrected) were measured with an XT4 melting point apparatus. ^{1}H NMR spectra were recorded on a Varian VXR 500 (500 MHz) spectrometer, using $CDCl_3$ as solvent and TMS as the internal standard. IR spectra were determined on a Nicolet 6700 spectrophotometer using KBr pellets. Microwave reactions were carried out in a Xianghu XH-100B microwave oven. TLC analysis was performed on 0.25 mm silica gel GF254 plates. All chemicals were purchased and used without further purification. 1,1-Dicyano-2-ferrocenylethene (**I**) (m.p. 99–101°C). IR (KBr; ν, cm^{-1}): 2190 (CN); 1629 (C=C); 1101, 992, 814) was prepared by Knoevenagel condensation of ferrocenecarbaldehyde (**II**) with equivalent amounts of malononitrile [15].

Synthesis of title complex (V). A mixture of compound **I** (2 mmol), compound **II** (2 mmol) and sarcosine (**III**) (2 mmol) in toluene (2 mL) was irradiated for 3 min at 120°C. This reaction was controlled with the temperature of microwave oven at 120°C and a power of 450 W. After the completion of the reaction (the reaction was followed by TLC), the mixture was allowed to cool to room temperature. The crude product was chromatographed on silica gel (200–300 mesh) using a mixture of petroleum ether and ethyl acetate (10 : 1) as eluent to afford the pure complex **V**. Yellow crystals, the yield was 39.8%. m.p. = 140–142°C.



Scheme 1.

^{1}H NMR ($CDCl_3$; δ, ppm): 2.04(3H, s., NCH_3), 2.67(1H, d., J = 10.0, FcCH–), 3.16–3.25 (2H, m., $NCHCH_2$–), 3.79 (1H, d., J = 10.5 Hz, NCH–), 4.18 (5H, s., C_5H_5Fe), 4.28 (5H, s., C_5H_5Fe), 3.95–4.34 (8H, m., FeC_5H_4). IR (KBr; ν, cm^{-1}): 3095, 2930, 2870, 2260, 1477, 1450, 1370, 1100, 1000, 830, 810.

Slow evaporation of the title compound in petroleum ether and ethyl acetate (10 : 1) yielded single crystals suitable for X-ray analysis.

X-ray crystal-structure V. An orange block crystal with approximate dimensions of 0.45 × 0.35 × 0.33 mm was mounted on a Bruker Smart 1000 CCD diffractometer equipped with a graphite monochromator data collection. The determination of the unit cell parameters and data collections were performed at 298(2) K, using graphite monochromated MoK_α (λ = 0.71073 Å) radiation. A total of 11536 reflections with 4069 unique ones with R_{int} = 0.0311 reflections were measured in the range of 2.74° ≤ θ ≤ 25.02° with an oscillation method. All data were corrected using the SADABS method. The structure was solved by direct methods using the SHELXL-97 program and refined by full-matrix leastsquares on F^2 [16]. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were added according to theoretical modes. The final refinement was performed by full matrix least-squares methods with anisotropic thermal parameters for non-hydrogen atoms on F^2. Crystal data: $C_{27}H_{25}N_3Fe_2$, Mr = 503.20, Orthorhombic, $P2_12_12_1$, a = 10.4873(9), b = 10.5251(10), c = 20.8587(19) Å, V = 2302.4(4) Å^3, ρ = 1.452 g cm^{-3}, Z = 4, T = 298(2) K. The final cycle of refinement gave R = 0.0402, wR = 0.1021 (the weighting scheme was $w = 1/[s^2(F_0^2) + (0.0526P)^2 + 0.7219P]$, where $P = (F_0^2 + 2Fc^2)/3$. The structure of title compound is listed in Fig. 1 and its conformations are given in Fig. 2.

Supplementary material for structure **V** has been deposited with the Cambridge Crystallographic Data Centre (CCDC no. 1583719; deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk or request@ccdc.cam.ac.uk).

RESULTS AND DISCUSSION

N-methyl-2,3-diferrocenyl-4,4-dicyanopyrrolidine (V) was afforded via [3 + 2] cycloaddition of the azomethine yield to 1,1-dicyano-2-ferrocenylethene (**I**). The steric barrier among reactant groups results in good regioselectivity, the ferrocenyl groups and cyano groups should be kept away as far as possible during the reaction, so only **V** is generated instead of (**IV**) (Scheme 2). The reaction of compound **I** with **II** and **III** was carried out under microwave irradiation conditions. We found that it took much less time than method of conventional heating reflux, which clearly indicates the advantage of this application of microwave irradiation. This method offers several advantages, such as short reaction time and simple procedure, etc.

The structures of **V** are confirmed using IR, ^{1}H NMR analysis. The spectroscopic data of the title compound **V** are found to be identical with the expected structure. The IR spectrum of the title compound shows a peak at about 2250 cm^{-1} due to the cyano group. In the ^{1}H NMR spectra of the product, the hydrogen atoms of the unsubstituted cyclopentadienyl moiety appear as a sharp singlet at about 4.18 and 4.28 ppm. The protons of the ferrocene substituted cyclopentadienyl moiety appear as multiplets at about 3.95–4.01 and 4.06–4.46 ppm. The –N–CH_3 protons of the pyrrolidine moiety resonate as a singlet at 2.04 ppm. The H proton of the pyrrolidine ring attached to the ferrocene core appears as a doublet at 2.67 (J = 10.0 Hz) and 3.79 (J = 10.5 Hz) which clearly

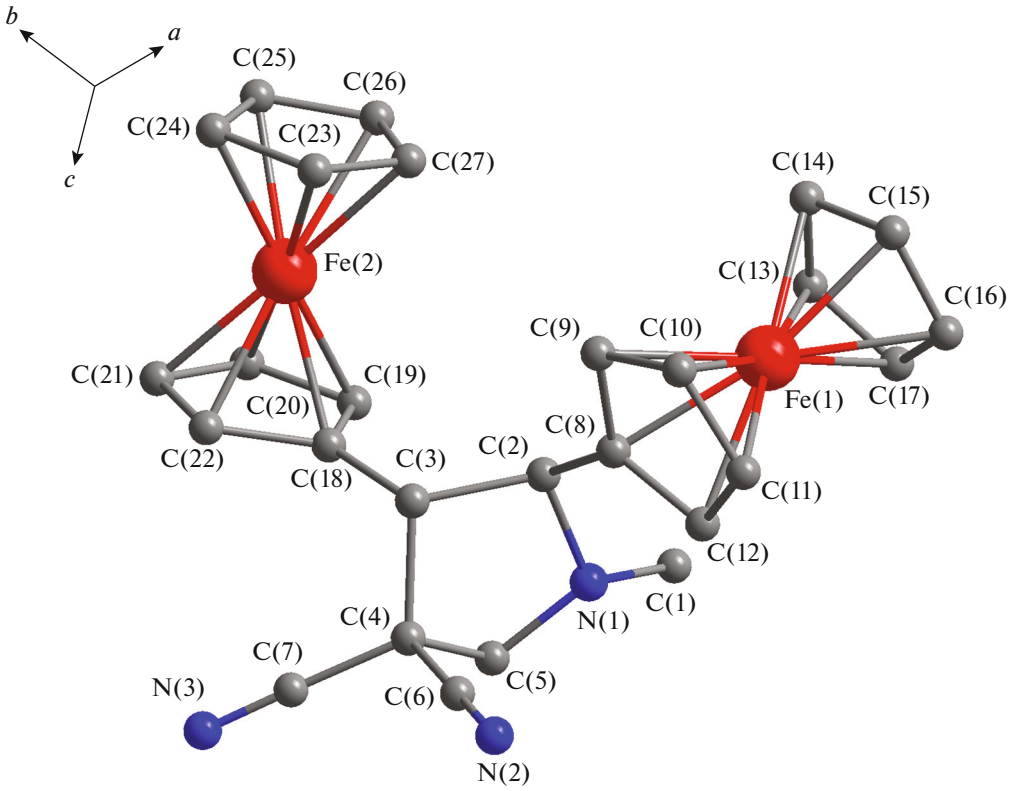


Fig. 1. ORTEP drawing of the structure of title compound **V**. Thermal ellipsoids are drawn at 30% probability level.

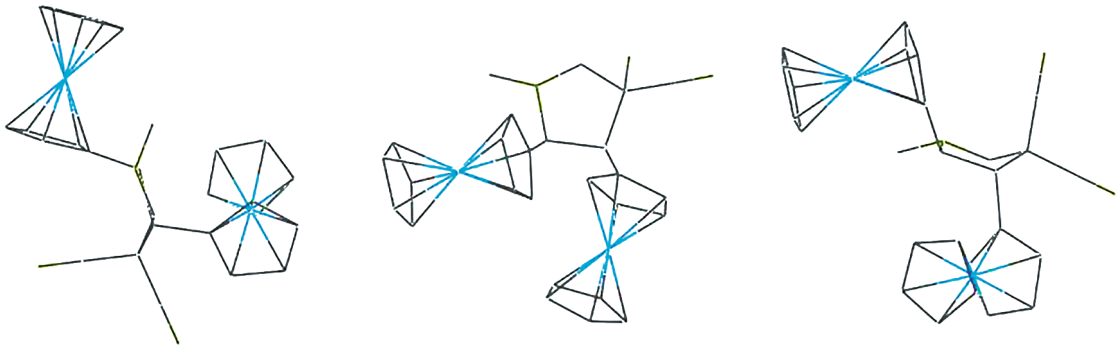
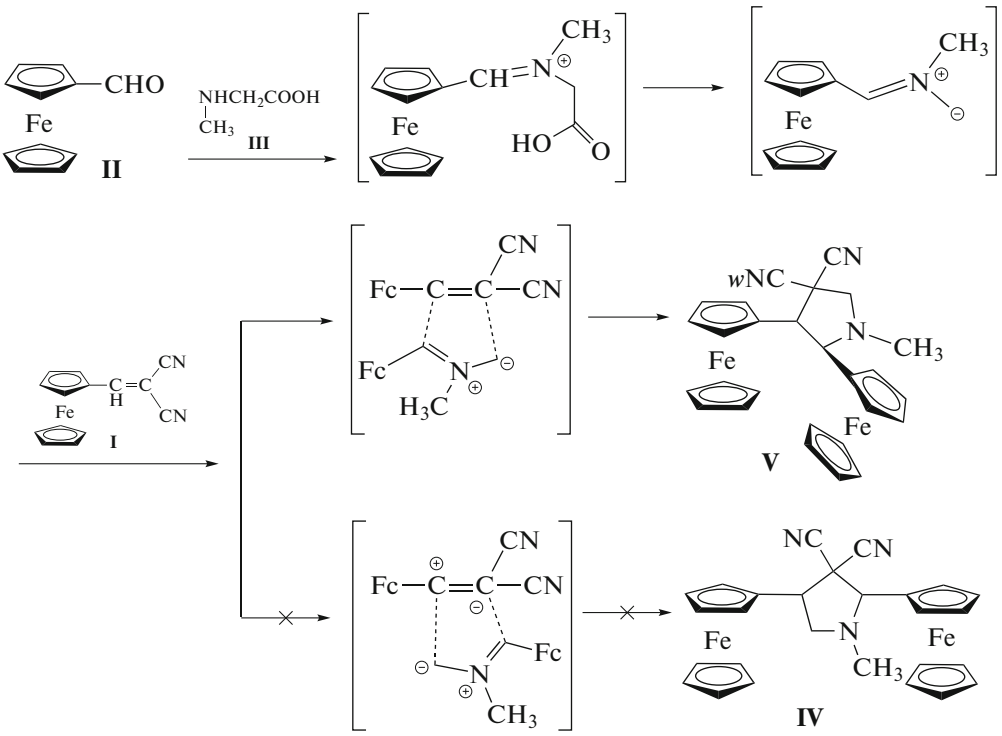


Fig. 2. View the conformations of compound **V**.

proves the regiospecificity in formation of the cycloadduct **V**. There is no evidence for the existence of other regioisomer (**IV**). If the other regioisomer (**IV**) was formed then the ^{1}H NMR spectrum would give a singlet and triplet for the pyrrolidine proton adjacent to the ferrocenyl moiety, respectively. Finally, the regio-specificity outcome of the cycloaddition (**V**) was determined unambiguously by single crystal X-ray analysis (Fig. 1).

It can be seen from Figs. 1 and 2, that in order to relieve strain, the pyrrolidine ring exists as an envelope conformation, the nitrogen atom and three carbon atoms of the pyrrolidine ring nearly exists in a plane, as shown by the torsion angle of C(5)–N(1)–C(2)–C(3) is 10.1(4), while the carbon atom with two cyano groups is outside the plane. The two ferrocene groups adopt a favored trans isomerism (Fig. 2). Possible mechanism for the formation of compound **V** is presented in Scheme 2.



Scheme 2.

In conclusion, we have developed a convenient method for the regioselective synthesis of *N*-methyl-2,3-diferrocenyl-4,4-dicyanopyrrolidine via a facile 1,3-dipolar cycloaddition. The reactions were carried out under microwave irradiation conditions. The structures of **V** has been determined by single crystal X-ray diffraction. Further investigation of the application scope is ongoing in our laboratory and will be reported in due course.

FUNDING

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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