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Original Scientific Paper

ULTRASOUND-ASSISTED SYNTHESIS OF NOVEL 3-(PYRIDINYLAMINO)-1-FERROCENYLPROPAN-1-ONES

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ABSTRACT

In this work we will report the formulation of novel 3-(pyridinylamino)-1-ferrocenylpropan-1-ones. A fruitful aza-*Michael* addition of pyridinamine moiety to a conjugated enone, 1-ferrocenylpropenone, has been accomplished by an ultrasonic irradiation of the mixture of these reactants. As the catalyst montmorillonite K-10 has been used and the reaction has been carried out as solvent-free, yielding ferrocene containing *Mannich bases*, compounds considered as important precursors in organic synthesis. The reaction score has been evaluated on three examples. The prepared products have been purified by column chromatography. In addition, a detailed characterization of the obtained 3-(pyridin-2-ylamino)-1-ferrocenylpropan-1-on and 3-(pyridin-3-ylamino)-1-ferrocenylpropan-1-on has been completed by IR and NMR spectroscopy, as well as elemental analyses.

Keywords: aza-*Michael* addition, Ultrasound irradiation, 3-(pyridinylamino)-1-ferrocenylpropan-ones, Mannich bases, Spectral characterization.

INTRODUCTION

Ferrocene has been discovered in 1951 (Kealy & Pauson, 1951), and since then its derivatives have been found applications in many areas, among which the most important are in material science, asymmetric catalysis, bioorganometallic chemistry, medicinal chemistry, and organic synthesis (Köpf-Maier et al., 1984; Houlton et al., 1991; Kowalski, 2018). The application of ferrocene derivatives in the medicinal investigations proved to be a fertile area of bioorganometallic chemistry. Although ferrocene is not biologically active, it possesses a unique feature to strongly affect the activity of the structures to which is bound for (Togni, 1996). The incorporation of ferrocene nucleus into biologically relevant molecules can significantly enhance molecular properties such as solubility, hydrophobicity, and lipophilicity of ''parent compounds'' (Jaouen, 2006; Gambino & Otero, 2012; Salas et al., 2013; Biot et al., 2012; Supan et al., 2012). In such a way, some ferrocenyl derivatives like ferroquine and ferrocifen occupied an important position in pharmaceutical and medicinal chemistry. Likewise, the presence of the organoiron unit in bioactive skeletons increases their original antimalarial and antitumoral activity. Thus, the ferrocene moiety was recognized as an attractive pharmacophore in drug design (N'Da, & Smith, 2014) and a multitude of reports dealing with derivatives of this metallocene have been appeared in the literature.

In continuation of our long-standing interest in the synthesis of novel Fc-containing (Fc = ferrocene) heterocyclic compounds, of potential biological interest (Pejović et al., 2012a; Pejović et al., 2017; Pejović et al., 2018a; Pejović et al., 2018b), and in design and optimizations of reactions conditions, we reported synthesis of bioactive 2-ferrocenoyl ethyl aryl amines and 1-ferrocenyl-3-(quinolinylamino)propan-1-ones, as it is presented on Scheme 1., (Damljanović et al., 2011; Pejović et al., 2012b; Minić et al., 2020a). These Mannich bases have been proved to be an excellent starting material for the synthesis of Fc derivatives (Minić et al., 2020a; Minić et al., 2015; Minić et al., 2017; Minić et al., 2018; Minić et al., 2019; Minić et al., 2020b; Pejović et al., 2015). Hence, the synthesis and spectral characterization of novel *Mannich bases* bearing ferrocenyl group and pyridinamine ring gained in this manner could be of great interest.

In agreement with above statement, herein, we report the ultrasound-assisted synthesis between three different pyridinamine and 1-ferrocenylpropenone. All formulated compounds have been washed by column chromatography and their predicted structure have been verified with spectroscopic data (^{1}H-NMR, ^{13}C-NMR, and IR), as well as by elemental analyses. Also, this synthetic approach gives rise to favorable starting materials for advance synthesis of Fc-containing compounds.

EXPERIMENTAL

Materials and measurements

All chemicals were commercially available and used as received, except the solvents, which were purified by distillation. Ultrasonic cleaner Elmasonic S 10 (Elma, Germany), 30W was used for the ultrasonically supported synthesis. Chromatographic

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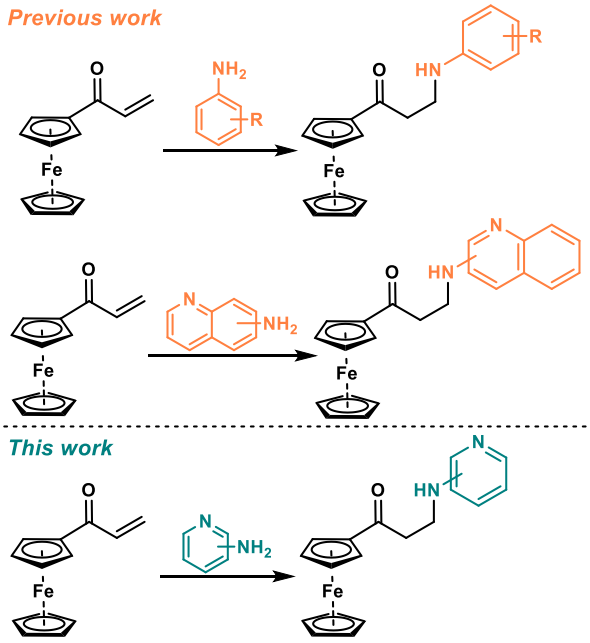
separations were carried out using silica gel 60 (Merck, 230–400 mesh ASTM), whereas silica gel 60 on Al plates, (Merck, layer thickness 0.2 mm) was used for TLC. Melting points were determined on a Mel-Temp capillary melting points apparatus, model 1001, and the given values have been uncorrected. The ^{1}H- and ^{13}C-NMR spectra of the samples in $CDCl_3$ have been recorded on a Varian Gemini (^{1}H- at 200 MHz, ^{13}C- at 50 MHz) NMR spectrometer. Chemical shifts are reported in ppm (δ) values relative to TMS (δ_H 0 ppm) in ^{1}H-, ^{13}C-NMR spectra. The coupling constants (J) are reported in Hz. Multiplicities of proton resonance are designated as singlet (s), a doublet (d), a doublet of doublets (dd), a triplet (t), a pseudo triplet (*pseudo* t), doublet of doublets of doublets (ddd), a quartet (q) and a multiplets (m). IR measurements were carried out with a Perkin–Elmer FTIR 31725-X spectrophotometer. Microanalyses of carbon, hydrogen and nitrogen were carried out with a Carlo Erba 1106 model microanalyzer; these results agreed satisfactorily with the calculated values.



Scheme 1. Synthesis of various *Mannich bases* bearing ferrocenyl group.

Synthesis and spectral characterization

*General procedure for the synthesis of 3-(pyridinylamino)-1-ferrocenylpropan-1-ones (**3a-c**)*

The 3-(pyridinylamino)-1-ferrocenylpropan-1-ones (**3a-c**) have been prepared following slightly modified formerly reported procedure (Pejović et al., 2012b; Minić et al., 2015; Minić et al., 2017; Minić et al., 2018; Minić et al., 2019). A test tube containing a well homogenized mixture of 1-ferrocenylpropenone (240 mg, 1 mmol), the analogous pyridinamine (**2a-c**, 2 mmol) and montmorillonite K-10 (100 mg, 0.42 m-eq.) has been placed in the ultrasonic cleaner for irradiations and the reaction outcome has been checked by TLC. Later, CH_2Cl_2 (10 ml) was added to the mixture, and the contents were filtered off. The solid residue was filtrated with water and brine, as well as dried over anh. Na_2SO_4. overnight. After the evaporation of the solvent, the crude mixture has been separated by chromatography on a SiO_2 column. The corresponding 3-(pyridinylamino)-1-ferrocenylpropan-1-ones (**3a-c**) have been washed from the column by a mixture of hexane and MeOH 9 : 1 (v/v). The obtained spectral data for 3-(pyridinylamino)-1-ferrocenylpropan-1-ones follow.

3-(Pyridin-2-ylamino)-1-ferrocenylpropan-1-on (***3a***). Dark red solid; mp 134 °C. Yield 60%. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.11 (dd, J = 5.1, 1.1 Hz, 1H, H-3'), 7.37 (ddd, J = 8.9, 7.1, 1.9 Hz, 1H, H-4'), 6.54 (ddd, J = 7.1, 5.1, 0.8 Hz, 1H, H-5'), 6.41 (d, J = 8.4 Hz, 1H, H-6'), 5.06 (s, 1H, NH), 4.77 (pseudo t, J = 1.9 Hz, 2H, H-4" and H-5"), 4.49 (pseudo t, J = 1.9 Hz, 2H, H-2" and H-3"), 4.10 (s, 5H, H-1"'), 3.77 (q, J = 6.1 Hz, 2H, H-3a and H-3b), 3.07 (t, J = 5.9 Hz, 2H, H-2a and H-2b). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 203.6 (C-1), 158.3 (C'), 147.9 (C'), 137.2 (C'), 112.7 (C'), 108.1 (C'), 78.9 (C"), 72.3 (C"), 69.7 (C"'), 69.2 (C"), 38.7 (C-3), 36.7 (C-2).IR (ATR, cm^{-1}): ν = 3200 (N-H) cm^{-1}; ν = 1671 (C=O) cm^{-1}. Anal. Calc. for $C_{18}H_{18}FeN_2O$: C, 64.69; H, 5.43; Fe, 16.71; N, 8.38; O, 4.79. Found: C, 64.71; H, 5.41; N, 8.36 %.

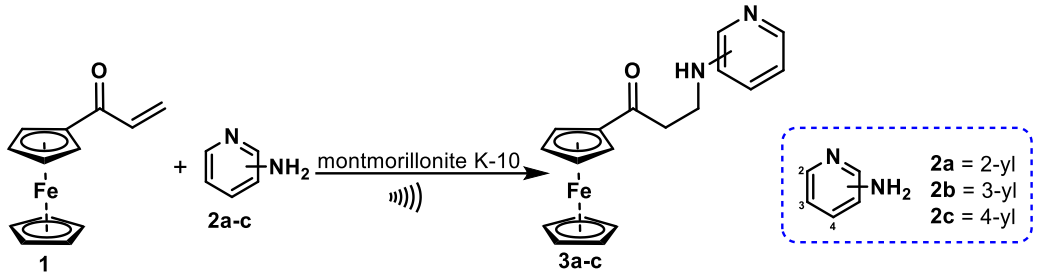
3-(Pyridin-3-ylamino)-1-ferrocenylpropan-on (***3b***). Dark red solid; mp 92 °C. Yield 75%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.08 = (d, J = 2.6 Hz, 1H, H-2'), 7.96 (d, J = 4.5 Hz, 1H, H-4'), 7.09 (dd, J = 8.3, 4.5 Hz, 1H, H-5'), 6.92 (d, J = 8.2 Hz, 1H, H-6'), 4.77 (pseudo t, J = 1.8 Hz, 2H, H-4" and H-5"), 4.53 – 4.48 (overlapped m, 3H, H-2", H-3" and NH), 4.12 (s, 5H, H-1"'), 3.57 (q, J = 5.6 Hz, 2H, H-3a and H-3b), 3.02 (t, J = 6.0 Hz, 2H, H-2a and H-2b). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 203.0 (C-1), 143.6 (C'), 138.7 (C'), 135.9 (C'), 123.6 (C'), 118.7 (C'), 78.5 (C"), 72.4 (C"), 69.7 (C"'), 69.1 (C"), 38.3 (C-3), 37.9 (C-2). IR (ATR, cm^{-1}): ν = 3211 (N-H) cm^{-1}; ν = 1665 (C=O) cm^{-1}. Anal. Calc. for $C_{18}H_{18}FeN_2O$: C, 64.69; H, 5.43; Fe, 16.71; N, 8.38; O, 4.79. Found: C, 64.70; H, 5.40; N, 8.40 %.

RESULTS AND DISCUSSION

Synthesis

As it has been declared in the introduction in the last decade our research group stated reaction conditions for the synthesis of 3-arylamino-1-ferrocenylpropan-1-ones in high yields. This reaction has yielded numerous compounds, which have been demonstrated to be both biological active agents and excellent starting materials (Damljanović et al., 2011; Pejović et al., 2012b; Minić et al., 2015; Minić et al., 2017; Minić et al., 2018; Minić et al., 2019; Minić et al., 2020a), see Scheme 1. Consequently, for required synthesis within this work we agreed to apply these already know reaction conditions (see Scheme 2). A test tube containing a well homogenized mix of 1-ferrocenylpropenone (240 mg, 1 mmol), the analogous pyridinamine (**2a**, 2 mmol) and montmorillonite K-10 (100 mg,

0.42 m-eq.) has been placed in the ultrasonic cleaner for 1h irradiations in the absence of solvent at ambient temperature. Later, the crude product has been purified by column chromatography (SiO_2/n-hexane–MeOH, 9 : 1, v/v) to give 3-(pyridin-2-ylamino)-1-ferrocenylpropan-1-on (**3a**) in only 10% yield. This result shows us that the reaction certainly occurs, but also that we need to and established the optimal parameters. Therefore, we set reaction under no different conditions, but this time reaction outcome has been monitored by TLC. Indeed, based on TLC plate, for the reaction to be fully done it was necessary much more time around 8 hours. Usual workup of the reaction and column chromatography (SiO_2/n-hexane–MeOH, 9 : 1, v/v), provided compound **3a** in 60% yield based on 1-ferrocenylpropenone.



Scheme 2. Synthesis of novel 3-(pyridinylamino)-1-ferrocenylpropan-1-ones (**3a-c**).

Reaction score has been evaluated on two additional examples and we discovered very interesting results (see Table 1). Under submitted conditions 3-(pyridin-3-ylamino)-1-ferrocenylpropan-1-on (**3b**) has been smoothly prepared in good yield 75% (see Table 1, entry 2), but when we used pyridine-4-amine as starting substrate the reaction has not proceed (see Table 1, entry 3). The explanation for these outcomes must be the different influence of electronic properties depending on the position of nitrogen atom in pyridinamine ring.

Table 1. Substrate scope for the production of 3-(pyridinylamino)-1-ferrocenylpropan-1-ones (**3a-c**)

Entry	Starting substrate	Time (h)	Product	Yield (%)[c]
1	pyridin-2-amine (**2a**)	8	**3a**	60
2	pyridin-3-amine (**2b**)	6	**3b**	75
3	pyridin-4-amine (**2c**)	10	**3c**	/

Spectral characterization

The newly obtained compounds **3a** and **3b** described in this paper have been found to be stable at the ambient temperature for a prolonged time and could safely be handled in air, but like other Fc derivatives, they should be stored in closed containers. To validate their structure detailed characterized by standard spectroscopic techniques (IR, ^{1}H- and ^{13}C-NMR), as well as elemental analyses has been done. All spectral data were completely consistent with the planned structures (for more data see Experimental part).

The IR spectra of compounds **3a** and **3b** contained characteristic vibrations of the N-H bonds at 3234 cm^{-1}. The strong band at 1670 cm^{-1} relating to absorptions of the C=O bond. Three sets of signals have been observed in the ^{1}H-NMR spectra. The first belongs to protons of the methylene groups, the second to protons of the ferrocene moiety and the third to the aromatic protons (see Figure 1).

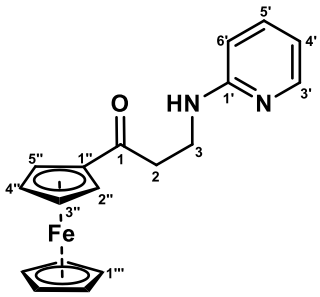


Figure 1. Labeled carbons atoms for NMR characterization.

The signals at ~ 3.57–3.77 and 3.02–3.07 ppm come from the protons of the methylene groups (H-3a, H-3b, H-2a, and H-2b, respectively). The broad singlets at ~ 5.06 ppm has been assigned to the NH protons. Likewise, the ^{1}H-NMR data for the newly produced compound **3a** and **3b** has been conventional for monosubstituted ferrocene (a typical intensity pattern of 2 : 2 : 5 for the H-atoms of Fc). Pseudo triplets at 4.48–4.77 ppm originate from the protons of the substituted cyclopentadiene rings (H-2'', H-3'', H-4'' and H-5''), and the singlets at ~ 4.10 ppm belong to the H-atoms of unsubstituted ferrocene cyclopentadiene rings (H-1'''). The signals of aromatic protons (H-2', H-3', H-4', H-5' and H-6') are positioned at the predicted chemical shifts (> 6.40 ppm) (for more data see Experimental part, Figure 2 and Figure 3).

Supplementary, signals assigned to the corresponding carbons of the synthesized compounds **3a** and **3b** appear in the expected regions of the ^{13}C NMR spectra. The corresponding signals originated from the carbonyl group (δ(C) around 203 ppm), aromatic core above 108 ppm, ferrocene moiety between 69 and 79 ppm and aliphatic carbons at *ca* 37 ppm. (for more data see Experimental part, Figure 4, and Figure 5).

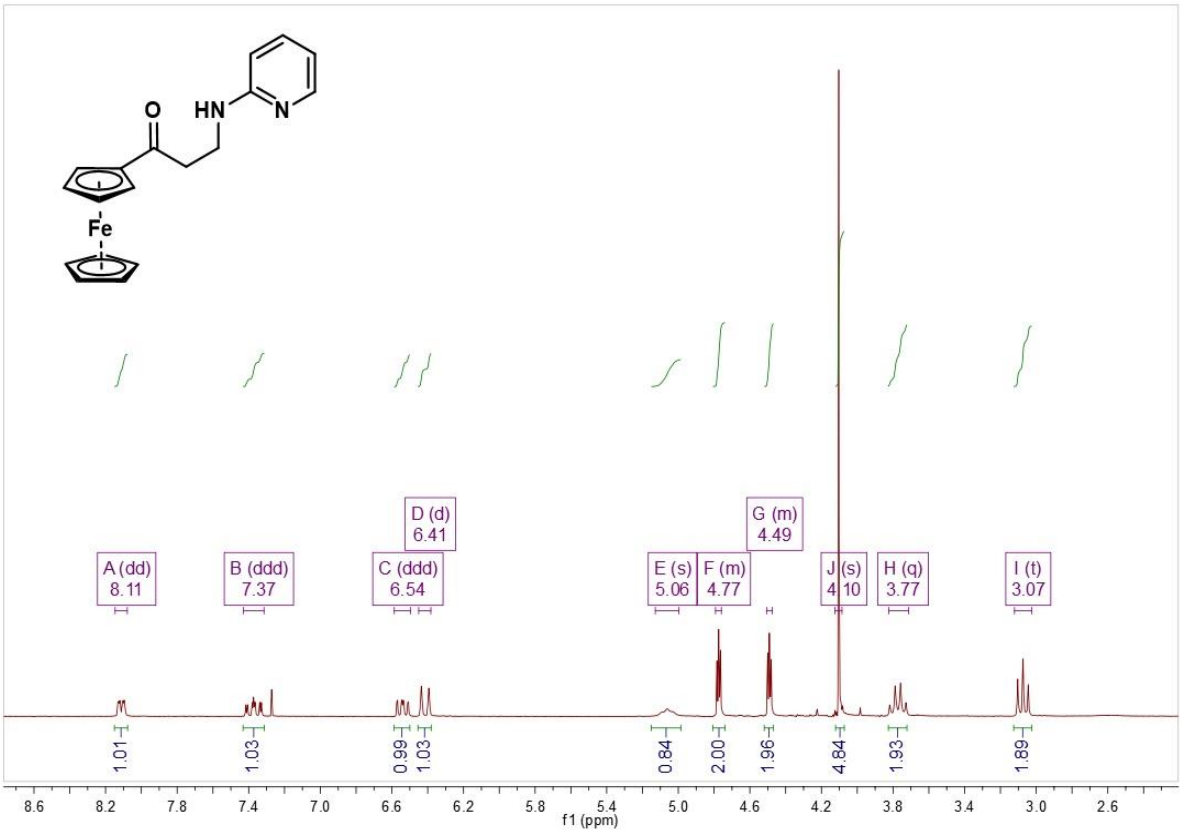


Figure 2. ^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **3a.**

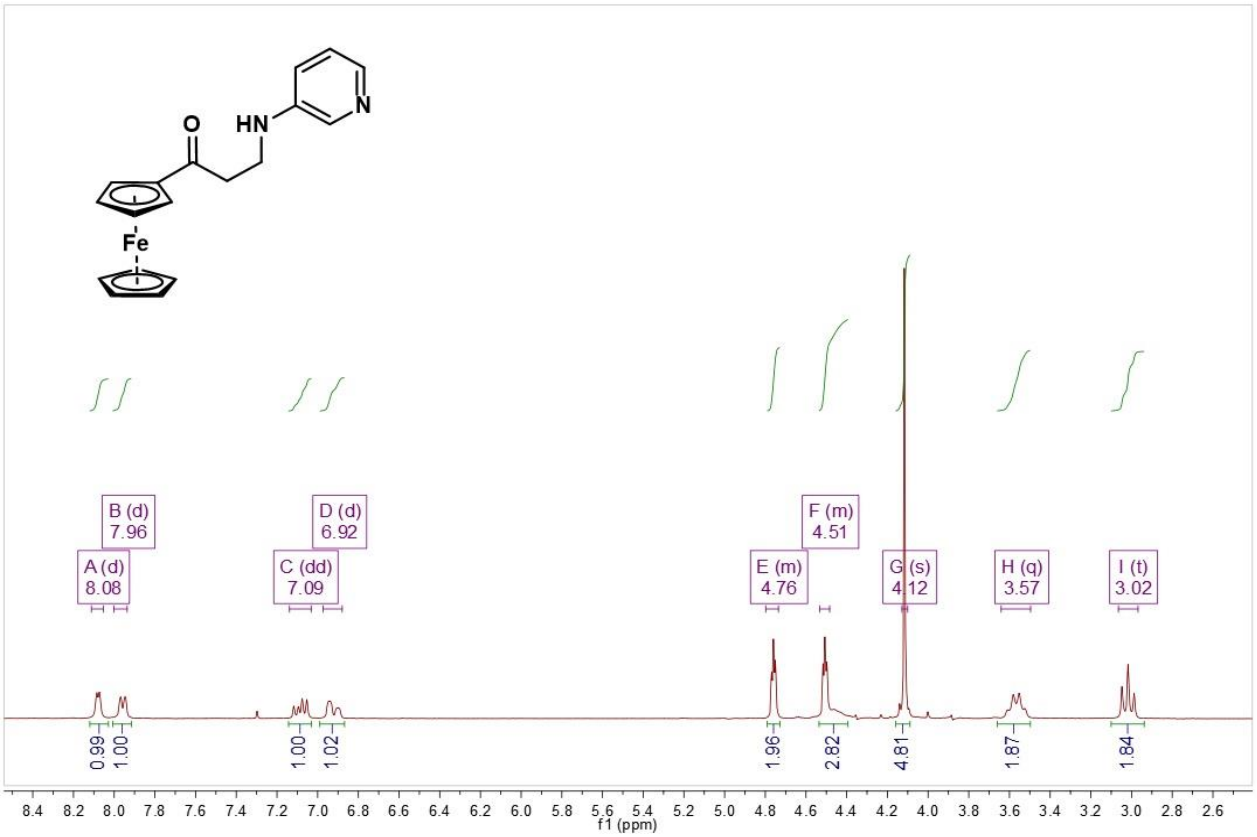


Figure 3. ^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **3b.**

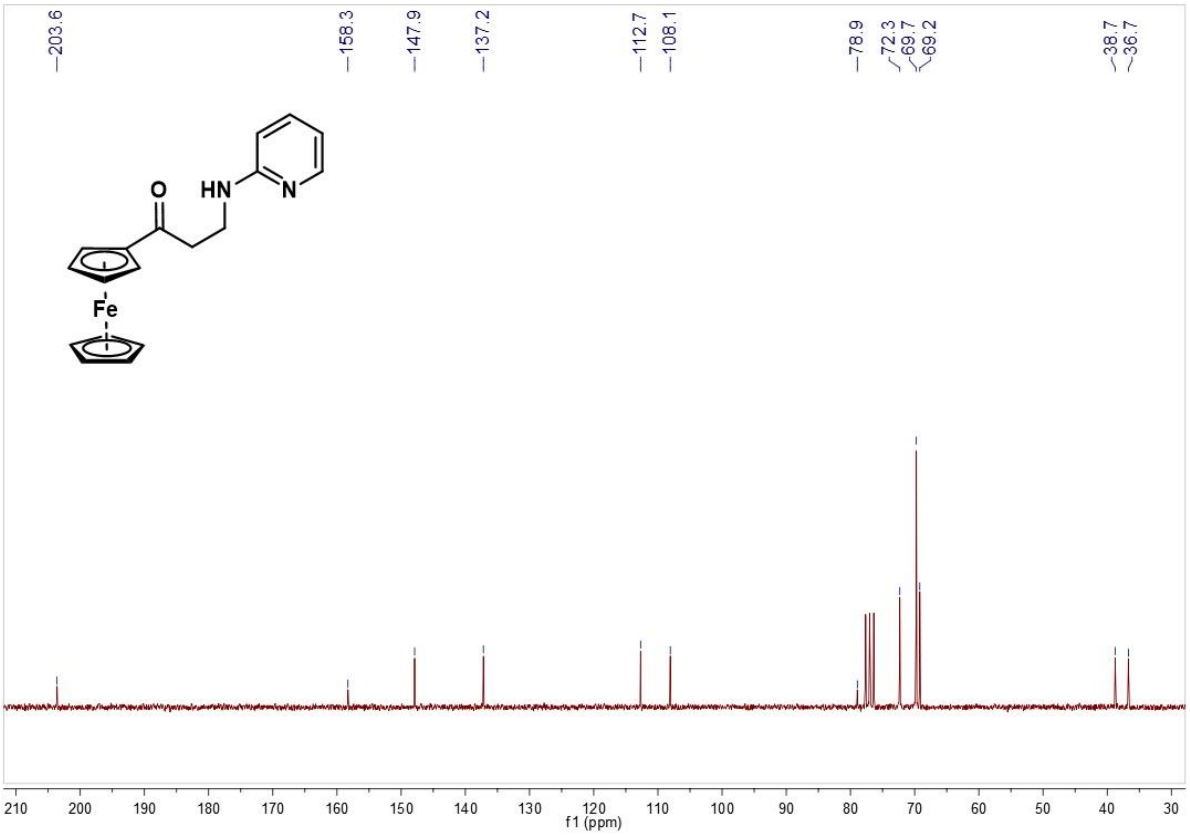


Figure 4. ^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **3a.**

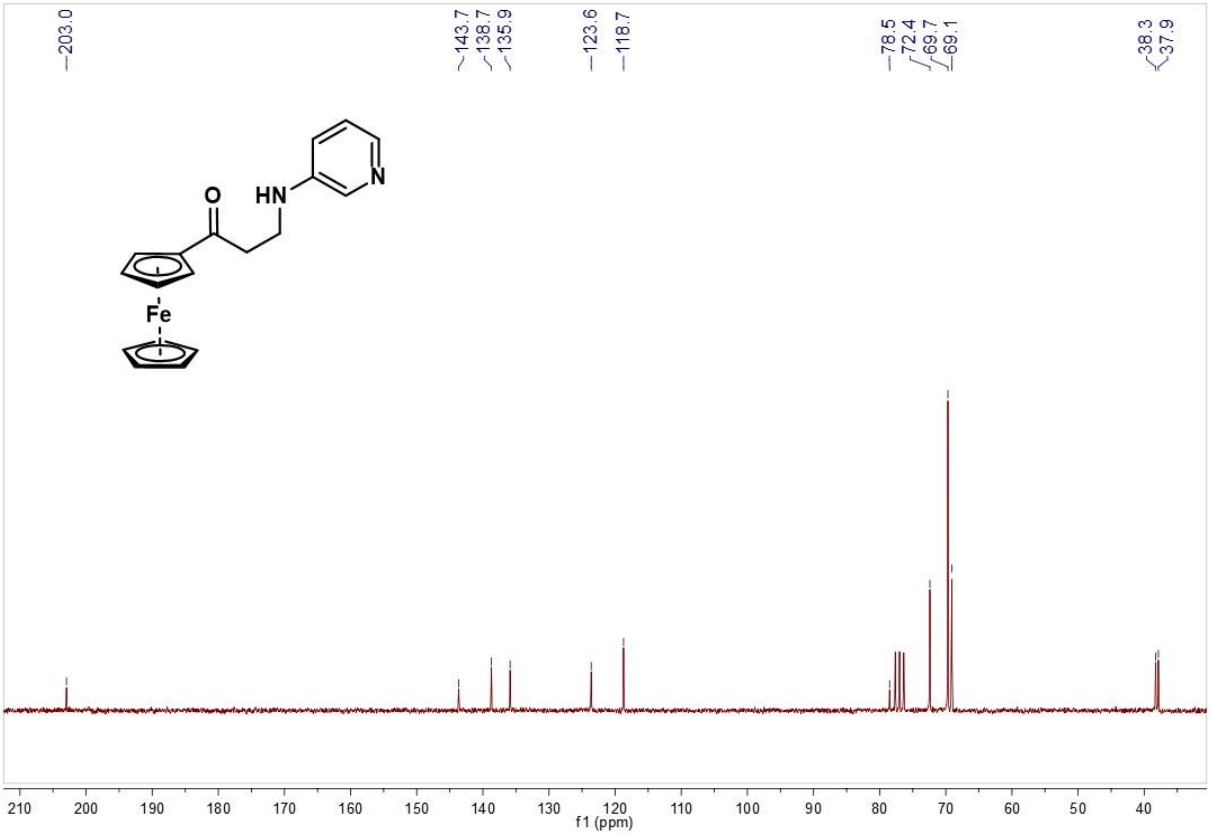


Figure 5. ^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **3b.**

CONCLUSION

In a nutshell, within this study first time synthesis of 3-(pyridin-2-ylamino)-1-ferrocenylpropan-1-on and 3-(pyridin-3-ylamino)-1-ferrocenylpropan-1-on has been submitted. Proposed structures of prepared molecules were undoubtedly confirmed by spectroscopic techniques (IR and NMR), as well as by elemental analyses. Added investigation to broaden this methodology for the synthesis of other ferrocenes is under development of our research group. In supplement, the synthesized molecules correspond to be interesting starting material for biological evaluation.

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