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-ferrocenylpropenone-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-ferrocenylpropenone-1-one and 3-(pyridin-3-ylamino)-1-ferrocenylpropenone-1-one has been completed by IR and NMR spectroscopy, as well as elemental analyses.

Keywords: aza-Michael addition, Ultrasound irradiation, 3-(pyridinylamino)-1-ferrocenylpropenone-1-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 ferrocin were occupied an important position in pharmaceutical and medicinal chemistry. Likewise, the presence of the organosilicon unit in bioactive skeletons increases their original antimalarial and antitumor 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 metalloocene have been appeared in the literature.

In continuation of our long-standing interest in the synthesis of novel Fe-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 arylamines 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 (1H-NMR, 13C-NMR, and IR), as well as by elemental analyses. Also, this synthetic approach gives rise to favorable starting materials for advance synthesis of Fe-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 1H- and 13C-NMR spectra of the samples in CDCl3 have been recorded on a Varian Gemini (H- at 200 MHz, 13C- at 50 MHz) NMR spectrometer. Chemical shifts are reported in ppm (δ) values relative to TMS (δH = 0 ppm) in 1H-, 13C-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.

![Previous work](image)

**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-ferrocenylpropane (240 mg, 1 mmol), the analogous pyridinamine (2a-c, 2 mmol) and montmorillonite K-10 (100 mg, 0.42 m-equiv.) has been placed in the ultrasonic cleaner for irradiations and the reaction outcome has been checked by TLC. Later, CH2Cl2 (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. Na2SO4. overnight. After the evaporation of the solvent, the crude mixture has been separated by chromatography on a SiO2 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-one (3a)** Dark red solid; mp 134 °C. Yield 60%. 1H NMR (200 MHz, CDCl3) 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-2” 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). 13C NMR (50 MHz, CDCl3) 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-1), 112.7 (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 C18H18FeN2O: 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-1-one (3b)** Dark red solid; mp 92 °C. Yield 75%. 1H NMR (200 MHz, CDCl3) 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). 13C NMR (50 MHz, CDCl3) 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 C18H18FeN2O: 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 known reaction conditions (see Scheme 2).

A test tube containing a well homogenized mix of 1-ferrocenylpropane (240 mg, 1 mmol), the analogous pyridinamine (2a, 2 mmol) and montmorillonite K-10 (100 mg,
0.42 m-equiv.) 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\textsubscript{2}/n-hexane–MeOH, 9 : 1, v/v) to give 3-(pyridin-2-ylamino)-1-ferrocenylpropenone (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\textsubscript{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).

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

| Entry | Starting substrate | Time (h) | Product | Yield (%) |
|-------|--------------------|----------|---------|-----------|
| 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 Fe derivatives, they should be stored in closed containers. To validate their structure detailed characterized by standard spectroscopic techniques (IR, \textsuperscript{1}H- and \textsuperscript{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\textsuperscript{-1}. The strong band at 1670 cm\textsuperscript{-1} relating to absorptions of the C=O bond. Three sets of signals have been observed in the \textsuperscript{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 \textsuperscript{13}C-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 \textsuperscript{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-one and 3-(pyridin-3-ylamino)-1-ferrocenylpropan-1-one 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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REFERENCES

Biot, C., Castro, W., Botte, C. Y. & Navarro, M. 2012. The therapeutic potential of metal-based antimalarial agents: Implications for the mechanism of action. Dalton Transactions, 41, pp. 6335-6349. doi:10.1039/C2DT12247B

Damljanović, I., Stevanović, D., Pejović, A., Vukićević, M., Novaković, S. B., Bogdanović, G. A., Mihajilov-Krstev, M. T., Radulović, N. & Vukićević, R. D. 2011. Antibacterial 3-(arylamino)-1-ferrocenylpropan-1-ones: Synthesis, spectral, electrochemical and structural characterization. Journal of Organometallic Chemistry, 696, pp. 3703-3713. doi:10.1016/j.jorganchem.2011.08.016

Gambino, D. & Otero, L. 2012. Perspectives on what ruthenium-based compounds could offer in the development of potential antiparasitic drugs. Inorganica Chimica Acta, 393, pp. 103–114. doi: 10.1016/j.ica.2012.05.028

Houlton, A., Roberts, R. M. G. & Silver, J. 1991. Studies on the anti-tumour activity of some iron sandwich compounds. Journal of Organometallic Chemistry, 418, pp. 107-112. doi:10.1016/0022-328X(91)86350-Y

Jaouen, G. 2006. Bioorganometallics: Biomolecules, Labeling, Medicine, John Wiley.

Kealy, T. J. & Pauson, P. L. 1951. A New Type of Organo-Iron Compound. Nature, 168, pp. 1039-1040. DOI:10.1038/1681039b0

Köpf-Maier, P., Köpf, H. & Neuse, E. W. 1984. Ferrocenium Salts—The First Antineoplastic Iron Compounds. Angewandte Chemie International Edition in English, 23, pp. 456-457. doi:10.1002/anie.198404561

Kowalski, K. 2018. Recent developments in the chemistry of ferroceny secondary natural product conjugates. Coordination Chemistry Reviews, 366, pp. 91-108. doi:10.1016/j.ccr.2018.04.008

Minci, A., Stevanović, D., Damljanović, I., Pejović, A., Vukićević, M., Bogdanović, G. A., Radulović, N. & Vukićević, R. D. 2015. Synthesis of ferrocene-containing six-membered cyclic ureas via α-ferrocenyl carbocations. RSC Advances, 5, pp. 24915-24919. doi. 10.1039/C5RA01383F

Minci, A., Stevanović, D., Vukićević, M., Bogdanović, G. A., D’hooghe, M., Radulović, N. & Vukićević, R. D. 2017. Synthesis of novel 4-ferrocenyl-1,2,3,4-tetrahydroquinolines and 4-ferrocenylquinolines via α-ferrocenyl carbenium ions as key intermediates. Tetrahedron, 73, pp 6268-6274. doi. 10.1016/j.tet.2017.09.014

Minci, A., Bugarinič, J., Ilić-Komatina, D., Bogdanović, G. A., Damljanović, I. & Stevanović, D. 2018. Synthesis of novel ferrocene-containing 1,3-thiazinan-2-imines: One-pot reaction promoted by ultrasound irradiation. Tetrahedron Letters, 59, pp. 3499-3502. doi:10.1016/j.tetlet.2018.08.029

Minci, A., Bugarinič, J., Pešić, M., & Ilić-Komatina, D. 2019. Novel 4-ferrocenyl-8-(phenylthio)-1,2,3,4-tetrahydroquinoline: design, synthesis and spectral characterization, UNIVERSITY THOUGHT - Publication in Natural Sciences, 9. DOI:10.5937/univth09-20839

Minci, A., Van de Walle, T., Van Hecke, K., Combrinck, J., Smith, P. J., Chibale, K. & D’hooghe, M. 2020a. Design and synthesis of novel ferrocene-quinoline conjugates and evaluation of their electrochemical and antiplasmodium properties, European Journal of Medicinal Chemistry, 187, pp. 111963. https://doi.org/10.1016/j.ejmech.2019.111963

Minci, A., Novaković, S. B., Bogdanović, G. A., Bugarinič, J., Pešić, M., Todosijević, A., Ilić-Komatina, D., Damljanović, I. & Stevanović, D. 2020b. Synthesis and structural characterizations of novel atropoisomeric ferrocene-containing six-membered cyclic ureas, Polyhedron, 177 pp. 114316. https://doi.org/10.1016/j.poly.2019.114316

NDa, D & Smith, P. 2014. Synthesis, in vitro antiplasmodial and antiproliferative activities of a series of quinoline–ferrocene hybrids. Medicinal Chemistry Research, 23, pp. 1214-1224. doi.org/10.1007/s00044-013-0748-4

Pejović, A., Damljanović, I., Stevanović, D., Vukićević, M., Novaković, S. B., Bogdanović, G. A., Radulović, N. & Vukićević, R. D. 2012a. Antimicrobial ferrocene containing quinolinones: Synthesis, spectral, electrochemical and structural characterization of 2-ferrocenyl-2,3-dihydroquinolin-4-(1H)-one and its 6-chloro and 6-bromo derivatives, Polyhedron, 31, pp. 789-795. https://doi.org/10.1016/j.poly.2011.11.006

Pejović, A., Stevanović, D., Damljanović, I., Vukićević, M., Novaković, S. B., Bogdanović, G. A., Mihajilov-Krstev, M. T., Radulović, N. & Vukićević, R. D. 2012a. Ultrasound-assisted synthesis of 3-(arylamino)-1-ferrocenylpropan-1-ones. Helvetica Chimica Acta, 95, pp. 1425-1441. doi:10.1002/hlca.201200009

Pejović, A., Dunneels, B., Desmet, T., Cham, B. T., Radulović, N. S., Vukićević, R. D. & D’hooghe, M. 2015. Synthesis and Antibacterial/Cytotoxic Assessment of Ferrocenyl Oxazinanes, Oxazinan-2-ones, and Tetrahydropyrimidin-2-ones, Synlett, 26, pp. 1195-1200. doi.10.1055/s-0034-130348

Pejović, A., Damljanović, I., Stevanović, D., Minci, A., Jovanović, J., Mihailović, V., Katanić, J. & Bogdanović, G. A. 2017. Synthesis, characterization and antimicrobial activity of novel ferrocene containing quinolines: 2-ferrocenyl-4-methoxyquinolines, 1-benzyl-2-ferrocenyl-2,3-dihydroquinolin-4-(1H)-ones and 1-benzyl-2-ferrocenylquinolin-4-(1H)-ones. Journal of Organometallic
Pejović, A., Minić, A., Bugarinović, J., Pešić, M., Damljanović, I., Stevanović, D., Mihailović, V., Katanić, J., & Bogdanović, G. A. 2018a. Synthesis, characterization and antimicrobial activity of novel 3-ferrocenyl-2-pyrazolyl-1,3-thiazolidin-4-ones, Polyhedron, 155, pp. 382–389. https://doi.org/10.1016/j.poly.2018.08.071

Pejović, A., Minić, A., Jovanović, J., Pešić, M., Ilić Komatina, D., Damljanović, I., Stevanović, D., Mihailović, V., Katanić, J. & Bogdanović, G. A. 2018b. Synthesis, characterization, antioxidant and antimicrobial activity of novel 5-arylidene-2-ferrocenyl-1,3-thiazolidin-4-ones, Journal of Organometallic Chemistry, 869, pp. 1-10. https://doi.org/10.1016/j.jorganchem.2018.05.014

Salas, P. F., Herrmann, C. & Orvig, C. 2013. Metalloantimalarials. Chemical Reviews, 113, pp. 3450-3492. doi.10.1021/cr3001252

Supan, C., Mombo-Ngoma, G., Dal-Bianco, M. P., Salazar, C. L. O., Issifou, S., Mazuir, F., Filali-Ansary, A., Biot, C., Ter-Minassian, D., Ramharter, M., Kremsner, P.G. & Lell, B. 2012. Pharmacokinetics of Ferroquine, a Novel 4-Aminoquinoline, in Asymptomatic Carriers of Plasmodium falciparum Infections. Antimicrobial Agents and Chemotherapy, 56, pp. 3165–3173. doi.10.1128/AAC.05359-11

Togni, A. 1996. Planar-Chiral Ferrocenes: Synthetic Methods and Applications. Angewandte Chemie International Edition in English, 35, pp. 1475-1477. doi.org/10.1002/anie.199614751