

THE PREPARATION AND CHARACTERIZATION OF SOME NOVEL FERROCENIL DERIVATIVES

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ABSTRACT

This paper provides a report on an easily performable synthesis *via* one-pot reaction, between the newly synthesized 3-arylamino-1-ferrocenylpropan-1-ols and PhNCO. We have used the acetic acid as the catalyst and ultrasound irradiation as the reaction promoter. We have evaluated the reaction score on three examples. In order to gain a more comprehensive insight into the role of α -ferrocenyl carbocation, we have described a plausible mechanism of the transformations in question. Moreover, we have purified the prepared by using column chromatography. Besides, we provide a detailed characterization of the new compounds (products and starting material), which was performed by IR, NMR and elemental analyses.

Keywords: Tetrahydropyrimidine ring, Ferrocene, Intramolecular cyclization, α -Ferrocenyl carbocation, Spectral characterization.

INTRODUCTION

Over the past few years, we have witnessed a radical change for modern organic chemistry, namely, raising awareness of the issues of environmental sustainability and efficiency. Consequently, one-pot reactions which involve various types of cascade and tandem reactions are being increasingly seen as a favourable approach due to their higher efficiency, operational simplicity, increased cost effectiveness and reduced generation of chemical waste. This is particularly striking in comparison with other synthetic methodologies (Hayashi 2016; Nicolaou et al., 2006; Motokura et al., 2005; Yang et al., 2016; Domling et al., 2012). In a similar vein, a new mainstream method has emerged, especially in the development of sustainable, frequently catalyst- or/and solvent-free versions of challenging reactions (Sarma et al., 2012a). Moreover, from the perspective of industrial manufacturing and “green” chemistry, such strategies would result in high yields of relatively pure products in shorter reaction times. Therefore, these strategies can be seen as not only eco-friendly, but also as financially viable options (Sharma et al., 2012b).

In contrast, heterocycles constitute one of the largest classes of organic compounds (Eicher et al., 2013). Heterocycles represent important structural motifs which are to be found extensively across a range of biologically active natural products, drug intermediates, pharmaceuticals and dye chemistry, as well as common versatile building blocks used for the synthesis of a variety of compounds (Taylor et al., 2016). For instance, at present, the most dominant among prescription medicaments constitute small heterocyclic molecules (containing diverse functional groups), or more complex structures containing a

heterocyclic core fragment (Taylor et al., 2016). Within the class of heterocycles, in recent years we have seen an increased interest of both chemists and biologists for urea derivatives, which have since been synthesized extensively. This specific class of compounds is characterized by a wide range of biological activities (Kashawa et al., 2009; Khan et al., 2008; Kaneko et al., 2007; Li et al., 2009; Tale et al., 2011; Fernandez & Caballero, 2006), which consequently resulted in a heightened interest for their synthesis. For this reason, the synthesis and characterization of novel cyclic ureas bearing ferrocenyl group obtained in this manner could be increasingly significant in the future.

Our team have recently reported synthesis of bioactive 2-ferrocenyl ethyl aryl amines (Damljanović et al., 2011; Pejović et al., 2012a). These results are a proof of our sustained interest in the synthesis of novel Fc-containing (Fc = ferrocene) heterocyclic compounds, which are of potential biological significance (Pejović et al., 2012b; Pejović et al., 2017; Pejović et al., 2018a; Pejović et al., 2018b), and in the design and optimizations of reactions conditions. 2-Ferrocenyl ethyl aryl amines - Mannich bases have demonstrated great initial results in the synthesis of Fc derivatives (Minić et al., 2017; Minić et al., 2018; Minić et al., 2019), notably in the synthesis of six-membered ureas (Minić et al., 2015; Minić et al., 2020a).

In view of this, we report the synthesis completed *via* one-pot reaction, between novel 3-arylamino-1-ferrocenylpropan-1-ols (which was obtained from corresponding Mannich bases), phenyl isocyanate, and acetic acid. All the above mentioned compounds used in this synthesis, including the products and the starting material, have been subjected to purification by column chromatography and their structure has been confirmed with the use of spectroscopic data (¹H-NMR, ¹³C-NMR, 2D-NMR and IR). Moreover, elemental analyses have been used in this

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process. Furthermore, this synthetic approach generates novel Fc-containing heterocyclic systems which may prove to be biologically relevant.

EXPERIMENTAL

Materials and measurements

All chemicals were commercially available and used as received, except that the solvents were purified by distillation. Chromatographic separations were carried out using Silica Gel 60 (Merck, 230–400 mesh ASTM), whereas Silica Gel 60 on Al plates, layer thickness 0.2 mm (Merck) was used for TLC. Melting points were determined on a Mel-Temp capillary melting points apparatus, model 1001 and are uncorrected. Microanalysis of carbon and hydrogen were carried out with a Carlo Erba 1106 microanalyser; their results agreed favorably with the calculated values. IR measurements were carried out with a Perkin–Elmer FTIR 31725-X spectrophotometer. NMR spectra were recorded on a Bruker Avance III 400 MHz (^1H at 400 MHz, ^{13}C at 101 MHz) and Varian Gemini (^1H at 200 MHz, ^{13}C at 50 MHz) NMR spectrometers. Chemical shifts are reported in ppm (δ) values relative to TMS (δ_{H} 0 ppm) in ^1H , ^{13}C and heteronuclear 2D NMR spectra.

Synthesis and spectral characterization

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

Ketones **3a-c** were synthesized by the known procedure (Pejović et al., 2012a; Minić et al., 2015; Minić et al., 2017; Minić et al., 2018; Minić et al., 2019). Spectral data of compounds **3a-c** follow.

1-Ferrocenyl-3-((2-iodophenyl)amino)propan-1-one (3a). Dark red solid; mp 162 °C. Yield 62%. ^1H NMR (400 MHz, CDCl_3) δ = 7.71 – 7.67 (m, 1H, CH_{Ar}), 7.30 – 7.25 (m, 2H, $2 \times \text{CH}_{\text{Ar}}$), 6.69 (d, J = 7.9 Hz, 1H, CH_{Ar}), 4.80 (pseudo t, J = 1.9 Hz, 2H, $2 \times \text{CH}_{\text{Cp}}$), 4.68 (t, J = 5.8 Hz, 1H, $\text{CH}_2\text{CH}_2\text{NH}$), 4.54 (pseudo t, J = 1.9 Hz, 2H, $2 \times \text{CH}_{\text{Cp}}$), 4.17 (s, 5H, $5 \times \text{CH}_{\text{Cp}}$), 3.65 (q, J = 6.2 Hz, 2H, $\text{CH}_2\text{CH}_2\text{NH}$), 3.11 – 3.05 (m, 2H, $\text{CH}_2\text{CH}_2\text{NH}$). ^{13}C NMR (101 MHz, CDCl_3) δ = 202.7 (C=O), 146.9 (C_{Ar}), 139.3 (C_{Ar}), 129.4 (C_{Ar}), 118.8 (C_{Ar}), 110.5 (C_{Ar}), 85.8 (C_{Ar}), 78.8 (C_{Cp}), 72.5 ($2 \times \text{C}_{\text{Cp}}$), 69.9 ($5 \times \text{C}_{\text{Cp}}$), 69.3 ($2 \times \text{C}_{\text{Cp}}$), 38.8 ($\text{CH}_2\text{CH}_2\text{NH}$), 38.2 ($\text{CH}_2\text{CH}_2\text{NH}$). IR (ATR, cm^{-1}): ν = 3210 (N-H) cm^{-1} ; ν = 1651 (C=O) cm^{-1} . Anal. Calc. for $\text{C}_{19}\text{H}_{18}\text{FeINO}$: C, 49.71; H, 3.95; Fe, 12.16; I, 27.64; N, 3.05; O, 3.48. Found: C, 49.76, H, 3.91, N, 3.12%.

1-Ferrocenyl-3-((3-iodophenyl)amino)propan-1-one (3b). Dark red solid; mp 156 °C. Yield 74%. ^1H NMR (400 MHz, CDCl_3) δ = 7.06 – 7.00 (m, 2H, $2 \times \text{CH}_{\text{Ar}}$), 6.94 – 6.85 (m, 1H, CH_{Ar}), 6.65 – 6.60 (m, 1H, CH_{Ar}), 4.81 (pseudo t, J = 1.9 Hz, 2H, $2 \times \text{CH}_{\text{Cp}}$), 4.54 (pseudo t, J = 1.9 Hz, 2H, $2 \times \text{CH}_{\text{Cp}}$), 4.30 (s, 1H, $\text{CH}_2\text{CH}_2\text{NH}$), 4.15 (s, 5H, $5 \times \text{CH}_{\text{Cp}}$), 3.55 (s, 2H,

$\text{CH}_2\text{CH}_2\text{NH}$), 3.03 (t, J = 6.0 Hz, 2H, $\text{CH}_2\text{CH}_2\text{NH}$). ^{13}C NMR (101 MHz, CDCl_3) δ = 203.3 (C=O), 149.0 (C_{Ar}), 130.8 (C_{Ar}), 126.4 (C_{Ar}), 121.3 (C_{Ar}), 112.6 (C_{Ar}), 95.4 (C_{Ar}), 78.7 (C_{Cp}), 72.5 ($2 \times \text{C}_{\text{Cp}}$), 69.9 ($5 \times \text{C}_{\text{Cp}}$), 69.3 ($2 \times \text{C}_{\text{Cp}}$), 38.5 ($\text{CH}_2\text{CH}_2\text{NH}$), 37.9 ($\text{CH}_2\text{CH}_2\text{NH}$). IR (ATR, cm^{-1}): ν = 3230 (N-H) cm^{-1} ; ν = 1663 (C=O) cm^{-1} . Anal. Calc. for $\text{C}_{19}\text{H}_{18}\text{FeINO}$: C, 49.71; H, 3.95; Fe, 12.16; I, 27.64; N, 3.05; O, 3.48. Found: C, 49.76, H, 3.99, N, 3.10%.

1-Ferrocenyl-3-((4-iodophenyl)amino)propan-1-one (3c). Dark red solid; mp 160 °C. Yield 56%. ^1H NMR (400 MHz, CDCl_3) δ = 7.54 – 7.37 (m, 2H, $2 \times \text{CH}_{\text{Ar}}$), 6.58 – 6.36 (m, 2H, $2 \times \text{CH}_{\text{Ar}}$), 4.77 (pseudo t, J = 2.0 Hz, 2H, $2 \times \text{CH}_{\text{Cp}}$), 4.54 (pseudo t, J = 2.0 Hz, 2H, $2 \times \text{CH}_{\text{Cp}}$), 4.29 (s, 1H, $\text{CH}_2\text{CH}_2\text{NH}$), 4.16 (s, 5H, $5 \times \text{CH}_{\text{Cp}}$), 3.56 (s, 2H, $\text{CH}_2\text{CH}_2\text{NH}$), 3.01 (t, J = 5.9 Hz, 2H, $\text{CH}_2\text{CH}_2\text{NH}$). ^{13}C NMR (101 MHz, CDCl_3) δ = 203.3 (C=O), 147.3 (C_{Ar}), 137.9 (C_{Ar}), 115.2 (C_{Ar}), 78.7 (C_{Ar}), 78.0 (C_{Cp}), 72.6 ($2 \times \text{C}_{\text{Cp}}$), 69.9 ($5 \times \text{C}_{\text{Cp}}$), 69.3 ($2 \times \text{C}_{\text{Cp}}$), 38.6 ($\text{CH}_2\text{CH}_2\text{NH}$), 38.0 ($\text{CH}_2\text{CH}_2\text{NH}$). IR (ATR, cm^{-1}): ν = 3190 (N-H) cm^{-1} ; ν = 1657 (C=O) cm^{-1} . Anal. Calc. for $\text{C}_{19}\text{H}_{18}\text{FeINO}$: C, 49.71; H, 3.95; Fe, 12.16; I, 27.64; N, 3.05; O, 3.48. Found: C, 49.71, H, 3.93, N, 3.12%.

General procedure for the synthesis of 3-(arylamino)-1-ferrocenylpropan-1-ols (4a-c)

Alcohols **4a-c** were synthesized by the known procedure (Minić et al., 2015; Minić et al., 2017; Minić et al., 2018; Minić et al., 2019). Spectral data of compounds **4a-c** follow.

1-Ferrocenyl-3-((2-iodophenyl)amino)propan-1-ol (4a). Yellow oil. Yield 97%. ^1H NMR (200 MHz, CDCl_3) δ = 7.66 – 7.62 (m, 1H, CH_{Ar}), 7.24 – 7.11 (m, 1H, CH_{Ar}), 6.57 (t, J = 8.8 Hz, 1H, CH_{Ar}), 6.47 – 6.36 (m, 1H, CH_{Ar}), 4.52 (pseudo t, J = 1.9 Hz, 2H, $2 \times \text{CH}_{\text{Cp}}$), 4.28 – 4.21 (m, 1H, $\text{CHOHCH}_2\text{CH}_2\text{NH}$), 4.17 (s, 7H, $7 \times \text{CH}_{\text{Cp}}$ *overlapped signals), 3.30 – 3.27 (m, 2H, $\text{CHOHCH}_2\text{CH}_2\text{NH}$), 2.24 – 2.12 (m, 1H, $\text{CHOHCH}_2\text{CH}_2\text{NH}$), 2.05 – 2.01 (m, 2H, $\text{CHOHCH}_2\text{CH}_2\text{NH}$). ^{13}C NMR (50 MHz, CDCl_3) δ = 147.3 (C_{Ar}), 138.9 (C_{Ar}), 129.3 (C_{Ar}), 118.4 (C_{Ar}), 110.5 (C_{Ar}), 93.3 (C_{Ar}), 85.4 (C_{Cp}), 68.3 (CHOH), 68.0 ($5 \times \text{C}_{\text{Cp}}$), 67.9 (C_{Cp}), 66.7 (C_{Cp}), 65.5 (C_{Cp}), 65.4 (C_{Cp}), 41.4 ($\text{CHOHCH}_2\text{CH}_2\text{NH}$), 36.7 ($\text{CHOHCH}_2\text{CH}_2\text{NH}$). IR (ATR, cm^{-1}): ν = 3280 (N-H) cm^{-1} ; ν = 3074 (O-H) cm^{-1} . Anal. Calc. for $\text{C}_{19}\text{H}_{20}\text{FeINO}$: C, 49.49; H, 4.37; Fe, 12.11; I, 27.52; N, 3.04; O, 3.47. Found: C, 49.52, H, 4.31, N, 3.10%.

1-Ferrocenyl-3-((3-iodophenyl)amino)propan-1-ol (4b). Yellow oil. Yield 98%. ^1H NMR (200 MHz, CDCl_3) δ = 7.03 – 6.77 (m, 3H, $3 \times \text{CH}_{\text{Ar}}$), 6.56 – 6.45 (m, 1H, CH_{Ar}), 4.55 – 4.39 (m, 1H, $\text{CHOHCH}_2\text{CH}_2\text{NH}$), 4.26 – 4.07 (m, 9H, $9 \times \text{CH}_{\text{Cp}}$ *overlapped signals), 3.26 – 3.09 (m, 2H, $\text{CHOHCH}_2\text{CH}_2\text{NH}$), 2.38 – 2.16 (m, 1H, $\text{CHOHCH}_2\text{CH}_2\text{NH}$), 2.07 – 1.75 (m, 2H, $\text{CHOHCH}_2\text{CH}_2\text{NH}$). ^{13}C NMR (50 MHz, CDCl_3) δ = 149.4 (C_{Ar}), 130.5 (C_{Ar}), 125.7 (C_{Ar}), 121.1 (C_{Ar}), 112.0 (C_{Ar}), 95.2 (C_{Ar}), 93.1 (C_{Cp}), 68.4 (CHOH), 68.2 ($5 \times \text{C}_{\text{Cp}}$), 67.9 (C_{Cp}), 67.9 (C_{Cp}), 66.6 (C_{Cp}), 65.4 (C_{Cp}), 40.9 ($\text{CHOHCH}_2\text{CH}_2\text{NH}$), 36.6

(CHOHCH₂CH₂NH). IR (ATR, cm⁻¹): $\nu = 3290$ (N-H) cm⁻¹; $\nu = 3080$ (O-H) cm⁻¹. Anal. Calc. for C₁₉H₂₀FeINO: C, 49.49; H, 4.37; Fe, 12.11; I, 27.52; N, 3.04; O, 3.47. Found: C, 49.44, H, 4.41, N, 3.01%.

1-Ferrocenyl-3-((4-iodophenyl)amino)propan-1-ol (4c). Yellow solid; mp 80 °C Yield 97%. ¹H NMR (200 MHz, CDCl₃) $\delta = 7.39$ (d, $J = 8.6$ Hz, 2H, 2 × CH_{Ar}), 6.37 (d, $J = 8.6$ Hz, 2H, 2 × CH_{Ar}), 4.55 – 4.41 (m, 1H, CHOHCH₂CH₂NH), 4.29 – 4.03 (m, 9H, 9 × CH_{Cp} *overlapped signals), 3.33 – 3.07 (m, 3H, 2H, CHOHCH₂CH₂NH and 1H, CHOHCH₂CH₂NH * overlapped signals), 2.08 – 1.80 (m, 2H, CHOHCH₂CH₂NH). ¹³C NMR (50 MHz, CDCl₃) $\delta = 147.9$ (C_{Ar}), 135.5 (C_{Ar}), 115.0 (C_{Ar}), 93.5 (C_{Ar}), 85.2 (C_{Cp}), 68.6 (CHOH), 68.3 (5 × C_{Cp}), 68.1 (C_{Cp}), 66.8 (C_{Cp}), 66.7 (C_{Cp}), 65.3 (C_{Cp}), 41.2 (CHOHCH₂CH₂NH), 36.9 (CHOHCH₂CH₂NH). IR (ATR, cm⁻¹): $\nu = 3300$ (N-H) cm⁻¹; $\nu = 3080$ (O-H) cm⁻¹. Anal. Calc. for C₁₉H₂₀FeINO: C, 49.49; H, 4.37; Fe, 12.11; I, 27.52; N, 3.04; O, 3.47. Found: C, 49.53, H, 4.33, N, 3.08%.

Synthesis of 1-aryl-4-ferrocenyl-3-phenyltetrahydropyrimidin-2(1H)-ones (5a-c)

Ureas **5a-c** were synthesized by the known procedure (Minić et al., 2015; Minić et al., 2020a). Spectral data of compounds **5a-c** follow.

4-(Ferrocenyl)-1-(2-iodophenyl)-3-phenyltetrahydropyrimidin-2(1H)-one (5a). **For example **5a** we obtained a mixture of two atropoisomers (in the text below labeled as **5a+5a'**), therefore, most of the signals in the NMR (¹H NMR and ¹³C NMR) spectra were double, which was in agreement with our previous studies (Minić et al., 2015; Minić et al., 2020).

Yellow oil. Yield 47%. Isomers ratio **5a** : **5a'** = 59.5 : 40.5 and it has been calculated based on ¹H NMR spectra. ¹H NMR (400 MHz, CDCl₃) $\delta = 7.91 - 7.84$ (m, 2H, 2 × CH_{Ar}), 7.55 (dt, $J = 8.7, 1.7$ Hz, 3H, 3 × CH_{Ar}), 7.49 (dt, $J = 6.4, 1.3$ Hz, 3H, 3 × CH_{Ar}), 7.45 – 7.17 (m, 8H, 8 × CH_{Ar}), 7.09 – 6.95 (m, 2H, 2 × CH_{Ar}), 5.28 (pseudo t, $J = 3.7$ Hz, 1H, NCHCH₂CH₂N), 5.22 (pseudo t, $J = 3.7$ Hz, 1H, NCHCH₂CH₂N), 4.51 (dt, $J = 2.4, 1.2$ Hz, 1H, CH_{Cp}), 4.36 (dt, $J = 2.4, 1.3$ Hz, 1H, CH_{Cp}), 4.22 – 4.12 (m, 3H, 3 × CH_{Cp}), 4.11 – 4.09 (m, 3H, 3 × CH_{Cp}), 3.78 (s, 5H, 5 × CH_{Cp}), 3.77 (s, 5H, 5 × CH_{Cp}), 3.63 – 3.58 (m, 2H, NCHCH₂CH₂N), 3.45 – 3.31 (m, 2H, NCHCH₂CH₂N), 2.82 – 2.59 (m, 2H, NCHCH₂CH₂N), 2.34 – 2.16 (m, 2H, NCHCH₂CH₂N). ¹³C NMR (101 MHz, CDCl₃) $\delta = 154.0$ (NCON), 153.3 (NCON), 146.4 (C_{Ar}), 145.8 (C_{Ar}), 143.9 (C_{Ar}), 143.5 (C_{Ar}), 143.3 (C_{Ar}), 143.2 (C_{Ar}), 129.8 (C_{Ar}), 129.5 (C_{Ar}), 129.4 (C_{Ar}), 129.3 (C_{Ar}), 128.8 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.1 (C_{Ar}), 126.3 (C_{Ar}), 126.2 (C_{Ar}), 126.0 (C_{Ar}), 125.6 (C_{Ar}), 100.3 (C_{Ar}), 99.4 (C_{Ar}), 88.9 (C_{Cp}), 88.8 (C_{Cp}), 69.9 (5 × C_{Cp}), 68.9 (5 × C_{Cp}), 68.8 (C_{Cp}), 68.5 (C_{Cp}), 66.9 (C_{Cp}), 66.8 (C_{Cp}), 66.6 (C_{Cp}), 64.5 (C_{Cp}), 64.4 (C_{Cp}), 64.4 (C_{Cp}), 58.8 (NCHCH₂CH₂N), 58.6 (NCHCH₂CH₂N), 45.9 (NCHCH₂CH₂N), 45.8 (NCHCH₂CH₂N), 31.1 (NCHCH₂CH₂N), 31.0

(NCHCH₂CH₂N). IR (ATR, cm⁻¹): $\nu = 1650$ (NCON) cm⁻¹. Anal. Calc. for C₂₆H₂₃FeIN₂O: C, 55.54; H, 4.12; Fe, 9.93; I, 22.57; N, 4.98; O, 2.85. Found: C, 55.60; H, 4.07; N, 4.94%.

4-(Ferrocenyl)-1-(3-iodophenyl)-3-phenyltetrahydropyrimidin-2(1H)-one (5b). Yellow solid; mp 103 °C. Yield 66%. ¹H NMR (400 MHz, CDCl₃) $\delta = 7.73$ (t, $J = 1.9$ Hz, 1H, CH_{Ar}), 7.52 – 7.40 (m, 5H, 5 × CH_{Ar}), 7.31 (ddd, $J = 8.1, 2.1, 1.0$ Hz, 1H, CH_{Ar}), 7.28 – 7.23 (m, 1H, CH_{Ar}), 7.05 (t, $J = 8.0$ Hz, 1H, CH_{Ar}), 5.20 (pseudo t, $J = 3.9$ Hz, 1H, NCHCH₂CH₂N), 4.22 – 4.18 (m, 2H, 2 × CH_{Cp}), 4.16 – 4.13 (m, 1H, CH_{Cp}), 4.07 (dt, $J = 2.5, 1.3$ Hz, 1H, CH_{Cp}), 3.77 (s, 5H, 5 × CH_{Cp}), 3.65 (td, $J = 11.6, 3.9$ Hz, 1H, NCHCH₂CH₂N), 3.53 (m, 1H, NCHCH₂CH₂N), 2.68 – 2.57 (m, 1H, NCHCH₂CH₂N), 2.25 – 2.17 (m, 1H, NCHCH₂CH₂N). ¹³C NMR (101 MHz, CDCl₃) $\delta = 153.6$ (NCON), 145.0 (C_{Ar}), 143.2 (C_{Ar}), 134.6 (C_{Ar}), 134.3 (C_{Ar}), 129.9 (C_{Ar}), 128.5 (C_{Ar}), 128.1 (C_{Ar}), 126.4 (C_{Ar}), 124.9 (C_{Ar}), 93.4 (C_{Ar}), 88.6 (C_{Cp}), 68.8 (5 × C_{Cp}), 68.4 (C_{Cp}), 68.2 (C_{Cp}), 67.0 (C_{Cp}), 64.4 (C_{Cp}), 58.6 (NCHCH₂CH₂N), 45.6 (NCHCH₂CH₂N), 31.0 (NCHCH₂CH₂N). IR (ATR, cm⁻¹): $\nu = 1640$ (NCON) cm⁻¹. Anal. Calc. for C₂₆H₂₃FeIN₂O: C, 55.54; H, 4.12; Fe, 9.93; I, 22.57; N, 4.98; O, 2.85. Found: C, 55.59; H, 4.08; N, 4.93%.

4-(Ferrocenyl)-1-(4-iodophenyl)-3-phenyltetrahydropyrimidin-2(1H)-one (5c). Yellow solid; mp 92 °C. Yield 74%. ¹H NMR (400 MHz, CDCl₃) $\delta = 7.63 - 7.58$ (m, 2H, 2 × CH_{Ar}), 7.46 – 7.36 (m, 4H, 4 × CH_{Ar}), 7.24 – 7.19 (m, 1H, CH_{Ar}), 7.10 – 7.05 (m, 2H, 2 × CH_{Ar}), 5.17 (pseudo t, $J = 3.9$ Hz, 1H, NCHCH₂CH₂N), 4.19 – 4.14 (m, 2H, 2 × CH_{Cp}), 4.10 (td, $J = 2.4, 1.3$ Hz, 1H, CH_{Cp}), 4.04 (dt, $J = 2.5, 1.3$ Hz, 1H, CH_{Cp}), 3.74 (s, 5H, 5 × CH_{Cp}), 3.61 (td, $J = 11.6, 3.9$ Hz, 1H, NCHCH₂CH₂N), 3.53 – 3.47 (m, 1H, NCHCH₂CH₂N), 2.65 – 2.54 (m, 1H, NCHCH₂CH₂N), 2.21 – 2.14 (m, 1H, NCHCH₂CH₂N). ¹³C NMR (101 MHz, CDCl₃) $\delta = 153.7$ (NCON), 143.7 (C_{Ar}), 143.2 (C_{Ar}), 137.5 (C_{Ar}), 128.5 (C_{Ar}), 128.0 (C_{Ar}), 127.6 (C_{Ar}), 126.3 (C_{Ar}), 89.6 (C_{Ar}), 88.6 (C_{Cp}), 68.8 (5 × C_{Cp}), 68.4 (C_{Cp}), 68.2 (C_{Cp}), 66.9 (C_{Cp}), 64.4 (C_{Cp}), 58.6 (NCHCH₂CH₂N), 45.5 (NCHCH₂CH₂N), 31.0 (NCHCH₂CH₂N). IR (ATR, cm⁻¹): $\nu = 1645$ (NCON) cm⁻¹. Anal. Calc. for C₂₆H₂₃FeIN₂O: C, 55.54; H, 4.12; Fe, 9.93; I, 22.57; N, 4.98; O, 2.85. Found: C, 55.58; H, 4.07; N, 4.91%.

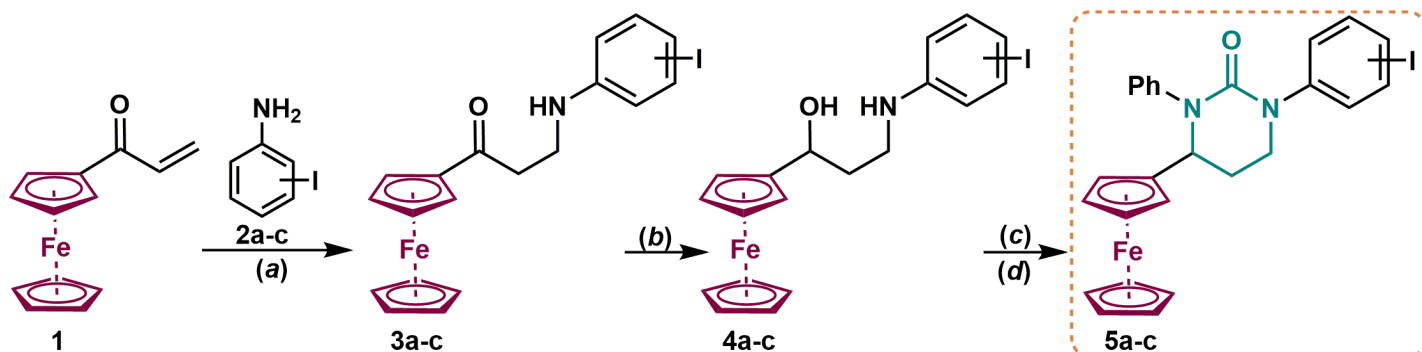
RESULTS AND DISCUSSION

Synthesis

Within the first phase of this synthesis, we made sure to come up with an appropriate method for the synthesis of 3-(arylamino)-1-ferrocenylpropan-1-ones. Our team have already designed and optimized reaction conditions for the synthesis of 3-arylamino-1-ferrocenylpropan-1-ones. On this occasion, which took place a few years ago, we managed to obtain high yields of the said compounds, and these proved to be both biological agents, as well as exquisite starting materials which can be used

for further chemical modifications (Damljanović et al., 2011; Pejović et al., 2012a; Pejović et al., 2012b; Minić et al., 2015; Minić et al., 2017; Minić et al., 2018; Minić et al., 2019; Minić et al., 2020a). In this manner, we adapted the protocol to make it suitable for the synthesis of target compounds through the usage

of iodoaniline as the arylamino moiety (see Scheme 1). After setting the reaction, we were delighted to see that under these conditions we were indeed able to successfully synthesize 2-ferrocenoyl ethyl aryl amines (**3a-c**) in the yields which were satisfactory (see Scheme 1 and Scheme 2).



Scheme 1. Synthesis of novel Fc-containing derivatives (**3**, **4** and **5**). Reagents and conditions: (a) **1** (1 mmol), iodoaniline (2 mmol), montmorillonite K-10 (100 mg), ultrasound irradiation 1 h, r.t.; (b) **3a-c** (1 mmol), MeOH (20 ml), NaBH₄ (5 mmol, up to 190 mg), r.t.; (c) **4a-c** (1 mmol), PhNCO (0.12 ml, 1.1 equivalents), ultrasound irradiation 1 h, r.t., then (d) AcOH (1 ml), ultrasound irradiation 1 h, r.t.

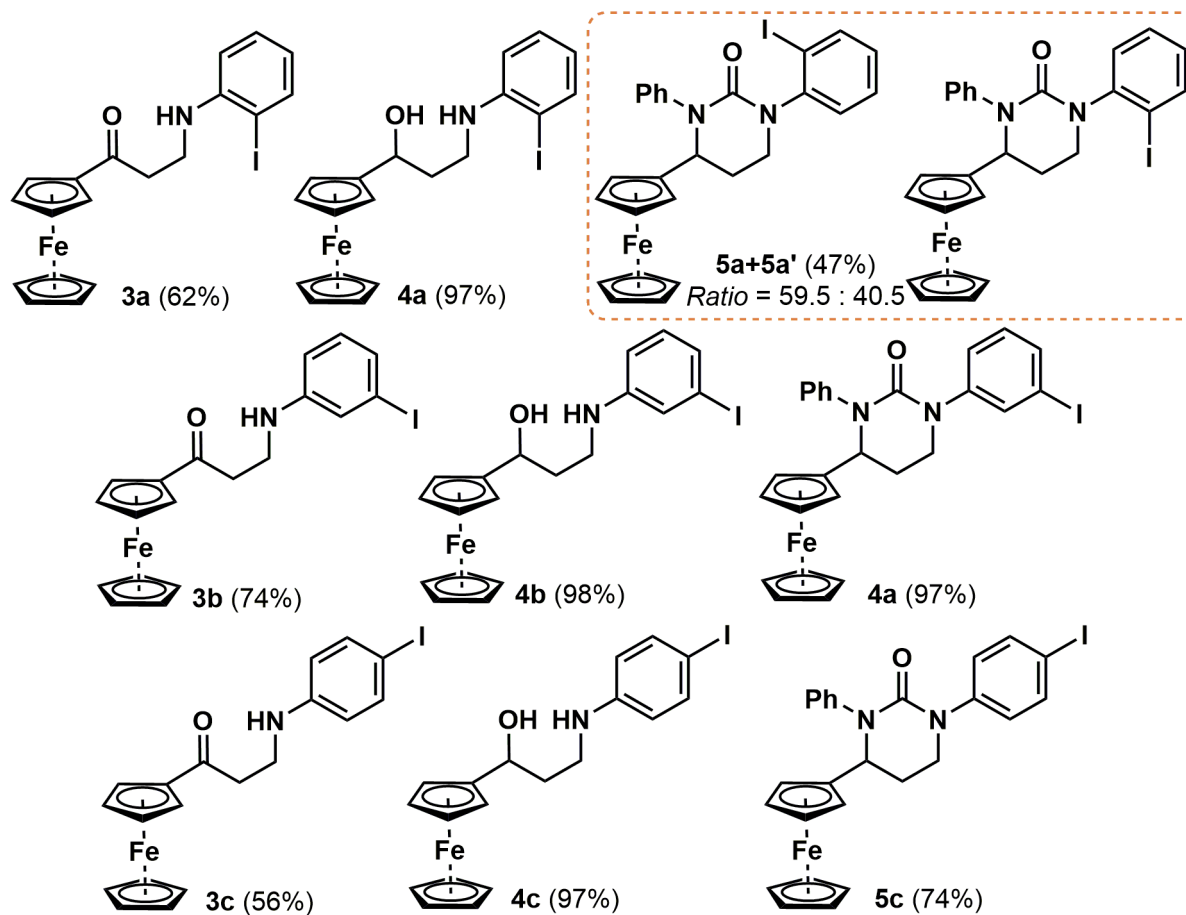
The following step was to convert the obtained ketones **3a-c** into the 3-(arylamino)-1-ferrocenylpropan-1-ols (**4a-c**). We utilized NaBH₄ (5 equivalents) in MeOH for this reaction and we were also able to synthesize target compounds in a successful manner. This means that we managed to obtain exquisite yields (98%), combined with a reduced reaction time and with the absence of sub products (see Scheme 1. and Scheme 2.). Our research team has previously reported on the method we utilized here (Minić et al., 2015; Minić et al., 2017; Minić et al., 2018; Minić et al., 2019; Minić et al., 2020b). It is essential to note that in organic chemistry γ -amino alcohols are generally regarded as versatile synthons. For that reason, the **4a-c** products we were able to obtain represent not only encouraging biological activity, but also remarkable starting material to be used for further synthesis of Fc-containing compounds. In this case, the focus is on an interest from a biological point of view (antibacterial, antimalarial, anti-inflammatory, antitumor etc.) (Minić et al., 2015; Minić et al., 2017; Minić et al., 2018; Minić et al., 2019; Minić et al., 2020a; Minić et al., 2020b; Pejović et al., 2015)

The last steps consisted of premising six-membered cyclic ureas **5a-c** bearing ferrocenyl group (see Scheme 1). A method which we opted for in this synthetic transformation is both efficient and involves mild reaction conditions. The method was earlier reported on by our research team (Minić et al., 2015; Minić et al., 2020a). We started the investigation by ultrasonating the mixture of 1,3-aminoalcohol (**4a-c**) and phenyl isocyanate (0.12 ml, 1.1 mmol). In the next step, we added 1 ml of glacial acetic acid, and irradiation continued for additional 1.5 h. Through the process of purification, we were

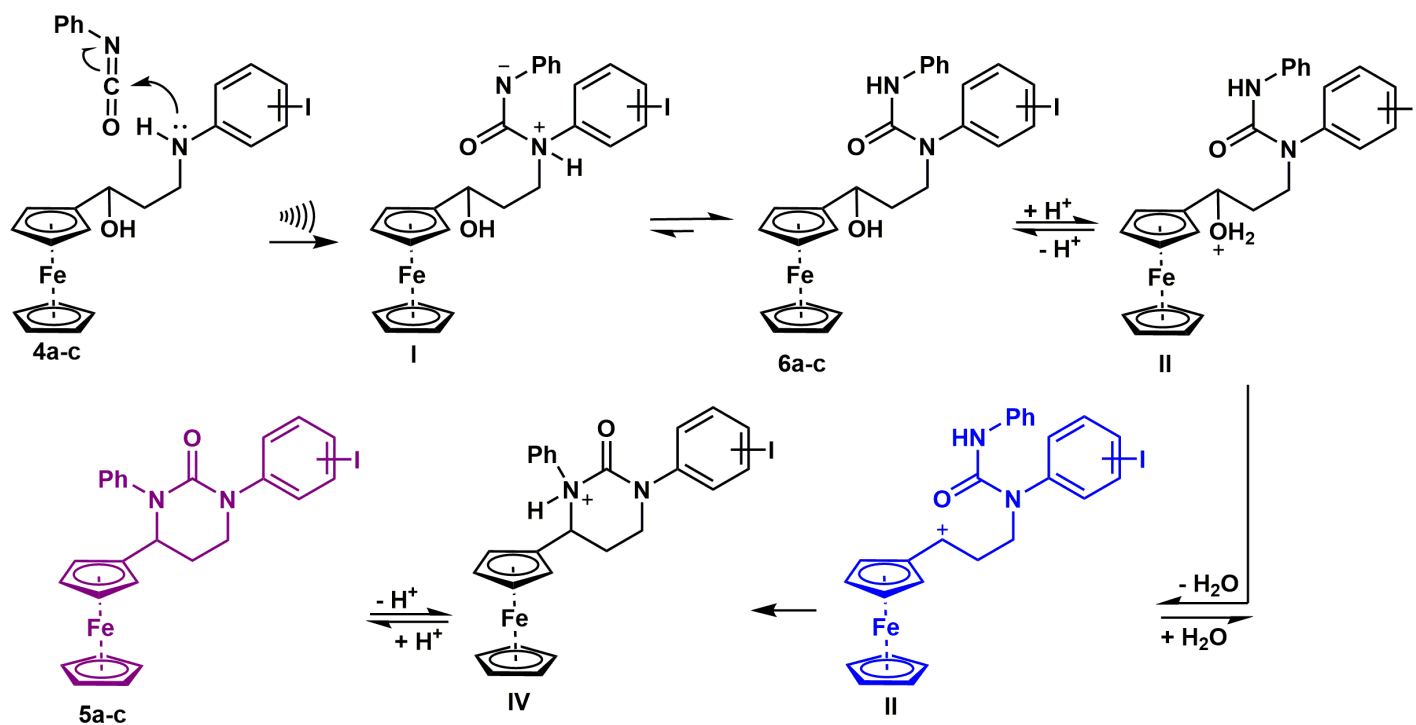
able to isolate the desired heterocyclic scaffold **5**, by using column chromatography in high purity (>95%, confirmed by NMR) and good yield (see Scheme 2). It is important to note that in the case of the example **5a** we were able to obtain the mixture of two atropoisomers (**5a+5a'**; see Scheme 2). This is the result which corresponds to previous study by our team (Minić et al., 2020a) However, regrettably, we haven't succeeded in separating these isomers.

Despite the fact that the reaction of 1,3-amino alcohols **4a-c** with phenyl isocyanate and the following intramolecular cyclization in the presence of acetic acid to cyclic ureas **5a-c** was carried out in "a one-pot" manner, we have previously established the existence of intermediates - the corresponding hydroxy ureas (**6a-c**) by carefully analyzing ¹H and ¹³C NMR spectra (see Scheme 3) (Minić et al., 2015; Minić et al., 2020a).

In order to get a more comprehensive insight into the role of α -ferrocenyl carbocation, we discussed the reaction mechanism. As demonstrated in Scheme 3, the beginning of the reaction is marked by the protonation of β -hydroxy ureas **6a-c** by acetic acid and dehydration of the resulting oxonium ions **II**, eventually giving α -ferrocenyl carbocations **III** (Wagner, G., & Herrmann, R., 1995). Finally, a nucleophilic attack of the carbamide nitrogen on the positive centre of α -ferrocenyl carbocations **III** forms cations **IV**, which yielded the target 1-aryl-4-ferrocenyl-3-phenyltetrahydropyrimidin-2(1H)-ones after deprotonations (**5a-c**).



Scheme 2. An overview of newly prepared Fc-derivatives **3**, **4** and **5**.



Scheme 3. A plausible reaction mechanism of the transformation of 1,3-amino alcohols **4a-c** into **5a-c**.

Spectral characterization

In order to confirm structure of the newly prepared molecules **3**, **4** and **5**, we have performed a detailed characterization by standard spectroscopic techniques (IR, ^1H and ^{13}C NMR), as well as elemental analyses. We have found all spectral data to be entirely compatible to the projected structures (for more data see Experimental part).

Within the IR spectra of **3a-c**, we have observed sharp, medium intensity absorption of NH stretching vibration below 3200 cm^{-1} , thereby demonstrating that all NH groups participate in H-bonding interactions. The CO stretching vibration band of the 1'-ferrocene-carbonyl group seem to be at approximately 1655 cm^{-1} . The ^1H and ^{13}C NMR spectra of compound **3a-c** demonstrate all the signals (for aliphatic, amino, ferrocenyl and aromatic protons) normally foreseen for the projected composition.

Infrared spectra of the Fc-containing 1,3-amino alcohols **4a-c** exhibit characteristic bands related to N-H stretching vibrations approximately 3290 cm^{-1} and O-H stretching vibrations approximately 3080 cm^{-1} . Furthermore, the lack of signal for C=O undeniably validates the occurrence of the reduction. The ^1H NMR spectra of **4a-c** comprises the signals which are typical of the aliphatic, hydroxy, ferrocene, amino, and aromatic protons found in the expected regions. In the ^{13}C NMR spectra of the **4a-c**, we can recognize the signals of the aliphatic, ferrocene and aromatic carbons in suitable regions. Additionally, the lack of signal which is associated with carbonyl group in ^{13}C NMR spectra of compound **4a-c** and the presence of signal at ~ 68.5 ppm, originated from C_{HOH} , unquestionably validates the projected product structure.

The IR spectra of the obtained compound **5a-c** comprises projected bands carbonyl diamide group. In the ^1H NMR spectra of product mixture **5a** + **5a'** the signals typical of the aromatic, ferrocene, and aliphatic protons can be found in pairs in the projected regions. The corresponding signal for compounds **5b** and **5c** has been observed, as well. In the ^{13}C NMR spectra of 1-aryl-4-ferrocenyl-3-phenyltetrahydropyrimidin-2(1H)-ones (**5a-c**) signals of the aliphatic, ferrocenyl, aromatic and carbonyl diamide carbons can be recognized in suitable regions (for example **5a** + **5a'** the majority of the signals can be recognized in pairs).

CONCLUSION

In conclusion, this paper presents the synthesis of three novel six-membered cyclic ureas bearing a ferrocenyl core starting from appropriate 1,3-amino alcohol. The protocol used is found to be practical, as well as convenient. Structures of all newly prepared compounds were undeniably validated using the standard spectroscopic techniques and elemental analyses. Finally, we find the synthesized compounds to be of potential interest for the bioactivity studies.

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