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Synthesis of 3-amido-3-ferrocenylpropionamides from diethyl 2-(ferrocenylmethylidene)malonate and amidines

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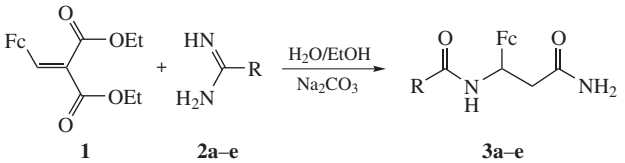
Diethyl 2-(ferrocenylmethylidene)malonate reacts with guanidines, amidines and *O*-methylisourea to afford 3-amido-3-ferrocenylpropionamides.

The compounds with β-dicarbonyl systems are used as 1,3-bis-electrophiles in cyclocondensations with N–C–N building blocks (*e.g.*, urea, guanidines, amidines) giving pyrimidine derivatives.[1–7] Incorporation of ferrocenyl substituents into such molecules provides unexpected properties unlike alkyl or aryl analogues. As recently reported,[8–11] 2-ferrocenylmethylidene-1,3-dicarbonyl compounds react with hydrazines[8,9] and amidines[10,11] forming mixtures of 1,2- and 1,3-insertion products of polynucleophilic reactants into molecules of the starting β-dicarbonyl compounds, *viz*., ethyl 3-(*N*′-acyl-*N*′-alkylhydrazino)-3-ferrocenylpropionates, 1-acyl-2-(*N*′-alkyl-*N*′-ethoxycarbonylhydrazino)-2-ferrocenylethanes,[8,9] or ethyl 3-(2-acetylamidino)-3-ferrocenylpropionates,[9] fragmentation–cycloaddition[8,9] and cycloaddition[11] products – ferrocenylpyrazole, pyrimidine and dihydropyrimidine derivatives. Ferrocenyl(dihydro)pyrimidines were tested *in vitro* against six human tumor cell lines U-251, PC-3, K-562, HCT-15, MCF-7 and SKLU-1 to assess their *in vitro* antitumor activity. The results suggest biological specificity towards PC-3 and K-562 cells for all compounds at doses 50 μM, which are lower than *cis*-platin IC_{50} in the two cell lines.[11]

These data prompt the conclusion that the fragmentation–cycloaddition processes will apparently take place in the reactions of polynitrogen nucleophilic reagents with olefins bearing no less than three electron-withdrawing groups.[8–12] The following issues should be addressed: assessment of the potential synthetic and practical applications of the fragmentation–cycloaddition reactions, their regioselectivity and investigations of the electronic factors impact on chemical characteristics of ferrocenylmethylidene-β-dicarbonylic substrates.

In the present work, the reactions of diethyl 2-(ferrocenylmethylidene)malonate **1** with guanidines, amidines and *O*-methylisourea **2a–e** are in the main focus. We found that, compound **1** reacts with excess of polyamines **2a–e** in aqueous ethanol in the presence of Na_2CO_3 at 80–85 °C to afford fragmentation products **3a–e** (Scheme 1).



Scheme 1

Products **3a–e** were isolated by chromatography on alumina and their structures were established by mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.† The ^{1}H NMR spectra of **3a–e** contain characteristic signals from protons of the methyl groups (for **3a**, **3d** and **3e**), signals for the protons of the ABX system of the CH_2CH fragments, as well as signals for the NH and NH_2 protons, the ferrocenyl and phenyl substituents protons signals were also detected. A characteristic feature of the ^{13}C NMR spectra of compounds **3a–e** is the high-field position of the signals for C_{ipsoFc} (δ ~80–82 ppm).

† *Reaction of diethyl 2-(ferrocenylmethylidene)malonate* **1** *with amidines* **2a**,**b**, *guanidines* **2c**,**d** *and* O-*methylisourea* **2e**. A mixture of compound **1** (5 mmol), guanidinium sulfate **2a**,**b**, amidine **2c**,**d** or *O*-methylisourea **2e** (10.5 mmol), ethanol (80 ml), H_2O (20 ml) and Na_2CO_3 (2.0 g) was stirred at 80 °C for 4 h. The solvents were removed *in vacuo*, the residues were dissolved in dichloromethane (50 ml). The solution was mixed with Al_2O_3 (activity III) (20 g) and the solvent was evaporated in air. This sorbent was applied on to a column with Al_2O_3 (the height of alumina is *ca*. 20 cm) and the reaction products were eluted from the column first with light petroleum and then with a 1:1 dichloromethane–light petroleum system to give compounds **3a–e**, respectively.

3-Acetylamino-3-ferrocenylpropionamide **3a**. Yield 0.62–0.76 g (40–48%), yellow crystals, mp 186–187 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.97 (s, 3H, Me), 2.57 (dd, 1H, CH_2, *J* 6.3 and 12.3 Hz), 2.78 (dd, 1H, CH_2, *J* 4.5 and 12.3 Hz), 4.12 (s, 5H, C_5H_5), 4.23 (m, 2H, C_5H_4), 4.31 (m, 2H, C_5H_4), 4.51 (dd, 1H, CH, *J* 4.5 and 6.3 Hz), 6.34 (br. s, 2H, NH_2), 8.80 (br. s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 18.32 (Me), 40.12 (CH_2), 56.39 (CH), 69.43 (C_5H_5), 69.21, 69.84 (C_5H_4), 80.11 (C_{ipso}Fc), 158.23, 164.18 (2C=O). MS, *m*/*z*: 314 $[M]^+$. Found (%): C, 57.47; H, 5.68; Fe, 17.82; N, 8.76. Calc. for $C_{15}H_{18}FeN_2O_2$ (%): C, 57.34; H, 5.77; Fe, 17.78; N, 8.92.

3-Benzoylamino-3-ferrocenylpropionamide **3b**. Yield 0.94–1.01 g (50–54%), yellow crystals, mp 202–203 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.59 (dd, 1H, CH_2, *J* 6.9 and 12.6 Hz), 2.75 (dd, 1H, CH_2, *J* 4.5 and 12.6 Hz), 4.13 (s, 5H, C_5H_5), 4.25 (m, 2H, C_5H_4), 4.32 (m, 2H, C_5H_4), 4.43 (dd, 1H, CH, *J* 4.5 and 6.9 Hz), 5.70 (br. s, 2H, NH_2), 7.62 (br. s, 1H, NH), 7.47–7.52 (m, 3H, Ph), 7.97 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 41.58 (CH_2), 59.34 (CH), 70.04 (C_5H_5), 68.95, 70.13 (C_5H_4), 82.61 (C_{ipso}Fc), 129.02, 132.61, 134.18 (Ph), 144.58 (C), 162.09, 164.36 (2C=O). MS, *m*/*z*: 376 $[M]^+$. Found (%): C, 63.96; H, 5.27; Fe, 14.99; N, 7.31. Calc. for $C_{20}H_{20}FeN_2O_2$ (%): C, 63.85; H, 5.36; Fe, 14.85; N, 7.44.

3-Ferrocenyl-3-ureidopropionamide **3c**. Yield 0.71–0.82 g (45–51%), yellow crystals, mp 176–177 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.39 (dd, 1H, CH_2, *J* 7.2 and 12.6 Hz), 2.69 (dd, 1H, CH_2, *J* 5.1 and 12.6 Hz), 4.12 (s, 5H, C_5H_5), 4.39 (dd, 1H, CH, *J* 5.1 and 7.2 Hz), 4.22 (m, 2H, C_5H_4), 4.31 (m, 2H, C_5H_4), 5.89 (br. s, 4H, $2NH_2$), 8.03 (br. s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 39.89 (CH_2), 50.12 (CH), 69.83 (C_5H_5), 69.51, 70.01 (C_5H_4), 80.02 (C_{ipso}Fc), 160.02, 164.31 (2C=O). MS, *m*/*z*: 315 $[M]^+$. Found (%): C, 53.18; H, 5.32; Fe, 17.83; N, 13.17. Calc. for $C_{14}H_{17}FeN_3O_2$ (%): C, 53.36; H, 5.44; Fe, 17.72; N, 13.33.

The X-ray diffraction analysis of single crystals of compound **3a** obtained by crystallization from CH_2Cl_2 ultimately confirmed its structure (Figure 1).‡ A characteristic feature of the crystal structure of **3a** is the presence of two molecules in the unit cell differing in the orientation of the ferrocenyl substituents.

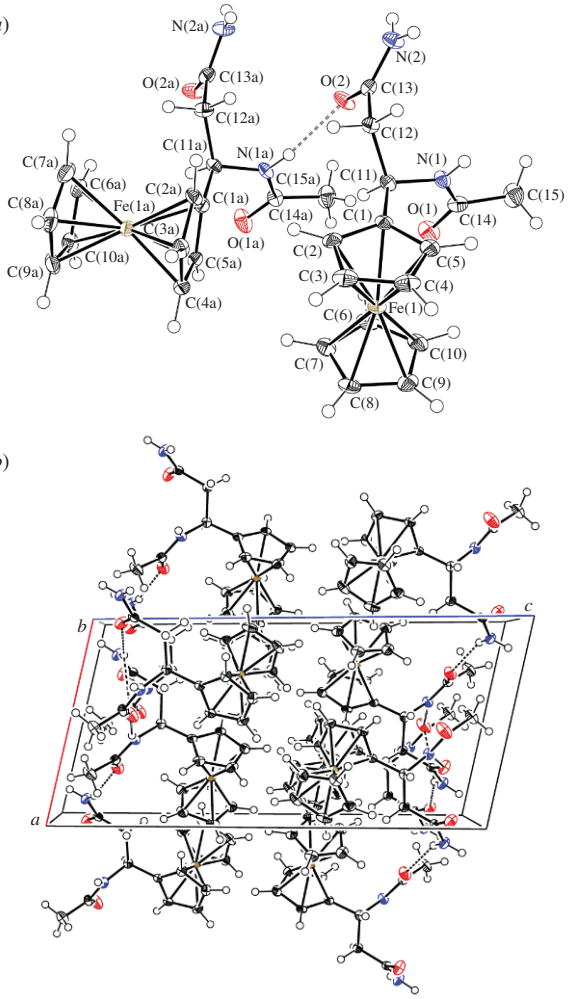
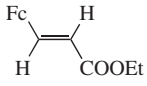


Figure 1 (*a*) Crystal structure and (*b*) crystal packing of compound **3a**. Selected bond lengths (Å) and angles (°): N(1)–C(11) 1.457(3), N(1a)–C(11a) 1.463(3), N(1)–C(14) 1.339(3), N(1a)–C(14a) 1.334(3), C(11)–C(12) 1.539(3), C(11a)–C(12a) 1.523(3), C(12)–O(2) 1.233(3), C(13a)–C(12a) 1.507(3), N(2)–C(13) 1.333(3), N(2a)–C(13a) 1.324(3), O(2)–H(1a) 2.03(2), O(1)–C(14) 1.230(3); O(1)–C(14)–N(1) 123.3(2), N(1)–C(11)–C(12) 108.7(2), C(12)–C(13)–N(2) 117.3(2), N(2)–C(13)–O(2) 122.5(2), N(1)–C(14)–C(15) 115.5(2), O(1)–C(14)–C(15) 121.2(2), C(1)–C(11)–N(1) 112.4(2), C(1a)–C(11a)–N(1a) 111.7(2), C(11a)–N(1a)–C(14a) 121.9(2), N(1a)–C(11a)–C(12a) 110.0(2), H(1a)–N(1a)–C(14a) 119(2), N(2a)-C(13a)-O(2a) 122.9(3).

One possible mechanism of formation of 3-amido-3-ferrocenylpropionamides **3a–e** is a fragmentation of the initial diethyl ferrocenylmethylidenemalonate **1** into ethyl 3-ferrocenylacrylate **4**, which upon cyclocondensation with amidines **2a–e** yields products **3a–e**. To verify this, the treatment of ethyl 3-ferrocenylacrylate **4** with amidines **2a–e** under similar conditions (EtOH/H_2O, Na_2CO_3, 80–82 °C) was performed. However, acrylate **4** did not undergo the cyclocondensation with amidines **2a–e** and remained unchanged even upon boiling of the reaction mixture for 24 h.



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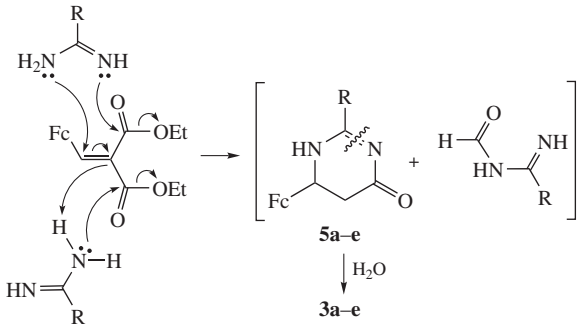
Based on these results, one may assume that compounds **3a–e** are formed in the three-component reaction with a simultaneous nucleophilic attack of two amidine **2** molecules on one molecule of diethyl(ferrocenylmethylidene)malonate **1** (Scheme 2).



Scheme 2

In conclusion, the one-step synthesis of the derivatives of 3-amido-3-ferrocenylpropionic acid based on the reaction of diethyl 2-(ferrocenylmethylidene)malonate with guanidines, amidines or *O*-methylisourea is described for the first time. This protocol provides a new and simple method for the preparation of 3-amino-3-ferrocenyl(or aryl)propionic acid derivatives which seem promising for the synthesis of new pharmacologically active substances.[7,11]

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3-(N′,N′-Dimethylureido)-3-ferrocenylpropionamide **3d**. Yield 0.79–0.91 g (44–53%), yellow crystals, mp 182–183 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.46 (dd, 1H, CH_2, *J* 12.3 and 15.6 Hz), 2.72 (dd, 1H, CH_2, *J* 4.5 and 15.6 Hz), 3.10 (s, 6H, 2Me), 4.20 (s, 5H, C_5H_5), 4.17 (m, 1H, C_5H_4), 4.22 (m, 1H, C_5H_4), 4.25 (m, 2H, C_5H_4), 4.34 (dd, 1H, CH, *J* 4.5 and 12.3 Hz), 4.89 (br. s, 2H, NH_2), 6.20 (br. s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.03 (2Me), 38.14 (CH_2), 56.18 (CH), 69.21 (C_5H_5), 68.78, 69.54 (C_5H_4), 80.83 (C_{ipso}Fc), 159.85, 164.38 (2C=O). MS, *m*/*z*: 343 $[M]^+$. Found (%): C, 56.07; H, 6.08; Fe, 16.38; N, 12.13. Calc. for $C_{16}H_{12}FeN_3O_2$ (%): C, 55.99; H, 6.17; Fe, 16.27; N, 12.24.

3-Ferrocenyl-3-(methoxycarbonylamino)propionamide **3e**. Yield 0.77–0.84 g (47–51%), yellow crystals, mp 179–181 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.63 (dd, 1H, CH_2, *J* 6.6 and 12.9 Hz), 2.85 (dd, 1H, CH_2, *J* 4.2 and 12.9 Hz), 3.61 (s, 3H, Me), 4.18 (s, 5H, C_5H_5), 4.28 (m, 2H, C_5H_4), 4.34 (m, 2H, C_5H_4), 4.53 (dd, 1H, CH, *J* 4.2 and 6.6 Hz), 6.06 (br. s, 2H, NH_2), 8.04 (br. s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 35.46 (Me), 40.24 (CH_2), 53.21 (CH), 69.84 (C_5H_5), 69.56, 70.12 (C_5H_4), 80.67 (C_{ipso}Fc), 162.43, 164.81 (2C=O). MS, *m*/*z*: 330 $[M]^+$. Found (%): C, 54.69; H, 5.34; Fe, 17.02; N, 8.32. Calc. for $C_{15}H_{18}FeN_2O_3$ (%): C, 54.57; H, 5.50; Fe, 16.91; N, 8.48.

‡ *Crystallographic data for* **3a**. Crystals of $C_{15}H_{18}FeN_2O_2$ (M = 314.16), are triclinic, space group $P\bar{1}$, at 130(2) K: a = 8.9053(5), b = 9.0583(5) and c = 18.5289(11) Å, α = 102.634(5)°, β = 102.425(5)°, γ = 91.273(4)°, V = 1420.55(14) Å^3, Z = 4, d_{calc} = 1.469 g cm^{-3}, λ(MoKα) = 0.71073 Å, F(000) = 1088, μ = 0.676 mm-1, index ranges $-14 \leqslant h \leqslant 14$, $-14 \leqslant k \leqslant 13$, $-22 \leqslant l \leqslant 21$, scan range $3.47 \leqslant \theta \leqslant 26.06°$, 5579 independent reflections, R_{int} = 0.0372, 10400 total reflections, 381 refinable parameters, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0382, wR_2 = 0.0788; R indices (all data): R_1 = 0.0654, wR_2 = 0.0855, goodness-of-fit on F^2 0.934, largest difference peak and hole 0.611/–0.385 eÅ^{-3}. The unit cell parameters and the X-ray diffraction intensities were recorded on a Gemini (detector Atlas CCD, Cryojet N_2) diffractometer. The structures of compound **3a** was solved by the direct method (SHELXS-97[13]) and refined using full-matrix least-squares on F^2.

CCDC 970624 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2014.

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