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One-pot three-component synthesis, structure and redox properties of ferrocenyl isoxazoles

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Dedicated to Professor Dr. Hans-Dieter Martin on the occasion of his 70th birthday

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ABSTRACT

A consecutive coupling-cycloaddition sequence of acid chlorides, terminal alkynes, and *in situ* generated nitrile oxides furnishes ferrocenyl substituted redox active isoxazoles in moderate to good yields. The structure was unambiguously assigned by X-ray structure analyses and the electronic structure was elucidated by computational methods. Redox potentials of all representatives are strongly effected by the electronic nature of the bridging isoxazoloyl moiety.

1. Introduction

Substituted isoxazoles have become an important motif in medicinal chemistry by virtue of their biological activity [1]. For instance, they have been found to be potent, selective agonists of human cloned dopamine D4 receptors [2], they exhibit $GABA_A$ antagonist [3], analgesic, antiinflammatory, ulcerogenic [4], COX-2 inhibitory [5], antinociceptive [6], and anticancer [7] activity. Therefore, many synthetic approaches have been reported for the formation of the isoxazole core, including reactions of hydroxylamine with 1,3-dicarbonyl compounds, α,β-unsaturated carbonyl compounds, and α,β-unsaturated nitriles [8]. In addition, [3 + 2] cycloadditions of alkynes and nitrile oxides represent an elegant and concise access to this class of compounds [9]. Although, these strategies are highly convergent, in many cases either strong bases or strong mineral acids are required, or prolonged heating at elevated temperatures is necessary. In addition, the observed regioselectivities of the heterocyclization are often poor. Metallocenes in their own right also exhibit a wide range of biological activity [10]. Among them, ferrocene has attracted special attention as a neutral, chemically stable and nontoxic unit in bioorganometallic entities [11]. It can be easily functionalized or oxidized to give stable ferricenium salts. Many ferrocenyl compounds display interesting antitumor, antimalarial, antifungal, anti-HIV and DNA-cleaving activity [12]. Therefore, the combination of isoxazole and ferrocene pharmacophores within the same molecule that also display interesting redox properties appears to be an attractive challenge for diversity-oriented synthesis in a one-pot fashion. As part of our program directed to design and develop new multi-component syntheses of heterocycles initiated by *Sonogashira* coupling [13], we have focused on coupling-cycloaddition sequences [14]. Here, we report a concise, consecutive three-component one-pot synthesis of 3,4,5-trisubstituted isoxazoles with ferrocenyl substituents, their structures and electronic properties.

2. Results and discussion

Sonogashira coupling [15] of acid chlorides with terminal alkynes represents a catalytic access to alkynones [16]. Just recently, we have established a modification, where 1 equiv. of triethylamine as the hydrochloric acid scavenging base proves to be most favorable for successful coupling under mild reaction conditions [17]. In turn, the resulting alkynones readily react with aromatic nitrile oxides as

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[1] X-ray structure analyses.

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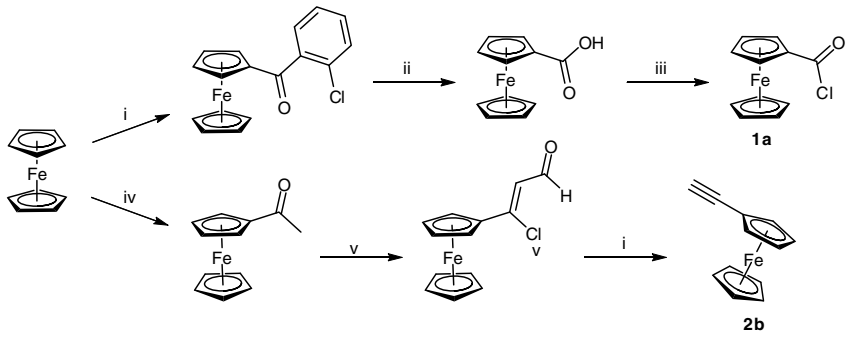


Scheme 1. Reagents and conditions: (i) $AlCl_3$, CH_2Cl_2, 0 °C, 2.5 h, 95%; (ii) KO^{t}Bu, DME, rfl., 1 h, 78%; (iii) $(COCl)_2$, CCl_4, rfl., 4 h, 98%; (iv) Ac_2O, H_3PO_4, 100 °C, 10 min, 66%; (v) $POCl_3$, DMF, NaOAc, 0 °C, 2 h, 77%; (vi) NaOH, dioxane, rfl., 5 min, 95%.

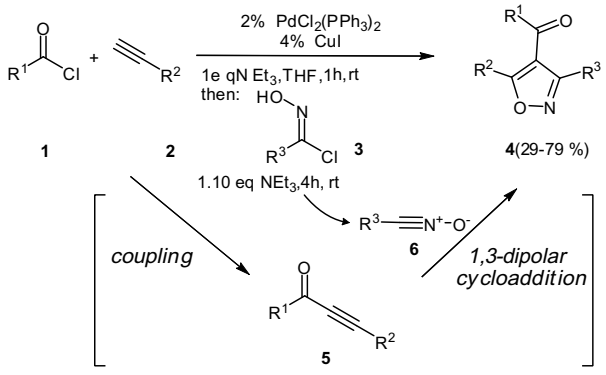
1,3-dipoles in a 1,3-dipolar cycloaddition to give isoxazoles in good to excellent yields [14]. Since aromatic nitrile oxides are usually unstable compounds, it is necessary to generate them *in situ* by dehydrochlorination of the corresponding hydroximinoyl chlorides with a suitable base. According to literature procedures these precursors are readily available from oximes by subsequent chlorination [18]. Interestingly, triethylamine as a base is sufficiently strong enough to achieve a mild generation of nitrile oxides that are prone to react with the present alkynones in a one-pot fashion.

Suitable ferrocene precursors, such as ferrocenyl acid chloride (**1a**) [19] and ethynylferrocene (**2a**) [20], are readily available from ferrocene in three steps (Scheme 1).

Therefore, upon reacting ferrocenoyl chloride (**1a**) or 2-thienoyl chloride **(1b)** and various terminal alkynes **2** under modified *Sonogashira* conditions for 1 h at room temperature, to furnish the expected alkynones **5**, the subsequent addition of hydroximinoyl chlorides **3** and triethylamine generating the nitrile oxides **6** gives rise to the formation of ferrocenyl substituted isoxazoles **4** in moderate to good yields as ruby red crystalline solids (Scheme 2, Table 1). Prolonged reaction times cause a slight decrease in yields in comparison with isoxazoles without organometallic substituents [14]. It is also noteworthy to mention that the cycloaddition step with ferrocenyl alkynones cannot be successfully performed under microwave heating.

In agreement with theory, the 1,3-dipolar cycloaddition under kinetic control [21] gives rise to the formation of **4** with excellent regioselectivity. Not even traces of the regioisomers **7** could be detected. The structures were unambiguously assigned by ^{1}H and ^{13}C NMR spectroscopy and later by X-ray structure analyses of the isoxazoles **4a**, **4c**, and **4d** (Figs. 1 and 2, Table 3) (see Supplementary material).

As a consequence of the substitution pattern, no peculiar resonances of the isoxazole core can be found in the proton NMR spectra. In each case, the ferrocene protons are relocated as a set of three signals consisting of a singlet (around δ = 4.10, 5H), and two triplets (around δ = 4.40 and 4.80, each 2H). The shifts of the carbon nuclei are readily assigned by 135-DEPT- and 2D NMR spectroscopy as well as by increment calculations. Carbon nuclei at ring position 5 appear in the carbon NMR spectra at δ 171, whereas the quaternary resonances at ring position 4 are detected at high field around δ 115 as a consequence of the polarization by the electron withdrawing effect of the adjacent carbonyl group. Finally, the imine type resonances at ring position 3 emerge at δ 160. The signals at δ 191 can be unambiguously assigned to the carbonyl carbon nuclei (Chart 1).



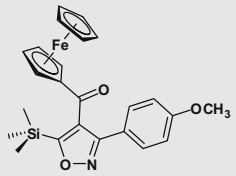
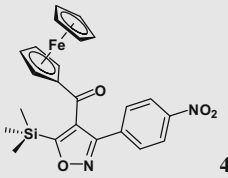
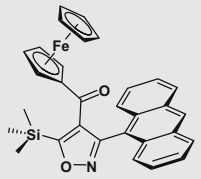
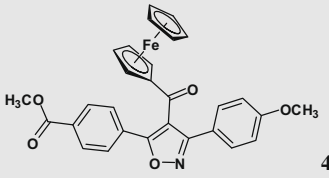
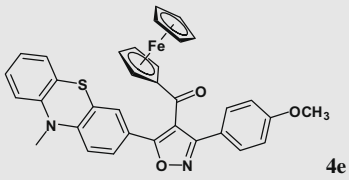
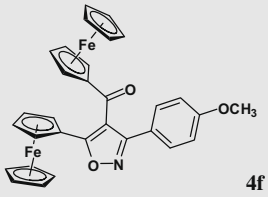
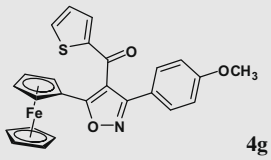
Scheme 2. One-pot three-component synthesis of isoxazoles **5** by a coupling-1,3-dipolar cycloaddition sequence.

Interestingly, compound **4c** crystallizes in two crystal modifications, where for one of the modifications two independent molecules are found in the unit cell (Fig. 1). Nevertheless, both crystal modifications support the same constitution as deduced from the spectroscopic data. Therefore, the different solid state structures arise from conformers and their packing in a crystal lattice. According to the X-ray structure analysis of compounds **4a**, **4c**, and **4d**, the ferrocenoyl moiety is distorted from coplanarity with respect to the isoxazole ring between 61° and 76°. However, the conformation of the ferrocene moiety in the crystal structures differs. For **4a** and **4d** the cyclopentadienyl rings are staggered (27.5° and 22.0°, resp.), while in the case of **4c** the two Cp rings are almost ecliptic (~2.5°). So the distortion of the Cp units is just a packing effect in the crystal.

The UV–Vis absorption spectra of the ferrocene derivatives **4** are characterized by the appearance of the weak absorption bands between 404 and 491 nm that can be assigned to ferrocenyl metal-to-ligand charge transfer bands. All ferrocenyl isoxazoles are fluorescence silent. The absence of fluorescence is even observed for the anthracene substituted derivative **4c**, although, anthracenes are known for their luminescent properties [22]. Here, the spatial proximity to the ferrocene moiety obviously opens an efficient channel for quenching of the fluorescence.

Electrochemical data for the ferrocene substituted isoxazoles **4** were obtained by cyclic voltammetry in dichloromethane solutions and were recorded in the anodic region (up to +1.4 V) showing distinct reversible oxidations stemming from the redox active ferrocenyl substituents (Table 2, Fig. 3). In all cases the first ferrocenyl centered oxidations are significantly shifted anodically by 85–308 mV in comparison to the parent compound ferrocene ($E^{0/+1}{}_{1/2}$ = 450 mV, in CH_2Cl_2). This can be plausibly rationalized by the electron withdrawing nature of the carbonyl functionality that renders the ferrocenyl part more difficult to oxidize. Isoxazole is by three orders of magnitude less basic than its constitutional isomer oxazole and, therefore, it can be considered to be a very weakly electron donating substituent [23]. Even a ferrocenyl substituent that is not directly bound to the carbonyl group, but to the isoxazole core as for compounds **4f** and **4g**, experiences a considerable anodic shift by conjugation of the carbonyl group through the π-system of the heterocycle (entries 7 and 8). In turn, the electron rich

Table 1
Coupling-1,3-dipolar cycloaddition synthesis of isoxazoles **4**.

Entry	Acid chloride **1**	Alkyne **2**	Hydroximinoyl chloride **3**	Isoxazole **4** (yield, %)[b]	Alkynone **5** (yield, %)
1	**1a**: R^1 = ferrocenyl	**2a**: $R^2 = Me_3Si$	**3a**: $R^3 = 4\text{-}MeOC_6H_4$	 **4a** (79)	**5a** (–)
2	**1a**	**2a**	**3b**: $R^3 = 4\text{-}O_2NC_6H_4$	 **4b** (29)	**5a** (33)
3	**1a**	**2a**	**3c**: R^3 = 10-anthranyl	 **4c** (62)	**5a** (–)
4	**1a**	**2b**: $R^2 = 4\text{-}MeO_2CC_6H_4$	**3a**	 **4d** (51)	**5b** (37)
5	**1a**	**2c**: R^2 = 10-methyl phenothiazin-3-yl	**3a**	 **4e** (51)	**5c** (24)
6	**1a**	**2d**: R^2 = ferrocenyl	**3a**	 **4f** (47)	**5d** (25)
7	**1b**: R^1 = 2-thienyl	**2d**	**3a**	 **4g** (53)	**5d** (41)

phenothiazinyl moiety in ring position 5 in compound **4e** is a remote donor to diminish the electron withdrawing power of the carbonyl group (entry 6). Hence, the oxidation of the ferrocenyl substituent is only shifted anodically by 85 mV vs. ferrocene.

In addition, isoxazoles **4e** and **4f** contain two redox active moieties, i.e. a 10-methyl phenothiazinyl (**4e**) and ferrocenyl substituent (**4f**) in close spatial proximity. Expectedly, two reversible oxidation waves can be found in the corresponding cyclic

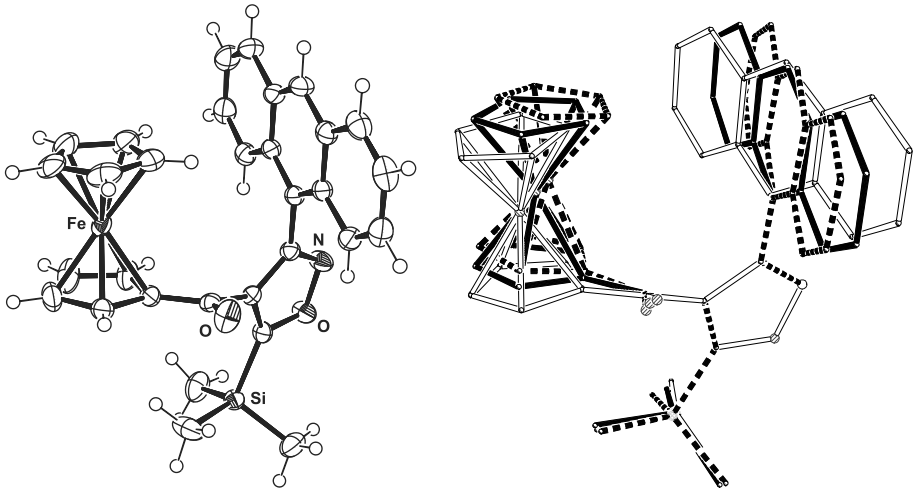


Fig. 1. ORTEP plot of isoxazole **4c** modification 1 (left); fit for structure **4c** as obtained from both crystal modifications (modification 1: dashed bonds; modification 2: black and hollow bonds; the fit was made by superimposition of the five atoms of the isoxazole core) where the modification 2 displays two independent molecules in the unit cell (right).

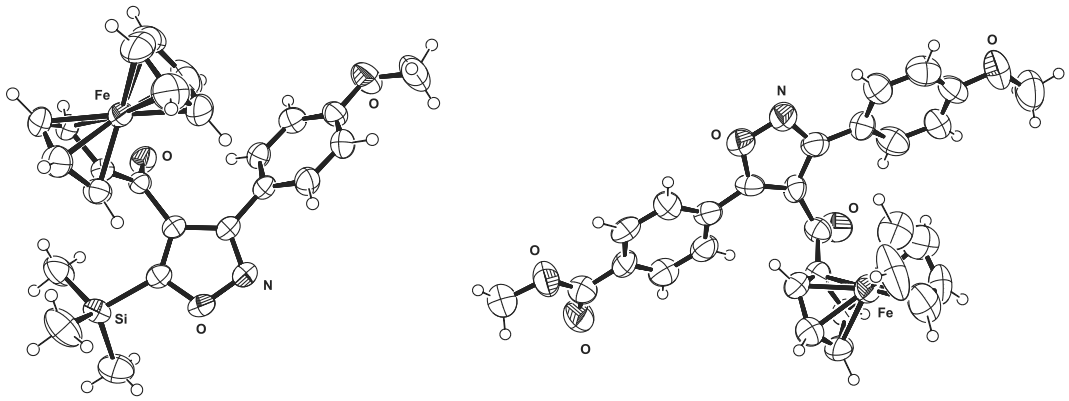
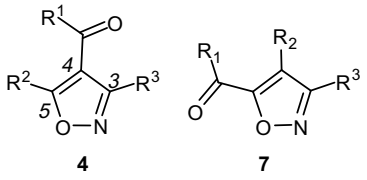


Fig. 2. ORTEP plots of isoxazoles **4a** (left) and **4d** (right, cocrystallized $CDCl_3$ was omitted for clarity).



4 **7**

Chart 1.

Table 2
Redox potentials of the isoxazoles **4** (recorded in CH_2Cl_2 at 20 °C, 0.1 M $^nBu_4NPF_6$, Pt as working electrode, Ag/AgCl as reference electrode, and Pt as counter electrode).

Entry	Isoxazole **4**	$E_{1/2}^{0/+1}$ (mV)	$E_{1/2}^{+1/+2}$ (mV)
1	Ferrocene	450	–
2	**4a**	698	–
3	**4b**	725	–
4	**4c**	758	–
5	**4d**	745	–
6	**4e**	535	764
7	**4f**	601	722
8	**4g**	749	–

voltammograms (entries 6 and 7, Fig. 3 right). In the case of the diferrocenyl substituted system **4f** the question lies at hand whether a through space interaction of the two inequivalent ferrocenyl units might influence their separate oxidation behavior.

Therefore, the electronic structure of the frontier orbitals was investigated by computational methods. Based upon a starting geometry from the X-ray structure analysis of **4a**, calculations were carried out using the B3LYP functional [24] and the 6-311 G++ SDD basis set for geometry optimization. As expected, the results clearly indicate, that the HOMO is localized on the ferrocenyl fragment (Fig. 4). The minimal energy difference to HOMO − 1 suggests that the highest occupied molecular orbitals are almost degenerate. HOMO − 2 is significantly lower in energy and it is predominantly localized on the anisyl isoxazole moiety, where as HOMO − 3 is represented by the ferrocenoyl part. The LUMO is delocalized over the isoxazole core and the ferrocenoyl substituent (Fig. 4).

Applying the same methodological protocol, the diferrocenyl substituted isoxazole **4f** was also computed. Pairwise, the highest occupied molecular orbitals indicate an energetic degeneracy of HOMO and HOMO − 1 on one hand and HOMO − 2 and HOMO − 3 on the other hand (Fig. 5). The energy gap between both pairs of orbitals is relatively small and indicate that the first one electron oxidations should display a relatively small separation. This is in good agreement with the recorded cyclovoltammetric data. Hence, the first oxidation should occur on the more electron rich ferrocene at ring position 5 of the isoxazole followed by the second oxidation

Table 3
X-ray structure data collection and refinement parameters for **4a**, **4c** (modifications 1 and 2), and **4d**.

	4a	**4c** (modification 1)	**4c** (modification 2)	**4d**
Empirical formula	$C_{24}H_{25}FeNO_3Si$	$C_{31}H_{27}FeNO_2Si$	$C_{31}H_{27}FeNO_2Si$	$C_{29}H_{23}FeNO_5 \cdot 0.5CDCl_3$
M (g/mol)	459.40	529.48	529.48	521.34
Temperature (K)	291(2)	200(2)	200(2)	291(2)
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Triclinic	Triclinic	Monoclinic
Space group	*Ia*	$P\bar{1}$	$P\bar{1}$	$P2_1/c$
Z	4	2	4	4
a (Å)	12.2582(16)	10.1838(2)	11.9488(8)	20.219(4)
b (Å)	9.3647(19)	10.8117(2)	12.7269(8)	5.9126(6)
c (Å)	19.761(3)	13.1426(1)	19.3795(12)	22.737(4)
α (°)	90	68.530(1)	91.982(2)	90
β (°)	103.379(16)	77.160(1)	105.845(2)	109.59(2)
γ (°)	90	76.880(1)	115.317(2)	90
Volume (Å^3)	2206.9(6)	1295.94(4)	2523.7(3)	2680.8(7)
D_{calc} (g/cm^3)	1.383	1.36	1.39	1.524
Absorption coefficient (mm^{-1})	0.763	0.66	0.68	0.789
Reflections collected	14127	13372	26771	11836
Observed reflections	3316 ($I > 2\sigma(I)$)	4892 ($I > 2\sigma(I)$)	8770 ($I > 2\sigma(I)$)	972 ($I > 2\sigma(I)$)
Independent reflections (R_{int})	3715 (0.0696)	5881 (0.0539)	12437 (0.0467)	4379 (0.1428)
Absorption correction	None	Semi-empirical from equivalents		None
Maximum and minimum transmission		0.89 and 0.83	0.95 and 0.88	
Refinement method	Full-matrix least-squares on F^2			
Data/restraints/parameters	3715/0/276	5881/0/328	12437/0/655	4379/0/349
Goodness-of-fit on F^2	1.00	1.03	1.10	0.88
Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.029$, $wR_2 = 0.067$	$R_1 = 0.037$, $wR_2 = 0.099$	$R_1 = 0.067$, $wR_2 = 0.130$	$R_1 = 0.044$, $wR_2 = 0.059$

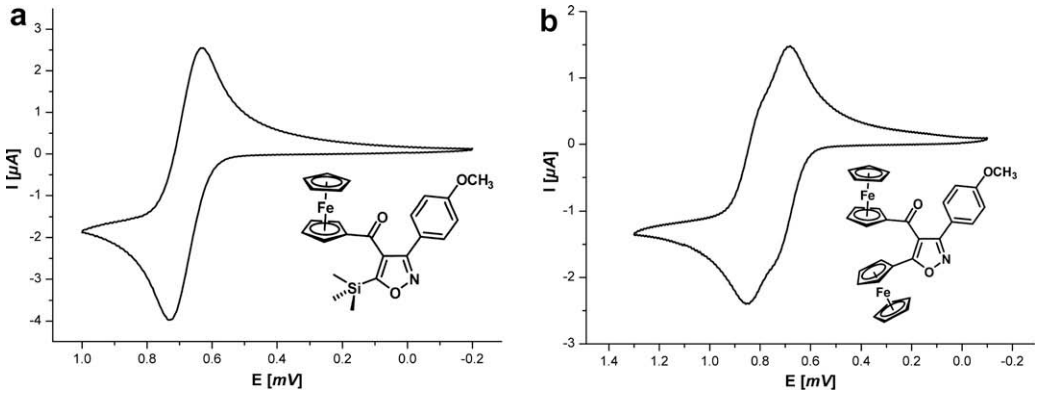


Fig. 3. Cyclic voltammograms of isoxazole **4a** (left) and **4f** (right) (recorded in dichloromethane at 20 °C, 0.1 m ^{n}Bu$_4$NPF$_6$, Pt as working electrode, Ag/AgCl as reference electrode, and Pt as counter electrode).

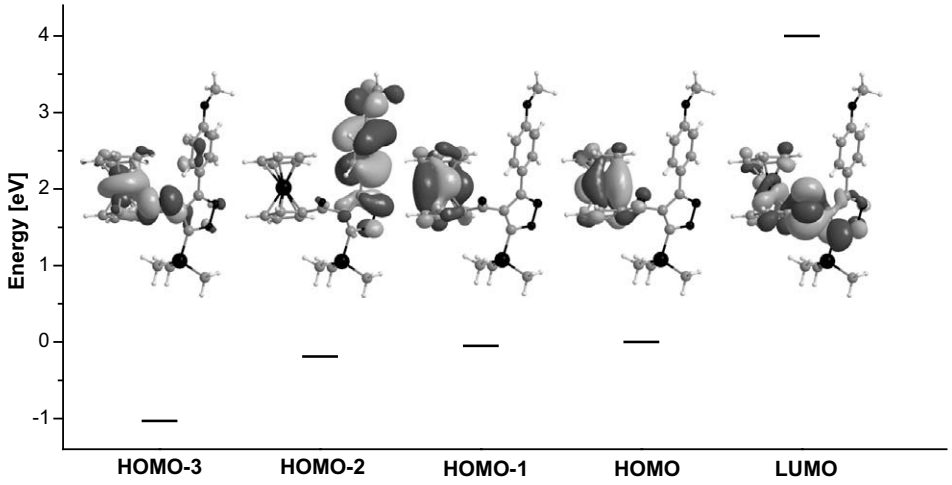


Fig. 4. DFT-computed frontier orbitals of the monoferrocenyl substituted isoxazole **4a**.

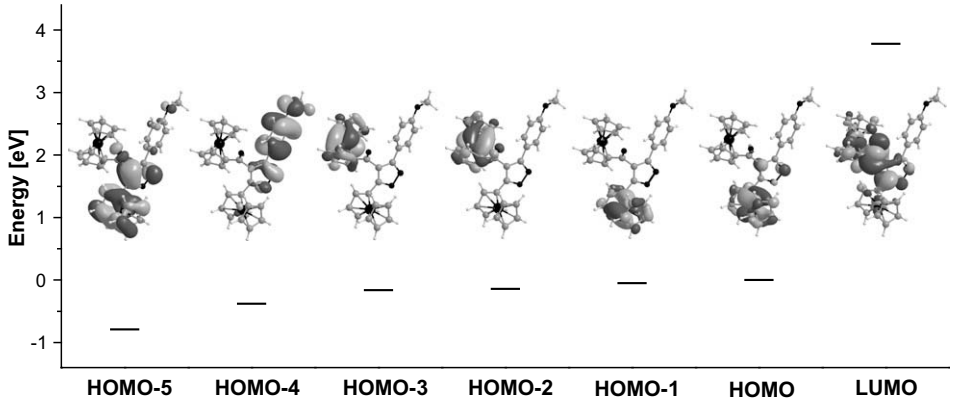


Fig. 5. DFT-calculated frontier orbitals of bisferrocenyl substituted isoxazole **4f**.

that is centered on the ferrocenoyl moiety. As computed for compound **4a** the LUMO of **4f** is delocalized over the isoxazole core and the ferrocenoyl substituent. Hence, the isoxazole carbonyl bridge does not support electronic communication of the ferrocenyl units, however, as a consequence of the substitution pattern and the electronic character of the isoxazole core the frontier orbital energies are relatively close.

3. Conclusion

In conclusion ferrocenyl substituted isoxazoles were prepared by a straightforward one-pot three-component synthesis in the sense of a consecutive coupling-cycloaddition sequence. The flexible synthetic strategy enables access to electronically diverse substituted ferrocenyl isoxazoles. As a consequence of the peculiar electronic nature of the central isoxazoloyl unit ferrocenyl substituents as redox active organometallic probes can be fine tuned by the substitution pattern on the isoxazoles. Furthermore, compounds like **4d** placing ether and ester masked phenol and acid moieties in ring position 3 and 5 can be considered as sections of polyesters with redox active sidechains. Further studies exploiting the synthetic potential of the three-component synthesis for addressing tailor-made molecular materials are currently underway.

4. Experimental

4.1. General information

All reactions involving water-sensitive compounds were carried out in flame-dried Schlenk glassware under nitrogen atmosphere unless stated otherwise. Reagents and catalysts were purchased reagent grade and used without further purification. Solvents were dried and distilled according to standard procedures. Aldoximes and corresponding hydroximinoyl chlorides **4** were synthesized according to literature procedures [18]. Flash column chromatography: silica gel 60, mesh 230–400, Merck. TLC: silica gel plates (60 F_{254} Merck, Darmstadt). ^{1}H-, ^{13}C-, DEPT-, NOESY-, COSY-, HMQC-, and HMBC spectra were recorded with Bruker ARX 250, Bruker DRX 300 or Bruker DRX 500 spectrometers by using $CDCl_3$ as solvent unless stated otherwise. The assignments of quaternary C, CH, CH_2 and CH_3 were made on the basis of DEPT spectra. Mass spectra were recorded with JEOL JMS-700 und Finnigan TSQ 700 spectrometers. The melting points (uncorrected) were measured with Stuart Scientific Melting Point Apparatus SMP3. Elemental analyses were carried out on a Perkin–Elmer CHN-Analyzer 2400 in the microanalytical laboratory of the Pharmazeutische Chemie of the Heinrich-Heine-Universität Düsseldorf. X-ray structures were measured with an Bruker Smart APEX or an Bruker Smart CCD.

4.2. General procedure for the one-pot three-component synthesis of isoxazoles *4*

In a 10 mL Schlenk tube $PdCl_2(PPh_3)_2$ (15 mg, 0.02 mmol) and CuI (8 mg, 0.04 mmol) were dissolved in degassed THF (5 mL). To this orange solution acid chloride **1** (1.00 mmol), alkyne **2** (1.00 mmol) and triethylamine (1.05 mmol) were added. The reaction mixture was stirred at room temp for 1 h. Finally, aryl hydroximinoyl chloride **3** (1.00 mmol) and triethylamine (1.1 mmol) were added to this suspension and the reaction mixture was stirred 4 h at room temp. The solvents were removed under reduced pressure and the residue was purified by silica gel flash column chromatography (hexane/ethyl acetate 50/1) to afford the analytically pure product **4** as a red solid and in some cases the alkynone **5** as a by product.

4.2.1. (3-(4-Methoxyphenyl)-5-(trimethylsilyl)-isoxazol-4-yl)-ferrocenylmethanone (*4a*)

According to the general procedure the reaction of 249 mg of acid chloride **1a**, 99 mg of alkyne **2a**, and 186 mg aryl hydroximinoyl chloride **3a** furnish 363 mg (79%) of **4a** as deep red crystals, mp. 147 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.28 (s, 9H), 3.79 (s, 3H), 3.92 (s, 5H), 4.46 (t, ^3J = 1.7 Hz, 2H), 4.60 (d, ^3J = 1.7 Hz, 2H), 6.93 (d, ^3J = 8.6 Hz, 2H), 7.71 (d, ^3J = 8.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −1.6 ($3CH_3$), 55.3 (CH_3), 69.7 (5CH), 71.0 (2CH), 72.6 (2CH), 81.4 (C_{quat}), 114.0 (2CH), 121.3 (C_{quat}), 128.6 (C_{quat}), 130.6 (2CH), 159.5 (C_{quat}), 160.9 (C_{quat}), 178.5 (C_{quat}), 195.3 (C_{quat}). EI MS (70 eV, *m/z* (%)): 459 ([M]$^+$, 13), 298 (18), 282 (42), 239 (18), 238 (100), 224 (10), 223 (52), 195 (19), 180 (10), 152 (19), 151 (10), 150 (11), 149 (80), 135 (35), 134 (12), 133 (12), 119 (15), 106 (13), 57 (13), 43 (14). IR (KBr): $\tilde{\nu}$ = 2957 cm^{-1} (w), 1638 (m), 1452 (m), 1376 (s), 1277 (s), 1176 (w), 1125 (m), 1073 (w), 1025 (m), 845 (s), 765 (w). UV–Vis (CH_2Cl_2): λ_{max} (ε) 240 (36500), 272 (22800), 358 (2200), 487 nm (1500). Anal. Calc. for $C_{24}H_{25}FeNO_3Si$ (459.4): C, 62.75; H, 5.49; N, 3.08. Found: C, 63.03; H, 5.37; N, 3.21%.

4.2.2. (3-(4-Nitrophenyl)-5-(trimethylsilyl)-isoxazol-4-yl)-ferrocenylmethanone (*4b*)

According to the general procedure the reaction of 249 mg of acid chloride **1a**, 99 mg of alkyne **2a**, and 201 mg aryl hydroximinoyl chloride **3b** furnish 138 mg (29%) of **4b** as a deep red solid, mp. 162 °C, and 103 mg (33%) of **5a**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.26 (s, 9H), 3.90 (s, 5H), 4.48 (t, ^3J = 1.6 Hz, 2H), 4.60 (d, ^3J = 1.6 Hz, 2H), 8.05 (d, ^3J = 9.0 Hz,

2H), 8.32 (d, ^3J = 9.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −0.8 ($3CH_3$), 68.5 (5CH), 70.2 (2CH), 72.3 (2CH), 82.4 (C_{quat}), 113.7 (C_{quat}), 124.4 (2CH), 126.2 (2CH), 135.1 (C_{quat}), 147.9 (C_{quat}), 159.2 (C_{quat}), 178.5 (C_{quat}), 193.9 (C_{quat}). EI MS (70 eV, *m/z* (%)): 474 ([M]$^+$, 22), 311 ([M+H]$^+$, 24), 310 ([M]$^+$, 100), 267 (21), 238 (53), 210 (10), 203 (16), 152 (12), 148 (25), 146 (13), 145 (11), 121 (13), 56 (10). IR (KBr): $\tilde{\nu}$ = 2959 cm^{-1} (m), 1639 (s), 1603 (w), 1570 (w), 1535 (s), 1458 (m), 1413 (w), 1347 (s), 1290 (s), 1126 (m), 1729 (s), 1073 (m), 1037 (w), 1014 (w), 918 (w), 854 (s), 832 (m), 743 (m), 729 (s), 708 (m), 683 (m), 539 (w). UV–Vis (CH_2Cl_2): λ_{max} (ε) 276 (22000), 355 (1200), 477 nm (400). Anal. Calc. for $C_{24}H_{25}FeNO_3Si$ (474.4): C, 58.24; H, 4.67; N, 5.91. Found: C, 58.32; H, 4.79; N, 5.83%.

4.2.3. (3-(9-Anthranyl)-5-(trimethylsilyl)-isoxazol-4-yl)-ferrocenylmethanone (**4c**)

According to the general procedure the reaction of 249 mg of acid chloride **1a**, 99 mg of alkyne **2a**, and 256 mg aryl hydroximinoyl chloride **3c** furnish 329 mg (62%) of **4c** as a deep red solid, mp. 138 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ −0.31 (s, 9H), 4.36 (s, 5H), 4.79 (m, 2H), 5.40 (m, 2H), 7.57–7.62 (m, 4H), 7.70–7.74 (m, 2H), 8.42–8.44 (m, 2H), 8.68 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −1.5 ($3CH_3$), 70.5 (5CH), 71.4 (2CH), 73.9 (2CH), 81.2 (C_{quat}), 105.5 (C_{quat}), 125.3 (2CH), 126.4 (2CH), 129.0 (4CH), 130.6 (CH), 132.8 (2 C_{quat}), 133.3 (C_{quat}), 134.1 (2C_{quat}), 157.1 (C_{quat}), 165.2 (C_{quat}), 194.2 (C_{quat}). EI MS (70 eV, *m/z* (%)): 531 ([$^{13}C_2$−M]$^+$, 11), 530 ([^{13}C−M]$^+$, 38), 529 ([M]$^+$, 100), 502 (12), 501 (36), 326 (33), 298 (13), 291 (11), 290 (15), 204 (18), 203 (94), 202 (14), 201 (12), 195 (43), 185 (14), 177 (13), 176 (21), 145 (11), 129 (18), 121 (18), 73 (25). IR (KBr): $\tilde{\nu}$ = 3049 cm^{-1} (m), 2960 (m), 1677 (m), 1636 (s), 1542 (m), 1443 (s), 1410 (w), 1375 (m), 1331 (w), 1257 (s), 1106 (m), 1036 (m), 897 (m), 845 (s), 781 (m), 759 (m), 732 (s), 693 (m), 638 (m), 611 (m), 582 (w), 550 (w). UV–Vis (CH_2Cl_2): λ_{max} (ε) 250 (26700), 257 (43600), 334 (11400), 349 (18600), 366 (29000), 386 (28000), 404 nm (14300). Anal. Calc. for $C_{31}H_{27}FeNO_2Si$ (529.5): C, 70.32; H, 5.14; N, 2.65. Found: C, 70.31; H, 5.20; N, 2.88%.

4.2.4. Methyl 4-(4-ferrocenoyl-3-(4-methoxyphenyl)isoxazol-5-yl)-benzoate (**4d**)

According to the general procedure the reaction of 249 mg of acid chloride **1a**, 161 mg of alkyne **2b**, and 186 mg aryl hydroximinoyl chloride **3a** furnish 267 mg (51%) of **4d** as a deep red solid, mp. 164 °C, and 138 mg (37%) of **5b**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.79 (m, 8H), 3.90 (s, 3H), 4.38 (s, 2H), 4.49 (s, 2H), 6.92 (d, ^3J = 8.4 Hz, 2H), 7.75 (d, ^3J = 8.3 Hz, 2H), 7.94 (d, ^3J = 8.0 Hz, 2H), 8.09 (d, ^3J = 8.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 52.3 (CH_3), 55.2 (CH_3), 69.6 (5CH), 70.7 (2CH), 73.2 (2CH), 79.6 (C_{quat}), 114.2 (2CH), 116.8 (C_{quat}), 120.7 (C_{quat}), 127.8 (2CH), 130.0 (2CH), 130.1 (2CH), 131.0 (C_{quat}), 131.9 (C_{quat}), 161.1 (C_{quat}), 161.5 (C_{quat}), 166.1 (C_{quat}), 166.6 (C_{quat}), 194.3 (C_{quat}). EI MS (70 eV, *m/z* (%)): 522 ([M+H]$^+$, 33), 521 ([M]$^+$, 100), 520 (20), 457 (10), 456 (36), 163 (19), 141 (10), 135 (18), 133 (11), 121 (18). IR (KBr): $\tilde{\nu}$ = 2959 cm^{-1} (m), 1729 (s), 1634 (m), 1527 (w), 1455 (m), 1278 (s), 1180 (w), 1123 (m), 1073 (m), 1026 (w), 840 (m), 774 (m), 743 (m), 696 (w), 604 (w), 583 (w), 524 (w). UV–Vis (CH_2Cl_2): λ_{max} (ε) 276 (34600), 353 (1200), 491 nm (900). Anal. Calc. for $C_{29}H_{23}FeNO_5$ (521.3): C, 66.81; H, 4.45; N, 2.69. Found: C, 66.59; H, 4.17; N, 2.76%.

4.2.5. (3-(4-Methoxyphenyl)-5-(10-methyl-10H-phenothiazinyl)-isoxazol-4-yl)ferrocenylmethan-one (**4e**)

According to the general procedure the reaction of 249 mg of acid chloride **1a**, 238 mg of alkyne **2c**, and 186 mg aryl hydroximinoyl chloride **3a** furnish 306 mg (51%) of **4e** as deep red crystals, mp. 121 °C, and 108 mg (24%) of **5c**.

^{1}H NMR (500 MHz, acetone-d_6): δ 3.42 (s, 3H), 3.77 (s, 3H), 4.29 (s, 5H), 4.66 (t, ^3J = 1.7 Hz, 2H), 4.99 (d, ^3J = 1.7 Hz, 2H), 6.82 (d, ^3J = 8.6 Hz, 2H), 6.95–7.02 (m, 3H), 7.15 (dd, ^3J = 7.6 Hz, ^3J = 1.2 Hz, 1H), 7.23 (t, ^3J = 7.7 Hz, 1H), 7.44 (d, ^3J = 8.6 Hz, 2H), 7.46 (d, ^3J = 1.7 Hz, 1H), 7.56 (dd, ^3J = 8.4 Hz, ^3J = 1.7 Hz, 1H). ^{13}C NMR (125 MHz, acetone-d_6): δ 37.0 (CH_3), 55.8 (CH_3), 72.1 (2CH), 72.2 (5CH), 74.9 (2CH), 83.0 (C_{quat}), 114.1 (2CH), 115.7 (C_{quat}), 116.3 (C_{quat}), 116.4 (CH), 116.8 (CH), 119.9 (C_{quat}), 123.9 (C_{quat}), 125.1 (CH), 125.4 (C_{quat}), 128.8 (CH), 129.8 (CH), 129.9 (2 CH), 132.5 (CH), 134.8 (CH), 146.6 (C_{quat}), 149.8 (C_{quat}), 160.0 (C_{quat}), 160.6 (C_{quat}), 168.1 (C_{quat}), 181.5 (C_{quat}). EI MS (70 eV, *m/z* (%)): 599 ([M+H]$^+$, 17), 598 ([M]$^+$, 42), 450 (30), 449 (100), 358 (14), 357 (58), 343 (13), 342 (53), 286 (22), 285 (10), 241 (30), 226 (19), 225 (21), 217 (15), 213 (10), 149 (12), 134 (18). IR (KBr): $\tilde{\nu}$ = 2963 cm^{-1} (m), 2183 (m), 1775 (w), 1686 (m), 1655 (m), 1618 (s), 1572 (m), 1544 (m), 1499 (m), 1451 (s), 1375 (w), 1334 (m), 1261 (s), 1104 (s), 1072 (s), 1024 (s), 871 (m), 803 (s), 748 (m), 699 (m), 673 (m), 606 (m), 578 (m). UV–Vis (CH_2Cl_2): λ_{max} (ε) 274 (31600), 322 (10900), 483 nm (900). Anal. Calc. for $C_{31}H_{25}Fe_2NO_2$ (598.6): C, 68.23; H, 4.38; N, 4.68. Found: C, 68.15; H, 4.56; N, 4.61%.

4.2.6. (3-(4-Methoxyphenyl)-5-(ferrocenyl)-isoxazol-4-yl)-ferrocenylmethanone (**4f**)

According to the general procedure the reaction of 249 mg of acid chloride **1a**, 211 mg of alkyne **2d**, and 186 mg aryl hydroximinoyl chloride **3a** furnish 292 mg (47%) of **4f** as a deep red solid, mp. 188 °C, and 106 mg (25%) of **5d**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.79 (s, 3H), 3.88 (s, 5H), 4.22 (s, 5H), 4.39 (m, 4H), 4.54 (m, 2H), 4.83 (m, 2H), 6.90 (d, ^3J = 8.6 Hz, 2H), 7.71 (d, ^3J = 8.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.2 (CH_3), 68.4 (2CH), 69.7 (5CH), 70.0 (5CH), 70.1 (C_{quat}), 70.4 (2CH), 70.8 (2CH), 72.7 (2CH), 80.0 (C_{quat}), 114.0 (2CH), 121.2 (2C_{quat}), 130.1 (2CH), 160.84 (C_{quat}), 160.87 (C_{quat}), 170.6 (C_{quat}), 194.2 (C_{quat}). EI MS (70 eV, *m/z* (%)): 572 ([M+H]$^+$, 34), 571 ([M]$^+$, 100), 569 (14), 506 (23), 505 (15), 386 (22), 317 (12), 286 (14), 238 (19), 223 (10), 186 (15), 185 (10), 129 (12), 121 (26), 43 (10). IR (KBr): $\tilde{\nu}$ = 2974 cm^{-1} (m), 1590 (w), 1520 (w), 1446 (w), 1262 (s), 1179 (w), 1084 (m), 1049 (s), 880 (m), 832 (m), 592 (w), 552 (w). UV–Vis (CH_2Cl_2): λ_{max} (ε) 251 (31600), 283 (19300), 364 (2100), 475 nm (1200). Anal. Calc. for $C_{31}H_{25}Fe_2NO_2$ (571.2): C, 65.18; H, 4.41; N, 2.45. Found: C, 65.41; H, 4.29; N, 2.39%.

4.2.7. (3-(4-Methoxyphenyl)-5-ferrocenyl-isoxazol-4-yl)(thiophen-2-yl)methanone (**4g**)

According to the general procedure the reaction of 147 mg of acid chloride **1b**, 211 mg of alkyne **2d**, and 186 mg aryl hydroximinoyl chloride **3a** furnish 287 mg (53%) of **4g** as a deep red solid, mp. 153 °C, and 142 mg (41%) of **5d**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (s, 3H), 4.11 (s, 5H), 4.38 (t, ^3J = 1.9 Hz, 2H), 4.76 (t, ^3J = 1.9 Hz, 2H), 6.84 (d, ^3J = 8.9 Hz, 2H), 6.91–6.95 (m, 2H), 7.38 (dd, ^3J = 3.8 Hz, ^3J = 1.1 Hz, 1H), 7.43–7.48 (m, 1H), 7.55 (d, ^3J = 8.9 Hz, 2H), 7.63 (dd, ^3J = 4.9 Hz, ^3J = 1.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.1 (CH_3), 55.3 (CH_3), 68.1 (CH), 69.3 (C_{quat}), 69.9 (CH, 5C), 70.5 (CH), 112.0 (C_{quat}), 114.1 (CH), 114.3 (CH), 114.8 (C_{quat}), 118.9 (C_{quat}), 120.5 (C_{quat}), 128.3 (CH), 129.4 (CH), 129.6 (CH), 130.1 (CH), 135.3 (CH), 135.5 (CH), 144.4 (C_{quat}), 155.8 (C_{quat}), 160.7 (C_{quat}), 160.8 (C_{quat}), 160.9 (C_{quat}), 161.5 (C_{quat}), 171.6 (C_{quat}), 182.6 (C_{quat}). EI MS (70 eV, *m/z* (%)): 469 ([M]$^+$, 100), 467 (15), 404 (61), 385 (13), 320 (7), 316 (11), 312 (38), 235 (16), 216 (10), 139 (14), 111 (10). IR (KBr): $\tilde{\nu}$ = 3110 cm^{-1} (w), 1598 (s), 1513 (m), 1456 (w), 1404 (s), 1353 (m), 1300 (s), 1228 (s), 1105 (w), 1079 (w), 1059 (w), 1040 (m), 1002 (m), 970 (s), 896 (w), 855 (s), 821 (s), 743 (s), 723 (s), 649 (w), 630 (w), 548 (w), 519 (m),

501 (s). UV–Vis (CH_2Cl_2): λ_{max} (ε) 269 (35600), 322 nm (51700), 388 nm (6700), 486 nm (6100). HRMS: calcd. for $C_{26}H_{21}NO_2S$: 469.0435. Found: 469.0428. Anal. Calc. for $C_{25}H_{19}FeNO_3S$ (469.4): C, 63.98; H, 4.08; N, 2.98. Found: C, 63.73; H, 4.00; N, 2.99%.

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Appendix A. Supplementary material

CCDC 698830, 699931, 699932, and 698831 contain the supplementary crystallographic data for (**4a**), (**4c** Modifikation 1), (**4c** Modifikation 2), and (**4d**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2008.10.050.

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