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Short Note

Ferrocenyl-*bis*-(1-(4-benzyl-5-morpholinooxazol-2-yl)-*N*-(4-(trifluoromethyl)benzyl)methanamine)

Roberto E. Blanco-Carapia, Enrique A. Aguilar-Rangel, Alejandro Islas-Jácome * and Eduardo González-Zamora *

Departamento de Química, Universidad Autónoma Metropolitana-Iztapalapa, Av. Ferrocarril San Rafael Atlixco 186, Col. Leyes de Reforma 1A Sección, Iztapalapa, Ciudad de Mexico C.P. 09310, Mexico
* Correspondence: aij@xanum.uam.mx (A.I.-J.); egz@xanum.uam.mx (E.G.-Z.)

Abstract: The new *bis*-heterocyclic compound ferrocenyl-*bis*-(1-(4-benzyl-5-morpholinooxazol-2-yl)-*N*-(4-(trifluoromethyl)benzyl)methanamine) (**1**) was synthesized in 73% overall yield in 1.5 hours via a pseudo-repetitive Ugi-Zhu five-component reaction, starting from 1,1′-ferrocenedicarboxaldehyde, 4-(trifluoromethyl)benzylamine, and 2-isocyano-1-morpholino-3-phenylpropan-1-one, in 1:2.1:2.2 proportions, respectively, using scandium(III) triflate as a Lewis-acid catalyst, microwaves as a heat source, and toluene as a solvent. The synthesized compound was characterized by 1D (^{1}H, ^{13}C, and ^{19}F) and 2D (COSY, HSQC, and HMBC) NMR, HRMS, and FT-IR.

Keywords: pseudo-repetitive multicomponent reactions; Ugi-Zhu reaction; MW-assisted reactions; ferrocene; 1,3-Oxazole; hybrid compounds

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1. Introduction

Ferrocene, one of the main sandwich-type metallocenes (η^5-$C_5H_5)_2$M(II), is constituted by a couple of cyclopentadienyl anions (Cp) coordinated to a central iron(II) atom [1] (Figure 1A). This 18e$^-$ organometallic complex Fe(Cp)$_2$ is the structural core of many molecules exhibiting a broad variety of interesting biological properties [2], mainly antimalarial agents [3], for instance, ferroquine [4] (Figure 1B). Additionally, the 1,3-oxazole is a five-membered heteroaromatic compound (Figure 1C), also present in a plethora of bioactive compounds and to date in-use drugs [5], but more interestingly, also in antimalarial agents [6], such as the compound shown in Figure 1D. In this context, it can be hypothesized that new compounds containing both pharmacophoric moieties (ferrocene and oxazole) may be tandem-hybrid molecules [7] with potential to be antimalarial therapeutics, as was recently mentioned by Aderibigbe and co-workers [8]. Moreover, it has been documented that the addition of fluorine atoms into bioactive compounds commonly enhance their pharmacokinetic profiles [9].

Multicomponent reactions (MCRs) are high convergent one-pot processes [10] involving sequential additions of three or more reactants that allow assembling complex polyheterocyclic compounds [11] eventually, with high chemical yields, remarkable atom economy, and with wide substrate scope, while saving the highest valued resources in organic synthesis (time and energy). MCRs are divided into two major groups, those involving the use of isocyanides as reagents (I-MCRs), and those that do not (NI-MCRs). The first ones have been considerably more explored than NI-MCRs. Thus, the Ugi four-component reaction (Ugi-4CR) is an I-MCR that makes use of carbonylic reagents (aldehydes or ketones), amines (1° or 2°) or ammonia, carboxylic acids or their surrogates, and isocyanides, toward the synthesis of almost all kinds of peptide-like compounds, for instance, open chain peptides, polyheterocyclic peptides, macrocyclic peptides, depsipeptides, peptoids, and peptidomimetics [12]. However, there are some variants of the Ugi-4CR, one of them avoiding the use of carboxylic acids as reagents (Ugi-3CR), which in turn has many subvariants, for instance, one that involves the use of aminoacid-derived isocyanides, to know,

the recently named Ugi-Zhu-three component reaction (Ugi-Zhu-3CR) [13]. Thus, herein, we described the synthesis of a ferrocene-based compound containing a couple of 1,3-oxazole motifs, and a couple of *p*-trifluoromethylphenyls via a Lewis-acid catalyzed and MW-assisted double Ugi-Zhu-3CR, which in turn may be considered as a pseudo repetitive Ugi-Zhu-five component reaction (pseudo-Ugi-Zhu-5CR) because amine and isocyanide reagents were both added in a stoichiometric ratio near 2:1 with respect to the aldehyde component, as will be discussed. It is important to note that pseudo-repetitive MCRs are almost unexplored, especially pseudo-repetitive Ugi-Zhu-5CRs; indeed there are only two reports to date [14,15].

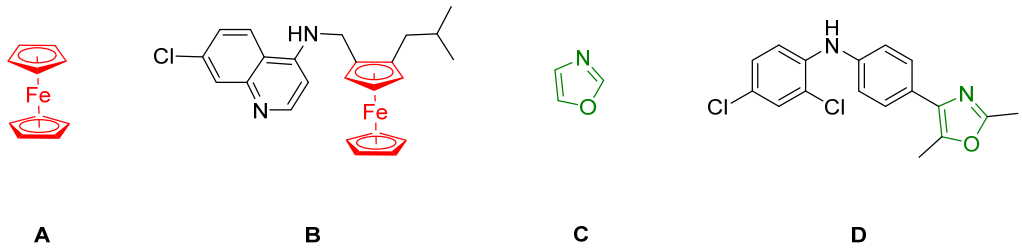


Figure 1. (**A**) Ferrocene, (**B**) Ferroquine, (**C**) 1,3-Oxazole, and (**D**) antimalarial agent.

2. Results and Discussion

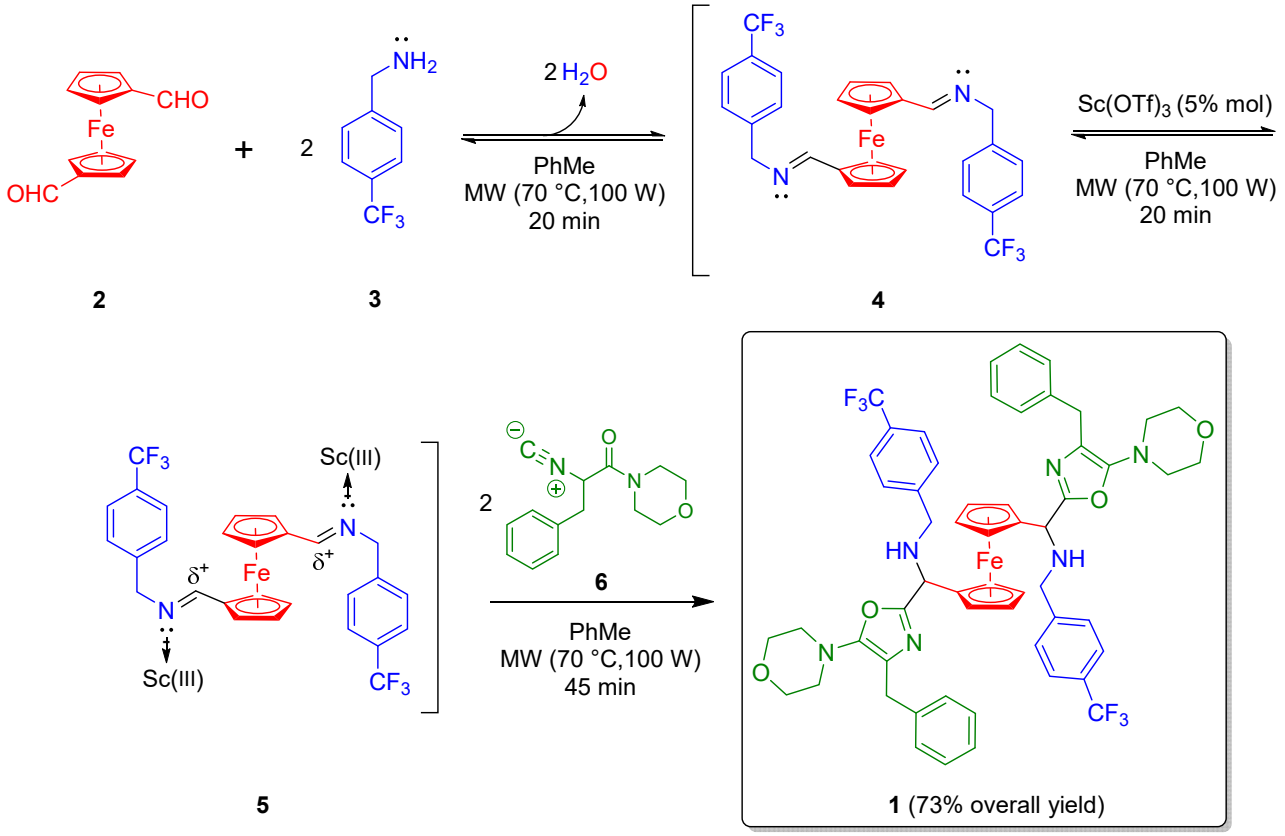
Ugi-Zhu reactions are carried out in three sequential steps, independently if they are three-component reactions (Ugi-Zhu-3CR), or pseudo-repetitive Ugi-Zhu-5CRs, and without losing their one pot nature. The first step is a reversible condensation between carbonylic components and amines to give the corresponding imines. The second one is an acid-catalyzed activation of the imines to form iminium cations (Bronsted- or Lewis-type iminium cations). Finally, the last step is an irreversible nucleophilic addition of isocyanides to the α-position of iminium cations, followed by a non-prototropic chain-ring tautomerization to assemble the 5-aminooxazole moiety.

Thus, with the aim of finding the optimal reaction conditions, parameters like solvent, catalyst, temperature, and stoichiometric ratios of reagents were screened. For synthesizing the ferrocenyl-*bis*-(1-(4-benzyl-5-morpholinooxazol-2-yl)-*N*-(4-(trifluoromethyl)benzyl) methanamine) **1** from 1,1′-ferrocenedicarboxaldehyde (**2**), 4-(trifluoromethyl)benzylamine (**3**), and the 2-isocyano-1-morpholino-3-phenylpropan-1-one (**4**), the first attempt was performed considering the classical Ugi-Zhu-3CR conditions [16], which were using methanol as a solvent, without additives, and at room temperature (Entry 1, Table 1). However, the reaction did not proceed, probably due to the low solubility of the ferrocene-containing dialdehyde **2** at such temperature. Then, just the reaction temperature was increased to 50 °C, using MW (100 W) as a heat source with the intention to solubilize better **2** and to accelerate the reaction, however, the desired compound **1** was observed only at trace level (Entry 2, Table 1). For this reason, we added scandium(III) triflate as a Lewis-acid catalyst, but the reaction profile was retained, leading to detection of the product at trace level again (Entry 3, Table 1). Then, the less polar solvent toluene was used instead of methanol because we found some time ago that the optimal reaction parameters for the synthesis of pyrrolo[3,4-*b*]pyridine-5-ones via an Ugi-Zhu-3CR were using toluene as a solvent, scandium(III) triflate as a Lewis acid catalyst, and MW as a heat source [17], yielding 25% this time (Entry 4, Table 1). Then, we performed further experiments increasing reaction temperatures in each step of the one pot process (Entries 5–7, Table 1). However, decomposition was observed at temperatures over 70 °C (Entry 7, Table 1). Thus, the best yield (73%) was reached at 70 °C (Entry 6, Table 1). We also tried varying the stoichiometric ratio, for instance, one of them 1:2.5:2.5 for dialdehyde, amines, and isocyanides, respectively, but many by-products were detected by TLC (Entry 8, Table 1). The synthetic methodology is depicted in the Scheme 1.

Table 1. Synthesis of the product **1.**

Entry	Solvent	Catalyst (5% mol)	Temperature (°C)	Yield [a] (%)
1	MeOH	-	rt	Nd
2	MeOH	-	50	Traces
3	MeOH	$Sc(OTf)_3$	50	Traces
4	PhMe	$Sc(OTf)_3$	50	25
5	PhMe	$Sc(OTf)_3$	60	49
6 [b]	PhMe	$Sc(OTf)_3$	70	73
7	PhMe	$Sc(OTf)_3$	85	Nd
8	PhMe	$Sc(OTf)_3$	70	Nd

[a] Calculated after purification by preparative TLC. [b] Optimal reaction conditions. Nd = Not determined.



Scheme 1. Synthesis of the symmetrical molecule 1 via a pseudo repetitive Ugi-Zhu-5CR.

3. Materials and Methods

3.1. General Information, Instrumentation, Software, and Chemicals

^{1}H, ^{13}C, and ^{19}F Nuclear Magnetic Resonance (NMR) spectra were acquired on a Bruker AMX Advance III spectrometer (500 MHz, Fällande, Uster, Switzerland). The solvent used for NMR experiments was deuterated chloroform ($CDCl_3$). Chemical shifts are reported in parts per million (δ/ppm). Coupling constants are reported in Hertz (J/Hz). Internal reference for NMR spectra was tetramethyl silane (TMS) at 0.00 ppm. Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). NMR spectra were analyzed using the MestReNova software Ver. 12.0.0-20080 (A Coruña, Spain). The infrared (IR) spectrum was acquired on a Perkin-Elmer 2000 spectrometer (Norwalk, CT, USA) using the Attenuated Total Reflectance (ATR) method. The maximum absorbance peaks are reported in reciprocal centimeters (ν_{max}/cm^{-1}), uncorrected. The IR spectrum was analyzed using the Origin software (Ver. 2018b, 9.55). The high-resolution mass spectroscopy (HRMS) spectrum was acquired by Electrospray Ionization (ESI) on a Micro-TOF II spectrometer Bruker

Daltonics GmbH (Bremen, Germany). The sample was injected directly (Apollo source) and analyzed by the time-of-flight method (TOF). The HRMS spectrum was analyzed using the Compass software (Ver. 1.5). Microwave-assisted reactions were performed in closed-vessel mode on a CEM Discover SP MW-reactor (Matthews, North Carolina, CA, USA). Reaction progress was monitored by thin-layer chromatography (TLC) and the spots were visualized under ultraviolet (UV) light (254 or 365 nm). Glass preparative plates (20 × 20 cm) coated with silica-gel 60 doped with UV indicator (F_{254}) were used to purify the product. Mixtures of hexanes (Hex) and ethyl acetate (EtOAc) in 3:1 (*v*/*v*) proportion were used to run TLC, preparative plates, and to measure the retention factor (R_f) value. All starting reagents and solvents were used as received (without further purification, distillation, nor dehydration). Chemical structures were drawn using the ChemDraw software (Ver. 15.0.0.106 Professional, Perkin Elmer Informatics, Cambridge, MA, USA). The purity of synthesized compound **1** (>99%) was assessed by ^{1}H-NMR.

3.2. Synthesis and Characterization of the Ferrocenyl-bis-(1-(4-benzyl-5-morpholinooxazol-2-yl)-N-(4-(trifluoromethyl)benzyl)methanamine) (**1**)

General Procedure (GP): 1,1′-ferrocenedicarboxaldehyde (0.5 mmol, 1.0 equiv.) and the 4-(trifluoromethyl)benzylamine (1.05 mmol, 2.1 equiv.) were placed in a sealed CEM Discover microware reaction tube (10 mL) and diluted in anhydrous toluene (2 mL). Then, the mixture was stirred and heated using microware irradiation (70 °C, 100 W) for 20 min, and scandium(III) triflate (0.025 mmol [5% mol], 0.05 equiv.) was added. The mixture was stirred and heated using microware irradiation (70 °C, 100 W) for 5 minutes, and the 2-isocyano-1-morpholino-3-phenylpropan-1-one (1.10 mmol, 2.2 equiv.) was added. The new mixture was stirred and heated using microware irradiation (70 °C, 100 W) for 45 min. Then, the solvent was removed to dryness under vacuum. The crude was extracted using EtOAc (3 × 10 mL) and $K_2CO_{3(aq)}$ [0.5 M] (3 × 10 mL). The organic layers were collected and washed with brine (3 × 10 mL). The new organic layer was dried using anhydrous Na_2SO_4, filtered over a celite pad, and concentrated to dryness under vacuum. The crude was purified by preparative TLC using a mixture of hexanes with ethyl acetate 3:1 (*v*/*v*) as the mobile phase to isolate the product **1** in 73 % yield as orange oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.0 Hz, 4H, H-17, H-17′, H-19, H-19′), 7.35 (d, *J* = 8.1 Hz, 4H, H-16, H-16′, H-20, H-20′), 7.29–7.26 (m, 8H, H-23, H-23′, H-24, H-24′, H-26, H-26′, H-27, H-27′), 7.21–7.16 (m, 2H, H-25, H-25′), 4.49 (s, 1H, H-12), 4.45 (s, 1H, H-12′), 4.24–4.23 (m, 1H, H-29), 4.21–4.20 (m, 1H, H-29′), 4.01–3.99 (m, 1H, H-32), 3.95–3.94 (m, 1H, H-32′), 3.88–3.86 (m, 1H, H-30), 3.85–3.83 (m, 4H, H-21, H-21′), 3.83–3.82 (m, 3H, H-30, H-30′, H-31, H-31′), 3.76–3.73 (m, 8H, H-2, H-2′, H-6, H-6′), 3.73–3.70 (m, 4H, H-14, H-14′), 3.00–2.97 (m, 8H, H-3, H-3′, H-5, H-5′), 2.04 (bs, 2H, NH-13, NH-13′) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 159.2 (C-9), 159.1 (C-9′), 151.4 (C-7, C-7′), 143.8 (C-15, C-15′), 139.5 (C-22, C-22′), 129.4 (C-18), 129.0 (C-18′), 128.5 (C-23, C-27), 128.4 (C-23′, C-27′), 128.3 (C-24, C-24′, C-26, C-26′), 126.2 (C-16, C-16′,C-20, C-20′), 125.2 (C-25, C-25′), 125.1 (C-17, C-17′, C-19, C-19′, C-33, C-33′), 123.1 (C-11, C-11′), 87.6 (C-28), 87.5 (C-28′), 69.1 (C-31, C-31′), 68.8 (C-32), 68.7 (C-32′), 68.6 (C-30, C-30′), 67.6 (C-29), 67.2 (C-29′), 66.8 (C-14, C-14′), 55.7 (C-12, C-12′), 51.3 (C-3, C-5), 51.2 (C-3′, C-5′), 31.8 (C-21, C-21′) ppm; ^{19}F-NMR (468.6 MHz, $CDCl_3$): δ -64.0 (CF_3) ppm; HRMS: (ESI$^+$) *m*/*z* calcd. for $[M–H]^+$ $C_{56}H_{53}F_6FeN_6O_4^+$ 1043.3383, found 1043.3334 (error = 4.6 ppm); FT-IR (ν_{max}): 2974, 2960, 1616, 1455, 1326, 1114, 1086, 1044, 879, 391 cm^{-1}. The Electronic Supplementary Material contains all NMR, HRMS and IR spectra.

4. Conclusions

A new highly symmetric *bis*-heterocycle structurally based on a metallocene unit was synthesized in 73% yield, which seems to be moderate. However, considering: (i) the molecular complexity and high molecular weight of the synthesized compound, (ii) many C–C, C–N, and C–O bonds were created in a one-pot manner, and iii) in the synthetic domino process, only a couple of water molecules were released, 73% overall yield results are very decent. This ferrocene-based compound, decorated with a couple of 1,3-oxazole

motifs and a couple of fluorinated phenyl rings, may be considered a potential candidate for further in silico, in vitro, and in vivo assays because it is well known that the rational placement of two or more pharmacophoric moieties, in the same structure, may result in tandem-hybrid molecules, which are high-valued compounds in medicinal chemistry mainly due to the inherent difficulty of their synthesis. In this context, the use of pseudo-repetitive MCRs to assemble complex and bigger molecules is a relatively new field, and worthy of all efforts to be continuously investigated.

Supplementary Materials: Copies of ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, 2D-NMR (COSY, HSQC, and HMBC), HRMS and FT-IR spectra.

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