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A two-step synthesis of ferrocenyl pyrazole and pyrimidine derivatives based on carbonylative Sonogashira coupling of iodoferrocene

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ABSTRACT

A new method for the synthesis of 3-substituted-1-ferrocenyl-2-propyn-1-ones was developed involving carbonylative Sonogashira coupling of iodoferrocene with terminal acetylenes. New ferrocenyl 1,3,5-trisubstituted pyrazoles and 2,4,6-trisubstituted pyrimidines were obtained by the addition-cyclocondensation reaction of the alkynones with hydrazines and guanidinium salts, respectively. The products were obtained with moderate to excellent yields and were characterised with various spectroscopic methods (^{1}H NMR, ^{13}C NMR IR, MS).

1. Introduction

The special properties of ferrocene, such as high stability, reversible change of the valence state, non-benzoic aromatic structure, low toxicity towards mammals and potential as an iron source, make its derivatives ideal candidates for drug design. According to the literature, different heterocyclic compounds possess valuable pharmaceutical properties, e.g. anticancer effects [1]. As in some cases the introduction of a ferrocenyl moiety was found to enhance the biological activity of the original compound [2], several derivatives with heterocyclic rings attached to the ferrocene core were synthesised [3–6]. Beside their pharmaceutical importance, these compounds may also serve as ligands in transition metal complexes [7] sometimes forming supramolecular assemblies [8].

As alkynones are versatile starting materials for the synthesis of a great variety of heterocycles [9,10], as a part of our ongoing research concerning palladium-catalysed carbonylation of iodoferrocene [11], a two-step synthesis of ferrocenyl pyrazoles and pyrimidines via carbonylative Sonogashira coupling was developed. The alkynone formation was followed by addition-cyclocondensation in the presence of hydrazines or guanidine derivatives. Although some ferrocenyl alkynones have been produced recently by Friedel-Crafts acylation of ferrocene with alkynoic acids [12], the methodology applying carbonylative Sonogashira coupling of iodoferrocene as key-reaction is unprecedented. Also, to the best of our knowledge, the use of an arginine derivative as nucleophilic reaction partner in the addition-cyclocondensation step has not been reported before.

2. Results and discussion

2.1. Carbonylative coupling of iodoferrocene (*1*) with terminal alkynes *2a–e*

Optimal conditions for the carbonylative coupling were determined in the reaction of iodoferrocene (**1**) with phenylacetylene (**2a**) (Scheme 1, Table 1).

Carbonylative coupling of aryl iodides and terminal alkynes is usually carried out in the presence of a palladium- or a copper-catalyst or both [13]. For the reaction of **1** and alkyne **2a**, the most widely used $PdCl_2(PPh_3)_2$+CuI catalytic system was chosen. The classic, non-carbonylative Sonogashira coupling reaction (Scheme 2) is supposed to follow the normal oxidative addition–reductive elimination process common to the Pd-catalysed C–C bond forming reactions [14]. The process is considered to involve a Pd(0) species (B) which is formed from the Pd(II) pre-catalyst via reductive elimination of a symmetric diyne from the Pd-diacetylide complex (A) generated from $PdCl_2(PPh_3)_2$ and the terminal alkyne or copper acetylide. The oxidative addition of the aryl halide gives a Pd(II) intermediate (C) which is supposed to react with a

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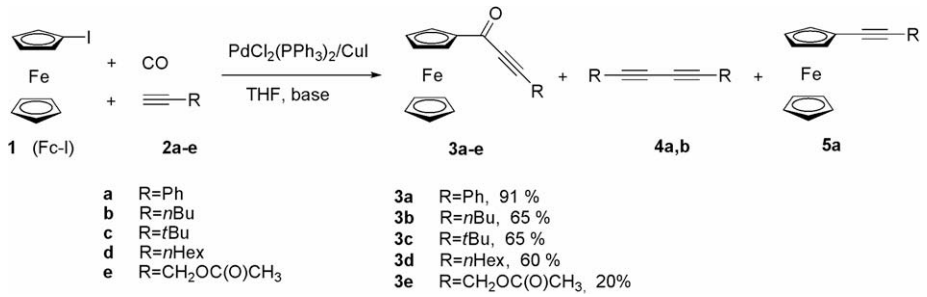
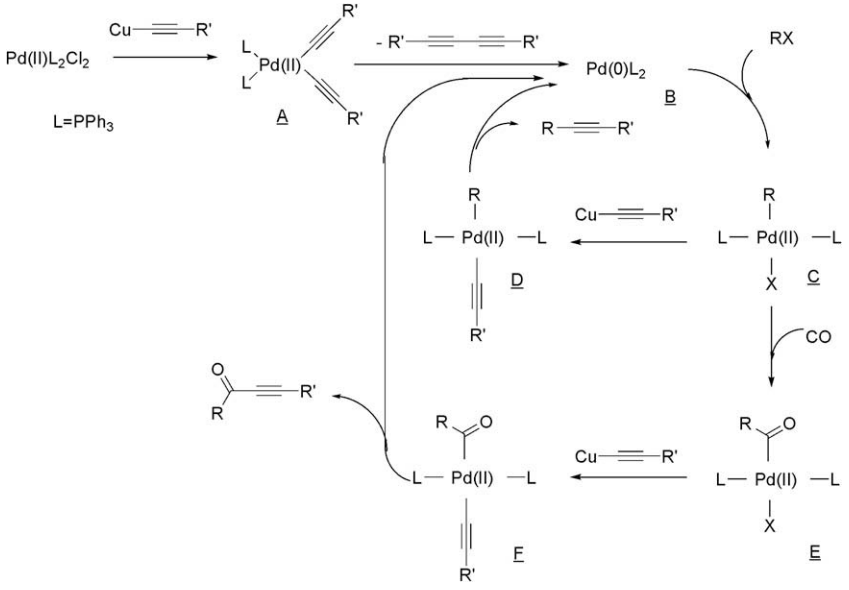


Scheme 1. Carbonylative coupling of **1** with alkynes **2a**–**e**.

Table 1
Carbonylative coupling of **1** with alkynes **2a** and **2b**.[a]

Entry	Alkyne	Alkyne/**1**	Cu/Pd/**1**	Pressure [bar]	Conv. of **1** [%][b]	Selectivity for **3a** or **3b** [%][c]
1	**2a**	1	0.02/0.05/1	1	19	100
2	**2a**	2.5	0.02/0.05/1	1	20	100
3[d]	**2a**	2.5	0.02/0.05/1	1	25	48[e]
4	**2a**	1	0.04/0.10/1	1	35	100
5	**2a**	1	0.04/0.10/1	15	60	100
6	**2a**	2.5	0.04/0.10/1	15	98	100
7	**2a**	2.5	0.02/0.05/1	15	68	100
8	**2a**	2.5	0/0.10/1	15	83	100
9	**2b**	2.5	0.02/0.05/1	1	51	100
10	**2b**	2.5	0.04/0.10/1	15	82	100

[a] Reaction conditions: $PdCl_2(PPh_3)_2$, CuI, Et_3N (**1**/base = 1/2), in THF; 60 °C, CO, 12 h.
[b] Determined by GC.
[c] Determined by GC, mmol **3a** or **3b**/mmol substrate **1**.
[d] With Cs_2CO_3 as the base, reaction time: 32 h.
[e] Compound **5a** was formed as side product.



Scheme 2. Supposed mechanism of direct and carbonylative Sonogashira coupling.

copper acetylide species in a transmetalation step leading to complex D. This is followed by reductive elimination of the product and regeneration of the catalytically active Pd(0) species. The reaction under carbonylation conditions may follow similar steps, except for a CO insertion reaction following the oxidative addition of the aryl halide resulting in the formation of an acyl complex E.

According to the literature, most of the reactions took place smoothly at room temperature and atmospheric carbon monoxide pressure, but these conditions were proved to be unsatisfactory in the case of iodoferrocene (**1**). At room temperature, no conversion of **1** was observed after 12 h. At the same time, according to the GC–MS measurements, phenylacetylene (**2a**) was totally converted into diyne **4a** [15]. This side reaction is often observed under similar conditions [16] and can be explained by a homo-coupling of the alkyne (Glaser reaction). At 60 °C homo-coupling remained the prevailing reaction, although alkynone **3a** was also formed in a low yield (Table 1, entry 1). The use of an excess of phenylacetylene did not lead to an increase in the conversion of **1** (entry 2). The

change of the base from Et_3N to Cs_2CO_3 resulted in a slightly better conversion, but was accompanied by a marked change of selectivity (entry 3). Beside **3a**, the formation of **5a**, [17] a product obtained *via* direct coupling of iodoferrocene and alkyne **2a**, was observed, too.

Even the use of larger amount (10 mol%) of the catalyst did not improve the results considerably (entry 4). However, at higher carbon monoxide pressure (15 bar) no homo-coupling was observed and alkynone **3a** was formed in moderate to high yields depending on molar ratios of the reactants and catalyst (entries 4–6). For an almost total conversion, an excess of phenyacetylene (**1**/**2a** ratio of 1/2.5) and 10 mol% catalyst had to be used (entry 6). Although the presence of the CuI co-catalyst is not essential (entry 8), its absence lowers the yield of alkynone **3a** considerably.

Similar conclusions could be drawn from the results of the reaction of **1** with 1-hexyne (**2b**) (entries 9, 10). It should be noted, however, that the difference in the outcome of the reactions at atmospheric and elevated pressures is not so great as it was observed with alkyne **2a**, though at atmospheric pressure the formation of diyne **4b** was observed here, too [18].

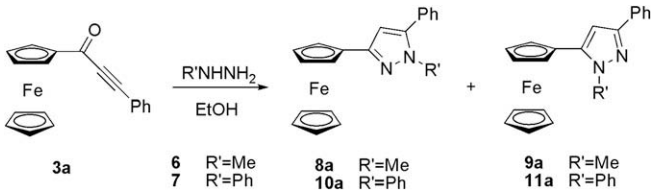
When the reactions were carried out under optimal conditions (entries 6, 10) alkynones **3a** and **3b** could be isolated in 91% and 65% yield, respectively.

Under the same conditions, alkynones **3c** and **3d** were produced in good yields (65% and 60%, respectively) (Scheme 1). However, the presence of an electron-withdrawing group in alkyne **2e** seems to hinder the reaction leading to **3e** in only 20% yield.

2.2. Synthesis of pyrazoles and pyrimidines

Alkynones were shown to be versatile intermediates in a number of cycloaddition and cyclocondensation reactions leading to a great variety of heterocyclic compounds [9–10]. Accordingly, alkynones obtained by the carbonylative Sonogashira reaction described above, were used as starting material for the synthesis of novel ferrocenyl pyrazoles and pyrimidines.

The use of alkynone **3a** and substituted hydrazines **6**,**7** as reaction partners led to isomeric mixtures of 1,3,5-trisubstituted pyrazoles (**8a, 9a** and **10a, 11a**, Scheme 3). Both reactivity of the hydrazines and regioselectivity of the reaction were determined by the electronic properties of the hydrazine reagents. Addition-cyclocondensation of **3a** with methylhydrazine (**6**) took place smoothly at room temperature, while in the case of the less nucleophilic phenylhydrazine (**7**), good results could be obtained only at higher temperature and in longer reaction time (Table 2, entries 1, 2).

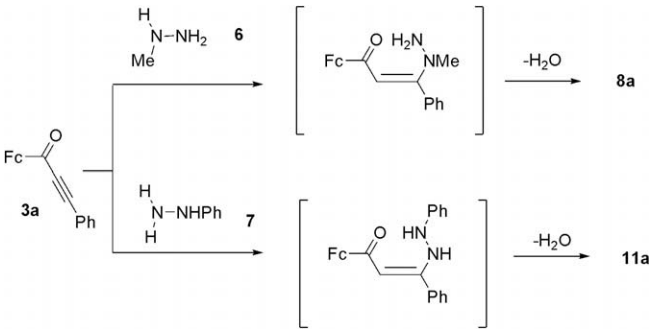


Scheme 3. Reaction of alkynone **3a** with hydrazines **6** and **7**.

Although pyrazoles were obtained as mixtures of regioisomers, the reactions took place with good regioselectivity leading to **8a** and **11a** as the main products by using hydrazines **6** and **7**, respectively (entries 1, 2). The formation of these major products can be rationalised by the initial conjugate addition of the more nucleophilic nitrogen of the hydrazine reagent, the substituted one in **6** and the unsubstituted one in **7**, to the triple bond of the alkynone **3a**, followed by cyclisation of the other hydrazine nitrogen onto the carbonyl group and dehydration (Scheme 4) [10].

The structures of the main products **8a** and **11a** were proved by NOESY experiments. Irradiation of the N–Me singlet of **8a** at 3.87 ppm resulted in an increase of the signal of aromatic protons of 7.47 ppm chemical shift. At the same time, no effect was obtained between the signals of the protons of the substituted cyclopentadienyl ring (at 4.69 ppm) and the methyl singlet at 3.87 ppm. In the NOESY spectrum of **11a** a crosspeak was observed between the protons of the substituted cyclopentadienyl ring (4.21 ppm) and aromatic protons of the N–Ph substituent (7.35 ppm) as well as between the singlet of 4-H (6.84) and the dd signal (7.94 ppm) of the *ortho* protons of the aromatic ring attached to C-3 of the pyrazole ring. The minor components (**9a** and **10a**) were detected by GC–MS [19].

The reaction of methylhydrazine and alkynones **3b** and **3d** led to isomeric pyrazoles **8b, d** and **9b, d,** respectively, in good yields and excellent selectivities towards isomers **8b, d** (Scheme 5, Table 2 entries 3, 5). The minor components (**9b, d**) were detected by

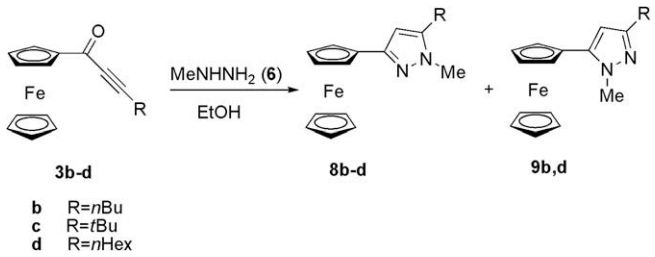


Scheme 4. Formation of different regioisomers in the reaction of **3a** with hydrazines **6** and **7**.

Table 2
Addition-cyclocondensation reactions of alkynones **3a–d** with hydrazines (**6**, **7**) and guanidinium salts (**12**, **13**).

Entry	Alkynone	Reagent	Solvent	R.time [h]	Conv. [%][a]	Product	Yield [%]	Isomer ratio (**8:9**) after isolation [a]
1[b]	**3a**	**6**	EtOH	4	98	**8a, 9a**	90	>99:1
2[c]	**3a**	**7**	EtOH	8	85	**10a, 11a**	78	4:96
3[b]	**3b**	**6**	EtOH	4	100	**8b, 9b**	98	97:3
4[b]	**3c**	**6**	EtOH	12	73	**8c**	56	>99:1
5[b]	**3d**	**6**	EtOH	4	81	**8d, 9d**	70	98:2
6[c,d]	**3a**	**12**	THF	24	53	**14a**	50	-
7[c,d]	**3a**	**13**	THF	24	44	**15a**	40	-
8[c,d]	**3b**	**12**	THF	24	47	**14b**	41	-
9[c,d]	**3b**	**13**	THF	24	39	**15b**	32	-

[a] Determined by GC.
[b] At room temperature.
[c] Reflux.
[d] In the presence of Cs_2CO_3.



Scheme 5. Reaction of alkynones **3b–d** with methylhydrazine (**6**).

GC–MS [20]. At the same time, **8c** was produced in 56% yield as a single isomer. However, in order to obtain this compound in an appropriate yield, a longer reaction time (12 h) had to be used.

Reaction of **3a** and **3b** and guanidinium salts **12** and **13** led to the 2,4,6-trisubstituted pyrimidines **14a,b** and **15a,b** in moderate yields (Scheme 6, Table 2, entries 7, 10) in accordance with the results of Müller et al. This approach was based on simple aryl-alkynones as starting compounds [21]. It should be mentioned, however, that our reactions described above were completely selective, and the unreacted alkynones **3a** and **3b** could be recovered upon separation of the products by column chromatography. Furthermore, the ring-closure reaction tolerates the presence of amido and ester functionalities in the protected arginine derivative, **13**.

3. Conclusions

3-Substituted 1-ferrocenyl-2-propyn-1-ones **3a–d** were obtained in good yields *via* carbonylative Sonogashira coupling of iodoferrocene (**1**) and terminal alkynes **2a–d** in the presence of the $PdCl_2(PPh_3)_2$/CuI catalytic system under moderate CO pressure.

New 1,3,5-trisubstituted ferrocenyl pyrazoles (**8a–d** and **11a**) were obtained in excellent yield and with high regioselectivity in the addition-cyclocondensation reaction of alkynones **3a–d** with substituted hydrazines. The use of methylhydrazine and phenylhydrazine led to different regioisomers of the 1,3,5-trisubstituted ferrocenyl pyrazoles. The use of guanidinium salts, such as the salt of the parent guanidine and N_α-benzoyl-arginine ethylester as reagents, resulted in the formation of new 2,4,6-trisubstitued ferrocenyl pyrimidines **14a,b** and **15a,b** with high selectivity but in moderate yields.

4. Experimental

4.1. Carbonylation of iodoferrocene (*1*) at atmospheric pressure

In a typical experiment a solution of iodoferrocene (**1**) (0.5 mmol), $PdCl_2(PPh_3)_2$ (0.025 or 0.05 mmol), CuI (0.01 or 0.02 mmol) were dissolved in THF (7.5 ml) under argon. Triethylamine (1 mmol), phenylacetylene (**2a**) or 1-hexyne (**2b**) (0.5 or 1.25 mmol) were added to the solution and the atmosphere was changed to carbon monoxide. The reaction was conducted at 60 °C for 12 h.

4.2. Carbonylation of iodoferrocene (*1*) at 15 bar

In a typical experiment a mixture of iodoferrocene (**1**) (0.5 mmol), $PdCl_2(PPh_3)_2$ (0.025 or 0.05 mmol), CuI (0.01 or 0.02 mmol), triethylamine (1 mmol), alkyne (**2a–e**) (0.5 mmol or 1.25 mmol) and THF (7.5 ml) were transferred under an inert atmosphere into a stainless steel autoclave. It was charged with carbon monoxide (15 bar at room temperature) and heated with stirring in an oil bath at 60 °C. After 12 h the solvent was removed in vacuo. The products were isolated by column chromatography (silica gel, eluent: toluene).

4.3. Synthesis of pyrazoles *8a–d* and *11a*

A 3-substituted 1-ferrocenyl-2-propyn-1-one (**3a–d**) (0.2 mmol) was reacted with methylhydrazine (**6**) or phenylhydrazine (**7**) (0.3 mmol) in EtOH (2 ml) at room temperature or at reflux, respectively, for the time indicated in Table 2. Evaporation of the solvent and column chromatography (silica gel, eluent: toluene:EtOAc = 8:1) led to the products.

4.4. Synthesis of pyrimidines *14a,b* and *15a,b*

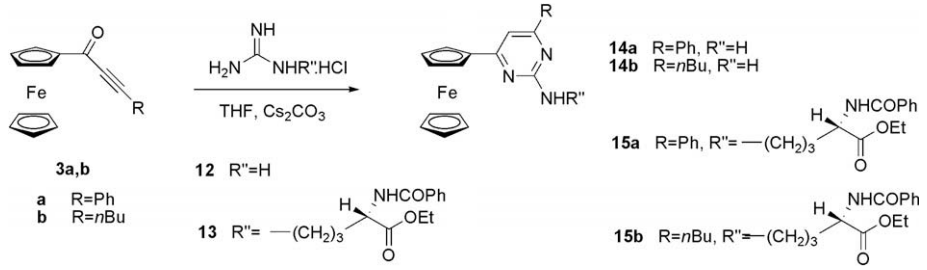
A 3-substituted 1-ferrocenyl-2-propyn-1-one (**3a** or **3b**) (0.2 mmol) was reacted with guanidine hydrochloride (**12**) or N_α-benzoyl-L-Arg-OEt.HCl (**13**) (0.4 mmol) in the presence of Cs_2CO_3 (0.4 mmol) in 10 ml THF at reflux temperature for 24 h. Evaporation of the solvent and column chromatography (silica gel, eluent: toluene:EtOAc = 4:1) led to the products.

4.5. Physical measurements

^1H and ^{13}C NMR spectra were recorded on a VARIAN INOVA 400 spectrometer at 400 and 100.58 MHz, respectively. Mass spectra were recorded on a HP-5971A MSD connected to a HP-5890/II gas chromatograph. Mass spectra of **15a,b** were recorded on an Autoflex II TOF/TOF (Bruker Daltonics, Bremen, Germany) instrument operated in reflector for MALDI TOF (matrix: 2,5-dihydroxybenzoic acid). IR spectra were made using an Avatar 330 FT-IR instrument. Samples were prepared as KBr pellets. Elemental analyses were measured on a 1108 Carlo Erba apparatus.

4.5.1. 1-Ferrocenyl-3-phenyl-2-propyn-1-one (*3a*)

^1H NMR (400 MHz, $CDCl_3$) δ: 7.62–7.65 (m, 2H, Ph); 7.38–7.50 (m, 3H, Ph); 4.99 (t, J = 1.9 Hz, 2H); 4.62 (t, J = 1.9 Hz, 2H); 4.28 (s, 5H). ^{13}C NMR ($CDCl_3$) δ: 181.1; 132.7; 130.3; 128.6; 120.6; 89.5; 87.7; 80.6; 73.2; 70.5 (7C). IR (cm^{-1}): 2202; 1605. MS (m/z/rel. int.): 314 (M^+)/100; 286/10; 222/8; 165/35; 56/10. Identical with the data reported in the literature [12]. Violet solid. M.p.:



Scheme 6. Reaction of alkynone **4** with guanidinium salts **13** and **14**.

104–105 °C. Anal. Calc. for $C_{19}H_{14}FeO$ (314.16): C, 72.64; H, 4.49. Found: C, 72.51; H, 4.56%. Yield: 91%.

*4.5.2. 1-Ferrocenyl-2-heptyn-1-one (**3b**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.89 (brs, 2H); 4.55 (brs, 2H); 4.23 (s, 5H); 2.44 (t, J = 7.5 Hz, 2H); 1.45–1.70 (m, 4H); 0.97 (t, J = 7.5 Hz, 3H). IR (cm^{-1}): 2206; 1613. ^{13}C NMR ($CDCl_3$) δ:181.8; 93.0; 80.8; 80.7; 73.2; 70.7; 70.6; 30.2; 22.2; 19.0; 13.7. MS (m/z/rel. int.): 294 (M^+)/100; 265/5; 251/2; 237/4; 223/10; 200/8; 121/20; 56/15. Red oil. Anal. Calc. for $C_{17}H_{18}FeO$ (294.17): C, 69.41; H, 6.17. Found: C, 69.60; H, 6.09%. Yield: 65%.

*4.5.3. 4,4-Dimethyl-1-ferrocenyl-2-pentyn-1-one (**3c**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.90 (brs, 2H); 4.60 (brs, 2H); 4.25 (s, 5H); 1.39 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 181.8; 93.1; 81.0; 79.2; 73.1; 70.8; 70.7; 30.6; 28.1. IR (cm^{-1}): 2222; 1621. MS (m/z/rel. int.): 294 (M^+)/100; 251/27; 200/13; 121/22; 56/9. Red solid. M.p.: 89–90 °C. Anal. Calc. for $C_{17}H_{18}FeO$ (294.17): C, 69.41; H, 6.17. Found: C, 69.07; H, 6.35%. Yield: 65%.

*4.5.4. 1-Ferrocenyl-2-nonyn-1-one (**3d**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.85 (brs, 2H); 4.58 (brs, 2H); 4.25 (s, 5H); 2.42 (t, J = 7.6 Hz, 2H); 1.22–1.70 (m, 8H); 0.88 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 181.8; 93.1; 80.8; 80.7; 73.2; 70.7; 70.6; 31.5; 28.8; 28.2; 22.8; 19.3; 14.3. IR (cm^{-1}): 2212; 1627. MS (m/z/rel. int.): 322 (M^+)/100; 223/5; 121/18; 56/7. Red oil. Anal. Calc. for $C_{19}H_{22}FeO$ (322.23): C, 70.82; H, 6.88. Found: C, 71.05; H, 6.65%. Yield: 60%.

*4.5.5. 4-Acetoxy-1-ferrocenyl-2-butyn-1-one (**3e**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.95 (s, 2H); 4.91 (brs, 2H); 4.62 (brs, 2H); 4.28 (s, 5H); 2.15 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 180.5; 170.2; 84.9; 83.9; 80.0; 73.7; 70.9; 70.8; 52.0; 20.8. IR (cm^{-1}): 2219; 1749; 1627. MS (m/z/rel. int.): 310 (M^+)/100; 268/7; 240/12; 158/21; 121/18; 56/15. Red solid. M.p.: 100–101 °C. Anal. Calc. for $C_{16}H_{14}FeO_3$ (310.13): C, 61.97; H, 4.55. Found: C, 62.16; H, 4.78%. Yield: 20%.

*4.5.6. 3-Ferrocenyl-1-methyl-5-phenyl-pyrazole (**8a**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39–7.48 (m, 5H); 6.36 (s, 1H); 4.69 (brs, 2H); 4.27 (brs, 2H); 4.11 (s, 5H); 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 149.7; 144.5; 130.8; 128.7; 128.6; 128.4; 103.7; 78.7; 69.4; 68.3; 66.5; 37.4. IR (cm^{-1}): 1565; 1478. MS (m/z/rel. int.): 342 (M^+)/100; 277/10; 221/4; 171/9; 121/8; 56/7. Orange solid. M.p.: 132–134 °C. Anal. Calc. for $C_{20}H_{18}FeN_2$ (342.22): C, 70.19; H, 5.30; N, 8.19. Found: C, 70.31; H, 5.42; N, 8.25%. Yield: 90%.

*4.5.7. 5-n-Butyl-3-ferrocenyl-1-methyl-pyrazole (**8b**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.02 (s, 1H); 4.62 (brs, 2H); 4.21 (brs, 2H); 4.02 (s, 5H); 3.71 (s, 3H); 2.55 (t, J = 7.2 Hz, 2H); 1.65 (quintet, J = 7.2 Hz, 2H); 1.42 (sextet, J = 7.2 Hz, 2H); 0.97 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 149.2; 144.0; 102.0; 79.5; 69.6; 68.4; 66.6; 36.1; 30.8; 25.6; 22.6; 14.0. MS (m/z/rel. int.): 322 (M^+)/100; 278/20; 257/7; 213/9; 140/10; 56/5. Anal. Calc. for $C_{18}H_{22}FeN_2$ (322.23): C, 67.09; H, 6.88; N, 8.69. Found: C, 67.28; H, 6.56; N, 8.89%. Yield: 98%. (Contains 3% of **9b**).

*4.5.8. 5-t-Butyl-3-ferrocenyl-1-methyl-pyrazole (**8c**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.03 (s, 1H); 4.63 (brs, 2H); 4.25 (brs, 2H); 4.09 (s, 5H); 3.94 (s, 3H); 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 151.8; 148.1; 101.3; 79.8; 69.5; 68.3; 66.4; 39.2; 31.1; 29.7. MS (m/z/rel. int.): 322 (M^+)/100; 305/34; 292/11; 241/7; 140/10; 56/3. Orange solid. M.p.: 96–98 °C. Anal. Calc. for $C_{18}H_{22}FeN_2$ (322.23): C, 67.09; H, 6.88; N, 8.69. Found: C, 66.85; H, 6.71; N, 8.95%. Yield: 56%.

*4.5.9. 3-Ferrocenyl-5-n-hexyl-1-methyl-5-pyrazole (**8d**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.04 (s, 1H); 4.62 (brs, 2H); 4.23 (brs, 2H); 4.05 (s, 5H); 3.74 (s, 3H); 2.57 (t, J = 7.4 Hz, 2H); 1.65 (t, J = 7.4 Hz, 2H); 1.28–1.40 (m, 6H); 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 149.2; 144.1; 102.1; 79.4; 69.6; 68.4; 66.6; 36.1; 31.8; 29.2; 28.6; 25.9; 22.8; 14.3. MS (m/z/rel. int.): 350 (M^+)/100; 278/15; 213/7; 140/10; 121/9; 56/5. Anal. Calc. for $C_{20}H_{26}FeN_2$ (350.29): C, 68.58; H, 7.48; N, 8.00. Found: C, 68.43; H, 7.56; N, 7.89%. Yield: 70%. (Contains 2% of **9d**).

*4.5.10. 1,3-Diphenyl-5-ferrocenyl-pyrazole (**11a**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (dd, J = 1.2 Hz, 8.4 Hz, 2H); 7.34–7.46 (m, 8H); 6.84 (s, 1H); 4.21 (brs, 2H); 4.15 (brs, 2H); 4.10 (s, 5H). ^{13}C NMR ($CDCl_3$) δ: 151.7; 143.1; 140.5; 133.2; 128.8; 128.6; 128.1; 127.8; 126.3; 125.8; 103.8; 74.9; 69.8; 68.7; 68.6. MS (m/z/rel. int.): 404 (M^+)/100; 339/6; 281/4; 254/4; 235/8; 202/5; 180/5; 152/5; 121/12; 77/8; 56/10. Anal. Calc. for $C_{25}H_{20}FeN_2$ (404.29): C, 74.27; H, 4.98; N, 6.93. Found: C, 74.12; H, 5.07; N, 7.05%. Yield: 78%. (Contains 4% of **10a**).

*4.5.11. 2-Amino-6-ferrocenyl-4-phenyl-pyrimidine (**14a**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99–8.03 (m, 2H); 7.45–7.51 (m, 3H); 7.12 (s, 1H); 5.06 (brs, 2H); 4.96 (t, J = 1.9 Hz, 2H); 4.45 (t, J = 1.9 Hz, 2H); 4.09 (s, 5H). ^{13}C NMR ($CDCl_3$) δ: 169.7; 164.9; 163.6; 138.2; 130.4; 128.9; 127.2; 104.2; 81.4; 70.9; 70.2; 68.2. MS (m/z/rel. int.): 355 (M^+)/100; 290/16; 207/11; 177/9; 145/11; 121/8; 89/6; 56/8. Dark red solid. M.p.: 159–160 °C. Anal. Calc. for $C_{20}H_{17}FeN_3$ (355.22): C, 67.62; H, 4.82; N, 11.83. Found: C, 67.49; H, 4.70; N, 11.95%. Yield: 50%.

*4.5.12. 2-Amino-4-n-butyl-6-ferrocenyl-pyrimidine (**14b**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.60 (s, 1H); 5.02 (brs, 2H); 4.85 (brs, 2H); 4.41 (brs, 2H); 4.04 (s, 5H); 2.58 (t, J = 7.4 Hz, 2H); 1.70 (quintet, J = 7.4 Hz, 2H); 1.41 (sextet, J = 7.4 Hz, 2H); 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 171.1; 168.1; 163.1; 106.7; 81.2; 70.8; 70.1; 68.1; 37.8; 31.1; 22.7; 14.1. MS (m/z/rel. int.): 335 (M^+)/100; 293/65; 228/7; 147/17; 121/13; 56/7. Dark red solid. M.p.: 114–115 °C. Anal. Calc. for $C_{18}H_{21}FeN_3$ (335.23): C, 64.49; H, 6.31; N, 12.53. Found: C, 64.53; H, 6.57; N, 12.22%. Yield: 41%.

*4.5.13. 2-(4-Benzoylamino-4-ethoxycarbonyl-butyl-amino)-6-ferrocenyl-4-phenyl-pyrimidine (**15a**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00–8.03 (m, 2H); 7.76–7.79 (m, 2H); 7.36–7.50 (m, 6H); 7.04 (s, 1H); 6.75 (d, J = 7.6 Hz, 1H); 5.18 (t, J = 7.1 Hz, 1H); 4.94–4.95 (m, 2H); 4.85–4.91 (m, 1H); 4.41 (brs, 2H); 4.21 (q, J = 7.1 Hz, 2H); 4.06 (s, 5H); 3.59 (q, J = 6.7 Hz, 2H); 2.10–2.20 (m, 1H); 1.90–2.03 (m, 1H); 1.74–1.87 (m, 2H); 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 172.8; 169.0; 167.3; 164.3; 162.9; 138.4; 134.2; 131.9; 130.3; 129.2; 128.8; 127.3; 127.2; 103.0; 81.9; 70.7; 70.1; 68.2; 61.9; 52.7; 41.4; 30.6; 26.0; 14.4. MS (m/z/rel. int.): 603 ($[M+H]^+$)/100. Dark red solid. M.p.: 66–67 °C. Anal. Calc. for $C_{34}H_{34}FeN_4O_3$ (602.51): C, 67.78; H, 5.69; N, 9.30. Found: C, 67.61; H, 5.75; N, 9.42%. Yield: 40%.

*4.5.14. 2-(4-Benzoylamino-4-ethoxycarbonyl-butyl-amino)-4-n-butyl-6-ferrocenyl-pyrimidine (**15b**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78–7.82 (m, 2H); 7.48–7.51 (m, 1H); 7.41–7.44 (m, 2H); 6.80 (d, J = 7.7 Hz, 1H); 6.48 (s, 1H); 5.12 (brs, 1H); 4.89 (brs, 2H); 4.85–4.90 (m, 1H); 4.38 (brs, 2H); 4.22 (q, J = 6.5 Hz, 2H); 4.04 (s, 5H); 3.52 (q, J = 7.0 Hz, 2H); 2.54 (t, J = 8.0 Hz, 2H); 1.74–2.20 (m, 4H); 1.72 (quintet, J = 8.0 Hz, 2H); 1.39 (sextet, J = 8.0 Hz, 2H); 1.28 (t, J = 6.5 Hz, 3H); 0.96 (t, J = 8.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 172.8; 170.9; 168.2; 167.8; 162.9; 134.2; 132.0; 128.8; 127.3; 105.9; 82.1; 70.5; 70.0; 68.1; 61.9; 52.6; 40.7; 37.8; 31.1; 30.5; 26.1; 22.6; 14.2; 14.1. MS (m/

z/rel. int.): 583 ([M+H]$^+$)/100. Dark red solid. M.p.: 47–48 °C. Anal. Calc. for $C_{32}H_{38}FeN_4O_3$ (582.52): C, 65.98; H, 6.57; N, 9.62. Found: C, 66.11; H, 6.61; N, 9.91%. Yield: 32%.

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[19] MS data for **9a**: MS (m/z/rel. int.): 342 (M$^+$)/100; 121/7; 56/8. MS data for **10a**: MS (m/z/rel. int.): 404 (M$^+$)/100; 339/4; 283/6; 281/6; 254/5; 202/8; 180/2; 152/2; 121/12; 77/8; 56/8.
[20] MS data for **9b**: MS (m/z/rel. int.): 360 (M$^+$)/100; 280/38; 265/46; 140/11; 121/22; 56/7. MS data for **9d**: MS (m/z/rel. int.): 322 (M$^+$)/100; 280/31; 265/25; 140/10; 121/17; 56/5.
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