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One-Pot Sonochemical Synthesis of Ferrocenyl Derivatives *via* a three-Component Reaction in aqueous Media

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Abstract

An ultrasound-assisted three-component, one-pot domino reaction with ferrocenecarboxaldehyde is herein reported. The sequence of reactions entails the allylindation and dehydrative alkylation of stabilized C- nucleophiles (e.g. electron-rich - (hetero)aromatics and stabilized enols) and N-nucleophiles (e.g. azoles). Sonochemical reactions have been performed in three different high-intensity reactors: a bath (20.3 kHz, 60W), as well as two cup horns working at 19.9 kHz (75W) and 300.5 kHz (70 W) giving a library of 18 new ferrocenyl derivatives.

Keywords

Ultrasound, Ferrocene, Domino reaction, Multi-component reaction, Indium, Aldehydes, Allylation.

1. Introduction

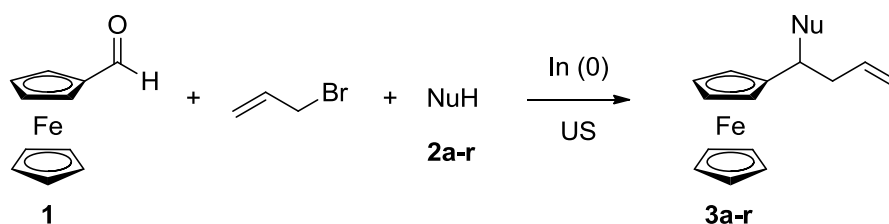
Ferrocene was discovered in 1951 [1], and immediately attracted research attention thanks to its peculiar structure, chemical and thermal stability, redox properties and the biological compatibility of some ferrocenyl derivatives. An intense and lively debate on the nature of this milestone in the history of organometallic chemistry has continued since its first synthesis. Ferrocenyl based ligands have found successful applications in metal catalysis [2,3], even in large scale applications for the industrial synthesis of optically active compounds [4]. Several biological functions for ferrocene

and its derivatives have been reported [5,6] as well as antitumor activity [7]. The ferrocene moiety has also found interesting uses in material science [8,9]. It is evident that the design of simple and efficient synthetic protocols for ferrocenyl derivatives and the use of multicomponent reactions (MCR) is a promising strategy [10,11].

A number of the Authors have recently and successfully dedicated study to MCRs by setting up a one-pot domino reaction that combines the allylindation of 1*H*-indole-3-carbaldehyde with dehydrative alkylation by C and N nucleophiles [12]. This methodology exploits the Barbier-type indium-mediated allylation of aldehydes, which was discovered in 1988 by Butsugan and co-workers [13], and which has been developed over the years to give general and efficient stereoselective protocols [14]. The alcohol formed as a result of the Barbier allylation is driven to *in situ* dehydration-Friedel-Crafts alkylation [15], due to the presence of a Lewis acid (In^{III} species, arising from the allylindation) in the reaction mixture.

Similar synthetic protocols, using metals or organometallic reagents, have been successfully carried out under ultrasound (US) irradiation. In 2006, Lee et al. described the advantages of sonochemical conditions in the indium mediated Reformatsky reaction [16]. The use of US allows mild reaction conditions to be used, generally reduces reaction time and affords high yields. More recently, a comprehensive literature survey has shown the beneficial effect of US in a classical coupling promoted by zero-valent metal species in heterogeneous mixtures [17].

In this piece of work, we successfully extend the domino allylindation-alkylation MCR protocol to ferrocenecarboxaldehyde **1** with a variety of nucleophiles **2a-r** (Scheme 1). Ultrasonic irradiation proved to be crucial for the transformation and a library of unknown derivatives **3a-r** have been synthesized in satisfactory to good yields.



Scheme 1. Three-component indium-mediated domino allylation of ferrocenecarboxaldehyde in the presence of nucleophiles.

2. Experimental

2.1 General

The reactions were performed using standard glassware, both under stirring on a standard heating plate and in three different high-intensity US probe reactors: an US-bath (20.3 kHz, 60W), and two cup horns working at 19.9 kHz (75W) [18] and 300.5 kHz (70 W) [19] all made by Danacamerini (Turin, Italy). Where air-sensitive reagents were used, reactions were performed in dried glassware under a nitrogen atmosphere. All solvents and indium powder (99.99%, 100 mesh) were purchased from Sigma-Aldrich and used as received without further purification. All reagents, if not otherwise specified, were used as received and stored under inert gas if necessary. Macherey-Nagel Polygram® sil G/UV 254 pre-coated plates were used for thin-layer chromatography (TLC) analyses. Column chromatography was performed on silica gel 60A (70–200 µm). ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) were measured on a Bruker AV400 spectrometer. Chemical shifts (δ) are expressed in parts per million (ppm) and coupling constants are given in hertz (Hz). Splitting patterns are indicated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet-doublet, td = triplet-doublet. Chemical ionization mass spectra (+ve mode) (CI+ -MS) were performed on a Finnigan-MAT TSQ70 with isobutane as the reactant gas.

2.2 Ultrasound-promoted domino allylindation-dehydrative alkylation of ferrocenecarboxaldehyde.

Ferrocenecarboxaldehyde **1** (214 mg 1 mmol), allylbromide (242mg, 2 mmol), a nucleophile (1 mmol) and indium powder (172 mg, 1.5 mmol) were dissolved in THF/H₂O (12 mL). Ultrasonic irradiation (cup horn: 19.9 kHz, 75W) was then applied to the reaction mixture for 3 h at room temperature. The crude products were filtered off in order to eliminate the unreacted Indium and then were purified using Combi-Flash Chromatography on silica (Hexane:EtOAc gradient from 0% to 100% of EtOAc).

3-(1-Ferrocenylbut-3-en-1-yl)-1*H*-indole (**3a**). Yellow oil. TLC (petroleum ether/dichloromethane, 6:4): *R_f* = 0.31. ¹H NMR (400 MHz, CDCl₃): δ = 7.90 (s, 1H, NH), 7.59 (d, *J* = 8.0 Hz, 1H, C7H), 7.35 (d, *J* = 8.0 Hz, 1H, C4H), 7.18 (t, *J* = 7.4 Hz, 1H, C6H), 7.08 (t, *J* = 7.4 Hz, 1H, C5H), 6.92 (s, 1H, C2H), 5.83 (m, 1H, C10H), 5.04 (d, *J* = 16.9 Hz, 1H, C11H), 4.95 (d, *J* = 10.0 Hz, 1H, C11H), 4.25 (m, 1H, C8H), 4.28-4.06 (m, 9H, Fc), 2.97 (m, 1H, C9H), 2.85 (m, 1H, C9H). ¹³C NMR (100 MHz, CDCl₃): δ = 138.3 (C10), 136.7 (C7a), 127.3 (C3), 122.2 (C6), 121.9 (C2), 120.5 (C3a), 120.1 (C7), 119.5 (C5), 115.9 (C11), 111.6 (C4), 94.95 (C12), 69.3-67.4 (Fc), 41.4 (C9), 37.6 (C8). ESI-MS: *m/z*: 356 [M+H]⁺.

3-(1-Ferrocenylbut-3-en-1-yl)-1-methyl-1*H*-indole (**3b**). Brown oil. TLC (*n*-hexane/dichloromethane 7/3 *R_f* = 0.22. ¹H NMR (400 MHz, CDCl₃): δ = 7.90 (s, 1H, NH), 7.63

(d, $J = 8.0$ Hz, 1H, C7H), 7.28 (d, $J = 8.0$ Hz, 1H, C4H), 7.21 (t, $J = 7.5$ Hz, 1H, C6H), 7.08 (t, $J = 7.5$ Hz, 1H, C5H), 6.79 (s, 1H, C2H), 5.83 (m, 1H, C10H), 5.06 (d, $J = 17.1$ Hz, 1H, C11H), 4.94 (d, $J = 10.1$ Hz, 1H, C11H), 4.32 (m, 1H, C8H), 4.16-4.06 (m, 9H, Fc), 3.74 (s, 3H, Me), 2.94 (m, 1H, C9H), 2.82 (m, 1H, C9H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 138.4$ (C10), 137.3 (C7a), 127.7 (C3), 126.6 (C2), 121.7 (C6), 120.1 (C7), 119.1 (C3a), 118.9 (C5), 115.8 (C11), 111.6 (C4), 94.0 (C12), 69.2-67.3 (Fc), 41.4 (C9), 37.4 (C8), 33.1 (Me). ESI-MS: m/z : 369 $[\text{M}+\text{H}]^+$.

2,5-Bis(1-Ferrocenylbut-3-en-1-yl)-1H-pyrrole (**3c**). Brown oil. TLC (*n*-hexane/dichloromethane, 1:1): $R_f = 0.41$. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.80$ (s, 1H, NH), 5.87 (m, 2H, C8H + C12H) 5.84 (s, 2H, C3H + C4H), 5.04 (m, 4H, C9H₂ + C13H₂), 4.16-4.07 (m, 18H, Fc), 3.75 (m, 2H, C6H + C10H), 2.77 (m, 2H, C7H + C11H), 2.58 (m, 2H, C7H + C11H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 137.8$ (C8, C12), 133.2 (C2, C5), 116.5 (C9, C13), 105.4 (C3, C4), 93.1 (C14, C24), 69.1-66.6 (Fc), 41.6 (C7, C11), 39.1 (C6, C10). ESI-MS: m/z : 543 $[\text{M}+\text{H}]^+$.

2,5-Bis(1-Ferrocenylbut-3-en-1-yl)furan (**3d**). Yellow oil. TLC (*n*-hexane/dichloromethane, 7:3): $R_f = 0.38$. ^1H NMR (400 MHz, CDCl_3): $\delta = 6.02$ (m, 2H, C3H + C4H) 5.78 (s, 2H, C8H + C12H), 5.05 (m, 2H, C9H C13H), 4.99 (m, 2H, C9H + C13H) 4.19-4.08 (m, 18H, Fc), 3.77 (m, 2H, C6H + C10H), 2.68 (m, 2H, C7H₂ C11H₂). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 155.8$ (C2, C5), 137.2 (C8, C12), 116.5 (C9, C13), 106.7 (C3, C4), 91.8 (C14, C24), 69.1-67.4 (Fc), 41.1 (C7, C11), 40.1 (C6, C10). ESI-MS: m/z : 545 $[\text{M}+\text{H}]^+$.

2-(1-Ferrocenylbut-3-en-1-yl)-5-methylfuran (**3e**). Yellow oil. TLC (*n*-hexane/dichloromethane, 7:3): $R_f = 0.39$. ^1H NMR (400 MHz, CDCl_3): $\delta = 5.95$ (d, $J = 3.0$ Hz, 1H, C4H), 5.91 (d, $J = 3.0$ Hz, 1H, C3H), 5.76 (m, 1H, C8H), 5.04 (dd, $J = 17.1, 1.6$ Hz, C9H), 4.97 (d, $J = 10.1$ Hz, 1H, C9H), 4.16-4.07 (m, 9H, Fc), 3.71 (m, 1H, C6H), 2.62 (m, 2H, C7H₂), 2.32 (s, 3H, Me). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 156.0$ (C5), 150.3 (C2), 137.3 (C8), 116.3 (C9), 106.4 (C4), 106.3 (C3), 92.1 (C11), 69.9-66.3 (Fc), 40.1 (C7), 38.4 (C6), 14.1 (Me). ESI-MS: m/z : 321 $[\text{M}+\text{H}]^+$.

1-(1-Ferrocenylbut-3-en-1-yl)-1H-pyrazole (**3f**). Orange oil. TLC (petroleum ether/ethyl acetate, 8:2): $R_f = 0.44$. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.53$ (d, $J = 1.3$ Hz, 1H, C3H), 7.42 (d, $J = 2.2$ Hz,

1H, C5H), 6.25 (t, $J = 2.0$ Hz, 1H, C4H), 5.64 (m, 1H, C8H), 5.21 (m, 1H, C6H), 5.05 (m, 2H, C9H₂), 4.26-4.10 (m, 9H, Fc), 2.93 (m, 2H, C7H₂). ¹³C NMR (100 MHz, CDCl₃): $\delta = 138.9$ (C3), 134.6 (C8), 128.1 (C5), 117.9 (C9), 105.4 (C4), 89.5 (C10), 69.3-67.4 (Fc), 62.6 (C6), 41.0 (C7). ESI-MS: m/z : 307 [M+H]⁺.

1-(1-Ferrocenylbut-3-en-1-yl)-3,5-dimethyl-1H-pyrazole (**3g**). Brown oil. TLC (petroleum ether/ethyl acetate, 8:2): $R_f = 0.45$. ¹H NMR (400 MHz, CDCl₃): $\delta = 5.79$ (s, 1H, C4H), 5.62 (m, 1H, C8H), 5.21 (m, 1H, C6H), 5.08 (d, $J = 16.4$ Hz, 1H, C9H), 4.98 (d, $J = 8.0$ Hz, 1H, C9H), 4.09-3.36 (m, 9H, Fc), 3.19 (m, 1H, C7H), 2.92 (m, 1H, C7H), 2.27 (s, 3H, Me), 2.23 (s, 3H, Me). ¹³C NMR (100 MHz, CDCl₃): $\delta = 147.2$ (C3), 138.7 (C5), 135.3 (C8), 117.6 (C9), 105.0 (C4), 90.1 (C10), 69.2-67.7 (Fc), 58.5 (C6), 40.0 (C7), 14.2 (Me), 12.0 (Me). ESI-MS: m/z : 335 [M+H]⁺.

1-(1-Ferrocenylbut-3-en-1-yl)-1H-imidazole (**3h**). Yellow Oil. TLC (chloroform/methanol/ammonium hydroxide, 95:4.5:0.5): $R_f = 0.37$. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.51$ (s, 1H, C2H), 7.01 (s, 1H, C5H), 6.91 (s, 1H, C4H), 5.57 (m, 1H, C8H), 4.96 (m, 3H, C6H + C9H₂), 4.18-4.03 (m, 9H, Fc), 2.88 (m, 1H, C7H), 2.68 (m, 1H, C7H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 133.8$ (C8), 132.5 (C2), 129.5 (C5), 120.1 (C4), 118.9 (C9), 89.10 (C10), 70.0-66.5 (Fc), 58.2 (C6), 41.3 (C7). ESI-MS: m/z : 307 [M+H]⁺.

1-(1-Ferrocenylbut-3-en-1-yl)-1H-1,2,4-triazole (**3i**). Brown oil. TLC (dichloromethane/ethyl acetate, 8:2): $R_f = 0.37$. ¹H NMR (400 MHz, CDCl₃): $\delta = 8.06$ (s, 1H, C3H), 7.93 (s, 1H, C5H), 5.60 (m, 1H, C8H), 5.22 (dd, $J = 9.2, 4.8$ Hz, 1H, C6H), 5.02 (m, 2H, C9H₂), 4.25-4.07 (m, 9H, Fc), 2.92 (m, 2H, C7H₂). ¹³C NMR (100 MHz, CDCl₃): $\delta = 152.0$ (C3), 143.0 (C5), 133.6 (C8), 118.9 (C9), 87.9 (C10), 69.3-67.4 (Fc), 61.0 (C6), 40.6 (C7). ESI-MS: m/z : 308 [M+H]⁺.

1-(1-Ferrocenylbut-3-en-1-yl)-1H-1,2,3-triazole (**3j**). Brown solid, m.p.: 68-69 °C. TLC (dichloromethane/ethyl acetate, 9:1): $R_f = 0.44$. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.68$ (m, 1H, C5H), 7.53 (m, 1H, C4H), 5.62 (m, 2H, C6H C8H), 5.05-5.01 (m, 2H, C9H₂), 4.28-4.09 (m, 9H, Fc), 2.97-2.92 (m, 2H, C7H₂). ¹³C NMR (100 MHz, CDCl₃): $\delta = 134.0$ (C4), 133.4 (C8), 122.3 (C5), 118.9 (C9), 87.7 (C10), 69.4-63.3 (Fc), 61.4 (C6), 41.0 (C7). ESI-MS: m/z : 308 [M+H]⁺.

1-(1-Ferrocenylbut-3-en-1-yl)-1*H*-indazole (**3k**). Orange oil. TLC (petroleum ether/ethyl acetate, 9:1): $R_f = 0.40$. $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 8.00$ (s, 1H, C3H), 7.72 (m, 1H, C4H), 7.42 (m, 1H, C7H), 7.36 (t, $J = 7.0$ Hz, 1H, C6H), 7.14 (t, $J = 7.0$ Hz, 1H, C5H), 5.62 (m, 1H, C10H), 5.45 (m, 1H, C8H), 5.05 (d, $J = 16.8$ Hz, 1H, C11H), 4.92 (d, $J = 10.0$ Hz, 1H, C11H), 4.44-4.14 (m, 9H, Fc), 3.28 (m, 1H, C9H), 3.06 (m, 1H, C9H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 139.7$ (C7a), 135.0 (C10), 133.2 (C3), 126.3 (C4), 124.3 (C3a), 121.5 (C7), 120.8 (C6), 117.8 (C11), 109.8 (C5), 89.9 (C12), 69.4-68.2 (Fc), 59.4 (C8), 39.9 (C9). ESI-MS: m/z : 357 $[\text{M}+\text{H}]^+$.

2-(1-Ferrocenylbut-3-en-1-yl)-2*H*-indazole (**3k'**). Orange oil. TLC (petroleum ether/ethyl acetate, 9:1): $R_f = 0.30$. $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 7.90$ (s, 1H, C3H), 7.75 (m, 1H, C7H), 7.64 (m, 1H, C4H), 7.28 (t, $J = 7.0$ Hz, 1H, C6H), 7.07 (t, $J = 7.0$ Hz, 1H, C5H), 5.66 (m, 1H, C10H), 5.51 (m, 1H, C8H), 5.11-5.00 (m, 2H, C11H₂), 4.12-4.39 (m, 9H, Fc), 3.1 (m, 2H, C9H₂). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 148.5$ (C7a), 134.1 (C10), 126.0 (C6), 121.9 (C5), 121.5 (C3), 120.6 (C4), 119.5 (C3a), 118.3 (C11), 118.1 (C7), 88.5 (C12), 69.4-67.3 (Fc), 64.4 (C8), 40.8 (C9). ESI-MS: m/z : 357 $[\text{M}+\text{H}]^+$.

3-(1-Ferrocenylbut-3-en-1-yl)-2-(4-bromophenyl)indolizine (**3l**). Yellow oil. TLC (petroleum ether/dichloromethane, 8:2): $R_f = 0.35$. $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 7.71$ (d, $J = 6.9$ Hz, 1H, C5H), 7.60 (d, $J = 8.0$ Hz, 2H, C10H + C14H), 7.44 (d, $J = 8.0$ Hz, 2H, C11H + C13H), 7.35 (d, $J = 9.0$ Hz, 1H, C8H), 6.62 (dd, $J = 9.0, 6.8$ Hz, 1H, C7H), 6.46 (s, 1H, C1H), 6.35 (t, $J = 6.8$ Hz, 1H, C6H), 5.52 (m, 1H, C17H), 4.92 (d, $J = 17.2$ Hz, 1H, C18H), 4.86 (d, $J = 10.0$ Hz, 1H, C18H), 4.42 (m, 1H, C15H), 4.15-3.91 (m, 9H, Fc), 2.87 (m, 2H, C16H₂). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 136.7$ (C8a), 136.6 (C12), 131.8 (C5), 128.2 (C3), 128.1 (C8), 124.0 (C6), 122.4 (C2), 121.0 (C9), 119.5 (C7), 116.8 (C1), 110.1 (C10, C14), 99.5 (C11, C13), 90.0 (C19), 77.4-66.8 (Fc), 36.8 (C15), 35.9 (C16). ESI-MS: m/z : 510 $[\text{M}+\text{H}]^+$.

1-(1-Ferrocenylbut-3-en-1-yl)imidazo[1,5-*a*]pyridine (**3m**). Yellow oil. TLC (ethyl acetate/methanol, 98:2): $R_f = 0.29$. $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 8.40$ (s, 1H, C3H), 7.69 (d, $J = 7$ Hz, 1H, C5H), 7.53 (d, $J = 9.0$ Hz, 1H, C8H), 7.09 (dd, $J = 9.2, 6.4$ Hz, 1H, C7H), 6.96 (t, $J = 7.0$

Hz, 1H, C6H), 5.87 (m, 1H, C11H), 5.10 (d, $J = 17.0$ Hz, 1H, C12H), 5.05 (d, $J = 9.2$ Hz, 1H, C12H), 4.58 (m, 1H, C9H), 4.41-4.25 (m, 9H, Fc), 3.37 (m, 1H, C10H), 3.04 (m, 1H, C10H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 135.2$ (C8a), 132.4 (C11), 130.3 (C1), 125.4 (C7), 124.9 (C3), 120.7 (C12), 118.6 (C8), 118.3 (C6), 111.4 (C5), 85.2 (C13), 70.0-69.2 (Fc), 63.2 (C9), 39.7 (C10). ESI-MS: m/z : 357 $[\text{M}+\text{H}]^+$.

5-(1-Ferrocenylbut-3-en-1-yl)benzene-1,2,4-triol (**3n**). Yellow oil. TLC (petroleum ether/ethyl acetate, 6:4): $R_f = 0.42$. ^1H NMR (400 MHz, CDCl_3): $\delta = 6.43$ (s, 1H, C6H), 6.11 (s, 1H, C3H), 5.73 (m, 1H, C9H), 5.02 (m, 2H, C10H₂), 4.27-4.08 (m, 9H, Fc), 3.95 (m, 1H, C7H), 2.89 (m, 1H, C8H), 2.56 (m, 1H, C8H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 187.6$ (C5), 184.3 (C1), 155.6 (C2), 154.5 (C4), 136.0 (C9), 128.5 (C6), 117.4 (C10), 108.4 (C3), 90.0 (C11), 69.3-66.9 (Fc), 39.8 (C8), 37.0 (C7). ESI-MS: m/z : 365 $[\text{M}+\text{H}]^+$.

1-(1-Ferrocenylbut-3-en-1-yl)naphthalene-2,7-diol (**3o**). Yellow oil. TLC (*n*-hexane/ethyl acetate, 7:3): $R_f = 0.28$. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.68$ (d, $J = 8.7$ Hz, 1H, C3H), 7.56 (d, $J = 8.7$ Hz, 1H, C6H), 7.44 (s, 1H, C8H), 6.97 (d, $J = 8.7$ Hz, 1H, C4H), 6.84 (d, $J = 8.7$ Hz, 1H, C5H), 5.79 (m, 1H, C9H), 5.67 (s, 1H, OH), 5.56 (s, 1H, OH), 5.12 (d, $J = 17$ Hz, 1H, C12H), 4.93 (d, $J = 10.1$ Hz, 1H, C12H), 4.30-4.12 (m, 10H, Fc + C9H), 2.97 (m, 2H, C10H₂). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 154.6$ (C2), 153.4 (C7), 137.4 (C11), 134.9 (C8a), 131.1 (C3), 129.0 (C6), 125.1 (C1), 120.8 (C4a), 117.7 (C8), 116.6 (C12), 114.9 (C4), 105.7 (C5), 91.5 (C13), 69.7-67.0 (Fc), 37.6 (C10), 36.7 (C9). ESI-MS: m/z : 399 $[\text{M}+\text{H}]^+$.

2-(1-Ferrocenylbut-3-en-1-yl)-5-(diethylamino)phenol (**3p**). Yellow oil. TLC (petroleum ether/ethyl acetate, 9:1): $R_f = 0.17$. ^1H NMR (400 MHz, CDCl_3): $\delta = 6.86$ (d, $J = 8.5$ Hz, 1H, C3H), 6.22 (dd, $J = 8.5, 2.5$ Hz, 1H, C4H), 6.12 (d, $J = 2.5$ Hz, 1H, C6H), 5.82 (m, 1H, C9H), 5.10 (d, $J = 17.2$ Hz, 1H, C10H), 5.00 (d, $J = 10.4$ Hz, 1H, C10H), 4.25 (m, 1H, C7H), 4.16-3.92 (m, 9H, Fc), 3.30 (q, $J = 7.0$ Hz, 4H, N-CH₂-), 2.86 (m, 1H, C8H), 2.67 (m, 1H, C8H), 1.15 (t, $J = 7.0$ Hz, 6H, Me). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 154.5$ (C1), 148.1 (C5), 138.2 (C9), 130.3 (C3), 118.2 (C2), 116.1 (C10), 105.2 (C4), 100.1 (C6), 94.0 (C11), 69.1-67.1 (Fc), 44.7 (N-CH₂-), 40.4 (C8), 39.9 (C7), 13.1 (Me). ESI-MS: m/z : 404 $[\text{M}+\text{H}]^+$.

3-(1-Ferrocenylbut-3-en-1-yl)-4-hydroxy-2*H*-chromen-2-one (**3q**). Brown oil. TLC (*n*-hexane/ethyl acetate, 7:3): $R_f = 0.27$. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.90$ (d, $J = 7.8$ Hz, 1H, C5H), 7.51 (t, $J = 7.6$ Hz, 1H, C7H), 7.30 (d, $J = 8.3$ Hz, 1H, C8H), 7.23 (t, $J = 7.6$ Hz, 1H, C6H), 6.80 (s, 1H, OH), 5.91 (m, 1H, C11H), 5.09 (d, $J = 16.9$ Hz, 1H, C12H), 5.02 (d, $J = 9.9$ Hz, 1H, C12H), 4.75-4.21 (m, 10H, Fc + C9H), 2.79 (m, 1H, C10H), 2.70 (m, 1H, C10H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 163.8$ (C2), 160.7 (C4), 152.9 (C8a), 132.1 (C7), 124.1 (C6), 123.3 (C5), 117.5 (C12), 116.7 (C11), 116.5 (C8), 116.5 (C4a), 108.9 (C3), 90.2 (C13), 70.3-66.1 (Fc), 37.8 (C10), 35.6 (C9). ESI-MS: m/z : 401 $[\text{M}+\text{H}]^+$.

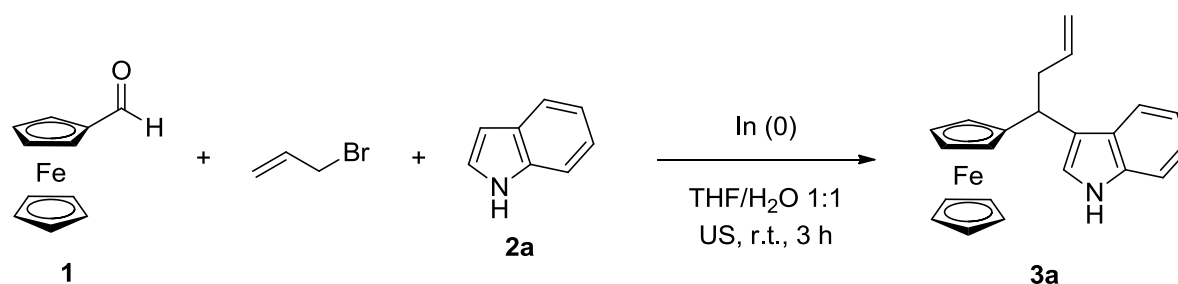
5-(1-Ferrocenylbut-3-en-1-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**3r**). Yellow oil. TLC (petroleum ether/ethyl acetate, 8:2): $R_f = 0.36$. ^1H NMR (400 MHz, CDCl_3): $\delta = 6.05$ (m, 1H, C9H), 5.40 (d, $J = 16.8$ Hz, C10H), 5.31 (d, $J = 10.4$ Hz, 1H, C10H), 4.21-4.10 (m, 10H, Fc + C7H), 3.50 (d, $J = 11.2$ Hz, 1H, C5H), 3.20 (s, 3H, Me), 2.95 (s, 3H, Me), 2.87 (m, 2H, C8H₂). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.1$ (C4), 167.7 (C6), 151.7 (C2), 136.0 (C9), 119.3 (C10), 87.6 (C11), 68.9-66.1 (Fc), 45.8 (C5), 36.1 (C8), 28.6 (Me), 28.3 (Me). ESI-MS: m/z : 395 $[\text{M}+\text{H}]^+$.

3. Results and Discussion

The domino allylindation-dehydrative alkylation was initially performed according to the successful procedure for indole-3-carboxyaldehyde [12], *i.e.* aldehyde (1 equiv), indium (1.4 equiv) allyl bromide (2 equiv) in THF/H₂O 1:1 at 50 °C for 8 h. A deep and careful investigation was carried out with the aim of selecting a better reaction solvent. A ready screening and survey of different solvents led us to the use of a THF/H₂O 1:1 mixture as our solvent of choice. An Achille's heel in our previous procedure was found as we recovered some homoallylic alcohol that had not reacted at the end of the reaction. Moreover, the dehydration product derived from homoallylic alcohol and which affords a butadiene derivative was detected in reaction mixtures when working with indole-3-carboxyaldehyde. Despite the similar functional groups, the reaction gave a useless and complex mixture of products. In the first step, the α -ferrocenyl carbocation was supposed to be the reaction intermediate. The capability of ferrocene nucleus to stabilize carbenium ions in an adjacent position to the cyclopentadienyl ring is well known [20], and as such the desired nucleophilic attack was expected according to an analysis of the electrophilicity parameters calculated by Mayr et al. [21].

In this context, the promoting effect of Bi (III) on the alkylation of α -ferrocenyl alcohols has recently been reported [22]. These premises prompted us to focus our investigation on the allylindation step of ferrocenecarboxaldehyde (FcCHO). The reaction was carried out in the absence of the nucleophile [i.e., FcCHO (1 equiv), indium (1.4 equiv) and allyl bromide (2 equiv)], in THF/H₂O 1:1 in order to evaluate the formation of homoallylic alcohol **3**(Nu=OH). Operating at room temperature, the clean alcohol (88% isolated yield) was formed very slowly after more than 20 h. A temperature of 50 °C gave a little improvement in reaction time (15 h), but we observed the formation of several side products and a prevalence of 1-ferrocenylbutadiene from dehydration. Higher temperature only gave a messy mixture of compounds. We conclude that the formation and stability of the alcohol is the bottleneck under conventional heating. In order to overcome these limitations, we used US to activate the metal surface [17, 23], removing the oxide layer of the metal surface and enhancing mass transfer. Preliminary trials were carried out in an US bath (20.3 kHz, 60W). US irradiation dramatically increased the rate of the reaction which went to completion in only 2 hours, affording the desired product in a 90% isolated yield, without any significant side products. Encouraged as we were by this result, we decided to investigate the effect of US on domino allylindation-dehydrative alkylation. Our model reaction is outlined as follows; 1*H*-indole as the nucleophile, a FcCHO/indium/allyl bromide/nucleophile ratio of 1:1.5:2:1, in 1:1THF/H₂O, at room temperature. The 1:1THF/H₂O mixture proved to be the solvent of choice under all conditions in the more efficient cup horn type probe reactors (Table 1).

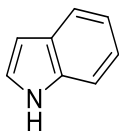
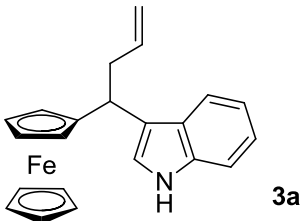
Table 1. US investigation of the domino allylindation-dehydrative alkylation of ferrocenecarboxaldehyde in the presence of 1*H*-indole. Reagents and conditions: **1** (1 mmol), allyl Br (2 mmol), **2a** (1 mmol), In (1.5 mmol), THF/H₂O 1:1 (6/6 mL), US, r. t., 3 h.

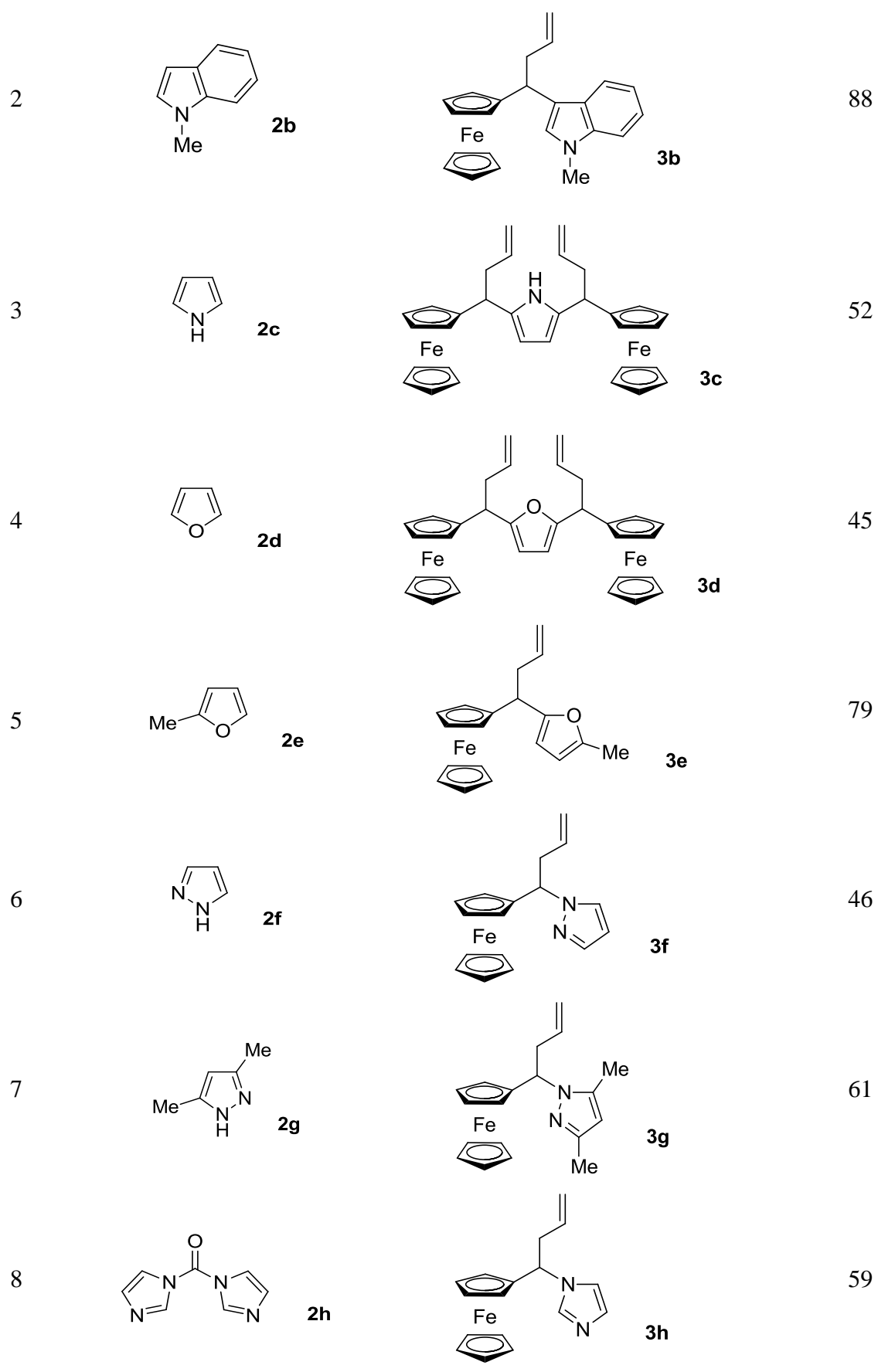


Probe US reactor	Isolated yield (%)
US-bath (20.3 kHz, 60W)	48
cup horn (19.9 kHz, 75W)	85
cup horn (300 kHz, 70W)	70

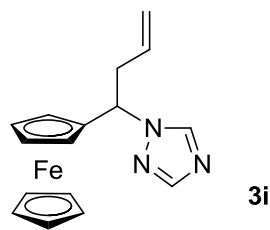
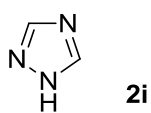
Three different US instruments were tested: a high power US bath (20.3 kHz) and two cup horns (19.9 kHz and 300.5 kHz). The best result was obtained with the 19.9 kHz cup-horn. Mass transfer was optimal under these conditions and indium powder reactivity favoured, affording the desired product **3a** in an 85% yield. The optimized protocol was then applied to a wide range of nucleophilic probes (*e.g.*, electron-rich (hetero)arenes and stabilized enols) (Table 2).

Table 2. Three-component US promoted indium-mediated domino allylation-alkylation of ferrocenecarboxaldehyde with electron-rich (hetero)arenes.

Entry	Nucleophile	Product	Isolated yield (%)
1	 2a	 3a	85

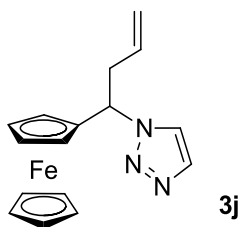
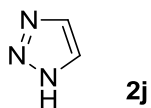


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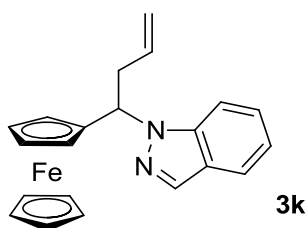
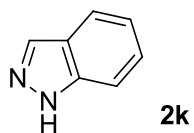
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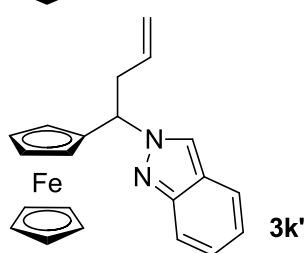


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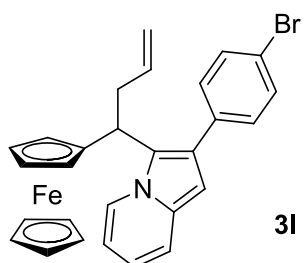
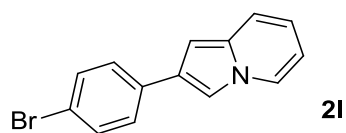


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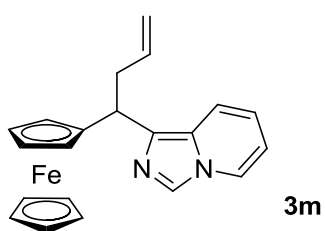
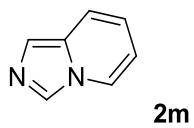
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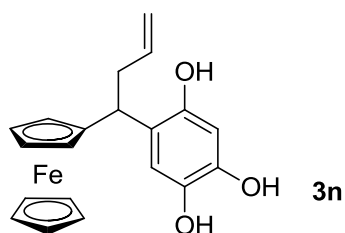
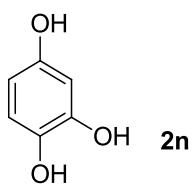
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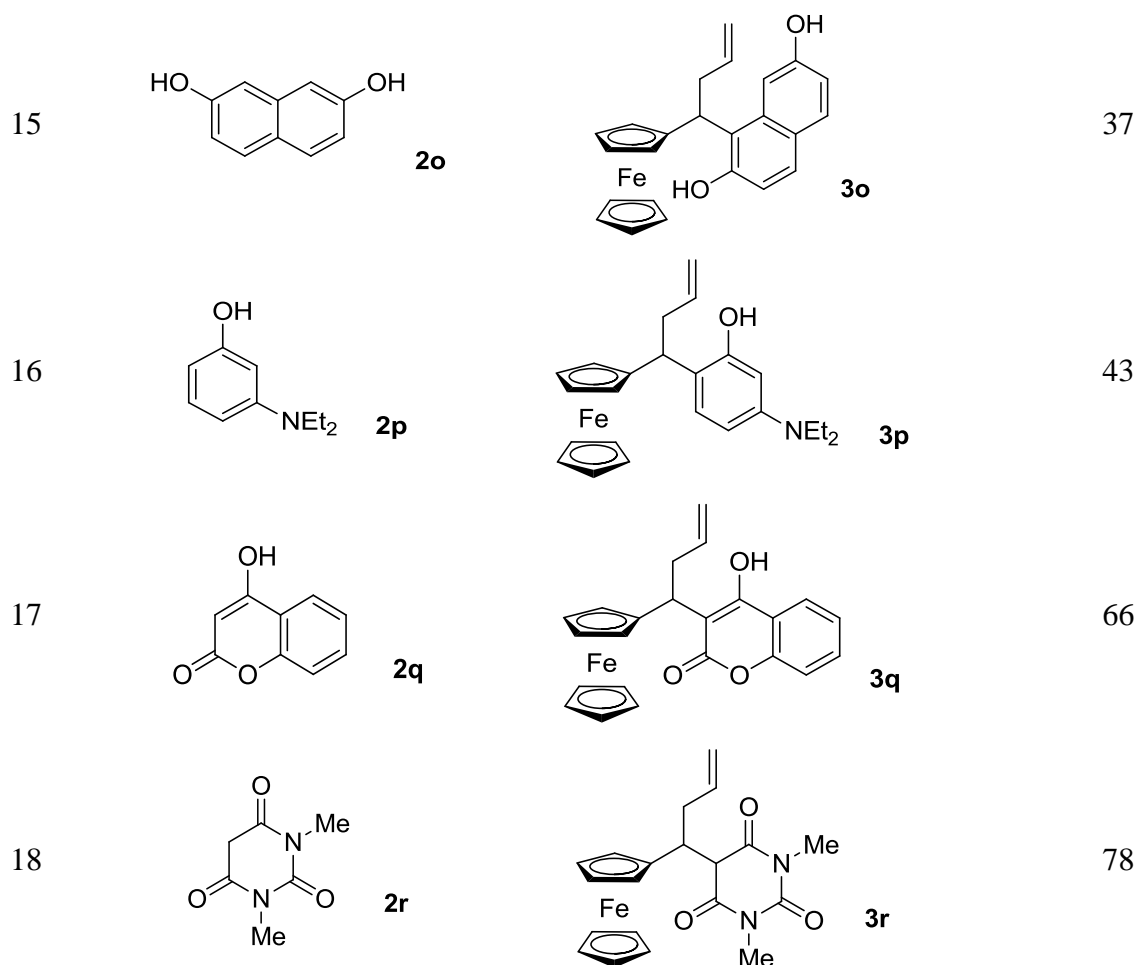


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Mono-alkylation did not take place with highly activated nucleophiles. In the case of pyrrole **2c** and furan **2d** (Table 2, Entries 3 and 4, respectively), the desired 1:1 adducts were not detected and only the *bis*-adducts **3c** and **3d** are formed. From a stereochemical point of view, *bis*-adducts **3c** and **3d** must be diastereoisomeric mixtures of C_2 and *meso* compounds, although ^1H and ^{13}C NMR spectra displayed no signal splitting. 2-Methylfuran **2e** only has one alpha position which is ready for nucleophilic attack (Table 2, Entry 5), so product **3e** was achieved in a good 79% yield.

Electron-poor azoles, for example, triazoles and benzofused analogues (Table 2, Entries 6-10), exhibited similar reactivity, affording the respective *N*-alkylated derivatives **3f-3j** in moderate-to-good yields while C-alkylation did not occur. These findings are consistent with classic azole chemistry. Accordingly, in free(NH) azole where (neutral) pyrrole-like and (base/nucleophilic) pyridine-like *N* atoms occur in the same molecule, an electrophile will always react with the latter [24]. The carbonyldiimidazole **2h** (Table 2, Entry 8) was used as the synthetic equivalent of imidazole. A regioselectivity issue occurred when benzopyrazole **2k** was used as an *N*-nucleophile. In fact, the equivalence of the two nitrogen atoms toward electrophilic attack lead to the formation of the N1 and N2 alkylation products **3k** and **3k'**, respectively, in equal amounts.

Pyrrolo[1,2-*a*]pyridines (or indolizines) and their aza-analogues (*viz.* imidazo[1,2-*a*]pyridines and imidazo[1,5-*a*]pyridines) result from the juxtaposition of electron-rich and electron-poor heterocyclic rings; their electrophilic substitution reactions take place on the five-membered ring at C-3 [25]. Thus, 2-(4-bromophenyl)indolizine gave the corresponding 3-alkylated compound **3l** in good yields (Table 2, Entry 12). Imidazo[1,5-*a*]pyridine **2m** (Table 2, Entry 13) is expected to be less selective, leading to a mixture of 1- (more favoured) and 3-substituted (less favoured) compounds. In this instance, however, the 1-substituted product **3m** was the sole reaction product.

We also examined the reactivity of electron-rich benzenoid compounds in order to assess the scope of our procedure. Highly activated poliphenol **2n** afforded the ferrocenyl adduct **3n** in satisfactory isolated yields (45 %) (Table 2, Entry 14); 2,7-dihydroxynaphthalene **2o**, that was inert in the thermal domino allylation-alkylation of indole-3-carboxyaldehyde [12], gave the product **3o** in a 37 % yield (Table 2, Entry 15); 3-(diethylamino)phenol **2p** reacted effectively to form **3p** in a 43 % yield (Table 2, Entry 16).

Enolates, that are derived from 1,3-dicarbonyl compounds, can undergo C and/ or O alkylation; the conditions that enhance the chemoselectivity of the reaction have been well established. Under our conditions, the use of 4-hydroxycoumarin **2q** and *N,N*-dimethyl barbituric acid **2r** afforded C-alkylated derivatives **3q** and **3r**, respectively, in good yields (Table 2, Entries 17 and 18 respectively).

4. Conclusions

In conclusion, a sonochemical, three-component, one-pot domino protocol for the synthesis of 18 new ferrocenyl derivatives has been described. Three US reactors have been compared and best results obtained in a cup-horn probe reactor (19.9 kHz). Full product characterization is reported as well as some considerations on key reaction mechanism steps.

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