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Regioselective synthesis of 1-azinyl-1′-isopropenylferrocenes

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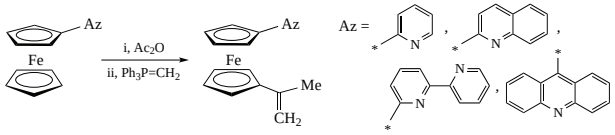
The Friedel–Crafts acetylation ($Ac_2O/AlCl_3$) reaction of azinylferrocenes occurs regioselectively at position 1′. Acetylated derivatives upon reaction with $Ph_3P{=}CH_2$ give the corresponding 1-azinyl-1′-isopropenylferrocenes.



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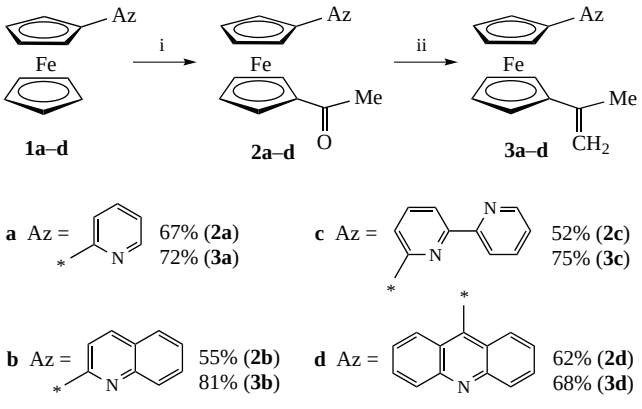
Owing to the exceptional electrochemical properties, substituted ferrocenes have been used in a wide range of material science applications.[1] Redox properties of the ferrocene moiety open up a new dimension for the construction of switchable motif for host–guest complexation,[2] nonlinear optical materials,[3] sol–gel[4] and micelle[5] actuation, biological recognition,[6] recyclable catalysts[7] and switchable dyes.[8] Olefins appended in ferrocene system allow one to create a highly conjugated two-dimensional p-electron system[9] providing a wide scope of useful materials.[10] Vinylferrocene, a monomer for metal-containing polymers,[10,11] is used for production of self-healing[4(a)] materials and composite colloidal crystal films.[12] Metal-containing polymers can participate in redox-responsive release from patchy nanocapsules,[13] catalysis modulating activity[14] and ion-selective membrane-gating through nanopores.[15] The presence of lipophilic ferrocene moiety in the drug structure modulates their physiological activity.[16]

To date, the Wittig reaction of phosphoranes and aldehydes/ketones[17] is most often employed for the synthesis of alkenylferrocenes. Alternatively, the McMurry coupling[18] ($TiCl_4/Zn$) between the appropriate benzophenones and acetylferrocenes was used in the synthesis of anticancer drugs as well as for reduction of aldehydes to obtain alcohol suitable for the following dehydration.[19]

The choice of azinylferrocenes is directly connected with the high efficiency of ferrocene derivatives in initiating mixtures for free-radical bulk polymerization of vinyl monomers.[20] Therefore, the synthesis of hetaryl-containing vinylferrocenes and study of their properties are of particular interest. To our knowledge, a protocol for the synthesis of non-symmetric azinyl-containing 1,1′-disubstituted vinylferrocenes has not been reported so far. In this work we have combined olefin and azine fragments on the ferrocene matrix by regioselective acylation followed by the Wittig reaction (Scheme 1).

The direct C–H functionalization of heteroarenes with ferrocenyllithium as a nucleophile (S_N^H reaction) generated azinylferrocenes **1**.[15(a)] The Friedel–Crafts acetylation ($Ac_2O/AlCl_3$) of compounds **1a**–**d** occurs exclusively at the 'free' Cp fragment to afford 1,1′-disubstituted products **2a**–**d** in good yields (see Scheme 1).[†] Apparently, an electron-withdrawing azine substituent would somewhat reduce the nucleophilicity of cyclopentadienyl ring, which is responsible for the regioselectivity of the process.[21] The steric bulkiness of these azine substituents



Scheme 1 *Reagents and conditions*: i, Ac_2O, $AlCl_3$, CH_2Cl_2, 0 °C; ii, $Ph_3P{=}CH_2$ (from $Ph_3PMe^+I^-$ and BuLi), Et_2O, room temperature.

† *1-Acetyl-1′-(pyridin-2-yl)ferrocene* **2a**. Acetic anhydride (0.283 ml, 6 mmol) was added to a solution of azinylferrocene **1a** (0.263 g, 1 mmol) in anhydrous CH_2Cl_2 (20 ml) at 0 °C followed by portionwise addition of $AlCl_3$ (0.399 g, 1.1 mmol) within 2 h, while the colour changed from red-orange to deep purple. After stirring at room temperature for 24 h, the mixture was poured into cold water and extracted with CH_2Cl_2. The extract was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (Al_2O_3, hexane/EtOAc, 9 : 1). The appropriate fractions were concentrated *in vacuo*. Yield of **2a**, 0.204 g (67%). Mp, 78 °C. R_f = 0.15. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.08 (s, 3H, Me), 4.40 (m, 2H, C_5H_4), 4.47 (m, 2H, C_5H_4), 4.59 (m, 2H, C_5H_4), 5.04 (m, 2H, C_5H_4), 7.19–7.22 (m, 1H, 5′-H), 7.54–7.56 (d, 1H, 3′-H, ^3J 7.9 Hz), 7.70–7.74 (m, 1H, 4′-H), 8.47–8.48 (d, 1H, 6′-H, ^3J 4.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.13 (Me), 68.35, 70.51, 71.12, 73.21, 80.28, 85.45 (Fc), 120.43, 121.28, 136.27, 149.11, 156.56 (Py), 200.44 (CO). IR (ν/cm^{-1}): 785.52, 1151.81, 1585.44, 1650.51 (CO). HRMS, *m*/*z* (%): 312.0662 [M + Li]$^+$ (100). Found (%): C, 66.98; H, 5.18; N, 4.60. Calc. for $C_{17}H_{15}FeNO$ (%): C, 66.89; H, 4.92; N, 4.59.

should also be considered. In previous reports, acylation of methyl- or bromoferrocenes with smaller substituents afforded mixtures of 1,2-, 1,3- and 1,1′-disubstituted derivatives.[1–3] In our case of azinylferrocenes, the regioselectivity is also attributed to the nature of the acetylating agent. For instance, on application of acetyl chloride or ethyl chloroformate, descent in the regioselectivity was observed. No products were formed when $(CF_3CO)_2O/AlCl_3$ and $AcOH/Al_2O_3$ systems were used. It should be noted that treatment of (quinoxalin-2-yl)ferrocene with $Ac_2O/AlCl_3$ system did not give the target 1′-acetyl derivative but occurred sluggishly at annealed benzene ring of the quinoxaline moiety. As for (phenanthrolin-2-yl)ferrocene, the target 1′-acetyl derivative was unstable towards column chromatography.

A general synthetic route to vinylferrocenes is based on the Wittig reaction of ferrocene carboxaldehyde with ylides.[17(*c*)] In this work, acetylferrocenes **2a**–**d** reacted at room temperature under an argon atmosphere with ylide obtained *in situ* from excess triphenylmethylphosphonium iodide and BuLi (see Scheme 1).‡ When reactivities of 1-acetyl-1′-azinylferrocenes **2a**–**d** and parent acetylferrocene in the Wittig olefination were compared, we indicated that isopropenyl derivatives **3a**–**d** were formed at room temperature, while the similar transformation of acetylferrocene required heating to 45 °C. Apparently, electron-withdrawing effect of hetaryl substituents in compounds **2** could enhance the electrophilicity of their carbonyl group. All obtained azinyl-substituted ferrocenes **2a**–**d** and **3a**–**d** are stable solid compounds coloured from orange to dark red. Their structures were confirmed by ^1H, ^{13}C NMR and IR spectroscopy, high resolution mass spectrometry (HRMS), and elemental analyses.

In conclusion, our study provides a method for the regioselective 1′-acetylation of mono-substituted azinyl-ferrocenes. The obtained acylated derivatives **2a**–**d** react with phosphorus ylides under mild conditions with formation of olefins **3a**–**d** enabling the design of redox and vinyl polymers.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.03.026.

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‡ *1-Isopropenyl-1′-(pyridin-2-yl)ferrocene* **3a**. A 1.6 M hexane solution of BuLi (0.71 ml, 1.14 mmol) was added to a suspension of methyl(triphenyl)phosphonium iodide (1.25 mmol) in anhydrous diethyl ether (5 ml) under argon at room temperature. After stirring for 15 min, a solution of acetylferrocene **2a** (1.0 mmol) in anhydrous diethyl ether (20 ml) was added. After stirring the reaction mixture at room temperature for 4 h, it was purified on Al_2O_3 using hexane–ethyl acetate mixture (9 : 1) as eluent. The eluate was concentrated to dryness *in vacuo*. Yield of **3a**, 0.218 g (72%). Mp, 84 °C. R_f = 0.5. For characteristics, see Online Supplementary Materials.