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Synthesis, Electrochemistry and Cytotoxicity of Ferrocene-Containing Amides, Amines and Amino-Hydrochlorides

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Abstract

Ferrocenylamides, Fc–(CH(sub2))subn–CONH(sub2) with n = 0 (3a), 1 (3b), 2 (3c), and 3 (3d) and Fc =ferrocenyl = FeII(C(sub5)H(sub5))(C(sub5)H(sub4)), were synthesised by reacting aqueous ammonia with the appropriate acid chlorides, Fc–(CH(sub2)subn–COCl, 2a–2d, under interfacial conditions. The acid chlorides were obtained from Fc–(CH(sub2))subn–COOH, 1a–1d, by treatment with SOCl9(sub2), (COCl)(sub2) or PCl(sub3). The effectiveness of the different chlorination reagents for these ferrocene acid derivatives is compared. The amides were subsequently treated with LiAlH4 to generate the amines Fc–(CH(sub2))subm–NH2 with m = 1 (4a), 2 (4b), 3 (4c), and 4 (4d); they may be stored as the hydrochloride salts but cold storage is preferable. A cyclic voltammetric study of the amides 3a–3d and amines 4a–4d in CH(sub3)CN/0.1 M [N(nBu)(sub4)][PF6] and the hydrochlorides 4a.HCl–4d.HCl in water containing 10 mM HCl and 1 M KCl showed the formal oxidation potential, Eo0 versus FcH/ FcH?, of the ferrocenyl group decreased non-linearly with increasing values of n. Formal redox potentials of the ferrocenylamides, –amines, –hydrochlorides, the precursor acids and of the related ferrocene-containing alcohols Fc–(CH(sub2))subn+1–OH, 5a–5d, are compared. The cytoxicity of Fc–CH(Sub2)–CONH9sub2), expressed as the concentration causing 50 % HeLa cell growth inhibition (the IC(sub50) value) was 39.7 lM, is almost the same as that of the alcohol Fc–CH9(sub2)–CH9sub2)–OH (IC5(sub0) = 35.0 lM). This Fc–CH(sub2)–CONH(sub2) cytotoxic result implies that the largest ferrocenyl group redox potential a radical-active cytotoxic ferrocene-containing compound can have to still possess cytotoxic activity against HeLa cancer cells is ca. -0.003 V versus FcH/FcH(sup+).