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Synthesis of benzyl- and benzhydrylferrocenes via Friedel–Crafts alkylation of ferrocene. Access to ferrocenyl bisphenols with high affinities for estrogen receptors

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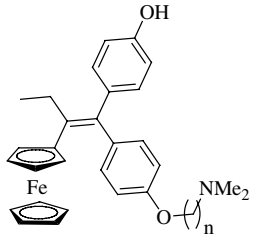
Abstract—Ferrocene reacts with methoxy-substituted benzyl- and benzhydryl alcohols in the presence of trifluoroacetic acid to afford methoxybenzyl- or benzhydrylferrocenes in 47–56% yield. Demethylation of these compound leads to the ferrocenyl phenols and bisphenols. Some of the synthesized compounds display high affinity for estrogen receptors ERα and ERβ.

The discovery of remarkable antiproliferative properties of ferrocifenes **1**[1,2] on both hormone-dependent and hormone-independent breast cancer cell lines prompted us to start a search for other ferrocene-based compounds exhibiting similar properties in the hope of finding new organometallic anticancer drugs. Benzyl- and benzhydryl (diphenylmethyl) ferrocenes containing hydroxyl groups in the phenyl rings are promising candidates since they are expected to display high affinity for estrogen receptors. In fact, it is known that some organic hydroxy-substituted di- and triarylmethanes display such affinity.[3–5] Replacement of one of the arene rings in these compounds by the potentially cytotoxic ferrocene moiety could lead to compounds exhibiting antiproliferative effects against breast cancer cells, depending on both types of estrogen receptors (ERα and ERβ), similar to those found for **1**.[1,2]

In principle, the introduction of benzyl or benzhydryl groups to ferrocene should be possible via Friedel–Crafts alkylation but this type of reaction usually leads to complex mixtures of mono- and polysubstituted ferrocenes.[6] It has been reported that reaction of ferrocene with benzhydryl alcohol in the presence of aluminum chloride at 120–140 °C (melt phase) resulted only in the formation of 1,1′-dibenzhydryl ferrocene and polysubstituted ferrocenes regardless of the ratio of the reactants used.[7] A similar reaction using benzyl alcohol instead of benzhydryl alcohol gave only a low yield (<20%) of substituted ferrocenes (presumably a mixture), which have not been purified and characterized.[7] A few substituted benzylferrocenes have been prepared by less direct routes, involving reactions of ferrocenecarboxaldehyde with aryllithiums and reduction of the resulting carbinols.[8,9] The carbenium salts obtained from these carbinols were also reacted with electron-rich arenes to give benzhydrylferrocenes.[10,11]



1: n = 3, 4

In this letter we report a simple, direct method for the introduction of substituted 4-methoxybenzyl or benzhydryl groups to ferrocene, giving good yields of

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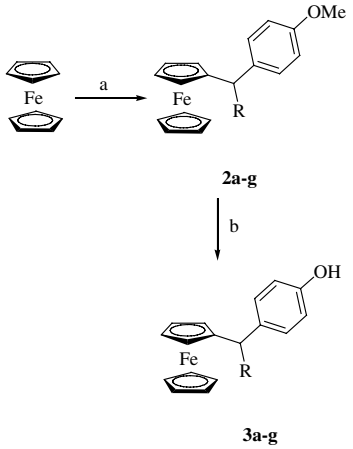
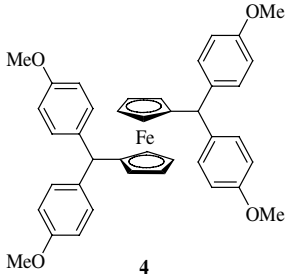
monosubstituted ferrocenes and demethylation of these compounds along with preliminary results on the biochemical properties of ferrocenyl bisphenols.

We have found that ferrocene reacts in CH_2Cl_2 at room temperature and in the presence of trifluoroacetic acid with benzyl- or benzhydryl alcohols to afford monoalkylated ferrocenes **2a**–**g** in 47–56% yield (Scheme 1).[12] More substituted ferrocenes were formed only in very low yields (<5%, calculated for disubstituted derivatives) and were easily separated from **2a**–**g** by column chromatography. No attempts were made to characterize these compounds. Only in the reaction of ferrocene with *p*′*p*′-dimethoxybenzhydrol we observe formation of a larger amount of the second product, identified as **4** (the isolated yields of **2g** and **4** in this reaction were 55% and 20%, respectively).



Scheme 1. Reagents and conditions: (a) (*p*-$MeOC_6H_4$)(R)CHOH, CF_3CO_2H, CH_2Cl_2, rt; (b) BBr_3, CH_2Cl_2, rt **2**–**3a** (R = H), **2**–**3b** (R = Me), **2c** (R = 6-MeO-2-naphthyl), **3c** (R = 6-HO-2-naphthyl), **2**–**3d** (R = *p*-$CF_3C_6H_4$), **2e** (R = *o*-$MeOC_6H_4$), **3e** (R = *o*-HOC_6H_4), **2f** (R = *m*-$MeOC_6H_4$), **3f** (R = *m*-HOC_6H_4), **2g** (R = *p*-$MeOC_6H_4$), **3g** (R = *p*-HOC_6H_4).



Strong protic acids such as trifluoromethanesulfonic or methanesulfonic acid have been recently applied in Friedel–Crafts reactions of ferrocene.[13,14] In comparison, the reaction described here proceeds under much milder conditions (solution of CF_3COOH in dichloromethane at room temperature). This is undoubtedly due to the easy ionization of the alcohols used in an acidic medium combined with the high nucleophilic activity of ferrocene.[6] On the other hand, the origins of the preferential formation of monosubstituted ferrocenes are not clear. In the reaction of ferrocene with benzhydryl alcohol in the presence of $AlCl_3$ the formation of polybenzhydrylferrocenes averaging 6–7 substituents per molecule has been observed,[7] indicating that steric effects are not important.

The corresponding hydroxy compounds **3a**–**g** have been obtained in 37–63% isolated yields by a routine demethylation of **2a**–**g** with BBr_3 in CH_2Cl_2 at rt.[15,16]

In a preliminary study of the biochemical properties of the three bisphenol complexes **3e**–**g** their relative binding affinities (RBA) were measured on both isoforms of the estrogen receptor (ERα and ERβ) using the radiochemical method previously described.[17] Lamb uterus cytosol was used as a source of ERα, while purified human ERβ (h-ERβ) was purchased from PanVera (USA). Interestingly all the three complexes showed significant recognition for the two forms of the estrogen receptor with a selectivity for ERβ (ratio RBA (ERβ)/RBA (ERα) between 1.5 and 3.4) (Table 1). These results are in agreement with the observation that the beta form of the estrogen receptor is more suitable to accommodate smaller ligands than its alpha form.[18] The RBA values found for **3g**, the complex with two *p*-hydroxyphenyl groups are remarkably high. For the three complexes, the RBA values are noticeably higher than the ones found for the xenoestrogen bisphenol A (0.4% for ERβ and 0.01% for ERα)[3] but comparable to the values found on ERα binding for some bisphenol sulfono derivatives.[5] Considering their high RBA values together with their structure, complexes **3e**–**g** are expected to be estrogenic. On the other hand, the presence of the ferrocenyl substituent could trigger off some cytotoxic effects. In vitro experiments on hormone-dependent and hormone-independent breast cancer cell lines, presently in progress, will help us to answer this question.

1. Conclusion

We have developed a simple and efficient method for the synthesis of methoxy- and hydroxy-substituted benzyl

Table 1. Relative binding affinities (RBA) for ERα and ERβ of ferrocenyl bisphenols **3e**–**g**

	RBA (%)		
	ERα	ERβ	RBA (ERβ)/RBA (ERα)
17β-Estradiol	100[a]	100[a]	1
3e	2.1 ± 0.1	7.5 ± 0.5	3.4
3f	4.6 ± 0.1	15.5 ± 0.5	3.3
3g	18.2 ± 1.5	28 ± 2	1.5

[a] Value by definition.

and benzhydryl ferrocenes via Friedel–Crafts alkylation of ferrocene. This method gives essentially monosubstituted ferrocenes. Di- and more substituted ferrocenes are formed only in small amounts and can be easily separated by flash chromatography. To the best of our knowledge, this reaction constitutes the first example of the selective monoalkylation of ferrocene by the Friedel–Crafts route. Interestingly, the three synthesized bisphenol derivatives of ferrocene exhibit a high affinity for the two forms of estrogen receptor.

Acknowledgements

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12. *General procedure*. CF_3CO_2H (0.3 mL) was added to a solution of ferrocene (2 mmol) and benzyl- or benzhydryl alcohol (1 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temperature for 20 min, poured into a saturated solution of $NaHCO_3$ (20 mL) and extracted three times with CH_2Cl_2 (60 mL). The monosubstituted ferrocenes **2a**–**g** were isolated by flash chromatography (pentane–dichloromethane 1:1). Yield (mp): **2a**, 50% (76–77 °C); **2b**, 55% (oil); **2c**, 47% (60–61 °C); **2d**, 56% (125–126 °C); **2e**, 47% (106–107 °C); **2f**, 55% (oil); **2g**, 55% (31–32 °C); **4**, 20% (118 °C (decomp.)). All new compounds were fully characterized.
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