Coupling of Low-order Organocopper Complexes with Organoiron Cations; Synthesis of Tamandron, a Novel Potentially Antiandrogenic Analogue of Tamoxifen

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Low-order alkyl, aryl and vinyl organocopper complexes react efficiently with tricarbonyl(cyclohexadienylium)iron cations; the low-order vinylcopper complex derived from an (*E*)-1-bromo-1-(4-alkoxyphenyl)-2-phenylbut-1-ene couples the bulky vinyl group regioselectively, and with retention of the double-bond stereochemistry, to the encumbered C-5 methylsubstituted position of a tricarbonyl(2-alkoxy-5-methylcyclohexadienylium)iron cation, thereby forming a chiral quaternary carbon centre, and providing access to tamandron, a novel potentially antiandrogenic analogue of tamoxifen.

A key objective in our programme to develop a selective drug for the treatment of prostate cancer is synthesis of a novel potentially antiandrogenic tamoxifen analogue **1**, which incorporates the testosterone *A*-ring, and which is herein referred to as tamandron.[1]

Our projected approach to tamandron (Scheme 1) demanded coupling of a bulky vinyl anion derived from the vinyl bromide **6** to the encumbered methyl substituted C-5 position of the organoiron cation **2a**. The (*E*)-vinyl bromides **6a**‡ and **b**‡ were prepared (>70% yield) from the aryl ketones[2] **5a** and **b**, respectively, using our recently discovered highly stereoselective ($E:Z$ = 20:1) bromide trapping reaction.[3] Therefore, we also sought to achieve this coupling whilst maintaining the integrity of the double-bond stereochemistry, despite the fact that α-aryl substituted vinyl anions undergo particularly facile stereomutation.[4]

However, although various organometallic reagents[5,6] deliver carbanions to the C-5 position of the 5-unsubstituted complex **3**, introduction of carbanions into the C-5 position of the methyl substituted complex **2a** has hitherto been restricted to enolate-type nucleophiles.[7] Indeed, attempted reaction of the vinylcadmium or vinylzinc[5] derivatives of **6a** with **2a** resulted in rapid deprotonation of the C-5 methyl group producing the C-5 methylene complex[8] **4a**; the vinyl anion therefore behaved as a base instead of a nucleophile. The prospect of coupling **6** with **2a** appeared even more remote when it was found that the vinylzinc derivative of **6a** also

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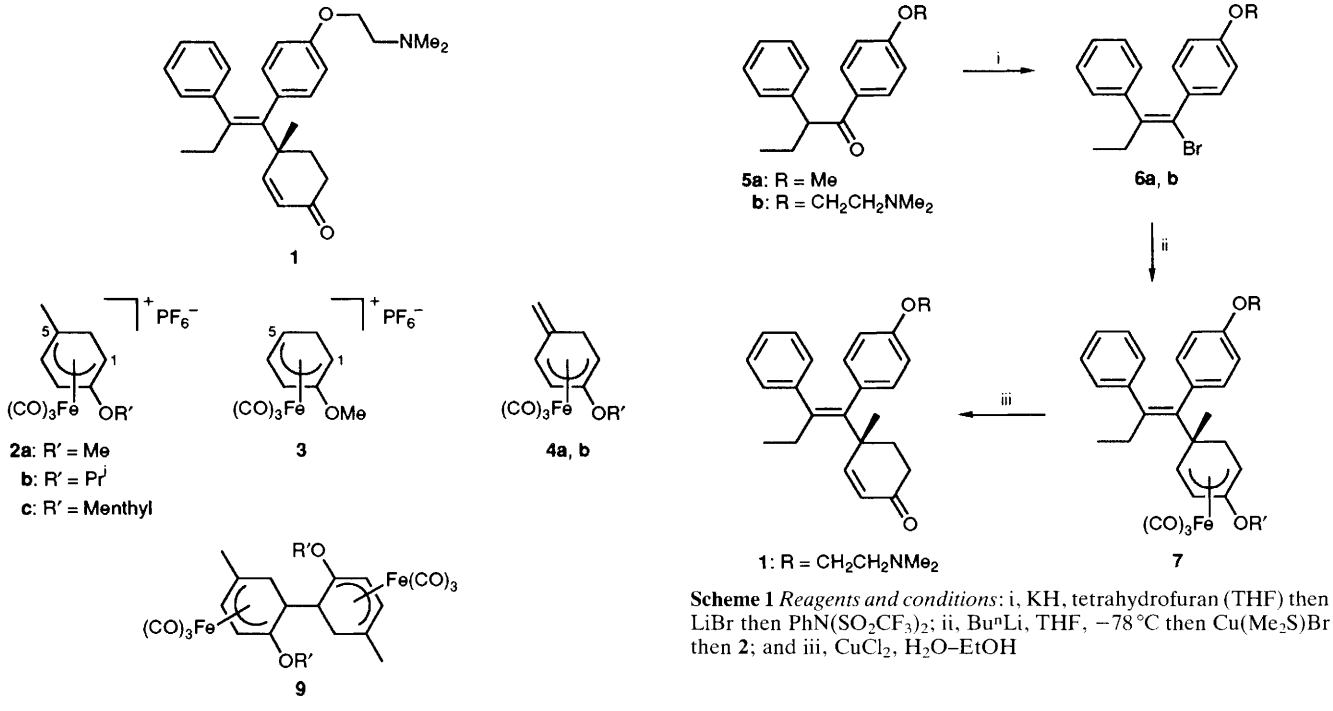
‡ New compounds isolated gave satisfactory elemental analyses.

Table 1 Coupling of vinylcopper complexes derived from **6a** with the organoiron cations 2a–c[a]

Entry	Organoiron cation	CuX	Order of 'cuprate'	Yield(%)[b] C-5 regioisomer **7**	C-1 regioisomer **8**	Homocoupled product **9**
1	**2a**	CuCN	2	4	48	5
2	**2b**	CuCN	2	9	8	15
3	**2b**	[Cu(thienyl)CN]Li	3	0.3	3	10
4	**2b**	$CuBr(Me_2S)$	1	42	5	0
5	**2c**	$CuBr(Me_2S)$	1	32	0	0

[a] All reactions were carried out according to Scheme 2, under an argon atmosphere. [b] Yields refer to isolated compounds for major products, or else were estimated from the proton NMR spectrum of the crude product.



Scheme 1 *Reagents and conditions*: i, KH, tetrahydrofuran (THF) then LiBr then $PhN(SO_2CF_3)_2$; ii, Bu^nLi, THF, −78 °C then $Cu(Me_2S)Br$ then **2**; and iii, $CuCl_2$, H_2O–EtOH

behaved as a base with the unsubstituted complex **3**, resulting in deprotonation from C-6 to liberate anisole.

In view of Pearson's[9] use of a second-order lithium divinylcuprate to deliver a simple vinyl group (H_2C=CH–) to an unsubstituted position of a tricarbonyl(cyclohexadienylium)iron cation, albeit in moderate yield (34%), and the fact that organocuprate nucleophiles have high affinity for carbon electrophiles and relatively low affinity for protons,[10] we were prompted to explore the reactions of various organocuprates and organocopper complexes derived from **6a** with **2** (Scheme 2 and Table 1).

Coupling of the second-order mixed lithium vinylcyanocuprate[11] derivative (entry 1) with the organoiron cation **2a** was achieved. However, the major coupled product was the C-1 regioisomer **8**,‡ but significantly some of the desired C-5 regioisomer **7**‡ was also formed. An interesting byproduct from this reaction was the homocoupled iron complex **9**,‡ isolated as bright-yellow crystals. Presumably this had formed by electron transfer from the cuprate complex to the organoiron cation and homocoupling of the resultant organoiron radical. Use of the isopropoxy organoiron complex[12] **2b** markedly reduced the unwanted coupling at C-1, but the yield of **7** was still poor (entry 2).

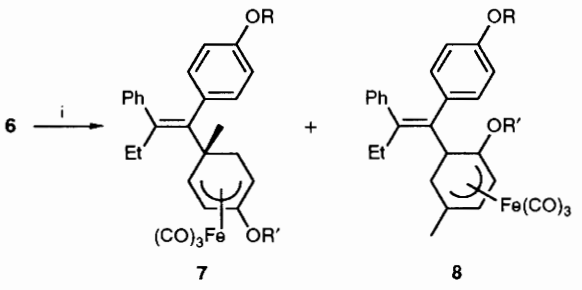
The mixed third-order dilithium vinyl(thienyl)cyanocuprate[13] (entry 3) was too reactive, displaying a more 'vinyllithium' than 'vinylcopper' character and giving mainly the deprotonated complex **4b** at the expense of nucleophilic attack.

It was therefore decided to 'tune down' the reactivity of the organocopper species by making a low-order vinylcopper derivative using copper(I) bromide(dimethyl sulfide).[14] This provided a completely soluble vinylcopper(dimethyl sulfide) derivative (entry 4), which introduced the bulky vinyl group into the methylsubstituted C-5 position with remarkable efficiency, and furthermore no homocoupled byproduct was formed. Importantly, by maintaining the reaction temperature at around −78 °C coupling was achieved with complete retention of the stereochemistry about the vinyl double-bond.

The (+)-menthoxy organoiron complex **2c**, which we have previously shown provides excellent regiocontrol and allows access to homochiral 4-methylcyclohexenone derivatives,[15] gave essentially complete regioselectivity for the methyl substituted C-5 position (entry 5).

In order to obtain tamandron **1** the low-order vinylcopper coupling reaction used the dimethylaminoethoxy vinyl bromide **6b** and the organoiron cation **2b**. This worked almost as well as for **6a**, and provided the key tamandron precursor **7** (R = $CH_2CH_2NMe_2$, R′ = Pri)‡ in 30% yield. The final decomplexation step on this compound, performed using copper(II) chloride dihydrate in ethanol,[16] provided the target molecule, tamandron, **1**‡ a colourless oil that afforded a white crystalline hydrochloride monohydrate derivative (m.p. 176–178 °C).

In addition another important point is that low-order organocopper complexes also deliver nucleophiles very efficiently into the C-5 position of the unsubstituted organoiron complex **3**. Thus, with the vinylcopper (dimethyl sulfide)



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Scheme 2 *Reagents and conditions*: i, Bu^{n}Li, THF, −78 °C then CuX then **2**

derivative of **6a**, the C-5 coupled product‡ was obtained in 78% isolated yield. This methodology also works exceptionally well for introducing more slender organic groups, and for the reaction of n-butylcopper(dimethyl sulfide) with **3** provided the coupled product tricarbonyl[2-methoxy-5α-(n-butyl)cyclohexadiene]iron in 86% isolated yield, previously prepared using second-order cuprate methodology in 33% yield.[9] Reaction of phenylcopper(dimethyl sulfide) with **3** provided exclusively the C-5 regioisomer tricarbonyl-(2-methoxy-5α-phenylcyclohexadiene)iron‡ in 96% isolated yield (m.p. 49–50 °C).

In conclusion, low-order organocopper complexes react efficiently with tricarbonyl(cyclohexadienylium)iron cations and a method has been developed that allows carbon nucleophiles, in addition to enolates,[7] and even very hindered carbon nucleophiles, to be introduced into an already substituted position of the dienyl ligand thereby forming a new quaternary carbon centre. This greatly extends the synthetic potential of this, already useful, type of organoiron complex, especially as recent developments in cuprate technology[17] allow the preparation of highly functionalised low-order organocopper complexes.

Tamandron **1** exhibited androgen receptor binding (IC_{50} = 12.5 μmol dm^{-3}; J. A. Houghton, unpublished results), which substantiates the prospect of developing an antiandrogenic tamoxifen analogue for the treatment of prostate cancer. The detailed results on the binding of tamandron to the androgen receptor will be published elsewhere, and the synthesis of the individual enantiomers of **1** employing the homochiral organoiron synthon[15] **2c** is currently underway.

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