ORGANOMETALLICS

Copper(I)-Mediated Synthesis of Ferrocenyl Alkyl Ethers[†]

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Summary: The copper(I)-mediated Ullman-type coupling of iodoferrocene and diverse alcoholates has been used for the preparation of a series of ferrocenyl alkyl ethers. In this manner oxygen-substituted ferrocenes that cannot be synthesized via the classical Williamson ether synthesis are accessible in good yields. The structure of three samples in the solid state is reported.

Introduction

In the last decades ferrocene has emerged as an essential motif in organometallic chemistry.¹ It has found numerous applications in academia and industry; the spectrum ranges from its use as a highly selective and efficient ligand in asymmetric homogeneous catalysis² to fuel additives for diesel engines.³

The field of oxygen-substituted ferrocenes is one aspect that is still not fully developed. This may be attributed to the sensitivity of the phenol analogue hydroxyferrocene⁴ or the tendency of oxygen electrophiles, e.g. peroxides or peresters, to irreversibly oxidize the iron center.⁵ Since 1959, when Nesmeyanov and co-workers reported on the synthesis of some ferrocenyl alkyl ethers via etherification of hydroxyferrocene,⁶ only a few new molecules have been prepared utilizing mostly primary alkyl halides or tosylates.⁷ To our knowledge, the successful application of neither secondary nor tertiary alkyl derivatives has been reported so far.

In contrast, ferrocenyl aryl ethers are easily accessible via copper(I)-mediated coupling of iodoferrocene and various phenols as demonstrated by Plenio et al. recently.⁸

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(3) Ferrocene is added to diesel fuel in order to improve combustion and to reduce the emission of soot.

(4) Nesmeyanov et al. report that hydroxyferrocene decomposes within several days when exposed to air.

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We report here on the copper(I)-mediated Ullman-type coupling of iodoferrocene with diverse alcoholates to give ferrocenyl alkyl ethers.

Results and Discussion

Recently, we have reported on novel planar chiral P,O-ferrocenes that show unrivaled activity for the Suzuki coupling of hindered substrates.⁹ For the synthesis of an enantiomerically enriched P,O-ferrocene we intended to apply enantiomerically pure ferrocenyl ethers. Scheme 1 summarizes our attempts to synthesize **3a** starting from iodoferrocene **2**.

All our attempts to prepare 3a via the classical Williamson ether synthesis failed; neither menthyl chloride, menthyl methansulfonate, nor menthyl 4-nitrobenzenesulfonate was successfully attacked by 1. As menthyl derivatives seem to be relatively inert toward a nucleophilic attack, we decided to use menthol as the nucleophile in a copper(I)-mediated Ullman-type coupling with iodoferrocene. At first an O-arylation protocol (CuI, 1,10-phenanthroline, Cs₂CO₃, toluene, 90 °C) published by Buchwald et al.¹⁰ was used. Unfortunately, this methodology did not result in the formation of desired 3a. Following this, a modified reaction protocol developed by Bolm et al. for the synthesis of nitrogensubstituted ferrocenes (CuI, KO'Bu, NMP, 70 °C)¹¹ was applied. This procedure allowed isolating 3a apart from unreacted 2 in approximately 10% yield; however, the product was contaminated with FcO'Bu (Fc = Fe(η^5 -C₅H₄)(η^5 - C_5H_5)). This prompted us to deprotonate menthol with sodium hydride prior to use rather than to apply menthol and a base in the coupling reaction, which indeed improved the yield of 3a (82%) significantly and avoided the formation of unwanted FcO^tBu.

The optimized reaction conditions (3.0 equiv of NaOR, 1.0 equiv of CuI, 0.2 equiv of 2,2'-bipyridine, 70 °C, 18 h) for the synthesis of ferrocenyl alkyl ethers were applied to several alcohols ROH to screen the synthetic potential of this coupling reaction (Table 1).¹²

As can be seen from Table 1 secondary (entries 1-6) and primary (entries 7-10) alcohols could successfully be applied in this Ullman-type coupling. Within this reaction, besides **3**,

[†]Dedicated to Professor Stefan Spange on the occasion of his 60th birthday.

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⁽¹²⁾ Changing the solvent to acetonitrile or dmso did not affect the yield positively.



^{*a*}(a) 1. AcOH, Cu₂O, CH₃CN, reflux, 3 h (93%); 2. KOH, H₂O, EtOH, reflux, 20 min; 3. HCl, H₂O, EtOH, ambient temperature, 10 min (95%); (b) base, menthylX (X = Cl, OS(O)₂CH₃, OS(O)₂-4-NO₂-C₆H₄), solvent, ambient temperature to 100 °C, 12–24 h; (c) CuI, 2,2'-bipyridine, NaOmenthyl, NMP, 70 °C, 18 h (82%).

 Table 1. Ullman-Type Coupling of Iodoferrocene and Various

 Alcohols to Ferrocenyl Alkyl Ethers^a



^{*a*} Reaction conditions: 1.0 equiv of iodoferrocene, 3.0 equiv of NaOR, 1.0 equiv of CuI, 0.2 equiv of 2,2'-bipyridine, NMP (5 mL/mmol iodoferrocene), 70 °C, 18 h. ^{*b*} Based on isolated material. ^{*c*} 0.1 equiv of CuI. ^{*d*} 2.0 equiv of NaOR.

only unreacted iodoferrocene $\mathbf{2}$ and ferrocene could be identified.

While the coupling of primary and secondary alcohols is well documented in the literature, to the best of our knowledge, the use of tertiary alcohols has not been reported so far,¹³ and hence, **2** was reacted with NaOR ($\mathbf{R} = {}^{t}\mathbf{Bu}$, Ph₃C, 1-adamantanyl). It was found that the coupling occurred but that the appropriate products were formed only in poor yields (<5%); however, in the case of $\mathbf{R} = 1$ -adamantyl the formation of the ferrocenyl ether was not observed.

Obviously, secondary alcohols show better results in this Ullman-type coupling reaction than primary ones. The

 Table 2. Comparison of Ullman-Type Coupling and Williamson

 Ether Synthesis



^{*a*} Based on isolated material. ^{*b*} Reaction conditions: 1.0 equiv of iodoferrocene, 3.0 equiv of NaOR, 1.0 equiv of CuI, 0.2 equiv of 2,2'-bipyridine, NMP (5 mL/mmol iodoferrocene), 70 °C, 18 h. ^{*c*} Reaction conditions: 1.0 equiv of FcOAc, 2.0 equiv of KOH, 2.0 equiv of RX (X = Br, Cl, OS(O)₂CH₃, OS(O)₂-4-NO₂-C₆H₄, DMF (7 mL/mmol FcOAc), 100 °C, 18 h.

Scheme 2. Ullman-Type Coupling of 1,1'-Diiodoferrocene and Menthol^a



 a (a) 1.0 equiv of 1,1'-diiodoferrocene, 6.0 equiv of NaOmenthyl, 2.0 equiv of CuI, 0.4 equiv of 2,2'-bipyridine, 10 mL of NMP, 70 °C, 18 h.

following order of reactivity can be established: secondary > primary > tertiary alcohols. Considering the secondary alcohols, it is obvious that steric hindrance at the β -carbons improves the yield of the reaction (Table 1, entries 1, 2, 5, and 6 vs 4) as long as the system is not overcrowded (Table 1, entry 3).

A beneficial property of this Ullman-type coupling is that chiral alcohols can be applied without any loss of stereoinformation. The reaction runs with full retention of configuration, which could be confirmed by NMR experiments and X-ray diffraction studies.

We also tried to perform this reaction catalytically based on copper(I) (Table 1, entry 1, 0.1 equiv of CuI), which resulted in a dramatic loss of activity. Nevertheless, the yield of this experiment revealed that this coupling reaction is at least substoichiometric concerning copper(I).

Compared to the classical Williamson ether synthesis the presented Ullman-type coupling is especially beneficial when sterically demanding alcohols are applied (Table 2, entries 1 and 2 vs 3 and 4). Obviously both synthesis methodologies are complementary.

Also 1,1'-diiodoferrocene was applied in this coupling reaction. Using excess menthol resulted in the formation of disubstituted ferrocene **5** besides **3a** (Scheme 2, ratio 1:1) as the only products. A ferrocene proving a 2-fold reaction

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Figure 1. ORTEP diagram of **3a**. Thermal ellipsoids are at 50% probability. Selected bond distances (Å) and angles (deg): D1–Fe1 1.6549(4), D2–Fe1 1.6529(4), C1–O1 1.365(2), O1–C11 1.442(3), D1–Fe1–D2 179.50(2), C1–O1–C11 117.67(19) (D1 = centroid C1–C5, D2 = centroid C6–C10).



Figure 2. ORTEP diagram of 3c. Thermal ellipsoids are at 50% probability. Selected bond distances (Å) and angles (deg): D1–Fe1 1.6563(3), D2–Fe1 1.6560(3), C1–O1 1.360(2), O1–C11 1.447(2), D1–Fe1–D2 179.17(2), C1–O1–C11 117.65(14) (D1 = centroid C1–C5, D2 = centroid C6–C10).

could not be identified. Unfortunately we were not able to separate the two ferrocenyl ethers by column chromatography. The formation of monosubstituted 3a can be explained by hydrodehalogenation (vide supra).¹⁴

It must be mentioned that the ferrocenyl ethers (**3a**, **3b**, and **3i**) tend to decompose slowly in solution, to give a paramagnetic species that could be removed by filtration.



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C1-C5, D2 = centroid C6-C10).

All new ferrocenes have been characterized by standard analytical methods including NMR spectroscopy, elemental analysis, and mass spectrometry. For **3a**, **3c**, and **3e** single crystals could be obtained by crystallization from *n*-pentane at -40 °C. Figures 1 to 3 show the results of the X-ray diffraction analyses. Representative bond distances (Å) and angles (deg) are given in the captions of these figures. The ferrocenyl moiety in **3c** exhibits a staggered conformation, whereas **3a** and **3e** show an almost eclipsed orientation of the two cyclopentadienyl rings.

Conclusion

Within this study the straightforward preparation of ferrocenyl alkyl ethers by an Ullman-type coupling of iodoferrocene and various alcohols has been developed, which is in the case of chiral alcohols highly diastereoselective. Primary and secondary alcohols can successfully be applied in this reaction, whereas tertiary alcohols are almost unreactive. A comparison of the developed coupling reaction with the classical Williamson ether synthesis revealed that both methodologies are complementary. Especially when secondary alcohols are applied, the respective ethers that are not accessible via etherification of ferrocenol can be isolated in good yields, which enriches this field of chemistry. Nevertheless, there is still a need for a rational synthesis route that utilizes tertiary alkyl derivatives.

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Supporting Information Available: Text and figures giving further experimental and spectroscopic details and CIF files giving crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data for **3a**, **3c**, and **3e** are also available from the Cambridge Crystallographic Database as file nos. CCDC 781730, 781732, and 781731.

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