



Mild hydrolytic cleavage of α -ferrocenylalkyl-*O*-methyl ethers

Sonia Pedotti*, Angela Patti

Istituto di Chimica Biomolecolare del CNR, Via Paolo Gaifami 18, 95126 Catania, Italy

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ABSTRACT

The conversion of α -ferrocenylalkyl-*O*-methyl ethers into the corresponding alcohols was successfully achieved by solvolysis in water/acetone mixtures. The content of water in the solvent markedly influenced the reaction rates. The reactivity of structurally different classes of ferrocenyl ethers was evaluated and in most cases high yields of ferrocenyl alcohols or diols were obtained in a few hours without any additive. Deprotection of less reactive substrates was accelerated in the presence of montmorillonite. The method is simple, environmentally benign and valuable in providing easy access to a variety of ferrocenyl derivatives through the use of the *-O*-methyl ether protective group.

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1. Introduction

Ferrocenes are an important group of organometallic compounds with applications in catalysis,¹ in materials science² and in the development of redox sensors.³ They also display interesting biological properties⁴ and some specifically designed ferrocenyl conjugates are valuable candidates for antimalarial⁵ or anticancer therapies.⁶

A large number of mono- or 1,1'-disubstituted ferrocenes can be prepared from α -ferrocenyl alcohols since they easily undergo, directly or through the corresponding acetates, the substitution of the hydroxyl group with a variety of nucleophiles.⁷ Such reactivity has been related with the formation of α -ferrocenylcarbocations as **1**, whose stabilization and conformationally constrained structure result from the direct participation of iron in charge delocalization.⁸ As a consequence of the structure of **1**, the displacement of hydroxyl (or acetate) group and the attack of the approaching nucleophile take place on the same *exo*-face so that the substitution leads to retention of configuration at the stereogenic α -carbon centre (Scheme 1a).

The synthesis of 1,2-disubstituted ferrocenes mostly relies on the selective metallation of substrates bearing suitable *ortho*-directing groups followed by quenching of the intermediate anion with different electrophiles⁹ (Scheme 1b). In relation with the configuration of the chiral carbon bearing the *ortho*-directing group, the sequence provides a versatile access to enantiopure derivatives with defined planar chirality. Among the different ferrocenes available as starting materials, chiral α -ferrocenyl alcohols

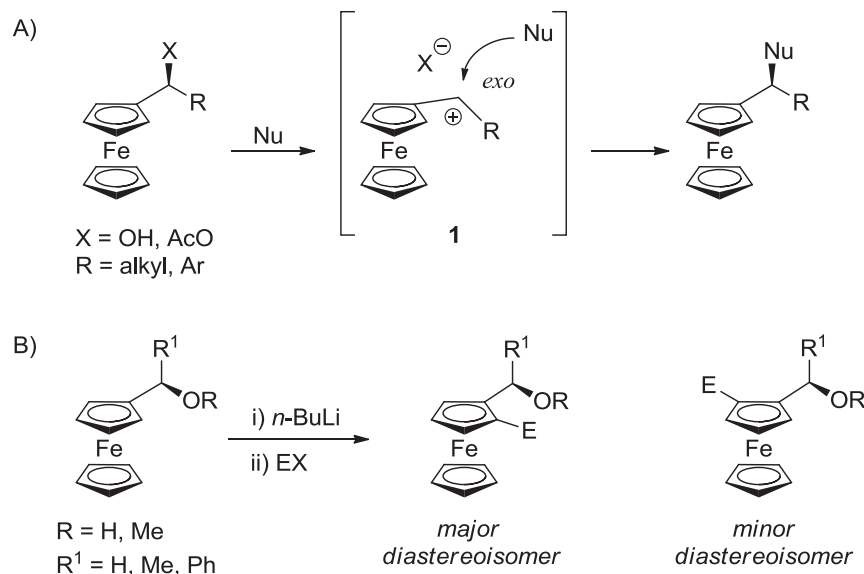
are straightforwardly available in enantiopure form from enzymatic resolution of their racemates¹⁰ or asymmetric reduction of the corresponding acylferrocenes¹¹ and good diastereoselectivity has been reported by Ueberbacher et al.¹² for their *ortho*-lithiation with 2.2 equiv of alkyllithium base.

In an alternative approach, *O*-methyl ethers of α -ferrocenyl alcohols have been employed as more stable substrates and Knochen's group described the highly diastereoselective *ortho*-introduction of halogens or aromatic and heteroaromatic substituents on different (α -methoxyarylmethyl) ferrocenes.¹³ The methoxy-directed lithiation has been also exploited for the preparation of some racemic 1,2- or 1,1',2,2'-functionalised ferrocenes from achiral *O*-methyl ethers of ferrocenemethanol and 1,1'-bis(hydroxymethyl)ferrocene, respectively.¹⁴ The ether functionality was retained in all the reaction products, may be due to the harsh conditions conventionally required for the cleavage of alkyl *O*-methyl ethers¹⁵ that could not be compatible with the ferrocenyl system.

Whereas the conversion of α -ferrocenyl alcohols into the corresponding *O*-methyl ethers readily occurs in the presence of acids or bases^{14a,16} and also cerium ammonium nitrate or ytterbium triflate has been recently shown effective catalyst for methanolysis,^{7e,17} the reverse reaction has not been investigated and the direct substitution of the α -methoxy group has been reported only with diphenylphosphine as nucleophile.^{13,18}

The development of a general protocol for deprotection of ferrocenyl methyl ethers to the corresponding alcohols could open up access to several ferrocenyl derivatives through a more extended use of the *O*-methyl ether protective group. Herein we describe the hydrolysis of α -ferrocenylalkyl-*O*-methyl ethers as a simple methodology for their conversion into alcohols and the extension of the

* Corresponding author. Tel.: +39 (0)957338329; fax: +39 (0)957338319; e-mail addresses: sonia.pedotti@cnr.it, sonia.pedotti@icb.cnr.it (S. Pedotti).



Scheme 1. (A) Nucleophilic substitutions at α -ferrocenyl carbon and (B) *ortho*-directed metallation for the synthesis of 1,2-disubstituted ferrocenyl derivatives.

procedure to 1,1'- and 1,2-disubstituted derivatives, in some case in the presence of montmorillonite as a catalyst. Mild conditions and high yields of the desired alcohols are attractive features of the process.

2. Results and discussion

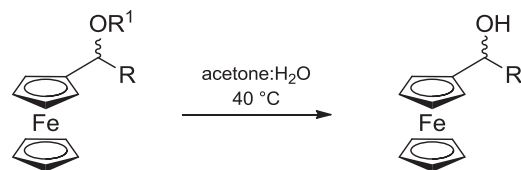
Solvolysis reactions have been mainly investigated for molecular systems able to give highly stabilized carbocations and the collection of solvolysis rate constants of several benzhydryl compounds has recently led to the construction of scales for nucleofugacity as a solvent-dependent parameter describing the ability of a given substituent to act as a leaving group that carries away the bonding electron pair in the heterolysis of carbon–X (X=O or halogen) bonds.¹⁹ In that study the *O*-methyl group was not considered and in the few reported examples of solvolysis of methyl ethers a reaction mechanism involving the formation of carbocation–MeOH pairs with significant lifetimes to be trapped by solvent has been suggested.²⁰

With respect to ferrocene derivatives, the solvolysis of α -ferrocenyl acetates or trimethylammonium iodides has been long reported^{7a,21} and related with the high stability of α -ferrocenylcarbocations, but the reaction has not been extended to other α -substituted compounds including *O*-methyl ethers.

At the onset of this study ferrocenyl ether **2a** was chosen as model substrate and left to stand in different water/acetone mixtures at 40 °C while the reaction course was monitored by TLC analysis. The formation of alcohol **3a** was evidenced in all cases and the efficiency of deprotection significantly increased in parallel with the water percentage in the solvent (Table 1), satisfactory conversions of **2a** being observed in mixtures containing more than 50% of water. Under vigorous stirring the initial suspensions of substrate turned into solutions with the progress of the reactions and, after addition of ethyl acetate, the alcohol **3a** was easily recovered in the organic phase. Neither the elimination product vinylferrocene nor bis(α -ferrocenylethyl) ether, derived from trapping of carbocation **1** by a molecule of **3a** and reported as a side-product in some nucleophilic substitutions of **2a** in an aqueous medium,^{7c} was detected in the reaction mixtures.

The solvolysis of a pure sample of (*R*)-**2a**^{7a} gave **3a** with the same configuration and enantiomeric purity as the starting ether, in

Table 1
Effect of water content on solvolysis of α -ferrocenylalkyl-*O*-methyl ethers^a



2a R = R¹ = Me

2b R = Me, R¹ = Et

2c R = H, R¹ = Me

3a R = Me

3c R = H

Entry	Substrate	Acetone/H ₂ O ratio ^b	Time (h)	Alcohol	(%) ^c
1	2a	5:1	20	3a	9
2	2a	1:1	20	3a	29
3	2a	1:2	4	3a	94
4	2a	1:5	4	3a	97
5	2b	1:5	20	3a	95
6	2c	1:5	20	3c	<5

^a Experimental conditions: substrate (5 mg/mL), solvent as indicated, 40 °C.

^b Vol/vol.

^c Isolated yields.

analogy with the general outcome reported for nucleophilic substitutions of other α -ferrocenyl derivatives.

In the optimal acetone/H₂O 1:5 mixture the solvolysis of ethoxy derivative **2b** proceeded effectively, albeit in a longer reaction time (compare entries 4 and 5), whereas methyl ether **2c** was quite unreactive under all of the tested conditions, in agreement with the relative solvolysis rates 1:10.5 reported for acetates of ferrocenylmethanol and α -ferrocenylethanol.^{21a}

The same reaction conditions were then applied to different *O*-methyl ethers from mono- and 1,1'-disubstituted α -ferrocenylalkylalcohols (Scheme 2 and Table 2). Monoether derivative **4a** were converted into the corresponding alcohols **3d** and **5a**, respectively, in high yields and reaction rates (entries 1 and 5). Phenyl derivative **2e** did not react at all (entry 2) at 40 °C, in contrast with solvolysis studies on *O*-acetates of α -ferrocenylalkylalcohols that evidenced increased reactivity on going

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