ORGANIC LETTERS

2004
Vol. 6, No. 21
3687−3690

Convenient Methods for the Synthesis of Ferrocene–Carbohydrate Conjugates

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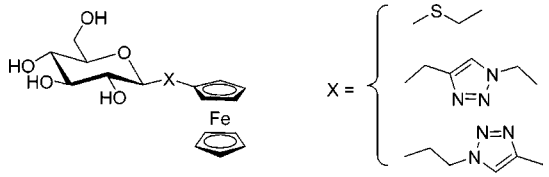
Received July 12, 2004

ABSTRACT



We report two methods for the attachment of mono- and disaccharides to one or both of the cyclopentadienyl rings in ferrocene. The first strategy involves the reaction in acidic media of thioglycosides with ferrocenemethanol or 1,1′-ferrocenedimethanol. The second method consists of the regiospecific catalytic cycloaddition of propargyl glycoside and azidomethyl and bis(azidomethyl)ferrocene leading to the 1,2,3-triazole derivatives. The inverse strategy was also explored. The electrochemical behavior of the synthesized ferrocene-containing glycoconjugates was investigated.

The possibility of building redox-switching or sensing systems of a molecular or supramolecular nature which can be controlled through the application of external stimuli has created a wide interest in metallocene derivatives such as ferrocene-bearing binding sites for molecular recognition.[1] In this regard, water-soluble ferrocenes are particularly of interest as their reversible and tunable redox properties could have biological applications, for example, in the development of biosensors. The covalent attachment of ferrocene and carbohydrate residues is a way to confer water-solubility and biocompatibility to the metallocene.[2]

In addition, water-soluble ferrocenes are useful for the development of ferrocene-containing drugs. It has been found, for example, that some ferrocenyl sugars possess antimalarial activity.[2i]

Normally, the conjugation between the carbohydrate and the ferrocene moieties has been performed via *O*, *S* and *N* acylation[2a,d,f,i−l] using 1-ferrocenecarbonyl chloride and 1,1′-ferrocene dicarbonyl chloride. Lewis acid promoted *O*-

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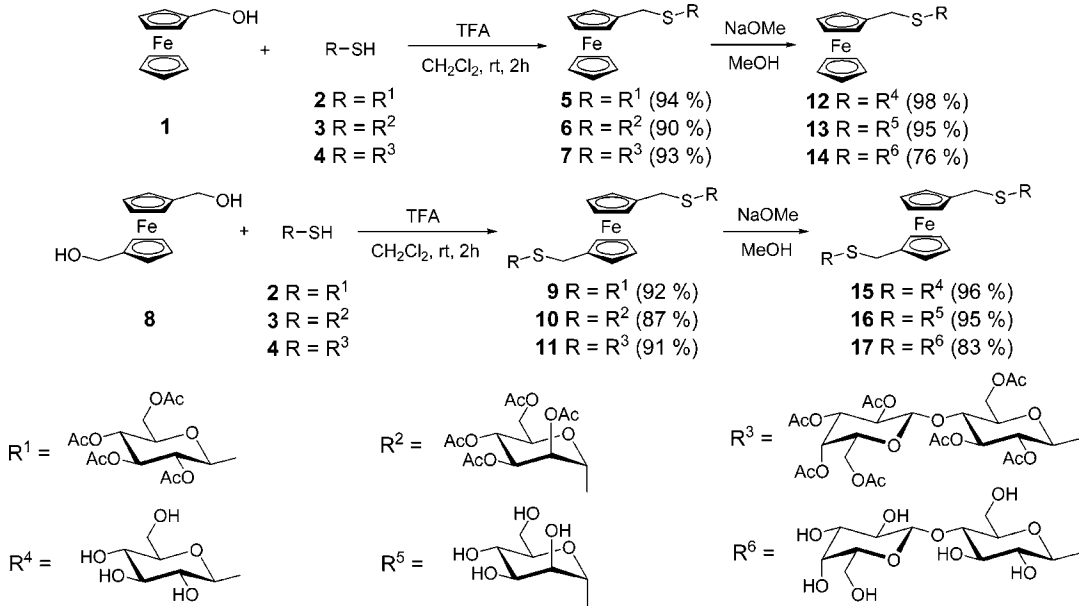
10.1021/ol048665j CCC: $27.50
Published on Web 09/17/2004

Scheme 1. Synthesis of Thioglycosylated Ferrocenes



glycosidation with a ferrocenyl derivative gave the ferrocenylamine−*O*-glucose conjugate in low yields.[2g] Also, a *C*-glycoside has been reported in which the glycopyranosyl unit is attached to one of the ferrocene cyclopentadienyl rings.[2b] 1-Ferrocenylmethyl tosylate has been used as well for connecting both moieties by means of nucleophilic substitution reactions giving rise to glycoconjugates attached by anomeric-*S* and nonanomeric-*O* linkages.[2a] In fact, the participation of the ferrocenyl group during the nucleophilic substitution reactions at the benzylic-like 1-ferrocenylmethyl position[3] provides a very reactive electrophilic carbon which allows the easy functionalization of that position. Thus, *O*-, *N*-, and *S*-ferrocenyl−carbohydrate conjugates have been synthesized from the methiodide salt of *N*,*N*-dimethylaminomethylferrocene by nucleophilic displacement of triethylamine by a carbohydrate derivative.[2a,c,g,h]

Due to our interest in developing carbohydrate-based biosensors, we became involved in exploring efficient and versatile methods that provide an easy access to ferrocene−carbohydrate conjugates. We have investigated two synthetic strategies. The first one is based on the reactivity of the 1-ferrocenylmethyl position that would allow the preparation of alkyl ferrocenylsulfides directly from hydroxymethylferrocene by reaction with thiol derivatives in acidic media.[4] The second strategy involves the copper(I)-catalyzed 1,3-dipolar cycloaddition reaction between a terminal alkyne and an azide. This reaction which leads only to the 1,4-disubstitued 1,2,3-triazole has demonstrated to be an extraordinarily efficient method for the construction of monovalent and multivalent bioconjugates.[5,6] Both strategies involve the use of easily available starting materials, both commercially and synthetically (see the Supporting Information). In this paper, we also describe the electrochemical behavior of both types of ferrocene−carbohydrate conjugates having sulfur and 1,2,4-triazole bridges.

The first synthetic strategy involved the treatment of 1-hydroxymethylferrocene (**1**) and the glycosyl thiols **2**−**4** with TFA in anhydro CH_2Cl_2 which led to the ferrocenylmethyl thio-*gluco*pyranoside, *manno*pyranoside, and lactoside **5**−**7** in 90−94% yields (Scheme 1). The reactions proceeded at room temperature and were kept for 2 h until TLC showed a complete disappearance of the starting material. Heating or long reaction times are not required as reported previously in former papers for similar acid-catalyzed thioalkyltions of **1**.[4] To synthesize divalent glycosyl-ferrocenes we carried out the reaction of the glycosyl thiols **2**−**4** with 1,1′-bis(hydroxymethyl)ferrocene (**8**) under similar conditions. The bis(glycosyl) ferrocene derivatives **9**−**11** were isolated after column chromatography in good yields (87−92%). Removal of the protecting groups of **5**−**7** and **9**−**11** with NaOMe

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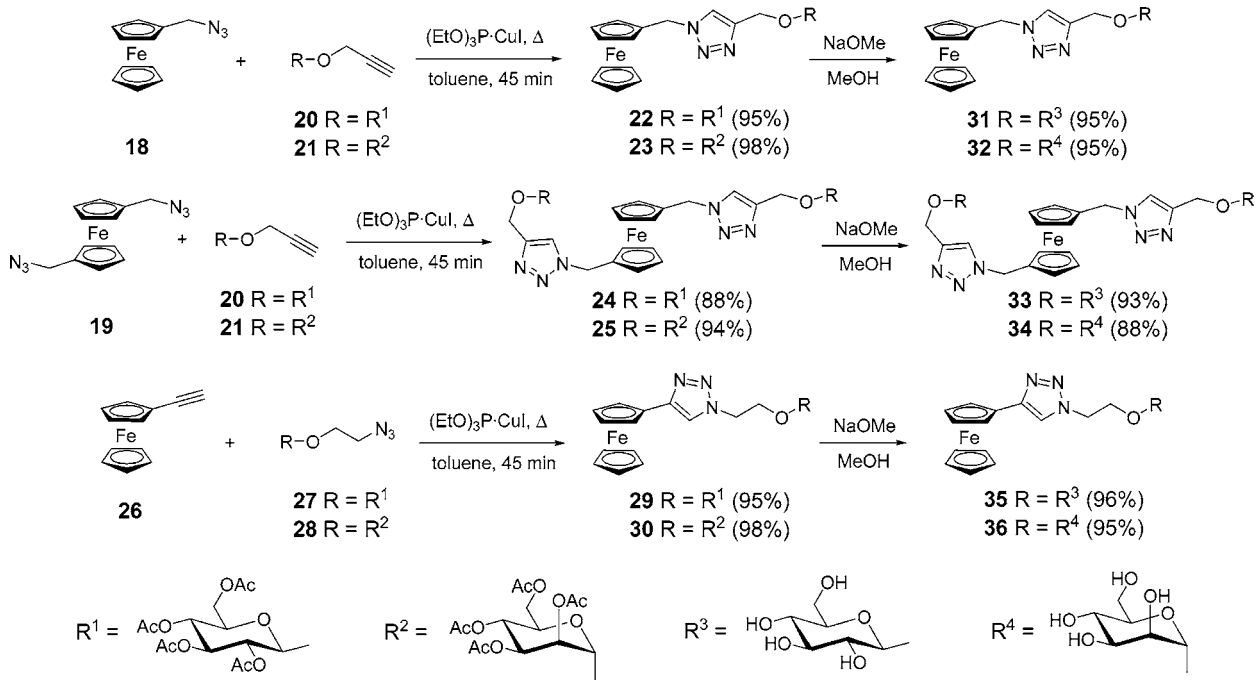
Scheme 2. Synthesis of 1,2,3-Triazole Derivatives



afforded the monovalent and divalent ferrocene−saccharide conjugates **12**−**17** having a methylenethio tether. Attempts to synthesize nonsymmetrical diglyco−ferrocene conjugates by subsequent reactions of **8** with two different thioglycosides failed. When we carried out the reaction of **8** with 0.5 equiv of **2** we isolated the dithioglucosylated ferrocene **9** suggesting an anchimeric assistance by the attached thioglycoside, likely through the formation of a sulfonium ion bridge intermediate.

Ferrocenes **1** and **8** efficiently reacted with sodium azide in acetic acid to give the corresponding azido derivatives **18** and **19** in 92 and 93% yield, respectively. We used these compounds to investigate the regiospecific coupling with alkyne derivatives of carbohydrates as an alternative method for the synthesis of carbohydrate−ferrocene conjugates. In previous reports, we have shown that the construction of neoglycoconjugates can be effectively performed by cycloaddition reactions of alkynes and azides using organic-soluble catalysts such as $(Ph_3P)_3$·CuBr and $(EtO)_3P$·CuI and bases such as DIPEA and DBU. These reaction conditions allow the formation of conjugates containing 1,4-disubstituted 1,2,3-triazole tethers.[6b] Thus, the reaction of propargyl glycosides **20** and **21** with azido ferrocenes **18** and **19** in toluene under reflux with catalytic amounts of $(EtO)_3P$·CuI afforded after 45 min and column chromatography the mono- and diglycosylated 1,2,3-triazoles **22-25** in 88−95% yields (Scheme 2). We found that the coupling reactions did not need a base to proceed efficiently. The same reaction conditions were used for the coupling of the 2-azidoethyl glycosides **27** and **28** and 1-ethynylferrocene **26** obtaining the corresponding monoglycosilated 1,2,3-triazoles **29** and **30** in almost quantitative yields.

Our interest in performing the reactions in protic solvents led us to carry out the reaction of the glucoside **27** with 1-ethynylferrocene **26** using the same catalyst but in methanol under reflux. In this case, the reaction needed 2 h for completion and the 1,2,3-triazole **29** was obtained in 59% yield. However, the reaction of the propargyl glucoside derivative **20** with 1-(azidomethyl)ferrocene **18** under the same conditions did not lead to the expected 1,2,3-triazole but to 1-(methoximethyl)ferrocene, as a result of the substitution of the azido group by methanol. Finally, de-*O*-acetylation of compounds **22**−**25**, **29**, and **30** by treatment with NaOMe gave the 1,2,3-triazole-tethered ferrocene−carbohydrate conjugates **31**−**36** in 88−96% yields having a glycoside attached to one and both cyclopentadienyl rings of the metallocene.

The electrochemical properties of ferrocene−carbohydrate conjugates **12**−**17** and **31**−**36** can be studied by cyclic voltammetry (CV) and differential pulse voltammetric (DPV). CV and DPV were performed using solutions of the conjugates (0.5 mM) prepared in water with 50 mM NaCl as a supporting electrolyte and using a glassy carbon working electrode, a Ag/AgCl (KCl 3 M) reference electrode, and a Pt wire counter electrode. The potential was scanned in the range of 0.05−0.50 V/s. Cyclic voltammograms of **12**−**17** and **31**−**36** showed reversible redox couples of ferrocene/ferricinium as shown in Figure 1. The values of the halfwave potential ($E_{1/2}$) for the oxidation of the ferrocene core and the diffusion coefficient (D_0) are shown in Table 1. Their differential pulse voltammograms reveal only one oxidation peak for each ferrocene derivative, meaning that in aqueous solution the conjugates are present in only one distinguishable form.[2k] ^{1}H NMR measurements of the disubstituted ferrocene **17** carried out at variable temperatures (+50 to −50 °C) in MeOD gave spectra showing as well only one distinguishable form. This indicates the absence of relevant restrictions (for

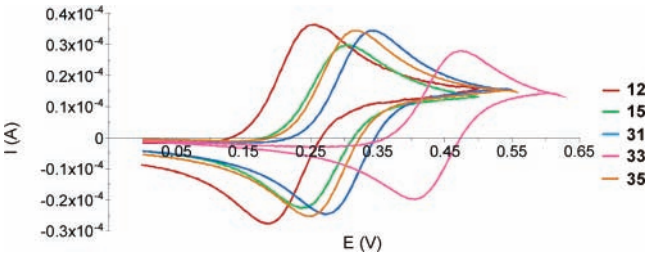


Figure 1. Cyclic voltammetry curves of the glucoside-containing conjugates (0.5 mM) in water with NaCl (50 mM) as supporting electrolyte, a glassy carbon working electrode, a Ag/AgCl reference electrode, and a Pt wire counter electrode with a scan rate at 0.1 V/s.

example, restrictions due to intramolecular hydrogen bonding) for the rotation of the cyclopentadienyl rings. As expected, the D_0 values decrease with increasing molecular weights. But there are no significant differences in $E_{1/2}$ in compared conjugates having the same tether and ferrocene cores. Thus, by changing the carbohydrate moiety there is barely an alteration of the $E_{1/2}$ value. However, the $E_{1/2}$ value of the ferrocene core as illustrated in Table 1 increases moving from the CH_2S tether to the CH_2-1,2,3-triazole-CH_2O tether. An increase of the $E_{1/2}$ value is generally associated with electron-acceptor property of the substitutent.[7] A slight decrease of $E_{1/2}$ is observed when the CH_2-1,2,3-triazole-CH_2O tether is substituted by the 1,2,3-triazole-CH_2CH_2O tether. This is possibly owing to some conjugation effect of ferrocenyl group with the 1,2,3-triazole ring in the oxidation products.[8] Also, the $E_{1/2}$ increases from the monoglycosylated ferrocenes to those that are diglycosylated. These effects can be attributed to the different degrees of shielding of the ferrocene core by the glycosyl-tether branches preventing solvent interactions, such that the ferrocenium ion resulting from the oxidation process is less stabilized by the solvent-shielding.[2k,7e]

Table 1. Electrochemical Data by Cyclic Voltammetry in Water with 50 mM NaCl, a Glassy Carbon Working Electrode, a Ag/AgCl Reference Electrode, and a Pt Wire Counter Electrode

compd	$E_{1/2}$ (V)	$D_0 \times 10^6$ (cm^2/s)
12	0.283	5.3 ± 0.4
13	0.287	5.2 ± 0.4
14	0.285	3.5 ± 0.2
15	0.333	3.5 ± 0.3
16	0.336	2.67 ± 0.16
17	0.336	2.92 ± 0.16
31	0.370	4.72 ± 0.23
32	0.376	5.3 ± 0.3
33	0.502	3.4 ± 0.2
34	0.509	3.3 ± 0.4
35	0.346	4.6 ± 0.3
36	0.353	4.7 ± 0.2

In summary, we report two convenient methods for the attachment of carbohydrates to one or both of the cyclopentadienyl rings in ferrocene. The first method involves the reaction in acidic media of 1-thioglycosides with ferrocenemethanol or 1,1′-ferrocenedimethanol. The second method involves the regiospecific catalytic cycloaddition of propargyl glycosides or 1-ethynylferrocene with azido ferrocene derivatives and 1,1′-bis(azidomethyl)ferrocene or azido-functionalized *O*-glycosides. The obtained water-soluble carbohydrate−ferrocene conjugates exhibit reversible oxidation and reduction of the Fe^{2+} center. The electrochemical studies also showed the dependence of the redox potential on the chemical nature of the tether and the number of substituents.

Acknowledgment. We thank the Spanish Ministry of Education and Science for financial support (Grant Nos. BQU2003-00330 and BQU2002-03477) and for a Ph.D. scholarship (J.M.C.-S.).

Supporting Information Available: Detailed experimental procedures, spectroscopic data, and ^{13}C NMR spectra for **5**−**7**, **9**−**17**, **22**−**25**, and **29**−**36**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048665J

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