New examples of template catalysis based processes: glycerol-like units as efficient promoters for dehydrative nucleophilic substitutions of ferrocenylmethanol

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Introduction

In the last three decades ferrocene and ferrocenyl derivatives have been extensively studied and they are frequently used for biological and non-biological applications.[1] The bio-organometallic chemistry of ferrocene based compounds with biomolecules[2] is also today intensively studied:[3,4] the main properties of the ferrocene unit in these compounds, related to their biological activity, are the small size, the high stability in aqueous and aerobic media, the relative lipophilicity, and the peculiar redox behavior. In the literature complex ferrocene derivatives with biological activity such as antifungal,[5–13] antimalerial,[14] anticancer,[15] antimicrobial,[16] anti-HIV-1,[17] antioxidant,[18] and PDE4 inhibitory activities[19] etc. are often reported, but it is important to underline that ferrocene itself exhibits interesting properties such as antianemic,[20] antiseptic,[21] or cytotoxic activities.[22,23]

By capitalizing on these observations we decided to synthetize and test simple ferrocene derivatives of glycerol, a fundamental widespread biological molecule able to confer to the ferrocene unit the necessary compatibility with the biological media.

The catalyzed condensation of ferrocenemethanol with alcohols to give the corresponding ethers by S_N1 reactions involving ferrocenylmethyl cations, is already well known, although new catalysts are still under investigation. This reaction is usually described as a protic or, more often, as a strong Lewis acid catalyzed process usually performed by using toxic and expensive chemicals like heavy metal salts of rare earth elements. In addition, the reaction is often performed in halogenated solvents and sometime subject to unfavorable equilibria. Several Brønsted acids, such as acetic acid and TFA,[24] sulfuric acid,[25] or Lewis acid like Yb(OTf)$_3$,[26] InBr$_3$,[27] CAN,[28] or Zn(OTf)$_2$, AgOTf, Bi(OTf)$_3$, Al(OTf)$_3$, are reported in the literature[29,30] as crucial catalysts for this reaction.

A different approach to the dehydrative nucleophilic substitutions of alcohols, such as ferrocenylethanol, was reported by Cozzi et al.[31] In this Letter the authors stressed that the reaction can slowly occur also without catalysis 'on water' under heterogeneous conditions. The uncommon reactivity observed was explained by assuming that the process is promoted by the presence of an appropriated cooperative network of hydrogen bonding at the interface of the organic substrate/water.

Following this original interpretation, we have investigated the reaction of glycerol and ferrocenylmethanol under neat homogenous conditions, thus finding a fast and efficiently nucleophilic substitution in the absence of solvent and acidic catalyst. This result prompted us to further investigate the reaction.

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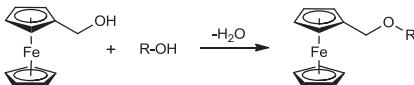   E-mail address: roberto.sebastiano@polimi.it (R. Sebastiano).

Results and discussion
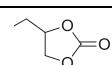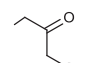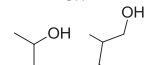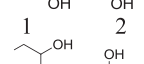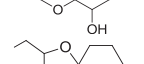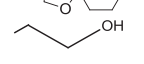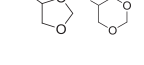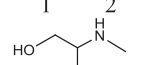
Ferrocenylmethyl derivatives **3a–l** were synthesized under different operative conditions as reported in Table 1. The experimental data collected have shown that: (1) the most reactive polyfunctionalized alcohols are those where, apart from the reactive C–OH group, the other two carbon atoms of the C3 unit possess oxygen atoms of either: (a) two additional hydroxyl groups (**2c**), or (b) one hydroxyl and one carbonyl group (**2b**),[32] or c) a cyclic carbonate group (**2a**). (2) In the case of hydroxyl ethers (**2d, 2e, 2g1, 2g2**), the reactivity is reduced till reaching zero for the tetraethylene glycol (**2j**) and glycidol (**2l**). (3) Among these derivatives, the presence of ethereal oxygen restricted to the 1,3-dioxolane ring favors the reactivity (**2e, 2g1**) whereas, on the contrary, the 'freely' rotating polyethers like tetraethylene glycol (**2j**) (also triethylene glycol and hexaethylene glycol were tested) are unreactive in the absence of acidic catalysts. (4) In regard to the vicinal diols tested, it is underlined that that glycerol (**2c**), digl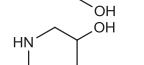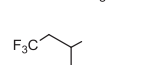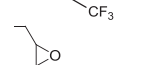ycerol (**2f**), and ethylene glycol (**2d**) show a significant difference of reactivity in terms of rate (see Table 1), despite their analogy in chemical functions and their similar dipolar moment values (2.56 D, 2.88 calcd D and 2.41 D, respectively).

Carbon dioxide and hexafluoroisopropanol effect

With the intent of favoring the slower reactions, while avoiding the direct use of metallic or protic catalyst, we tested the effect of carbon dioxide. This compound in fact is a weak acid able, in principle, to favor the formation of the ferrocenylmethyl carbocation (Fc–CH$_2^+$) reacting as Lewis acid on the ferrocenylmethanol. Carbon dioxide is also able to react with the water (formed during the reaction and virtually always present in these hygroscopic substrates) and with the substrates to form, respectively, carbonic acid and the corresponding carbonic acid monoesters, in equilibrium with the free form of the gas. In all cases the carbon dioxide should have acted as an indiscriminate acidic catalyst and should

Table 1
Synthesis of substituted ferrocenylmethyl ethers and amine

R **2,3**	Catalyst	T (°C)	Time	**1** Conv.[a] (%)	**3** Yield[a] (%)	Pseudo first order $k_{obs.}$[e] (min^{-1})
a	No	60	30′	99	97	1.17×10^{-1}
	CO$_2$		30′	96	92	1.10×10^{-1}
b	No	90	1 h	100	89[g]	
c	No	60	22 h	98	88, 10	3.50×10^{-3}
	CO$_2$	60	4.5 h	98	89, 9	1.44×10^{-2}
	No	90	2 h	100	72, 24	
d	No	60	42 h	92	54	
	CO$_2$	60	18 h	96	62	
	No	90	18 h	99	66	
e	No	60	21 h	58	57	
	No	90	15 h	99	98	
f	No	60	120 h	95	80	9.0×10^{-5}
	CO$_2$		24 h	75	73	4.0×10^{-3}
g	No	60	114 h	32	22, 9	5.64×10^{-5}
	CO$_2$	60	110 h	29	20, 8	5.19×10^{-5}
	No	90	12 h	100	60, 40	
h	No	90	6 h	0	0	
	H$^+$	90	6 h	2[b]	1[b]	
	HFIP	50	8 h	95[c]	88[c]	
i	No	90	6 h	0	0	
	H$^+$	90	6 h	0[2b]	0[2b]	
	HFIP	50	8 h	94[c]	90[c]	
j	No	90	6 h	0	0	
	CO$_2$	90	6 h	0	0	
	HFIP	50	4 h	95[d]	92[d]	
	p-Cl-PhOH	50	6 h	2[d]	1[d]	
k	No	50	18 h	90	80[f]	
l	No	60	4 h	0.0	0.0	

[a] Typical molar ratio FcCH$_2$OH/substrate = 1/10, but similar results with just a little loss of selectivity were obtained also with the ratio 1/5.
[b] Until 5% on molar of acetic acid.
[c] Molar ratio FcCH$_2$OH/substrate/HFIP = 1/2/10.
[d] Molar ratio FcCH$_2$OH/substrate/Cat. = 1/2/5.
[e] Molar ratio FcCH$_2$OH/substrate = 1/120.
[f] Slowly formed only in the absence of other nucleophilic reactants.
[g] Small amount of di-substituted derivative.

have favored all the reactions. Surprisingly, though, we observe that: (a) carbon dioxide improves the nucleophilic substitution only in those cases in which the substrates are vicinal glycols like ethylene glycol, glycerol, or diglycerol, (b) it does not promote the reactivity of the most unreactive substrates like polyethyleneglycols or isoserinol, (c) in the case of the glycerol carbonate or that of the glycerol formals, the presence of carbon dioxide inhibits to some extent the reaction (see $k_{obs.}$ in Table 1).

On the basis of the papers published by Mayr and co-workers[33] and Trillo et al.[34] where it is reported that appropriated fluorinated alcohols are able to promote nucleophilic substitutions without the presence of Brønsted or Lewis acid as the catalyst, we investigated also the effect of the hexafluoroisopropanol (HFIP): as unreactive substrates we have chosen tetraethylene glycol (**2j**), serinol (**2h**), and isoserinol (**2i**) (it should be noted that these last two derivatives are almost unreactive also in the presence of a catalytic amount of protic acid). As expected, the reactions were strongly favored when in the presence of just a few equivalents of HFIP, and in a short time the corresponding ferrocenyl derivatives were obtained in high yields and with high selectivity (see Table 1 reactions **h–j**).

The experimental results here reported require the following considerations: (1) the dehydrative nucleophilic substitutions of the ferrocenyl methanol in the absence of acidic catalysis require, as a necessary condition, the presence of vicinal oxygenated or fluorinated alcohol, (2) vicinal hydroxyl ethers structurally not restricted (like PEGs) are not reactive, (3) relevant differences of reactivity are observed between similar subclasses of reactants in which the same functional groups are present (like glycerol, diglycerol, and ethylene glycol). These results suggest that these reactions are controlled by a common property present in all the poly oxygenated/fluorinated alcohols investigated, which acts with different efficiencies depending on the chemical structure of the molecules. This common factor can be identified in the potential ability of these molecules to build up intra and inter molecular structured networks of hydrogen bonds able, in principle, to stabilize the transition state of a process where the breaking of a C–OH bond is involved. In these cases we can talk about template-catalyzed processes. This interpretation is supported by the results obtained in the presence of HFIP. In fact the catalytic properties of this compound (as other fluorinated alcohols) are attributed to its ability to form a strong network of hydrogen bonding with the reactants.[35,36] In order to exclude that the catalytic effect observed with HFIP was due to its weak 'acidity' (pK_a = 9.3), we have performed the reaction between ferrocenylmethanol and tetraethylene glycol (**2j**) in the presence of *p*-Cl-phenol (pK_a = 9.4) under the same experimental conditions: as expected, no significant reaction was observed in this last case (see Table 1, reaction **j**).
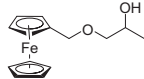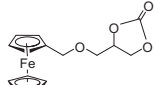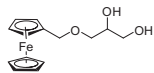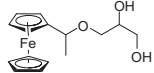
Also the unexpected behavior of carbon dioxide can be justified by admitting that these processes are based on template catalysis. In fact, as recently shown by Buxing and co-workers[37] in a theoretical work, the carbonic acid monoester of the ethylene glycol can build complex hydrogen bond networks able to stabilize several conformations of the molecule. Similar behavior can be admitted for the substrates here investigated: when in the presence of vicinal diols, carbon dioxide is involved as a carbonic acid monoester of the substrates in the hydrogen bonding network generated between the reactants so as to favor the reaction of dehydrative nucleophilic substitution while, on the contrary, in the other cases investigated, its presence shows a perturbing effect on the process, also in the case of the glycerol carbonate where all the ionic dissociation processes, included the carbonic acid deprotonation, are strongly favored.

Antifungal activity

Four ferrocene derivatives were tested on the two fungi *Botrytis cinerea* and *Penicillium* spp. by performing two sets of in vitro growth inhibition experiments: in the first case the effects of the compounds were studied by applying them on the surface of the solidified cultural growth medium (surface treatment) whereas, in the second case, the products were dissolved in the cultural growth medium before solidification (inclusion treatment). The fungal growth inhibition values (FGI%, see experimental part) of all the ferrocene derivatives tested are mentioned in Table 2. Despite the structural simplicity, all the products tested have shown a bioactivity toward the fungi, comparable with that of much more complex molecules reported in the literature which require often a complex synthesis procedure. From the analysis of the collected data, it is clear that the compound **3h** is the most effective for growth inhibition by surface treatment as well as, in almost all cases, by inclusion treatment, with a higher significant activity toward the *Penicillium*, as compared with the *Botrytis cinerea*.

In conclusion, the dehydrative nucleophilic substitution of ferrocenylmethanol to give ethers can occur in the absence of acidic catalyst and in homogeneous media. The reaction is promoted by

Table 2
Antifungal activity of ferrocenylmethyl ethers

Compounds			Fungal growth inhibition (FGI %) *Penicillium* spp.		*Botrytis cinerea* spp.	
			Surface	Inclusion	Surface	Inclusion
3m		(a)	77.0(100)	84.2(100)	68.1(100)	62(100)
		(b)	46.2(100)	58.2(100)	35.3(100)	30.1(100)
		(c)	74.6(1)	46.8(1)	117.1(1)	153(1)
3a		(a)	72.2(93.8)	72.6(86)	44.1(65)	39.0(63)
		(b)	40.2(87)	40.2(69)	17.2(49)	14.0(47)
		(c)	96.1(1.3)	96.9(2.1)	316(2.7)	390(2.6)
3c (1+2)		(a)	53.9(70)	56.0(66)	59.1(87)	57.6(93)
		(b)	23.2(50)	24.6(42)	27.2(77)	25.7(85)
		(c)	213.8(2.9)	196.4(4.2)	173(1.5)	184(1.2)
3n (1+2)		(a)	50.6(65)	59.6(71)	66.5(98)	38.2(62)
		(b)	21.0(45)	27.3(47)	33.8(96)	14.7(49)
		(c)	244.1(3.3)	169.5(3.6)	125(1.1)	404(1.1)

For each experiment, are reported three data: (a) FGI% at [sample] = 250 µg/mL, (b) FGI% at [sample] = 62.5 µg/mL; and (c) IC_{50} (µg/mL). The numbers in brackets are the corresponding normalized values, respect to the best values in the column.

the presence of compounds able to generate an appropriate hydrogen bonding network with the reactants, so as to favor the process, probably at the level of transition state energy and geometry. Also a thermodynamic contribution due to a possible 'seizure' by these compounds of the water formed during the reactions, so to affect its nominal activity, cannot be excluded.[38]

Poly oxygenated glycerol-like C3 units appear to be very efficient reactants/promoters of the process as well as hexafluoro-isopropanol, which make possible reactions with inert substrates like serinol or tetraethylene glycol that typically do not react with ferrocenylmethanol in the absence of acidic catalyst. All these experimental results suggest that the reactions described here are template catalysis based processes.

Some of the derivatives synthesized here, despite their structural simplicity, are bioactive toward the fungi as inhibitors of the growth, with comparable efficiency in respect to the more complex ferrocenyl derivatives. Because of the cleanness of the reactions, the absence of acid or metallic cations, the biocompatibility of glycerol and some glycerol derivatives, the synthetic method here presented lends itself to industrial applications at low environmental impact.

Acknowledgments

Supplementary data

Supplementary data associated with this article can be found, in the online version.

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