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Synthesis in ionic liquids only: access to α-oxo-γ-thio-esters via Mukaiyama coupling

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ABSTRACT

Ionic liquids are solvents general enough to conduct a multi-step process in organic synthesis. We show that both the preparation of starting materials (thioacetals and enoxysilane) as well as their coupling can be realized in such medium.

Owing to their unique properties, ionic liquids (ILs) nowadays are widely examined as eco-compatible solvents for organic synthesis.[1] Many successful applications have been disclosed, including modern aspects such as enantioselective,[2] catalytic,[3] or multicomponent reactions.[4] Nevertheless one can observe that in most of these reports only one single model reaction is generally studied (and generally carried out on few model compounds); to the best of our knowledge, no multi-step or all-step syntheses in ILs have been described so far.[5] We believe that time has come to this type of research, that is the search for processes in which no other solvents than ILs are used even for multi-step syntheses or for the preparation of starting materials. With this ambition in mind, we recently embarked mainly on two approaches, that is peptide[6] and Mukaiyama couplings, calling this approach 'synthesis in ILs only' (*SILO*).

In this Letter we describe our results in the field of Mukaiyama couplings leading to α-oxo γ-thio-esters, where both partners of the Mukaiyama reaction, that is thioacetals and pyruvate enoxysilane, are prepared in ionic liquids. Their coupling is also realized in such a solvent. Thus, the full synthetic pathway does not require any other solvents than ionic liquids, consisting in an unprecedented approach in organic synthesis.

In the first part we summarize the background of this study, which was initiated because of the puzzling role of the solvent during the construction of ulosonic derivatives by Mukaiyama reactions. In the second part are depicted our preliminary results regarding the SILO approach.

From the ulosonic puzzle...

Our interest for the construction of bioactive materials in the ulosonic series, via Mukaiyama reaction of ethyl 2-(trimethylsilyloxy)acrylate with epoxyaldehydes such as **1**,[7] led us to search for alternative media as solvents for this transformation. Indeed, the role of the solvent in these studies appeared rather puzzling. For example it has been shown in our laboratory that a Lewis acid as catalyst in aqueous medium (sodium dodecyl sufate, SDS) led to aldol derivatives without any oxirane-ring opening (Scheme 1),[8] while chlorinated solvents mainly afforded products arising from ring expansion.[7] In the latter case, even the workup procedure could exert strong influence, giving in some cases access to fluorinated intermediates such as compound **2** as depicted in Scheme 1.[9] In order to avoid any fluorinated products, it would be worthwhile to find either catalyst-free conditions or to replace $BF_3{\cdot}Et_2O$ by another catalyst. Unfortunately, only this Lewis acid could give substantial amount of adducts when employed in molecular solvents.[10]

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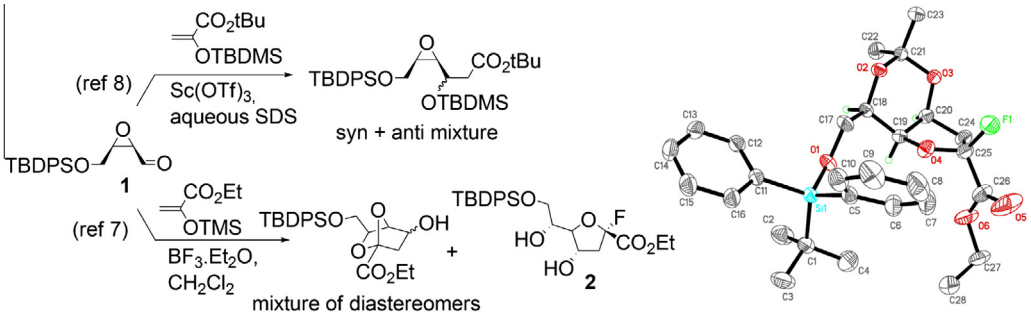


Scheme 1. Construction of ulosonic structures by Mukaiyama couplings. Molecular view of isopropylidene derivative of compound **2** in the solid state (thermal ellipsoids at 50% probability); hydrogen atoms are omitted for clarity excepted on asymmetric carbons. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-969490.

ILs have already been used either as solvents or promoters for Mukaiyama couplings; for example it has been shown that aldolizations could be performed at room temperature in the absence of any activation.[11] Also the role of the IL structure was examined and it was found that better results were observed for cations bearing a long carbon chain (omim vs hmim) and for chloride anions with respect to hexafluorophosphates.[11] More recently, Gaumont et al. showed that Mukaiyama aldol reactions leading to dihydropyranones were promoted either by ionic liquids or ionic additives.[12] In this study, thiazolinium salts were the best catalysts. Interestingly, only the Mukaiyama process was observed without any hetero Diels-Alder cycloaddition.[12] Inspired by these results, we examined ionic liquids as solvents for the same type of transformations from the *cis*-epoxyaldehyde depicted in Scheme 1. New materials were obtained as traces that were not identified. Although not satisfactory from a preparative point of view, this result incited us to focus on this IL strategy since full conversion was observed without the need for any catalyst. The major aims were to find catalyst-free conditions (or to avoid the use of $BF_3{\cdot}Et_2O$), to improve the overall yield of the transformations, and eventually to realize all steps in ILs.

To ionic liquid solution?

We focused on a strategy recently published by Bolm,[13] who described the synthesis of α-oxo-γ-thio-esters by reaction of ethyl pyruvate enoxysilane onto thioacetals. Aldolizations were carried out at 0 °C in dichloromethane, in the presence of scandium triflate as catalyst, with best results as high as 62%.[13] We thus embarked on a project in which both precursors as well as the reaction itself would be realized in ionic liquids (Fig. 1).

Synthesis of thioacetals

Thioacetals are generally prepared by condensation of a parent carbonyl compound with thiols in the presence of a Lewis acid. For example CuCl, CuBr, CuI, $Pd(acac)_2$ et $Co(acac)_3$ were successfully used in acetonitrile.[14] Also, $Sc(OTf)_3$ was immobilized in imidazolium ILs such as [bmim][PF_6] and [bmim][BF_4], and used as catalyst for the preparation of thioacetals with better performance than in molecular solvents such as dichloromethane (faster reaction rate as well as better yields).[15] We used this last method to obtain the targeted thioacetals (Table 1). We selected two commercial hydrophobic ionic liquids,[16] [bmim][PF_6] and [emim][NTf_2], as model solvents for this study, for their low melting point, viscosity, and hygroscopy. We did not consider hydrophilic ILs possessing halide anions that are known as non-innocent species because of their nucleophilic and reducing properties.

A series of *para*-substituted benzaldehydes was transformed into the corresponding thioacetals with good performance. The reaction is rather fast for electroenriched aromatic rings and gives 76–99% yield after purification by column chromatography. Reaction rate is lower for electron poor compounds as well as for the dimethylamino substituted substrate, for which complexation of the Lewis acid by the nitrogen lone pair occurs. Even a more sterically demanding compound such as 1-naphtaldehyde was converted to the corresponding thioacetal in 65% yield. Aliphatic and conjugated starting materials are also conveniently protected by this method. As previously mentioned, we verified that the transformation was less efficient in organic molecular solvents.

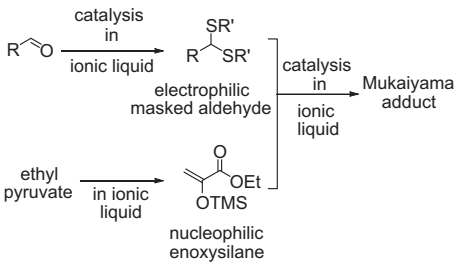
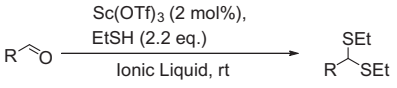
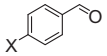
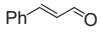


Figure 1. General strategy.

Table 1
Synthesis of thioacetals in ILs in the presence of $Sc(OTf)_3$



Aldehyde	X	Ionic liquid	Reaction time (yield)
	X = H	[bmim][PF_6]	10 min (78%)
		[emim][NTf_2]	10 min (99%)
	X = OMe	[bmim][PF_6]	10 min (98%)
		[emim][NTf_2]	10 min (85%)
	X = Me	[bmim][PF_6]	60 min (76%)
		[emim][NTf_2]	20 min (84%)
	X = NO_2	[bmim][PF_6]	105 min (79%)
		[emim][NTf_2]	>16 h[a] (55%)
	X = COMe	[bmim][PF_6]	60 min (48%)
	X = NMe_2	[bmim][PF_6]	240 min (25%)
		[emim][NTf_2]	240 min (33%)
		[bmim][PF_6]	60 min (65%)
		[emim][NTf_2]	45 min (82%)
		[bmim][PF_6]	15 min (99%)
		[emim][NTf_2]	20 min (82%)
t-BuCHO		[bmim][PF_6]	30 min (89%)

[a] Reaction was not complete after 16 h.

We believe that the use of [bmim][PF_6] and [emim][NTf_2] as solvents, which are hydrophobic ILs, has the advantage to remove water from the reaction mixture, thus preventing any subsequent hydrolysis of the formed thioacetal. Although significant differences in yield and/or reaction rates could be observed between reactions run in [emim][NTf_2] and in [bmim][PF_6] with several substrates, no clear trend could be established.

We also examined CuBr, a cheaper and less toxic catalyst than $Sc(OTf)_3$, in the same transformation on benzaldehyde. However in these conditions the reaction requires a longer duration and the yield is significantly lower (Scheme 2). This can be easily rationalized using HSAB theory: Cu(I), which is a much softer acid than Sc(III), interacts not only with the oxygen of the carbonyl group (hard base), but also with the sulfur atom of ethanethiol (soft base), thus slowing down the thioacetalization reaction.

Finally, the epoxyaldehyde **1** was used as substrate in the thioacetalization reaction in ionic liquid. However, concomitant nucleophilic opening of the epoxide by ethanethiol was consistently observed, giving access to a highly functionalized carbohydrate derivative in rather good yield and in pure diastereomeric form (Scheme 3).

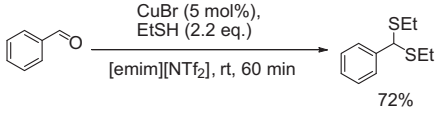
Synthesis of ethyl pyruvate enoxysilane

This compound has been prepared in 1992, starting from ethyl pyruvate.[17] More recently, Smietana and Mioskowski described a new method for the preparation of enoxysilanes in ILs.[18] In the presence of bis-trimethylsilylacetamide (BSA), aldehydes and ketones are transformed into their corresponding silyl enol ether in ionic medium such as [NBu_4][Br]. The reaction is carried out at the mp of the IL (ca 100 °C) and requires heating for 4 h to give the target enoxysilanes in 75–90% yield. We decided to adapt this method to ethyl pyruvate, and were delighted to obtain the corresponding enoxysilane in rather good yield (Scheme 4, 62% after purification by bulb-to-bulb distillation). This method presents some advantages like neutral conditions (no need to add base such as DMAP), simplicity, and atom economy.

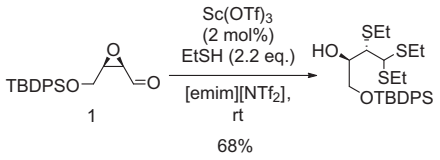
Imidazolium based ionic liquids[16] [omim][NTf_2] and [emim][NTf_2] were also assessed as solvents in this reaction, and were found to give the target enoxysilane with acceptable, if somewhat lower, yields. This observation is crucial for our future studies, since we plan to realize the whole synthetic pathway (i.e. preparation of both precursors as well as the coupling reaction) in the same ionic solvent. The better yield obtained in [NBu_4][Br] could be due to reaction of bromide ion with BSA giving a transient highly reactive bromosilane.

Mukaiyama couplings

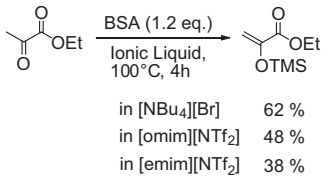
Finally, we focused on the coupling in ionic medium of the previously obtained pyruvate enoxysilane with thioacetals. After checking various ionic solvents, we observed that the pyruvate enoxysilane was not stable in the presence of BF_4^- and PF_6^- anions (presumably because of trace amounts of HF produced by the hydrolysis of BF_4^- or PF_6^-), but could be used in NTf_2^- containing ILs. As imidazolium cations proved to be convenient for many organic reactions, we decided to test those couplings in [emim][NTf_2]. Our main results are depicted in Scheme 5.



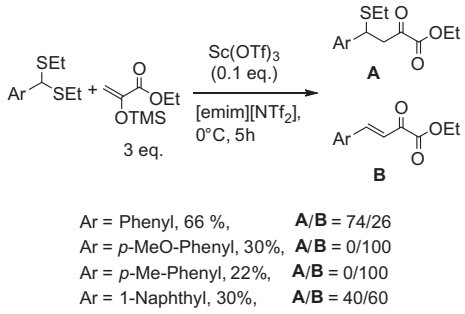
Scheme 2. Synthesis of thioacetals in IL in the presence of CuBr.



Scheme 3. Thioacetalization of **1** in IL in the presence of $Sc(OTf)_3$.



Scheme 4. Synthesis of ethyl pyruvate enoxysilane in ILs.



Scheme 5. Mukaiyama couplings in ILs.

Two main compounds were obtained in our experiments. We were delighted to obtain the expected coupling adduct **A** starting from benzaldehyde and naphtaldehyde derivatives, along with the corresponding elimination product **B**. The latter was the only product from *p*-methoxy and *p*-methyl congeners, while *p*-nitro derivative yielded a complex and inseparable mixture, in which both **A** and **B** were detected by NMR. One can explain the reactivity by electronic effects, electron donating groups (MeO and Me) stabilizing the carbocationic form thus facilitating the elimination process. Nevertheless, both compounds **A** and **B** come from the same coupling reaction, thus proving that [emim][NTf_2] is a convenient solvent for such a synthetic step. We are currently focusing on conditions which could improve the chemoselectivity of this last step.

In conclusion, we show that ILs are solvents general enough to conduct a multi-step process in organic synthesis. Both the preparation of starting materials (thioacetals and pyruvate enoxysilane) and their coupling are realized in such medium. Figure 2 summarizes the whole synthetic process for the best model substrate.

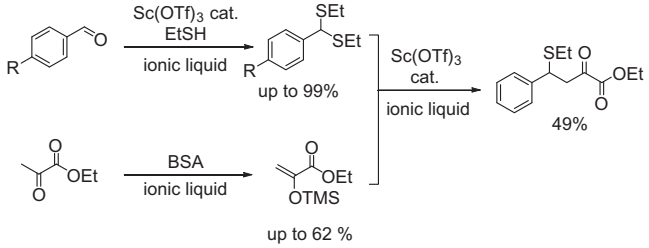


Figure 2. *SILO* for the preparation of α-oxo γ-thio-esters.

The full synthetic pathway described herein does not require any other solvents than ionic liquids, consisting in an unprecedented approach in organic synthesis. The search for multi-step processes avoiding the use of volatile organic solvents is of growing importance,[19] and we believe that our approach can give new insights in this field. Studies are currently underway to perform the entire synthetic sequence without extraction of the intermediate compounds from the ionic liquid.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.024.

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