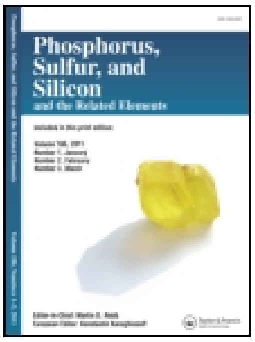

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Ionic liquids as an alternative reaction medium for HMDST based synthesis of thioaldehydes

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ABSTRACT

Reaction of bis(trimethylsilyl)sulfide (HMDST) with aldehydes can be efficiently carried out in various ionic liquids, under $CoCl_2.6H_2O$ or TfOTMF catalysis, leading to the formation of thioaldehydes, which are trapped as Diels-Alder cycloadducts. When 1,3-cycloheaxadiene was used, a stereoselective entry to the *endo* isomer was always obtained.

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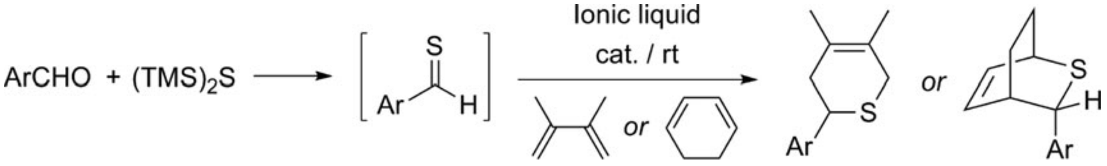
GRAPHICAL ABSTRACT



Introduction

Organic sulfur compounds play an important role in different fields. They represent very reactive and efficient intermediates in many chemical processes for the synthesis, for instance, of pharmaceutically active compounds.[1] Very recently, phenyl propyl thioketone has been isolated from seagrasses and identified as a novel antibacterial compound.[2] They participate also in obtaining molecules used in food chemistry as additives and aromas.[3] In fact it is well known that chemicals which contain sulfur atoms often have a peculiar odour, depending on the nature of the sulfurated functional groups, i.e. sulfide, di- or higher sulfides, thiol, heterocyclic systems or thiocarbonyl derivatives.

In addition, it has been well established that the hetero Diels-Alder reaction is a very useful method for the preparation of six-membered heterocycles containing different heteroatoms, including sulfur and selenium. In fact carbon-chalcogen double bonds have been recognized as reactive groups, and in particular thiocarbonyl derivatives represent very valuable compounds to react as efficient heterodienophiles in cycloaddition reactions, including 1,3-dipolar cycloadditions.[4] During the course of our studies in the chemistry of thiocarbonyl derivatives, we reported an efficient and direct conversion of a carbonyl function into a thiocarbonyl group through the reactivity with bis(trimethylsilyl)sulfide, $(Me_3Si)_2S$ (HMDST).[5] Using this procedure, we have successfully obtained a wide series of thioaldehydes, thioketones and thioacylsilanes, and we have elucidated their behaviour as heterodienophiles with acyclic and cyclic dienes.

Although other efficient methods for the direct conversion of a C=O into a C=S group are described,[6] such as for instance the use of Lawesson's reagent or H_2S/HCl, the *n*-BuLi catalyzed reaction of a silyl sulfide, to date the conversion of a carbonyl group into a thiocarbonyl moiety in room temperature ionic liquids (RTILs) has not been yet reported. Thus, the development of new, alternative methodologies to access C=S containing systems under mild conditions, using non hazardous materials, is highly desirable.

In this context, a growing interest has been focused in the use of ionic liquids as solvents or catalysts in different chemical reactions.[7] They are salts that are liquids at room temperature or below. RTILs found wide application because of their negligible vapor pressure, lack of inflammability, chemical stability, good solvating ability and recyclability. They are made of positive and negative ions, and each ionic liquid shows peculiar chemical and physical properties depending on the kind of cation and anion. The most commonly used cations are based on *N,N'*-dialkylimidazolium species, and they show a different behaviour as a function of the nature of the relative anion. Reactions performed in ionic liquids often show higher yields, rate enhancement and selectivity with respect to traditional solvents.[7] Some papers dealing with the synthesis of organochalcogenides in ILs are also reported.[8] To the best of our knowledge no example is described for thionation reactions using ionic liquids as solvents.

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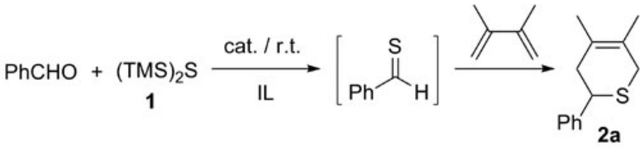
Dedicated to Professor B. S. (Raj) Thyagarajan for his retirement from the Editorial Board of Phosphorus Sulfur and Silicon and the Related Elements



cat.: **A** = $CoCl_2 \cdot 6H_2O$; **B** = TfOTMS

Entry	Ionic liquid	cat.	Yield (%)
1	[bmim][BF_4]	**A** / **B**	78 (A); 71 (B)
2	[bmim][PF_6]	**A** / **B**	72 (A); 73 (B)
3	[emim][TfO]	**A** / **B**	65 (A); 69 (B)
4	[emim][CH_3OSO_3]	**A** / **B**	75 (A); 67 (B)
5	[hmim][$N(Tf)_2$]	**A**	51
6	[bmpl][$N(Tf)_2$]	**A** / **B**	43 (A); 78 (B)
7	[bmpl][$N(CN)_2$]	**A** / **B**	--

Scheme 1

Results and discussion

In order to develop a clean thionation method, in this communication we would like to report the use of ionic liquids as novel reaction media for the conversion of aldehydes into thioaldehydes, which reacted as heterodienophiles in Diels-Alder cycloadditions.

As a model substrate to evaluate the best reaction conditions, we performed a set of experiments using benzaldehyde and bis(trimethylsilyl)sulfide **1** under $CoCl_2 \cdot 6H_2O$ or silyl triflate (TfOTMS) catalysis and 2,3-dimethyl-1,3-butadiene as trapping agent (Scheme 1).[9] We considered different ionic liquids, which are liquid at room temperature and stable under the used conditions. All imidazolium derivatives, with different alkyl chains (butyl-methyl [bmim], ethyl-methyl [emim] and hexyl-methyl [hmim]) and various counter ions were efficient in promoting the thionation of PhCHO and the cycloaddition of the transient thioaldehyde with the diene (Scheme 1, entries 1–5), as demonstrated by the good yields of the corresponding dihydrothiopyran derivative **2a**. When the reaction was performed in pyrrolidinium derivatives, only in [bmpl][$N(Tf)_2$] was observed the formation of the cycloadduct (Scheme 1, entry 6), while in [bmpl][$N(CN)_2$] any amount of the desired product was observed (Scheme 1, entry 7). This result can suggest the influence of the cation in such reactions. The ionic liquids used can be potentially recycled up to three times.[10]

These findings point out that the use of ionic liquids to promote this thionation is suitable, and that the conditions are mild enough to trap thiobenzaldehyde with the diene. With the aim of evaluating the generality of this new protocol, differently substituted aromatic and aliphatic aldehydes were reacted under $CoCl_2 \cdot 6H_2O$ catalysis in selected ionic liquids. The results are summarized in Table 1.

All aromatic aldehydes react smoothly, and the reaction appears to be general (Table 1, entries 2–6). The yields were generally good, comparable with those obtained in traditional solvents, and a rate enhancement was observed in ionic liquids. Also aliphatic thioaldehydes were formed under the present conditions, but they demonstrated unreactive towards the diene, leading to the formation of trimers and oligomeric material (Table 1, entries 7, 8), thus confirming their low reactivity in Diels-Alder reactions.

Table 1. Synthesis of thioaldehydes in ionic liquids and their trapping by 2,3-dimethyl-1,3-butadiene.

Entry	Ionic Liquid	Aldehyde	Adduct[a]	Yield %[b]
1	[bmim][BF_4]	C_6H_5CHO	2a	78
2	[bmim][BF_4]	p-$CF_3C_6H_4CHO$	2b	63
3	[bmim][BF_4]	o-$CF_3C_6H_4CHO$	2c	68
4	[bmim][BF_4]	p-$NO_2C_6H_4CHO$	2d	57
5	[emim][TfO]	p-$CHOC_6H_4CHO$	2e	61
6	[emim][TfO]	p-$CHOC_6H_4CHO$	3[c]	70
7	[bmim][BF_4]	CH_3CH_2CHO	—[d]	—
8	[bmim][BF_4]	$CH_3CH(Ph)CHO$	—[d]	—

[a] Products **2a**, **2e**, **3** have been previously reported in the literature.[5c] For **2b,c** see ref. 8.

[b] Isolated products.

[c] Bisadduct **3** [1,4-bis(3,6-dihydro-4,5-dimethyl-2H-thiopyranyl)benzene] was obtained with a ratio aldehyde:HMDST:diene = 1:4:4.

[d] Trimers were formed as major products.

Even though it is reported that ionic liquids usually are effective in promoting cycloadditions of carbon or nitrogen containing dienophiles,[11] in our case alkanethials proved to be unreactive, as already observed in traditional solvents.[5c]

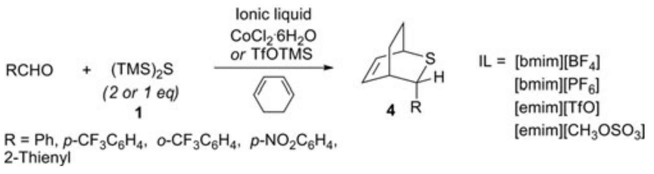
Then we turned our attention towards the reaction with 1,3-cyclohexadiene in order to evaluate the stereochemical outcome of the cycloaddition. The reaction with thiobenzaldehyde, generated under $CoCl_2 \cdot 6H_2O$ or TfOTMS catalysis with aldehyde:HMDST ratio of 1:2, occurs with a high preference for the formation of the *endo* adduct **4** (Scheme 2, R = Ph), as previously observed by us in acetonitrile.[5c]

When PhCHO and HMDST were reacted in equimolar ratio in the presence of TfOTMS as catalyst, the *endo* adduct was again the major isomer isolated. This result was different from what we obtained in CH_3CN, where the *exo* adduct was predominant when aldehydes/HMDST were used in 1:1 molar ratio under TfOTMS catalysis.[5c] This behaviour was observed with a representative series of differently substituted aromatic and heteroaromatic aldehydes (Scheme 2).

Finally, in order to verify whether ionic liquids could behave also as catalysts, aldehydes were treated with HMDST and the diene in different ILs. Whilst it is reported that Diels-Alder cycloadditions can be performed under ionic liquids catalysis,[11] no example is described of thionation induced by ILs.

A series of imidazolium derivatives were then used to study the effect of changing the alkyl chain and the nature of the anion, but only [emim][TfO] was able to promote the conversion of PhCHO and p-$CF_3C_6H_4CHO$ into the corresponding thioaldehydes, isolated as cycloadducts with cyclohexadiene, even in a little bit lower yield with respect to the catalyzed reaction.

Theoretically, different interactions have to be considered for reactions in ILs, like for example the ability of the cation to act



Scheme 2

as hydrogen bond donor and the counter anion as hydrogen acceptor, solvent effects, as well as their basic or acid character.[12] Therefore various factors can affect either thionation and cycloaddition, as well as the behaviour of ILs as promoters of such reactions. These effects are at present not fully understood, and further investigations will be necessary.

Conclusions

In summary, we have shown that direct formation of thioaldehydes, and their trapping with dienes, are possible using ionic liquids as solvents under mild conditions, through reaction of silyl sulfide with aldehydes. Further studies to extend the thionation to different carbonyl compounds and to try to elucidate the interaction between the ionic liquids and the substrates are now under investigation.

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9. *Typical procedure.* A mixture of 0.5 mL of ionic liquid (maintained under high vacuum prior to use), benzaldehyde (30 mg, 0.28 mmol) and 2,3-dimethyl-1,3-butadiene (46 mg, 0.56 mmol) was treated under inert atmosphere at room temperature with HMDST (100 mg, 0.56 mmol) and $CoCl_2 \cdot 6H_2O$ (14 mg, 0.056 mmol) (or TfOTMS, 12 mg, 0.056 mmol). The progress of the reaction was monitored by TLC (petroleum ether/diethyl ether 10:1). After completion of the reaction (2–3 h), the mixture was diluted with diethyl ether. The organic phase was then washed with NH_4Cl (3×1 mL) and extracted with diethyl ether (3×2 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated under vacuum. TLC purification (petroleum ether/diethyl ether 50:1) afforded 44 mg (78%) of 4,5-dimethyl-2-phenyl-3,6-dihydro-2H-thiopyran **2a**.[5c] 4,5-dimethyl-2- (4- (trifluoromethyl)-phenyl)-3,6-dihydro-2H-thiopyran **2b**. ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.73 (3H, s), 1.77 (3H, s), 2.45–2.55 (2H, m), 2.91 (1H, bd, $J = 16.8$ Hz), 3.42 (1H, bd, $J = 16.8$ Hz), 4.02 (1H, dd, $J = 8.4$ Hz, 4.5 Hz), 7.45 (2H, ap d, $J = 8.3$ Hz), 7.61 (2H, ap d, $J = 8.3$ Hz). MS, m/z (I_{rel}, %): 272 (26) [M^+], 239 (16), 190 (59), 82 (100). 4,5-dimethyl-2- (2- (trifluoromethyl)phenyl)-3,6-dihydro-2H-thiopyran **2c**. ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.72 (3H, s), 1.74 (3H, s), 2.33–2.51 (2H, m), 2.93 (1H, bd, $J = 17.0$ Hz), 3.44 (1H, d, $J = 17.0$ Hz), 4.16 (1H, dd, $J = 10.0$ Hz, 4.5 Hz), 7.30–7.38 (1H, m), 7.50–7.56 (1H, m), 7.79–7.83 (1H, m), 7.95–8.01 (1H, m). MS, m/z (I_{rel}, %): 272 (24) [M^+], 239 (12), 190 (62), 82 (100).
10. The same thionation reaction was performed using as a medium the recovered IL/catalyst system just by adding more reagents, without the addition of more catalyst. Under these conditions the formation of the product **2a** was observed, even if in lower yield.
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