Investigations Towards the Chemoselective Thioacetaliztion of Carbonyl Compounds by Using Ionic Liquid [bmim]Br as a Recyclable Catalytic Medium

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Abstract: The ionic liquid based on the 1-*n*-butyl-3-methylimidazolium cation has been prepared and used as an efficient catalytic medum for the chemoselective thioacetalization of carbonyl compounds. Furthermore, recycling and reuse of this ionic liquid medium has been demonstrated. Moreover, the use of this catalytic medium not only avoids the generation of waste but also provides a green process with minimal hazards.

Keywords: aldehydes; 1-*n*-butyl-3-methylimidazolium bromide; chemoselectivity; ionic liquid; thioacetalization; thioacetals

Introduction

Thioacetalization is a well-studied process for the conversion of carbonyl compounds to the corresponding thioacetals. Thioacetals are frequently used as important protecting groups for carbonyl compounds in the total synthesis of natural/synthetic organic compounds, including multifunctional complex molecules, because of their enhanced stability under acidic conditions compared to *O*,*O*-acetals.[1] Further, dithiolanes and dithianes also act as blocking groups for the electrophilic substitution of carbonyl compounds. To date, many attempts for improvement of this process using different Lewis acid catalyst systems have been reported.[2] Very recently $NiCl_2$[3] and $CoCl_2$[4] have been introduced for the chemoselective thioacetalization of aldehydes. However, there are very few methods known in the literature that do not require a solvent as the reaction medium.[5] Thus, there is an immense demand to develop an alternative and improved procedure to reduce the amount of toxic waste and by-products by employing less toxic and environmentally compatible materials. In continuation of our efforts in this direction, we have recently introduced *N*-bromosuccinimide and scandium triflate as efficient catalysts for such purposes.[6]

In recent years, stringent environmental constraints have been coming into force, as a result, a large number of organic reactions and catalytic processes require the development of new methodologies with alternative solvents and catalysts.[7] In view of this, ideal solvents need to have low volatility with chemical and physical stability. Furthermore, it is desirable that the solvent can be recycled and reused, and also can be handled with ease. In addition, the solvent should allow a more selective and rapid transformation. Hence, the use of non-volatile solvents and non-metallic catalysts is an area of considerable importance that could contribute to the economical and environmental aspects.

In the last few years, room temperature ionic liquids (RTILs), particularly those based on 1,3-dialkylimidazolium cations, have been recognized as a possible replacement for conventional organic solvents because of their unique physical and chemical behaviour.[8] The RTILs are completely non-volatile, and can usually be recycled and reused. Moreover, their Lewis and Brönsted acidities make them useful catalysts in organic reactions. By utilizing their Lewis and Brönsted acidic properties, dialkylimidazolium ionic liquids have been recently used as catalysts as well as media in some organic transformations like the Diels–Alder reaction,[9] esterification reactions,[10] and towards the synthesis of 1,5-benzodiazepines.[11] In continuation of our interest in the thioacetalization of carbonyl compounds,[6] we decided to investigate the possibility to realize the thioacetalization of carbonyl compounds in ionic liquids in the absence of any catalyst.

Results and Discussion

The reaction of benzaldehyde (1 mmol) with ethanethiol (2.5 mmol) has been carried out in three different flasks with 1.5 mL each of the ionic liquids: $[bmim]BF_4$ (**a**), [bmim]Br (**b**), and $[bmim]PF_6$ (**c**) [$bmim^+ = 1$-*n*-butyl-3-methylimidazolium cation]. The ionic liquids **a** and **c** have been prepared and purified by the procedure as described in the literature.[12] On the other hand, **b** has been prepared by heating 1-methylimidazole (1 equiv.) and 1-bromobutane (1.2 equivs.) under a nitrogen atmosphere at 80 °C for 12 h to obtain a brown-coloured,

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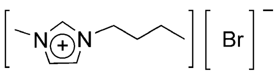
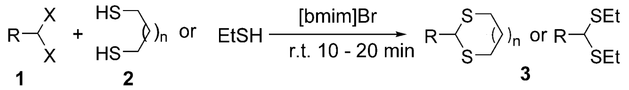


b

viscous liquid (hygroscopic), which is washed several times with ethyl acetate and dried at 80 °C under high vacuum.[13]

It is observed (by TLC) that benzaldehyde is converted to the corresponding thioacetal in about 10 min by employing ionic liquid **b**. On the other hand, there is no detectable thioacetal formation by the ionic liquids **a** and **c** even after prolong reaction times (60 min). This observation is interesting as the Brönsted and Lewis acidity of these ionic liquids is very similar. This finding suggested that the ionic liquid **b** by itself could possibly catalyze such a reaction process or may be effective because of some related factors. One such possibility is the coexistence of more than one type of anion in the ionic liquid employed. This is likely because of the HBr which is likely to be formed during the preparation of this ionic liquid by dehydrobromination of 1-bromobutane in the presence of 1-methylimidazole or could also be due to a wet ionic liquid (as this ionic liquid is hygroscopic). To clarify these assumptions, we have carried out the reaction of benzaldehyde (1 mmol) with ethanethiol (2.5 mmol) in a 10-mL round-bottom flask with 1.5 mL of ionic liquid [bmim]Br which has been previously washed with $NaHCO_3$ before it is used for the reaction.[14] It is observed that even after 1 h there is no formation of the thioacetal (as seen by TLC). However, treatment of the reaction mixture with a catalytic amount of HBr solution in water, led to a quantitative conversion of benzaldehyde to the corresponding thioacetal within 10–15 min. This finding is in conjunction with a recent report that describes a method for the determination of Brönsted acidity in an ionic liquid.[15] Therefore, it is believed that the higher Brönsted acidity of HBr in the ionic liquid together with the formation of a possible hydrogen bonding interaction between the most acidic hydrogen at position 2 of the imidazolium cation with the oxygen of the carbonyl compound may be responsible for the acidic property of this system.

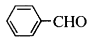
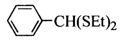
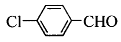
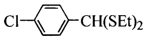
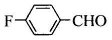
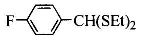
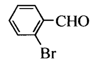
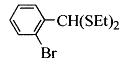
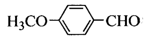
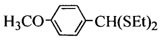
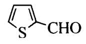
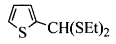
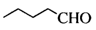
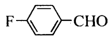
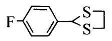
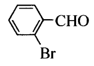
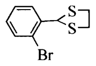
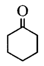
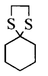
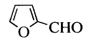
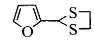
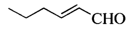
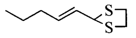
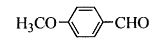
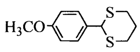
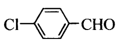
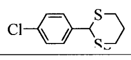
This process has been extended to different carbonyl compounds to examine the efficiency, scope, and generality of this reaction and the results are summarized in Table 1 (see Scheme 1).



R = aryl, alkyl, heterocyclic
XX = O
n = 0, 1

Scheme 1.

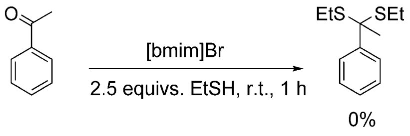
Table 1. Thioacetalization of carbonyl compounds in the ionic liquid[bmim]Br.

Entry	Aldehyde 1	Product 3[a]	Time [min]	Yield [%][b]
a			10 (5 h)[c]	95 (89)[c]
b			12 (4 h)[c]	93 (79)[c]
c			13	92
d			20	85
e			20 (4 h)[c]	95 (91)[c]
f			10	90
g			15	90
h			10	89
i			20	85
j			20	90
k			10	80
l			15	81
m			20	75
n			20	70

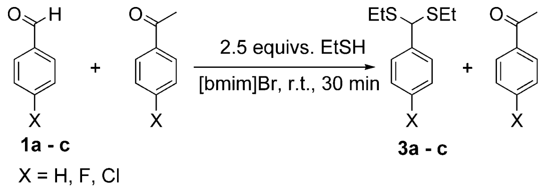
[a] All products were characterized by ^1H NMR, IR and mass spectroscopy.[2,3]
[b] Isolated yields after column chromatography on silica gel.
[c] Ref.[4]

It is worthwhile to note that the reaction proceeds with both activated and weakly activated aromatic aldehydes (with electron-donating and -withdrawing groups at the *ortho* and *para* positions **1b–e**) in almost quantitative yields in short reaction times (entries **b–e**). Moreover, heterocyclic and aliphatic aldehydes (entries **f** and **g**) provide their corresponding thioacetals in high yields. Further, it has been observed that acid-sensitive substrate such as furfural (entry **k**) also forms its thioacetal in almost quantitative yield without the formation of any side-products, while this reaction under acidic conditions is usually known to be problematic.[16] This process is also useful for the conversion of carbonyl functionality to the corresponding 1,3-dithiolanes and 1,3-dithianes (**1h–n**) which can act as blocking groups for electrophilic substitution at the carbonyl carbon.

Moreover, it is interesting to observe that aromatic ketones have not produced the corresponding thioketals under the same reaction conditions even after a prolonged reaction time; however, cyclic ketones like cyclohexanone (**1j**) provide the thioketal in almost quantita-



Scheme 2.



Scheme 3.

tive yield and this could be attributed to the stereoelectronic factors (Scheme 2). To explain this phenomena the electron density at the carbonyl carbon has been calculated using semi-empirical molecular orbital calculations by the AM1 method of the MOPAC 6.0 package. The electron densities for cyclohexanone and acetophenone are 0.231 and 0.267, respectively. Therefore, due to the higher electron density around the carbonyl carbon of an aromatic ketone is less susceptible to nucleophilic attack.

Further, we have carried out the reaction of different substituted aldehydes and ketones with ethanethiol to unravel the chemoselectivity of this reaction process. When equimolar mixtures of an aldehyde and ketone have been treated with ethanethiol (2.5 equivs.), it is observed that the thiol selectively adds to the aldehyde and whereas the ketone is almost completely recovered (Scheme 3). This is also explained by taking into account the electron density at the carbonyl carbon of acetophenone (0.267) and benzaldehyde (0.223). It is well-known that ketones are less reactive than aldehydes due to the presence of alkyl groups that provide electron density through the sigma bond. In addition, the transition state of an aldehyde after its reaction has a lower energy than that of ketone because of steric crowding, and thus a ketone has a lower reactivity than the aldehyde.

The chemoselectivity has been further demonstrated by carrying out a reaction with an equimolar mixture of an aliphatic aldehyde and ketone with ethanethiol and it is observed that the thioacetal of aliphatic aldehyde alone is obtained as shown in Scheme 4.

Recyclability of the ionic liquid has also been examined by extracting the product with ether, the remaining ionic liquid is further washed with ether and is recycled in subsequent runs. It is observed that there is no loss of activity of the ionic liquid even up to 3 or 4 subsequent runs. Alternatively, if the products are liquids they can be isolated by distillation under reduced pressure, particularly for reaction of more than 5 mmol scale.

Conclusion

In conclusion, we have demonstrated the preparation of the ionic liquid [bmim]Br, and its application for the chemoselective thioacetalization of carbonyl compounds. The present method offers high yields and enhanced reaction rates with chemoselectivity. The use of this ionic liquid as a catalytic medium could replace the conventional procedures involving boron trifluoride etherate or lithium perchlorate-diethyl ether.[17] This methodology reduces the generation of wastes and also avoids safety-related problems. Further, the absence of a catalyst and recyclability of the non-volatile ionic liquid are the remarkable features of the present method, and it is expected to address the problem of environmental concerns.

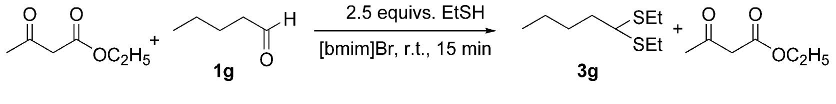
Experimental Section

General Remarks

All reagents were obtained from commercial sources and used without further purification. Solvents for chromatography are of technical grade and were distilled before use. ^{1}H NMR spectra were recorded at 200 MHz and 300 MHz and chemical shifts are given in δ units relative to the tetramethylsilane (TMS) signal as an internal reference in $CDCl_3$. Coupling constants (J) are reported in hertz (H). Electron-impact (EI) mass spectra were recorded in the form of m/z (intensity relative to base 100) on a VG 7070H Micromass mass spectrometer at 200 °C, 70 eV, with a trop current of 200 μA and 4 KV acceleration. Melting points have been recorded on an Electrothermal melting point apparatus. IR spectra were recorded neat on a refractive spectrophotometer. Analytical TLC of all reactions was performed on Merck prepared plates (silica gel 60 F-254 on glass). Column chromatography was performed using Acme silica gel (100–200 mesh).

Synthesis of 1-*n*-Butyl-3-methylimidazolium Bromide

To *N*-methylimidazole (10 mL, 0.125 mmol) solution, *n*-bromobutane (16 mL, 0.15 mmol) was added and then the mixture was heated at 80 °C for 12 h. After allowing the reaction mixture to cool, the brown-coloured, viscous product was washed



Scheme 4.

with ethyl acetate (5 × 20 mL) and volatile materials was evaporated under high vacuum to obtain the 1-*n*-butyl-3-methylimidazolium bromide [**b**] as a brown-coloured liquid. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.98$ (t, 3H, $J = 7.4$ Hz), 1.30–1.50 (m, 2H), 1.80–2.00 (m, 2H), 4.20 (s, 3H), 4.40 (t, 2H, $J = 7.4$ Hz), 7.60 (s, 1H), 7.80 (s, 1H), 10.40 (s, 1H); IR (neat): $\nu =$ 3440, 3142, 3072, 2960, 2864, 1552, 1488, 800, 768, 624 cm^{-1}; FAB (+ve): $m/z = 139$ $(M-Br)^+$ (100%), 357 $(C_8H_{15}N_2)_2Br$ (4%).

General Procedure for Thioacetalization of Carbonyl Compounds in [bmim]Br

To a stirred solution of the appropriate aldehyde (1 mmol) in the ionic liquid [bmim]Br (1.5 mL) was added ethanethiol (2.5 mmol) or 1,2-ethandithiol (1.2 mmol) or 1,3-propanedithiol (1.2 mmol) at room temperature. The reaction mixture was stirred at room temperature for the appropriate time (see Table 1). After completion of the reaction as indicated by TLC, ether (3 × 5 mL) was added to the reaction mixture with vigorous stirring for 5 min. The mixture was allowed to stand for further 5 min and the clear supernatant liquid was decanted. The combined ether layers were concentrated Under vacuum to obtain the crude product which was purified by short silica gel column chromatography (eluent: ethyl acetate/*n*-hexane) to furnish the corresponding thioacetal. The ionic liquid layer was further washed with ether (2 × 3 mL), volatile materials were evaporated under vacuum and the ionic liquid recycled in subsequent runs. The products were characterized by their NMR, IR, and MS analysis. The spectral data of all the products were identical with those of authentic samples.[2,3]

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[14] The ionic liquid was dissolved in water and to this was added $NaHCO_3$ in small amounts with vigorous stirring until no bubbling was observed from the ionic liquid water mixture, then methanol was added to this mixture and water was removed azeotropically at 80 °C under high vacuum, later dichloromethane was added, the mixture filtered and the filtrate dried on sodium sulfate, finally concentration under vacuum at 80 °C provided the neutral ionic liquid.

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