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Chemoselective thioacetalization and transthioacetalization of carbonyl compounds catalyzed by immobilized scandium(III) triflate in ionic liquids

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Abstract—Immobilized scandium triflate [Sc(OTf)$_3$] in ionic liquids has been found to be an extremely efficient and recyclable catalyst for the thioacetalization and transthioacetalization of both aromatic and aliphatic aldehydes. Significant rate acceleration and chemoselectivity was achieved by employing this catalytic system. © 2003 Elsevier Science Ltd. All rights reserved.

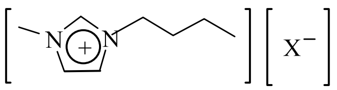
Thioacetalization and transthioacetalization are well studied processes for the conversion of carbonyl compounds and their *O*,*O*-acetals to the corresponding thioacetals. Thioacetals are important protecting groups for the total synthesis of complex natural products because of their enhanced stability under acidic conditions compared to *O*,*O*-acetals.[1] Transthioacetalization of acetals is a useful transformation for the preparation of *S*,*S*-acetals[2] and, in comparison to thioacetalization of carbonyl compounds, is a rapid and cleaner reaction process. In general thioacetals are prepared by protic or Lewis acid catalyzed condensation of carbonyl compounds and their *O*,*O*-acetals with thiols.[3–10] However, there are some disadvantages of these methods, e.g. long reaction times; reflux temperatures; poor selectivity when applied to mixtures of aldehydes and ketones; and the catalyst cannot be recovered and reused.

In a previous report, we demonstrated that scandium triflate is an efficient and recyclable catalyst for thioacetalization.[11] However, disadvantages of this process are difficulties in recovering the catalyst quantitatively after each run and drying the catalyst at high temperature and pressure. A further limitation is the use of the highly volatile solvent, dichloromethane, in this reaction.

Recently, there have been a considerable number of reports regarding ionic liquids and their use for immobilizing catalysts thereby improving the stability of and facilitating the recovery of the catalyst.[12] In this process, a catalyst having a polar or ionic character can be immobilized without structural modification and the ionic solution containing the catalyst can be separated from reagents and products.

Scandium triflate immobilized in ionic liquids has been used for Friedel–Crafts[13] and Diels–Alder[14] reactions. Herein, we wish to report thioacetalization and transthioacetalization of carbonyl compounds and their *O*,*O*-acetals using an efficient and recyclable catalytic system, Sc(OTf)$_3$ immobilized in air and moisture stable ionic liquids.

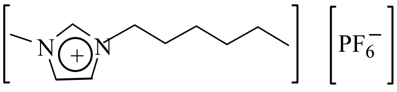
The ionic liquids [bmim][X] **1a**–**b** ([bmim]$^+$ = 1-butyl-3-methylimidazolium cation; **1a**: X = PF$_6$; **1b**: X = BF$_4$)



[bmim][X] (**1a-b**)

a: X= PF$_6$

b: X= BF$_4$



[hmim][PF$_6$] (**2**)

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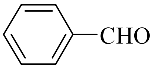
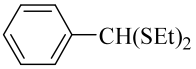
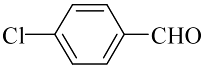
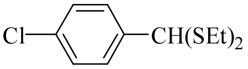
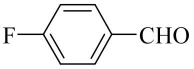
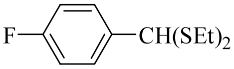
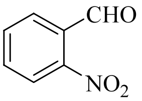
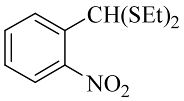
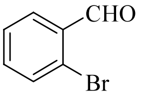
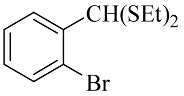
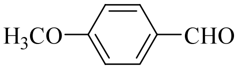
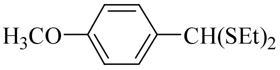
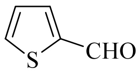
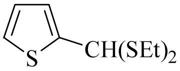
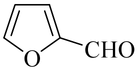
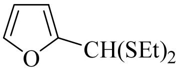
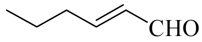
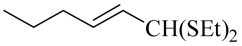
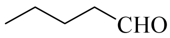
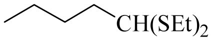
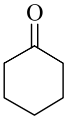
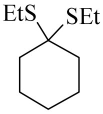
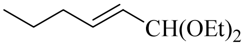
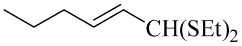
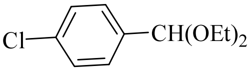
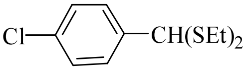
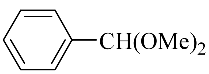
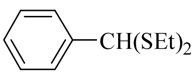
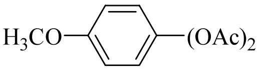
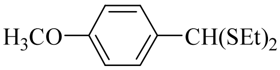
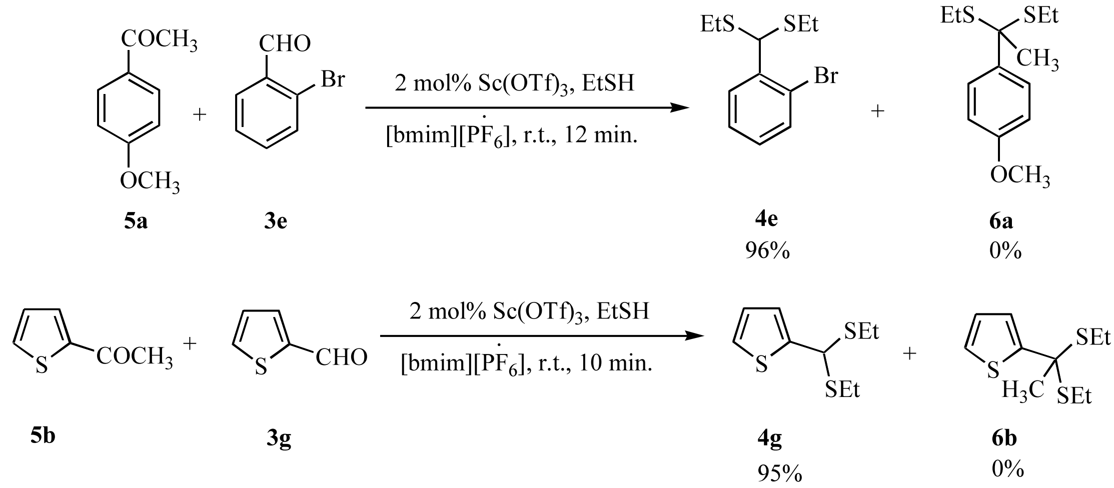
and [hmim][PF_6] ([hmim]$^+$ = 1-hexyl-3-methylimidazolium cation) were prepared by stirring a mixture of *N*-methylimidazole with 1.2 equiv. of *n*-butyl or *n*-hexyl chloride at 78°C for 30 h under nitrogen followed by the metathesis reaction of these imidazolium halides with 1.3 equiv. of HPF_6 in water and $NaBF_4$ in acetone

Table 1. Thioacetalization and transthioacetalization of carbonyl compounds using $Sc(OTf)_3$ immobilized in ionic liquid **1a**

Entry	Aldehyde/Acetal **3**	Product **4** [a]	(Ref)	Time (min)	Yield (%)[b]
a			(6)	9	95 (92, 94, 95)[c]
b			(19)	10 (20)[d]	93 (93)[d]
c				10	95
d				10	91
e				12	97
f			(6)	10 (35)[d]	90 (80)[d]
g				8	95
h			(20)	10	92
i			(11)	15 (50)[d]	90 (87)[d]
j			(11)	15 (50)[d]	90 (90)[d]
k			(6)	15	90
l				12	90
m				10	91
n				8	95
o				9	92

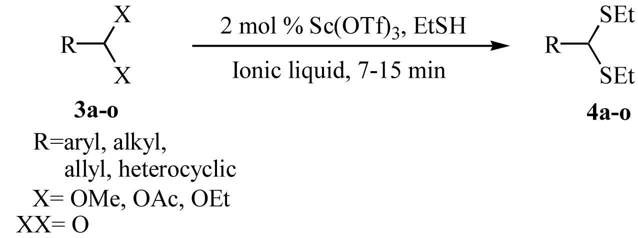
[a] All products were characterised by ^1H NMR, IR and mass spectroscopy. [b] Isolated yields after column chromatography on silica gel. [c] Isolated yield with reused catalyst. [d] Time and yield with $Sc(OTf)_3$(4 mol %) in CH_2Cl_2.[11]



Scheme 1.

for 2 days. Purification of these ionic liquids was carried out as described in the literature.[15]

Initially, benzaldehyde (1 mmol) and scandium triflate (2 mol%) in [bmim][PF$_6$] **1a** (1 ml) was treated with 2.2 equiv. of ethanethiol to furnish the corresponding thioacetal in 95% yield in 9 min. A wide range of aldehydes and acetals derived from aromatic, and aliphatic aldehydes also formed thioacetals with ethanethiol in short reaction times and high yields.[16] The generality of the process was investigated with a wide range of aromatic, aliphatic and heterocyclic aldehydes and the results are illustrated in Table 1.



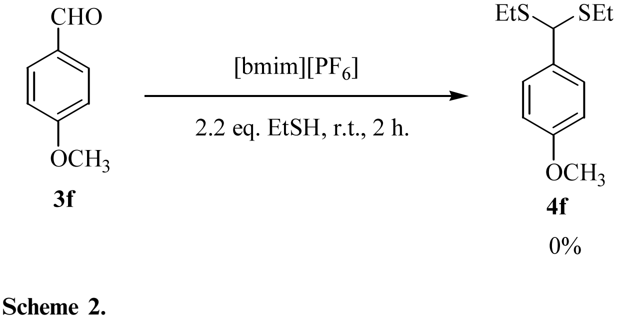
The activity of several ionic liquids (**1a**–**b** and **2**) was evaluated for thioacetalization with similar behavior being observed. Sc(OTf)$_3$ is partially soluble in ionic liquids and exists as a suspension in [bmim][PF$_6$] (**1a**) and [hmim][PF$_6$] (**2**), whereas in the hydrophilic ionic liquid [bmim][BF$_4$] (**1b**), it is highly soluble and is totally immobilized. The products were obtained in excellent yields using these ionic liquids. Moreover, the ionic liquid phase containing Sc(OTf)$_3$ was effectively quantitatively recovered and reused three times by simple extraction of the product with Et$_2$O (Table 1, see entry **a**).

It is interesting to note that reaction rates and yields for the thioacetalization process in ionic media are faster and much improved in comparison to those reported in non-ionic media, i.e. in dichloromethane where 4 mol% of the catalyst is required (Table 1, products **4b**, **4f**, **4i**, **4j**).[11]

Moreover, this procedure is highly chemoselective, providing selective protection of an aldehyde in the presence of a ketone, c.f. the use of mixtures of the aldehydes (**3e** and **3g**) and ketones (**5a** and **5b**) as shown in Scheme 1.

The catalytic activity of the ionic liquid [bmim][PF$_6$] (**1a**)[17] has also been investigated for this type of reaction in the absence of Sc(OTf)$_3$ but no reaction occurred even after a prolonged reaction time (Scheme 2).

In conclusion, we have demonstrated that ionic liquids act as a versatile media not only for efficient catalyst recycling but also for enhancing the rate of the reaction and improving selectivity in scandium(III) triflate catalyzed thioacetalization. In the present process the immobilized catalytic system has been reused three times without any change in catalytic activity. Hence this new technique involving the application of an ionic liquid could have potential to address intrinsic problems (low catalytic activity, selectivity and the structure modification of the catalyst) of homogenous catalysis. Moreover, in this reaction the ionic liquid was used in stoichiometric amounts, which addresses a problem of environmental and economical sustainability.



Scheme 2.

Acknowledgements

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16. **Typical experimental procedure**: To a stirred solution of scandium triflate (2 mol%) and the appropriate aldehyde or acetal (1 mmol) in the ionic liquid (1 ml) at room temperature was added ethanethiol (2.2 mmol). The mixture was stirred at room temperature for the appropriate time (see Table 1). After completion of the reaction as indicated by TLC, the ionic liquid was extracted with Et$_2$O. The ether layer was washed with aqueous 2N NaOH, extracted, dried (Na$_2$SO$_4$), concentrated in vacuo and the crude product purified by silica gel column chromatography to furnish the corresponding thioacetal.
    Spectroscopic data; Compound **4b**; ^{1}H NMR (300 MHz; CDCl$_3$); $\delta = 1.20$–1.30 (t, $J = 7.2$ Hz, 6H), 2.45–2.70 (m, 4H), 4.90 (s, 1H), 7.30 (d, $J = 8.1$ Hz, 2H), 7.40 (d, $J = 8.1$ Hz, 2H). Compound **4d**; ^{1}H NMR (300 MHz; CDCl$_3$); $\delta = 1.20$–1.40 (t, $J = 7.2$ Hz, 6H), 2.45–2.80 (m, 4H), 5.65 (s, 1H), 7.25 (dd, $J = 7.4$ Hz, 1H), 7.40 (dd, $J = 7.4$ Hz, 1H), 7.80 (d, $J = 7.4$ Hz, 1H), 7.95 (d, $J = 7.4$ Hz, 1H). IR (CHCl$_3$) ν cm^{-1}; 3070, 2967, 2925, 2870, 1560, 1452, 1373, 1263, 1220, 1155, 1020, 972, 852, 743, 700. FAB MS $m/z = 256$ (M–H). Compound **4e**; ^{1}H NMR (300 MHz; CDCl$_3$); $\delta = 1.40$ (t, $J = 7.2$ Hz, 6H), 2.40–2.80 (m, 4H), 5.40 (s, 1H), 7.10 (dd, $J = 7.4$ Hz, 1H), 7.30 (dd, $J = 7.4$ Hz, 1H), 7.60 (d, $J = 7.4$ Hz, 1H), 7.85 (d, $J = 7.4$ Hz, 1H). IR (CHCl$_3$) ν cm^{-1}; 3067, 2967, 2925, 2870, 1566, 1451, 1375, 1264, 1220, 1153, 1020, 972, 852, 744. FAB MS $m/z = 290$ (M–H) Compound **4g**; ^{1}H NMR (300 MHz; CDCl$_3$); $\delta = 1.20$ (t, $J = 7.2$ Hz, 6H), 2.50–2.90 (m, 4H), 5.20 (s, 1H), 6.75 (t, $J = 4.4$ Hz, 1H), 7.05 (d, $J = 5.2$ Hz, 1H), 7.30 (dd, $J = 5.2$ Hz, 1H). IR (CHCl$_3$) ν cm^{-1}; 3074, 2967, 2925, 2870, 1793,1672, 1446, 1375, 1262, 1151, 1041, 974, 849, 703. FAB MS $m/z = 217$ (M–H).
17. Imidazolium ionic liquid [bmim][PF$_6$] has been selected, as it is stable in air and moisture. Although organoaluminate imidazolium ionic liquids are known to possess Lewis acid properties and can catalyze such reactions in the absence of a Lewis acid but they are not stable to air and moisture.[12] Therefore, since these are chemically not inert their applications are limited and the desired chemoselectivity cannot be achieved.
    Spectroscopic data of [bmim][PF$_6$][15,18]; ^{1}H NMR (400 MHz; neat); $\delta = 0.75$ (t, $J = 7.3$ Hz, 3H), 1.20 (m, 2H), 1.75 (m, 2H), 3.80 (s, 3H), 4.10 (t, $J = 7.3$ Hz, 2H), 7.30 (d, $J = 14.6$ Hz, 2H) 8.30 (s, 1H). IR (neat); 3168 and 3124 [ν(C–H) aromatic]; 2964, 2935, and 2877 [ν(C–H) aliphatic]; 1571 and 1465 [ν(C=C)]; 835 [ν(PF)] cm^{-1}.
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