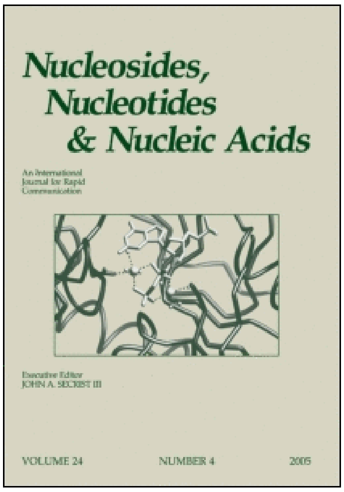

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TRANSPROTECTION OF SILYL ETHERS OF NUCLEOSIDES IN $FeCl_3$ BASED IONIC LIQUIDS

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▫ *Ionic liquid mediated deprotection of tert-butyldimethyl silyl (TBDMS) ethers derived from various primary and secondary alcohols have been studied and the reaction conditions optimized. Deprotection of the silyl ethers in $FeCl_3$ based ionic liquids in presence of acetic anhydride yielded the acetate esters of the corresponding alcohols in good yields. The transprotection methodology was extended to the silyl ethers of nucleosides to yield the corresponding acetylated products.*

Keywords Protected Nucleosides, Ionic Liquid, Desilylation, Acylation

INTRODUCTION

Among the silyl protecting groups, the *tert*-butyldimethyl silyl (TBDMS) ethers of the alcohols provide low-cost and synthetic advantages. Additionally, the TBDMS ethers are stable to hydrogenolysis, Jones oxidation, mild chemical reductions and THP ether cleavage. One of the key feature of TBDMS ethers is their ability to be cleaved selectively in the presence of the other silyl protecting group(s).[1] Survey of the literature indicated that the protocols used for the cleavage of silyl ethers either employ Lewis acids or water in presence of acid or base.[2–4] The literature methodologies were of limited utility and interest to us, as our goal was to develop a protocol that was non-hydrolytic. This is because most of the -OH and -NH protecting groups employed routinely in nucleoside chemistry are sensitive towards acid and base hydrolysis. $FeCl_3$ is reported to act as an efficient Lewis acid catalyst. With the growing interest in applications of the ionic liquids,[5–9] we considered it worthy to use 1-*b*utyl-3-*m*ethyl*im*idazolium chloride [bmim]$ClFeCl_3$, $N = 0.35–0.60$ ionic liquid for the desilylation of silyl ethers.

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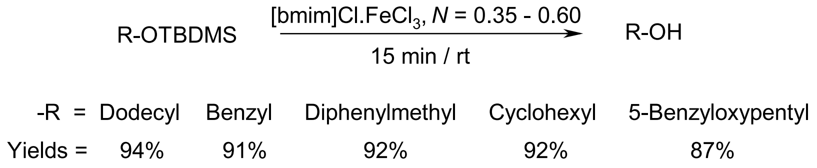
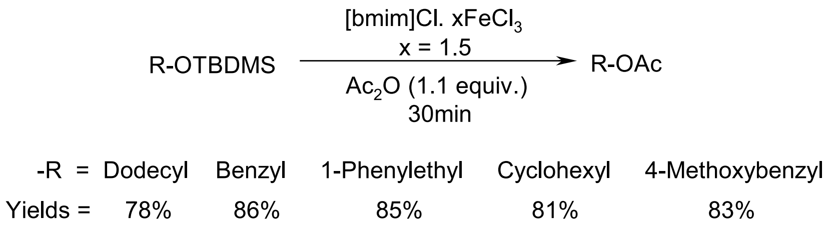


SCHEME 1 [bmim]ClFeCl$_3$, $N = 0.60$ mediated desilylation of TBDMS ethers.

RESULTS AND DISCUSSION

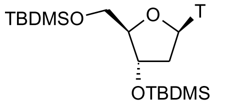
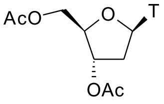
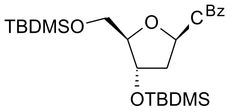
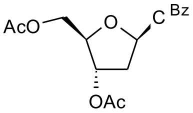
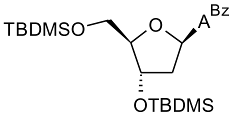
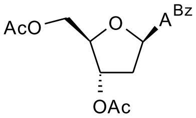
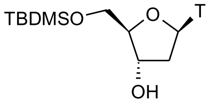
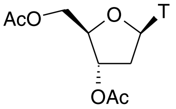
The [bmim]Cl.xFeCl$_3$ system is liquid when the apparent mole fraction of FeCl$_3$, N in the ionic liquid is in the range $N = 0.35–0.60$.[10] We conducted the experiments using benzyloxy-*tert*-butyldimethylsilane as a model substrate. The ionic liquids of different Lewis acidities were added in the stiochiometric amounts to the reaction mixture (1 mol equiv. used for each reaction). The reactions were stopped after 30 min, and were assayed on GC to quantify the extent of conversion obtained at different Lewis acidities. The extent of conversion was dependent on the Lewis acidity of the ionic liquid. Thus, the ionic liquid with $N = 0.35$ provided 12% conversion, while the reaction with $N = 0.50$ showed 22% conversion within 30 min. Extending the reaction time to 24 h improved the conversion to 45% ($N = 0.50$). The ionic liquid [bmim]FeCl$_3$, $N = 0.60$ proved to be superior to all other ionic liquids with 100% conversion in 30 min. Therefore, we chose [bmim]ClFeCl$_3$, $N = 0.60$ ionic liquid in our deprotection studies.

Next, we studied the effects of using a molar equivalence of ionic liquid with $N = 0.60$ in the reaction mixtures. We quantified the extent of conversion in each case by arbitrarily fixing the time at 30 min. The results indicated that the conversion was directly dependent on the molar stoichiometry of the ionic liquid in the reaction. An increase in the molar stoichiometry from 0.25 equivalent to 0.50 equivalent increased the conversion from 18 to 43%. A further increase in the molar equivalence to 0.75 resulted in a 72% conversion. The conversion was found to be quantitative with 1 mol equivalent of ionic liquid. The reaction time was further optimized via desilylation of benzyloxy-*tert*-butyldimethyl-silane using 1 mol equivalent of ionic liquid. The progress of the reaction was monitored at 5, 10, 15, and 20 min. A 62% conversion was observed after 5 min, which increased to 89% after 10 min. The conversions reached a maximum of 100% within 15 min. These



SCHEME 2 [bmim]ClFeCl$_3$, $N = 0.60$ mediated transprotection of TBDMS ethers.

TABLE 1 Transprotection of Silylated Nucleosides in [bmim]ClFeCl$_3$, $N = 0.60$ in Presence of Acetic Anhydride[a]

Entry	Silylated nucleoside	Product	Yields (%)[b]
1			76
2			88
3			72
4[c]			62

[a] 2 mol equiv. of [bmim]ClFeCl$_3$, $N = 0.60$/2.2 mol equiv. of Ac$_2$O/30 min/rt.
[b] Isolated yields.
[c] Reaction carried out for 3 h.

being the optimal conditions for desilylation, the protocol was utilized for silyl ethers derived from primary, secondary and cyclic secondary alcohols to evaluate the success of our methodology. Gratifyingly, excellent desilylation of a variety of molecules was accomplished under the optimized conditions (Scheme 1).*

Furthermore, we studied the desilylation reaction in the presence of acetic anhydride. Interestingly, we observed a rapid transprotection of silylated substrates which furnished acetylated products in good yields (Scheme 2).* Extension of this

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**Preparation of 1-butyl-3-methylimidazolium chloride, [bmim]Cl:* The mixture of 100 mmol 1-methylimidazole and 400 mmol 1-chlorobutane in 12 mL dried toluene was refluxed under nitrogen atmosphere for 24 h to obtain a viscous liquid forming the lower layer. The reaction mixture was cooled to 0°C overnight to yield the solid quaternary salt (1-butyl-3-methylimidazolium chloride). The excess unreacted toluene and 1-chlorobutane was decanted and the salt washed with diethyl ether (3 × 10 mL). The salt was further purified by recrystallization from acetonitrile/ethyl acetate to yield the pure product. Melting point: 66–68°C. *Preparation of [bmim]Cl.xFeCl$_3$:* Appropriate quantities of 1-butyl-3-methylimidazolium chloride and FeCl$_3$ (depending on the Lewis acidity of the ionic liquid required) were mixed in a round bottom flask and stirred under cold conditions (0–10°C) to avoid local overheating. Upon stirring (30 min), the two solids fused together, resulting in the formation of a clear ionic liquid, [bmim]ClFeCl$_3$, $N = 0.35–0.60$. *General procedure for desilylation:* To 2 mmol of [bmim]ClFeCl$_3$, $N = 0.60$ ionic liquid, 2 mmol of silyl ether was added and the mixture was stirred at room temperature under inert atmosphere. The reaction mixture was quenched by adding aqueous saturated NaHCO$_3$ and extracted with diethyl ether (3 × 5 mL). The combined organic layer was dried over anhydrous Na$_2$SO$_4$ and evaporated under reduced pressure. The products were purified by silica gel chromatography to furnish the alcohol. *General procedure for transprotection:* To 5 mmol of [bmim]Cl.FeCl$_3$, $N = 0.60$ ionic liquid, 5 mmol of silyl ether, and 5.5 mmol of acetic anhydride were added and the mixture was stirred at room temperature under inert atmosphere. The reaction mixture was worked up as described above to furnish the acylated product.

protocol to TBDMS protected 2′-deoxyribonucleosides furnished acetylated products in 62–88% yields (Table 1).* The protocol used 2 mol equivalent of [bmim]Cl.FeCl$_3$, N = 0.60 and 2.2 mol equivalent of Ac$_2$O for the disilyl derivatives to yield the nucleoside diacetates. The optimal time for the reaction was 1 h; however, the monosilyl derivative took a longer time (entry 4, Table 1).

CONCLUSION

The [bmim]ClFeCl$_3$, N = 0.60 ionic liquid served as an efficient solvent-catalyst system for achieving the desilylation of alcohols. The desilylation protocol in [bmim]Cl.xFeCl$_3$ has been optimized for the Lewis acidity and reaction time. The FeCl$_3$ based ionic liquid was efficient in promoting the desilylation reaction of silyl ethers of nucleosides in presence of acetic anhydride, generating the corresponding acetate esters.

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