



An Efficient Conversion of Alcohols to Alkyl Bromides Using Pyridinium Based Ionic Liquids: A Green Alternative to Appel Reaction

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Pyridinium based ionic liquids namely 4-alkylpyridinium bromides were prepared and used for the conversion of alcohols to alkyl bromides in the presence of *p*-toluenesulphonic acid in the absence of volatile organic compounds. This solvent free procedure promises to be a much improved and environmentally benign alternative to the Appel reaction.

Keywords: Appel reaction, Ionic liquid, Solvent free synthesis, Alkylbromides, Aliphatic alcohol.

INTRODUCTION

Alkyl halides are widely used as industrial solvents and also as essential precursors for the preparation of a variety of fine chemicals. The classical procedure for the conversion of alcohols to alkyl halides is termed as the Appel reaction and in the classical example requires the use of NaBr and H₂SO₄ under harsh reaction conditions [1]. Being an environmentally unacceptable process, this synthesis has limited synthetic applicability today. A direct conversion of alcohols to alkyl halides is difficult due to poor leaving group characteristics of the hydroxyl group, however several improved procedures have been reported to overcome this drawback. An elegant procedure for the conversion was reported wherein triphenylphosphine and tetrahaloalkanes were used [2]. Other notable synthetic procedures are the Mitsunobu reaction [3], the reaction of 2,4,6-trichloro-[1,3,5]-triazine (TCT) in DMF followed by addition of CH₂Cl₂ solution of the reactant alcohol [4], the reaction of alcohol with 2,3-trichloro-5,6-dicyanobenzo-quinone in the presence of triphenyl phosphine, CH₂Cl₂ and a phase transfer catalyst [5]. ROMP-gel supported triphenyl-phosphine [6], phosphorus(V) mediated nucleophilic substitution reaction [7] and finally the use of fluororous phosphine [8] besides others. The previously reported procedures suffer from the use of toxic and expensive reagents and further the use of triphenylphosphine makes product recovery difficult and time consuming specially due to the *in situ* formation of the phosphine oxide. In order to avoid the use of triphenylphosphine, an elegant phosphine free halogenation protocol using a visible light photoredox catalyst Ru(bpy)₃Cl₂ was reported [9].

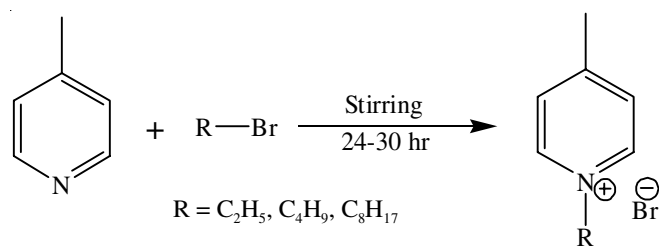
The need for environmentally acceptable processes has fuelled great interest towards the use of benign reagents especially the use of ionic liquids to promote reactions. Generally reactions promoted by ionic liquids results in reduced reaction time, simplifies product recovery and greatly improves turn over. Leadbeater *et al.* [10] used imidazolium based ionic liquids, which played the dual role as a reagent and as a solvent in microwave mediated technique for the conversion of alcohols to the alkyl halides in the presence of mineral acids. Ren and Wu [11] used 1,3-dimethylimidazolium halide as reagent for the conversion of *n*-butanol and *n*-octanol to the corresponding halide in the presence of bronsted acids such as HCl, H₂SO₄ and CH₃SO₃H. Petten *et al.* [12] used halodehydrogenation technique using ionic liquid for the conversion of long chain alcohols to their respective alkyl halides, Ranu and Jana [13] reported a stereoselective one pot conversion combining the use of ionic liquid and ultrasound and finally a stereoselective one pot conversion of N,N'-diisopropylcarbodiimide was reported [14] besides others [15,16].

EXPERIMENTAL

GC/MS was carried out on a Perkin Elmer Clarus 600 gas chromatograph and Clarus 600C mass spectrometer (column 30.0 m × 250 μm). ¹H was done on a Bruker 300 MHz instrument using CDCl₃ as the solvent, 4-methylpyridine, ethylbromide, *n*-butylbromide, *n*-octylbromide, substrate alcohols and *p*-toluenesulphonic acid were purchased from Sigma Aldrich and were used as received. The ionic liquids, 1-*n*-alkyl-4-methylpyridinium bromide, were prepared from 4-methylpyridine and characterized.

Thermogravimetric analysis (TGA): TGA experiments were performed using a TGA-DSC1, Mettler Toledo instrument. The samples were weighed and placed in a platinum crucible. They were then heated in a stream of nitrogen atmosphere, from room temperature to 700 °C with a heating rate usually of 10 °C/min.

General method for preparation of ionic liquids: Three different pyridinium based ionic liquids namely 1-ethyl-4-methyl pyridinium bromide, 1-*n*-butyl-4-methyl pyridinium bromide and 1-*n*-octyl-4-methyl pyridinium bromide were prepared by simply mixing 4-methylpyridine (γ -picoline) and the appropriate alkyl halide and stirring the mixture in the dark for 20-24 h (Scheme-I). The yield of the ionic liquids was found to be almost quantitative.



Scheme-I

1-Ethyl-4-methylpyridinium bromide: m.f.: C₈H₁₂NBr, white solid, melting range 250-300 °C; ¹H NMR (300 MHz, CDCl₃, Me₄Si) (δ _H ppm): 9.322 (2H, d, *J* = 6.6 Hz, pyr-CH), 7.756 (2H, d, *J* = 6.3 Hz, pyr-CH), 4.803 (2H, q, *J* = 7.2 Hz, CH₂), 2.503 (3H, s, CH₃), 1.532 (3H, t, *J* = 7.2 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) (δ ppm): 158.53, 143.85, 128.72, 56.12, 22.03, 17.03.

1-*n*-Butyl-4-methyl pyridinium bromide: m.f.: C₁₀H₁₆NBr, nature: white waxy solid, melting range 110-280 °C; ¹H NMR (300 MHz, CDCl₃, Me₄Si) (δ _H ppm): 9.363 (2H, d, *J* = 6.6 Hz, pyr-CH), 7.840 (2H, d, *J* = 6.0 Hz, pyr-CH), 4.812 (2H, t, *J* = 7.2 Hz, CH₂), 2.577 (3H, s, CH₃), 1.972-1.872 (2H, m, CH₂), 1.381-1.282 (2H, m, CH₂), 0.853 (3H, t, *J* = 7.2 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) (δ ppm): 158.51, 144.17, 128.70, 60.59, 33.51, 22.08, 19.09, 13.36.

1-*n*-Octyl-4-methyl pyridinium bromide: m.f.: C₁₄H₂₄NBr, nature: light pink waxy solid, melting range 300-400 °C; ¹H NMR (300 MHz, CDCl₃, Me₄Si) (δ _H ppm): 9.338 (2H, d, *J* = 6.3 Hz, pyr-CH), 7.893 (2H, d, *J* = 6.3 Hz, pyr-CH), 4.872 (2H, t, *J* = 7.5 Hz, CH₂), 2.645 (3H, s, CH₃), 2.022-1.941 (2H, m, CH₂), 1.300-1.204 (10H, m, CH₂), 0.824 (3H, t, *J* = 6.9 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) (δ ppm): 158.54, 144.11, 128.75, 60.93, 31.69, 31.45, 28.82, 25.84, 22.35, 22.09, 13.87.

General procedure for the conversion: A mixture of 5 mmol alcohol, 5 mmol *p*-toluenesulphonic acid, 5 mmol 1-*n*-butyl-4-methylpyridiniumbromide was heated in an oil bath with constant stirring to different temperatures (Table-2), the progress of the reactions monitored by GC after 0.5, 1.0, 1.5, 2.5 and 5 h. In the GC experiments, aliquots of reaction mixture drawn, diluted with 1 mL of diethylether, solution filtered and GC recorded. After complete conversion as indicated by GC, 25 mL of *n*-hexane was added to precipitate out the ionic liquid. The filtrate on evaporation of the solvent afforded the bromides,

which could be identified by running GC with authentic sample. Products were examined for their purity by TLC using silica gel plates and *n*-hexane:petroleum ether (40-60) (9:1) as the eluent.

Recovery of 1-*n*-butyl-4-methylpyridinium-*p*-toluenesulphonate: After separation of the products, the precipitated ionic liquid was found to be transformed to the *p*-toluenesulphonate. For further purification, 25 mL petroleum ether (40-60 °C) was added to this and stirred for 5 min to remove any trace of alkyl bromides. The petroleum ether layer on evaporation afforded the 1-*n*-butyl-4-methyl-pyridinium-*p*-toluenesulphonate, which was recovered and stored in dessicator. The recovered product was identified as the sulphonate form by ¹H NMR spectra. ¹H NMR (300 MHz, CDCl₃): δ _H ppm 8.915 (d, 2H, *J* = 6.3 Hz, ArH), 7.740-7.685 (m, 4H, ArH), 7.112 (d, 2H, *J* = 7.8 Hz, ArH), 4.612 (t, 2H, *J* = 7.2 Hz, 2H, NCH₂), 2.520 (s, 3H, ArCH₃), 2.303 (s, 3H, ArCH₃), 1.867-1.767 (m, 2H, CH₂), 1.292-1.192 (m, 2H, CH₂), 0.840 (t, 3H, *J* = 7.2 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ ppm 158.38, 143.51, 139.58, 128.50, 125.50, 60.44, 32.94, 21.61, 20.93, 18.79, 13.10. The sulphonate form of the ionic liquid was converted to the bromide form by treatment with 30 % HBr.

RESULTS AND DISCUSSION

In all reported synthetic methods, the imidazolium based ionic liquids were used as the promoter. These ionic liquids are costly, less effective and the methods reported requires high pressure and long reaction time and the procedures are limited to a few selected alcohols and could not be generalized. Search for inexpensive, efficient and environmentally benign methods for carrying out the Appel reaction is still being explored. In order to overcome the disadvantages associated with the use of imidazolium based ionic liquids, we examined the possibility of the use of pyridinium based ionic liquids for promoting the Appel reaction for the conversion of alcohols to the alkyl bromides. The results reported herein indicate the superiority of pyridinium based ionic liquids *vis-a-vis* imidazolium counterparts. The pyridinium based ionic liquids used in this study were prepared by a simple reported procedure [17] using low-cost and easily available starting compounds. Three different ionic liquids were prepared starting from 4-methylpyridine and corresponding alkyl halides namely 1-ethyl-4-methylpyridiniumbromide [1-E-4-MPyr]Br, 1-*n*-butyl-4-methyl-pyridinium bromide [1-*n*-B-4MPyr]Br and 1-*n*-octyl-methylpyridinium-bromide [1-*n*-O-4-Mpyr]Br and characterized. Results indicate that all the ionic liquids have thermal stability upto 250 °C. Thermogravimetric curves of the three ionic liquids indicate that 1-*n*-butyl-4-methyl pyridinium-bromide had a melting range of 110-280 °C and this being close to the melting range of usual ionic liquids was considered to be the most appropriate of the three ionic liquids for the present synthesis. The TGA curves are shown in Fig. 1.

The ionic liquids were used as a promoter for a solvent free conversion of a variety of alcohols to the corresponding bromides. Initially the efficiency of the individual ionic liquids were screened for their utility. The conversion of octan-1-ol to 1-bromooctane using the three ionic liquids individually was examined as a model reaction and the results summarized

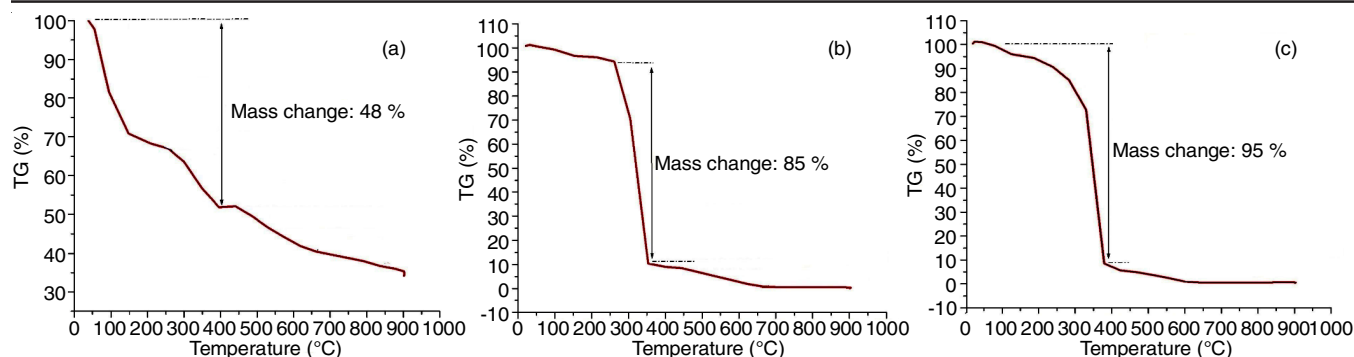


Fig. 1. TGA curve of (a) 1-*n*-butyl-4-methylpyridiniumbromide (b) 1-ethylpyridiniumbromide (c) 1-*n*-octylpyridiniumbromide

in Table-1. Results indicates the better efficiency, in terms of better yield of products, of 1-*n*-butyl-4-methyl-pyridiniumbromide [1-*n*-B-4Mpyr]Br over other ionic liquids used. Consequently all subsequent reactions were carried out with using [1-*n*-B-4Mpyr]Br.

TABLE-1
EFFICIENCY OF DIFFERENT PYRIDINIUM BASED IONIC LIQUID FOR CONVERSION OF OCTAN-1-OL TO *n*-OCTYLBROMIDE AFTER 5 h OF REACTION TIME

Entry	Ionic liquid	Reaction temp. (°C)	% Conversion after 5 h*
1	1-Butyl-4-methylpyridinium bromide	130	100
2	1-Ethyl-4-methylpyridinium -bromide	130	65
3	1-Octyl-4-methylpyridinium -bromide	130	70

*% conversion obtained from GC experiments.

In a typical procedure, an equimolar mixture of alcohol, *p*-toluenesulphonic acid and 1-*n*-butyl-4-methylpyridinium-bromide was taken in a round bottom flask and heated to the optimized temperature for range of reaction time. The progress

of the reaction was monitored by GC of aliquots drawn from the reaction mixture at time intervals of 0.5, 1.5, 2.5 and 5 h. The reaction is shown in **Scheme-II** and results obtained for a variety of alcohols summarized in Table-2. The reaction time and temperature necessary for complete conversion, varied with the nature of the substrate alcohol.

Conclusion

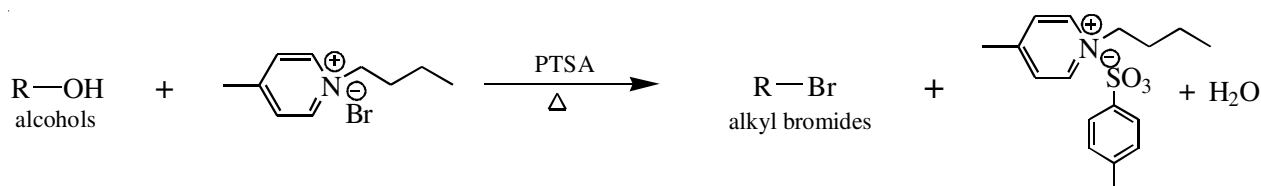
The use of pyridinium based ionic liquid for the Appel reaction offers an easy access to the alkylbromides. The products could be isolated by simple filtration of the precipitated ionic liquids. The precuts were identified performing GC with authentic sample. The ionic liquids could be recycled. Simple reaction condition, absence of costly reagents, high turnover of products makes this procedure an improved practical alternative to the conventional Appel reaction.

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TABLE-2
SYNTHESIS OF ALKYL BROMIDES FROM ALCOHOLS USING AS THE IONIC LIQUID [1-B-4-M-Pyr]Br AS THE BROMINATING AGENT

Entry	Reactants	Products	Reaction temp. (°C)	Time (h)	Conversion (%)
1	Butan-1-ol	<i>n</i> -Bromobutane	100	5.0	100
2	Pentan-1-ol	<i>n</i> -Bromopentane	130	5.0	100
3	Pent-2-ol	2-Bromopentane	120	7.0	100
4	Hexan-1-ol	<i>n</i> -Bromohexane	130	4.0	100
5	Cyclohexanol	Bromocyclohexane	140	5.0	100
6	Heptan-1-ol	<i>n</i> -Bromoheptane	130	5.0	100
7	Octan-1-ol	<i>n</i> -Bromooctane	140	2.5	100
8	Benzyl alcohol	Benzyl Bromide	140	0.5	100
9	4-chlorobenzyl alcohol	4-Chlorobenzyl Bromide	140	1.0	100



Where $\text{R} = \text{CH}_3(\text{CH}_2)_n$ where $n = 3, 4, 5, 6, 7$

$= \text{C}_6\text{H}_{11}, \text{C}_6\text{H}_5\text{CH}_2, 4\text{-ClC}_6\text{H}_4\text{CH}_2$

Scheme-II: Conversion of alcohols to alkylbromides using pyridinium based ionic liquids

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