Direct Halogenation of Alcohols and Their Derivatives with *tert*-Butyl Halides in the Ionic Liquid [pmIm]Br under Sonication Conditions – A Novel, Efficient and Green Methodology

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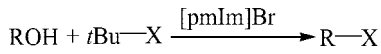
A novel halogenating reagent system for direct halogenation of alcohols has been developed. *tert*-Butyl bromide, chloride and iodide in combination with the ionic liquid [pmIm]Br have been found to convert alcohols into the corresponding bromides, chlorides and iodides under sonication conditions (or heating) in good yields. Although a variety of primary and secondary alcohols participated in this reaction without any difficulty, tertiary alcohols remained inert. Several alcohol derivatives such as OTMS, OTBDMS, OAc, OTS and OTHP are also transformed into the corresponding halides in one-pot fashion by this procedure. A plausible rationale for this transformation is also presented.

Introduction

Alkyl halides, particularly bromides and iodides, are very useful intermediates in organic synthesis, being frequently used for ionic or radical carbon–carbon coupling, substitution, elimination and rearrangement reactions. Alkyl halides are readily available from the corresponding alcohols by different procedures.[1] Because of the lower leaving ability of the hydroxy group, however, procedures for direct conversion of alcohols into alkyl halides under mild conditions are very limited.[2a,2b] Of all the available methods for direct halogenation under neutral conditions,[3] the most widely used are triphenylphosphane/carbon tetrahalide[3a] and a few other similar phosphorus-based reagents such as triphenylphosphane with trihaloimidazole.[3b] However, these systems generally require elevated temperatures and long reaction times. Another serious drawback with these reagents is the generation of triphenylphosphane oxide as a by-product that is very difficult to remove from the reaction mixture by means other than repeated chromatography or precipitation, ultimately resulting in loss of product. An efficient, mild and direct halogenation procedure through the use of a simple and benign reagent and involving a simple purification process would thus be highly desirable, and we would like to report here that *tert*-butyl halides in combination with the easily available ionic liquid [pmIm]Br (*n*-pentylmethylimidazolium bromide) serve as very effective halogenating agents for conversion of alcohols into their corresponding halides (Scheme 1).



Scheme 1. Halogenation of alcohols

2. Results and Discussion

The experimental procedure is very simple. A mixture of alcohol and *tert*-butyl halide in the ionic liquid [pmIm]Br was sonicated in an ultrasonic bath (for bromides and iodides) or heated at 60 °C (for chlorides) for a certain period of time as required to complete the reaction (TLC). At room temperature the reaction did not proceed without sonication. The product was isolated from the reaction mixture by direct distillation under reduced pressure. Alternatively, if the reaction was carried out in smaller scale, the product could be isolated by extraction of the reaction mixture with ether, followed by filtration through a short column of silica gel. The ionic liquid remaining in the reaction vessel could be recycled for subsequent runs. The products isolated by distillation were very pure and did not require further purification, and the crude products obtained through extraction were also reasonably pure (> 95 %), just one short column chromatographic separation providing the analytically pure compounds.

A variety of structurally diverse alcohols were converted into their corresponding bromides, iodides and chlorides by this procedure, through treatment with *tert*-butyl bromide, iodide and chloride, respectively. Although alkyl bromides

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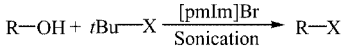
and iodides were obtained very cleanly by sonication (Table 1), the formation of chlorides from alcohols under these conditions was not very smooth. The chlorinations appeared sluggish or incomplete under sonication conditions, but considerable improvement was observed when the reactions were carried out by conventional heating at 60 °C, in contrast to the bromination and iodination reactions, which were found to be messy with heating. All chlorinations were therefore carried out under heating conditions, and the results are summarized in Table 2. Although chlorination proceeded satisfactorily with many substrates under these conditions, a few alcohols that had easily produced bromides and iodides under sonication conditions (entries 6, 8, 9, 12 and 13 in Table 1) did not undergo clean chlorinations, these being associated with mixtures of undesired (and unidentified) side products. However, in general, primary, secondary, benzylic and allylic alcohols underwent smooth conversions into the corresponding bromides and iodides by this procedure. Hindered alcohols such as isoborneol (entry 8, Table 1) were also converted into the corresponding *exo* halides. The primary allylic diol (entry 6, Table 1) was converted into the dibromide and the diiodide without any difficulty, but several tertiary alcohols such as 3-methylpentan-3-ol, 1,1-diphenylethanol and 1-methyl-1-phenylethanol remained inactive under sonication conditions even after 12 h, while heating at 60–70 °C for long periods induced the formation of dehydrated olefins. The acid-sensitive molecule 2-thiophenemethanol (entry 9, Table 1), which was not converted into the corresponding bromide/iodide in satisfactory yields by conventional brominating and iodinating reagents such as PBr_3, Ph_3P/CBr_4 or Ph_3P/I_2/imidazole, such treatment always being associated with considerable polymerization and decomposition, was successfully transformed into the corresponding bromide and iodide by this reagent. Many hydroxy-protected derivatives such as OTMS, OTBDMS, OAc, OTS and OTHP derivatives underwent direct conversions into the corresponding halides by this procedure. The results are presented in Table 3.

Table 1. Halogenation of alcohols by *tert*-butyl halides in [pmIm]Br



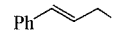
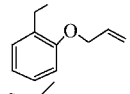
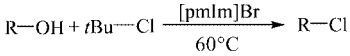
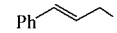
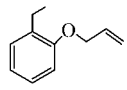
Entry	Alcohol R	X = Br Time/h ; Yield(%)[a]		X = I Time/h ; Yield(%)[a]		Ref.
1	$PhCH_2$	0.8	93	0.7	92	6, 3e
2	$(p\text{-Cl})C_6H_4CH_2$	1.0	95	0.75	85	7, 8
3	$(p\text{-OMe})C_6H_4CH_2$	1.0	92	0.8	89	9, 10
4	$n\text{-}C_5H_{11}$	2	82	4.5	83	3e
5		1.2	92	0.3	85	6, 3f
6		1.6	87	0.5	70	11, 12
7		1.1	90	1.0	92	
8	 (Isoborneol)	2	82 (*exo*)	0.5	75 (*exo*)	17
9		1.5	78	0.7	72	13, 12
10	$c\text{-}C_5H_9$	2	82	1.5	82	3e
11	$c\text{-}C_6H_{11}$	2	84	2.2	80	3e
12		1	87	0.4	93	3f
13		1.3	87	0.5	85	14, 12

Table 2. Chlorination of alcohols by *tert*-butyl chloride in [pmIm]Br



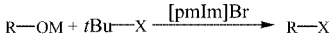
Entry	Alcohol R	Time/h ; Yield(%)[a]		Ref.
1	$PhCH_2$	3	87	6
2	$(p\text{-Cl})C_6H_4CH_2$	3	87	6
3	$(p\text{-OMe})C_6H_4CH_2$	3	85	15
4	$n\text{-}C_5H_{11}$	10	55	3e
5		3.5	82	6
6		5.0	82	16
7	$c\text{-}C_5H_9$	3.75	72	3e
8	$c\text{-}C_6H_{11}$	4	73	3e

[a] The yields refer to pure isolated products characterized by spectroscopic data (IR, ^1H and ^{13}C NMR).

The reactions are in general very clean, reasonably fast and high-yielding. At room temperature with stirring only, halogenation was not initiated. Other open-chain tertiary halides such as *tert*-amyl bromide are also effective, but *tert*-butyl halides were chosen because of their easy availability and better efficiency. Primary and secondary halides such as *n*-butyl bromide and *sec*-butyl bromide, however, were not effective at all.

To ascertain the course of this novel halogenation reaction a few investigative experiments were carried out (Figure 1). It was observed that halogenation by *tert*-butyl halide did not proceed at all in organic solvents such as dichloromethane, acetonitrile, THF or DMF in the absence of an ionic liquid under sonication or heating conditions, although marginal conversion (10–20 %) was observed in DMSO. However, other similar ionic liquids such as [pmIm]BF_4 or [pmIm]I were also equally effective. On the other hand, the reaction was not initiated with the ionic liquid [pmIm]Br alone in the absence of *tert*-butyl bromide. Use of *tert*-butyl bromide in the absence of an ionic liquid also could not push the reaction more than 20 %, so a combination of *tert*-butyl halide and ionic liquid is essential for the reaction to proceed and it is now clear that the halogenating

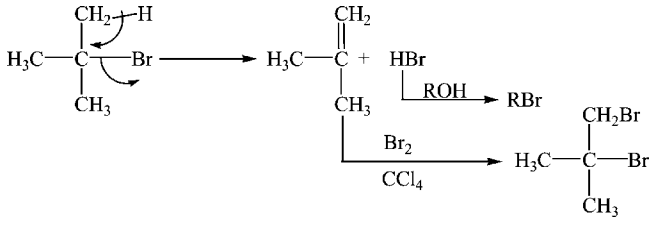
Table 3. Halogenation of alcohol derivatives by *tert*-butyl halides in [pmIm]Br



Entry	Alcohol derivatives	X = Br[a]		X = I[a]		X = Cl[b]		Ref.
		Time/h;	Yield(%)[c]	Time/h;	Yield(%)[c]	Time/h;	Yield(%)[c]	
1	$PhCH_2OTMS$	1.3	94	0.7	95	3	82	3e
2	$PhCH_2OTBDMS$	1.8	87	1	87	3	89	3e
3	$PhCH_2OAc$	1.6	95	0.6	92	2.5	84	3e
4	$PhCH_2OTs$	1.5	92	0.8	90	2.5	86	3e
5	$PhCH_2OTHP$	5	80	3.5	82	10	80	3e
6		2.1	82	2	75	5	75	3e
7		2.5	82	2.5	78	3	89	3e
8		6	75	3.8	74	12	66	3e
9		2.3	85	2.1	80	3.5	82	3e
10		2	80	2.3	82	4	78	3e

[a] The reaction was carried out under sonication conditions. [b] The reaction was carried out at 60 °C. [c] The yields refer to pure isolated products characterized by spectroscopic data (IR, ^1H and ^{13}C NMR).

source is the *tert*-butyl halide, as the bromination takes place with the same efficiency even when *tert*-butyl bromide is used in combination with other non-bromine-containing ionic liquids such as [pmIm]I or [pmIm]BF_4. Presumably, *tert*-butyl bromide (or halide) in combination with ionic liquid readily generates 2-methylpropene together with HBr, which subsequently brominates alcohols. The presence of 2-methylpropene was established by passing the gas coming out from the reaction vessel through a solution of bromine in carbon tetrachloride, upon which 1,2-dibromo-2-methylpropane was formed and isolated as a colourless liquid. The identity of this compound was confirmed by comparison of its spectroscopic data (IR, ^1H and ^{13}C NMR) with those reported[5] (Scheme 2). Bromination was also observed when free HBr was passed through benzyl alcohol in [pmIm]Br under sonication conditions. This observation supports our prediction of the participation of HBr as the active brominating species in this procedure with *tert*-butyl bromide/[pmIm]Br. It may be mentioned that the primary



Scheme 2. Mechanism of halogenation

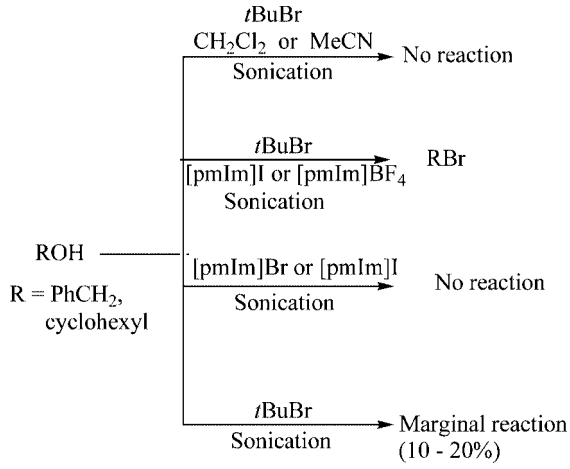


Figure 1. Attempted bromination under different conditions

and secondary halides failed to initiate halogenation, as liberation of HBr (or HX) from these is not facile.

3. Conclusion

This procedure with *tert*-butyl halide in combination with the ionic liquid [pmIm]Br provides a simple and efficient methodology for bromination, iodination and chlorination of primary and secondary alcohols. To the best of our knowledge we are not aware of use of any tertiary halide in halogenation reactions, and this is most probably the first report of this kind. The other significant improvements offered by this procedure are: [a] simple purification, avoiding organic solvents and rigorous chromatography, [b] reasonably fast reaction, [c] high yields of products, [d] mild and neutral reaction condition tolerable to sensitive molecules, and [e] involvement of no toxic and expensive reagent, thus providing a green process. We believe this methodology should find suitable applications in organic synthesis.

4. Experimental Section

General: The ionic liquids [pmIm]Br, [pmIm]I and [pmIm]BF_4 were prepared by a reported procedure.[4] *tert*-Butyl halides are commercial materials and were distilled before use. IR spectra were run as thin films. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 300 MHz and at 75 MHz respectively. The ultrasonic bath used was manufactured by Julabo, Germany (35 KHz).

General Procedure for Bromination and Iodination of Alcohols. Representative Procedure for Bromination of Benzyl Alcohol: A mixture of benzyl alcohol (540 mg, 5 mmol) and *tert*-butyl bromide (820 mg, 6 mmol) in the ionic liquid [pmIm]Br (2.0 g) was sonicated in an ultrasonic bath for 0.8 h (TLC). Direct distillation of the reaction mixture under reduced pressure produced the product, benzyl bromide (800 mg, 93 %) as a colourless liquid. The product was easily identified by comparison of its spectra (^1H and ^{13}C NMR) with those of an authentic sample.[6]

This procedure was followed for bromination and iodination of all alcohols and alcohol derivatives listed in Table 1, Table 2 and Table

3, although iodination of a few sensitive substrates was carried out with the temperature of the ultrasonic bath maintained at 20 °C (Table 1) and for chlorination the reaction mixture was heated at 60 °C in place of sonication, other experimental conditions being kept identical.

All the products were properly characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopic data. Many of these compounds are known (references given in tables) and so are easily identified by comparison with reported data. A few compounds for which spectroscopic data are not available are provided below in the order of their entries in the Tables.

1-Allyloxy-2-(bromomethyl)benzene (entry 7, X = Br, Table 1): Colourless liquid; R_f =.60. ^{1}H NMR: δ = 4.60 (s, 2 H), 4.62–4.67 (m, 2 H), 5.28–5.32 (m, 1 H), 5.45–5.52 (m, 1 H), 6.03–6.15 (m, 1 H), 6.85–6.95 (m, 2 H), 7.24–7.36 ppm (m, 2 H). ^{13}C NMR: δ = 29.4, 69.2, 112.6, 117.6 (2 C), 121.2, 130.4 (2 C), 131.2, 133.3 ppm. IR: ṽ = 1608, 1512, 1251, 1031, 831 cm^{-1}. $C_{10}H_{11}BrO$ (226.00): C 52.89, H 4.88; found: C 52.72, H 4.82.

1-Allyloxy-2-(iodomethyl)benzene (entry 7, X = I, Table 1): Yellowish liquid; R_f = 0.60. ^{1}H NMR: δ = 4.53 (s, 2 H), 4.64–4.65 (m, 2 H), 5.31–5.35 (m, 1 H), 5.50–5.55 (m, 1 H), 6.07–6.18 (m, 1 H), 6.85–6.95 (m, 2 H), 7.24–7.36 ppm (m, 2 H). ^{13}C NMR: δ = 1.4 (*C*H$_2$I), 68.7, 112.2, 117.3, 120.8, 127.7, 129.5, 130.2, 133.0, 156.1 ppm. IR: ṽ = 1603, 1510, 1460, 1250, 1030, 827 cm^{-1}. $C_{10}H_{11}IO$ (273.99): C 43.82, H 4.05; found: C 43.80, H 4.10.

Acknowledgments

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