Pentylpyridinium Tribromide: A Vapor Pressure Free Room Temperature Ionic Liquid Analogue of Bromine

José Salazar,* Romano Dorta*

Departamento de Química, Universidad Simón Bolívar, Caracas 1080A, Venezuela Fax +58(212)9063961; E-mail: jsalazar@usb.ve; E-mail: rdorta@usb.ve *Received 26 February 2004*

Abstract: The synthesis and characterization of the room temperature ionic liquid pentylpyridinium tribromide (2) is described. Tribromide 2 was used as a vapor pressure free bromine analogue for the bromination of ketones, aromatics, alkenes, and alkynes. The brominations were carried out in the absence of organic solvents and in most cases the only extraction solvent needed was water. Selectivities and reactivities were shown to be superior to current protocols. The spent reagent pentylpyridinium bromide (1) was easily recycled.

Key words: pentylpyridinium tribromide, room temperature ionic liquid, solvent-free brominations

Bromine is widely used for the functionalization of organic and inorganic substrates. However, bromine is a hazardous chemical that is difficult to manipulate due to its toxicity and high vapor pressure. Half a century ago, Djerassi and Scholz introduced the pyridinium hydrobromide perbromide (PHP) salt as an alternative, readily weighable, and selective ketone brominating agent.¹ PHP proved also useful for the bromination of alkenes² and aromatics,³ as catalyst for aziridinations,⁴ and for the stereoselective alkene bromination in water suspension.⁵ On the other hand, alkylpyridinium salts are well-documented and commercially available room temperature ionic liquids (RTIL's). The combination of an alkylpyridinium cation with the tribromide anion should therefore lead to a RTIL bromine analogue. Brominations in classic RTIL media, such as [BMI]PF₆, which replace environmentally problematic chlorinated solvents, have been recently demonstrated.⁶ We disclose here the synthesis, full characterization, and reactivity of pentylpyridinium tribromide (2), a proton free RTIL bromine analogue that does not have any measurable vapor pressure. Furthermore, 2 is a rare example of a RTIL which integrates the function of solvent and reagent.7

Adding molecular bromine dropwise under mechanical stirring to powdered pentylpyridinium bromide $(1)^8$ exothermically formed the red liquid pentylpyridinium tribromide $(2)^9$ (Equation 1) which displayed a density of 1.79 g cm⁻³ and a viscosity of $\eta_{35-500} = 0.038$ Pa s at 25 °C (constant over a shear velocity range between 35 s⁻¹ and 500 s⁻¹).¹⁰ The UV–Vis spectrum showed a characteristic ab-

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Equation 1

sorption at $\lambda = 268$ nm ($\epsilon = 1.14 \times 10^4$ L mol⁻¹ cm⁻¹). The conductivity of the neat RTIL **2** was $\kappa = 8.09$ mS cm⁻¹.

Excess bromine was likewise readily absorbed by **2**. However, under high vacuum the excess was efficiently removed leaving pure **2**. Even after prolonged heating at 70°C under vacuum ($<10^{-2}$ mmHg), **2** was recovered unaltered without loss of bromine. The ionic nature of **2** thus effectively eliminates any noxious residual bromine vapor pressure.¹¹ RTIL **2** is hydrophobic forming two phases with water contrasting the highly hydrophilic and hygroscopic character of salt **1**. Likewise, it forms two phases with CHCl₃, alkanes, aromatic solvents, and ethers. RTIL **2** also showed an extended shelf life of at least 3 months so far.

RTIL 2 was then tested as brominating agent for a series of organic substrates and the results are summarized in Table 1. In general the brominations were performed in air without solvent and in some cases mechanical stirring was necessary. Although the reactions were slightly exothermic, no special precautions were taken for cooling. Reactions giving hydrophobic and water tolerant products (entries 3 and 5-10) were quenched by adding water. This caused precipitation of the products as solids or oils, which were readily separated and washed with fresh portions of water and then dried (either with Na_2SO_4 or in vacuo). The aqueous phase containing highly water soluble 1 (and HBr, in the case of monobrominations) was easily concentrated in vacuo to recycle 1 which then could be used to regenerate RTIL 2 with bromine (Equation 1). We emphasize that no organic solvents are needed in these protocols and that water should only be used to quench and extract the mixtures at the end of the reactions. The presence of water during the reactions had only detrimental effects on selectivity and reactivity. On the other hand, reactions leading to water sensitive or water miscible products (entries 1, 2 and 4) were extracted with Et₂O.^{12a}

Ketones were cleanly and selectively monobrominated by **2** without the formation of side products (entries 1 and 2). Ether extraction allowed the separation of the products

Substrate Entry Products Isolated yield (%) 1 85 2 92 3 85 4 93 90^[a] 5 6 81 7 90 8 84 9 92 COOE OOEt 90 10 COOF Br 94 6

Table 1Solvent-Free Brominations Using Pentylpyridiniumtri-bromide 2 at Room Temperature

^a Reaction performed in the presence of aq Na₂CO₃ (1 M).

from bromide 1, which after in vacuo treatment was recycled with one equivalent of bromine to afford 2. Aromatics¹³ were brominated by 2 with complete selectivity and in excellent yields: Phenol was cleanly monobrominated in the absence of a solvent at room temperature by 2 within 20 minutes affording exclusively *p*-bromophenol (entry 4).^{12a} The simplicity and selectivity of this phenol bromination protocol compare favorably with current methods which use solvents and tend to lead to mixtures of isomers and polybromination. Likewise, anisole is monobrominated in the presence of one equivalent of 1 M aq Na₂CO₃ (needed to prevent hydrolysis of the methoxy function) in excellent isolated yield exclusively in the para position. This reaction was slower than the phenol bromination (ca. 1.5 h) and the liquid hydrophobic product was separated from the aqueous phase without the need of any extraction solvent. Finally, bromination of N,N-dimethylaniline (entry 6) afforded p-bromo-N,N-dimethylaniline as the only product in 81% isolated yield (water was used to quench the reaction and to precipitate the product as microcrystals). Alkenes and alkynes were selectively dibrominated by 2 in substance. For example, addition of 2 to cyclohexene led to a biphasic product mixture, which was easily separated.^{12b} Dibromination of phenylacetylene afforded one sole isomer in excellent yields, while ethylpropiolate led to a *cis-trans* mixture in a 94:6 ratio (entries 10, 11). Again, by simple addition of water at the end of the reactions the products were separated from **1**.

In summary, an ionic liquid bromine analogue was synthesized and characterized which is safer, easier to use, and which displayed vastly improved reactivity and selectivity patterns as compared to current bromination techniques. This new functional RTIL **2** may be classified as 'green' for the following reasons: (1) it eliminates toxic bromine vapors, (2) the bromine carrier **1** is readily recycled, and (3) it minimizes the use of organic solvents in the bromination protocols. Furthermore, **2** was shown in this preliminary screening to brominate very selectively and in good to excellent yields a wide variety of substrates including ketones, aromatics, alkenes, and alkynes.

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- (9) **Pentylpyridinium Tribromide (2).** Bromine (64.48 g, 404.7 mmol) was added over 30 min to solid crushed pentylpyridinium bromide (**1**, 93.07 g, 404.4 mmol) under mechanical stirring and cooling in a water bath affording a deep red liquid. After stirring for 2 h the liquid was left in vacuo overnight. Yield: 156 g (99%); mp 0 °C; $\kappa = 8.09$ mS cm⁻¹; d = 1.79 g cm⁻³; η_{35-500} 0.038 Pa s (all at 25° C). ¹H NMR (CD₂Cl₂): $\delta = 0.80-1.00$ (m, 3 H), 1.30–1.55 (m, 4 H), 2.00–2.15 (m, 2 H), 4.60–4.75 (m, 2 H), 8.10–8.20 (m, 2 H), 8.50–8.65 (m, 1 H), 8.80–8.95 (m, 2 H). ¹³C NMR (400.14 MHz, CD₂Cl₂): $\delta = 13.62$ (s), 22.12 (s), 28.20 (s), 31.33 (s), 63.14 (s), 129.08 (s), 144.42 (s), 145.86 (s). Anal. Calcd for C₁₀H₁₆NBr₃: C, 30.80; H, 4.14; N, 3.59. Found: C, 30.95; H, 4.11; N, 3.71.
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- (12) Representative Procedures (a) p-Bromophenol: To crystalline phenol (1.03 g, 10.9 mmol) was added dropwise 2 (4.04 g, 10.3 mmol) over 20 min. The first few drops of 2 caused the phenol crystals to melt and to form a limpid reaction solution. The resulting orange syrup was left stirring for another 20 min during which time the color changed to yellow. Extraction with $Et_2O(4 \times 20 \text{ mL})$ yielded a colorless oil (1.66 g, 93%) and spectroscopic data corresponded to pure *p*-bromophenol. The yellowish ionic liquid phase was dried under high vacuum, identified as pure 1 (1 is liquid when moist)⁸ by ¹H NMR (1.99 g, 8.6 mmol), and reacted with 1 equiv of Br₂ to regenerate 2. Note: We do not recommend the use of recycled 2 from monobrominations that could contain traces of HBr in acid-sensitive reactions. (b) 1,2-Dibromocyclohexane: Tribromide 2 (5.00 g, 12.8 mmol) was added dropwise to neat cyclohexene (1.05 g, 12.8 mmol) over 25 min yielding a viscous orange mixture which was left stirring for 2 h. To the resulting yellow biphasic system (heavy phase: 1,2-dibromocyclohexane) was added water (10 mL) for easier phase separation. The organic product was dried with a small amount of Na₂SO₄, filtered and left for 5 min under high vacuum to remove traces of bromine leaving a colorless liquid (2.60 g, 84%). Spectroscopic data corresponded to a pure sample of 1,2dibromocyclohexane.
- (13) For examples, see: (a) Smith, M. B.; Guo, L. C.; Okey, S.; Stenzel, J.; Yanella, J.; LaChapelle, E. *Org. Lett.* **2002**, *4*, 2321. (b) Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T.; Patel, B. K. *Org. Lett.* **2000**, *2*, 247.