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Design of ionic liquids as a medium for the Grignard reaction

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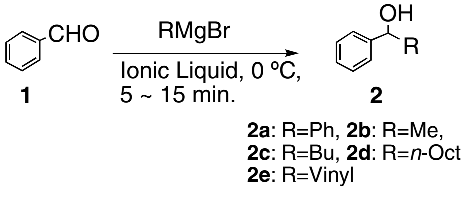
Abstract—Design of novel phosphonium ionic liquids that are compatible with Grignard reagents have been investigated; several types of phosphonium salts that have an alkyl ether moiety have been synthesized and their capability evaluated as solvents for Grignard reagents. It has been established that even basic aliphatic Grignard reagent-mediated reactions are possible when methoxyethyl(tri-*n*-butyl)phosphonium bis(trifluoromethanesulfonyl)imide is used as the solvent.

Ionic liquids are widely recognized as greener solvents, suitable for use in organic reactions and providing possibilities for improvement in control of product distribution, enhanced reactivity, ease of product recovery, catalyst immobilization, and recycling.[1] We have been interested in the use of ionic liquids in organic synthesis in both chemical and biochemical reactions, and have shown several excellent examples of the recyclable use of enzymes or iron salt catalysts using these liquids as reaction media.[2] Ionic liquids have heretofore been considered inappropriate for strong base-mediated reactions. However, recently, several examples have been reported showing the possibility of using these liquids as reaction media for strong base-mediated reactions such as the Grignard reaction.[3–5]

Clyburne and co-workers made the first breakthrough on this problem, demonstrating that Grignard reactions took place in a mixture of phosphonium ionic liquid and tetrahydrofuran (THF).[3] The authors showed that a number of reactions were possible in the phosphonium ionic liquids including addition of carbonyl, benzyne reaction, halogenation, and coupling reactions.[3] But there was still the serious limitation that aryl Grignard reagents were only applicable in the phosphonium ionic liquid solvent system.[3] Wilhelm and Jurcik[4a] and Handy[4b] reported that the use of 2-arylated-imidazolium salts and 2-alkylated-imidazolium salts is a solution to this issue and Grignard reactions were accomplished in these 2-substituted imidazolium type ionic liquid solvent systems. Further, Chan reported the first preparation of ethyl magnesium iodide in pure ionic liquid, *N*-butylpyridinium tetrafluoroborate ([bpy][BF_4]).[5] These reports prompted us to investigate the most suitable design of ionic liquids for the Grignard reaction. Herein we wish to report our successful design of phosphonium salt ionic liquids that are applicable to various types of Grignard reagent mediated reactions. Wilhelm and jurcik[4a] and Handy[4b] reported that use of 2-alkylated or arylated-imidazolium salts is essential to accomplish the Grignard reaction in an imidazolium ionic liquid solvent system. Therefore, we initially tested the reaction of benzaldehyde with phenylmagnesium bromide (PhMgBr) in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide ([Bmim][Tf_2N]) or 1-butyl-2,3-dimethylimidazolium bis(trifluoromethanesulfonyl)imide ([Bdmim][Tf_2N]) (Eq. 1).



(1)

As anticipated, and as shown in Table 1, no reaction took place when PhMgBr was reacted with benzaldehyde in conventional ionic liquid, [Bmim][Tf_2N] (entry 2) and desired product **2a** ($R = \text{Ph}$) was obtained for the [Bdmim][Tf_2N] solvent system (entry 3). These results clearly showed that the strong acidity of the 2-proton of the imidazolium salt caused decomposition of the Grignard reagents.[4] Furthermore, it was also found that **2a** was obtained in good yield by using diethyl-1-methoxyethylammonium bis(trifluoro-

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Table 1. Results of the Grignard reaction in an ionic liquid solvent system

Entry	Solvent	RMgBr	Yield of **2**[a] (%)	
		(R)	**A**[b]	**B**[c]
1	THF[d]	Ph	95[d]	98[d]
2	[Bmim][Tf_2N]	Ph	0	0
3[b]	[Bdmim][Tf_2N]	Ph	86[d]	80[d]
4	**DEME**[e]	Ph	88[d]	87[d]
5	**P1**[f]	Ph	<64[h]	—
6	**P2**[g]	Ph	92	89[d]
7	**IL1a**	Ph	95	94
8	**IL2a**	Ph	55	61
9	**IL1a**	Me	74	56
10	**IL1a**	Bu	71	76
11	**IL1a**	*n*-Oct	81	67
12	**IL1a**	Vinyl	93	66
13	**IL1a**[i]	Ph	97	81
14	**IL1a**[j]	Ph	87	—
15	**IL1a**[j]	Bu	66	—
16	**P2**[j]	Ph	79	—

[a] Isolated yield. All results are average data after the reaction was carried out with 3 repetitions.

[b] Condition A: 0.6 mL of 1.0 M THF solution of RMgBr was mixed with 1.0 mL of IL, then the aldehyde (0.5 mmol) was added immediately to the mixture.

[c] Condition B: a solution of 0.6 mL of 1.0 M THF solution of RMgBr and IL (1.0 mL) was stored at 0 °C for 1 h under argon, then the aldehyde (0.5 mmol) was added to the mixture.

[d] It took at least 15 min. to complete the reaction when the reaction was carried out in THF.

[e] **DEME**:$Et_2(MeOCH_2CH_2)N][Tf_2N]$.

[f] **P1**: $[(n\text{-Hex})_3(n\text{-}C_{14}H_{29})P][Tf_2N]$.

[g] **P2**: $[n\text{-}Bu_3(Me)P][Tf_2N]$.

[h] It was very difficult to isolate the product from the reaction mixture due to high solubility of the IL in Et_2O or hexane.

[i] Recycled IL (5 times) was used as solvent.

[j] Condition C: THF was removed under vacuum from the THF solution of PhMgBr (0.6 mmol) at 0 °C, then 1.0 mL of IL solution of PhCHO (0.5 mmol) was added and stirred for 5 min at 0 °C under argon.

methane-sulfonyl)imide (DEME)[6] as a reaction medium (entry 4). Very recently, it has been reported that oxygen atoms from anions like decanoate can stabilize a Grignard reagent.[7]

Clyburne and co-workers explained the reason that Grignard reaction is possible in their phosphonium ionic liquid **P1** (tetradecyl(trihexyl)phosphonium bis(trifluoromethanesulfonyl)imide) using kinetic arguments: the acidic C–H site of the α position of the phosphonium cation might be protected by the long, non-rigid alkyl chain.[3] We confirmed that the desired Grignard reaction was indeed possible in **P1** (entry 5), however, we soon recognized a serious drawback: isolation of the product was very difficult from this solvent **P1** due to its high solubility in both ether and hexane. This caused significant reduction of the chemical yield of the product in a small scale experiment, although the reaction itself proceeded very smoothly in this solvent.

With these preliminary results in mind, we attempted to design a novel phosphonium type of ionic liquid (Fig. 1).[8] Since it is well known that Grignard reagents are stabilized by complexation with an ether oxygen functional group,[9] we simply hypothesized that introduction of an appropriate alkyl ether functional group on the phosphonium salts might contribute to stabilization of the reagents.

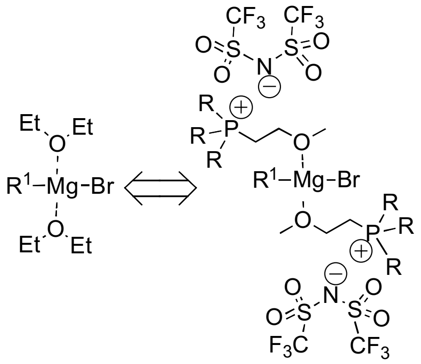

Figure 1. Working hypothesis for designing ionic liquids appropriate for Grignard reaction.

From the standpoint of realizing an easy work-up process, hydrophobic salts are far preferable. On this basis, we attempted to prepare room temperature ionic liquids by combining phosphonium cations with two types of anions, bis(trifluoromethanesulfonyl)imide (Tf_2N) and its cyclic analogue NDSHFPI, because it was well recognized that bis(trifluoromethanesulfonyl)imide salts provide hydrophobic ionic liquids (Fig. 2).[10] Among 10 phosphonium salts prepared, six types were obtained as liquids and four as solids at room temperature (25 °C). As shown in Figure 2, all Tf_2N salts were found to be liquid at rt, while the combination of NDSHFPI anion tended to give solid salts at rt. Although all salts showed the desired hydrophobic properties, **IL1a**[11] and **IL2a**[11] possess preferable properties as a solvent, being soluble in neither hexane nor ether. This made it possible to realize easy extraction of the product from

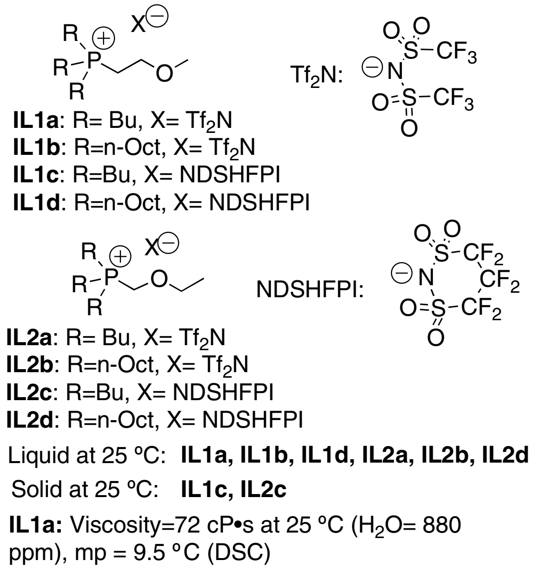

Figure 2. List of novel phosphonium salts prepared.

the ionic liquid mixture. On the other hand, tri(*n*-octyl)phosphonium salts, **IL1b**, **IL1d**, **IL2b**, and **IL2d**, were easily dissolved in both ether and hexane, so it was assumed that isolation of the reaction products from these solvents might be difficult. We thus chose **IL1a** and **IL2a** as appropriate solvents for the present project and evaluated each of them as a solvent for Grignard reaction with benzaldehyde.

Typically the reaction was carried out as follows (Condition A): 0.6 mL of 1.0 M THF solution of PhMgBr was mixed with 1.0 mL of IL, then benzaldehyde (0.5 mmol) was immediately added to the mixture at 0 °C. After 5 min stirring at 0 °C, the reaction was quenched by the addition of 0.1 mL of water and the organic products were then extracted with 25% ether in hexane to afford,[12] after purification on silica gel thin layer chromatography (TLC), the desired product **2a** (R = Ph) in good yield. After the work up process, the ionic layer was washed with water to remove magnesium salt derived from the Grignard reagent, then dried under reduced pressure at 60 °C for 3 h prior to use in the next reaction. It was confirmed that **IL1a** could be recycled and reused many times without any difficulty. With the intention of investigating the stability of Grignard reagent in the phosphonium salt ionic liquid, we also conducted the reaction under Condition B: a solution of 0.6 mL of 1.0 M THF solution of RMgBr and IL (1.0 mL) was stored at 0 °C for 1 h under argon, then the aldehyde (0.5 mmol) was added to the mixture.

We found that use of methyl(tir-*n*-butyl)phosphonium bis(trifluoromethanesulfonyl)imide, **P2**,[13] also gave good results and alcohol **2a** was obtained in excellent yield because this solvent had poor solubility in ether and hexane (entry 6). This was an unexpectedly good result for us because **P2** possesses the acidic C–H site of the α position of phosphonium cation, though it was explained by kinetic arguments that the reason the Grignard reaction is possible in **P1** is due to the protective effect of the long, non-rigid alkyl chains. As expected, we found that methoxyethyl(tri-*n*-butyl)phosphonium bis(trifluoromethanesulfonyl)imide (**1L1a**) worked best when PhMgBr reacted with benzaldehyde at 0 °C; the reaction proceeded very rapidly and benzaldehyde was consumed completely in less than 5 min (entry 7), while at least 15 min was required to complete the reaction when it was carried out in THF under the same temperature conditions (entry 1). Since **IL1a** is highly viscous compared to THF and it was suggested that the Grignard reaction might involve an electron transfer pathway,[9,7] this acceleration seems to be an important character of the ionic liquid medium.

A significant stabilization effect of the ionic liquid was observed when PhMgBr was stored in **IL1a** for 1 h at 0 °C (entry 7, condition B), while, in contrast, PhMgBr lost its activity gradually in the simple phosphonium salt **P2** (entry 6). It was further found that the position of ether oxygen at the alkyl group reflected on the capability of the phosphonium salt. Stability of PhMgBr in ionic liquid **IL2a** was obviously inferior to that in **IL1a** (entry 8). We speculate that this lower stability of PhMgBr in **IL2a** might be due to the increased acidity of the α-position of the phosphonium center. It was possible to use highly basic aliphatic Grignard reagents in our **IL1a** solvent system (entries 9–12); the desired products were obtained in excellent to good yield if the reactions were carried out in **IL1a**. We thus succeeded in showing that our design was indeed effective for preparing phosphonium ionic liquid that is appropriate for the use of Grignard reaction. Use of **IL1a** facilitated product separation due to the triphasic nature of water, ionic liquid, and ether (or hexane) combinations. Further, it was confirmed that **IL1a** was recyclable after drying of the solvent under vacuum following the work-up process (entry 13).

Although attempts to generate the Grignard reagent in pure **IL1a** by the reaction of PhBr with magnesium metal were unsuccessful, we finally established that the reaction proceeded in a THF free **IL1a** solvent system (Condition C): a THF solution of PhMgBr (0.6 mmol) was placed in a flask under argon, then THF was removed under vacuum at 0 °C. To the resulting PhMgBr solid was added a **IL1a** (1.0 mL) solution of benzaldehyde (0.5 mmol) and the mixture was stirred for 5 min at 0 °C. After the usual work-up process, we obtained the desired product **2a** in 87% yield (entry 14). To our delight, we succeeded in obtaining **2b** (*R* = Bu) using more basic BuMgBr instead of PhMgBr under the same conditions (entry 15). On the contrary, a significant reduction of the chemical yield of **2a** was recorded; 79% of **2a** was obtained when **P2** was used as solvent in the reaction of PhMgBr (entry 16). These results confirmed that the presence of ether oxygen on the side arm of the phosphonium salt contributes to stabilizing the Grignard reagent as we hypothesized. This might be the most important advantage of **IL1a**.

In summary, we demonstrated that introduction of alkyl ether moiety on the side arm of phosphonium salt ionic liquid was quite effective in improving the capability of the phosphonium salt ionic liquids as a solvent for Grignard reaction, and we were able to apply the solvent for even aliphatic Grignard reagent mediated reaction. We also succeeded in demonstrating the ether free Grignard reaction in an ionic liquid solvent system. Since solvent polarity conditions of **IL1a** are completely different from many conventional organic solvents, we are hopeful of obtaining unique results with further investigation.

Acknowledgments

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Supplementary data

Experimental details for preparation of ionic liquids **IL1a** and **IL2a** with NMR spectra (^{1}H, ^{13}C, ^{31}P, and ^{19}F) are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.010.

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11. Preparation of **IL1a** was carried out as follows: To an ethanol (20 mL) solution of 1-bromo-2-methoxyethane (4.68 g, 40 mmol) was added tributylphosphine (7.5 g, 37 mmol) and the resulting mixture was stirred for 22 h at 80 °C. After being cooled to room temperature (rt), hexane was added to form a precipitate, which was removed by filtration. The resulting filtrate was evaporated under vacuum to give the bromine salt (12.31 g, 36 mmol) in 97% yield. The salt was dissolved in ethanol (18 mL) and lithium bis(trifluoromethanesulfonyl)imide (11.37 g, 40 mmol) powder was added, then the mixture was stirred at rt for 17 h to form lithium bromide as a precipitate. The precipitate was removed by filtration, the filtrate was washed with hexane 3 times and the solvent removed using lyophilization. The resulting oil was dissolved in acetone and treated with active charcoal, and the charcoal was then removed by filtration. The filtrate was passed through active alumina (Type II) and dried under vacuum at 50 °C for 5 h to give **IL1a** (19.15 g, 35 mmol) as colorless oil in 95% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.979 (9H, t, $J = 6.85$ Hz), 1.45–1.55 (12H, m), 2.10–2.20 (6H, m), 2.53 (2H, q, $J = 5.95$ Hz), 3.36 (3H, s), 3.75 (2H, dt, $J = 14.2$ Hz, $J = 5.95$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.00, 19.16 (d, $J_{C\text{–}P} = 46.7$ Hz), 19.98 (d, $J_{C\text{–}P} = 46.7$ Hz), 23.24 (d, $J_{C\text{–}P} = 4.78$ Hz), 23.60 (d, $J_{C\text{–}P} = 16.2$ Hz), 58.82, 65.08 (d, $J_{C\text{–}P} = 7.64$ Hz), 119.80 (q, $J_{C\text{–}F} = 315.5$ Hz); ^{31}P NMR (202.46 MHz, $CDCl_3$) δ 39.08 (d, $J_{P\text{–}C} = 26.1$ Hz); ^{19}F NMR (170.6 MHz, $CDCl_3$, C_6F_6) δ 92.91; IR (neat) 2937, 2878, 1400, 1194, 1057, 738 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{34}OP$: 261.1670. Found: 261.1666. Viscosity = 72 cPs at 25 °C (H_2O = 880 ppm), mp = 9.5 °C (DSC). Compound **IL2a** was prepared through a similar route from ethoxymethylchloride in 97% overall yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (9H, t, $J = 7.0$ Hz), 1.23 (t, 3H, $J = 7.0$ Hz), 1.49–1.59 (6H, m), 2.15–2.21 (6H, m), 3.69 (2H, q, $J = 7.0$ z), 4.29 (2H, dd, $J = 3.0$ Hz, $J = 2.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) d 13.04, 16.83, 17.19, 23.20, 23.60, 23.72, 23.86, 59.47(d, $J_{C\text{–}P} = 65.8$ Hz) 70.33 (d, $J_{C\text{–}P} = 13.3$ Hz), 119.80 (q, $J_{C\text{–}F} = 315.5$ Hz); ^{31}P NMR (202.46 MHz, $CDCl_3$) δ 37.20 (d, $J_{P\text{–}C} = 26.1$ Hz); ^{19}F NMR (170.6 MHz, $CDCl_3$, C_6F_6) δ 82.91; IR (neat) 2939, 2877, 1468, 1193, 1057, 617 cm^{-1}. Since ionic liquids, **IL1b**, **IL1d**, **IL2a**, **IL2b**, and **IL2d**, showed poor properties as reaction media, we did not attempt further purification.
12. Since **IL1a** does exhibit slight solubility in ether, over the course of extraction workup, the volume of the IL remaining will decrease. Fortunately, the use of 25% ether in hexane solution was sufficient to extract the products from the IL.
13. For this novel ionic liquid, please contact Dr. Katsuhiko Tsunashima of Nippon Kagaku Industry Co., Ltd Tel.: +81 3 3636 8090; fax: +81 3 3636 8071. E-mail: katsuhiko.tsunashima@nippon-chem.co.jp.