Grignard reagents in ionic liquids†

Man Chun Law,[ab] Kwok-Yin Wong[a] and Tak Hang Chan*[ab]

Received (in Cambridge, UK) 22nd February 2006, Accepted 10th April 2006
First published as an Advance Article on the web 3rd May 2006
DOI: 10.1039/b602718k

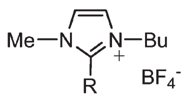
Grignard reagents were generated from magnesium and organic iodides in the ionic liquid *n*-butylpyridinium tetrafluoroborate, [bpy][BF$_4$], and they showed different reactivity from classical Grignard reagents in organic solvents.

Because of concerns for the environment, there has been considerable recent research into replacing volatile organic solvents as reaction media.[1] Water,[2] supercritical carbon dioxide[3] and room temperature ionic liquids[4] are the most commonly explored "clean" media for organic reactions. However, reactive compounds such as Grignard reagents are well known to react vigorously with water or carbon dioxide. Those two "clean" media therefore cannot be used for the preparation or reactions of such reactive organometallic reagents.[5] The study of organometallic reactions in room temperature ionic liquids (RTILs) has thus far been limited to the less reactive allylmetal reagents or their variations.[6] Recently, *preformed* phenylmagnesium bromide in THF was found to be stable in phosphonium ionic liquids and can undergo the reactions normally expected of Grignard reagents.[7,8] Attempts to generate the Grignard reagent in phosphonium based ionic liquids, however, were unsuccessful.[7] Because of our general interest in organometallic reactions in clean media, we examined the generation and reactions of Grignard reagents in ionic liquids.[5,6,9]

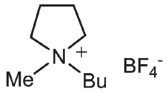
When we examined the reaction of magnesium metal with ethyl iodide in imidazolium based ionic liquid [bmim][BF$_4$] (**1a**), there was no reaction whatsoever, as expected. When [bdmim][BF$_4$] (**1b**) was used instead so that the acidic proton in the imidazolium moiety was replaced with a methyl group, a colour change from colorless to green and then red was observed at 80 °C. The reaction mixture however reverted to a colourless solution when the temperature was decreased to room temperature. Similar results were also obtained with pyrrolidinium based (**2**) and phosphonium based (**3**) ionic liquids. In all cases, quenching the reaction mixture at any stage with benzaldehyde did not lead to any products, and the aldehyde was recovered completely.

We then attempted the reaction of magnesium metal and ethyl iodide in *pure* [bpy][BF$_4$] (**4**). To our delight, the reaction proceeded well and was reproducible. The magnesium metal dissolved, accompanied by an obvious colour change from colourless to red. The red colour persisted indicating the formation of an ethylmagnesium intermediate. The purity of [bpy][BF$_4$] was critical in getting reproducible results because the presence of bromide ion, from the precursor [bpy][Br], was detrimental to the formation of the Grignard reagent. When ethyl iodide was replaced by ethyl bromide, there was no reaction even with the addition of activators such as iodine. We found that magnesium turnings were not as effective as magnesium powder (~325 mesh). The use of Rieke-magnesium[10] has not been examined.

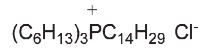
When the ethylmagnesium reagent thus generated was reacted with benzaldehyde followed by the normal aqueous workup, the product was found, to our surprise, to be a mixture of the iodo-compound **7** and the pinacol **8**. The relative yields of **7** and **8** depended on the ratio of benzaldehyde to the amount of magnesium–ethyl iodide used (Table 1). When the ratio was 1 : 3 : 3 (entry 1), a high yield (81%) of the adduct **7** could be obtained. As the amounts of Mg–EtI were reduced relative to the aldehyde, the pinacol **8** was obtained in higher yield (entries 1 to 3). Previously, for Grignard reactions in organic solvents, the formation of pinacol was suggested to be due to a radical intermediate initiated by MgI formed from the Mg–MgI$_2$ (1 : 1) mixture.[11] In the present case with [bpy][BF$_4$] as solvent, no pinacol product **8** was formed when benzaldehyde was added to a Mg alone or to Mg–MgI$_2$ mixture (entries 4 and 5).[12] This



1a: R=H
1b: R=Me

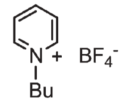


2



$(C_6H_{13})_3\overset{+}{P}C_{14}H_{29}\ Cl^-$

3



4

Table 1 Magnesium-mediated cross coupling of ethyl iodide with benzaldehyde according to Scheme 1

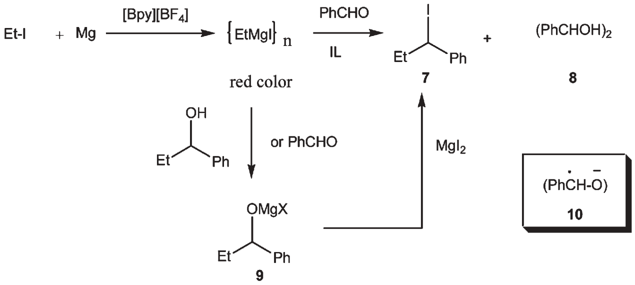
Entry	Mole ratio PhCHO : Mg : EtI	Additive	Yield (%)[a] 7	Yield (%)[a] 8
1	1 : 3 : 3	—	(81)	—
2	1 : 2 : 2	—	8.4	42.3
3	1 : 1 : 1	—	21	62.6
4	1 : 2 : —	—	0	0
5	1 : 2 : —	MgI$_2$	0	0
6	— : 1 : 1	1-Phenyl-1-propanol	5	0
7	— : 1 : 1	1-Phenyl-1-propanol + MgI$_2$	(100)	0

[a] Isolated yields in parentheses. After 1 h stirring of magnesium powder and ethyl iodide in purified [bpy][BF$_4$] (2 mL), benzaldehyde (1mmol, for entries 1, 2, 4 and 5) was added to the reaction mixture for 12 h at rt. Entry 3: 0.5 mmol of benzaldehyde was used. Entry 5: MgI$_2$ (2 mmol) was added in place of EtI. Entries 6 and 7: equivalent amounts of additives were added to reaction mixture in place of benzaldehyde.

---

[a] *Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Hum, Hong Kong, China. E-mail: bcchanth@polyu.edu.hk; Fax: +852-2364-9932; Tel: +852-2766-5605*
[b] *Department of Chemistry, McGill University, Montreal, Quebec, Canada. E-mail: tak-hang.chan@mmcgill.ca; Fax: +1-514-398-3797; Tel: +1-514-398-2094*

† Electronic supplementary information (ESI) available: Experimental procedures, ^{1}H and ^{13}C spectra of compound **7**. See DOI: 10.1039/b602718k



Scheme 1 The formation of **7** may be derived from the expected alcoholate adduct **9** under the reaction conditions.

indicates that the ethylmagnesium intermediate in the IL was responsible for the formation of both **7** and **8**, but with different concentration dependence. At a lower concentration of the ethylmagnesium intermediate, radical transfer to benzaldehyde to form the ketyl radical intermediate **10** leading to pinacol **8** was preferred.

Indeed, when we quenched the ethylmagnesium species in the [bpy][BF$_4$] mixture with 1-phenyl-1-propanol (**11a**) instead of benzaldehyde, a small amount of adduct **7** was obtained (entry 6). This suggested that in the rather polar ionic liquid [bpy][BF$_4$], the conditions were sufficiently acidic for a nucleophilic displacement of the alkoxide by iodide (from, for example, magnesium iodide). In support of such a possibility, addition of magnesium(II) iodide in the above experiment led to complete transformation of 1-phenyl-1-propanol to **7**.

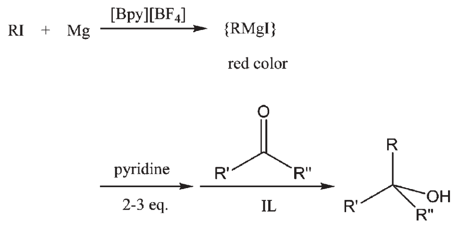
Because the formation of **7** is likely due to the Lewis acidic nature of the reaction media, we examined the reaction of the ethylmagnesium species with benzaldehyde under less acidic conditions. After the formation of the ethylmagnesium intermediate as described, pyridine was added to the reaction mixture. Benzaldehyde was then added. Afterwards, the mixture was quenched with water. Under such conditions, 1-phenyl-1-propanol (**11a**) was obtained (Table 2). The yield of **11a** depended critically on the amount of pyridine added and the concentration of the presumed Grignard reagent. The optimal ratio of pyridine to ethylmagnesium reagents appeared to be between 1.3 : 1 and 2 : 1 (entry 4). Excess or insufficient amount of pyridine reduced the yield. Triethylamine can be used to replace pyridine (entry 7). On the other hand, if the concentration of the ethylmagnesium reagent was reduced, the reaction gave poor yields of **11a** even in the presence of pyridine (entry 1). Other aryl aldehydes can be used but the yields were poorer. When alkyl aldehydes were used, complex mixtures were obtained with complete consumption of the starting aldehydes. Finally, when *n*-butyl iodide or allyl iodide was used in place of ethyl iodide, the corresponding adduct **11b** or **11c** was obtained respectively in good yield. When phenyl iodide was used, the presumed phenylmagnesium species was generated as evident by the persistent red colour. However, quenching of the reaction mixture with benzaldehyde gave a complex mixture as product with complete consumption of the starting benzaldehyde. Finally, ketones such as benzophenone, acetophenone or acetones were unreactive towards the ethylmagnesium species in [bpy][BF$_4$], with the starting ketone recovered completely. This reactivity pattern is distinctly different from the reactions of Grignard reagents with carbonyl compounds in conventional organic solvents, and also different from preformed Grignard reagents (in THF) in the phosphonium ionic liquids.[7,8]

In view of the rather different reactivity of the organomagnesium species generated in the ionic liquid [bpy][BF$_4$] from those in conventional organic solvents, it is likely that the organomagnesium species in [bpy][BF$_4$] may have a different structure. In organic solvents, the majority of organomagnesium RMgX structures exist as a monomeric compound with magnesium in a distorted tetrahedral environment of four ligands. Two of the ligands, L, are generally Lewis bases such as ethers and tertiary amines. EtMgBr is known to exist as EtMgBr·(Et$_2$O)$_2$ in an ethereal solvent.[13] It is also known that organomagnesium compounds have a certain tendency towards association as dimeric or oligomeric compounds in concentrated solution or weakly basic solvents.[14] EtMgBr with Et$_3$N as ligand was found to be a simple dimeric compound (Et$_3$NMgEt)$_2$(μ-Br)$_2$.[15] For EtMgI with ligand L, it is likely to be in the form of (EtMgL)$_2$(μ-I)$_2$.[14] On the other hand, solvent-free organomagnesium compounds were usually obtained as polymeric materials (Et$_2$Mg)$_n$.[16] With [bpy][BF$_4$] as solvent, there is no coordinating ligand L. The ethylmagnesium

Table 2 Magnesium-mediated cross coupling of organic iodide with aldehydes according to Scheme 2

Entry	R′	R″	R	Mole ratioMg : RI : L	Solvent[b]/ml	Additive (L)	Time/h	Yield (%)[a]
1	Ph	H	Et	1 : 1 : 2	2	Pyridine	12	59
2	Ph	H	Et	1.5 : 1.5 : 3	1	Pyridine	2	55
3	Ph	H	Et	1.5 : 1.5 : 3	2	Pyridine	12	22
4	Ph	H	Et	1.5 : 1.5 : 2	2	Pyridine	12	83
5	Ph	H	Et	1.5 : 1.5 : 2	2	Pyridine	12	0[c]
6	Ph	H	Et	1.5 : 1.5 : 1.5	1	Pyridine	3	13
7	Ph	H	Et	1.5 : 1.5 : 2	2	Et$_3$N	12	74
8	*p*-NCPh	H	Et	3 : 3 : 4	3	Pyridine	12	44
9	*p*-ClPh	H	Et	3 : 3 : 4	2	Pyridine	12	51
10	*n*-C$_7$H$_{15}$	H	Et	1.5 : 1.5 : 2	1	Pyridine	12	—[e]
11	Ph	Me	Et	1.5 : 1.5 : 2	1	Pyridine	12	0[d]
12	Ph	Ph	Et	1.5 : 1.5 : 2	1	Pyridine	12	0[d]
13	Ph	H	*n*-Bu	1.5 : 1.5 : 2	1	Pyridine	12	80
14	Ph	H	Allyl	1.5 : 1.5 : 2	1	Pyridine	12	91
15	Ph	H	Ph	1.5 : 1.5 : 2	1	Pyridine	12	—[e]

[a] Isolated yields. [b] Pure [bpy][BF$_4$] was used except in entry 5. [c] Entry 5: impure [bpy][BF$_4$] containing [bpy][Br] was used. [d] Entries 11 and 12: ketones were found to be unreacted and fully recovered. [e] Entry 15: a complex mixture of products resulted and was unidentified. [f] Reaction conditions: addition of the carbonyl compound (in mmol, as specified in the Table) to the reaction mixture after 1 h stirring of magnesium powder and organic iodide for the specified reaction time at rt.



11a: R=Et, R'=Ph, R''=H;
11b: R=*n*-Bu, R'=Ph, R''=H;
11c: R=allyl, R'=Ph, R''=H.

Scheme 2

Table 3 Chemical shifts of methylene protons of various ethylmagnesium compounds in different solvents[17a,b]

Compound	Et_3N^a	Et_2O^a	THF^a	DBE^b	CD_3CN^c
EtMgBr	−0.51	−0.61	−0.71	—	—
EtMgI	—	—	—	−0.62	—
Et_2Mg	—	−0.67	−0.78	—	—
EtMg species in [bpy][BF_4]	—	—	—	—	0.45

^{a} Reference 17*a*. ^{b} Reference 17*b*. ^{c} This work, 1.5 M solution in [bpy][BF_4] with 2 mmol of pyridine dissolved in CD_3CN.

species generated is likely to have an oligomeric structure $\{EtMgI\}_n$. This hypothesis is consistent with our ^1H NMR studies (Table 3). In general, the methylene protons of ethylmagnesium halide in coordinating solvents such as ether or THF appear as a clear quartet at about −0.5 to −0.7 ppm. The ethylmagnesium species in [bpy][BF_4], when observed directly, showed only broad absorption and did not show any clear quartet in the −0.5 to −0.7 ppm region. This is consistent with the polymeric structure. When the species was dissolved in a weakly coordinating solvent such as CD_3CN, the NMR signals sharpened, but there was still no quartet in the −0.5 to −0.7 ppm region. Upon addition of pyridine, a clear methylene quartet appeared at 0.45 ppm, much lower field than −0.5 to −0.7 ppm. This is consistent with the fact that pyridine is a coordinating ligand; de-aggregation of the ethylmagnesium species in the IL thus occurred upon addition of pyridine leading to the observed NMR signals.

In conclusion, we demonstrated that organomagnesium species can be generated in the ionic liquid [Bpy][BF_4]. They showed a distinctly different reactivity pattern from Grignard reagents in conventional organic solvents. This suggests that for reactive organometallic reagents in ionic liquids, we cannot extrapolate their expected chemistry from conventional organic solvents. Careful investigation for each case is warranted.

We thank NSERC of Canada, the RGC of Hong Kong (PolyU 5002/03P) as well as the University Grants Committee Area of Excellence Scheme in Hong Kong (Project No AoE/P-10/01) for financial support of this research.

Notes and references

1 (*a*) *Green Chemistry: Theory and Practice*, P. T. Anastas and J. C. Warner, Oxford Science Publications, Oxford, 1998; (*b*) *Clean Solvents: Alternative Media for Chemical Reactions and Processing*, ed. M. Abraham and L. Moens, ACS Symposium Series No. 819, American Chemical Society, Washington, DC, 2001.
2 *Organic Reactions in Aqueous Media*, C. J. Li and T. H. Chan, John Wiley & Sons, New York, 1997.
3 *Chemical Synthesis Using Supercritical Fluids*, P. Jessop, Wiley-VCH, Weinheim, 1999.
4 *Ionic Liquids: Industrial Applications to Green Chemistry*, R. D. Rogers and K. R. Seddon, Oxford University Press, Washington, 2002.
5 For the rather extensive study of less reactive organometallic reactions in aqueous media, see for example: (*a*) C. J. Li and T. H. Chan, *Tetrahedron*, 1999, **55**, 11149; (*b*) C. Petrier and J. L. Luche, *J. Org. Chem.*, 1983, **50**, 910; (*c*) C. C. K. Keh, C. Wei and C. J. Li, *J. Am. Chem. Soc.*, 2003, **125**, 4062 and references therein.
6 (*a*) M. C. Law, K. Y. Wong and T. H. Chan, *Green Chem.*, 2002, **4**, 161; (*b*) C. M. Gordon and C. Ritchie, *Green Chem.*, 2002, **4**, 124; (*c*) T. Kitazume and K. Kasai, *Green Chem.*, 2001, **3**, 30; (*d*) C. M. Gordon and A. Mccluskey, *Chem. Commun.*, 1999, 1431.
7 B. Gorodetsky, T. Ramnial, N. R. Branda and J. A. C. Clyburne, *Chem. Commun.*, 2005, 325.
8 V. Jurcik and R. Wilhelm, *Green Chem.*, 2005, **7**, 844.
9 (*a*) M. C. Law, K. Y. Wong and T. H. Chan, *Green Chem.*, 2004, **6**, 241; (*b*) M. C. Law, K. Y. Wong and T. H. Chan, *J. Org. Chem.*, 2005, **70**, 10434.
10 R. D. Rieke and P. M. J. Hudnall, *J. Am. Chem. Soc.*, 1972, **94**, 7178.
11 M. Gomberg and W. E. Bachmann, *J. Am. Chem. Soc.*, 1927, **49**, 236.
12 (*a*) W. C. Zhang and C. J. Li, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3131; (*b*) W. C. Zhang and C. J. Li, *J. Org. Chem.*, 1999, **64**, 3230.
13 (*a*) L. J. Guggenberger and R. E. Rundle, *J. Am. Chem. Soc.*, 1964, **86**, 5344; (*b*) L. J. Guggenberger and R. E. Rundle, *J. Am. Chem. Soc.*, 1968, **90**, 5375.
14 W. E. Lindsell, in *Comprehensive Organometallic Chemistry II*, ed. E. W. Abel, F. G. A. Stone and G. Wilkinson, Pergamon/Elsevier, Oxford, 1995, **vol. 1**, pp. 57–127.
15 J. Toney and G. D. Stucky, *Chem. Commun.*, 1967, 1168.
16 E. J. Weiss, *J. Organomet. Chem.*, 1965, **4**, 101.
17 (*a*) G. Westera, C. Blomberg and F. J. Bickelhaupt, *J. Organomet. Chem.*, 1978, **155**, C55; (*b*) H. W. H. J. Bodewitz, C. Blomberg and F. Bickelhaupt, *Tetrahedron*, 1972, **29**, 719.