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Organotin reagents supported on ionic liquid: highly efficient catalytic free radical reduction of alkyl halides

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ABSTRACT

Ionic liquid-supported organotin reagents were prepared in good yield and demonstrated a convenient catalytic free radical reduction of alkyl halides. A variety of alkyl and aryl halides could be reduced in high to excellent yields and selectively to afford the desired products with simple work-up procedure.

1. Introduction

During the past decades, a number of reactions using organotin compounds[1] (Stille coupling, radical dehalogenation, etc.) have emerged as a result of the increasing demand to develop more versatile and efficient synthetic methods. However, despite that such impressive synthetic potential, organotin reagents have been avoided for the synthesis of health care products and pharmacologically active substances. They have undoubtedly a bad reputation because of their toxicity and the difficulties of removing organotin residues[2] from reaction products. Recently, efforts have been done to overcome these problems, leading, for example, to the use of solid-phase synthetic methods,[3] phosphonium grafted organotins,[4] and other modified organotin reagents.[5]

As a part of our ongoing research program on the discovery of potentialities of TSILs (task-specific ionic liquids) by supporting organotin reagents on ionic liquid,[6] we examined the activity of organotin hydride in the reduction of alkyl halide[7]—one of the important applications of organotin reagents. One approach to minimize the pollution of organotin residue is with free radical catalytic organotin hydride reactions, employing only a catalytic amount of organotin hydride. For example, the in situ regeneration of an organotin hydride is possible by employing hydrogenosilanes or with sodium borohydride.[8] Herein, we would like to report a very simple method to reduce selectively alkyl halide. Moreover, thanks to the organotin reagents supported on ionic liquid, by simple extraction and filtration, the desired product could be easily isolated.

Typically, classical dehalogenation reaction using trialkyl hydride requires an excess amount of the organotin reagent. During the purification, some precautions must be taken to avoid the contamination of the product by organotin residue. If organotin hydride could be immobilized in an ionic liquid and used in a catalytic amount (recycled by an external reducing agent), this contamination could be limited (Fig. 1).

The organotin reagents incorporated on ionic liquid are constructed as shown in Scheme 1. Initially, treatment of the imidazole with 1-bromo-6-chlorohexane gave **1**, which was stannylated with Bu_2SnPhH[6] to afford **2**[6] which was methylated by methyl iodide to give the ionic liquid **3**.[6] Conversion of **3** into **4**[9] was achieved by treatment with HCl in ether. Finally, $NaBH_4$ reduction of **4** in the presence of methanol led to the organotin hydride **5**.[10]

We showed that the reductions of alkyl and aryl halides by **4** were very efficient with 65–97% good yield of isolated product. After a standard work-up procedure,[11] the pure products were isolated in good yields.

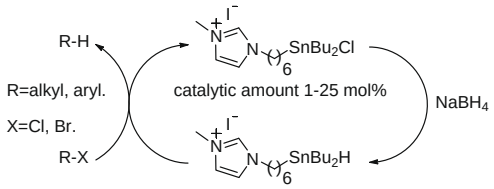

Figure 1. Organotin hydride in catalytic amount catalyzed dehalogenation reaction.

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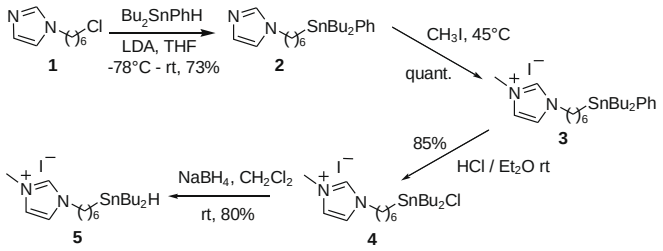
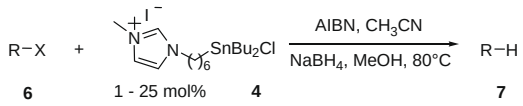


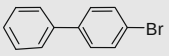
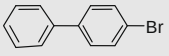
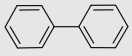
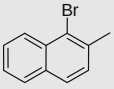
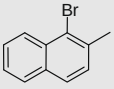
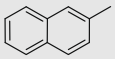
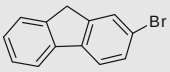
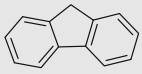
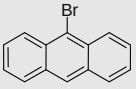
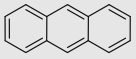
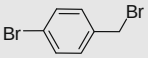
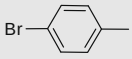
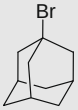
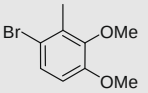
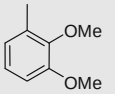
Scheme 1. Preparation of organotin reagents supported on ionic liquid.

In an initial study, without organotin reagent **4** and AIBN, $NaBH_4$ (1.5 equiv) could not reduce the aryl halides as shown in Table 1, entries 1 and 3. No trace of the desired product was obtained. In the presence of **4**, **6a**, **6b** could be easily reduced in excellent yield (Table 1, entries 2 and 4). As an extension, aryl bromides of different structures (2-fluorenyl, 9-anthracenyl, and 3,4-dimethoxy-2-methylphenyl) could be also reduced but required higher organotin catalyst charge and longer reaction times (entries 5, 6, and 10). Interestingly, in the case of 9-anthracenyl bromide (entry 6), the formation of dimerized product 9,9′-bianthracenyl was observed as the result of a coupling reaction. Furthermore, the hexadecylchloride could also be reduced with long-reaction time to afford the pure product in high yield (entry 8). Despite, total and clean conversion of the reduction of adamantyl bromide (entry 9), the product was isolated in moderate yield (65%) possibly due to high volatility. Taking advantage of the reactivity difference between an aryl and a benzyl bromide by applying an appropriated reaction time (3 h), we could reduce selectively the more reactive one by employing 1 mol % of organotin reagent **4** (entry 7) to yield **7e** (70%). Surprisingly, without AIBN (entries 5 and 8), the conversion into the dehalogenated product is 5% (entry 5), and 30% (entry 8). It is plausible that organotin radical could be formed by thermal homolysis but in very low concentration. Although AIBN is not so stable at 80 °C, it could promote the formation of organotin radical that is more stable at high concentration than under purely thermal conditions. In addition, the role of the counter anion (I^-) was also tested. As demonstrated in our recent trials, dehalogenation of hexadecylchloride was carried out in the presence of BF_4^- vs I^- counter anion (conversion 55% vs 100% (81% yield) (Table 1, entry 8)). I/Br,Cl exchange is strongly possible under these reaction conditions (CH_3CN, MeOH, 80 °C) and could result in an enhanced reactivity. Besides, in the case of **6c**, counter anion exchange could not be carried out (BF_4^-/I^-) because the same reduction rate of 2-fluorenylbromide was observed (entry 5) (91% yield (100% conversion) vs 93% yield (100% conversion)). Analysis by ICP-AES[13] of the **7h** (entry 10) showed that the concentration in residual tin was <5 ppm. In all reactions (Table 1, entries 2, 4–10), ^1H NMR and ^{119}Sn NMR analyses showed no contamination by organotin byproducts.

Furthermore, by employing directly the organotin hydride **5** in the radical dehalogenation reaction, the aryl halides could be reduced chemoselectively to afford **9a**, **9b** in good yield without touching the ester function (Table 2). Analysis by ICP-AES[13] of **9a** indicated that the concentration in residual tin was <8 ppm. In all reactions (Table 2, entries 1 and 2), ^1H NMR and ^{119}Sn NMR analyses showed no contamination by organotin byproducts.

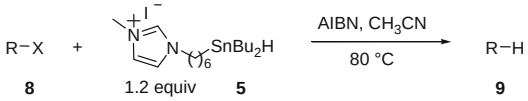
Table 1
Catalytic reduction of halides with organotin hydride in situ supported on ionic liquid

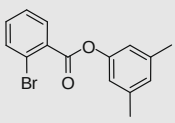
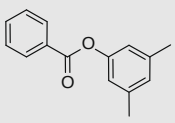
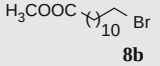
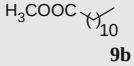


Entry	**4** (equiv)	Substrate		Time (h)	Product[12]		Yield[a] (%)
1[b]	0		**6a**	14	—		0
2	0.1		**6a**	8		**7a**	95
3[b]	0		**6b**	24	—		0
4	0.25		**6b**	24		**7b**	96
5	0.25		**6c**	24		**7c**	93[c] (91)[d]
6	0.25		**6d**	4		**7d**	—[e]
7	0.01		**6e**	3		**7e**	70
8	0.15		**6f**	36		**7f**	81[f] (55)[g]
9	0.25		**6g**	3		**7g**	65
10	0.1		**6h**	22		**7h**	83

[a] Isolated yield.
[b] In the absence of **4** and AIBN.
[c] Without AIBN under the same condition (5% conversion by ^1H NMR).
[d] 91% yield by utilizing **4** with the counter anion BF_4^-.
[e] Isolated product as unseparable mixture of anthracene (21% yield) and 9,9′-bianthracene (50% yield)
[f] Without AIBN under the same conditions (30% conversion by ^1H NMR).
[g] By utilizing **4** with the counter anion BF_4^- (55% conversion by ^1H NMR).

Table 2
Reduction of halides with organotin hydride supported on ionic liquid[15]



Entry	Substrate	Time (h)	Product[14]	Yield[a] (%)
1	 **8a**	24	 **9a**	62
2	 **8b**	6	 **9b**	80

[a] Isolated yield.

2. Conclusion

In conclusion, the new ionic liquid-supported organotin reagents **4** and **5** were prepared in very high yield and demonstrated a convenient catalytic free radical reduction of alkyl halides. A variety of alkyl and aryl halides could be reduced in high to excellent yields and selectively to afford the desired product with simple work-up procedure.

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References and notes

1. (a) Neumann, W. P. *Synthesis* **1987**, 665; (b) Curran, D. P. *Synthesis* **1988**, 417; (c) Curran, D. P. *Synthesis* **1988**, 489; (d) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; (e) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704; (f) Su, W.; Urgaonkar, S.; McLaughlin, P. A.; Verkade, J. G. *J. Am. Chem. Soc.* **2004**, *126*, 16433; (g) *Organotin Chemistry*; Davies, A. L., Ed., 2nd Ed.; Wiley-VCH: Weinheim, New York, 2004; (h) Li, J.-H.; Liang, Y.; Wang, D.-P.; Liu, W.-J.; Xie, Y.-X.; Yin, D.-L. *J. Org. Chem.* **2005**, *70*, 2832; (i) Calo, V.; Nacci, A.; Monopoli, A.; Montingelli, F. *J. Org. Chem.* **2005**, *70*, 6040; (j) Garcia-Martinez, J. C.; Lezutekong, R.; Crooks, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 5097; (k) Lee, K.; Gallagher, W. P.; Toskey, E. A.; Chong, W.; Maleczka, R. E., Jr. *J. Organomet. Chem.* **2006**, *691*, 1462; (l) Chiappe, C.; Pieraccini, D.; Zhao, D.; Fei, Z.; Dyson, P. J. *Adv. Synth. Catal.* **2006**, *348*, 68.
2. (a) Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471; (b) Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449; (c) Curran, D. P.; Chang, C. T. *J. Org. Chem.* **1989**, *54*, 3140; (d) Farina, V. *J. Org. Chem.* **1991**, *56*, 4985; (e) Crich, D.; Sun, S. X. *J. Org. Chem.* **1996**, *61*, 7200; (f) Renaud, P.; Lacote, E.; Quaranta, L. *Tetrahedron Lett.* **1998**, *39*, 2123; (g) Edelson, B. S.; Stoltz, B. M.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 6729; (h) Salomon, C. J.; Danelon, G. O.; Mascaretti, O. A. *J. Org. Chem.* **2000**, *65*, 9220; (i) Studer, A.; Amreim, S. *Synthesis* **2002**, 835; (j) Bergbreiter, D. E.; Walker, S. A. *J. Org. Chem.* **1989**, *54*, 5138; (k) Light, J.; Breslow, R. *Tetrahedron Lett.* **1990**, *31*, 2957; (l) Vedejs, E.; Duncan, S. M.; Haight, A. R. *J. Org. Chem.* **1993**, *58*, 3046; (m) Rai, R.; Collum, D. B. *Tetrahedron Lett.* **1994**, *35*, 6221; (n) Clive, D. L. J.; Yang, W. *J. Org. Chem.* **1995**, *60*, 2607; (o) Suga, S.; Manabe, T.; Yoshida, J.-I. *Chem. Commun.* **1999**, 1237; (p) Han, X.; Hartmann, G. A.; Brazzale, A.; Gaston, R. D. *Tetrahedron Lett.* **2001**, *42*, 583; (q) Clive, D. L. J.; Wang, J. *J. Org. Chem.* **2002**, *67*, 1192; (r) Stien, D.; Gastaldi, S. *J. Org. Chem.* **2004**, *69*, 4464.
3. (a) Gerlach, M.; Jördens, F.; Kuhn, H.; Neumann, W. P. *J. Org. Chem.* **1991**, *56*, 5971; (b) Dumarin, G.; Ruel, G.; Kharboutli, J.; Delmond, B.; Connil, M.-F.; Jousseaume, B.; Pereyre, M. *Synlett* **1994**, 952; (c) Enholm, E. J.; Schulte, J. P., II *Org. Lett.* **1999**, *1*, 1275; (d) Zhu, X.; Blough, B. E.; Carroll, F. I. *Tetrahedron Lett.* **2000**, *41*, 9219; (e) Cossy, J.; Rasamison, C.; Gomez Pardo, D. *J. Org. Chem.* **2001**, *66*, 7195; (f) Chrétien, J.-M.; Zammattio, F.; Le Grognec, E.; Paris, M.; Cahingt, B.; Montavon, G.; Quintard, J.-P. *J. Org. Chem.* **2005**, *70*, 2870; (g) Chrétien, J. M.; Mallinger, A.; Zammattio, F.; Le Grognec, E.; Paris, M.; Montavon, G.; Quintard, J.-P. *Tetrahedron Lett.* **2007**, *48*, 1781.
4. Poupon, J. C.; Marcoux, D.; Cloarec, J. M.; Charette, A. B. *Org. Lett.* **2007**, *9*, 3591.
5. (a) Olofsson, K.; Kim, S.-Y.; Larhed, M.; Curran, D. P.; Halberg, A. *J. Org. Chem.* **1999**, *64*, 4539; (b) Fouquet, E.; Pereyre, M.; Rodriguez, A. L. *J. Org. Chem.* **1997**, *62*, 5242; (c) Fouquet, E.; Pereyre, M.; Roulet, T. *J. Chem. Soc., Chem. Commun.* **1995**, 2387.
6. Vitz, J.; Mac, D. H.; Legoupy, S. *Green Chem.* **2007**, *9*, 431.
7. Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009.
8. (a) Lipowitz, J.; Bowman, S. A. *J. Org. Chem.* **1973**, *38*, 162; (b) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554; (c) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303; (d) Hays, D. S.; Fu, G. C. *Tetrahedron* **1999**, *55*, 8815; (e) Gallagher, W. P.; Terstiege, I.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 3194; (f) Gallagher, W. P.; Maleczka, R. E., Jr. *J. Org. Chem.* **2005**, *70*, 841.
9. *1-((Dibutylchlorostannyl)hexyl)-3-methyl-1H-imidazol-3-ium iodide* (**4**): To a solution of **3** (1.25 g, 2.07 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of HCl 2 M in ether (1.1 mL, 2.2 mmol) at 0–5 °C over a period of 5 min. The mixture was stirred for 2 h at rt, then treated with H_2O (10 mL). To this mixture CH_2Cl_2 (20 mL) was added and the organic phase was washed with H_2O (3 × 20 mL), and the aqueous phase was washed with CH_2Cl_2 (3 × 10 mL), the combined organic phase was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield **4** (988 mg, 85%) as a yellow viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.10 (s, 1H), 7.42–7.40 (m, 2H), 4.34 (t, J = 7.3 Hz, 2H), 4.12 (s, 3H), 1.31–1.99 (m, 22 H), 0.92 (t, J = 7.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.6, 123.7, 123.4, 50.2, 37.1, 32.6, 29.9, 28.6, 26.8, 25.9, 25.4, 18.5, 18.1, 13.7; ^{119}Sn NMR (149 MHz, $CDCl_3$): δ +105.7; IR (neat): 3082, 2953, 2920, 2853, 1579, 1462, 1166, 678, 519 cm^{-1}. HRMS calcd. for $C_{18}H_{36}N_2Cl^{120}Sn$ 435.1589. Found: 435.1595.
10. *1-((Dibutylstannyl)hexyl)-3-methyl-1H-imidazol-3-ium iodide* (**5**)To a suspension of $NaBH_4$ (25 mg, 0.65 mmol) in CH_2Cl_2 (5 mL), a solution of **4** (122 mg, 0.22 mmol) in mixture of CH_2Cl_2 (5 mL) and MeOH (20 μL) was added slowly at 0 °C. The resulting mixture was stirred for 1 h at rt. To this mixture CH_2Cl_2 (10 mL) was added and the organic phase was washed with H_2O (3 × 10 mL), and the aqueous phase was washed with CH_2Cl_2 (3 × 10 mL), the combined organic phase was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield **5** (92 mg, 80%) as a yellow viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.11 (s, 1H), 7.39–7.42 (m, 2H), 5.29 (m, 1H), 4.33 (t, J = 7.6 Hz, 2H), 4.11 (s, 3H), 1.28–1.99 (m, 22 H), 0.92 (t, J = 7.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.2, 123.2, 121.6, 50.2, 36.7, 33.4, 30.2, 29.8, 27.5, 27.1, 25.8, 13.7, 8.2, 8.1; IR (neat): 2954, 2925, 2852, 1806, 1463, 1376, 1169, 676 cm^{-1}; ^{119}Sn NMR (149 MHz, $CDCl_3$): δ −88.3; HRMS calcd. for $C_{18}H_{37}N_2{}^{120}Sn$ 401.1979. Found: 401.1975.
11. *Representative procedure for the reduction of halides using organotin hydride* **4** (Table 1). 1-(Bromomethyl)-4-methylbenzene **6e** (Table 1, entry 7).A mixture of **6e** (472 mg, 1.89 mmol, 1 equiv), organotin chloride **4** (10.6 mg, 0.019 mmol, 0.01 equiv), $NaBH_4$ (107 mg, 2.84 mmol, 1.5 equiv), AIBN (3 mg, 0.019 mmol, 0.01 equiv), CH_3CN (2 mL), and MeOH (20 μL) was placed in a Schlenk tube which was then evacuated and back filled with nitrogen five times. The solution was heated under reflux for required time, the conversion was checked by ^{1}H NMR. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in Et_2O (10 mL) and filtered over a short pad of silica gel to afford the desired product (70%).
12. ^{1}H NMR of **7a–h** and the corresponding commercially available product were identical.
13. ICP-AES measurements were carried out at UT2A (Ultra Traces Analyses Chimiques), Hélioparc Pau—Pyrénées 2, avenue du président Angot F-64053 PAU Cedex 9, France.
14. ^{1}H NMR of **9a**, **9b** and the corresponding commercially available product were identical.
15. *Representative procedure for the reduction of halides using tin hydride* **5** (Table 2). 3,5-dimethylphenyl 2-bromobenzoate **8a** (Table 2, entry 1).A mixture of methyl 3,5-dimethylphenyl 2-bromobenzoate **8a** (48 mg, 0.16 mmol, 1.0 equiv), organotin hydride **5** (100 mg, 0.19 mmol, 1.2 equiv), AIBN (0.016 mmol, 2.6 mg, 0.1 equiv), and CH_3CN (1 mL) was placed in a Schlenk tube which was then evacuated and back filled with nitrogen five times. The solution was heated under reflux for required time, the conversion was checked by ^{1}H NMR. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in Et_2O (10 mL) and filtered over a short pad of silica gel to give a pure product in 62%.