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A new diphenylphosphinite ionic liquid (IL-$OPPh_2$) as reagent and solvent for highly selective bromination, thiocyanation or isothiocyanation of alcohols and trimethylsilyl and tetrahydropyranyl ethers

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Abstract—A new diphenylphosphinite ionic liquid (IL-$OPPh_2$) is introduced. This ionic liquid is used as both a reagent and a solvent to convert alcohols and trimethylsilyl and tetrahydropyranyl (THP) ethers into their corresponding alkyl bromides, thiocyanates or isothiocyanates in the presence of Br_2 and SCN^- at 80 °C. In this ionic liquid, bromination and thiocyanation of alcohols occurs highly selectively in the presence of trimethylsilyl and THP-ethers and also between different classes of alcohols. The use of this ionic liquid allows easy separation of the desired products from the phosphinate by-product.
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The importance of green reactions in organic synthesis has encouraged scientists to explore the use of ionic liquids (ILs) as novel solvents, catalysts, reagents, and also in separation processes.[1–6] ILs usually possess unique properties, such as nonvolatility, nonflammability, and a wide temperature range over the liquid phase. Their miscibility with polar organic solvents and nonmiscibility with water and less polar organic solvents offer the potential for easy separation.[7]

The conversion of alcohols to alkyl halides and alkyl thiocyanates has been widely studied with tertiary phosphines,[8,9] via the Mitsunobu reaction,[10] using PPh_3/Br_2 or phenylene alkylphosphite/Br_2/AgSCN[11] and using in situ generated $PPh_3(SCN)_2$.[12] One of the major disadvantages often encountered with these systems is the difficulty of removing by-products, in particular, phosphine oxides. A number of approaches have been developed to solve this problem. One proposed solution is the use of cross-linked,[13] or noncross linked polystyrene carrying a phosphine group,[14] or PEG-bound reagents.[15] In addition, the use of diphenyl(2-pyridyl)phosphine,[16] (*p*-dimethylaminophenyl)-diphenylphosphine,[17] diphos-1,2-bis(diphenylphosphino-ethane),[18] silicaphosphine,[19] tris[4-(1*H*,1*H*-perfluorooctyloxyphenyl)-phosphine,[20] 4-diphenyl phosphanyl benzoic acid 2-trimethylsilanyl-ethyl ester (DPPBE)[21] as other sources of phosphines for this purpose have been reported.

In continuation of our work on the synthesis of removable phosphines,[19] we now introduce a new diphenylphosphinite ionic liquid **2** that can act both as a solvent and a reagent for the efficient conversion of alcohols and trimethylsilyl and THP ethers to their corresponding alkyl bromides and alkyl thiocyanates or isothiocyanates. This reagent is readily prepared from 1-(2-hydroxypropyl)-3-methylimidazolium hexafluorophosphate **1**.[22] Thus, the reaction of **1** with PPh_2Cl (1 equiv) and triethylamine (1.5 equiv) in CH_2Cl_2 furnished this new diphenylphosphinite ionic liquid **2** in 90% yield (Scheme 1).[23] The ^{31}P NMR spectrum of **2** in $CDCl_3$ showed two resonances at $\delta_P = 22.15$ and -144.3 for the two P atoms.

This ionic liquid is air and water stable and is a liquid at 80–81 °C. We applied the mixture of IL-$OPPh_2$ **2** and Br_2 for the efficient conversion of alcohols and trimethylsilyl and THP ethers to their corresponding bromides and its combination with Br_2 and KSCN for the

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Keywords: Triphenylphosphine; Ionic liquid; Alcohol; Trimethylsilyl ether; Tetrahydropyranyl ether; Halogenation; Thiocyanation.

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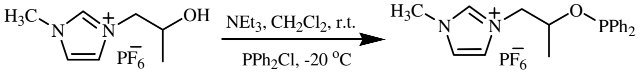
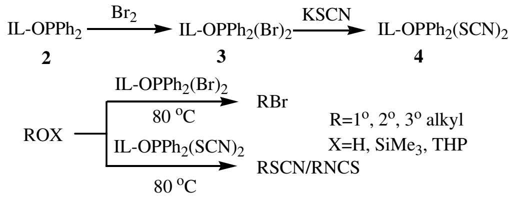


1

IL-OPPh₂ 2

Scheme 1.



Scheme 2.

preparation of alkyl thiocyanates or isothiocyanates without using an organic solvent (Scheme 2). Treatment of **2** with Br_2 (1 equiv) gives IL-$OPPh_2(Br)_2$ **3**. Its ^{31}P NMR spectrum of which in $CDCl_3$ shows two resonances at $\delta_P = 30.37$ and -144.3 ppm. When IL-$OPPh_2(Br)_2$ **3** was treated with KSCN (1 equiv), the formation of IL-$OPPh_2(SCN)_2$ **4** occurred. The ^{31}P NMR resonance of **4** in $CDCl_3$ appeared at $\delta_P = 38.61$ ppm. This chemical shift is very similar to that which has been reported for $PPh_3(SCN)_2$ ($\delta_P = 39.0$ ppm).[11b] Addition of an alcohol (1 equiv) to either of these ionic liquids gave the corresponding bromide, thiocyanate or isothiocyanate together with the formation of the corresponding phosphinate which could easily be separated by extraction of the desired product with diethyl ether.

The optimized ratio of benzyl alcohol/IL-$OPPh_2$/Br_2 to convert benzyl alcohol to its corresponding bromide was found to be 1/1.5/1.5.[24] Here, IL-$OPPh_2$ acts as both a solvent and a reagent. Using this method, primary, secondary, and tertiary alcohols were converted into their bromides in excellent yields (Table 1, entries 1–8). We also used this diphenylphosphinite ionic liquid for the successful conversion of trimethylsilyl and tetrahydropyranyl ethers to the corresponding bromides in very good yields under the same reaction conditions as applied for alcohols (Table 1, entries 9–14).

Table 1. Conversion of alcohols and trimethylsilyl and THP-ethers to bromides in the presence of IL-$OPPh_2$ and Br_2 at 80 °C

Entry	ROX	Time (h)	Isolated yield[a] (%)
1	$PhCH_2OH$	Immediately	95
2	PhCH(OH)Ph	5	89
3	p-C_6H_5–$C_6H_4C(CH_3)_2OH$	10	86
4	$PhCH(OH)CH_2CH_3$	0.5	90
5	$CH_3(CH_2)_6CH_2OH$	2	96
6	$CH_3(CH_2)_5CH(OH)CH_3$	14	88
7	p-CH_3O–$C_6H_4CH_2OH$	Immediately	97
8	p-NO_2–$C_6H_4CH_2OH$	3	95
9	$PhCH_2OSiMe_3$	1	87
10	$PhCH(OSiMe_3)Ph$	9	78
11	p-C_6H_5–$C_6H_4C(CH_3)_2OSiMe_3$	12	69
12	$PhCH_2OTHP$	2	89
13	PhCH(OTHP)Ph	10	85
14	p-C_6H_5–$C_6H_4C(CH_3)_2OTHP$	24	73

[a] All the products are known compounds and were identified by comparison of their physical and spectral data with those of authentic samples.[8,9]

In continuation of our work on the use of in situ generated $PPh_3(SCN)_2$ for the preparation of thiocyanates,[12] we used the combination of IL-$OPPh_2(Br)_2$ and KSCN at 80 °C for the synthesis of IL-$OPPh_2(SCN)_2$. We used KSCN instead of NH_4SCN because of its solubility in our ionic liquid. This ionic liquid was then used as the reagent and solvent for the conversion of alcohols and trimethylsilyl and tetrahydropyranyl ethers to the corresponding thiocyanates or isothiocyanates (Scheme 2).

Optimization of the reaction conditions showed that for a mixture of benzyl alcohol/IL-$OPPh_2(Br)_2$/KSCN, the stoichiometric ratio of 1/1.5/3 was the most suitable for the conversion of benzyl alcohol to benzyl thiocyanate.[25] We applied these optimized conditions for the reaction of structurally different alcohols (Table 2).

Table 2. Conversion of alcohols and trimethylsilyl and THP-ethers to thiocyanates and isothiocyanates in the presence of IL-$OPPh_2$, Br_2 and KSCN at 80 °C

Entry	ROX	Time (h)	RSCN/ RNCS[a]	Isolated yield[c] (%)
1	$PhCH_2OH$	0.5	100/0	98
2	PhCH(OH)Ph	9	20/80	91[b]
3	p-C_6H_5–$C_6H_4C(CH_3)_2OH$	15	0/100	82
4	$PhCH(OH)CH_2CH_3$	1	16/84	93[b]
5	$CH_3(CH_2)_6CH_2OH$	2	100/0	90
6	$CH_3(CH_2)_5CH(OH)CH_3$	20	23/77	88[b]
7	p-CH_3O–$C_6H_4CH_2OH$	0.1	100/0	90
8	p-NO_2–$C_6H_4CH_2OH$	7	100/0	95
9	$PhCH_2OSiMe_3$	2	100/0	83
10	$PhCH(OSiMe_3)Ph$	12	21/79	80[b]
11	p-C_6H_5–$C_6H_4C(CH_3)_2OSiMe_3$	16	0/100	72
12	$PhCH_2OTHP$	3	100/0	83
13	PhCH(OTHP)Ph	13	17/83	89[b]
14	p-C_6H_5–$C_6H_4C(CH_3)_2OTHP$	24	0/100	79

[a] GC and NMR yield using n-octane as internal standard.

[b] A mixture of thiocyanate and isothiocyanate was obtained.

[c] All the products are known compounds and were identified by comparison of their physical and spectral data with those reported in the literature.[10–12]

Table 3. Selective reactions of different binary mixtures with IL-$OPPh_2(Br_2)$ **3** (conditions A) and IL-$OPPh_2(SCN)_2$ **4** (conditions B)[a]

Entry	Binary Mixture	Conditions	Time (h)	Yield[b] (%)
1		A	0.5	100
	$PhCH_2OH$			0
	$CH_3(CH_2)_5CH(OH)CH_3$			100
		B	1	0
2		A	1	100
	$PhCH_2OH$			0
	p-C_6H_5–$C_6H_4C(CH_3)_2OH$			95
		B	2	5
3		A	8	90
	PhCH(OH)Ph			10
	p-C_6H_5–$C_6H_4C(CH_3)_2OH$			94
		B	10	6
4		A	<1 min	100
	$PhCH_2OH$			0
	$PhCH_2OSiMe_3$			100
		B	0.5	0
5		A	5	91
	PhCH(OH)Ph			9
	$PhCH(OSiMe_3)Ph$			95
		B	11	5
6		A	<1 min	100
	$PhCH_2OH$			0
	$PhCH_2OTHP$			100
		B	<1 min	0
7		A	7	100
	PhCH(OH)Ph			0
	PhCH(OTHP)Ph			100
		B	10	0
8		A	12	89
	p-C_6H_5–$C_6H_4C(CH_3)_2OH$			11
	p-C_6H_5–$C_6H_4C(CH_3)_2OTHP$			90
		B	16	10

[a] The stoichiometry of the binary mixture of IL-$OPPh_2/Br_2$ and IL-$OPPh_2/Br_2/KSCN$ is 1.5/1.5 and 1.5/1.5/3.

[b] GC yield using *n*-octane as internal standard.

The formation of only thiocyanates from 1° alcohols and isothiocyanates from 3° alcohols with this reagent system is shown in Table 2. We also used this ionic phosphinite for the successful conversion of trimethylsilyl and tetrahydropyranyl ethers to the corresponding thiocyanates or isothiocyanates in high yields under the same reaction conditions as applied for alcohols (Table 2, entries 9–14).

Bromination and thiocyanation reactions in these ionic liquids were found to be highly selective for primary alcohols in the presence of secondary alcohols. In a binary mixture of benzyl alcohol and 2-octanol, the primary alcohol was converted quantitatively to its bromide or thiocyanate, while the secondary alcohol remained intact (Table 3, entry 1). Excellent selectivity was also observed for the conversion of 1° and 2° alcohols in the presence of a 3° alcohol (Table 3, entries 2 and 3). Similarly, this method showed excellent selectivity for the conversion of 1° and 2° alcohols to the corresponding bromides and thiocyanates in the presence of trimethylsilyl ethers (Table 3, entries 4 and 5) and THP-ethers (Table 3, entries 6–8).

The use of this new and easily prepared ionic liquid **2** as an air and water stable phosphine reagent and also a green solvent provides an attractive and practical method for the clean conversion of alcohols and trimethylsilyl and tetrahydropyranyl ethers into bromides and thiocyanates or isothiocyanates. The excellent selectivity of this method can also be considered as an advantage.

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23. *Procedure for the preparation of ionic liquid* **2**: To a flask containing the dried ionic liquid **1**[22] (1.15 g, 4 mmol) was added CH_2Cl_2 (5 mL), followed by triethylamine (0.94 mL, 6.03 mmol). The resultant mixture was cooled to −20 °C, followed by the dropwise addition of a solution of PPh_2Cl (0.73 mL, 4 mmol) in 5 mL of CH_2Cl_2. The reaction mixture was left to stir for 1 h and was then quenched with 5 N NaOH (1.45 mL), followed by water (2 mL). The aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford 89% of **2** as a white solid (mp 80–81 °C). ^{1}H NMR 250 MHz ($CDCl_3$): δ (ppm): 1.20 (3H, d, $J = 5.4$ Hz, $-CH_3$), 3.60 (3H, s, N–CH_3), 3.84 (2H, m), 4.12 (1H, m), 6.76 (2H, s C(4,5)–H), 7.16–7.64 (10H, m), 10.01 (1H, s, C(2)–H); ^{13}C NMR 60 MHz ($CDCl_3$): δ (ppm): 20.4 ($-CH_3$), 34.5 (N–CH_3), 58.6 (N–CH_2), 72.0 ($CHOPPH_2$), 123.1, 123.2 (C4/5), 129.2, 129.5, 131.1, 137.4, 140.4; ^{31}P NMR 202 MHz ($CDCl_3$): δp (ppm): 22.15, −144.30.
24. *Typical procedure for the conversion of benzyl alcohol to benzyl bromide*: To a flask containing ionic liquid **2** (0.705 g, 1.5 mmol), Br_2 (0.075 mL, 1.5 mmol) was added dropwise. The red color of Br_2 immediately disappeared. Then benzyl alcohol (0.1 mL, 1 mmol) was added at 80 °C. GC and TLC of the reaction mixture showed immediate completion of the reaction. The mixture was cooled to room temperature and benzyl bromide was extracted with diethyl ether (3 × 5 mL). Evaporation of ether, followed by chromatography on a short column of silica gel using *n*-hexane/ethyl acetate (10/1) as eluent, gave benzyl bromide as a colorless liquid (0.256 g, 94% yield, bp 196–197 °C, lit.[19] bp 196–198 °C).
25. *Typical procedure for the conversion of benzyl alcohol to benzyl thiocyanate*: To a flask containing ionic liquid **2** (0.705 g, 1.5 mmol), Br_2 (0.075 mL, 1.5 mmol) was added dropwise. The red color of Br_2 disappeared immediately, and then KSCN (0.29 g, 3 mmol) and benzyl alcohol (0.1 mL, 1 mmol) were added at 80 °C. GC and TLC of the reaction mixture showed the immediate completion of the reaction after the addition of benzyl alcohol. The mixture was cooled to rt and benzyl thiocyanate was extracted with diethyl ether (3 × 5 mL). Evaporation of the ether and chromatography on a short silica gel column using *n*-hexane/ethyl acetate (5/1) as eluent gave benzyl thiocyanate in 94% yield (mp 39.5–40 °C, lit.[12] mp 39–40 °C).