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Ionic liquid/PPh_3 promoted cleavage of diphenyl disulfide and diselenide: a straight-forward metal-free one-pot route to the synthesis of unsymmetrical sulfides and selenides

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ABSTRACT

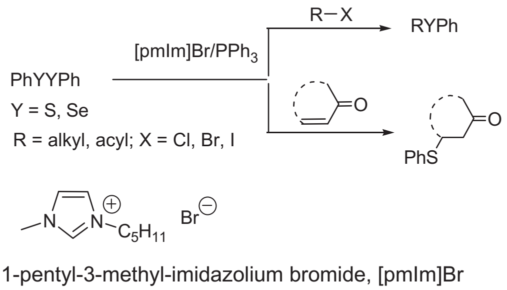
A metal-free cleavage of diphenyl disulfide and diphenyl diselenide has been achieved using ionic liquid/triphenyl phosphine (PPh_3) and a convenient protocol for the one-pot synthesis of unsymmetrical sulfides and selenides by condensing 'in situ' generated thiolate or selenate anion with alkyl halides has been developed. In addition, 1,4-conjugate addition of the generated thiolate anions to activated alkenes has also been demonstrated. The ionic liquid, 1-methyl-3-pentyl imidazolium bromide, [pmIm]Br plays a crucial role in promoting the course of the reactions and shows superior activity and selectivity compared to other solvents. The [pmIm]Br has been reused for at least five times without appreciable loss of activity.

Organic sulfides and selenides have been extensively used in organic synthesis and pharmaceutical industries[1a–c] and as a food supplement.[1d,e] A number of protocols are available in the literature for the preparation of organic sulfides and selenides.[2] In another aspect, conjugate addition of thiols to the activated alkenes leads to various biologically important organo sulfides. Commonly used reagents for this conjugate addition reaction are strong bases,[3] Lewis acids[4], and ionic liquids, or quaternary ammonium salts.[5] However, with a few exceptions most of these are two-step procedures and involve malodorous and toxic thiols and handling of unstable reagents in addition to strong basic or acidic reagents.

Thus, an alternative efficient and milder procedure for the synthesis of organic sulfides and selenides avoiding toxic and malodorous thiols is highly desirable. One of the straightforward options is the cleavage of disulfides and diselenides and subsequent reaction of thiolates or selenates with alkyl halides or conjugated alkenes in the presence of a mild catalyst. A few reagents have been developed for the cleavage of disulfide and diselenide, which include $Zn/ZnCl_2$,[6] $Zn/RuCl_3$,[7] lanthanum metal,[8] indium(I) iodide,[9] reduction with $NaBH_4$[10], or phosphine.[11] Although, PPh_3[11c] was reported to reduce the disulfide bond the subsequent reaction of the thiolate anion has not been explored to the best of our knowledge.

Besides being used as the reaction medium,[12] ionic liquids also have the potential to promote the course of a reaction[13] by acting as catalysts.[14] Here, we report a simple procedure for a facile cleavage of diphenyl disulfide and diselenide mediated by [pmIm]Br/PPh_3 and subsequent reaction with alkyl halides and activated alkenes leading to the synthesis of unsymmetrical sulfides, selenides, and 1,4-addition products, respectively (Scheme 1).

Initially, we have selected the synthesis of benzyl phenyl sulfide as a model reaction for the optimization of various reaction parameters. The results are summarized in Table 1. It was observed that PPh_3 failed to initiate the reaction in the absence of [pmIm]Br, whereas in other organic solvents the reaction either did not initiate (Table 1, entries 1 and 2) or proceeded marginally (Table 1, entries 3 and 4). When the same reaction was carried out in ethanol the corresponding benzyl ethyl ether was formed as a major



Scheme 1. PPh_3/ionic liquid mediated reaction of diphenyl disulfide and diselenide with alkyl halide and activated alkene.

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Table 1
Optimization of reaction conditions

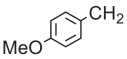
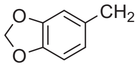
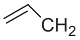
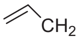
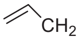
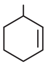
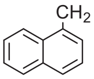
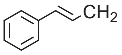
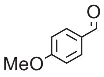
$$PhCH_2Br + PhSSPh \xrightarrow[75\ ^{o}C,\ 8\ h]{PPh_3,\ Solvent} PhCH_2SPh$$

Entry	Solvent	PPh_3	Product	Yield[a] (%)
1	Toluene	1.1 equiv	—	0
2	CH_2Cl_2	1.1 equiv	—	0
3	CH_3CN	1.1 equiv	$PhCH_2SPh$	20
4	THF	1.1 equiv	$PhCH_2SPh$	40
5	EtOH	1.1 equiv	$PhCH_2SPh + PhCH_2OEt$	60 (10:90)
6	Dioxan + H_2O (1:1)	1.1 equiv	$PhCH_2SPh + PhCH_2OH$	75 (15:85)
7	[pmIm]Br (40 mol %)	1.1 equiv	$PhCH_2SPh$	84
8	[pmIm]Br (1 mmol)	1.1 equiv	$PhCH_2SPh$	90
9	[pmIm]Br (40 mol %)	0.5 equiv	$PhCH_2SPh$	35
10	[pmIm]Br (20 mol %)	1.1 equiv	$PhCH_2SPh$	25

[a] Isolated yield. Amount of PPh_3 and [pmIm]Br was calculated with respect to alkyl bromide.

Table 2
Synthesis of alkyl phenyl sulfides, selenides, and alkyl thiobenzoates, selenobenzoates in a one-pot reaction

$$R{-}X + PhYYPh \longrightarrow RYPh$$

Entry	R	X	Y	Time (h)	Yield[a] (%)	Ref.
1	$PhCH_2$	Cl	(a) S (b) Se	2.5 4.0	80 78	9b 6a
2	$PhCH_2$	Br	(a) S (b) Se	1.5 3.5	84 80	9b 6a
3	$PhCH_2$	I	(a) S (b) Se	1.5 3.0	88 82	9b 6a
4		Br	(a) S (b) Se	2.0 4.0	82 74	9b 9a
5		Br	(a) S (b) Se	2.5 3.0	78 70	9b 9a
6	$PhCH_2CH_2$	Br	(a) S (b) Se	4.0 5.5	80 75	4h 9a
7	$PhCH_2CH_2$	I	S	4.0	75	4h
8		Cl	(a) S	3.0	76	9b
9		Br	(a) S (b) Se	3.0 5.0	83 72	9b 9b
10		I	S	2.5	84	9b
11	$(CH_3)_2CH$	Br	(a) S (b) Se	5.5 6.0	70 72	2f 6c
12	PhCH(Me)	Br	(a) S (b) Se	4.5 5.0	75 70	4h 9b
13		Br	(a) S (b) Se	5.0 6.0	76 73	16 9a
14		Br	S	3.5	80	17
15		Br	Se	5.0	80	6c
16	CH_2CO_2Et	Br	Se	4.5	86	6a
17	MeCO	Cl	(a) S (b) Se	3.0 4.5	80 74	9b 18
18	MeCO	Cl	(a) S (b) Se	2.0 3.0	85 84	9b 9a
19	PhCO	Cl	(a) S (b) Se	2.0 3.5	82 80	9b 8a
20	cHex-CO	Cl	(a) S (b) Se	2.5 4.0	82 85	9b 9b
21		Cl	(a) S (b) Se	3.0 3.5	84 80	9b 19

A mixture of substrate, diphenyl diselenide or diphenyl disulfide, (1 mmol), [pmIm]Br (0.4 mmol), and PPh_3 (0.7 mmol) was heated at 75 °C.

[a] Yields refer to those of pure isolated products.

product along with 10% of the desired product (Table 1, entry 5). As PPh_3 was reported[11c] to cleave the disulfide bond in dioxane–water solvent mixture we have tried this condition for our condensation reaction and we found that benzyl alcohol was produced as the major product (Table 1, entry 6).

It was found that PPh_3 mediated cleavage of diphenyl disulfide and the subsequent condensation of the thiolate anion proceeded efficiently in [pmIm]Br (40 mol %) at 75 °C and no other side product was isolated. The diphenyl diselenide was also found to produce benzyl phenyl selenide by the same sequence of reactions in excellent yield. The above studies clearly demonstrate the crucial role of [pmIm]Br in the cleavage of diphenyl disulfide and subsequent reaction of thiolate/selenate ion.

To explore the general applicability and scope of this procedure, the reaction of 'in situ' generated phenyl thiolate and selenate anion was carried out with various alkyl halides, allyl halides, and acid chlorides under the optimized reaction conditions. Briefly, in a simple experimental procedure[15] PPh_3 was added to a mixture of diphenyl disulfide or diselenide, and alkyl halide in [pmIm]Br and the reaction mixture was heated at 75 °C till completion of reaction (TLC). Extraction of the product with diethyl ether followed by evaporation of solvent lead to a crude product, which was purified by column chromatography to provide pure unsymmetrical sulfides and selenides in good yields. The results are summarized in Table 2. All the reactions were successfully carried out under the reaction conditions, giving alkyl aryl sulfides, selenides, and alkyl thiobenzoates and selenobenzoates in high yields (70–86%) at a reasonable time period (1.5–6 h).

Encouraged by the reactivity and effectiveness of this [pmIm]Br/PPh_3 reagent system toward the synthesis of unsymmetrical sulfides and selenides, we have attempted the 1,4-conjugate addition of phenyl thiolate and phenyl selenate anion with activated alkenes.

We have observed that, the phenyl thiolate anion generated by the cleavage of diphenyl disulfide also underwent clean conjugate addition with conjugated alkenes under similar reaction conditions to provide the corresponding 1,4-addition products in high yields. The results for thio-Michael addition are presented in Table 3. A variety of conjugated alkenes (e.g., aldehydes, ketones, esters, and nitriles) took part in this reaction producing the corresponding 1,4-addition products.

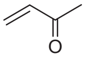
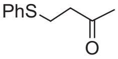
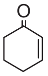
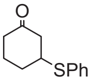
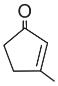
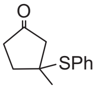
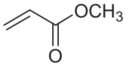
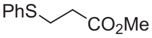
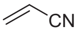
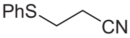
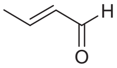
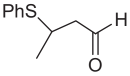
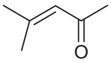
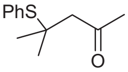
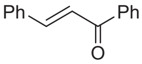
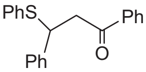
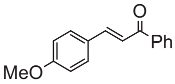
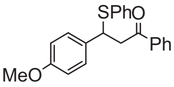
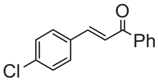
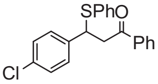
We observed that α,β-unsaturated ketones with substitution at β-position (Table 3, entries 3 and 7) also participated in this reaction without any difficulty. However, this reagent system is unable to initiate the 1,4-conjugate addition of phenyl selenate anion to activated alkenes under similar reaction conditions.

In general, the cleavage of both diphenyl disulfide and diphenyl diselenide by triphenyl phosphine in ionic liquid is very clean and considerably fast. This protocol offered a one-pot synthesis of unsymmetrical sulfides and selenides by condensing 'in situ' generated thiolate or selenate anion with alkyl halides. Moreover generated thiolate anion underwent addition reaction with various conjugated alkenes to produce 1,4-addition products in high yields. The results are summarized in Table 3. All the products are obtained in high purity and were characterized by their spectroscopic (IR, ^1H NMR and ^{13}C NMR) data. The PPh_3 here acts as a catalyst. Without PPh_3 the cleavage reaction did not proceed at all.

The ionic liquid was reused for five times without appreciable loss of activity. The mechanism of this reaction is interesting since phosphorus, being a second-row element, has the potential for va-

Table 3

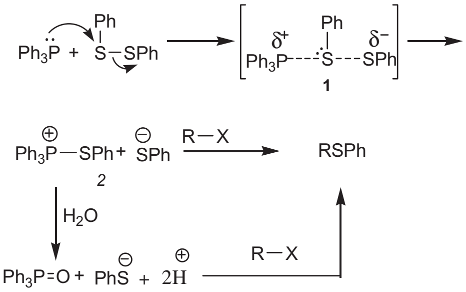
[pmIm]Br/PPh_3-promoted cleavage of diphenyl disulfide followed by 1,4-addition to conjugated alkenes

Entry	Michael acceptor	Product	Time (h)	Yield[a] (%)	Ref.
1			4.0	80	4a
2			5.0	78	5b
3			6.0	75	20
4			4.5	80	5c
5			7.0	68	5c
6			6.0	72	5a
7			6.5	75	5a
8			7.0	70	5b
9			7.0	72	4d
10			6.5	76	4d

A mixture of conjugated alkene (1 mmol), diphenyl disulfide (0.7 mmol), [pmIm]Br (0.4 mmol) was heated at 75 °C.

[a] Yields refer to those of pure isolated products characterized by spectroscopic data (IR, ^1H and ^{13}C NMR).

lence expansion. Following a reported reaction pathway,[11c] an addition–elimination mechanism has been proposed as outlined in Scheme 2. The nucleophile, PPh_3 attacks the sulfur or selenium atom to produce an intermediate **1** which underwent a facile cleavage to release thiolate or selenate anion. These anions underwent subsequent reactions to provide unsymmetrical sulfides, selenides, and 1,4-addition products. As the reaction did not proceed in the absence of ionic liquid it has a vital role in this reaction. Although we do not have any experimental data regarding the precise function of ionic liquid we believe that the ionic liquid acts as solvent, promoter, and stabilizer for the intermediates **1**, **2**, and other charged species via involvement of its imidazolium and bromide ions. It is likely that because of the hygroscopic nature of the ionic liquid, the moisture absorbed from air releases thiolate anion from Ph_3P^+-SPh (**2**),[11c] which then reacts with other electrophiles to yield the final product. In the course of the reaction PPh_3 is converted into triphenyl phosphine oxide and thus 1 equiv of PPh_3 is required to carry out the reaction.



Scheme 2. Possible mechanism for the cleavage of diphenyl disulfide and subsequent reaction.

In summary, we have demonstrated a simple metal-free one-pot procedure for the synthesis of unsymmetrical sulfides, selenides, and 1,4-thio-adducts by the [pmIm]Br/PPh_3 mediated cleavage of diphenyl disulfide and diphenyl diselenide and subsequent condensation. Thus, this protocol avoided the use of expensive metal catalysts usually used for this reaction, volatile organic solvents and toxic thiols. Certainly, the present protocol offers a novel and green alternative to the existing procedures.

Acknowledgments

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Supplementary data

Supplementary data (general experimental procedure and characterization data of all products listed in Tables 2 and 3) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.047.

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15. *Representative procedure for the synthesis of benzyl phenyl sulfide* (Table 2, entry 2a). A mixture of benzyl bromide (171 mg, 1 mmol), diphenyl disulfide (131 mg, 0.6 mmol), PPh_3 (184 mg, 0.7 mmol), and [pmIm]Br[21] (94 mg, 0.4 mmol) was stirred at 75 °C for 1.5 h (TLC). The reaction mixture was extracted with Et_2O, and the organic layer was washed with brine (2 × 5 mL) and dried (Na_2SO_4). Evaporation of solvent left the crude product which was purified by column chromatography over silica gel (hexane) to afford the pure product, benzyl phenyl sulfide (168 mg, 84%) as a colorless liquid; IR (neat) 3058, 3028, 2923, 1581, 1495, 1479, 1452, 1438, 1238, 1090, 1068, 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.21 (s, 2H), 7.32–7.41 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.5, 127.6, 128.0, 129.0 (2C), 129.3 (2C), 129.5 (2C), 130.3 (2C), 136.9, 137.9. The spectroscopic (FT-IR, ^1H NMR and ^{13}C NMR) data are in good agreement with the reported values.[9b] The remaining ionic liquid was washed with ether, dried under vacuum, and reused five times without appreciable loss of catalytic activity.

    The similar procedure was used to carry out all the reactions listed in Tables 2 and 3 and in case of 1,4-addition reaction (Table 3), activated alkenes were used in place of alkyl halides. All the products are known in the literature and were properly characterized by spectroscopic (IR, ^1H NMR and ^{13}C NMR) data. These spectroscopic data are in good agreement with the reported values (references provided in Tables 2 and 3).

    Although this procedure was described on mmol scale, gram-scale reactions also provided uniform results. It was also observed that use of [bmim]Br in place of [pmim]Br provided comparable results.
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21. This ionic liquid was prepared by the reaction of *N*-methylimidazole and pentyl bromide following a reported procedure (Namboodiri, V. V.; Varma, R. S. *Org. Lett*. **2002**, *4*, 3161–3163).