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An indium–TMSCl promoted reaction of diphenyl diselenides and aldehydes: novel routes to selenoacetals and alkyl phenyl selenides

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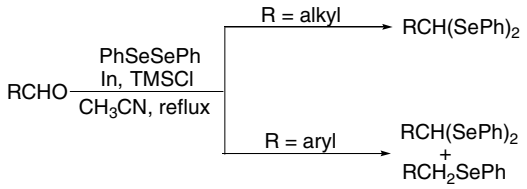
Abstract—The reaction of diphenyl diselenides with aldehydes in the presence of In–TMSCl has been investigated. Aliphatic aldehydes provide the corresponding selenoacetals, whereas aromatic aldehydes lead predominantly to alkyl phenyl selenides under the same reaction conditions. This constitutes a new approach for the synthesis of selenoacetals and selenides from aldehydes.

Indium metal and its derivatives have been found to have great potential for a variety of organic transformations and have generated new interesting chemistry.[1] As a part of our program to develop new synthetic procedures using indium reagents,[1e,2] we have investigated In–TMSCl[2o] and discovered a very interesting reaction of diphenyl diselenides with aldehydes promoted by this reagent. Aliphatic aldehydes when heated under reflux with diphenyl diselenides in the presence of In–TMSCl in acetonitrile produced the corresponding selenoacetals whereas from aromatic aldehydes, alkyl phenyl selenides under the same reaction conditions were produced (Scheme 1).

Selenoacetals are versatile intermediates in organic synthesis and have played a crucial role in the development of organoselenium chemistry.[3] They are stable in basic and mildly acidic conditions, inert to Grignard reagents and thus have similar properties to their oxygen and sulfur analogues. They are also useful for carbonyl protection.[3] Usually, selenoacetals are prepared from the corresponding carbonyl compounds by reaction with selenols or $[B(SeMe)_3]$ under the catalysis of protic or Lewis acids.[4] Alternatively, they can be prepared by exchange reactions between *O*-acetals and tris(phenylseleno)borane.[5] However, all these reagents—selenols and tris(alkylseleno)borane—are usually prepared from dialkyl diselenides.[4] Thus, a method involving dialkyl diselenides directly would be more convenient and practical.



Scheme 1.

Organic selenides are of considerable interest in academia as well as in industry because of their wide involvement in organic synthesis[6a] and their biological activities.[6b] Although a number of procedures for the synthesis of dialkyl/alkyl aryl selenides have been reported,[7] most use alkyl halides as starting materials. To the best of our knowledge, no method is available starting from aldehydes. Thus, the present protocol (Scheme 1) provides new routes for the synthesis of selenoacetals and alkyl phenyl selenides.

The experimental procedure is very simple.[8] A solution of diphenyl diselenide, an aldehyde and trimethylsilyl chloride in acetonitrile is heated under reflux in the presence of indium metal for a period of time (Table 1), standard work-up and extraction with ether providing the product.

Keywords: Selenoacetal; Selenides; Indium; Trimethylsilyl chloride; Aldehydes.
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Table 1. Synthesis of selenoacetals and aryl phenyl selenides

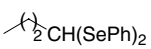
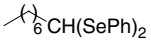
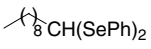
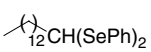
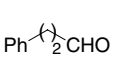
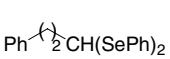
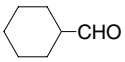
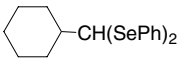
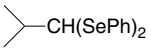
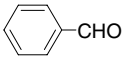
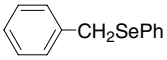
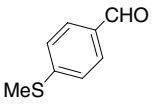
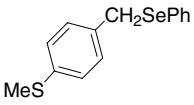
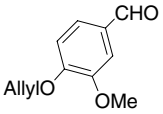
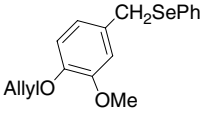
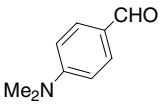
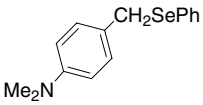
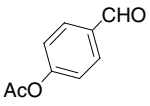
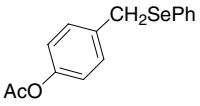
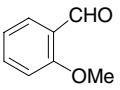
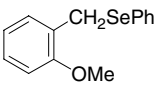
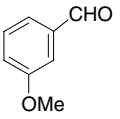
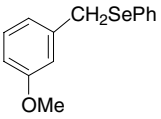
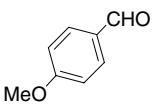
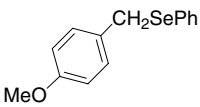
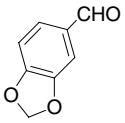
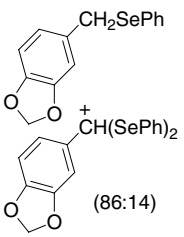
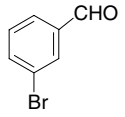
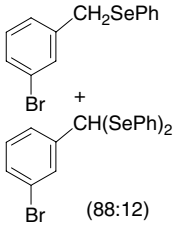
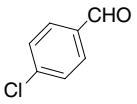
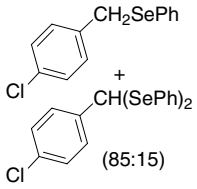
Entry	Aldehyde	Time (h)	Product	Yield[a] (%)	Ref.
1		2.0		70	
2		2.5		78	
3		2.5		72	
4		2.5		76	
5		4.5		75	
6		2.0		71	
7		2.0		80	
8		7.0		75	2j
9		5.5		76	
10		3.5		72	
11		2.5		65	
12		2.5		75	
13		3.0		73	
14		3.5		72	
15		3.5		74	
16		4.0		80	2j

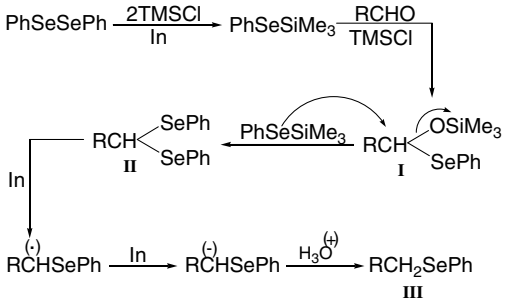
Table 1 (*continued*)

Entry	Aldehyde	Time (h)	Product	Yield[a] (%)	Ref.
17		7.0	 (88:12)	70	
18		6.5	 (85:15)	75	2j

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

A wide range of structurally diverse aliphatic and aromatic aldehydes underwent reactions with diphenyl diselenides using this procedure to produce the corresponding products. The results are summarized in Table 1. All the aliphatic aldehydes produced the corresponding selenoacetals (entries 1–7), whereas aromatic aldehydes furnished exclusively (entries 8–15) or predominantly (entries 16–18) the corresponding aryl phenyl selenides. In the reactions of aromatic aldehydes where a mixture of aryl phenyl selenides and selenoacetals was produced, the proportion of selenides was increased at the cost of selenoacetals after longer periods although 100% conversion was not achieved. However, an isolated pure selenoacetal of 3-bromobenzaldehyde was converted to the corresponding selenide under the same reaction conditions after 6 h. When the reactions of aliphatic aldehydes were allowed to proceed for longer periods, no alkyl selenides were obtained. Thus, it seems that the reactions of aliphatic aldehydes stopped at the selenoacetal stage, whereas the reactions of aromatic aldehydes proceeded further to produce selenides. The exact reason for this difference of reactivity is not clear. We found that a radical quencher considerably affects the course of the reaction of aromatic aldehydes.

Thus, when the reaction of 2-methoxybenzaldehyde (entry 13) was carried out in the presence of a quencher, 4-hydroxy TEMPO under reflux for 5 h, the formation of the corresponding selenide was considerably diminished, a 1:1 mixture of selenoacetal and selenide being obtained whereas in the normal reaction the selenide was obtained as the only isolable product after 3 h. In contrast, the quencher had no effect on the conversion of an aliphatic aldehyde (decanal, entry 3) to the selenoacetal. Thus, we speculate that a free radical is involved in the formation of aryl phenyl selenides. Based on these observations, we propose the reaction course shown in Scheme 2. As indium metal is well known to initiate radical processes,[1e] it may be that the initially formed selenoacetal **II** undergoes radical cleavage followed by anion formation leading to selenides **III** in reactions of aromatic aldehydes.



Scheme 2.

In general, the reactions were very clean, fast and high yielding. The products were obtained in high purity. Although a few aromatic aldehydes (entries 16–18) led to mixtures of selenides and selenoacetals, these could be separated by careful column chromatography. Various functional groups such as OAc, OMe, SMe, *O*-allyl, NMe_2, Cl and Br survived under the reaction conditions intact. The reactions did not proceed at all either in the absence of TMSCl or in the absence of In metal, that is, the combined In–TMSCl reagent is essential for this reaction. Replacement of TMSCl with BF_3 did not give the products. Indium(I) iodide which is very efficient for the cleavage of diphenyl diselenides[2j,k,p] was also ineffective. Acetonitrile was found to be the best solvent, whereas in methylene chloride the reaction was very slow, and in THF poor yields of the product were obtained. Finally, ketones remained completely inert under these experimental conditions.

In conclusion, the present procedure[8] using In–TMSCl provides a new route for the synthesis of selenoacetals and aryl phenyl selenides from aldehydes. The significant features of this procedure are (a) simple one-pot operation, (b) use of stable and readily available diphenyl diselenide, (c) rapid reaction and (d) high isolated yields of products. Thus, it provides a better and practical alternative to the existing procedures[4,5,7] and we believe that it will find useful applications in organic synthesis.

Acknowledgements

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8. *General experimental procedure for the synthesis of selenoacetals and aryl phenyl selenides. Representative procedure for 1,1-diphenylselenooctane (entry 2).*
To a stirred solution of diphenyl diselenide (1 mmol, 312 mg) and trimethylsilyl chloride (2 mmol, 218 mg) in dry acetonitrile (3 mL) was added octanal (1 mmol, 128 mg) and the mixture was stirred for 2 min at room temperature. The reaction mixture was then heated under reflux with indium metal (1 mmol, 115 mg, cut into small pieces) for 2.5 h. After completion of the reaction (TLC), acetonitrile was evaporated in vacuo and the residue was extracted with ether (3×10 mL). The combined ether extract was then washed with brine, dried (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography over silica gel (hexane–ether 98:2) to furnish 1,1-diphenylselenooctane as a yellow liquid (331 mg, 78%); IR (neat): 1436, 1475, 1578 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.78 (t, $J = 6.6$ Hz, 3H), 1.13–1.18 (m, 7H), 1.46–1.49 (m, 3H), 1.80–1.89 (m, 2H), 4.40 (t, $J = 6.5$ Hz, 1H), 7.16–7.22 (m, 6H), 7.48–7.51 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9, 22.5, 28.2, 28.7, 28.9, 31.6, 36.9, 44.0, 127.8 (2C), 128.9 (4C), 130.3 (2C), 134.5 (4C). Anal. Calcd for $C_{20}H_{26}Se_2$: C, 56.61; H, 6.18. Found: C, 56.37; H, 6.03.
This procedure was followed for all the aldehydes listed in Table 1. As mentioned earlier, aliphatic aldehydes produced the corresponding selenoacetals (entries 1–7) and aromatic aldehydes provided aryl phenyl selenides (entries 8–15) or mixtures of aryl phenyl selenides and selenoacetals (entries 16–18). The known compounds (entries 8, 16 and 18) were identified by comparison of their spectral data with those reported (Table 1), and the new compounds (entries 1–7, 9–15 and 17) were properly characterized from their IR, ^1H NMR and ^{13}C NMR spectroscopic data and elemental analysis. The data for two representative compounds are presented below:
1,1-Diphenylselenobutane (entry 1): Yellow liquid; IR (neat): 1437, 1475, 1578 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (t, $J = 7.35$ Hz, 3H), 1.51–1.64 (m, 2H), 1.87–1.94 (m, 2H), 4.49 (t, $J = 6.60$ Hz, 1H), 7.24–7.30 (m, 6H), 7.56–7.59 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.2, 21.4, 43.7, 47.9, 127.8 (2C), 128.8 (4C), 130.2 (2C), 134.5 (4C). Anal. Calcd for $C_{16}H_{18}Se_2$: C, 52.19; H, 4.93. Found: C, 51.97; H, 4.88.
4-Methylthiophenylmethyl phenyl selenide (entry 9): Yellow solid, mp 55–57 °C; IR (KBr): 1438, 1475, 1577 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H), 4.06 (s, 2H), 7.08–7.24 (m, 7H), 7.41–7.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.6, 31.7, 126.6 (2C), 127.2, 128.3, 128.8 (2C), 129.2 (2C), 130.2, 133.5 (2C), 135.4. Anal. Calcd for $C_{14}H_{14}SSe$: C, 57.33; H, 4.81. Found: C, 57.25; H, 4.73.