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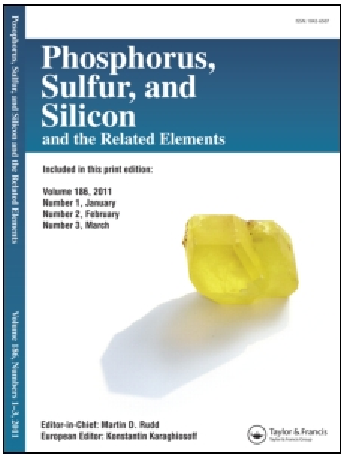

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Mixed Acetals as New Precursors for Selenium Electrophiles

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Mixed Acetals as New Precursors for Selenium Electrophiles

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A wide range of precursors for selenium electrophiles is already known, but the requirements for the development of polymer-bound selenium reagents are different. Herein we report mixed acetals as new precursor molecules for the synthesis of selenium electophiles under very mild reaction conditions. The use of $(MeOCH_2Se)_2$ allows a very fast access to these mixed acetals. Chiral precursor molecules can be synthesized as well and employed in efficient stereoselective selenenylation reactions.

Keywords: selenium electrophiles; mixed acetals; stereoselective synthesis

For three decades now, selenium reagents have attracted growing interest for their application in organic synthesis.[1] In particular, the oxidative functionalization of not or only slightly activated C=C -double bonds and the cyclisation of unsaturated alcohols, amines and carbonyl

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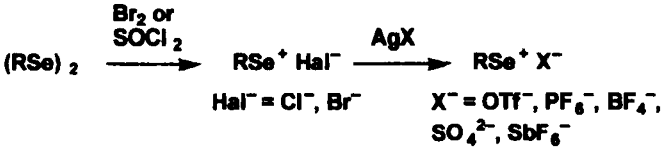
derivates offer a wide range of applications. Selenium electrophiles are highly potent for such transformations because of their high anti-Markovnikov selectivity, their mild reaction conditions as well as their ability to undergo a wide range of further reactions leading to even higher functionalized compounds.[2]

The most commonly employed selenium reagents are the seleneyl halides. Some of them are commercially available but because of their sensibility towards hydrolysis, more complex seleneyl halides are prepared easily in situ by addition of bromine or thionyl chloride to the corresponding diselenides as shown in Scheme 1. These halides can subsequently be converted to selenium electrophiles with other counter ions by addition of appropriate silver salts.



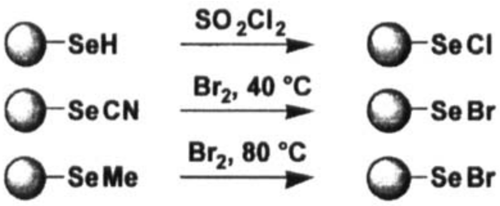
$$(RSe)_2 \xrightarrow{Br_2 \text{ or } SOCl_2} RSe^+\,Hal^- \xrightarrow{AgX} RSe^+\,X^-$$

$Hal^- = Cl^-, Br^-$

$X^- = OTf^-, PF_6^-, BF_4^-, SO_4^{2-}, SbF_6^-$

SCHEME 1. Synthesis of selenium electrophiles.

For the generation of selenium electrophiles on solid-support other precursors than the widely used diselenides have to be employed. Various precursor molecules have already been investigated and selenols,[3] selenocyanates,[4] as well as methylselenides[5] have been used to generate selenium electrophiles under relatively harsh reaction conditions as shown in Scheme 2.



SCHEME 2. Synthesis of selenium electrophiles on solid support.

We introduce now mixed acetals of type **1** as very versatile new precursor moieties for the generation of selenenyl bromides **2** under mild reaction conditions using bromine at 0 °C. Such derivatives have been synthesized previously,[6] but only been used for the synthesis of selenium-stabilized carbanions.[7] They can be prepared easily by MOM-protection of the selenols as shown in Scheme 3.[6] Additional synthetic approaches are based on treatment of the selenols with dimethylacetal or dihydropyrane in the presence of a Lewis acid.[8] Selenostannanes can be used as precursors by reaction either with dimethoxymethane and boron trifluoride etherate or with MOMCl and cesium fluoride.[9] But the introduction of the whole moiety in only one step is more straightforward. We therefore prepared the diselenide $MeOCH_2SeSeCH_2OMe$ **3** from Na_2Se_2 and MOMCl in 60 – 80% yield.[10] Diselenide **3** can react with lithiated aryl derivatives under direct formation of the corresponding mixed acetals **1**. The yields of this reaction are after optimization usually in the range of 70 – 85%.

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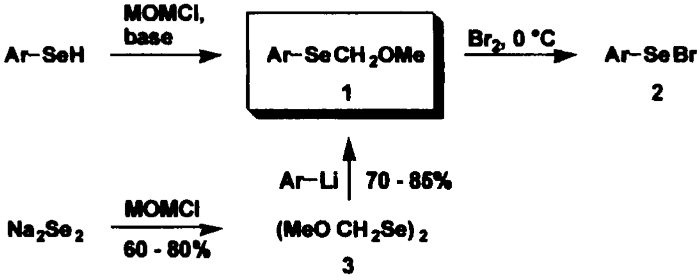

SCHEME 3. Synthesis of mixed acetals 1.

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The efficiency of the electrophile formation is high as the yields of the subsequent addition reactions are indicating. We have performed also the synthesis of a variety of chiral selenium electrophile precursors containing the mixed acetal moiety by reacting a lithiated compound with diselenide 3. We found that the purification of these compounds is much easier than of the corresponding diselenides and their stabilities are higher as well. The reactions of the selenium electrophiles generated from these precursors with alkenes are summarized in Scheme 4 and Table 1.

The methoxyselenenylation of styrene using the corresponding selenenyltriflates as electrophiles is still the most efficient reaction leading to products 6 in 87% *de*. However, the use of selenenylbromides as electrophilic reagents in selenocyclizations have been improved and the compounds 5 can be synthesized in up to 75% *de*.

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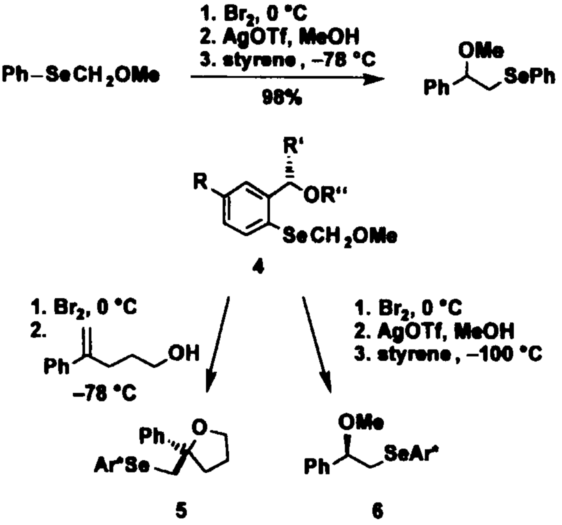

SCHEME 4. Reactions of selenium electropiles with alkenes.

TABLE 1. Selenenylations with electrophiles generated from 4.

R	R'	R''	product	(yield)	(*de*)[a]
H	Me	CH_2OMe	5	98%	53%
OMe	Me	H	5	26%	57%
OMe	Me	CH_2OMe	5	74%	75%
H	Et	H	6	65%	87%
OMe	Me	H	6	73%	87%

[a] Determined by HPLC after radical cleavage of the selenium moiety (*ee* of the cleavage product)

In conclusion, we have prepared mixed acetals in a one step synthesis using the diselenide $(MeOCH_2Se)_2$ 3. These compounds are

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new selenium electrophile precursor molecules. The corresponding electrophiles can be generated efficiently under mild reaction conditions (bromine, 0 °C). We showed that highly stereoselective addition reactions are possible using precursor molecules of type **4**. Investigations of employing this methodology in the preparation of polymer-bound electrophiles are currently performed in our laboratory.

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[10] 230 mg (10 mmol) sodium, 790 mg (10 mmol) selenium powder, and 128 mg (1 mmol) naphthaline were refluxed in 10 ml abs. THF under nitrogen for 7 h. After cooling to 0°C, 845 mg (10.5 mmol) chloromethyl methylether was added and the mixture treated in an ultrasonic bath for 12 h. The reaction mixture was quenched with 2 ml sat. aq. NH_4Cl, the organic solvent was removed in vacuo and the aqueous phase extracted with *tert.*-butyl methyl ether (3 x). Flash chromatography (*tert.*-butyl methyl ether: pentane 1:4) yielded 750 to 1000 mg (60-80%) **3** (yellow oil).Selected spectroscopic data: ^{1}H-NMR: δ (ppm) 5.31 (s, 4H), 3.40 (s, 6H). ^{13}C-NMR: δ (ppm) 76.7, 57.3. ^{77}Se-NMR: δ (ppm) 365.5. IR (NaCl) $\tilde{\nu}$ = 2989, 2926, 2817, 2002, 1445, 1416, 1260, 1179, 1083, 926, 868, 800 cm^{-1}. HRMS for $C_4H_{10}O_2Se_2$ calc. 249.9011 found 249.9015.