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N-Phenylselenosaccharin (NPSSac): a new electrophilic selenium-containing reagent

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Dedicated to Professor Marcello Tiecco in the occasion of his 70th birthday

Abstract—A new reagent *N*-phenylselenosaccharin (NPSSac) was simply prepared and used as a source of the electrophilic phenylselenyl group. This relatively stable new compound was able to react with a series of electron rich organic molecules like alkenes in the presence of external or internal nucleophiles, activated aromatic substrates, or enolizable carbonyl derivatives, under very mild experimental conditions.

It is well established that selenium-containing organic molecules allow chemo-, regio-, and stereoselective reactions to be effected under mild experimental conditions. Selenium can be introduced into an organic molecule, typically as a phenylselenyl group, as electrophile, nucleophile, or a radical. On the other hand, this heteroatom can be removed both by oxidation to selenoxide, which undergoes β-hydrogen abstraction and *syn*-elimination, or by the action of an appropriate reducing agent.[1] In the last two decades great attention has been devoted to find better sources of electrophilic selenium species. In particular, two different solutions were chosen, one that used direct sources of the PhSe group like phenylselenenyl chloride or bromide (PhSeX, X = Cl, Br), or *N*-phenylselenophthalimide (NPSP).[2] The other preferred to prepare in situ the electrophilic phenylselenium reagent by the oxidation of PhSeSePh with several oxidizing agents like ammonium persulfate,[3] hypervalent iodine species,[4] or metal-containing oxidizing agents.[5]

Unfortunately all of these methods have some peculiar disadvantages. For instance, in the addition reactions to alkenes, the halide anion can cause unfavorable competition with other nucleophiles. On the other hand, the acidity conditions generated in the preparations of electrophilic phenylselenium, sometimes match with the stability of the substrates.

In search of better reaction conditions, a particular but expensive silver salt, silver triflate (AgOTf), was frequently employed, to prepare in situ the highly electrophilic benzeneselenenyl triflate free from halide anions.[6] More recently, starting from chiral non racemic halogenated selenium reagent, the use of AgOTf allowed the production of the corresponding aryl selenenyl triflate.[7] Unlikely in many cases, the stoichiometric amount of trifluoromethanesulfonic acid formed, is not completely compatible with the stability of the materials employed.

In the light of these observations it should be of interest to find out new arylselenenylating agents, which are easy to prepare starting from more common starting materials, free from halogen anions and able to produce almost neutral reaction conditions. A good candidate capable of reaching these goals is the stable silver saccharin (AgSac)[8] that could react in principle, with any aryl selenenyl halide to produce the corresponding *N*-arylselenosaccharin and the AgX as completely insoluble salt. Thus as depicted in Scheme 1, we have realized this process starting from a slight excess of commercially available PhSeCl or PhSeBr, in anhydrous CH_2Cl_2 and using AgSacc as a source of Ag cations able to hide the halide anions. In the meantime the sulfonamide anion liberated is scarcely nucleophile and generated free saccharin, a very weak acid species.

Keywords: Selenium; Electrophilic selenenylation; Selenosaccharin; Addition reactions.
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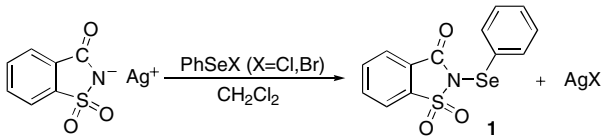


Scheme 1.

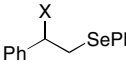
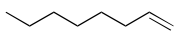
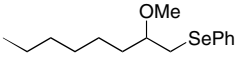
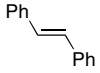
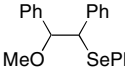
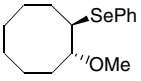
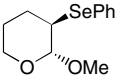
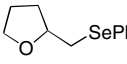
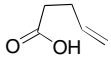
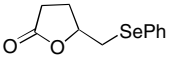
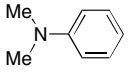
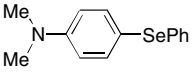
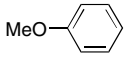
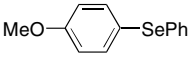
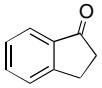
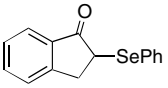
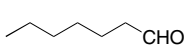
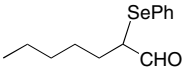
After filtration of the AgX formed, a pale yellow solution of *N*-phenylselenosaccharin (NPSSac) **1** was indeed recovered and used without any further manipulation, to promote a series of phenylselenenylation reactions.

In a parallel experiment a solution of our reagent in CH_2Cl_2 was evaporated and the solid separated, washed with cold and dry hexane to remove traces of PhSeSePh formed. The white solid recovered, dried under reduced pressure in the presence of P_2O_5, can be dissolved both in CH_2Cl_2, or in CH_3CN and used immediately or stored at −18 °C and employed in a successive experiment.[9]

The electrophilic character of compound **1** is also confirmed by the spectral data. The ^1H NMR spectra of NPSSac in CD_3CN shows the aromatic protons near selenium, at lower chemical shifts (0.3 ppm) with respect to those of PhSeSePh. Moreover, the ^{77}Se NMR of compound **1** shows a signal at 734 ppm with a deshielding of almost 300 ppm with respect to the ^{77}Se-resonance of PhSeSePh.

As reported in Table 1 a series of phenylselenenylation reactions of the electron-rich molecules have been carried out in very mild conditions. In particular we have found that all the transformations are described in Table 1, unless the experiment carried out using the azido anion as a nucleophile, entry 1, product **1c**, proceed with a higher conversion and good yields, when a catalytic amount (5%) of anhydrous camphorsulfonic acid was added. This acid probably facilitates the detachment of the electrophilic selenium from nitrogen and the consequent formation of the scarcely nucleophilic sulfonamide saccharin.

Table 1. Phenylselenenylation of electron rich molecules promoted by *N*-phenylselenosaccharin (NPSSac) at 25 °C

Entry	Substrate	Reaction products		Solvent/time (h)	Yield[a] (%)
1			X = OH **1a**	CH_2Cl_2/2	67[b]
			=OMe **1b**	CH_2Cl_2/1	93
			=N_3 **1c**	CH_3CN/8	75[b]
2			**2a**	CH_3CN/1	65[b]
3			**3a**	CH_2Cl_2/1	56[c]
4			**4a**	CH_2Cl_2/2	75
5			**5a**	CH_2Cl_2/2	65[d]
6			**6a**	CH_2Cl_2/1	92
7			**7a**	CH_2Cl_2/1	89
8			**8a**	CH_2Cl_2/3	87[e]
9			**9a**	CH_2Cl_2/3	80[e]
10			**10a**	CH_3CN/20	72
11			**11a**	CH_3CN/20	91

[a] Yields based on isolated products after flash chromatography.
[b] Reactions started at 0 °C; a 5:1 mixture of regioisomers was recovered.
[c] *Erythro*.
[d] In CH_3CN a 1:1 mixture of diastereoisomers was recovered (75% yield).
[e] Five percent by GC–MS analysis of the *ortho*-derivative was detected.

Briefly as reported in Table 1, using NPSSac, it is possible to functionalize terminal or internal olefins, entries from 1 to 5, in the presence of different nucleophiles like H_2O, MeOH or NaN_3, entry 1.

The cyclofunctionalization of alkenes bearing an internal nucleophiles (entries 6 and 7) or the phenylselenenylation of activated aromatic substrates (entries 8 and 9) were also realized in a high yield. Finally, the direct α-phenylselenenylation of an enolizable ketone or an aldehyde (entries 10 and 11) is possible, leaving these reactions running for a longer time, but still obtaining a high reaction conversion.[10,11]

The representative examples reported in this letter show the ability of our new reagent to produce the electrophilic PhSe group, starting from cheap and easily available materials like $AgNO_3$ and saccharin.[8] Moreover, the almost neutral reaction conditions generated can be adjusted on demand by adding a catalytic amount of camphorsulfonic acid.

It is important to observe that the properties and the reactivity of NPSSac are very similar to those showed by the commercially available *N*-phenylselenophthalimide (NPSP).[2] It is our opinion, however, that the silver salt of saccharin can potentially combine with all the alkyl- or aryl-selenyl chloride or bromide generated from the corresponding dialkyl- or diaryl-diselenide derivatives and for these reasons our method should be considered for wide applications in organic synthesis.

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9. *N*-Phenylselenosaccharin **1**: In a 150 ml RB 3-necked flask equipped with an argon inlet was placed phenylselenenyl chloride, (1.0 g, 5.2 mmol) dispersed in 3 ml of anhydrous hexane. Dry CH_2Cl_2 (20 ml) was then added and to this stirred solution, under Ar atmosphere, solid silver saccharin (1.45 g, 5.0 mmol) was added portionwise, at room temperature. The initial red brown solution decolorized and after 3 h stirring, a consistent amount of white AgCl was separated and a pale yellow solution appeared. As described in the test the precipitate can be filtered off and the resulting solution is ready for use. In order to better characterize NPSSac **1**, after the evaporation of the solvent, the solid obtained (1.3 g, 81% yield) was in part crystallized from a mixture of CH_2Cl_2–hexane to obtain a stable solid. Compound **1**: colorless crystals; mp 151–154 °C (dec); IR (CCl_4), cm^1: 3010 (w), 1747 (s), 1342 (s), 1180 (s); ^1H NMR (400 MHz, CD_3CN): $\delta = 8.05–7.90$ (m, 4H, aromatic nucleus of saccharin), 7.90–7.85 (m, 2H, *ortho*-aromatic PhSe), 7.67–7.63 (m, 3H, *meta*- and *para*-aromatic PhSe); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 160.0$ (s); 148.1 (s); 139.4 (s); 135.6 (d); 134.7 (d); 132.3 (d); 129.4 (d); 127.5 (s); 125.8 (d), 125.1 (d); 120.9 (d); ^{77}Se NMR (76.28 MHz, THF-d_8): $\delta = 734$.
10. The reactions described were carried out in CH_2Cl_2 or in CH_3CN on a 0.5 mmol scale. The external nucleophile was added in a slight excess (30%) referred to the amount of the starting material. Unless the preparation of the phenylseleno-azide starting from styrene, entry 1, product **1c**, all the reactions proceeded in the presence of 5% of camphorsulfonic acid. After the time indicated in Table 1 the reactions were quenched with water extracted with CH_2Cl_2 and washed with a dilute solution of sodium bicarbonate. The longer reaction time observed for both carbonyl derivatives, Table 1 entries **10** and **11**, is probably due to the initial equilibrium reaction that produces the more reactive, enol forms.
11. All the compounds are stable enough to be purified by standard flash chromatography, using a mixture of hexane–*tert*-butyl methyl ether as eluant. Products **1a**,[12] **1b**,[3] **1c**,[13] **2a**,[2] **3a**,[14] **4a**,[2] **5a**,[15] **6a**,[4] **7A**,[4] **8a**,[16] **9a**[17] and **11a**[18] have spectral data consistent with those previously reported. Compound **10a** is fully characterized.[19]
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18. Wang, W.; Wang, J.; Li, H. *Org. Lett.* **2004**, *6*, 2817–2820.
19. Physical data of compound **10a**: ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.80–7.20$ (m, 9H), 4.2 (dd, $J^1 = 7.6$ Hz, $J^2 = 2.7$ Hz, 1H), 3.65 (dd, $J^1 = 18.1$ Hz, $J^2 = 7.6$ Hz, 1H), 3.15 (dd, $J^1 = 18.1$ Hz, $J^2 = 2.7$ HZ, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 203.2 (s, C–O); 152.2 (s); 135.5; 135.3; 135.0; 129.0; 128.4; 127.7; 127.5; 126.2; 124.4; 43.3 (d); 35.1 (t); GC–EIMS: m/z 288 (M^+) (19), 207 (13), 157 (11), 131 (93), 103 (55), 77 (100), 51 (74). Anal. Calcd. for $C_{15}H_{12}OSe$: C, 62.72; H, 4.21. Found: C, 62.69; H, 4.25.