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Reaction of Dess–Martin periodinane with 2-(alkylselenyl)pyridines. Dehydration of primary alcohols under extraordinarily mild conditions

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ABSTRACT

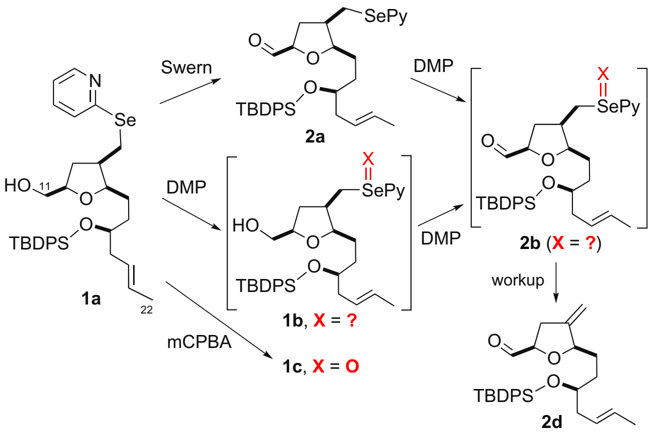
Dess–Martin periodinane oxidizes very rapidly 2-pyridylseleno derivatives RR′CHCH$_2$SePy in CHCl$_3$ or CH$_2$Cl$_2$ and more chemoselectively than mCPBA. Tetravalent selenanes, RR′CHCH$_2$Se(OAc)$_2$Py, seem to be formed. Treatment of these intermediates with aqueous NaHCO$_3$ gives rise to irreversible hydrolysis and elimination to terminal alkenes. As the OH/SePy exchange can be performed in minutes, the overall process is an exceptionally efficient procedure for the dehydration of primary alcohols.

In connection with a total synthesis of amphidinolide K,[1] the oxidation of the OH group of fragment C11–C22 (**1a**, Scheme 1) was required. Under standard Swern conditions[2] **2a** was obtained. However, to our initial surprise, the treatment of **1a** with Dess–Martin periodinane (DMP)[3] gave almost quantitatively a Se derivative (**1b**, the characterization of which will be explained below), which was not identical to the selenoxide (**1c**) we obtained as a major compound, among by-products, from **1a** and 3-chloroperoxybenzoic acid (mCPBA). A second equivalent of DMP was necessary to form the aldehyde at C11 (conversion of **1b** to **2b**); **2a** and DMP also gave **2b**, which could not be isolated but it gave an elimination product (**2d**) during the workup.

The equimolar reaction of the 2-pyridylseleno group (2-pyridylselenenyl, SePy) with DMP can be viewed as a simple redox process ($\mathrm{I^{V} + Se^{II} \rightarrow I^{III} + Se^{IV}}$). However, a search of the literature indicated that there is no precedent for the use of hypervalent iodine reagents for the oxidation of RSeAr or RSeHet.[4] There are, of course, many important studies on the preparation of SeAr derivatives,[5] their oxidation with peroxyacids or peroxides, and their *syn*-eliminations.[6]

From the TBS-monoprotected derivative of hexane-1,6-diol (**3**) and PySeSePy in toluene or CH$_2$Cl$_2$, we prepared quickly and quantitatively, at rt, 2-pyridylselenide **3a** by the addition of a solution of PMe$_3$ in toluene.[7] When the reaction of **3a** with DMP (Scheme 2) was monitored by ^{1}H NMR spectroscopy in CDCl$_3$, upfield and downfield shifts were noted for the acetoxy groups but neither Ac$_2$O nor AcOH was formed, as confirmed by the addition of small amounts into independent NMR tubes. The triplet of the CH$_2$ group close to the Se atom and the proton signals of the pyridine ring underwent downfield shifts, with broadening of some peaks. We supposed that an unstable species such as selenane **3b** had been formed.[8] Attempts to purify or isolate it from the reaction mixture accelerated its decomposition.

On the other hand, from **3a** and mCPBA, **3c** was obtained as the major compound, most NMR signals of which could be easily assigned from the final reaction mixture.[9] Intermediate **3c** gave **3d** on treatment with aq NaHCO$_3$. All these facts, which we hypothesized to occur as shown in Scheme 2, ran in parallel to those mentioned for **1a**.



Scheme 1. Oxidations of **1a**.

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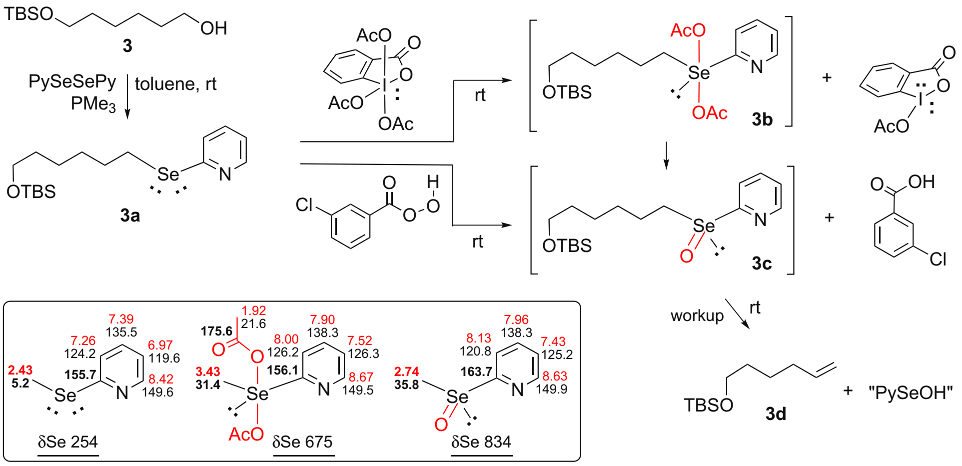


Scheme 2. Conversion, at rt, of **3a–d**. Relevant ^{1}H, ^{13}C and ^{77}Se NMR chemical shifts in $CDCl_3$ of model compounds.

To confirm or discard the initial formation of selenanes, we prepared PySeMe, which could simplify the NMR analysis of the reaction mixtures. Furthermore, its $PySe(OAc)_2Me$ and PySe(O)Me derivatives were expected to be more stable (at least, a β-elimination is not possible). The ^{77}Se NMR peak of PySeMe (254 ppm downfield to Me_2Se)[10] was shifted to 675 ppm when DMP was added, whereas it was shifted to 834 ppm with mCPBA (Scheme 2, bottom). The corresponding $^{1}H/^{13}C$/gCOSY/HSQC/HMBC NMR spectra were also different (see also Scheme 2). Everything pointed out that, in the reactions of SePy derivatives with DMP, λ^4 selenanes were the first noticeable intermediates.[11] Therefore, in Scheme 1, we believe that X means two magnetically equivalent AcO groups.

The trend of Se(IV) to be linked by single bonds to its ligands (rather than by double bonds) is paradigmatic and understandable for all elements down within each group of the periodic table. There seems that the two-electron transfer between I(V) and Se(II) eventually gives rise to the transfer of two AcO groups.

In this context, we carried out additional experiments to examine whether (1) the oxidation of SePy by DMP was more rapid or not than that of alcohols, (2) oxidizing agents other than peroxides and DMP could carry out the same transformation, (3) the SePy group is more suitable than SeAr groups, and (4) DMP has advantages or not in relation to peroxides.

With regard to question 1, we treated an equimolar mixture of alcohol **3** and its SePy derivative **3a** with 0.8 equiv of DMP. Only **3a** reacted to give **3b**, while the alcohol was recovered unchanged (see also the conversion of **1a** to **1b**).

Regarding question 2, standard oxidizing reagents such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and ammonium cerium(IV) nitrate (CAN), in moist or anhydrous CH_2Cl_2 or CH_3CN, did not affect the SePy group. IBX, a DMP precursor, did not react at all in CH_2Cl_2 (where it is insoluble) or in CH_3CN; even by heating **3a** and IBX (2.0 equiv) in Me_2SO-d_6 for 5 h at 50 °C, the conversion was very low (only a trace of **3d** was detected by TLC).[12] The Swern reagent (Me_2SO, ClCOCOCl), under standard conditions,[2] did not react with **3a** either.

Concerning question 3, in competition experiments between $PhCH_2CH_2CH_2SePy$ (see **4a**, in Table 1) and its SePh analogue ($PhCH_2CH_2CH_2SePh$) with a defect of DMP, only **4a** was oxidized. Its *o*-nitro derivative, $PhCH_2CH_2CH_2SeC_6H_4$(*o*-NO_2), [5] hardly reacted.[13] Thus, DMP reacts very selectively with SePy.

As far as question 4 is concerned, the reaction of SePy groups with H_2O_2 is not recommendable in general, since secondary reactions may occur.[14] Moreover, the reaction of **4a** with commercial mCPBA was slower than with DMP, under identical conditions. However, when mCPBA was previously purified (removing 3-chlorobenzoic acid), the reaction was completed as quickly as with DMP (ca. 30 min in $CDCl_3$). Thus, both the reagents are similarly useful for the oxidation of SePy. Nevertheless, a key point was to examine whether these oxidants are compatible or not with other sensitive groups, especially with double bonds prone to epoxidation.[15] When we treated a mixture of 0.10 mmol of **4a** and 0.10 mmol of cyclohexene with 0.10 mmol of pure mCPBA in a NMR tube in $CDCl_3$, at rt for a few minutes, 40% of **4a** was oxidized to **4b** while 50% of cyclohexene was converted to its epoxide.[16] Therefore, mCPBA does not distinguish between a cis-disubstituted double bond and the SePy group. In the cases of **1a** and **5a** we noted partial epoxidations of the double bonds with mCPBA. In sharp contrast, DMP reacts very selectively with the SePy group.

Not all the solvents were appropriate. At 0.1–0.2 M concentrations, with **3a** and 1.2 equiv of DMP, the reaction was completed in $CHCl_3$ in around 30 min and in CH_2Cl_2 within 50 min; in 9:1 CH_2Cl_2–toluene the reaction was slower, but still efficient. On the other hand, the oxidation process did not progress in THF, in CH_3CN, or in 1:1 CH_2Cl_2–pyridine, as if coordinating solvents interacted with the iodine atom of DMP, disturbing the approach of the SePy group.

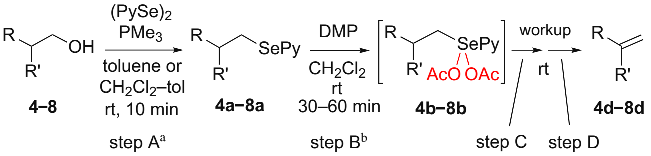
Treatment of **3b** with aqueous $NaHCO_3$ or Na_2CO_3, or with methanolic NEt_3, at rt, quickly gave the elimination product (**3d**). Most likely, **3b** is hydrolyzed to **3c**, which undergoes the known spontaneous *syn*-elimination to give **3d**, as indicated in Scheme 2.

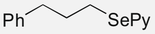
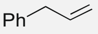
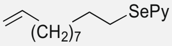
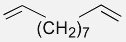
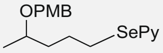
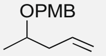
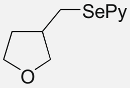
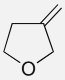
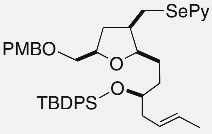
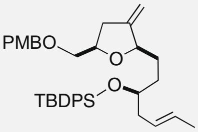
With the optimum conditions in hand, we investigated substrates **4a**–**8a**. Table 1 shows the results for SePy derivatives arising from primary alcohols, prepared by means of a simple reaction with PySeSePy and PMe_3 (which gives $O{=}PMe_3$ and PySeH as coproducts). In practice, 1.10 equiv of DMP was enough for a full conversion, but 1.20 equiv was added if the commercial sample had a purity <97% when checked by ^{1}H NMR. Without isolation, they were shaken with a slightly alkaline aqueous solution, as mentioned above. The organic layer contained only the alkene or unsaturated compound.

This very mild procedure can be applied to molecules containing C–C double bonds (entries 2 and 5), without precautions. As expected, the procedure was compatible with common protecting groups (see entries 3 and 5, as well as **1b**). Double bond isomerization was not observed in the case of entries 4 and 5.

In summary, after the conversion of primary alcohols to SePy derivatives with PySeSePy/PMe_3 in 90–98% yields, oxidation with DMP affords λ^4 selenanes. With a basic workup, they are hydro-

Table 1
From primary alcohols to alkenes or unsaturated compounds



Entry	SePy derivative	Yield, % step A	Alkene or unsaturated compd	Yield, % B–D
1	 **4a**	93	 **4d**	95
2	 **5a**	98	 **5d**	90
3	 **6a**	95	 **6d**	99
4	 **7a**	93	 **7d**	95[c]
5	 **8a**	98	 **8d**	95[d]

[a] Alcohols **4**–**8** (1.0 mmol) in toluene or CH$_2$Cl$_2$ (ca. 5 mL), a commercially available toluene solution of Me$_3$P (1.0 M, 1.2 mL), and a solution of PySeSePy in toluene or CH$_2$Cl$_2$ (1.1 mmol in 2.0 mL) were mixed at 0 °C or at rt. Stirring the mixture under Ar for 10 min, washing with water, and filtering through a small pad of silica gel, gave **4a**–**8a**.

[b] DMP (1.1–1.2 equiv) was added to the SePy derivative (0.20 mmol of **4a**–**8a**) in CH$_2$Cl$_2$ (1–2 mL). After stirring for 30–60 min at rt (or 1–2 h if the reaction was carried out in 9:1 CH$_2$Cl$_2$–toluene), TLC indicated that the substrate had been consumed. A vigorous stirring of the final solutions with aq NaHCO$_3$ for 10–60 min or shaking them strongly for a few minutes with aq Na$_2$CO$_3$ left pure organic solutions of **4d**–**8d**.

[c] Conversion percentage as observed by ^{1}H NMR (the product is too volatile to be isolated operating at 0.1–1.0 mmol scales).

[d] 2.0 equiv of DMP was used (step B) in this case.

lyzed and converted spontaneously in situ to olefins in 90–99% yields. The full process can be carried out at rt within 1 h (for the most simple cases) or 2 h. DMP can be considered an alternative to mCPBA (and to peroxides in general) that can be used in the presence of double bonds prone to epoxidation. Thus, a new application of DMP (not shared by DDQ, CAN or IBX) has been disclosed: it oxidizes SePy groups in the presence of alcohols and double bonds.

The overall process seems an academic exercise on red-ox reactions involving trivalent and pentavalent P, divalent and tetravalent Se, and pentavalent and trivalent iodine (three elements in a diagonal that is parallel to that of the borderline metals or semimetallic elements). In practice, we have discovered by accident the mildest procedure for the dehydration of primary alcohols reported to date, to the best of our knowledge.

Acknowledgments

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8. The involvement of a *N*-acetylpyridinium acetate of the selenoxide (instead of **3b**) was ruled out on the basis of the NMR spectra, as the well-known downfield shifts expected for all pyridine protons and β and γ carbons as well as upfield shifts of the α carbons, if a N-acylation had taken place, were not observed.
9. The protons of the CH$_2$ group linked to Se of **3a** (a triplet at δ 3.17) were split and appeared at 3.23 ppm (ddd) and 3.10 ppm (ddd), indicating that a new

stereocenter (Se) had been created (see **3c**). The carbon signal of that CH_2 was shifted from 25.8 to 50.4 ppm, while C2 and C3 of the pyridine ring were shifted from 155.7 and 125.4 ppm to 160.9 and 122.1 ppm, respectively.

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11. (a) There are few reported diarylselenium bis(carboxylates), cf.: Todo, H.; Miyagawa, N.; Yokoyama, M. *Chem. Lett.* **1992**, 1677–1678, and references therein. The ^{77}Se chemical shifts of PhSeMe (202 ppm), $PhSe(OAc)_2Me$ (658 ppm) and PhSe(=O)Me (832 ppm) are parallel to those obtained by us in the pyridine series (shown in Scheme 2). We also confirmed this pattern for other SePy derivatives not included here for the sake of simplification; e.g., $PySeCH_2CH_2Ph$ (347 ppm), $PySe(OAc)_2CH_2CH_2Ph$ (709 ppm) and $PySe(=O)CH_2CH_2Ph$ (853 ppm); for very recent, representative examples of tetrasubstituted Se compounds (λ^4 selenanes) of type $R_2Se(OR)_2$, see: (b) Back, T. G.; Kuzma, D.; Parvez, M. *J. Org. Chem.* **2005**, *70*, 9230–9236; (c) Back, T. G.; Moussa, Z.; Parvez, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1268–1270.
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13. As the deactivating electronic effect of the Py and 2-nitrophenyl groups on the Se oxidation should be similar, the reactivity differences may be attributed to the steric effect of the NO_2 group (which may hinder the approach required for the electronic transfer) and to the cooperation of the lone pair of the pyridine nitrogen atom in the chelation of the pentavalent iodine. This last statement is confirmed by the fact that SePy is oxidized more rapidly than SePh.
14. (a) In fact, Toshimitsu et al. (Ref. 6c) already reported that ozone was preferable to H_2O_2. In our hands, oxidation of **4a** with H_2O_2 was slow (even with a large excess and gentle stirring of the biphasic system); when after 2–3 h, aq $NaHCO_3$ was added to the reaction mixture, **4c** partially returned to **4a**. Related redox reactions, which look like disproportionations, were described with SePh groups, see: Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 1396–1403, and references therein (selenenic acid PhSeOH, formed partially by elimination from $RCH_2CH_2Se(O)Ph$, was oxidised to seleninic acid $PhSeO_2H$ while the selenoxide was reduced to RCH_2CH_2SePh); (b) it is also known that $ArSeO_2H$ (and their precursors ArSeSeAr/ArSeX) catalyse Baeyer–Villiger and epoxidation reactions of H_2O_2: Ten Brink, G.-J.; Fernandes, B. C. M.; Van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A., *J. Org. Chem.* **2001**, *66*, 2429–2433, and references therein; oxidations of SeAr groups with H_2O_2 have been clearly counter-indicated in some instances: (c) Blay, G.; Cardona, L.; Collado, A. M.; García, B.; Morcillo, V.; Pedro, J. R. *J. Org. Chem.* **2004**, *69*, 7294–7302 (significant epoxidation of the double bond of an unsaturated o-$NO_2C_6H_4Se$ derivative); (d) Lu, L.; Zhang, W.; Carter, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 7253–7255, and references therein (the o-$NO_2C_6H_4Se$ oxidation with peroxides proved problematic in complex molecules with sensitive groups).
15. For an over-oxidation in situ of the resulting elimination product (from a bis-o-$NO_2C_6H_4Se$ derivative) by the mCPBA excess, see: Blay, G.; Cardona, M. L.; García, B.; Pedro, J. R. *J. Org. Chem.* **1991**, *56*, 6172–6175.
16. As it could be expected, an excess of mCPBA (0.22 mmol) added to a mixture of **4a** (0.10 mmol) and cyclohexene (0.10 mmol) in $CDCl_3$, gave quantitatively, after the workup, both **4d** and cyclohexene epoxide.