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Oxidation of organoselenium compounds. A study of chemoselectivity of phenylacetone monooxygenase

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ABSTRACT

Organoselenium acetophenones oxidation using enzymatic reactions has been developed and chemoselectivity of phenylacetone monooxygenase (PAMO) with selenium-containing ketones has been explored. We discovered that this biocatalyst prefers selenium oxidation, which leads to selenoxide in excellent conversion, over Baeyer–Villiger oxidation.

1. Introduction

Organoselenium compounds are very useful synthetic tools in organic synthesis, they are regularly employed in the preparation of many organic compounds including natural products [1]. Among the various types of organoselenium compounds, selenoxides are frequently used as versatile intermediates. In addition, these compounds are known as mild oxidant reagents of several organic compounds oxidation (olefins, thiols, sulfides, phosphines, hydrazines, amines, alcohols, catechols) and selenoxide can also be used as catalysts in hydrogen peroxide activation for bromide anions oxidation [2]. Moreover, selenoxides that have a β-hydrogen atom suffer the well-known β-elimination reaction, which has been used to prepare alkenes and α,β-unsaturated ketones [3]. In the absence of a β-hydrogen atom, the selenoxide is stable and easily isolable.

Selenoxides are generally prepared from the corresponding selenides using common oxidants such as hydrogen peroxide [4], ozone [5], *tert*-butyl hydroperoxide [6], oxyridines [7], sodium metaperiodate [8], *m*-CPBA [9], (dichloroiodo)benzene [7], *N*-chlorosuccinimide [10], *tert*-butyl hypochloride [9] or nitrogen oxides [11]. These methods usually are carried out with great amounts of organic solvents [12]. Despite of the organoselenium compounds versatility, very few studies about the enzymatic oxidation of selenium have been published to date [13]. In addition, enzyme-catalyzed transformations are environmentally friendly reactions, due to their wide applications under mild conditions. An interesting class of enzymes that catalyzes a variety of oxidations are the Baeyer–Villiger monooxygenases (BVMOs): flavin-containing and NAD(P)H-dependent enzymes that catalyze the incorporation of one oxygen into organic substrates [14].

BVMOs are known to perform the aldehydes and ketones oxidation to their corresponding esters, the heteroatoms oxygenation (sulfur, phosphorus, nitrogen, boron, selenium) and even epoxidation reactions [15]. BVMOS have gained strong interest, mainly due to its high performance for selective oxidation [16]. One example is the chemoselective transformation of heterocyclic ketones into lactones leaving the hetoroatom (ex. sulfur) untouched [17]. Usually, sulfoxidation reaction is chosen as an easy model to evaluate the BVMOs activity [16]. Among the BVMOs, phenylacetone monooxygenase (PAMO) is a very interesting biocatalyst, which offers unique and attractive features such as thermostability and organic solvent tolerance [18]. Therefore, this study was aimed at evaluating the chemoselectivity of PAMO in organoselenium acetophenones biooxidation. In addition, another purpose of this study is also to determine the behavior of the selenium-containing ketones towards catalytic conditions using a monooxygenase.

2. Experimental

2.1. General

Oxidation reactions were performed using purified enzymes. Recombinant phenylacetone monooxygenase (PAMO) from *Thermobifida fusca* [19] was overexpressed and purified as previously described (gift from Prof. M.W. Fraaije) [20]. Glucose-6-phosphate

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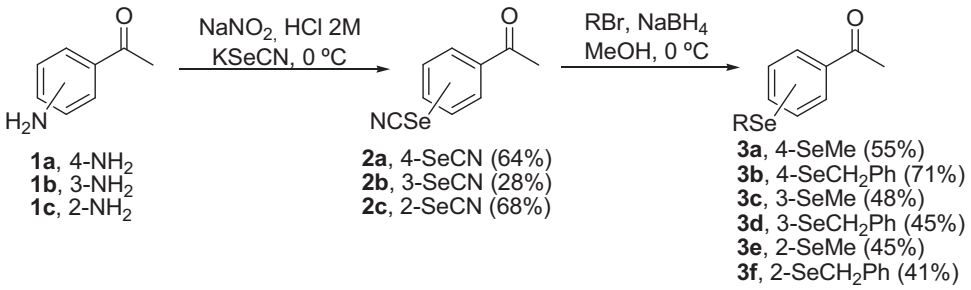


Scheme 1.

dehydrogenase from *Leuconostoc mesenteroides*, glucose-6-phosphate and NADPH were purchased from Sigma–Aldrich. The organoselenium acetophenones (**3a**–**f**) were synthesized as previously described [21].

2.2. General procedure for oxidation of the organoselenium acetophenones (*3a–f*) using monooxygenase (PAMO)

To an erlenmeyer flask (100 mL) containing the starting material solution (0.047 mmol in 190 μL of DMSO) was added Tris/Cl aqueous buffer at pH 9.0 (50 mM, 19 mL), glucose-6-phosphate (0.1 mmol), NADPH (0.002 mmol), glucose-6-phosphate dehydrogenase (0.62 mM) and PAMO (2.5 mM). Reactions were shaken at 30 °C for 24 h, and then extracted with dichloromethane (3 × 5 mL). The organic phase was dried over $MgSO_4$, and the solvent was evaporated under vacuum. The crude reaction was purified by preparative thin-layer chromatography (eluent: ethyl acetate).

2.3. General procedure for oxidation of the organoselenium acetophenones (*3a–f*) using sodium periodate [22]

Methanol (3 mL) and water (1 mL) were mixed in a 50 mL round-bottomed 5 flask containing organoselenium acetophenones (**3a**–**f**). The reaction was cooled at 0 °C and sodium periodate (1 mmol) was then added. The mixture was shaken at 0 °C for 1 h and dichloromethane (5 mL) was added, and the resulting solution 10 was washed with aqueous NaCl saturated solution (2 × 5 mL). The organic phase was dried over $MgSO_4$, and the solvent was evaporated under vacuum. The crude reaction was purified by preparative thin-layer chromatography (eluent: ethyl acetate) providing the desired product (65–90%).

2.3.1. 1-(4-(Methylseleninyl)phenyl)ethanone (*4a*), orange solid

^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.65 (s, 6H), 7.85 (d, J = 8.6 Hz, 2H), 8.11 (d, J = 8.6 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 26.74, 37.43, 125.79, 129.35, 139.45, 147.18, 197.03. HRMS [ESI(+)], calcd $[M+Na]^+$: 252.9744, found: 252.9735.

2.3.2. 1-(4-(Benzylseleninyl)phenyl)ethanone (*4b*), orange solid

^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.64 (s, 3H), 3.98 (d, J = 11.4 Hz, 1H), 4.23 (d, J = 11.4 Hz, 1H), 6.94–6.97 (m, 2H) 7.24–7.30 (m, 3H), 7.49 (d, J = 8.4, 2H), 7.99 (d, J = 8.4, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 26.76, 59.08, 125.30, 126.50, 128.71, 128.78, 139.40, 197.18. HRMS [ESI(+)], calcd $[M+H]^+$: 307.0237, found: 307.0233.

2.3.3. 1-(3-(Methylseleninyl)phenyl)ethanone (*4c*), orange oil

^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.67 (s, 6H), 7.65–7.72 (m, 1H), 30 7.98 (d, J = 7.2 Hz, 1H), 8.11 (d, J = 5.6 Hz, 1H), 8.30 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 26.74, 125.28, 129.75, 130.14, 130.97, 138.23, 196.77. HRMS [ESI(+)], calcd $[M+H]^+$: 230.9924, found: 230.9919.

2.3.4. 1-(3-(Benzylseleninyl)phenyl)ethanone (*4d*), orange oil

^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.51 (s, 3H), 3.95 (d, J = 11.4 35 Hz, 1H), 4.19 (d, J = 11.2 Hz, 1H), 6.88–6.93 (m, 2H), 7.21–7.27 (m, 3H), 7.52–7.61 (m, 2H), 7.81 (d, J = 0.8 Hz, 1H), 8.05 (dd, J = 1.6 and 5.6 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 26.59, 58.63, 126.02, 128.54, 129.44, 129.88, 130.30, 130.74, 137.58, 40 140.29, 196.74. HRMS [ESI(+)], calcd [M+H]+: 307.0237, found: 307.0241.

2.3.5. 1-(2-(Methylseleninyl)phenyl)ethanone (*4e*), orange solid

^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.72 (s, 6H), 7.68 (dt, J = 1.4 and 6.2 Hz, 1H), 7.90 (dt, J = 1.2 and 6.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 26.37, 38.33, 126.06, 130.76, 130.89, 134.67, 199.74. HRMS [ESI(+)], calcd [M+H]+: 230.9924, found: 230.9915.

2.3.6. 1-(2-(Benzylseleninyl)phenyl)ethanone (*4f*), orange solid

^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.70 (s, 3H), 4.02 (d, J = 11 Hz, 50 1H), 4.14 (d, J = 11 Hz, 1H), 7.06–7.18 (m, 5H), 7.55–7.7 (m, 2H), 7.94–8.1 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 26.45, 58.77, 127.13, 127.81, 128.12, 129.80, 130.54, 198.50. HRMS [ESI(+)], calcd [M+H]+: 307.0237, found: 307.0225.

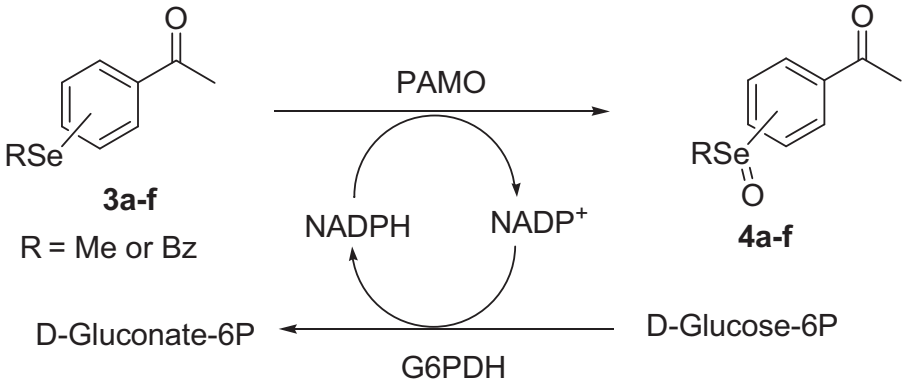
3. Results and discussion

Initially, in order to evaluate the chemoselectivity between selenium oxidation and Baeyer–Villiger (BV) oxidation catalyzed by PAMO, six selenium-containing acetophenones (**3a**–**f**) were selected as substrates. The organoselenium acetophenones (**3a**–**f**) were prepared from commercially available *ortho-*, *meta-* and *para-*amino-acetophenones (**1a**–**c**) (Scheme 1). The *in situ* preparation of diazonium salt from **1a**–**c** followed by the addition of KSeCN afforded the selenocyanate acetophenones (**2a**–**c**) (28–68%). Then, the alkylation of the selenium atom was carried out with $NaBH_4$ and the appropriate alkyl halide to give the organoselenium acetophenones (**3a**–**f**) (41–71%) [21].

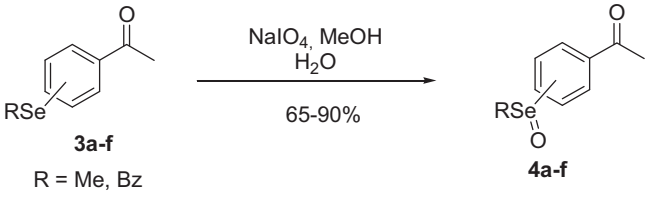
With organoselenium acetophenones in hands, we started the investigation on PAMO-catalyzed reactions (Scheme 2). The oxidation reactions were coupled to a second enzymatic reaction catalyzed by glucose-6-phosphate dehydrogenase (G6PDH), in order to regenerate the consumed NADPH [23]. All oxidations were carried out in a Tris/Cl aqueous buffer at pH 9.0 (Table 1). The buffer was saturated with oxygen for 5 min; otherwise the conversions would be low.

The organoselenium acetophenones (**3a**–**d**) oxidation reaction gave the corresponding selenoxides (**4a**–**d**) in high conversion after 24 h reactions. In all these reactions, PAMO was chemoselective by only catalyzing selenium oxidation, leaving the ketone moiety intact. While a NAD(P)H-regenerating system was employed, no product from a Baeyer–Villiger reaction was observed.

On the other hand, the PAMO-catalyzed reaction of 4-hydroxyacetophenone, which contains an electron donor group, yield ester (4-hydroxyphenyl acetate) in excellent conversion (>99%) (see supporting material). As the methylselane and

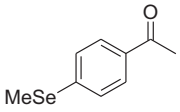
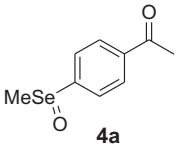
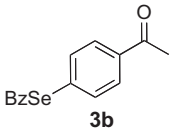
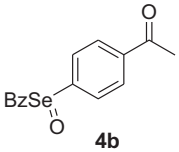
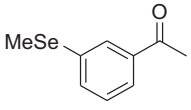
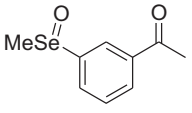
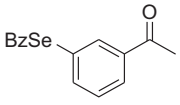
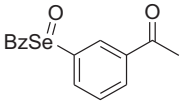
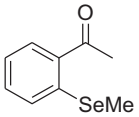
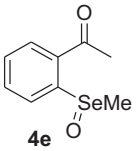
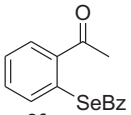
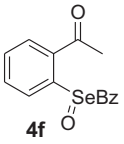


Scheme 2.



Scheme 3.

Table 1
Oxidation reaction of organoselenium acetophenones (**3a**–**f**) mediated by PAMO.[a]

Entry	Substrate	Product	Conversion (%)[b]
1	 **3a**	 **4a**	>99
2	 **3b**	 **4b**	>99
3	 **3c**	 **4c**	76
4	 **3d**	 **4d**	>99
5	 **3e**	 **4e**	(–)[c]
6	 **3f**	 **4f**	(–)[c]

[a] Reactions were carried out by using selenide **3a**–**f** (0.047 mmol in 190 μL of DMSO) in presence of Tris–HCl buffer at pH 9.0 (50 mM, 19 mL), G6P (0.1 mmol, 27 mg), NADPH (0.002 mmol, 1.6 mg), G6PDH (0.62 mM) and PAMO (2.5 mM).
[b] Conversion was measured by ^{1}H NMR (the reaction mixture was analyzed by NMR).
[c] No reaction was observed.

benzylselane groups are moderate electron donor groups, we expected that PAMO was able to oxidize the carbonyl group (BV-oxidation) instead selenium atom. However, PAMO easily transformed the selenium moieties into the corresponding selenoxides, which contain an electron-withdrawing group, preventing the subsequent BV-oxidation. When the starting materials were **3e** and **3f**, no reaction was observed. These results can be attributed to the proximity of the two moieties (organoselane and ketone group), which result in steric hindrance (Table 1, entries 5 and 6). Selenoxides leads to racemization process in the presence of water, even in basic condition. Therefore, we could not determine the enantiomeric excess value for those compounds [24].

We also performed the chemical oxidation of **3a**–**f** in order to obtain the organoselenoxides (**4a**–**f**). The oxidation of **3a**–**f** was carried out with sodium periodate, methanol and water at 0 °C, which led to the selenoxides in 65–90% yield (Scheme 3).

4. Conclusions

In conclusion, the present results demonstrate that oxidation mediated by PAMO is a good way to oxidize selenides to selenoxides from organoselenium acetophenones. The oxidation reactions were chemoselective and most of the conversions were very efficient (up to >99% conversion). This study provides a new enzyme-based approach to perform mild oxidation of selenium-containing compounds using aqueous medium and biocatalyst (monooxygenase).

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcatb.2011.07.018.

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