Organic LETTERS

Organoselenium-Catalyzed Mild Dehydration of Aldoximes: An Unexpected Practical Method for Organonitrile Synthesis

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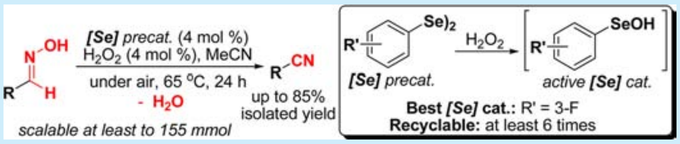
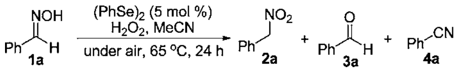
S *Supporting Information*



ABSTRACT: Areneselenenic acids (ArSeOH), readily generated from diaryl diselenides and H_2O_2 by in situ oxidation, were found to be effective and reusable catalysts for dehydration of aldoximes, leading to a practical and scalable preparation of useful organonitriles under mild conditions.

Organoselenium compounds have attracted much interest in synthetic chemistry not only because they are important reagents and synthons in organic, pharmaceutical, and natural product synthesis and materials science[1] but also because many of them exhibited significant biochemical and pharmaceutical activities, such as antitumor, antibacterial, antiaging, and antithyroid properties,[2] most possibly due to the fact that selenium is an ecofriendly element and a necessary trace element metabolizable in organisms.[3] Organoselenium compounds can also act as effective catalysts,[4−13] e.g., oxidation type reactions such as epoxidation,[4] dihydroxylation,[5] halohydroxylations,[6] and haloamidations of alkenes,[7] Baeyer−Villiger oxidation,[8] oxidation[9] and halogenation[10] of sp^2 and sp^3 C−H bonds, allylic amination,[11] and oxidation of amines,[12] as well as other types of reactions such as Diels−Alder, Baylis−Hillman, and thioacetalization reactions, etc.[1] In addition to developing novel methods for the synthesis and applications of useful organoselenium compounds,[14] we are also interested in organoselenium catalysis and recently reported a Baeyer−Villiger oxidation of methylenecyclobutanones and a dihydroxylation reaction of cyclohexene.[13] Herein we report the first organoselenium-catalyzed dehydration reaction of aldoximes, which can be readily conducted under mild conditions by using diaryl diselenides $(ArSe)_2$ and H_2O_2 as the effective and green precatalysts, providing a practical and scalable method for synthesis of useful organonitriles.[15]

Since organoselenium compounds are known to be good oxidation catalysts,[4−13] we initially attempted the oxidation of the readily available aldoximes intending to develop a new method for the synthesis of nitroalkanes because they are also a class of useful compounds in chemistry[16] and the known methods still have limitations such as production of undesired wastes.[17] Thus, benzaldoxime **1a** was first treated with aqueous H_2O_2 (30% w/w) under air in the presence of $(PhSe)_2$. Contrary to our expectations, the reaction gave no target phenylnitromethane **2a** but varying yields of benzaldehyde **3a** and benzonitrile **4a** instead (eq 1). Clearly, in addition to the usual hydrolysis of **1a** to **3a**, an aldoxime dehydration reaction also occurred to afford the unexpected nitrile **4a**. More interestingly, a higher yield of **4a** was obtained when a lower amount of H_2O_2 was used (eq 1, entry 3). Since aldoxime dehydration to nitriles was usually performed by using excess amounts of dehydrating reagents or under transition-metal catalysis,[18] this new finding led us to investigate the reaction to develop a greener and more practical method for organonitriles from the aldoximes.



(1)

entry	H_2O_2	**2a:3a:4a**
1	1 equiv	0:57:28
2	2 equiv	0:44:0
3	0.5 equiv	0:44:37

Based on our experience on organoselenium catalysis and to minimize potential byproduct formation due to high catalyst loadings,[13] catalytic activities of lower amounts of $(PhSe)_2$ and H_2O_2 were then investigated. The reaction of 1 mol % of $(PhSe)_2$ and 10 mol % of H_2O_2 indeed gave a much lower yield of **3a** and a slightly lower yield of **4a** (Table 1, entry 1). A detailed screening on precatalyst loadings was then undertaken,[19] showing that 4 mol % of both $(PhSe)_2$ and H_2O_2 could gave a rather good result (85% **4a**, entry 2). In contrast, no reaction occurred in the absence of $(PhSe)_2$ or H_2O_2 (entries 3 and 4), showing that they

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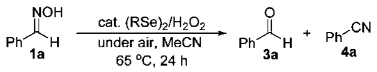
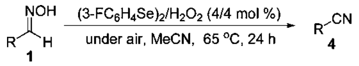
Table 1. Catalyst and Condition Optimization[a]



entry	$(PhSe)_2$ (mol %)	H_2O_2(mol %)	**3a**[b] (%)	**4a**[b] (%)
1	$(PhSe)_2$ (1)	10	16	25
2	**$(PhSe)_2$ (4)**	**4**	**7**	**85 (74)**
3	$(PhSe)_2$ (4)	0	0	0
4	$(PhSe)_2$ (0)	4	0	0
5	$(C_6H_5CH_2Se)_2$ (4)	4	9	50
6	$(c\text{-}C_6H_{11}Se)_2$ (4)	4	7	82
7	$(1\text{-}C_{10}H_7Se)_2$ (4)	4	8	34
8	$(4\text{-}MeOC_6H_4Se)_2$ (4)	4	7	65
9	$(4\text{-}Me_2NC_6H_4Se)_2$ (4)	4	7	23
10	$(3,5\text{-}(CF_3)_2C_6H_3Se)_2$ (4)	4	6	29
11	$(3\text{-}ClC_6H_4Se)_2$ (4)	4	8	72
12	$(2\text{-}FC_6H_4Se)_2$ (4)	4	7	58
13	$(4\text{-}FC_6H_4Se)_2$ (4)	4	9	73
14	**$(3\text{-}FC_6H_4Se)_2$ (4)**	**4**	**8**	**91 (81)**

[a] **1a** (5 mmol), a diselenide, and H_2O_2 (30% w/w aqueous solution) were stirred in commercial MeCN (5 mL) under air. [b] GC yields based on **1a** with biphenyl used as the internal standard. Isolated yields are shown in parentheses.

Table 2. Organoselenium-Catalyzed Aldoxime Dehydration Reaction for Organonitrile Synthesis[a]



entry	**1**: R	**4**: yield[b] (%)
1	**1a**: C_6H_5	**4a**: 81
2	**1b**: $4\text{-}FC_6H_4$	**4b**: 70
3	**1c**: $2\text{-}ClC_6H_4$	**4c**: 78
4	**1d**: $3\text{-}ClC_6H_4$	**4d**: 80
5	**1e**: $4\text{-}ClC_6H_4$	**4e**: 81
6	**1f**: $4\text{-}BrC_6H_4$	**4f**: 80
7	**1g**: $4\text{-}CF_3C_6H_4$	**4g**: 82
8	**1h**: $4\text{-}MeC_6H_4$	**4h**: 73
9	**1i**: $3\text{-}MeC_6H_4$	**4i**: 81
10	**1j**: $4\text{-}MeOC_6H_4$	**4j**: 76
11	**1k**: $4\text{-}t\text{-}BuC_6H_4$	**4k**: 74
12	**1l**: $1\text{-}C_{10}H_7$	**4l**: 82
13	**1m**: $4\text{-}CH_2{=}CHCH_2OC_6H_4$	**4m**: 66
14	**1n**: $2,4,6\text{-}Me_3C_6H_2$	**4n**: <5[c]
15[d]	**1o**: $n\text{-}C_6H_{13}$	**4o**: 85
16[d]	**1p**: $n\text{-}C_8H_{17}$	**4p**: 76
17	**1q**: $E\text{-}C_6H_5CH{=}CH$	**4q**: 71
18[e]	**1r**: *i*-Pr	**4r**: <5
19[e]	**1s**: $c\text{-}C_6H_{11}$	**4s**: <5
20[e]	**1t**: *t*-Bu	**4t**: <5

[a] **1** (5 mmol), $(3\text{-}FC_6H_4Se)_2/H_2O_2$ (0.2/0.2 mmol, 4/4 mol %) in commercial MeCN (5 mL) was stirred under air and monitored by TLC and/or GC. [b] Isolated yields based on **1**. [c] 85% aldehyde **3n** recovered. [d] 155 mmol scale. Nitriles purified by vacuum distillation. [e] Also tested at 80 °C. Aldoximes were recovered.

are both essential for the reaction and that a new organoselenium species may be generated as the active catalyst of the reaction. Screening on precatalyst loadings also showed that the $(PhSe)_2/H_2O_2$ ratio is crucial for the reaction, for other ratios gave only low to moderate yields of **4a**.[19]

We next investigated a series of diselenides to identify the best organoselenium precatalyst since different substitutents have been known to affect the catalyst's activity and reaction efficiency.[8] The readily available dialkyl diselenides with different electronic properties to $(PhSe)_2$ were first tested. Although $(PhCH_2Se)_2$ gave an inferior result compared to $(PhSe)_2$ (50%, entry 5), the slightly more bulky $(c\text{-}C_6H_{11}Se)_2$ gave a similar result with $(PhSe)_2$ (82%, entry 6). A more bulky $(1\text{-}C_{10}H_7Se)_2$ was then tested, but it gave a low yield of **4a** (34%, entry 7). We next investigated electron-rich and -deficient $(ArSe)_2$ with different substituents such as 4-methoxy, 4-amino, trifluoromethyl, 3-chloro, and 2- or 4-fluoro groups (entries 8−13). Unfortunately, these $(ArSe)_2$ only gave low to moderate yields of **4a** (23−73%), all lower than that of $(PhSe)_2$. To our surprise, the *meta*-fluoro analogue $(3\text{-}FC_6H_4Se)_2$ was found to be the best precatalyst, giving a high conversion of **1a** and a good isolated yield of **4a** (81%, entry 14). The reason for the higher catalytic activity of $(3\text{-}FC_6H_4Se)_2$ was not clear but may be attributed to fine-tuning of the electronic property of the phenyl ring by the *meta*-F group. As shown in the table, $(c\text{-}C_6H_{11}Se)_2$ and $(4\text{-}FC_6H_4Se)_2$ gave similar results to $(PhSe)_2$ and $(3\text{-}FC_6H_4Se)_2$, whereas other diselenides, either with sterically more bulky substituents or with substituents of strong electron-rich or -deficient properties, usually gave lower yields of **4a**. The optimal reaction (entry 14) was also tested under N_2 to give a similar result (83% **4a**),[19] revealing that air does not affect the reaction. Thus, the conditions and operation of the reactions can be simplified by being carried out under air.

$(3\text{-}FC_6H_4Se)_2$ and the optimized conditions were then employed to extend the scope of the reaction (Table 2). Like **1a** (entry 1), electron-deficient and -rich aromatic aldoximes, including those with slightly bulky *ortho*-substituents (entries 3, 12) and a terminal vinyl group (entry 13), reacted efficiently under the standard conditions to give moderate to good yields of the target nitriles (entries 2−13). In contrast, the more bulky 2,4,6-trimethylphenyl aldoxime **1n** gave aldehyde **3n** as the major product, with only a trace of **4n** detected (entry 14). In addition, primary aliphatic and vinylic aldoximes could also be dehydrated efficiently under the same conditions to give similarly good results (entries 15−17), showing a relatively high tolerance of the method. However, the reactions of secondary and tertiary aliphatic aldoximes **1r−t** were not successful even at a higher temperature, giving only a trace amount of the nitriles with recovery of the aldoximes (entries 18−20). The ineffective reactions of **1n,r−t** may be attributed to the bulky substituents that hindered the interaction of the substrates and catalyst, in analogy to the results of bulky catalysts (Table 1, entries 7, 10, and 11). It is noteworthy that although the reactions of aliphatic aldoximes were conducted on a much larger scale of 155 mmol (Table 2, entries 15 and 16), they were still very efficient under the standard conditions and afforded good yields of the nitriles by vacuum distillation,[19] showing the scalability and practicality of the present aldoxime dehydration method.

During the above studies, we also found that distillation of the reaction mixtures not only afforded good yields of the target aliphatic nitriles but also gave a deep yellow and sticky oily residue containing the nonvolatile organoselenium catalyst (Table 2, entries 15 and 16). Therefore, the possibility of catalyst recycling and reuse were investigated by recharging the freshly used flask containing the catalyst residue with a new quantity of aldoximes. As shown in Figure 1, in 25 mmol scale reactions of **1a**, **1b**, **1d**, or **1o** under the standard conditions, the organoselenium catalyst could be reactivated by H_2O_2[20] and then reused at least four to six times without obvious loss of its catalytic activity, affording moderate to good yields of **4a**, **4b**, **4d**,

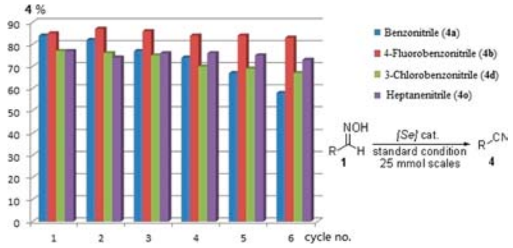
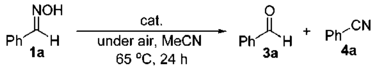


Figure 1. Organoselenium catalyst recovery and reuse in large scale reactions under the standard conditions.[19]

or **4o** in each cycle.[19] These results clearly revealed the recyclability of the organoselenium catalyst and high practicality of the method.

The active organoselenium catalyst and mechanism of this interesting aldoxime dehydration reaction were our next concern. Since equal amounts of $(ArSe)_2$ and H_2O_2 were found to be the best precatalyst, we believe areneselenenic acids (ArSeOH, **5**) that can be produced from diselenides via oxidation by H_2O_2[21] may be generated in situ as the active catalyst, but ArSeOH are also notoriously unstable compounds difficult to be obtained pure.[22] To certify this hypothesis and originally to develop more effective precatalysts, during catalyst screening we also tested alkyl phenyl selenides because PhSeOH is the side product of the well-known selenoxide *syn*-elimination reactions.[22,23] As shown in Table 3, model reactions of **1a** using *i*-PrSePh or EtSePh as the precatalysts indeed gave rather good yields of **4a** (entries 1 and 2), showing that PhSeOH, the selenoxide *syn*-elimination byproduct of *i*-PrSePh and EtSePh, is most possibly the active catalyst in the reaction. In contrast, incomplete reaction of *c*-C_6H_{11}SePh gave a much lower yield of **4a** (entry 3). These results showed a rate order of *i*-PrSePh > EtSePh > *c*-C_6H_{11}SePh in dehydration of **1a**, which in comparison is in good agreement with the rate order of selenoxide *syn*-elimination reactions of *i*-PrSePh > EtSePh > *c*-C_6H_{11}SePh (also the rate order of PhSeOH formation) as documented in the literature,[23a] further supporting that ArSeOH is indeed the active catalyst of the reaction. On the contrary, negative results were observed in the reactions of PhSePh, which is incapable of undergoing selenoxide *syn*-elimination (entry 4), $(PhS)_2$, $(PhTe)_2$, and other usual oxyacids containing no selenium (entries 5−7). Selenium as well as the in situ generated PhSeOH, but not other elements or the acidity of the acids, are clearly the key to facilitate an efficient aldoxime dehydration reaction, further excluding the possibility of a Bronsted acid catalyzed process. More interestingly, PhSeBr that can hydrolyze to afford PhSeOH could also catalyze the reaction efficiently in the presence of water (entry 8), whereas PhSeBr alone is not a good precatalyst, giving only a low yield of **4a** (entry 9). The results also indicated that PhSeOH, generated by hydrolysis of PhSeBr, rather than PhSeBr itself, should be a more active catalyst for the reaction.

Table 3. Determination of the Active Organoselenium Catalyst via Alternative Protocols[a]

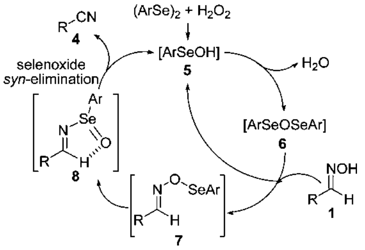


entry	catalysts (mol %)	3a[b] (%)	4a[b] (%)
1	*i*-PrSePh (8), H_2O_2 (8)	<3	87
2	EtSePh (8), H_2O_2 (8)	<3	79
3	*c*-C_6H_{11}SePh (8), H_2O_2 (8)	6	42
4	PhSePh (8), H_2O_2 (8)	5	9
5	$(PhS)_2$ (4), H_2O_2 (4)	5	6
6	$(PhTe)_2$ (4), H_2O_2 (4)	7	10
7[c]	other oxyacids (8)	<3	0
8	PhSeBr (8), H_2O (8)	15	81
9	PhSeBr (8)	11	38

[a] **1a** (5 mmol) and a catalyst were stirred in commercial MeCN (5 mL) under air. [b] GC yields based on **1a** with biphenyl used as the internal standard. [c] Oxyacids 4-$CH_3C_6H_4SO_3H$, AcOH, CF_3CO_2H, H_2SO_4 (50%), and CF_3SO_3H (15%) were tested.

A possible mechanism of the present aldoxime dehydration reaction is shown in Scheme 1. Thus, ArSeOH (**5**) may be generated from $(ArSe)_2$ via oxidation by H_2O_2,[21] which is then converted to the corresponding selenenic anhydride ArSeOSeAr (**6**). Then, **6** may react with aldoxime (**1**) to give a mixed anhydride **7**. We deduce **6** rather than **5** should be the more active species in this step because it has been well-documented that the unstable **5** can readily convert to **6** by self-condensation and **6** can also react with various nucleophiles effectively to regenerate **5** and condensation products.[22] In addition, the moisture-sensitive and more active PhSeBr, which should be more reactive than PhSeOH in condensation with **1**, showed a much lower catalytic activity than its hydrolysis product PhSeOH (Table 3, entries 8 and 9). This result explains that **6** was quickly formed as the more reactive organoselenium species. Upon formation of **7**, it may undergo a rearrangement to give its selenoxide isomer **8** to facilitate a selenoxide *syn*-elimination process to give product nitriles **4** and regenerate **5**. The key role of both PhSeOH and selenium observed in control reactions (Table 3) also supports that an elimination reaction of intermediate **8** analogous to the well-known selenoxide *syn*-elimination[22,23] most likely took place in the reaction. Although this mechanism remains to be fully clarified and alternative processes may also exist, Scheme 1 should be the most likely mechanism based on the above experimental findings and the related literatures.[21−23]

Scheme 1. Possible Mechanism for Organoselenium-Catalyzed Aldoxime Dehydration Reaction



In conclusion, we have developed a mild and simple aldoxime dehydration reaction by using recyclable organoselenium catalysts generated in situ from the readily available $(ArSe)_2$ and the green oxidant H_2O_2, which provided a practical and scalable new method for synthesis of the useful organonitriles form the readily available aldoximes. To our knowledge, this may be the first example of an organoselenium-catalyzed dehydration reaction. Deeper mechanistic studies and further extension of the present dehydration method are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, condition screening table, product characterization, and ^{1}H and ^{13}C NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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