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Synthesis of Selenoesters via Aldol Condensation and/or Conjugate Reduction and Their Antiviral Activities

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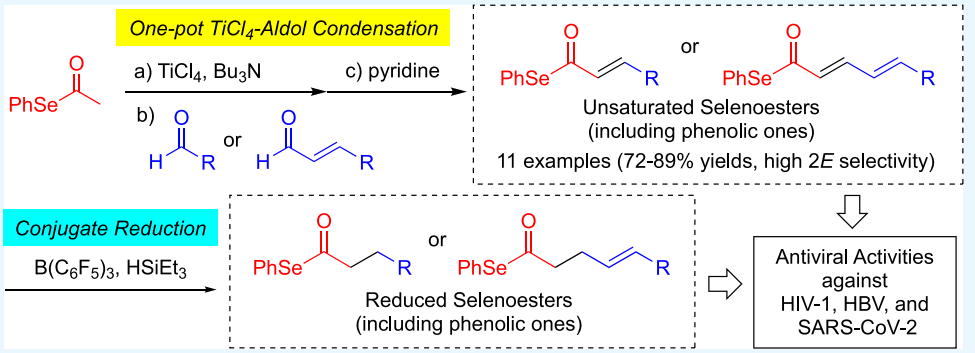

ABSTRACT: A variety of unsaturated selenoesters (including phenolic ones) were produced in good to high yields and with high *E*/*Z* ratios using $TiCl_4$-promoted aldol condensation between *Se*-phenyl selenoacetate and their respective aldehydes without aqueous workup. A representative phenolic unsaturated selenoester was applied to acylation of tyrosine methyl ester without protection of the phenolic hydroxy groups to furnish the corresponding amino acid conjugate. The conjugate reduction of the unsaturated selenoesters including phenolic ones and selenocoumarin with $HSiEt_3$ was catalyzed by $B(C_6F_5)_3$ to afford the corresponding saturated selenoesters in good to high yields. This method was also applicable to the reduction of a saturated selenoester to the corresponding *O*-silyl hemiselenoacetal in a high yield. Moreover, most acyclic unsaturated selenoesters were found to show good multiple antiviral activities against HIV-1, HBV, and SARS-CoV-2.

1. INTRODUCTION

Organoselenium compounds have been proven to have an array of biological activities such as being anti-inflammatory, antitumor, antimicrobial, and others.[1,2] The selenocysteine moiety included in glutathione peroxidase (GPx) helps to maintain a healthy redox status of cells and protects against cellular damage by reactive oxygen species (ROS).[2b] Cancer cells are more susceptible to compounds with Se than those without Se, and tumor drug-resistant cells have been easily targeted by combining selenium-containing compounds with conventional chemotherapeutic agents.[2c,2] Some organoselenium compounds have also been shown to be potent antiviral[2c] and antioxidant agents.[3] Selenoesters are one of the prominent classes of organoselenium compounds showcasing carbonic anhydrase (CA) inhibitory activity.[4] There have been limited reports on the potential antiviral activities of selenoesters.[2c,5] Thus, this forms part of the objectives of this research to investigate these potential prospects and to help increase the chemical space of potential antiviral especially anti-COVID-19 agents which could be crucial in the continuous global fight against the pandemic.

Another potential application of selenoesters is their use in the synthesis of amino acid conjugates via amidation.[2a] The introduction of polyhydroxy unsaturated groups such as a catechol group with an unsaturated aliphatic arm to amino acids such as tyrosine and cysteine via amidation has been shown to be a good strategy for the synergistic antioxidant effect of the resulting amino acid conjugates.[6]

We recently reported the one-pot synthesis of multi-unsaturated thioesters mainly dienyl and trienyl thioesters via the $TiCl_4$-promoted aldol condensation between *S*-aryl thioacetate and an enal or dienal (Scheme 1a).[7a] Prior to this recent report, we had successfully developed the one-pot synthesis of *β*,*β*-disubstituted *α*,*β*-unsaturated ketones or thioesters via the $TiCl_4$-promoted aldol condensation between simple ketones or between ketones and *S*-phenyl thioacetate and their subsequent conjugate reduction.[7b] In light of the success of this synthetic approach especially to unsaturated thioesters, we decided to apply this method in the synthesis of

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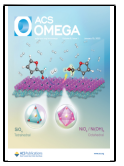

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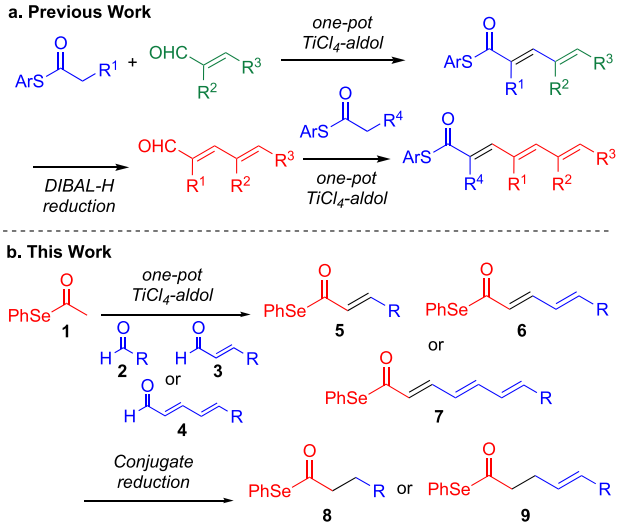
Scheme 1. $TiCl_4$-Promoted Aldol Condensation for the Synthesis of Unsaturated Thioesters and Selenoesters



its close chalcogen relative derivatives, unsaturated selenoesters **5**−**7**. This was followed by the conjugate reduction of unsaturated selenoesters **5** and **6** to obtain the corresponding reduced selenoesters **7** and **8**, respectively (Scheme 1b). Selenoesters are generally prepared from the corresponding selenol and acyl donors.[8] Rather surprisingly, no work has been done on the synthesis of unsaturated selenoesters and their corresponding saturated selenoesters with aliphatic or aryl terminal using aldol condensation and conjugate reduction, respectively.

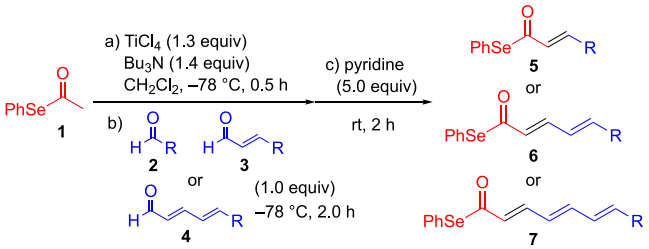
Herein, we report the use of the $TiCl_4$-promoted aldol condensation method to obtain various α,β-unsaturated selenoesters and the subsequent conjugate reduction with Et_3SiH as a reductant and $B(C_6F_5)_3$ as a catalyst to give their saturated counterparts. These selenoesters have been shown to have good antiviral activities against HIV-1, HBV, and COVID-19 for the first time.

2. RESULTS AND DISCUSSION

A variety of unsaturated selenoesters **5**−**7** were successfully synthesized via the $TiCl_4$-promoted aldol condensation of *Se*-phenyl selenoacetate (**1**) with their corresponding aldehyde **2**, enal **3**, and dienal **4**. The method consists of three steps: formation of a Ti-enolate intermediate from **1** with $TiCl_4$ and Bu_3N, aldolization with aldehyde **2**−**4**, and elimination of oxytitanium species from the titanium aldolate intermediate. The addition of pyridine is a key to promote the last elimination step. The reaction and workup procedure are as reported in our previous report on the synthesis of unsaturated thioesters.[7a] The products were obtained by column chromatography in 76 to 89% yields and with a 2*E*/2*Z* ratio of 97:3 to 100:0 (Table 1). A gram-scale synthesis of compound **5a** also gave 88% yield (see the Supporting Information).

The next step was to verify the feasibility of this method in the synthesis of phenolic selenoesters. We initially expected that the aldolization step proceeded faster than the protonation of the Ti-enolate intermediate by the hydroxy group, but the reaction was unsuccessful. We therefore tried to protect the hydroxy group(s) with methoxymethyl (MOM) groups and found that the $TiCl_4$-promoted aldol condensation proceeded well. However, an attempt to deprotect the MOM group(s) under the standard deprotection conditions (HCl in methanol) resulted in decomposition of the selenoester. This prompted us to develop a tentative protection method using Me_3SiCl and Bu_3N. By virtue of the fact that the Ti-aldol condensation method is compatible with trialkylammonium salts, phenolic aldehydes **2b**−**c** and enal **3f** were protected with Me_3SiCl (1.3 equiv) and Bu_3N (1.4 equiv) in a different flask and were subjected without isolation to the *Se*-phenyl selenoacetate-derived Ti-enolate. This was followed by treatment with pyridine for the elimination step to afford monoenyl selenoester products **5b**−**c** and dienyl selenoester product **6f** in 72−84% yields after purification by column chromatography. The Me_3Si groups were deprotected during the workup. Similarly, catecholic aldehyde **2d** was also tentatively protected by this method but with the use of Me_3SiCl (4.0 equiv) and Et_3N (4.0 equiv) instead of Bu_3N and successfully converted to its corresponding monoenyl selenoester **5d** in 83% yield (Table 2). In this case, Et_3N gave better results compared to Bu_3N. We speculate that the steric bulkiness of Bu_3N hinders the silylation of the second hydroxy group of the catechol after

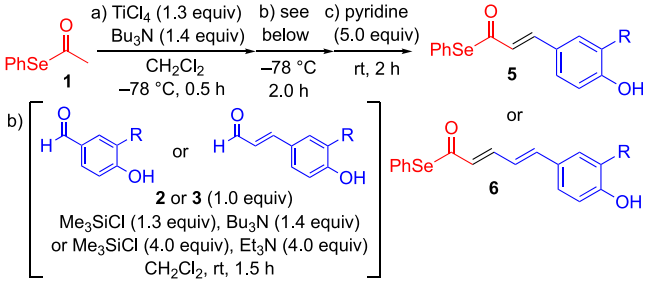
Table 1. $TiCl_4$-Promoted Aldol Condensation of *Se*-Phenyl *Se*lenoacetate with Benzaldehyde, Enals, or Dienal



entry	2−4	R	5−7	yield (%)[a]	2E/2Z
1	**2a**	Ph	**5a**	87	100:0
2	**3a**	Ph	**6a**	78	98:2
3	**3b**	4-MeC_6H_4	**6b**	88	97:3
4	**3c**	4-$MeOC_6H_4$	**6c**	85	97:3
5	**3d**	4-BrC_6H_4	**6d**	89	98:2
6	**3e**	4-$NO_2C_6H_4$	**6e**	76	97:3
7	**4a**	Ph	**7a**	77	98:2

[a]Isolated yields.

Table 2. $TiCl_4$-Promoted Aldol Condensation of *Se*-Phenyl *Se*lenoacetate with Phenolic Aldehydes



entry	2 or 3	R	5 or 6	yield (%)[a]	2E/2Z
1	**2b**	H	**5b**	72	100:0
2	**2c**	OMe	**5c**	78	100:0
3	**2d**	OH	**5d**	83	100:0
4	**3f**	OMe	**6f**	84	97:3

[a]Isolated yields.

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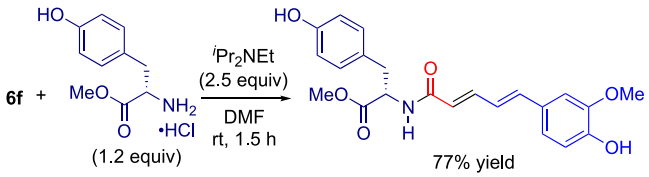
the silylation of the first hydroxy group, thus leading to lower yields of the final product **5d**.

The dienyl phenolic selenoester **6f** served as a good acyl donor in amidation with tyrosine methyl ester without protection of the phenolic hydroxy groups to give the respective amino acid conjugate in 77% yield (Scheme 2).

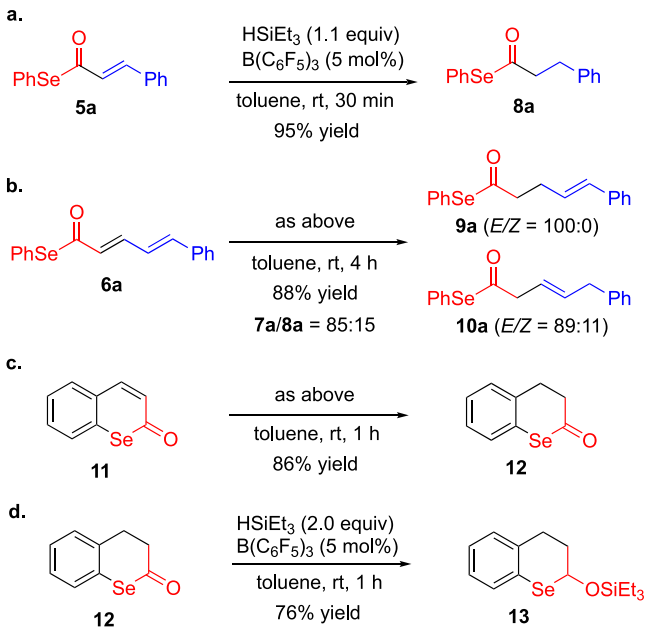
Scheme 2. Acylation of Tyrosine Methyl Ester with 6f



The resulting amino acid conjugate is anticipated to be a potential antioxidant by virtue of its phenolic groups and dienyl moiety and also because similar phenolic cinnamoyl tyrosine was reported to have high antioxidant activity.[6] Thus, unsaturated selenoesters are potentially applicable to peptide acylation such as native chemical ligation.[9]

We next explored the conjugate reduction of the *α,β*-unsaturated selenoesters to extend the chemical space of the selenoesters. According to our previous report on the reaction of enones,[10] the conjugate reduction of **5a** using $HSiCl_3$ and Lewis base catalyst was first investigated, but the reaction failed. This might have been due to the relatively lower Lewis basicity of the carbonyl oxygen of **5a** compared to that of enones. Therefore, several other methods of conjugate reduction were examined. It then turned out that the method using $HSiEt_3$ as a reductant and $B(C_6F_5)_3$ as a catalyst, reported by Piers and coworkers,[11] successfully gave saturated selenoester **8a** in 95% yield (Scheme 3a). The dienyl selenoester **6a** was also successfully reacted under the same conditions to afford **9a** and **10a** in 88% yield as a mixture of 1,4- and 1,6-reduction products in an 85 to 15 ratio (Scheme 3b). In addition, this method was also found to be applicable

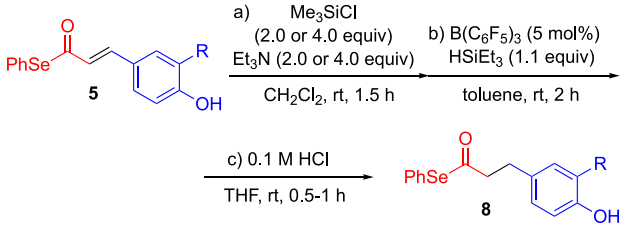
Scheme 3. Reduction of Selenoester 5a, 6a, Selenocoumarin 11, and Dihydroselenocoumarin 12



to the reduction of selenocoumarin (**11**), establishing a practical method for the synthesis of dihydroselenocoumarin[12] (**12**) (Scheme 3c). We further made a finding that hydrosilylation of selenoesters with Et_3SiH as the reductant and $B(C_6F_5)_3$ as the catalyst gave the corresponding selenoacetals, as shown in Scheme 3d. To our knowledge, this is the first example of the synthesis of *O*-silyl hemiselenoacetals by the reduction of selenoesters.[13] The synthetic potential of silicon enolate intermediates of the conjugate reduction as well as the biological activity of selenoacetals are currently under investigation.

Subsequently, we investigated the conjugate reduction of the phenolic cinnamoyl selenoesters **5b–d** under the above conditions. However, we faced the challenge of the presence of hydroxy groups again, even though we expected that silylation of hydroxy groups[14] would proceed faster than the conjugate reduction.[15] Thus, we investigated the tentative protection of the hydroxy group **5b–d** with Me_3SiCl and Et_3N (Table 3). Unlike Ti-aldol condensation, the ammonium salt

Table 3. Conjugate Reduction of Phenolic Cinnamoyl Selenoesters with Tentative Protection of Hydroxy Group(s)



entry	5	R	8	yield (%)[c]
1[a]	**5b**	H	**8b**	82
2[a]	**5c**	OMe	**8c**	82
3[b]	**5d**	OH	**8d**	46

[a]With Me_3SiCl (2.0 equiv) and Et_3N (2.0 equiv). [b]With Me_3SiCl (4.0 equiv) and Et_3N (4.0 equiv). [c]Isolated yields.

was incompatible to the reduction conditions. Thus, after treatment with Me_3SiCl and Et_3N, the mixture was passed through a short column of deactivated silica gel, and the eluent was concentrated under vacuum and subjected to the $B(C_6F_5)_3$-catalyzed conjugate reduction. After the acidic workup, the corresponding saturated selenoesters **8b–d** were obtained in good to high yields (Table 3).

Finally, the antiviral activity of some representative selenoesters against HIV-1, SARS-CoV-2, and Hepatitis B viruses (HBV) were investigated using the MTT [3-(4,5-dimetylthiazol-2-yl)-2,5-diphenyltetrazolium bromide],[16] WST-8 [2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2*H*-tetrazolium monosodium salt],[17] and PCR (polymerase chain reaction)[18] assays, respectively (see Table 4 and Supporting Information). Abacavir and lamivudine served as the reference standards for the anti-HIV-1 bioassay and remdesivir and lopinavir as the reference standards for the anti-SARS-CoV-2 bioassay. To our delight, all the tested selenoesters were found to exert antiviral activities. Especially, compound **5a** had the highest or the second highest activities for all viruses with comparable potencies to the reference standards. Compounds **5c**, **6a**, and **6c** also had similar high activities to HIV-1.[19,20] Compound **6f** exhibited the highest activity to SARS-CoV-2 with compounds **5c** and

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Table 4. Antiviral Activities of Representative Selenoesters against HIV-1, SARS-CoV-2, and Hepatitis B Virus

selenoester	anti-HIV-1_{LAI} activity ($EC_{50}/\mu M$)	cytotoxicity[a] ($CC_{50}/\mu M$)	anti-SARS-CoV-2 activity ($EC_{50}/\mu M$)	cytotoxicity[b] ($CC_{50}/\mu M$)	anti-HBV activity ($EC_{50}/\mu M$)	cytotoxicity[c] ($CC_{50}/\mu M$)
5a	3.1 ± 0.2	33.2 ± 1.7	5.7 ± 0.4	97.0 ± 1.6	1.6 ± 0.5	>100
5b	4.5 ± 0.4	33.7 ± 0.6	12.8 ± 0.1	>100	7.4 ± 0.3	>100
5c	3.3 ± 0.1	35.1 ± 0.0	7.3 ± 1.8	>100	19.7 ± 1.8	>100
5d	7.3 ± 0.5	33.4 ± 0.2	7.7 ± 0.2	>100	2.4 ± 0.8	>100
6a	2.9 ± 0.1	29.5 ± 1.9	18.5 ± 2.9	99.4 ± 1.3	16.3 ± 0.7	>100
6b	4.3 ± 0.3	32.9 ± 1.0	11.3 ± 1.5	>100	3.7 ± 1.4	>100
6c	3.4 ± 0.3	28.5 ± 0.3	11.2 ± 0.5	>100	32.0 ± 4.6	>100
6d	6.5 ± 0.8	29.5 ± 0.2	9.9 ± 2.8	>100	6.7 ± 1.8	>100
6e	6.7 ± 0.2	29.3 ± 0.1	12.3 ± 3.2	88.2 ± 6.6	4.2 ± 0.4	>100
6f	6.9 ± 0.9	31.9 ± 0.9	5.3 ± 1.0	>100	6.3 ± 0.1	>100
8a	8.7 ± 1.1	34.7 ± 0.5	17.9 ± 1.9	>100	2.8 ± 0.3	>100
11	>100	>100	>100	>100	>50	>100
12	>100	>100	>100	>100	>50	>100
abacavir	2.6 ± 0.5	>100				
lamivudine	3.1 ± 0.2	>100				
remdesivir			1.9 ± 0.3	>100		
lopinavir			>100	>100		

[a]Against MT-2 cells. [b]Against VeroE6 cells. [c]Against HepG 2.2.15 cells.

5d following suit with comparable activities to the same virus. Compounds **5d**, **6b**, and **8a** had high activities to HBV. Interestingly, both selenocoumarin (**11**) and the dihydroselenocoumarin (**12**) had no antiviral potency to all viruses.[21]

Cytotoxicity studies of the selenoesters against the target cells for these antiviral bioassays were also conducted and the selenoesters showed no significant or low cytotoxicities to the cells (Table 4). The selenoesters also proved to be less cytotoxic to other crucial cell lines such as the human hepatocyte-derived cell lines (HLE and Li-7) and the human kidney-derived cell line (HEK-293) via the MTT bioassay or WST-8 bioassay (see Supporting Information, Table S1).

The presence of a cinnamoyl moiety could be required for higher antiviral activity in almost all three cases as proved from the comparison of the antiviral activities of selenoester **5a** to its corresponding reduced and saturated selenoester **8a** (aside from the results of **8a** against HBV compared to other selenoesters). In addition, the fact that the selenocoumarins were inactive against all viruses demonstrates the relevance of an acyclic unsaturated group for antiviral activity. For anti-SARS-CoV-2 activity, the presence of a catechol or vanillin-derived unsaturated group could be pivotal as evidenced from the results of **6f**, **5c**, and **5d** in that respective order of potency.[22] Interestingly, when we evaluated the antiviral activity of compound **5a** against five infectious SARS-CoV-2 variants of concern (VOCs; Alpha, Beta, Gamma, Delta, and Omicron/BA.5), compound **5a** showed comparable antiviral activity against Alpha and Delta variants to that against the wild-type Wuhan strain (see Supporting Information Table S2). However, compound **5a** had a decreased activity against certain variants (such as Beta, Gamma, and Omicron/BA.5) which have immune escape amino acid mutations in the receptor binding domain (RBD; such as K417N/T and E484K/A mutations) of viral Spike protein and less susceptible to the neutralization antibody elicited by SARS-CoV-2 Wuhan-based mRNA vaccination, suggesting that compound **5a** possibly binds to the RBD of SARS-CoV-2 Spike protein and exerts a protective effect against SARS-CoV-2 infection to the target cells, as the neutralization antibody does. Further evaluation regarding this finding will provide new insight into the understanding of the novel antiviral mechanism and optimization of compounds. Further studies are being continued to arrive at some deductions of the possible SAR of the selenoesters for anti-HBV activity.[23]

3. CONCLUSIONS

In summary, we have demonstrated that unsaturated and saturated selenoesters (including the phenolic ones) can be made readily available via $TiCl_4$-promoted aldol condensation and conjugate reduction methods. This is the first time selenoesters are being produced by these two methods. They hold valuable synthetic applications and are potentially bioactive against HIV-1, SARS-CoV-2, and HBV. With the selenoester **5a** being the most potent against all three viruses, extended studies are intended to be continued to explore the possible SAR of the selenoester phenyl ring of **5a** using electron-donating and electron-withdrawing groups. Further studies are also to be continued to elucidate further the molecular mechanisms for the antiviral activities and to explore other possible synthetic utilities and bioactivities of the selenoesters.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c06784.

Experimental procedures; ^1H and ^{13}C NMR spectra of new compounds; and bioassay procedures (PDF)

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Author Contributions

A.B. designed and synthesized molecules, performed the compound characterization, and co-wrote the manuscript. M.A. performed the antiviral bioassays and cytotoxicity tests and co-wrote the manuscript. M.S. supervised the design, synthesis, and characterization of molecules and co-wrote the manuscript.

Notes

The authors declare no competing financial interest.

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