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Catalyst and Additive-Free Selective Ring-Opening Selenocyanation of Heterocycles with Elemental Selenium and TMSCN

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Abstract: A catalyst and additive-free strategy for selective ring-opening selenocyanation of saturated heterocycles with elemental selenium and TMSCN is developed, affording a series of aliphatic selenocyanates and selenaheterocycles. In the case of unprotected unstrained N-heterocycles, the reactions offer ammonium selenonitriles that prove to be an efficient selenonitrile reagent.

Keywords: Ring-Opening; Selenocyanation; Heterocycles; Elemental Selenium; Radical

Ring-opening reactions of readily available saturated heterocycles based on C-heteroatom bond cleavage have emerged as a powerful strategy to construct valuable scaffolds in past decades. In particular, ring-opening reactions of small saturated heterocycles[1] and bridged heterocycles[2,3] have been extensively investigated, mainly because their huge ring strain can significantly derive ring-opening to proceed. The most successful small heterocycles employed in ring-opening reactions have been the epoxides[1a,b,c,d,4] and aziridines,[1a,h,i,5] which can be subjected to the attack from a series of nucleophilic reagents to furnish aliphatic alcohols and amines respectively. Nevertheless, C-heteroatom bond cleavage in five- or six-membered rings is usually a rather challenging task due to their negligible ring strain.[6]

Aliphatic selenocyanates have found many important applications in organic synthesis,[7] halide receptors[8] and pharmaceutical (Figure 1).[9] In contrast, the reported approaches to access aliphatic selenocyanates remained rare. The most common method for the preparation of aliphatic selenocyanates relied on nucleophilic displacement of electrophilic reagents such as alkyl halides and tosylates with KSeCN (Scheme 1a).[10] However, KSeCN is easily deliquescent and poorly soluble in most organic solvents. Obviously, the present synthetic methods are completely inadequate to meet the increasing demand for versatile aliphatic selenocyanates Elemental selenium will undoubtedly be an attractive surrogate of KSeCN due to its storage stability, cheapness, commercial availability and ease of handling. Herein, we disclose a strategy for the selective ring-opening reaction of saturated heterocycles with elemental selenium and TMSCN under catalyst and additive-free conditions, unlocking a facile route to aliphatic selenocyanates as well as selenium-containing heterocycles (Scheme 1b).

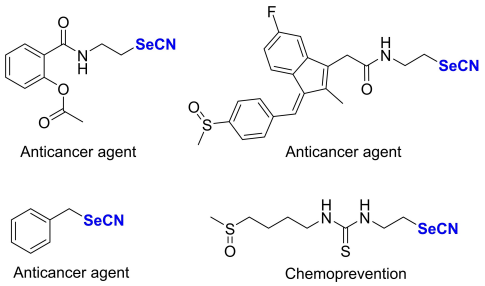
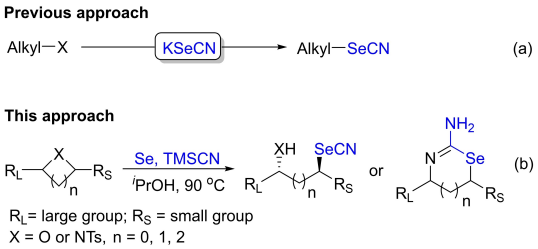


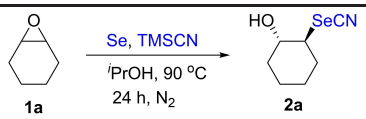
Figure 1. Anti-cancer active molecules containing SeCN group.

We initiated our work by selecting cyclohexene oxide (**1a**) as the model substrate (Table 1). After



Scheme 1. Methods for the synthesis of aliphatic selenocyanates.

Table 1. Reaction condition optimization.[a]

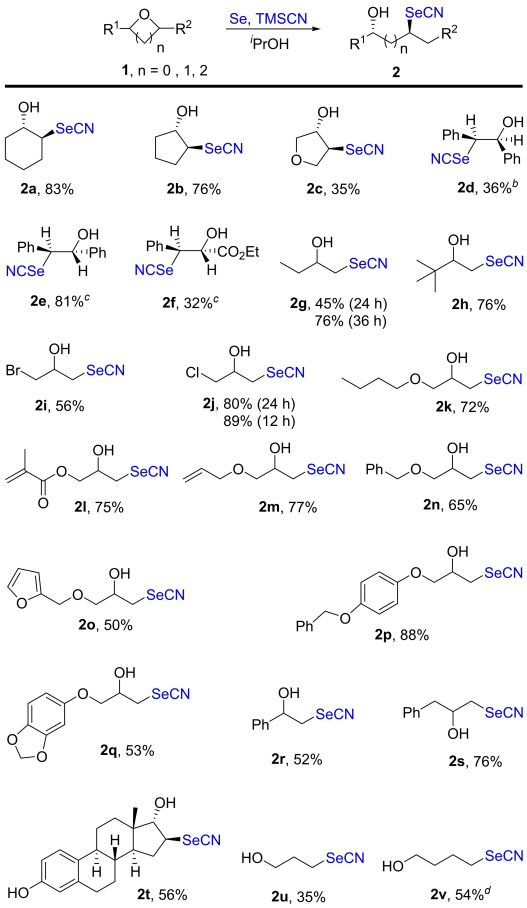


Entry	Change in condition	Yield[b] (%)
1	**None**	83
2	70 °C instead of 90 °C	50
3	80 °C instead of 90 °C	81
4	100 °C instead of 90 °C	80
5	DMSO instead of ^{i}PrOH	43
6	DMF instead of ^{i}PrOH	47
7	THF instead of ^{i}PrOH	77
8	CH_3CN instead of ^{i}PrOH	33
9	Toluene instead of ^{i}PrOH	69
10	air instead of N_2	76
11	O_2 instead of N_2	70
12	12 h instead of 24 h	79
13	36 h instead of 24 h	78
14	DMF instead of TMSCN	0
15	malononitrile instead of TMSCN	0
16	2 equiv Se powder was used	65
17	1 equiv Se powder was used	41

[a] General conditions: **1a** (0.5 mmol), Se powder (1.5 mmol), TMSCN (1.0 mmol), ^{i}PrOH (2 mL), 90 °C, 24 h, N_2.
[b] Isolated yield.

systematic examination of all reaction parameters, *trans* β-hydroxy selenocyanate (**2a**) was isolated in 83% yield with single stereoselectivity when the model reaction was carried out in ^{i}PrOH at 90 °C for 24 h under N_2 atmosphere (entry 1). Lower or higher reaction temperature did not improve the reaction efficiency at all (entries 2–4). Other solvents (entries 5–9) resulted in an inferior yield. The investigation on reaction atmosphere (entries 10 and 11) demonstrated that the presence of O_2 had a negative impact on reaction efficiency. The reaction was slightly affected by the reaction time (entries 12 and 13). The use of other organic CN sources such DMF and malononitrile led to no formation of the desired product (entries 14 and 15). It was found that the use of an overdose of Se powder was essential for the high yield probably because Se powder acted as not only the selenium source but also the reductant and part of Se powder was converted into other selenium-containing moiety (entries 16 and 17).

β-Hydroxy (amino) selenides[11] are one of the most important class of organic selenium-containing compounds, which are widely employed in pharmaceutical chemistry[12] and organic synthesis.[13] Under the optimized conditions, a wide range of β-hydroxy selenocyanates were prepared from various epoxides in the presence of Se powder and TMSCN (Scheme 2). Symmetric epoxides reacted well to provide the desired products (**2a**–**2c**) with 35%-83% yields. In addition to the desired product **2c**, large amount of



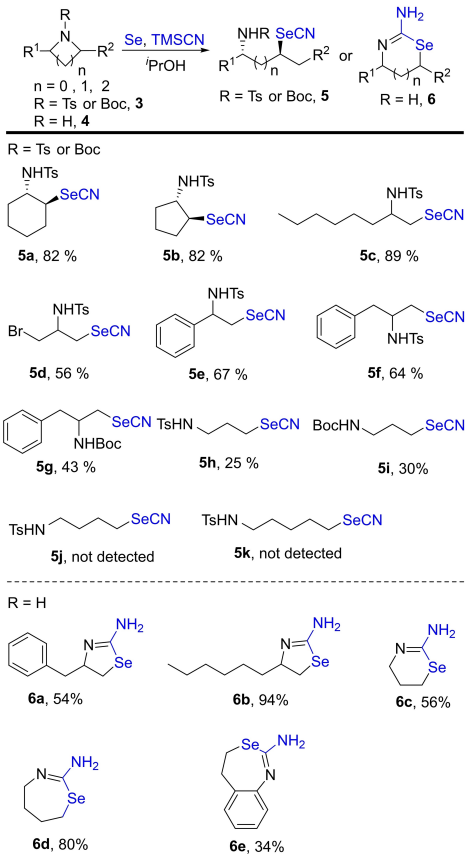
Scheme 2. The scope of ring-opening reactions of saturated O-heterocycles. Reaction conditions: **1** (0.5 mmol), Se powder (1.5 mmol), TMSCN (1.0 mmol), ^{i}PrOH (2 mL), 90 °C, 24 h, N_2, isolated yields. [b]Using *cis*-epoxide as a substrate. [c]Using *trans*-epoxide as a substrate. [d]Se powder (0.5 mmol), TMSCN (1.0 mmol), THF (2 mL), 120 °C, 24 h.

side products with uncertain structure was detected in the reaction of **1c**, Se powder and TMSCN. These side products may be generated from the ring opening reaction of the THF-moiety. The reaction of *cis*-stilbene yielded a product (**2d**) with a different configuration from that (**2e**) obtained from the reaction of *trans*-stilbene oxide. Furthermore, *trans*-stilbene led to much better reaction efficiency than *cis*-stilbene oxide mostly due to the less steric hindrance. Unsymmetric epoxides were also amenable to reaction, providing the corresponding β-hydroxy selenocyanates (**2f**–**2t**) with moderate to good yields in most cases. The "SeCN" moiety preferred to attack the less sterically hindered carbon atom of unsymmetric epoxides, thus leading to excellent regioselectivity. It should be worth to note that halogens (**2j** and **2k**) remained intact under the optimized reaction conditions. This protocol was also applicable for ring-opening selenocyanation of bioactive derivatives (**2q** and **2t**). In addition to epoxides, both four-membered and five-membered oxygen heterocycles proved to be suitable substrates, affording 35% yield of γ-hydroxy selenocyanate (**2u**) and 54% yield of δ-hydroxy selenocyanate (**2v**) respectively.

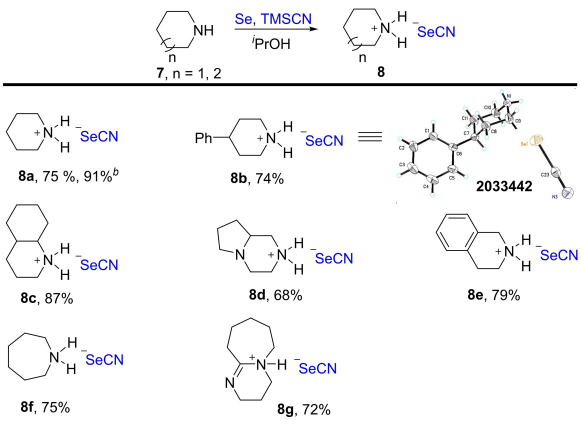
The success of preparation of β-hydroxy selenocyanates encourage us to explore the possibility of constructing β-amino selenocyanates from N–Ts-substituted aziridines (Scheme 3). To our delight, a series of substituted aziridines successfully underwent ring opening with selenium powder and TMSCN to offer the target products with excellent regio and stereoselectivities (**5a**–**5g**). γ-Amino selenocyanates (**5h** and **5i**) could be accessed from Ts- or Boc-protected azetidine. Based on these results, it could be concluded that the protecting groups on nitrogen atom showed significant influence on the reaction outcome for aziridines, while both Ts- and Boc-protecting groups gave comparable yields for azetidines. However, the transformation didn't occur when Ts-protected pyrrolidine or piperidine was employed as the substrate (**5j** and **5k**). Interestingly, in the case of unprotected saturated N-heterocycles, the reactions didn't give the desired selenocyanates but selenium-containing heterocycles (**6a**–**6e**).

Switching the heterocycles to unprotected six or seven membered N-heterocycles, the ring-opening reaction failed, but good yields of ammonium selenonitriles were isolated (Scheme 4). It's worth to note that the reaction of piperidine performed on 20 mmol-scale gave better yield than small-scale reaction, and the product **8a** could be isolated by recrystallization instead of column chromatography. The structure of **8b** was further confirmed by single crystal X-ray diffraction.[14]

Several control experiments were conducted to gain insight into the ring-opening selenocyanation. The formation of **2a** or **8a** was inhibited by the addition of

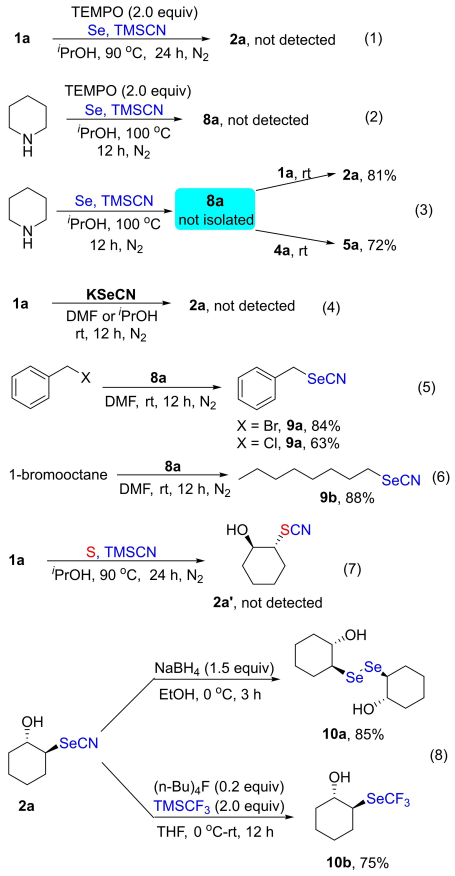


Scheme 3. The scope of ring-opening reactions of saturated N-heterocycles. Reaction conditions: **3** or **4** (0.5 mmol), Se powder (1.5 mmol), TMSCN (1.0 mmol), ^{i}PrOH (2 mL), 100 °C, 24 h, N_2, isolated yields.



Scheme 4. The scope of the synthesis of N-heterocycles. Reaction conditions: **7** (0.5 mmol), Se powder (1.5 mmol), TMSCN (1.0 mmol), ^{i}PrOH (2 mL), 100 °C, 24 h, N_2, isolated yields. [b]Piperidine (30 mmol), Se powder (20 mmol), TMSCN (30 mmol), ^{i}PrOH (30 mL), 100 °C, 24 h, N_2.

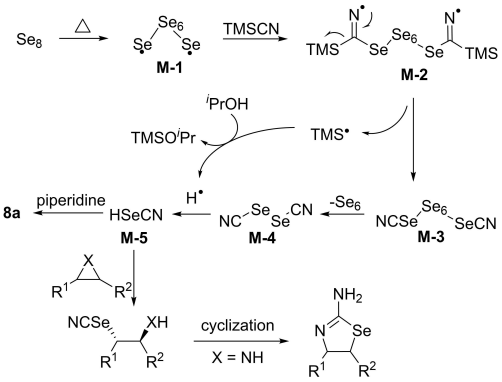
TEMPO, suggesting that a radical process was involved (Scheme 5.1 and 5.2). In-situ generated



Scheme 5. Control experiments and applications of **8a** and **2a**.

product **8a** could react well with **1a** or **4a** to afford the corresponding selenocyanation product, indicating that "HSeCN" may act as the key intermediate (Scheme 5.3). It is noted that **8a** is very chemically and physically stable, and is not deliquescent. On the contrary, using KSeCN to replace **8a** led to no reaction under the similar reaction conditions (Scheme 5.4). The contrary results suggested **8a** was more reactive than KSeCN probably because the hydrogen proton of **8a** could adhere to the O(N) atom of heterocycles, thus promoting ring-opening reaction together with "SeCN" anion. In addition, we used **8a** as a selenonitrile reagent for the synthesis of aliphatic selenocyanates from alkyl halides. To our delight, the reactions of alkyl bromide or alkyl chloride with **8a** successfully furnished the desired products **9a** and **9b** (scheme 5.5 and 5.6). In a word, **8a** is a better selenonitrile reagent than KSeCN. In the case of elemental sulfur, ring opening of **1a** did not occur to give the desired product **2a**' (Scheme 5.7). The synthetic application of product **2a** was demonstrated by the synthesis of diselenide **1a** and $SeCF_3$-containing compound **10b** (Scheme 5.8).

Based on the above observation and previous work,[12,15] a plausible reaction pathway is proposed in Scheme 6. At the beginning, selenium biradical (**M-1**)



Scheme 6. A plausible mechanism.

in situ generated from Se_8 undergoes radical addition with TMSCN to give intermediate **M-2**, followed by release of two TMS radicals to afford **M-3**. On one hand, the reaction between TMS radical and ^{i}PrOH yields TMSO^{i}Pr and a hydrogen radical. On the other hand, **M-3** releases a Se_6 moiety to form **M-4** which then reacts the hydrogen radical to generate the key intermediate **M-5**. The intermediate **M-5** enables the selective ring-opening of heterocycles to produce the selenocyanation product. Owing to the strong nucleophilicity of free amino group, the selenocyanation products bearing free amino group can be further cyclized to give selenium-containing heterocycles. In the case of unstrained N-heterocycles, their tension is not enough to drive the ring-opening reaction, but ammonium selenonitriles were formed from the reaction between N-heterocycles and **M-5**.

In summary, a catalyst and additive-free three-component reaction of heterocycles, selenium powder and TMSCN has been developed. The heterocycles from strained three-membered rings to unstrained five-membered rings could undergo selective ring-opening selenocyanation, enabling the scalable and diverse synthesis of various aliphatic selenocyanates including β to δ-hydroxy selenocyanates and β to γ-amino selenocyanates, as well as selenium-containing heterocycles. Most of the synthesized aliphatic selenocyanates was found to be physically and chemically stable. Control experiments have shown that this three-component reaction involved HSeCN as a key intermediate. Moreover, this protocol develops a new and efficient selenonitrile reagent which can be applied in the construction of aliphatic selenocyanates from alkyl halides and heterocyclic compounds. The facile synthesis of aliphatic selenocyanates from easily available precursors will pave the way to explore their potential pharmaceutical and physiological function.

Experimental Section

The Reaction of Saturated Heterocycles, Elemental Selenium and TMSCN

A 25 mL Schlenk tube equipped with a stir bar was charged with saturated heterocycle (0.5 mmol), selenium powder (1.5 mmol), TMSCN (1.0 mmol), and ^{i}PrOH (2 mL). The tube was fitted with a rubber septum, then the septum was replaced by a Teflon screwcap. The reaction mixture was preheated to 90 °C (100 °C in the case of N-heterocycle) in a heating mantle and stirred under N_2 atmosphere for 24 h. After cooling down, the reaction mixture was diluted with 2 mL of ethyl acetate, filtered through a pad of silica gel, followed by washing the pad of the silica gel with the same solvent (20 mL), concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel to provide the corresponding product.

Acknowledgements

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