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Convenient and Rapid Synthesis of 3-Selenocyanato-4*H*-chromen-4-ones

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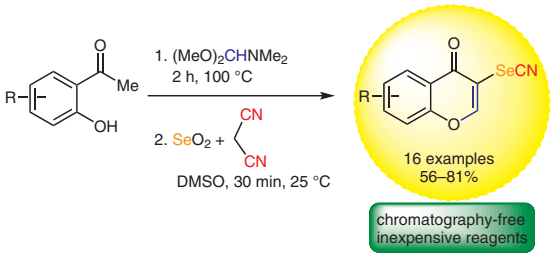

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Abstract A sequential one-pot, simple and convenient method is described for the synthesis of 3-selenocyanato-4*H*-chromen-4-ones by addition, first of DMF-DMA and then of triselenodicyanide as electrophile.

Key words selenocyanate, chromones, triselenodicyanide, selenium dioxide, malononitrile, electrophile addition, oxidation, rearrangement

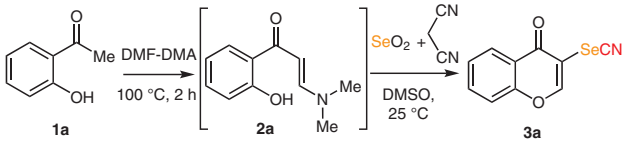
Organic selenocyanates (RSeCN) interest medicinal chemists because of their remarkable activities as antileishmanial[1] and cancer chemopreventive agents.[2] The chemical field has known organoselenocyanates for almost a century, but recent advances led to a revival of interest in these compounds. Compared to the arylselanyl group, the SeCN functional group offers the advantage of being an air- and moisture-stable intermediate. They behave like pseudohalides, where the CN acts as a leaving group.[3a–c] They can also be transformed by base- or $NaBH_4$-mediated decyanation.[3d] For the selenocyanation of electron-rich arenes, potassium selenocyanate (KSeCN) is typically used as radical source with an oxidant such as cerium ammonium nitrate[4a] or $K_2S_2O_8$,[4b] or as an electrophilic source with *N*-iodosuccinimide[4c] or *N*-chlorosuccinimide.[4d] The disadvantage with most of these methods is that they require odorous, air-sensitive and expensive potassium selenocyanate, along with tedious product purification by column chromatography.

Developing a more attractive industry-compatible process requires a straightforward, odorless, inexpensive and scalable method. Triselenodicyanide [$Se(SeCN)_2$] represents an ideal electrophilic source,[5] especially considering its simple and cheap generation from malononitrile and odorless selenium dioxide. So far, this reagent has only been employed for the direct selenocyanation of activated nitrogen-containing heterocycles (indoles[6a] and imidazoheterocycles[6b]). In continuation of our research centered on efficient one-pot synthesis,[6c] we investigated the reactivity of triselenodicyanide in a one-pot two-step procedure for the selenocyanation of chromones from *o*-hydroxyacetophenones. Chromone structures, widely found in many natural products, are valued in pharmacology notably for their antiallergic, anti-inflammatory, antidiabetic, antitumoral, and antimicrobial properties.[7] We hypothesized that combining selenocyanates with chromones could enhance these biological properties. Selenation for chromones has so far only concerned the introduction of arylselanyl groups[8] in the C3-position; to our knowledge, no C3-selenocyanation has been performed to date.

To validate the sequential one-pot procedure, we first optimized the insertion of the dimethylamino group to activate the enaminone **2a**[9] thus-formed for the subsequent addition of the electrophilic selenocyanate. The *o*-hydroxyacetophenone (**1a**) was heated with different equivalents of *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) under neat conditions at temperatures ranging from 80 °C to 120 °C; and the reaction was monitored by LC–MS. The best result was obtained at 100 °C in two hours with 1 equivalent of DMF-DMA. We then explored the electrophilic addition of triselenodicyanide without prior isolation of the intermediate. Using a previously optimized solvent system (DMSO, 1 $mol.L^{-1}$),[6b] we tested different amounts of SeO_2 and malononitrile at room temperature for one hour (Table 1, entries 1–4). With a SeO_2/malononitrile proportion of 1:0.5, low conversion of **1a** was obtained (31%). Moderate conversion was obtained with a proportion of 2:1 (Table 1, entry 2). Surprisingly, increasing the amount of malononitrile decreased the conversion, probably due to the formation of unreactive selenium-based intermediate. An excellent NMR conversion was obtained with SeO_2/malononitrile proportion of 3:1 after only 30 minutes at room temperature (Table 1, entry 4). Addition of three volumes of

water precipitated the pure selenocyanated product to give 76% yield. Lower conversion was obtained when the reaction was conducted with anhydrous DMSO under nitrogen atmosphere, probably due to lower SeO_2 solubility in the absence of water (Table 1, entry 5).

Table 1 Optimization of the Reaction Conditions[a]



Entry	SeO_2 (equiv)	Malononitrile (equiv)	Yield (%)[b]
1	1	0.5	31
2	2	1	72
3	2	2	39
4	3	1	100 (76)[c]
5	3	1	78[d]

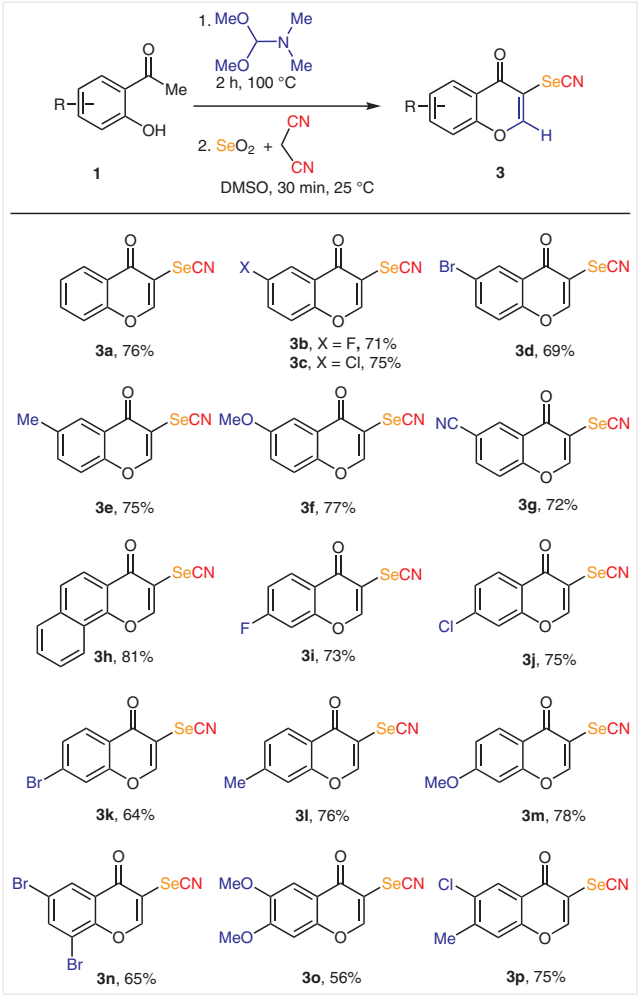
[a] Reaction conditions: *o*-hydroxyacetophenone (**1a**; 0.5 mmol, 1 equiv), DMF-DMA (1 equiv) at 100 °C for 2 h. Then a preprepared solution of SeO_2 and malononitrile in DMSO (0.5 mL) at 25 °C for 20 min was added under air atmosphere. The reaction mixture was stirred for a further 1 h.
[b] ^{1}H NMR yield of **3a** (isolated yield).
[c] Reaction time was 30 minutes.
[d] The reaction was performed with anhydrous DMSO under nitrogen atmosphere.

Next, we examined the scope of our selenocyanation method with variously decorated *o*-hydroxyacetophenones (Scheme 1).[10]

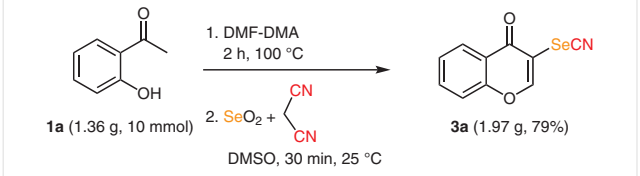
The selenocyanation led to good yields and tolerated numerous functional groups such as halogen (**3b**, **3c**, **3d**, **3i**, **3j**, **3k**), methyl (**3e**, **3l**), alkoxy (**3f**, **3m**) or nitrile groups (**3g**). Both electron-rich and electron-deficient substituents were well tolerated. Only the *o*-hydroxyacetophenone bearing a NO_2 group at the *para* position of the phenol did not react. The relative positioning of the substituent on the aromatic ring (*ortho*, *meta* or *para* position) did not affect the efficiency of the reaction. Replacing the phenyl moiety by a naphthalene led to a better yield of 3-cyanoselenatochromone (**3h**, 81%). In contrast, the yield in the presence of two hydrophilic substituents (two methoxy) was moderate (**3o**, 56%).

To further explore the applicability of the procedure, we performed a gram-scale synthesis of **3a** with 10 mmol of *o*-hydroxyacetophenone. This reaction was accomplished with a slight increase in yield (79%) without changing the reaction time (Scheme 2).

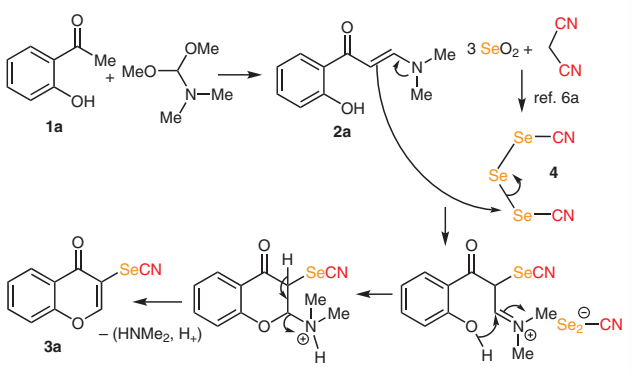
We suggest the following mechanism to explain our experimental results (Scheme 3). First, the *o*-hydroxyacetophenone (**1a**) is converted into the enaminone **2a** with DMF-DMA. Meanwhile, the reaction between three equivalents of selenium dioxide and one equivalent of malononitrile gives the triselenodicyanide **4**.[6a] The enaminone **2a** reacts on the most electrophilic selenium of **4** atom, leading to an iminium salt. Cyclization with phenol may occur, leading to a new iminium salt. After elimination of the volatile dimethylamine, the 3-selenocyanato-4*H*-chromen-4-one (**3a**) is isolated.



Scheme 1 Scope of the synthesis of 3-selenocyanato-4*H*-chromen-4-ones. *Reagents and conditions*: a mixture of *o*-hydroxyacetophenone **1a–p** (1 mmol, 1 equiv) and DMF-DMA (1 equiv) was heated for 2 h at 100 °C; then a preprepared solution of SeO_2 (3 equiv) and malononitrile (1 equiv) in DMSO (1 mL) stirred at 25 °C for 20 min was added at 25 °C. The reaction mixture was stirred for 30 min under air atmosphere. Isolated yield is provided based on **1a–p**.

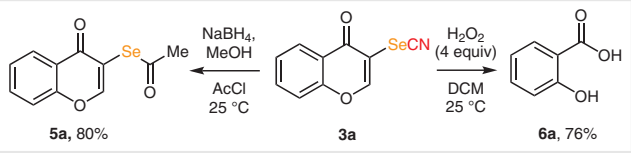


Scheme 2 Gram synthesis



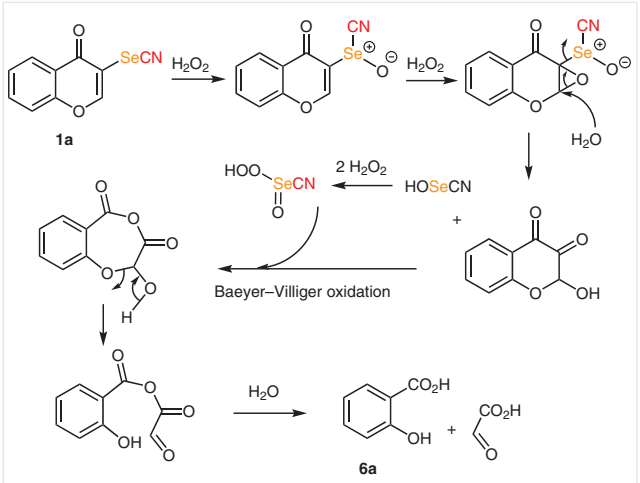
Scheme 3 Suggested mechanism of the reaction

To demonstrate the utility of the selenocyanated chromones, two transformations of the SeCN functional group were explored (Scheme 4). The 3-selenocyanato-4*H*-chromen-4-one (**3a**) was converted into (**5a**) bearing a seleno ester group in 80% yield via a reduction with $NaBH_4$ into a selenolate followed by addition of an electrophile (acetyl chloride). The chromen-4-one (**3a**) was then subjected to H_2O_2 oxidation (1 equiv) in dichloromethane. To our surprise, no selenoxide was isolated; instead only the unexpected *o*-hydroxybenzoic acid appeared. The reaction was not completed even after one day at room temperature. Adding 3 equivalents of H_2O_2, allowed complete conversion into *o*-hydroxybenzoic acid with a 76% yield.



Scheme 4 Transformations of the selenocyanated group in **5a** and **6a**

Assuming that the chromone first lost the double bond and the SeCN group and that the ketone was secondly converted into carboxylic acid, a cascade reaction of several oxidations and rearrangements could be involved. The proposed mechanism is based on previous studies on the oxidative rearrangement of selenium (Scheme 5).[11] The selenocyanate group could first be oxidized by H_2O_2into selenoxide species. A polarizable double bond further oxidized would be easily convertible into epoxide by H_2O_2. Then addition of water on position 2 could open this activated epoxide, inducing the expulsion of 'HOSeCN'. HOSeCN could then be further oxidized by the excess of H_2O_2 into CNSe(O)OOH (cyanoperseleninic acid). Perseleninic acid is known as a selective oxidant able to perform Baeyer–Villiger reactions.[12] The Baeyer–Villiger oxidation of the diketone could give the acid anhydride derivative. The hemiacetal formed upon opening of the seven-membered ring could expulse the oxoacetic acid and the *o*-hydroxybenzoic acids in the presence of water. The requirement of four equivalents of H_2O_2 for complete reaction is in agreement with the mechanism described. These successive oxidation steps demonstrate that these chromone-4-ones with a selenium on position 3 could be compounds of interest due to their antioxidant properties.



Scheme 5 Mechanism for the peroxidation of selenium

In summary, we have developed an efficient approach for the preparation of 3-selenocyanato-4*H*-chromen-4-ones using readily available selenium dioxide and 2-hydroxyacetophenones. This one-pot two-step reaction leads to good yields with easy purification by simple filtration. The method uses odorless and inexpensive starting materials. Oxidation of the core of the chromones gives the *o*-hydroxybenzoic acid by rearrangement of the selenium. This result indicates that insertion of SeCN in position 3 of chromones could increase their antioxidant properties.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609340.

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(10) **3-Selenocyanato-4*H*-chromen-4-ones 3; General Procedure**: A mixture of *o*-hydroxyacetophenone (**1a**; 136 mg, 1 mmol, 1 equiv) and dimethylformamide dimethylacetal (120 mg, 1 mmol, 1 equiv) was heated for 2 h at 100 °C. After cooling to 25 °C, a preprepared solution of malononitrile (66 mg, 1 mmol, 1 equiv) and SeO_2 (332 mg, 3 mmol, 3 equiv) in DMSO (1 mL), stirred at 25 °C for 20 min, was added at 25 °C. The reaction mixture was stirred for a further 30 min, then H_2O was added (3 mL). The resulting precipitate was filtered off, washed with H_2O (3 × 10 mL) and dried under a fume hood overnight at 25 °C to give the pure product **3a**.

3-Selenocyanato-4*H*-chromen-4-one (3a): brown solid; yield: 76%; mp 136–137 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.26 (s, 1 H), 8.20 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.79 (dt, *J* = 8.4, 1.7 Hz, 1 H), 7.56 (dt, *J* = 8.4 Hz, 1 H), 7.51 (dt, *J* = 7.1, 1.1 Hz, 1 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 174.3 (CO), 156.7 (C), 153.1 (CH), 135.1 (CH), 126.5 (CH), 125.9 (CH), 122.0 (C), 118.6 (CH), 112.7 (C), 100.0 (CN). HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_5NO_2Se$: 251.9559; found: 251.9557.

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