Selenochromanes *via* tandem homolytic addition/substitution chemistry†

Maree K. Staples[ab] and Carl H. Schiesser*[ab]

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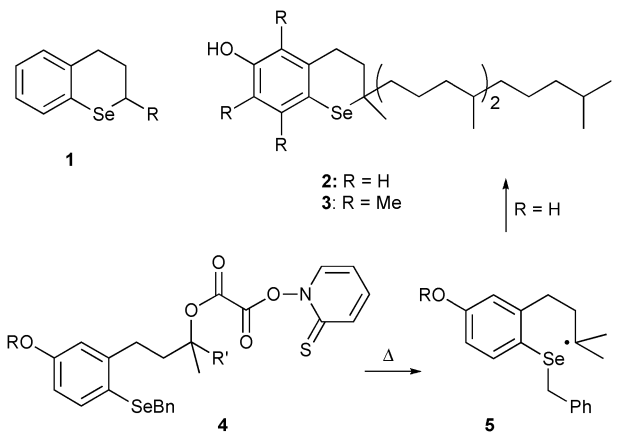
Selenochromanes and analogues are conveniently prepared through a tandem homolytic addition/substitution sequence involving suitably substituted olefins.

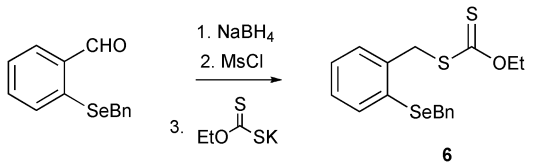
As part of an ongoing interest in the synthesis of selenium-containing heterocycles of biological relevance,[1] we required methodology for the preparation of the selenochromane scaffold **1**, such as found in the analogue **2** of selenotocopherol **3**. Having developed free radical homolytic substitution methods for the construction of selenium-containing rings,[2] our initial work focused on the preparation of suitable precursors to achieve that aim. For example, **2** was prepared by thermolysis of the pyridinethioneoxycarbonyl (PTOC) ester precursor **4**, presumably *via* an intramolecular homolytic substitution reaction involving the tertiary carbon-centred radical **5** (Scheme 1).[3]

Despite the success of the route depicted in Scheme 1, preparation of the precursor **4** is somewhat laborious, largely because of chain homologation steps necessary for the construction of the six-membered ring from commercially-available starting materials such as 3-hydroxybenzoic acid.

We reasoned that compounds such as **1** should be available through a one-pot sequence involving *intermolecular* homolytic addition (double chain homologation) followed by *intramolecular* homolytic substitution at selenium. To the best of our knowledge this had not been attempted for the construction of six-membered selenium-containing rings.



Scheme 1



Scheme 2

Xanthates (dithiocarbonates) are versatile radical precursors that have found application in the contruction of small molecules as well as polymers and can be used in the presence or absence of chain-carrying reagents such as tributyltin hydride.[4,5] We chose to explore the utility of benzylic xanthates such as **6** in the tandem chemistry described above; **6** was conveniently prepared from 2-(benzylseleno)benzaldehyde[6] by simple borohydride reduction followed by mesylation and reaction with potassium ethyl xanthate (Scheme 2).

With xanthate **6** in hand, we turned our attention to developing a protocol for the formation of selenochromanes such as **1**. Initial experiments involved the reaction of **6** with methyl acrylate **7**, in toluene, under thermolysis or photolysis conditions, with and without the addition of dilauryl peroxide as initiator. In the absence of photolysis, none of the reactions attempted afforded anything other than partially polymerized methyl acrylate as a thick jelly, even at temperatures up to 200 °C (sealed tube). Under photolysis conditions, dilauryl peroxide proved to be unnecessary.

To our delight, when a solution of **6** (0.35 M) and 3 equivalents of **7** (R = CO_2Me) in toluene was irradiated with a low-pressure mercury lamp at 200 °C for 4 h, methyl 3,4-dihydro-2*H*-1-benzoselenin-2-carboxylate **1** (R = CO_2Me) was obtained in 33% yield and was isolated as a colourless oil after flash chromatography (Scheme 3).‡ As expected, reduction in temperature required longer reaction times to achieve similar yields; optimum conditions appeared to be about 12 h at 80 °C (Scheme 3, entry 3), with further increases in time providing no increase in the yield of **1** (R = CO_2Me).§ This is an excellent outcome as it affords an important ring system, functionalized at a key position,¶ from readily available starting materials in yields that exceed those from the multi-step sequence described above.[3]

Under the optimum reaction conditions described above 1-heptene and styrene failed to react, while methyl methacrylate **8** and *N*-benzyl maleimide **9** afforded the corresponding selenochromanes **10**,‡ **11**‡ in 25% and quantitative‖ yield respectively, while benzyl acrylate and maleic anhydride **12** afforded **13** in 22% isolated yield, and **14**** in high conversion (Scheme 4). These results highlight the importance of

[a] *School of Chemistry, The University of Melbourne, Victoria 3010, Australia. E-mail: carlhs@unimelb.edu.au; Fax: +61 3 9347 8189; Tel: +61 3 8344 2432*
[b] *Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Victoria 3010, Australia*

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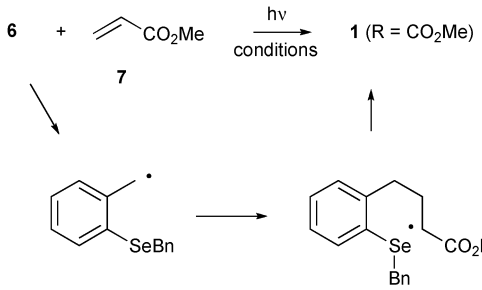
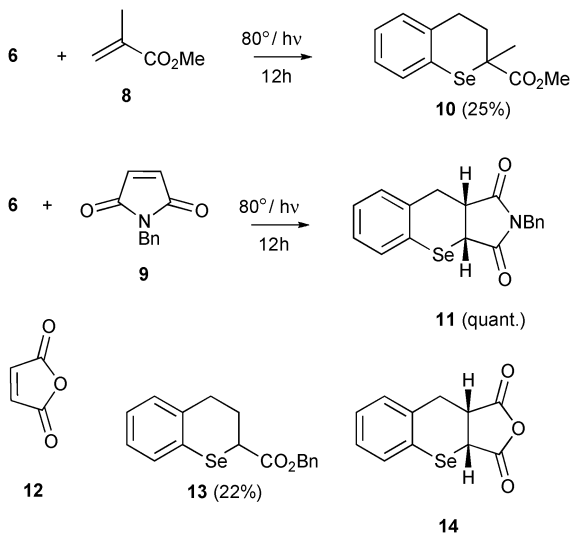


Entry	Temp (°C)	Time (h)	Yield (%)
1	20	2	0
2	80	6	15
3	80	12	40
4	120	2	18
5	120	6	31
6	200	1	14
7	200	2	35
8	200	4	33

Scheme 3

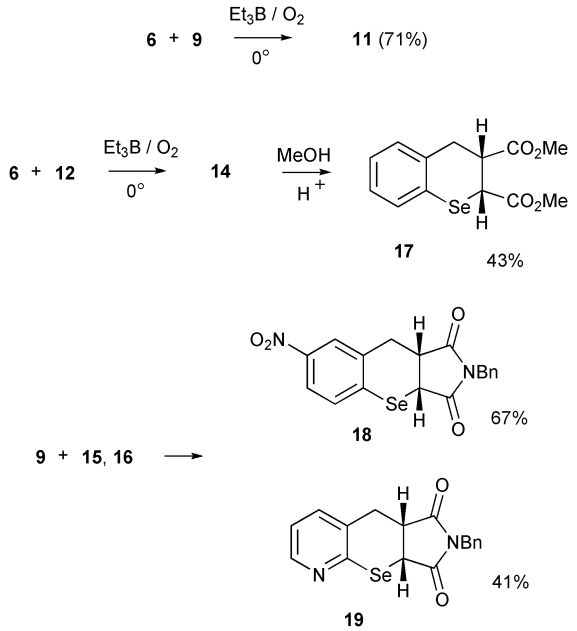


Scheme 4

electron-withdrawing groups in the initial addition step involving the weakly nucleophilic benzyl radical. It should be noted that the addition of benzyl radical to **9** has been reported previously.[7]

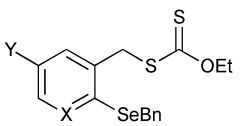
To briefly explore the general versatility of this chemistry, the preparation of selenochromane analogues requiring benzylic radicals with differing electron demand was next explored. To that end, xanthates **15**, **16** were prepared from ethyl 2-(benzylseleno)-5-nitrobenzoate[8]‡ and ethyl 2-(benzylseleno)nicotinate[9] respectively by reduction, mesylation and reaction with potassium ethyl xanthate. At the same time we explored more convenient methods for the initiation of these radicals and eventually turned to the low-temperature borane methods originally developed by Brown.[10]

To our delight, xanthates **6**, **15**, **16** reacted smoothly with **9**, as well as maleic anhydride **12** at 0 °C, in dichloromethane, initiated with Et_3B/O_2 under standard conditions.[11] In the case of **6**, the product **11** was isolated after 30 min in 71% yield



Scheme 5

(chromatography),§ while the corresponding reaction with maleic anhydride afforded an insoluble solid that was converted to the corresponding diester **17**‡ in 43% overall yield by treatment with acidic methanol followed by chromatography.



15 (X = CH, Y = NO_2)
16 (X = N, Y = H)

The remaining xanthates **15**, **16** afforded the corresponding selenochromanes **18**,‡ **19**‡ in 40–70% yield (Scheme 5), while none of the xanthates reacted with methyl acrylate **7** under these conditions. It is interesting to note that diminished yields seem to correspond with the less reactive radicals such as that derived from **16**.

We are currently exploring the scope and utility of this novel chemistry, together with its application to key targets, and will report the outcome of this work, in full, in due course.

Generous support by the Australian Research Council through the Centres of Excellence Scheme is gratefully acknowledged.

Notes and references

‡ This is a new compound. Analytical data are provided in the Electronic Supporting Information.

§ Experimental procedure for the preparation of **1** (R = CO_2Me): *O*-ethyl-*S*-(2-(benzylseleno)benzyl) dithiocarbonate (209 mg, 0.55 mmol) and methyl acrylate (76 μL, 0.82 mmol) were dissolved in toluene (1.5 mL) in a Pyrex tube after "degassing" by bubbling a steady stream of nitrogen through the solvent. The reaction vessel was sealed and irradiated for 12 h with a 125 W medium pressure mercury lamp at a distance of 15 cm while maintaining the temperature at 80 °C. (Temperature control was made possible by placing the sealed tube in a preheated silicone oil bath during irradiation.) The product was purified by flash chromatography (5% ethyl acetate/petroleum spirits) to give a colourless oil (0.22 mmol, 40%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 1H), 7.20–7.04 (m, 3H), 4.24–4.18 (m, 1H),

3.74 (s, 3H), 2.96–2.87 (m, 1H), 2.74–2.64 (m, 1H), 2.20–2.12 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.13, 138.24, 129.26, 128.77, 128.40, 127.06, 125.83, 52.55, 35.43, 31.32, 25.69; ^{77}Se NMR ($CDCl_3$) δ 305.168; IR (neat) cm^{-1}: 2949.1, 1731.0, 1433.6, 1307.4, 1234.7, 1157.6; MS (EI) *m*/*z* (relative intensity) 256 (66), 195 (31), 169 (23), 115.1 (100), 89.1 (18); HRMS calcd for $C_{11}H_{12}O_2Se$ [M + Ag] 362.90480, found 362.90491.

Experimental procedure for the preparation of **11**: Ethyl-*S*-(2-(benzylseleno)benzyl) dithiocarbonate (52 mg, 0.14 mmol) and *N*-benzyl maleimide (51 mg, 0.27 mmol) were dissolved in dichoromethane (300 μL). Triethylborane in cyclohexane (1 M, 1.1 equivalents) was added *via* syringe (with the needle under the surface of the solution), followed by an equivalent volume of air. The reaction mixture was stirred for 30 min and then diluted with dichloromethane (1 mL), washed with water (1 mL) and brine (1 mL). The solution was dried ($MgSO_4$) and the solvent removed *in vacuo*. The desired product was isolated as colourless needles (34 mg, 71%) after flash chromatography (10% ethyl acetate/petroleum spirits, increasing to 20%). Mp 193 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.40 (m, 1H), 7.28–7.05 (m, 6H), 6.71 (d, J = 7.3, 2H), 4.49 (q, J = 14.6, 2H), 4.27 (d, J = 9.5, 1H), 3.60 (dt, J = 4.6, 9.4, 1H), 3.39 (dd, J = 4.2, 13.9, 1H), 2.93 (dd, J = 5.0, 13.9, 1H); ^{13}C NMR ($CDCl_3$) δ 176.81, 176.68, 137.00, 134.86, 131.90, 129.65, 128.47, 128.42, 128.38, 128.18, 127.36, 127.25, 43.28, 42.48, 36.91, 35.20; ^{77}Se NMR ($CDCl_3$) δ 320.312; IR (neat) cm^{-1}: 1773.9, 1698.8, 1426.6, 1395.3, 1339.8, 1168.2; MS (EI) *m*/*z* (relative intensity) 357.1 (94), 276.1 (12), 195 (75), 186 (30), 168.9 (30), 115 (100), 106.1 (29), 91.1 (100), 89 (24), 65 (21); Anal. Calc. for $C_{18}H_{15}NO_2Se$: C 60.68, H 4.24; found C 60.79, H 4.01%.

¶ Selenochromanes bearing functionality, as opposed to alkyl or aryl substitution, at the 2-position are novel.

‖ By ^{1}H NMR assessment; isolated in 71% yield after chromatography.

** This is a highly insoluble compound in most organic solvents. Conversion estimated from the ^{1}H NMR spectrum of the crude reaction mixture.

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