Nucleophilic Ring Opening of Mono-Activated Cyclopropanes with Arylselenolates Generated from Diselenides in the Presence of a Zn/$AlCl_3$ System

Mohammad Nazari, Barahman Movassagh*

Department of Chemistry, K. N. Toosi University of Technology, P. O. Box 16315-1618, Tehran, Iran
Fax +98(21)22853650; E-mail: bmovass1178@yahoo.com

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Abstract: An efficient one-pot synthesis of γ-arylselenenyl ketones, acids, and nitriles is presented. The method uses Zn/$AlCl_3$-promoted cleavage of diselenides and subsequent ring-opening of mono-activated cyclopropanes.

Key words: mono-activated cyclopropanes, ring opening, diselenides, zinc selenolates, zinc

Organoselenium compounds have found wide utility due to their effects on numerous reactions, often affording stereo- and regioselectivity and excellent yields under relatively mild reaction conditions.[1] Organoselenium compounds are also promising pharmacological agents in view of their antioxidant, antitumor, antimicrobial, and antiviral properties.[2]

Among the methods for the introduction of a selenium moiety into organic molecules, the use of selenide anions (selenolates) is especially convenient and common. Although, selenolates are weak bases, they are nevertheless powerful, soft nucleophiles[3] because of the high polarizability of the selenium atom. In general, methods for the preparation of selenide anions include reductive cleavage of the Se–Se bond by various agents such as sodium borohydride,[4a] sodium,[4b] samarium diiodide,[4c] lithium aluminum hydride,[4d] reaction of Grignard reagents with selenium,[4e] and reaction of selenols with sodium hydride or even with aqueous sodium hydroxide under certain conditions.[4f]

The nucleophilic cleavage of electron-deficient cyclopropane derivatives has been widely applied in organic synthesis and is known as the homologous (or 1,5) version of the classical Michael addition,[5] which has found many applications in the total synthesis of natural products.[5,6] Unlike doubly-activated cyclopropanes, the corresponding reaction of mono-activated analogues is limited to highly strained bicyclic systems.[7,8]

To the best of our knowledge, there are only two reports describing procedures for generating either sodium or lithium phenylselenolate as the nucleophilic reagent for ring opening of mono-activated cyclopropanes.[9,10] However, these methods generally result in poor yields of products. Furthermore, the clean and efficient generation of selenolates continues to cause practical problems owing to the malodorous nature of certain compounds such as benzeneselenol,[4e,g,h] the need for toxic solvents such as HMPA,[4e,h] the use of alkali metals or very strong bases such as sodium hydride,[4e,g,h] which are incompatible with substrates having base-sensitive substituents, and the lack of required reactivity of some of these salts.[4a]

As part of our ongoing work on the application of zinc selenolates in chemical reactions,[11] we describe herein the use of the Zn/$AlCl_3$ system for the reductive cleavage of diaryl diselenides followed by nucleophilic ring-opening of a cyclopropyl ring, mono-activated with either ketone, aldehyde, acid, or nitrile functionalities (Scheme 1). We found that zinc selenolate (**2a**), generated from reductive cleavage of diphenyl diselenide in the presence of Zn/$AlCl_3$, reacts smoothly with cyclopropyl methyl ketone (**3a**) to give the corresponding γ-phenylselenenyl ketone (**4a**) in very good yield. After optimization of the reaction conditions (solvent, temperature and molar ratios), and in order to probe the generality of our methodology further, we ran the reaction with different mono-activated cyclopropanes and various arylselenolates, generating the corresponding ring-opened products.[12] The choice of zinc selenolate as the ring-opening reagent is particularly attractive for two reasons. Firstly, it is a highly potent nucleophile which is able to react with mono-activated cyclopropanes bearing sensitive functionalities under mild reaction conditions. Secondly, the arylselenenyl functionalized chain products can be easily manipulated and/or the arylselenenyl group can be removed under mild reaction conditions.

The results of this study are illustrated in Table 1. Simply stirring diselenides **1** with zinc dust in the presence of anhydrous aluminum chloride in acetonitrile under an air atmosphere at 70 °C generated the zinc selenolate **2**. This was followed by addition of mono-activated cyclopropanes **3**, which gave the desired products **4**, after work-up, with yields ranging from 48–90% (Table 1). Different diaryl diselenides react with a variety of cyclopropane derivatives, mono-activated by ketone, aldehyde, acid, ester, and nitrile functionalities. The reaction of the diselenides with cyclopropyl methyl ketone (entries 1, 6, and 9) took place faster and gave higher yields than the others, while cyclopropanecarbonitrile (entries 3 and 8) required longer reaction times and gave lower yields. Because of the dominant nucleophilic acyl-oxygen cleavage reaction of zinc selenolates with esters,[9] the reaction with cyclopropanes

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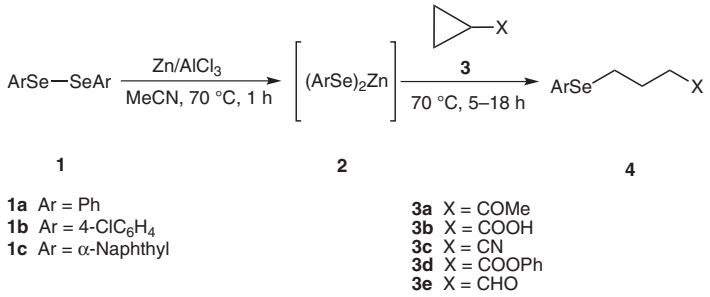

Scheme 1

Table 1 Reaction of Mono-Activated Cyclopropanes with Diaryl Diselenides in the Presence of $Zn/AlCl_3$

Entry	Diselenide **1**	Cyclopropyl **3**	Product **4**		Time (h)	Yield (%)[a]
1	**1a**	**3a**	PhSe(CH2)3COMe	**4a**[9]	5	87
2	**1a**	**3b**	PhSe(CH2)3COOH	**4b**[4e]	16	73
3	**1a**	**3c**	PhSe(CH2)3CN	**4c**[9]	18	48
4	**1a**	**3d**	PhSe(CH2)3COOPh	**4d**[9]	18	–
5	**1a**	**3e**	PhSe(CH2)3CHO	**4e**	8	67
6	**1b**	**3a**	4-ClC6H4Se(CH2)3COMe	**4f**	6	90
7	**1b**	**3b**	4-ClC6H4Se(CH2)3COOH	**4g**	16	75
8	**1b**	**3c**	4-ClC6H4Se(CH2)3CN	**4h**	17	55
9	**1c**	**3a**	α-NaphthylSe(CH2)3COMe	**4i**	6	84
10	**1c**	**3b**	α-NaphthylSe(CH2)3COOH	**4j**	17	70

[a] Isolated yield.

activated by an ester moiety (entry 4) was unsuccessful; in this case we obtained phenol in nearly quantitative yield.

In conclusion, the present method introduces a simple Zn/$AlCl_3$-promoted one-pot procedure for ring opening of different mono-activated cyclopropanes under neutral, and relatively mild reaction conditions, without the need for using an inert atmosphere. The method generates synthetically useful γ-arylselenenyl ketones, acids, nitriles and aldehydes in moderate to excellent yields. This approach offers significant advantages over previously reported procedures with regards to operation and yields, and thus presents an efficient alternative to the existing methods.[9,10]

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(12) **General Procedure**: A mixture of diaryl diselenide (0.5 mmol) and zinc powder (3.0 mmol) in anhydrous MeCN (15 mL), was stirred at 70 °C. After 15 min, anhydrous $AlCl_3$ (3.0 mmol in 2 mL anhydrous MeCN) was added cautiously. The mixture was stirred for 1 h at 70 °C, until the yellow solution turned colorless. The mono-activated cyclopropane (1.1 mmol) was then added to the solution and the mixture was stirred at 70 °C for the period of time specified in Table 1. The progress of reaction was monitored with TLC. After the reaction was complete, the solution was filtered and the solvent was evaporated. Aqueous HCl (10%) was added to the crude product and the mixture was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Purification by preparative TLC (silica gel; *n*-hexane–EtOAc, 3:1) gave the corresponding arylselenenyl-functionalized ring-opened product. All novel compounds were characterized by ^1H and ^{13}C NMR, IR, mass spectroscopy, and elemental analysis. Compound **4e**: IR (neat): 1723, 2725, 2825 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.06 (quin, *J* = 6.9 Hz, 2 H), 2.64 (t, *J* = 6.9 Hz, 2 H), 2.98 (t, *J* = 7.0 Hz, 2 H), 7.23–7.61 (m, 5 H), 9.80 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.9, 27.5, 29.3, 127.5, 129.4, 129.6, 132.7, 201.8 ppm. LRMS: *m*/*z* (%) = 227 (25) $[M + 2]^+$, 225 (12) $[M]^+$, 185 (45), 183 (22), 171 (32), 169 (15), 157 (78), 155 (42), 123 (53), 105 (31), 91 (100), 77 (78), 71 (58), 55 (45), 41 (49). Anal. Calcd for $C_{10}H_{12}OSe$: C, 52.87; H, 5.32. Found: C, 52.95; H, 5.35. Compound **4f**: IR (neat): 1714 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.96 (quin, *J* = 7.1 Hz, 2 H), 2.13 (s, 3 H), 2.59 (t, *J* = 7.0 Hz, 2 H), 2.91 (t, *J* = 7.2 Hz, 2 H), 7.24 (d, *J* = 8.5 Hz, 2 H), 7.43 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.9, 27.5, 30.0, 42.9, 128.2, 129.2, 133.1, 134.0, 207.7 ppm. LRMS: *m*/*z* (%) = 278 (7) $[M + 4]^+$, 276 (15) $[M + 2]^+$, 274 (7) $[M]^+$, 191 (4), 156 (3), 125 (3), 85 (100), 43 (86). Anal. Calcd for $C_{11}H_{13}ClOSe$: C, 47.93; H, 4.75. Found: C, 47.83; H, 4.39. Compound **4g**: mp 100–101 °C. IR (KBr disk): 1709, 2450–3500 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.99 (quin, *J* = 7.2 Hz, 2 H), 2.51 (t, *J* = 7.2 Hz, 2 H), 2.94 (t, *J* = 7.3 Hz, 2 H), 7.24 (d, *J* = 8.5 Hz, 2 H), 7.43 (d, *J* = 8.5 Hz, 2 H), 11.50 (br s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8, 27.1, 33.5, 127.7, 129.3, 133.3, 134.2, 179.3 ppm. LRMS: *m*/*z* (%) = 280 (10) $[M + 4]^+$, 278 (24) $[M + 2]^+$, 276 (11) $[M]^+$, 192 (21), 156 (16), 112 (24), 87 (100), 43 (44). Anal. Calcd for $C_{10}H_{11}ClO_2Se$: C, 43.27; H, 3.99. Found: C, 43.16; H, 3.83. Compound **4h**: IR (neat): 2246 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.00 (quin, *J* = 7.0 Hz, 2 H), 2.51 (t, *J* = 7.0 Hz, 2 H), 2.99 (t, *J* = 7.1 Hz, 2 H), 7.27 (d, *J* = 8.5 Hz, 2 H), 7.45 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.1, 25.7, 26.4, 118.8, 127.0, 129.5, 133.9, 134.7 ppm. LRMS: *m*/*z* (%) = 261 (50) $[M + 4]^+$, 259 (100) $[M + 2]^+$, 257 (52) $[M]^+$, 191 (14), 156 (14), 112 (11), 68 (14), 41 (27). Anal. Calcd for $C_{10}H_{10}ClNSe$: C, 46.44; H, 3.90; N, 5.42. Found: C, 46.73; H, 4.15; N, 5.58. Compound **4i**: IR (neat): 1714 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.96 (quin, *J* = 7.1 Hz, 2 H), 2.13 (s, 3 H), 2.59 (t, *J* = 7.1 Hz, 2 H), 2.99 (t, *J* = 7.1 Hz, 2 H), 7.40 (t, *J* = 7.7 Hz, 1 H), 7.50–7.62 (m, 2 H), 7.78–7.89 (m, 3 H), 8.40 (d, *J* = 8.4 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.0, 27.5, 29.7, 43.1, 125.8, 126.2, 126.6, 127.5, 128.3, 128.7, 129.2, 132.3, 134.1, 134.3, 207.9 ppm. LRMS: *m*/*z* (%) = 292 (17) $[M + 2]^+$, 290 (10) $[M]^+$, 207 (6), 165 (6), 141 (6), 128 (15), 115 (17), 85 (100), 43 (99). Anal. Calcd for $C_{15}H_{16}OSe$: C, 61.86; H, 5.54. Found: C, 62.17; H, 5.76. Compound **4j**: IR (neat): 1708, 2400–3500 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.01 (quin, *J* = 7.2 Hz, 2 H), 2.53 (t, *J* = 7.3 Hz, 2 H), 3.02 (t, *J* = 7.2 Hz, 2 H), 7.41 (t, *J* = 7.7 Hz, 1 H), 7.51–7.63 (m, 2 H), 7.80–7.90 (m, 3 H), 8.45 (d, *J* = 8.4 Hz, 1 H), 11.41 (br s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.0, 27.1, 33.8, 125.8, 126.3, 126.7, 127.6, 128.5, 128.7, 129.1, 132.5, 134.1, 134.4, 179.3 ppm. LRMS: *m*/*z* (%) = 294 (87) $[M + 2]^+$, 292 (47) $[M]^+$, 208 (38), 141 (14), 128 (100), 115 (65), 87 (67), 43 (24). Anal. Calcd for $C_{14}H_{14}O_2Se$: C, 57.35; H, 4.81. Found: C, 56.99; H, 5.03.