A novel synthetic method for β-keto esters

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A novel synthetic method for the preparation of β-keto esters has been developed. α-Phenylseleno acetate was treated with LDA to produce a selenium-stabilised carbanion, which reacted with aldehydes, followed by selenoxide *syn*-elimination, to give β-keto esters.

Keywords: α-phenylseleno acetate, selenoxide *syn*-elimination, β-keto esters, aldehydes

β-Keto esters are an important class of 1,3-dicarbonyl compounds and have a long history of use in synthesis. Many methods have been developed for the preparation of β-keto esters.[1]

Over the past 30 years, organoselenium reagents have been increasingly utilised in highly selective organic reactions.[2] Selenium-stabilised carbanions have played an important role in organic synthesis because of their easy availability and because they are particularly good nucleophiles, allowing the formation of new carbon–carbon bonds when they react with compounds bearing an electrophilic carbon atom.[3,4]

Our research group has been interested in the application of organoselenium reagents in the organic synthesis.[5] We have found that β-hydroxyselenides, the addition products of α-phenylseleno acetate and aldehydes, can be conveniently converted into β-keto esters by selenoxide *syn*-elimination (Scheme 1).

The α-selenocarbanion readily obtained according to Sharpless (LDA, THF, –78°C) react at this temperature with aldehydes producing β-hydroxyselenides **2** in high yield.[7] The β-hydroxyselenides **2** may be converted to β-keto esters **3** by oxidation with hydrogen peroxide in good yield. The results are shown in Table 1.

In summary, we have developed a novel synthetic method for the conversion of aldehydes to β-keto esters. The β-hydroxyselenides, the addition products of α-phenylseleno acetate and aldehydes, may be conveniently converted in good yield to β-keto ester by reaction with hydrogen peroxide.

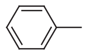
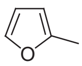
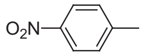
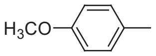
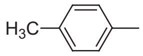
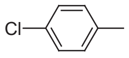
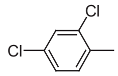
Experimental

^{1}H NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ with TMS as the internal standard. IR spectra were recorded on a Bruker Tenson 27 spectrometer. EIMS were run on a HP 5989B mass spectrometer. Microanalysis was carried out on a Carlo Erba 1106. THF for preparation of β-hydroxyselenides was purified by the standard method[6] before use.

Typical procedure for the preparation of β-*hydroxyselenides* **2a–i**

β-Hydroxyselenides 2 were prepared according to literature procedure.[7] Under an N_2 atmosphere, LDA (2 mmol) is rapidly added at –78°C to a α-phenylseleno acetate (2 mmol) solution in THF (20 ml). After 2 h benzaldehydes (2 mmol) is added and the resulting solution stirred for 1 h at –78°C and rise to room temperature about 1 h. Usual work up and purification on preparative layer chromatography on silica gel to afford **2a** (84%).

Table 1 Synthesis of β-keto ester

Compound	R	Yield/%[a]
3a		93
3b		80
3c		90
3d		83
3e		94
3f		89
3g		87
3h	$PhCH_2$-	82
3i	$(CH_3)_2CHCH_2$-	71

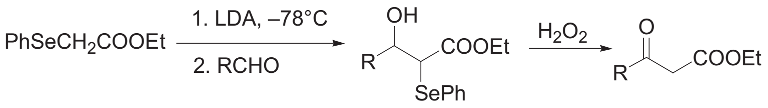
[a]Yields are of pure isolated products.

2a: Yield 84%; oil.[7] IR ν (cm^{-1}): 3420, 3030, 2979, 1727, 1578, 1257. ^{1}H NMR δ (ppm): 1.18(t, J = 7.1 Hz, 3H), 3.49(d, J = 7.8 Hz, 1H), 3.50(s, 1H), 4.10(q, J = 7.1 Hz, 2H), 4.62(d, J = 7.8 Hz, 1H), 7.18–7.65 (m, 10H). MS (m/z): 350(M$^+$), 323, 304, 193, 166, 106, 91, 77.

2b: Yield 70%; oil. IR ν (cm^{-1}): 3410, 3130, 2984, 1732, 1571, 1247. ^{1}H NMR δ (ppm): 1.24(t, J = 7.1 Hz, 3H), 3.59(m, 2H), 4.16 (q, J = 7.0 Hz, 2H), 5.23(d, J = 5.8 Hz, 1H), 6.58(d, d, J = 3.6, 1.02 Hz, 1H), 7.24(d, J = 3.7 Hz, 1H), 7.60(d, J = 0.9 Hz, 1H). MS (m/z): 341(M$^+$), 314, 295, 183, 110, 97, 67. Anal. Calcd. for $C_{15}H_{16}O_4Se$: C 53.11, H 4.75. Found: C 53.20, H 4.71%.

2c: Yield 81%; oil. IR ν (cm^{-1}): 3410, 3030, 2982, 1717, 1616, 1531, 1351, 1186. ^{1}H NMR δ (ppm): 1.08(t, J = 7.1 Hz, 3H), 3.50(s, 1H), 3.61(d J = 8.0 Hz, 1H), 4.06(q, J = 7.1 Hz, 2H), 4.88(d, J = 8.1 Hz, 1H), 7.20–7.39 (m, 5H), 7.71(d, J = 8.9 Hz, 2H), 8.18(d J = 9.0 Hz, 2H). MS (m/z): 395(M$^+$), 368, 349, 238, 211, 152, 120, 76. Anal. Calcd. for $C_{17}H_{17}NO_5Se$: C 51.79, H 4.35, N 3.55. Found: C 51.88, H 4.29, N 3.60%.

2d: Yield 75%; oil. IR ν (cm^{-1}): 3421, 3030, 2988, 1714, 1587, 1257, 1197. ^{1}H NMR δ (ppm): 1.16(t, J = 7.1 Hz, 3H), 3.49(m, 2H), 3.77(s, 3H), 4.1(q, J = 7.1 Hz, 2H), 4.54(d, J = 7.8 Hz, 1H), 7.19–7.34 (m, 5H), 7.58(d J = 8.8 Hz, 2H), 7.72(d, J = 8.8 Hz, 2H). MS (m/z): 380(M$^+$), 365, 353, 322, 223,196, 137, 122, 71. Anal. Calcd. for $C_{18}H_{20}O_4Se$: C 57.00, H 5.31. Found: C 56.87, H 5.24%.



1 **2** **3**

Scheme 1

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2e: Yield 86%; oil. IR ν (cm^{-1}): 3414, 3030, 2984, 1724, 1589, 1236. ^{1}H NMR δ (ppm): 1.18(t, J = 7.2 Hz, 3H), 2.41(s, 3H), 3.49(m, 2H), 4.06(q, J = 7.1 Hz, 2H), 4.57(d, J = 7.8 Hz, 1H), 7.27(m, 5H), 7.57(d, J = 8.1 Hz, 2H), 7.75(d, J = 8.1 Hz, 2H). MS (m/z): 364(M^+), 337, 318, 207, 180, 121, 97, 77. Anal. Calcd. for $C_{18}H_{20}O_3Se$: C 59.51, H 5.55. Found: C 59.45, H 5.51%.

2f: Yield 83%; oil. IR ν (cm^{-1}): 3401, 3030, 2982, 1714, 1582, 1351, 1186. ^{1}H NMR δ (ppm): 1.19(t, J = 7.1 Hz, 3H), 3.50(m, 2H), 4.12(q, J = 7.2 Hz, 2H), 4.74(d, J = 7.9 Hz, 1H), 7.19–7.34(m, 7H), 7.58(d J = 8.1 Hz, 2H). MS (m/z): 384(M^+), 338, 303, 227, 142, 111, 75. Anal. Calcd. for $C_{17}H_{17}ClO_3Se$: C 53.21, H 4.47. Found: C 53.34, H 4.46%.

2g: Yield 76%; oil. IR ν (cm^{-1}): 3424, 3037, 2983, 1729, 1589, 1569, 1197. ^{1}H NMR δ (ppm): 1.22(t, J = 7.2 Hz, 3H), 3.49(m, 2H), 4.1(q, J = 7.1 Hz, 2H), 5.78(d, J = 8.1 Hz, 1H), 7.29–7.82(m, 8H). MS (m/z): 419(M^+), 383, 355, 261, 189, 175, 145, 139, 109, 75. Anal. Calcd. for $C_{17}H_{16}Cl_2O_3Se$: C 48.83, H 3.86. Found: C 48.75, H 3.82%.

2h: Yield 73%; oil. IR ν (cm^{-1}): 3406, 3030, 2957, 1723, 1584, 1272. ^{1}H NMR δ (ppm): 1.25(t, J = 7.2 Hz, 3H), 2.27(d, J = 6.4 Hz, 2H), 3.50(m, 1H), 3.60(s, 1H), 4.18(q, J = 7.2 Hz, 2H), 4.54 (d, J = 7.6 Hz, 1H), 7.15–7.79(m, 10H). MS (m/z): 364(M^+), 337, 318, 207, 180, 121, 97, 77. Anal. Calcd. for $C_{18}H_{20}O_3Se$: C 59.51, H 5.55. Found: C 59.42, H 5.51%.

2i: Yield 71%; oil. IR ν (cm^{-1}): 3412, 2961, 2873, 1731, 1467, 1370, 1182. ^{1}H NMR δ (ppm): 0.92(d, J = 6.0 Hz, 6H), 1.07 (t, J = 7.2 Hz, 3H), 1.80(m, 1H), 2.38(m, 2H), 3.51(m, 2H), 4.10 (m, 3H), 7.19(m, 3H), 7.37(m, 2H). MS (m/z): 330(M^+), 303, 284, 173, 146, 131, 73. Anal. Calcd. for $C_{15}H_{22}O_3Se$: C 54.71, H 6.73. Found: C 54.66, H 6.67%.

General procedure for the preparation of β-*keto esters* **3a–i**

30% H_2O_2 (2 ml) was added to β-Hydroxyselenides **2** (1 mmol) in THF (20 ml). The mixture was stirred for 1 h at room temperature and 2 h at 50°C. Upon completion of the reaction (monitored by tlc), the mixture was added to $CHCl_3$ (30 ml) and washed with H_2O (20 ml × 2). The mixture was purified by preparative layer chromatography on silica gel to afford the β-keto esters **3**.

3a: Yield 93%; oil.[1b] IR ν (cm^{-1}): 3063, 2983, 1742, 1688, 1624, 1598, 1326, 1148. ^{1}H NMR δ (ppm): 1.25(t, J = 7.2 Hz, 3H), 4.00 (s, 2H), 4.21(q, J = 7.1 Hz, 2H), 7.47(m, 3H), 7.95(d, J = 7.3 Hz, 2H). MS (m/z): 192(M^+), 146, 120, 105, 77, 51.

3b: Yield 80%; oil. [1c] IR ν (cm^{-1}): 3135, 2984, 1741, 1679, 1571, 1369, 1155. ^{1}H NMR δ (ppm): 1.26(t, J = 7.1 Hz,3H), 3.85(s, 2H), 4.21(q, J = 7.1 Hz, 2H), 6.58(d, d, J = 1.7, J = 3.6 Hz, 1H), 7.28(d, J = 3.7 Hz, 1H), 7.62(d, J = 0.7 Hz, 1H). MS (m/z): 182(M^+), 154, 137, 110, 95, 81, 67, 53.

3c: Yield 90%; oil. [1d] IR ν (cm^{-1}): 3114, 2992, 1739, 1696, 1621, 1594, 1349, 1217. ^{1}H NMR δ (ppm): 1.35(t, J = 7.2 Hz, 3H), 4.04 (s, 2H), 4.23(q, J = 7.1 Hz, 2H), 8.27(d, J = 9.0 Hz, 2H), 8.34(d, J = 8.9 Hz, 2H). MS (m/z): 237(M^+), 191, 174, 150, 120, 104, 92, 76, 69.

3d: Yield 83%; oil.[1b] IR ν (cm^{-1}): 2981, 1739, 1679, 1602, 1576, 1368, 1174. ^{1}H NMR δ (ppm): 1.25(t, J = 7.2 Hz, 3H), 3.87(s, 3H), 3.94(s, 3H), 4.20(q, J = 7.2 Hz, 2H), 6.94(d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.8 Hz, 2H). MS (m/z): 222(M^+), 176, 150, 135, 119, 105, 91, 77, 57.

3e: Yield 94%; oil. [1b] IR ν (cm^{-1}): 3054, 2983, 1743, 1685, 1609, 1572, 1367, 1187. ^{1}H NMR δ (ppm): 1.26(t, J = 7.1 Hz, 3H), 2.42(s, 3H), 3.97(s, 2H), 4.20(q, J = 7.1 Hz, 2H), 7.28(d, J = 8.0 Hz, 2H), 7.84(d, J = 8.1 Hz, 2H). MS (m/z): 206(M^+), 160, 134, 120, 119, 91, 77, 65.

3f: Yield 89%; oil. [1b] IR ν (cm^{-1}): 2983, 1742, 1689, 1623, 1589, 1570, 1490, 1198. ^{1}H NMR δ (ppm): 1.26(t, J = 7.1 Hz, 3H), 3.96(2H), 4.21(q, J = 7.2 Hz, 2H), 7.46(d, J = 8.7 Hz, 2H), 7.89(d, J = 8.7 Hz, 2H). MS (m/z): 226(M^+), 180, 154, 141, 139, 111, 75.

3g: Yield 87%; oil. IR ν (cm^{-1}): 3092, 2983, 1744, 1701, 1629, 1584, 1473, 1374, 1197. ^{1}H NMR δ (ppm): 1.25(t, J = 7.1 Hz, 3H), 4.03(s, 2H), 4.19(q, J = 7.1 Hz, 2H), 7.32(m, 1H), 7.60(d, 1H), 7.45(s, 1H). MS (m/z): 260(M^+), 227, 225, 197, 175, 173, 145, 109, 75. Anal. Calcd. for $C_{11}H_{10}Cl_2O_3$: C 50.60, H 3.86. Found: C 50.47, H 3.80%.

3h: Yield 82%; oil. [1c] IR ν (cm^{-1}): 3063, 2927, 1743, 1718, 1656, 1584, 1495, 1454, 1367, 1171. ^{1}H NMR δ (ppm): 1.26(t, J = 7.1 Hz, 3H), 3.38(s, 2H), 3.78(s, 2H), 4.20(q, J = 7.1 Hz, 2H), 7.21(m, 3H), 7.48(d, J = 7.2 Hz, 2H). MS (m/z): 206(M^+), 160, 134, 119, 91, 77.

3i: Yield 71%; oil. [1b] IR ν (cm^{-1}): 2962, 1775, 1732, 1629, 1467, 1370, 1183. ^{1}H NMR δ (ppm): 0.98(d, 6H), 1.28(t, J = 7.2 Hz, 3H), 1.46(m, 1H), 2.50(d, 2H), 3.50(s, 2H), 4.25(q, J = 7.1 Hz, 2H). MS (m/z): 172(M^+), 126, 100, 85, 57, 43.

This work was supported by the Science Foundation of Hangzhou Normal College (No.131901, No. 131001).

Received 26 February 2007; accepted 10 March 2007
Paper 07/4509 doi: 10.3184/030823407X198311

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