Synthesis of Highly Functionalized β-Lactams. Alkynylation of 2-Oxoazetidin-1-yl Malonates

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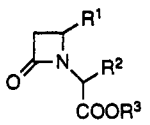
Nonfused 2-oxoazetidines of type **1** have been extensively used for the synthesis of various antibiotics having a fused-bicyclic β-lactam system as a basic molecular feature.[1] In some of these syntheses the construction of the bicyclic framework is completed through cyclization reactions involving an acetylenic functionality situated on one of the 2-oxoazetidine's appendages.[2-6] We conceived



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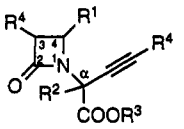

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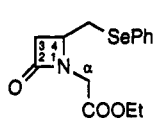
2-oxoazetidines of type **2** as potential intermediates for the synthesis of bicyclic β-lactams. These compounds are characterized by an acetylenic group directly linked to the α-carbon atom of a (2-oxoazetidin-1-yl)acetic acid system and a functionalized tether R^1. This paper describes the synthesis of the highly functionalized alkynyl-(2-oxoazetidin-1-yl)malonates **7** and **8** as well as the structurally related alkynyl(phthaloyl)malonate **9**.

Starting materials **4** and **5** were prepared by ethoxy carbonylation of ethyl (4-((phenylseleno)methyl)-2-oxoazetidin-1-yl)acetate (**3**) and *tert*-butyl(4-*tert*-butylthio)-2-oxoazetin-1-yl)acetate,[7] respectively, as described in the Experimental Section. These compounds as well as diethyl 2-phthalimidomalonate were alkynylated on their α-carbon atom by treatment of their lithium or sodium enolate with [(trimethylsilyl)ethynyl](phenyl)iodonium triflate (**6**) in an inert organic solvent to give the corresponding ethynylated products **7–9** in high yield.[8] In a typical experiment a solution of the (2-oxoazetidinyl)malonate **4** and *n*-BuLi in THF at 0 °C was added to a solution of [(trimethylsilyl)ethynyl](phenyl)iodonium triflate (**6**) in THF at −78 °C, and the reaction mixture was allowed to



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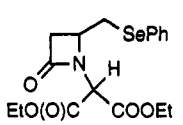

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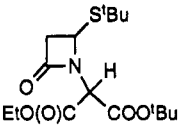

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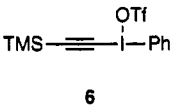

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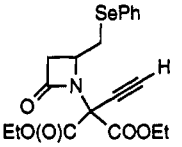

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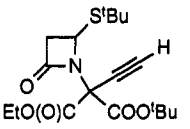

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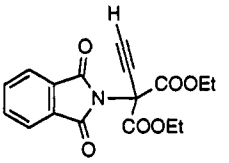

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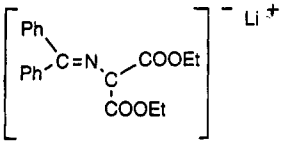
warm to ambient temperature and worked up to give the alkynyl(2-oxoazetidin-1-yl)malonates **7** in 93% yield.

In contrast to the related alkynylation of the (alkylideneamino)malonate **10** which affords the ((trimethylsilyl)ethynyl)malonate **11**, in which the alkyne group is protected by a TMS group,[9] the alkynylation of (2-oxoazetidin-1-yl)malonates **4** and **5** and of diethyl 2-phthalimidomalonate directly affords the terminal alkynes **7–9**.



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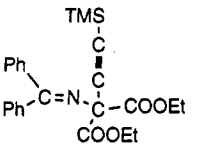

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Experimental Section

General experimental conditions were given in a previous paper.[9]

Ethyl (4-((Phenylseleno)methyl)-2-oxoazetidin-1-yl)acetate (3). To a suspension of 4-((phenylseleno)methyl)-2-oxoazetidine[10] (283 mg, 1.1 mmol) and ethyl bromoacetate (0.17 mL, 1.5 mmol) in benzene (50 mL) was added 18-crown-6 (46 mg, 0.18 mmol) and powdered KOH (87 mg, 1.5 mmol). The reaction mixture was stirred at room temperature for 2 h. Ether (60 mL) was added, the solid was filtered over Celite, and the organic layer was evaporated. Flash chromatography (EtOAc/Hex, 2:3) of the residue afforded the title compound **3** (258 mg, 72%): IR (neat) 1763, 1751, 1738 (C=O) cm^{-1}; ^1H NMR (270 MHz) δ 1.41 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.66 (dd, J = 14.8, 2.4 Hz, 1H, azetidinone 3-CH*H*), 3.06–3.15 (m, 3H, azetidinone 3-C*H*H and CH_2Se), 3.71 (d, J = 18.0 Hz, 1H, NCH*H*), 4.00–4.07 (m, azetidinone 4-CH), 4.09 (d, J = 18.0 Hz, NC*H*H), 4.17 (q, J = 7.1 Hz, 2H, CH_2CH_3), 7.27–7.29 (m, 3H, Ar), 7.51–7.55 (m, 2H, Ar).

Diethyl (4-((Phenylseleno)methyl)-2-oxoazetidin-1-yl)-malonate (4). To a cold (−78 °C) solution of LHMDS [(1.92 mmol), obtained from HMDS (0.4 mL) and *n*-BuLi (1 equiv, 1.5 M in hexane)] in dry THF (2 mL) was added a solution of 1-((ethoxycarbonyl)methyl)-4-((phenylseleno)methyl)azetidin-2-one (313 mg, 0.96 mmol) in THF (1 mL) and DMPU (0.25 mL). The solution was maintained at −78 °C for 45 min and ethyl chloroformate (0.1 mL, 1 mmol) was added. The solution was stirred at −78 °C for 1 h and at −40 °C for 1 h. Acetic acid (0.06

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mL in 0.5 mL of THF) was added, the reaction mixture was warmed to 0 °C, and ethyl acetate (10 mL) was added. The solution was washed with brine, dried, and evaporated. Flash chromatography (Hex/EtOAc, 7:3) afforded the title compound 4 (295 mg, 74%): IR (neat) 1778, 1751, 1745 (C=O) cm^{-1}; ^1H NMR (270 MHz) δ 1.25 (t, J = 7.2 Hz, CH_2CH_3), 1.30 (t, J = 7.2 Hz, CH_2CH_3), 2.66 (dd, J = 15.1, 2.7 Hz, 1H, azetidinone 3-CH*H*), 3.00 (dd, J = 12.7, 9.6 Hz, CH*H*Se), 3.10 (dd, J = 15.1, 5.25 Hz, azetidinone 4-C*H*H), 3.41 (dd, J = 12.7, 4.1 Hz, C*H*HSe), 4.18–4.29 (m, $2CH_2CH3$ and azetidinone 4-CH), 5.19 (s, 1H, NCH), 7.26–7.29 (m, 3H, Ar), 7.50–7.56 (m, 2H, Ar).

***tert*-Butyl Ethyl (4-(*tert*-Butylthio)-2-oxoazetidin-1-yl)-malonate (5).** To a cold (−78 °C) solution of LHMDS [(7 mmol) obtained from HMDS (1.45 mL) and *n*-BuLi (1 equiv, 1.5 M in hexane)] in dry THF (8 mL) was added solution of *tert*-butyl (4-(*tert*-butylthio)-2-oxoazetidin-1-yl)acetate (940 mg, 3.5 mmol) in THF (4 mL) and DMPU (0.82 mL). The solution was maintained at −78 °C for 1 h and ethyl chloroformate (0.35 mL, 4 mmol) was added. The solution was stirred at −78 °C for 1 h and at −40 °C for an additional 1 h. Acetic acid (0.58 mL in 5 mL of THF) was added, the reaction mixture was warmed to 0 °C, and ethyl acetate (50 mL) was added. The solution was washed with 5% aqueous $NaHCO_3$ and then with water and dried. Flash chromatography (Hex/EtOAc, 4:1) afforded the azetidinone 5 (975 mg, 81%) as a 1:1 diastereoisomeric mixture: IR (neat) 1763–1785 (br, C=O), 1739–1751 (br, C=O) cm^{-1}; ^1H NMR (270 MHz) δ 1.32 (two t, J = 7.1 Hz and J = 7.05 Hz, CH_2CH_3), 1.34 and 1.35 (two s, $C(CH_3)_3$), 1.50 and 1.51 (two s, 9H, $SC(CH_3)_3$), 3.05 (dd, J = 15.0, 2.3 Hz, 1H, azetidinone 3-CH*H*), 3.54 and 3.58 (two dd, J = 15.0, 5.1 Hz and J = 14.9 5, 4.85 Hz, 1H, azetidinone 3-C*H*H), 4.25 and 4.29 (two q, J = 7.3 Hz and J = 7.1 Hz, 2H, CH_2CH_3), 4.80 and 4.86 (two s, 1H, NCH), 5.15 and 5.21 (two dd, J = 4.9, 2.3 Hz and J = 4.9, 2.3 Hz, 1H, azetidinone 4-CH). Anal. Calcd for $C_{16}H_{27}NO_5S$: C, 55.65; H, 7.83; N, 4.06; S, 9.27. Found: C, 55.80; H, 7.58; N, 3.97; S, 8.94.

Diethyl Ethynyl(4-((phenylseleno)methyl)-2-oxoazetidin-1-yl)malonate (7). To a stirred solution of 2-oxoazetidine 4 (96 mg, 0.23 mmol) in dry THF (3 mL) at 0 °C was added *n*-BuLi (1 equiv, 1.5 M in hexane). After 20 min at 0 °C, the dark reaction mixture was added dropwise (15 min) to a cold (−78 °C) stirred solution of [(trimethylsilyl)ethynyl](phenyl)iodonium triflate (124 mg, 0.23 mmol) in THF (3 mL). The reaction mixture was allowed to warm to room temperature and the solvent was evaporated. The residue was taken up in CH_2Cl_2 (10 mL), washed with water, dried, and evaporated. Flash chromatography (Hex/EtOAc, 7:3) afforded the title compound 7 (92.7 mg, 93%): IR (neat) 3268 (C≡CH), 2122 (C≡C), 1770, 1751, 1735 (C=O) cm^{-1}; ^1H NMR (400 MHz) δ 1.30 (q, J = 7.2 Hz, CH_2CH_3), 1.32 (q, J = 7.15 Hz, CH_2CH_3), 2.60 (dd, J = 15.1, 2.6 Hz, 1H, azetidinone 3-CH*H*), 2.64 (s, 1H, C≡C), 2.96 (dd, J = 12.6, 10.4 Hz, CH*H*Se), 3.10 (dd, J = 15.1, 5.4 Hz, azetidinone 3-C*H*H), 3.44 (dd, J = 12.6, 3.45 Hz, C*H*HSe), 4.09–4.19 (m, azetidinone 4-CH), 4.27–4.37 (m, CH_2CH_3), 7.27–7.29 (m, 3H, Ar), 7.52–7.56 (m, 2H, Ar). Anal. Calcd for $C_{19}H_{21}NO_5Se$: C, 54.03; H, 4.98; N, 3.32. Found: C, 53.75; H, 4.98; N, 3.22.

***tert*-Butyl Ethyl Ethynyl(4-(*tert*-butylthio)-2-oxoazetidin-1-yl)malonate (8).** To a stirred solution of 2-oxoazetidine 5 (220 mg, 0.64 mmol) in dry THF (8 mL) at −78 °C was added *n*-BuLi (1 equiv, 1.5 M in hexane). After 20 min at −78 °C, a solution of [(trimethylsilyl)ethynyl](phenyl)iodonium triflate (287 mg, 0.64 mmol) in THF (3 mL) was added. The reaction mixture was kept at −60 °C until TLC indicated consumption of the starting material (~1 h). Flash chromatography (Hex/EtOAc, 4:1) of the product obtained after evaporation afforded the title compound 8 (180 mg, 92%): mp 75 °C (hexane); IR (neat) 3260 (C≡CH), 2123 (C≡C), 1760, 1757, 1755 (C=O) cm^{-1}; ^1H NMR (400 MHz) δ 1.35 (m, $CO_2C(CH_3)_3$ and CH_2CH_3), 1.52 and 1.53 (two s, 9H, $SC(CH_3)_3$), 2.67 and 2.68 (two s, 1H, C≡CH), 3.01 (dd, J = 14.8, 1.95 Hz, 1H, azetidinone 3-CH*H*), 3.54 and 3.57 (two dd, J = 14.85, 4.7 Hz and J = 14.8, 4.7 Hz, 1H, azetidinone 3-C*H*H), 4.29–4.37 (m, CH_2CH_3), 5.07 and 5.09 (two dd, J = 4.75, 1.95 Hz and J = 4.65, 1.95 Hz, azetidinone 4-CH). Anal. Calcd for $C_{18}H_{27}NO_5S$: C, 58.58; H, 7.36; N, 3.79; S, 8.67. Found: C, 58.25; H, 7.13; N, 3.84; S, 8.55.

Diethyl Ethynylphthalimidomalonate (9). Procedure 1. To a stirred solution of diethyl phthalimidomalonate (200 mg, 0.66 mmol) in dry glyme (8 mL) at −78 °C was added *n*-BuLi (1 equiv, 1.14 M in hexane). After 30 min at −78 °C, a solution of [(trimethylsilyl)ethynyl](phenyl)iodonium triflate (355 mg, 0.66 mmol) in glyme (2 mL) was added. The reaction mixture was kept at −50 °C until the starting material was consumed (TLC, 30 min). Flash chromatography (Hex/EtOAc, 7:3) of the product obtained after evaporation afforded the title compound 9 (141 mg, 70%). **Procedure 2.** To a stirred solution of diethyl phthalimidomalonate (118 mg, 0.39 mmol) in dry toluene (3 mL) at room temperature was added NaH (14 mg, 0.43 mmol, 80% in paraffin). After 30 min [(trimethylsilyl)ethynyl](phenyl)-iodonium triflate (213 mg, 0.39 mmol) was added in four portions. Flash chromatography (Hex/EtOAc, 7:3) of the product obtained after evaporation afforded the title compound 9 (84 mg, 70%): mp 98 °C; IR (Nujol) 3273 (C≡CH), 2128 (C≡C), 1760, 1732, 1723 (C=O) cm^{-1}; ^1H NMR (80 MHz) δ 1.35 (t, J = 7.1 Hz, 6H, CH_3), 2.74 (s, 1H, C≡CH), 4.39 (q, J = 7.2 Hz, 4H, CH_2), 7.68–7.95 (m, 4H, Ph). Anal. Calcd for $C_{17}H_{15}NO_6$: C, 62.01; H, 4.59; N, 4.25. Found: C, 61.89; H, 4.58; N, 4.07.

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Supplementary Material Available: Copies of ^1H NMR spectra of 3 and 4 (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.