Alkynyltrifluoroborates as Versatile Tools in Organic Synthesis: A New Route to Spiroketal.

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General

All reactions were carried out under an Ar atmosphere using oven dried glassware and standard syringe and septa techniques. All work-up, wash, and chromatographic solvents were distilled prior to use. Diethyl ether and THF were distilled from Na/benzophenone under Ar.

Benzyl protected alkynols **1** were prepared according to the standard procedure from corresponding alcohols and benzyl bromide in the presence of NaH in THF¹. Starting alkynols, lactones and BF₃·Et₂O are commercially available and were used without further purification.

Gas chromatography was used to monitor the progress of reactions (Hewlett-Packard HP 6890 series equipped with flame ionization detector; capillary column with 5 % phenyl-methyl-siloxane as stationary phase (30 m × 0.32 mm I.D., 0.25 μm film thickness) and helium as a carrier gas). Chiral gas chromatography analyses were performed using fused silica capillary column with 20% of permethylated β-cyclodextrin in poly(35% diphenyl/ 65% dimethylsiloxane) as the stationary phase (30 m × 0.25 mm I.D., 0.25 μm film thickness).

Flash chromatographic purifications were performed using Merck Kieselgel 60 (230-400 mesh).

¹H-NMR and ¹³C-NMR data were recorded on Varian Unity-200, Varian Unity Inova-400, Bruker Avance 400, and Bruker Avance 500 in CDCl₃ and all chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane as internal standard (¹H) or relative to CDCl₃ (¹³C). Peak multiplicates in ¹H-NMR spectra are abbreviated as s (singlet), d (doublet), t (triplet), m (multiplet), and bs (broad singlet).

Interaction constants *J* are given in Hz (rounded to one decimal place).

Gas chromatography-mass spectrometry was performed on a Carlo Erba GC 8000 series gas chromatograph (capillary column with 5 % phenyl-methyl-siloxane as stationary phase, 30 m × 0.25 mm I.D., 0.25 μm film thickness) and Fisons MD 800 mass detector (quadrupole mass spectrometer using 70 eV electron impact ionization).

Infrared spectra were recorded with a Bruker IFS 88 and a Bruker Equinox 55 Fourier-transform infrared spectrometers. Absorption maxima are expressed in wavenumbers (cm⁻¹) with possible abbreviation br (broad).

Synthesis of Alkynones 3:

To a solution of alkyne **1** (8 mmol) in dry THF (25 ml) at -78°C, *n*BuLi (5 ml, 1.6M, 8 mmol) was slowly added, maintaining an argon atmosphere. The reaction mixture was stirred for 20 min, allowed to warm to about -30°C, cooled to -78°C again, and BF₃·Et₂O (1 ml, 7.9 mmol) was added dropwise. Stirring was continued for 10 min, and then lactone **2** (7.2 mmol) was added in one portion via syringe. The resulting mixture was allowed to warm to room temperature within 1 h, a solution of saturated NH₄Cl – NH₃ (aq.) 2:1 (5 ml) was added, the mixture was poured into water (50 ml), and extracted with Et₂O (4× 25 ml). The combined ethereal layers were washed with brine, dried briefly with MgSO₄, and evaporated to afford the crude product as a slightly yellow oil. The crude material was purified by chromatography on silica gel (hexane / 10-30% EtOAc) to yield the alkynone **3**.

Synthesis of Spiroketal 4:

Alkynone **3** (5 mmol) was dissolved in 50 ml of anhydrous EtOH or EtOAc, and 250 mg of 10% Pd/C was added. The mixture was stirred under H₂ (1 atm) at room temperature while monitoring the progress of reaction by GC. After the completion of reaction, the catalyst was filtered off, washed with the same solvent used for the reaction, and the most of the solvent was distilled off under atmospheric pressure. The residue could be then either directly distilled under reduced pressure to furnish the desired product **4**, or diluted with water (in the case of EtOH), extracted three times with pentane, dried over Na₂SO₄, and after evaporation of volatiles distilled under reduced pressure.

In some cases, the pre-formed diastereomeric and/or spiroketal/hemiketal mixtures were converted into the more stable *E*-isomers (**4b**, **4d**, **4g**, **4i** and **4k**), or *E,E/E,Z*-mixtures (**4e** and **4n**) respectively, before the isolation: After the most of the solvent was distilled off, a few drops of 2N HCl was added, and the mixture was stirred for approx. 5 min, diluted with pentane, extracted once with satd. aq. NaHCO₃, and the organic phase was dried over Na₂SO₄. Further work-up followed the standard procedure described above.

The yields reported below for each of the spiroketals **4** represent isolated yields (GC purity in parenthesis).

Selected analytical data:

Detailed analytical data of new α -alkynones **3k-n** are summarized below, while those of **3a-j** were reported previously.² All spiroketals **4** (including individual isomers) were identified by GC-MS and their spectra were in accordance with those reported in literature.³⁻¹⁶ Examples of selected MS, GC-IR, ¹H-NMR, and ¹³C-NMR spectra are enclosed.

3k 2-Benzyloxy-11-hydroxyundec-4-yn-6-one:

¹H NMR (400 MHz, CDCl₃): δ = 1.32 (d, 3H, J = 6.1 Hz), 1.39 (m, 2H), 1.56 (m, 2H), 1.69 (m, 2H), 2.55 (dd, 1H, J = 17.2 and 6.6 Hz), 2.56 (t, 2H, J = 7.3 Hz), 2.66 (dd, 1H, J = 17.2 and 5.4 Hz), 3.62 (t, 2H, J = 6.6 Hz), 3.76 (ddq, 1H, J = 6.6, 6.1 and 5.4 Hz), 4.57 (m, 2H), 7.25-7.37 (m, 5H). ¹³C NMR (100 MHz, CDCl₃): δ = 19.73, 23.69, 25.07, 26.59, 32.31, 45.35, 62.55, 70.79, 72.60, 82.05, 90.73, 127.59 (2C), 127.69, 128.41 (2C), 138.10, 187.99. IR (CCl₄): 3397 (br, OH), 2215 (C $\equiv$ C), 1675 (C=O) cm⁻¹.

3l 1-Benzyloxy-7-hydroxynon-2-yn-4-one:

¹H NMR (400 MHz, CDCl₃): δ = 0.95 (t, 3H, J = 7.5 Hz), 1.49 (m, 2H), 1.72 (m, 1H), 1.89 (m, 1H), 2.76 (m, 2H), 3.54 (m, 1H), 4.33 (s, 2H), 4.62 (s, 2H), 7.26-7.38 (m, 5H). ¹³C NMR (100 MHz, CDCl₃): δ = 9.85, 30.37, 30.45, 41.85, 56.93, 72.09, 72.32, 85.35, 87.81, 128.11 (2C), 128.13, 128.53 (2C), 136.69, 187.48. IR (CCl₄): 3418 (br, OH), 2215 (C $\equiv$ C), 1681 (C=O) cm⁻¹.

3m 2-Benzyloxy-8-hydroxyundec-3-yn-5-one:

¹H NMR (400 MHz, CDCl₃): δ = 0.93 (t, 3H, J = 7.0 Hz), 1.30-1.55 (m, 4H), 1.52 (d, 3H, J = 6.7 Hz), 1.72 (m, 1H), 1.89 (m, 1H), 2.75 (m, 2H), 3.63 (m, 1H), 4.36 (q, 1H, J = 6.7 Hz), 4.51 (d, 1H, J = 11.6 Hz), 4.78 (d, 1H, J = 11.6 Hz), 7.25-7.37 (m, 5H). ¹³C NMR (100 MHz, CDCl₃): δ = 14.00, 18.78, 21.30, 30.95, 39.80, 41.94, 64.22, 70.71, 71.07, 84.03, 91.39, 127.93, 127.97 (2C), 128.47 (2C), 137.23, 187.65. IR (CCl₄): 3425 (br, OH), 2212 (C $\equiv$ C), 1679 (C=O) cm⁻¹.

3n 2-Benzyloxy-10-hydroxyundec-4-yn-6-one:

¹H NMR (400 MHz, CDCl₃): δ = 1.18 (d, 3H, J = 6.1 Hz), 1.31 (d, 3H, J = 6.1 Hz), 1.39-1.85 (m, 4H), 2.45 (dd, 1H, J = 16.6 and 5.1 Hz), 2.58 (m, 2H), 2.66 (dd, 1H, J = 16.6 and 7.4 Hz), 3.73 (ddq, 1H, J = 7.4, 6.1 and 5.1 Hz), 3.96 (m, 1H), 4.57 (s, 3H), 7.24-7.37 (m, 5H). ¹³C NMR (100 MHz, CDCl₃): δ = 19.75, 20.01, 23.59, 26.62, 38.28, 44.82, 68.11, 70.79, 72.58, 82.03, 91.00, 127.50, 127.62 (2C), 128.32 (2C), 138.08, 188.11. IR (CCl₄): 3417 (br, OH), 2215 (C $\equiv$ C), 1675 (C=O) cm⁻¹.

4a 1,6-Dioxaspiro[4.5]decane:⁴

EtOAc, 15 h; distillation (Kugelrohr, 125°C air bath / 50 Torr) afforded 505 mg (71%) of clear liquid (GC $\approx$ 100%).

GC-MS (EI); m/z (%): 142 (10) [M^+], 141 (2), 112 (11), 111 (6), 101 (21), 100 (14), 99 (2), 98 (6), 97 (20), 87 (100), 86 (29), 85 (9), 84 (61), 83 (21), 55 (45), 41 (47).

4b 7-Methyl-1,6-dioxaspiro[4.5]decane:⁵

EtOAc, 14 h, run from 50.8 mmol **3b**; distillation (60.5°C / 14 Torr) afforded 6.07 g of (*E*)-**4b** (76%) as clear liquid (GC 98%).

GC-MS (EI); m/z (%):

(*E*)-**4b**: 156 (5) [M^+], 155 (2), 141 (3), 126 (3), 115 (10), 114 (5), 113 (3), 112 (19), 97 (27), 87 (98), 86 (16), 85 (11), 84 (100), 69 (12), 41 (31).

(*Z*)-**4b**: MS-spectrum was nearly identical with that of (*E*)-**4b**.

4c 2-Methyl-1,6-dioxaspiro[4.4]nonane:⁶

EtOH, 17 h; distillation (Kugelrohr, 125°C air bath / 50 Torr) afforded 572 mg (80%) of clear liquid (GC 99%, mixture of two isomers 1:1). MS-spectra were closely similar for both isomers.

GC-MS (EI); m/z (%): 142 (12) [M^+], 141 (5), 127 (24), 112 (11), 101 (41), 100 (24), 98 (47), 97 (23), 87 (100), 85 (34), 83 (37), 69 (7), 59 (7), 56 (71), 55 (43), 41 (23).

4d (5*S*,7*S*)-7-Methyl-1,6-dioxaspiro[4.5]decane:^{5,7}

EtOAc, 24 h; distillation (Kugelrohr, 130°C air bath / 50 Torr) afforded 484 mg (62%) of clear liquid (GC 99%, ee >98%). MS-spectrum was identical with that of (*E*)-**4b**. See Example 1.

4e 2,7-Dimethyl-1,6-dioxaspiro[4.5]decane:⁸

EtOH, 15 h; distillation (Kugelrohr, 140°C air bath / 35 Torr) afforded 578 mg (68%) of clear liquid (GC 98%, mixture of *E,E* and *Z,E*-isomer 1:1). Analytical samples of *E,E*-**4e**, *Z,E*-**4e**, and *E,Z/Z,Z*-mixture were obtained from the crude reaction mixture by liquid chromatography (SiO₂ deactivated with 6% H₂O; pentane/Et₂O 99:1 – 90:10). MS-spectra were closely similar for all isomers. See Example 2.

GC-MS (EI); m/z (%): 170 (4) [M^+], 155 (5), 126 (20), 115 (16), 111 (12), 101 (100), 100 (28), 98 (91), 97 (32), 85 (17), 83 (44), 69 (22), 55 (41).

4f 1,7-Dioxaspiro[5.5]undecane:⁹

EtOAc, 22 h; distillation (Kugelrohr, 140°C air bath / 35 Torr) afforded 493 mg (63%) of clear liquid (GC 97%).

GC-MS (EI); m/z (%): 156 (14) [M^+], 126 (3), 111 (30), 101 (88), 100 (55), 99 (9), 98 (100), 83 (55), 55 (94).

4g 2-Methyl-1,7-dioxaspiro[5.5]undecane:¹⁰

EtOH, 28 h; distillation (Kugelrohr, 140°C air bath / 35 Torr) afforded 553 mg (65%) of (*E*)-**4g** as clear liquid (GC 98%).

GC-MS (EI); m/z (%):

(*E*)-**4g**: 170 (21) [M^+], 155 (3), 140 (2), 126 (16), 125 (13), 115 (52), 114 (28), 112 (51), 111 (20), 101 (93), 100 (37), 98 (100), 97 (39), 83 (50), 73 (16), 69 (27), 55 (62).

(*Z*)-**4g**: MS-spectrum was nearly identical with that of (*E*)-**4g**.

4h 2-Methyl-1,6-dioxaspiro[4.5]decane:^{5,7}

EtOH, 26 h; run from 12.5 mmol **3h**; distillation (Kugelrohr, 125°C air bath / 40 Torr) afforded 1.42 g (73%) of clear liquid (GC 98%, mixture of two isomers 1:2). MS-spectra were closely similar for both isomers.

GC-MS (EI); m/z (%): 156 (6) [M^+], 155 (2), 141 (5), 126 (2), 112 (17), 111 (18), 101 (100), 100 (44), 98 (61), 85 (13), 83 (55), 55 (48).

4i (2*S*,6*R*)-2-Methyl-1,7-dioxaspiro[5.5]undecane:¹⁰

EtOH, 26 h; distillation (Kugelrohr, 140°C air bath / 35 Torr) afforded 547 mg (64%) of (2*S*,6*R*)-**4i** as clear liquid (GC 99%, ee >98%). MS-spectrum was identical with that of (*E*)-**4g**. See Example 3.

4j 1,7-Dioxaspiro[5.6]dodecane:¹¹

EtOH, 40 h; distillation (Kugelrohr, 140°C air bath / 20 Torr) afforded 462 mg (54%) of clear liquid (GC ≈100%). See Example 4.

GC-MS (EI); m/z (%): 170 (7) [M^+], 125 (5), 115 (21), 112 (20), 111 (49), 101 (80), 98 (95), 97 (26), 83 (41), 73 (11), 69 (28), 55 (100).

4k 2-Methyl-1,7-dioxaspiro[5.6]dodecane:¹²

EtOH, 18 h; run from 8.1 mmol **3k**; distillation (Kugelrohr, 160°C air bath / 20 Torr) afforded 1.24 g (83%) of (*E*)-**4k** as clear liquid (GC ≈100%).

GC-MS (EI); m/z (%): 184 (11) [M^+], 169 (5), 154 (7), 140 (8), 115 (100), 112 (93), 97 (49).

4l 2-Ethyl-1,6-dioxaspiro[4.4]nonane (*Chalcogran*):¹³

EtOH, 24 h; distillation (Kugelrohr, 130°C air bath / 35 Torr) afforded 593 mg (76%) of clear liquid (GC ≈100%, mixture of two isomers 1:1). MS-spectra were closely similar for both isomers.

GC-MS (EI); m/z (%): 156 (3) [M^+], 155 (3), 128 (8), 127 (100), 115 (5), 98 (25), 97 (15), 87 (32), 85 (27), 69 (10), 55 (16).

4m 2-Methyl-7-propyl-1,6-dioxaspiro[4.4]nonane:^{3,14}

EtOH, 37 h; run from 2.95 mmol **3m**; distillation (Kugelrohr, 150°C air bath / 25 Torr) afforded 318 mg (58%) of clear liquid (GC ≈100%, mixture of four isomers 3:3:2:4). MS-spectra were closely similar for all isomers. See Example 5.

GC-MS (EI); m/z (%): 184 (2) [M⁺], 169 (4), 141 (100), 129 (12), 112 (25), 111 (26), 101 (52), 99 (7), 98 (4), 85 (68), 83 (32), 55 (38), 43 (24).

4n 2,8-Dimethyl-1,7-dioxaspiro[5.5]undecane:^{15,16}

EtOAc, 24 h; distillation (Kugelrohr, 160°C air bath / 25 Torr) afforded 549 mg (60%) of clear liquid (GC 98%, mixture of *E,E*- and *E,Z*-isomer 1:1).

GC-MS (EI); m/z (%):

(*E,E*)-**4n**: 184 (12) [M⁺], 169 (4), 140 (16), 115 (94), 114 (38), 112 (100), 97 (52), 69 (50), 55 (62), 43 (77), 41 (56).

(*E,Z*)-**4n** and (*Z,Z*)-**4n**: MS-spectra were closely similar with that of (*E,E*)-**4n**.

Literature:

¹ For example see: Dupont, J.; Donato, A.J. *Tetrahedron Asymm.* **1998**, 9, 949-954.

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³ For overview and examples of spiroketal fragmentations see: Francke, W.; Kitching, W. *Curr. Org. Chem.* **2001**, 5, 233-251, and references cited therein.

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Example 1: **GC analyses:** **GC-MS:**

MS-spectra were closely similar for both isomers.

GC-IR:

Example 2: **GC analyses:** **GC-MS:**

MS-spectra were closely similar for all isomers.

GC-IR:

^1H and ^{13}C -NMR spectra:

Frequency (MHz) 500.13
Solvent BENZENE-D6

4e - Isomer 2

Frequency (MHz) 125.77
Solvent BENZENE-D6

4e - Isomer 2

Example 3: **GC analyses:** **GC-MS:**

MS-spectra were closely similar for both isomers.

GC-IR:

^1H and ^{13}C -NMR spectra:

Example 4: **GC analyses:** **GC-MS:**

GC-IR: ¹H and ¹³C-NMR spectra:

Example 5: **GC analyses:** **GC-MS:**

MS-spectra were closely similar for all isomers.

GC-IR:

The numbering of isomers follows the retention times order.

¹H and ¹³C-NMR spectra:

Frequency (MHz) 125.77
Solvent BENZENE-D6

4m