3-Halotetrahydropyran-4-one derivatives from homopropargyl acetal

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Supplementary Information

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Full experimental details, ^1H and ^{13}C NMR, IR and HRMS characterization of compounds **8**, **9**, **10**, **11**, **12a**, **12b**, **13** and **14** and copies of ^1H and ^{13}C NMR spectra of compounds **7** – **14**.

3-Bromo-4-methoxy-6-(4-methoxyphenyl)-2,2-dimethyl-3,6-dihydro-2H-pyran (**8**)

Gold catalyst **1** (12.1 mg, 5 mol%) in dry nitromethane (2.0 ml) was added a solution of acetal **2**^[1] (79 mg, 0.32 mmol) in nitromethane (2.0 ml) and stirred for 3 min. NBS (58 mg, 1 equiv.) was added in one portion and the reaction continued for 15 min. Dichloromethane (20 ml) and a solution of NaHCO_3 (saturated, 10 ml) were added. The aqueous phase was extracted with additional dichloromethane (10 ml) and the combined organic phases were dried over MgSO_4 . The concentrated crude material was purified flash (VersaFlash) chromatography (2% EtOAc in *n*-pentane) to give **8** (52 mg, 50%) as a colourless oil; R_f = 0.18 (5% EtOAc in *n*-pentane). ^1H NMR (400 MHz, CDCl_3) δ 7.39 (d, J = 8.7 Hz, 2H, H_{Ar}), 6.89 (d, J = 8.7 Hz, 2H, H_{Ar}), 5.26 (br s, 1H, H-6), 4.69 (d, J = 1.9 Hz, 1H, H-5), 4.24 (br s, 1H, H-3), 3.80 (s, 3H, $\text{CH}_3\text{OC}_{Ar}$), 3.59 (s, 3H, CH_3O), 1.52 (s, 3H, CH_3C), 1.49 (s, 3H, CH_3C). ^{13}C NMR (100 MHz, CDCl_3) δ 159.6 (C_{Ar}), 152.4 (C-4), 133.9 (C_{Ar}), 129.0 (C_{Ar}), 114.0 (C_{Ar}), 99.0 (C-5), 73.8 (C-2), 72.9 (C-6), 55.3 ($\text{CH}_3\text{OC}_{Ar}$), 54.8 (CH_3O), 54.4 (C-3), 30.0 (CH_3C), 22.5 (CH_3C). IR (neat, cm^{-1}) 2336 (w), 1611 (m), 1512 (s), 1370 (m), 1246 (s), 1172 (s), 1102 (s), 1028 (s).

3,5-Dibromo-4-methoxy-2-(4-methoxyphenyl)-6,6-dimethyl-3,6-dihydro-2H-pyran (**9**) and 3,5-Dibromo-4-methoxy-6-(4-methoxyphenyl)-2,2-dimethyl-3,6-dihydro-2H-pyran (**10**)

The gold catalyst **1** (8.0 mg, 5 mol%) was dissolved in dry nitromethane (1.0 ml) and added a solution of acetal **2**^[1] (50 mg, 0.20 mmol) in nitromethane (1.0 ml). After 3 min stirring, NBS (72 mg, 2 equiv.) was added in one portion. The reaction continued for 15 min before addition of a solution of NaHCO_3 (saturated, 10 ml) and dichloromethane (20 ml). The aqueous phase was extracted with dichloromethane (10 ml), and the combined organic phases were dried over MgSO_4 . The concentrated

crude material was purified through flash (VersaFlash) chromatography (2% EtOAc in *n*-pentane) to afford **9** (25 mg, 31%) and **10** (12 mg, 15%) as colourless oils.

9: R_f = 0.37 (5% EtOAc in *n*-pentane). ^1H NMR (400 MHz, CDCl_3) δ 7.31 (d, J = 8.7 Hz, 2H, H_{Ar}), 6.92 (d, J = 8.9 Hz, 2H, H_{Ar}), 4.93 (d, J = 1.6 Hz, 1H, H-2), 4.64 (d, J = 2.0 Hz, 1H, H-3), 3.86 (s, 3H, CH_3O), 3.82 (s, 3H, $\text{CH}_3\text{OC}_{Ar}$), 1.60 (s, 3H, CH_3C), 1.50 (s, 3H, CH_3C). ^{13}C NMR (100 MHz, CDCl_3) δ 159.2 (C_{Ar}), 148.6 (C-4), 130.7 (C_{Ar}), 127.3 (C_{Ar}), 114.5 (C-5), 113.5 (C_{Ar}), 77.9 (C-6), 71.8 (C-2), 57.5 ($\text{CH}_3\text{OC}_{Ar}$), 55.3 (CH_3O), 50.6 (C-3), 29.3 (CH_3C), 24.0 (CH_3C). IR (neat, cm^{-1}) 2935 (w), 1642 (w), 1614 (w), 1513 (s), 1461 (w), 1305 (m), 1247 (s), 1159 (m), 1095 (m), 1033 (m). HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{18}\text{O}_3\text{Br}_2$ (M^+) 403.9617, obsd 403.9618.

10: R_f = 0.29 (5% EtOAc in *n*-pentane). ^1H NMR (400 MHz, CDCl_3) δ 7.38 (d, J = 8.7 Hz, 2H, H_{Ar}), 6.89 (d, J = 8.5 Hz, 2H, H_{Ar}), 5.17 (d, J = 1.1 Hz, 1H, H-6), 4.49 (d, J = 1.3 Hz, 1H, H-3), 3.88 (s, 3H, CH_3O), 3.80 (s, 3H, $\text{CH}_3\text{OC}_{Ar}$), 1.56 (s, 3H, CH_3C), 1.49 (s, 3H, CH_3C). ^{13}C NMR (100 MHz, CDCl_3) δ 159.9 (C_{Ar}), 149.4 (C-4), 131.5 (C_{Ar}), 130.0 (C_{Ar}), 113.9 (C_{Ar}), 108.0 (C-5), 77.6 (C-6), 74.3 (C-2), 57.9 (CH_3O), 55.2 ($\text{CH}_3\text{OC}_{Ar}$), 53.9 (C-3), 29.6 (CH_3C), 22.5 (CH_3C). IR (neat, cm^{-1}) 2937 (w), 1652 (w), 1612 (w), 1513 (m), 1461 (w), 1304 (m), 1238 (m), 1173 (m), 1001 (m), 734 (s). HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{18}\text{O}_3\text{Br}_2$ (M^+) 403.9617, obsd 403.9624.

1-(1-Ethoxybut-3-ynyl)-4-methoxybenzene (**11**)

The title compound was isolated as the main product in an attempted gold-catalysed cyclization/iodination sequence of homopropargyl acetal **3**.^[1] Gold-catalyst **1** (8.0 mg, 5 mol%) was dissolved in DCM (1.0 ml), added NIS (94 mg, 2 equiv.) and stirred for a few minutes. A solution of homopropargyl acetal **3** (54 mg, 0.22 mmol) in DCM (1.0 ml) was added over 5 min. A rapid conversion of **3** was observed, and after 15 min the reaction was added triethylamine (5 drops), before the mixture was filtered through Celite and concentrated. The residue was purified by flash (VersaFlash) chromatography (3% EtOAc in *n*-pentane). Compound **11** (18 mg, 41%) was isolated as a colourless oil; R_f = 0.50 (3% EtOAc in *n*-pentane). ^1H NMR (400 MHz, CDCl_3) δ 7.26 (app d, J = 9.0 Hz, 2H, H_{Ar}), 6.89 (app d, J = 9.0 Hz, 2H, H_{Ar}), 4.37 (t, J = 6.7 Hz, 1H, H-1), 3.81 (s, 3H, CH_3O), 3.39 (dq, J = 7.0, 2.0 Hz, 2H, CH_3CH_2), 2.69 (ddd, J = 16.6, 6.6, 2.6 Hz, 1H, H-2), 2.52 (ddd, J =

16.2, 6.8, 2.7 Hz, 1H, H-2), 1.95 (t, $J = 2.6$ Hz, 1H, H-4), 1.18 (t, $J = 7.0$ Hz, 3H, CH_3CH_2). ^{13}C NMR (100 MHz, CDCl_3) δ 159.3 (C_{Ar}), 133.2 (C_{Ar}), 127.8 (C_{Ar}), 113.7 (C_{Ar}), 81.1 ($\text{CH}_2\text{C}_{\text{alkyne}}$), 79.6 (HCC_{Ar}), 69.8 ($\text{HC}_{\text{alkyne}}$), 64.2 (OCH_2CH_3), 55.2 ($\text{CH}_3\text{OC}_{\text{Ar}}$), 28.1 ($\text{CH}_2\text{C}_{\text{alkyne}}$), 15.2 (CH_3CH_2). IR (neat, cm^{-1}) 3291 (w), 2973 (w), 1612 (m), 1511 (s), 1246 (s), 1173 (m), 1091 (s), 1034 (m), 830 (m). HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{13}\text{O}_2$ ($\text{M}-\text{C}_3\text{H}_3$) $^+$ 165.0910, obsd 165.0913.

General procedure for acid catalysed hydrolysis of dihydropyrans 8 and 9:

Experiments were performed with $\text{TsOH}\cdot\text{H}_2\text{O}$, according to the protocol described by Bae and co-workers.^[2] Weaker acids, such as CSA and TFA were tested, as well. The amount of acid and the reaction times were also varied in modified protocols.

General procedure for the preparation of esters 12a,b:

A solution of 1-(4-methoxyphenyl)buta-2,3-dien-1-ol in DCM ($c = 200$ mM) was added DMAP (0.05 equiv.) and NEt_3 (2.0 equiv.) at 0°C and stirred for 15 min. The acyl chloride or anhydride reactant (3.0 equiv.) was added at 0°C and the mixture was stirred at rt for 20 hrs. Diethyl ether (20 mL/mmol alcohol) was added and the solution was treated with HCl (1 M, 20 mL/mmol alcohol), brine (20 mL/mmol alcohol), aq. NH_3 (6%, 2 x 20 mL/mmol alcohol) and brine (2 x 15 mL/mmol alcohol). The organic phase was dried over Na_2SO_4 and concentrated.

1-(4-Methoxyphenyl)-2-methylbuta-2,3-dien-1-yl benzoate (12a).

The title compound was prepared according to the *General procedure above* from 1-(4-methoxyphenyl)buta-2,3-dien-1-ol (0.24 g, 1.26 mmol), DMAP (8 mg, 0.06 mmol, 0.05 equiv.), NEt_3 (0.26 g, 2.52 mmol, 2.0 equiv.) and benzoyl chloride (0.53 g, 3.78 mmol, 3.0 equiv.). Flash chromatography (n -pentane/EtOAc 10:1) afforded **12a** (0.32 g, 87%) as a colourless clear oil; $R_f = 0.44$ (n -hexane/EtOAc 4:1). ^1H NMR (400 MHz, CDCl_3) δ : 8.10-8.08 (m, 2 H, H_{Ar}), 7.56-7.52 (m, 1 H, H_{Ar}), 7.45-7.41 (m, 2 H, H_{Ar}), 7.40-7.38 (m, 2 H, H_{Ar}), 6.90-6.88 (m, 2 H, H_{Ar}), 6.36 (t, $J = 2.4$ Hz, 1 H, ArCH), 4.86-4.75 (m, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 1.69 (t, $J = 3.2$ Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ : 206.4 ($\text{C}=\text{C}=\text{C}$), 165.5 (COPh), 159.5 ($\text{CH}_3\text{OC}_{\text{Ar}}$), 133.0 ($p\text{-C}_{\text{Ar}}$), 130.6

(CHC_{Ar}), 130.4 (O₂CC_{Ar}), 129.7 (2 x *o*-C_{Ar}), 128.5 (2 x *o*-C_{Ar}), 128.4 (2 x *m*-C_{Ar}), 113.8 (2 x *m*-C_{Ar}), 99.4 (C=C=CH₂), 76.9 (CH₂), 76.2 (CH), 55.3 (OCH₃), 15.2 (CH₃). IR (neat, cm⁻¹) 2953 (br), 2836 (w), 1960 (w), 1716 (s), 1511 (m), 1450 (m), 1243 (s), 1116 (m), 707 (s). HRMS (ESI) calcd for C₁₉H₁₈O₃Na [M+Na]⁺ 317.1148, obsd 317.1143.

1-(4-Metoksyfenyl)-2-metylbuta-2,3-dien-1-yl acetate (12b).

The title compound was prepared according to the *General procedure above* from 1-(4-methoxyphenyl)buta-2,3-dien-1-ol (0.15 g, 0.79 mmol), DMAP (5 mg, 0.04 mmol, 0.05 equiv.), NEt₃ (0.16 g, 1.57 mmol, 2.0 equiv.) and acetic acid anhydride (0.24 g, 2.36 mmol, 3.0 equiv.). Flash chromatography (*n*-pentane/EtOAc 10:1) afforded product **12b** (0.14 g, 76%) as a yellow oil; *R*_f = 0.41 (*n*-hexane/EtOAc 4:1). ¹H NMR (400 MHz, CDCl₃) δ: 7.32-7.28 (m, 2 H, H_{Ar}), 6.91-6.89 (m, 2 H, H_{Ar}), 6.12 (t, *J* = 2.4 Hz, 1 H, ArCH), 4.83-4.81 (m, 2 H, CH₂), 3.83 (s, 3 H, OCH₃), 2.12 (s, 3 H, O₂CCH₃), 1.63 (t, *J* = 3.0 Hz, 3 H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ: 206.1 (C=C=C), 170.0 (CO₂), 159.5 (CH₃OC_{Ar}), 130.4 (CHC_{Ar}), 128.6 (2 x *o*-C_{Ar}), 113.8 (2 x *m*-C_{Ar}), 99.3 (C=C=CH₂), 76.7 (CH₂), 75.6 (CH), 55.3 (OCH₃), 21.2 (O₂CCH₃), 15.1 (CH₃). IR (neat, cm⁻¹) 2934 (br), 2837 (w), 1960 (w), 1736 (s), 1512 (m), 1369 (m), 1226 (s), 1172 (s), 838 (s). HRMS (ESI) calcd for C₁₄H₂₀O₃N [M+NH₄]⁺ 250.1438, obsd 250.1434.

General procedure for the preparation of iodo-compounds 13 and 14:

The gold catalyst **1** (4.6 mg, 0.01 mmol, 0.05 equiv.) in DCM (0.60 mL) was left at rt without stirring for 5 min. Allene **12a** or **12b** (0.12 mmol), NIS (33.0 mg, 0.15 mmol, 1.25 equiv.) and water (0.06 mL, 5 vol%) in DCM (0.60 mL) were added and the solution was stirred for 2 hrs at rt. The mixture was filtered through Na₂SO₄ and concentrated. Flash chromatography (*n*-pentane/EtOAc 10:1) afforded products **13** and **14**.

2-Hydroxy-3-iodo-1-(4-methoxyphenyl)-2-methylbut-3-en-1-yl benzoate (13)

The title compound was prepared from allene **12a** and NIS in DCM in the presence of gold catalyst **1** as described in the *General procedure above*, affording the product as an orange oil (31.2 mg, 59%),

$R_f = 0.65$ (*n*-hexane/EtOAc 4:1). ^1H NMR (400 MHz, CDCl_3) δ : 8.07-8.05 (m, 2 H, H_{Ar}), 7.60-7.55 (m, 1 H, H_{Ar}), 7.49-7.46 (m, 2 H, H_{Ar}), 7.44-7.40 (m, 2 H, H_{Ar}), 6.89-6.86 (m, 2 H, H_{Ar}), 6.47 (d, $J = 2.2$ Hz, 1 H, CHH_a), 6.27 (s, 1 H, ArCH), 5.97 (d, $J = 2.2$ Hz, 1 H, CH_bH), 3.79 (s, 3 H, OCH_3), 2.45 (s, 1 H, OH), 1.37 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ : 165.3 (CO_2), 159.7 ($\text{CH}_3\text{OC}_{Ar}$), 133.2 ($p\text{-C}_{Ar}$), 130.0 (O_2CC_{Ar}), 129.7 (2 x $o\text{-C}_{Ar}$), 129.5 (2 x $o\text{-C}_{Ar}$), 128.5 (2 x $m\text{-C}_{Ar}$), 128.0 (CHC_{Ar}), 127.1 (CH_2), 117.6 (CI), 113.5 (2 x $m\text{-C}_{Ar}$), 78.9 (CH), 78.5 (COH), 55.2 (OCH_3), 23.8 (CH_3). IR (neat, cm^{-1}) 3494 (br), 2926 (br), 2844 (w), 1704 (m), 1611 (m), 1512 (m), 1245 (s), 1025 (s), 709 (s); HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{23}\text{O}_4\text{NI}$ $[\text{M}+\text{NH}_4]^+$ 456.0666; obsd 456.0667.

3-Iodo-2-(4-methoxyphenyl)-2-methylbut-3-enal (14)

The title compound was prepared according to the *General procedure* above from gold catalyst **1** (6.6 mg, 0.01 mmol, 0.05 equiv.) in DCM (0.70 mL), allene **12b** (40.0 mg, 0.17 mmol), NIS (48.0 mg, 0.21 mmol, 1.25 equiv.) in water (0.09 mL, 5 vol%) and DCM (1.00 mL) as a yellow oil (24.2 mg, 45%), $R_f = 0.42$ (*n*-hexane/EtOAc 4:1). ^1H NMR (400 MHz, CDCl_3) δ : 9.76 (s, 1 H, OCH), 7.24-7.21 (m, 2 H, H_{Ar}), 6.97-6.94 (m, 2 H, H_{Ar}), 6.26 (d, $J = 2.8$ Hz, 1 H, CH_aH), 6.18 (d, $J = 2.8$ Hz, 1 H, CHH_b), 3.84 (s, 3 H, OCH_3), 1.67 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ : 196.9 (OCH), 159.7 ($\text{CH}_3\text{OC}_{Ar}$), 130.3 (C_{Ar}), 129.0 (2 x $o\text{-C}_{Ar}$), 128.3 (CH_2), 115.6 (CI), 114.4 (2 x $o\text{-C}_{Ar}$), 62.7 (CH_3C), 55.3 (CH_3O), 21.2 (CH_3),). IR (neat, cm^{-1}) 2935 (br), 2835 (w), 1723 (s), 1605 (m), 1509 (s), 1250 (s), 1029 (s), 827 (s). HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{17}\text{O}_2\text{NI}$ $[\text{M}+\text{NH}_4]^+$ 334.0298; obsd 334.0298.

Reference

1. Aaseng, J. E.; Iqbal, N.; Sperger, C. A.; Fiksdahl, A. **2014**, submitted.
2. Bae, H J.; Jeong, W.; Lee, J. H.; Rhee, Y. H. *Chem.-- Eur. J.* **2011**, *17*, 1433.

^1H and ^{13}C -spektra of compounds **7a**, **7b**, **8**, **9**, **10**, **11**, **12a**, **12b**, **13** and **14**

Fig. 1 ^1H NMR spectrum of **7a** in CDCl_3

Fig. 2 ^{13}C NMR spectrum of **7a** in CDCl_3

Fig. 3 ¹H NMR spectrum of **7b** in CDCl₃

Fig. 4 ¹³C NMR spectrum of **7b** in CDCl₃

Fig. 5 ^1H NMR spectrum of **8** in CDCl_3

Fig. 6 ^{13}C NMR spectrum of **8** in CDCl_3

Fig. 7 ^1H NMR spectrum of **9** in CDCl_3

Fig. 8 ^{13}C NMR spectrum of **9** in CDCl_3

Fig. 9 ^1H NMR spectrum of **10** in CDCl_3

Fig. 10 ^{13}C NMR spectrum of **10** in CDCl_3

Fig. 11 ^1H NMR spectrum of **12a** in CDCl_3

Fig. 12 ^{13}C NMR spectrum of **12a** in CDCl_3

Fig. 13 ¹H NMR spectrum of **12b** in CDCl₃

Fig. 14 ¹³C NMR spectrum of **12b** in CDCl₃

Fig. 15 ^1H NMR spectrum of **13** in CDCl_3

Fig. 16 ^{13}C NMR spectrum of **13** in CDCl_3

Fig. 17 ^1H NMR spectrum of **14** in CDCl_3

Fig. 18 ^{13}C NMR spectrum of **14** in CDCl_3