Synthesis of 3-Aryl-Substituted Tetrahydropyran-4-ones and Tetrahydrothiopyran-4-ones

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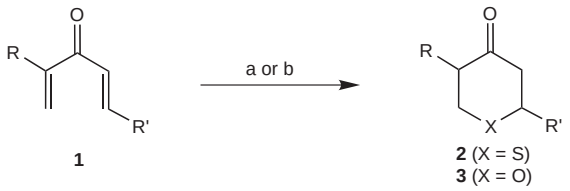
Abstract: A series of tetrahydropyran-4-one and tetrahydrothiopyran-4-one derivatives with 3-aryl or 3,6-diaryl substituents were prepared by double conjugate addition of water or H_2S to divinyl ketones. These starting materials were accessed in two steps by conversion of lithiated α-bromostyrene derivatives with acrolein or cinnamaldehyde and subsequent oxidation of the divinylalcohols with MnO_2.

Key words: building blocks, conjugate addition, heterocyclic compounds, pyran derivatives, thiopyran derivatives

Successful drug development is often dependent on the availability of heterocyclic building blocks with a specific substitution pattern. In the course of a research program in a medicinal chemistry context tetrahydropyran-4-ones **3** and tetrahydrothiopyran-4-ones **2** were required for the preparation of novel enzyme inhibitors. Of course, many procedures[1] have been reported to access tetrahydropyran-4-one derivatives[2] and their sulfur analogues,[3] however, our requirement for an electron-rich aryl substituent in the 3-position has not been addressed in the literature so far. The obvious first approach to our target structures is the α-arylation of the unsubstituted heterocyclic ketone, which failed, however, due to decomposition by E1cb elimination of the respective enolates. Therefore, we envisioned to build up the heterocycle by double conjugate addition of water (X = O) or sulfane (X = S) to a divinylketone[4] with the accurate aryl substitution pattern (Scheme 1).



Scheme 1 Synthesis of 3-aryl-substituted tetrahydropyran-4-ones **3** and -thiopyran-4-ones **2** by double conjugate addition. *Reagents and conditions*: (a) for **2**: NaHS-hydrate, 2-methoxyethanol (2-ME), 50 °C, 5 h; (b) for **3**: KOH, H_2O, CH_2Cl_2, 40 °C, 2–3 d. For yields and substituents, see Table 1.

Reaction conditions were optimized with model compound **1a** (R = Ph, R′ = H). Although sulfides, as soft nucleophiles, should cleanly undergo conjugate additions, yields turned out to be highly dependent on the reaction conditions, particularly on the solvent. Best results were achieved with NaHS in 2-methoxyethanol (2-ME)[5] or Na_2S in THF–H_2O (1:1) at elevated temperatures (45–55 °C). Yields for products **2a**–**f** are collated in Table 1. They are, however, dependent on the purity of the respective divinylketone **1** (see below).

Table 1 Yields and Substituents R and R′ in the Synthesis of Tetrahydropyran-4-ones **3** (X = O) and Tetrahydrothiopyran-4-ones **2** (X = S)

Product	R	R′	X	Yield (%)
2a	Ph	H	S	70
2b	3,4-$(MeO)_2C_6H_3$	H	S	65
2c	3-EtO-4-$MeOC_6H_3$	H	S	59
2d	3,4-$(MeO)_2C_6H_3$	Ph	S	60 (dr 4:1)
2e	3-EtO-4-$MeOC_6H_3$	Ph	S	48 (dr 9:1)
2f	4-$MeOC_6H_4$	Ph	S	57 (dr 3:1)
3a	Ph	H	O	50
3b	3-EtO-4-$MeOC_6H_3$	H	O	25

All compounds were of course obtained as racemates. For products **2d**–**f** mixtures of two diastereoisomers were obtained with moderate stereoselectivity. The relative configuration was assigned based on ^3J(H,H) coupling constants. The *trans* isomer is the major diastereomer in all three cases (**2d**: *trans*/*cis* 4:1; **2e**: *trans*/*cis* 9:1; **2f**: *trans*/*cis* 3:1). For the pyranone series, various acidic and basic reaction conditions with different solvent–water mixtures, even with phase-transfer catalysis have been investigated. Surprisingly, only with the system KOH–H_2O–CH_2Cl_2 at 50 °C the racemic pyranones **3a** and **3b**[6] were formed, though, yields are not fully satisfying. Nevertheless, products of specific interest were prepared batchwise in total yields of 50 g (thiacycle **2**) and 20 g (oxacycle **3**), respectively, by using the conditions depicted in Scheme 1.

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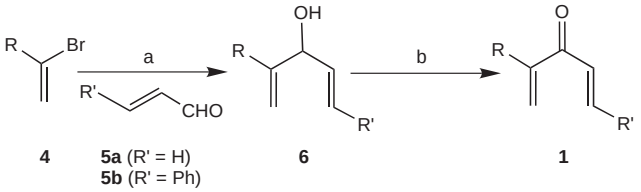

Scheme 2 Synthesis of divinylketones **1** from α-bromostyrenes **4**. *Reagents and conditions*: (a) 1. *n*-BuLi, THF, 1.5 h, –78 °C; 2. aldehyde **5**, 1.5 h, –78 °C; (b) excess MnO_2, CH_2Cl_2, 60 min, 23 °C.

Table 2 Yields and Substituents R and R′ in the Synthesis of Divinylketones **1**

R	R′	Product **6**	Product **1**
Ph	H	**6a** (78%)	**1a** (90%)
3,4-$(MeO)_2C_6H_3$	H	**6b** (62%)	**1b** (56%)
3-EtO-4-$MeOC_6H_3$	H	**6c** (64%)	**1c** (74%)
3,4-$(MeO)_2C_6H_3$	Ph	**6d** (63%)	**1d** (72%)
3-EtO-4-$MeOC_6H_3$	Ph	**6e** (48%)	**1e** (64%)
4-$MeOC_6H_4$	Ph	**6f** (74%)	**1f** (83%)

Starting divinylketones **1** were prepared by a two-step sequence from α-bromostyrene derivatives **4** (Scheme 2, Table 2). Whereas the parent compound **4a** (R = Ph) is commercially available, donor-substituted congeners **4b** [R = 3,4-$(MeO)_2C_6H_3$], **4c** (R = 3-EtO-4-$MeOC_6H_3$) and **4f** (R = 4-$MeOC_6H_4$) were prepared by addition of HBr to the respective alkyne under strictly anhydrous conditions. Lithium–bromine exchange of compounds **4** with *n*-BuLi proceeded smoothly at –78 °C and was followed by treatment of the reaction mixture with freshly distilled acrolein (**5a**) or cinnamaldehyde (**5b**) to yield the divinylalcohols **6a–f** in good to reasonable yields after chromatographic purification.[7] Compounds **6d–f** are obtained as single diastereoisomers with the double bond configuration being *E* [olefinic ^3J(H,H)]. Oxidation to the ketones was achieved with MnO_2 (commercial activity). The oxidant was added portionwise to a suspension in CH_2Cl_2 until almost no starting material **6** was detectable by TLC, which normally took one hour and 20–30 equivalents of MnO_2.[8] The products are generally pure by ^{1}H NMR without further chromatography, and are again obtained exclusively with *E* double-bond configuration. If the conversion is not complete, the remaining starting material **6** might be hardly separable from the product of the next step (**2** or **3**). On the other hand, prolonged reaction times result in overoxidation to an epoxide. Divinylketones **1a–c**, which derive from acrolein (**5a**) are highly reactive and neither stable at ambient conditions nor at low temperatures. They even decompose significantly upon chromatography on SiO_2. Therefore, they were directly converted further to the heterocyclic products **2** and **3**. Actually, the low stability of divinylketones **1** might be the major reason for the moderate yields of compounds **3a** and **3b**.

In conclusion, tetrahydrothiopyran-4-ones **2** with an aromatic substituent in the 3-position are conveniently accessed by double conjugate addition of sulfide to the respective divinylketone **1**. The respective oxacycles **3** can be similarly achieved from compounds **1** and water, however, in lower yields. The divinylketones **1** are accessed from α-bromostyrene derivatives **4** with a specific aromatic substitution pattern. Overall yields allow for the preparation of final products on multigram scale.

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(5) **3-(3-Ethoxy-4-methoxyphenyl)tetrahydrothiopyran-4-one (2c).**
$NaHS·9H_2O$ (2.7 g, 13 mmol) was added to a solution of dienone **1c** (1.9 g, 8.2 mmol) in 2-methoxyethanol (120 mL). The reaction mixture was stirred at 50 °C for 5 h and then poured onto H_2O (80 mL). After extraction with EtOAc (4 × 80 mL) the combined organic layers were washed with H_2O (80 mL), dried ($MgSO_4$), and all volatile materials removed in vacuum. Chromatography of the residue on SiO_2 (PE–EtOAc, 2:1, R_f = 0.31) gave the title compound **9** (1.29 g, 4.84 mmol, 59%) as a colorless solid, mp 103–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (t, *J* = 7.0 Hz, 3 H, CH_3), 2.76–2.92 (m, 2 H), 2.98–3.17 (m, 3 H), 3.24 (dd, *J* = 13.6 Hz, *J* = 10.6 Hz, 1 H), 3.86 (s, 3 H), 3.90 (dd, *J* = 10.6 Hz, *J* = 4.8 Hz, 1 H), 4.04–4.13 (m, 2 H), 6.71 (d, *J* = 1.9 Hz, 1 H, Ar-H), 6.74 (dd, *J* = 8.2 Hz, *J* = 2.0 Hz, 1 H, Ar-H), 6.85 (d, *J* = 8.2 Hz, 1 H, Ar-H) ppm. ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ = 14.82 (CH_3), 30.75 (CH_2), 36.74 (CH_2), 44.23 (CH_2), 55.93 (OCH_3), 58.90 (CH), 64.36 (CH_2), 111.47 (CH), 113.30 (CH), 120.55 (CH), 129.86 (C), 148.19 (C),

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148.64 (C), 207.69 (C=O) ppm. IR (ATR): 2926 (w), 1703 (vs), 1588 (m), 1514 (s), 1444 (m), 1422 (m), 1344 (m), 1306 (m), 1243 (vs), 1182 (m), 1155 (m), 1137 (s), 1111 (m), 1042 (m), 1019 (s), 980 (m), 857 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 266 (53) [M^+], 178 (100), 150 (26), 91 (5), 77 (7), 28 (9). Anal. Calcd for $C_{14}H_{18}O_3S$ (266.35): C, 63.13; H, 6.81. Found: C, 63.01; H, 6.79.

(6) **3-(3-Ethoxy-4-methoxyphenyl)tetrahydropyran-4-one (3b).**
KOH (4.34 g, 77.5 mmol) was added to a solution of **1c** (4.50 g, 19.4 mmol) in CH_2Cl_2–H_2O (1:1, 200 mL). The reaction mixture was vigorously stirred at 40 °C for 3 d and then poured into a mixture of H_2O (100 mL) and aq solution of citric acid (c = 20%, 25 mL). The resulting mixture was extracted with CH_2Cl_2 (2 × 80 mL). The combined organic layers were washed with H_2O (30 mL) and dried ($MgSO_4$). After removal of all volatile materials in vacuum, the residue was chromatographed on SiO_2 (PE–EtOAc, 2:1, R_f = 0.23) to give title compound **3b** (1.21 g, 4.83 mmol, 25%) as a light-yellow oil, which solidified after one day, mp 65–67 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.45 (t, *J* = 7.0 Hz, 3 H, CH_3), 2.59–2.65 (m, 2 H, CH_2), 3.71 (dd, *J* = 8.2 Hz, *J* = 5.9 Hz, 1 H, CH), 3.85 (s, 3 H, OCH_3), 3.93–4.13 (m, 4 H, 2 CH_2), 4.16–4.25 (m, 2 H, CH_2), 6.76–6.87 (m, 3 H, Ar-H) ppm. $^{13}C\{^1H\}$-NMR (62 MHz, $CDCl_3$): δ = 14.81 (CH_3), 41.84 (CH_2), 55.94 (OCH_3), 57.48 (CH), 64.39 (CH_2), 68.52 (CH_2), 73.20 (CH_2), 111.62 (CH), 113.57 (CH), 120.99 (CH), 127.39 (C), 148.29 (C), 148.77 (C), 206.11 (C=O) ppm. IR (ATR): 2973 (m), 2934 (w), 1715 (vs), 1589 (m), 1517 (vs), 1474 (w), 1433 (m), 1424 (w), 1389 (m), 1339 (w), 1309 (w), 1251 (vs), 1167 (m), 1094 (m), 1045 (m), 1020 (s), 969 (m), 924 (m), 887 (m), 851 (m), 822 (m), 693 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 250 (100) [M^+], 222 (4), 178 (72), 150 (34), 107(6), 91 (5), 77 (7), 28 (12). Anal. Calcd for $C_{14}H_{18}O_4$ (250.29): C, 67.18; H, 7.25. Found: C, 67.09; H, 7.29.

(7) **2-(3-Ethoxy-4-methoxyphenyl)-1,4-pentadien-3-ol (6c).**
Under an inert atmosphere (N_2) *n*-BuLi (154 mmol, 77.0 mL of a 2 M solution in pentane) was added dropwise at –78 °C to a solution of bromoolefin **4c** (18.0 g, 70.0 mmol) in abs. THF (250 mL) over a period of 30 min. The reaction mixture was further stirred at –78 °C for 1.5 h. Then freshly distilled acrolein (**5a**, 10.5 g, 187 mmol) was dropwise added over a period of 10 min. After being stirred for a further 1.5 h at –78 °C, the reaction mixture was allowed to warm up to r.t. and washed with sat. aq NH_4Cl (300 mL) and with H_2O (100 mL). The layers were separated, and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over $MgSO_4$. After filtration and removal of solvent, the residue was chromatographed on SiO_2 [PE–EtOAc, 5:1, R_f (PE–EtOAc, 2:1) = 0.31] to give **6c** (10.5 g, 44.8 mmol, 64%) as a colorless solid, mp 30–32 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (t, *J* = 7.0 Hz, 3 H, CH_3), 2.18 (br d, *J* = 3.5 Hz, 1 H, OH), 3.87 (s, 3 H, OCH_3), 4.06–4.15 (m, 2 H, OCH_2), 5.08 (br s, 1 H, 3-H), 5.17 (dt, *J* = 10.3 Hz, *J* = 1.4 Hz, 1 H, *E*-5-H), 5.32 (br t, *J* = 1.0 Hz, 1 H, 1-H), 5.33 (br s, 1 H, 1-H), 5.34 (dt, *J* = 17.2 Hz, *J* = 1.4 Hz, 1 H, *Z*-5-H), 5.96 (ddd, *J* = 17.2 Hz, *J* = 10.4 Hz, *J* = 5.6 Hz, 1 H, 4-H), 6.81–6.84 (m, 1 H, Ar-H), 6.98–7.01 (m, 2 H, Ar-H) ppm. $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 14.83 (CH_3), 55.94 (OCH_3), 64.35 (OCH_2), 74.75 (CH), 111.25 (CH), 112.01 (CH), 112.51 (CH_2), 115.73 (CH_2), 119.38 (CH), 132.03 (C), 139.19 (CH), 148.02 (C), 149.22 (C), 149.55 (C) ppm. IR (ATR): = 3435 (br m), 2934 (w), 1579 (w), 1511 (s), 1441 (w), 1249 (s), 1211 (m), 1178 (w), 1137 (m), 1025 (s), 921 (w), 810 (w), 775 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 234 (48) [M^+], 177 (100), 149 (14), 117 (7), 77 (6). Anal. Calcd for $C_{14}H_{18}O_3$ (234.29): C, 71.77; H, 7.74. Found: C, 71.44; H, 8.09.

(8) **2-(3-Ethoxy-4-methoxyphenyl)-1,4-pentadien-3-one (1c).**
MnO_2 (25.0 g, 287 mmol) was added portionwise to a solution of **6c** (2.00 g, 8.55 mmol) in CH_2Cl_2 (60 mL) at ambient temperature. The progress of the reaction was monitored by TLC [product **1c**: R_f (SiO_2, PE–EtOAc, 2:1) = 0.45]. After being stirred for 60 min at 23 °C, the reaction mixture was filtered with vacuum through SiO_2 to separate MnO_2, the residue was washed several times with EtOAc (total ca. 600 mL). The filtrate was concentrated under vacuum to give **1c** as a yellow oil (1.47 g, 6.33 mmol, 74%) with 90–95% purity by ^{1}H NMR. The product decomposes under ambient conditions. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (t, *J* = 7.0 Hz, 3 H, CH_3), 3.88 (s, 3 H, OCH_3), 4.10 (q, *J* = 7.0 Hz, 2 H, OCH_2), 5.87 (dd, *J* = 10.5 Hz, *J* = 1.5 Hz, 1 H, *E*-5-H), 5.87 (s, 1 H, 1-H), 5.89 (s, 1 H, 1-H), 6.34 (dd, *J* = 17.4 Hz, *J* = 1.6 Hz, 1 H; *Z*-5-H), 6.73 (dd, *J* = 17.3 Hz, *J* = 10.5 Hz, 1 H, 4-H), 6.84–6.93 (m, 3 H, ArH) ppm. $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ = 14.77 (CH_3), 55.97 (OCH_3), 64.40 (OCH_2), 111.25 (CH), 112.44 (CH), 120.50 (CH), 121.93 (CH_2), 129.44 (C), 130.35 (CH_2), 134.45 (CH), 148.04 (C), 148.30 (C), 149.64 (C), 193.97 (C=O) ppm. IR (ATR): 2932 (br m), 2186 (w), 1671 (m), 1604 (m), 1514 (s), 1398 (w), 1255 (s), 1141 (m), 1028 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 232 (100) [M^+], 177 (89), 149 (43), 117 (5), 89 (8), 77 (4), 55 (16). HRMS (EI, 70 eV): *m/z* calcd for $C_{14}H_{16}O_3$: 232.1099; found: 232.1099 [M^+].

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