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Synthesis of unsymmetrically 2,6-disubstituted 2,3-dihydrothiopyran-4-ones

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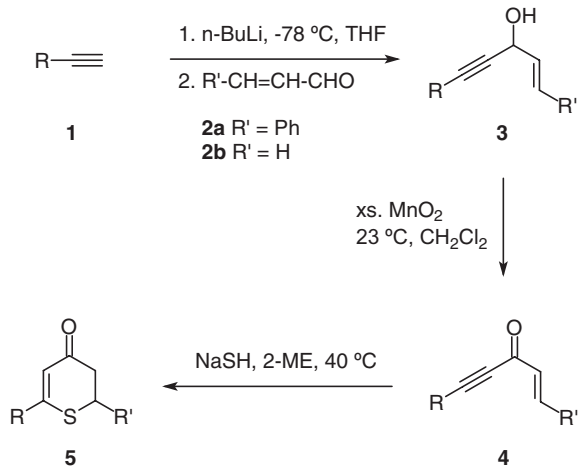
Abstract—A series of 2,3-dihydrothiopyran-4-one derivatives with unequal substituents in the 2- and 6-position have been prepared by double conjugate addition of sulfide to enynones. These starting materials were accessed in two steps from terminal alkynes and α,β-unsaturated aldehydes.

Dihydrothiopyran-4-one derivatives **5** are important building blocks for the synthesis of heterocyclic compounds[1] and organic materials for electronic applications.[2] They have been accessed by oxidation of the respective tetrahydrothiopyran-4-ones by a halogenation–dehydrohalogenation sequence with various chlorinating[3] and fluorinating[4] reagents. Since this oxidation was reported to proceed without any significant regioselectivity, only symmetrically substituted compounds of this class have been reported in the literature so far. In the course of a project related to the pharmaceutical application we were looking for dihydrothiopyran-4-ones **5** with unsymmetrical 2,6-disubstitution as heterocyclic building blocks. An obvious retrosynthetic approach to these compounds is the double conjugate addition of sulfide to an enynone **4** with the appropriate substitution pattern. It was however not clear whether an initial conjugate addition to the triple bond of these starting materials would lead to a *Z*-configurated donor–acceptor substituted olefin, which of course would be the precondition for the formation of the heterocyclic ring in the second conjugate addition to the C–C double bond. Conjugate addition reactions of nitrogen nucleophiles have been reported in the literature to give enaminones with a *E*-configurated C–C double bond,[5] which is of course the thermodynamically more favoured situation. And indeed, in our hands, the conversion of enynones **4** with primary amines led to the exclusive formation of enaminones with two C–C double bonds. No piperidone derivatives were detected. Therefore we conclude, that at least for *N*-nucleophiles the conjugate addition to the C–C triple bond is the predominating process.

Enynones **4** (Scheme 1) were prepared starting from a series of terminal alkynes **1** by deprotonating them with one equivalent of *n*-BuLi in THF and further conversion with cinnamaldehyde **2a** or acroleine **2b**. After aqueous work-up and chromatographic purification allylic alcohols



Scheme 1. Synthesis of dihydrothiopyrones **5** from alkynes **1** via allylalcohols **3** and vinylketones **4**, for yields and substituents R and R′ see Table 1. 2-ME = 2-methoxyethanol.

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3 were obtained,[6] which were subsequently oxidized with an excess (10–30 equiv) MnO_2 at 23 °C in CH_2Cl_2. The progress of this reaction was followed by TLC, and after full conversion as achieved (5–30 min), materials containing manganese were simply removed by filtration to yield the double Michael acceptors **4**, which were analytically pure without further purification.[7] Yields for both steps are generally very good, in some cases even quantitative (Table 1). Alcohols **3a**–**i** and ketones **4a**–**i** originating from cinnamaldehyde **2a** (R′ = H) are exclusively obtained with the C–C double bond in *E*-configuration.

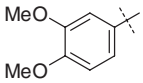
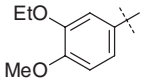
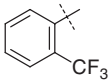
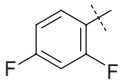
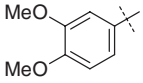
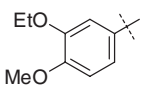
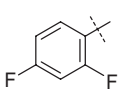
Whereas vinylketones **4a**–**i** with R′ = Ph show reasonable stability, their congeners **4j**–**k** deriving from acroleine (R′ = H) tend to decompose within an hour at ambient conditions and can even not be stored at lower temperatures and must therefore be further converted directly after filtration.

The result of the double thia-Michael reaction was highly dependent on the solvent applied. Best results were achieved with 2-ME at moderate temperatures (40–55 °C) within a few hours (4–16 h). After aqueous workup, products were purified by column chromatography on SiO_2.[8] The yields of derivatives with R′ = Ph (**5a**–**i**) range from satisfying (60% for **5g**) to excellent (96% for **5b**). For R = Ph (**5a**) and electron rich aromatics (**5b** and **5c**) yields are reaching 90%. Electron deficient phenyl (**5d** and **5e**) and electron rich (**5f**) and poor heteroaryl (**5g**) as well as an aliphatic (**5h**) gave yields from 60% to 85%. If trimethylsilyl acetylene **1i** is used as starting material, the R = TMS group is retained in alcohol **3i** and ketone **4i**. Cyclization with $NaSH{\cdot}9H_2O$ leads to ring closure, but the TMS group is lost presumably due to the strong nucleophilicity of sulfide. In this case the final product **5i** is unsubstituted in the 6-position (R = H).

Yields for compounds **5j**–**l** without a substituent in the 2-position are not satisfying at all (8–36%). This might actually originate from the low stability of the respective starting materials **4j**–**l**, which decompose under the reaction conditions.

In conclusion, 2,3-dihydrothiopyran-4-one derivatives with unequal substituents in the 2- and 6-position (R, R′) are conveniently accessed from terminal alkynes and α,β-unsaturated aldehydes in a three step sequence. The ring closure is achieved from enynones with sulfide. Electron rich and deficient aromatic and heteroaromatic as well as aliphatic substituents have been introduced in the 6-position (R). The yields over three steps range from 40% to 80%. Congeners without a substituent in the 2-position (R′ = H) are more difficult to prepare, which is mainly due to the instability of the enynone intermediate product. Overall yields in these cases are much lower (6–20%).

Table 1. Yields and substituents R and R′ in the synthesis of dihydrothiopyrones **5**

Entry	R	R′	Yield of **3** (%)	Yield of **4** (%)	Yield of **5** (%)
a	Ph	Ph	89	96	94
b		Ph	94	84	96
c		Ph	79	99	92
d		Ph	78	99	84
e		Ph	66	99	65
f		Ph	51	99	81
g		Ph	92	75	60
h	*t*-Bu	Ph	85	99	85
i	TMS, H[a]	Ph	98	97	70
j		H	71	77	36
k		H	67	62	16
l		H	71	99	8

[a] TMS acetylene **1i** was used as starting material. The TMS group was retained in alcohol **3i** and ketone **4i** (R = TMS), but lost in the final product **5i** (R = H).

Acknowledgements

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6. Representative experimental procedure, (*E*)-1-(2,4-difluorophenyl)-3-hydroxy-5-phenyl-4-penten-1-yne (**3e**): *n*-BuLi (3.62 mmol, 1.80 ml of a solution in pentane, 2.0 mol dm^{-3}) was added at −78 °C to a solution of 2,4-difluorophenylacetylene (**1e**, 500 mg, 3.62 mmol) in abs. THF (9 ml). After further stirring (−78 °C, 90 min), cinnamaldehyde (**2a**, 530 mg, 3.98 mmol) was added, and the resulting mixture stirred for 90 min at −78 °C. Then a saturated, aqueous NH_4Cl-solution (20 ml) was added, the layers were separated, and the aqueous phase extracted with CH_2Cl_2 (20 ml). The combined organic layers were dried ($MgSO_4$), filtered and the solvent stripped off. The residue was chromatographed (SiO_2, hexanes/EtOAc 2:1, $R_f = 0.50$) to yield the title compound **3e** (642 mg, 2.38 mmol, 66%) as light yellow crystals, mp 64–66 °C. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.82$ (br s, 1H, OH), 5.29 (d, $J = 5.6$ Hz, 1H, 3-H), 6.36 (dd, $J = 15.8$, 6.0 Hz, 1H, 4-H), 6.81 (t, $J = 8.2$ Hz, 1H, Ar–H), 6.83 (d, $J = 15.6$ Hz, 1H, 5-H), 6.84 (d, $J = 1.9$ Hz, 1H, Ar–H), 7.21–7.45 (m, 6H, Ar–H) ppm. $^{13}C\{^1H\}$ NMR (62 MHz, $CDCl_3$): $\delta = 63.41$ (s, CH, C-4), 78.88 (s, C, C-2), 93.03 (s, C, C-1), 104.31 (t, $^2J = 25.8$ Hz, CH, C-3′), 107.40 (dd, $^2J = 15.9$ Hz, $^4J = 4.0$ Hz, C, C-1′), 111.63 (dd, $^2J = 21.9$ Hz, $^4J = 3.8$ Hz, CH, C-5′), 126.91 (s, 2CH), 127.62 (s, CH), 128.23 (s, CH), 128.67 (s, 2CH), 132.37 (s, CH), 134.53 (dd, $^3J = 9.7$ Hz, $^3J = 2.6$ Hz, CH, C-6′), 136.05 (s, C), 162.91 (dd, $^1J = 252$ Hz, $^3J = 11.3$ Hz, C, C–F), 163.19 (dd, $^1J = 266$ Hz, $^3J = 10.9$ Hz, C, C–F) ppm. IR (ATR): $\lambda^{-1} = 3298$ (w, br), 1649 (w), 1610 (w), 1587 (w), 1502 (m), 1424 (m), 1322 (w), 1294 (w), 1267 (m), 1217 (m), 1140 (m), 1101 (m), 1075 (w), 1057 (w), 1007 (m), 964 (m), 891 (w), 852 (m), 819 (m), 754 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 270 (100) [M^+], 251 (46), 220 (30), 193 (8), 165 (76), 151 (19), 138 (48), 127 (52), 104 (55), 91 (43), 77 (30). Anal. Calcd for $C_{17}H_{12}F_2O$ (270.28): C, 75.55; H, 4.47. Found: C, 75.54; H, 4.48.
7. Representative experimental procedure (*E*)-1-(2,4-difluorophenyl)-3-oxo-5-phenyl-4-penten-1-yne (**4e**): MnO_2 (2.9 g, 33 mmol) was portionwise added to a solution of alcohol **3e** (450 mg, 1.66 mmol) in CH_2Cl_2 (15 ml). The suspension was stirred for 30 min at 23 °C, then filtered through SiO_2. The residue was washed several times with EtOAc and the combined filtrates were evaporated to yield the analytically pure title compound **4e** (440 mg, 1.64 mmol, 99%) as a light yellow solid, mp 110–112 °C. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 6.86$ (d, $J = 16.1$ Hz, 1H, 4-H), 6.91–6.99 (m, 2H, Ar–H), 7.43–7.47 (m, 3H, Ar–H), 7.59–7.67 (m, 3H, Ar–H), 7.99 (d, $J = 16.1$ Hz, 1H, 5-H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta = 83.74$ (s, C, C-2), 90.95 (t, $^3J = 2.4$ Hz, C, C-1), 104.81 (dd, $^2J = 25.1$ Hz, $^2J = 24.5$ Hz, CH, C-3′), 105.58 (dd, $^2J = 15.9$ Hz, $^4J = 4.0$ Hz, C, C-1′), 112.35 (dd, $^2J = 22.5$ Hz, $^4J = 5.9$ Hz, CH, C-5′), 128.34 (s, CH), 128.80 (s, 2CH), 129.12 (s, 2CH), 131.33 (s, CH), 134.03 (s, C), 135.84 (dd, $^3J = 10.0$ Hz, $^3J = 1.7$ Hz, CH, C-6′), 149.33 (s, CH), 164.35 (d, $^1J = 256.7$ Hz, C, C–F), 164.45 (d, $^1J = 256.7$ Hz, C, C–F), 177.91 (s, C=O, C-3) ppm. IR (ATR): $\lambda^{-1} = 2215$ (m), 1632 (m), 1604 (m), 1496 (m), 1446 (w), 1425 (w), 1317 (m), 1267 (m), 1224 (m), 1174 (m), 1139 (w), 1093 (m), 1000 (w), 973 (m), 963 (m), 847 (m), 756 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 267 (100) [M^+−H], 249 (55), 239 (59), 220 (17), 165 (45), 137 (14), 102 (33), 77 (21), 51 (5). Anal. Calcd for $C_{17}H_{10}F_2O$ (268.26): C, 76.11; H, 3.76. Found: C, 76.01; H, 3.83.
8. Representative experimental procedure, 6-(2,4-difluorophenyl)-2,3-dihydro-2-phenylthiopyran-4-one (**5e**): $NaHS{\cdot}9H_2O$ (194 mg, 0.76 mmol) was added to a solution of ketone **4e** (100 mg, 0.37 mmol) in 2-ME (13 ml). The mixture was stirred for 3 h at 55 °C, then washed with a saturated, aqueous solution of NH_4Cl (40 ml). The organic layer was extracted with EtOAc (3 × 25 ml), and the combined organic phases dried ($MgSO_4$). After filtration, the solvent was stripped off, and the residue purified by chromatography (SiO_2, hexanes/EtOAc 2:1, $R_f = 0.56$) to yield the title compound **5e** (74 mg, 0.24 mmol, 65%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.99$ (dd, $J = 16.4$, 3.3 Hz, 1H, 3-H), 3.18 (dd, $J = 16.4$, 13.9 Hz, 1H, 3-H), 4.78 (dd, $J = 13.9$, 3.3 Hz, 1H, 2-H), 6.48 (d, $J = 1.6$ Hz, 1H, 5-H), 6.86–6.97 (m, 2H, Ar–H), 7.33–7.45 (m, 5H, Ar–H), 7.51–7.60 (m, 1H, Ar–H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta = 44.01$ (s, CH_2, C-3), 47.14 (s, CH, C-2), 105.07 (t, $^2J = 26.0$ Hz, CH, C-3′), 111.90 (dd, $^2J = 21.6$ Hz, $^4J = 4.1$ Hz, CH, C-5′), 121.42 (dd, $J = 13.4$, 4.9 Hz, C, C-1′), 124.56 (d, $^4J = 5.1$ Hz, CH, C-5), 127.58 (s, 2CH), 128.75 (s, CH), 129.12 (s, 2CH), 131.21 (dd, $^3J = 9.9$ Hz, $^3J = 3.4$ Hz, CH, C-6′), 137.46 (s, C), 153.01 (d, $^3J = 1.9$ Hz, C, C-6), 159.75 (dd, $^1J = 255.9$ Hz, $^3J = 12.4$ Hz, C, C–F), 163.92 (dd, $^1J = 254.1$ Hz, $^3J = 12.0$ Hz, C, C–F), 194.65 (s, C=O, C-4) ppm. IR (ATR): $\lambda^{-1} = 3062$ (w), 1650 (vs), 1608 (s), 1558 (m), 1496 (s), 1453 (w), 1425 (m), 1264 (br s), 1143 (s), 1100 (s), 975 (m), 917 (w), 850 (m), 813 (w), 733 (m), 698 (m), 619 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 302 (84) [M^+], 274 (13), 225 (5), 198 (51), 170 (100), 126 (9), 104 (32), 91 (6), 77 (7), 28 (14). Anal. Calcd for $C_{17}H_{12}F_2OS$ (302.34): C, 67.54; H, 4.00. Found: C, 67.30; H, 4.09.