

Functionalization of Unprotected Uracil Derivatives Using the Halogen-Magnesium Exchange

Supporting Information

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General: All reactions involving the use of Grignard reagents were carried out under an argon atmosphere in dried glassware using Schlenk techniques. The high vacuum (oil pump) was measured to be 3×10^{-2} mbar or better. As not otherwise stated, the starting materials were purchased from commercial sources and used without further purification. 6-iodouracil (**1c**) was prepared according to the literature¹ and additionally purified by silica gel filtration (eluent: CH₂Cl₂:MeOH; 19:1). 5-methyl-barbituric acid (**4a**),² 6-iodopurine (**10**),³ *S*-phenyl benzenesulfonothioate⁴ and CuCN•2LiCl in THF⁵ were prepared according to literature known procedures. Benzaldehyde, cyclohexane carbaldehyde and TMSCl were distilled under reduced pressure and stored under an argon atmosphere upon use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

The reactions of all uracil and purine derivatives were monitored by TLC of reaction aliquots quenched with MeOH (silica plates; CH₂Cl₂:MeOH-mixtures, in almost all cases 19:1) versus the starting material and/or commercial uracil (equivalent for the quenched Grignard reagent). Analogously, the extractions in course of workups were always monitored by TLC to ensure completeness of the extractions and the content of the collected organic fractions. As not otherwise stated, yields refer to isolated yields of compounds estimated to be >95 % pure by NMR.

Preparation of LiCl in THF (0.5 M)

LiCl (5.25 g, 125 mmol) was placed in a 500 mL Schlenk-flask equipped with a magnetic stirring bar and a glass stopper. For all purposes, teflon grease should be employed. The salt is heated at 150 °C in an oil bath for 4 h. Then, after cooling to rt, the stopper is changed to a rubber septum

¹ Pfeleiderer, W.; Deiss, H. *Israel J. Chem.* **1968**, 6, 603.

² Puckett, W. E.; Pews, R. G. *J. Fluorine Chem.* **1989**, 42, 179.

³ Elion, G. B.; Hitchings, G. H. *J. Am. Chem. Soc.* **1956**, 78, 3508.

⁴ Fujili, K.; Tanifuji, N.; Sasaki, Y.; Yokoyama, T. *Synthesis* **2002**, 343.

⁵ Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, 53, 2390.

and absolute THF (250 mL) is added. Afterwards, the septum is replaced again by a glass stopper and the suspension is left stirring over night at rt. After at least 12 h, the LiCl has completely dissolved; the stirring is stopped and the solution is left for some more time to become completely clear (little particles and insoluble impurities settle down by that way). The solution is stored under Ar upon use.

1. Preparation of the functionalized uracil derivatives of type 3

a) Typical procedure for the triple metallation of 5-iodouracil (1a) (TP1):

5-Iodouracil (**1a**; 476 mg, 2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. Applying vigorous stirring, the substrate was dried for 15 min in high vacuum to exclude the presence of water in the hygroscopic substrate. Then, a solution of LiCl in THF (0.50 M; 8.00 mL; 4.00 mmol, 2.00 equiv) was added and after stirring for some minutes at rt, the substrate dissolved to give a clear and colourless solution. The solution was cooled to -20 °C and MeMgCl (3.00 M in THF; 1.33 mL, 4.00 mmol, 2.00 equiv) was added dropwise. Strong bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, the resulting, clear solution was stirred at -20 °C for further 20 min. Afterwards, *i*-PrMgCl·LiCl (1.32 M in THF; 1.82 mL, 2.40 mmol, 1.20 equiv) was added slowly and the resulting mixture was allowed to warm up to room temperature. After one hour, a thick, greyish slurry had formed and the TLC of the mixture did show only traces of 5-iodouracil. The mixture was cooled to -20 °C and the respective electrophile was added at this temperature, then the mixture was allowed to warm up to rt. After the completion of the reaction, it was quenched by addition of MeOH (2.0 mL), the mixture was subjected to workup and purification (see examples).

b) Typical procedure for the triple metallation of 5-bromouracil (1b) (TP2):

5-Bromouracil (**1b**; 382 mg, 2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. A solution of LiCl in THF (0.50 M; 8.00 mL; 4.00 mmol, 2.00 equiv) was added and after stirring for some minutes at rt, the substrate dissolved to give a clear, pale yellow solution. The solution was cooled to -20 °C and MeMgCl (3.00 M in THF; 1.33 mL, 4.00 mmol, 2.00 equiv) was added dropwise. Strong bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, the resulting, clear solution was stirred at -20 °C for further 20 min. Afterwards, (*i*-Pr)₂Mg·LiCl⁶ (0.42 M in THF; 5.24 mL, 2.20 mmol, 1.10 equiv) was added slowly and the resulting mixture was allowed to warm up to room temperature. After one hour, a clear, greyish solution had formed and the TLC of the mixture did show only traces of 5-bromouracil. The mixture was cooled to -20 °C and the respective electrophile was added at this temperature, then the mixture was allowed to warm up to rt. After the completion of the reaction, it was quenched by addition of MeOH (2.0 mL) the mixture was subjected to workup and purification (see examples).

⁶ This reagent can be prepared either by addition of dioxane to *i*-PrMgCl·LiCl and subsequent centrifugation or by CAREFUL combination of *i*-PrMgCl (in THF) and *i*-PrLi (neat) at low temperature, for more detailed information, see: Krasovskiy, A.; Straub, B.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, 45, 15.

c) Typical procedure for the triple metallation of 6-iodouracil (1c) (TP3):

6-Iodouracil (**1c**; 476 mg, 2.00 mmol) was placed in a dry and argon-flushed Schlenk- tube equipped with a magnetic stirring bar and a septum. A solution of LiCl in THF (0.50 M; 8.00 mL; 4.00 mmol, 2.00 equiv) was added and after stirring for some minutes at rt, the substrate dissolved to give a clear, slightly yellow solution. The solution was cooled to -25 °C and MeMgCl (3.00 M in THF; 1.33 mL, 4.00 mmol, 2.00 equiv) was added dropwise. Strong bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, the resulting, clear solution was stirred at -25 °C for further 20 min. Afterwards, *i*-PrMgCl·LiCl (1.32 M in THF; 1.82 mL, 2.40 mmol, 1.20 equiv) was added slowly and the resulting mixture was stirred at the same temperature. After one hour, a clear, greyish solution had formed and the TLC of the mixture did show mainly the exchanged species, traces of 6-iodouracil and traces of an unidentified byproduct. The respective electrophile was added at this temperature, and then the mixture was allowed to warm up to rt. After the completion of the reaction, it was quenched by addition of MeOH (2.0 mL) and the mixture was subjected to workup and purification (see examples).

Preparation 5-(1-hydroxy-2,2-dimethylpropyl)pyrimidine-2,4(1*H*,3*H*)-dione (3a): According to **TP1**, the trimagnesiased reagent **2a** was prepared from 5-iodouracil (**1a**) (476 mg, 2.00 mmol) and reacted with *t*-BuCHO (224 mg, 2.60 mmol, 1.30 equiv). After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca 5-6 (indicator paper). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na₂SO₄) and the volume was, after filtration, reduced in *vacuo* to ca. 30-40 mL giving a suspension of the white product, that was cooled and subsequently filtered. After drying in high vacuum, the product **3a** was obtained as a colorless, crystalline solid (307 mg, 1.55 mmol, 77 %).

mp.: 256.3-259.0 °C

¹H-NMR (dmsO-d₆, 300 MHz): δ [ppm] = 0.79 (s, 9 H); 4.27 (s, 1 H); 4.87 (brs, 1 H); 7.09 (s, 1 H); 10.86 (brs, 2 H).

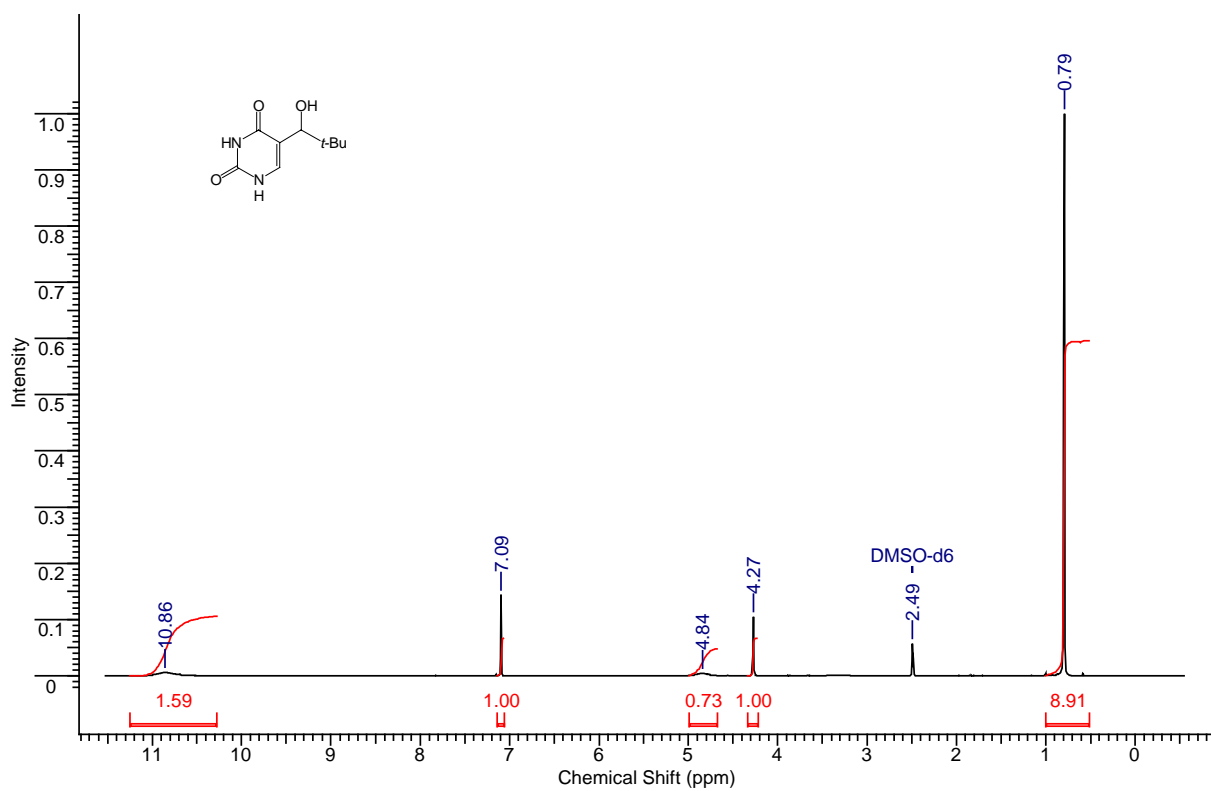
¹³C-NMR (dmsO-d₆, 75 MHz): δ [ppm] = 164.1; 151.0; 139.0; 114.4; 70.9; 35.9; 25.5.

IR (KBr): ν [cm⁻¹] = 3434 (w); 3102 (w); 3080 (w); 2984 (w); 2984 (w); 2952 (m); 2906 (m); 2872 (w); 1702 (s); 1648 (vs); 1500 (w); 1482 (m); 1464 (m); 1446 (m); 1424 (m); 1392 (w); 1376 (w); 1362 (m); 1232 (w); 1206 (m); 1188 (m); 1136 (w); 1050 (m); 1012 (m); 954 (w); 906 (w); 864 (s); 826 (m); 780 (m); 770 (m); 742 (m); 650 (s).

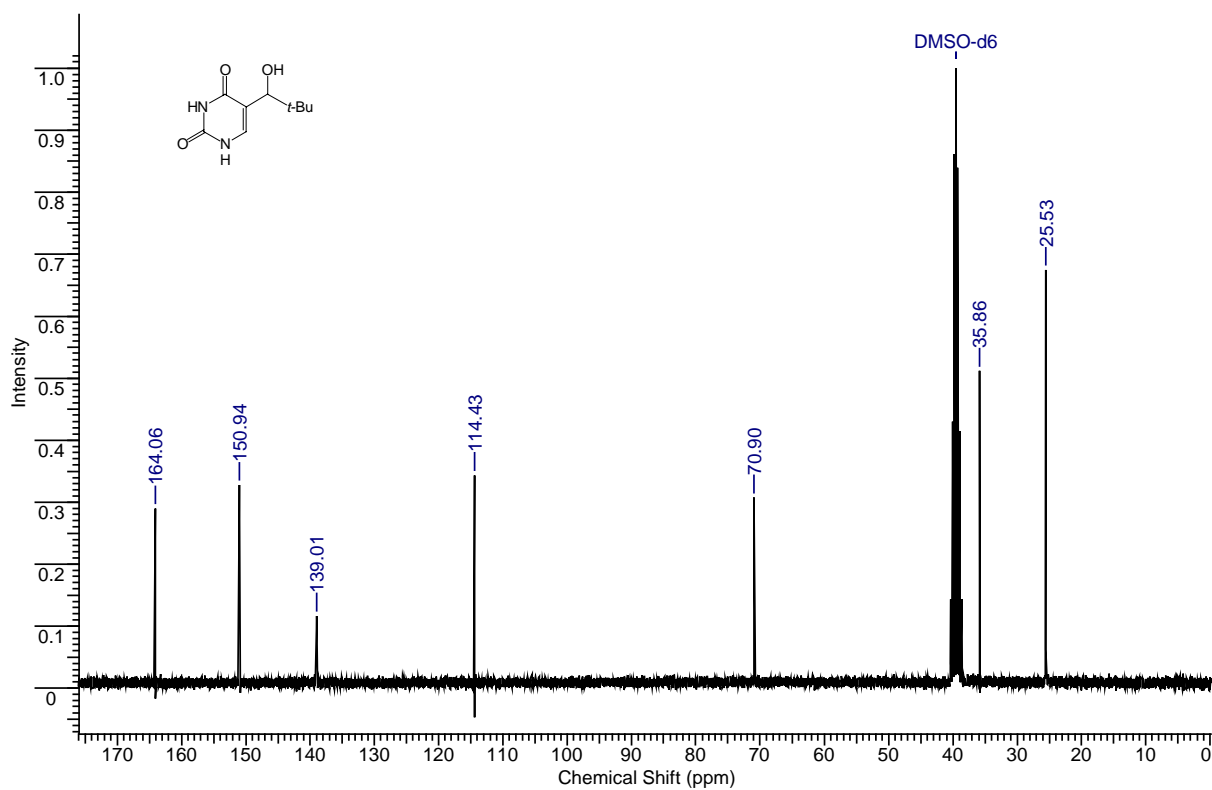
MS (EI): (m/z) (%) = 183 ([M-CH₃]⁺; 1); 165 (8); 142 (85); 141 (100); 137 (5); 124 (9); 113 (7); 98 (18); 70 (8); 57 (16).

HR-MS (C₈H₁₁N₂O₃, [M-CH₃]⁺): calculated: 183.0770 found: 183.0771.

¹H-NMR of pure product:



¹³C-NMR of pure product:



Preparation 5-[hydroxy(phenyl)methyl]pyrimidine-2,4(1*H*,3*H*)-dione (3b): According to **TP1**, the trimagnesiated reagent **2a** was prepared from 5-iodouracil (**1a**) (476 mg, 2.00 mmol) and reacted with benzaldehyde (276 mg, 2.60 mmol, 1.30 equiv). After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca 5-6 (indicator paper). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na₂SO₄) and the volume was, after filtration, reduced in *vacuo* to ca. 30-40 mL giving a suspension of the white product, that was cooled and subsequently filtered. After drying in high vacuum, the product **3b** was obtained as a colorless, crystalline solid (339 mg, 1.56 mmol, 78 %).

mp.: 272.9-274.2 °C

¹H-NMR (dmsO-d₆, 300 MHz): δ [ppm] = 5.48 (s, 1 H); 5.60 (brs, 1 H); 7.18-7.35 (m, 6 H); 10.78 (brs, 1 H); 11.01 (brs, 1 H).

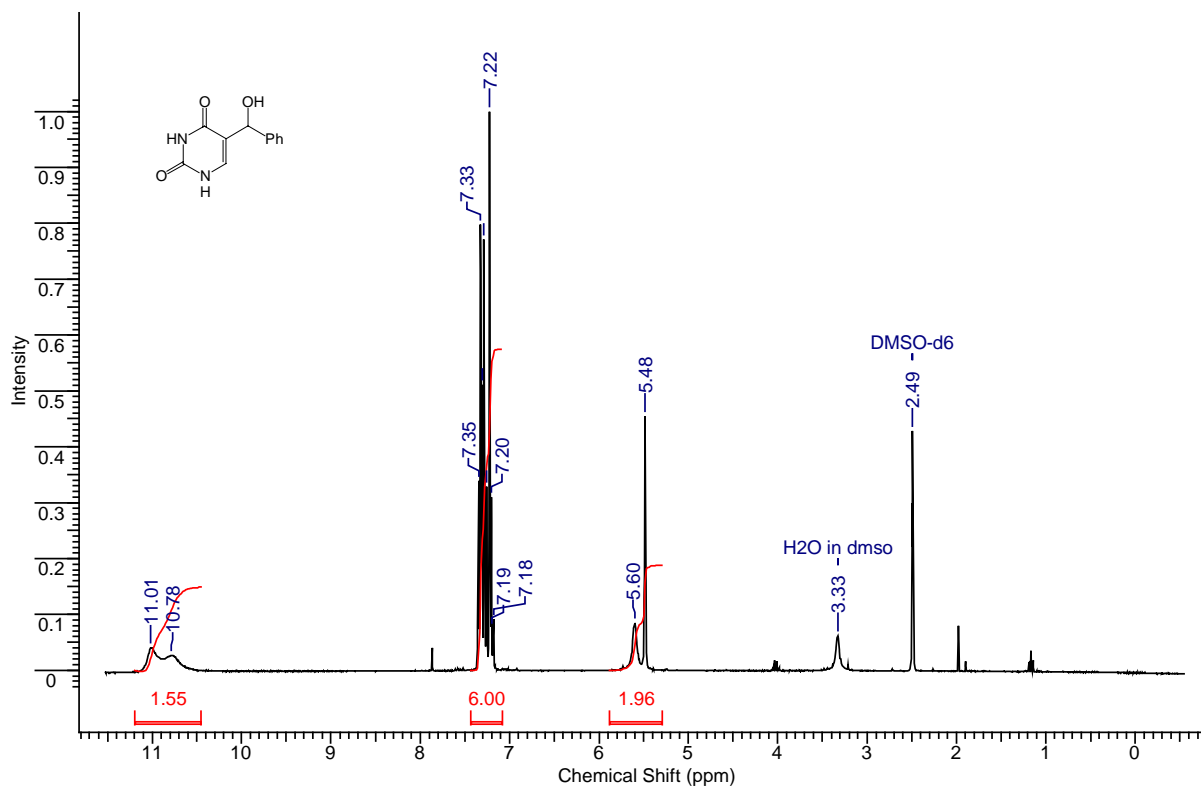
¹³C-NMR (dmsO-d₆, 75 MHz): δ [ppm] = 67.3; 116.2; 126.5; 126.9; 127.9; 137.7; 143.9; 151.1; 163.2.

IR (KBr): ν [cm⁻¹] = 3562 (m); 3472 (w); 3204 (m); 3082 (m); 3028 (m); 2876 (m); 2814 (m); 1712 (s); 1698 (s); 1658 (vs); 1488 (m); 1468 (m); 1446 (m); 1426 (m); 1374 (w); 1364 (w); 1338 (w); 1232 (s); 1220 (m); 1190 (m); 1142 (m); 1130 (w); 1078 (w); 1042 (m); 1024(m); 874 (m); 826 (m); 808 (m); 784 (m); 762 (s); 746 (s); 696 (vs); 662 (s); 624 (w); 606 (w).

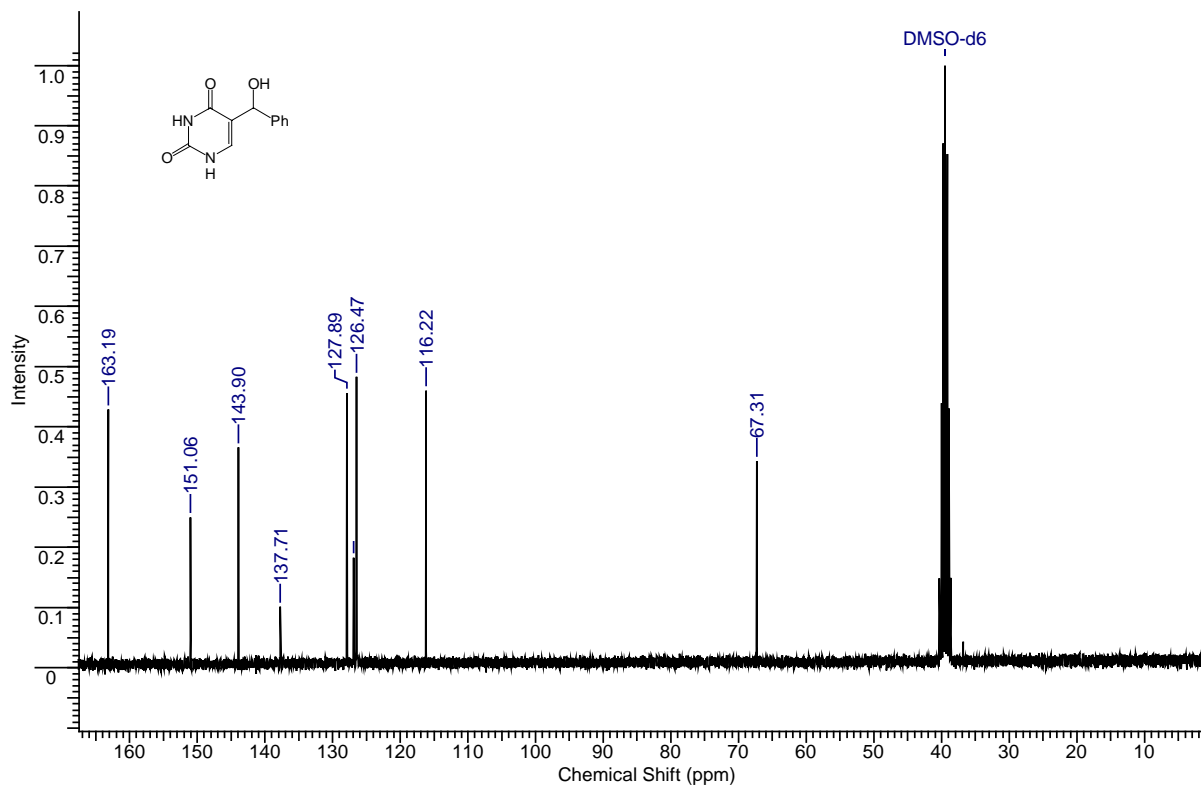
MS (EI): (m/z) (%) = 218 (M⁺; 49); 200 (100); 171 (23); 141 (13); 139 (17); 130 (24); 129 (37); 112 (15); 105 (10); 102 (37); 98 (8); 78 (8).

HR-MS (C₁₁H₁₀N₂O₃): calculated: 218.0691 found: 218.0683.

¹H-NMR of pure product:



¹³C-NMR of pure product:



Preparation 5-[cyclohexyl(hydroxy)methyl]pyrimidine-2,4(1*H*,3*H*)-dione (3c): According to **TP1**, the trimagnesiased reagent **2a** was prepared from 5-iodouracil (**1a**) (476 mg, 2.00 mmol) and reacted at $-20\text{ }^{\circ}\text{C}$ with cyclohexane carbaldehyde (291 mg, 2.60 mmol, 1.30 equiv). After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca 5-6 (indicator paper). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na_2SO_4) and the volume was, after filtration, reduced in *vacuo* to ca. 30-40 mL giving a suspension of the white product, that was cooled and subsequently filtered. After drying in high vacuum, the product **3c** was obtained as a colorless, crystalline solid (314 mg, 1.40 mmol, 70 %).

mp.: 270.1-273.0 $^{\circ}\text{C}$

^1H -NMR (dms- d_6 , 300 MHz): δ [ppm] = 0.80-1.25 (m, 5 H); 1.35-1.70 (m, 6 H); 7.18-7.35 (m, 6 H); 4.18 (t, $J = 5.1\text{ Hz}$, 1H); 4.72 (d, $J = 5.1\text{ Hz}$, 1 H); 7.11 (s, 1 H); 10.67 (brs, 1H); 10.94 (brs, 1H).

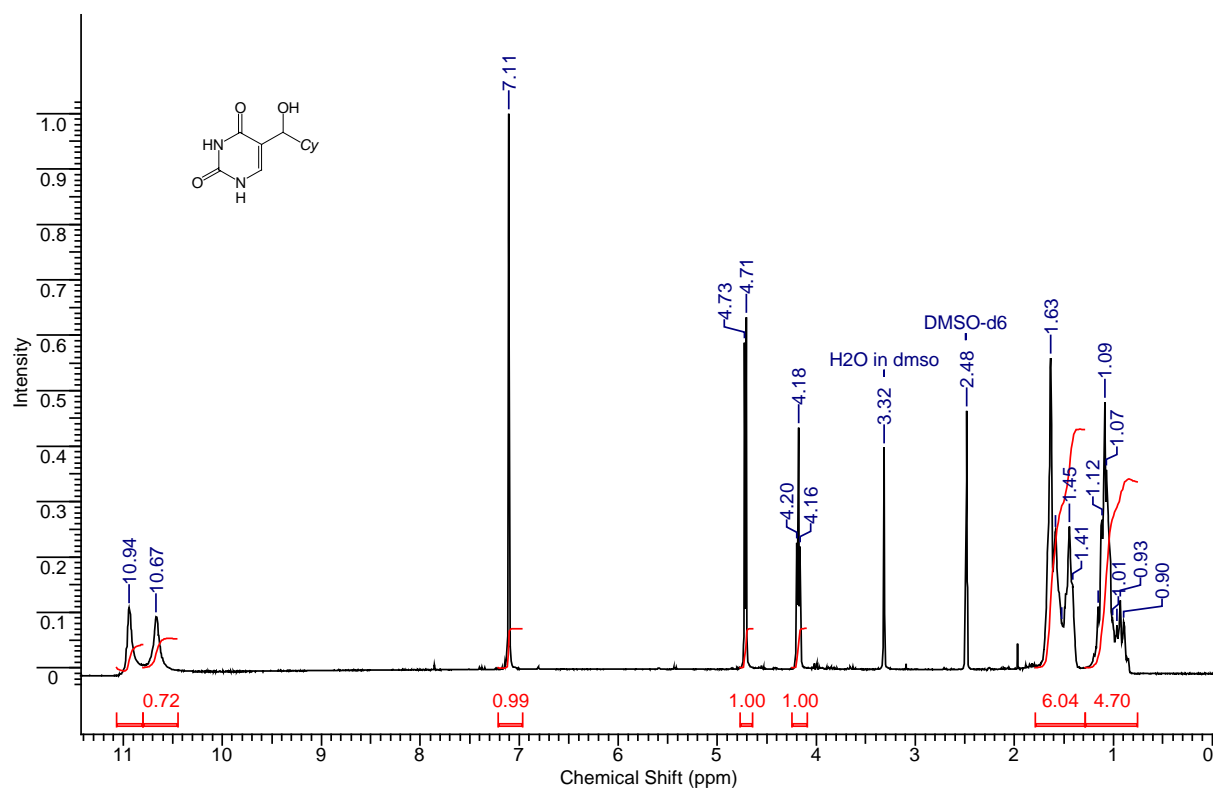
^{13}C -NMR (dms- d_6 , 75 MHz): δ [ppm] = 25.7; 25.9; 26.2; 26.9; 29.3; 42.3; 69.3; 115.0; 137.8; 151.1; 163.6.

IR (KBr): ν [cm^{-1}] = 3444 (w); 3158 (m); 3084 (m); 3022 (m); 2920 (s); 2866 (m); 2850 (m); 2806 (w); 1712 (s); 1650 (vs); 1504 (m); 1466 (m); 1450 (s); 1422 (s); 1380 (m); 1368 (m); 1344 (w); 1306 (w); 1230 (s); 1210 (m); 1174 (w); 1134 (w); 1092 (w); 1066 (w); 1026 (m); 956 (w); 890 (m); 850 (s); 814 (m); 786 (s); 774 (s); 756 (m); 680 (s); 620 (w).

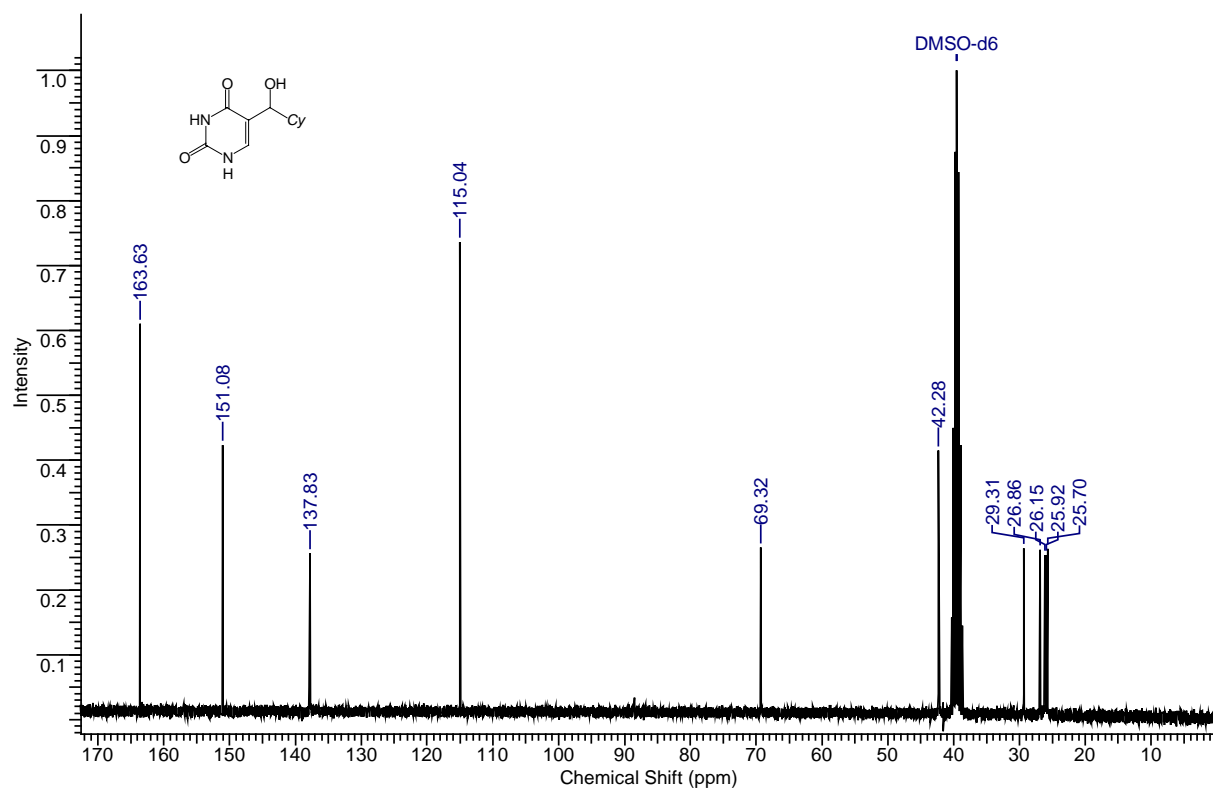
MS (EI): (m/z) (%) = 206 ($[\text{M}-\text{H}_2\text{O}]^+$; 11); 141 (100); 126 (27); 125 (9); 106 (11); 81 (26); 55 (7).

HR-MS ($\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$; $[\text{M}-\text{H}_2\text{O}]^+$): calculated: 206.1055 found: 206.1044.

¹H-NMR of pure product:



¹³C-NMR of pure product:



Preparation 5-[hydroxy(2-thienyl)methyl]pyrimidine-2,4(1*H*,3*H*)-dione (3d): According to **TP 1** the trimagnesiated reagent **2a** was prepared from 5-iodouracil (**1a**) (476 mg, 2.00 mmol) and reacted at -20 °C with thiophene-2-carbaldehyde (291 mg, 1.30 equiv). After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca 5-6 (indicator paper). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na₂SO₄) and evaporated. After recrystallization from MeOH and drying in high vacuum, the product was obtained as pale beige, crystalline solid (246 mg, 1.10 mmol, 55 %).

mp.: 208.6-210.0 °C

¹H-NMR (dmso-d₆, 300 MHz): δ [ppm] = 5.72 (d, *J* = 5.1 Hz, 1 H.); 5.95 (d, *J* = 5.1 Hz, 1 H); 6.92 (2 × s, 2 H; overlaid signals); 7.28 (brs, 1H); 7.36 (t, *J* = 3.1 Hz, 1H); 10.79 (brs, 1H); 11.12 (brs, 1H).

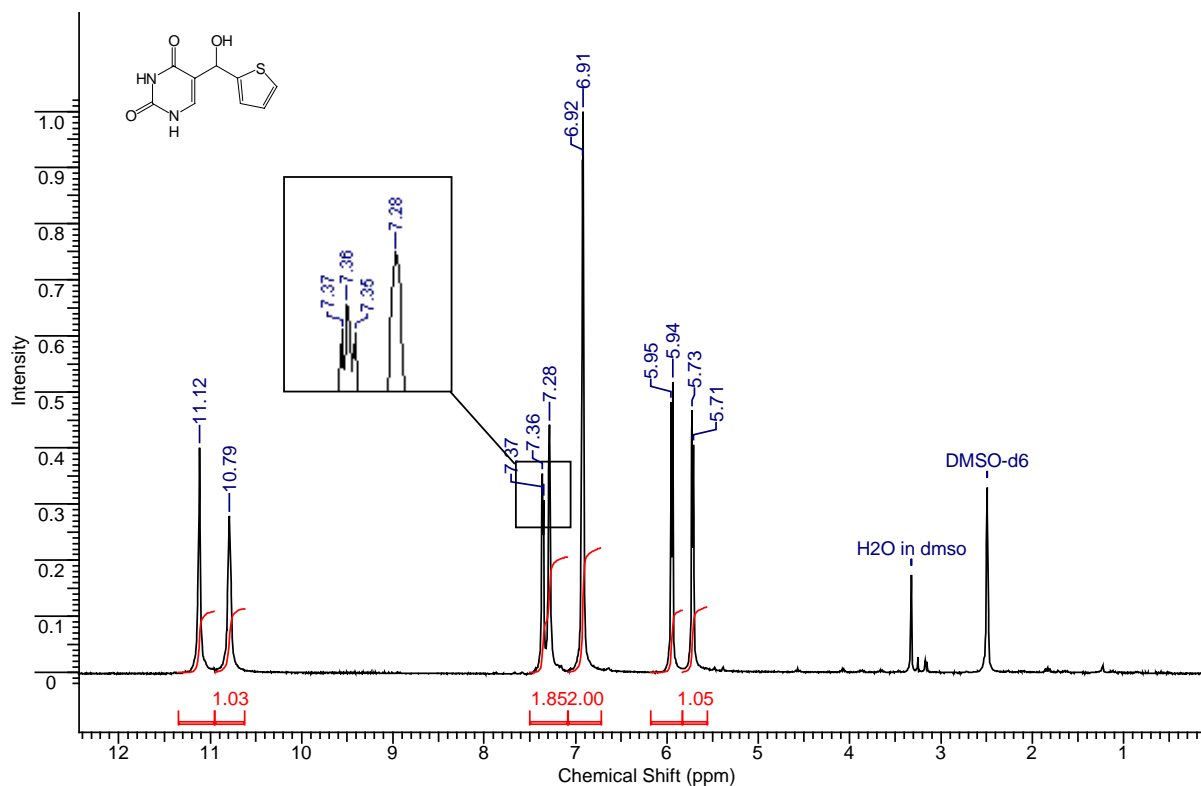
¹³C-NMR (dmso-d₆, 75 MHz): δ [ppm] = 63.4; 115.9; 124.0; 124.5; 126.5; 137.9; 148.5; 151.0; 163.1.

IR (KBr): ν [cm⁻¹] = 3472 (m); 3098 (m); 2992 (m); 2954 (m); 2824 (m); 1692 (s); 1652 (vs); 1506 (m); 1452 (m); 1426 (s); 1394 (m); 1360 (m); 1298 (w); 1228 (s); 1210 (s); 1164 (w); 1140 (m); 1018 (m); 1006 (m); 954 (w); 890 (m); 856 (m); 842 (m); 826 (m); 778 (s); 742 (m); 686 (s); 656 (s); 626 (m); 612 (w).

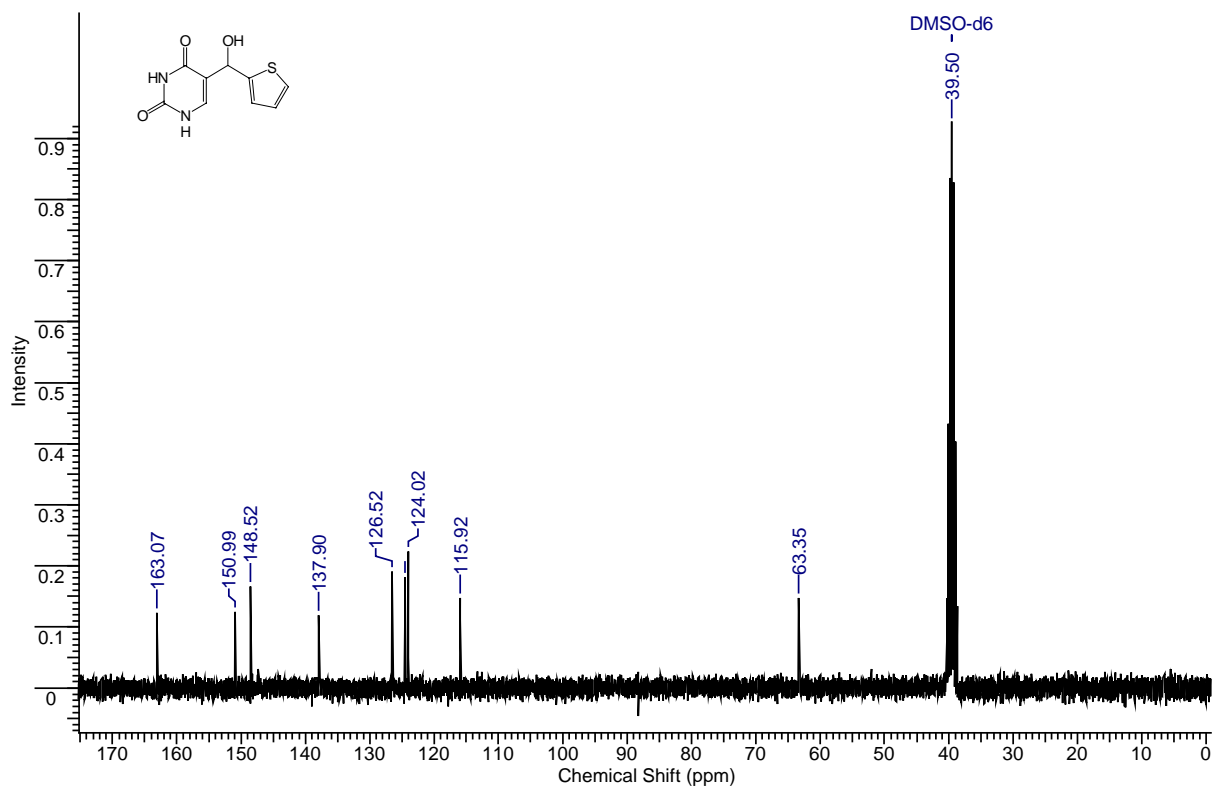
MS (EI): (m/z) (%) = 224 (M⁺; 54); 208 (72); 206 (100); 178 (17); 140 (32); 137 (19); 136 (61); 135 (51); 112 (47); 108 (38); 85 (42); 45 (22).

HR-MS (C₉H₈N₂O₃S): calculated: 224.0256 found: 224.0235.

¹H-NMR of pure product:



¹³C-NMR of pure product:



Preparation of 5-allylpyrimidine-2,4(1*H*,3*H*)-dione (3e): According to **TP 1**, the trimagnesiased reagent **2a** was prepared from 5-iodouracil (**1a**) (476 mg, 2.00 mmol) and reacted with allyl bromide (315 mg, 2.60 mmol, 1.30 equiv) in the presence of CuCN·2LiCl (1.00 M in THF; 0.02 mL, 1.00 mol%) (the catalyst is added first). After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca 6-7 (indicator paper). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na₂SO₄) and the volume was, after filtration, reduced in *vacuo* to ca. 30-40 mL giving a suspension of the crystalline product, that was cooled and subsequently filtered. After drying in high vacuum, the product **3e** was obtained as a colorless, crystalline solid (256 mg, 1.68 mmol, 84 %).

mp.: 279.5-281.3 °C (decomposition)

¹H-NMR (dmsO-d₆, 300 MHz): δ [ppm] = 2.90 (d, *J* = 6.4 Hz, 2 H); 4.96-5.06 (m, 2 H); 5.76-5.89 (m, 1 H); 7.14 (s, 1 H); 10.67 (brs, 1 H); 10.99 (brs, 1 H).

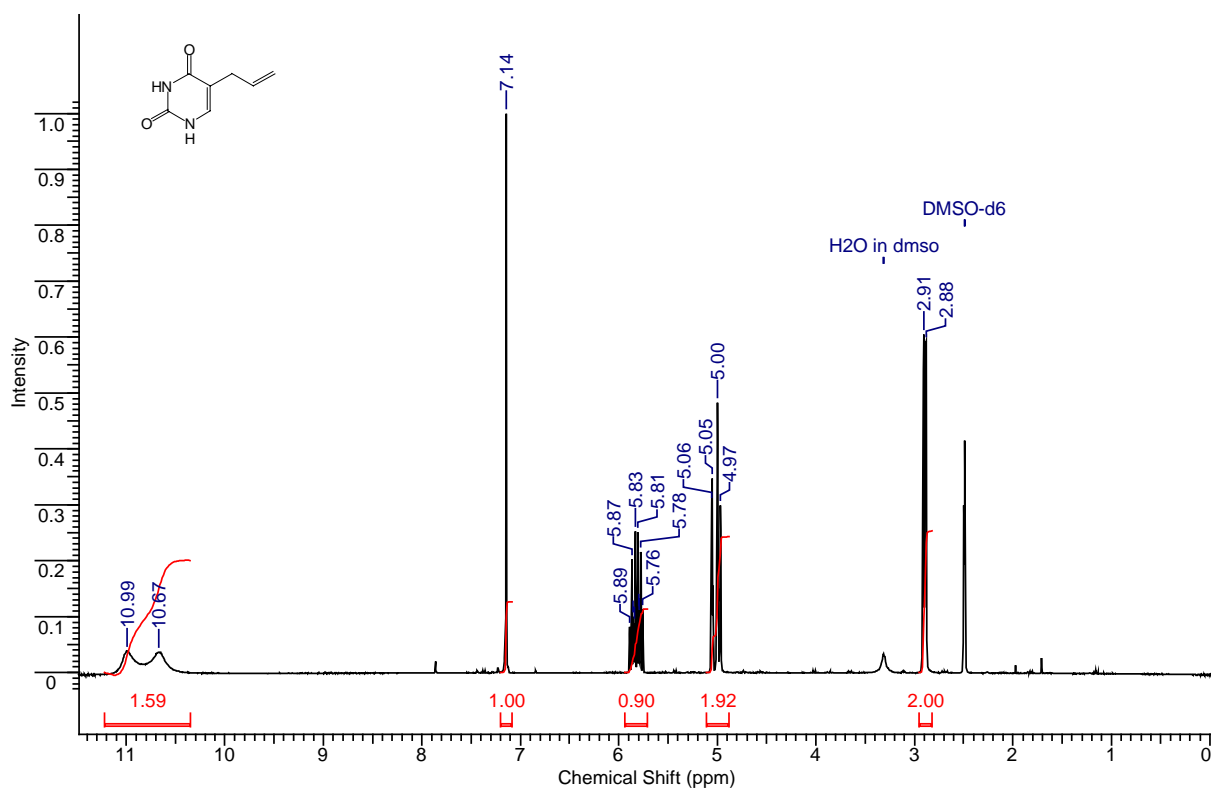
¹³C-NMR (dmsO-d₆, 75 MHz): δ [ppm] = 29.9; 110.3; 115.9; 135.9; 138.2; 151.3; 164.1.

IR (KBr): ν [cm⁻¹] = 3216 (m); 3152 (m); 3074 (m); 3016 (m); 2896 (m); 2864 (m); 2826 (m); 1792 (w); 1728 (m); 1700 (m); 1660 (vs); 1484 (s); 1448 (s); 1428 (s); 1372 (m); 1338 (w); 1284 (w); 1234 (s); 1190 (s); 1130 (w); 1116 (w); 1006 (m); 996 (w); 952 (w); 930 (m); 918 (s); 898 (m); 864 (m); 820 (m); 796 (m); 776 (m); 758 (s); 746 (s); 656 (m); 612 (w).

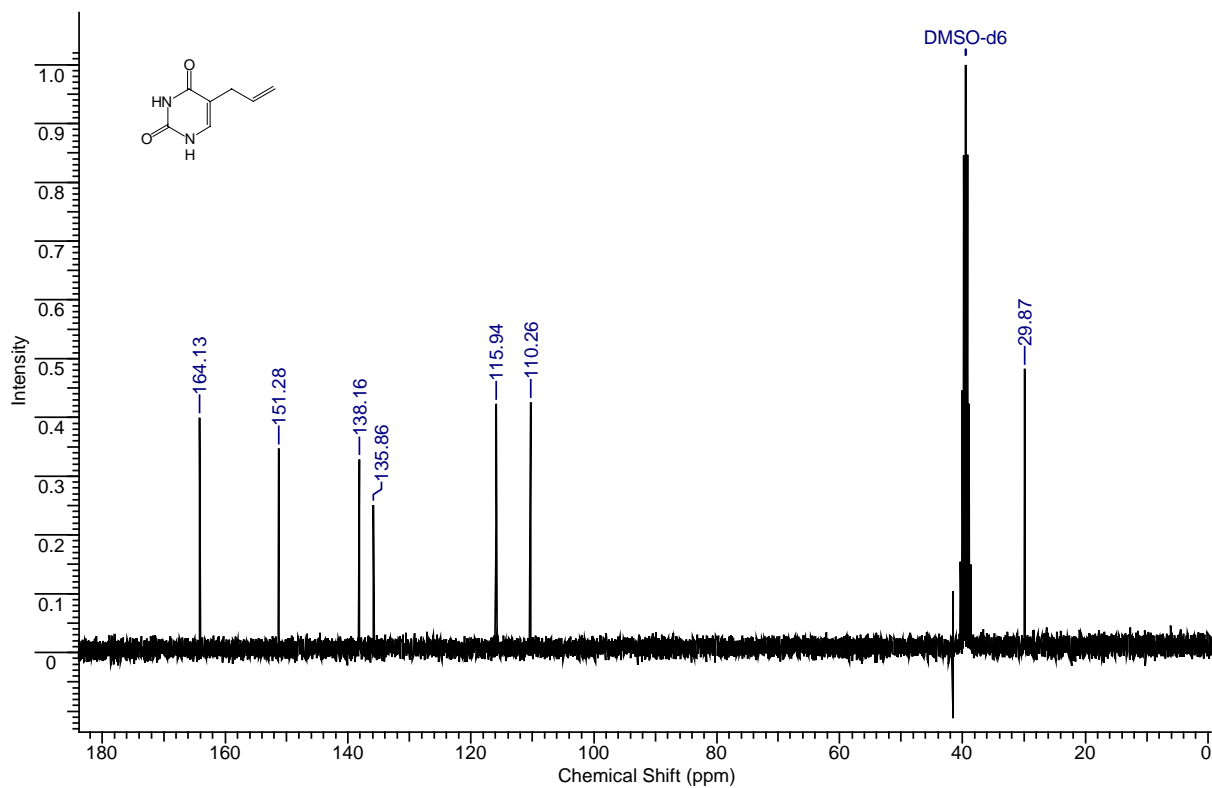
MS (EI): (m/z) (%) = 152 (M⁺; 40); 137 (10); 109 (26); 94 (10); 80 (100); 66 (17); 54 (12); 53 (21); 52 (22); 51 (12).

HR-MS (C₇H₈N₂O₂): calculated: 152.0586 found: 152.0595.

¹H-NMR of pure product:



¹³C-NMR of pure product:



Preparation of 5-(2-methyl-2-propenyl)-2,4(1*H*,3*H*)-pyrimidinedione (3f): According to **TP2**, the trimagnesiated reagent **2b** was prepared from 5-bromouracil (**1b**) (382 mg, 2.00 mmol) and reacted at $-20\text{ }^{\circ}\text{C}$ with 3-bromo-2-methyl-1-propene (743 mg, 5.50 mmol, 2.75 equiv) in the presence of $\text{CuCN}\cdot 2\text{LiCl}$ (1.00 M in THF; 0.02 mL, 1.00 mol%). Afterwards, the mixture was warmed up to rt and stirred at that temperature till TLC indicated completion of the reaction. After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca 6-7 (indicator paper). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na_2SO_4) and the volume was, after filtration, reduced in *vacuo* to ca. 30-40 mL giving a suspension of the crystalline product, that was cooled and subsequently filtered. The residue was washed with little cold CH_2Cl_2 , and after drying in high vacuum, a first batch of the product was obtained as a colorless, crystalline solid. Reducing the volume of the mother liquor and cooling of the same did give another crop of the crystalline, colorless product (allover 180 mg, 1.08 mmol, 54 %).

mp.: 271.3-274.0 $^{\circ}\text{C}$

^1H -NMR (dms- d_6 , 300 MHz): δ [ppm] = 1.64 (s, 3 H); 1.84 (s, 2 H); 4.71 (s, 1 H); 4.62 (s, 1 H); 7.16 (s, 1 H); 10.68 (brs, 1 H); 10.01 (brs, 1 H).

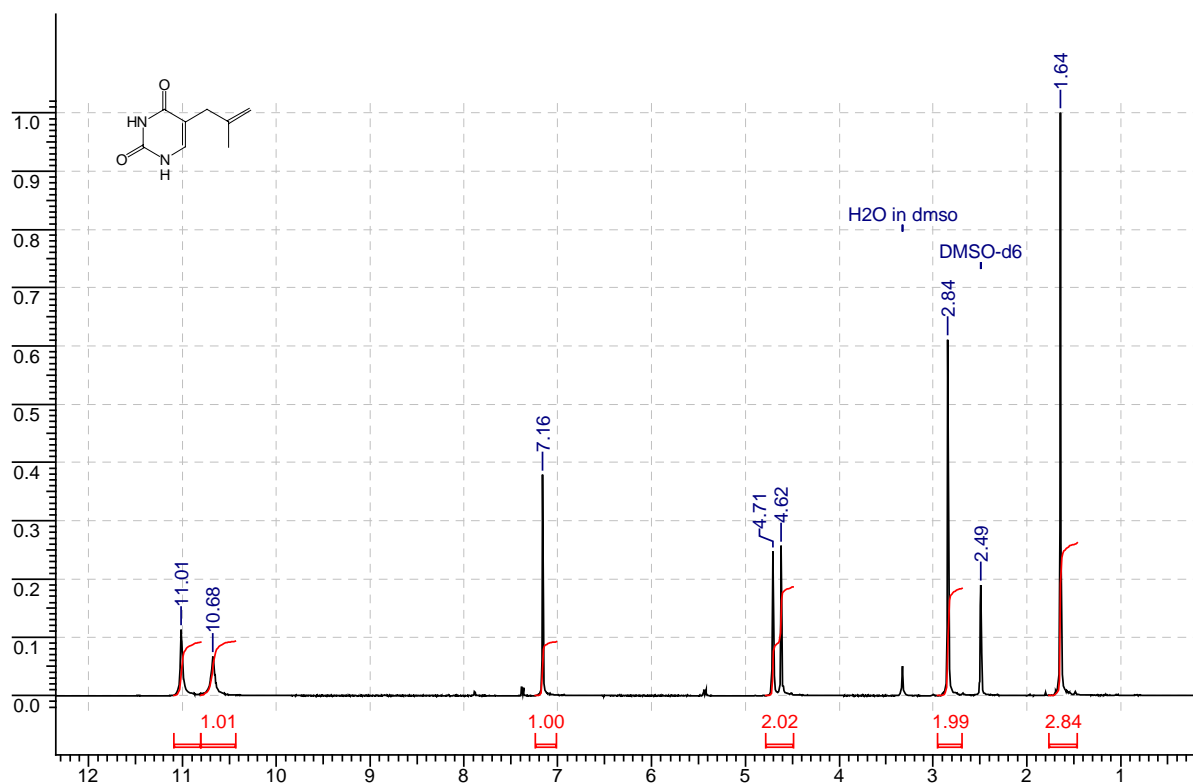
^{13}C -NMR (dms- d_6 , 75 MHz): δ [ppm] = 22.2; 33.4; 109.7; 111.2; 138.9; 143.4; 151.4; 164.3.

IR (KBr): ν [cm^{-1}] = 3204 (m); 3164 (m); 3126 (m); 3066 (m); 3026 (m); 2968 (m); 2934 (m); 2906 (m); 2868 (m); 2820 (m); 2724 (w); 1728 (m); 1660 (vs); 1650 (vs); 1488 (m); 1448 (s); 1424 (s); 1374 (m); 1342 (m); 1244 (s); 1228 (m); 1206 (s); 1138 (w); 1014 (w); 950 (w); 918 (m); 902 (s); 834 (w); 804 (w); 765 (w); 742 (w); 640 (w).

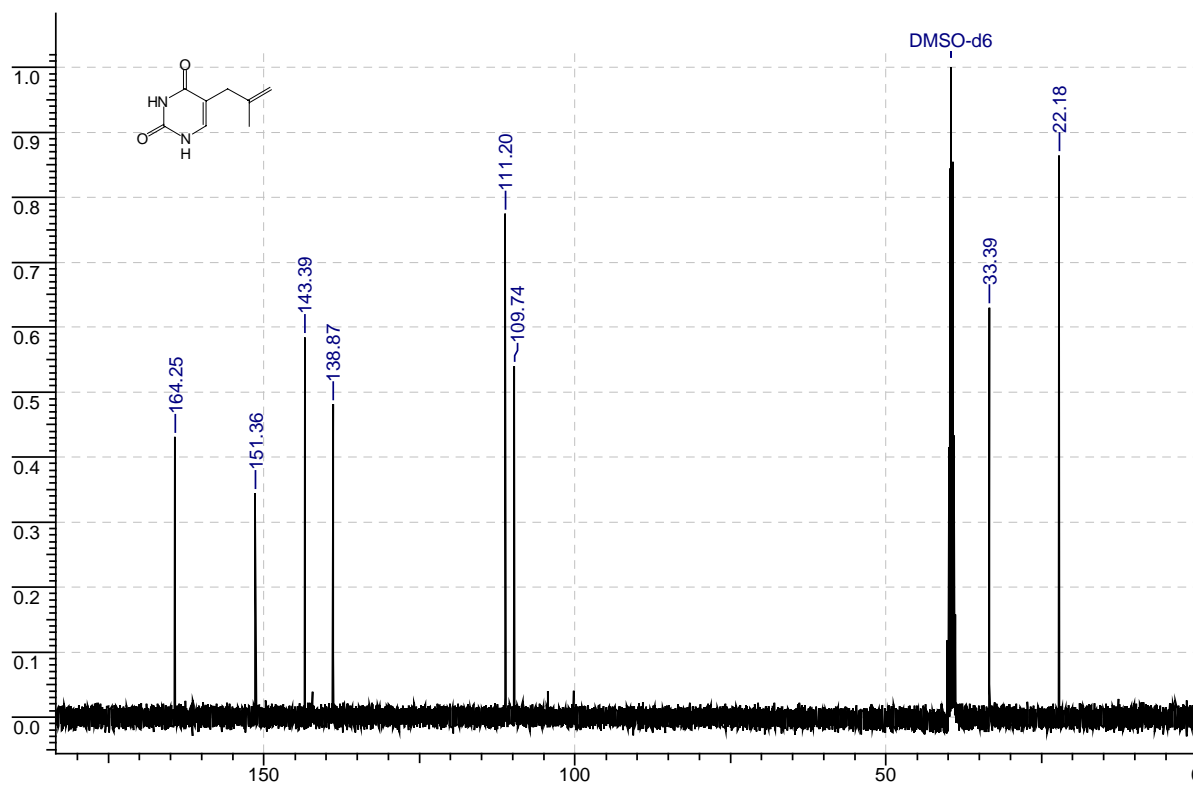
MS (EI): (m/z) (%) = 166 (M^+ , 100); 151 (28); 123 (82); 108 (24); 94 (52); 81 (31); 80 (68); 55 (13); 41 (15).

HR-MS ($\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2$): calculated: 166.0742 found: 166.0734.

¹H-NMR of pure product:



¹³C-NMR of pure product:



Preparation of 5-(trimethylsilyl)-2,4(1*H*,3*H*)-pyrimidinedione (3g): According to **TP 1** the trimagnesiased reagent **2a** was prepared from 5-iodouracil (**1b**) (476 mg, 2.00 mmol) and reacted at chlorotrimethylsilane (719 mg, 6.60 mmol, 3.30 equiv). Afterwards, the mixture was warmed up to rt and stirred at that temperature till TLC indicated completion of the reaction. It was quenched by addition of MeOH (2.0 mL) and transferred to a separation funnel containing a mixture of HCl (1.0 M; 20 mL) and sat. aq. NH₄Cl (20 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 40 mL) and EtOAc (3 × 40 mL), the combined organic layers were dried (Na₂SO₄) and evaporated in *vacuo*. Recrystallization from MeOH afforded **3g** as colorless, crystalline solid (286 mg, 1.45 mmol, 72 %).

mp.: 339.3-346.6 °C (decomposition)

¹H-NMR (dmso-*d*₆, 300 MHz): δ [ppm] = 0.13 (s, 9 H); 7.12 (s, 1 H); 10.89 (brs, 2 H).

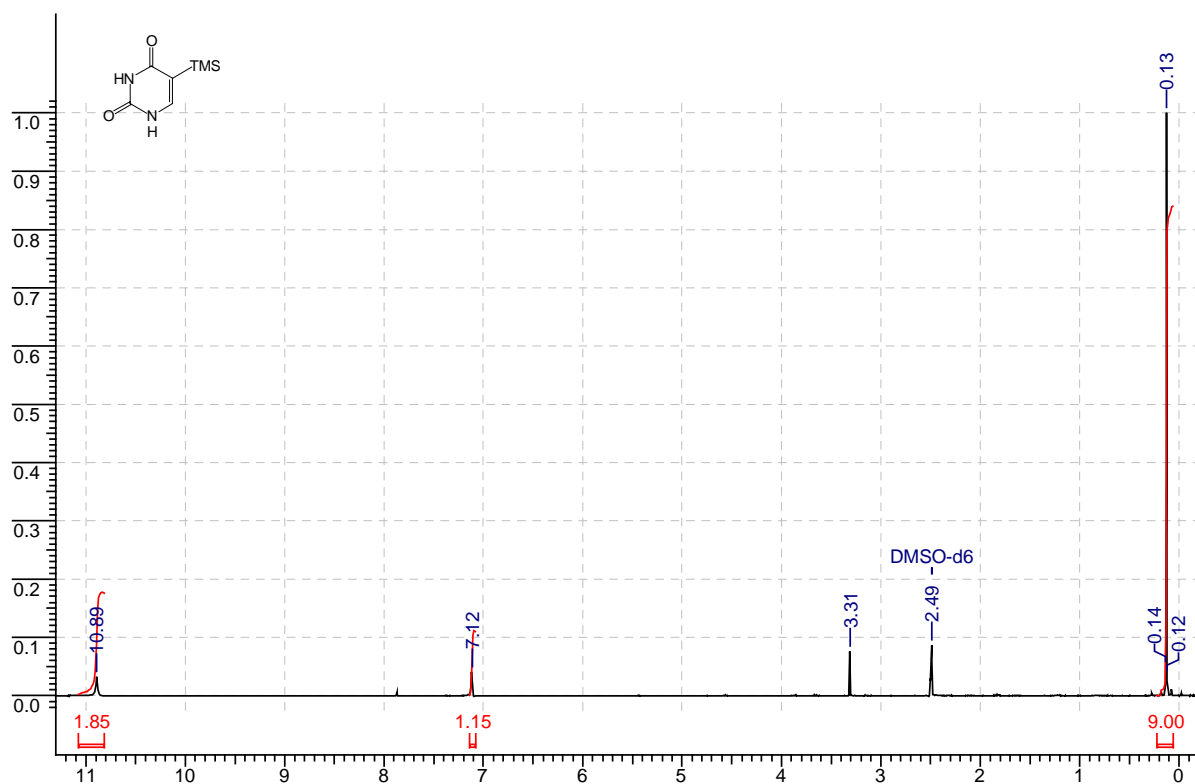
¹³C-NMR (dmso-*d*₆, 75 MHz): δ [ppm] = -1.6; 107.0; 146.1; 151.7; 166.6.

IR (KBr): ν [cm⁻¹] = 3214 (m); 3088 (m); 2956 (m); 1721 (vs); 1661 (vs); 1614 (s); 1438 (m); 1348 (m); 1248 (m); 1162 (w); 1071 (m); 1012 (w); 843 (s); 785 (m); 756 (w); 697 (w); 667 (w); 614 (m); 554 (m); 473 (m).

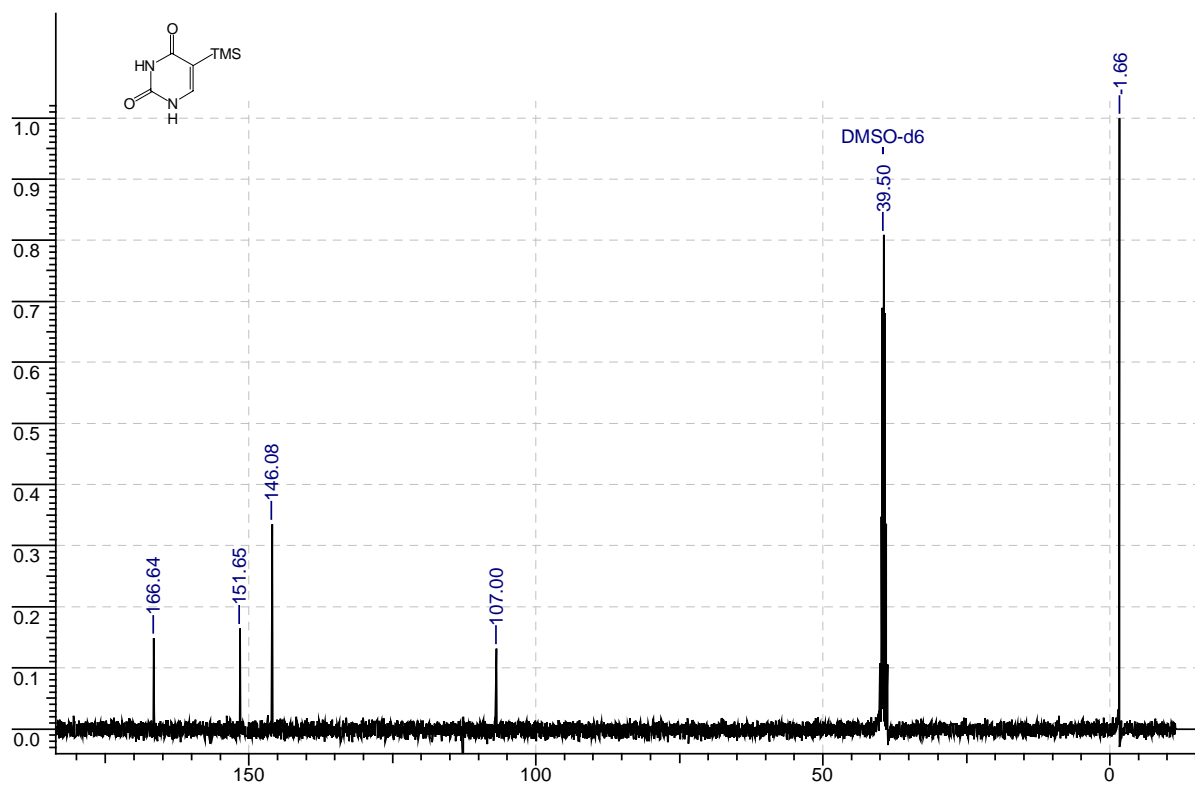
MS (EI): (m/z) (%) = 184 (M⁺; 4); 169 (100); 100 (7); 83 (4); 74 (29); 43 (4).

HR-MS (C₇H₁₂SiN₂O₂): calculated: 184.0668 found: 184.0648.

^1H -NMR of pure product:



^{13}C -NMR of pure product:



Preparation of 5-(phenylsulfanyl)-2,4(1*H*,3*H*)-pyrimidinedione (3h): According to **TP1**, the trimagnesiased reagent **2a** was prepared from 5-iodouracil (**1a**) (476 mg, 2.00 mmol) and reacted at –20 °C with *S*-phenyl benzenesulfonothioate (650 mg, 2.60 mmol, 1.30 equiv; in 4.0 mL THF). After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca 5-6 (indicator paper). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na₂SO₄) and evaporated in *vacuo*. The crude product was suspended in little heptane, some drops of EtOAc were added and the suspension was sonicated for 30 min. After filtration and drying in high vacuum, the product **3h** was obtained as off white solid (337 mg, 1.53 mmol, 77 %; purity by ¹H-NMR: 92 %; impurity: 8 % 5-iodouracil; see below).

mp.: 273.0-274.2 °C

¹H-NMR (dmsd-d₆, 400 MHz): δ [ppm] = 7.12-7.30 (m, 5 H); 7.91 (s, 1 H); 11.37 (brs, 2H).

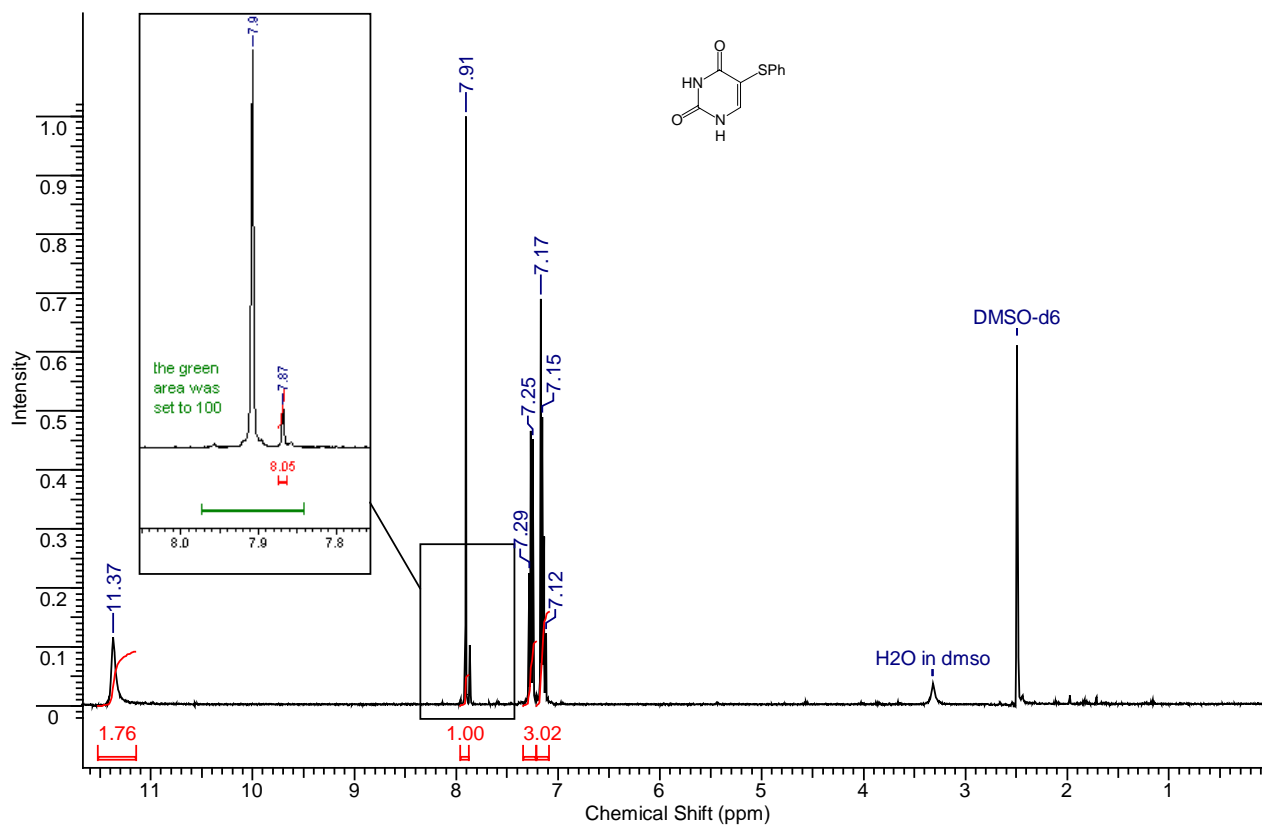
¹³C-NMR (dmsd-d₆, 100 MHz): δ [ppm] = 101.9; 125.5; 126.3; 128.9; 136.7; 148.9; 151.2; 162.2.

IR (KBr): ν [cm⁻¹] = 3164 (m); 3058 (m); 2876 (m); 1744 (vs); 1679 (vs); 1610 (s); 1584 (m); 1480 (m); 1438 (m); 1423 (m); 1326 (w); 1220 (m); 1175 (w); 1075 (w); 1025 (w) 998 (w); 815 (w); 786 (w); 760 (m); 733 (m); 686 (m); 615 (w); 551 (w).

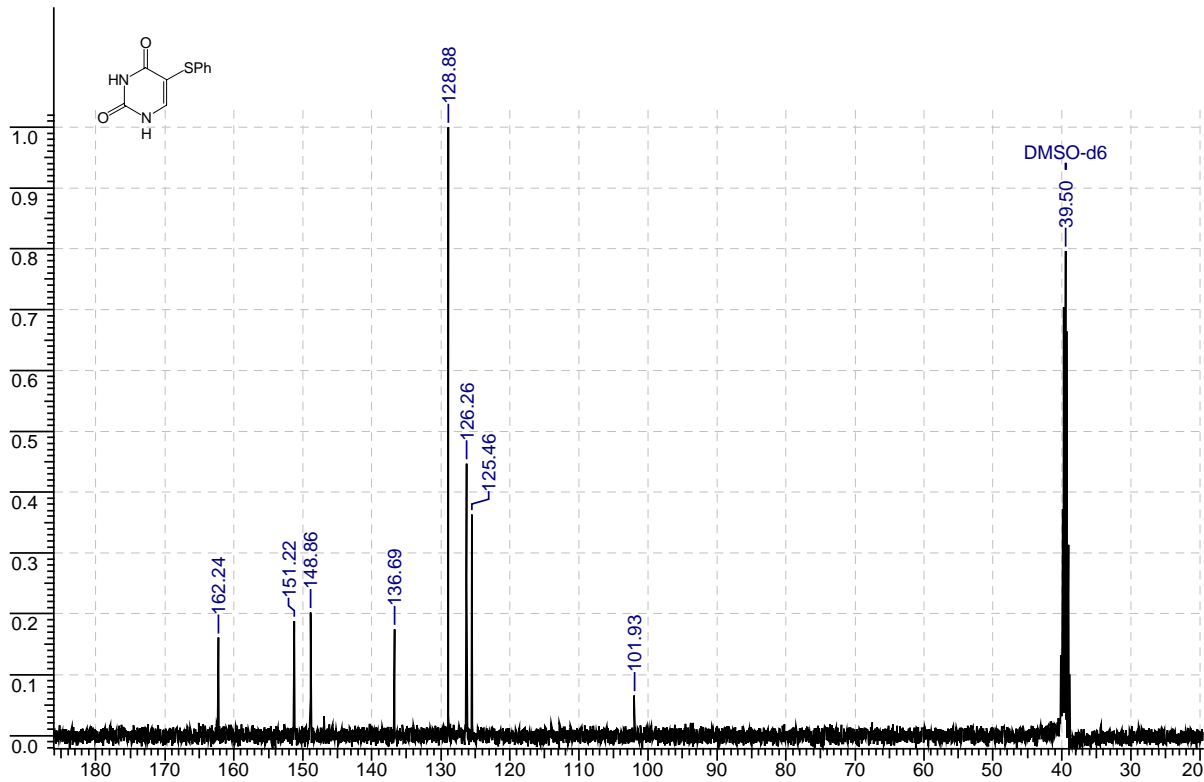
MS (EI): (m/z) (%) = 220 (M⁺; 100); 177 (4); 149 (36); 121 (29); 117 (7); 105 (5); 77 (10); 51 (7).

HR-MS (C₁₀H₈N₂O₂S): calculated: 220.0306 found: 220.0291.

¹H-NMR of pure product:



¹³C-NMR of pure product:



Preparation of 5-(methylthio)pyrimidine-2,4(1*H*,3*H*)-dione (3i): According to **TP1**, the trimagnesiated reagent **2a** was prepared from 5-iodouracil (**1a**) (476 mg, 2.00 mmol) and reacted at -20 °C with *S*-methyl methanesulfonylthioate (328 mg, 2.60 mmol, 1.30 equiv). Afterwards, the mixture was warmed up to rt and stirred at that temperature till TLC indicated completion of the reaction. After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca. 5-6 (indicator paper). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na₂SO₄) and evaporated. Recrystallization from MeOH afforded the product as a colorless, crystalline solid which was dried in high vacuum (202 mg, 1.28 mmol, 64 %).

mp.: 303.7-304.9 °C

¹H-NMR (dmsO-d₆, 400 MHz): δ [ppm] = 2.20 (s, 3 H); 7.41 (s, 1 H); 11.03 (s, 1 H); 11.26 (s, 1H).

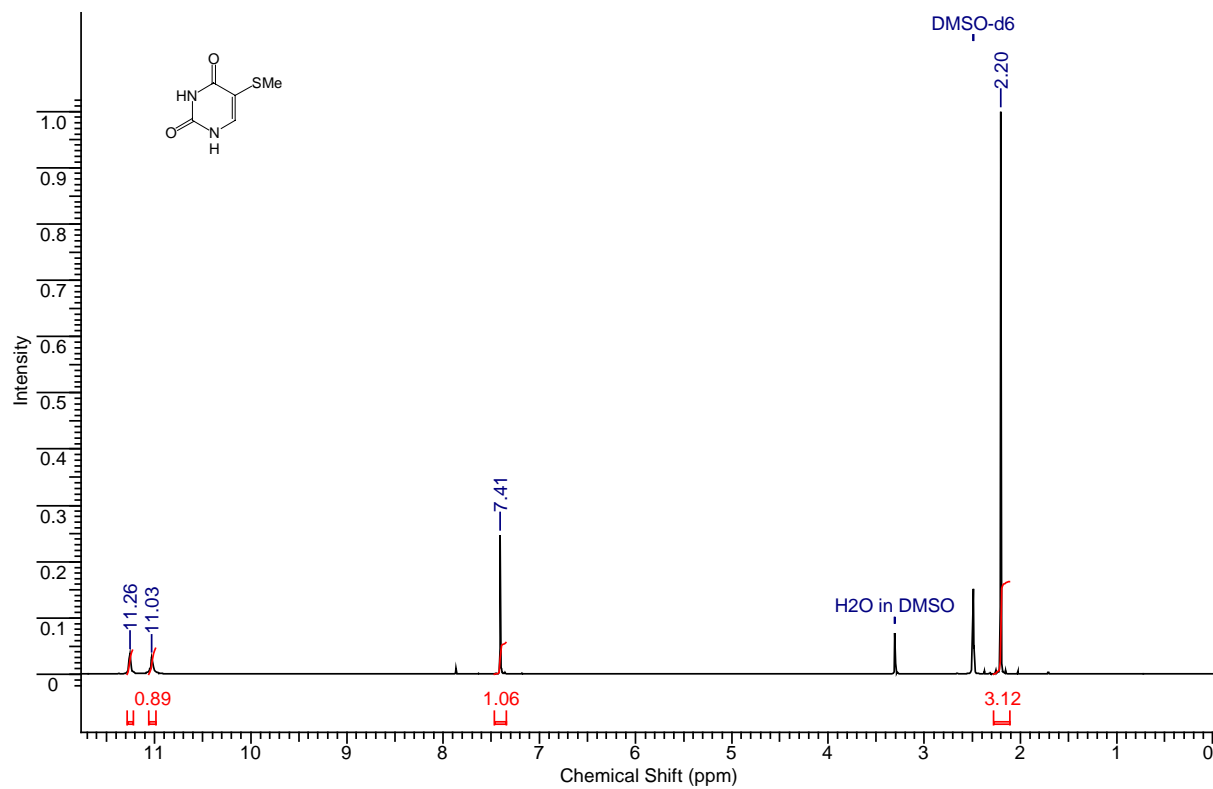
¹³C-NMR (dmsO-d₆, 100 MHz): δ [ppm] = 16.5; 108.4; 141.4; 151.7; 163.1.

IR (KBr): ν [cm⁻¹] = 3447 (w); 3204 (m); 3014 (s); 2819 (m); 1728 (vs); 1664 (vs); 1612 (s); 1474 (m); 1427 (s); 1353 (m); 1316 (w); 1244 (m); 1158 (w); 1090 (m); 1018 (w); 985 (w); 964 (w); 899 (w); 868 (m); 810 (m); 778 (m); 758 (m); 677 (s); 624 (w); 551 (m).

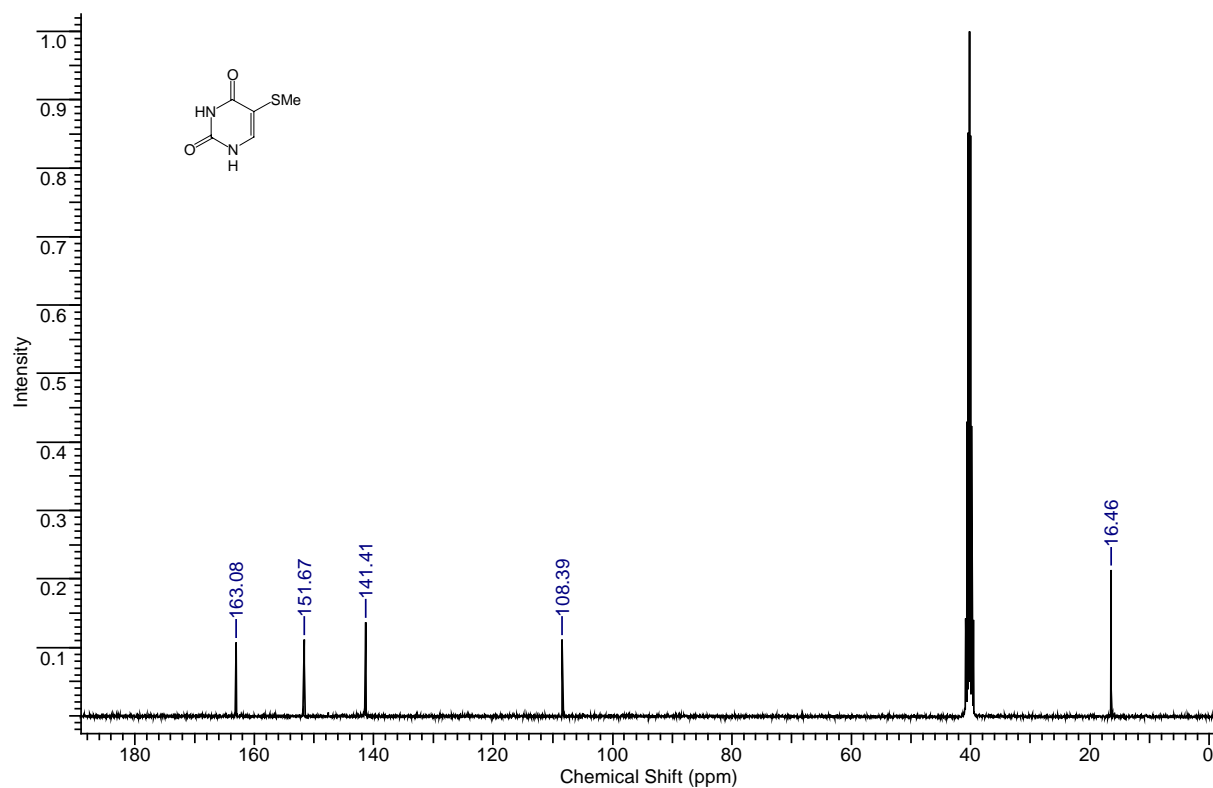
MS (EI): (m/z) (%) = 158 (M⁺; 100); 125 (42); 115 (15); 88 (12); 72 (18); 69 (24); 60 (9); 45 (23).

HR-MS (C₅H₆N₂O₂S): calculated: 158.0150 found: 158.0153.

¹H-NMR of pure product:



¹³C-NMR of pure product:



Preparation of 6-allylpyrimidine-2,4(1*H*,3*H*)-dione (3j): According to **TP3**, the trimagnesiased reagent **2c** was prepared from 6-iodouracil (**1c**) (476 mg, 2.00 mmol) and reacted with allyl bromide (315 mg, 2.60 mmol, 1.30 equiv) in the presence of CuCN·2LiCl (1.00 M in THF; 0.02 mL, 1.00 mol%). After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca 6-7 (indicator paper). The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na₂SO₄) and evaporated. Filter column chromatography (*l* = ca. 6 cm, Ø = ca. 3 cm; silica; CH₂Cl₂:MeOH; 19:1) afforded the desired product as colorless, crystalline solid (195 mg, 1.28 mmol, 64 %).

mp.: 188.2-190.1 °C

¹H-NMR (dmso-*d*₆, 400 MHz): δ [ppm] = 3.05 (d, *J* = 6.8 Hz, 2 H); 5.13-5.22 (m, 2 H); 5.27 (s, 1 H); 5.80-5.90 (m, 1 H); 10.83 (brs, 1 H); 10.90 (brs, 1 H).

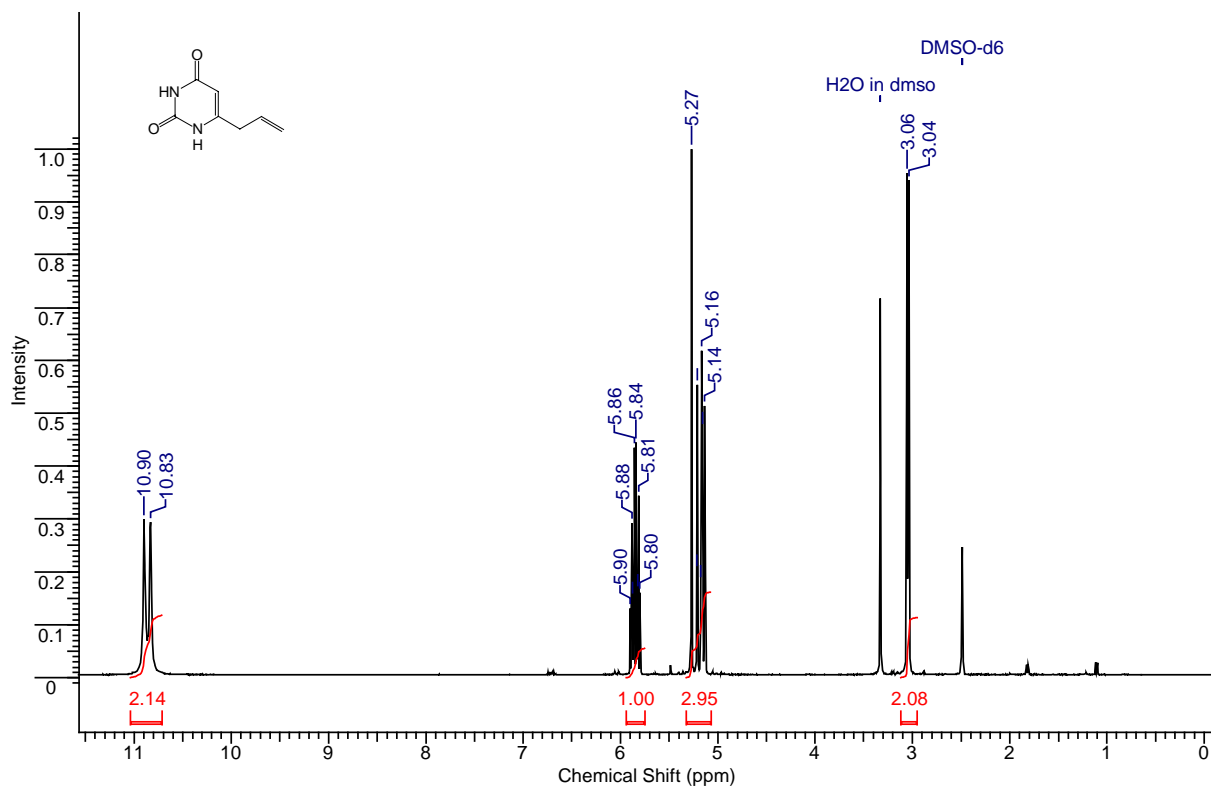
¹³C-NMR (dmso-*d*₆, 100 MHz): δ [ppm] = 35.8; 98.1; 118.8; 132.4; 151.6; 154.6; 164.12.

IR (KBr): ν [cm⁻¹] = 2982 (m); 2932 (m); 2854 (m); 2810 (m); 1712 (s); 1640 (vs); 1530 (m); 1504 (s); 1450 (s); 1422 (vs); 1372 (s); 1322 (m); 1282 (m); 1238 (m); 1168 (m); 1046 (w); 1020 (m); 992 (m); 970 (m); 942 (s); 924 (m); 904 (m); 850 (s); 816 (vs); 760 (vs); 728 (m); 616 (s).

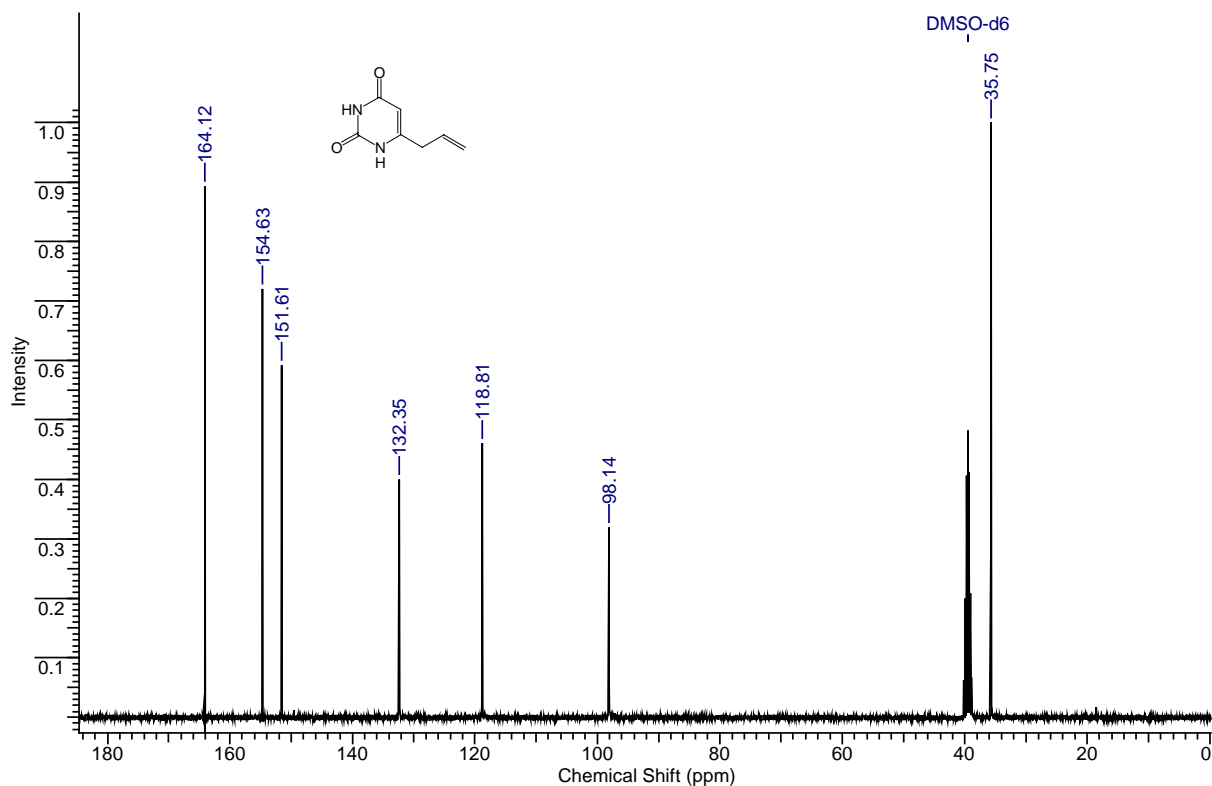
MS (EI): (m/z) (%) = 152 (M⁺; 100); 124 (36); 109 (34); 81 (42); 80 (46); 68 (48); 67 (35); 53 (8); 41 (10).

HR-MS (C₇H₈N₂O₂S): calculated: 152.0586 found: 152.0581.

¹H-NMR of pure product:



¹³C-NMR of pure product:



Preparation of 6-(1-hydroxy-2,2-dimethylpropyl)pyrimidine-2,4(1*H*,3*H*)-dione (3k):

According to **TP 3** the trimagnesiated reagent **2c** was prepared from 6-iodouracil (**1c**) (476 mg, 2.00 mmol) and reacted with *t*-BuCHO (224 mg, 2.60 mmol, 1.30 equiv). After quenching with MeOH, the mixture was transferred to a separation funnel containing water (40 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca 5-6 (indicator paper). The aqueous layer was extracted with EtOAc, the completeness of the reaction was checked by TLC of the fractions. The combined organic layers were dried (Na₂SO₄) and evaporated. Filter column chromatography (*l* = ca. 6 cm, Ø = ca. 3 cm; silica; CH₂Cl₂:MeOH; 19:1) afforded the desired product as colorless, crystalline solid (253 mg, 1.28 mmol, 64 %).

mp.: 188.2-190.1 °C

¹H-NMR (dmsO-d₆, 400 MHz): δ [ppm] = 0.86 (s, 9 H); 3.90 (d, *J* = 4.6 Hz, 1 H); 5.33 (s, 1 H); 5.57 (d, *J* = 4.6 Hz, 1 H); 10.48 (s, 1 H); 10.94 (s, 1 H).

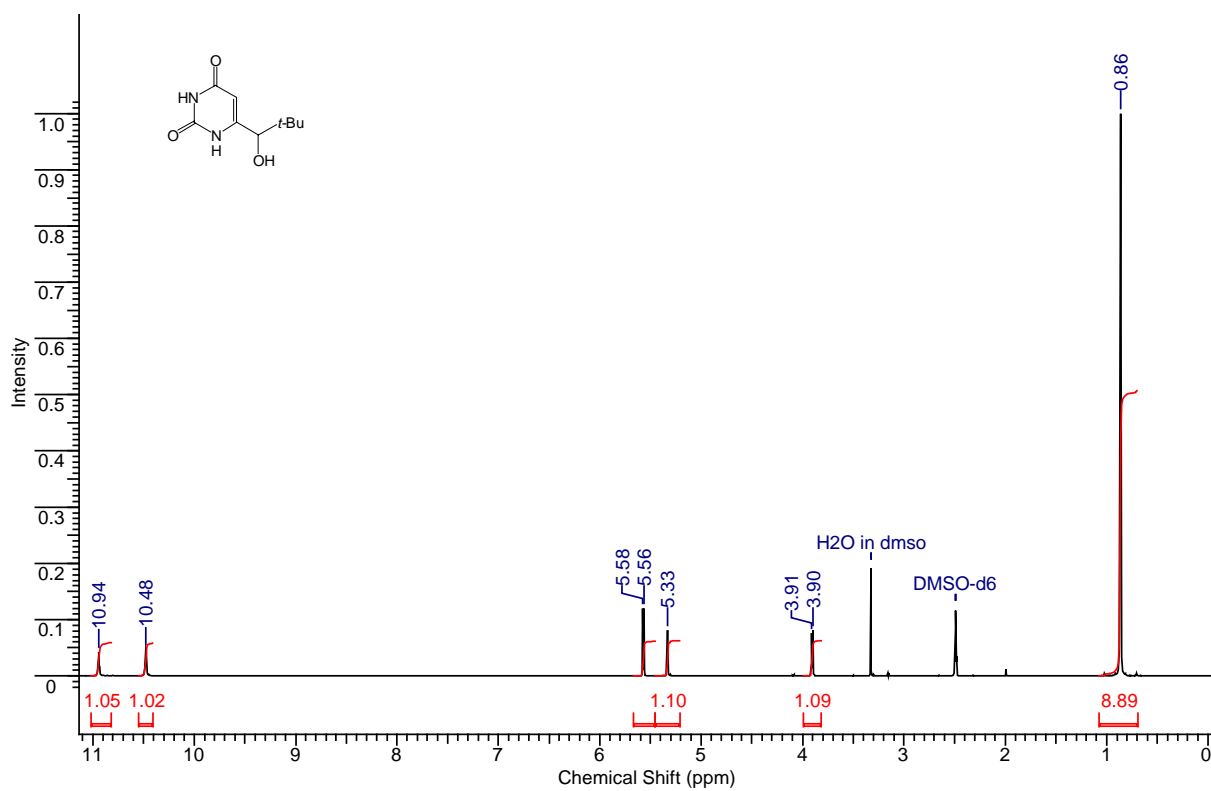
¹³C-NMR (dmsO-d₆, 100 MHz): δ [ppm] = 25.7; 35.1; 75.6; 97.9; 151.2; 158.0; 164.0.

IR (KBr): ν [cm⁻¹] = 3154 (m); 2976 (m); 2964 (m); 2954 (m); 2904 (m); 2870 (m); 2824 (m); 1694 (vs); 1672 (s); 1642 (vs); 1614 (vs); 1496 (s); 1480 (m); 1464 (m); 1422 (vs); 1386 (m); 1366 (m); 1304 (m); 1234 (m); 1158 (w); 1088 (s); 1056 (m); 1016 (m); 966 (m); 876 (m); 840 (m); 828 (s); 792 (m); 776 (s); 764 (s); 748 (m); 714 w); 620 (m); 604 (w).

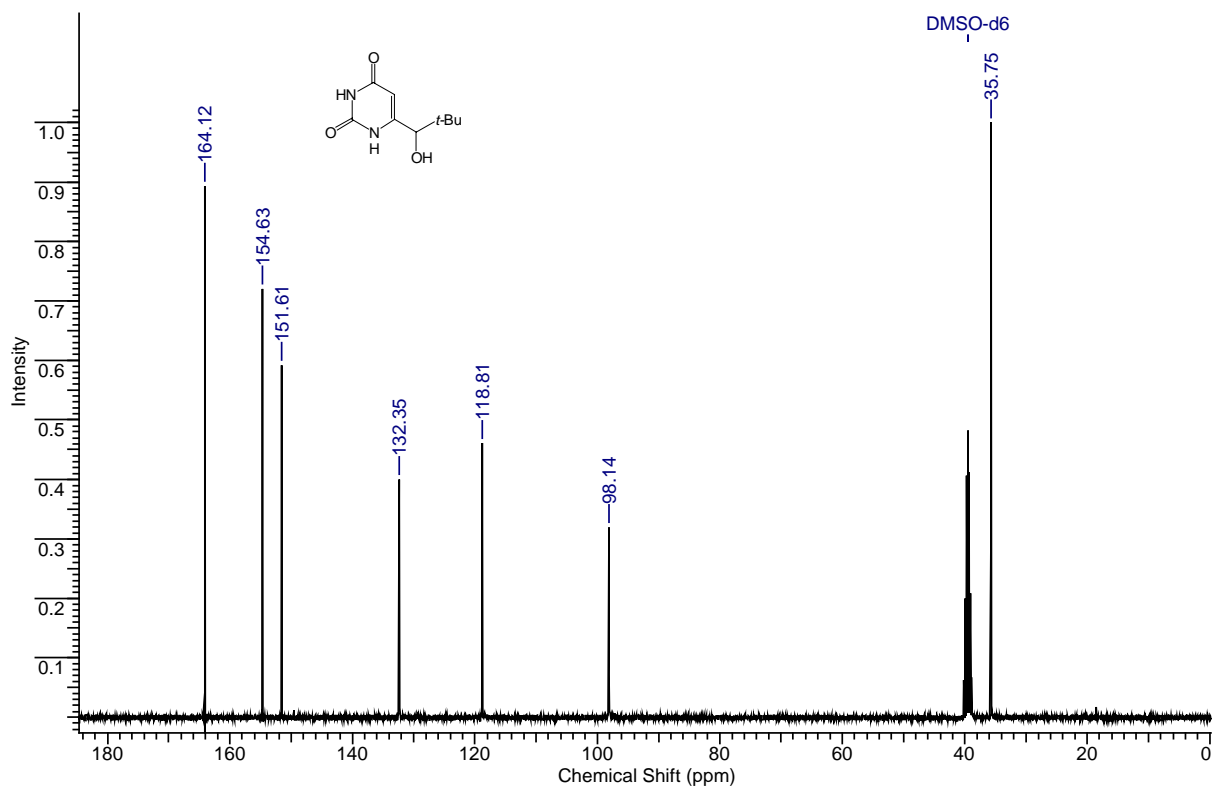
MS (EI): (m/z) (%) = 198 (M⁺; 8); 142 (100); 140 (6); 125 (4); 114 (7); 98 (4); 71 (9); 68 (13); 57 (64).

HR-MS (C₉H₁₅N₂O₃; [M+H]⁺): calculated: 199.1083 found: 199.1075.

¹H-NMR of pure product:



¹³C-NMR of pure product:



2. Synthesis of the HEPT- and Emivirine-precursors 8 and 9

a) Chlorinations of the 5-Alkyl-barbituric acids of type 4

Synthesis of 6-chloro-5-methylpyrimidine-2,4(1H,3H)-dione (5a):

5-Methyl-barbituric acid⁷ (**4a**; 7.10 g, 50 mmol) was placed under N₂ in a Schlenk-flask equipped with a magnetic stirring bar, a reflux condenser and a bubbler on top. POCl₃ (45.0 mL, 75.2 g, 490 mmol, 9.80 equiv) was carefully added, the substrate suspended and then, carefully H₃PO₄ (85 %; 3.5 mL) was added. The resulting mixture was then refluxed (100 °C) for 45 min. [**Note: Longer reaction times have to be strictly avoided, as in this case big amounts of 2,4,6-trichloro-5-methylpyrimidine are formed as side product and, by that way, the yield of the desired product is drastically diminished (3h → 10 %!)**]. Then, the mixture was shortly left for cooling and was poured portionwise on ice. The resulting slurry was then subjected for 30 min to sonication which led to the formation of a fine, white solid that was subsequently filtered and washed with little water. Cooling of the mother liquor afforded another 2-3 crops of the crude product. As TLC of the crops showed, the very first fraction usually only contains the byproduct, whereas the later ones contain the already nearly clean product. The collected product 'fractions' were washed with diethylether (400 mL; to remove 2,4,6-trichloro-5-methylpyrimidine). After recrystallization from MeOH and drying in high vacuum, the desired product **5a** was obtained as a crystalline powder (5.23 g, 32.7 mmol, 65 %). From the ether eluate of the washing, the solvent was removed and 2,4,6-trichloro-5-methylpyrimidine was received as colourless, crystalline solid (1.85 g, 9.40 mmol, 19 %, identified by ¹H-NMR and GC-MS measurements.). (So, the total recovery is 84 %)

mp.: 273.8-275.0 °C (decomposition)

¹H-NMR (dmso-d₆, 400 MHz): δ [ppm] = 1.78 (s, 3 H); 11.26 (s, 1H); 11.77 (brs, 1 H).

¹³C-NMR (dmso-d₆, 100 MHz): δ [ppm] = 10.7; 105.9; 140.6; 149.6; 163.1.

IR (KBr): ν [cm⁻¹] = 3072 (m); 2990 (m); 2912 (m); 2820 (m); 2768 (m); 1708 (s); 1646 (vs); 1624 (vs); 1510 (s); 1482 (s); 1428 (vs); 1382 (s); 1286 (s); 1226 (m); 1210 (m); 1184 (m); 1062 (s); 1010 (m); 872 (s); 778 (s); 754 (vs); 728 (s); 610 (m).

MS (EI): (m/z) (%) = 162 (M⁺; ³⁷Cl; 29); 160 (M⁺; ³⁵Cl; 54); 117 (17); 82 (100); 52 (26); 44 (18).

⁷ Also, the dihydrate, which primarily is obtained by the reaction of urea and diethyl-2-methylmalonate as described in ref. [2], can be used directly. The addition of H₃PO₄ is then unnecessary. However, the addition of POCl₃ in this case should be conducted very careful.

HR-MS (C₅H₅ClN₂O₂): calculated: 160.0040

found: 160.0026.

Synthesis of 6-chloro-5-isopropylpyrimidine-2,4(1*H*,3*H*)-dione (5b**)⁸:**

5-Isopropyl-barbituric acid (**4b**; 4.25 g, 25.0 mmol) was placed under N₂ in a Schlenk-flask equipped with a magnetic stirring bar, a reflux condenser and a bubbler on top. POCl₃ (11.3 mL, 18.9 g, 124 mmol, 4.96 equiv) was carefully added, the substrate suspended and then, carefully H₃PO₄ (85 %; 1.75 mL,) was added. The resulting mixture was then refluxed (100 °C) for 3 h. Then, the mixture was shortly left for cooling and was poured portionwise on ice. The resulting slurry was then subjected for 30 min to sonication which led to the formation of a fine, white solid that was subsequently filtered and washed with water (20 mL). Recrystallization from EtOH gave the desired product **5b** as colourless plates (3.00 g, 15.9 mmol, 63 %).

mp.: 242.3-245.2 °C

¹H-NMR (dmso-d₆, 400 MHz): δ [ppm] = 1.17 (d, *J* = 7.1 Hz, 6 H); 3.00 (sept, *J* = 7.1 Hz, 1 H); 11.19 (s, 1 H); 11.69 (s, 1 H).

¹³C-NMR (dmso-d₆, 100 MHz): δ [ppm] = 19.7; 27.1; 113.9; 140.1; 149.5; 162.2.

IR (KBr): ν [cm⁻¹] = 3020 (m); 2978 (m); 2966 (m); 2928 (m); 2900 (s); 2874 (s); 2846 (s); 2770 (m); 1722 (s); 1702 (s); 1670 (vs); 1650 (vs); 1606 (vs); 1494 (s); 1470 (m); 1446 (s); 1424 (vs); 1380 (s); 1364 (m); 1352 (m); 1306 (w); 1278 (s); 1224 (m); 1196 (w); 1184 (m); 1154 (m); 1110 (w); 1054 (s); 1036 (s); 910 (s); 852 (m); 788 (s); 758 (vs); 728 (vs); 670 (m).

MS (EI): (m/z) (%) = 190 (M⁺; ³⁷Cl; 14); 188 (M⁺; ³⁵Cl; 38); 175 (35); 173 (100); 159 (19); 153 (18); 132 (24); 130 (74); 115 (7); 94 (22); 68 (9); 66 (9).

HR-MS(C₇H₉ClN₂O₂): calculated: 188.0358

found: 188.0362.

⁸ Analogously to *J. Med. Chem.***1986**, 29, 151, except the workup which was slightly modified.

b) Iodinations of the 6-chloro-5-alkyl uracils of type 5⁹

General: We found these reactions to be strongly dependent on the quality of the hydriodic acid used. Even though the reactions proceed always in a spot-to-spot manner (as seen by TLC), iodine and other impurities contained in the acid decrease the quality of the crude product dramatically. Thus, the purification becomes more difficult, resulting in lower yields.

The hydriodic acid employed should be therefore absolutely clean to receive optimum results. The optical appearance of the reagent should be that of a light yellow, clear solution, smoking at the air. Purification of contaminated solutions can be achieved, for example, by stirring the respective solution over red phosphorus until the upstanding solution shows the desired colour and storing the resulting mixture overnight in the fridge, to allow the phosphorus to settle down.

Synthesis of 6-iodo-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**6a**):

6-chloro-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**5a**⁹; 1.44 g, 9.00 mmol), NaI (6.75 g, 45.0 mmol, 5.00 equiv) and HI (54 %, 23.0 mL) are placed in a tube equipped with a magnetic stirring bar and a Teflon stopper. The resulting mixture was stirred for 1 d at rt. Then, the suspension was filtered employing reduced pressure, washed with EtOAc and water until a pale yellow to white solid was obtained (crude yield 2.00 g, 88 %). Recrystallization from EtOAc:MeOH (ca. 9:1) afforded **6a** as off white solid (1.61 g, 6.39 mmol, 71 %)

mp.: ~ 250.0 °C (decomposition)

¹H-NMR (dmsO-d₆, 400 MHz): δ [ppm] = 1.89 (s, 1 H); 11.19 (s, 1 H); 11.30 (s, 1 H).

¹³C-NMR (dmsO-d₆, 100 MHz): δ [ppm] = 17.8; 110.9; 114.2; 150.5; 160.9.

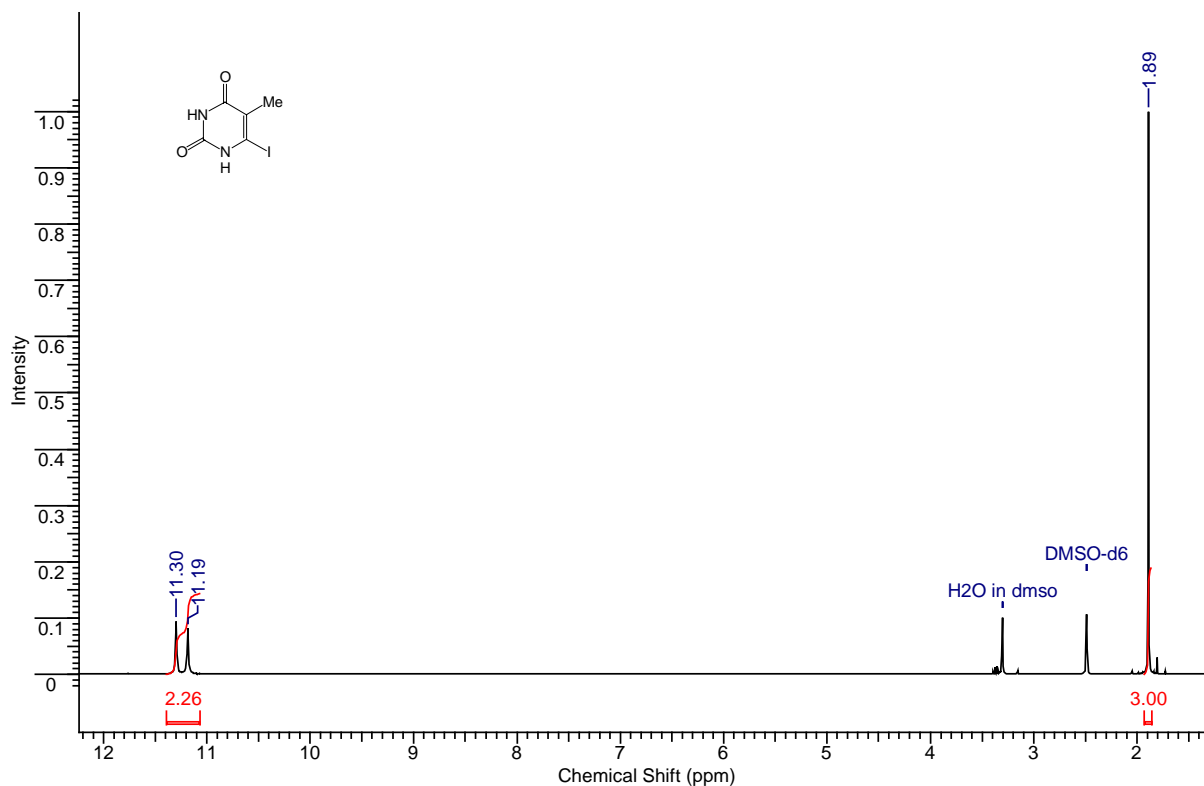
IR (KBr): ν [cm⁻¹] = 3148 (w); 3006 (m); 2810 (m); 1702 (s); 1658 (s); 1634 (vs); 1598 (s); 1494 (m); 1470 (m); 1426 (s); 1378 (s); 1274 (m); 1212 (m); 1200 (m); 1180 (m); 1038 (s); 986 (m); 856 (s); 840 (s); 760 (s); 750 (vs); 710 (s); 646 (m); 632 (m).

MS (EI): (m/z) (%) = 252 (M⁺; 100); 207 (6); 127 (10); 82 (47); 52 (15); 44 (40).

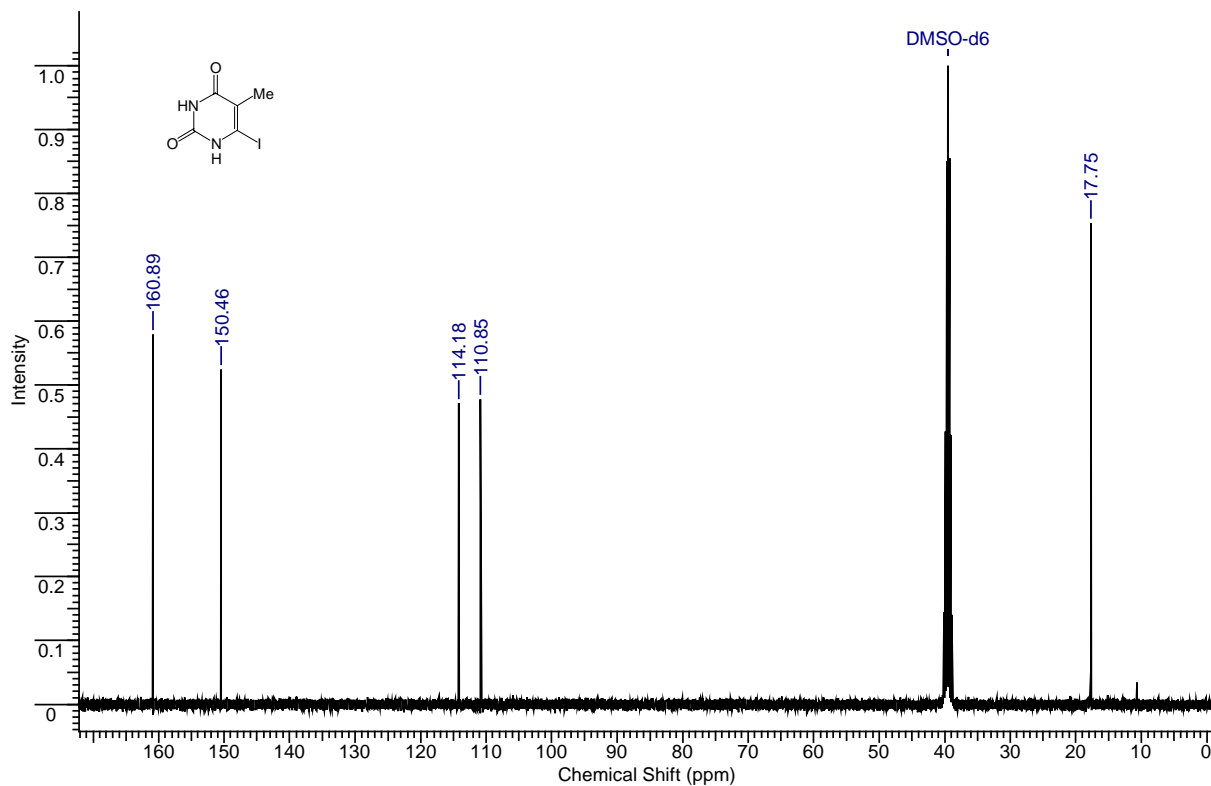
HR-MS (C₅H₅IN₂O₂): calculated: 251.9396 found: 251.9378.

⁹ A similar iodination method is known for other pyrimidines, see: *J. Med. Chem.* **2002**, 45, 3639.

¹H-NMR of pure product:



¹³C-NMR of pure product:



Synthesis of 6-iodo-5-isopropylpyrimidine-2,4(1*H*,3*H*)-dione (6b):

6-chloro-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**5b**^o; 3.12 g, 16.5 mmol), NaI (12.4 mg, 82.5 mmol, 5.00 equiv) and HI (54 %, 41.3 mL) are placed in a tube equipped with a magnetic stirring bar and a Teflon stopper. The resulting mixture was stirred for 3 d at rt. Then, the suspension was filtered employing reduced pressure, washed with water and CH₂Cl₂ until a white solid was obtained (crude yield 3.83 g, 83 %). It was dissolved in EtOAc, dried (Na₂SO₄) and evaporated in *vacuo*. Recrystallization from heptane:EtOAc (ca. 2:3) afforded **6b** as a colourless, crystalline solid (3.50 g, 12.5 mmol, 76 %)

mp.: 251.3-255.2 °C

¹H-NMR (dmsO-d₆, 400 MHz): δ [ppm] = 1.15 (d, *J* = 7.0 Hz, 6 H); 2.83 (sept, *J* = 7.0 Hz, 1 H); 11.19 (s, 1 H); 11.69 (s, 1 H).

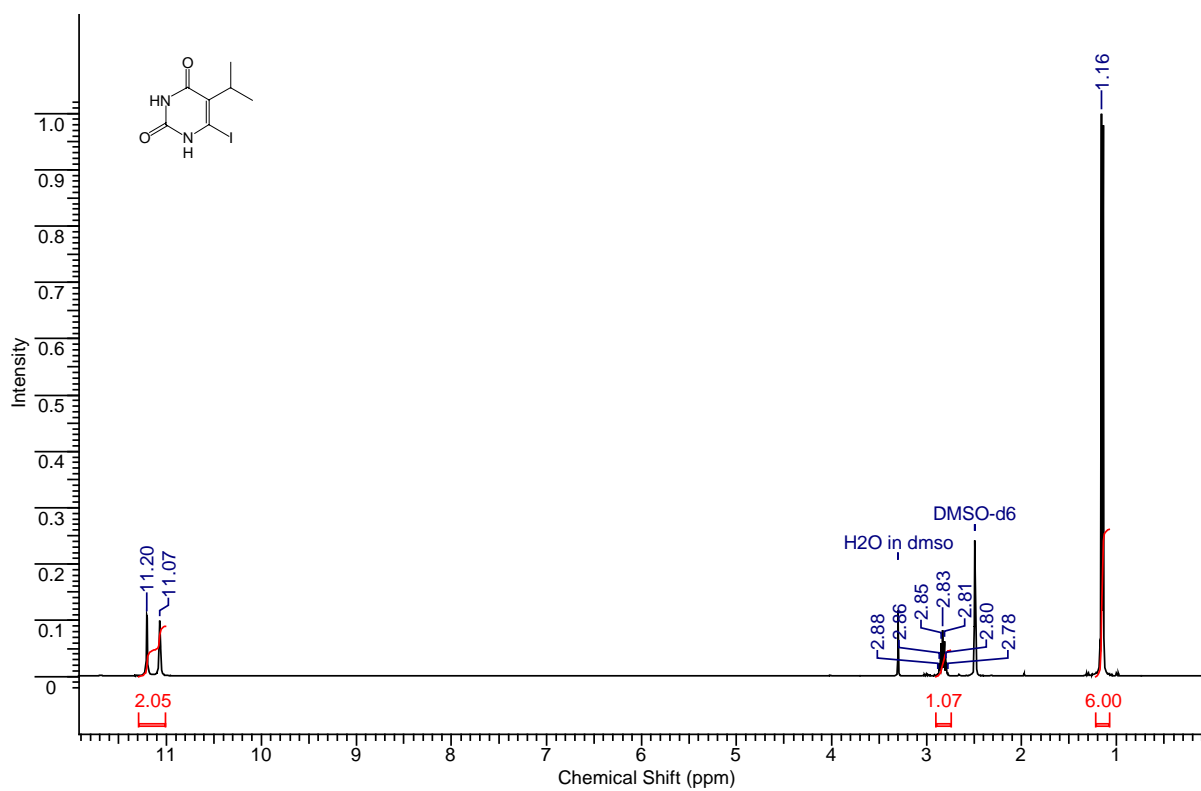
¹³C-NMR (dmsO-d₆, 100 MHz): δ [ppm] = 19.8; 35.7; 110.9; 121.5; 150.3; 159.3.

IR (KBr): ν [cm⁻¹] = 3110 (m); 2996 (m); 2976 (m); 2956 (m); 2922 (m); 2844 (m); 1720 (s); 1666 (s); 1648 (vs); 1582 (s); 1484 (m); 1466 (m); 1446 (s); 1418 (vs); 1376 (m); 1358 (m); 1348 (m); 1302 (w); 1266 (m); 1220 (m); 1178 (m); 1148 (m); 1108 (w); 1044 (s); 1024 (s); 892 (m), 866 (m); 840.00 (s); 784 (m); 752 (s); 722 (s); 652 (m).

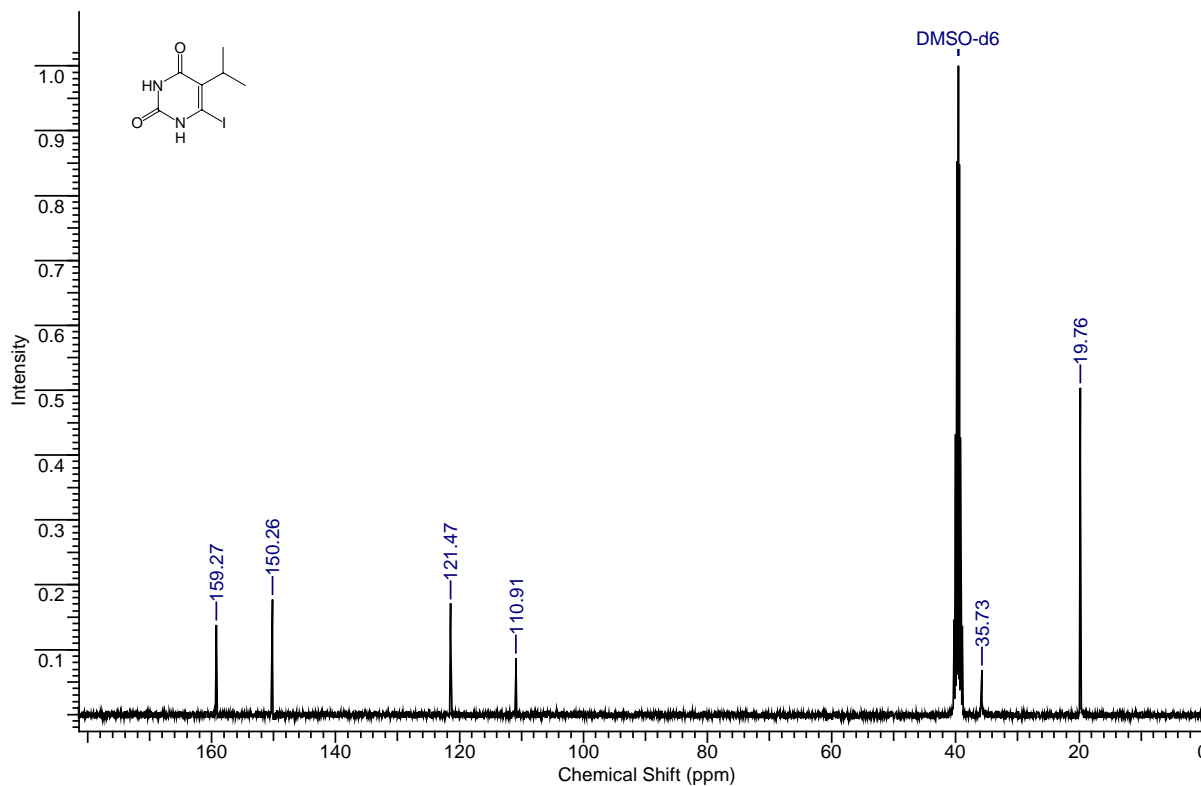
MS (EI): (m/z) (%) = 280 (M⁺; 32); 265 (100); 251 (16); 222 (27); 153 (21); 110 (10); 94 (24); 68 (6); 52 (4).

HR-MS (C₇H₉IO₂N₂): calculated: 279.9709 found: 279.9700.

¹H-NMR of pure product:



¹³C-NMR of pure product:



c) Exchange on 5-alkyl-6-iodo uracils of type 6 and subsequent reactions with electrophiles

Typical procedure for the synthesis of the Grignard reagents of type 7 (TP6):

The 5-alkyl-6-iodouracil was placed in a dry and argon-flushed Schlenk tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M; 2.00 equiv) was added leading to a clear and colourless solution. The solution was cooled to -30 °C and MeMgCl (3.00 M in THF, 2.00 equiv) was added dropwise. Strong bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, the resulting, clear solution was stirred at -30 °C for further 20 min. Afterwards, *i*-PrMgCl·LiCl (1.30 M in THF, 1.30 equiv) was added slowly and the resulting mixture was allowed to stir at -30 °C for 1 h. The exchange reaction was monitored by TLC versus the starting material.

Synthesis of 5-methyl-6-(phenylthio)pyrimidine-2,4(1*H*,3*H*)-dione (8):

The Grignard reagent **7a** was synthesized according to **TP6** from 6-iodo-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**6a**; 504 mg, 2.00 mmol). Then, *S*-phenyl benzenesulfonothioate (700 mg, 2.80 mmol, 1.40 equiv) in THF (4.0 mL) was added dropwise and the resulting mixture was warmed up to rt. After 1 h, TLC monitoring showed nearly complete consumption of the Grignard reagent (Note: Longer reaction times should be avoided, as the product seems to decompose by time in this mixture at rt.). MeOH (2.0 mL) was added and the mixture was transferred to a separation funnel containing water (30 mL). By careful addition of 2.0 M HCl, the pH of the mixture was adjusted to ca 6-7 (indicator paper). The aqueous layer was extracted with CH₂Cl₂ (3×40 mL). The combined organic layers were dried (Na₂SO₄) and evaporated in *vacuo*. Column chromatography (silica; CH₂Cl₂:MeOH, 19:1) afforded **8** as a colourless, crystalline solid (187 mg, 0.80 mmol, 40 %)

mp.: 244.6-245.8 °C

¹H-NMR (dmsO-d₆, 400 MHz): δ [ppm] = 1.89 (s, 3 H); 7.32-7.41 (m, 5 H); 10.92 (s, 1 H); 11.23 (s, 1 H).

¹³C-NMR (dmsO-d₆, 100 MHz): δ [ppm] = 12.7; 113.8; 128.3; 130.3; 130.4; 132.1; 143.5; 151.2; 164.3.

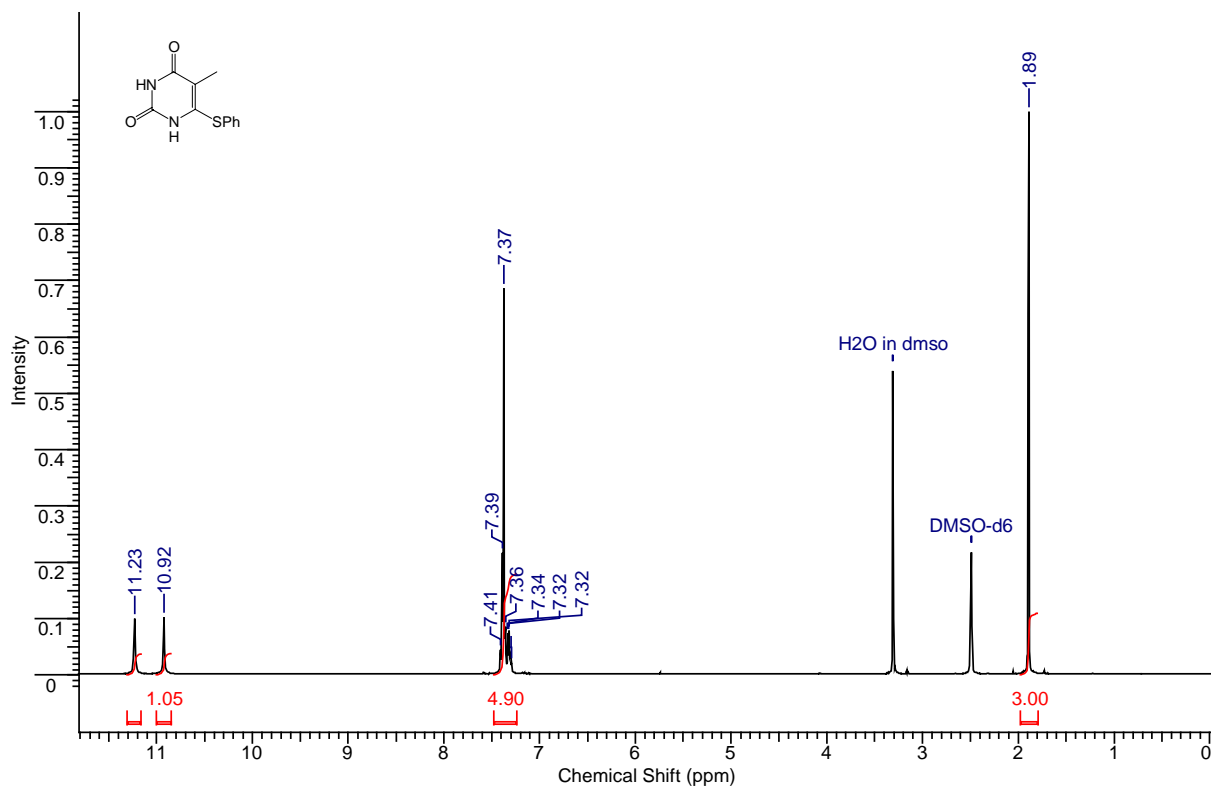
IR (KBr): ν [cm⁻¹] = 3204 (m); 1700 (s); 1652 (s); 1634 (s); 1590 (s); 1574 (s); 1470 (s); 1440 (s); 1418 (s); 1386 (s); 1376 (s); 1328 (m); 1304 (m); 1280 (m); 1202 (m); 1174 (m); 1156 (m); 1066

(m); 1044 (s); 1026 (m); 1004 (m); 980 (m); 886 (m); 842 (m); 816 (s); 768 (m); 754 (m); 740 (vs); 706 (s); 684 (vs); 644 (s); 614 (m).

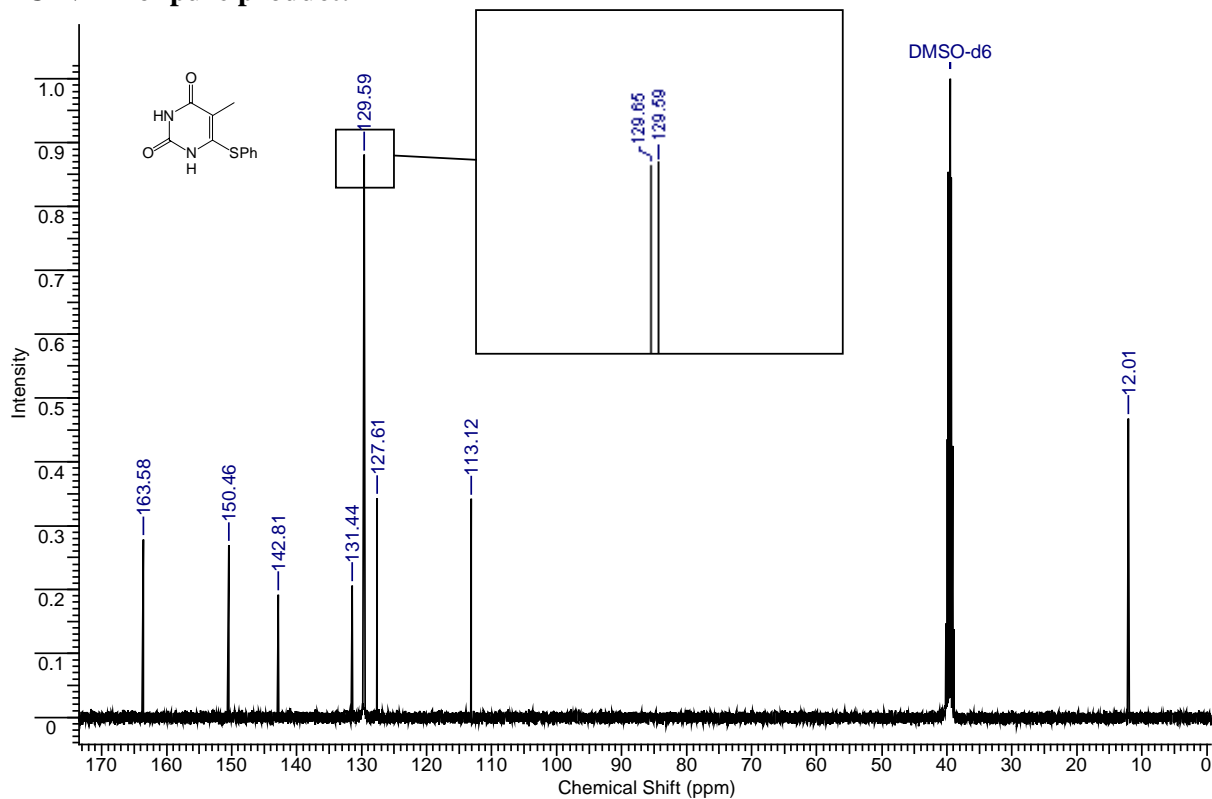
MS (EI): (m/z) (%) = 234 (M^+ ; 100); 207 (10); 201 (12); 156 (34); 110 (28), 109 (14); 82 (35); 44 (16).

HR-MS($C_{11}H_{10}N_2O_2S$): calculated: 234.0463 found: 234.0454.

¹H-NMR of pure product:



¹³C-NMR of pure product:



Synthesis of 6-benzyl-5-isopropylpyrimidine-2,4(1H,3H)-dione (9):

The Grignard reagent **7b** was synthesized according to **TP6** from 6-iodo-5-isopropylpyrimidine-2,4(1H,3H)-dione (**6b**; 560 mg, 2.00 mmol). Then, CuI·2LiCl¹⁰ (0.75 M in THF; 3.47 mL, 2.60 mmol, 1.30 equiv) was slowly added and the resulting mixture was warmed up to rt. After 0.5 h, the mixture was cooled again to -30 °C, then benzyl bromide (479 mg, 2.80 mmol, 1.40 equiv) was added slowly and after 20 min at -30 °C, the solution was allowed to warm up to rt. After 3 h, TLC monitoring showed nearly complete consumption of the Grignard reagent. MeOH (2.0 mL) was added and the mixture was transferred to a separation funnel containing water (20 mL) and sat. aq. NH₄Cl (20 mL). The aqueous layer was extracted with DCM (3 × 40 mL), the completeness was checked by TLC of the fractions. The combined organic layers were dried (Na₂SO₄) and evaporated in *vacuo*. Column chromatography (silica; CH₂Cl₂:MeOH, 19:1) afforded **9** as a colourless, crystalline solid (278 mg, 1.14 mmol, 57 %)

mp.: 231.5-233.2 °C

¹H-NMR (dmso-d₆, 400 MHz): δ [ppm] = 1.05 (d, *J* = 6.9 Hz, 6 H); 2.80 (sept, *J* = 6.9 Hz, 1 H); 3.75 (s, 2 H); 7.20-7.34 (m, 5 H); 10.70 (s, 1 H); 10.88 (s, 1 H).

¹³C-NMR (dmso-d₆, 100 MHz): δ [ppm] = 20.1; 26.4; 35.2; 113.9; 126.6; 128.0; 128.6; 137.0; 148.4; 150.9; 163.8.

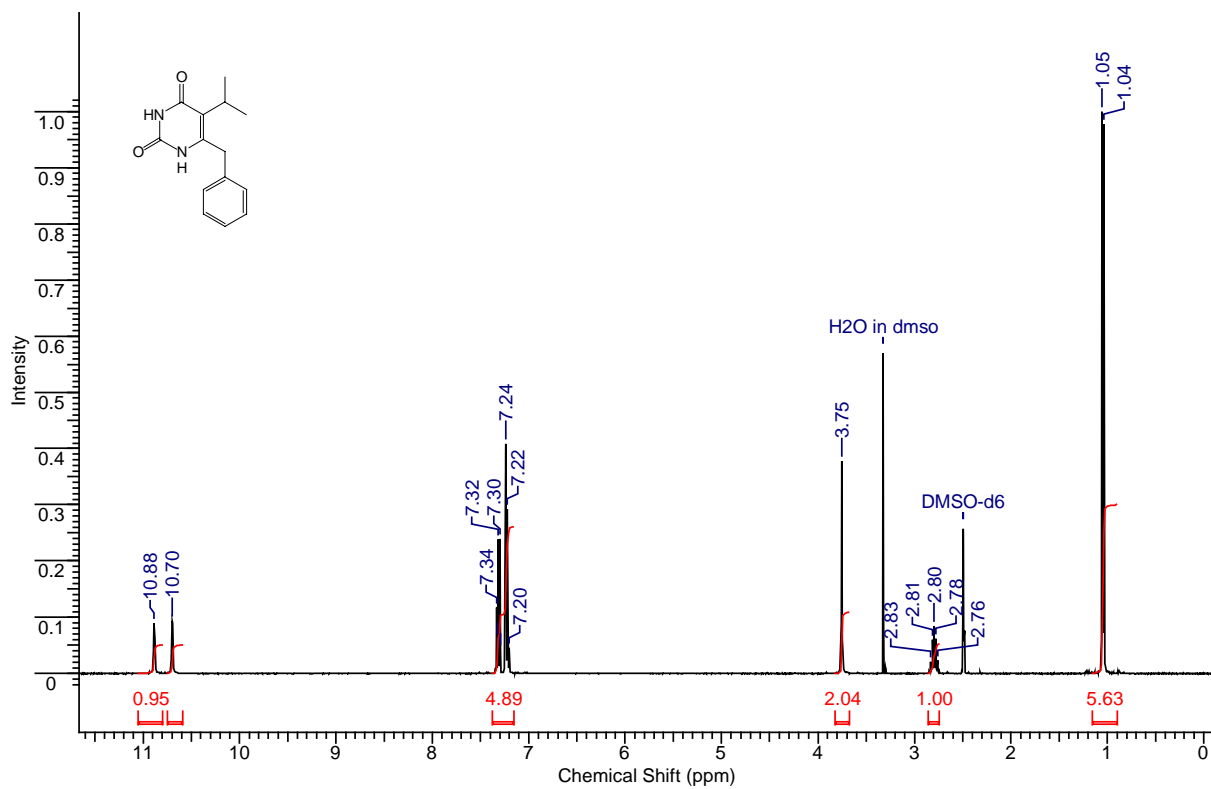
IR (KBr): ν [cm⁻¹] = 3108 (m); 3090 (m); 3068 (m); 3034 (m); 2980 (m); 2958 (m); 2942 (m); 2926 (m); 2868 (w); 2826 (w); 1726 (s); 1682 (m); 1640 (vs); 1620 (s); 1604 (s); 1586 (m); 1506 (m); 1496 (m); 1460 (s); 1440 (m); 1410 (s); 1376 (m); 1358 (m); 1328 (w); 1314 (w); 1290 (m); 1278 (m); 1242 (w); 1192 (m); 1170 (w); 1156 (m); 1112 (w); 1086 (m); 1046 (m); 1032 (m); 986 (w); 934 (w); 898 (w); 802 (s); 776 (s); 756 (s); 724 (s); 702 (vs); 640 (m); 626 (w); 612 (m).

MS (EI): (m/z) (%) = 244 (M⁺; 51); 299 (100); 186 (14); 153 (4); 118 (4); 91 (13); 69 (11).

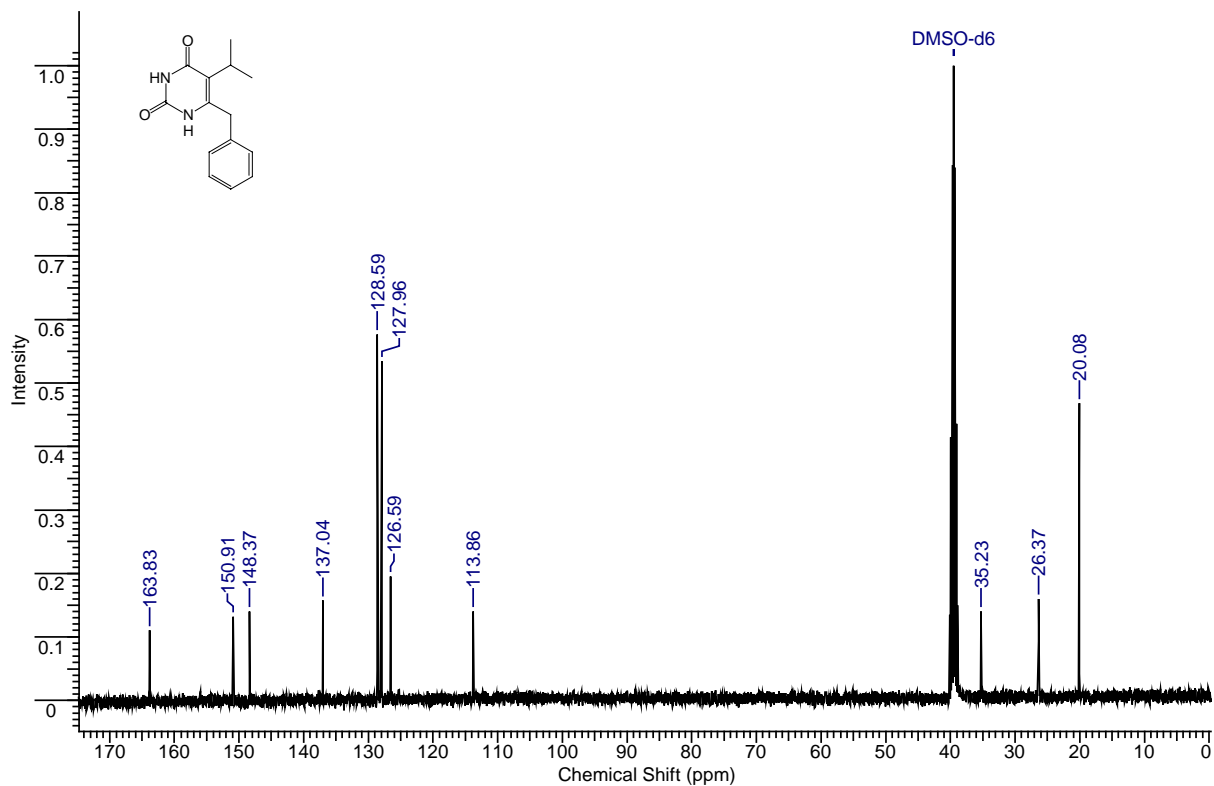
HR-MS(C₁₄H₁₆N₂O₂): calculated: 244.1212 found: 244.1222.

¹⁰ Prepared in analogy to CuCN·2LiCl from CuI and LiCl.

¹H-NMR of pure product:



¹³C-NMR of pure product:



3. Synthesis of 6-(phenylthio)-9H-purine

6-iodopurine (**12**; 246 mg, 1.00 mmol) was placed in a dry and argon-flushed Schlenk tube equipped with a magnetic stirring bar and a septum. Applying vigorous stirring, the substrate was dried for 15 min in high vacuum, to exclude the presence of water in the hygroscopic substrate. Then, a solution of LiCl in THF (0.50 M; 2.00 mL; 1.00 equiv) and dry THF (2.00 mL) was added and the resulting suspension was cooled to -30 °C. Then, MeMgCl (0.33 mL, 3.00 M in THF, 1.00 equiv) was added dropwise. Bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, the resulting, clear yellow solution was stirred at -20 °C for further 20 min. Afterwards, *i*-PrMgCl-LiCl (0.80 mL, 1.32 M in THF, 1.05 equiv) was added slowly and the resulting mixture was allowed to warm up to room temperature. After one hour, an orange slurry had formed and the TLC of the mixture did show only traces of the starting material and traces of an unidentified byproduct. The mixture was cooled to -30 °C again and *S* phenyl benzenesulfonothioate (275 mg, 1.10 mmol, 1.10 equiv; in 2.0 mL THF) was added at this temperature, then the mixture was allowed to rt. The reaction was monitored using TLC. After the completion of the reaction, it was quenched by addition of sat. aq. NH₄Cl (2.0 mL, **not more!**), which resulted in the precipitation of the contained salts. The slurry was, directly in the Schlenk tube, extracted with EtOAc until TLC of the organic layer did not show any content under UV (10 times, 10 mL each). The combined organic layers were dried and evaporated in *vacuo*. Column chromatography (silica; CH₂Cl₂:MeOH, 19:1) afforded **14** as a yellow, crystalline solid (125 mg, 0.55 mmol, 55 %).

mp.: 231.5-233.2 °C

¹H-NMR (dms_o-d₆, 400 MHz): δ [ppm] = 7.49 (m, 3 H); 7.61 (m, 2 H); 8.50 (2 × s, 2 H); 13.59 (brs, 1 H).

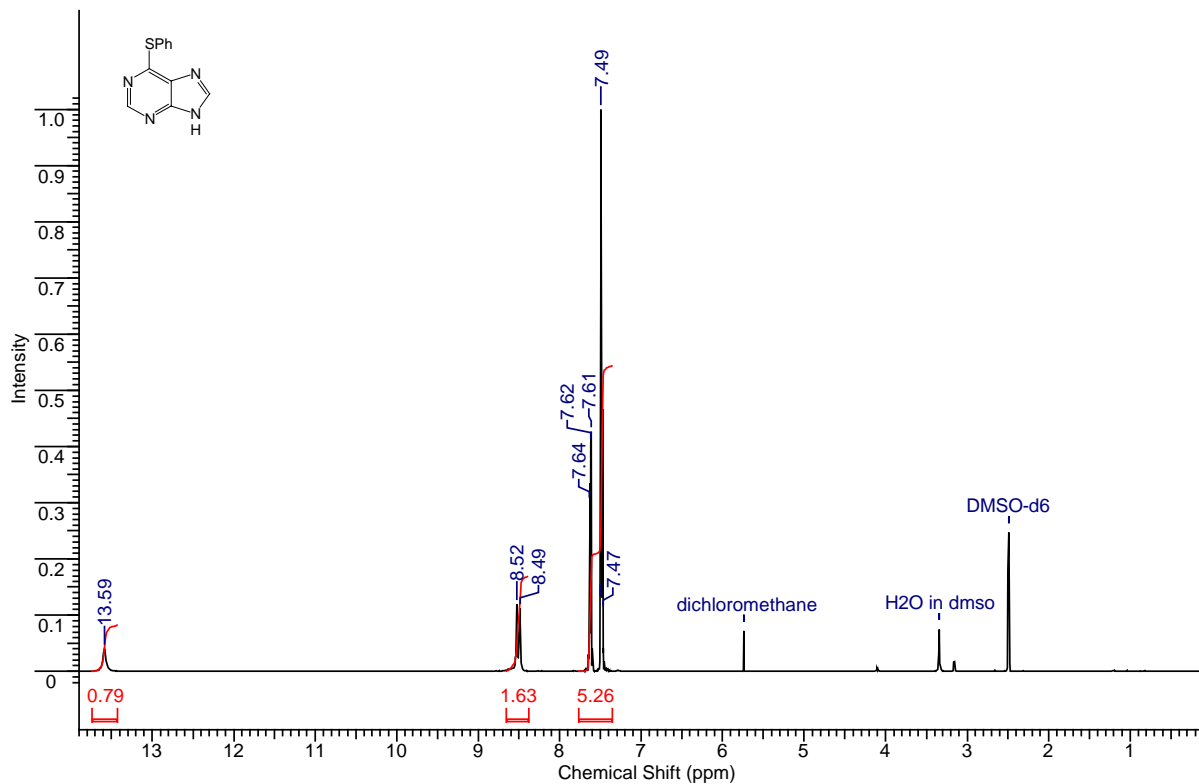
¹³C-NMR (dms_o-d₆, 100 MHz): δ [ppm] = 127.0; 129.4; 129.5; 129.7; 135.5; 143.5; 149.7; 151.6; 158.0.

IR (KBr): ν [cm⁻¹] = 3122 (w); 3076 (w); 3064 (w); 2960 (m); 2816 (m); 2800 (m); 2696 (w), 2658 (w), 2522 (w); 1590 (m); 1560 (vs); 1472 (m); 1444 (w); 1434 (m); 1418 (m); 1384 (m); 1320 (m); 1278 (w); 1234 (vs); 1218 (m); 1176 (w); 1166 (w); 1150 (w); 1070 (w); 1024 (w); 994 (s); 948 (w); 920 (s); 888 (m); 856 (vs); 838 (s); 792 (m); 750 (s); 704 (m); 686 (s), 670 (m); 640 (vs); 632 (s); 608 (s).

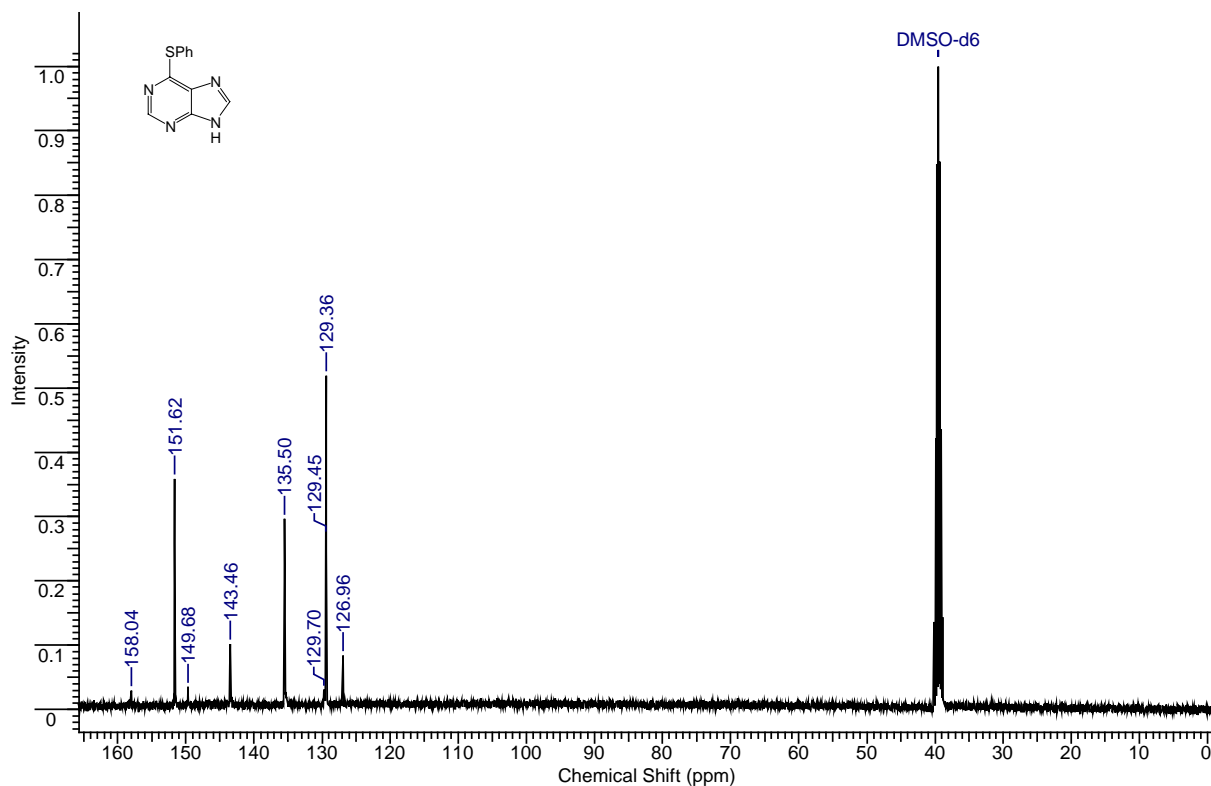
MS (EI): (m/z) (%) = 227 ([M-H]⁺; 100); 207 (23); 200 (4); 146 (4), 109 (5); 77 (5); 65 (4); 44 (4).

HR-MS (C₁₁ H₇ N₄S; [M-H]⁺): calculated: 227.0384 found: 227.0391.

¹H-NMR of pure product:



^{13}C -NMR of pure product:



Region from 120 to 160 ppm:

