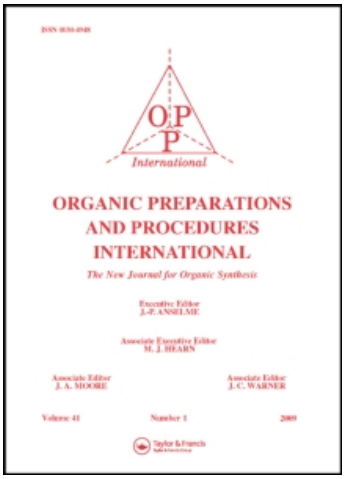

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AN IMPROVED PREPARATION OF 2, 2, 4, 4-TETRAMETHYL-6-AMINOTHIOCHROMAN, A KEY INTERMEDIATE TO UREA AND THIOUREA HETEROAROTINOIDS FOR ANTICANCER STUDIES

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AN IMPROVED PREPARATION OF 2,2,4,4-TETRAMETHYL-6-AMINO-THIOCHROMAN, A KEY INTERMEDIATE TO UREA AND THIOUREA HETEROAROTINOIDS FOR ANTICANCER STUDIES

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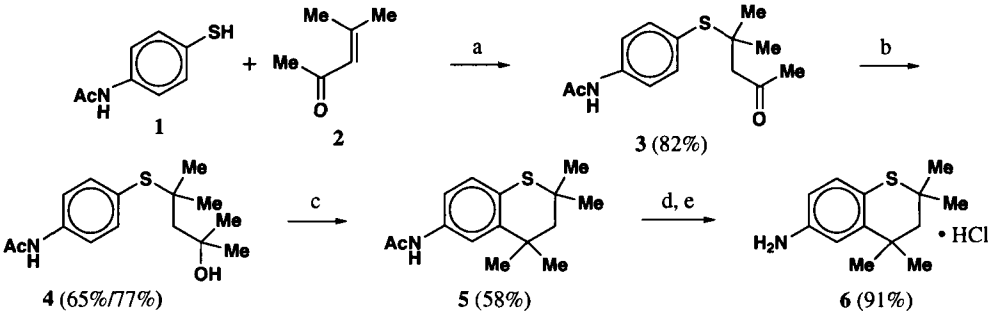
The synthesis of urea and thiourea analogs of the title aminothiochroman **6** is an area of current research for potential anticancer compounds of the heteroarotinoid class mimicking retinoids.[1,2] The recently reported preparation[1,3,4] of this late stage intermediate, however, suffers from a low overall yield of 5.3% from mesityl oxide that is limited by the nitration step and to a lesser degree upon the reduction employed in its preparation. Especially problematic was the 26% yield of the nitration step which introduced the nitrogen atom of the eventual amine moiety of the 6-aminothiochroman intermediate **6**. The 40% yield in the reduction of the nitro group with Fe/HOAc offered cost advantages and a greater ease of workup over the previously employed $TiCl_3$/HOAc method (50%)[4] which justified the lesser yield. These combined poor yields necessitated increasing the scale of the previous steps which limited both the throughput for the preparation of *in vivo* testing quantities of a single compound and the potential to prepare multiple other urea and thiourea analogs from **6**. The improved synthesis reported here is shorter and affords a higher overall yield of **6** that circumvents the nitration and the obligatory reduction by incorporating the nitrogen from the start of the synthesis.

Incorporating a nitrogen *para* to the sulfur in the starting thiophenol can formally be achieved with a nitro, amino, or protected amino substituent in the thiophenol. A nitro group (*i.e.* 4-nitrothiophenol) would be problematic in the subsequent Grignard reaction, that converts the methyl ketone to a dimethylcarbinol, since Grignard reagents are known to add to nitroaromatics.[5] An amine group was of concern especially in the $AlCl_3$ promoted cyclization of the carbinol. An acetamido substituted thiophenol, while having its own potential limitations, seemed to offer more possibilities of success and hence its use was examined prompted by its commercial availability.



a) $CHCl_3/Et_3N$; b) MeLi; c) $AlCl_3$/chlorobenzene; d) HCl aq-Ethanol; e) $NaHCO_3$

Commercially available 4-acetamidothiophenol (**1**) undergoes 1,4-addition to mesityl oxide (**2**)[1] to give ketone **3** in 82% yield. Treatment of **3** with methylmagnesium bromide afforded the expected salt, but failed to undergo further reaction with the keto group to give carbinol **4**. Substituting methyllithium for methylmagnesium bromide was however successful[6] and afforded **4** in a yield of 65% (77% based on recovered **3**). Cyclization of **4** with $AlCl_3$ in chlorobenzene gave 2,2,4,4-tetramethyl-6-acetamidothiochroman **5** in 58% yield. The literature cyclized an otherwise unsubstituted thiophenol ether in 93% in CS_2.[1] This better yield might be due to a solvent effect or a substituent effect (*i.e.* 4-acetamido). We chose not to work with significant volumes of flammable and noxious CS_2. Hydrolysis[7] of **5** with HCl provided 2,2,4,4-tetramethyl-6-aminothiochroman hydrochloride **6·HCl** in 91% yield which was neutralized with $NaHCO_3$ in quantitative yield to give crystalline 2,2,4,4-tetramethyl-6-aminothiochroman **6** (28% overall yield; 33% based on recovered **3**). The compound identity was confirmed by comparison of its ^1H NMR spectrum to that published and by the elemental analysis of its HCl salt.

This synthesis provides two benefits. First is the five-fold improvement in the yield of a key intermediate in the synthesis of a family of anti-cancer compounds of current interest. Second, it demonstrates an approach to overcome the limitation of the Grignard chemistry of intermediate **3** resulting from poor solubility and reactivity of the magnesium salt of **3** by using methyllithium in place of methylmagnesium bromide. Other heteroarotinoid analogs prepared from this intermediate are currently under study.

EXPERIMENTAL SECTION

Silica gel 230-400 mesh from EM Science was employed for column chromatography. TLC plates were silica gel 60 F-254 from EMD Chemicals Inc. Acetamidothiophenol (95%) was obtained from Acros and used as received, and mesityl oxide was obtained from Sigma-Aldrich and distilled prior to use. Melting points were obtained on a Fisher-Johns melting point apparatus. ^{1}H NMR spectra were obtained on Bruker DPX 300 Supercon NMR Spectrometer. Mass spectra were obtained in either electrospray positive ion mode (ESI) or atmospheric pressure chemical ionization (APCI) in positive or negative ion mode as noted on an Applied Biosystems Single Quadrupole Mass Spectrometer model API 150EX. Elemental analyses were obtained from Atlantic Microlab, Inc., Norcross, GA 30091.

4-Methyl-4-(4-acetamidophenylthio)-2-pentanone (3).- 4-Acetamidothiophenol **1** (25 g, 142 mmol purity corrected) and mesityl oxide **2** (freshly distilled, 16.9 mL, 148 mmol) were dissolved/suspended in 300 mL of $CHCl_3$ with magnetic stirring under argon. The pale yellow slurry was cooled in an ice water bath, and Et_3N (6.9 mL) added which afforded a solution. After stirring for 15 min at 0-5°C and for 1 h at room temperature, the resulting grey slurry was heated at reflux to yield a dark brown homogeneous solution. TLC (see below) analysis after 13 h of heating at reflux indicated some starting material remained. More mesityl oxide (0.845 mL) and Et_3N (0.345 mL) were added, and, after 4 h, additional mesityl oxide (0.42 mL) and Et_3N (0.17 mL) were added and heating was continued for 2 h. When TLC analysis indicated little 4-acetamidothiophenol remained, the reaction mixture was cooled to room temperature and chromatographed on silica gel 60 (1000 g), eluting with CH_2Cl_2/EtOAc/abs. EtOH v/v/v: 75:25:0.5, 4050 mL followed by (75:25:1, 3450 mL). On the basis of TLC analysis, highly pure product eluted in the 3050 to 6500 mL fraction. The product containing fractions (TLC) were combined, evaporated *in vacuo*, and the resulting oil evaporated from CH_2Cl_2 twice in order to remove residual ethanol by azeotropic distillation. The resulting oil was dried *in vacuo* overnight to afford **3** as a pale yellow solid (30.1 g, 82%), mp 46-49°C; TLC: R_f 0.48, EtOAc/CH_2Cl_2 1:1, uv, phosphomolybdic acid (PMA) visualization. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (s, 6, $C(CH_3)_2$), 2.15 (s, 3, $COCH_3$), 2.19 (s, 3, $NHCOCH_3$), 2.65 (s, 2,-CH_2CO), 7.46 (dm, 2, J = 8.7 Hz, Ar-H), 7.52 (dm, 2, J = 8.7 Hz, Ar-H); MS ESI: Calcd for $C_{14}H_{19}NO_2S$, M = 265. Found 266 (M+H). *Anal.* Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28. Found C, 63.10; H, 7.21; N, 5.37.

2,4-Dimethyl-4-(4-acetamidophenylthio)-2-pentanol (4).- Pentanone **3** (34.8 g, 131 mmol) was dried by azeotropic distillation from anhydrous benzene (4 x 200 mL portions) followed by vacuum drying overnight at room temperature. The resulting oily residue was dissolved in anhydrous THF (2L) and cooled to – 40 ± 5°C under dry argon. As the solution was stirred mechanically, methyllithium (245 mL of a 1.6 M solution in ethyl ether) was added over 5 min. A precipitate started to form after 100 mL of the methyllithium had been added. After 1.5 h, more methyllithium (245 mL, 1.6 M in ethyl ether) was added. The reaction mixture was allowed to warm slowly to –5°C to –10°C over 1 h and was stirred for another 5 h at –5°C. Water (1L) was

added slowly and cautiously at –5°C to 0°C under argon. The mixture was acidified with 1 N HCl (780 mL), and sodium hydroxide (1 N, 1 mL portions) was subsequently added until the pH of the mixture was 7. The resulting two phases were separated, and the aqueous phase was further extracted with EtOAc (2 x 500 mL). The combined organic extracts were washed with water (2 x 500 mL) and brine (500 mL) and dried [Na_2SO_4] under argon overnight. Filtration and solvent evaporation yielded crude **4** that was purified by silica gel 60 flash chromatography (1200 g) eluting with a stepwise gradient of CH_2Cl_2/EtOAc/abs. EtOH v/v/v: 70:30:1, 3700 mL; 60:40:2, 2050 mL; 60:40:3, 3000 mL. On the basis of TLC analysis, highly pure product eluted in the 3300 to 6750 mL fraction. The product containing fractions (TLC) were combined, evaporated *in vacuo*, and evaporated from CH_2Cl_2 twice to remove residual ethanol azeotropically. The resulting residue was dried *in vacuo* overnight to obtain alcohol **4** as a pale yellow solid (23.8 g, 65%; 77% based on recovered **3**), mp 138-141°C, crystallized from benzene; TLC: R_f 0.2, CH_2Cl_2/EtOAc/abs. EtOH (70:30:1, v/v/v); UV, PMA. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (s, 6, $C(CH_3)_2$), 1.35 (s, 6, $C(CH_3)_2$), 1.78 (s, 2, CH_2), 3.44 (s, 1, OH), 7.42 (br s, 1, NH), 7.50 (dm, 2, J = 8.8 Hz, Ar-H), 7.54 (dm, 2, J = 8.8 Hz, Ar-H), MS APCI: Calcd for $C_{15}H_{23}NO_2S$, M = 281. Found 282 (M+H), 280 (M-H).

Anal. Calcd for $C_{15}H_{23}NO_2S$: C, 64.02; H; 8.24; N, 4.98; S, 11.39. Found: C, 64.05; H, 8.39; N, 4.96; S, 11.30.

2,2,4,4-Tetramethyl-6-acetamidothiochroman (5).- Alcohol **4** (18.5 g, 65.9 mmol) and chlorobenzene (1655 mL) under dry argon in a three-necked, 5 L, round-bottomed flask fitted with a mechanical stirrer and a condenser were stirred and heated at 70-75°C in an oil bath until the alcohol completely dissolved. Anhydrous aluminum chloride (34.5 g, 259 mmol) weighed in a dry nitrogen atmosphere, was cautiously added in one portion to the hot reaction mixture resulting in a hazy mixture. After 2 h at 70-75°C, the reaction mixture was cooled in an ice water bath and poured into ice/water (500 mL/1500 mL) cooled in an ice water bath. Ice was added to the brown oily residue remaining in the reaction flask, followed by 5% wt/v sodium bicarbonate (500 mL), and the resulting emulsion added to the workup which was stirred magnetically for 30 min at ambient temperature. The phases were separated, and the aqueous phase (pH 4) was further extracted with $CHCl_3$ (2 x 500 mL) and EtOAc (700 mL). All organic extracts were combined, washed with distilled water (2 x 500 mL) and brine (500 mL) and stirred over sodium sulfate under argon overnight. Filtration and solvent evaporation yielded the crude product (22.6 g) that was purified by silica gel 60 column chromatography (1017 g) eluting with a stepwise gradient of CH_2Cl_2/EtOAc/abs. EtOH, v/v/v: 900:100:1.25, 2500 mL; 850:150:2.5, 1400 mL; 850:150:5, 2000 mL; 850:150:10, 1200 mL. On the basis of TLC analysis, fractions eluted from 4100 to 6500 mL contained product **5**. The product containing fractions (TLC) were combined, evaporated *in vacuo*, and the resulting oil was evaporated twice from CH_2Cl_2 to remove residual ethanol. The resulting oil was dried *in vacuo* overnight to afford **5** as a pale yellow solid (10.0 g, 58%), mp 104-107°C, crystallized from EtOH/H_2O; TLC: R_f 0.5, CH_2Cl_2/EtOAc/abs. EtOH

(70:30:1, v/v/v) UV, PMA.; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (s, 6, $C(CH_3)_2$), 1.40 (s, 6, $C(CH_3)_2$), 1.93 (s, 2, CH_2), 2.15 (s, 3, $COCH_3$), 7.06 (d, 1, J = 8.4 Hz, Ar-H-8), 7.20 (dd, 1, J = 2.3, 8.4 Hz, Ar-H-7), 7.35 (br s, 1, NH), 7.57 (d, 1, J = 2.3 Hz, Ar-H-5); MS APCI: Calcd for $C_{15}H_{21}NOS$, M = 263. Found 264 (M+H), 262 (M-H).

Anal. Calcd for $C_{15}H_{21}NOS$: C, 68.40; H, 8.04; N, 5.32; S, 12.17. Found: C, 68.56; H, 8.00; N, 5.35; S, 12.10.

2,2,4,4-Tetramethyl-6-aminothiochroman (6).- Acetamido derivative **5** (10.2 g, 38.3 mmol) was dissolved in absolute ethanol (570 mL). Distilled water (15 mL) was added, and the mixture heated at reflux under argon. Concentrated HCl (340 mL) was added dropwise over 15 min to the refluxing mixture. After 1.5 h, the reaction mixture was cooled in an ice water bath and added to cold distilled water (2.5 L) in an ice water bath. The hazy solution that resulted was extracted with EtOAc (500 mL) to remove neutral products. The EtOAc extract was washed with 1N HCl (100 mL and 50 mL), and the washes were added to the cooled aqueous acidic phase. Sodium hydroxide (10 N, 360 mL) was added followed by CH_2Cl_2 (500 mL). The pH was adjusted to pH 7.5 with sodium hydroxide (10 N or 1 N) and hydrochloric acid (6 N or 1 N). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (1 x 500 mL and 2 x 300 mL). The organic extract was washed with H_2O (3 x 300 mL) and rotary evaporated. Excess HCl (50 mL, 1 N) was added to the resulting oily residue. The resulting solution was evaporated *in vacuo* to obtain a pale yellow solid that was again dissolved in HCl (25 mL, 1 N) to obtain a solution that was evaporated *in vacuo* to yield amine hydrochloride **6•HCl** (9.1 g, 91%); mp 165°C (sample melted and re-solidified then melted from 275 to 290°C) crystallized from methanol/benzene; TLC R_f 0.58 EtOAc/hexanes (4:6, v/v), UV, PMA, [R_f 0.24 for acetamido derivative **5**]; ^{1}H NMR (d_6-DMSO, 300 MHz): δ 1.34 (s, 6, $C(CH_3)_2$), 1.38 (s, 6, $C(CH_3)_2$), 1.94 (s, 2, CH_2), 7.09 (dd, 1, J = 2.2, 8.3 Hz, Ar-H-7), 7.18 (d, 1, J = 8.3 Hz, Ar-H-8), 7.50 (d, 1, J = 2.2 Hz, Ar-H-5), 10.14 (br s, 3, NH_3^+);

Anal. Calcd for $C_{13}H_{20}ClNS$: C, 60.56; H, 7.82; N, 5.43; S, 12.44. Found: C, 60.65; H, 7.94; N, 5.46; S, 12.38.

Amine hydrochloride (**6•HCl**, 8.45 g, 32.8 mmol) was partially dissolved in 700 mL of H_2O. Sodium bicarbonate (100 mL, 5% wt/v) was added, and the resulting emulsion was extracted with CH_2Cl_2 (3 x 200 mL). The extract was washed with H_2O (100 mL) and brine (100 mL) and stirred magnetically over sodium sulfate for 1 h. Filtration and solvent evaporation yielded an oil that was evaporated twice from CH_2Cl_2 to remove residual H_2O by azeotropic distillation. The resulting oil was dried *in vacuo* overnight to afford free amine **6** as a pale yellow solid (7.5 g, >100%); mp 35-65°C; TLC: R_f 0.61, CH_2Cl_2 /hexanes/EtOH (80:20:2, v/v/v). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (s, 6, $C(CH_3)_2$), 1.38 (s, 6, $C(CH_3)_2$), 1.89 (s, 2, CH_2), 6.47 (dd, 1, J = 2.5, 8.2 Hz, Ar-H-7), 6.76 (d,1, J = 2.5 Hz, Ar-H-5), 6.93 (d, 1, J = 8.2 Hz, Ar-H-8). MS ESI: 222.6 (M+1), $C_{13}H_{21}NS$ calcd M = 221.

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SYNTHESIS OF NOVEL 5-SUBSTITUTED-6-METHYL-4-[5-CHLORO-3-METHYL-1-PHENYL-1*H*-PYRAZOL-4-YL]-3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONES

Submitted by (06/16/06)

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Derivatives of dihydropyrimidones (DHPMS) exhibit a wide range of biological activities and are antihypertensive, antitumor and anti-inflammatory agents.[1] Recently, appropriately functionalized DHPMs have emerged as orally active antihypertensive agents[2] or A_{1a} adrenoceptor-selective antagonists.[3] A very recent highlight in this context has been the identification of the structurally rather simple DHPM *monastrol* as a mitotic kinesin Eg5 motor protein