Supporting Information

Synthesis of 3-amino-thiochromanes from 4-benzyl 2-thiazolines, via an unprecedented intramolecular electrophilic aromatic substitution

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General Information:
NMR spectra were recorded on a Bruker DRX 400 spectrometer. Chemical shifts (δ) are reported in ppm (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad) and are indicated in ppm using TMS as internal standard. Coupling constants (J) are given in Hertz.
Mass spectra were obtained on a GC/MS Saturn 2000 spectrometer and HRMS on a Waters QTOF micro spectrometer. IR spectra were recorded with a Perkin Elmer 16 PC FT-IR instrument. Analytical data were obtained using a THERMOQUEST NA 2500 instrument. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.
X-ray diffraction experiments were performed with graphite-monochromatized MoKα radiation on a Bruker-Nonius Kappa CCD area detector diffractometer.


Preparation of the 3-amino-thiochromanes 3a,b and 6a-e. General procedure:
1 mmol of starting material (thiazoline 3, thiazolinium salt 4, or disulfide 2 or 5) was placed in aqueous 5N HCl (5 mL) and heated at 100°C, in air, until reaction completion. After
evaporation under vacuum, the residue was washed with acetone and the resulting solid filtrated and dried to afford the 3-amino-thiochromane as a hydrochloride.

(S)-3-Aminothiochromane hydrochloride 3a

Prepared from thiazoline 1a (150 mg, 0.86 mmol); reaction time = 5 days; yield = 86%.
Prepared from disulfide 2a (50 mg, 0.28 mmol); reaction time = 4 days; yield = 88%.
Formula: C₉H₁₂NSCl
Molecular weight: 201.72 g.mol⁻¹
Aspect: red powder
[α]D²⁰ -17 (c = 0.45, MeOH); for the (R)-3a: [α]D²⁰ + 18 (c = 1.00, MeOH)
mp 214 °C

¹H NMR (250 MHz, D₂O) δ (ppm) 2.96 (dd, J = 6.1, 17.1 Hz, 1H), 3.08 (dd, J = 6.4, 13.6 Hz, 1H), 3.20 (dd, J = 4.3, 17.1 Hz, 1H), 3.33 (dd, J = 3.1, 13.6 Hz, 1H), 4.02 – 4.09 (m, 1H), 7.07 – 7.17 (m, 4H).

¹³C NMR (63 MHz, D₂O) δ (ppm) 28.8, 32.1, 44.7, 125.5, 126.5, 127.6, 129.0, 130.2, 131.1.

HMRS (ESI) calcd. for C₉H₁₂NS, 166.0690; found, 166.0698.

Elemental analysis : Calc. for C₉H₁₂NSCl + 0.3 HCl: H 5.83, C 50.83, N 6.59; found: H 5.69, C 50.77, N 6.65.


X-ray crystallographic data

Single crystals of aminothiochromane (S)-3a suitable for X-ray crystallographic analysis were obtained by slow evaporation of methanol. X-ray diffraction experiments for monocrystal of 3a were performed at 291 K with graphite–monochromatized Mo Kα radiation on an Bruker–Nonius Kappa CCD area detector diffractometer. Formula C₉H₁₂ClNS, M = 201.71, crystal system orthorhombic, space group P2₁2₁2₁ (no. 19), a = 5.3668(11) Å, b = 6.2152(12) Å, c = 29.035(6) Å, U = 968.5(3) Å³, T = 291 K, Z = 4, calculated density = 1.383 g/cm³, μ = 0.55 mm⁻¹, 15838 reflections measured, 2871 unique (Rint = 0.069) which were used in all calculations. The final wR(F²) was 0.141 (all data).
Single crystals of aminothiochromane \((R)\)-3a suitable for X-ray crystallographic analysis were obtained by slow evaporation of methanol. X-ray diffraction experiments for monocrystal of 3a were performed at 291 K with graphite–monochromatized Mo K\(\alpha\) radiation on a Bruker–Nonius Kappa CCD area detector diffractometer. Formula C\(_9\)H\(_{12}\)ClNS, \(M = 201.71\), crystal system orthorhombic, space group \(P2_12_12_1\) (no. 19), \(a = 5.3436(12)\) Å, \(b = 6.2291(19)\) Å, \(c = 29.214(8)\) Å, \(U = 972.4(4)\) Å\(^3\), \(T = 291\) K, \(Z = 4\), calculated density = 1.378 g/cm\(^3\), \(\mu = 0.55\) mm\(^-1\), 39910 reflections measured, 4476 unique (\(R_{int} = 0.021\)) which were used in all calculations. The final \(wR(F_2)\) was 0.085 (all data).

\((S)\)-3-Amino-7-hydroxythiochromane hydrochloride 3b

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\begin{align*}
\text{HCl-H}_2\text{N} & \quad \text{OH} \\
\text{3b} & \\
\end{align*}
\]

Prepared from thiazoline 1b (150 mg, 0.86 mmol); reaction time = 10 days; yield = 36%.

Formula: C\(_9\)H\(_{12}\)NOSCl

Molecular weight: 217.72 g.mol\(^-1\)

Aspect: red powder

\([\alpha]_D^{20} + 61\) (c = 0.23, MeOH)

\(^1\)H NMR (500 MHz, D\(_2\)O) \(\delta\) (ppm) 2.78 (dd, \(J = 5.2, 13.5\) Hz, 1H), 2.96 (dd, \(J = 4.5, 10.5\) Hz, 1H), 2.99 (dd, \(J = 3.8, 13.5\) Hz, 1H), 3.20 (dd, \(J = 2.5, 10.5\) Hz, 1H), 3.90 – 3.95 (m, 1H), 6.47 – 6.90 (m, 4H).

\(^{13}\)C NMR (125 MHz, D\(_2\)O) : \(\delta\) (ppm) 28.6, 31.3, 44.7, 112.4, 113.0, 120.6, 131.2, 132.2, 154.4.

HMRS (ESI) calcd. for C\(_9\)H\(_{12}\)NOS, 182.0640; found, 182.0646.

\((S)\)-3-(Methylamino)thiochromane hydrochloride 6a

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\begin{align*}
\text{HCl-H}_2\text{N} & \quad \text{Me} \\
\text{6a} & \\
\end{align*}
\]

Prepared from thiazolinium salt 4a (50 mg, 0.08 mmol); reaction time = 5 days; yield = 69%.

Formula: C\(_{10}\)H\(_{14}\)NOSCl

Molecular weight: 215.74 g.mol\(^-1\)
Aspect: white powder

$[\alpha]_D^{20} - 36$ (c = 0.10, MeOH)

$\text{mp 191 °C}$

$\text{H NMR (400 MHz, D}_2\text{O)} \delta (\text{ppm}) 2.74 (s, 3H), 3.05 (dd, J = 5.0, 17.3 \text{ Hz, 1H}), 3.15 (dd, J = 5.8, 13.8 \text{ Hz, 1H}), 3.23 (dd, J = 4.3, 17.3 \text{ Hz, 1H}), 3.40 (dd, J = 3.1, 13.8 \text{ Hz, 1H}), 3.89 - 3.95 (m, 1H), 7.07 - 7.17 (m, 4H).

$\text{C NMR (125 MHz, D}_2\text{O)} \delta (\text{ppm}) 27.2, 30.4, 30.6, 52.0, 125.5, 126.6, 127.7, 128.4, 130.3, 131.1.$

$\text{HMRS (ESI)}$ calc. for C$_{10}$H$_{14}$NS, 180.0847; found, 180.0847.

(S)-3-(Butylamino)thiochromane hydrochloride 6b

Prepared from thiazolinium salt 4b (50 mg, 0.18 mmol); reaction time = 5 days; yield = 87%.
Prepared from disulfide 5b (30 mg, 0.06 mmol); reaction time = 3 days; yield = 84%.

Formula: C$_{13}$H$_{20}$NSCl
Molecular weight: 257.82 g.mol$^{-1}$

Aspect: white powder

$[\alpha]_D^{20} + 26$ (c = 0.40, MeOH).

$\text{mp 194 °C}$

$\text{H NMR (400 MHz, D}_2\text{O)} \delta (\text{ppm}) 0.77 (t, J = 7.2 \text{ Hz, 3H}), 1.25 (sx, J = 7.2 \text{ Hz, 2H}), 1.48 - 1.58 (m, 2H), 2.94 (dd, J = 6.2, 17.3 \text{ Hz, 1H}), 2.98 - 3.09 (m, 3H), 3.16 (dd, J = 4.5, 17.3 \text{ Hz, 1H}), 3.27 (dd, J = 2.7, 13.6 \text{ Hz, 1H}), 3.84 - 3.90 (m, 1H), 6.98 - 7.08 (m, 4H).

$\text{C NMR (63 MHz, D}_2\text{O)} \delta (\text{ppm}) 12.6, 19.2, 27.4, 31.0, 45.2, 51.3, 125.6, 126.6, 127.6, 129.0, 130.5, 131.0.$

$\text{HMRS (ESI)}$ calcd. for C$_{13}$H$_{20}$NS, 222.1316; found, 222.1326.

Elemental analysis: Calc. for C$_{13}$H$_{20}$NSCl + 1.4 HCl: H 6.98, C 50.55, N 4.53; found: H 7.00, C 50.29, N 4.63.
(S)-3-(Benzylamino)thiochromane hydrochloride 6c

Prepared from thiazolinium salt 4c (100 mg, 0.28 mmol); reaction time = 14 days; yield = 89%. Prepared from disulfide 5c (25 mg, 0.07 mmol); reaction time = 4 days; yield = 98%.

Formula: C_{16}H_{18}NSCl

Molecular weight: 291.84 g mol^{-1}

Aspect: light blue powder

[^\alpha]D^20 + 33 (c = 0.32, MeOH)

^1H NMR (400 MHz, D_{2}O) δ (ppm) 3.04 (dd, J = 5.9, 17.1 Hz, 1H), 3.17 (ddd, J = 1.0, 6.7, 13.6 Hz, 1H), 3.25 (dd, J = 4.6, 17.1 Hz, 1H), 3.36 (dd, J = 2.8, 13.6 Hz, 1H), 3.96 – 4.01 (m, 1H), 4.27 – 4.37 (m, 2H), 7.08 – 7.16 (m, 4H), 7.44 (s, 5H).

^{13}C NMR (63 MHz, D_{2}O) δ (ppm) 27.6, 31.1, 48.8, 51.0, 125.6, 126.7, 127.7, 129.0, 129.3, 129.8, 129.9, 130.3, 130.5, 131.0.

HMRS (ESI) calcd. for C_{16}H_{18}NS, 256.1160; found, 256.1154.

Elemental analysis: Calc. for C_{16}H_{18}NSCl + 2 HCl: H 5.53, C 52.68, N 3.84; found: H 5.01, C 52.31, N 3.83.

(S)-2-(thiochromane-3)aminoacetic acid hydrochloride 6d

Prepared from thiazolinium salt 4d (170 mg, 0.42 mmol); reaction time = 5 days; yield = 83%. Prepared from disulfide 5d (100 mg, 0.28 mmol); reaction time = 4 days; yield = 68%.

Formula: C_{11}H_{14}NO_{2}SCl

Molecular weight: 259.75 g mol^{-1}

Aspect: light brown powder

[^\alpha]D^20 + 14.8 (c = 0.40, MeOH).

mp 209 °C.

^1H NMR (400 MHz, D_{2}O) δ (ppm) 3.07 (dd, J = 6.4, 16.8 Hz, 1H), 3.17 (dd, J = 7.0, 13.9 Hz, 1H), 3.25 (dd, J = 4.0, 16.8 Hz, 1H), 3.36 (dd, J = 2.9, 13.9 Hz, 1H), 3.89 (AB, J = 16.8
Hz, 1H), 3.95 (AB, J = 16.8 Hz, 1H), 4.01 – 4.07 (m, 1H), 7.07 – 7.11 (m, 1H), 7.12 – 7.17 (m, 3H).

$^{13}$C NMR (63 MHz, D$_2$O) δ (ppm) 27.6, 30.9, 45.8, 52.1, 125.6, 126.6, 127.7, 129.0, 130.4, 131.0, 169.4.

**Elemental analysis:** Calc. for C$_{11}$H$_{14}$NSO$_2$Cl + 0.6 HCl: H 5.23, C 46.91, N 4.97; found: H 5.23, C 46.78, N 5.20.

(S)-3-(2-Hydroxyethyl)aminothiochromane hydrochloride 6e

![Chemical Structure](image)

Prepared from thiazolinium salt 4e (100 mg, 0.32 mmol); reaction time = 7 days; yield = 82%.

Formula: C$_{11}$H$_{16}$NSCl

Molecular weight: 245.77 g.mol$^{-1}$

Aspect: light brown powder

[α]$^D$$_{20}$ −1.1 (c = 1.0, MeOH).

mp 203 °C.

$^1$H NMR (500 MHz, D$_2$O) δ (ppm) 3.02 (dd, J = 6.0, 17.2 Hz, 1H), 3.14 (dd, J = 6.7, 13.5 Hz, 1H), 3.20 - 3.27 (m, 3H), 3.34 (dd, J = 3.0, 13.5 Hz, 1H), 3.78 (t, J = 5.2 Hz, 1H), 3.96 - 4.01 (m, 1H), 7.04 – 7.14 (m, 4H).

$^{13}$C NMR (125 MHz, D$_2$O) δ (ppm) 27.4, 31.0, 46.8, 51.5, 56.5, 125.6, 126.6, 127.6, 129.0, 130.4, 131.0.

HMRS (ESI) calc. for C$_{11}$H$_{16}$NSO, 210.0953; found, 210.0943.

**Elemental analysis:** Calc. for C$_{11}$H$_{16}$NSOCl + 2 HCl: H 5.69, C 41.46, N 4.40; found: H 5.62, C 41.29, N 4.55.
$^1$H NMR and $^{13}$C NMR spectra of 3-amino-thiochromanes 3a,b and 6a-e:

3a:
3b:
6a:
6b:
6c:
6d:
6e: