Supporting Information

for

The rapid generation of isothiocyanates in flow

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Experimental part
Experimental

General experimental procedures: $^1$H and $^{13}$C NMR spectra were recorded on either Bruker-Avance 400 or Varian VNMRS-600 instruments using CDCl$_3$ as internal reference. HSQC, HMBC and NOESY experiments were used in aiding the structural assignment. IR spectra were recorded neat on a Perkin Elmer RX1 spectrometer (ATR sampling) with the intensities of the characteristic signals being reported as weak (w, <20% of tallest signal), medium (m, 21–70% of tallest signal) and strong (s, >70% of tallest signal). Low and high resolution mass spectrometry was performed using the indicated techniques on either a Thermo-Finnigan Trace GC–MS or Waters LCT Premier XE and Waters TQD instruments equipped with Acquity UPLC and a lock-mass electrospray ion source.

**General flow procedure for the conversion of chloroximes into isothiocyanates:**
A solution of a chloroxime substrate was prepared in 2 mL MeCN (0.25–0.5 M) and injected into a sample loop mounted on the R2-flow unit. This solution was subsequently pumped at a flow rate of 0.2 mL/min into a heated Omnifit glass column (50 °C, 10 cm length, 6.6 mm i.d.) placed in a glass jacket on the R4-flow unit. This glass column was filled with a mixture of the immobilised base (SiO$_2$-pyridine, 1.2 equiv [or 2.5 equiv in case of entries 13, 14, 15 in Table 2]) and the immobilised thiourea (QP-TU or QS-MTU, 1.2 equiv). After passing this reactor column the reaction mixture was collected, concentrated by evaporation of the solvent and analysed by $^1$H NMR spectroscopy. If the product purity was below 90% column chromatography was performed as indicated below (10% EtOAc/90% hexanes).
4-Bromophenylisothiocyanate (1b):

Isolated as white solid after evaporation of the solvent (198 mg, 93%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.46 (2H, d, $J = 8.0$ Hz), 7.08 (2H, d, $J = 8.0$ Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 137.0 (C), 132.8 (2CH), 130.5 (C), 127.2 (2CH), 120.8 (C); IR (neat) ν/cm$^{-1}$ 3082.4 (w), 2168.4 (m), 2067.7 (s), 1579.8 (m), 1477.6 (s), 1400.0 (s), 1066.7 (m), 923.0 (m), 816.6 (s); GC–MS: 212.8 (M$^+$); HRMS–ESI: calculated for C$_7$H$_5$BrNS: 213.9326, found: 213.9308 (M$^+$H$^+$).

Spectroscopic data are in accordance with published data from supplier [1].

4-Methoxyphenylisothiocyanate (2b):

Isolated as white solid after evaporation of the solvent (146 mg, 89%). $^1$H NMR (CDCl$_3$, 600 MHz) δ 7.15 (2H, d, $J = 9.0$ Hz), 6.84 (2H, d, $J = 9.0$ Hz), 3.80 (3H, s); $^{13}$C NMR (CDCl$_3$, 150 MHz) δ 158.6 (C), 133.9 (C), 126.9 (2CH), 123.6 (C), 114.8 (2CH), 55.6 (CH$_3$); IR (neat) ν/cm$^{-1}$ 2835.1 (w), 2068.9 (s), 1602.0 (m), 1501.3 (s), 1461.9 (m), 1104.9 (m), 1031.3 (m), 926.8 (m), 825.7 (s); ASAP–MS: 165.0 (M$^+$); HRMS–AP$^+$: calculated for C$_8$H$_7$NOS: 165.0248, found: 165.0249 (M$^+$).

Spectroscopic data are in accordance with published data from supplier [1].

Phenylisothiocyanate (3b):

Isolated as colourless oil after evaporation of the solvent (122 mg, 91%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.27 (2H, t, $J = 8.0$ Hz), 7.20 (1H, m), 7.10-7.16 (2H, m); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 135.3 (C), 131.3 (C), 129.6 (2CH), 127.3 (CH), 125.7 (2CH); IR (neat) ν/cm$^{-1}$ 2171.9 (m), 2050.5 (s), 1590.4 (s), 1489.0 (s), 1451.6 (w), 1069.9 (w),
925.0 (m), 904.8 (m), 746.5 (s), 682.1 (s); ASAP–MS: 136.0 (M + H⁺); HRMS–AP⁺: calculated for C₇H₅NS: 135.0143, found: 135.0147 (M⁺).

Spectroscopic data are in accordance with published data from supplier [1].

2-Chloro-5-nitrophenylisothiocyanate (4b) [2]:

Isolated as white solid after evaporation of the solvent (117 mg, 78%). ¹H NMR (CDCl₃, 400 MHz) δ 8.09 (1H, s), 8.06 (1H, d, J = 8.0 Hz), 7.60 (1H, d, J = 8.0 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 146.9 (C), 142.1 (C), 138.7 (C), 131.5 (C), 130.9 (CH), 122.2 (CH), 121.5 (CH); IR (neat) ν/cm⁻¹ 3095.7 (w), 2010.1 (s), 1519.6 (s), 1511.1 (s), 1463.8 (m), 1057.3 (m), 891.9 (s), 837.8 (s), 739.2 (s); ASAP–MS: 215.0 (M + H⁺); HRMS–AP⁺: calculated for C₇H₃ClN₂O₂S: 213.9604, found: 213.9591 (M⁺).

4-Nitrophenylisothiocyanate (5b):

Isolated as white solid after evaporation of the solvent (68 mg, 76%). ¹H NMR (CDCl₃, 400 MHz) δ 8.24 (2H, d, J = 8.8 Hz), 7.35 (2H, d, J = 8.8 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 145.8 (C), 140.4 (C), 137.9 (C), 126.4 (2CH), 125.3 (2CH); IR (neat) ν/cm⁻¹ 2101.0 (s), 1603.1 (w), 1584.7 (s), 1518.9 (s), 1485.7 (m), 1335.7 (s), 1105.9 (m), 850.4 (s), 745.9 (m); ASAP–MS: 180.0 (M⁺); HRMS–AP⁺: calculated for C₇H₄N₂O₂S: 179.9993, found: 179.9990 (M⁺).

Spectroscopic data are in accordance with published data from supplier [1].
1-Isothiocyanato-2-methylbenzene (6b):
Isolated as colourless oil after evaporation of the solvent (140 mg, 94%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.13-7.24 (4H, m), 2.38 (3H, s); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 135.3 (C), 135.0 (C), 130.7 (CH), 130.3 (C), 127.4 (CH), 126.9 (CH), 125.9 (CH), 18.4 (CH$_3$); IR (neat) ν/cm$^{-1}$ 2062.8 (s), 1598.2 (w), 1485.2 (m), 1459.8 (m), 1114.2 (w), 927.2 (s), 787.9 (m), 749.5 (s), 672.2 (m); ASAP–MS: 149.0 (M$^+$); HRMS–AP$^+$: calculated for C$_8$H$_7$NS: 149.0299, found: 149.0296 (M$^+$).
Spectroscopic data are in accordance with published data from supplier [1].

2,4-Dichloro-1-((4-isothiocyanato-3-methoxyphenoxy)methyl)benzene (7b):
Isolated as white solid after evaporation of the solvent (155 mg, 91%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.54 (1H, d, $J = 2.0$ Hz), 7.45 (1H, d, $J = 7.6$ Hz), 7.25 (1H, dd, $J = 2.0, 8.0$ Hz), 6.87 (1H, dd, $J = 2.0, 8.4$ Hz), 6.82 (1H, d, $J = 8.4$ Hz), 6.72 (1H, d, $J = 2.0$ Hz), 5.04 (2H, s), 3.88 (3H, s); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 149.2 (C), 148.0 (C), 136.5 (C), 134.2 (C), 132.9 (C), 132.2 (C), 130.7 (CH), 129.2 (CH), 126.5 (CH), 123.6 (C), 119.4 (CH), 112.0 (CH), 111.7 (CH), 69.8 (CH$_2$), 56.2 (CH$_3$); IR (neat) ν/cm$^{-1}$ 2844.8 (w), 2126.0 (s), 1587.4 (m), 1505.3 (s), 1378.0 (m), 1260.0 (s), 1238.0 (s), 1216.8 (m), 1176.5 (s), 1127.8 (s), 1019.1 (s), 832.4 (s), 800.0 (m); ASAP–MS: 340.0 (M$^+$ + H$^+$); HRMS–AP$^+$: calculated for C$_{15}$H$_{11}$NO$_2$Cl$_2$S: 338.9888, found: 338.9911 (M$^+$).

9-Isothiocyanatoanthracene (8b) [3]:
Isolated as yellow solid after evaporation of the solvent (200 mg, 85%). $^1$H NMR (CDCl$_3$, 600 MHz) δ 8.37 (1H, s), 8.28 (2H, d, $J = 9.0$ Hz), 8.01 (2H, d, $J = 9.0$ Hz), 7.61 (2H, t, $J$
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\text{= 7.8 Hz), 7.53 (2H, t, } J = 7.8 \text{ Hz); } ^{13}\text{C NMR (CDCl}_3, 150 \text{ MHz) } \delta 137.7 \text{ (C), 131.6 (C), 129.0 (CH), 128.0 (C), 127.5 (CH), 126.7 (CH), 126.3 (CH), 123.2 (CH), 122.4 (C); IR (neat) } \nu/\text{cm}^{-1} 3052.0 \text{ (w), 2114.2 (s), 1710.0 (w), 1673.8 (w), 1442.0 (w), 886.7 (m), 777.3 (m), 730.0 (s); ASAP–MS: 236.0 (M}^+\text{); HRMS–AP}^+: \text{ calculated for C}_{15}\text{H}_9\text{NS: 235.0456, found: 235.0430 (M}^+\text{).}
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1-Isothiocyanatotridecane (9b):

Isolated as colourless oil after evaporation of the solvent (171 mg, 89%). \(^1\text{H NMR (CDCl}_3, 400 \text{ MHz) } \delta 3.44 \text{ (2H, t, } J = 6.4 \text{ Hz), 1.63 (2H, m), 1.15-1.40 (20H, m), 0.81 (3H, t, } J = 6.8 \text{ Hz); } ^{13}\text{C NMR (CDCl}_3, 100 \text{ MHz) } \delta 129.0 \text{ (C), 45.1 (CH}_2\text{), 31.9 (CH}_2\text{), 30.0 (CH}_2\text{), 29.7 (CH}_2\text{), 29.64 (CH}_2\text{), 29.61 (CH}_2\text{), 29.5 (CH}_2\text{), 29.4 (CH}_2\text{), 29.36 (CH}_2\text{), 28.8 (CH}_2\text{), 26.6 (CH}_2\text{), 22.7 (CH}_2\text{), 14.1 (CH}_3\text{); IR (neat) } \nu/\text{cm}^{-1} 2921.3 \text{ (s), 2852.2 (m), 2084.8 (s), 1455.2 (m), 1345.3 (m), 721.0 (w); ASAP–MS: 242.2 (M}^+\text{); HRMS–AP}^+: \text{ calculated for C}_{14}\text{H}_{28}\text{NS: 242.1942, found: 242.1948 (M}^+\text{).}
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Benzylisothiocyanate (10b):

Isolated as colourless oil after evaporation of the solvent (100 mg, 84%). \(^1\text{H NMR (CDCl}_3, 400 \text{ MHz) } \delta 7.30-7.45 \text{ (5H, m), 4.72 (2H, s); } ^{13}\text{C NMR (CDCl}_3, 100 \text{ MHz) } \delta 134.3 \text{ (C), 132.2 (C), 129.0 (2CH), 128.4 (CH), 126.9 (2CH); IR (neat) } \nu/\text{cm}^{-1} 2166.1 \text{ (m), 2079.9 (s), 1495.8 (m), 1453.8 (m), 1438.1 (m), 1346.3 (m), 1028.0 (w), 696.3 (s); GC–MS: 148.9 (M}^+\text{).}
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Spectroscopic data are in accordance with published data from supplier [1].
(E)-(2-Isothiocyanatovinyl)benzene (11b) [4]:
Isolated as colourless oil after evaporation of the solvent (104 mg, 81%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.30-7.38 (5H, m), 6.67 (1H, d, $J$ = 14.0 Hz), 5.58 (1H, d, $J$ = 14.0 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 134.1 (C), 133.7 (C), 131.6 (CH), 129.0 (CH), 128.9 (2CH), 126.3 (2CH), 115.4 (CH); IR (neat) v/cm$^{-1}$ 2099.6 (s), 1625.5 (w), 1447.4 (w), 932.8 (m), 746.3 (m), 689.8 (m); ASAP–MS: 162.0 (M$^+$H$^+$); HRMS–AP$^+$: calculated for C$_9$H$_7$NS: 161.0299, found: 161.0293 (M$^+$).

5-(2-Isothiocyanatopropyl)benzo[d][1,3]dioxole (12b):
Isolated as white solid after evaporation of the solvent (192 mg, 87%). $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 6.77 (1H, d, $J$ = 7.8 Hz), 6.68 (1H, s), 6.65 (1H, d, $J$ = 7.8 Hz), 5.95 (2H, s), 3.90 (1H, m), 2.75-2.86 (2H, m), 1.36 (3H, d, $J$ = 6.6 Hz); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ 147.8 (C), 146.7 (C), 131.5 (C), 130.3 (C), 122.5 (CH), 109.5 (CH), 108.4 (CH), 101.0 (CH2), 55.3 (CH), 43.5 (CH$_2$), 21.3 (CH$_3$); IR (neat) v/cm$^{-1}$ 2886.2 (w), 2088.0 (s), 1501.8 (s), 1487.9 (s), 1442.0 (s), 1332.1 (m), 1246.4 (s), 1190.1 (m), 1100.3 (m), 1035.8 (s), 926.7 (s), 807.6 (m); ASAP–MS: 222.0 (M$^+$H$^+$); HRMS–AP$^+$: calculated for C$_{11}$H$_{11}$NO$_2$S: 221.0511, found: 221.0519 (M$^+$).

rac-(2S,4S)-Ethyl 5-(4-bromophenyl)-4-isothiocyanato-4-methyl-3,4-dihydro-2H-pyrrole-2-carboxylate (13b):
Isolated after column chromatography (10% EtOAc, 90% hexanes) as colourless oil (134 mg, 73%). $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 7.89 (2H, d, $J$ = 9.0 Hz), 7.59 (2H, d, $J$ = 9.0 Hz), 4.67 (1H, app. t, $J$ = 7.8 Hz), 4.28 (2H, q, $J$ = 7.2 Hz), 2.73 (1H, dd, $J$ = 8.4,
13.2 Hz), 2.65 (1H, dd, \( J = 7.2, 13.2 \) Hz), 1.71 (3H, s), 1.33 (3H, t, \( J = 7.2 \) Hz); \(^{13}\text{C} \) NMR (CDCl\(_3\), 150 MHz) \( \delta \) 172.1 (C), 170.6 (C), 136.6 (C), 131.9 (2CH), 129.9 (2CH), 129.4 (C), 126.3 (C), 71.0 (C), 69.8 (CH), 61.8 (CH\(_2\)), 44.9 (CH\(_2\)), 25.9 (CH\(_3\)), 14.2 (CH\(_3\)); IR (neat) v/cm\(^{-1}\) 2980.9 (w), 2055.9 (s), 1735.9 (s), 1588.0 (m), 1487.2 (m), 1271.1 (m), 1192.5 (s), 1106.9 (m), 1071.8 (m), 1010.1 (m), 833.3 (m); LC–MS: 368.9 (M + H\(^+\)); HRMS–AP\(^+\): calculated for C\(_{15}\)H\(_{16}\)O\(_2\)BrN\(_2\)S: 367.0110, found: 367.0117.

**rac-(2S,4S)-Ethyl 4-isothiocyanato-4-methyl-5-(3-nitrophenyl)-3,4-dihydro-2H-pyrrole-2-carboxylate (14b):**

Isolated after purification by column chromatography (10% EtOAc, 90% hexanes) as yellow oil (117 mg, 71%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 8.88 (1H, t, \( J = 2.4 \) Hz), 8.33-8.38 (2H, m), 7.67 (1H, t, \( J = 8.0 \) Hz), 4.75 (1H, app. t, \( J = 8.0 \) Hz), 4.31 (2H, q, \( J = 7.2 \) Hz), 2.80 (1H, dd, \( J = 8.4, 13.2 \) Hz), 2.71 (1H, dd, \( J = 7.6, 13.2 \) Hz), 1.75 (3H, s), 1.35 (3H, t, \( J = 7.2 \) Hz); \(^{13}\text{C} \) NMR (CDCl\(_3\), 100 MHz) \( \delta \) 171.3 (C), 170.4 (C), 148.5 (C), 138.1 (C), 134.0 (CH), 132.4 (C), 129.9 (CH), 125.9 (CH), 123.6 (CH), 71.2 (C), 70.0 (CH), 62.0 (CH\(_2\)), 44.9 (CH\(_2\)), 25.9 (CH\(_3\)), 14.2 (CH\(_3\)); IR (neat) v/cm\(^{-1}\) 2981.7 (w), 2064.0 (s), 1710.4 (s), 1529.9 (s), 1446.1 (m), 1348.1 (s), 1186.6 (m), 1096.4 (m), 911.3 (m), 734.7 (m); ASAP–MS: 334.1 (M + H\(^+\)); HRMS–AP\(^+\): calculated for C\(_{15}\)H\(_{16}\)O\(_4\)N\(_3\)S: calculated for C\(_{15}\)H\(_{16}\)O\(_4\)N\(_3\)S: 334.0862, found: 334.0881 (M + H\(^+\)).
rac-(2S,4R)-Ethyl 4-isothiocyanato-4-methyl-5-(3-nitrophenyl)-3,4-dihydro-2H-pyrrole-2-carboxylate (15b):

Isolated after column chromatography (10% EtOAc, 90% hexanes) as yellow oil (188 mg, 76%). $^1$H NMR (CDCl$_3$, 600 MHz) δ 8.83 (1H, s), 8.36 (1H, d, $J$ = 8.4 Hz), 8.28 (1H, d, $J$ = 8.4 Hz), 7.67 (1H, t, $J$ = 8.4 Hz), 5.05 (1H, dd, $J$ = 5.4, 8.4 Hz), 4.28 (2H, q, $J$ = 7.2 Hz), 2.85 (1H, dd, $J$ = 8.4, 13.2 Hz), 2.60 (1H, dd, $J$ = 5.4, 13.2 Hz), 1.82 (3H, s), 1.35 (3H, t, $J$ = 7.2 Hz); $^{13}$C NMR (CDCl$_3$, 150 MHz) δ 171.3 (C), 170.8 (C), 148.4 (C), 138.2 (C), 134.0 (CH), 132.5 (C), 129.8 (CH), 125.7 (CH), 123.6 (CH), 77.3 (C), 71.0 (CH), 62.0 (CH$_2$), 44.5 (CH$_2$), 27.1 (CH$_3$), 14.1 (CH$_3$); IR (neat) ν/cm$^{-1}$ 2036.2 (s), 1737.8 (s), 1531.1 (s), 1349.4 (s), 1190.0 (m), 1094.2 (m), 911.9 (m), 732.0 (s); ASAP–MS: 334.1 (M + H$^+$); HRMS–AP$^+$: calculated for C$_{15}$H$_{16}$O$_4$N$_3$S: 334.0862, found: 334.0872 (M + H$^+$).

References:

1. See the corresponding compound at www.sigmaaldrich.com