Supporting Information for

Solvent- and Halide-free Synthesis of Pyridine-2-yl Substituted Ureas through Facile C–H Functionalization of Pyridine N-oxides

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Table of Contents

1 General remarks...............................................................................................................................2
2 Experimental procedures .................................................................................................................3
  2.1. General procedure for the synthesis of N-pyridine-2-yl substituted urea 4 (GP1)........3
  2.2. Synthesis of the starting pyridine N-oxides 1 .................................................................11
  2.3. Synthesis of the starting cyanamide 2c .............................................................................16
  2.4. Optimization of the reaction conditions (full data).............................................................17
3 NMR spectra..................................................................................................................................18
  3.1. Spectra of N-pyridine-2-yl substituted ureas 4 .................................................................18
  3.2. Spectra of substituted pyridine 1-oxides 1 ........................................................................44
  3.3. Spectrum of cyanamide 2c ..................................................................................................58
4 X-ray data ......................................................................................................................................59
  4.1. X-ray structure of 3-(6-Bromopyridin-2-yl)-1,1-dimethylurea (4o) ..............................59
  4.2. X-ray structure of 3-(6-Chloropyridin-2-yl)-1,1-dimethylurea (4p) .............................62
  4.3. X-ray structure of 3-(2-Methoxypyridin-3-yl)-1,1-dimethylurea (5t) .........................65
1 General remarks

NMR spectra were recorded at ambient temperature with a Bruker Avance III 400 instrument at 400.13 MHz (1H NMR) and 100.61 MHz (13C NMR, DEPT-135). Chemical shifts (δ) are given in ppm relative to resonances of solvents (1H: δ = 7.26 for the residual CHCl₃ peak, δ = 2.50 for the residual DMSO-d₅ peak; 13C: δ = 77.0 for CDCl₃, δ = 39.5 for DMSO-d₆). Spin-spin coupling constants (J) are given in Hz. Multiplicities of signals are described as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. The multiplicities of signals in 13C NMR spectra were determined by the DEPT-135 technique. Mass spectra were recorded with a Bruker MicroTOF (ESI) and Bruker maXis HRMS-ESI-QTOF instruments. Mass spectra from TLC plates were recorded employing a Camag TLC-MS interface and a Bruker MicroTOF (ESI) instrument. Infrared spectra were recorded with a Perkin-Elmer spectrum ASCII PEDS 1.60 FT-IR spectrometer. X-ray diffraction data were collected at an Xcalibur Eos diffractometer using Mo-Kα (λ = 0.071073 nm) radiation. The structures were solved by direct methods using the SHELXS and refined with the SHELXL¹ incorporated in the OLEX2 program package.² Chromatographic separation was carried out on Macherey-Nagel silica gel 60 (0.063–0.210 mm). Analytical TLC was performed on unmodified Merck ready-to-use plates (TLC silica gel 60 F254). Detection was achieved with a UV lamp. Melting points were determined in capillaries with a Stuart SMP 30 apparatus. The solvents were used as received, without purification. The commercially available compounds dimethylcyanamide, diethylcyanamide, piperidine-1-carbonitrile, pyrrolidine-1-carbonitrile, morpholine-4-carbonitrile, pyridine 1-oxide, 2-picoline 1-oxide were used as received without further purification.

2 Experimental procedures

2.1 General procedure for the synthesis of N-pyridine-2-yl substituted urea 4 (GP1)

\[
\begin{align*}
\text{R}^1-N & \quad + \quad \text{MeSO}_3\text{H} \\
\text{N} & \quad \rightleftharpoons \quad \text{O} \\
\text{R}^2-N & \quad \rightarrow \quad \text{R}^3-N \\
\end{align*}
\]

A mixture of substituted pyridine N-oxide 1 (1.00 mmol) and cyanamide 2 (1.50 mmol) was stirred at r.t. for 2 min and methanesulfonic acid (96.0 mg, 1.00 mmol) was then added dropwise within 3 min. The reaction mixture was then stirred at 60 °C for 2 h, cooled down, diluted with saturated aq. Na₂CO₃ (5.0 mL) and aq. NaCl (20 mL), and extracted with EtOAc (4 × 15 mL). Combined organic fractions were dried over anhydrous Na₂SO₄, filtered, and concentrated on a rotary evaporator. The crude product was subjected to column chromatography on silica gel (EtOAc/hexane, gradient from 50% to pure EtOAc) to give target urea 4 in good to excellent yields.

1,1-Dimethyl-3-(pyridin-2-yl)urea (4a): From pyridine 1-oxide (1a) (95.0 mg, 1.00 mmol) and dimethylcyanamide (2a) (105 mg, 1.50 mmol), compound 4a (147 mg, 89%) was obtained according to GP1 as a yellow oil, which was then crystalized in the freezer to give pale yellow solid, m.p. = 42.6–43.5 °C, lit. 4 m.p. = 44–47 °C (EtOAc/hexane), Rₜ = 0.25 (EtOAc). ¹H NMR (400 MHz, CDCl₃): δ = 3.00 (s, 6 H, NCH₃), 6.88 (ddd, J = 7.3, 5.0, 0.9 Hz, 1 H), 7.30 (br. s, 1 H), 7.60 (ddd, J = 8.5, 7.3, 1.9 Hz, 1 H), 8.02 (dt, J = 8.5, 0.9 Hz, 1 H), 8.14 (ddd, J = 5.0, 1.9, 0.9 Hz, 1 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 36.3 (2 C, CH₃), 113.0 (CH), 118.1 (CH), 138.0 (CH), 147.3 (CH), 152.8 (C), 154.8 (C) ppm. NMR data are consistent with previously reported. ³ HRMS (ESI), m/z: [M + H]⁺ calcd. for C₈H₁₂N₃O: 166.0975; found: 166.0977.

1,1-Diethyl-3-(pyridin-2-yl)urea (4b): From pyridine 1-oxide (1a) (95.0 mg, 1.00 mmol) and diethylcyanamide (2b) (147 mg, 1.50 mmol), compound 4b (141 mg, 73%) was obtained according to GP1 as a brownish oil, Rₜ = 0.30 (EtOAc). ¹H NMR (400 MHz, CDCl₃): δ = 1.19 (t, J = 7.2 Hz, 6 H, CH₃), 3.35 (q, J = 7.2 Hz, 4 H, NCH₂), 6.88 (ddd, J = 7.3 5.0, 0.9 Hz, 1 H), 7.16 (br. s, 1 H), 7.59 (ddd, J = 8.5, 7.3, 1.9 Hz, 1 H), 8.05 (dt, J = 8.5, 0.9 Hz, 1 H), 8.14 (ddd, J = 5.0, 1.9, 0.9 Hz, 1 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 13.8 (2 × CH₃), 41.5

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(2 × CH₂), 113.1 (CH), 118.0 (CH), 138.0 (CH), 147.3 (CH), 152.9 (C), 153.7 (C) ppm. NMR data are consistent with previously reported.⁵ HRMS (ESI), m/z: [M + H]^+ calcd. for C₁₀H₁₆N₃O⁺: 194.1288; found: 194.1280.

1,1-Dipropyl-3-(pyridin-2-yl)urea (4c): From pyridine 1-oxide (1a) (95.0 mg, 1.00 mmol) and dipropylcyanamide (2c) (189 mg, 1.50 mmol), compound 4c (175 mg, 79%) was obtained according to GP1 as a brownish oil, which was then crystallized in the freezer to give pale brown solid, m.p. = 38.5–39.4 °C (EtOAc/hexane), R_f = 0.50 (EtOAc). Compound 4c is mentioned in lit.⁵, but analytical data are absent. IR (KBr, pellet): \( \tilde{\nu}_{\text{max}} \) 3225 (w), 2965 (m), 2930 (m), 2875 (m), 1660 (m), 1575 (m), 1535 (m), 1435 (s), 1405 (m), 1305 (s), 1230 (m), 1165 (m), 1105 (w), 895 (w), 782 (m) cm⁻¹. \(^1\)H NMR (400 MHz, CDCl₃): \( \delta \) = 0.93 (t, J = 7.4 Hz, 6 H, CH₃), 1.55–1.71 (m, 4 H, CH₂(CH₃)), 3.18–3.30 (m, 4 H, NCH₂), 6.89 (ddd, J = 7.3, 5.0, 1.0 Hz, 1 H), 7.16 (br. s, 1 H), 7.60 (ddd, J = 8.5, 7.3, 1.9 Hz, 1 H), 8.06 (dt, J = 8.5, 1.0 Hz, 1 H), 8.15 (ddd, J = 5.0, 1.9, 1.0 Hz, 1 H) ppm. \(^{13}\)C NMR (101 MHz, CDCl₃): \( \delta \) = 11.3 (2 × CH₃), 21.7 (2 × CH₂), 49.4 (2 × CH₂), 113.2 (CH), 118.1 (CH), 138.0 (CH), 147.2 (CH), 152.9 (C), 154.1 (C) ppm. HRMS (ESI), m/z: [M + H]^+ calcd. for C₁₂H₂₀N₃O⁺: 222.1601; found: 222.1600.

N-(Pyridin-2-yl)pyrrolidine-1-carboxamide (4d): From pyridine 1-oxide (1a) (95.0 mg, 1.00 mmol) and pyrrolidine-1-carbonitrile (2d) (144 mg, 1.50 mmol), compound 4d (176 mg, 92%) was obtained according to GP1 as a pale yellow solid, m.p. = 116.5–116.9 °C (EtOAc/hexane), lit.⁶ m.p. = 154–155 °C, R_f = 0.30 (EtOAc). \(^1\)H NMR (400 MHz, CDCl₃): \( \delta \) = 1.96–1.99 (m, 1 H, NCH₂CH₂), 3.47–3.50 (m, 1 H, NC(CH₂)₂), 6.92 (ddd, J = 7.3, 5.0, 1.0 Hz, 1 H), 6.99 (br. s, 1 H, NH), 7.63 (ddd, J = 8.5, 7.3, 1.9 Hz, 1 H), 8.11 (dt, J = 8.5, 1.0 Hz, 1 H), 8.18 (ddd, J = 5.0, 1.9, 1.0 Hz, 1 H) ppm. \(^{13}\)C NMR (101 MHz, CDCl₃): \( \delta \) = 25.4 (2 × CH₂), 45.7 (2 × CH₂), 112.9 (CH), 118.0 (CH), 137.9 (CH), 147.3 (CH), 152.7 (C), 153.0 (C) ppm. NMR data are consistent with previously reported.⁶ HRMS (ESI), m/z: [M + H]^+ calcd. for C₁₀H₁₄N₃O⁺: 192.1131; found: 192.1127.

N-(Pyridin-2-yl)piperidine-1-carboxamide (4e): From pyridine 1-oxide (1a) (95.0 mg, 1.00 mmol) and piperidine-1-carbonitrile (2e) (165 mg, 1.50 mmol), compound 4e (172 mg, 83%) was obtained according to GP1 as a pale yellow solid, m.p. = 84.2–84.8 °C (EtOAc/hexane), lit.⁷ m.p. = 85 °C, R_f = 0.50 (EtOAc). \(^1\)H NMR (400 MHz, CDCl₃): \( \delta \) = 1.17–1.88 (m, 6 H), 3.39–3.47 (m, 4 H, NCH₂), 6.86 (ddd, J = 7.3, 5.0, 1.0 Hz, 1 H), 7.51 (br. s, 1 H, 6 Wei, Y.; Liu, J.; Lin, S.; Ding, H.; Liang, F.; Zhao, B. Org. Lett. 2010, 12, 4220–4223.
NH), 7.58 (ddd, J = 8.5, 7.3, 1.9 Hz, 1 H), 7.98 (dt, J = 8.5, 0.9 Hz, 1 H), 8.13 (ddd, J = 5.0, 1.9, 0.9 Hz, 1 H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 24.2\) (CH\(_2\)), 25.6 (2 \(\times\) CH\(_2\)), 45.1 (2 \(\times\) CH\(_2\)), 113.2 (CH), 118.0 (CH), 137.9 (CH), 147.3 (CH), 153.0 (C), 153.9 (C) ppm. HRMS (ESI), m/z: [M + Na]\(^+\) calcd. for C\(_{11}\)H\(_{15}\)N\(_3\)NaO\(^+\): 228.1107; found: 228.1099.

**N-(Pyridin-2-yl)morpholine-4-carboxamide (4f):** From pyridine 1-oxide (1a) (95.0 mg, 1.00 mmol) and morpholine-4-carbonitrile (2f) (168 mg, 1.50 mmol), compound 4f (164 mg, 89%) was obtained according to GP1 as a colorless solid, m.p. = 92.6–93.1 °C (EtOAc/hexane), lit.\(^8\) m.p. = 92 °C, \(R_f\) = 0.35 (EtOAc). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 3.45–3.51\) (m, 4 H), 3.65–3.71 (m, 4 H), 6.92 (m, 1 H), 7.62 (m, 1 H), 7.66 (br. s, 1 H, NH), 7.98 (d, \(J = 8.4\) Hz, 1 H), 8.15 (d, \(J = 4.2\) Hz, 1 H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 44.1\) (2 \(\times\) CH\(_2\)), 66.4 (2 \(\times\) CH\(_2\)), 113.4 (CH), 118.4 (CH), 138.1 (CH), 147.3 (CH), 152.6 (C), 154.2 (C) ppm. HRMS (ESI), m/z: [M + H]\(^+\) calcd. for C\(_{10}\)H\(_{14}\)N\(_3\)O\(_2\)+: 208.1081; found: 208.1084.

**1,1-Dimethyl-3-(6-methylpyridin-2-yl)urea (4g):** From 2-methylpyridine 1-oxide (1g) (109 mg, 1.00 mmol) and dimethylcyanamide (2a) (105 mg, 1.50 mmol), compound 4g (147 mg, 82%) was obtained according to GP1 as a pale yellow oil, \(R_f\) = 0.30 (EtOAc). IR (KBr, thin film): \(\nu_{max}\) 3355 (w), 2925 (w), 1670 (s), 1580 (m), 1530 \(\tilde{\nu}\) (s), 1455 (s), 1400 (m), 1305 (m), 1180 (m) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 2.40\) (s, 3 H, CCH\(_3\)), 3.03 (s, 6 H, NCH\(_3\)), 6.77 (d, \(J = 7.4\) Hz, 1 H), 7.28 (br. s, 1 H, NH), 7.52 (dd, \(J = 8.3, 7.4\) Hz, 1 H), 7.85 (d, \(J = 8.3\) Hz, 1 H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 23.7\) (CCH\(_3\)), 36.4 (2 \(\times\) NCH\(_3\)), 110.0 (CH), 117.6 (CH), 138.5 (CH), 152.2 (C), 154.9 (C), 156.0 (C) ppm. HRMS (ESI), m/z: [M + H]\(^+\) calcd. for C\(_9\)H\(_{14}\)N\(_3\)O\(_2\)+: 180.1131; found: 180.1132.

**1,1-Dimethyl-3-(4-methylpyridin-2-yl)urea (4h):** From 4-methylpyridine 1-oxide (1h) (109 mg, 1.00 mmol) and dimethylcyanamide (2a) (105 mg, 1.50 mmol), compound 4h (140 mg, 78%) was obtained according to GP1 as a gray solid, m.p. = 100.1–100.4 °C (EtOAc/hexane), \(R_f\) = 0.25 (EtOAc). IR (KBr, pellet): \(\tilde{\nu}_{max}\) 3215 (w), 3175 (w), 3020 \(\tilde{\nu}\) (w), 2975 (w), 2920 (w), 2800 (w), 1665 (s), 1610 (m), 1575 (s), 1530 (s), 1425 (m), 1365 (s), 1300 (m), 1185 (s), 995 (w), 830 (m), 785 (s), 750 (s), 625 (s) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 2.29\) (s, 3 H, CCH\(_3\)), 3.00 (s, 6 H, NCH\(_3\)), 6.72 (d, \(J = 5.0\) Hz, 1 H), 7.21 (br. s, 1 H, NH), 7.87 (s, 1 H), 8.00 (d, \(J = 5.0\) Hz, 1 H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 2.29\) (s, 3 H, CCH\(_3\)), 3.00 (s, 6 H, NCH\(_3\)), 6.72 (d, \(J = 5.0\) Hz, 1 H), 7.21 (br. s, 1 H, NH), 7.87 (s, 1 H), 8.00 (d, \(J = 5.0\) Hz, 1 H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 21.3\) (CH\(_3\)), 36.3 (2 \(\times\) NCH\(_3\)), 113.5 (CH), 119.5 (CH), 146.9 (CH), 149.4 (C), 152.8 (C), 154.9 (C) ppm. HRMS (ESI), m/z: [M + H]\(^+\) calcd. for C\(_9\)H\(_{14}\)N\(_3\)O\(_2\)+: 180.1131; found: 180.1127.

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1,1-Dimethyl-3-(3-methylpyridin-2-yl)urea (4i): From 3-methylpyridine 1-oxide (1i) (109 mg, 1.00 mmol) and dimethylcyanamide (2a) (105 mg, 1.50 mmol), compound 4i (115 mg, 64%) was obtained according to GP1b as a yellowish solid, m.p. = 61.2–61.7 °C, R_f = 0.20 (EtOAc). IR (KBr, pellet): \( \tilde{\nu}_{\text{max}} \) 3260 (m), 3020 (m), 2950 (m), 2920 (m), 1675 (s), 1590 (s), 1520 (s), 1475 (s), 1370 (s), 1305 (s), 1265 (m), 1180 (m), 1125 (w), 1035 (w), 835 (m), 745 (w), 660 (w), 560 (w), 520 (w) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 2.24 \) (s, 3 H, CCH\(_3\)), 3.02 (s, 6 H, NCH\(_3\)), 7.10 (br. s, 1 H, NH), 7.45 (dd, \( J = 8.5, 1.8 \) Hz, 1 H, H-4), 7.94 (d, \( J = 8.5 \) Hz, 1 H, H-3), 7.99 (br. s, 1 H, H-6) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta = 17.6 \) (CCH\(_3\)), 36.4 (2 × NCH\(_3\)), 112.6 (CH), 127.4 (C), 138.8 (CH), 147.1 (CH), 150.6 (C), 155.0 (C) ppm. HRMS (ESI), m/z: [M + H\(^+\)] calcd. for C\(_9\)H\(_{14}\)N\(_3\)O: 180.1131; found: 180.1124.

3-(6-Benzylpyridin-2-yl)-1,1-dimethylurea (4j): From 2-benzylpyridine 1-oxide (1j) (185 mg, 1.00 mmol) and dimethylcyanamide (2a) (105 mg, 1.50 mmol), compound 4j (181 mg, 71%) was obtained according to GP1 as a colorless solid, m.p. = 90.5–90.9 °C (EtOAc/hexane), R_f = 0.50 (EtOAc). IR (KBr, pellet): \( \tilde{\nu}_{\text{max}} \) 3215 (w), 3060 (w), 3025 (w), 2960 (w), 2930 (w), 2890 (w), 1555 (s), 1640 (s), 1580 (m), 1530 (m), 1450 (s), 1410 (m), 1303 (m), 1190 (m), 740 (m), 700 (m) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 3.03 \) (s, 6 H, NCH\(_3\)), 4.00 (s, 2 H, PhCH\(_2\)), 6.73 (d, \( J = 7.4 \) Hz, 1 H), 7.14 (s, 1 H, NH), 7.17–7.24 (m, 3 H, H-Ar), 7.26–7.32 (m, 2 H, H-Ar), 7.53 (dd, \( J = 8.3, 7.4 \) Hz, 1 H), 7.88 (d, \( J = 8.3 \) Hz, 1 H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta = 36.4 \) (2 × CH\(_3\)), 44.1 (CH\(_2\)), 110.5 (CH), 117.5 (CH), 126.3 (CH), 128.4 (2 × CH), 129.0 (2 × CH), 138.5 (CH), 139.4 (C), 152.3 (C), 154.9 (C), 158.8 (C) ppm. HRMS (ESI), m/z: [M + H\(^+\)] calcd. for C\(_{15}\)H\(_{18}\)N\(_3\)O: 256.1444; found: 256.1444.

3-(4-Methoxypyridin-2-yl)-1,1-dimethylurea (4k): From 4-methoxypyridine 1-oxide (1k) (125 mg, 1.00 mmol) and dimethylcyanamide (2a) (105 mg, 1.50 mmol), compound 4k (168 mg, 86%) was obtained according to GP1 as a colorless solid, m.p. = 47.0–47.2 °C, R_f = 0.15 (EtOAc). IR (KBr, pellet): \( \tilde{\nu}_{\text{max}} \) 3260 (m), 3135 (w), 3035 (w), 2980 (w), 2940 (w), 1665 (s), 1600 (s), 1575 (s), 1515 (s), 1450 (s), 1430 (s), 1415 (s), 1370 (m), 1315 (m), 1305 (m), 1260 (w), 1200 (s), 1180 (s), 1035 (m), 1025 (m), 995 (w), 875 (w), 845 (w), 810 (w), 800 (w), 780 (m), 755 (w) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 3.01 \) (s, 6 H, NCH\(_3\)), 3.83 (s, 3 H, OCH\(_3\)), 6.47 (dd, \( J = 5.8, 2.1 \) Hz, 1 H, H-5), 7.24 (br. s, 1 H, NH), 7.70 (d, \( J = 2.1 \) Hz, 1 H, H-3), 7.94 (d, \( J = 5.8 \) Hz, 1 H, H-6) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta = 36.3 \) (2 × NCH\(_3\)), 55.1 (OCH\(_3\)), 97.0 (CH), 106.8 (CH), 148.0 (CH), 154.5 (C), 154.9 (C), 167.3 (C) ppm. HRMS (ESI), m/z: [M + H\(^+\)] calcd. for C\(_9\)H\(_{14}\)N\(_3\)O\(_2\): 196.1081; found: 196.1088.

3-(6-Benzylpyridin-2-yl)-1,1-dimethylurea (4j):

3-(4-Methoxypyridin-2-yl)-1,1-dimethylurea (4k):
1,1-Dimethyl-3-(4-nitropyridin-2-yl)urea (4l): From 4-nitropyridine 1-oxide (1l) (140 mg, 1.00 mmol) and dimethylcyanamide (2a) (105 mg, 1.50 mmol), compound 4l (164 mg, 78%) was obtained according to GP1 as an orange solid, m.p. = 124.7–125.1 °C (EtOAc/hexane), \( R_f = 0.40 \) (EtOAc). IR (KBr, pellet): \( \tilde{\nu}_{max} \) 3330 (m), 3145 (w), 2940 (w), 1665 (s), 1585 (m), 1530 (s), 1415 (m), 1380 (m), 1360 (m), 1270 (m), 1175 (m), 875 (s), 745 (m), 695 (m) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 3.06 \) (s, 6 H, NCH\(_3\)), 7.51 (s, 1 H, NH), 7.59 (dd, \( J = 5.4, 1.5 \) Hz, 1 H), 8.38 (d, \( J = 5.4 \) Hz, 1 H), 8.80 (d, \( J = 1.5 \) Hz, 1 H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta = 36.4 \) (2 × CH\(_3\)), 106.2 (CH), 110.7 (CH), 149.4 (CH), 154.1 (C), 155.0 (C), 155.3 (C) ppm. HRMS (ESI), \( m/z \): [M + H]+ calcd. for C\(_{8}\)H\(_{11}\)N\(_4\)O\(_3\): 211.0826; found: 211.0822.

3-(5-Methoxypyridin-2-yl)-1,1-dimethylurea (4m): From 5-methoxypyridine 1-oxide (1m) (125 mg, 1.00 mmol) and dimethylcyanamide (2a) (105 mg, 1.50 mmol), compound 4m (140 mg, 72%) was obtained according to GP1 as a yellowish solid, m.p. = 103.0–130.5 °C, \( R_f = 0.3 \) (EtOAc). IR (KBr, pellet): 3270 (m), 3020 (w), \( \tilde{\nu}_{max} \) 2940 (m), 2850 (w), 1660 (s), 1590 (s), 1510 (s), 1485 (s), 1390 (s), 1370 (s), 1280 (s), 1245 (m), 1175 (m), 1120 (m), 1070 (w), 1020 (m), 850 (w), 825 (w), 750 (w), 685 (w) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 3.02 \) (s, 6 H, NCH\(_3\)), 3.81 (s, 3 H, OCH\(_3\)), 7.07 (br. s, 1 H, NH), 7.22 (dd, \( J = 9.1, 2.9 \) Hz, 1 H), 7.87 (d, \( J = 2.9 \) Hz, 1 H), 7.97 (d, \( J = 9.1 \) Hz, 1 H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta = 36.3 \) (2 × NCH\(_3\)), 55.9 (OCH\(_3\)), 113.6 (CH), 123.7 (CH), 133.6 (CH), 146.6 (C), 151.9 (C), 155.0 (C) ppm. HRMS (ESI), \( m/z \): [M + Na]+ calcd. for C\(_{9}\)H\(_{13}\)N\(_3\)NaO\(_2\): 218.0900; found: 218.0900.

3-(5-Cyanopyridin-2-yl)-1,1-dimethylurea (4n): From 3-cyanopyridine 1-oxide (1n) (120 mg, 1.00 mmol) and dimethylcyanamide (2a) (105 mg, 1.50 mmol), compound 4n (152 mg, 80%) was obtained according to GP1 as a yellowish solid, m.p. = 158.5–159.5 °C, \( R_f = 0.5 \) (EtOAc). IR (KBr, pellet): 3425 (m), 2225 (m), \( \tilde{\nu}_{max} \) 1675 (s), 1600 (m), 1580 (m), 1520 (s), 1470 (m), 1385 (m), 1370 (m), 1315 (m), 1270 (w), 1200 (w), 1170 (m), 1355 (w), 1110 (w), 1075 (w), 1020 (w), 950 (w), 850 (w), 750 (w), 580 (w) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 3.08 \) (s, 6 H, NCH\(_3\)), 7.50 (br. s, NH), 7.87 (d, \( J = 8.9 \) Hz, 1 H), 8.24 (d, \( J = 8.9 \) Hz, 1 H), 8.47 (d, \( J = 1.8 \) Hz, 1 H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta = 36.4 \) (2 × CH\(_3\)), 103.2 (CN), 112.5 (CH), 117.1 (C), 140.9 (CH), 151.4 (CH), 153.8 (C), 155.3 (C) ppm. HRMS (ESI), \( m/z \): [M + Na]+ calcd. for C\(_{9}\)H\(_{10}\)N\(_3\)NaO\(_2\): 213.0747; found: 213.0738.

3-(6-Bromopyridin-2-yl)-1,1-dimethylurea (4o): From 2-bromopyridine 1-oxide (1o) (174 mg, 1.00 mmol) and dimethylcyanamide (2a) (105 mg, 1.50 mmol),
compound 4o (167 mg, 68%) was obtained according to GP1 as a yellowish solid, m.p. = 96.1–96.3 °C (EtOAc/hexane), \( R_f = 0.55 \) (EtOAc). IR (KBr, pellet): \( \tilde{\nu}_{\text{max}} \) 3325 (m), 3050 (w), 2930 (w), 1680 (s), 1560 (s), 1595 (m), 1570 (s), 1525 (s), 1440 (s), 1395 (s), 1305 (m), 1265 (w), 1245 (w), 1190 (m), 1160 (m), 1130 (m), 1070 (w), 980 (w), 885 (w), 775 (s), 620 (m) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 3.03 \) (s, 6 H, NCH\(_3\)), 7.09 (d, \( J = 7.7 \) Hz, 1 H), 7.14 (br. s, 1 H, NH), 7.48 (dd, \( J = 8.3 \) Hz, 1 H), 8.03 (d, \( J = 8.3 \) Hz, 1 H) ppm. \(^1\)C NMR (101 MHz, CDCl\(_3\)): \( \delta = 36.2 \) (2 × CH\(_3\)), 111.2 (CH), 121.5 (CH), 138.5 (C), 140.0 (CH), 152.8 (C), 154.1 (C) ppm. HRMS (ESI), \( m/z \): [M + Na]\(^+\) calcd. for C\(_8\)H\(_{10}\)BrN\(_3\)NaO\(_2\): 265.9899; found: 265.9891.

3-(6-Chloropyridin-2-yl)-1,1-dimethylurea (4p): From 2-chloropyridine 1-oxide (1p) (130 mg, 1.00 mmol) and dimethylcyanamide (2a) (105 mg, 1.50 mmol), compound 4p (126 mg, 63%) was obtained according to GP1 as a pale yellow solid, m.p. = 73.2–74.1 °C (EtOAc/hexane), \( R_f = 0.55 \) (EtOAc). IR (KBr, pellet): \( \tilde{\nu}_{\text{max}} \) 3330 (m), 2930 (w), 1680 (s), 1660 (s), 1590 (s), 1570 (s), 1515 (m), 1440 (s), 1400 (s), 1305 (m), 1250 (m), 1180 (m), 1155 (s), 1135 (m), 985 (m), 780 (w), 750 (w), 625 (m) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 3.00 \) (s, 6 H, NCH\(_3\)), 6.90 (d, \( J = 7.6 \) Hz, 1 H), 7.18 (s, 1 H, NH), 7.54 (t, \( J = 8.1 \) Hz, 1 H), 7.96 (d, \( J = 8.3 \) Hz, 1 H) ppm. \(^1\)C NMR (101 MHz, CDCl\(_3\)): \( \delta = 36.3 \) (2 × CH\(_3\)), 110.9 (CH), 117.8 (CH), 140.5 (CH), 148.3 (C), 152.7 (C), 154.2 (C) ppm. HRMS (ESI), \( m/z \): [M + Na]\(^+\) calcd. for C\(_8\)H\(_{10}\)ClN\(_3\)NaO\(_2\): 222.0405; found: 222.0462.

3-(4-Cyanopyridin-2-yl)-1,1-dimethylurea (4q): From 4-cyanopyridine 1-oxide (1q) (120 mg, 1.00 mmol) and dimethylcyanamide (2a) (105 mg, 1.50 mmol), compound 4q (137 mg, 72%) was obtained according to GP1 as a pale yellow solid, m.p. = 98.5–99.1 °C, \( R_f = 0.25 \) (EtOAc, 5 : 1). IR (KBr, pellet): \( \tilde{\nu}_{\text{max}} \) 3440 (m), 3155 (w), 3105 (w), 3085 (w), 2935 (w), 2880 (w), 2821 (w), 2235 (w), 1675 (s), 1610 (m), 1555 (s), 1510 (s), 1415 (s), 1365 (s), 1295 (m), 1265 (m), 1215 (m), 1155 (s), 880 (w), 855 (w), 750 (w), 655 (w), 530 (w) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 3.06 \) (s, 6 H, NCH\(_3\)), 7.12 (dd, \( J = 5.1, 1.4 \) Hz, 1 H), 7.32 (br. s, 1 H, NH), 8.31 (dd, \( J = 5.1, 0.8 \) Hz, 1 H), 8.39 (dd, \( J = 1.4, 0.8 \) Hz, 1 H) ppm. \(^1\)C NMR (101 MHz, CDCl\(_3\)): \( \delta = 36.4 \) (2 × CH\(_3\)), 115.2 (CH), 116.7 (C), 119.4 (CH), 122.0 (C), 148.6 (CH), 153.5 (C), 154.1 (C) ppm. HRMS (ESI), \( m/z \): [M + Na]\(^+\) calcd. for C\(_9\)H\(_{10}\)N\(_4\)NaO\(_2\): 213.0747; found: 213.0749.

3-(2-Cyanopyridin-2-yl)-1,1-dimethylurea (4r): From 2-cyanopyridine 1-oxide (1r) (120 mg, 1.00 mmol) and dimethylcyanamide (2a) (105 mg, 1.50 mmol), compound 4r (158 mg, 83%) was obtained according to GP1 as a colorless solid,
m.p. = 122.1–122.5 °C, \( R_f = 0.50 \) (EtOAc). IR (KBr, pellet): \( \tilde{\nu}_{\text{max}} \) 3405 (m), 3120 (w), 3070 (w), 2945 (w), 2245 (w), 1670 (s), 1575 (s), 1530 (s), 1455 (s), 1400 (m), 1310 (m), 1170 (m), 985 (w), 800 (m), 755 (w), 625 (w), 550 (w), 460 (w) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 3.07 \) (s, 6 H, N\(\text{CH}_3\)), 7.27 (br. s, NH), 7.32 (dd, \( J = 7.5, 0.6 \) Hz, 1 H), 7.74 (dd, \( J = 8.5, 7.5 \) Hz, 1 H), 8.34 (dd, \( J = 8.5, 0.6 \) Hz, 1 H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta = 36.4 \) (2 × CH\(_3\)), 117.0 (CN), 117.1 (CH), 122.8 (CH), 130.9 (C), 138.7 (CH), 153.8 (C), 154.2 (C) ppm.

HRMS (ESI), \( m/z \) : [M + Na]\(^+\) calcd. for C\(_9\)H\(_{10}\)N\(_4\)NaO\(_3\): 213.0747; found: 213.0748.

**Methyl 2-(3,3-dimethylureido)isonicotinate (4s):** From 4-(methoxycarbonyl)pyridine 1-oxide (1s) (153 mg, 1.00 mmol) and dimethylcyanamide (2a) (105 mg, 1.50 mmol), compound 4s (176 mg, 79%) was obtained according to GP1 as a colorless solid, m.p. = 93.5–94.1 °C, \( R_f = 0.30 \) (EtOAc). IR (KBr, pellet): \( \tilde{\nu}_{\text{max}} \) 3365 (m), 3145 (w), 3085 (w), 3010 (w), 2950 (w), 1720 (s), 1665 (s), 1570 (s), 1535 (s), 1440 (m), 1415 (s), 1370 (m), 1310 (m), 1255(m), 1230 (m), 1170 (m), 1105 (m), 975 (w), 760 (m), 690 (w), 625 (m) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 3.07 \) (s, 6 H, N\(\text{CH}_3\)), 3.92 (s, 3 H, O\(\text{CH}_3\)), 7.25 (s, 1 H, NH), 7.50 (dd, \( J = 5.1, 1.5 \) Hz, 1 H), 8.31 (dd, \( J = 5.1, 0.7 \) Hz, 1 H), 8.61 (dd, \( J = 1.5, 0.7 \) Hz, 1 H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta = 36.4 \) (2 × CH\(_3\)), 52.4 (O\(\text{CH}_3\)), 112.7 (CH), 117.5 (CH), 139.3 (C), 148.0 (CH), 153.6 (C), 154.6 (C), 165.6 (C) ppm. HRMS (ESI), \( m/z \) : [M + H]\(^+\) calcd. for C\(_{10}\)H\(_{14}\)N\(_3\)O\(_3\): 224.1030; found: 224.1023.

From 2-methoxypyridine 1-oxide (1t) (500 mg, 4.00 mmol) and dimethylcyanamide (2a) (420 mg, 6.00 mmol), a mixture of 5t and 4t (702 mg, 5 : 1) was obtained according to GP1.

**3-(2-Methoxypyridin-3-yl)-1,1-dimethylurea (5t):** Recrystallization (2 times) of the mixture of 5t and 4t from Et\(_2\)O/hexane gave 5t (328 mg, 42%) as a colorless solid, m.p. = 72.9–73.1 °C, \( R_f = 0.30 \) (EtOAc). IR (KBr, pellet): \( \tilde{\nu}_{\text{max}} \) 3455 (m), 3115 (w), 3060 (w), 3020 (w), 2990 (w), 2955 (w), 2895 (w), 2850 (w), 1675 (s), 1600 (w), 1585 (w), 1520 (s), 1455 (s), 1400 (m), 1360 (m), 1290 (w), 1270 (w), 1245 (m), 1200 (w), 1170 (m), 1105 (m), 1020 (m), 795...
(m), 795 (m), 760 (w), 745 (w), 605 (w), 505 (w), 495 (w) cm⁻¹. **¹H NMR** (400 MHz, CDCl₃): δ = 3.01 (s, 6 H, NCH₃), 3.98 (s, 3 H, OCH₃), 6.84 (dd, J = 7.8, 5.0 Hz, 1 H, H-5), 6.92 (br. s, 1 H, NH), 7.73 (dd, J = 5.0, 1.6 Hz, 1 H, H-6), 8.38 (dd, J = 7.8, 1.6 Hz, 1 H, H-4) ppm. **¹³C NMR** (101 MHz, CDCl₃): δ = 36.2 (2 × NCH₃), 53.6 (OCH₃), 117.3 (CH, C-5), 124.2 (C, C-3), 125.0 (CH, C-4), 138.2 (CH, C-6), 152.7 (C, C-2), 155.3 (CO) ppm. **HRMS** (ESI), m/z: [M + H]⁺ calcd. for C₉H₁₄N₃O₂⁺: 196.1081; found: 196.1076.

3-(6-Methoxypyridin-2-yl)-1,1-dimethylurea (4t): Compound 4t was not isolated in pure form. NMR data extracted from the NMR spectra of the mixture of 5t and 4t. **¹H NMR** (400 MHz, CDCl₃): δ = 2.89 (s, 6 H, NCH₃), 3.69 (s, 3 H, OCH₃), 6.23 (dd, J = 7.9, 0.6 Hz, 1 H, H-5), 7.39 (t, J = 7.9 Hz, 1 H, H-4), 7.47 (dd, J = 7.9, 0.6 Hz, 1 H, H-3) ppm. **¹³C NMR** (101 MHz, CDCl₃): δ = 35.9 (2 × NCH₃), 53.0 (OCH₃), 103.2 (CH, C-5), 104.1 (CH, C-3), 140.3 (CH, C-4), 150.4 (C, C-2), 154.4 (CO) 162.4 (C, C-6) ppm.
2.2. Synthesis of the starting pyridine N-oxides 1

*General procedure for the N-oxidation of pyridine 1 (GP2)*

![Chemical Structure]

Aq. H₂O₂ (75 mL, 30 %) was added in one portion to the solution of the substituted pyridine (30 g) in glacial CH₃CO₂H (160 mL) and the mixture was stirred at 80 °C for 12 h. Solution was then cooled down and concentrated on a rotary evaporator. The residue was worked up in 2 different ways.

a) The residue was alkalized with saturated aq. Na₂CO₃ (100 mL) and solid K₂CO₃ until pH = 8, and the resulting solution was then extracted with EtOAc (4 × 75 mL). Combined organic fractions were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated on a rotary evaporator. The crude product was purified by vacuum distillation or recrystallization from a suitable solvent.

b) The residue was diluted with acetone (100 mL) and the precipitate was filtered off.

**4-Methylpyridine 1-oxide (1h):** From 4-methylpyridine (30.0 g, 322 mmol), compound 1h was obtained according to GP2a. Crude product was purified by recrystallization from acetone/hexane mixture to give 1h (16.6 g, 47%) as a pale gray solid, m.p. = 182–183 °C, lit.⁹ m.p. = 180–181 °C. ¹H NMR (400 MHz, CDCl₃): δ = 2.29 (s, 3 H, CH₃), 7.02 (m, 2 H), 8.04 (m, 2 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 20.1 (CH₃), 126.6 (2 × CH), 137.4 (C), 138.5 (2 × CH) ppm. HRMS (ESI), m/z: [M + H]+ calcd. for C₆H₈NO+: 110.0600; found: 110.0604.

**3-Methylpyridine 1-oxide (1i):** From 3-methylpyridine (33.0 g, 354 mol), compound 1i was obtained according to GP2a. Crude product was purified by vacuum distillation to give 1i (16.6 g, 43%) as a colorless liquid (b.p. = 132–134, 5 mbar), which was then crystallized in the freezer to form colorless solid, m.p. = 36.5–37.5 °C, lit.¹⁰ m.p. = 37–38 °C. ¹H NMR (400 MHz, CDCl₃): δ = 2.18 (s, 3 H, CH₃), 6.94–7.09 (m, 2 H), 7.90–7.98 (m, 2 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 18.0 (CH₃), 125.1 (CH), 126.9 (CH), 136.3 (CH), 136.6 (C), 139.0 (CH) ppm. HRMS (ESI), m/z: [M + Na]+ calcd. for C₆H₂NaNO+: 132.0420; found: 132.0415.

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2-Benzylpyridine 1-oxide (1j): From 2-benzylpyridine (15.0 g, 89.0 mmol), compound 1j was obtained according to GP2a. Crude product was purified by recrystallization from hexane to give 1j (11.8 g, 72%) as a colorless solid, m.p. = 99–100 °C, m.p. = 99–100 °C, lit.\textsuperscript{11} m.p. = 98–99 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 4.20\) (s, 2 H, CH\textsubscript{2}), 6.88 (m, 1 H), 7.03–7.10 (m, 2 H), 7.25–7.32 (m, 2 H), 8.21 (m, 1 H) ppm. \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): \(\delta = 36.2\) (CH\textsubscript{2}), 123.3 (CH), 125.1 (CH), 125.6 (CH), 126.8 (CH), 126.8 (2 × CH), 129.4 (2 × CH), 136.1 (C), 139.1 (CH), 151.6 (C) ppm. HRMS (ESI), \(m/z\): [M + Na]\textsuperscript{+} calcd. for C\textsubscript{12}H\textsubscript{11}NaNO\textsuperscript{+}: 208.0733; found: 208.0730.

3-Methoxypyridine 1-oxide (1m): From 3-methoxypyridine (4.00 g, 36.7 mmol), compound 1m was obtained according to GP2a. The crude product was purified by recrystallization from the mixture of acetone and hexane to give 1m (3.82 g, 83%) as a colorless solid, m.p. = 102.0–102.6 °C, lit.\textsuperscript{10} m.p. = 100–101 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 3.76\) (s, 3 H, OCH\textsubscript{3}), 6.80 (dd, \(J = 8.7, 1.9\) Hz, 1 H), 7.08 (dd, \(J = 8.7, 6.4\) Hz, 1 H), 7.79 (m, 1 H), 7.89 (t, \(J = 1.9\) Hz, 1 H) ppm. \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): \(\delta = 55.9\) (OCH\textsubscript{3}), 112.6 (CH), 125.2 (CH), 127.6 (CH), 132.2 (CH), 157.8 (C) ppm. HRMS (ESI), \(m/z\): [M + Na]\textsuperscript{+} calcd. for C\textsubscript{6}H\textsubscript{7}NNaO\textsubscript{2}: 148.0369; found: 148.0369.

3-Cyanopyridine 1-oxide (1n): From 3-cyanopyridine (15.0 g, 144 mmol), compound 1n was obtained according to GP2b. The crude product was purified by recrystallization from acetone to give 1n (12.5 g, 72%) as a colorless solid, m.p. = 176.5–177.0 °C, lit.\textsuperscript{10} m.p. = 174–175 °C. \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}): \(\delta = 7.60\) (ddd, \(J = 7.8, 6.6, 0.6\) Hz, 1 H), 7.81 (ddd, \(J = 0.9, 1.5, 7.8\) Hz, 1 H), 8.48 (ddd, \(J = 6.6, 1.9, 0.9\) Hz, 1 H), 8.86 (ddd, \(J = 1.9, 1.5, 0.6\) Hz, 1 H) ppm. \textsuperscript{13}C NMR (101 MHz, DMSO-d\textsubscript{6}): \(\delta = 112.0\) (C), 114.9 (C), 127.4 (CH), 128.3 (CH), 141.6 (CH), 143.2 (CH) ppm. HRMS (ESI), \(m/z\): [M + Na]\textsuperscript{+} calcd. for C\textsubscript{6}H\textsubscript{4}N\textsubscript{2}NaO\textsuperscript{+}: 143.0216; found: 143.0213.

2-Bromopyridine 1-oxide (1o): From 2-bromopyridine (15.0 g, 95.0 mmol), compound 1o was obtained according to GP2a. The crude product was purified by recrystallization from acetone/hexane mixture to give 1o (8.30 g, 50%) as a pale brown solid, m.p. = 62–63 °C, lit.\textsuperscript{12} m.p. = 132–135 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 7.02\) (ddd, \(J = 8.1, 7.5, 1.4\) Hz, 1 H), 7.17 (ddd, \(J = 7.5, 6.5, 1.9\) Hz, 1 H), 7.56 (ddd, \(J = 8.1, 1.9, 0.4\) Hz, 1 H), 8.25 (ddd, \(J = 6.5, 1.4, 0.4\) Hz, 1 H) ppm. \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): \(\delta = 124.5\) (CH), 125.5 (CH), 130.7 (CH), 132.6 (C), 140.1 ppm.

(CH) ppm. NMR data are consistent with previously reported.\textsuperscript{13} HRMS (ESI), \textit{m/z}: [M + H]\(^+\) calcd. for C\textsubscript{5}H\textsubscript{5}BrNO\(^+\): 173.9549; found: 173.9550.

\textbf{2-Chloropyridine 1-oxide (1p):} From 2-chloropyridine (30.0 g, 264 mmol), compound \textit{1p} was obtained according to GP2a. The crude product was purified by recrystallization from acetone/hexane mixture to give \textit{1p} (17.4 g, 51\%) as a pale gray solid, m.p. = 67–68 °C, lit.\textsuperscript{14} m.p. = 66–68 °C. \(^1\text{H} \text{NMR} \) (400 MHz, CDCl\(_3\)): \(\delta = 7.13–7.22 \) (m, 2 H), 7.46 (m, 1 H), 8.30 (m, 1 H) ppm. \(^{13}\text{C} \text{NMR} \) (101 MHz, CDCl\(_3\)): \(\delta = 123.9 \) (CH), 125.7 (CH), 127.1 (CH), 140.5 (CH), 141.9 (C) ppm. HRMS (ESI), \textit{m/z}: [M + H]\(^+\) calcd. for C\textsubscript{5}H\textsubscript{5}ClNO\(^+\): 130.0054; found: 130.0051.

\textbf{4-Cyanopyridine 1-oxide (1q):} From 4-cyanopyridine (15.0 g, 144 mmol), compound \textit{1q} was obtained according to GP2b. The crude product was purified by recrystallization from methanol to give \textit{1q} (11.7 g, 68\%) as a colorless solid, m.p. = 227–228 °C, lit.\textsuperscript{15} m.p. = 220–222 °C. \(^1\text{H} \text{NMR} \) (400 MHz, DMSO-\(d_6\)): \(\delta = 7.91 \) (m, 2 H), 8.38 (m, 2 H) ppm. \(^{13}\text{C} \text{NMR} \) (101 MHz, DMSO-\(d_6\)): \(\delta = 106.3 \) (C), 116.6 (C), 129.7 (2 \(\times\) CH), 140.0 (2 \(\times\) CH) ppm. HRMS (ESI), \textit{m/z}: [M + H]\(^+\) calcd. for C\textsubscript{6}H\textsubscript{5}N\textsubscript{2}O\(^+\): 121.0396; found: 121.0398.

\textbf{2-Cyanopyridine 1-oxide (1r):} From 2-cyanopyridine (15.0 g, 144 mmol), compound \textit{1r} was obtained according to GP2a. The crude product was purified by recrystallization from methanol to give \textit{1r} (10.8 g, 62\%) as a colorless solid, m.p. = 119–120 °C, lit.\textsuperscript{16} m.p. = 116 °C. \(^1\text{H} \text{NMR} \) (400 MHz, DMSO-\(d_6\)): \(\delta = 7.47 \) (td, \(J = 7.9, 1.0\) Hz, 1 H), 7.69 (ddd, \(J = 7.9, 6.7, 2.0\) Hz, 1 H), 8.08 (ddd, \(J = 7.9, 2.0, 0.5\) Hz, 1 H), 8.45 (ddd, \(J = 6.7, 1.0, 0.5\) Hz, 1 H) ppm. \(^{13}\text{C} \text{NMR} \) (101 MHz, DMSO-\(d_6\)): \(\delta = 112.6 \) (C), 124.5 (C), 125.3 (CH), 130.3 (CH), 132.1 (CH), 140.0 (CH) ppm. HRMS (ESI), \textit{m/z}: [M + H]\(^+\) calcd. for C\textsubscript{6}H\textsubscript{5}N\textsubscript{2}O\(^+\): 121.0396; found: 121.0401.

\textbf{4-Nitropyridine 1-oxide (1l):} A mixture of pyridine 1-oxide (10.2 g, 107 mmol), concentrated H\textsubscript{2}SO\(_4\) (22.7 mL, 417 mmol), and fumaring HNO\(_3\) (11.4 mL) was heated at 130 °C for 5 hours.


The resulting solution was poured into ice, alkalized with saturated aq. Na₂CO₃, and extracted with dichloromethane (3 × 30 mL). Combined organic fractions were dried over anhydrous Na₂SO₄ and concentrated on a rotary evaporator. The crude product was purified by recrystallization from acetone to give 1l (9.60 g, 64%) as a yellow solid, m.p. = 160.5–161.5 °C, lit.¹⁷ m.p. = 163 °C. ¹H NMR (400 MHz, CDCl₃): δ = 8.10 (m, 2 H), 8.25 (m, 2 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 120.8 (2 × CH), 140.1 (2 × CH), 142.1 (C) ppm. HRMS (ESI), m/z: [M + H]⁺ calcd. for C₅H₅N₂O₃+: 141.0295; found: 141.0290.

4-Methoxypyridine 1-oxide (1k): 4-Nitropyridine 1-oxide (1l) (3.00 g, 21.4 mmol) was added by portions to the freshly prepared solution of MeONa, which was obtained from Na (900 mg, 39.1 mmol) and methanol (100 mL). The resulting mixture was heated at 65 °C for 4 h, methanol was distilled off on a rotary evaporator and the residue was diluted with DCM (50 mL). Precipitate was filtered off, washed with DCM (50 mL), mother liquor was concentrated and the crude product was recrystallized from ethyl acetate/hexane mixture to give 1k (1.83 g, 68%) as a dark green solid, m.p. = 82.5–84.0 °C, lit.¹⁸ m.p. = 81.5–82.5 °C. ¹H NMR (400 MHz, CDCl₃): δ = 3.85 (s, 3 H, CH₃), 6.77–6.82 (m, 2 H), 8.09–8.14 (m, 2 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 56.0 (OCH₃), 111.6 (2 × CH), 139.9 (2 × CH), 157.8 (C) ppm. HRMS (ESI), m/z: [M + H]⁺ calcd. for C₆H₈NO₂⁺: 126.0550; found: 126.0554.

2-Methoxypyridine 1-oxide (1t): Solution of 2-chloropyridine 1-oxide (1p) (13.4 g, 103 mmol) in methanol (30 mL) was slowly added to the freshly prepared solution of MeONa, which was obtained from Na (2.62 g, 114 mmol) and methanol (45 mL). The resulting mixture was stirred under reflux for 2 h. Methanol was distilled off on a rotary evaporator, the residue was diluted with DCM (50 mL) and precipitate was filtered off. Mother liquor was concentrated and the crude product was recrystallized from ethyl acetate/hexane to give 1t (8.70 g, 67%) as a colorless solid, m.p. = 59–60 °C, lit.¹⁹ m.p. = 77–78 °C. ¹H NMR (400 MHz, CDCl₃): δ = 3.69 (s, 3 H, CH₃), 6.53–6.63 (m, 2 H), 6.94 (m, 1 H), 7.85 (d, J = 6.3 Hz, 1 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 56.4 (CH₃), 107.4 (CH), 116.8 (CH), 127.3 (CH), 139.0 (CH), 157.8 (C) ppm. HRMS (ESI), m/z: [M + H]⁺ calcd. for C₆H₅NO₂⁺: 126.0550; found: 126.0552.

**4-Carboxypyridine 1-oxide:** From 4-carboxypyridine (15.0 g, 122 mmol), 4-carboxypyridine 1-oxide (11.0 g, 65%) was obtained according to GP2b as a colorless solid, m.p. = 264–265 °C, lit.\(^ {20} \) m.p. = 258–259 °C. \(^ {1}H\) NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 7.81\) (m, 2 H), 8.28 (m, 2 H), 13.51 (br. s, 1 H, OH) ppm. \(^ {13}C\) NMR (101 MHz, DMSO-\(d_6\)): \(\delta = 126.7\) (C + CH), 139.3 (2 × CH), 164.8 (C) ppm. HRMS (ESI), \(m/z\): [M + H]\(^ +\) calcd. for C\(_6\)H\(_6\)NO\(_3\): 140.0342; found: 140.0345.

\(\text{4-(Methoxycarbonyl)pyridine 1-oxide (1s)}\): SOCl\(_2\) (40 mL) was added dropwise to the suspension of 4-Carboxypyridine 1-oxide (11.1 g, 79.4 mmol) in methanol (150 mL) and the resulting mixture was stirred at r.t. for 2 h. Solvent was distilled off on a rotary evaporator and the crude product was recrystallized from acetone/hexane to give 1s (8.75 g, 72%) as a colorless solid, m.p. = 106–107 °C, lit.\(^ {21} \) m.p. = 116.5–118.5 °C. \(^ {1}H\) NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 3.83\) (s, 3 H, CH\(_3\)), 7.89 (m, 2 H), 8.43 (m, 2 H) ppm. \(^ {13}C\) NMR (101 MHz, DMSO-\(d_6\)): \(\delta = 53.0\) (CH\(_3\)), 126.9 (CH), 127.6 (C), 139.8 (CH), 163.7 (C) ppm. HRMS (ESI), \(m/z\): [M + H]\(^ +\) calcd. for C\(_7\)H\(_8\)NO\(_3\): 154.0499; found: 154.0496.


2.3. Synthesis of the starting cyanamide 2c

Dipropylcyanamide (2c): Cyanamide (10.51 g, 250 mmol) was added in one portion to the solution of freshly prepared MeONa (13.5 g, 250 mmol) in MeOH (100 mL) and resulted mixture was stirred at r.t. for 15 h. Methanol was removed on a rotary evaporator, the residue was suspended in MeCN (100 mL) and 1-bromopropane (123 g, 1.00 mol) was added. Reaction mixture was stirred under reflux for 2 d, cooled down, and precipitate was filtered off. Vacuum distillation of the filtrate gave cyanamide 2c (6.02 g, 19%) as a colourless liquid, b.p. = 84–85 °C (10 mbar), lit.\(^2^2\) b.p. = 60 °C (1 Torr). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 0.96\) (t, \(J = 7.5\) Hz, 6 H, NCH\(_3\)), 1.66 (sextet, \(J = 7.5\) Hz, 4 H, CH\(_2\)CH\(_3\)), 2.94 (t, \(J = 7.5\) Hz, 4 H, NCH\(_2\)) ppm. \(^13\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 11.0\) (2 × CH\(_3\)), 21.0 (2 × CH\(_2\)CH\(_3\)), 53.2 (2 × NCH\(_2\)), 117.9 (CN) ppm. NMR data are consistent with previously reported.\(^2^3\) HRMS (ESI), \(m/z\): [M + Na]\(^+\) calcd. for C\(_7\)H\(_{14}\)N\(_2\)Na\(^+\): 149.1049; found: 149.1051.


### 2.4. Optimization of the reaction conditions (full data)

![ReactionDiagram]

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*– conversion of the starting material was estimated by ¹H NMR; †– molar ratio of target- and by-product
3 NMR spectra

3.1. Spectra of \(\text{N-pyridine-2-yl substituted ureas} \ 4\)
SI 28
NOESY NMR of 3-(4-Methoxypyridin-2-yl)-1,1-dimethylurea (4fa)
SI 37
$^1$H-$^{13}$C HSQC NMR of 3-(2-Methoxypyridin-3-yl)-1,1-dimethyl urea (5t):

$^1$H-$^{13}$C HMBC NMR of 3-(2-Methoxypyridin-3-yl)-1,1-dimethyl urea (5t):
$^1$H$^{15}$N HSQC NMR of 3-(2-Methoxypyridin-3-yl)-1,1-dimethylurea (5t):

$^1$H$^{15}$N HMBC NMR of 3-(2-Methoxypyridin-3-yl)-1,1-dimethylurea (5t):
$^1$H and $^{13}$C NMR spectra of the mixture of 3-(2-methoxypyridin-3-yl)-1,1-dimethylurea (5t, major) and 3-(6-methoxypyridin-2-yl)-1,1-dimethylurea (4t, minor):
$^1$H–$^{13}$C HSQC NMR of the mixture of 3-(2-methoxypyridin-3-yl)-1,1-dimethylurea (5t, major) and 3-(6-methoxypyridin-2-yl)-1,1-dimethylurea (4t, minor):

$^1$H–$^{13}$C HMBC NMR of the mixture of 3-(2-methoxypyridin-3-yl)-1,1-dimethylurea (5t, major) and 3-(6-methoxypyridin-2-yl)-1,1-dimethylurea (4t, minor):
$^1$H–$^{15}$N HSQC NMR of the mixture of 3-(2-methoxypyridin-3-yl)-1,1-dimethylurea (5t, major) and 3-(6-methoxypyridin-2-yl)-1,1-dimethylurea (4t, minor):

$^1$H–$^{15}$N HMBC NMR of the mixture of 3-(2-methoxypyridin-3-yl)-1,1-dimethylurea (5t, major) and 3-(6-methoxypyridin-2-yl)-1,1-dimethylurea (4t, minor):
3.2. Spectra of substituted pyridine 1-oxides 1

![Spectra of substituted pyridine 1-oxides 1](image-url)
3.3. Spectrum of cyanamide 2c
4 X-ray data

4.1. X-ray structure of 3-(6-Bromopyridin-2-yl)-1,1-dimethylurea (4α)

CCDC: 1473656

Table S1. Crystal data and structure refinement

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SI 59
Final R indexes [all data]  
\[ R_I = 0.0657, \quad wR_2 = 0.1016 \]

Largest diff. peak/hole / e Å\(^{-3}\)  
0.90/−0.84

**Table S2.** Fractional Atomic Coordinates (×10\(^4\)) and Equivalent Isotropic Displacement Parameters (Å\(^2\)×10\(^3\)). \(U_{eq}\) is defined as 1/3 of the trace of the orthogonalised \(U_{ij}\) tensor.

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**Table S3.** Anisotropic Displacement Parameters (Å\(^2\)×10\(^3\)). The Anisotropic displacement factor exponent takes the form: -2π\(^2\) [h\(^2\)a\(^2\)U\(_{11}\)+2hka*b*U\(_{12}\)+…]

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**Table S4.** Bond Lengths

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Table S5. Bond Angles

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<td>123.0(3)</td>
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<td>115.6(3)</td>
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<td>Br(1)</td>
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<td>N(3)</td>
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</tr>
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<td>C(6)</td>
<td>N(2)</td>
<td>121.4(3)</td>
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<td>C(6)</td>
<td>N(2)</td>
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<td>C(1)</td>
<td>C(2)</td>
<td>122.8(3)</td>
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<td>C(2)</td>
<td>C(1)</td>
<td>118.0(3)</td>
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Table S6. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3)

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
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<th>z</th>
<th>U(eq)</th>
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</thead>
<tbody>
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<td>H(2)</td>
<td>2036</td>
<td>2758</td>
<td>7018</td>
<td>17</td>
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<tr>
<td>H(4)</td>
<td>7979</td>
<td>4915</td>
<td>5925</td>
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<td>H(2A)</td>
<td>7040</td>
<td>3104</td>
<td>4654</td>
<td>19</td>
</tr>
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<td>H(7A)</td>
<td>-2696</td>
<td>1415</td>
<td>4710</td>
<td>26</td>
</tr>
<tr>
<td>H(7B)</td>
<td>-71</td>
<td>892</td>
<td>5170</td>
<td>26</td>
</tr>
<tr>
<td>H(7C)</td>
<td>634</td>
<td>1392</td>
<td>4083</td>
<td>26</td>
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<td>H(3)</td>
<td>9018</td>
<td>4125</td>
<td>4418</td>
<td>22</td>
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<td>H(8A)</td>
<td>2206</td>
<td>1699</td>
<td>7781</td>
<td>35</td>
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<tr>
<td>H(8B)</td>
<td>-378</td>
<td>1185</td>
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<td>H(8C)</td>
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<td>1903</td>
<td>7395</td>
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</table>
4.2. X-ray structure of 3-(6-Chloropyridin-2-yl)-1,1-dimethylurea (4p)

CCDC: 1473657

Table S7. Crystal data and structure refinement for
Empirical formula \( \text{C}_8\text{H}_{10}\text{ClN}_3\text{O} \)
Formula weight 199.64
Temperature/K 100.01(10)
Crystal system monoclinic
Space group \( \text{P}2_1/c \)
a/Å 4.1274(3)
b/Å 20.8167(12)
c/Å 10.4887(6)
\( \alpha/^{\circ} \) 90
\( \beta/^{\circ} \) 95.909(5)
\( \gamma/^{\circ} \) 90
Volume/Å\(^3\) 896.38(9)
\( Z \) 4
\( \rho_{\text{calc}}/\text{g/cm}^3 \) 1.479
\( \mu/\text{mm}^{-1} \) 0.387
\( F(000) \) 416.0
Crystal size/mm\(^3\) 0.28 × 0.2 × 0.12
Radiation MoK\( \alpha \) (\( \lambda = 0.71073 \))
2\( \Theta \) range for data collection/° 5.528 to 58.2
Index ranges \(-5 \leq h \leq 5, -28 \leq k \leq 16, -13 \leq l \leq 8 \)
Reflections collected 4077
Independent reflections 2078 [\( R_{\text{int}} = 0.0240, R_{\text{sigma}} = 0.0470 \)]
Data/restraints/parameters 2078/0/120
Goodness-of-fit on \( F^2 \) 1.075
Final R indexes [\( I \geq 2\sigma (I) \)] \( R_1 = 0.0416, wR_2 = 0.0926 \)
Final R indexes [all data] \( R_1 = 0.0552, wR_2 = 0.1028 \)
Largest diff. peak/hole / e Å\(^{-3}\) 0.37/-0.43
Table S8. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{Å}^2 \times 10^3$). $U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$ tensor.

<table>
<thead>
<tr>
<th>Atom</th>
<th>$x$</th>
<th>$y$</th>
<th>$z$</th>
<th>$U_{eq}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl$^{(1)}$</td>
<td>5537.8(12)</td>
<td>4909.1(2)</td>
<td>1674.0(5)</td>
<td>22.90(16)</td>
</tr>
<tr>
<td>O$^{(1)}$</td>
<td>7371(3)</td>
<td>2415.9(7)</td>
<td>5469.6(12)</td>
<td>19.1(3)</td>
</tr>
<tr>
<td>N$^{(1)}$</td>
<td>5908(4)</td>
<td>3763.9(8)</td>
<td>2691.8(15)</td>
<td>16.0(3)</td>
</tr>
<tr>
<td>N$^{(3)}$</td>
<td>9078(4)</td>
<td>1742.1(8)</td>
<td>3978.3(15)</td>
<td>18.0(4)</td>
</tr>
<tr>
<td>N$^{(2)}$</td>
<td>6651(4)</td>
<td>2719.8(8)</td>
<td>3356.9(15)</td>
<td>16.6(4)</td>
</tr>
<tr>
<td>C$^{(6)}$</td>
<td>7712(4)</td>
<td>2293.2(9)</td>
<td>4338.8(18)</td>
<td>15.5(4)</td>
</tr>
<tr>
<td>C$^{(1)}$</td>
<td>5346(4)</td>
<td>3323.5(9)</td>
<td>3576.1(17)</td>
<td>14.7(4)</td>
</tr>
<tr>
<td>C$^{(2)}$</td>
<td>3553(4)</td>
<td>3460(1)</td>
<td>4603.4(18)</td>
<td>17.8(4)</td>
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<tr>
<td>C$^{(5)}$</td>
<td>4736(4)</td>
<td>4344.7(10)</td>
<td>2836.6(17)</td>
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<tr>
<td>C$^{(4)}$</td>
<td>3008(4)</td>
<td>4542.3(10)</td>
<td>3829.0(19)</td>
<td>20.0(4)</td>
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<tr>
<td>C$^{(7)}$</td>
<td>10476(5)</td>
<td>1302.7(10)</td>
<td>4973.0(18)</td>
<td>19.7(4)</td>
</tr>
<tr>
<td>C$^{(3)}$</td>
<td>2424(4)</td>
<td>4077.4(10)</td>
<td>4718.1(19)</td>
<td>21.9(5)</td>
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<tr>
<td>C$^{(8)}$</td>
<td>9736(5)</td>
<td>1594.7(11)</td>
<td>2674.8(18)</td>
<td>23.5(5)</td>
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</table>

Table S9. Anisotropic Displacement Parameters ($\text{Å}^2 \times 10^3$). The Anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2a^2U_{11} + 2hka*b*U_{12} + \ldots]$.

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<tr>
<th>Atom</th>
<th>$U_{11}$</th>
<th>$U_{22}$</th>
<th>$U_{33}$</th>
<th>$U_{12}$</th>
<th>$U_{13}$</th>
<th>$U_{23}$</th>
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<td>33.5(3)</td>
<td>16.1(3)</td>
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<td>-0.8(3)</td>
<td>1.7(3)</td>
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<tr>
<td>O$^{(1)}$</td>
<td>30.9(7)</td>
<td>18.3(7)</td>
<td>8.2(7)</td>
<td>1.6(7)</td>
<td>1.6(7)</td>
<td>0.8(7)</td>
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<td>N$^{(1)}$</td>
<td>20.9(8)</td>
<td>16.0(8)</td>
<td>11.0(8)</td>
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<td>0.9(6)</td>
<td>-0.6(7)</td>
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<tr>
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<td>18.1(9)</td>
<td>9.6(8)</td>
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<td>1.8(6)</td>
<td>4.8(7)</td>
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<td>N$^{(2)}$</td>
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<td>14.4(8)</td>
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<td>15.1(9)</td>
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</tr>
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<td>20.6(11)</td>
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<td>18.8(8)</td>
<td>15.7(9)</td>
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Table S10. Bond Lengths

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Table S11. Bond Angles

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<td>N(3)</td>
<td>C(8)</td>
<td>124.53(17)</td>
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<td>115.98(14)</td>
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Table S12. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3)

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<td>20</td>
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<td>5191</td>
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<td>H(4)</td>
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<td>4963</td>
<td>3894</td>
<td>24</td>
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<td>1364</td>
<td>5105</td>
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<td>30</td>
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<td>H(8C)</td>
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</table>
### 4.3. X-ray structure of 3-(2-Methoxypyridin-3-yl)-1,1-dimethylurea (5t)

![X-ray structure diagram]

**CCDC: 1473655**

**Table S13. Crystal data and structure refinement**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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</tr>
<tr>
<td>Temperature/K</td>
<td>100.01(10)</td>
</tr>
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<td>Crystal system</td>
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</tr>
<tr>
<td>Space group</td>
<td>P2₁/c</td>
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<td>7.3261(5)</td>
</tr>
<tr>
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</tr>
<tr>
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<tr>
<td>β/°</td>
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</tr>
<tr>
<td>γ/°</td>
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</tr>
<tr>
<td>Volume/Å³</td>
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</tr>
<tr>
<td>Z</td>
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</tr>
<tr>
<td>(\rho_{\text{calc}})/g/cm³</td>
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</tr>
<tr>
<td>(\mu)/mm⁻¹</td>
<td>0.099</td>
</tr>
<tr>
<td>F(000)</td>
<td>832.0</td>
</tr>
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<td>Crystal size/mm³</td>
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</tr>
<tr>
<td>Radiation</td>
<td>MoKα (λ = 0.71073)</td>
</tr>
<tr>
<td>2θ range for data collection/°</td>
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</tr>
<tr>
<td>Index ranges</td>
<td>-9 ≤ h ≤ 10, -27 ≤ k ≤ 27, -17 ≤ l ≤ 18</td>
</tr>
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Reflections collected: 29572
Independent reflections: 4907 [R_{int} = 0.0493, R_{sigma} = 0.0394]
Data/restraints/parameters: 4907/0/259
Goodness-of-fit on F^2: 1.050
Final R indexes [I>=2σ(I)]: R_1 = 0.0542, wR_2 = 0.1212
Final R indexes [all data]: R_1 = 0.0737, wR_2 = 0.1325
Largest diff. peak/hole / e Å^-3: 0.32/-0.25

### Table S14. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3)

The Equivalent Isotropic Displacement factor exponent takes the form: -2π^2 [h^2 a^2 * U_{11} + 2hka*b* U_{12} + ...]

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### Table S15. Anisotropic Displacement Parameters (Å^2×10^3)

The Anisotropic displacement factor exponent takes the form: -2π^2 [h^2 a^2 * U_{11} + 2hka*b* U_{12} + ...]

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Table S18. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3)

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