Supplementary Information

Mechanosynthesis of pharmaceutically relevant sulfonyl-(thio)ureas

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Table of contents

1. Experimental Section 1
   1.1 Mechanosynthesis by copper-catalysed coupling 2
   1.2 Base-assisted mechanosynthesis using K₂CO₃ 2
   1.3 Gram-scale synthesis 2
   1.4 Pathway B for the synthesis of tolbutamide (1a) 3
2. Summary of ¹H and ¹³C NMR and HR-MS data 3
3. Selected Fourier-transform attenuated total reflectance (FTIR-ATR) spectra 6
4. Selected ¹H and ¹³C NMR spectra 13

1. Experimental Section

Mechanosynthesis of sulfonyl-(thio)ureas was carried out in a Retsch MM400 mill at a frequency of 30 Hz using a 10 mL stainless steel milling jar and a single ball made of the same material (10 mm diameter). Gram-scale synthesis reactions were carried out in a 25 mL stainless steel milling jar. ¹H and ¹³C NMR spectra were recorded on a Varian MERCURY plus-300 or plus-400 spectrometer (300 or 400 MHz) with chemical shifts (δ) given in parts per million (ppm). The molecular weights of the pure products were determined using high-resolution mass spectra (HRMS). FT-IR spectra were collected using a Fourier Transform-Infrared Attenuated Total Reflection PerkinElmer UATR Two spectrometer in the range 400 cm⁻¹ to 4000 cm⁻¹.
1.1 Mechanosynthesis by copper-catalysed coupling

A mixture of 0.50 mmol of sulfonamide, 0.50 mmol isocyanate (1 equiv), 0.025 mmol (5% mol) of CuCl and nitromethane as the grinding liquid (η= 0.25 mL mg⁻¹) was milled at a frequency of 30 Hz for 2 hrs. After the reaction, 3 mL of deionized water and 20 mg of Na₂H₂EDTA-2H₂O were added to the green coloured crude mixture which was then milled for further 10 minutes at a frequency of 25 Hz. The resulting white product was purified by vacuum filtration and dried in air in all cases, except for glibenclamide 3b where the formation of the sideproduct dicyclohexylurea requires chromatography.

1.2 Base-assisted mechanosynthesis using K₂CO₃

A mixture of 0.50 mmol of sulfonamide and 0.50 mmol of K₂CO₃ (1 equiv) was milled at a frequency of 30 Hz for 1hr. Then, 0.50 mmol isocyanate or isothiocyanate (1 equiv) was added and subsequently milled for another 2 hrs at 30 Hz. 20 mL of deionized water and dilute HCl was added to the crude mixture. The pH of the resultant suspension was set to pH=3 using pH paper and left to stir for 15 mins. The product was isolated via vacuum filtration and dried in air in all cases, except for the sulfonyl-urea 1d where the formation of the sideproduct diphenylurea requires chromatography.

1.3 Gram-scale synthesis

For gram-scale synthesis of tolbutamide (1a) 5.0 mmol of sulfonamide, 5.0 mmol isocyanate (1 equiv), 0.25 mmol (5% mol) of CuCl and nitromethane as the grinding liquid (η= 0.25 mL mg⁻¹) was milled at a frequency of 30 Hz for 2 hrs. The reaction was carried out using two 10 mm diameter stainless steel balls in a 25 mL stainless steel jar. After the reaction, 15 mL of deionised water and 200 mg of Na₂H₂EDTA.2H₂O were added to the green coloured crude mixture which was then milled for 10 minutes more at a frequency of 25 Hz. The white product was purified via vacuum filtration and dried in air.

For the gram-scale synthesis of 1b, a mixture of 5.0 mmol of sulfonamide and 5.0 mmol of K₂CO₃ (1 equiv) was milled at a frequency of 30 Hz for 1 hour. Then, 5.0 mmol isothiocyanate (1 equiv) was added and subsequently milled for another 2 hrs at 30 Hz.
mL of deionized water and dilute HCl were added to the crude mixture. The pH of the resultant suspension was set to pH=3 using pH paper and left to stir for 15 mins. The product was purified via vacuum filtration and dried in air.

1.4 Pathway B for the synthesis of tolbutamide (1a)

The mechanosynthesis of tolbutamide 1a (93% yield) was also explored by milling p-toluenesulfonyl-isocyanate and n-butyl-amine (retrosynthetic pathway B in the main paper). The high reactivity and moisture sensitive nature of p-toluenesulfonyl-isocyanate meant that reaction mixture preparation had to be done in a glovebox. Sulfonyl-isocyanates (mostly liquids) in general are less ideal, in terms of ease of handling and toxicity, as compared to sulfonamides (mostly solids).

2. Summary of 1H and 13C NMR and HR-MS data

N-(butylcarbamoyl)-4-methylbenzenesulfonamide 1a

White powder (92% yield); 1H-NMR (400 MHz, DMSO-d6) δ 0.79 (t, J = 7.20 Hz, 3H), δ 1.11-1.18 (m, 2H), δ 1.23-1.30 (m, 2H), δ 2.37 (s, 3H), δ 2.88-2.93 (m, 2H), δ 6.41 (t, J = 5.80 Hz, 1H), δ 7.38 (d, J = 8.00 Hz, 2H), 7.75 (d, J = 7.6 Hz, 2H), δ 10.45 (s, 1H); 13C-NMR (300 MHz, DMSO-d6) δ 14.0, 19.7, 21.5, 31.7, 39.2, 127.6, 129.8, 137.9, 143.9, 151.7. HRMS: Calculated for C12H18N2NaO3S [M+Na]: 293.0930; measured: 293.0925.

4-methyl-N-(phenylcarbamothioyl)benzenesulfonamide 1b

White powder (91% yield); 1H-NMR (400 MHz, DMSO-d6) δ 2.38 (s, 3H), δ 7.16 (t, J = 7.26 Hz, 1H), δ 7.39-7.43 (m, 4H), δ 7.28-7.36 (m, 2H), δ 7.81 (d, J = 8.37 Hz, 2H), δ 10.14 (s, 1H); 13C-NMR (300 MHz, DMSO-d6) δ 21.5, 119.4, 124.5, 126.2, 128.2, 129.0, 129.9, 138.5, 144.3, 178.0; HRMS: Calculated for C14H14N2NaO2S2 [M+Na]: 329.0389; measured: 329.0390.
4-methyl-N-(4-nitrophenoxy)carbamothioyl)benzenesulfonamide 1c

Yellow powder (80% yield); \textsuperscript{1}H-NMR (400 MHz, DMSO-\textit{d6}) \(\delta\) 2.31 (s, 3H), \(\delta\) 7.18 (d, \(J = 8.12\) Hz, 2H), \(\delta\) 7.63 (d, \(J = 8.40\) Hz, 2H), \textit{7.95-8.04} (m, 4H), \(\delta\) 9.66 (s, 1H); \textsuperscript{13}C-NMR (300 MHz, DMSO-\textit{d6}) \(\delta\) 21.1, 118.6, 124.9, 127.9, 128.3, 140.0, 142.1, 147.8, 183.0; \textbf{HRMS}: Calculated for C\(_{14}\)H\(_{12}\)N\(_3\)O\(_4\)S\(_2\) [M+Na]: 350.0275; measured: 350.0272.

4-methyl-N-(phenylcarbamoyl)benzenesulfonamide 1d

\textsuperscript{1}H-NMR (400 MHz, DMSO-\textit{d6}) \(\delta\) 2.37, \(\delta\) 2.37 \(\delta\) 2.37 \(\delta\) 6.99 (t, \(J = 4.00\) Hz, 1H), \(\delta\) 7.20-7.33 (m, 2H), \(\delta\) 7.82 (d, \(J = 7.84\) Hz, 2H), \(\delta\) 8.78 (s, 1H), \(\delta\) 10.63 (s, 1H); \textsuperscript{13}C-NMR (300 MHz, DMSO-\textit{d6}) \(\delta\) 21.5, 119.3, 123.5, 126.1, 127.9, 129.9, 137.7, 138.6, 144.1, 150.0 ppm. \textbf{HRMS}: Calculated for C\(_{14}\)H\(_{14}\)N\(_2\)NaO\(_3\)S [M+Na]: 313.0617; measured: 313.0614.

N-(cyclohexylcarbamoyl)-4-methylbenzenesulfonamide 1e

White powder (88% yield); \textsuperscript{1}H-NMR (400 MHz, DMSO-\textit{d6}) \(\delta\) 1.02-1.25 (m, 5H), \(\delta\) 1.22-1.66 (m, 5H), \(\delta\) 2.37 (s, 3H), \(\delta\) 3.25 (d, \(J = 7.28\) Hz, 1H), \(\delta\) 6.30 (d, \(J = 8.40\) Hz, 1H), \(\delta\) 7.38 (d, \(J = 8.00\) Hz, 2H), \(\delta\) 7.75 (d, \(J = 7.60\) Hz, 2H), \(\delta\) 10.26 (s, 1H); \textsuperscript{13}C-NMR (300 MHz, DMSO-\textit{d6}) \(\delta\) 21.5, 24.6, 25.4, 32.7, 48.5, 127.6, 129.9, 137.9, 144.0, 150.9. \textbf{HRMS}: Calculated for C\(_{14}\)H\(_{20}\)N\(_2\)NaO\(_3\)S [M+Na]: 319.1087; measured: 319.1082.

4-methyl-N-(propylcarbamoyl)benzenesulfonamide 1f

White powder (86% yield) \textsuperscript{1}H-NMR (400 MHz, DMSO-\textit{d6}) \(\delta\) 0.73 (t, \(J = 7.00\) Hz, 3H), \(\delta\) 1.28-1.32 (m, 2H), \(\delta\) 2.37 (s, 3H), \(\delta\) 2.84-2.91 (m, 2H), \(\delta\) 6.42 (t, \(J = 5.80\) Hz, 1H), \(\delta\) 7.38 (d, \(J = 8.00\) Hz, 2H), \(\delta\) 7.75 (d, \(J = 7.60\) Hz, 2H), \(\delta\) 10.46 (s, 1H); \textsuperscript{13}C-NMR (300 MHz, DMSO-\textit{d6}) \(\delta\) 11.4, 21.4, 23.0, 41.2, 127.6, 129.7, 137.7, 143.7, 151.7; \textbf{HRMS}: Calculated for C\(_{11}\)H\(_{16}\)N\(_2\)NaO\(_3\)S [M+Na]: 279.0774; measured: 279.0764.
4-chloro-N-(propylcarbamoyl)benzenesulfonamide 2a

![Chemical structure of 2a]

White powder (92% yield); $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ 0.73 (t, $J = 7.48$Hz, 3H), $\delta$ 1.26-1.35 (m, 2H) $\delta$ 2.85-2.89 (m, 3H), $\delta$ 6.51 (t, $J = 5.80$Hz, 1H), $\delta$ 7.67 (d, $J = 8.36$Hz, 2H), $\delta$ 7.88 (d, $J = 7.96$Hz, 2H), $\delta$ 10.66 (s, 1H); $^{13}$C-NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.5, 22.9, 41.4, 129.6, 129.7, 138.5; HRMS: Calculated for C$_{10}$H$_{13}$ClN$_2$NaO$_3$S [M+Na]: 299.0228; measured: 299.0229.

N-(butylcarbamoyl)-4-chlorobenzenesulfonamide 2b

![Chemical structure of 2b]

Off-white powder (92% yield); $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ 0.79 (t, $J = 7.20$Hz, 3H), $\delta$ 1.10-1.18 (m, 2H), $\delta$ 1.22-1.30 (m, 2H), $\delta$ 2.88-2.93 (m, 2H), $\delta$ 6.50 (t, $J = 5.80$Hz, 1H), $\delta$ 7.67 (d, $J = 8.00$Hz, 2H), 7.88 (d, $J = 8.00$Hz, 2H), 7.47-7.50 (m, 1H), $\delta$ 10.64 (s, 1H); $^{13}$C-NMR (300 MHz, DMSO-$d_6$) $\delta$ 13.9, 19.7, 31.1, 31.7, 129.6, 129.7, 138.4, 151.7; HRMS: Calculated for C$_{11}$H$_{15}$ClN$_2$NaO$_3$S [M+Na]: 313.0376; measured: 313.0376.

4-chloro-N-(cyclohexylcarbamoyl)benzenesulfonamide 2c

![Chemical structure of 2c]

White powder (91% yield); $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.03-1.22 (m, 5H), $\delta$ 1.46-1.66 (m, 5H), $\delta$ 3.26 (d, $J = 7.28$Hz, 1H), $\delta$ 6.39 (d, $J = 8.40$Hz, 1H), $\delta$ 7.66 (d, $J = 8.28$Hz, 2H), $\delta$ 7.88 (d, $J = 8.64$Hz, 2H), $\delta$ 10.44 (s, 1H); $^{13}$C-NMR (300 MHz, DMSO-$d_6$) $\delta$ 24.6, 25.4, 32.7, 48.6, 129.6, 129.7, 138.4; HRMS: Calculated for C$_{13}$H$_{17}$ClN$_2$NaO$_3$S [M+Na]: 339.0541; measured: 339.0541.

5-chloro-2-methoxy-N-(4-sulfamoylphenethyl)benzamide 3a

![Chemical structure of 3a]

White powder (74% yield); $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.89 (t, $J = 7.04$Hz, 2H), $\delta$ 3.48-3.53 (m, 2H), $\delta$ 3.79 (s, 3H), $\delta$ 7.14 (d, $J = 8.96$Hz, 2H), $\delta$ 7.29 (s, 2H), $\delta$ 7.43 (d, $J = 8.24$Hz, 2H), $\delta$ 7.47-7.50 (m, 1H), $\delta$ 7.62 (d, $J = 2.48$Hz, 1H), $\delta$ 7.74 (d, $J = 8.12$Hz, 2H), $\delta$ 8.25 (t, $J = 5.52$Hz, 1H); $^{13}$C-NMR (300 MHz, DMSO-$d_6$) $\delta$ 35.1, 56.7, 114.6, 124.8, 125.3, 126.1, 129.6, 130.0, 131.2, 142.5, 144.1, 156.1, 164.0. HRMS: Calculated for C$_{16}$H$_{17}$ClN$_2$NaO$_3$S [M+Na]: 391.0490; measured: 391.0478.
5-chloro-N-(4-(N-(cyclohexylcarbamoyl)sulfamoyl)phenethyl)-2-methoxybenzamide 3b

White powder; $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 1.03-1.22 (m, 5H), δ 1.46-1.66 (m, 5H), 2.89 (t, $J$ = 7.04Hz, 2H), $\delta$ 3.26 (d, $J$ = 7.28Hz, 1H), δ 3.48-3.53 (m, 2H), δ 3.79 (s, 3H) δ 7.14 (d, $J$ = 8.96Hz, 2H), δ 7.43 (d, $J$ = 8.24Hz, 2H), δ 7.47-7.50 (m, 1H), δ 7.62 (d, $J$ = 2.84Hz, 1H), δ 7.74 (d, $J$ = 8.12Hz, 2H), δ 8.25 (t, $J$ = 5.52Hz, 1H); $^{13}$C-NMR (300 MHz, DMSO-$d_6$) δ 24.6, 25.4, 31.2, 32.7, 35.1, 48.5, 56.7, 114.6, 124.7, 125.3, 127.7, 129.8, 129.9, 131.9, 138.6, 145.7, 150.8, 156.1, 164.0; HRMS: Calculated for C$_{23}$H$_{28}$ClN$_3$O$_5$S [M+Na]: 516.1330; measured: 516.1331.

3. Selected Fourier-transform attenuated total reflectance (FTIR-ATR) spectra

According to powder X-ray diffraction the crude reaction mixtures were amorphous and we were not able to detect product formation by solid-state diffraction methods. However, comparisons of FTIR-ATR spectra of crude reaction mixtures from both base-assisted and copper-catalysed reactions showed that all of the iso(thio)cyanate had been consumed by the disappearance of the characteristic absorption band around 2200 cm$^{-1}$.

![Figure S1. FTIR-ATR spectra for n-butylisocyanate reactant and the freshly prepared crude reaction mixture from the synthesis of tolbutamide (1a) via base-assisted and copper-catalysed routes. The disappearance of the isocyanate stretching band at 2200 cm$^{-1}$ is evident in both cases.](image-url)
Figure S2. FTIR-ATR spectra for phenyl-isothiocyanate reactant and the freshly prepared crude reaction mixture from the synthesis of the sulfonil-thiourea 1d via base-assisted mechanochemical route. The disappearance of the thioisocyanate stretching band at ca. 2000 cm$^{-1}$ is evident.

Figure S3. FTIR-ATR spectra for cyclohexyl-isocyanate reactant and the freshly prepared crude reaction mixture from the synthesis of glibenclamide (3b) via copper-catalysed mechanochemical route. The disappearance of the isocyanate stretching band at ca. 2000 cm$^{-1}$ is evident.
FTIR-ATR spectrum of N-(butylcarbamoyl)-4-methylbenzenesulfonamide 1a

FTIR-ATR spectrum of 4-methyl-N-(phenylcarbamothioyl)benzenesulfonamide 1b
FTIR-ATR spectrum of 4-methyl-N-(4-nitrophenylcarbamothioyl)benzenesulfonamide 1c

FTIR-ATR spectrum of 4-methyl-N-(phenylcarbamoyl)benzenesulfonamide 1d
FTIR-ATR spectrum of \( N \)-(cyclohexylcarbamoyl)-4-methylbenzenesulfonamide 1e

FTIR-ATR spectrum of 4-methyl-\( N \)-(propylcarbamoyl)benzenesulfonamide 1f
FTIR-ATR spectrum of 4-chloro-N-(propylcarbamoyl)benzenesulfonamide 2a

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N-(butylcarbamoyl)-4-chlorobenzenesulfonamide 2b

Electronic Supplementary Material (ESI) for Chemical Communications
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4-chloro-N-(cyclohexylcarbamoyl)benzenesulfonamide 2c
4. Selected $^1$H and $^{13}$C NMR spectra

![NMR spectra](image)

**Figure S4.** $^1$H (top) and $^{13}$C (bottom) NMR spectra for sulfonyl-urea 1a (tolbutamide).
Figure S5. $^1$H (top) and $^{13}$C (bottom) NMR spectra for sulfonyl-thiourea 1b.
Figure S6. $^1$H (top) and $^{13}$C (bottom) NMR spectra for sulfonyl-thiourea 1c.
Figure S7. $^1$H (top) and $^{13}$C (bottom) NMR spectra for sulfonyl-urea 1d. In this case the competing side-reaction of isocyanate coupling to form diphenylurea was difficult to avoid and the crude product contained 93% yield of 1d, calculated from the $^1$H NMR spectrum.
Figure S8. $^1$H (top) and $^{13}$C (bottom) NMR spectra for sulfonyl-urea 1e.
Figure S9. $^1$H (top) and $^{13}$C (bottom) NMR spectra for sulfonyle-urea 1f.
Figure S10. $^1$H (top) and $^{13}$C (bottom) NMR spectra for sulfonil-urea 2a (chlorpropamide).
Figure S11. $^1$H (top) and $^{13}$C (bottom) NMR spectra for sulfonyl-urea 2b.
Figure S12. $^1$H (top) and $^{13}$C (bottom) NMR spectra for sulfonyl-urea 2c.
Figure S13. $^1$H (top) and $^{13}$C (bottom) NMR spectra for the glibenclamide precursor $3a$, obtained by mechanochemical amide synthesis.
**Figure S14.** $^1$H (top) and $^{13}$C (bottom) NMR spectra for glibenclamide (3b) obtained by mechanochemical amide coupling and mechanochemical copper-catalysed coupling.