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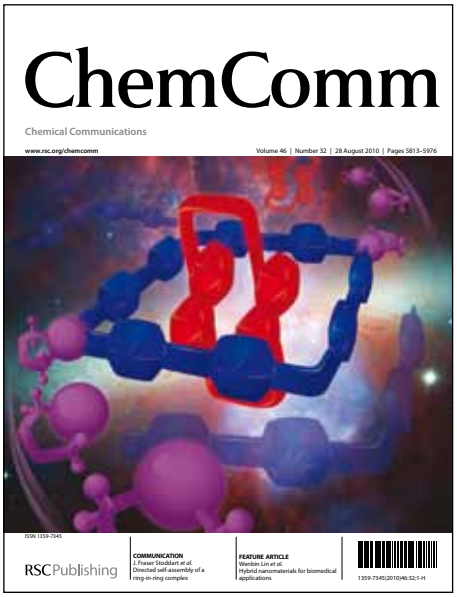

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ARTICLE TYPE

Mechanosynthesis of pharmaceutically relevant sulfonyl-(thio)ureas

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We demonstrate the first application of mechanochemistry to conduct the synthesis of sulfonyl-(thio)ureas, including known anti-diabetic drugs tolbutamide, chlorpropamide and glibenclamide, in good to excellent isolated yields by either stoichiometric base-assisted or copper-catalysed coupling of sulfonamides and iso(thio)cyanates.

Mechanochemical reactions,[1] induced or sustained by mechanical force, represent one of the most successful modes of solvent-free synthesis. Whereas mechanochemistry has led to important improvements across chemical synthesis (*e.g.* pharmaceutical materials, metallodrugs,[2] metal-organic frameworks,[3] nanoparticles[4]), organic synthesis is one of the most rapidly developing areas of its application.[5] Several groups have demonstrated the potential of mechanochemistry in important areas of organic chemistry, including organo-[6] and transition metal-catalysed reactions,[7] (oligo)peptide synthesis[8] and enantioselective transformations.[9] Importantly, Bonnamour *et al.* have recently demonstrated the synthesis of a relatively complex molecular target Leu-enkephaline[10] using exclusively solvent-free synthetic steps. Recently, we used mechanochemistry for solvent-free click coupling of amines with iso(thio)cyanates to form (thio)ureas, providing a simple means for the desymmetrization of diamines and accessing chiral organocatalysts.[11]

We now expand the mechanochemical reactivity of iso(thio)cyanates for the solvent-free synthesis of anti-diabetic[12] sulfonyl-ureas (Figure 1a) and related sulfonyl-thioureas. Whereas mechanosynthesis of sulfonyl-(thio)ureas has never previously been demonstrated, our work is inspired by the explicit calls from the pharmaceutical industry to develop cleaner, more efficient and low-solvent synthetic procedures.[13]

We considered two routes (Figure 1b) for the mechanosynthesis of sulfonyl-ureas: coupling of sulfonamides with isocyanates (A) and coupling of sulfonyl-isocyanates with amines (B). The corrosive nature of sulfonyl-isocyanates[14] led us to select A[15] as the route more compatible with green chemistry.[16]

We first explored the reaction of *p*-toluenesulfonamide with *n*-butyl isocyanate, expected to generate the 1st generation anti-diabetic drug tolbutamide (**1a**, Figure 1a). Milling‡ of pure reagents did not lead to a reaction, most likely due to the poorly nucleophilic nature of sulfonamides, caused by the highly electron-withdrawing sulfonyl group.[17] To activate the sulfonamide group, we explored a two-step approach in which the sulfonamide was first deprotonated by milling with one equivalent of K_2CO_3 and then milled in the same pot with one equivalent of isocyanate (Figure 1c). This procedure gave **1a** in 88% yield after simple workup with aqueous HCl and filtration. Using 0.5 equivalents of K_2CO_3 gave **1a** in 92% isolated yield, indicating that carbonate can be used as a divalent base.

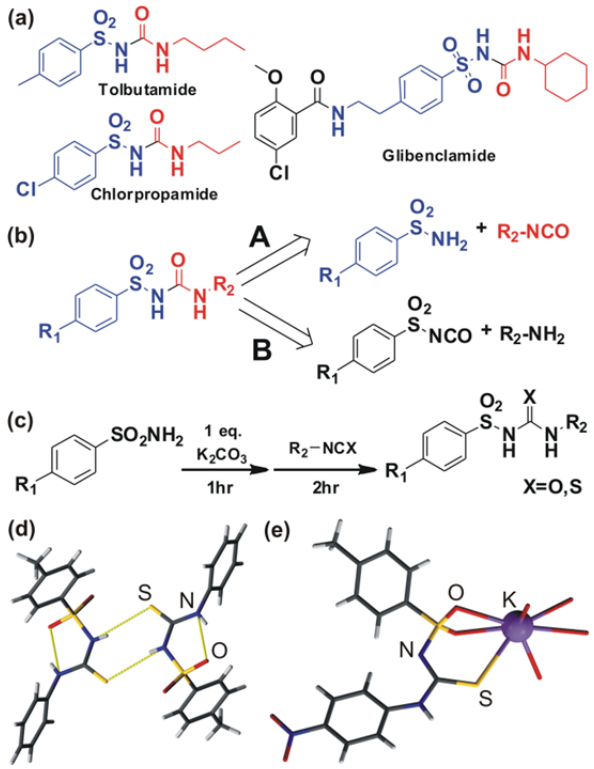

Figure 1. (a) Pharmaceutically relevant sulfonyl-ureas; (b) retrosynthetic routes to sulfonyl-ureas; (c) base-assisted one-pot mechanosynthesis of sulfonyl-(thio)ureas. Fragment of crystal structure of: (d) **1b** and (e) potassium salt of **1c**, with the environment of K^+ simplified for clarity.

The protocol was readily applicable to aromatic isocyanates and isothiocyanates, giving sulfonyl-(thio)ureas **1b-d** (Table 1).

Table 1. Results of two-step mechanosyntheses‡ of sulphonyl-(thio)ureas using one equivalent of K_2CO_3

Compound	R_1	R_2-NCO or R_2-NCS	Yield (%)
1b	Me	phenyl-NCS	91[a]
1c	Me	4-NO_2-phenyl-NCS	80[a]
1d	Me	phenyl-NCO	93[b]

[a]Isolated yield after aqueous workup; [b] based on ^{1}H NMR.

That all reactions took place by milling, rather than upon

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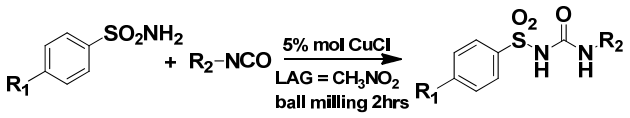
subsequent work-up, was confirmed by Fourier-transform infrared attenuated total reflectance (FTIR-ATR, see ESI) spectra of crude reaction mixtures, which exhibited complete disappearance of iso(thio)cyanate. Formation of **1b** was confirmed by X-ray structural characterisation of single crystals grown after workup. Also, recrystallisation from acetone of the crude reaction mixture from the synthesis of sulfonyl-thiourea **1c** gave single crystals of its potassium salt, confirming the role of K_2CO_3 in sulfonamide deprotonation (Figure 1d,e).

After demonstrating the synthesis of sulfonyl-(thio)ureas by using mechanochemistry, we explored synthetic procedures that might allow circumventing the use of stoichiometric base. In 1990, Cervello and Sastre reported the coupling of *p*-toluenesulfonamide with isocyanates using CuCl as a catalyst.[18] The reactions were performed in *N*,*N*-dimethylformamide (DMF) and took between 16 to 24 hours. Intrigued by this report, we explored if **1a** could be synthesized by direct mechanochemical coupling of *p*-toluenesulfonamide and *n*-butylisocyanate with a CuCl catalyst (Scheme 1, R_1 = methyl, R_2= *n*-butyl).



Scheme 1. Copper-catalysed LAG mechanosynthesis of sulfonyl-ureas

Indeed, the catalytic coupling took place and provided **1a** in good yield (68%) after only 2 hours milling with 5 mol% CuCl. With 20 mol% CuCl, yield was improved to 91% (Table 2, Entry 2).

Table 2. Selected results of optimisation and catalyst screening for the copper-catalysed mechanosynthesis‡ of **1a**.

entry	catalyst	loading (%mol)	time (h)	grinding liquid[a]	yield (%)[b]
1	CuCl	5	2	-	68
2	CuCl	20	2	-	91
3	CuCl	5	2	CH_3CN	54
4	CuCl	5	2	DMF	79
5	CuCl	5	2	toluene	85
6	CuCl	5	2	acetone	86
7	CuCl	5	2	CH_3NO_2	90
8	$CuCl_2$	5	2	Neat	86
9	$CuCl_2.2H_2O$	5	2	Neat	84
10	$Cu(acetate)_2{\cdot}H_2O$	5	2	Neat	83
11	CuBr	5	2	Neat	36
12	Cu powder	10	2	Neat	88
13	Cu_2O	5	2	Neat	75
14	-[c]	-[c]	2	CH_3NO_2	87
15	$NiCl_2$	5	2	Neat	18
16	$ZnCl_2$	5	2	Neat	10
17	$MgCl_2$	5	2	Neat	-
18	AgCl	5	2	Neat	-
19	$FeCl_2{\cdot}2H_2O$	5	2	Neat	-
20	$FeCl_3{\cdot}6H_2O$	5	2	Neat	-

a) LAG[18] with η= 0.25 mL mg^{-1}; b) isolated yield; c) using one 10 mm diameter brass ball in a 10 mL stainless steel jar.

To optimise the reaction conditions we conducted liquid-assisted grinding (LAG) with different catalytic liquid additives (Table 2, Entries 3-7).[19] It was previously proposed that catalytic amounts of a liquid can be used to modify and optimise mechanochemical reactions.[2,20] Indeed, LAG allowed the reaction to be rapidly improved to 90% isolated yield of **1a** at a 5 mol% catalyst loading (Table 2, Entry 7). Reaction mixtures after milling were amorphous, as evidenced by X-ray powder diffraction patterns which did not exhibit any sharp features. The product was isolated by adding aqueous EDTA to remove the metal catalyst and filtration.

The coupling was catalysed not only by Cu(I) but also by Cu(II) additives and even copper powder; water did not seem to affect the reactivity (Table 2, Entries 8-13). The reaction also proceeded without external copper reagents,[7] simply by using a brass milling ball (Table 2, Entry 14). We also explored catalytic activity of Zn, Mg, Ni(II), Ag(I) and Fe chlorides (Entries 15-20). The reaction took place only with $ZnCl_2$ and $NiCl_2$, providing tolbutamide in poor yield (10% and 18%, respectively).

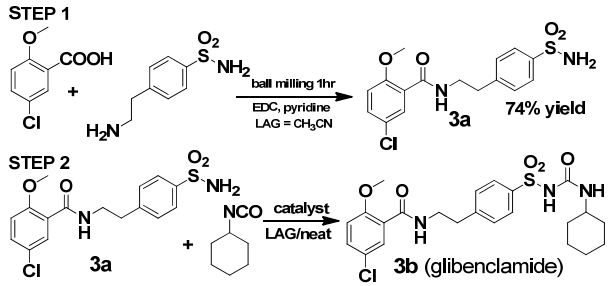
The LAG protocol (Scheme 1) provided further tolbutamide analogues, including the 1st generation drug chlorpropamide (**2a**, Figure 1a), in high isolated yields (Table 3). Catalytic coupling was, however, not applicable to aromatic isocyanates. Using the syntheses of **1a** and **1b** as examples of CuCl-catalysis and base-assisted grinding, respectively, we explored the scale-up of these reaction protocols. The two compounds were isolated in >1 gram amounts with yields of 95% (**1a**) and 80% (**1b**) (see ESI).

Table 3. Results of mechanosynthesis‡ of tolbutamide analogues using CuCl catalyst (5 mol%) and LAG with nitromethane (η= 0.25 mL mg^{-1})

Product	R_1	R_2	Yield (%)[a]
1e	Me	Cy	88
1f	Me	n-Pr	86
2a	Cl	n-Pr	92
2b	Cl	n-Bu	92
2c	Cl	Cy	91

[a]isolated yields after aqueous workup.

Lastly, we set our sights on the 2nd generation drug glibenclamide (**3b**, Figure 1a), which we envisaged could be obtained from the simple starting material p-(2-aminoethyl)benzenesulfonamide in two mechanochemical steps (Scheme 2).



Scheme 2. Synthesis of glibenclamide (**3a**) in two mechanochemical steps

First, we used our previously described[21] mechanochemical amide coupling protocol to form the precursor **3a** in 74% isolated yield, comparable to solution synthesis (81%). The identity of **3a** was also confirmed by crystal structure determination (see ESI).

Next, **3b** was obtained by mechanochemical copper-catalysed coupling of **3a** with cyclohexylisocyanate.¶ Conversion reached completion only with excess isocyanate (Table 4) due to a side-reaction forming dicyclohexylurea which cannot be simply separated from **3b** (product after aqueous EDTA workup contains 92% **3b**).‡ However, quantitative conversion of **3a** into **3b** was achievable with only 5 mol% catalyst (Table 4, Entry 11), demonstrating the potential of mechanochemistry for the synthesis of glibenclamide.

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Table 4. Results of the Cu-catalysed mechanochemical‡ coupling of **3a** with cyclohexylisocyanate to form glibenclamide (**3b**).

Entry	Catalyst	Isocyanate	Catalyst loading (% mol)	Time (h)	LAG or neat[a]	Conversion of **3a** (%)[b]
1	CuCl	1.0 eq	5	2	Neat	54
2	CuCl	1.0 eq	5	2	DMF	60
3	CuCl	1.0 eq	20	2	Neat	43
4	Cu powder	1.0 eq	20	2	Neat	38
5	CuCl	1.0 eq	20	2	CH_3NO_2	83
6	CuCl	1.0 eq	20	4	CH_3NO_2	87
7	Cu_2O	1.0 eq	20	2	Neat	50
8	$CuCl_2.2H_2O$	1.0 eq	20	2	Neat	30
9	$CuCl_2$	1.0 eq	20	2	Neat	48
10	CuCl	1.2 eq	20	2	CH_3NO_2	100
11	CuCl	1.2 eq	5	2	CH_3NO_2	100
12	CuCl	1.1 eq	5	2	CH_3NO_2	68
13	CuCl	1.0 eq	5	2	CH_3NO_2	66
14	-	1.0 eq	-	2	CH_3NO_2	-

[a]LAG with η= 0.25 mL mg^{-1}; [b]determined using ^{1}H NMR.

In summary, we demonstrated two[15] mechanochemical, room temperature procedures for the synthesis of sulfonyl-(thio)ureas, an important family of pharmaceutically relevant molecules. First generation anti-diabetic drugs tolbutamide and chlorpropamide were isolated in >90% yield *via* a catalytic mechanochemical procedure which was also incorporated into a two-step mechanochemical protocol for making the more complex second generation drug glibenclamide in ~70% overall yield. Both Cu-catalysed and base-assisted protocols were readily scaled to 1 gram. By demonstrating the mechanosynthesis of molecules used in treating a wide-spread disease, such as diabetes[12] (estimated[22] to be affecting ~5% of world population), the presented work aims to encourage further development of mechanochemical methods for cleaner, more efficient synthesis of medicinal targets. We are currently exploring the metal-catalysed coupling of sulphonamides and isocyanates.

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Notes and references

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† Electronic Supplementary Information (ESI): experimental procedures, FTIR-ATR, ^{1}H and ^{13}C NMR, HR-MS and crystallographic data in CIF format. See DOI: 10.1039/b000000x/

‡ In a typical procedure the reaction was milled in a 10 mL stainless steel jar with one 10 mm diameter ball made of stainless steel or brass, using a Retsch MM400 mill operating at 30Hz. Aqueous workup and filtration were sufficient for the purification of all compounds except **1d** and **3b** where moisture-induced isocyanate dimerisation yielded small amounts of a urea sideproduct whose separation requires chromatography.

¶ Synthesis of pharmaceutially relevant sulfonyl-ureas in solution requires stoichiometric base and excess isocyanate for sulfonamide-isocyanate coupling, see: H. Ruschig, W. Aumüller, G. Korger, H. Wagner, J. Scholz, A. Bander, "New benzene sulfonyl ureas; composition and process for lowering blood sugar therewith" US2968158 A (1961).

Crystal data. **1c** (K^+ salt, acetone solvate): $C_{14}H_{12}KN_3O_4S_2 \cdot 1.25(CH_3)_2CO$, CCDC 965656, triclinic, a=7.366(1) Å, b=16.466(3) Å, c=18.699(3) Å, α=107.650(2)°, β=93.736(2)°, γ=96.762(2)°, V=2134.1(6) Å^3, space group $P\bar{1}$, Z=4, R_1=0.0582, wR_2=0.1269 ($I>2\sigma_I$), S=0.965; **1b**:$C_{14}H_{14}N_2O_2S_2$, CCDC 965657, triclinic, a=7.557(4) Å, b=9.922(5) Å, c=11.266(6) Å, α=106.421(6)°, β=103.828(6)°, γ=98.312(6)°, V=766.0(7) Å^3, space group $P\bar{1}$, Z=2, R_1=0.0533, wR_2=0.1281 ($I>2\sigma_I$), S= 0.973; **2a**: $C_{13}H_{17}ClN_2O_3S$, CCDC 965659, monoclinic, a=9.3333(8) Å, b=16.065(1) Å, c=19.644(2) Å, β=97.580(1)°, V=2919.6(4) Å^3, space group $P2_1/c$, Z=8, R_1=0.0336, wR_2=0.0836 ($I>2\sigma_I$), S=1.026; **3a**: $C_{16}H_{17}ClN_2O_4S$, CCDC 965658, triclinic, a=9.634(2) Å, b=10.046(2) Å, c=10.667(2) Å, α=64.209(3)°, β=69.198(2)°, γ=72.313(2)°, V=855.1(3) Å^3, space group $P\bar{1}$, Z=2, R_1=0.0388, wR_2=0.0922 ($I>2\sigma_I$), S=0.989;

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