Synthetic Methods

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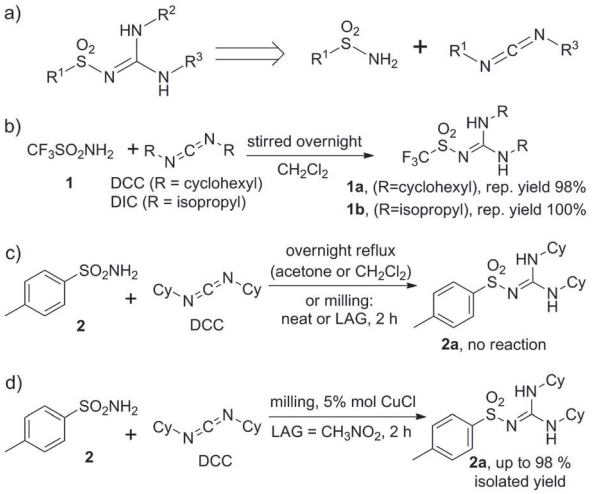
Development of C–N Coupling Using Mechanochemistry: Catalytic Coupling of Arylsulfonamides and Carbodiimides**

*Davin Tan, Cristina Mottillo, Athanassios D. Katsenis, Vjekoslav Štrukil, and Tomislav Friščić**

Abstract: *Reported herein is the mechanochemical synthesis of sulfonyl guanidines, a family of molecules which are relevant as pharmaceuticals and herbicides, by direct coupling of sulfonamides and aromatic or aliphatic carbodiimides. Attempts to conduct the coupling in solution have either failed or given very low conversions, thus demonstrating mechanochemistry as the necessary component for the discovery of this synthetic strategy.*

Mechanochemistry[1] is a rapidly developing approach to environmentally friendly and solvent-free synthesis, and offers excellent atom efficiency, reduction in energy consumption,[2] and can expand the scope of chemical reactions by allowing reactivity independent[3] of solubility. Selectivity and stoichiometric control shown in mechanochemical reactions[4,5] offer an opportunity for exhaustive[6] or site-selective derivatization[7] of small molecules. The recent reports[8,9] of multistep or multicomponent syntheses of complex targets[10] suggest mechanochemistry can provide solvent-free chemistry with synthetic freedoms akin to those of solution synthesis. Such development is particularly attractive to pharmaceutical industries which demand more efficient and cleaner synthetic methods.[11] However, a persistent critique of mechanosynthesis is that, with rare exceptions,[12] its focus is on improving known chemistry rather than on reaction discovery. Consequently, mechanochemical reactions are often perceived as a tool for making greening known solution-based reactivity, rather than as a means for reaction discovery.

We now demonstrate mechanochemistry as the enabling element of a new one-step route to *N*-sulfonylguanidines, a family of molecules which have significant potential as herbicides and pharmaceuticals,[13–15] by catalytic coupling of sulfonamides and carbodiimides (Scheme 1 a). Such coupling



Scheme 1. a) A potential retrosynthetic route to *N*-sulfonylguanidines. b) Reported coupling of **1** with DCC and DIC. c) Initial attempts to react **2** and DCC by solution synthesis, neat milling, or LAG. d) Successful LAG[20,21] synthesis catalyzed by 5 mol% CuCl.

is not normally observed because of poor sulfonamide nucleophilicity. The unusual exception to this is trifluoromethylsulfonamide (**1**), which was recently found[16] to react with di(cyclohexyl)carbodiimide (DCC) and diisopropylcarbodiimide (DIC; Scheme 1 b). Normally, *N*-sulfonylguanidines are obtained from activated sulfonyl or carbodiimide derivatives.[14,17,18] Recently, however, we demonstrated the efficient copper-catalyzed mechanochemical coupling of sulfonamides and isocyanates,[19] and speculated as to whether similar reactivity might be applicable to carbodiimides.

We first attempted the coupling of *p*-tolylsulfonamide (**2**) with DCC to form the *N*-sulfonylguanidine **2a** (Scheme 1 c). Attempts to conduct the coupling in solution or by milling were not successful. These included liquid-assisted grinding (LAG),[20,21] a mechanochemical technique which uses substoichiometric amounts of a liquid to enhance reactivity and base-assisted synthesis, which previously enabled the mechanosynthesis of sulfonyl-thioureas by milling **2** first with K_2CO_3 and then with the electrophile.[19]

Next, we attempted neat milling and LAG in the presence of CuCl, which was previously shown to catalyze the mechanochemical coupling of sulfonamides and isocyanates.[19] As shown by ^{1}H NMR spectroscopy, adding 5 mol% of CuCl to the reaction mixture resulted in 81%

[*] D. Tan, C. Mottillo, Dr. V. Štrukil, Prof. Dr. T. Friščić
Department of Chemistry and FRQNT Centre for Green Chemistry and Catalysis, McGill University
801 Sherbrooke St. W. H3A 0B8 Montreal (Canada)
E-mail: tomislav.friscic@mcgill.ca
Dr. V. Štrukil
Laboratory for Physical Organic Chemistry
Division of Organic Chemistry and Biochemistry
Ruđer Bošković Institute, Zagreb (Croatia)
A. D. Katsenis
Laboratory of Inorganic Chemistry, Department of Chemistry
National and Kapodistrian University of Athens (Greece)

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conversion to **2a** after 2 hours of neat milling, while 2 hours of LAG, using nitromethane ($\eta = 0.25\ \mu L\,mg^{-1}$),[20] gave **2a** in 98% yield (Scheme 1d). The product was isolated by a simple protocol[19] in which the crude reaction mixture is briefly (5 min) milled with aqueous sodium ethylenediaminetetraacetate to quench the reaction and remove the metal catalyst by complexation. The water-insoluble **2a** is isolated as a white solid by filtration. That **2a** forms mechanochemically rather than during work-up is evidenced by Fourier-transform attenuated total reflectance (FTIR-ATR) spectra (Figure 1a), which revealed the absence of the carbodiimide band at 2120 cm^{-1} in the freshly milled reaction. If the milling was performed without CuCl, the carbodiimide signal was clearly visible, thus confirming that the reaction requires the copper additive. Formation of **2a** was confirmed by X-ray crystallography using single crystals grown after work-up (see the Supporting Information).

We also attempted the copper-catalyzed synthesis of **2a** in CH_2Cl_2 or acetone solution. After an overnight reflux no trace of **2a** was detected and the reactant **2** was retrieved, thus highlighting the importance of milling for the copper-catalyzed coupling. The inability to reproduce this catalytic coupling in solution provided an opportunity to explore a novel reaction using mechanochemistry only. We first compared it to the recently reported[16] catalyst-free coupling of **1** with DCC and DIC. We readily conducted both of these reactions by neat milling and by LAG (Table 1).

Different carbodiimides were used to compare CuCl-catalyzed mechanochemical coupling of **2** to that of the catalyst-free coupling of **1**. The latter readily reacted with all explored carbodiimides except di(trimethylsilyl)carbodiimide (Table 1) and the aromatic di(*p*-tolyl)carbodiimide (DPTC). In contrast, CuCl-catalyzed coupling of **2** readily proceeded with DCC, DIC, and DPTC (**2a–c**), but not with sterically hindered carbodiimides involving *tert*-butyl and trimethylsilyl groups (Table 2). An identical pattern of reactivity was observed for *p*-chlorophenylsulfonamide (**3**), which exhibited no reactivity on its own, but with CuCl readily yielded the *N*-sulfonylguanidines **3a–c** by using DCC, DIC, and DPTC (Table 2).

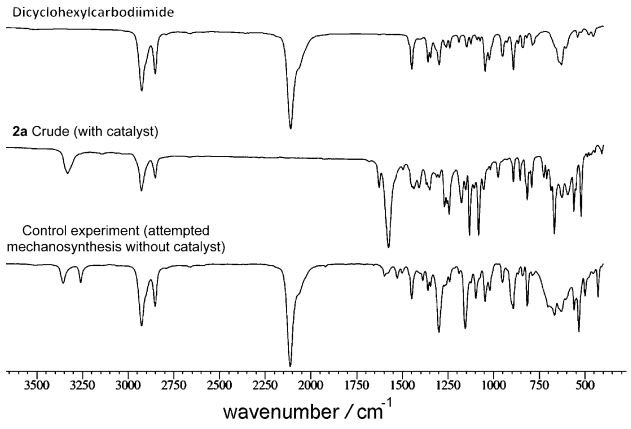
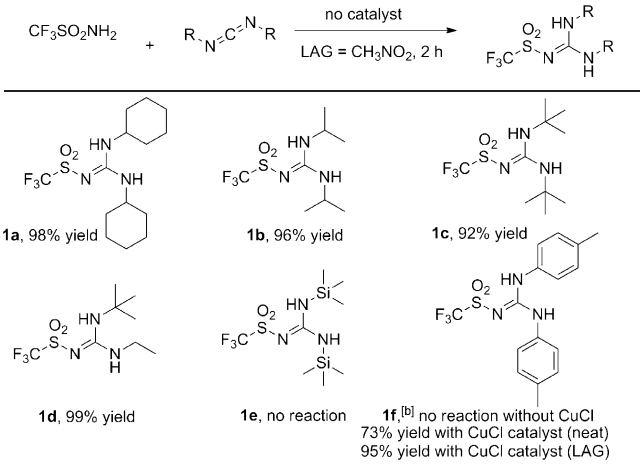


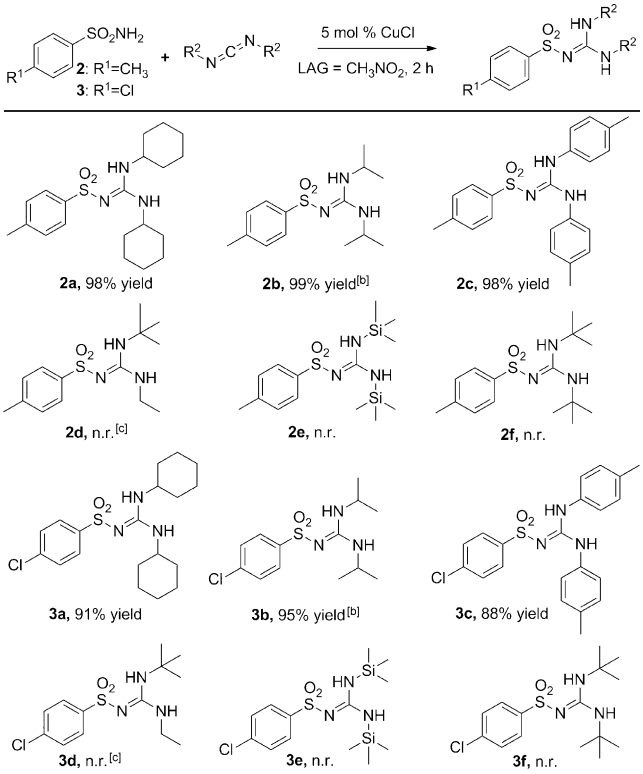
Figure 1. FTIR-ATR spectra for mechanosynthesis of **2a**: DCC (top); freshly milled mixture of DCC and **2** with 5 mol% CuCl (middle), and without CuCl (bottom).

Table 1: Catalyst-free coupling of **1** with carbodiimides.[a]



[a] For reaction conditions please see the Supporting Information. The yields reported are those of the isolated product. [b] Synthesis of **1f** was only possible with 10 mol% CuCl.

Table 2: CuCl-catalyzed coupling of *p*-tolyl- (**2**) and *p*-chlorophenylsulfonamide (**3**) with different carbodiimides.[a]



[a] For reaction conditions please see the Supporting Information. The yields reported are those of the isolated product. [b] Used 10 mol% CuCl. [c] The reaction did not proceed even if the sulfonamide was first milled with K_2CO_3.

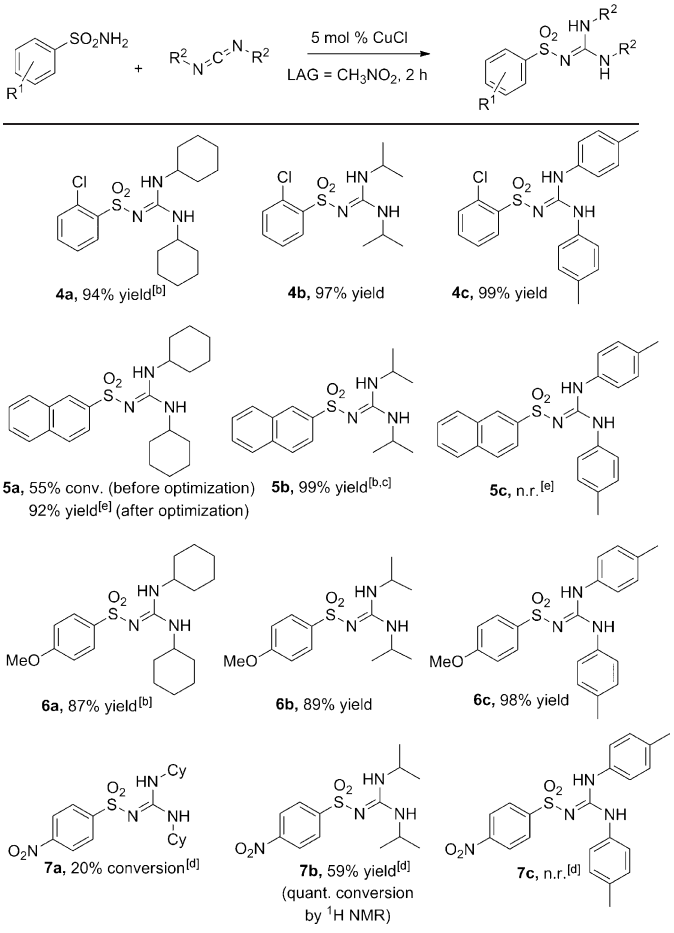
These comparisons confirm that **1** is unique in its ability to directly react with carbodiimides and suggest its reactivity is limited to aliphatic substrates. In contrast, the CuCl-catalyzed coupling is general with respect to the sulfonamide and tolerates aromatic carbodiimides. Indeed, 10 mol% of CuCl also enabled the coupling of **1** with DPTC, which was

previously not achievable in solution or mechanochemically (Table 1).[16] To verify the importance of CuCl in enabling the coupling of aromatic carbodiimides, we explored the reaction of **1** with di(*o*-tolyl)carbodiimide (DOTC). While the reaction did not take place without CuCl, milling with 5 mol% CuCl gave 73% conversion into the *N*-sulfonylguanidine as evidenced by ^{1}H NMR and MS data (see the Supporting Information).

Next, we explored the applicability of the mechanochemical copper-catalyzed coupling to other commercially available arylsulfonamides (Table 3). No reactivity was observed without CuCl. With CuCl, reactions readily took place in almost all cases, thus providing *N*-sulfonylguanidines in excellent yields after simple optimization. Select products were characterized by X-ray crystallography (see the Supporting Information). We also attempted syntheses of **3b**, **4c**, and **6b** in solution. After 18 hours at reflux in acetone, using 10 mol% CuCl, the conversion into **3b** and **6b** was 8% and 5%, respectively, whereas no conversion was observed for **4c**.

The 2-naphthyl- (**5**) and *p*-nitrophenylsulfonamide (**7**) exhibited poorer mechanochemical reactivity than other tested sulfonamides (Table 3). In principle, LAG should allow the optimization of mechanochemical reactions by switching the catalytic liquid[21] in a similar way that solvent switching can affect solution synthesis. To investigate how a poorly behaving LAG coupling can be optimized, we focused on the reaction of **5** with DCC and explored increasing the catalyst amount, reaction time, and different liquid additives at $\eta = 0.25\ \mu L\,mg^{-1}$ (Table 4). Quantitative conversion (from ^{1}H NMR and FTIR-ATR data) and 92% yield of **5a** were obtained using acetone as a grinding liquid with 10 mol% CuCl (Tables 3 and 4).

Table 3: Mechanochemical CuCl-catalyzed coupling of different commercially available arylsulfonamides with DCC, DIC, and DPTC.[a]



[a] For reaction conditions please see the Supporting Information. The yields reported are those of the isolated product. [b] Used 10% CuCl. [c] Used 1.1 equiv carbodiimide. [d] Used 20% CuCl. [e] Optimized reaction conditions: 10 mol% CuCl, acetone ($\eta = 0.25\ \mu L\,mg^{-1}$), 4 h milling.

Table 4: Optimization of copper-catalyzed LAG synthesis of **5a**.

Entry	CuCl (mol%)	*t* [h]	LAG	Conv. [%][a]
1	5	2	CH_3NO_2	36
2	10	2	CH_3NO_2	55
3	10	4	CH_3NO_2	75
4	20	2	CH_3NO_2	50
5	20	2	acetone	84
6	10	4	acetone	>95[b]
7	10	2	2-butanone	79
8	10	2	acetonitrile	43
9	10	2	cyclohexanone	61
10	10	2	*N*,*N*-dimethylformamide	47
11	10	2	neat	58

[a] Based on ^{1}H NMR spectroscopy. [b] Yield of the isolated product was 92%.

Syntheses of **3a** and **3b** were also conducted at 5 mmol scale, thus yielding the expected products in 1.9 g (96%) and 1.5 g (87%) amounts, respectively, and demonstrating the applicability of mechanochemical synthesis for gram-scale reaction.

In conclusion, we used mechanochemistry to establish a previously not known catalytic route[22] for one-step synthesis of *N*-sulfonylguanidines from arylsulfonamides and carbodiimides. This chemistry presents mechanosynthesis not only as a tool for enhancing known procedures, but also as a means to discover and develop synthetic pathways which are difficult to access in solution. Attempts to conduct the coupling reaction in solution have so far been either unsuccessful or gave very poor conversions. This outcome indicates that the sulfonamide–carbodiimide coupling is not impossible in solution, but is greatly favored in a mechanochemical environment, possibly as a result of a higher effective concentration of the catalyst in the absence of bulk solvent. As the addition of a base did not induce catalyst-free reactivity between sulfonamides and carbodiimides,[19] we suggest that the role of CuCl might be largely in activating the carbodiimide, for example, by coordinating to its π system. We are now performing reaction screens and computational studies to elucidate the mechanism of this and related[19,23] mechanochemical coupling procedures.

Experimental Section

General Information: Syntheses of *N*-sulfonylguanidines were 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 (7 or 10 mm). Gram-scale reactions were carried out in a 25 mL stainless steel milling jar. In a typical experiment, a mixture of 0.50 mmol of sulfonamide, 0.50 mmol carbodiimide (1 equiv), 0.025–0.050 mmol (5–10 % mol) of CuCl, and CH_3NO_2 as the grinding liquid ($\eta = 0.25\ \mu L\,mg^{-1}$) was milled for 2 h. After the reaction, 3 mL water and 20–40 mg of $Na_2H_2EDTA{\cdot}2H_2O$ were added to the crude reaction mixture, followed by 10 min of milling. The product was separated by vacuum filtration and dried. For gram-scale syntheses, 5.0 mmol of sulfonamide, 5.0 mmol carbodiimide, 0.50 mmol CuCl (10 % mol) and CH_3NO_2 ($\eta = 0.25\ \mu L\,mg^{-1}$) were milled for 2 h, using three 10 mm diameter balls in a 25 mL jar. After the reaction, 15 mL of water and 400 mg of $Na_2H_2EDTA{\cdot}2H_2O$ were added to the crude reaction mixture, which was then milled for 10 min. The product was separated by vacuum filtration and dried. Details of all experiments, ^{1}H,^{13}C NMR spectroscopy, and MS, TGA/DSC, and FTIR-ATR data are given in the Supporting Information. CCDC 995641 (**2a**), 995642 (**3b**), 995643 (**4a**), 995644 (**5b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[20] η is the ratio of added liquid (in μL) to the mass of reactants (in mg), typically between 0.1–1 $\mu L\,mg^{-1}$; a) The herein reported reactions use 50 μL per 0.2 g of reactants ($\eta = 0.25\ \mu L\,mg^{-1}$).

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[23] While the exceptional reactivity of **1** has not yet been explained,[16] a search of the Cambridge Structural Database (V5.34) shows that it exhibits an unusually short S–N bond (1.55–1.57 Å) compared to other sulfonamides in our study (1.59–1.62 Å).

