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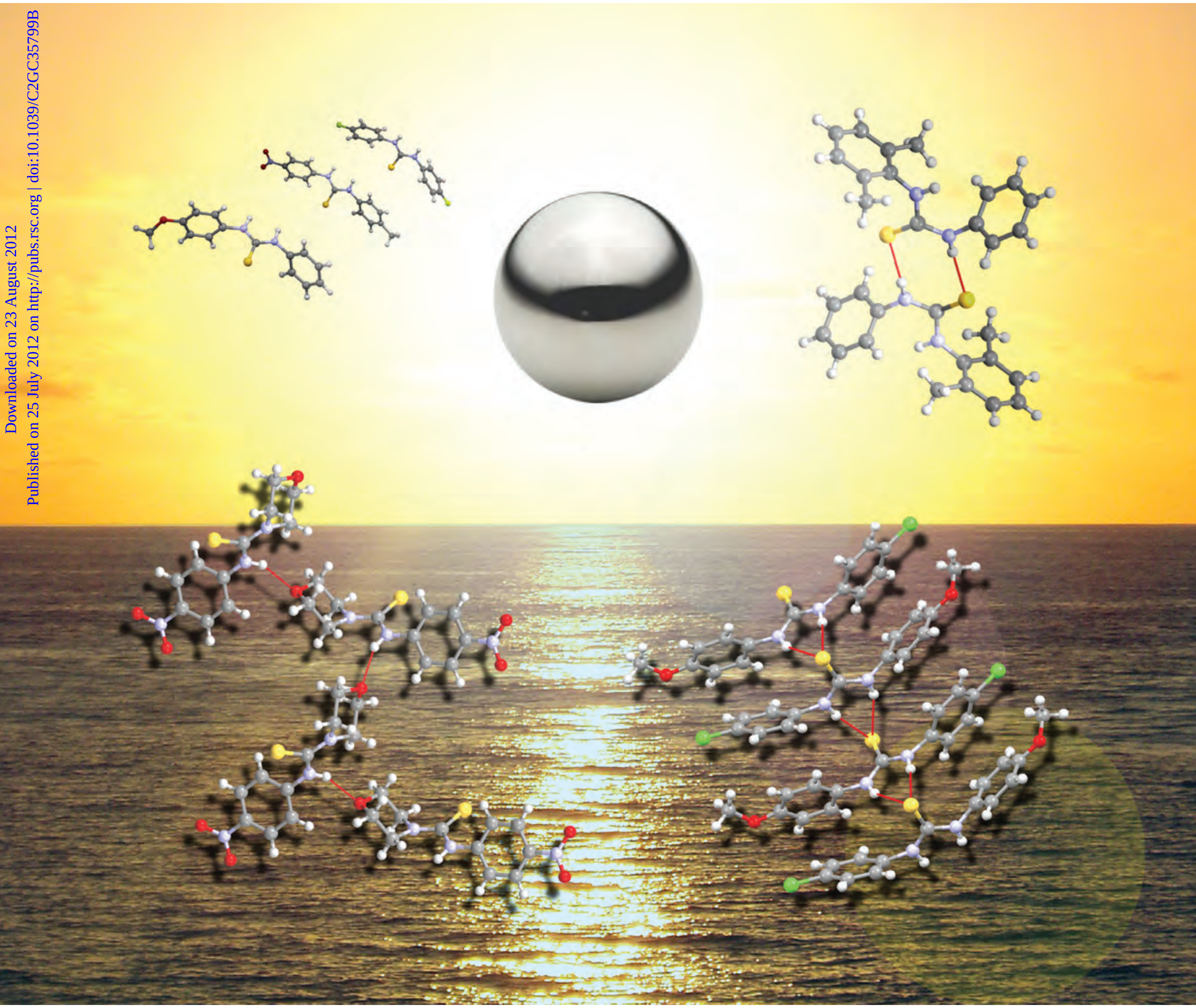
Volume 14 | Number 9 | September 2012 | Pages 2355–2648



ISSN 1463-9262

RSC Publishing

COVER ARTICLE
Friščić, Eckert-Maksić *et al.*
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1463-9262(2012)14:9;1-M

Green Chemistry

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Cite this: *Green Chem.*, 2012, **14**, 2462

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PAPER

A model for a solvent-free synthetic organic research laboratory: click-mechanosynthesis and structural characterization of thioureas without bulk solvents†

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Received 24th May 2012, Accepted 24th July 2012
DOI: 10.1039/c2gc35799b

The mechanochemical click coupling of isothiocyanates and amines has been used as a model reaction to demonstrate that the concept of a solvent-free research laboratory, which eliminates the use of bulk solvents for either chemical synthesis or structural characterization, is applicable to the synthesis of small organic molecules. Whereas the click coupling is achieved in high yields by simple manual grinding of reactants, the use of an electrical, digitally controllable laboratory mill provides a rapid, quantitative and general route to symmetrical and non-symmetrical aromatic or aromatic–aliphatic thioureas. The enhanced efficiency of electrical ball milling techniques, neat grinding or liquid-assisted grinding, over manual mortar-and-pestle synthesis is demonstrated in the synthesis of 49 different thiourea derivatives. Comparison of powder X-ray diffraction data of mechanochemical products with structural information found in the Cambridge Structural Database (CSD), or obtained herein through single crystal X-ray diffraction, indicates that the mechanochemically obtained thiourea derivatives are pure in a chemical sense, but can also demonstrate purity in a supramolecular sense, *i.e.* in all structurally explored cases the product consisted of a single polymorph. As an extension of our previous work on solvent-free synthesis of coordination polymers, it is now demonstrated that such polymorphic and chemical purity of selected thiourea derivatives, the latter being evidenced through quantitative reaction yields, can enable the direct solvent-free structural characterization of mechanochemical products through powder X-ray diffraction aided by solid-state NMR spectroscopy.

Introduction

Mechanochemical reactions,[1] *i.e.* reactions initiated or sustained through mechanical force, are becoming increasingly important in the context of environmentally-friendly synthesis,[2] particularly as a means to conduct solvent-free and low-energy synthesis.[3] This is evidenced by a rapidly growing number of research areas where mechanochemistry has been successfully applied for the improvement of reaction efficiency: supramolecular synthesis[4] of hydrogen- or halogen-bonded materials,[5] including pharmaceutical cocrystals[6] and salts,[7] photoreactive, chromophoric or luminescent cocrystals,[8] the synthesis of coordination compounds, clusters and polymers,[9] metallodrugs[10] and porous metal–organic frameworks.[11] However, the dominant area of application of mechanosynthesis in a laboratory is organic synthesis,[12] including asymmetric catalysis.[13] Significant advances in the mechanosynthesis of organic compounds have recently been achieved through the application of metal-based catalysis,[14] catalytic supramolecular templating[15] and reversible covalent bonding.[16] A mechanochemical approach to click-chemistry was first reported by the Stolle group, who demonstrated solvent-free polymer synthesis using a 1,3-dipolar Huisgen cycloaddition in a ball mill,[17] and our group recently demonstrated the mechanochemical thiourea click-coupling as a highly-efficient route to thiourea organocatalysts.[18]

Whereas laboratory-scale mechanochemical synthesis is often conducted by manual mortar-and-pestle techniques,[19] the application of a digitally controlled laboratory mill allows a higher

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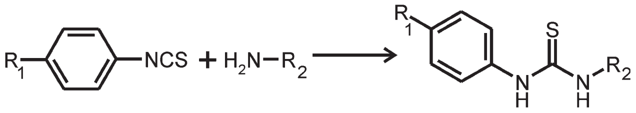
† Electronic supplementary information (ESI) available: Details of experiments and instrumental techniques, ^1H and ^{13}C solution NMR spectra of mechanochemical products, selected ^{13}C solid-state CP-MAS NMR spectra, FTIR-ATR spectra, PXRD patterns and crystallographic data in CIF format. (All crystallographic data, except for the **1e-SC** and **1e-PXRD** structures have been deposited with the Cambridge Structural Database, CCDC deposition numbers 883638–883645). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2gc35799b

level of reproducibility through clearly delineated reaction conditions such as reaction time, impact force (which is readily defined through selection of grinding ball weight and size) and grinding intensity (which is defined by milling frequency).[20] The increasing popularity of mechanochemistry in recent synthetic literature is related to the high energy- and solvent-efficiency of milling reactivity compared to conventional laboratory techniques (*e.g.* microwave-assisted solution synthesis)[21] as well as to the development of new modified mechanochemical methods, such as liquid-assisted grinding (LAG)[22–24] or ion- and liquid-assisted grinding (ILAG).[25]

From the environmental point of view, these mechanochemical techniques, when coupled with state-of-the-art methods of solid-state analysis, could enable the development of a laboratory research methodology that obviates the need for bulk solvent throughout the entire synthesis and analysis sequence. The viability of such a "solvent-free research laboratory" concept was recently demonstrated in the synthesis of coordination polymers based on simple and rigid organic ligands.[26a] From the synthetic side, the ability of mechanochemical reactions to achieve quantitative reaction yields is central to the development of solvent-free research, as it provides an environmentally more acceptable process and prevents the loss of reaction yield inherent to solution-based crystallization or chromatographic methods.[18,27] From the analytical side, two instrumental techniques of outstanding importance for solvent-free laboratory research are structural characterization from laboratory powder X-ray diffraction (PXRD)[28] data and solid-state NMR spectroscopy,[29] both of which offer the opportunity to avoid bulk solvents in post-synthetic structural analysis, in particular for single crystal growth and NMR sample preparation. Different groups have pointed to the ability of mechanochemistry, when coupled with PXRD and solid-state NMR, to enable solvent-free laboratory research in the areas of metal–organic materials, specifically coordination polymers,[26] and hydrogen-bonded cocrystals, including model pharmaceutical materials.[30]

We have now explored how the concepts of solvent-free research[26a,31] can be transferred into the arena of organic synthesis, by focusing on the click-mechanochemical coupling of amines and isothiocyanates leading to simple and rigid molecules in the form of symmetrically and non-symmetrically *N*,*N*′-disubstituted thioureas (Scheme 1).

Thioureas have been selected as target compounds due to their importance and the simplicity of mechanochemical preparation. The significance of thioureas lies in their pharmaceutically-relevant physiological activity encompassing antibacterial,[32] antimalarial,[33] antiviral[34] and antitumor[35] behavior, as well as in their organocatalytic activity[36] and applications in anion sensing and transport.[37] The importance of thioureas as organocatalysts is growing, with reported applications in enantioselective Morita–Baylis–Hillman reactions, Michael additions, nitroaldol condensations, acetalisations of aldehydes and ketones and Friedel–Crafts alkylations.[36] Consequently, a simple, efficient and high-yielding procedure for the synthesis of thioureas is desirable from both economic and environmental points of view. The rapid and quantitative mechanosynthesis of chiral thiourea organocatalysts using the mechanochemical amine–isothiocyanate click coupling was recently demonstrated on a gram scale.[18] Besides the efficient synthesis of important organocatalysts, this previous work also demonstrated that click mechanosynthesis provides simple access to both mono- and bis-thioureas based on sterically and electronically hindered diamines. The superior control of product stoichiometry using click-mechanochemical synthesis resembled similar observations previously made in the mechanosynthesis of coordination compounds[26] and cocrystal synthesis.[38]



Scheme 1 The synthesis of *N*,*N*′-disubstituted thioureas through primary amine–isothiocyanate coupling.

The simplicity of the reaction, the potential importance of the products in catalysis and anion binding studies, and their inherently rigid structure make the amine–isothiocyanate coupling a very suitable test reaction for exploring two important principles of the proposed solvent-free research laboratory in organic synthesis: avoiding bulk solvents in quantitative synthesis, and structural characterization without the need to grow macroscopic single crystals from bulk solvents.

The solvent-free approach to the synthesis of thioureas was first put forward by Kaupp, who investigated the synthesis of non-symmetrical *N*-methyl-*N*′-arylthioureas through solvent-free solid–solid and solid–gas reactions of amines with isothiocyanates.[39] The reactions were conducted over a period of one day, with occasional manual grinding in the case of a solid reactant. Subsequently, Li and Wang described the solid-state synthesis of several *N*,*N*′-diaryl thioureas from aromatic isothiocyanates and amines in a microwave oven and by manual grinding.[40] Steed's group has reported the use of mechanochemical grinding for the synthesis of a podand anion receptor through a related reaction of coupling amines with isocyanates.[41] The supramolecular solid-state chemistry of thioureas has recently become of interest as a means for the structural interpretation of solution-phase catalytic activity, as well as because of the recently introduced use of thioureas as hydrogen-bonding templates for directing the solid-state photodimerisation of olefins.[42] Consequently, thioureas represent a set of target molecules whose structural studies in the solid state[43] could be particularly gratifying.

The current broad study demonstrates the generality of mechanochemical thiourea synthesis, regardless of the physical state of the reactants, their substituent-controlled reactivity or steric hindrances. Specifically, we now report a successful quantitative synthesis of 49 symmetrical and non-symmetrical *N*,*N*′-diaryl or *N*-aryl-*N*′-alkyl thiourea derivatives through mechanochemical amine–isothiocyanate coupling. The quantitative reaction after mechanochemical treatment was evidenced through the absence of the characteristic isothiocyanate 2200 cm^{-1} stretching band in the Fourier-transform attenuated total reflection (FTIR-ATR) spectra of products. Quantitative yields were also verified by high-pressure liquid chromatography (HPLC) analysis of selected samples. While high reaction efficiencies have been obtained in simple manual grinding procedures, the laboratory mill enabled each synthesis to be conducted in quantitative yield. The products of ball milling were all highly crystalline solids, making them amenable to direct solvent-free structural characterization by PXRD structure solution.

Results and discussion

General reactivity of aromatic and aliphatic primary amines

The click-mechanochemical methodology was first tested on the reaction of *p*-substituted aromatic isothiocyanates with differently *p*-substituted anilines as representatives of typical aromatic amines (Table 1). As aliphatic amine reactants were explored isopropylamine, 3-dimethylaminopropylamine and benzylamine, the latter being a representative of a reactant with benzylic character. All reactions were conducted using the 1 : 1 stoichiometric ratio of the reactants, with the exception of reactions involving isopropylamine. Due to its volatility which prevented efficient handling, isopropylamine was always used in excess (Table 1).

Table 1 Reactions of aromatic isothiocyanates with aromatic, aliphatic and benzylic (Bn) amines[a]

Entry	Product	R_1, R_2	Reactant physical state (isothiocyanate/amine)[b]	Yield[c] (manual, milled)/%
1	**1a**	OMe, 4-OMe-Ph	Liquid, solid	>99, >99
2	**1b**	OMe, 4-Me-Ph	Liquid, solid	>99, >99
3	**1c**	OMe, Ph	Liquid, liquid	82, >99[d]
4	**1d**	OMe, 4-F-Ph	Liquid, liquid	88, >99[d]
5	**1e**	OMe, 4-Cl-Ph	Liquid, solid	90[e], >99[d]
6	**1f**	OMe, i-Pr	Liquid, liquid	>99, >99[f]
7	**1g**	OMe, 3-(NMe_2)-Pr	Liquid, liquid	95, >99
8	**1h**	OMe, Bn	Liquid, liquid	>99, >99
9	**2a**(**1c**)	H, 4-OMe-Ph	Liquid, solid	>99, >99
10	**2b**	H, 4-Me-Ph	Liquid, solid	>99, >99
11	**2c**	H, Ph	Liquid, liquid	>99, >99
12	**2d**	H, 4-F-Ph	Liquid, liquid	>99, >99
13	**2e**	H, 4-Cl-Ph	Liquid, solid	>99, >99[d]
14	**2f**	H, i-Pr	Liquid, liquid	>99, >99[f]
15	**2g**	H, 3-(NMe_2)-Pr	Liquid, liquid	>99, >99
16	**2h**	H, Bn	Liquid, liquid	>99, >99
17	**3a**(**1d**)	F, 4-OMe-Ph	Liquid, solid	>99, >99
18	**3b**	F, 4-Me-Ph	Liquid, solid	>99, >99
19	**3c**(**2d**)	F, Ph	Liquid, liquid	>99, >99
20	**3d**	F, 4-F-Ph	Liquid, liquid	>99, >99
21	**3e**	F, 4-Cl-Ph	Liquid, solid	75, 97[d], >99[g]
22	**3f**	F, i-Pr	Liquid, liquid	>99, >99[f]
23	**3g**	F, 3-(NMe_2)-Pr	Liquid, liquid	>99, >99
24	**3h**	F, Bn	Liquid, liquid	>99, >99
25	**4a**	NO_2, 4-OMe-Ph	Solid, solid	>99, >99
26	**4b**	NO_2, 4-Me-Ph	Solid, solid	>99, >99
27	**4c**	NO_2, Ph	Solid, liquid	>99, >99
28	**4d**	NO_2, 4-F-Ph	Solid, liquid	>99, >99
29	**4e**	NO_2, 4-Cl-Ph	Solid, solid	98, >99[d]
30	**4f**	NO_2, i-Pr	Solid, liquid	>99, >99[f]
31	**4g**	NO_2, 3-(NMe_2)-Pr	Solid, liquid	>99, >99
32	**4h**	NO_2, Bn	Solid, liquid	>99, >99

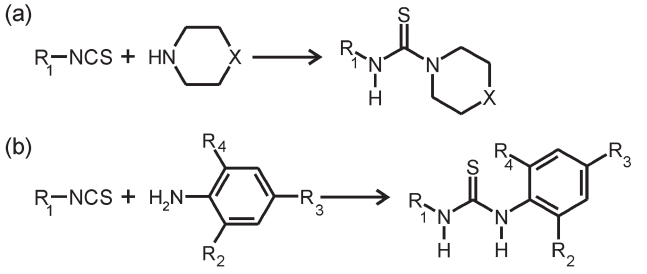
[a] The reaction time for manual grinding was typically 15–20 minutes while ball milling was conducted for 10 minutes at 30 Hz using a single stainless steel ball (12 mm diameter, m = 7.056 g). LAG experiments were carried out using 50 μL of acetonitrile as the liquid phase. [b] At 25 °C. [c] Isolated yield. In reactions where ^{1}H NMR indicated a conversion lower than quantitative, the yield was calculated from the corresponding NMR intensities of the product and unreacted isothiocyanate or amine. [d] 15 minutes of neat ball milling. [e] 45 minutes manual grinding. [f] Three-fold excess (six-fold for manual grinding and five-fold for ball milling in the case of thiourea **4f**) of isopropylamine was used due to its high volatility (b.p. 32 °C). [g] 15 minutes of LAG.

Although the presence of a substituent at the *para* position in both aromatic reactants was expected to provide insight into possible substituent effects on mechanochemical reactivity, all investigated reactions were found to proceed rapidly (within 10–20 minutes) to quantitative yield, with little or no observable substituent effect. Since many of the reagents used in this study are liquids at room temperature, the viability of the grinding synthetic procedure was first explored by simply combining the reagents in a mortar and conducting the reactions manually using a pestle. The manual mechanical agitation of the reaction mixtures resulted in a quantitative conversion of the starting materials into the desired thiourea derivative in almost all cases (Table 1).

The only exceptions were the coupling reactions involving the most electron rich aromatic isothiocyanate, 4-methoxyphenyl isothiocyanate (Table 1, entries 3, 4, 5 and 7), and some of the reactions involving the electron poor amines, such as 4-chloro- and 4-fluoroaniline (Table 1, entries 4, 5, 21 and 29). Such behaviour is consistent with the reduced electrophilic nature of the isothiocyanate moiety in 4-methoxyphenyl isothiocyanate, and the lowered nucleophilic character of 4-halogenated aniline. However, in all quantitative yields were achieved by replacing the manual methodology with 10 – 30 minutes milling in a laboratory mechanical mill. Aliphatic amines are generally very good nucleophiles and as such gave the corresponding thioureas **1f–1h**, **2f–2h**, **3f–3h** and **4f–4h** in quantitative (*i.e.* 99% and higher) yields.

Reactions of sterically hindered amines and anilines

The excellent yields of reactions involving 4-substituted aromatic isothiocyanates with aliphatic amines and 4-substituted anilines encouraged the exploration of the sensitivity of mechanochemical coupling to steric hindrance. Reactants used for that purpose were the more sterically hindered secondary amines piperidine, morpholine and thiomorpholine (Scheme 2a), as well as 2,4- and 2,6-disubstituted anilines (Scheme 2b). In the case of secondary aliphatic amines, the application of a laboratory mill led to the formation of each aliphatic amine product in quantitative yield, as established by HPLC (Table 2). The manual grinding reactions involving cyclic secondary amines have not been conducted due to potential complications related to the known propensity of such molecules to react with atmospheric carbon dioxide. However, the manual grinding and ball milling



Scheme 2 Synthesis of non-symmetrical (a) aromatic–aliphatic thioureas starting from sterically hindered secondary amines and (b) aromatic thioureas starting from sterically hindered primary aromatic amines.

Table 2 Mechanochemical reactivity of the model 4-substituted aromatic isothiocyanates with cyclic secondary amines[a]

Entry	Product	R_1, X	Reactant physical state[b]	Yield/%
1	**1i**	4-OMe-Ph, CH_2	Liquid, liquid	>99[c]
2	**1j**	4-OMe-Ph, O	Liquid, liquid	>99
3	**1k**	4-OMe-Ph, S	Liquid, liquid	>99
4	**2i**	Ph, CH_2	Liquid, liquid	>99[d]
5	**2j**	Ph, O	Liquid, liquid	>99
6	**2k**	Ph, S	Liquid, liquid	>99[e]
7	**3i**	4-F-Ph, CH_2	Liquid, liquid	>99[d]
8	**3j**	4-F-Ph, O	Liquid, liquid	>99
9	**3k**	4-F-Ph, S	Liquid, liquid	>99
10	**4i**	4-NO_2-Ph, CH_2	Solid, liquid	>99[d]
11	**4j**	4-NO_2-Ph, O	Solid, liquid	>99
12	**4k**	4-NO_2-Ph, S	Solid, liquid	>99

[a] Ball milling was conducted for 10 minutes at 30 Hz by using a single stainless steel ball (12 mm diameter, *m* = 7.056 g) and 40 μL of acetonitrile as the liquid phase. [b] At 25 °C. [c] 15 minutes ball milling and 50 μL of acetonitrile. [d] Neat grinding. [e] 45 μL of acetonitrile.

Table 3 Mechanochemical reactivity of 4-substituted aromatic isothiocyanates towards sterically hindered 2,4- and 2,6-dimethylanilines[a]

Entry	Product	R_1, R_2, R_3, R_4	Reactant physical state[b]	Yield[c] (manual, milled)/%
1	**1l**	4-OMe-Ph, Me, Me, H	Liquid, liquid	94[d], >99[e]
2	**1m**	4-OMe-Ph, Me, H, Me	Liquid, liquid	>99[f]
3	**2l**	Ph, Me, Me, H	Liquid, liquid	>99, >99[g]
4	**2m**	Ph, Me, H, Me	Liquid, liquid	>99
5	**3l**	4-F-Ph, Me, Me, H	Liquid, liquid	97, >99[g]
6	**3m**	4-F-Ph, Me, H, Me	Liquid, liquid	>99
7	**4l**	4-NO_2-Ph, Me, Me, H	Solid, liquid	98, >99[g]
8	**4m**	4-NO_2-Ph, Me, H, Me	Solid, liquid	>99[f]

[a] The reaction time for manual grinding was typically 15–20 minutes while ball milling was conducted for 10 minutes at 30 Hz using a single stainless steel ball (12 mm diameter, *m* = 7.056 g) and 50 μL of acetonitrile as the liquid phase. [b] At 25 °C. [c] Isolated yield. For reactions where ^{1}H NMR indicated a conversion lower than quantitative, the yield was calculated from the corresponding NMR intensities of the product and unreacted isothiocyanate or amine. [d] 45 minutes of manual grinding. [e] 40 minutes ball-milling. [f] 15 minutes ball-milling. [g] Neat grinding.

methodologies have been compared for the reactions of the sterically hindered aliphatic i-propylamine, revealing that quantitative yields are readily obtained by both approaches (Table 1, entries 6, 14, 22 and 30).

As evident from Table 3, excellent yields of non-symmetrical thioureas have also been obtained in the case of sterically hindered anilines. Again, the application of a laboratory mill improved reaction yields to the quantitative level.

Single crystal structure determination: supramolecular (polymorphic) purity of selected thiourea derivatives

The characterization of prepared thioureas using powder X-ray diffraction suggested that, for all thioureas with available crystal structures, the mechanochemical product consisted of a single polymorphic form. Specifically, this was evident from the comparison of the PXRD pattern measured for the ground product with the patterns simulated from the crystallographic data available in the Cambridge Structural Database (CSD, thioureas **1a** (CCDC code WEFQEE), **2c** (CCDC code ZEYBIO) and **2j** (CCDC code TABYUQ)) (Fig. 1).

To further verify the polymorphic purity of the thiourea products, which is helpful when attempting structural characterization from PXRD data, a selection of molecules was analyzed by conventional single crystal X-ray diffraction. The preparation of required single crystals was simplified by the quantitative yields of mechanochemical reactions which allowed diffraction-quality samples to be obtained by simple recrystallization of the ground reaction mixtures from methanol. In this way, the crystal and molecular structures have been determined for *N*,*N*′-bis(4-fluorophenyl)thiourea (**3d**), *N*-(4-nitrophenyl)-*N*′-morpholinothiourea (**4j**), *N*-(4-methoxyphenyl)-*N*′-piperidinothiourea (**1i**) and *N*-phenyl-*N*′-thiomorpholinothiourea (**2k**) (Table 4). In all cases, except **4j**, the simulated PXRD pattern corresponded to the one measured for the mechanochemical product.

The crystal structure of *N*,*N*′-bis(4-fluorophenyl)thiourea (**3d**, Fig. 2a) was found to resemble that of the orthorhombic polymorph of the simple *N*,*N*′-bis(phenyl)thiourea (**2c**) (CCDC code ZEYBIO), in which the molecules stack head-to-tail to form zigzag tapes involving twin N–H···S contacts of 3.52 Å. The N–H···S contacts can be interpreted as hydrogen-bonding

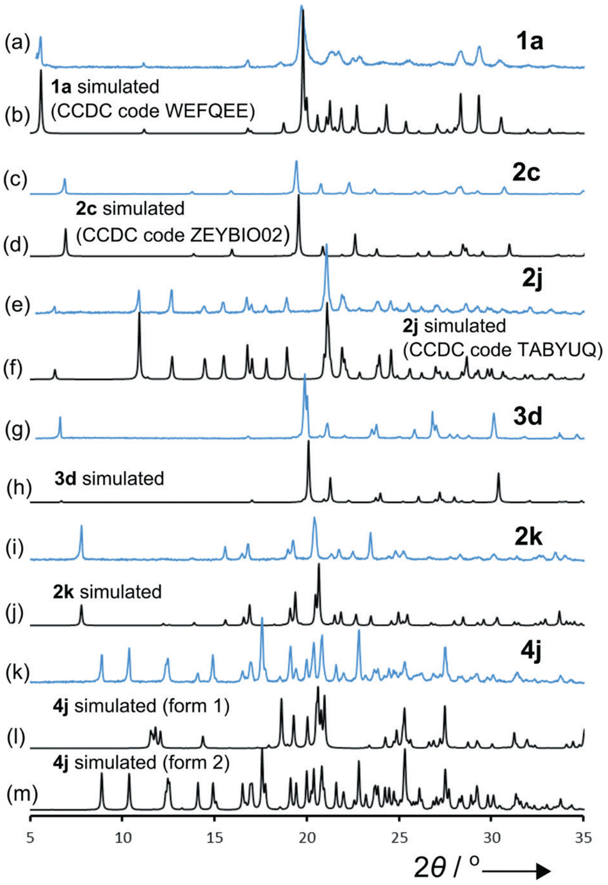


Fig. 1 Comparison of measured (blue) and simulated (black) PXRD patterns for selected mechanochemically prepared thioureas.

Table 4 General and crystallographic parameters for mechanochemical thiourea products characterised by single crystal X-ray diffraction

Compound	**1i**	**2k**	**3d**	**4j** (form 1)	**4j** (form 2)	**1e-SC**
Formula	$C_{13}H_{18}N_2OS$	$C_{11}H_{14}N_2S_2$	$C_{13}H_{10}F_2N_2S$	$C_{11}H_{13}N_3O_3S$	$C_{11}H_{13}N_3O_3S_1$	$C_{14}H_{13}ClN_2OS$
M_r	250.35	238.36	264.29	267.30	267.30	292.77
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Monoclinic	Orthorhombic	Orthorhombic
Space group	Cc	$P2_1/c$	$Pnma$	$P2_1/n$	$Pca2_1$	$Pbcm$
a (Å)	10.4930(2)	11.5813(3)	8.3457(1)	10.2252(2)	21.221(1)	5.6100(6)
b (Å)	14.6391(4)	9.3856(3)	26.4224(2)	10.5172(3)	8.0908(4)	7.9500(8)
c (Å)	9.0779(2)	10.8926(4)	5.3071(6)	11.1949(2)	28.647(2)	32.010(3)
β (°)	113.021(1)	101.21(3)	90	90.788(2)	90	90
V (Å^3)	1283.39(5)	1161.4(2)	1170.3(1)	1203.79(5)	4918.6(4)	1427.6(3)
T (K)	180(2)	180(2)	180(2)	180(2)	291(2)	293(2)
Z	4	4	4	4	16	4
μ(MoKα) (mm^{-1})	0.238	0.427	0.284	0.273	0.268	0.406
Reflections measured	10 115	14 713	8268	11 967	35 514	14 424
Independent reflections	4498	3390	1882	4139	9571	1693
R_{int}	0.0394	0.0460	0.0346	0.0300	0.1164	0.0451
R_1 ($I > 2\sigma(I)$)	0.0441	0.0472	0.0364	0.0330	0.0471	0.0452
wR_2 ($I > 2\sigma(I)$)	0.1048	0.0987	0.0856	0.0957	0.0911	0.1106
R_1 (all data)	0.0655	0.0773	0.0559	0.0462	0.1498	0.0697
wR_2 (all data)	0.1198	0.1109	0.0924	0.0980	0.1249	0.1210
S	1.121	1.029	1.065	1.021	1.008	1.086
Flack parameter	0.10(7)	—	—	—	0.5(1)	—

interactions to a bifurcated sulfur acceptor. The N–H⋯S hydrogen bonds have been recognized as a characteristic part of the solid-state assembly of thiourea molecules.[43] The same zigzag motif as observed in **3d** is encountered in the majority of *N*,*N*′-diarylthiourea crystal structures found in the Cambridge Structural database (CSD). The thiourea derivatives derived from secondary amines, *N*-phenyl-*N*′-thiomorpholinothiourea (**2k**), *N*-(4-methoxyphenyl)-*N*′-piperidinothiourea (**1i**) and *N*-(4-nitrophenyl)-*N*′-morpholinothiourea (**4j**), are not expected to form the zigzag tape supramolecular motifs due to the presence of only one N–H moiety per molecule. Indeed, in the herein determined crystal structures of *N*-phenyl-*N*′-thiomorpholinothiourea (**2k**) and *N*-(4-methoxyphenyl)-*N*′-piperidinothiourea (**1i**) the zigzag tapes based on twin N–H⋯S interactions are replaced by chains displaying only single N–H⋯S interactions (Fig. 2b,c). The N⋯S separations in these two cases are shorter than observed in zigzag tapes of diarylthioureas: 3.30 Å (for **2k**, the N–H⋯S contacts are also accompanied by short C–H⋯S contacts of 3.7 Å, Fig. 2b) and 3.46 Å (for **1i**, Fig. 2c).

In contrast, the solid-state structure of **4j** did not exhibit short N–H⋯S interactions. Instead, the molecules are associated into zigzag chains through N–H⋯O hydrogen bonds (2.96 Å) between the N–H groups of each thiourea moiety and the oxygen atom of the morpholine ring in neighbouring molecules (Fig. 2d). The formation of N–H⋯O rather than N–H⋯S hydrogen-bonding motifs in **4j** is surprising as the crystal structure of **2j**, which contains a phenyl and a morpholine substituent (CCDC code TABYUQ),[44] exhibits only N–H⋯S interactions analogous to those in **1i** and **2j**. Moreover, as the PXRD pattern simulated for the crystal structure of **4j** was evidently different from the pattern of the mechanochemically obtained product, we attempted a PXRD structure determination procedure. The PXRD pattern indexing procedure suggested the mechanochemical product with a large unit cell (a = 21.224 Å, b = 8.104 Å, c = 28.655 Å, V = 4928.9 Å^3) corresponding to the orthorhombic system with Z = 16 and implying four different molecules in the asymmetric unit. As such a structural problem would represent a considerable challenge even for conventional PXRD structure solution procedures, we turned to a solution-based polymorph screening.

Recrystallisation of the mechanochemical product from ethyl acetate provided single crystals that exhibited a crystallographic unit cell identical to the one indicated by PXRD pattern indexing. Structure determination revealed that the space group is non-centrosymmetric ($Pca2_1$) with four independent molecules in the asymmetric unit (Z' = 4) held by the expected N–H⋯S hydrogen bonds. The molecules in this solid-state structure of **4j** (polymorph 2) form two crystallographically distinct hydrogen-bonded chains. Each chain consists of two alternating crystallographically distinct molecules of **4j**, accounting for the observed Z' = 4 (Fig. 3). Although crystal structure determination for this material was not attempted from powder diffraction data, it was pleasing to observe that the PXRD indexing procedure initially yielded the correct unit cell size and crystallographic parameters.

Structural characterization from PXRD data

The apparent crystallinity and purity of mechanochemically obtained thioureas in a chemical, as well as a supramolecular sense (*i.e.* the appearance of the product in one dominant polymorphic crystalline form) are key for crystal structure determination from PXRD data. Whereas the polymorphic purity of mechanochemically prepared thioureas was indicated by previous and current single crystal X-ray crystallography studies, PXRD analysis revealed that roughly 40% of them (22 compounds) display diffraction patterns of sufficient quality for structural characterization. The criterion for pattern quality was a typical diffraction peak width at half maximum of 0.4° or less, based on previous experience.[26a,30] Consequently, crystal structure determination was attempted on a selection of five mechanochemically prepared thiourea derivatives: *N*-(4-methoxyphenyl)-*N*′-phenylthiourea (**1c**), *N*-(4-chlorophenyl)-*N*′-(4-methoxyphenyl)thiourea (**1e**), *N*-(4-nitrophenyl)-*N*′-(4-methylphenyl)

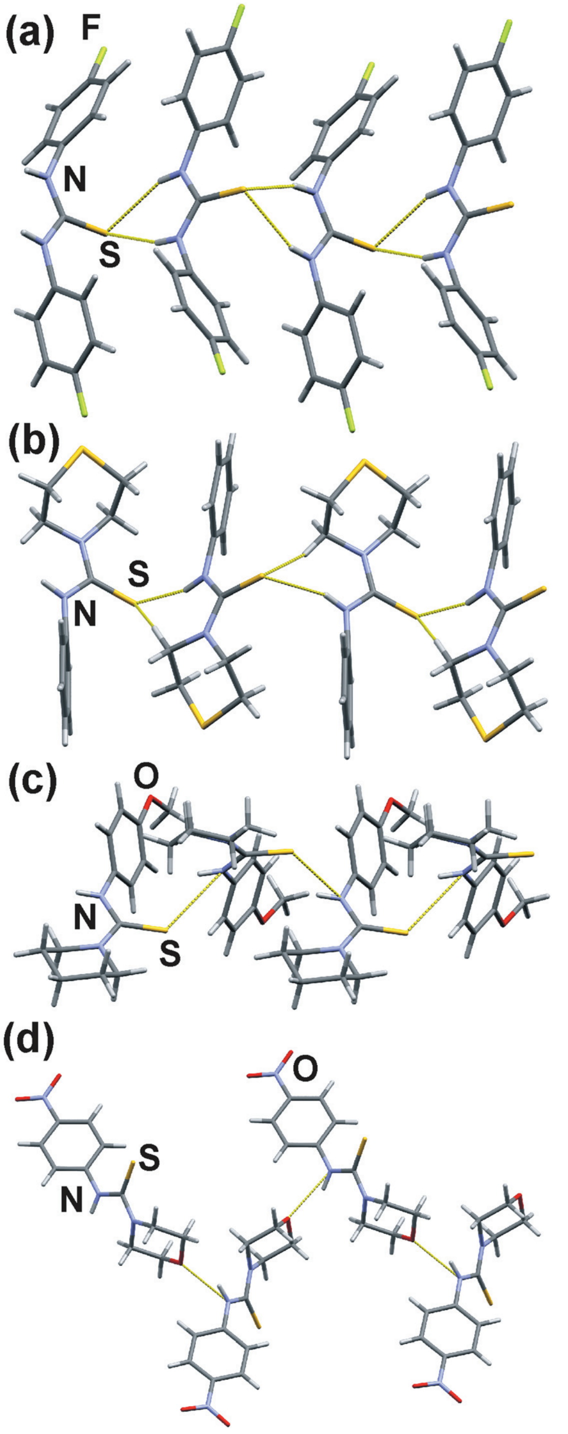


Fig. 2 Assembly of molecules *via* N–H···S hydrogen bonds in the crystal structures of compounds: (a) *N*,*N*′-bis(4-fluorophenyl)thiourea (**3d**); (b) *N*-phenyl-*N*′-thiomorpholinothiourea (**2k**); (c) *N*-(4-methoxyphenyl)-*N*′-piperidinothiourea (**1i**) and (d) polymorph 1 of *N*-(4-nitrophenyl)-*N*′-morpholinothiourea (**4j**). The N–H···S hydrogen bonds are shown as yellow dotted lines.

thiourea (**4b**), *N*-(4-fluorophenyl)-*N*′-(isopropyl)thiourea (**3f**) and *N*-phenyl-*N*′-(2,6-dimethylphenyl)thiourea (**2m**). In order to conduct solvent-free structural analysis in a typical laboratory environment, which would be in accordance with the previously explained concept of a solvent-free laboratory,[26a] structure determination was limited to measurements conducted on a laboratory instrument in the simple flat-plate data collection mode. The structure indexing procedure was conducted using either DICVOL04 or DIVOL06[45] within the DASH[46,47] package distributed by the Cambridge Crystallographic Data Centre (CCDC). Indexing provided satisfactory unit cell parameters for all datasets and structure solution was pursued using the simulated annealing techniques in DASH.

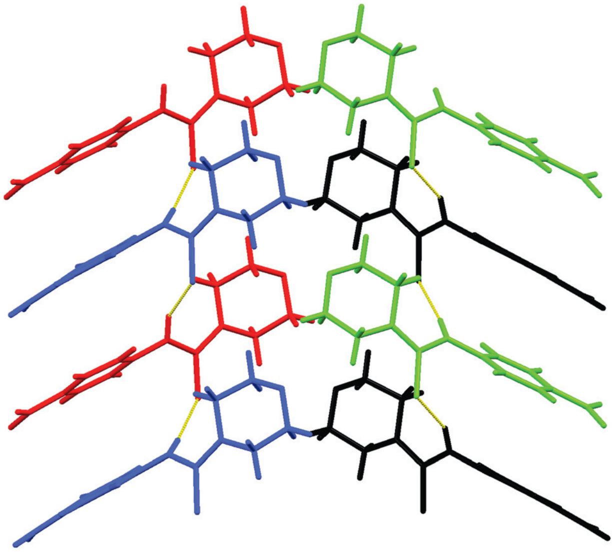


Fig. 3 The assembly of four crystallographically independent types of **4j** molecules in the crystal structure of the **4j** polymorph 2. The crystallographically distinct molecules are colour coded, and N–H···S hydrogen bonds are shown as yellow dotted lines.

Crystal structure solution provided plausible preliminary solutions for compounds **1c**, **4b**, **3f** and **2m**. However, numerous attempts at solving the structure of *N*-(4-chlorophenyl)-*N*′-(4-methoxyphenyl)thiourea **1e** did not yield a reasonable solution, most likely due to problems of preferred orientation when using flat-plate scans. The visual inspection, as well as the indexing of the PXRD pattern indicated that **1e** should be isostructural to the previously reported symmetrical *N*,*N*′-bis(4-methoxyphenyl)-thiourea (**1a**) (CCDC code WEFQEE).[48] This enabled an alternative approach to elucidating the crystal structure of **1e**, by applying a suitable space group to the unit cell previously reported for bis(4-methoxyphenyl)thiourea. The isostructurality and the reduction in molecular symmetry on going from *N*,*N*′-bis-(4-methoxyphenyl)thiourea (**1a**) to *N*-(4-chlorophenyl)-*N*′-(4-methoxyphenyl)thiourea (**1e**) implied that the most suitable choices of the space group would involve either a disordered structure with the full retention of space group symmetry, or a fully ordered structure with a reduced space group symmetry. This dilemma was resolved with the aid of solid-state magic angle spinning (MAS) cross-polarization (CP) ^{13}C NMR spectroscopy. The ^{13}C CP-MAS solid-state NMR spectrum of **1e** (Fig. 4) strongly indicated only one molecule per asymmetric unit (*i.e.* $Z' = 1$). The NMR signal for the carbon atom of the methoxy group was particularly sharp, which clearly indicated only one crystallographically independent type of molecule. This indicated space groups $P2_12_12$, $P2_12_12_1$ and $Pna2_1$ as potential candidates.

The preliminary crystal structures for **1c**, **4b**, **3f**, **1e** and **2m** were reasonable both in terms of the molecular geometry as well as in terms of supramolecular interactions. The preliminary structures displayed either the characteristic thiourea N–H···S motif of hydrogen bonds bifurcated on the sulfur acceptor (for **1c**, **4b** and **3f**) or the formation of a known $R_2^2(8)$ hydrogen bonded motif composed of N–H···S interactions (for **2m**). The three potential space group choices for **1e** all yielded the crystal structure composed of molecular stacks held by bifurcated N–H···S hydrogen bonds. The choice of $Pna2_1$ led to stacks composed of molecules oriented in parallel, whereas for the $P2_12_12$ and $P2_12_12_1$ space groups the molecules were aligned in an alternating, antiparallel fashion.

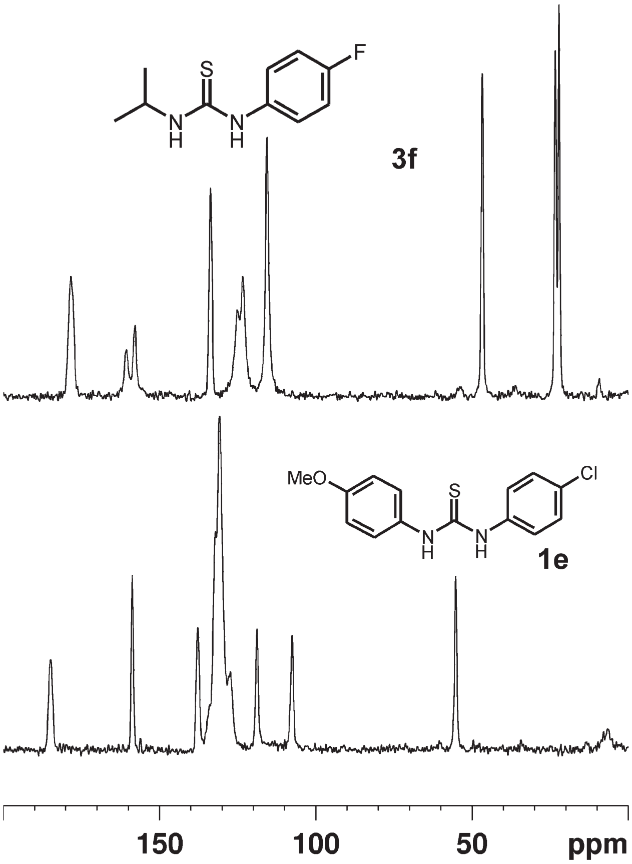


Fig. 4 Solid-state ^{13}C CP-MAS NMR spectra for the compounds **3f** (top) and **1e** (bottom).

The initial structure solution for **3f**, however, indicated the existence of two crystallographically independent molecules in the unit cell ($Z' = 2$). Whereas crystal structures with $Z' > 1$ are well known, their occurrence is generally considered unusual. Similarly to the case of **1e**, we employed solid-state CP-MAS ^{13}C NMR spectroscopy to verify the correctness of the crystallographic determination. All recorded solid-state CP-MAS NMR spectra, including that of **3f**, exhibited a slightly broad singlet for the thiourea carbon atom, consistent with $Z' = 1$ and the presence of two quadrupolar nitrogen nuclei. The signals for 4-methyl and 4-methoxy groups, where present in the molecular structure, were sharp singlets. For compound **3f**, the solid-state NMR spectrum (Fig. 4) revealed three sharp signals in the region characteristic for aliphatic groups, which strongly suggested only one crystallographically independent isopropyl group in the crystal structure and, therefore, $Z' = 1$. Consequently, we concluded that the structure of **3f** obtained from PXRD data was erroneous. The initial structural models for four (**1c**, **1e**, **2m** and **4b**) out of five molecules were considered suitable for Rietveld refinement. The refinement was conducted using the Topas software[49] and, by using rigid body restraints for the phenyl rings, provided reliable and reasonable crystal structures for compounds **1c**, **2m** and **4b** (Table 5, Fig. 5 and 6).

For compound **1e**, the careful Rietveld refinement indicated that the $P2_12_12$ model was superior to the $P2_12_12_1$ or the $Pna2_1$ one. However, in order to verify the correctness of the $P2_12_12$ structure, we resorted to single crystal structure determination. Whereas the single crystal growth experiments consistently provided very thin plates, those grown from a methanol–acetone solution were found suitable for single crystal X-ray diffraction. Structure determination procedure revealed a unit cell identical to that expected from powder diffraction experiments. However, the space group was determined as *Pbcm*, identical to that of the symmetrical *N*,*N′*-bis(4-methoxyphenyl)thiourea (**1a**) structure WEFQEE.[48] This highly symmetrical space group requires the molecule of **1e** to be disordered over a mirror plane, which is inconsistent with the order inferred by solid-state ^{13}C CP-MAS NMR.

Table 5 Crystallographic parameters for the crystal structures of thioureas **1c**, **1e**, **2n** and **4b** determined from PXRD data

Compound reference	**1e-PXRD**	**2m**	**1c**	**4b**
Chemical formula	$C_{14}H_{13}Cl_1N_2O_1S_1$	$C_{15}H_{16}N_2S_1$	$C_{14}H_{14}N_2O_1S_1$	$C_{14}H_{13}N_3O_2S_1$
Formula mass	292.79	256.37	258.34	287.34
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Orthorhombic
a (Å)	7.9168(4)	12.6721(3)	28.494(2)	14.5044(9)
b (Å)	31.787(2)	9.7973(3)	5.5557(3)	13.6232(9)
c (Å)	5.5767(3)	12.1009(3)	8.1430(4)	7.1408(3)
β (°)	90	115.223(1)	90.748(4)	90
Unit cell volume (Å^3)	1403.4(1)	1359.12(6)	1289.0(1)	1411.0(1)
Temperature (K)	293	293	293	293
Space group	$P2_12_12$	$P2_1/n$	$P2_1/c$	$Pna2_1$
Z	4	4	4	4
ρ_{calc} (g cm^{-3})	1.39	1.25	1.33	1.35
R_p	0.0367	0.0293	0.0395	0.040
R_{wp}	0.0501	0.0406	0.0522	0.053
X	0.559	0.571	0.975	0.732

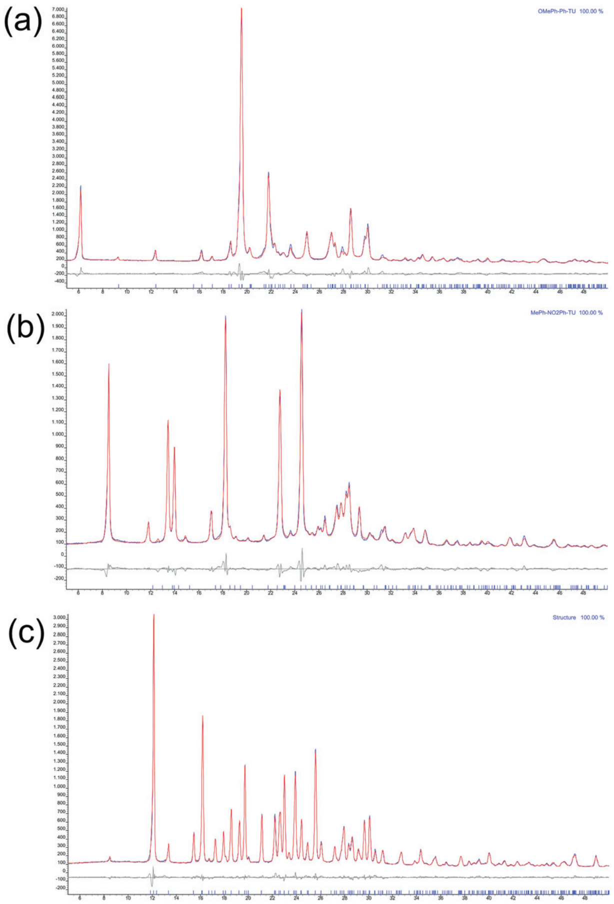


Fig. 5 Rietveld fits of experimental (blue line) and simulated (red line) PXRD patterns and for compounds: (a) **1c**, (b) **4b** and (c) **2m**. The difference between experimental and calculated patterns is shown in grey.

It is possible that the inconsistency between single crystal X-ray diffraction and solid-state NMR is a result of single crystals being composed of micro-scale domains of different orientation. Whereas the structure of each individual domain would be organized so as to provide a sharp NMR signal, the different orientations of the domains lead to a pseudo-centrosymmetric average structure being observed using single crystal X-ray diffraction. Although single crystal structure determination provided only an averaged distribution of the phenyl ring substituents in the crystal structure of **1e**, the inspection of the overall molecular packing allowed verification of the model structures based on powder diffraction. The projections of the structure along the crystallographic (010) and (001) directions clearly revealed correspondence to the structure obtained by powder X-ray structure determination in the $P2_12_12$ space group. Consequently, single crystal analysis indicates the validity of the structure indicated by Rietveld refinement. As a further confirmation of the non-centrosymmetric structure deduced by combination of PXRD structure determination and solid-state NMR, we compared the PXRD pattern simulated for the structure of **1e** obtained by single crystal diffraction to the measured one. Following Rietveld refinement, the fit of the structure in the *Pbcm* space group was considerably worse than that obtained for the structure in the $P2_12_12$ space group (see ESI†).

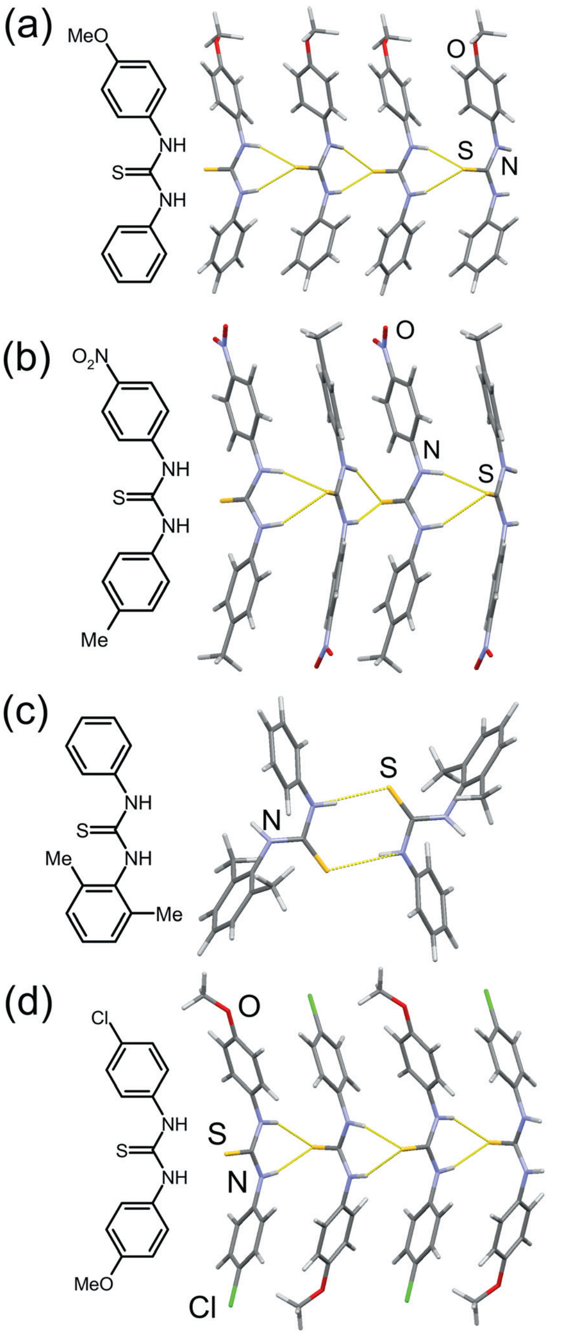


Fig. 6 Fragments of crystal structures determined from PXRD data along with molecular diagrams for (a) **1c**, (b) **4b**, (c) **2m** and (d) **1e**.

Self-assembly of simple bis(aryl)thioureas in the solid-state

The structures of **1c**, **1e**, **2m** and **4b** determined from PXRD data provide insight into the supramolecular chemistry of simple bis(aryl)thioureas in the solid state. According to the recent edition of the CSD, the crystal structures of pure symmetrical and non-symmetrical bis(aryl)thioureas have been poorly studied, with 12 and 7 chemically distinct examples recorded in the database, respectively.[48,50,51] The four PXRD structures provided herein illustrate three different types of self-assembly motifs based on N–H···S hydrogen bonds (Fig. 6): corrugated chains of molecules aligned head-to-head (parallel molecular dipoles) in **1c**; corrugated chains of head-to-tail aligned molecules (antiparallel molecular dipoles) in **1e** and **4b**; and discrete dimers based on the $R_2^2(8)$ supramolecular synthon in **2m**. The comparison of PXRD patterns for all bis(aryl)thioureas synthesized herein (Fig. 7) reveals that these structures could be representative of two families of solid-state structures adopted by symmetrical as well as non-symmetrical *p*-substituted bis(aryl) thioureas. We propose that these structural families, designated I and II, are based on the corrugated chains of molecules held by bifurcated N–H···S hydrogen bonds observed in structures **1c**, **1e** and **4b** and in previously reported structures of symmetrical bis (aryl)thioureas. In the structural family I these supramolecular chains are juxtaposed so as to form parallel stacks (Fig. 8).

Such supramolecular architecture gives rise to a characteristic (200) reflection at the Bragg angle range 5–7° in the PXRD pattern which corresponds to the width of the supramolecular stack. The (200) reflection also corresponds to the lattice separation between sulfur atoms in neighboring hydrogen-bonded stacks, which explains the pronounced intensity of this reflection.

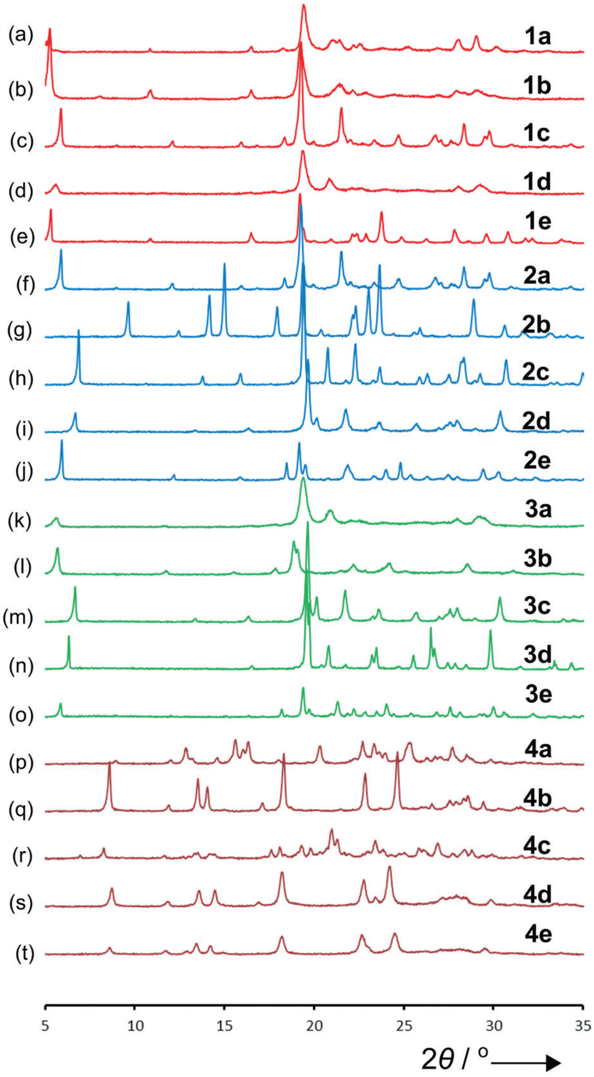


Fig. 7 Comparison of PXRD patterns for the simple *p*-substituted *N*,*N′*-diaryl(thioureas) prepared by click-mechanochemical coupling. Inspection of the patterns indicates that most compounds belong to the structural family I, while **2b** and **4b–4e** form the structural family II. The PXRD pattern of **4a** does not belong to either of the structural families.

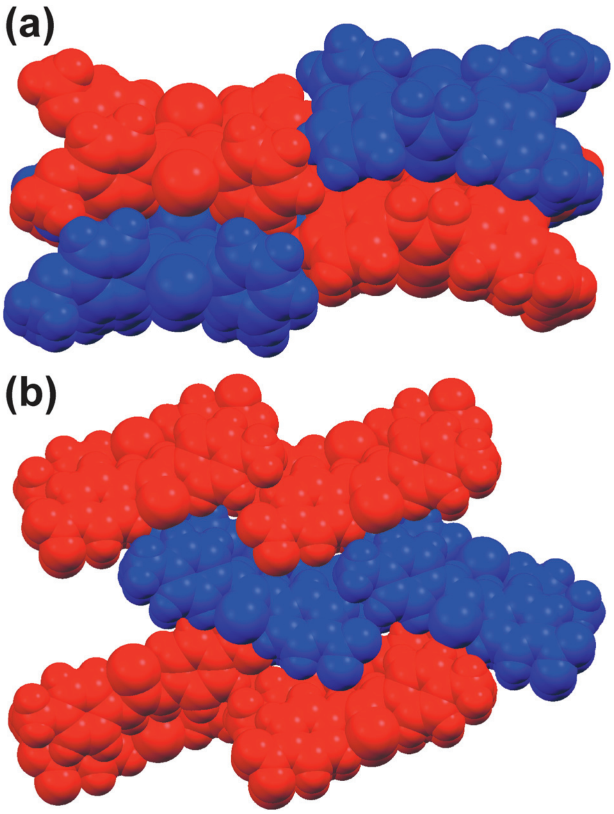


Fig. 8 Arrangement of molecules in two structural families of *p*-phenyl substituted thioureas, viewed along the N–H···S hydrogen-bonded chains: (a) structural family I and (b) structural family II.

The structural family II is characterised by a characteristic (110) reflection at the Bragg angle range 8–10° in the PXRD pattern. The (110) plane again corresponds to the separation between strongly scattering sulfur atoms in nearest-neighbour hydrogen-bonded molecular stacks which are now arranged in a herringbone pattern with an angle of 44° between neighbouring stacks (Fig. 8). The inspection of PXRD patterns for bis(aryl)-thioureas containing 2,4-dimethylphenyl or 2,6-dimethylphenyl moieties does not reveal such a clear division into structural families (Fig. 9). This could be the result of the formation of discrete $R_2^2(8)$ hydrogen-bonded dimers, as the ones observed for **2m**, instead of infinite hydrogen-bonded stacks. Presumably, the three-dimensional crystallographic arrangement of discrete molecular dimers would be more sensitive to changes to molecular structure than the assembly of one-dimensional hydrogen-bonded chains.

Conclusions

Mechanochemical milling was used to conduct quantitative synthesis of 49 different monothioureas based on variously substituted aromatic, aliphatic, heterocyclic, primary, as well as

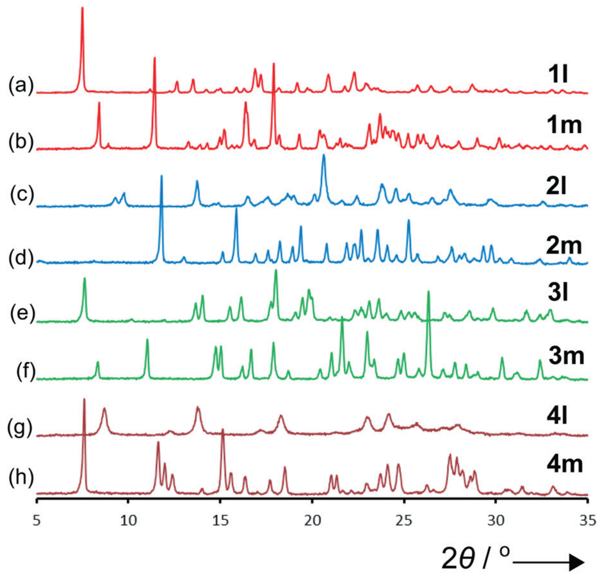


Fig. 9 Comparison of PXRD patterns for the *N*,*N*′-diaryl(thioureas) substituted with 2,4-dimethyl- or 2,6-dimethylphenyl groups.

secondary amine building blocks. This extensive synthetic investigation demonstrated the efficiency and functional group tolerance of mechanochemical synthesis in conducting thiourea click coupling reactions either in a completely solvent-free environment (manual and mechanochemical neat grinding), or in the presence of a catalytic amount of a liquid phase (liquid-assisted grinding, LAG). A large proportion (at least 40%) of the mechanochemically synthesized products displayed high quality powder diffraction patterns that, in principle, should be amenable to solvent-free crystal structure determination from laboratory X-ray powder diffraction data. This possibility was explored by attempting structural characterization on five randomly selected target molecules, relying exclusively on conventional laboratory X-ray powder diffraction data. Structural characterization was straightforward in three out of five cases (60%). One more structure was accessible through a more involved procedure requiring crystallographic experience. Structure determination failed in only one out of five explored cases. The correctness of the structural characterization could be verified through simple one-dimensional ^{13}C solid-state NMR measurements.[52]

Structural and spectroscopic characterization of thioureas directly from a mechanochemical synthesis demonstrates the viability of a solvent-free approach to the synthesis and analysis of small rigid organic molecules. Whereas this current study is limited to simple organic reactivity at a proof-of-principle level, we hope it will encourage the further development of solvent-free research procedures in more complex synthetic systems.‡

We acknowledge the financial support of the Unity Through Knowledge fund (project no. 63/10) and support of the Ministry of Science, Education and Sport of Croatia (Projects No. 098-0982933-2920). McGill University, the FQRNT Centre for Self-Assembled Chemical Structures, the NSERC Discovery Grant program, Canada Foundation for Innovation Leaders Opportunity Fund, and the FQRNT Nouveaux Chercheurs program are acknowledged for support.

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‡ We believe the presented model of solvent-free organic synthesis could be employed in research, as well as in the teaching laboratory environment, as it is amenable to a variety of solid-state analysis techniques normally available in the latter context, such as FTIR-ATR or Raman spectroscopy (see ESI, Fig. S50–S54†).

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