## COMMUNICATION

## Desymmetrisation of aromatic diamines and synthesis of non-symmetrical thiourea derivatives by click-mechanochemistry $\dagger$

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*ortho-* and *para-*Phenylenediamines were desymmetrised and quantitatively transformed into mono- and bis-(thio)ureas or mixed thiourea–ureas through a one-pot mechanochemical click reaction sequence; mechanochemical desymmetrisation proceeds quantitatively without excess reagents and allows the controlled extension of a molecular structure by combining normally competing reactions.

Mono-functionalization of small symmetrical molecules is an important goal of laboratory and industrial chemistry,<sup>1</sup> as it enables the desymmetrisation of simple precursors into nonsymmetrical and/or chiral building blocks for organic synthesis<sup>2</sup> or the design of advanced materials (liquid crystals,<sup>3</sup> oligo- and polymers based on donor-acceptor units).4,5 While procedures for such desymmetrisation of small molecules cover a broad range of reactions, including classical organic transformations,<sup>6</sup> solidphase transformations,<sup>2,7</sup> metal-based<sup>8</sup> and enzymatic<sup>9</sup> catalysis, the development of new and efficient desymmetrisation routes remains a challenge. This is reflected in the fact that a majority of synthetic molecules contain an even number of carbons, being derived by dimerisation or symmetrical functionalisation of precursors.<sup>10</sup> Mono-functionalization of symmetrical molecules often implies poor atom efficiency due to byproducts or excess starting materials, making the challenge of efficient desymmetrisation increasingly relevant in Green Chemistry due to the growing need to maximise atom economy and minimise the use of solvents, energy and production of waste.11

We now present a methodology for the selective and nearquantitative mono- and difunctionalisation of aromatic *ortho*and *para*-phenylenediamines using mechanochemistry.<sup>12,13</sup> Recently, we described<sup>14</sup> how the click<sup>15</sup> coupling of amines and isothiocyanates can be improved to >99% isolated yield by mechanochemical liquid-assisted grinding (LAG). We noted that *ortho*-phenylenediamine (*o*-pda, Scheme 1) can be selectively reacted



**Scheme 1** Synthesis of symmetrical and non-symmetrical *o*-phenylenediamine (thio)urea derivatives by ball milling (Table 1).

with either one or two equivalents of phenyl isothiocyanate to vield the non-symmetrical amino-thiourea 1b or the symmetrical bis-thiourea **2b** in 95% and >99% (quantitative) yields, respectively.<sup>14</sup> This indicated that the excellent control of the stoichiometric composition of the product in mechanochemistry, established for cocrystals and coordination polymers,<sup>16</sup> could also be valid for simple organic reactions. We now confirm such stoichiometric control in mechanochemical click-thiourea coupling and demonstrate that it provides a facile and clean one-pot route to desymmetrisation of aromatic diamines, and to the synthesis of symmetrical and non-symmetrical bis-(thio)ureas that are in solution obtained in poor yields.<sup>17</sup> We focus on aromatic (thio)ureas derived from o-pda, as these compounds have found extensive applications in organic and supramolecular chemistry as catalysts and anion sensors.17,18

First, we explored the click-mechanochemical reactivity of *o*-pda with equimolar aryl isothiocyanate (Scheme 1). After 30 minutes of LAG (methanol, solid-to-liquid ratio<sup>19</sup>  $\eta$  = 0.25  $\mu$ L mg<sup>-1</sup>), the mono-thioureas **1a-d** were synthesized in an excellent  $\geq 98\%$  yield (Table 1).§ The synthesis of bisthioureas by the amine-isothiocyanate coupling in the 1:2 molar ratio required longer reaction time:  $N^1, N^2$ -bis[N-(4-methoxyphenyl)-thiocarbamoyl]-1,2-diaminobenzene (2a) was obtained in  $\geq 95\%$  yield after 9 hours, whereas the phenyl (2b), *p*-chloro (2c) and p-nitro (2d) derivatives quantitatively formed after 3 hours of LAG. The selective mechanosynthesis of mono- and bis(thioureas) by simply varying the ratio of reagents clearly indicates the click-mechanochemical thiourea coupling as a clean route for the desymmetrisation of o-pda. The excellent yields of 1a-d revealed an opportunity to synthesise non-symmetrical bis(thioureas) using a one-pot click-mechanochemical procedure which obviates conventional solvent-based isolation and purification of the mono-thiourea intermediate. The reaction of mono-thioureas 1a ( $R^1 = OCH_3$ ) and 1d ( $R^1 = NO_2$ ) with

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 Table 1
 Reaction conditions and yields for the click-mechanochemical desymmetrisation of *o*-pda

Compound	$\mathbf{R}^1$	$\mathbb{R}^2$	X,Y	Conditions <sup>a</sup>	Yield <sup>b</sup> /%
1a	OCH <sub>3</sub>	_	S,-	LAG, 30 min	≥ 98
1b	Н		S,-	Neat, 30 min	$\geq 95^{14}$
1c	Cl		S,-	LAG, 30 min	$\geq 99$
1d	$NO_2$		S,-	LAG, 30 min	$\geq 98 \ (78)^{18}$
1e	Н		O,-	Neat, 30 min	78
2a	OCH <sub>3</sub>	OCH <sub>3</sub>	S,S	LAG, 540 min	$\geq 95$
2b	Н	Н	S,S	LAG, 180 min	$\geq 99^{14}$
2c	Cl	Cl	S,S	LAG, 180 min	$\geq 99$
2d	$NO_2$	$NO_2$	S,S	LAG, 180 min	$\geq 99 \ (54)^{21}$
2e	$OCH_3$	Cl	S,S	LAG, 180 min	≥ 99
2f	OCH <sub>3</sub>	$NO_2$	S,S	LAG, 180 min	$\geq 99$
2g	$NO_2$	Cl	S,S	LAG, 180 min	$\geq 97$
2ĥ	Н	$NO_2$	S,S	LAG, 30/180 min	$68 \ge 99$
2i	Н	Н	0,0	Neat, 30 min	$\geq 99 \ (96)^{20}$
2j	$OCH_3$	Н	S,O	Neat, 180 min	$\geq 99$
2k	Η	Н	S,O	Neat, 180 min	$\geq 99$
21	Cl	Н	S,O	Neat, 180 min	$\geq 99$
2m	$NO_2$	Н	S,O	Neat, 180 min	$\geq 99$
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<sup>*a*</sup> A single 12 mm diameter stainless steel ball was used in all experiments, frequency of 30 Hz. <sup>*b*</sup> Based on <sup>1</sup>H NMR analysis.

*p*-chloro or *p*-nitro isothiocyanate afforded non-symmetrical bis-thioureas 2e-g in  $\ge 99\%$  yield after 3 hours.

In solution, *o*-pda-based bis-ureas are generally obtained in higher yields than the corresponding bis-thioureas.<sup>17</sup> To compare reported solution results with mechanochemistry, we investigated the reactions of o-pda and mono-urea 1e with phenyl isocyanate under milling conditions used for bis-thioureas 2a-g. Milling o-pda and phenyl isocyanate in a molar ratio of 1:2 yielded quantitatively 2i, a known anion sensor,<sup>20</sup> in 30 minutes. The 1:1 reaction, however, yielded a mixture of mono-urea 1e (78%), bis-urea 2i (12%) and o-pda (10%), demonstrating the uniqueness of click-mechanochemical thiourea coupling for the desymmetrisation of o-pda. Furthermore, milling 1e with one equivalent of *p*-nitrophenyl isothiocyanate for 30 minutes yielded the mixed urea-thiourea 2m in  $\geq 99\%$  yield. The analogous reaction of the mono-thiourea 1b yielded the bisthiourea 2h in only 68% yield (Table 1), revealing enhanced reactivity of the urea 1e compared to the analogous thiourea 1b.

The selective conversion of *o*-pda into non-symmetrical aminomono(thioureas) provided an opportunity to synthesize mixed urea-thioureas in a one-pot, two-step solvent-free process. Addition of one equivalent of phenyl isocyanate to mono-thioureas **1a-d** mechanochemically synthesized from *o*-pda, followed by three hours of milling quantitatively yielded the mixed urea-thioureas **2j-m**. The same compounds could also be prepared by a "reverse" mechanosynthesis starting from the mono-urea **1e**, but without the obvious advantage of conducting the synthesis from *o*-pda in a one-pot, solvent-free manner.<sup>22</sup>

Next, we explored the desymmetrisation of the sterically less hindered *para*-phenylenediamine (*p*-pda). Presumably due to reduced steric hindrance, selective desymmetrisation of *p*-pda was more tantalising. As a model reaction, we used the synthesis of the *p*-methoxy derivative **3a** ( $\mathbb{R}^1 = OCH_3$ , Scheme 2). The solution synthesis yielded 78% of **3a**. Mechanochemical milling of a neat equimolar mixture of *p*-methoxyphenyl isothiocyanate and *p*-pda resulted in only 65% conversion to **3a**, along with 17% of bis-thiourea **4a** and 18% of unreacted *p*-pda (Scheme 2, Table 2). The yield was increased using LAG with ethyl acetate



Scheme 2 Mechanochemical desymmetrisation of *p*-phenylenediamine.

 
 Table 2
 Optimisation of the reaction conditions for the mechanosynthesis of 3a from *p*-phenylenediamine

Entry	Grinding material <sup>a</sup>	Conditions <sup>b</sup>	Yield <sup>c</sup> / %
1	Steel	Neat	65
2	Steel	LAG – methanol	70
3	Steel	LAG – water	36
4	Steel	LAG – DMF	70
5	Steel	LAG – cyclohexane	74
6	Steel	LAG – EtOAc	88
7	Steel	LAG – EtOAc, 8 mm ball	91
8	Teflon	Neat	67
9	Teflon	LAG – EtOAc	93
10	Teflon	$LAG - EtOAc$ , <sup>d</sup> $m(NaCl) = 10 \times m(p-pda)$	95
11	Teflon	$LAG - EtOAc$ , $dm(NaCl) = 20 \times m(p-pda)$	$\geq 96$
12	Teflon	$LAG - EtOAc$ , <sup>e</sup> $m(NaCl) = 20 \times m(p-pda)$	$\geq 97$

<sup>*a*</sup> Grinding jars and balls. <sup>*b*</sup> A single 12 mm diameter stainless steel or 10 mm Teflon grinding ball, 30 minutes, 30 Hz frequency,  $\eta =$ 0.25 µL mg<sup>-1</sup> (for LAG). <sup>*c*</sup> From <sup>1</sup>H NMR <sup>*d*</sup> Diluted with NaCl. <sup>*e*</sup> Diluted with NaCl,  $\eta = 0.8 \,\mu\text{L mg}^{-1}$ . The  $\eta$  value is the ratio of the added liquid and the total mass of reactants,<sup>19</sup> not including the NaCl diluent.

as the grinding liquid. Reducing the diameter of the milling ball from 12 mm to 8 mm increased the conversion to 91%. Using Teflon grinding media/jar also improved the conversion (93%).

To further increase the yield of **3a**, we resorted to sample dilution. To preserve the environmentally-friendly nature of the process, we used NaCl as a diluent that can be readily washed away with water. The sample dilution strategy followed by simple aqueous workup (see ESI<sup>‡</sup>) gave the pure 3a in an excellent 97% isolated yield (Table 2, entry 12). This approach was not successful for the *p*-nitrophenyl derivative **3b**, yielding a mixture of the mono-thiourea 3b, bis-thiourea 4b and p-pda. Such a result can be explained by higher reactivity of *p*-nitrophenyl isothiocyanate compared to its *p*-methoxy analogue. The 1:2 milling with *p*-pda quantitatively yielded the symmetrical bis-thioureas 4a ( $R^1$ ,  $R^2 = OCH_3$ ) and 4b ( $R^1$ ,  $R^2 = NO_2$ ) after only 30 minutes. Milling 4a and p-chloro or p-nitrophenyl isothiocyanate quantitatively yielded the non-symmetrical 4c  $(R^1 = OCH_3, R^2 = Cl)$  and 4d  $(R^1 = OCH_3, R^2 = NO_2)$ , respectively (Scheme 2).

To understand the differences in reactivity of *o***-pda** and mono-thioureas **1a–d**, which are key to the efficient clickmechanochemical desymmetrisation of *o***-pda**, we turned to density functional theory (DFT) at the B3LYP/6-311 + G(d,p)// B3LYP/6-31G(d) level.<sup>23</sup> Several conformations of monothioureas **1a–d** were optimised, whereby the thermodynamically most stable structures adopted the *trans*-orientation of the N–H thiourea protons. These structures are characterized by an N–H…N intramolecular hydrogen bond (IMHB) between the NH<sub>2</sub> acceptor and thiourea moiety as the donor. For example, in **1d**-*trans* the N···N distance is 2.924 Å. The second most stable structure of mono-thiourea **1d** has no IMHB and is less stable by 3.8 kJ mol<sup>-1.24</sup>



Fig. 1 HOMO-1 contours of (a) mono-thiourea 1b and (b) monourea 1e.

Formation of the IMHB could account for the reduced reactivity of mono-thioureas by imposing steric hindrance to the approach of the isothiocyanate reactant. Presumably, a combination of such molecular reactivity and the absence of solubility-imposed limitations under mechanochemical conditions enables the quantitative mono-functionalization of *o*-pda. Frontier molecular orbital (FMO) analysis of mono-thiourea–isothiocyanate pairs provided a suitable explanation for different reactivity of mono-thioureas **1a–d** compared to their urea analogues. The analysis indicated that the most important interactions involve the HOMOs (*e.g.* HOMO and HOMO-1) of mono-thioureas and the LUMOs of isothiocyanates (Tables S6 and S7 in ESI‡).

The HOMO analysis of **1a–d** reveals much larger orbital coefficients on sulfur compared to the nitrogen of the  $-NH_2$  group (illustrated for **1b**, Fig. 1a). The relative sizes of the molecular orbital coefficients on the chalcogen and amino nitrogen atoms in the HOMO-1 of mono-thioureas and -ureas are substantially different (Fig. S31 in ESI‡). Ureas exhibited a larger coefficient on the NH<sub>2</sub> nitrogen atom (shown for **1e**, Fig. 1b) and, presumably, a greater propensity for isocyanate addition.

Click-mechanochemical thiourea coupling enabled the quantitative and selective desymmetrisation of *ortho-* and *para*-phenylenediamines. To the best of our knowledge, our work is the first to demonstrate the controlled extension of a molecular structure in a purely mechanochemical sequence that combines competing bond-forming reactions: the thiourea synthesis and the urea synthesis. The described reactivity avoids the need to isolate intermediates and allows the building-up of non-symmetrical molecules in >95% yield over two steps. Our report complements previously reported multi-step mechanosyntheses which exploit non-competing reactions or involve purification steps.<sup>25</sup>

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## Notes and references

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- 22 Milling 1e with *p*-chlorophenyl isothiocyanate for 30 min gave 2l in 65% yield, with quantitative conversion achieved after 3 hours of milling. Under identical conditions *p*-methoxyphenyl isothiocyanate and 1e did not react (most of the reagents remained unreacted).
- 23 To evaluate the effect of the thiourea substituent on reactivity, Mulliken population analysis for the most stable conformer of **1a-d** was carried out. The analysis did not reveal any significant effect of the substituent on the charges on the NH<sub>2</sub> nitrogen atom.
- 24 The *cis*-conformer **1d**-*cis* displays an IMHB between the NH<sub>2</sub> group and the sulphur atom (N–H···S distance 3.360 Å), but is less stable than **1d**-*trans* by 17.6 kJ mol<sup>-1</sup> (see ESI<sup>‡</sup>).
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