Mechanochemistry

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Trapping Reactive Intermediates by Mechanochemistry: Elusive Aryl *N*-Thiocarbamoylbenzotriazoles as Bench-Stable Reagents**

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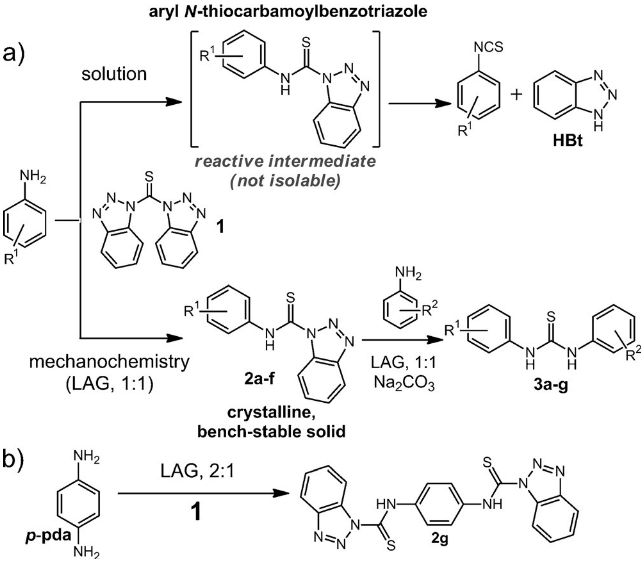
***Abstract:** Monitoring of mechanochemical thiocarbamoylation by in situ Raman spectroscopy revealed the formation of aryl N-thiocarbamoylbenzotriazoles, reactive intermediates deemed unisolable in solution. The first-time isolation and structural characterization of these elusive molecules demonstrates the ability of mechanochemistry to access otherwise unobtainable intermediates and offers a new range of masked isothiocyanate reagents.*

Mechanochemistry has emerged as an efficient means for rapid, solvent-free, and energy-efficient synthesis.[1] In organic synthesis,[2] neat and liquid-assisted grinding (LAG)[3] has provided rapid and clean access to a number of transformations, excellent control of reaction stoichiometry, and previously unknown reactivity.[4–6] We now demonstrate the ability of mechanochemistry to access reactive intermediates considered unisolable in solution. We describe the first synthesis and isolation of aryl *N*-thiocarbamoylbenzotriazoles (**2a**–**g**, Scheme 1) as bench-stable solids by milling bis(benzotriazolyl)methanethione (**1**)[7] with anilines (Table 1). Mechanochemical isolation of **2a**–**g** allows their use as reagents for the controlled solvent-free synthesis of thioureas (**3a**–**g**) without using corrosive isothiocyanates.



Scheme 1. a,b) In contrast to solution chemistry,[14–16] mechanochemical reactions of **1** and anilines give *N*-thiocarbamoylbenzotriazoles (**2a**–**g**) as stable solids which, upon milling with anilines and a base, afford thioureas (**3a**–**g**).

Table 1: LAG synthesis of aryl *N*-thiocarbamoylbenzotriazoles **2a**–**g** and thioureas **3a**–**g**.[a]

Compound	R^1	R^2	Yield of isolated product [%]
2a	4-Br	–	99
2b	4-Cl	–	98
2c	4-CH_3	–	98
2d	4-OCH_3	–	99
2e	2-NH_2	–	98
2f	4-NH_2	–	99
2g[b]	4-NH_2	–	99
3a	4-Br	4-Br	97[c]
3b	4-Cl	4-Cl	97
3c	4-CH_3	4-CH_3	98
3d	4-OCH_3	4-OCH_3	98
3e	4-OCH_3	4-Cl	97[d]
3f	4-Cl	4-Br	99[c,d]
3g	4-Br	2-NH_2	98[d,e]

[a] 10 min LAG with CH_3CN ($\eta = 0.25\ \mu L\,mg^{-1}$), 10 mm ball. [b] 2 equiv of **1**. [c] 45 min LAG. [d] Two-step synthesis. [e] 30 min LAG.

As part of our interest in the mechanosynthesis of ureas and thioureas,[8,9] we applied the recently introduced technique of in situ Raman spectroscopy monitoring of mecha-

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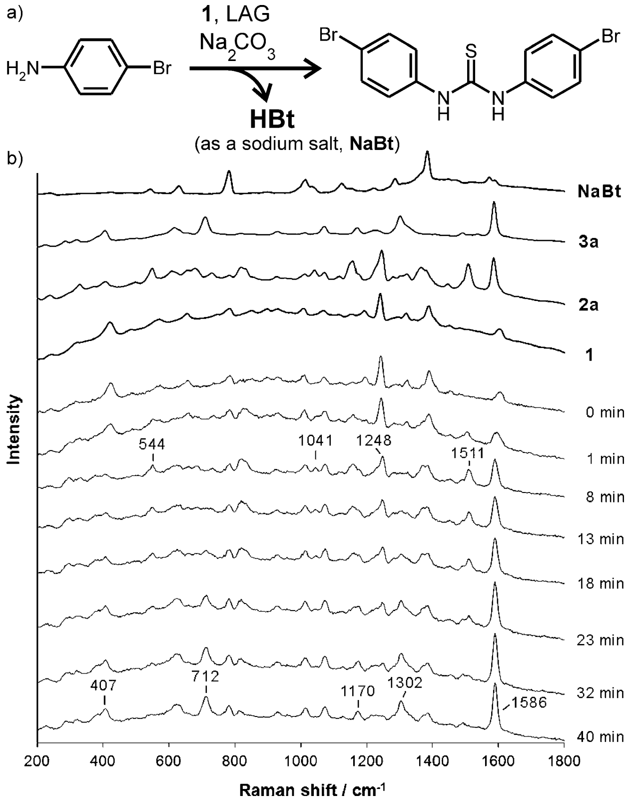

Figure 1. a) Mechanochemical base-assisted reaction of **1** and *p*-bromoaniline to form the thiourea **3a** and b) in situ collected Raman spectra for this reaction.

nochemical reactions[10–13] to the mechanosynthesis of **3a** by milling **1** with two equivalents of 4-bromoaniline in the presence of Na$_2$CO$_3$ (Figure 1a). While **1** is a known reagent for base-catalyzed thioacylations and thiocarbamoylations in solution,[7,14] thereby giving benzotriazole (HBt) as a by-product, its mechanochemical reactivity is still unexplored. Monitoring the reaction in situ reveals that characteristic bands of **1** are completely replaced with those of **3a** (e.g. 407, 712, 1170, 1302 cm^{-1}, Figure 1b) within 40 min. A characteristic band of the by-product HBt sodium salt also appears at 1380 cm^{-1}. However, the spectra also revealed an unknown intermediate with bands at 544, 1041, 1159, 1248, and 1511 cm^{-1}, appearing about 2 min into milling and disappearing concomitantly with the appearance of **3a**.

Katritzky et al. proposed that **1** reacts with anilines in solution via reactive aryl *N*-thiocarbamoylbenzotriazole intermediates that are not isolable due to their rapid fragmentation into isothiocyanates (Scheme 1).[14–16]

Speculating that the herein observed intermediate might be the elusive *N*-thiocarbamoylbenzotriazole, we repeated the milling without a base, and with only one equivalent of aniline. Under these conditions the intermediate was obtained as the only product (see the Supporting Information). Solution ^{1}H NMR spectroscopy and thin-layer chromatography revealed this product deteriorates quickly in organic solvents into HBt and 4-bromophenylisothiocyanate. However, a ^{1}H NMR spectrum recorded immediately after dissolution was consistent with the generation of *N*-thiocarbamoylbenzotriazole **2a** (Scheme 1, Table 1). Intrigued by the possibility of mechanochemically accessing such elusive molecules, we conducted LAG of **1** with a series of substituted anilines (Table 1, Scheme 1a,b). In all cases, LAG followed by simple aqueous washing gave crystalline solids, which were identified as *N*-thiocarbamoylbenzotriazoles **2a–g** by cross-polarization magic angle spinning (CP-MAS) ^{13}C and ^{15}N solid-state NMR spectroscopy (SSNMR, Figure 2a), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), and, where possible, structure determination from synchrotron powder X-ray diffraction (PXRD) data (Figure 2b,c and Figure 3a–d). Solid-state characterization was mandated by the instability of **2a–g** in solution: the ^{1}H NMR spectra in CDCl$_3$, [D$_6$]DMSO, or CD$_3$CN reveals degradation to isothiocyanates in minutes (see the Supporting Information). The 2-amino derivative **2e** decomposed in solution into 2-mercaptobenzimidazole (**4**) and HBt. In contrast, the compounds were stable in the solid state: FTIR-ATR spectra of mechanochemically prepared **2a–d** did not change after storage for more than 1 year.[17]

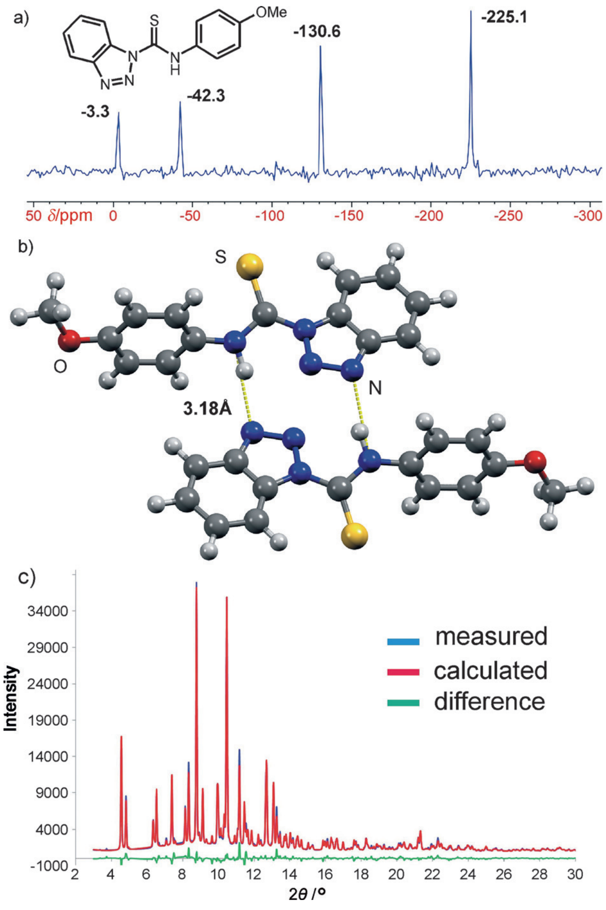

Figure 2. a) ^{15}N NMR CP-MAS SSNMR spectrum of **2d**; b) a centrosymmetric pair of **2d** molecules in the crystal structure, based on PXRD data; and c) final Rietveld fit for the crystal-structure determination of **2d** by PXRD.

The CP-MAS ^{13}C SSNMR spectra of **2a–g** reveal the signal of the thiocarbonyl group shifted downfield by about 2–

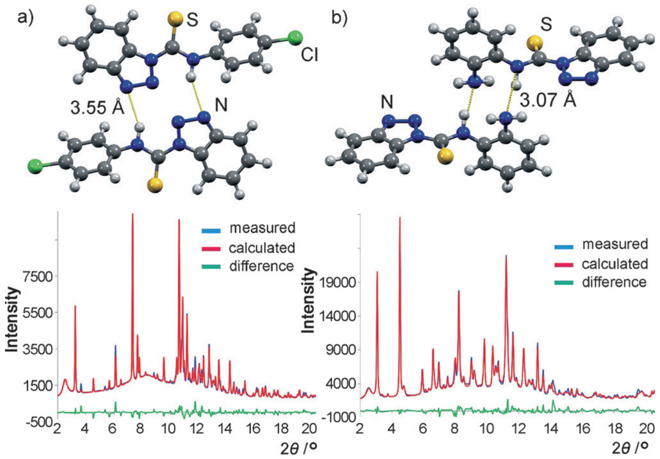

Figure 3. Centrosymmetric arrangement of molecules (top) and the final Rietveld fits (bottom) for the crystal structures of a) **2b** and b) **2e**, determined from PXRD data.

5 ppm relative to that of **1**. The spectrum of **2f** reveals signal twinning, thus suggesting $Z'=2$.[18] With the exception of **2f**, the ^{13}C SSNMR spectra for all the compounds are consistent with one molecule per asymmetric unit ($Z'=1$).

The ^{15}N CP-MAS SSNMR spectra of **2d** and **2g** (Figure 2a, see also the Supporting Information) showed four signals, consistent with four non-equivalent nitrogen atoms per molecule. TGA shows **2a–d** to be stable to approximately 120 °C, with the first decomposition event corresponding to elimination of aryl isothiocyanate, followed by loss of HBt. DSC of **2a–d** reveals a melting signal at 90–105 °C. Compound **2e** also undergoes an exothermic event at 92 °C, as a result of cyclization to **4** with loss of HBt, as confirmed by TGA and PXRD (see the Supporting Information). Crystal structures of **2b**, **2d**, and **2e** were determined from synchrotron PXRD data collected at the Canadian Light Source (CLS) beamline 08B1-1 ($\lambda=0.6897$ Å). Indexing gave monoclinic unit cells with $Z=4$. Determination of the structure using TOPAS revealed $Z'=1$, in agreement with SSNMR spectroscopic analysis. **2d**, **2b**, and **2e** are nonplanar, with the angle between the phenyl and benzotriazolyl substituents being 83°, 65°, and 86°, respectively. The thione and benzotriazole groups are nearly coplanar in all cases. The molecules form centrosymmetric pairs with long N−H⋯N interactions between the thiocarbamoyl group and benzotriazole (**2b**, **2d**) or 2-aminophenyl (**2e**) groups of neighboring molecules (Figures 2 and 3).

Amino-substituted *N*-thiocarbamoylbenzotriazoles, such as **2e** and **2f**, are attractive as precursors for catalytically interesting aminothioureas[19] and amino-substituted isothiocyanates. Both **2e** and **2f** were readily obtained by milling **1** with one equivalent of either *ortho*- (***o*-pda**) or *para*-phenylenediamine (***p*-pda**). The ^{1}H NMR spectrum of **2f** in [D$_6$]DMSO reveals rapid decomposition to the tentatively identified *p*-aminophenyl isothiocyanate (see the Supporting Information).[20] Although stable for weeks, solid **2f** slowly degrades on prolonged standing, as shown by ^{1}H NMR and FTIR-ATR spectroscopy.

The bis-*N*-thiocarbamoylbenzotriazole **2g** was quantitatively obtained by LAG of ***p*-pda** with two equivalents of **1** (Scheme 1b). Attempted analogous synthesis of the bis-*N*-thiocarbamoylbenzotriazole **5** from ***o*-pda** and two equivalents of **1** yielded the bisthione **6**, probably as a result of an intramolecular cyclization of the expected product (Figure 4a,b, see also the Supporting Information). The alternative path, cyclization of **2e** into **4** followed by reaction with **1**, was dismissed because **1** and **4** do not react on milling.

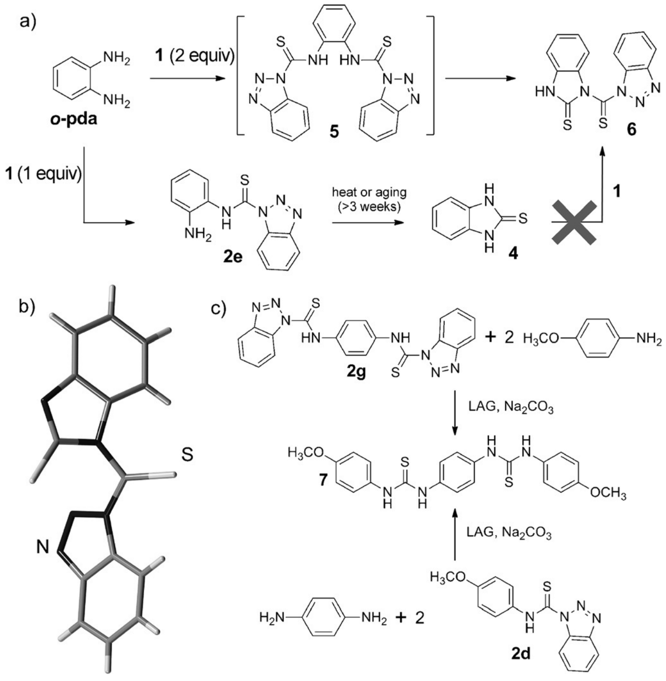

Figure 4. a) Mechanochemical reaction of ***o*-pda** with **1** in a 1:1 stoichiometric ratio yields **2e** (which slowly degrades into **4**) and milling in 1:2 ratio affords **6**, most likely by intramolecular cyclization of the expected **5**. b) Molecular structure of **6** from single-crystal X-ray diffraction. c) The use of mechanochemically prepared aryl *N*-thiocarbamoylbenzotriazoles as masked isothiocyanates.

Compounds **2a–d** represent masked aryl isothiocyanates that are useful in thiourea mechanosynthesis. Milling **2a–d** with anilines and Na$_2$CO$_3$ gave **3a–g** in near quantitative yields (Table 1). Symmetrical **3a–d** were also obtained by milling **1** with two equivalents of an aniline and Na$_2$CO$_3$, while nonsymmetrical **3e–g** were obtained by a two-step one-pot procedure from **1**, thus confirming the structures of **2a–d**. Similarly, **2g** allows the synthesis of bisthioureas: milling **2g** with *p*-anisidine and Na$_2$CO$_3$ gave **7** quantitatively after 3 h. The same product was obtained in 98 % yield by milling **2d** and ***p*-pda** with Na$_2$CO$_3$ for 45 min (Figure 4c).

In summary, real-time monitoring revealed the utility of mechanochemistry to trap and quantitatively synthesize molecules too reactive to access in solution. Solid-state analysis enabled the first structural, physical, and chemical identification of aryl thiocarbamoylated benzotriazoles and, in combination with structure determination from PXRD data, full structural characterization of members of this compound family. In addition to providing a new family of bench-stable thiocarbamoylation reagents, this also establishes mechanochemistry as a means to circumvent solvent-induced limitations of traditional synthesis.

Experimental Section

In a typical experiment, 200 mg of an equimolar mixture of **1** and a substituted aniline was milled for 10 min with dry CH_3CN (50 µL, $\eta = 0.25\ \mu L\,mg^{-1}$)[3] with a 10 mm stainless-steel ball in a Retsch MM400 mill at 30 Hz. The crude mixture was meticulously scraped from the jar and suspended in 10 mL distilled water by vigorous stirring for 30 min. The solid was filtered off, washed, and dried in air. **1** and **6** were also characterized by ^{1}H and ^{13}C NMR spectroscopy as well as single-crystal X-ray diffraction. See the Supporting Information for PXRD, FTIR, SSNMR, TGA/DSC, TLC, MS, solution degradation, and in situ monitoring data.

Crystallographic data: **1**: monoclinic, $P2_1/c$, $a = 8.747(5)$, $b = 7.370(5)$, $c = 19.079(12)$ Å, $V = 1228.6(13)$ Å^3, $Z = 4$, $R_1 = 0.0338$, $wR_2 = 0.0814$ (1795 data, $I \geq 2\sigma_I$); **6**: triclinic, $P\bar{1}$, $a = 7.1962(11)$, $b = 7.8855(12)$, $c = 12.7962(19)$ Å, $\alpha = 98.710(2)$, $\beta = 104.144(2)$, $\gamma = 93.099(2)°$, $V = 692.85(18)$ Å^3, $Z = 2$, $R_1 = 0.0484$, $wR_2 = 0.0987$ (1861, with $I \geq 2\sigma_I$); **2b**: monoclinic, $P2_1/n$, $a = 21.7933(7)$, $b = 14.7693(9)$, $c = 3.9624(1)$ Å, $\beta = 97.125(3)°$, $V = 1265.5(1)$ Å^3, $Z = 4$, $R_{exp} = 0.40\,\%$, $R_p = 2.73\,\%$, $R_{wp} = 3.84\,\%$; **2d**: monoclinic, $P2_1/n$, $a = 17.6266(8)$, $b = 8.9650(4)$, $c = 8.6183(5)$ Å, $\beta = 100.034(4)°$, $V = 1341.1(1)$ Å^3, $Z = 4$, $R_{exp} = 2.00\,\%$, $R_p = 4.98\,\%$, $R_{wp} = 6.46\,\%$; **2e**: monoclinic, $P2_1/c$, $a = 13.0760(3)$, $b = 12.0177(7)$, $c = 8.1421(9)$ Å, $\beta = 98.25(2)°$, $V = 1266.3(3)$ Å^3, $Z = 4$, $R_{exp} = 1.64\,\%$, $R_p = 3.85\,\%$, $R_{wp} = 5.53\,\%$. CCDC 1050984 (**1**), 1050985 (**6**), 1050986 (**2b**), 1050987 (**2d**), and 1050988 (**2e**) 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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[16] Alkyl and heteroaryl derivatives can be isolated from solution.[15]

[17] The presence of acetonitrile in LAG does not affect the integrity of **2a–g**, as established by PXRD analysis of crude reaction mixtures immediately after milling, which revealed only HBt and **2a–g**. Attempts to synthesize **2a** or **2d** by stirring **1** with 4-bromoaniline or *p*-anisidine in CH_2Cl_2 failed, only yielding a mixture of **2d**, the isothiocyanate, and HBt. Reactions in acetonitrile gave only HBt and respective isothiocyanate (Figures S41–S44). Such observations confirm that the reactivity of the catalytic liquid in LAG can be different from that in a bulk solvent: T. Friščić, A. V. Trask, W. Jones, W. D. S. Motherwell, *Angew. Chem. Int. Ed.* **2006**, *45*, 7546; *Angew. Chem.* **2006**, *118*, 7708.

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