

Mechanochemically Assisted Synthesis of Hexaazatriphenylenehexacarbonitrile

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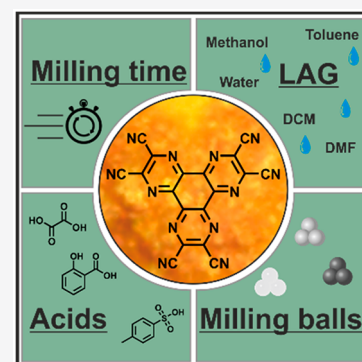


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Supporting Information

ABSTRACT: 1,4,5,8,9,11-hexaazatriphenylenehexacarbonitrile (HAT-CN) was synthesized mechanochemically at room temperature. The coupling of hexaketocyclohexane and diaminomaleonitrile was conducted in 10 min by vibratory ball milling. The effects of milling parameters, acids, dehydrating agents, and liquid-assisted grinding were rationalized. With 67%, the yield of this mechanochemical approach exceeds that of state-of-the-art wet-chemical syntheses while being superior with respect to time-, resource-, and energy-efficiency as quantified via green metrics.



INTRODUCTION

1,4,5,8,9,11-Hexaazatriphenylenehexacarbonitrile (HAT-CN) is a hydrogen-free trigonal planar conjugated aromatic compound, with a composition close to the C_2N stoichiometry. It is promising in OLED (organic light-emitting diode) architectures, where it can be used either as a protective layer,¹ as a doping material in hole injection layers,^{1–4} or even as a standalone interlayer.^{5,6} It also finds applications in organic solar cells,^{7–10} for the directed growth of graphene^{5,11–14} and the synthesis of porous carbon materials with high N-content.¹⁵ HAT-CN is commonly synthesized by a two-step reaction of hexaketocyclohexane and diaminomaleonitrile (Figure 1).¹⁶ We would like to note that, although it is

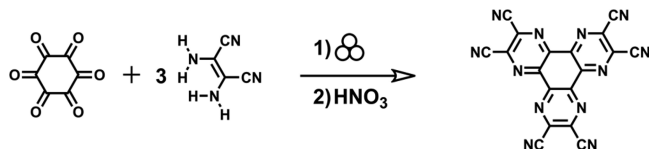


Figure 1. Synthetic pathway to obtain HAT-CN. Hexaketocyclohexane and diaminomaleonitrile are coupled in a condensation reaction with subsequent oxidation steps.

commonly referred to as hexaketocyclohexane octahydrate, this is not representative of the structure of the molecule. Crystallographic studies of Weigand and co-workers have shown that the molecule is, in fact, dodecahydroxycyclohexane dihydrate.¹⁷ However, since the community knows it as hexaketocyclohexane, we have decided to stick to the terminology for consistency. In the literature synthesis, first published by Czarnik et al.,¹⁶ both starting materials are

coupled in refluxing acetic acid (118 °C). The obtained raw product consists only of 50% HAT-CN and requires purification. Oschatz et al. refined the synthetic procedure by purification using hot nitric acid as well as refluxing acetonitrile to obtain pure HAT-CN (for more details, see [Supporting Information](#), chapter 2.4).¹⁵ This two-step reaction requires 2 days of work, of which 7 h are taken up by pure heating time. Additionally, high amounts of hazardous solvents are required to obtain around 50% yield.^{11,18} All of these factors render the synthesis neither sustainable, scalable, or economically viable. Within this contribution, we present a facile, cheap, time-resource-, and energy-efficient alternative based on mechanochemistry.^{19–28} Compared to the traditional wet-chemical approach, the reaction mixture requires no external heating. The activation energy is provided by the colliding milling balls inside ball mills, and the reactions run in the absence of solvents within minutes.^{29–33}

RESULTS AND DISCUSSION

With this contribution, we present a fast mechanochemically assisted synthesis of HAT-CN in as little as 10 min of milling, followed by a second step utilizing hot HNO_3 . The yields after those two steps are even higher than in traditional syntheses. We were able to completely omit the use of acetic acid and

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acetonitrile applying a mechanochemical approach, thus vastly improving the synthesis. Adapting the liquid phase protocol, we first investigated the reaction under strongly acidic conditions. However, the use of *p*-toluenesulfonic acid only leads to a low yield of 29% (Table 1, entry 2). The use of

Table 1. Screening of Solid Acids and Reaction Conditions^a

entry	additive	pK _a	yield [%]
1	sulfuric acid ^b	−3.00	11
2	<i>para</i> -toluene sulfonic acid monohydrate	−2.80	29
4	oxalic acid	1.23	41
5	KHSO ₄	1.92	35
6	salicylic acid	2.75	25
7	benzoic acid	4.20	0
8	ascorbic acid	5.25	0
9	P ₂ O ₅		0
10	FeCl ₃ anhydride		0
11	MgSO ₄		17
12	none		48
13 ^c	none		49

^aAll approaches were milled for 10 min at 35 Hz in a 10 mL ZrO₂ vial containing 0.40 g of hexaketocyclohexane, 1.10 g of diaminomaleonitrile, and a Ø = 10 mm ZrO₂ milling ball. Acids sorted by pK_a.
^bSulfuric acid is a liquid, and MgSO₄ was added as a bulk material.
^cMilled for 60 min

sulfuric acid gave even lower yields of 11% (Table 1, entry 1). These disheartening results lead to a change of mind, as we understood that the acid strength is not the decisive factor in this reaction. Following this realization, other acids were tested, which are solid but, in some cases, very weak regarding their pK_a. Some of the weaker organic solvents did not show any yield (Table 1, entries 7 and 8), but the use of oxalic acid leads to a significant improvement. It was the most efficient conversion, yielding 41% HAT-CN after mere 10 min of mixing (Table 1, entry 5). As the results were inconsistent regarding the used acids pK_a (see Table 1, entries 1–8), we hypothesized that the milling additive might play a crucial role and tested additives from a rheological perspective. Magnesium sulfate, phosphorus pentoxide, and other additives were used to shift the equilibrium of the condensation reaction due to their dehydrating properties.^{33,34} This screening gave yields of only a maximum of 17% (Table 1, entries 9–11). Following this result, we conducted the condensation reaction under neat conditions (i.e., acid-free and additive-free, however, please note that hexaketocyclohexane contains crystal water), mixing only the starting materials in the ball mill. This resulted in a yield of 48%. This simplified the reaction greatly but requested a further investigation, as the reaction appeared to run entirely different from what was known from the liquid phase (Table 1, entry 12). Longer milling periods of up to 60 min did not show a significantly enhanced conversion (Table 1, entry 13). To test the scalability, the approach was performed in bigger vials with higher quantities, leading to the same conversion as the smaller scale batches (Table S1, entry 12). During this screening, we observed that the reaction mixture in the neat approach appeared to be mud-like. We concluded that the water formed during the condensation leads to this appearance. As water might act physically or chemically as a self-accelerating side product, liquid-assisted grinding using water was tested (Figure 2).

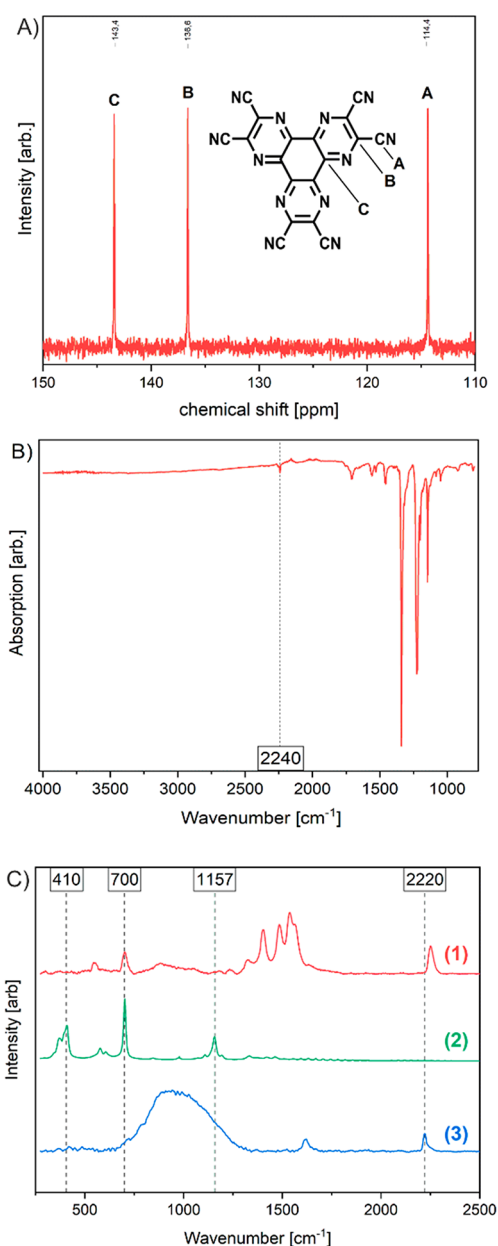


Figure 2. Spectroscopic analysis of HAT-CN. (A) ¹³C{¹H} NMR (300 MHz, CO(CD₃)₂) spectrum of pure HAT-CN. (B) IR spectrum of HAT-CN. (C) Stacked Raman spectra of HAT-CN and the starting materials used in the synthesis of HAT-CN. (1) Raman spectrum of HAT-CN. (2) Raman spectrum of hexaketocyclohexane. (3) Raman spectrum of diaminomaleonitrile.

We have investigated the influence of small quantities of various liquids (liquid-assisted grinding (LAG) with η between 0.1 and 0.5).^{35,36} For a first try, a η of 0.2 was used. This led to no product formation (Table 2, entry 2). The raw mixture appeared not to be a dark brown paste but a slurry, leading to the conclusion that a η of 0.2 was too high. Smaller amounts of water enhanced the yield significantly up to 67% (Table 2, entries 3 and 4). Please note that, even under neat conditions, i.e., η of 0, there is still crystal water from the hexaketocyclohexane present. As LAG with a η of 0.1 seemed to be the optimum, further investigations of LAG showed that small amounts of protic solvents like methanol and ethanol enhance the reaction rate by a small margin but not as efficient

Table 2. Screening of Liquid-Assisted Grinding and One-Pot Two-Step Process^a

entry	LAG additive	LAG amount [η]	yield [%]
1			48
2	H ₂ O	0.2	0
3	H ₂ O	0.1	67
4	H ₂ O	0.05	62
5	methanol	0.1	45
6	ethanol	0.1	50
7	toluol	0.1	29
8	DCM	0.1	36
9	DMF	0.1	19
10 ^b	H ₂ O	0.1	47
11 ^c			0

^aAll approaches were milled for 10 min at 35 Hz in a 10 mL ZrO₂ vial containing 0.40 g of hexaketocyclohexane, 1.10 g of diaminomaleonitrile, and 1 \emptyset = 10 mm ZrO₂ milling ball. ^b0.42 g of diaminomaleonitrile (stoichiometric amount) was used ^cAfter the first step, the solution workup was replaced by adding 1 mL of 30% HNO₃ (9.36 mmol) to the milling vessel and milling the mixture for another 10 min at 30 Hz.

as water (Table 2, entries 5 and 6). Water appears to be a critical additive, which may function as a stabilizing agent. Switching to common, aprotic organic solvents like DCM and toluene (Table 2, entries 7 and 8), the yields are lowered drastically, supporting the suspicion that the water is involved in the reaction not as a solvent, as the solubility of both starting materials in water is poor compared to the other used LAG additives. Using DMF as an additive led to a drastic decrease in conversion, which might be because of side reactions. Therefore, we could conclude that polar protic solvents are beneficial for this condensation reaction.

To verify the merit of our approach in terms of sustainability, we calculated the green metrics (cf. Supporting Information, section 3). The stoichiometric approach has a 795-times better mass productivity and process mass intensity compared to the solution-based protocol. In addition, the reaction time is strongly reduced, and thus, the global warming potential of the process can be reduced by 78%. Overall, the sustainability of the reaction has been vastly increased by the use of mechanochemistry.

Analogously to the conventional route, the presented synthesis also involves a workup with HNO₃. As reported for the conventional route, this serves as a purification step to dissolve unreacted or incompletely reacted (1- or 2-fold condensation, excess diaminomaleonitrile) reaction products. We attempted to substitute this liquid phase workup with a second treatment inside the ball mill. Oxidizing agents like potassium peroxydisulfate, sodium perchlorate, sodium percarbonate, or liquid HNO₃ (Table 2, entry 11 and Table S2) were employed in a one-pot two-step process, but no product could be isolated for any of them. In the mechanochemical approach, however, this treatment is crucial for another reason. As our analysis shows that no HAT-CN but an intermediate is formed during the milling process. This intermediate must be an adduct of the two starting materials in a pre-coordinated fashion, as the starting materials themselves are not stable under 30% HNO₃ conditions (for a detailed discussion, see Supporting Information, section 2.4). If the intermediate is exposed to the same conditions, however, it is transferred into HAT-CN and precipitating from the solution.

This observation shows strong parallels with the accelerated aging, described by Friščić et al.³⁷ For comparison, the conventional liquid-phase synthesis already shows HAT-CN formed after the coupling in refluxing acetic acid (cf. Supporting Information, section 2.4). This points toward a different mechanistic pathway of the mechanochemical and the liquid-phase synthesis.

Overall, we were able to significantly improve the synthesis of HAT-CN by performing the condensation reaction in as little as 10 min inside a ball mill. Thus, making it significantly more sustainable by completely avoiding acetic acid and acetonitrile. The use of water as a liquid-assisted grinding additive led to a yield of up to 67%, significantly outperforming the state of the art. To further enhance the environmental compatibility, we conducted the reaction without any excess diaminomaleonitrile, leading to less product but overall better green metrics. The product mass intensity is lower by a factor of up to 795. With our synthetic pathway, 78% CO₂ equivalents can be saved. Our synthetic approach does not rely on high excesses of one starting material, solvents, or high temperatures and, therefore, is more cost- and time-efficient than the traditional way, while giving improved yields.

EXPERIMENTAL SECTION

General Information. All reagents were obtained from commercial suppliers and were used without purification. Acids and solvents for the LAG were used in the anhydrous form if not mentioned otherwise. Water used in LAG was taken from a tap for the deionized form. The mechanochemical step was carried out in a Retsch MM400 and Retsch MM500 nano/vario ball mill. Commercial milling vessels out of zirconium dioxide were used. Zirconium dioxide (Type ZY-S) milling balls with a diameter of 10 mm were purchased from Sigmund Lindner GmbH. The average weight of one milling ball is 3.19 \pm 0.05 g. Nuclear magnetic resonance spectroscopy was recorded on a Bruker BRUKER Avance III HD 300 MHz NMR spectrometer. As a solvent and internal standard, acetone-*d*₆ was used. Fourier transform infrared spectroscopy (FT-IR) was carried out on a SHIMADZU IR Spirit with a QATR-S ATR unit. Each sample was measured with 15 scans with a resolution of 4 in the range from 400 to 4000 cm⁻¹. Elemental analysis was carried out on a vario Micro cube from Elementar Analysensysteme GmbH at 1200 °C. Raman spectra were obtained using a RENISHAW inVia Qontor Raman microscope with 50 \times object (NA = 0.50, 8.2 mm free working distance). The wavelength for the measurement was 785 nm with 0.001–10% laser power dependent on the sample. The exposure time varied between 20s and 2 accumulations and 15 and 20 accumulations, of which the latter resulted in the best spectra.

Synthesis of 1,4,5,8,9,11-Hexaazatriphenylenehexacarbonitrile. In a typical synthesis, the reactants were placed in a 10 mL ZrO₂ milling vial together with a \emptyset = 10 mm ZrO₂ milling ball. Then, 0.400 g (1.30 mmol, 1 equiv) of hexaketocyclohexane-octahydrate, 1.10 g (10.20 mmol, 7.84 equiv) of diaminomaleonitrile and the respective additives were added (for detailed information, see section 1 of the Supporting Information). The mixture was milled for 10 min at 35 Hz in a Retsch MM500 mixer ball mill (MBM). After the milling, the raw mixture was transferred into a flask and stirred in 30% HNO₃ in a 110 °C oil bath for an hour. After cooling, the orange-solid HAT-CN was filtered, washed with water, and dried. An evenly bright yellow solid was isolated (0.3319 g, 0.864 mmol) in 67% yield. ¹³C{¹H} NMR (300 MHz, CO(CD₃)₂): δ 143.4, 136.6, 114.4 ppm. FT-IR: ν 2240, 1340, 1226, 1146 cm⁻¹. Raman: ν 2253, 1400, 1480, 1540, 700 cm⁻¹. HRMS (MALDI-TOF, TCNQ): M⁺ 384.7 *m/z*. Elemental analysis: 54.6%, C; 43.1%, N; 0.4%, H; 0%, S. The melting point is reported to be >500 °C and was not further explored for analysis.

Upscaling the Synthesis of 1,4,5,8,9,11-Hexaazatriphenylenehexacarbonitrile in the MM-500. To check the scalability of

this reaction, a bigger batch of the reactants was placed in a 45 mL ZrO₂ milling vial together with 22 Ø = 10 mm ZrO₂ milling balls. Then, 2.50 g (8.01 mmol, 1 equiv) of hexaketocyclohexane-octahydrate and 6.84 g (63.27 mmol, 7.90 equiv) of diaminomaleonitrile were placed in the milling vessel. The mixture was milled for 10 min at 35 Hz in a Retsch MM500 mixer ball mill (MBM). After the milling, the raw mixture was transferred into a flask and stirred in 30% HNO₃ in a 110 °C oil bath for an hour. After cooling, the orange-solid HAT-CN was filtered, washed with water, and dried. An evenly bright yellow solid was isolated (1.7625 g, 4.5870 mmol) in 57% yield. ¹³C{¹H} NMR (300 MHz, CO(CD₃)₂): δ 143.4, 136.6, 114.4 ppm. FT-IR: ν 2240, 1340, 1226, 1146 cm⁻¹. Raman: ν 2253, 1400, 1480, 1540, 700 cm⁻¹.

Synthesis of 1,4,5,8,9,11-Hexaazatriphenylenehexacarbonitrile in a One-Pot Two-Step Approach. The reactants were placed in a 10 mL ZrO₂ milling vial together with a Ø = 10 mm ZrO₂ milling ball. Then, 0.400 g (1.30 mmol, 1 equiv) of hexaketocyclohexane-octahydrate and 1.10 g (10.20 mmol, 7.84 equiv) of diaminomaleonitrile were placed in the milling vessel. The mixture was milled for 10 min at 35 Hz in a Retsch MM500 mixer ball mill (MBM). After the milling, various oxidative agents were added (according to Table S2) to the milling vial, and the milling was continued. The volume of HNO₃ required to oxidize the raw mixture leads to slurry grinding. After the milling, the raw mixture was washed with water and dried. A dark brown paste was obtained, which did not show any traces of HAT-CN. Other oxidants such as Kaliummonoperoxosulfat, sodium perchlorate, or sodium percarbonate show similar results.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.1c00253>.

Screening experiments with different additives; ¹H NMR spectra; MALDI-MS spectra and EA comparison; mechanistic consideration, green metrics calculation (PDF)

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Notes

The authors declare no competing financial interest.

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