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Altering Copper-Catalyzed A³-Couplings by Mechanochemistry; One-Pot Synthesis of 1,4-Diamino-2-butynes

Mathias Turberg,⁺ Karen J. Ardila-Fierro,⁺ Carsten Bolm^{*} and José G. Hernández^{*}

Abstract: The ability of mechanochemistry to alter an established chemical selectivity is here demonstrated. A copper(I)-catalyzed mechanochemical aldehyde-alkyne-amine-coupling using calcium carbide as the acetylene source, allows a selective access to 1,4-diamino-2-butynes, which contrasts classical approaches providing propargylamine-type products. Solventless milling conditions were found essential to unmask a new A³-coupling product composition.

In recent years, the use of mechanical energy to induce or facilitate chemical transformations has become an important approach in chemical synthesis.^[1] One unique feature of mechanochemistry is the possibility to alter chemical reactivity, thereby allowing to access otherwise disallowed or unfavorable products. For example, exertion of mechanical forces by sonication and pulling has led to the discovery of the anti-Woodward-Hoffmann electrocyclic ring opening of benzocyclobutene,^[2] the trapping of a diradical transition state,^[3] and recently to an alternative retro-Diels-Alder product composition in furan/maleimide adducts.^[4,5] Thus, activation of chemical systems by ball milling has also unmasked reaction pathways that differ from their solution-based thermal counterparts, clearly highlighting a synthetic value of mechanochemistry.^[6]

From a practical perspective, the implementation of ball milling techniques offers the possibility to carry out chemical reactions in the absence of bulk reaction media. This allows reacting substances of very poor solubility or to combine reaction partners of different solubility profiles. In this context, calcium carbide (CaC₂) has recently proven useful as a solid replacement of hazardous and difficult to handle acetylene gas.^[7-9] However, due to the poor solubility of CaC₂ in organic solvents,^[10] procedures for CaC₂ upgrading often require threephasic reaction mixtures,^[9m] superbasic reaction media,^[9n] high temperatures,^[9c,i] and long reaction times.^[9c,k] Challenged by the current limitations for utilizing CaC₂ as a surrogate for acetylene, we surmised that the application of mechanochemical techniques to the valorization of CaC2 could overcome the abovementioned practical drawbacks. Additionally the development of a solventless alternative for the activation of CaC₂ in ball mills was foreseen as an opportunity to help discovering new chemical reactivity.

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-diamino-2-butynes (major product)

Scheme 1. Solution-based and mechanochemical Cu-catalyzed A³-coupling using calcium carbide as the acetylene source.

As a starting point, we focused on the aldehyde-alkyneamine-coupling (A³-coupling), a well-established and convenient atom-economical multicomponent reaction to access synthetically valuable propargylamines.^[11,12] In 2012, Zhang and co-workers reported the use of CaC₂ as an acetylene surrogate in such couplings.^[13] Heating a mixture of aldehydes, amines and CaC₂ in undried acetonitrile led to the formation of terminal propargylamines as major product (Scheme 1a). Being attracted by this work we decided to study a mechanochemical activation of CaC_2 by ball milling and its application in an A³-coupling (Scheme 1b). On the one hand, milling of CaC₂ could help breaking its crystal structure, thereby accelerating its availability for the reaction. In addition, solventless condensations of amines and carbonyl compounds should provide the conditions for the activation of CaC₂ without the use of wet solvents or added water. Controlling the neat mechanochemical reaction conditions was anticipated to prevent quenching of charged chemical species (e.g., by water), leading to a change in the established product composition of the A³-coupling by mechanochemistry (Scheme 1b).

At the onset of this study, we tested the mechanochemical A3-coupling between benzaldehyde (1a), pyrrolidine (2a) and calcium carbide by ball milling (Table 1). To prevent any reaction between 1a and 2a before the milling had started and to protect calcium carbide from reacting with atmospheric moisture, 1a and CaC₂ were sealed inside glass ampules (for details see Figure S1, Supporting Information).^[14] An initial milling experiment at 25 Hz in the absence of a catalyst enabled crushing the glass ampules and mixing of the reagents. Disappointingly, ¹H NMR analysis of the crude reaction mixture revealed no new product. (Table 1, entry 1). On the other hand, under identical milling conditions the presence of copper iodide (20 mol %) favored the consumption of starting materials after only 90 min of milling.^[15] Now, however, to our surprise, the mechanochemical reaction afforded 1,4-diamino-2-butyne 3a as the major product (Table 1, entry 2). Such reactivity stands in stark contrast to the previous observations by Zhang and coworkers, who obtained the typical propargylamine 4a in undried acetonitrile (at 80 °C after 18-72 h).^[13,16] In fact, it was reported that in solution 4a was formed exclusively and "no bis-substituted propargylic amine product

Table 1. Screening of the mechanochemical	Cu-catalyzed A ³ -coupling. ^[a]
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Ph +	N_{H} + CaC ₂ $\frac{\text{catalyst}}{\text{ball milling}}$ 2a		+ $\stackrel{\bigvee}{{\xrightarrow}}_{Ph}$ =
Entry	Catalyst (mol %)	Conversion [%] ^[b]	Yield 3a:4a ^[b]
1	-	-	-
2	Cul (20)	>99	85:11
3	CuBr (20)	>99	85:10
4	CuCl (20)	83	47:46
5	CuBr ₂ (20)	99	79:14
6	Cu(BF ₄) ₂ ·6H ₂ O	96	16:74
7 ^[c]	Cul (20)	98	44:31
8 ^[d]	Cul (20)	95	82:13
9	Cul (10)	>99	88:12
10	Cul (5)	98	83:13
11 ^[e]	Cul (20)	>99	74:6

[a] **1a** (53.1 mg, 0.5 mmol), **2a** (35.6 mg, 0.5 mmol), CaC₂ (33 mg; 0.5 mmol) [technical grade, 74.24% purity, corresponding to approx. 0.8 equiv.] and catalyst were milled for 90 min in a 10 mL stainless steel milling jar with one 10 mm milling ball of the same material; **1a** and CaC₂ were loaded into the milling jar in sealed glass ampules. [b] Determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [d] Water (1.2 equiv.) was added in the milling jar. [d] After 30 min of milling. [e] LAG reaction (MeCN); $\eta = 0.25 \,\mu$ L/mg.

was observed even with inorganic base present in the reaction system^{*.[13]} Indeed, repeating the protocol in solution using undried or dry acetonitrile led predominantly to the formation of **4a** (for details see ESI). Additionally, in the ball mill only trace quantities of the Glaser-Hay homocoupling product were detected.^[17] Consequently, the high selectivity of the reaction by milling and, in particular, the change in product composition by mechanochemistry requested a deeper study of the mechanochemical Cu-catalyzed A³-coupling.

First, a variety of Cu^I and Cu^{II} salts were screened as potential catalysts for the mechanochemical A³-coupling. Copper (I) bromide was found to catalyze the reaction to a similar extend compared to Cul, providing 3a as the major product after 90 min of milling at 25 Hz (3a:4a; 85:10; Table 1, entry 3). Conversely, copper (I) chloride proved less effective as catalyst in terms of reactivity and selectivity, affording both 1.4-diamino-2-butyne 3a and propargylamine 4a (Table 1, entry 4). On the other hand, when copper (II) bromide was tested as catalyst the selectivity towards product 3a was regained (Table 1, entry 5). Using $Cu(BF_4)_2 \cdot 6H_2O$ in the mechanochemical reaction led preferentially to the formation of propargylamine 4a over 3a (3a:4a; 16:74; Table 1, entry 6). This change in selectivity was attributed to the crystalline water contained in the copper (II) salt. Thus, the presence of water during the milling could have aided quenching of the mono anionic intermediate obtained after the first addition of C₂²⁻ to the iminium ion, thus preferentially providing 4a. To test this hypothesis, a mixture of 1a, 2a, CaC₂ and Cul was milled in the presence of 1.2 equiv. of added water (Table 1, entry 7). Under these conditions, the formation of the mono-substituted propargylic amine 4a was favored compared

with the same reaction in the absence of water (Table 1, entries 2 and 7), thereby supporting our hypothesis on the role of water on the selectivity of the reaction with CaC2. Next, to evaluate the product composition of the mechanochemical reaction over time, an experiment was halted after 30 min of milling. The analysis of the reaction mixture revealed traces of unreacted starting materials. However, the ratio 3a:4a (82:13) was comparable with the milling experiment carried out for 90 min (Table 1, entries 2 and 8). Decreasing the catalyst loading proved possible, as shown by using copper (I) iodide in 5.0 mol % or 10 mol %, which afforded primarily 1,4-diamino-2-butyne 3a without the need for lengthening the milling time (Table 1, entries 9-10). Finally, a liquid-assisted grinding (LAG) experiment was carried out.^[18,19] Repeating the copper-catalyzed reaction in the presence of catalytic amounts of undried MeCN, a solvent typically used in solvent-based protocols with CaC2, still maintained the preference of the LAG reaction towards the bissubstituted propargylic product 3a (Table 1, entry 11).

Having identified the best milling parameters as 90 min of milling at 25 Hz, the substrate scope of the mechanochemical A³-coupling was investigated (Scheme 2). In general, the synthetic protocol involved milling of a mixture of 1:2: CaC₂ (1: 1: 1 equiv.) with Cul (10 mol %) as the catalyst. Under these conditions, aromatic aldehydes bearing halogen substituents were tolerated. For example, p-fluorobenzaldehyde (1b) reacted with pyrrolidine (2a) and CaC₂ to afford the corresponding 1,4diamino-2-butyne 3b in 67% after column chromatography (Scheme 2). Similarly, the use of p-chloro and pbromobenzaldehyde led to the formation of products 3c and 3d in 75% and 79% yield, respectively (Scheme 2). Additionally, oand m-bromobenzaldehyde were successfully tested as substrates in the mechanochemical A³-coupling, leading to 1,4diamino-2-butynes 3e and 3f in up to 72% yield (Scheme 2). p-Tolualdehyde (1g), 4-carbomethoxybenzaldehyde (1h) and panisaldehyde (1i) proved suitable for the reaction as well. In these cases, the corresponding bis-substituted propargylic products 3g-i were obtained in yields ranging from 72% to 81% (Scheme 2). Employing 3,5-bis(trifluoromethyl)benzaldehyde (1j) as a substrate gave product 3j in 72% yield (Scheme 2). Interestingly, the expected product 3k was not detected when 2cyanobenzaldehyde (1k) was used as substrate. Instead, unprecedented isoindolinone 5 was obtained in 75% yield (Scheme 2). This result suggests that intramolecular hydrolysis of the nitrile group occurs faster than the addition of the carbide anion to the iminium ion intermediate. Moreover, reacting polyaromatic aldehydes such as 11 and 1m afforded 1-naphthyland 9-phenanthryl-substituted 1,4-diamino-2-butynes 3I and 3m in 56% and 76%, respectively (Scheme 2). Pivaldehyde (1n) was also compatible with the milling conditions and gave 3n in 57% yield. Replacing pyrrolidine with piperidine (2b) was also possible leading to the formation of product 3o in 75% yield. Conversely, primary amines only provided the corresponding imine whereas acyclic secondary amines (e.g., diethylamine) gave the desired 1,4-diamino-2-butynes in low yields. In general, most of the products 3 appeared homogeneous by thin-layer chromatography and NMR spectroscopy, however the presence of diastereomers or rotamers cannot be excluded,^[20] (for a detailed study on 3m see Supporting Information).

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Scheme 2. Substrate scope for the mechanosynthesis of symmetric 1,4diamino-2-butynes **3**. Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), CaC_2 (33 mg; 0.5 mmol) [technical grade, 74.24% purity, corresponding to approx. 0.8 equiv.] and Cul (10 mol %) were milled for 90 min in a 10 mL stainless steel milling jar with one 10 mm milling ball of the same material. The use of 20 mol% of Cul led to similar yields. ^[a] Experiment carried out on a 1.0 mmol scale.

From a practical point of view, the one-pot mechanosynthesis of symmetric 1,4-diamino-2-butynes **3** is significantly more advantageous compared to reported approaches in solution, which required two-step protocols^[20a] or higher catalyst loadings at high temperatures.^[20b] Additionally, due to the simplicity of the mechanochemical strategy to enable the formation of two new N–C bonds and two new C–C bonds in one step, we decided to carry out intermolecular competition experiments with pyrrolidine (**2a**), substituted benzaldehydes and CaC₂ to attempt the synthesis of unsymmetric 1,4-diamino-2-butynes **3** (Scheme 3; top).^[21]

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Scheme 3. Applications of the mechanochemical Cu-catalyzed A³-coupling. *Top*: mechanosynthesis of unsymmetric 1,4-diamino-2-butynes. *Bottom*: mechanosynthesis of **3s** by ball milling.

Reacting a mixture of benzaldehyde (1a), p- fluorobenzaldehyde (**1b**), **2a**, CaC₂ (0.25 : 0.25 : 0.5 : 0.5 mmol) and Cul (10 mol %) led to full conversion of the aldehydes 1a and 1b, with preferential formation of the unsymmetric 1,4-diamino-2-butyne 3p (3a / 3b / 3p; 1.0 / 0.7 / 2.2). Replacing 1a with ptolualdehyde (1g) or p-anisaldehyde (1i) generated, once again, the unsymmetric diamino-2-butynes 3q-r as major products 3; top). Finally, the usefulness of (Scheme the mechanochemical Cu-catalyzed A³-coupling to prepare 1Dpolymeric materials containing 1,4-diamino-2-butyne units was tested. Pleasingly, reacting terephthaldehyde (1s), 2a and CaC₂ under the standard reaction conditions led to the formation of a polymeric material in 40% yield (Scheme 3; bottom). Analysis of the sample by NMR spectroscopy and High Resolution Mass Spectrometry (HRMS) revealed that 3s (with n = 1) was predominant in the mixture.

A plausible mechanism to explain the formation of symmetric and unsymmetric **3** is shown in Scheme 4.



Scheme 4. Plausible mechanism for the mechanochemical $\mathsf{A}^3\text{-}\text{coupling}.$

In summary, mechanochemistry enabled altering the typical product composition of copper-catalyzed A³-couplings. The mechanical milling of the reagents in the absence of solvent favored the formation of 1,4-diamino-2-butynes over the typically generated propargylamines. This one-pot mechanochemical reaction simplifies the existing procedures for the preparation of valuable 1,4-diamino-2-butynes,^[22] and rises the degree of complexity in the field of mechanochemical multicomponent

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reactions.^[23] The application of mechanical forces by ball milling also permits exploring otherwise dormant chemical reactivity.

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Keywords: mechanochemistry • A³-coupling • calcium carbide • 1,4-diamino-2-butynes

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Different is always better: Mechanochemical activation of aldehydes, amines and calcium carbide in the presence of copper (I) iodide enabled the unprecedented formation of 1,4-diamino-2-butynes under solventless conditions.

Mathias Turberg, Karen J. Ardila-Fierro, Carsten Bolm* and José G. Hernández*

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