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Article

# Investigation of Mechanochemical Sonogashira Couplings—From Batch Solution to Continuous Reactive Extrusion through Ball-Milling Optimization

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**ABSTRACT:** Solvents used to run chemical reactions on a process scale are the largest contributors to hazardous waste in active pharmaceutical ingredient (API) process manufacturing. Frequently, the solvents providing optimal reaction performance are toxic and environmentally damaging. The rapid emergence of mechanochemistry as a practical tool for organic synthesis has piqued the interest of process chemists as a potential method that could reduce solvent use and perform organic transformations in a safer and environmentally friendly manner. Reactive extrusion has become a viable option for chemists to perform multigram-scale reactions in a continuous manner. Herein, we demonstrate the use of small-scale ball-milling experiments as a screening and optimizing system to allow translation of a Sonogashira coupling reaction from small-scale to twin-screw extrusion for implementation at a larger scale.

**KEYWORDS:** *mechanochemistry, catalysis, Sonogashira, reactive extrusion, scale-up*



## INTRODUCTION

Heterocyclic compounds are extremely common in FDA-approved pharmaceuticals but are often cost drivers in large-scale manufacturing (Figure 1).[1] To date, there are a multitude of methods that have been developed to functionalize heterocyclic cores at both the early and late stages of an active pharmaceutical ingredient (API) synthesis. Many of these processes rely on large quantities of solvents, tedious manipulations, and/or long reaction times. They often generate impurities that can carry through or negatively impact downstream steps. The use of transition metal catalysis has helped alleviate some of these problems but has not solved the issues around solvent use and the environmental impact of pharmaceutical preparations.

With a growing focus on developing more environmentally friendly and process-scale amenable methods, chemists have worked to incorporate flow-chemistry methods, greener solvents, and waste reduction into their processes.[2,3] One of the emerging techniques of interest is the implementation of mechanochemistry, a method that uses mechanical force to conduct chemical reactions as defined by IUPAC.[4−6] Many research groups have translated powerful transition metal-catalyzed reactions from the solution phase into the solid state, but many of them stop at the small scale or have limited substrate compatibility.[7−13] To date, many published methods lack large-scale examples or have limited compatibility with substrates relevant to pharmaceutical research. In addition to the exploration of mechanochemistry for catalysis, many research groups have explored methods for large-scale mechanochemical synthesis, namely, in the area of reactive extrusion.[14−16] Browne and co-workers have performed extensive work to increase the scale of metal-catalyzed mechanochemical reactions through the implementation of reactive extrusion.[10] Mack and co-workers have also explored reactive extrusion with nucleophilic aromatic substitution and Knoevenagel reactions and have found success.[17]

Browne and co-workers have outlined safety considerations to ensure a specific chemical reaction of interest can be translated to a mechanochemical environment.[6] On the ball-mill scale (10 mg to 5 g), considerations of pressure build-up, reactivity with the surface of the milling vessel, and shock sensitivity are included in the list of traditional safety parameters such as thermal runaway, air and moisture sensitivity, and others. These same considerations outlined by Browne et al. can be used to inform scale-up to extrusion, where pressure and thermal limitations are more relaxed due to the design of extrusion equipment. However, air and moisture sensitivity are now of greater concern than they were on the ball-mill scale due to the inability to enclose the reaction system.

The introduction of mechanochemistry to the synthesis of APIs has the potential not only to make the process more environmentally friendly but to reduce cost as well. We were interested in evaluating this developing technology for the scalable synthesis of pharmaceutically relevant heterocyclic cores via palladium-catalyzed reactions. We chose the Sonogashira reaction, a frequently employed entry into

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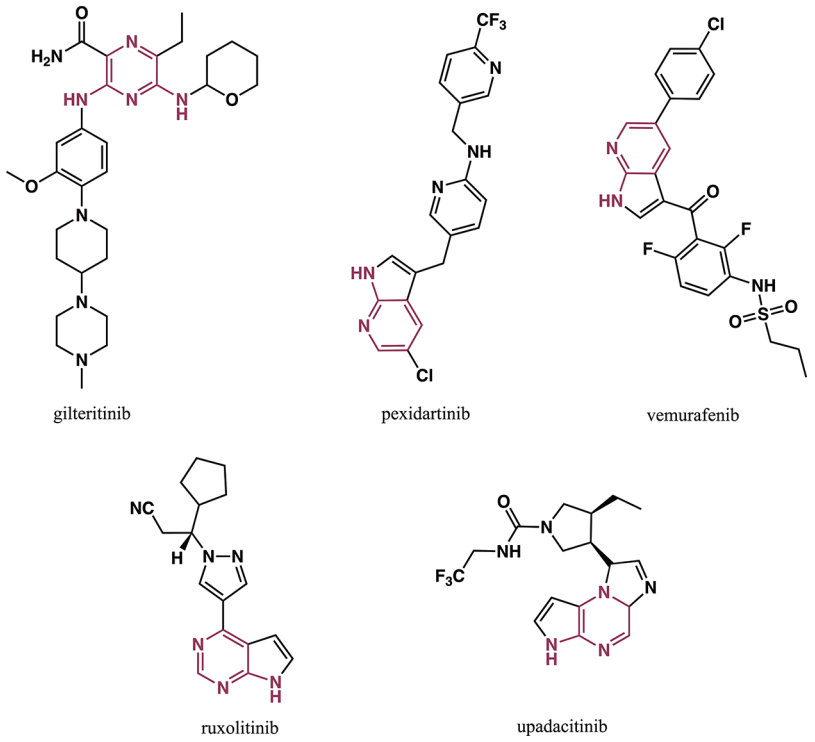
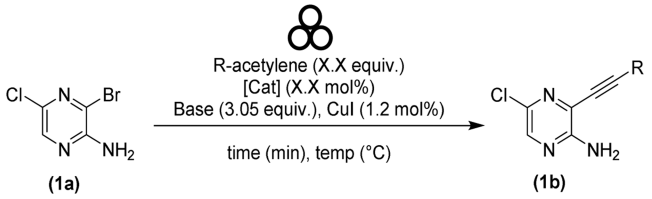



**Figure 1.** Selected FDA-approved drugs containing aminopyrazine and azaindole moieties. Adapted from Kumar et al.[1]

**Table 1. Optimization of Mechanochemical Sonogashira Coupling with 3-Bromo-5-chloropyrazin-2-amine**[a]




| entry | base | R= (equiv) | cat. (mol %) | temperature (°C) | time (min) | conversion (%)[b] | purity (pa %)[c] |
|---|---|---|---|---|---|---|---|
| 1 | $Et_3N$ | TMS (1.1) | $Pd(PPh_3)_4$ (0.2) | 25 | 240 | ≥99 | 97 |
| 2 | $Et_3N$ | TMS (1.5) | $Pd(PPh_3)_4$ (0.2) | 25 | 240 | ≥99 | 98 |
| 3 | DABCO | TMS (1.5) | $Pd(PPh_3)_4$ (0.2) | 25 | 240 | 45 | 42 |
| 4 | $K_2CO_3$ | TMS (1.5) | $Pd(PPh_3)_4$ (0.2) | 25 | 240 | 23 | 22 |
| 5 | $K_2CO_3$ | TMS (1.5) | $Pd(PPh_3)_4$ (0.2) | 45 | 120 | 12 | 11 |
| 6 | $K_2CO_3$ | TES (1.5) | $Pd(PPh_3)_4$ (0.2) | 45 | 120 | 91 | 89 |
| 7 | $K_2CO_3$ | TES (1.5) | $Pd(PPh_3)_4$ (0.2) | 45 | 30 | 67 | 66 |
| 8 | $K_2CO_3$ | TES (1.5) | $Pd(PPh_3)_4$ (0.2) | 90 | 30 | ≥99 | 97 |
| 9 | $K_2CO_3$ | TES (1.1) | $Pd(PPh_3)_4$ (0.2) | 90 | 30 | ≥99 | 97 |
| 10 | $K_2CO_3$ | TES (1.1) | $Pd(OAc)_2$ + $PPh_3$ (0.2 + 0.6) | 90 | 30 | 96 | 95 |
| 11[d] | $K_2CO_3$ | TES (1.1) | $Pd(OAc)_2$ + $PPh_3$ (0.5 + 1.5) | 90 | 30 | ≥99 | 99 |

[a]Reactions were performed on a 0.25 g scale of heteroarene and performed in a 15 mL stainless-steel milling jar with three (3) 3/16th″ stainless-steel balls. All reactions were treated with ethyl acetate and filtered; purities and conversions are of the filtered reaction mixtures. [b]High-performance liquid chromatography (HPLC) area conversions. [c]Purities reported are peak area percents with respect to full HPLC trace, including the starting material. [d]Reaction performed in triplicate. The data shown is an average of trials. The ball-milling symbol was adapted from Hanusa and co-workers.[37]

azaindoles and related heterocycles.[18−23] The goals of this study were to identify solvent-free mechanochemical reaction conditions that achieved high conversion and purity and to minimize post-reaction manipulations to enable streamlined process manufacturing.

## RESULTS AND DISCUSSION

**Optimization in Ball Milling.** Our initial screenings were performed on 3-bromo-5-chloropyrazin-2-amine with trimethylsilyl (TMS) acetylene as the selected coupling partner. This substrate proved interesting as we hoped to be able to invoke high chemoselectivity while leaving a reactive handle for additional arene modification.

The launch point for our reaction conditions was adapted from solution-based Sonogashira reactions[24] and, to our delight, provided good conversion after 4 h of milling (Table 1, Entry 1). These results were encouraging; however, the large loadings of liquid reagents caused the reaction mixture to be a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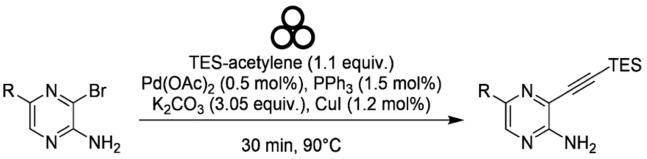
mobile slurry that could leak from the milling jar and make the post-reaction handling problematic.[25] To bring our reaction more in line with traditional mechanochemical systems, a change to solid bases was explored. Mechanochemical Suzuki and Sonogashira couplings in previous reports have implemented DABCO and potassium carbonate as bases with high success, which gave us the confidence to employ them in our system.[13,26,27] Exchanging triethyl amine with these solid bases gave moderate results in initial screening but gave a lead toward conditions that are better suited for mechanochemical processing. In hopes of keeping reaction processing simple after milling, potassium carbonate was pursued as the base of interest. Inorganic bases and salts would be insoluble in an organic filtration, which would eliminate the need for an aqueous workup and further reduce solvent waste production. In hopes of improving our results, we turned to previous reports by Mack,[28−30] Browne,[10] Ito,[9] and others,[31−34] which have shown that elevated temperatures can help promote mechanochemical reactions without significant degradation of the reactants. At elevated temperatures, we began to see more promising results when using potassium carbonate, but our upper-temperature threshold was limited by our coupling partner, TMS-acetylene (Table 1, Entry 5). A pivot from TMS-acetylene (boiling point: 53 °C) to triethylsilyl (TES) acetylene (boiling point: 136 °C) was made, which would allow access to higher temperatures for our milling trials. At elevated temperatures, we observed conversions and purities comparable to multihour reactions in half the time (Table 1, Entry 6). A further increase in temperature allowed for the shortening of the reaction time to 30 min with higher conversions and purity (Table 1, Entry 8). These shortened times gave us conditions that would be better for extrusion where the reaction mixture has limited time in the extruder barrel.

During our initial efforts in conducting reactions in an extruder, we found that the air sensitivity of $Pd(PPh_3)_4$ was a significant limitation. Thus, the more stable $Pd(OAc)_2/PPh_3$ system was evaluated in comparison. Consistent with the studies of Amatore and Jutand, the use of a 3:1 L/Pd ratio gave comparable conversions to trials where $Pd(PPh_3)_4$ was used.[35,36] This precatalyst system was implemented as our ideal palladium source in subsequent studies. Despite these advancements in our system, full consumption of **1a** was not observed with our new catalyst system. Therefore, a slight increase in palladium loading from 0.2 to 0.5 mol % was used to encourage the consumption of any remaining starting material (Table 1, Entry 11).

**Substrate Scope.** With optimum conditions in hand, we sought to expand our substrate scope to include other decorated heteroarenes (Table 2). 3-Bromopyrazin-2-amine and 3-bromo-5-methylpyrazin-2-amine also gave high conversion to the predicted alkynylated product under our optimized conditions with lower catalyst loading (0.2 mol %). Various halides are compatible; however, chemoselectivity erodes as the carbon halide bond strengths are weakened. 3,5-Dibromopyrazin-2-amine performed well with high conversions but also showed the presence of a bisalkynylated product, which can be easily separated by chromatography. Bromoiodopyrazine reacts initially at the C−I bond when forming a monoalkynylated product, followed by the C−Br bond to form the bisalkynylated product as the minor product. The exchange of a halide group for another reactive handle such as a methyl ester provided difficulties in chemoselectivity. The reaction

**Table 2. Pyrazine Substrate Scope for Mechanochemical Sonogashira Coupling**[a]




| entry | R= | conversion (%)[b] | purity (pa %)[c] | yield (%)[d] |
|---|---|---|---|---|
| 1 | Cl (1a) | ≥99 | 99 | 92 |
| 2[e] | H (2a) | ≥99 | 99 | 90 |
| 3[e] | Me (3a) | ≥99 | 99 | 87 |
| 4 | I (4a) | 88 | 62 | 49[f] |
| 5 | Br (5a) | 92 | 86 | 71 |
| 6 | COOMe (6a) | ≥99 | 54 | 20 |

[a]Reactions were performed on a 0.25 g scale of heteroarene and performed in a 15 mL stainless-steel milling jar with three (3) 3/16th″ stainless-steel balls. All reactions were treated with ethyl acetate and filtered; purities and conversions are of filtered samples before purification. [b]HPLC area conversion. [c]Purities reported are peak area percents with respect to full HPLC trace, including the starting material. [d]Isolated yield. [e]Reactions used 0.2 mol % $Pd(OAc)_2$ and 0.6 mol % triphenylphosphine. [f]Product yield is reflective of 3-bromo-5-((triethylsilyl)ethynyl)pyrazin-2-amine.

fully consumed the starting pyrazine but produced a multitude of products such as the desired alkynylated product, amide coupled product, and even a portion of a hydrolysis product, leading to low yields of the desired alkynylated product. Despite the side product formation seen with some substrates, all desired monoalkyne substrates can be purified by column chromatography.

When exploring the utility of this method on other nitrogen-containing heterocycles, we applied our optimized conditions to pyridines. Unfortunately, the use of potassium carbonate led to extremely poor conversions, unlike what we observed in our pyrazine studies (Table 3, Entry 1). Because DABCO showed promising activity in early optimization experiments for pyrazines (Table 1, Entry 3), we investigated its effectiveness for this substrate. With a slight increase in alkyne, copper, and catalyst, the coupling reaction performs extremely well with high conversion and purity (Table 3, Entry 2). We hypothesize the formation of a DABCO-Cu-$PPh_3$ complex based on findings from Borchardt and co-workers, which is unique to the mechanochemical environment.[38] This complex could serve as a more active source of copper to participate in the coupling reaction.

The DABCO conditions were then applied to several pyridine substrates (Table 4). Excellent conversions and high in-process purities were observed for both 2- and 3-bromopyridines bearing an unprotected amino group ortho to the bromide. High chemoselectivity was achieved in 2-chloropyridine-derived substrates (Entries 1 and 5). For a 5-fluoropyridine-derived substrate, a minor amount of an SNAr byproduct was observed, but this did not affect the performance of the catalyst (Entry 8).

**Reactive Extrusion Development.** After optimized conditions were established in our small-scale ball-milling trials, we began to explore extrusion conditions for large-scale Sonogashira reactions using a Liestritz Nano 16 twin-screw extruder. Optimization of reactive extrusion processes may include traditional variables like temperature, time (in this case, residence time), and feed rate alongside extrusion-


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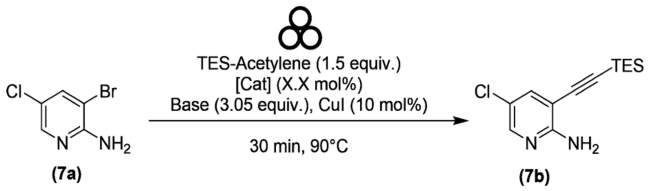
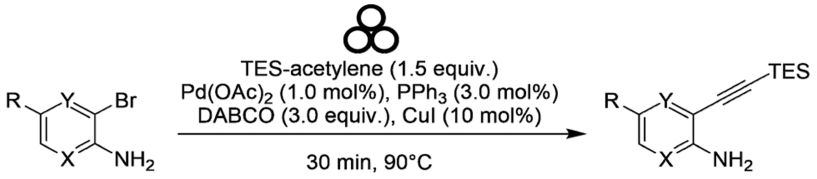
**Table 3. Optimization Screening for Mechanochemical Sonogashira Coupling with 3-Bromo-5-chloropyridin-2-amine**[a]




| entry | Cat. (mol %) | base | conversion (%)[b] | purity (pa %)[c] |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ + $PPh_3$ (1.0 + 3.0) | $K_2CO_3$ | 10 | 10 |
| 2 | $Pd(OAc)_2$ + $PPh_3$ (1.0 + 3.0) | DABCO | ≥99 | 86 |

[a]Reactions performed on 0.25 g of pyridine and performed in a 15 mL stainless-steel milling jar with three (3) 3/16th″ stainless-steel balls. All reactions were treated with tetrahydrofuran (THF) and filtered; purities and conversions are of filtered samples. [b]HPLC area conversion. [c]Purities reported are peak area percents with respect to full HPLC trace, including the starting material.

**Table 4. Pyridine Substrate Scope for Mechanochemical Sonogashira Coupling**[a]




| entry | R= | X= | Y= | conversion (%)[b] | purity (pa %)[c] | yield (%)[d] |
|---|---|---|---|---|---|---|
| 1 | Cl (7a) | N | CH | ≥99 | 86 | 88 |
| 2 | Me (8a) | N | CH | ≥99 | 87 | 66 |
| 3 | H (9a) | N | CH | 99 | 88 | 72 |
| 4 | F (10a) | N | CH | ≥99 | 94 | 74 |
| 5 | Cl (11a) | CH | N | ≥99 | 85 | 58 |
| 6 | Me (12a) | CH | N | ≥99 | 91 | 77 |
| 7 | H (13a) | CH | N | ≥99 | 90 | 75 |
| 8 | H[e] (14a) | CH | N | ≥99 | 88 | 67 |

[a]Reactions were performed on a 1.00 mmol scale of heteroarene and performed in a 15 mL stainless-steel milling jar with three (3) 3/16th″ stainless-steel balls. All reactions were treated with tetrahydrofuran and filtered; purities and conversions are of filtered samples before purification. [b]HPLC area conversion. [c]Purities reported are peak area percents with respect to full HPLC trace, including the starting material. [d]Isolated yield. [e]Fluorine location is in position 5. The starting material is 2-bromo-5-fluoropyridin-3-amine.

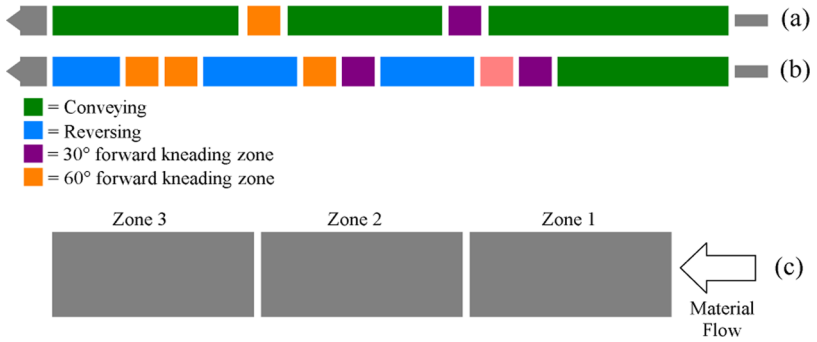



**Figure 2.** Illustration of screw configurations (a, b) and barrel heating zones (c) for reactive extrusion in Nano 16 (not to scale).

focused variables such as screw geometry, screw element arrangement, feeder type, die temperature, and screw speed.[17] We chose to initially implement a mild screw configuration in comparison to those used in the work of Browne and Mack[10,17] to give us an opportunity to increase to a more aggressive configuration in the cases of low reaction conversion. Our initial screw configuration (Figure 2a) was tested on a proprietary substrate and showed poor conversions when tested with a temperature gradient across the barrel (zone 1 50 °C, zone 2 70 °C, zone 3 90 °C) as well as an isothermal barrel (90 and 110 °C). We reasoned that our screw design was not imparting enough mechanical force to the reagents and stunting reactivity; therefore, a more aggressive screw design was implemented (Figure 2b).[16,39] The screw design includes three unique kneading segments, each containing two kneading elements: two forward kneading elements in the first (30°), one forward and one neutral kneading element in the second (30 and 60°), and two neutral kneading elements in the last (60°). These elements are separated by narrow pitch conveying elements to increase the residence time of the reactive material. (Images of the extruder, screw elements, screw designs, and other equipment are


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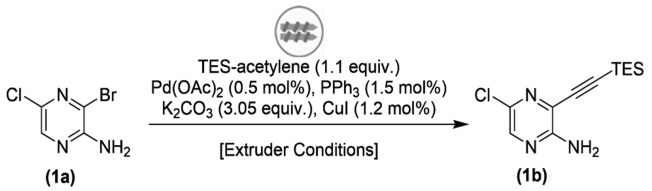
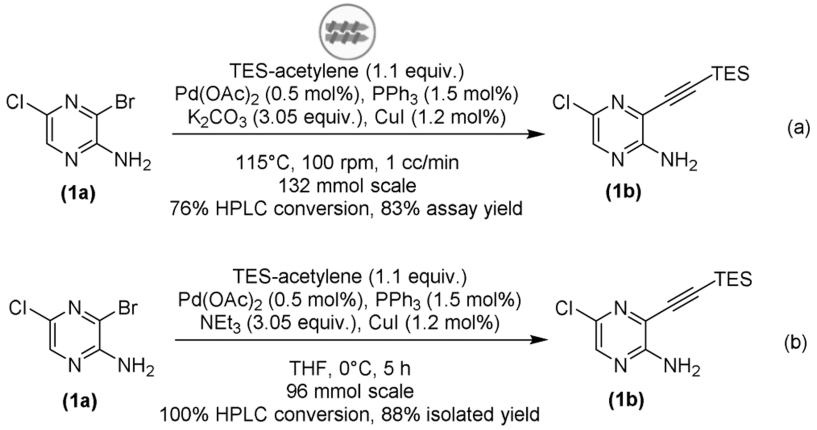
**Table 5. Optimization of Extrusion Conditions for Sonogashira Coupling with 3-Bromo-5-chloropyrazin-2-amine Using the Nano 16 Extruder[a]**




| entry | temperature (°C) | screw speed (rpm) | feed rate ($cm^3$/min) | conversion (%)[b] | purity (pa %)[c] | bisalkyne (pa %) |
|---|---|---|---|---|---|---|
| 1[d] | 100 | 150 | 1 | 32 | 31 | 0 |
| 2[e] | 100 | 150 | 1 | 73 | 71 | 0 |
| 3 | 110 | 150 | 1 | 80 | 77 | 0 |
| 4 | 115 | 150 | 1 | 86 | 82 | 0 |
| 5 | 120 | 150 | 1 | 94 | 86 | 4.7 |
| 6 | 120 | 300 | 1 | ≥99 | 79 | 16 |
| 7[f,g] | 115 | 100 | 1 | 65 | 64 | 1.4 |
| 8[f,h,i] | 115 | 100 | 1 | 73 (83[j]) | 75 | 0.9 |

[a]Reactions performed on a 40 g scale of heteroarene; the unused reaction blend was stored. [b]HPLC area conversion. [c]Purities reported are peak area percents with respect to full HPLC trace, including the starting material. [d]Extruder die became blocked; the sample was taken from the extruder barrel opening. [e]Extrudate from die taken for sampling. [f]Continuous run performed on 120 g of total preblend. [g]Sampling performed before carbon treatment. [h]Sampling performed after carbon treatment. [i]Average of two trials. [j]Assay yield of alkynyl-pyrazine. The extrusion symbol was adapted from Browne and co-workers.

**Scheme 1. Comparison of Reactive Extrusion (a) and Solution (b) Processes in the Synthesis of 5-Chloro-3-((triethylsilyl)ethynyl)pyrazin-2-amine**




included in the Supporting Information and discussed in greater detail.)

Our initial trial using 3-bromo-5-chloropyrazin-2-amine was performed at 100 °C, informed by prior experiments performed on a proprietary substrate. Typically, a die is used at the end of an extruder to shape the extrudate into a desired form while the material is processed. Due to the consistency of our small-scale reaction mixtures, we saw it was advantageous to use a die at the end of the extruder to aid in sample collection; however, the extrudate blocked the exit port and began backfilling the barrel until the system totally seized. Despite the unexpected setback, we were able to gain insight into our reaction system. Small samples were taken from the extruder in zone 1 and from the die, which showed good conversion after the material completely traveled through the barrel (Table 5, Entry 2). In subsequent trials, the die was removed, and the samples were collected from the end of the barrel as thick runoffs. We found through optimization that a temperature of 115 °C was ideal for our reaction system. Additionally, a low feed rate with a screw speed of 150 rpm gave us approximately 86% conversion to a single product (Table 5, Entry 4). At higher temperatures, we observed increased formation of the bisalkyne product due to the reaction at the remaining halide handle (Table 5, Entries 5 and 6). Since the unreacted aryl halide was easier to separate from the product than the bisalkyne byproduct, we conducted further optimization at 115 °C. Ultimately, a choice had to be made between using a higher feed rate and screw speed to reduce residence time in combination with high temperatures or a slower speed and feed rate at the lower temperature to increase residence time.

Ultimately, an isothermal barrel at 115 °C, a slower screw speed of 100 rpm, and a feed rate of 1cc/min were implemented as optimum for this system (Table 5, Entries 7 and 8). These conditions gave a conversion of 73%, which was slightly lower than what was observed in our optimization trials. There was approximately 20 g of extrudate (of the 120−125 g total blend loaded) processed before the system reached a steady state. Such losses are common in continuous processes and become negligible on larger material inputs.


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**Figure 3.** Illustration of Screw Configuration Comparisons for Nano 16 (a) and Process 11 (b) extruders (not to scale).

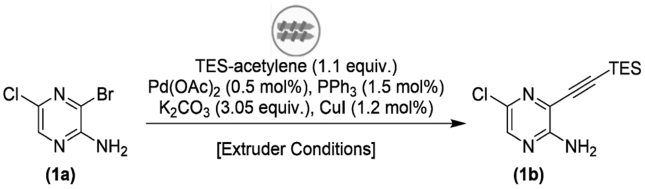
Treatment of the crude extrudate with EtOAc and activated carbon afforded 83% solution assay yield after filtration, which compares well with the result obtained from a solution-based process (Scheme 1). These simple workup conditions would be readily scalable. It is also important to note that these conditions do not require the use of grinding auxiliaries or liquid-assisted grinding aids, which can add additional considerations to the workup.[10]

**Generality of Extrusion Conditions.** To determine the ability to translate the optimized conditions across multiple extruder models, we performed the Sonogashira coupling in an extruder with different parameters. Comparison experiments were performed on a Process 11 benchtop extruder which has an 11 mm screw diameter and 440 mm screw length, seven unique heating zones, and uses a bilobe screw design. Also, the Process 11 extruder does not allow for the bottom loading of the preblend that we implemented in the Nano 16 extruder, so the reaction preblend is fed from the top using a volumetric feeder. This feeder has a twin-screw dispensing mechanism similar to that of the actual extruder, so caution was taken to prevent over-reaction. Reaction pre-blends were only lightly mixed to allow for the feeder to not cause premature reactions. A screw design was assembled to be as close to that of the Nano 16 design utilized in our optimum conditions as possible (Figure 3).

Some key differences are the lack of reversing elements and the angles between kneading elements from the Nano 16 to the Process 11 extruders due to the change from a trilobe screw shape to a bilobe shape.[39] In order to implement a screw design that was as similar as we could control, we substituted 60° kneading elements in our trilobe design with 90° elements and used 60° elements as our lower energy kneading elements given that there is no direct translation from the 30° elements on a bilobe system. We also spaced our elements as best as possible due to the changes in screw length (see the Supporting Information).

Our initial trial in the Process 11 extruder gave promising results with a conversion of 73%, and the only observed species in the extrudate were the starting material and monoalkynylated product (Table 6, entry 1). In a second extrusion trial, the extrudate appeared in two forms: a solid, hardened black material that was followed by a thick black oil, similar to the previous trial and trials performed in the Nano 16 extruder. Interestingly, the solid extrudate was fully converted to only monoalkynylated pyrazine. The oily extrudate had about 10% remaining starting material in the sample, along with monoalkynylated pyrazine. Additionally, there is no observation of the bisalkynylated material in either of these extrudate samples (Table 6, Entries 2 and 3). We attribute the additional starting material to variations in the feed rate due to the fill in the feeder and our inability to tune the feed rate over time. A gravimetric feeder alleviates this challenge by altering the feed rate to match the mass of the preblend remaining in the feed chamber.

**Table 6. Exploration of Extrusion Conditions for Sonogashira Coupling with 3-Bromo-5-chloropyrazin-2-amine Using the Process 11 Extruder**[a]




| entry | temperature (°C) | screw speed (rpm) | feed rate (% motor speed) | conversion (%)[b] | purity (pa %)[c] | bisalkyne (pa %) |
|---|---|---|---|---|---|---|
| 1 | 70/115 | 100 | 15 | 73 | 68 | 0 |
| 2[d] | 70/115 | 50 | 15 | ≥99 | 89 | 0 |
| 3[e] | 70/115 | 50 | 15 | 89 | 86 | 0 |

[a]Reaction performed on a 40 g scale of heteroarene. [b]HPLC area conversion. [c]Purities reported are peak area percents with respect to full HPLC trace, including the starting material. [d]Solid extrudate sample. [e]Liquid/oil extrudate sample.

The solid extrudate obtained from these experiments is amenable to straightforward workup using the procedure outlined in the previous section: extraction with a solvent such as EtOAc, carbon treatment, and filtration. This would reduce the number of workup operations and volume of the solvent used in a typical, large-scale workup.[24]

## CONCLUSIONS

We have developed platform-independent mechanochemical conditions for Sonogashira cross-couplings of decorated heterocyclic aryl halides of pharmaceutical interest. Small-scale optimization in a ball mill allowed us to identify conditions amenable to solid-state chemistry while also using readily available reagents. Engineering optimization of extrusion parameters enabled a scalable version of the reaction to be conducted in twin-screw extruders. The optimized conditions proved successful at the decagram scale in two different extruder platforms, highlighting the adaptability of this technology through modification of screw design, barrel temperature, and feed rate. Assay yields were comparable to standard solution-based methods for the reaction, and reaction times and workup efficiency were superior. Additionally, the solvent used was reduced in reactions using **1a** from 9 V of tetrahydrofuran (THF) in the solution process to 6 V of EtOAc and a 63% reduction when compared to work by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Rozema and co-workers (from 16 to 6 V).[24] Finally, reactions could be conducted without rigorous exclusion of air at <1 mol % Pd loading in the extruder.[40,41]

The prospect of reactive extrusion as a viable technique for performing mechanochemical reactions on scale is inspired by engineering expertise in the fields of hot-melt extrusion and granulation. Using equations developed for hot-melt extrusion,[42,43] we believe that these reactions can be taken from lab-scale extrusion showcased in our study (40 g) to process scales and potentially commercial scale with minimal optimization or engineering challenge. The ability to add reactive extrusion to the process chemist's toolbox adds to the versatility to perform challenging reactions in an efficient and safe way.[44]

Performing a reaction in solution vs. mechanochemically can require additional user input and operation ranging from prep time (solvent sparging, reactor sparging, solvent swaps post reaction, reaction monitoring over time) to true reaction time, and in some cases, product isolation and purification.[10,14,17,45,46] Furthermore, extrusion reactions can be simpler to perform as the material is automatically fed at a controlled rate, temperature, and speed are monitored by onboard software, and reaction material collection is simplified by placing a collection receptacle at the end of the extruder barrel. Despite advancements in both mechanochemistry and extrusion, there are still limitations in the areas of in-process analysis, in situ monitoring by methods other than Raman/IR, and methods to fully dissect reaction kinetics. There are opportunities where reactive extrusion can overcome some of these limitations (in-process analysis in models such as the Process 11 extruder can be done by stopping the extruder, opening the barrel, and sampling directly from the reaction mixture), but there are still many advancements to be made in the field to make this a sharper tool for process scientists. Mechanochemical reactions can be more attractive to academic and industry chemists alike due to their ease of use, efficiency in time, and reagent consumption, alongside the long-lasting impacts of solvent reduction.

## EXPERIMENTAL SECTION

**General Information.** All reagents and solvents were purchased from commercial vendors and used without purification unless noted otherwise. $^{1}$H NMR spectra were recorded on a 400 MHz Bruker spectrometer, and chemical shifts were referenced to the NMR solvent. $^{13}$C NMR spectra were obtained at 101 MHz and referenced to the NMR solvent. Purity results reported by HPLC.

Milling equipment, heating apparatus, and twin-screw extruder details and images are expanded upon in the Supporting Information.

HPLC samples were analyzed using an Agilent 1200 system equipped with a UV-DAD detector. Suitable HPLC methods were developed for the analysis of the reactants and products. The HPLC columns for Sonogashira reaction monitoring were Thermo Hypersil BDS C18, 250 × 4.6 mm, 5.0 $\mu$m columns. The mobile phases for the solvent-free Sonogashira couplings were 0.1 mM ammonium acetate in water (mobile phase A) and acetonitrile (mobile phase B). More details about the HPLC method are included in the Supporting Information.

**General Ball-Milling Procedure for Pyrazines.** A 15 mL Formtech Scientific smart-snap stainless-steel jar was equipped with three (3), 3/16″ stainless-steel balls (0.5 g/ball). The jar was then charged with a heteroarene substrate (250 mg, 1.00 equiv), $K_2CO_3$ (3.05 equiv), TES-acetylene (1.1 equiv), CuI (1.2 mol %), $PPh_3$ (1.5 mol %), and $Pd(OAc)_2$ (0.5 mol %). The jar was closed and then placed in a custom heating band.[47] The assembled milling equipment was placed in the ball-mill (SPEX 8000M) jar clamp and attached to the PID heating apparatus. After closing the mill door, milling and heating of the reaction was begun simultaneously. The reaction was heated to 90 °C for 30 min. After the milling cycle was completed, the mill door was opened, and the apparatus was allowed to cool for 15 min prior to further manipulation. The jar was disconnected from the PID, removed from the mill clamp, and removed from the heating band. The jar was then opened, and the jar halves were treated with a total of 10 mL of EtOAc. The resulting suspension was vacuum-filtered through a pad of Celite into a 40 mL vial. The jar and Celite pad were rinsed with an additional 4 mL of solvent. The filtrate was then concentrated and purified by ISCO column chromatography (heptane:ethyl acetate) for removal of palladium and other impurities when necessary. The product-containing fractions were combined, concentrated, and analyzed by NMR, HPLC, and HRMS.

**General Ball-Milling Procedure for Pyridines.** A 15 mL Formtech Scientific smart-snap stainless-steel jar was equipped with three (3), 3/16″ stainless-steel balls (0.5 g/ball). The jar was then charged with a heteroarene substrate (1.00 mmol, 1.00 equiv), DABCO (3.05 equiv), TES-acetylene (1.5 equiv), CuI (10 mol %), $PPh_3$ (3.0 mol %), and $Pd(OAc)_2$ (1.0 mol %). The jar was closed and then placed in a custom heating band.[47] The assembled milling equipment was placed in the ball-mill (SPEX 8000M) jar clamp and attached to the PID heating apparatus. After closing the mill door, milling and heating of the reaction were begun simultaneously. The reaction was heated to 90 °C for 30 min. After the milling cycle was completed, the mill door was opened, and the apparatus was allowed to cool for 15 min prior to further manipulation. The jar was disconnected from the PID, removed from the mill clamp, and removed from the heating band. The jar was then opened, and the jar halves were treated with a total of 10 mL of THF. The resulting suspension was vacuum-filtered through a pad of Celite into a 40 mL vial. The jar and Celite pad were rinsed with an additional 4 mL of solvent. The filtrate was then concentrated and purified by ISCO column chromatography (heptane:EtOAc or heptane:acetone) for the removal of palladium and other impurities. The product-containing fractions were combined, concentrated, and dried in a vacuum oven with a dry nitrogen bleed at 45 °C for 8 h to ensure the removal of residual DABCO. The dried samples were analyzed by NMR, HPLC, and HRMS.

**General Reactive Extrusion Procedure for the Nano 16 Extruder.** A large ceramic mortar was charged with 3-bromo-5-chloropyrazin-2-amine (40 g, 1.0 equiv), $K_2CO_3$ (3.05 equiv), TES-acetylene (1.5 equiv), CuI (1.2 mol %), $PPh_3$ (1.5 mol %), and $Pd(OAc)_2$ (0.5 mol %). The reagents were gently ground using a ceramic pestle to create a homogenous mixture and then added to the extruder plunger with a funnel and spatula. The material was tapped down using a Teflon rod to ensure full packing and even surface height. Any additional preblend was stored in a media bottle.[48] The plunger was loaded onto the extruder from the bottom of the barrel and locked in place. The barrel of the extruder was preheated to 115 °C in all zones prior to material feeding. The main drive was started at 100 rpm, and the material was fed into the extruder barrel at a rate of 1 cm$^3$/min. The reaction mixture was allowed to pass through the extruder and was


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collected in a large glass crystallization dish. The extrudate was treated with 190 mL of EtOAc and vacuum-filtered into a 1000 mL round-bottomed flask through a pad of Celite. The Celite was washed with 50 mL of EtOAc. The resulting filtrate was then stirred with DARCO G60 activated carbon (8.00 g) for 2 h, followed by filtration through a second pad of Celite. The resulting filtrate was held as a solution in a tared media bottle without further manipulation. The isolated material was analyzed by NMR and HPLC.

**General Reactive Extrusion Procedure for the Process 11 Extruder.** A 500 mL beaker was charged with 3-bromo-5-chloropyrazin-2-amine (40 g, 1.0 equiv), $K_2CO_3$ (3.05 equiv), TES-acetylene (1.1 equiv), CuI (1.2 mol %), $PPh_3$ (1.5 equiv), and $Pd(OAc)_2$ (0.5 mol %). The reagents were gently mixed with a spatula and loaded into a volumetric feeder, which was fixed over zone 1. The barrel was fitted with a Teflon block in place of a die to prevent material blockage. The barrel of the extruder was preheated to 70 °C in zones 2 and 3 and 115 °C in all remaining zones prior to material feeding. The screws were started at 50 rpm, and the material was fed into the extruder barrel at 15% of the feeder motor speed. The reaction mixture was allowed to pass through the extruder and was collected in a 500 mL beaker. The extrudate was treated with 350 mL of EtOAc and vacuum-filtered into a 1000 mL vacuum flask through a pad of Celite. The filtrate was then stirred with DARCO G60 activated carbon (9.00 g) for 2 h, followed by filtration through a second pad of Celite. The resulting filtrate was concentrated into oil and dried under a high vacuum overnight to afford the isolated reaction mixture. The isolated material was analyzed by HPLC. Details about the Process 11 twin-screw extruder can be found in the Supporting Information as well as previous reports by the Mack group.[17]

**Solution Procedure for the Sonogashira Coupling Reaction with 1a.** A 500 mL jacketed reactor was charged with pyrazine **1a** (20 g, 96 mmol, 1.0 equiv), CuI (0.219 g, 1.2 mol %), $PPh_3$ (0.151 g, 0.6 mol %), and $Pd(OAc)_2$ (0.041 g, 0.2 mol %). The reactor was sealed with septa at open necks, and the atmosphere was evacuated with nitrogen gas. A 250 mL addition funnel with THF (160 mL) and $Et_3N$ (41 mL, 294 mmol, 3.05 equiv) was sparged with nitrogen gas for 1 h. An addition funnel was fitted to the reactor and the reactor was chilled to 0 °C. The THF/$Et_3N$ solution was added in one charge, and the solution was allowed to cool to 0 °C. In a separate 60 mL addition funnel, THF (22 mL) and triethylsilyl acetylene (18.9 mL, 106 mmol, 1.1 equiv) were combined and sparged with nitrogen gas for 1 h. The addition funnel was equipped to the reactor with a nitrogen line and added dropwise to the reaction mixture. The internal temperature of the reaction was held between 0 and 5 °C during the addition of the alkyne solution. After roughly 1 h, the addition of TES-alkyne was complete, and the reaction progress was monitored hourly. After 4 h, no starting material was observed by HPLC. The reaction mixture was drained into a 500 mL Erlenmeyer flask and filtered by vacuum into a 1000 mL round-bottomed flask. The reaction mixture was then concentrated into crude oil, which was purified by ISCO (330 g column, 95/5% heptane/EtOAc 5 min, 95/5% to 85/15% heptane/EtOAc 10 min, 85/15% heptane/EtOAc 7 min). Fractions were collected and concentrated to afford a yellow crystalline solid (22.6 g, 88% yield).

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.3c00200.

Used equipment supported by pictures of ball milling and extrusion equipment, used chemicals, analytical spectra (PDF)

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### Author Contributions

S.C.C. conceptualized the study's early stages; M.M.M. and R.H.H. performed exploratory reactions and made the initial discovery; M.M.M., R.H.H., and I.R.S. performed reaction optimization; M.C.H., H.G., I.R.S., S.C.C., R.H.H., and J.M. envisioned and designed optimization experiments for ball milling and extrusion reactions; A.R., C.S., and D.B. designed screw configurations, operated twin-screw extruder, and oversaw extrusion trials; A.R., C.S., D.B., I.R.S., R.H.H., and S.C.C. performed extrusion trials, collected extrudates, and performed the analysis of extrudates; A.R., C.S., and D.B. performed extruder modifications; R.H.H. and I.R.S. performed substrate-scope experiments; M.M.M., R.H.H., I.R.S., and S.C.C. performed data collection and interpretation; I.R.S., R.H.H., M.C.H., J.M., H.G., and S.C.C. drafted, edited, and



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compiled the manuscript; and S.C.C. and I.R.S. oversaw the project team.

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### Notes

The authors declare no competing financial interest.

The AbbVie Process Safety group performed extensive safety tests before extrusion scale-up reactions were performed. This information has been outlined in the Supporting Information.

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## ■ ABBREVIATIONS

HPLC, high-performance liquid chromatography; NMR, nuclear magnetic resonance spectroscopy; TMS, trimethylsilyl; TES, triethylsilyl; THF, tetrahydrofuran; rpm, rotations per minute; DABCO, 1,4-diazabicyclo[2.2.2]octane

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