ChemPlusChem

Full Papers
doi.org/10.1002/cplu.202000451

Mechanochemical Synthesis of N-Aryl Amides from O-Protected Hydroxamic Acids

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Dedicated to Prof. Len Barbour, Prof. Jon Steed, Prof. Bill Jones, and the many young talents they have mentored.

Two robust and efficient mechanochemical protocols for the synthesis of an array of *N*-arylamides have been developed. This was achieved by a C–N cross-coupling between *O*-pivaloyl hydroxamic acids and aryl iodides or aryl boronic acids, in the presence of a stoichiometric amount of a copper mediator. The effectiveness of this method is highlighted by the high-yielding (up to 94%), scalable (up to 8 mmol), and rapid (20 minutes) synthesis of *N*-aryl amides (15 examples), using a variety of deactivated and sterically encumbered substrates, whilst employing mild conditions and in the absence of solvents. In addition, it was determined that whilst the *O*-pivaloyl hydroxamic acid precursors can be synthesised mechanochemically, iron contamination originating from the steel jars was found to occur which can hinder the efficacy of this process. Furthermore, 3D printing was used to produce custom milling jars that could successfully accommodate a scaled-up version of the two protocols.

Introduction

The amide functionality has proven to be extremely important in most areas of organic chemistry and is present in a vast number of contemporary pharmaceuticals, agrochemicals, polymers, as well as natural products and biological molecules.[1–3] Since there is an intrinsic need for large scale production of amide-bearing compounds, it is imperative that improved and sustainable methods are developed to provide high atom efficiency, low energy consumption, and minimal waste, whilst maintaining acceptable yields.[4] It is noted that within the pharmaceutical industry alone, amides constitute by far the most abundant functionality (16% of all reactions within the sector), and subsequently, synthetic routes that provide access to this moiety are the most commonly used in the sector.[5,6] Aryl amides can be problematic to synthesise due to the reduced reactivity/nucleophilicity of the amine. Furthermore, it has been reported that around 85% of the chemicals that are being used are solvents,[4] of which a large percentage are never recycled, ending up in the environment as pollutants. Large database searches have revealed that the most prevalent solvents employed in amide couplings are dichloromethane (DCM) and *N*,*N*-dimethylformamide (DMF), used in 36% and 47% of the reactions respectively.[7] It is widely accepted that both of these solvents pose issues,[8] both in handling them and discarding them to the environment.[9,10] Thus, it is now becoming increasingly important for chemists to seriously consider implementing alternative and greener methods for synthesising compounds and mechanochemistry is a great means to achieve this. Traditionally, mechanochemistry was considered as a technique of less versatility and scope for chemists, and as a result, it hasn't been widely accepted by the synthetic community as a plausible method of inducing chemical reactions. However, this is now rapidly changing, as researchers are starting to recognise the versatility and potential mechanochemistry has to offer, mainly due to the advent of green chemistry and the need to find more environmentally friendly and sustainable methods of producing chemicals, both in research laboratories[11–13] and on an industrial scale.[14] These realisations have led to rapid developments in key areas of synthetic organic chemistry spanning from catalysis and coupling reactions[15] to more niche topics such as fullerene chemistry,[16] photocatalysis, and supramolecular chemistry.[17] Through this apparent era of 'mechanochemical enlightenment', it has become clear that an optimised mechanochemical protocol can not only provide improved performance compared to equivalent batch reactions but it can also unlock new mechanistic pathways which lead to products previously unattainable through batch techniques.[18,19] Amides have understandably been a target for mechanochemical synthesis with activated carboxylic acids (carbodiimides, for example), peptides, and materials being common themes.[20] Herein we describe two mechanochemical protocols for the high yielding *N*-amidation of aryl iodides (protocol **A**) and aryl boronic acids (protocol **B**) by *O*-protected hydroxamic acids,

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/cplu.202000451

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mediated by the stoichiometric presence of a Cu(I/II) species (Scheme 1).

Results and Discussion

There are several examples in the literature[21–23] (see Scheme 1 for comparison of literature methods and work presented here) where protected hydroxamic acids are converted into amides, and it is clear that high temperatures, inert atmospheres, harsh solvents and moderate to long reaction times are in most cases indispensable to achieve the desired outcome. Additionally, only one of the reports[21] employs aryl halides, where the starting reagent *N*-methoxybenzamide undergoes a double oxidative C–C and C–N bond formation to afford a cyclic phenanthridinone, circumventing the formation of a secondary amide. The most common coupling partners used in those reactions are boronic acids. Our main goal for this study was to find a set of more benign and sustainable reaction conditions that could be implemented with mechanochemistry. Initially, the possibility of using ball milling as a means to gain access to the *O*-pivaloyl protected hydroxamic acids starting materials was examined (Scheme 2).

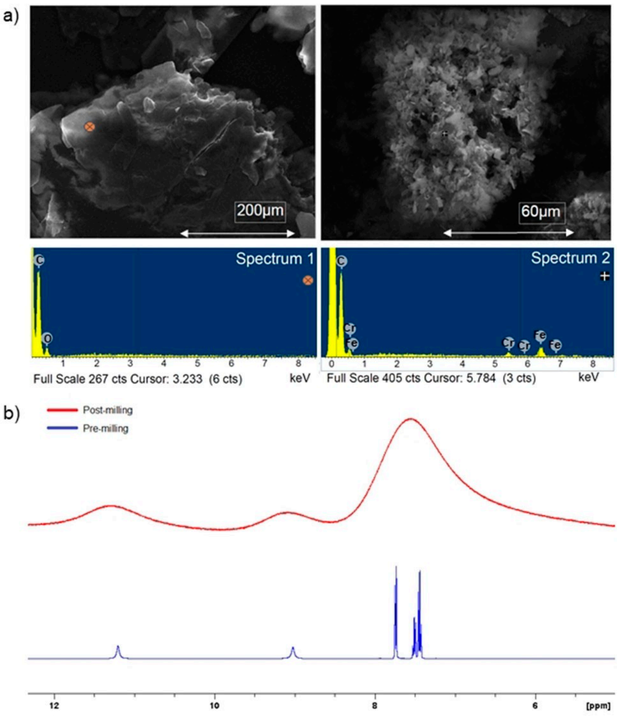

Figure 1. a) SEM/EDX analysis of pristine and milled benzohydroxamic acid clearly shows that iron and chromium leaches from the steel jars to the sample. Spectra and images are representative of the entire sample (nine images and spectra recorded). b) Pre-milled and post-milled ^{1}H-NMR spectra of benzohydroxamic acid illustrating peak broadening due to the presence of paramagnetic Fe(III).

It was found, that although it was possible to achieve comparable yields with reduced reaction times by applying the mainstream solution-based conditions[23,24] to the ball mill, in the absence of a solvent, iron leaching from the steel jars occurs during the milling process. It has been shown that iron particles which become dislodged during the milling process can then be oxidised to form Fe(II) and Fe(III) species.[25] We found that when this occurs, the Fe-hydroxamate complex becomes unreactive and due to the paramagnetic nature of Fe(III), during NMR analysis we observed reduced relaxation times, which causes an extreme broadening of the NMR peaks (Figure 1 and Supporting Information S1.3). Furthermore, energy dispersive x-ray spectroscopy (EDX) analysis with a scanning electron microscope (SEM) of pristine and milled benzohydroxamic acid samples confirmed the presence of iron and chromium in the latter sample, both of which are contained within the steel jars that were used (Figure 1). It is interesting to note that Mocci *et al.*[26] do not mention leaching of iron during their hydroxamic acid mechanochemical synthesis. We can only speculate

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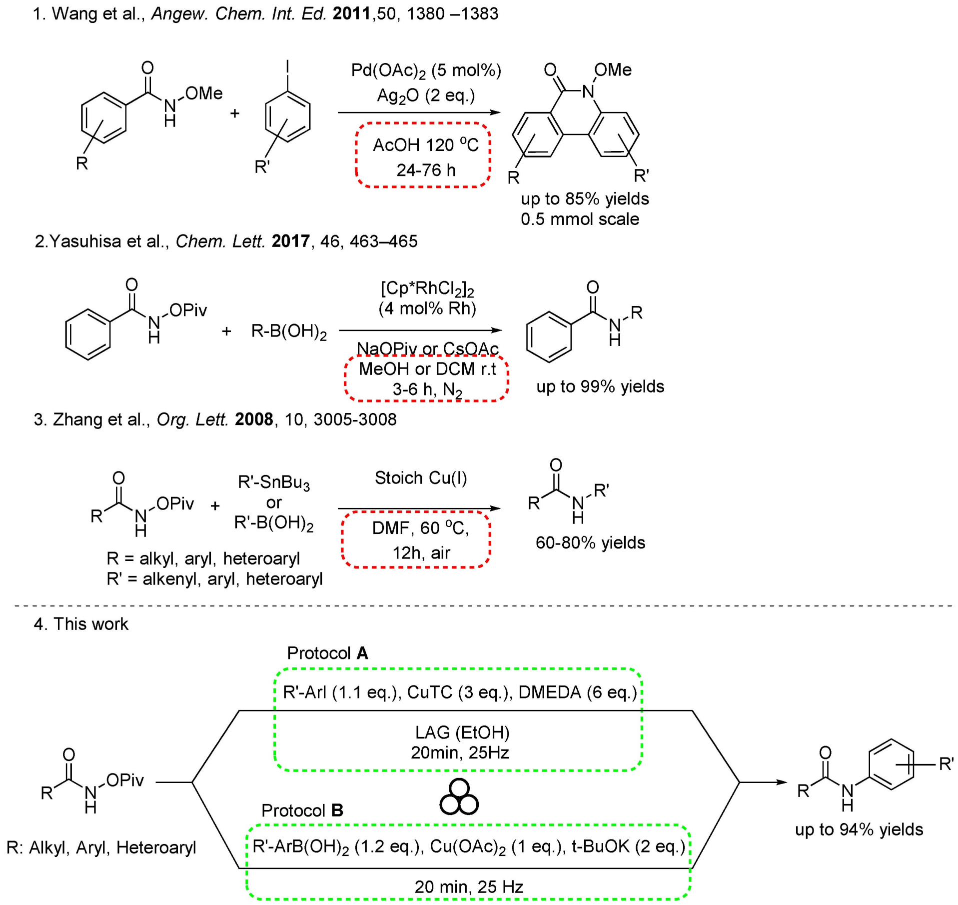
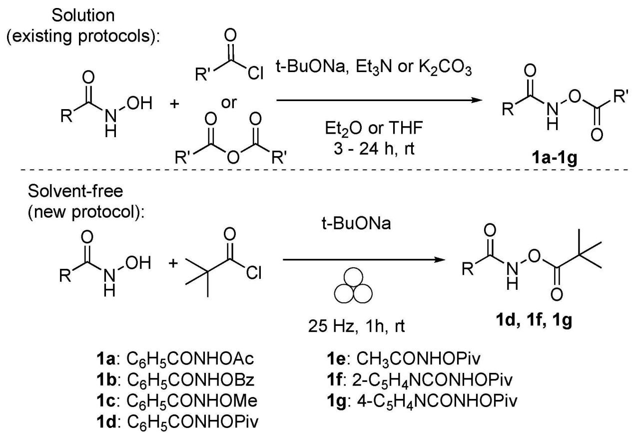
Gareth Lloyd completed his MSc at Stellenbosch University, South Africa under the supervision of Len Barbour. A PhD followed at Durham, UK under the supervision of Jon Steed. An independent position as a Herchel Smith Fellow at Cambridge, UK under the mentorship of Bill Jones began his interest in mechanochemistry. The Lloyd/Vilela collaboration ensued upon a move for Gareth further north to Scotland and Heriot-Watt University as a Research Fellow. Gareth recently moved to the new School of Chemistry at the University of Lincoln.

Len, Jon, Bill, Dave and Pete inspired an interdisciplinary and collaborative work environment. Mary Jones and Emmanouil Broumidis are co-supervised by Gareth and Filipe, and work across a number of teams. The researchers within the teams, who bring this scientific effort to fruition, are continuously inspiring new ideas and projects, like this one. This paper is the brainchild of Emmanouil, and couples the Vilela group interests of polyaryls and photocatalysis with the Lloyd group interests of mechanochemistry and hydroxamic acids.



Scheme 1. Comparison between previous *N*-benzamide synthetic contributions using *O*-protected hydroxamic acids and current work.



Scheme 2. Most common synthesis conditions of various *O*-protected hydroxamic acids involves the use of solvents such as diethyl ether (Et_2O) or tetrahydrofuran (THF).

that ageing of the steel-constructed jars may be the cause of our observation of leaching and we advise when using mechanochemistry to be aware of this issue with steel grinding jars, as leaching of iron or chromium may not only interfere with the reactants but also catalyse reactions[27,28] both of which may lead to inaccurate results. Unsurprisingly, this leaching occasionally caused interference with the reaction leading to inconsistent results, as hydroxamic acids and their derivatives are well-known siderophores and iron sequesters.[29,30] As such, in order to reliable obtain the desired *O*-protected hydroxamic acids we opted to use traditional batch procedures, although we believe that future research endeavours focusing on addressing this issue are required to allow iron sensitive chemistries to work reliably under mechanochemical conditions using steel grinding jars. Use of jars made out of different materials such as Teflon (PTFE) may be a way to circumvent this issue, however, the aforementioned reaction did not work, perhaps due to the softness of PTFE in comparison to steel.

For the optimisation of the Ullmann coupling (protocol **A**, Scheme 1), we were interested in determining the optimal conditions for the preparation of *N*-phenylbenzamide (**2a**). Although this compound is trivial, the starting materials are relatively cheap, easily available, and allow for ease of testing and optimisation of the initial reaction conditions. These include the determination of an appropriate catalyst/promoter, base (if required), ligand, and protecting group for the hydroxamic acid. It was found that by using 3 equivalents (eq.) of copper (I) thiophene-2-carboxylate (CuTC), *N,N'*-dimethylethylenediamine (DMEDA) (6 eq.), *O*-pivaloyl protected benzohydroxamic acid and iodobenzene the Ullmann-type transformation (protocol **A**) proceeded to give the best results under liquid-assisted grinding (LAG, EtOH, $\eta = 0.16\ \mu L/mg$)[31] mechanochemical transformations. No other additives were deemed necessary. All mechanochemical reactions were carried out using a 10 mL steel jar with 2 steel balls (8 mm in diameter), and the optimised reaction was complete in under 20 minutes, which is significantly less than comparable batch reactions (Scheme 1). With these optimal conditions in hand, we proceeded to investigate whether the use of LAG is necessary (Table 1).

A range of solvents was tested spanning a wide spectrum of polarities. It immediately became obvious that using small amounts of EtOH has a profound effect on the efficiency of the reaction (entry 3). When the reaction was performed without any solvent, (entry 1) the yield dropped significantly, highlighting the importance of LAG in this mechanochemical synthesis.[32] The use of water as a LAG additive (entry 2) further reduced the overall yield, while DMF (entry 4) offers a substantial conversion but lower than EtOH. Non-polar solvent LAG did not affect the yield. Olefins and alkynes are known to act as π-Lewis base ligands that can coordinate with various copper species and enhance the yields of Ullmann oxidative couplings.[33] Moreover, it was recently found[12,34] that olefins can be used as effective molecular dispersants for solid-state Pd promoted cross-coupling reactions. For those reasons 3-hexyne was used to test whether any enhancement could be observed. The overall yield of the reaction (entry 5) was no different than the LAG-free benchmark. We also noticed that the two best LAG additives (EtOH and DMF) were found to dissolve all components of the mixture fairly well, albeit when we tried applying the same reaction protocol in solution the reactivity was reduced significantly (Supporting Information S1.6). After establishing that EtOH is the most efficient LAG additive, we wanted to examine the respective reactivity of bromo- and chloro-benzene as coupling partners. It was found that under the aforementioned optimal reaction conditions bromobenzene only afforded **2a** at a yield of 16% while chlorobenzene was completely unreactive (SI, S1.2). This was not unexpected, as aryl iodides are known to be the most reactive aryl halides towards Ullmann couplings.[35] Commercial grinding jars are available in a range of materials therefore further optimisation may be achieved by changing the jars used. The reaction was repeated for jars and 8 mm balls made out of Teflon (PTFE) and poly(methyl methacrylate) (PMMA). It was found that stainless steel and Teflon had comparable performances, and the acrylic jars and balls did not perform as well (SI S1.7).

Table 1. Investigation of LAG effects on the yield of **2a**.[a]

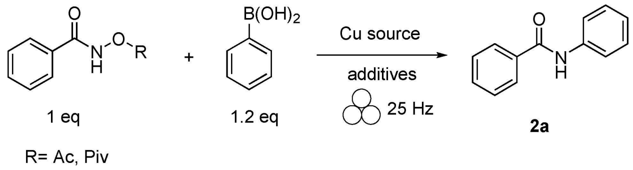
Entry	LAG[b]	Yield [%][c]
1	Neat	65
2	Water	46
3	Ethanol	94
4	Dimethylformamide (DMF)	88
5	3-Hexyne	66
6	Toluene	65

[a] 10 mL stainless-steel jar with two 8 mm diameter stainless-steel balls were used for the ball-milling reactions. An average of two runs is reported for the ball-milling reactions. [b] $\eta = 0.16$ μL/mg, based on adding 100 μL of solvent in 618 mg of reactants. [c] Yield of isolated product.

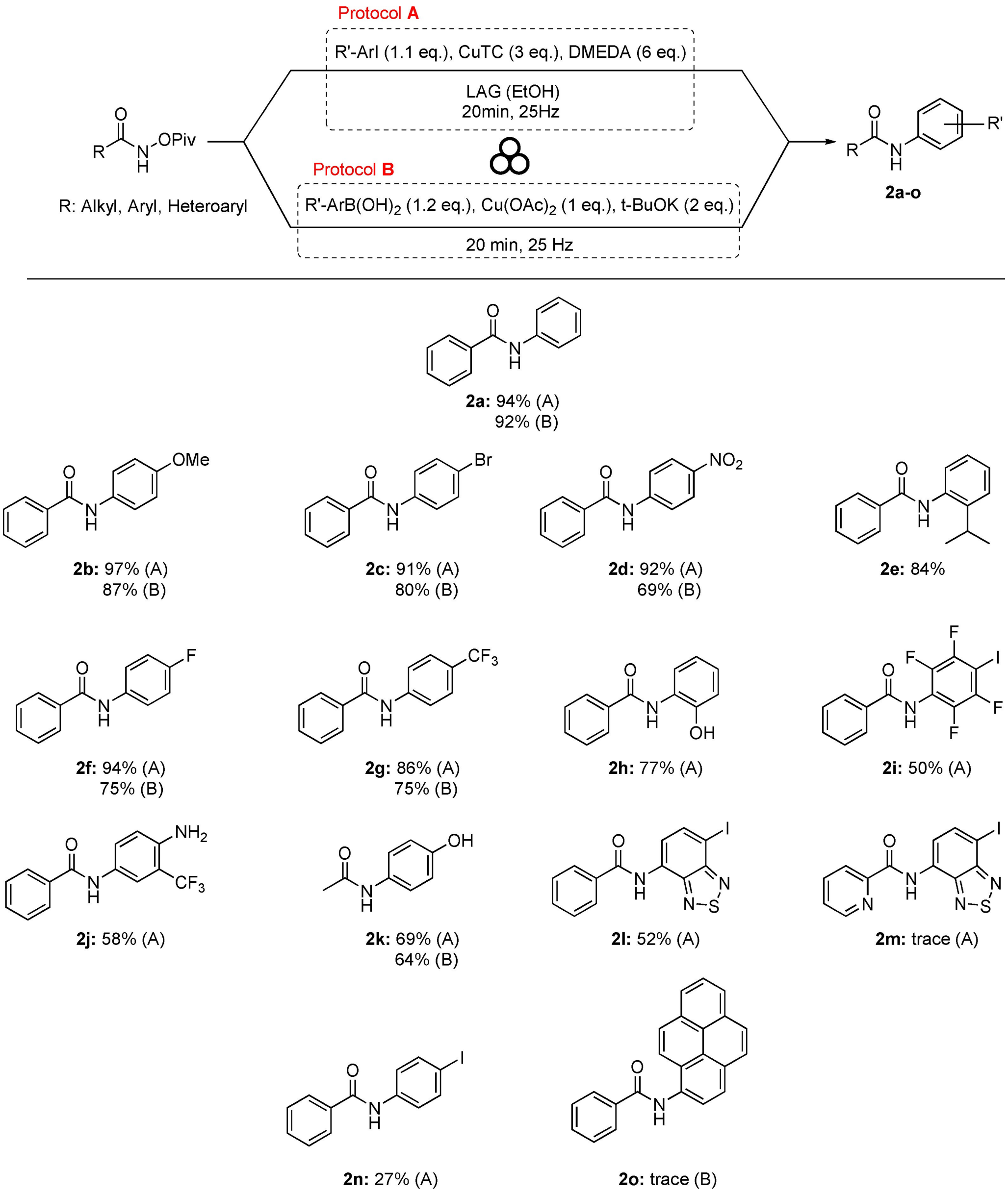
In order to extend the utility of the *O*-protected hydroxamic acid starting materials, and inspired by previously reported[31] solution-based *N*-amidations, we developed a separate, mechanochemical Chan-Lam type coupling procedure (protocol **B**), which uses arylboronic acids as the coupling partner together with a stoichiometric amount of $Cu(OAc)_2$ as a mediator. We initiated our optimisation (Scheme 3), by adopting the conditions that were developed for solution-based chemistry by Zhang *et al.*[36] We found that both acetyl (**1a**) and pivaloyl (**1d**) *O*-protected hydroxamic acids were effective coupling partners affording **2a** in a 90% and 92% yield, respectively. The presence of a base was deemed necessary for the reaction to proceed to completion and after a base screening, 2 equivalents of potassium *tert*-butoxide (*t*-BuOK) was found to be the best choice (SI S1.1).

In contrast with the Ullmann protocol **A**, the addition of a LAG solvent did not improve the reaction efficacy with a reduction in the overall yield when EtOH was used as a LAG component (SI S1.1). The minimum amount of time for the reaction to go to completion was determined to be 20 minutes, which is comparable with the corresponding time for protocol **A**. It was observed that when the $Cu(OAc)_2$ equivalents were less than one, the reaction did not proceed to completion. This result is in line with most Chan-Lam coupling procedures in the literature,[37] where a stoichiometric amount of copper is required. Overall, the optimised conditions were determined to be 1 eq. of **1d**, 1 eq. of $Cu(OAc)_2$ and 2 eq. of *t*-BuOK which afforded product **2a** in high yield (92%) after 20 minutes of milling. For comparison, when applying these conditions to a solution-based set-up using various solvents and heating the reaction mixture we found that even after 16 hours the reaction was not complete and thin-layer chromatography (TLC) analysis revealed many side-products and unreacted starting material (SI, S1.6). Finally, the optimised protocols (**A** and **B**) were applied to a range of different aryl iodides and aryl boronic acids to explore their effectiveness and versatility (Scheme 4).

Overall, both protocols **A** and **B** proved to be highly efficient and provided access to moderate to high yielding *N*-arylamides. Compounds bearing electron-deficient functional groups (**2d**, **2f**, **2g**, **2i**, **2j**, **2l**, **2m**) and sterically encumbering functional groups (**2e**, **2h**, **2i**, **2o**) were accessed, although **2m** and **2o** only in trace amounts. Furthermore, protocol **A** also works by varying the starting *O*-protected hydroxamic acid, as demonstrated by the use of *N*-(pivaloyloxy)acetamide **1e** and *N*-(pivaloyloxy)picolinamide **1f** to give the commercial pharmaceutical paracetamol, **2k**, in moderate yield and traces of **2m**. Interestingly, when diiodo aryl starting materials were used only



Scheme 3. Chan-Lam reaction parameters that were explored for optimisation under mechanochemical conditions (protocol **B**).



Scheme 4. Reaction scope using the optimised protocols **A** and **B**.

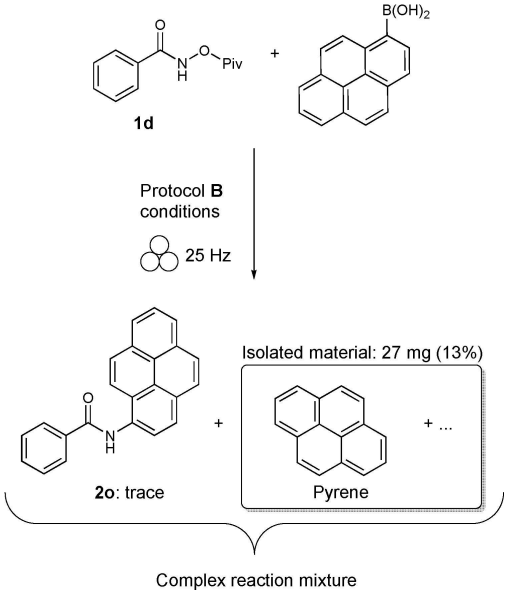
the monosubstituted compounds were formed (**2i**, **2l**, **2m**, **2l**), even when the CuTC and DMEDA equivalents were doubled. Similar results were observed under solution conditions.

Heteroaryl **1f** was used to afford compound **2m**, but only a trace amount (<5% yield) was isolated and when N-(pivaloyloxy)isonicotinamide (**1g**) was used the reaction failed. Similarly, when these heteroaryl starting materials were used in conjunction with protocol **B** conditions, the reaction did not work. We postulate that this lack of reactivity stems from the pyridyl moiety binding to the copper mediator. Interestingly, when 1,4-diiodobenzene was used under protocol **A** conditions, compound **2n** was isolated (27% yield) and no traces of diamide were detected in the reaction mixture. Even when we used 2 eq. of **1d** only the monoamide **2n** formed, despite having a second iodine available for further cross-coupling. This apparent inertness of **2n** towards protocol **A**'s Ullmann-like conditions was further established when we used a pure sample of **2n** as the halide source and it did not react with **1d**. Similar results were observed when 1,4-dibromobenzene and 4,7-diiodobenzo[c][1,2,5]thiadiazole were used for the formation of **2c** and **2l**, respectively. Overall, this selective reactivity towards aryl dihalides expands the scope of the method and makes it possible to synthesise halogen bearing N-benzamides which can be then used for further synthetic modifications.

We postulated that the donor-acceptor (D–A) type compound, **2l**, could be used for photochemical applications. This was demonstrated by using it as a photosensitiser for the mechanochemically-assisted solid-state photocatalytic (MASSPC)[38] conversion of anthracene to anthracene-endoperoxide (SI S1.8, S1.9) which was subsequently catalytically decomposed to anthraquinone.[39]

Since polycyclic aromatic hydrocarbons (PAHs) are known for their low solubility in most organic solvents, due to strong intermolecular π-π interactions which stem from their extended planar structures,[40] we decided to use pyrene-1-boronic acid as a coupling partner to **1 d** to gain access the corresponding *N*-benzamide **2 o** via protocol **B**. Unexpectedly, after 20 minutes of milling, TLC analysis of the reaction mixture showed a multitude of trailing spots, indicating a deviation from the expected outcome. Upon subjecting the reaction mixture to mass spectrometry (MS) analysis, it was revealed that the target amide **2 o** was present amongst other side-products. Purification of the crude reaction mixture via preparative thin layer chromatography, afforded 27 mg of a yellow solid (13 % yield), however, we were not able to isolate amide **2 o**. Interestingly, upon analysis, the isolated yellow solid was found to be primarily pyrene and although it was contaminated with other by-products it was reasonably pure (Scheme 5).

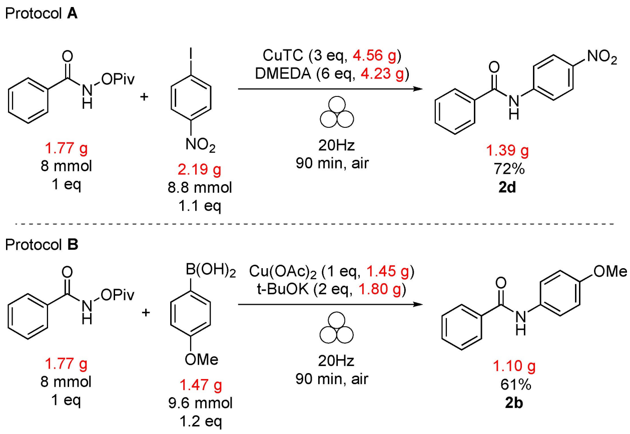
We postulate that the formation of pyrene can be the result of a protodeboronation side-reaction which may have been catalysed by the presence of $Cu(OAc)_2$. A solution-based copper catalysed protodeboronation procedure under basic conditions was reported in 2014,[41] however, to the best of our knowledge, this is the first example of a mechanochemical protodeboronation reaction. Although historically protodeboronations have been considered of lesser importance by organic chemists, recently this reaction has found a variety of applications in synthetic procedures[42,43] and thus the aforementioned example may form a stepping stone for further development of such solventless protodeboronations. In general, protocol **B** gave slightly lower yields than protocol **A**, which can be rationalised since we know that side-reactions such as protodeboronations may occur, under protocol's **B** conditions.



Scheme 5. Mechanochemical reaction between **1 d** and pyrene-1-boronic acid under protocol **B** conditions leads to the formation of pyrene as the major isolatable product.

We found that both protocols are scalable up to the gram scale with only slight modifications (Scheme 6). Machining[44] and 3D printing of custom milling jars[45] are examples of customisation techniques mechanochemists have used in the past to adjust the milling jars to their needs. To accommodate the large quantity of reactants, custom milling jars were made using a commercial 3D printer that uses methacrylate photopolymers to produce the desired object via a stereolithographic (SLA) printing technique.[46] The 3D printed jar that was used was printed using a commercial form 2 SLA printer along with tough v5 resin, both made by Formlabs. The jars had an internal volume of 70 mL, a wall thickness of 10 mm and could easily accommodate the reactants, which combined had a mass of 12.75 g and 6.49 g for protocols **A** and **B**, respectively. The milling frequency was reduced to 20 Hz in order to ensure that the printed jars could withstand the prolonged milling forces, as it was found that at 25 Hz cracks would form on the inner surface of the jars after about 30–45 minutes of milling. As a result of the lower milling frequency, the reaction time to completion increased from 20 minutes to about 90 minutes, for both protocols.

Initially, 25 × 8 mm Teflon balls with a total mass of 6 g were used (protocol **A**), but the mixture remained unreactive. However, when 6 ZrO_2 balls of variable diameter (6–15 mm) were used with a total mass of 16.11 g, the reaction gave product **2 d** at 72 % yield. This agrees with the studies made by Fischer *et al.*,[47] which showed that the total energy input of each collision during the milling process has a higher impact on the reactivity than the number of collisions during the milling process. Similarly, by using the mixed ZrO_2 balls, protocol **B** was successfully used at gram scale and afforded **2 b** at 61 %. In both cases, the yield diminished slightly, as would be expected for a scaled reaction.



Scheme 6. Gram-scale synthesis using protocols **A** and **B**. The scaling of the reaction reduces the yield slightly.

Conclusion

We report here the synthesis of amides using two mechanochemical protocols. As a comparison to previously reported methodologies, we believe that these methods add to the current knowledge base. As early as 2008, Gao and Wang[48] used potassium peroxymonosulfate, also known as oxone, as an environmentally friendly non-toxic oxidant to synthesise a range of aromatic benzamides by oxidative amidation of aldehydes with anilines under mechanochemical, solvent-free conditions. Other notable amide synthesis examples include mechanochemically activating carboxylic acids using *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) for the chemoselective and high yielding synthesis of aromatic amides and dipeptides, developed by Štrukil *et al.*[49] A similarly enticing report emerged in 2013 by Bonnamour *et al.*[50] demonstrating a method that uses EtOAc LAG mechanochemistry to access a variety of peptides in high yields after 20 minutes of milling, compared to traditional solution syntheses which primarily use harsh solvents such as DMF. Finally, a more recent example from 2020 by Dayaker *et al.*,[11] introduced a copper-catalysed milling synthesis affording a plethora of carbamoyl-amides in high yields, whilst analogous batch experiments required high temperatures to work, while producing unwanted by-products not seen under mechanochemical conditions. These examples are a small part of an ongoing effort[20] for utilising mechanochemical techniques to form amide and peptide bonds and they all operate under the same principles as our study, offering high yielding amide syntheses, minimal ecological impact, chemoselectivity, minimisation of unwanted by-products, and synthesis of difficult-to-access amides (e.g. aryl amides).

In summary, we developed two high yielding and scalable mechanochemical protocols that provide access to various secondary *N*-arylamides from readily available *O*-protected hydroxamic acids, iodoaryls, and arylboronic acids. As the industrial community recognises the need for the development for new and sustainable amidation methodologies, this work acts as a proof of concept that may encourage other researchers to delve into solvent-free syntheses of amides and utilise the many benefits mechanochemistry has to offer compared to the traditional batch-based chemistries. Protocol **B** produced lower yields than protocol **A**, most likely due to protodeboronation acting as a side-reaction. In addition, we identified and highlighted the fact that iron leaching originating from the steel milling jars should be taken into account when using reactants with high affinity for iron such as hydroxamic acids or when iron contamination may alter the reaction outcome. Moreover, we utilised SLA 3D printing to produce jars that were suitable for scaling up the new synthetic protocols. Finally, in order to expand the scope of the methodology that was developed, further work is currently underway that aims to synthesise efficient BTZ-containing *N*-arylamides for MASSPC singlet oxygen generation.

Experimental Section

Preparation of *N*-aryl benzamides

Mechanochemical preparation

Protocol **A**: To a stainless steel ball mill jar (10 mL internal volume) *N*-(pivaloyloxy)benzamide (88.5 mg, 0.400 mmol, 1 eq.) was added, followed by the corresponding phenyl iodide (0.44 mmol, 1.1 eq.), copper (I) thiophene-2-carboxylate (228.2 mg, 1.200 mmol, 3 eq.) and *N*,*N*′-dimethylethylenediamine (211.6 mg, 2.400 mmol, 6 eq.). In addition to these reagents, EtOH ($\eta = 0.16\ \mu L/mg$) was added to the jar, along with two steel balls (8 mm in diameter). The jar was sealed and milled for 20 minutes at 25 Hz. After the completion of the reaction was confirmed by TLC ($CHCl_3$: EtOAc, 90 : 10), the jar was opened and the reaction mixture was passed through a short silica plug (eluted with 5 mL $CHCl_3$: EtOAc, 80 : 20). The resulting solution was evaporated under reduced pressure, and the residue was recrystallised to afford the title compound (**2**_).

Protocol **B**: To a stainless steel ball mill jar (10 mL internal volume) *N*-(pivaloyloxy)benzamide (88.5 mg, 0.400 mmol, 1 eq.) was added, followed by the corresponding phenyl boronic acid (0.48 mmol, 1.2 eq.), copper(II) acetate (72.7 mg, 0.400 mmol, 1 eq.) and potassium *tert*-butoxide (89.77 mg, 0.800 mmol, 2 eq.). In addition to these reagents, two steel balls were added to the jar (8 mm in diameter). The jar was then sealed and milled for 20 minutes at 25 Hz. After the completion of the reaction which was confirmed by TLC ($CHCl_3$: EtOAc, 90 : 10), the jar was opened and the reaction mixture was passed through a short silica plug (eluted with 5 mL $CHCl_3$: EtOAc, 80 : 20). The resulting solution was evaporated under reduced pressure, and the residue was recrystallised to afford the title compound (**2**_).

Gram scale mechanochemical preparations

Protocol **A**: To an SLA 3D printed milling jar (70 mL internal volume) *N*-(pivaloyloxy)benzamide (1.77 g, 8.00 mmol, 1 eq.) was added, followed by 1-iodo-4-nitrobenzene (2.19 g, 8.80 mmol, 1.1 eq.), copper (I) thiophene-2-carboxylate (4.56 g, 24.0 mmol, 3 eq.) and *N*,*N*′-dimethylethylenediamine (4.23 g, 48.0 mmol, 6 eq.), along with 4 ZrO_2 balls of variable diameter (6–15 mm) with a total mass of 16.11 g. The jar was sealed and milled for 90 minutes at 20 Hz. After the completion of the reaction was confirmed by TLC ($CHCl_3$: EtOAc, 90 : 10), the jar was opened and the reaction mixture was passed through a short silica plug (eluted with 10 mL $CHCl_3$: EtOAc, 80 : 20). The resulting solution was evaporated under reduced pressure, and the residue was recrystallised to afford **2d** as a yellow powder (1.39 g, 72 %).

Protocol **B**: To an SLA 3D printed milling jar (70 mL internal volume) *N*-(pivaloyloxy)benzamide (1.77 g, 8.00 mmol, 1 eq.) was added, followed by 4-methoxyphenylboronic acid (1.47 g, 9.60 mmol, 1.2 eq), copper(II) acetate (1.45 g, 8.00 mmol, 1 eq.) and potassium *tert*-butoxide (1.80 g, 16.0 mmol, 2 eq). In addition to these reagents, 4 ZrO_2 balls of variable diameter (6–15 mm) with a total mass of 16.11 g were added. The jar was sealed and milled for 90 minutes at 20 Hz. After the completion of the reaction was confirmed by TLC ($CHCl_3$: EtOAc, 90 : 10), the jar was opened and the reaction mixture was passed through a short silica plug (eluted with 10 mL$CHCl_3$: EtOAc, 80 : 20). The resulting solution was evaporated under reduced pressure, and the residue was recrystallised to afford **2b** as a white powder (1.10 g, 61 %).

Acknowledgements

The University of Edinburgh Mass Spectrometry Service is acknowledged for acquiring invaluable mass spectra. Sam Goldwater (Lincoln) is thanked for assistance with SEM and EDX. E.B. would like to thank Heriot-Watt University (HWU) and the CRITICAT EPSRC Centre for Doctoral Training for funding. G.O.L. would like to thank the Royal Society of Edinburgh/Scottish Government Personal Research Fellowship scheme. M.J. would like to thank HWU and EPSRC for PhD funding from the EPSRC DTP. This project has been supported by the HWU Energy Academy 2016 Fledge Award (Dr. Susana Garcia-Lopez (HWU) is thanked for being a co-I on this grant).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Amidation · cross-coupling · mechanochemistry · solvent-free synthesis · sustainable chemistry

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Manuscript received: June 8, 2020
Revised manuscript received: July 27, 2020
Accepted manuscript online: July 28, 2020