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Flow-through mechanochemical synthesis by reactive extrusion

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Chemical reactions are conventionally carried out in solution, wherein solvents assume a pivotal role in facilitating the dissolution of reagents and thereby enabling molecular interactions. However, this conventional approach is associated with substantial solvent consumption, waste production, and environmental and safety concerns, while also necessitating protracted reaction times. In recent years, there has been an increase in the study of various mechanochemical methods, with the flow-through mechanochemical approach *via* reactive extrusion (REX) emerging as one of the most promising alternatives. This process employs screws (single, twin or multiple) to generate mechanical energy (shear, compression and friction) to drive chemical reactions, offering precise control over temperature, mixing and residence time. Typically, REX is performed with minimal or no solvents, which significantly reduces its environmental impact. Furthermore, it ensures shorter reaction times and higher yields. In this review, a comprehensive analysis is conducted on the role of screw configuration, temperature control, and residence time in optimising the outcomes of various reaction types.

1. Introduction

Flow-through mechanochemical synthesis by reactive extrusion refers to a continuous or semi-continuous process in which mechanical forces are used to induce chemical reactions during extrusion, usually without solvents or with minimal solvent use. Instead of traditional solvent-based thermal activation, mechanochemical transformations are driven by mechanical energy with shear, compression and friction, generally carried out in ball mills (IUPAC definition).[1] Extruder screws (single, twin or multiple) can mix, grind and press the reacting solid (or semi-solid) mixture through the barrel under suitable modular heating.

In recent years, mechanochemistry has become the focus of research due to its numerous advantages. It has been shown that yields can be increased, and reactions can proceed faster than in solution, resulting in shorter reaction times and better stereochemical control and selectivity.[2,3] In addition, mechanochemical reactions allow the use of insoluble starting materials, whereby any liquids behave as lubricants.[4] Since Aristotle's students discovered that grinding cinnabar with a bronze or copper mortar could lead to the formation of mercury,[5] mechanochemistry has evolved into various mechanised technologies such as mechanical grinding (including ball- and pan-milling), ultrasonic irradiation and reactive extrusion.[6]

In 2019, IUPAC identified the top ten emerging technologies in chemistry that have the potential to change our world and make it more sustainable.[7] One of these is reactive extrusion (REX). The extrusion process has mainly been used to produce polymers[8] or for drug formulation,[9] but more recently scientists have begun to explore the possibilities of using the extruder as a reactor to produce both organic and inorganic compounds, *i.e.* metal–organic frameworks (MOFs).[7,10–16]

The standard configuration of an extruder comprises a feeder (which may be either volumetric or gravitational) and a heatable barrel. Within this barrel, one (single-screw extrusion or SSE) or two (twin-screw extrusion or TSE) screws are employed to convey the material along the inner barrel (Fig. 1).

The screws can perform both co-rotating and counter-rotating movements. An access port for gases or liquid reagents can be fitted along the barrel and an optional die can be attached at the end of the extruder to mould the material if required.[17] In the case of TSE, the screw can be modulated with three different sections. The conveying section moves the material flow along the screw. The reverse section counteracts the tendency of the flow to move in a forward direction and thus facilitates mixing. The kneading section improves the mixing shear and can be positioned at 30, 60, 90°.[18,19] Extrusion technology enables solvent-free chemical reactions, which could significantly reduce the impact on the environment.[20] In addition, REX has been shown to reduce hazardous waste, lower energy consumption and minimise emissions of volatile organic compounds (VOCs), thereby engendering a safer and more environmentally friendly production. This feature must

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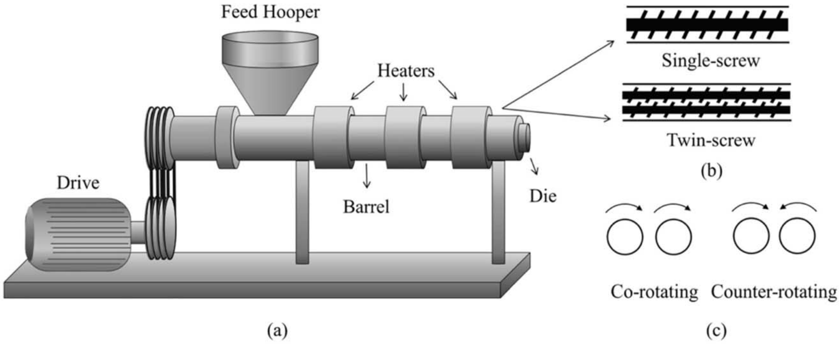


Fig. 1 (a) Structure of extruder; (b) single-screw and twin-screw; (c) rotation directions.

be taken into account, as the pharmaceutical industry, for example, produces around 25 to 100 kg of waste per kg of product, where waste consists mainly of solvents.[21] REX enables continuous processes with a significant reduction in reaction time compared to batch procedures.[22] This enables the exposure of the organic material to elevated temperatures for a brief period, thereby averting the potential for thermal degradation. As with flow chemistry, reactive extrusion facilitates precise control of parameters, encompassing temperature control, homogenous mixing, controlled and defined residence time and *in situ* monitoring.

The use of analytical techniques such as near-infrared spectroscopy (NIR), Raman, and Fourier-transform infrared spectroscopy (FT-IR) is an optional addition. While the entire system is exposed to a certain pressure during batch processing, only a small amount of the material is exposed to these phenomena in the extruder.

This ensures to drastically reduce safety issues concerning the risks of fire, explosion and/or development of toxic gases, thus ensuring greater overall operational safety.[23,24]

Another example of a semi-continuous flow reactor is the DYNO®-mill, an agitator bead mill that uses high-speed beads to generate shear forces and impact energy for grinding and mixing. It often requires the use of solvents to enhance efficiency. However, its scalability is limited as an increase in production capacity usually requires the use of larger or multiple mills. Additionally, the DYNO®-mill is primarily suited for particle size reduction and dispersing applications, but only few articles about chemical reactions are reported.[25–28] In contrast, extruders represent a more suitable industrial alternative, as they enable continuous processing through adjustable throughput and multi-screws configurations.[29] In fact, multi-screw extruders offer better mixing capabilities, greater throughput and longer residence time.[30] In addition, extruders offer greater versatility and are suitable for a variety of applications such as chemical reactions, polymer processing and blending without the risk of metal contamination observed in mills using metal balls and jars.[31]

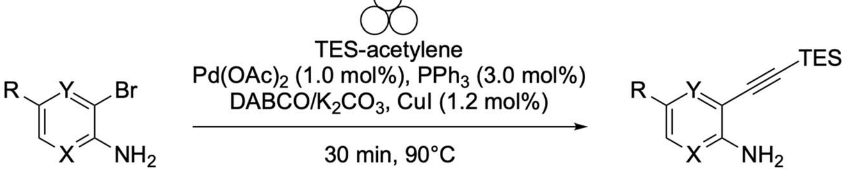
This review provides a comprehensive overview of these mechanochemical transformations, describing in detail the transfer of cross-coupling, halogenation, amidation, nucleophilic substitution and condensation reactions to continuous flow processes using TSE.

2. Transition metal-catalysed reactions

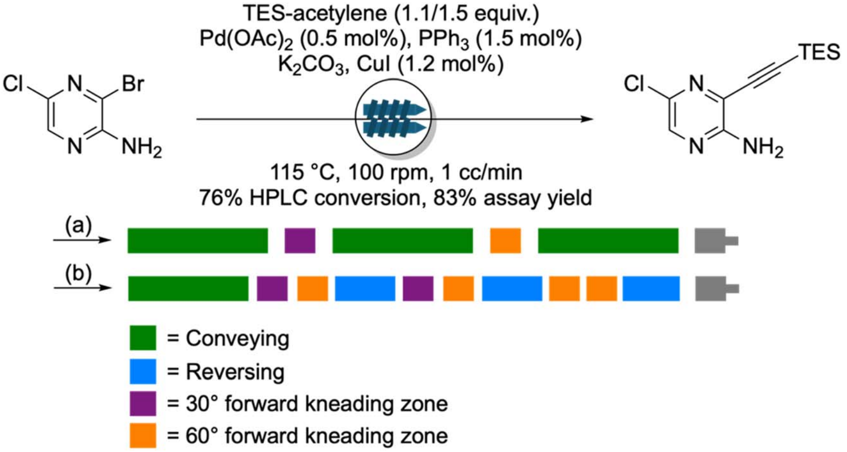
Mechanochemical cross-coupling strategies have been effectively translated into continuous flow processes *via* twin-screw extrusion, as recently illustrated by Hastings *et al.*[32] (2023), Chantrain *et al.*[33] (2024) and Bolt *et al.*[13] (2022).

Hastings and co-workers implemented a Sonogashira-coupling reaction *via* TSE, initially optimising mechanochemical parameters in a ball-mill setup including base, temperature, and catalyst. The authors thoroughly analysed the reaction between a pyrazine/pyridine substrate and trimethylsilyl- (TMS) or triethylsilyl- (TES) acetylene (Scheme 1). They identified that solid and inorganic bases (*e.g.* K_2CO_3) improved sustainability by avoiding aqueous workups, and that switching from TMS- (b.p. = 53 °C) to TES-acetylene (b.p. = 136 °C) helped to achieve higher temperatures, resulting in higher yields.

Since the catalyst used in the batch process, $Pd(PPh_3)_4$, is also sensitive to air, it was decided to test a pre-catalyst system,



Scheme 1 General reaction scheme for mechanochemical Sonogashira coupling. The nature of R depends on X and Y: when X = N and Y = CH, R = Cl, Me, H or F; when X = CH and Y = N, R = Cl, Me and H; when both X and Y = N, R = Cl, H, Me, I, Br, COOMe.



Scheme 2 Optimal extrusion conditions for Sonogashira coupling with 3-bromo-5-chloropyrazin-2-amine. Screw configuration: (a): standard; (b): more aggressive.

$Pd(OAc)_2/PPh_3$. Translation to TSE revealed that soft screw configuration failed to ensure effective mixing, even under both gradient (50/70/90 °C) and isothermal (90 and 110 °C) temperature profiles.

Only by implementing a more aggressive screw design (Scheme 2) and operating at 110 °C, 150 rpm, and a feed rate of 1 cc min^{-1} they were able to achieve high conversion, with an 83% solution assay after EtOAc/activated carbon treatment, comparable to solution-phase processes but with reduced solvent consumption and toxicity.

In parallel, Chantrain *et al.* and Bolt *et al.* developed two different synthetic protocols for Suzuki–Miyaura reactions using a direct mechanochemical strategy, where catalysis was achieved by using palladium and nickel respectively.

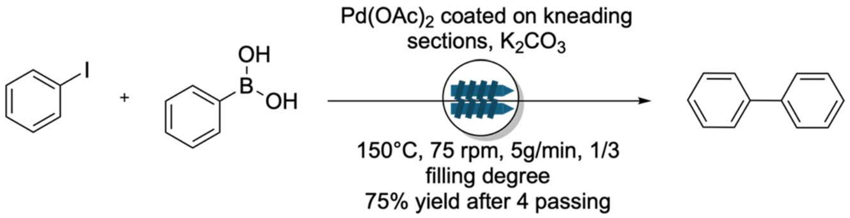
Chantrain *et al.* initially focused on a Suzuki–Miyaura coupling reaction between an iodobenzene derivative and a phenylboronic acid under classic conditions: $Pd(OAc)_2$ (5 mol%), K_2CO_3, Ethanol (liquid-assisted grinding), 150 rpm and 60 °C, resulting in moderate yields (58%) but with degradation of the catalyst after just one cycle. This reaction had previously been explored in mechanochemical conditions (*e.g.* ball-milling) eliminating the need for solvents and hazardous catalyst complexes, while concomitantly yielding only minor side reactions.[34]

To reduce the catalyst loss, the researchers were inspired by Wohlhemuth's work[35] when they attempted to coat the kneading section of the screw with 500 nm thick layers of Cu, Ni, Au and Pd over a length of 9 cm per screw. After an optimisation process, they found that the screws had to be made of low chromium steel to avoid deactivation of the catalyst and abrasion. A comprehensive temperature screening (from room temperature to 200 °C), showed that a moderate conversion (36%) occurred at 150 °C, while higher temperatures led to trimerization of the phenylboronic acid.

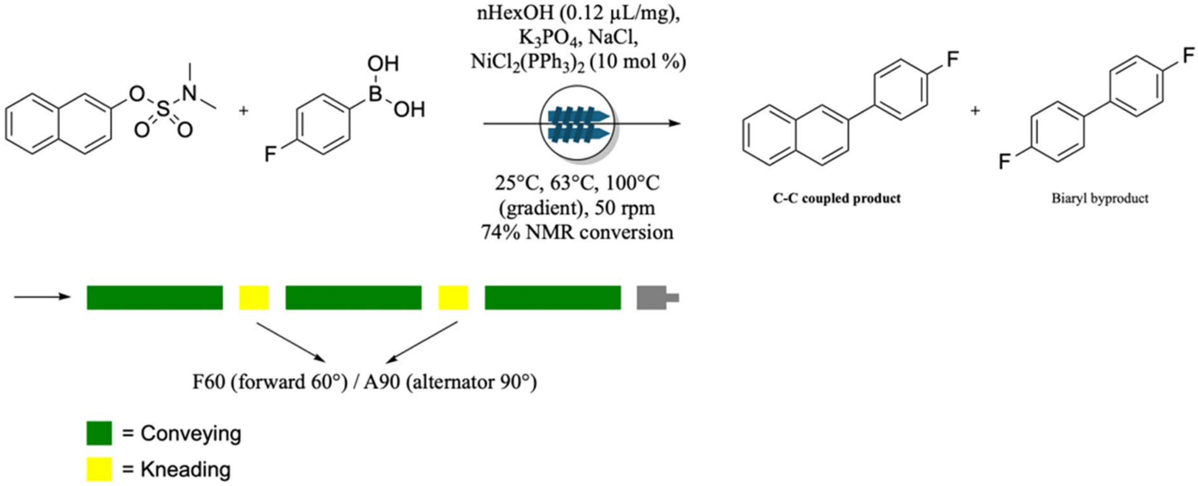
Screw speed and residence time were found to be critical too. Optimal extrusion conditions were found working at 150 °C, 75 rpm, and a filling degree of 1/3 of the barrel volume, with the coated kneading segments forming localised catalytic hotspots. An increase in extruder passages from two to four was fundamental (Scheme 3), resulting in an overall yield of 75% (with the addition of iodobenzene during the second and third passages to improve flowability).

Inspired by earlier work,[36–39] Bolt *et al.* thoroughly investigated the Suzuki–Miyaura reaction between an aryl (pseudo) halide and a boronic acid/ester species. Instead of relying on palladium, which is both expensive and less abundant, they adopted an earth-abundant nickel-based catalyst system, $NiCl_2(PPh_3)_2$. Their initial parameter optimization was conducted in a ball mill under standard solution-phase conditions[40] (10 mol% $NiCl_2(PPh_3)_2$, K_3PO_4 as base, and ethanol as LAG), accompanied by a systematic study on activating groups. Among those tested, sulfamates emerged as the best activating group, delivering an initial yield of 35%.

After further investigation on varied LAG agents, temperatures (from room temperature to 130 °C) and substrate scopes, the research group identified the optimal mechanochemical



Scheme 3 Optimal extrusion conditions for the palladium-catalysed Suzuki–Miyaura.



Scheme 4 Optimal extrusion condition for the nickel-catalysed Suzuki–Miyaura.

conditions as 4 hours of milling at 30 Hz and 100 °C for standard substrates, with electron-rich alkoxy-substituted substrates requiring higher temperatures (120–130 °C) for effective conversion.

A preliminary translation of this protocol into a TSE setup, using a screw configuration incorporating both 60° and 90° kneading sections (Scheme 4), a feed rate set by 50 rpm, and *n*-hexanol as LAG, resulted in a total NMR conversion of 74% (residence time: 3 min). This successful adaptation allowed a remarkable 200-fold scale-up, showcasing the potential of using nickel catalysis as a cost-effective and sustainable alternative for cross-coupling reactions.

3. Halogenation reactions

Halogenation reactions continue to attract considerable attention due to the central role of organohalides in various synthetic transformations, including nucleophilic substitution,[41] cross-coupling, and atom transfer radical cyclisation (ATRC) reactions.[42,43]

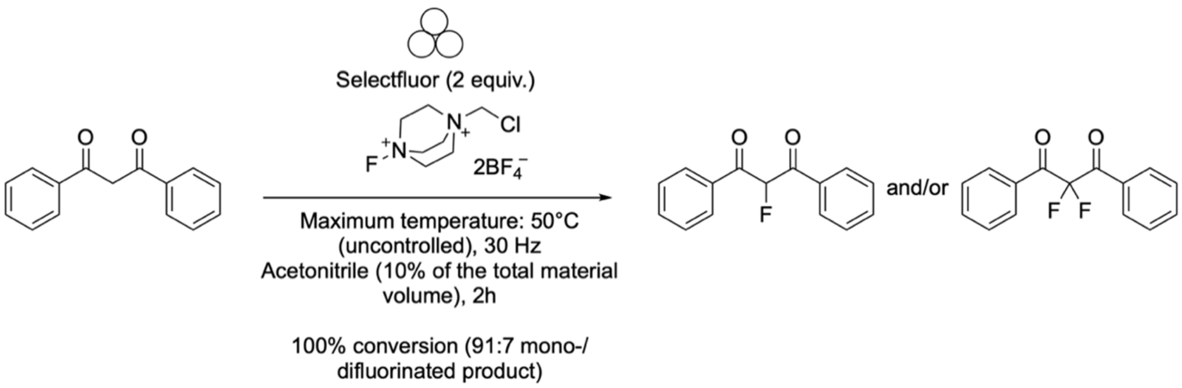
In 2017, Howard *et al.* reported one of the first attempts for the fluorination of diketones derivatives.[44]

Initially, they explored the stoichiometric reaction between solid dibenzoylmethane and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor or F-TEDA) in ball-mill using a frequency of 30 Hz and reaching a maximum temperature of 50 °C, thus resulting in a 53% of monofluorinated product with only 4% of difluorinated. The mere augmentation of the amount of Selectfluor to 2 equivalents resulted in a concomitant increase in yield, achieving 87% of mono- and 11% of di-fluorinated products. The exploration of LAG's behaviour was fundamental. The use of acetonitrile as grinding auxiliary (10% of the total volume of all materials in the jar) and the increase of reaction time to 2 hours resulted in full conversion with an impressive selectivity for mono-fluorinated product (91 : 7 ratio).

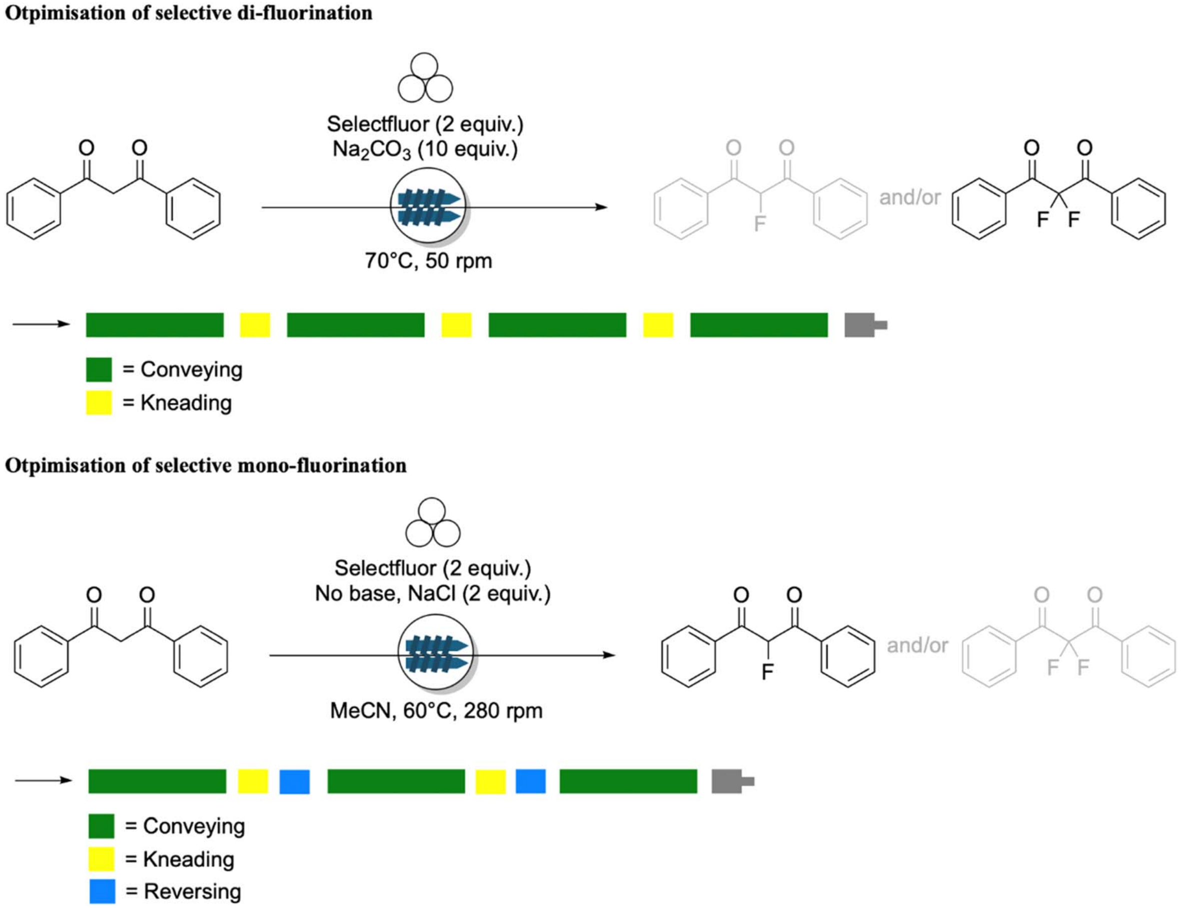
A substrate scope analysis was also performed, which showed that all reactions occurred in less than 3.5 hours, which is the minimum reaction time required for batch reaction processes (Scheme 5).

To improve scalability and sustainability, Cao and co-workers[45] reported in 2018 a transfer of this reaction from mixer mill to TSE.

Initially, the reaction was studied at different temperatures using a standard screw configuration with a screw speed of



Scheme 5 Optimisation of conditions for the selective mono-fluorination of dibenzoylmethane in mixer mill.



Scheme 6 Optimal extrusion condition for selective mono- and di-fluorination of dibenzoylmethane.

50 rpm and Na_2CO_3 as base and grinding auxiliary. It was reported that an optimal temperature of 70 °C was achieved, resulting in 54% of yield. The recirculation of the mixture thrice within the extruder was found to enhance the yield to 61%.

The addition of a reverse section after each kneading zone (Scheme 6) along with an adjustment in the addition of sodium chloride, prevented the obstruction phenomenon, and with a screw speed of 280 rpm, gave an 83% yield of difluorinated compound, with only 3% of monofluorinated.

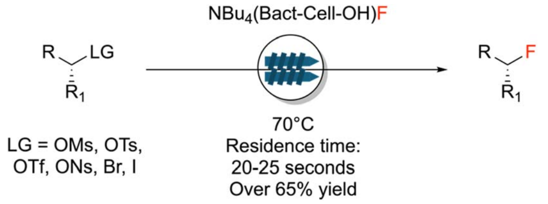
As previously observed, the utilisation of acetonitrile as a liquid additive resulted in enhanced selectivity towards the monofluorinated compound, thereby facilitating full conversion with an overall yield of 81% monofluorinated product at 60 °C.

Since the electrophilic fluorination process using Selectfluor is associated with drawbacks relating to the equivalents of reagents utilised, as well as difficulties in synthesis and atom economy, Said *et al.*[46] (2020) investigated the potential of a nucleophilic fluorination approach employing a diverse polysaccharide-supported TBAF.

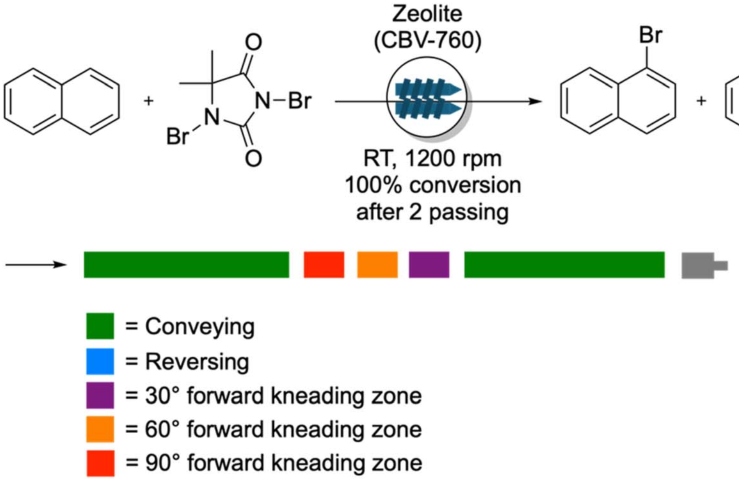
Following a period of extensive experimentation, four stable solid complexes were obtained: NBu_4(Bact-cell-OH)F, NBu_4(Pla-cell-OH)F, NBu_4(Pec-OH)F and NBu_4(Sta-OH)F. Subsequently, the focus shifted towards a systematic optimisation of fluorination reactions. In this context, 3-(biphenyl-4-yloxy)propyl methanesulfonate was utilised as the substrate, with a batch mode of operation being employed. This research led to the identification of acetonitrile and 70 °C as the optimal operating conditions.

The authors demonstrated the applicability of this reaction in a continuous mode using their in-house built extruder with NBu_4(Bact-Cell-OH)F as the complex (Scheme 7). A substrate scope was performed, with the barrel temperature maintained at 70 °C, obtaining good to excellent yield (over 65%).

In contrast, the work of Ardila-Fierro *et al.*[47] presents an innovative approach to the solid-state bromination of naphthalene through mechanochemical methods, emphasising both catalyst design and process intensification.[47]



Scheme 7 Optimal extrusion condition for nucleophilic fluorination reaction.



Scheme 8 Optimal extrusion condition for bromination of naphthalene.

Given the solid nature of naphthalene at room temperature, the study focused on its bromination using four solid brominating agents: *N*-bromosaccharin (NBSacc), *N*-bromophthalimide (NBPth), *N*-bromosuccinimide (NBS), and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH). Initial experiments conducted *via* ball milling (2 hours at 30 Hz, without catalyst) demonstrated very limited reactivity. These findings underscored the pivotal function of catalysis in facilitating the reaction.

FAV-type zeolites were selected as catalysts due to their intrinsic porosity and Brønsted acidic sites. Among the brominating agents tested, DBDMH was identified as the most promising candidate due to its low cost, high bromine content (two bromine atoms per molecule) and improved atom economy. An optimisation study showed that a stoichiometric ratio of DBDMH favoured monobromination, while an excess led to undesirable dibromination and, importantly, the zeolite catalyst proved to be recyclable with little loss of activity.

The optimized conditions were transferred to a TSE platform on which a pre-grinded solid mixture was extruded at 1200 rpm at room temperature (Scheme 8). The presence of a zeolite catalyst allowed complete conversion within only two extrusion cycles (using 2 equivalents of DBDMH) and minimized byproduct formation (the only by-product detected was 5,5-dimethylhydantoin, a low toxicity material that can be easily recycled).

4. Multicomponent reaction (MCRs)

Multicomponent reactions (MCRs), defined as reactions involving the simultaneous coupling of at least three distinct reactants into a single product that integrates the atoms of all starting material, have emerged as a powerful tool in synthetic and pharmaceutical chemistry.[48,49]

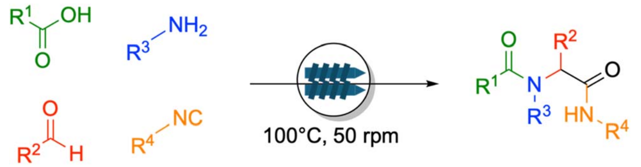
El-Remaily *et al.*[50] reported a mechanochemical Ugi reaction between an aldehyde, an aromatic amine, an aromatic acid and an isocyanide.

Initially, the reaction (R^1, R^2, R^3 = Ph and R^4 = *t*Bu) was optimized in solution using various solvents (water, methanol, ethanol, acetonitrile and *N*,*N*-dimethylformamide), with water affording the most favourable yield (66%).

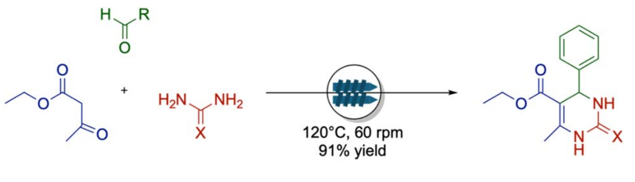
The translation to solvent-free condition allowed further optimization, with a maximum yield (77%) obtained at 100 °C for 60 minutes, but leading to thermal degradation.

After recognizing the limitations of batch processing, the protocol was adapted to TSE, so that the inherent shear and compression between screws not only improved mixing but also facilitated the evaporation of water, which is the major by-product. Under these conditions, raising the temperature to 100 °C at 50 rpm for a residence time of 15–20 minutes resulted in a marked yield improvement up to 93%, with substrate variation having negligible impact on the outcome (Scheme 9).

In another work, Carvalho *et al.*[51] revisited the historic Biginelli reaction, originally introduced in 1893 that was carried out in ethanol with an acid catalyst. Under conventional



Scheme 9 Optimal extrusion condition for Ugi reaction. R^1 = Ph, Bn, EtPh, Me; R^2 = Ph, iBu, Me, Et; R^3 = Ph, 4-MeO-Bn, Et; R^4 = *t*Bu, 4-MeO-Bn, Cy.



Scheme 10 Optimal extrusion condition for Biginelli reaction. X = O or S, R = C_6H_5, 4-Cl–C_6H_4, 4-CH_3–C_6H_4, 4-OCH_3–C_6H_4.

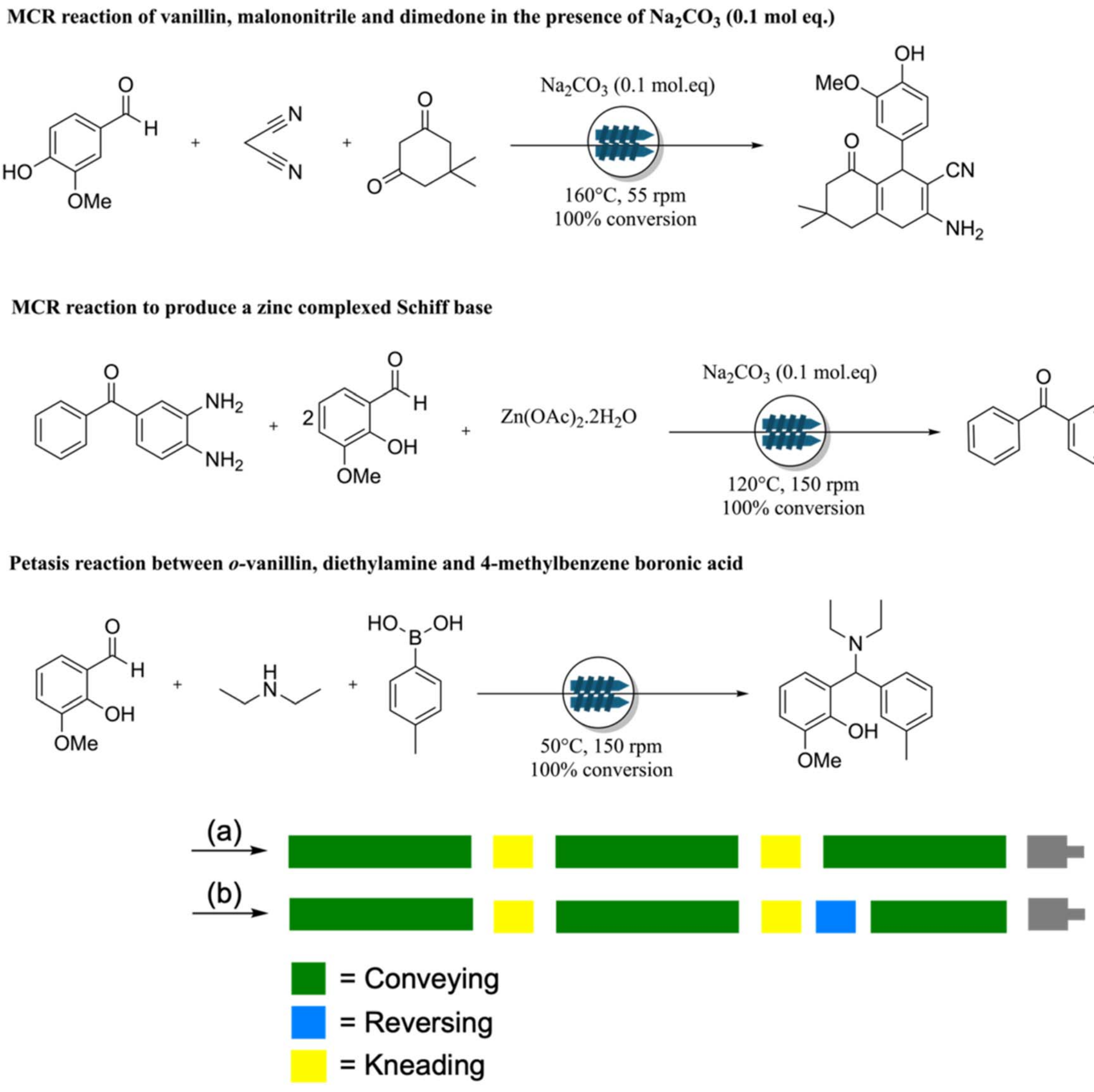
conditions, however, this reaction suffers from long reaction times and low yields. Although excellent results were previously achieved with the ball mill process, the switch to twin-screw extrusion in 2019 enabled a more efficient process. The conditions at room temperature were insufficient, but by increasing to 120 °C and a screw speed of 60 rpm, a yield of 88% was achieved. Finally, 120 °C and 50 rpm with a residence time of 9–11 minutes (91% of yield) were found to be the optimum conditions (Scheme 10). The evaluation of the substrate spectrum for the different aromatic aldehydes showed a uniform product formation.

Further broadening the scope of mechanochemical MCRs in TSE, in 2017 Crawford *et al.*[52] provided a suite of examples that highlight the method's versatility.

Their work demonstrated that a simultaneous Knoevenagel condensation and Michael addition, using vanillin, malononitrile and dimedone, could be carried out as a MCR in TSE, with optimum condition at 160 °C and 55 rpm in the presence of Na_2CO_3 (0.1 mol eq.), yielding full conversion with water as the only by-product (Scheme 11).

Subsequently, the authors investigated the formation of a Schiff base as a consequence of the variation of temperature from RT to 160 °C and screw speeds, thus resulting in 120 °C, 55 rpm with Na_2CO_3 as the best condition (Scheme 11).

A final example of a MCR translated into TSE was the Petasis reaction, a three-component reaction between 4-methylbenzene boronic acid, diethylamine and *o*-vanillin. This was the first example of a non-condensation reaction carried out in a twin-screw extruder. Instead of a standard screw configuration, which led to unsuccessful results (partial conversion), the addition of 90° kneading sections and a series of reverse segments (Scheme 11) led to prolonged mixing and high shear kneading, resulting in a complete reaction at 50 °C and 150 rpm (residence time: 7 minutes).



Scheme 11 Optimal extrusion condition for several examples of MCRs. (a) = Standard screw configuration for the first two reactions; (b) = alternative screw configuration for Petasis reaction.

5. Condensation reactions

In 2017, Crawford *et al.*[53] firstly reported the translation of several condensation reactions from batch processing to TSE conditions.

For instance, they investigated a Knoevenagel reaction between barbituric acid and three different aldehydes (vanillin, veratraldehyde, 5-bromovanilin) and observed similar reactivity trends under ball-milling conditions. When adapted to TSE, a systematic optimization of temperature (from RT to 160 °C) and screw speed (30–250 rpm) was undertaken. No product formation was observed at room temperature, partial conversion occurred above 40 °C, and full conversion was achieved at 160 °C using a standard screw configuration operating at 55 rpm (Scheme 12).

Crawford's elevated operating temperature prompted Andersen *et al.*[54] to conduct a series of tests in 2021 with the objective of minimising the environmental impact. Their findings revealed that the incorporation of 10% of water into the stoichiometric reaction between vanillin and barbituric acid resulted in complete conversion, with an isolated yield of 95% at a temperature of 60 °C (Scheme 12).

Similarly, the condensation between vanillin and malononitrile reached full conversion at 120 °C with 55 rpm, with the lower temperature being essential to prevent malononitrile polymerisation observed at higher temperatures. To demonstrate the versatility of TSE with substrates in different physical states, Crawford *et al.* also examined a reaction between vanillin and liquid ethyl cyanoacetate (in the presence of Na_2CO_3 10 mol%), achieving full conversion at 160 °C with 55 rpm (Scheme 13).

Additionally, they reported the imine formation between 4,4′-oxydianiline and *o*-vanillin, which was completed under TSE conditions at 120 °C and 55 rpm within 2 minutes. The same reaction in solution (methanol) would have required several hours at reflux (Scheme 13).

Furthermore, the authors investigated a Michael addition between veratraldehyde and dimedone. Under ball milling conditions (at 25 Hz for 60 minutes), the reaction produced only approximately 7.5% of yield; however, optimisation in TSE at 150 °C and 55 rpm increased the yield to 80%. Adjustments to the screw configuration, including the introduction of reverse segments, ultimately led to complete conversion at 120 °C and 200 rpm, although more than one product was observed (unidentified by-products). Finally, an aldol condensation between ninhydrin and dimedone, conducted with Na_2CO_3 as base, achieved 80% conversion at 75 °C and 55 rpm, while increasing the temperature to 100 °C under standard screw configuration resulted in full conversion (Scheme 14).

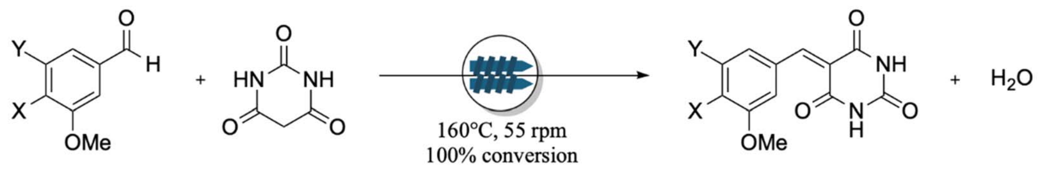
In another study, Crawford *et al.*[55] extended the application of TSE to the synthesis of hydrazones by reacting a furfural derivative and 1-aminohydantoin hydrochloride. Conventionally, solution-based synthesis is too expensive because it requires many purification steps, large amounts of expensive organic solvents, and different recovery cycles for solvent and excess reactants.

Given the significant interest in *N*-acylhydrazones in the field of medicinal chemistry, the authors previously demonstrated the feasibility of producing these compounds mechanochemically.[56]

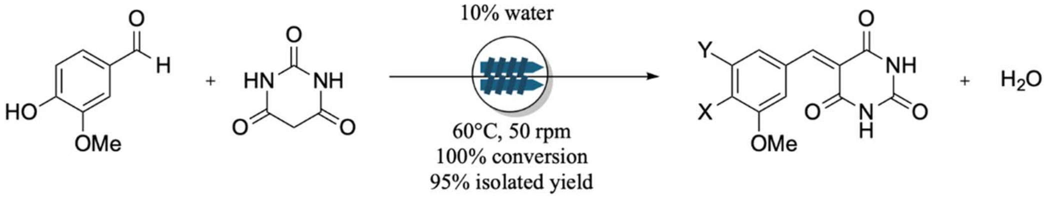
The present study focuses on the scalability of the process in terms of TSE.

The study commenced with the stoichiometric condensation of *p*-nitrobenzaldehyde with benzhydrazide or phenylacetic hydrazide, utilising a screw configuration comprising two kneading and three conveying zones, with a residence time of less than two minutes and a temperature ranging from 20 to 150 °C.

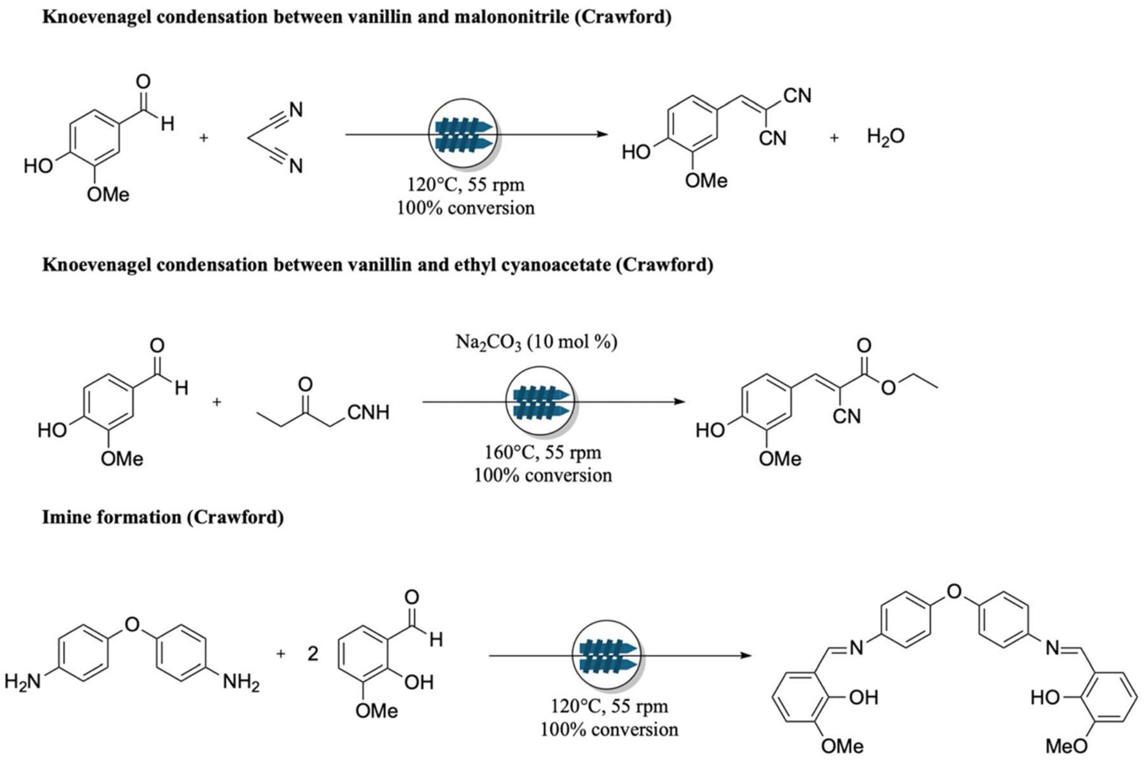
Knoevenagel reaction between barbituric acid and three different aldehydes (Crawford)



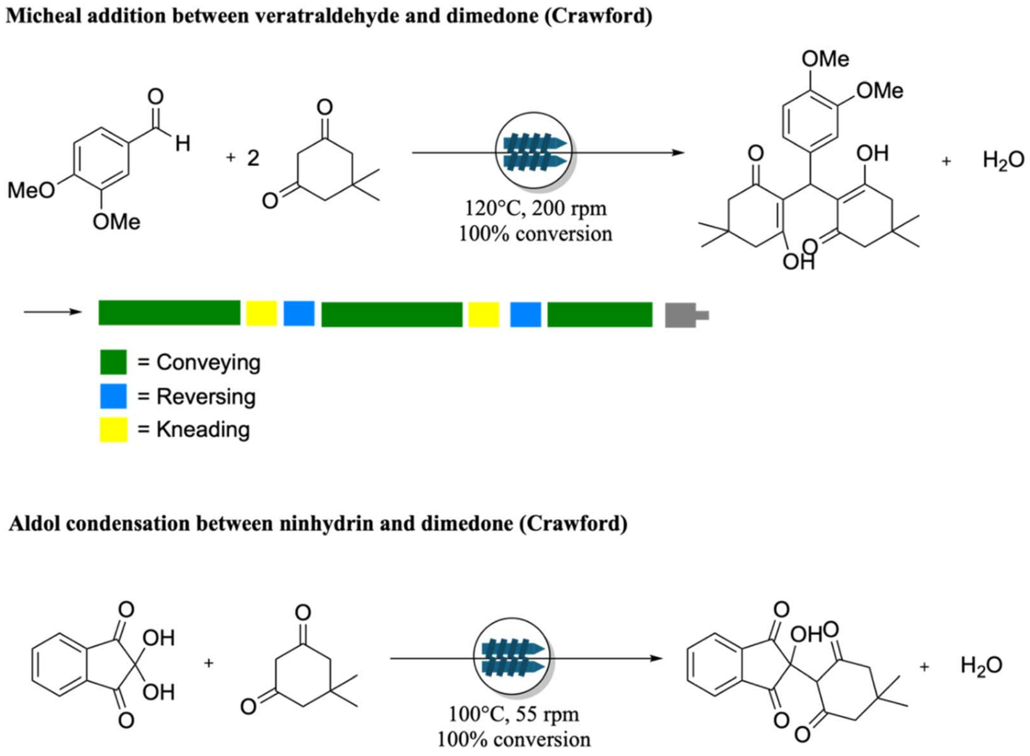
Knoevenagel reaction between barbituric acid and vanillin (Andersen)



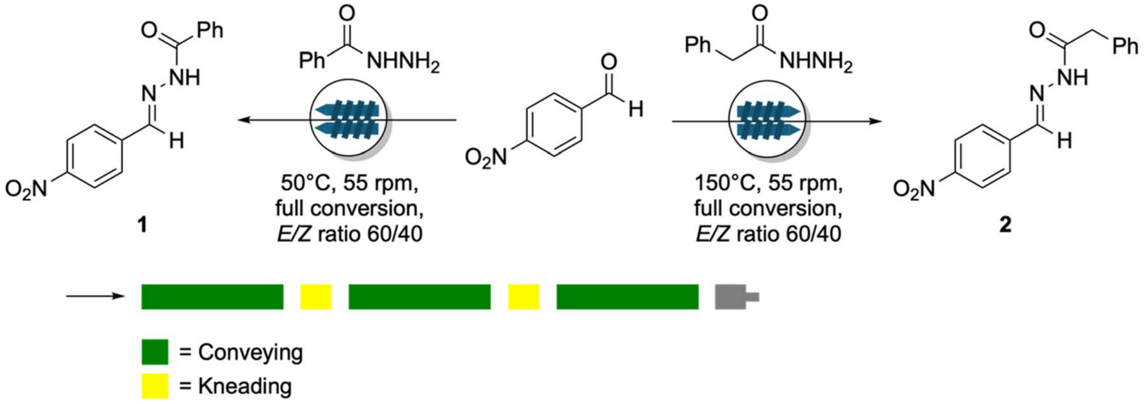
Scheme 12 Optimal extrusion condition for several condensation reaction.



Scheme 13 Optimal extrusion condition for several condensation reactions.



Scheme 14 Optimal extrusion condition for several condensation reactions. Micheal addition reaction required an alternative screw configuration to improve yields (with unidentified by-products).



Scheme 15 Optimal extrusion condition for *N*-acylhydrazones syntheses.

The formation of products **1** and **2** was characterised by full conversion at 55 rpm, 50 °C and 150 °C, respectively (Scheme 15). It was demonstrated that, since the initial temperature is lower than the melting points of the starting materials, an actual solid-state reaction is occurring. Furthermore, it was established that a greater mechanical stress or mixing is required to obtain the reaction.

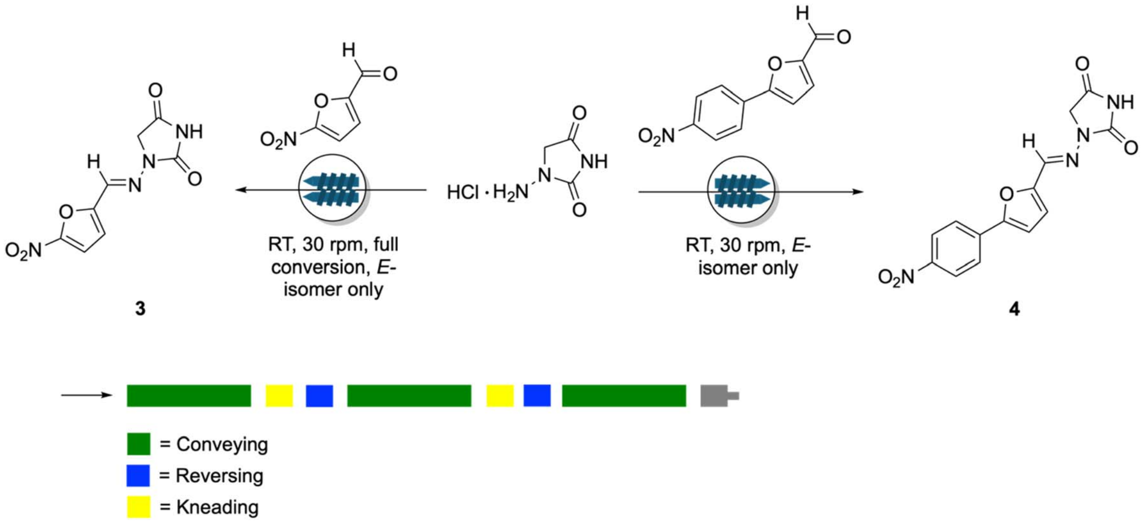
Subsequently, an attempt was made to directly produce two active pharmaceutical ingredients (APIs), namely nitrofurantoin (**3**) and dantrolene (**4**), starting from 1-aminohydantoin hydrochloride and 5-nitro-2-furaldehyde (for product **3**) or 5-(4-nitrophenyl)-furfural (for product **4**). An alternative screw configuration was required, adding a reverse section after each kneading zone in order to increase the residence time up to 40 minutes. The ideal condition set up was with 30 rpm and room temperature, leading to *E*-isomer only (Scheme 16).

Finally, in 2020, Cao *et al.*[57] reported the synthesis of perylene diimides (PDIs) in TSE.

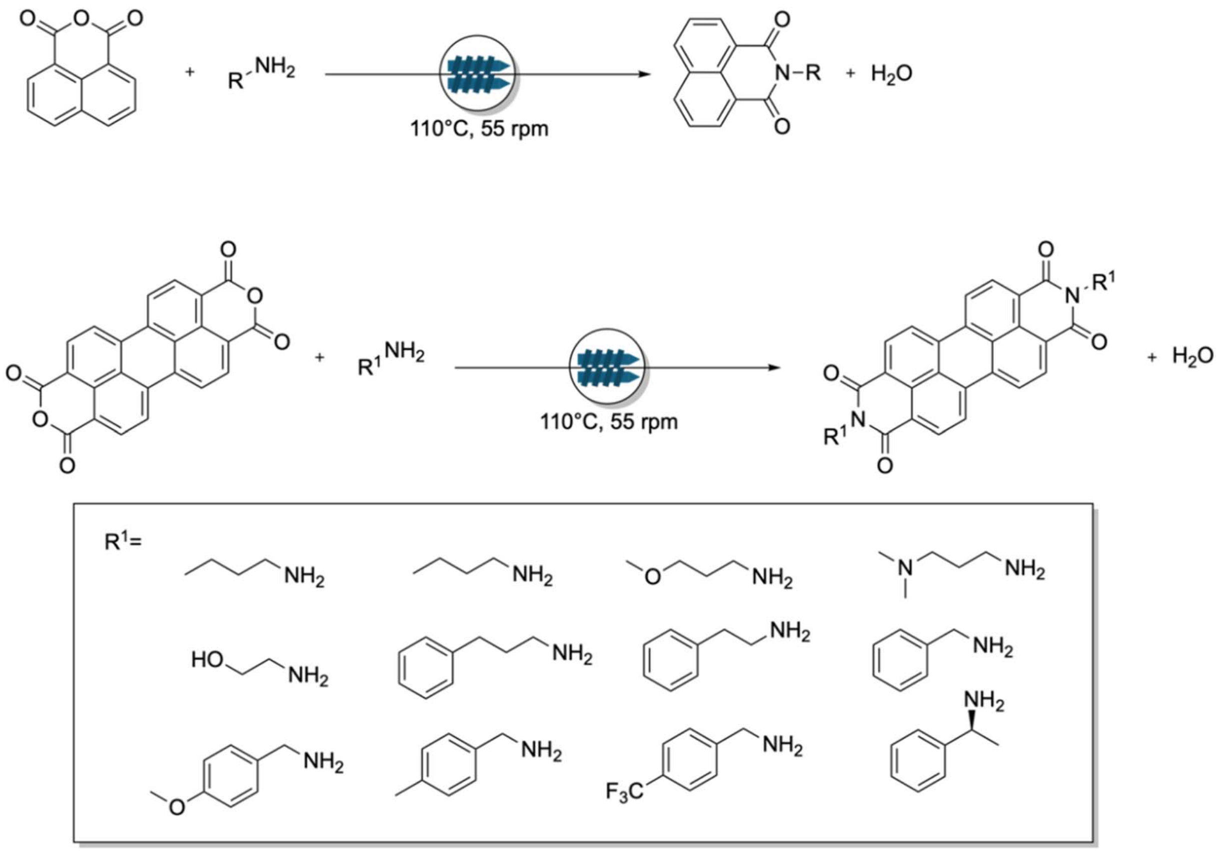
Conventionally, these compounds have been synthesised using the Langhals method, which involves the use of perylene-3,4,9,10-tetracarboxylic dianhydride (PTCDA) and anilines/aliphatic primary amines at temperatures in excess of 160 °C in high boiling solvents (*e.g.* imidazole, quinoline, *N*-methyl-2-pyrrolidone), with $Zn(OAc)_2$ serving as a promoter.

To address these drawbacks, Unterlass *et al.*[58] have previously reported a hydrothermal protocol which employs water as a solvent at 200 °C under autogenous pressure (17 bar) over a period of 4 hours, with the addition of an Hünig base. However, it should be noted that this protocol is not applicable in cases where the reactants are not water-soluble.

Kaupp and co-workers[59] have translated this to mechanochemistry, using a mixer mill, and subsequently an oven-heating of the jar at 110 °C to obtain complete conversion. Applying this temperature to the extruder and utilising screws with two reverse sections (to retard the flow) at 55 rpm resulted in full conversion. Consequently, they investigated the applicability to other amines/anilines with PTCDA (Scheme 17),



Scheme 16 Optimal extrusion condition for nitrofurantoin and dantrolene syntheses.



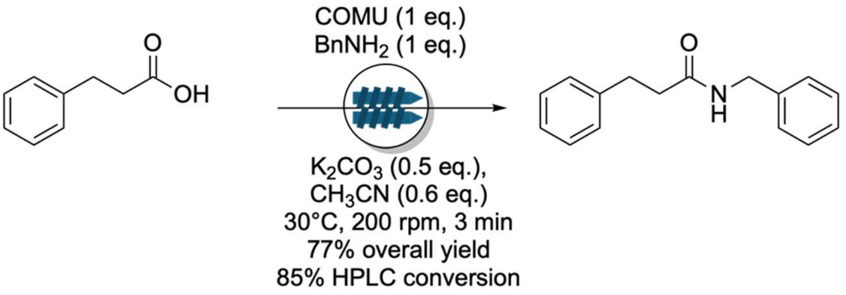
Scheme 17 Optimal extrusion condition for PDIs syntheses. R= 4-EtO-Ph, 4-MeO-Bz, EtPh.

observing that varying temperatures were required (*e.g.* up to 150 °C) and, in some cases, an additive was required too (*e.g.* inorganic bases: Na_2CO_3 and K_2CO_3).

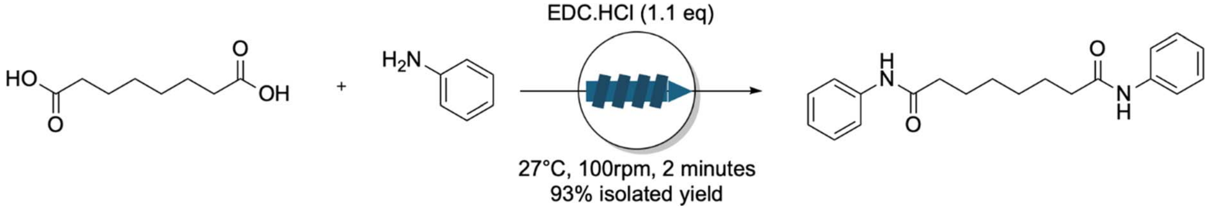
6. Amidation reaction

Amidation reactions are usually carried out in hazardous solvents such as dichloromethane (DCM) and *N*,*N*-dimethylformamide (DMF). To address this problem, several alternative mechanochemical strategies have recently been developed that aim to reduce or avoid solvents, as required by the 12 principles of green chemistry.

In 2009, Lamaty and co-workers[60] pioneered the solvent-free mechanochemical synthesis of amides using coupling agents under ball-milling conditions, achieving high yields in less than 1 hour. In 2023, Lamaty[61] translated this approach to a TSE platform operated at 30 °C and 200 rpm, enabling continuous processing. They evaluated different coupling agents and liquid-assisted grinding (LAG) additives to improve the flowability of the mixture (Scheme 18), ultimately identifying COMU, K_2CO_3, and acetonitrile as the optimal combination for large-scale synthesis (77% overall yield, 85% conversion). This method was further evaluated through the synthesis of two APIs such as teriflunomide (immunomodulatory agent) and moclobemide (antidepressant drug).



Scheme 18 Optimal extrusion condition for amidation reaction with coupling-agent.



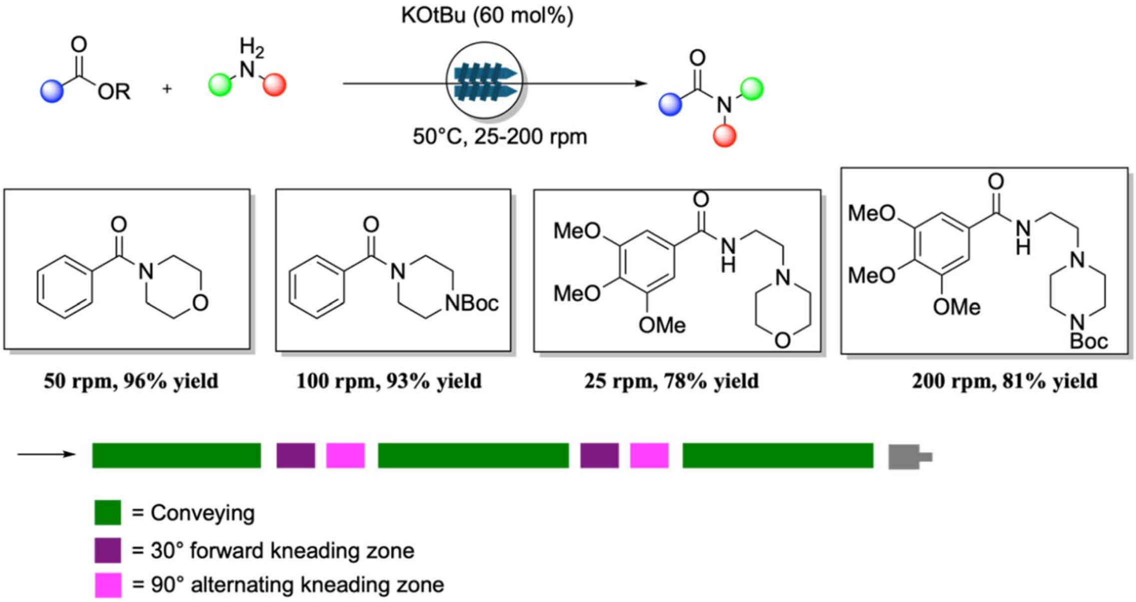
Scheme 19 Optimal extrusion condition for amidation reaction (Atapalkar *et al.*).

Similarly, in 2023, Atapalkar *et al.* reported a better approach to synthesising amides using coupling agents in a single-screw extruder. They optimised a model reaction involving suberic acid and aniline at 27 °C, varying the coupling agent.[62]

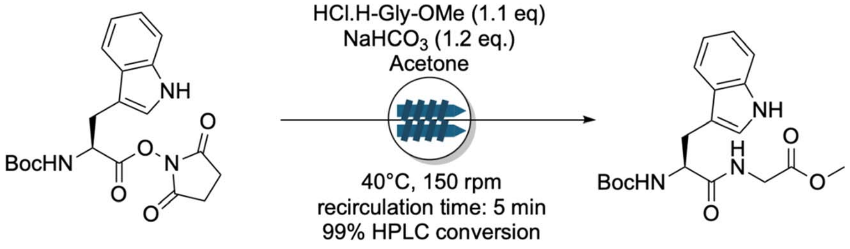
1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) demonstrated superior performance compared to *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 1,1′-carbonyldiimidazole (CDI). The best result was obtained using EDC·HCl at 27 °C and 100 rpm (Scheme 19), with a total reaction time of two minutes and an isolated yield of 93%.

Furthermore, the authors investigated the scope of the reaction with various aromatic and aliphatic diacids and amines, including primary and secondary ones. They also reported scaling up the process to 50 g h^{-1} using a larger screw reactor, enabling them to produce 100 g of amides with an isolated yield of almost 90%.

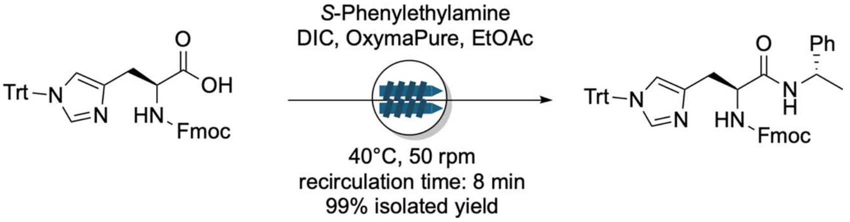
In contrast, Bolt *et al.*[63] (2024) introduced a coupling agent-free protocol based on direct amidation of esters, initially optimised *via* ball-milling using KO*t*Bu (60 mol%) and then successfully adapted to TSE. Remarkably, their approach also achieved a 98% yield under mild conditions (50 °C, 200 rpm) with no solvents (Scheme 20). To overcome processing limitations related to material rheology and torque resistance, they identified Na_2SO_4 as an effective grinding auxiliary, enabling



Scheme 20 Optimal extrusion condition for amidation reaction from esters (coupling-agent free).



Scheme 21 Optimal extrusion conditions for the peptide synthesis model reaction (Yeboue).



Scheme 22 Optimal extrusion condition for the peptide synthesis model reaction (El-dine).

a continuous 7 hours run synthesizing up to 500 g of product. While the Lamaty and Atapalkar strategies rely on coupling agents to synthesize different amides, Bolt's methodology offers a highly scalable and cheaper route, underscoring the versatility of mechanochemistry for amide bond formation.

Peptides, including dipeptides and tripeptides, have also been synthesized under a corotating vertical twin screw extruder, as reported by Yeboue *et al.* (2018)[64] and El Dine *et al.* (2024).[65]

Yeboue *et al.* investigated the formation of the dipeptide Boc-Trp-Gly-OMe by reacting Boc-Trp-OSu with HCl·H-Gly-OMe in the presence of $NaHCO_3$. Due to the absence of a molten phase, the mixture's flowability was improved by introducing additives, with acetone proving to be the most effective. The reaction was initially carried out at 40 °C and 50 rpm in recirculation mode (residence time: 5 minutes), achieving a 73% HPLC conversion. Increasing the temperature to 100 °C and the screw speed to 150 rpm led to higher conversions. However, extending the recirculation time to 10 minutes while maintaining the screw speed at 150 rpm allowed for full conversion even at the lower temperature of 40 °C (Scheme 21).

More recently, El-dine *et al.* reported a peptide synthesis using coupling agents, focusing on a model reaction between Fmoc-His(Trt)-OH and *S*-phenylethylamine.

The initial reaction was carried out with DMF as a liquid-assisted grinding (LAG), employing *N*,*N*′-diisopropylcarbodiimide (DIC) as the coupling agent and ethyl cyano(hydroxymino)acetate (OxymaPure) as an additive. Under these conditions (40 °C and 50 rpm), a 99% conversion was achieved by HPLC analysis.

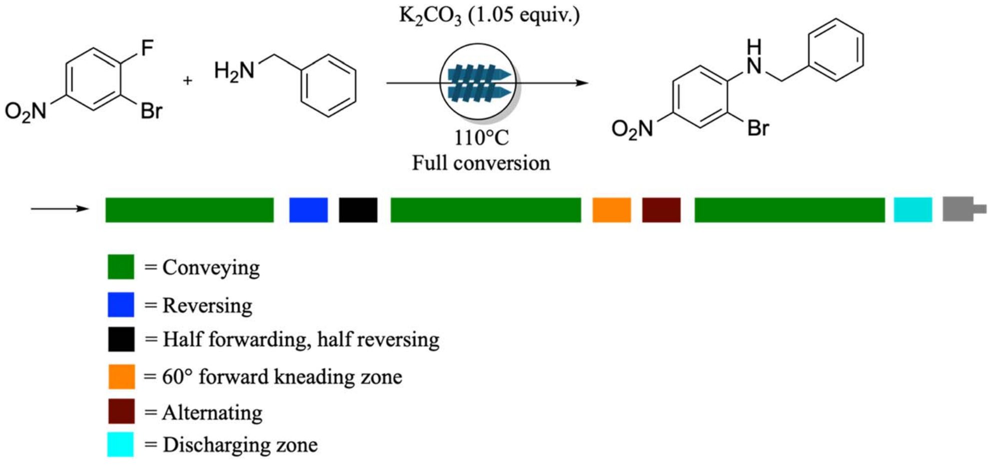
Given the environmental concerns associated with DMF, alternative solvents were screened (*e.g.* cyrene, anisole, 2-methyl tetrahydrofuran, ethyl acetate). Among these, ethyl acetate (EtOAc) emerged as the most effective, maintaining a 99% conversion. A systematic evaluation of different coupling agents and additives confirmed that DIC in combination with EtOAc provided the optimal outcome. The best overall conditions consisted of 1.2 eq. of DIC, 5.0 eq. of EtOAc, and a recirculation time of 8 minutes at 40 °C, resulting in a 99% isolated yield (Scheme 22).

Both model reactions achieved high conversions under mild conditions, with optimizations enabling solvent replacement and shorter reaction times.

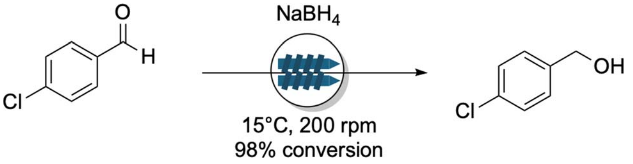
7. Nucleophilic substitution

Aromatic nucleophilic substitution is preferably performed in polar, aprotic solvents such as *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMAc) or *N*-methylpyrrolidone (NMP) which all display reproductive toxicity and for safety reasons they should be avoided; so the translation into TSE conditions could be a viable solution to this problem.

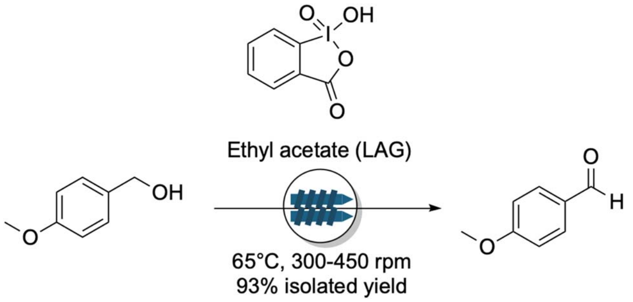
In 2021 Andersen *et al.*[54] started to test the reaction by ball milling, resulting in poor conversion at low temperatures (<40 °C) but full conversion at 110 °C. In transitioning to TSE, pulse experiments were used to determine the residence time in the



Scheme 23 Optimal extrusion condition for aromatic nucleophilic substitution.



Scheme 24 Optimal extrusion condition for the reduction of 4-chlorobenzaldehyde.



Scheme 25 Optimal extrusion condition for the oxidation of 4-methoxybenzyl alcohol.

extruder ranged between 10 to 16 minutes. With an alternative screw configuration (Scheme 23), they achieved full conversion at 110 °C with K_2CO_3 (1.05 eq.).

8. Oxidation and reduction reactions

Oxidation and reduction reactions are fundamental transformation in chemistry, playing an important role in the synthesis of a wide range of materials.

In 2017, Isoni *et al.*[66] investigated the exothermic reduction of poorly water-soluble aromatic aldehydes using $NaBH_4$.

They performed an initial screening in a batch mode using a cooking blender, varying the equivalents of $NaBH_4$, mixing methods, and the presence of solvents. Their results showed that the optimal conditions involved 0.26 equivalents of $NaBH_4$ with aqueous sodium hydroxide, achieving 96% NMR conversion in less than one minute.

To translate this reaction to TSE conditions, they focused on 4-chlorobenzaldehyde and obtained a 98% conversion at 200 rpm and 15 °C barrel temperature, maintained by a jacket to prevent thermal runaway (Scheme 24).

Since the oxidation of alcohols is typically carried out in dimethyl sulfoxide (DMSO) under batch conditions, Sharma *et al.*[62] (2019) introduced a mechanochemical approach for oxidising 4-methoxybenzyl alcohol to its corresponding aldehyde using 2-iodoxybenzoic acid (IBX), thereby avoiding the use of DMSO.

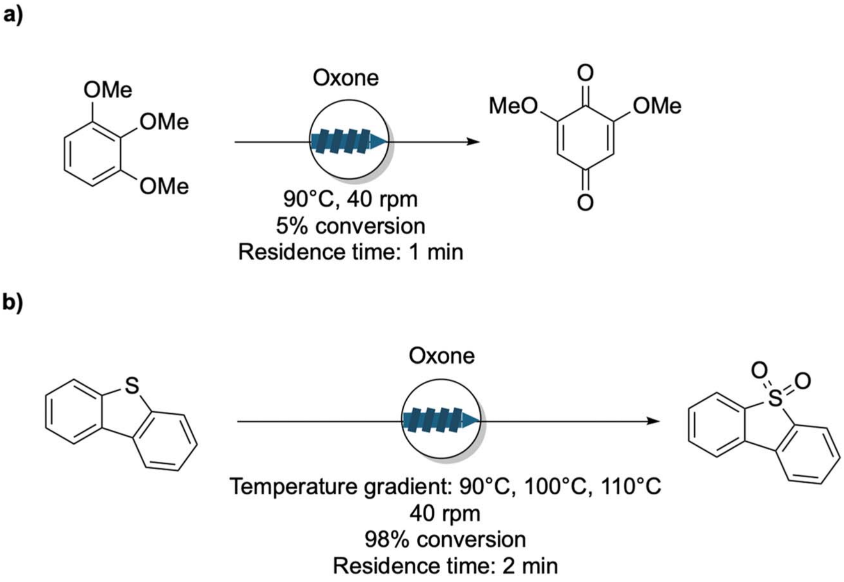
To improve the flowability of the reaction mixture, they employed ethyl acetate as a LAG.

The optimal conditions were found to be 65 °C and 300–450 rpm, with a residence time of 60 seconds, resulting in a 93% isolated yield (Scheme 25).

In 2022, Calcio Gaudino *et al.*[14] reported the oxidation of lignin-like methoxylated aromatics and organosulfur compounds in a single-screw extruder (SSE). They employed Oxone ($2KHSO_5$, $KHSO_4$, and K_2SO_4) as the oxidant due to its safer degradation products compared to the other oxidants.

The mechanochemical oxidation of lignin-like methoxylated aromatics was first demonstrated by Collom *et al.*[67] in 2013. They obtained quinone as the only product following a prolonged reaction time of seven days. When this reaction was transferred to SSE, a quinone yield of 5% was achieved in just 1 minute at 90 °C and 40 rpm (Scheme 26a).

Additionally, the oxidation of dibenzothiophene to sulfone was carried out in the extruder using a temperature gradient (90 °C, 100 °C, 110 °C) with an excess of oxone. This process



Scheme 26 Optimal extrusion condition for oxidation reactions: (a) oxidation of 1,2,3-trimethoxybenzene and (b) of dibenzothiophene.

afforded a 40% yield in 1 minute at 40 rpm, which increased dramatically to 98% when the residence time was doubled to 2 minutes (Scheme 26b).

9. Conclusion

In summary, the transfer of various mechanochemical reactions such as transition metal-catalysed cross-couplings (*e.g.* Sonogashira, Suzuki–Miyaura), halogenations, amidations, nucleophilic substitutions, oxidations, reductions and various condensation processes, into continuous flow systems *via* twin-screw extrusion (TSE) is remarkably promising for sustainable synthesis, as it offers competitive yields, shorter reaction times and better control of reaction parameters.

Nevertheless, there are some critical issues that still hinder the widespread adoption of this technology. Transferring conventional solution phase protocols to TSE conditions requires careful optimisation of physical and mechanical parameters, including temperature, screw speed and screw configuration. These parameters are strictly related to kinetic aspects, such as residence time and mixing effects, which can limit reaction efficiency. One promising solution to these challenges is the evolution of extruder architecture, particularly the adoption of multi-screw extruders, such as quad- or even octa-screw configurations. These systems offer better control over the rheological behaviour of reaction mixtures as the surface area available for shearing, mixing and kneading is significantly increased, which directly correlates with improved reaction homogeneity and scalability. In addition, multi-screw designs have been shown to alleviate problems associated with incomplete mixing, hot-spot formation or poor axial transport by decoupling feeding and transport and by enabling more complex modular screw geometries. In addition, improved control of residence time facilitates optimised fine-tuning of reaction kinetics, enabling the exploration of slower or multi-step reaction cascades.[68–71]

In conclusion, while TSE is already a promising pillar for greener continuous flow organic synthesis, the future lies in the convergence of mechanochemistry and advanced engineering solutions. This will overcome the technological and practical differences that currently make it impossible to compare data in the literature. It is recommended that future research efforts include not only the exploration of the chemical compatibility of these systems, but also the development of comprehensive scale-up models and digital twins. Their integration has the potential to facilitate the control of extrusion-based synthesis with improved predictive accuracy and industrial reliability.

Conflicts of interest

All authors declare no conflicts of interest.

Data availability

The data and references used in this review have been included in the text.

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