



**QUEEN'S
UNIVERSITY
BELFAST**

Organic synthesis by Twin Screw Extrusion (TSE): continuous, scalable and solvent-free

Crawford, D. E., Miskimmin, C. K. G., Albadarin, A. B., Walker, G., & James, S. L. (2017). Organic synthesis by Twin Screw Extrusion (TSE): continuous, scalable and solvent-free. DOI: 10.1039/C6GC03413F

Published in:
Green Chemistry

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

Publisher rights

© 2017 Royal Society of Chemistry.

This work is made available online in accordance with the publisher's policies. Please refer to any applicable terms of use of the publisher.

General rights

Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

A solvent-free, continuous and scalable method of carrying out condensation reactions by Twin Screw Extrusion (TSE)

D. E. Crawford,^{a*} C. K. G. Miskimmin,^a Ahmad B. Albadarin,^b Gavin Walker^b and S. L. James^{a*}

Mechanochemistry provides a way to reduce or eliminate the use of solvents by carrying out reactions through the grinding of neat reagents. Until recently a significant drawback of this form of synthesis has been the limited ability to scale up. However, it has been shown that twin screw extrusion (TSE) may overcome this problem as demonstrated in the continuous synthesis of co-crystals, Metal Organic Frameworks (MOFs) and Deep Eutectic Solvents (DES), in multi kg_{hr}⁻¹ quantities. TSE has provided a means to carry out mechanochemical synthesis in a continuous, large scale and efficient fashion, which is adaptable into a manufacturing process. Herein, we highlight the potential of this technique for organic synthesis by reporting four condensation reactions, the Knoevenagel condensation, imine formation, Aldol reaction and the Michael addition, to produce analytically pure products, most of which did not require any post synthetic purification or isolation. Each reaction was carried out in the absence of solvent and the water byproduct was conveniently removed as water vapour during the extrusion process due to the elevated temperatures used. Furthermore, the Knoevenagel condensation has been studied in detail to gain insight into the mechanism by which these mechanochemical reactions proceed. The results point to effective wetting of one reactant by another as being critical for these reactions to occur.

Introduction

Mechanochemical synthesis, conducted by grinding two or more solid reagents together to instigate a chemical reaction, has become of great interest for reducing or eliminating the use of hazardous and toxic substances in chemical synthesis and materials processing.¹⁻⁵ Avoiding toxic solvents not only decreases potential hazards, but can also reduce the overall cost of a process.⁵ A variety of materials and compounds have been prepared mechanochemically including metal alloys,⁶ metal organic frameworks (MOFs),⁷ and organic compounds from reactions such as the Knoevenagel condensation⁸⁻¹⁰ and Wittig reaction,¹¹ amongst others.¹²

However, two main drawbacks of mechanochemical synthesis are the general lack of both temperature control and scalability.¹ Generally, ball milling or grinding in a mortar and pestle do not allow control of the temperature. Temperature normally only increase incidentally due to the frictional forces experienced in the milling process. Takacs reports that planetary ball milling can result in temperatures exceeding 200 °C, and there is currently very limited control of this temperature rise which can have a dramatic influence on the overall process.¹³ Cryomills can be used, which allow milling to be conducted at -196 °C. However this approach is not suitable for all milling investigations. Alternatively, ball mill jars can be modified to allow for thermal bath fluids to be circulated around a jacket to regulate both high and low temperatures. Overall, however, temperature control in ball milling is currently not widely available. With regard to scalability, typically, the maximum quantity of product obtained is of the order of several hundred grams, through the use of planetary ball mills. Larger industrial scale ball mills are widely used, however, these are applied primarily for material processing, on the tonne scale and have not been demonstrated for chemical synthesis.¹⁴ Overall, there is a need to be able to control the

temperature of mechanochemical processes as well as improve their scalability if mechanochemistry is to become widely applicable as a manufacturing technique.

Recently, in order to overcome these drawbacks, twin screw extrusion (TSE), previously used extensively in the food, polymer and pharmaceutical industries,¹⁵ has shown great potential for the efficient, continuous mechanochemical synthesis of fine chemicals, including co-crystals² and metal organic frameworks (MOFs).³ This technique involves the conveyance of material through a confined space (barrel) by the rotation of a pair of modulated, intermeshing, co- or counter-rotating screws (Figure 1).¹⁶ The use of modular screws allows the screw configuration to be customised to meet the specific needs of a given process. Modifying this parameter allows control of the total shear and compressive forces experienced by the material as it moves along the extruder barrel¹⁶ and thus the screw design can potentially be manipulated to instigate and optimise a given chemical reaction. Furthermore, the temperature, screw speed and feed rate of the starting reagents can all be varied, with the latter having a direct effect on the overall compression force experienced by the material.¹⁶

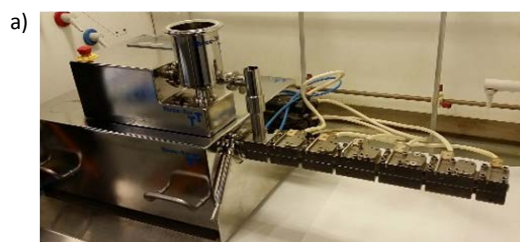


Figure 1: a) Twin screw extruder and b) intermeshing co-rotating screws encased in the extruder barrel.

The first use of TSE technique in chemical synthesis was in hot melt extrusion to form co-crystals.² Co-crystal research to date has been directed towards the formation of pharmaceutically relevant mixtures, for example Amgen report the synthesis of the AMG 517 – sorbic acid co-crystal via TSE.² Those authors also highlight additional advantages of employing TSE in addition to benefits related to the process efficiency. They report that the cocrystals obtained exhibit enhanced properties (compared to solution grown cocrystals), including a higher surface area ($2.9 \text{ m}^2\text{g}^{-1}$ vs. $0.9 \text{ m}^2\text{g}^{-1}$), thereby eliminating the need for post-synthesis processing involving milling.

More recently we have demonstrated the synthesis of Metal Organic Frameworks (MOFs),³ Deep Eutectic Solvents (DESs)⁴ and discrete metal complexes by TSE.³ In most cases (with exception of HKUST-1 and $[\text{Ni}(\text{Salen})]^{3-}$), the reactions were carried out without added solvent and gave materials of similar or superior quality to those prepared by conventional means. Notably, the fast reaction times involved in TSE (0.5 – 4 minutes) meant that the problematic thermal degradation typically observed in the conventional 12-hour preparation of the choline chloride : D-fructose DES, as a consequence of fructose caramelisation, was avoided.⁴ The elimination or reduction of solvent use not only provided more sustainable synthetic processes but also dramatically increased the Space Time Yields (STYs) compared to conventional processes. The STY (kg of product obtained per m^3 of reactor volume per day) is a parameter which indicates the overall efficiency of a process. For the synthesis of MOFs, STYs were up to three orders of magnitude greater than for the reported conventional syntheses³ and for the preparation of DESs, four orders of magnitude greater than for the standard batch heating procedure.⁴

Along with an increasing interest in the formation of inorganic and coordination compounds by mechanochemical means, there has also been a keen interest in carrying out organic synthesis this way, and a diverse range of organic reactions has been demonstrated, mainly through ball milling.¹² In particular, several successful mechanochemical condensation reactions have been reported, including the Knoevenagel condensation and Aldol reaction.^{8,9,17,10} Other examples of organic reactions performed mechanochemically include the Wittig reaction, Diels–Alder, click and Suzuki reactions,

some of which usually require quite stringent conditions in their conventional solution-based synthesis such as the use of dry solvents and inert atmospheres. However, there are several examples where ball milling has been done successfully without such rigorous conditions.¹⁸

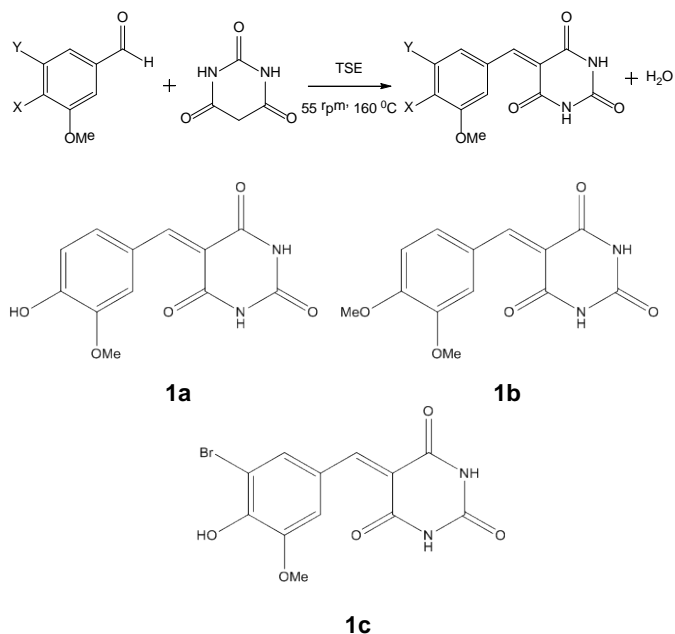
Some research into the scaling up of mechanochemical organic reactions has been carried out, particularly by Stolle *et al.* who investigated the Knoevenagel condensation between vanillin and barbituric acid, scaling up from mixer to planetary ball mills.⁹ Stolle considered factors such as milling frequency and time, as well as vessel size and shape, ball diameter, weight and reagent fill level, finding that they all had important effects on the reaction process. The maximum scale of this study was 400 g (using four 100 g grinding stations).⁹

As the formation of co-crystals and inorganic materials has been scaled up to a continuous manufacturing process through the use of TSE, it is interesting to investigate organic synthesis by this technique. Here, we report four condensation reactions successfully carried out on large scales by TSE, specifically the Knoevenagel condensation, imine formation, the Aldol reaction and finally a Michael addition. Each product was synthesised without any added solvent and analytically pure products were obtained without any post process purification.

Results and Discussion

Knoevenagel Condensation

Kaupp *et al.* first investigated the Knoevenagel condensation between vanillin and barbituric acid in the solid state,¹⁰ and Stolle *et al.* successfully highlighted the potential of this system to be carried out on a larger scale mechanochemically, via planetary ball milling.^{8,9} We therefore chose this as the first organic reaction to be studied by twin screw extrusion, and subsequently extended it to include the reaction of barbituric acid with two other aldehydes, veratraldehyde and 5-bromovanillin (Scheme 1). Comparison between the three aldehydes provides insight as to whether reactant melting points (Table 1) are important factors in this type of synthesis (*i.e.* the aldehyde of lowest melting point could be expected to react most readily) or whether electronic substituent effects dominate as in solution (*i.e.* the aldehyde with electron donating substituents would be expected to react most readily). Furthermore, the Knoevenagel reaction between vanillin and malononitrile was also investigated to determine the effect of replacing the activated methylene reactant, barbituric acid, with a compound of substantially lower melting point.



Scheme 1: Reaction of three different aldehydes with barbituric acid in the solid state, by Twin Screw Extrusion (TSE).

Table 1: Melting points of the various starting reagents.

Reagent	Melting point ($^{\circ}\text{C}$)
Veratraldehyde	40-43
Vanillin	81-83
5-Bromovanillin	162-166
Barbituric Acid	245
Malononitrile	32

For comparison with the TSE results, all three reactions were initially carried out by ball milling as well as in anhydrous d^6 -DMSO, and were monitored by ^1H NMR spectroscopy, allowing any differences in the reactivities of the aldehydes in the solid state and in solution to be determined. Interestingly, it was found that a similar trend in reactivity was observed for both of these methods, with the reaction between vanillin and barbituric acid occurring most rapidly, whilst the reaction involving 5-bromovanillin was the slowest.

With respect to the solution based reactions, the conversion vs. time graphs (Figure 2) show that the reactions are slow (several days) and do not actually go to completion, and from *ca.* day 25, the conversion curves plateau in each case. We believe that each reaction reaches equilibrium at these maximum conversions. As the main aim of this work did not involve investigating each reaction in terms of its kinetic behaviour, the corresponding reaction rates in d^6 -DMSO were not calculated. However, the equilibrium conversions for each of the three reactions and the time required to reach equilibrium were compared to give an indication of how these reactions were proceeding in solution.

Comparison of the conversion vs. time curves established that all three reactions reached equilibrium on the same day – day 25. However, a trend was established upon comparison of these equilibrium conversions, which indicated that superficially the rate

of reaction of the Knoevenagel condensation is dependent on the electronic substituents present on the aromatic ring, as expected with conventional solution reactions.¹⁹ However, as these systems are in equilibrium, the most that can be said at this stage is that the equilibrium tends to lie more in favour of the desired product when there is an electron-donating substituent *para* to the aldehyde, as is the case with vanillin. When a methoxy group (veratraldehyde) is in *para* position, which is considered to be slightly less electron donating (compared to a hydroxyl group), the equilibrium conversion is *ca.* 20 % lower.

However, the key result comes from comparison of the equilibrium conversions for the reactions involving vanillin and 5-bromovanillin. The addition of an electron withdrawing group to the aromatic ring hinders the conversion to product. In this case, this is not as significant as one would expect due to the *para*-hydroxyl group still present in 5-bromovanillin.

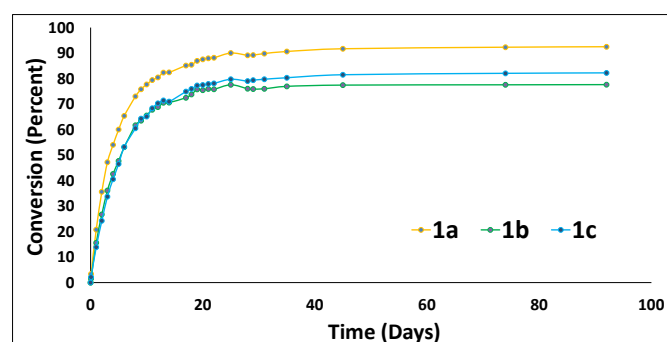


Figure 2: Graph outlining the conversion as a variance of time, for the three Knoevenagel condensations with barbituric acid in anhydrous d^6 -DMSO.

In regards to the ball mill reactions between barbituric acid and each of the three aldehydes, it was seen that the reactions went to completion. The reaction of vanillin and barbituric acid was complete after 60 minutes at 25 Hz whilst the reaction involving veratraldehyde required 90 minutes to reach 100 %. However, at 90 minutes (maximum milling time available) the conversion observed for the reaction between 5-bromovanillin and barbituric acid was only 72.8 % (Table 2). Hutchings *et al.* reported that for the milling-induced Knoevenagel condensation, a feedback mechanism based on both the chemical and physical properties of the system was in operation, with which there was a significant dependency on the temperature reached inside the ball mill as well as the changes in rheology of the reaction mixture during milling.²⁰ Therefore, restarting the ball milling process to prolong reaction time would disrupt the temperature and possibly the rheology of the mixture, leading to inaccurate results.

Furthermore, *pseudo*-sigmoidal kinetics are observed for each of these ball milling reactions in accordance with the results published by Hutchings *et al.* (Figure 3), suggesting that the same feedback mechanism is also operating in the Knoevenagel condensation between veratraldehyde or 5-bromovanillin and barbituric acid.²⁰

Table 2: Conversion to product via ball milling, as determined by ^1H NMR spectroscopy.

Time (mins)	Conversion to Product (%)		
	1a	1b	1c
30	66.59	12.13	54.40
60	99.29	90.50	76.80
90	-	98.61	77.30

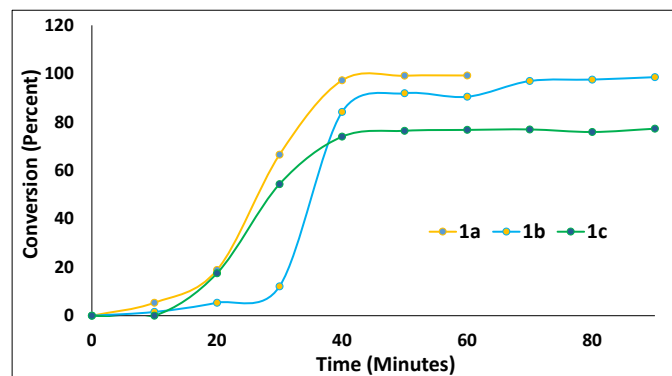


Figure 3: Graph showing the conversion versus time for the three Knoevenagel condensations with barbituric acid by ball milling.

The results observed here are surprising as it was expected that the ball milling reactions would show dependency on the melting points of each aldehyde, with veratraldehyde of lowest melting point reacting first. This expectation was based on previous ball milling investigations carried out by James and Pichon.²¹ However, this is not the case as vanillin reacts fastest. If we consider the time required for the reactions to go to completion, a trend of $\text{OH} < \text{OMe} < \text{Br}$ is observed, and one would immediately assume the reactions occur based on the effect of the electronic substituents. However, considering the unconventional shapes of the conversion curves, it can be presumed that the mechanism by which these reactions are proceeding in the solid state is not straightforward and requires further investigation which is beyond the scope of this work.

With our main goal involving the scale-up of these reactions into a continuous, high yielding process, we next investigated the Knoevenagel condensation via twin screw extrusion and showed that **1a-c** could be synthesised successfully via this technique. Colour changes were seen upon the reaction of each aldehyde with barbituric acid, *i.e.* from white to orange (Figure 4) which gave an indication that the reaction was proceeding. Characterisation was carried out by ^1H NMR spectroscopy, PXRD and elemental analyses, to show that in each optimised reaction, an analytically pure product was obtained as described in detail below (Figures 5 and 6).



Figure 4: Mixture of vanillin and barbituric acid before extrusion (left) and the extruded product, **1a** (right).

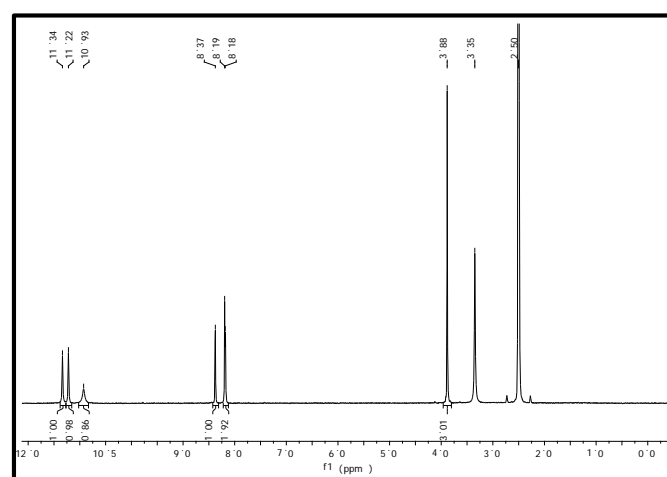
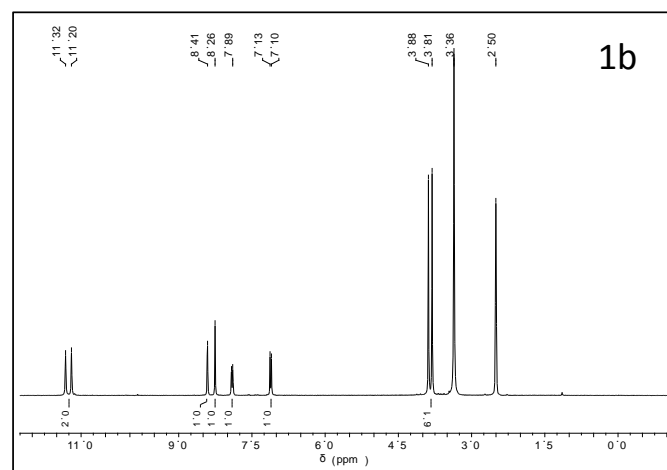
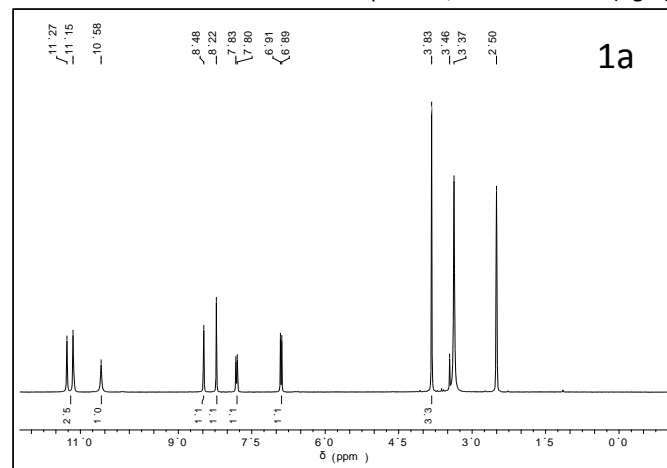


Figure 5: ^1H NMR spectra of **1a-c** in d^6 -DMSO.

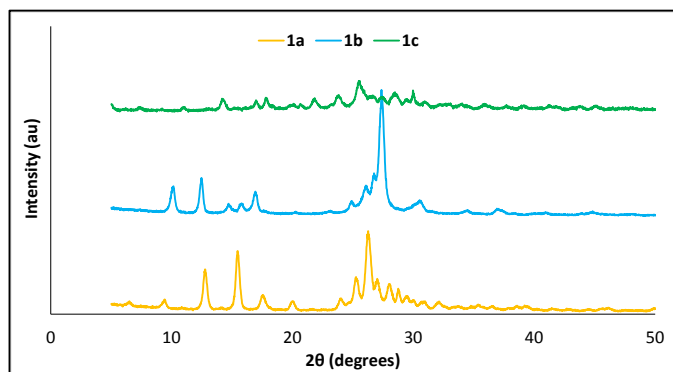


Figure 6: PXRD patterns of products **1a-c** prepared by Twin Screw Extrusion (TSE).

TSE allows precise temperature control across the different heating zones making up the extruder barrel. Therefore, experiments were carried out between room temperature and 160 °C. This range allowed investigation of the reactions below reactant melting points or above the melting point of the aldehyde. A standard screw speed of 55 rpm was initially employed as it provides efficient mixing as well as a reasonable residence time (*i.e.* the time required to travel along the length of the extruder) of *ca.* 2 minutes.

At room temperature, the starting materials were recovered with no trace of product, even after several passes through the extruder. Above 40 °C partial conversion to products was observed. However, for all three reactions, 100 % conversion was achieved at 160 °C, which is significantly higher than the melting points of veratraldehyde and vanillin, but similar to that of 5-bromovanillin.

We then optimised the screw speed. Increasing the screw speed results in greater mixing of the material and a greater shear and mechanical energy being applied to the material, but also reduces the residence time, which may then be too short for complete reaction. Longer residence times are achievable by altering the screw configuration, as will be discussed below for the Michael addition. Figure 7 shows the screw configuration employed for the Knoevenagel condensations, which consisted largely of conveying sections (with channel depth decreasing from one conveying section to the next) and kneading segments containing combinations of 30°, 60° and 90° orientations of the segments, with greater angles applying the greater shear to the material.

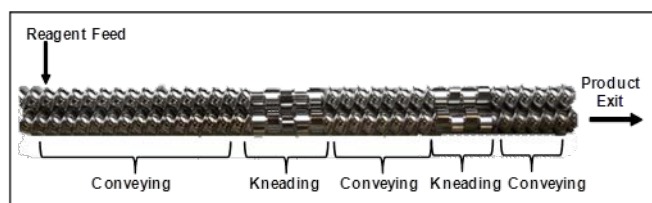


Figure 7: Screw geometry employed in the twin screw extrusion of the Knoevenagel condensation.

Screw speeds of 30 – 250 rpm were investigated, with speeds > 200 rpm resulting in residence times of < 30 seconds. However, the

screw speed of 55 rpm resulted in optimum mixing (indicated by complete conversions) with a residence time of *ca.* 2 minutes. At 30 rpm, the residence time was slightly longer at just over 2 minutes, however the highest conversions obtained were between 95 – 98 %. Therefore, the better mixing at 55 rpm may have improved contact between the reactive surfaces of the materials.

Table 3 reports the feed rates optimised for each reaction when the extrusion processes were carried out at 160 °C and 55 rpm, with the highest feed rate of 0.5 kg hr⁻¹ being found for the reaction between vanillin and barbituric acid. The limiting factor preventing greater feed rates was the high levels of torque recorded as a result of over-feeding the extruder barrel. However, the level of torque with which an extruder can withstand, increases as the size of the extruder increases. We employed a small extruder (12 mm, 40:1 L/D) to fit a standard fume cupboard.

After each process was optimised, its efficiency was then assessed by considering the throughput rate and the Space Time Yields (Table 3). Twin screw extrusion has been shown to result in high STYs, *e.g.* in synthesis of MOFs,³ as a result of the low free volume present in the extruder barrel and removing or reducing the amount of solvent. This is again the case in this work with all three Knoevenagel condensations producing high STYs with the highest being for the reaction between vanillin and barbituric acid (> 250,000 kg m⁻³ day⁻¹).

Table 3: Feed rate, throughput rate and Space Time Yield for each extrusion process in the synthesis of **1a-c**.

Product	Feed Rate (kg hr ⁻¹)	Throughput Rate (kg hr ⁻¹)	Space Time Yield (kg m ⁻³ day ⁻¹)
1a	0.599	0.520	258,385
1b	0.254	0.228	113,291
1c	0.433	0.398	197,942

Again, as with the ball mill reactions, the ease of reactions did not correlate with the reactant melting points. Therefore, DSC analysis was conducted on stoichiometric mixtures of each aldehyde with barbituric acid at various heating rates (for full details see ESI) to gain greater insight to the effects of heating on these mixtures.

It was observed that a reaction was initiated in each case whilst the reactants were being analysed in the open DSC pan, indicated by the presence of an endothermic peak representing the product. As an example, Figure 8 shows a DSC curve of a mixture of vanillin and barbituric acid with a peak at *ca.* 300 °C which corresponds to melting of the corresponding product.

In addition, peaks are present representing melting of the starting materials at *ca.* 80 °C for vanillin and *ca.* 260 °C for barbituric acid. There appears to be an initial shoulder on the endothermic peak for the melting of vanillin. We believe this peak shape is due to a combination of surface and bulk melting of the aldehyde.

The most revealing part of the DSC curve is the region from 120 to 160 °C, which shows two exothermic peaks and one endothermic peak. This indicates that more than one process is occurring. The

endothermic peak can be assigned to the Knoevenagel reaction occurring, as supported by literature.²² Several possibilities such as solidification of the formed product, polymerisation of the starting material or hydration of barbituric acid – to form its known hydrate - were considered for the exothermic peaks, but these were subsequently ruled out after further investigation.

Nevertheless, as these reactions are each between a solid and a melt reactant, it was proposed that the wettability of the reagents may be key to explaining why conditions of 160 °C and 55 rpm were essential for complete conversion. Wettability experiments were conducted with vanillin or veratraldehyde, each in a melt phase, dropped onto a compressed disc of barbituric acid (Figure 9). The contact angles were measured with time at the respective melting points of each aldehyde as well as at 155 °C to mimic the extrusion and DSC processes. Unfortunately, as 5-bromovanillin does not melt until 164 °C, so it was not possible to obtain similar data for this material.

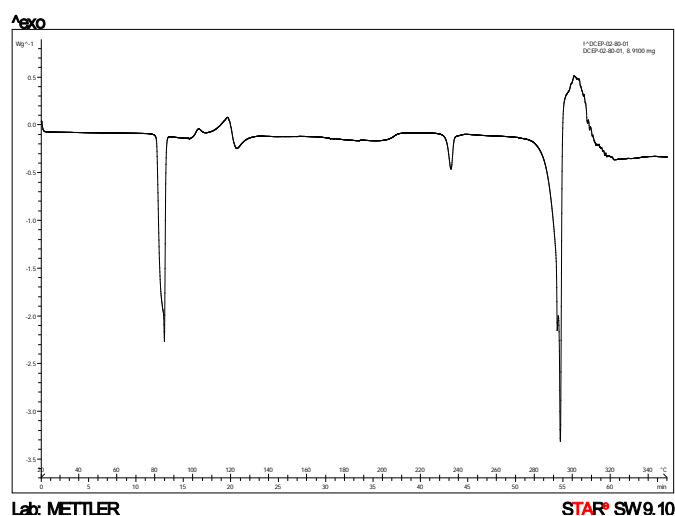


Figure 8: DSC curve of the vanillin and barbituric acid at a heating rate of 5 °C/min.

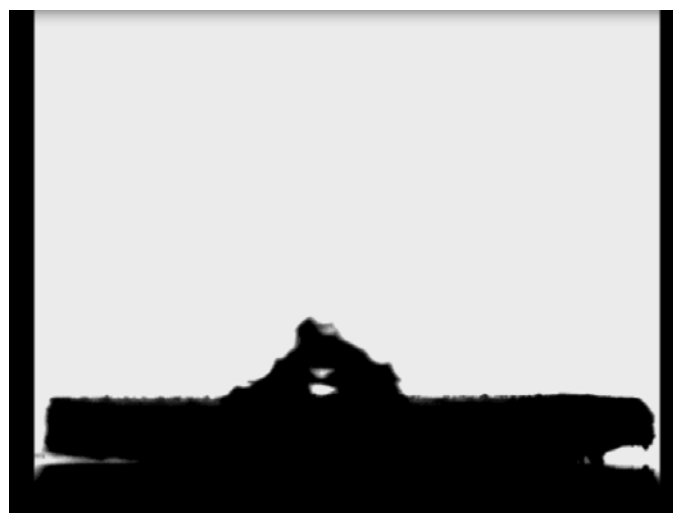


Figure 9: Aldehyde dropped onto a compressed disc of barbituric acid.

Figure 10 shows that at their respective melting points, the contact angles of both vanillin (54.9°) and veratraldehyde (68°) each decrease to *ca.* 11° within 3 seconds. In fact, within the first second of contact with barbituric acid, the contact angle of vanillin decreases by *ca.* 35°, and veratraldehyde undergoes a more dramatic decrease of *ca.* 50°. More crucially, for experiments conducted at 155 °C the initial contact angles are very similar for both aldehydes (34° for veratraldehyde and 31° for vanillin), and they decrease to similar angles (8° for veratraldehyde and 11° for vanillin), within the same time period. In addition, Figure 11 highlights the time required for each aldehyde to reach a contact angle of 20° (when reagents are considered to have high wettability), at these various temperatures. At each aldehyde's respective melting point, vanillin takes a greater time (1.2 seconds) than veratraldehyde (0.8 seconds) to reach 20°. However, at 155 °C the time required to reach 20° is exactly the same for both vanillin and veratraldehyde (0.5 seconds).

Therefore, as at 155 °C, the contact angles measured for each aldehyde and the times required to reach a low angle of 20° were the same, we suggest that for the Knoevenagel condensation under these conditions it is the wettability of the reagents that is vital for the reaction to proceed to completion. Decreasing the temperature of the reaction or even the time in the extruder would significantly hinder the wetting of barbituric acid by the aldehyde, thereby slowing the reaction.

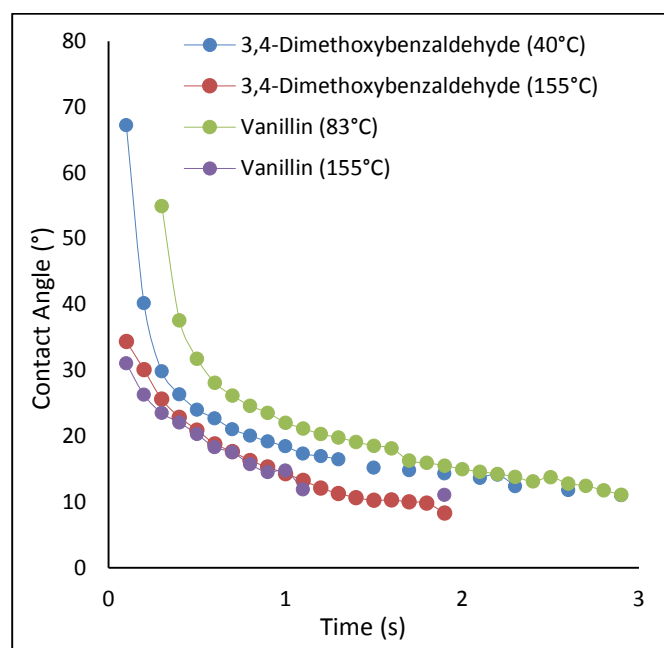


Figure 10: Graph of contact angle versus time measured between barbituric acid and both vanillin and between barbituric acid and veratraldehyde at the aldehydes' respective melting points and at and at 155 °C.

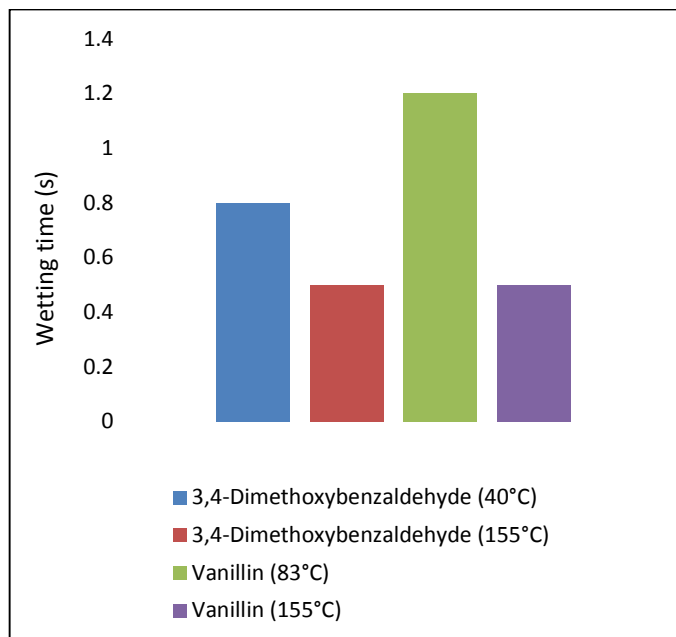
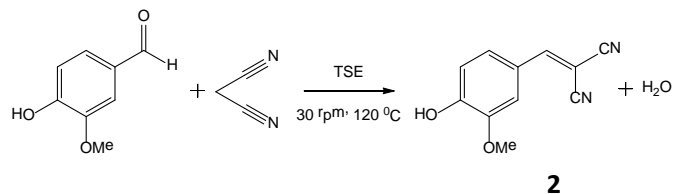


Figure 11: Bar chart representing the wetting time required for vanillin and veratraldehyde to reach an optimum contact angle of 20 °, at both their respective melting temperatures as well as 155 °C.

The reaction between vanillin and malononitrile was also carried out by TSE. Malononitrile, an alternative activated methylene compound, has a lower melting point (32 °C) than barbituric acid (164 °C), allowing us to investigate the effect of this reagent on the previous reactions. Again, Kaupp reported this solvent-free reaction in the presence of Na_2CO_3 (0.1 mol. eq.) (Scheme 2) by ball milling.¹⁰ Unfortunately we could not reproduce this reaction in the ball mill, obtaining instead a mixture of unidentified products together with the starting materials. However, in our hands the reaction was successful by TSE as discussed below.

Preliminary extrusion experiments were carried out without the presence of a catalyst at barrel temperatures from ambient temperature up to 160°C. However, malononitrile was suspected to have polymerised upon heating (a common phenomenon with this reagent)²³ and no product was observed. Therefore, Na_2CO_3 (0.1 mol. eq.) was employed during the subsequent experiments. ^1H NMR spectroscopy and PXRD analysis (Figures 12 and 13) indicated that complete conversion to product, **2**, occurred at a screw speed of 55 rpm (as before), but at a lower temperature (120 °C) than required for the reactions with barbituric acid (160°C). A maximum feed rate of 0.21 kg hr^{-1} was achieved, with a throughput rate of 0.196 kg hr^{-1} , corresponding to a high STY of $98 \times 10^3 \text{ kg m}^{-3} \text{ day}^{-1}$.

Inclusion of a catalyst means that a direct comparison of the required process temperatures for the Knoevenagel condensations involving barbituric acid versus malononitrile cannot be made. However, one key observation to come from the latter reaction is that it is not simply the formation of a melt phase that results in a complete conversion, as the process temperature (120°C) was much greater than the melting points of either reagent.



Scheme 2: Knoevenagel condensation carried out by TSE, 55 rpm, 120 °C.

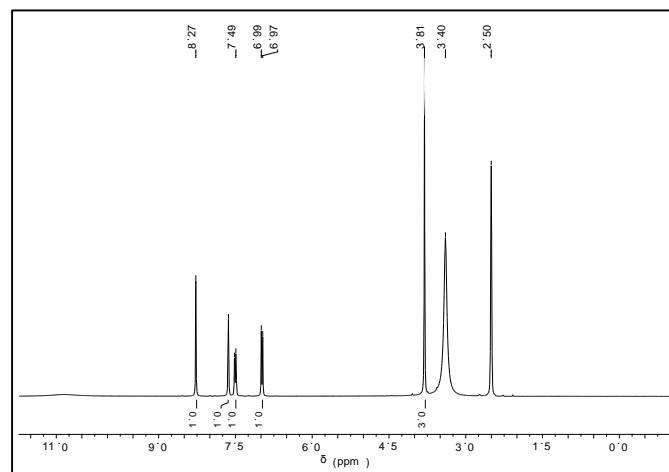


Figure 12: ^1H NMR spectrum of **2** in d^6 -DMSO.

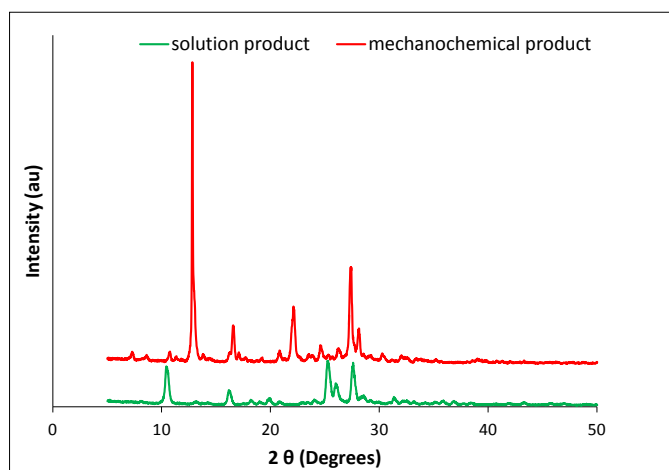
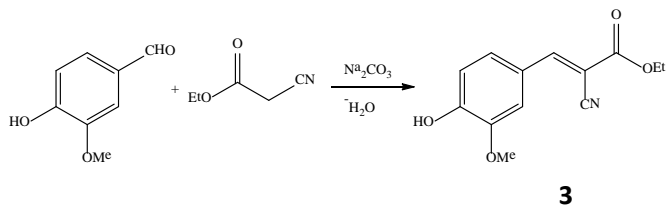


Figure 13: PXRD patterns of **2** prepared in solution, and by twin screw extrusion.

Finally, to explore whether extrusion can be applied to mixtures of solid and liquid reagents, we next investigated the reaction between solid vanillin and liquid ethyl cyanoacetate in the presence of Na_2CO_3 (10 % mol.) (Scheme 3). A syringe pump was used to feed ethyl cyanoacetate into the extruder and a volumetric feeder supplied the solid mixture of vanillin and Na_2CO_3 (Figure 14). The feed rates were optimised as 1.74 ml min^{-1} and 2.9 g min^{-1} respectively, resulting in a slightly longer residence time of 6 – 7 minutes (compared to the previous Knoevenagel condensations with residence times of ca. 2 minutes). The product of this reaction has been investigated as a potential photostabiliser in sunscreen products.²⁴



Scheme 3: Knoevenagel condensation reaction to prepare **3**.

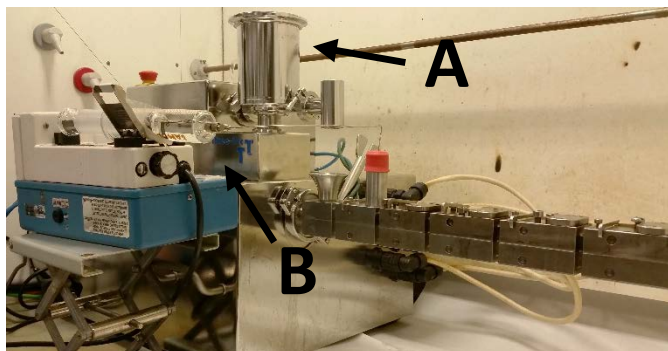


Figure 14: Twin screw extruder with a volumetric feeder (A) (feeding vanillin and Na_2CO_3), and a syringe pump (B) (feeding ethyl cyanoacetate) attached.

Extrusion experiments were carried out to optimise the temperature and screw speed required to achieve 100 % conversion to product (Figures 15 and 16). A complete reaction was achieved at 160 °C with a screw speed of 55 rpm. A throughput rate of 0.11 $\text{kg}\cdot\text{hr}^{-1}$ was achieved, which resulted in a Space Time Yield (STY) of 55,650 $\text{kg}\cdot\text{m}^{-3}\cdot\text{day}^{-1}$. The catalyst, Na_2CO_3 , was not removed from the extrudate before analysis (to ensure the reaction did not proceed during purification). Allowing for 0.1 mol. eq. Na_2CO_3 in the extrudate, pure product was obtained as indicated by elemental analysis. It must be noted that in solution morpholine (more difficult to remove than Na_2CO_3) is conventionally used to catalyse this reaction.

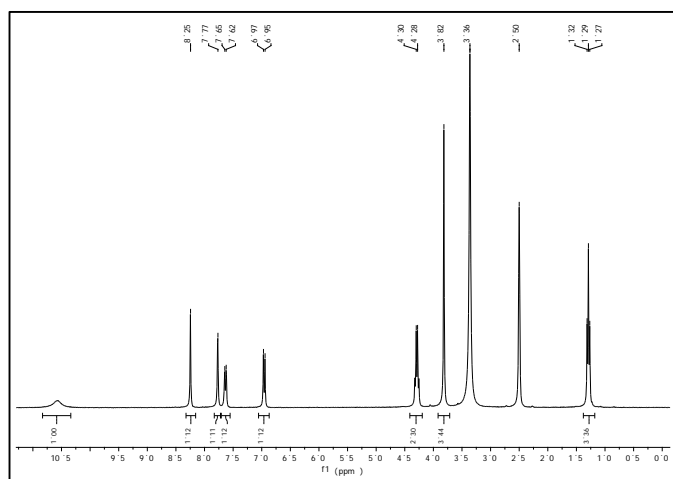


Figure 15: ^1H NMR spectrum of **3** in d^6 -DMSO.

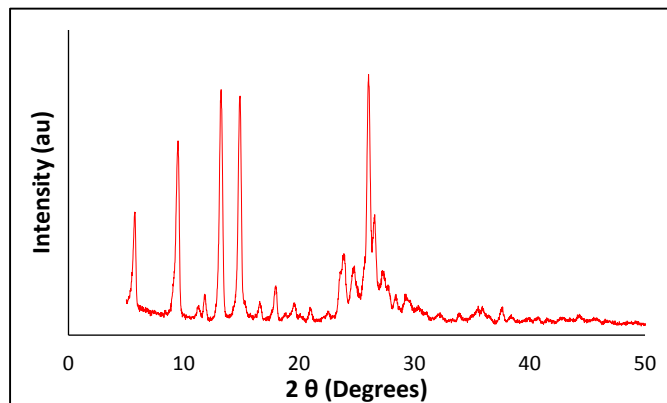


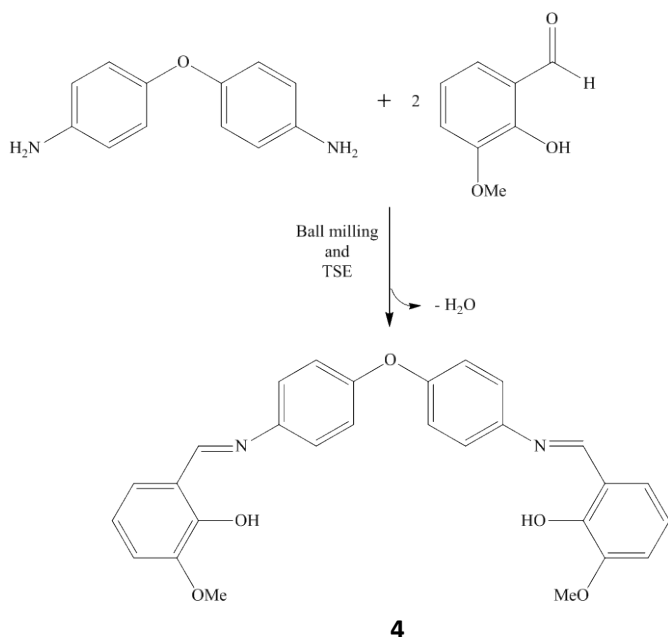
Figure 16: PXRD pattern of **3** prepared by twin screw extrusion.

To summarise regarding the Knoevenagel condensations, the above study represents the first step in scaling up solvent-free organic synthesis by extrusion. The technique was found to be applicable to a range of reactions, including those between a solid and a liquid as well as reactions involving reagents of varying melting points. In most examples, post synthetic purification was not required, and in these cases, TSE was shown to produce analytically pure compounds with high Space Time Yields. Furthermore, it was demonstrated that the reactions involving barbituric acid occurred through a physical process dependent on the wettability of barbituric acid.

Imine Formation

Solvent-free C-N bond formation has been reported extensively in the literature, including the formation unsymmetrical aromatic diimines as well the synthesis of salen H_2 from two liquids (salicylaldehyde and ethylene diamine), both reactions being conducted by ball milling. Herein, we report the formation of a C-N bond by TSE as demonstrated through the synthesis of a diimine **4** (Scheme 4). The solution reaction involves refluxing 4,4'-oxydianiline with 2 equivalents of *ortho*-vanillin in methanol for several hours.²⁵

The imine formed within 30 minutes of ball milling at 25 Hz, without the addition of solvent. The reaction was subsequently scaled from 0.5 g per batch (by ball milling) to 0.03 $\text{kg}\cdot\text{hr}^{-1}$ via twin screw extrusion, producing the desired Schiff base as a bright orange powder (Figure 17). Again, temperature, screw speed and feed rate were optimised individually for this reaction and an analytically pure product (as indicated by elemental analysis) was obtained by extruding at 120 °C, 55 rpm with a feed rate of 0.79 $\text{g}\cdot\text{min}^{-1}$ (Figures 18 and 19). No post synthetic purification was needed.



Scheme 4: Mechanochemical imine formation (**4**) by ball milling at 25 Hz for 30 minutes and by TSE at 55 rpm, 120 °C.



Figure 17: Orange solid (**4**) produced from the twin screw extrusion of 4,4'-oxydianiline and 2 equivalents of *ortho*-vanillin.

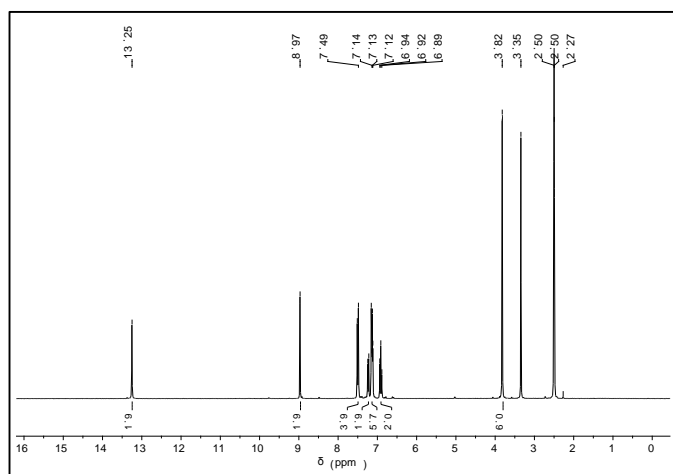


Figure 18: ^1H NMR spectrum of the Schiff base, **4** in d^6 -DMSO.

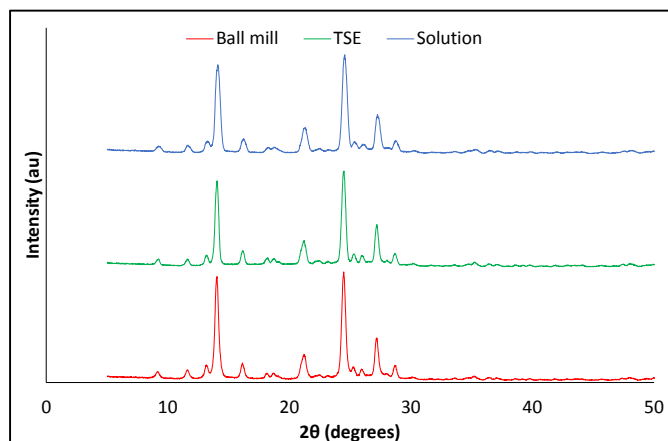


Figure 19: PXRD patterns of the Schiff base prepared in solution, by ball milling and twin screw extrusion.

Only partial reaction (28 % conversion) occurred at room temperature, as determined by ^1H NMR spectroscopy. At room temperature, the screw speed was increased to 100, 150 and 250 rpm to encourage greater conversion, however this actually resulted in lower conversions as a result of the shorter residence times.

Table 4 highlights the temperatures and feed rates investigated as well as the conversions to **4** (as determined by ^1H NMR spectroscopy). Moderate temperatures of 40 - 80 °C resulted in significant conversions to product of up to 99 %. However, it was quickly identified that increasing the temperature further allowed a greater feed rate and 100 % conversion. This was considered to be more advantageous than employing a lower temperature, and consequently at 120 °C, 55 rpm (with a residence time of *ca.* 30 – 60 seconds), a feed rate of 0.79 gmin^{-1} was achieved. This is almost double the feed rate of the experiment carried out at 80 °C.

Table 4: Variation of temperature and feed rate on the extrusion of 4,4'-oxydianiline with *o*-vanillin.

Temperature (°C)	Screw Speed (rpm)	Feed Rate (gmin^{-1})	Conversion (%)
25	55	- ^a	0
40	55	- ^a	80
80	55	- ^a	99
80	55	0.45	0
80	55	0.73	45
80	55	0.79	70
100	55	0.79	91
120	55	0.79	100

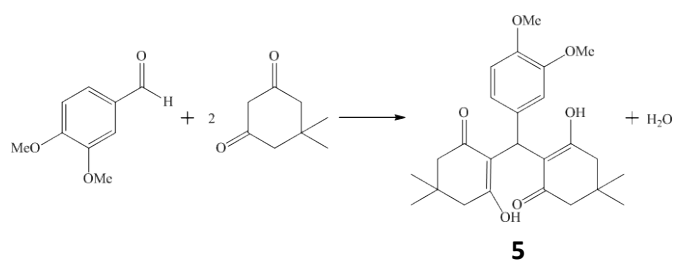
^a Reagents were fed manually.

Therefore, the formation of a C-N bond has been carried out as a solvent-free continuous process, made possible by TSE. Analytically pure product (as determined by elemental analysis) is obtained after *ca.* 2 minutes without any post-synthetic workup being required. Furthermore, a throughput rate of 0.03 kg hr^{-1} was achieved resulting in a high STY of 14,900 $\text{kg m}^{-3}\text{day}^{-1}$.

Michael Addition

Michael additions are another subset of organic reactions that have been reported to proceed efficiently by ball milling, for example, the reaction between vanillin and dimedone as reported by Kaupp *et al.*¹⁰ Herein, we report a related reaction between veratraldehyde and dimedone (2 equivalents) by TSE (Scheme 5).

Unfortunately, initial ball mill experiments were unsuccessful. Milling of the starting materials at 25 Hz for 60 minutes resulted in a low conversion to product of only 7.5 %. Experiments employing Liquid Assisted Grinding (CHCl₃ or H₂O) and/or catalysts (CaCl₂ and SmBr₃·6H₂O, reported to work in the solution reactions)^{26,27} were also unsuccessful. In fact the use of CaCl₂ was observed to hinder the ball mill reaction, resulting in a conversion to product of < 1.5 %.



Scheme 5: Michael addition carried out mechanochemically to form **5**.

However, the control over temperature and screw configuration offered by extrusion methods encouraged us to attempt this reaction in the extruder.

At room temperature and screw speeds of 30 – 250 rpm, no reaction was observed to occur with a white solid consisting of the starting materials being retrieved. However, a slight temperature increase to 40 °C resulted in a significant change in the properties of the extrudate, producing a golden yellow liquid which rapidly formed a glass on cooling. However, ¹H NMR spectroscopy indicated that the extrudate still consisted mainly of starting reagents (< 5 % conversion to product).

Increasing the temperature further did increase the conversion to product, *e.g.* at 150 °C and 55 rpm a conversion of 80 % was achieved. Increasing the temperature above 160 °C resulted in a brown viscous liquid, which is believed to result from the thermal degradation of one of the reagents. Therefore, as degradation was observed at high temperatures, and increasing screw speed resulted in insufficient residence times, the screw configuration was then changed to determine if this could drive the reaction to completion.

The alternative screw configuration consisted of conveying and kneading segments as before, but with the addition of reverse conveying segments (Figure 20). These segments retard the flow of material through the extruder increasing the residence time.¹⁶ They were strategically positioned after each kneading section, to hold material in the high shear kneading sections for a prolonged period of time.

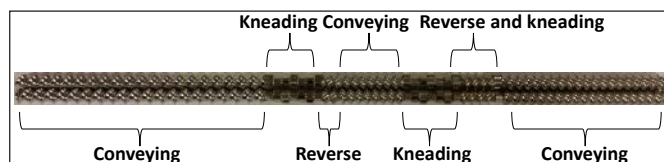


Figure 20: Alternative screw configuration employed, containing reverse conveying segments that retard the flow of material.

Using this configuration, complete conversion to product was achieved at 120 °C and 200 rpm to produce a beige/yellow solid. However, repetition of this result proved difficult with conversions to product being observed thereafter between 97 – 98 %. After some consideration, the problem was identified to be inefficient premixing before extrusion. The reagents were of similar particle size (*ca.* 300 μm) and consistencies but it was only when they were premixed in a planetary ball mill in the absence of any grinding media (170 rpm, 5 minutes), followed by extrusion at 120 °C, 200 rpm, that 100 % conversion to product was achieved, and was found to be reproducible. It must be noted that no reaction had occurred after mixing in the planetary ball mill, as determined by ¹H NMR spectroscopy.

Although there was 100 % conversion of starting materials, more than one product was observed to form in this reaction. The dihydroxyl compound (**5**) was the major product, and unidentified byproducts were present in trace amounts. The same mixture of products, in the same ratio, was observed to form regardless of the synthetic technique or catalyst used, *i.e.* the same result was obtained from both solvent-based and mechanochemical experiments. Therefore, the formation of these byproducts in the extruder was not considered to be a significant drawback compared to the solution-based method. A sample of the obtained extrudate was purified by column chromatography (eluent system CH₂Cl₂:EtOH 9:1) to produce an analytically pure white solid (**5**) as determined by ¹H NMR spectroscopy, PXRD and elemental analysis (Figures 21 and 22).

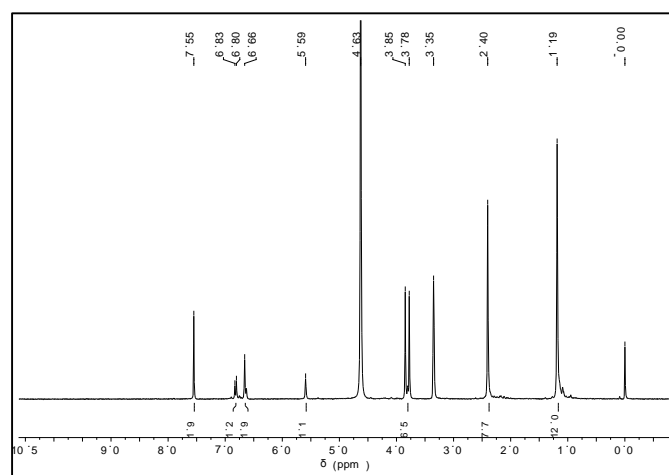


Figure 21: ¹H NMR Spectrum of **5** in MeOD.

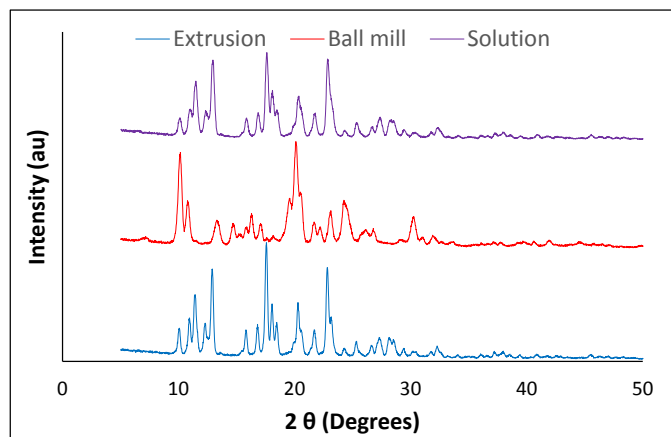


Figure 22: PXRD patterns of the **5** prepared in solution, by ball milling and twin screw extrusion.

As expected, the residence time of the optimised process was longer at *ca.* 12 minutes, due to the presence of reverse conveying segments (compared with 2 minutes for the standard screw configuration in the Knoevenagel condensations). An optimised feed rate of 0.12 kg hr⁻¹ resulted in an overall throughput rate of 0.07 kg hr⁻¹. A Space Time Yield of 35 x 10³ kg m⁻³ day⁻¹ was determined for these conditions.

When this reaction is conducted in solution, catalysts such as CaCl₂ or SmBr₃·6H₂O are utilised. The catalyst and the temperature determine the final product obtained from the reaction.^{26,27} The dihydroxyl product (**5**) obtained in this work is typically formed at room temperature in solution. However, at reflux an alternative xanthene compound (**5'**) is isolated instead (Figure 23). Therefore, not only have we demonstrated that TSE can be used to carry out Michael additions, but it is also the first example where extrusion gives different chemoselectivity to that observed in solution.

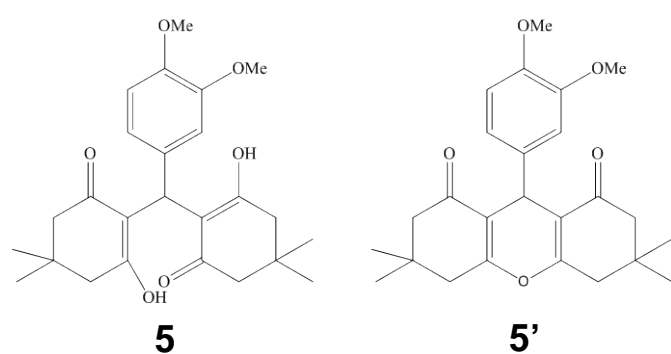
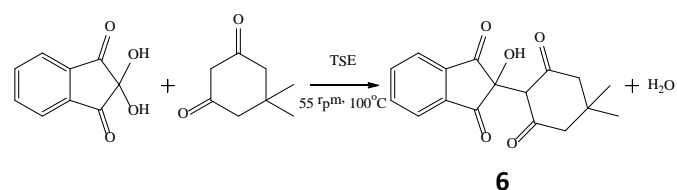


Figure 23: Possible products from the Michael Addition.

Aldol Condensation

Aldol condensations have been investigated extensively by ball milling, and demonstrate chemoselectivity for one product in many cases. Kaupp *et al.* reported the reaction between ninhydrin and dimedone by ball milling, to produce a substituted 1,3 indandione (**6**)

(Scheme 6).²⁸ We were able to reproduce this result by ball milling and therefore subsequently investigated it by twin screw extrusion. Initial results showed that the reaction would not go to completion without the presence of Na₂CO₃ (0.1 mol. eq.), even when an alternative screw configuration was employed to prolong residence time (as with the Michael Addition).



Scheme 6: Aldol condensation carried out by TSE at 55 rpm, 100 °C to form **6**.

At 75 °C and 55 rpm, a conversion to product of 80 % was achieved, but increasing the temperature to 100 °C gave 100 % conversion to product. At this temperature, screw speeds of 30 - 200 rpm were investigated, and 100 % conversion to product was observed at 55 rpm (Figures 24 and 25).

A standard screw configuration was employed, and it was observed that the residence time in this case was unusually long at 12 minutes, in comparison to *ca.* 2 minutes (as in the Knoevenagel condensations). Furthermore, a significant increase in torque was also observed. This is believed to result from a change in the rheological properties of the material during the course of the reaction. Due to this high torque, the feed rate was kept low at 0.8 g min⁻¹, to prevent an obstruction occurring along the barrel, disrupting the continuous process. A throughput rate of 63.6 g hr⁻¹ was obtained, resulting in a Space Time Yield (STY) of 32 x 10³ kg m⁻³ day⁻¹.

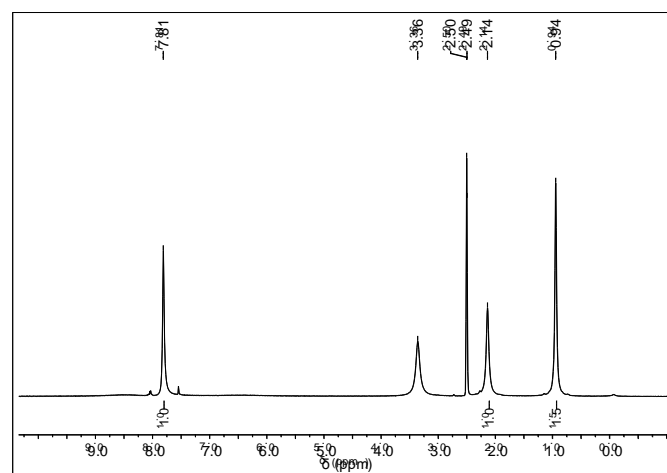


Figure 24: ¹H NMR spectrum of the 1,3 indandione, **6** in d⁶-DMSO.

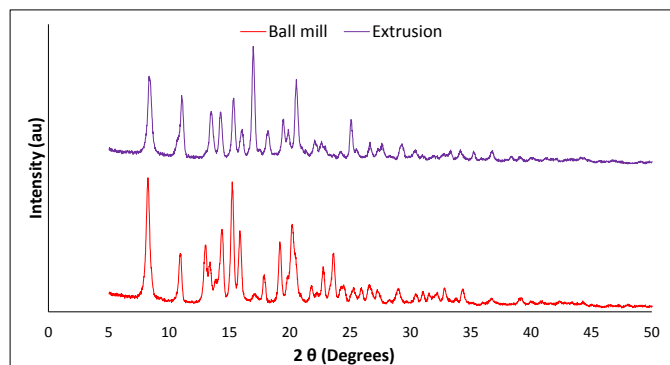


Figure 25: PXRD patterns of the ball mill and extrusion products of the aldol reaction.

The reported conventional synthesis involves refluxing in water overnight.²⁹ However, we found that refluxing in water for 3 days, even in the presence of 0.1 mol. eq. Na_2CO_3 did not result in a complete reaction. Ultrasound irradiation has also been employed to carry out this reaction,³⁰ however this is still very difficult to scale up, supporting the use of extrusion for the large scale, continuous synthesis of a substituted 1,3 indandione (**6**).

Conclusions

In conclusion, we have demonstrated through a variety of condensation reactions that organic synthesis can be conducted as a large scale, continuous process under solvent-free conditions. In most cases, post process purification was not required and high throughput rates (ca. 0.5 kg hr^{-1}) and Space Time Yields (up to $260 \times 10^3 \text{ kg m}^{-3} \text{ day}^{-1}$) were achieved. The physical mechanism by which some of the Knoevenagel condensations took place was studied and identified as involving wetting of the barbituric acid by the liquid aldehyde as a key process. Furthermore, the first extrusion example of a reaction (Michael addition) that is chemoselective for one product has also been presented.

Acknowledgements

We thank EPSRC for funding (EP/L019655/1).

Notes and references

- G. A. Bowmaker, *Chemical communications (Cambridge, England)*, 2013, **49**(4), 334.
- C. Medina, D. Daurio, K. Nagapudi and F. Alvarez-Nunez, *Journal of pharmaceutical sciences*, 2010, **99**(4), 1693.
- D. Crawford, J. Casaban, R. Haydon, N. Giri, T. McNally and S. L. James, *Chem. Sci.*, 2015, **6**(3), 1645.
- D. E. Crawford, L. A. Wright, S. L. James and A. P. Abbott, *Chemical communications (Cambridge, England)*, 2016, **52**(22), 4215.
- S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friscic, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed and D. C. Waddell, *Chemical Society reviews*, 2012, **41**(1), 413.
- D. R. Maurice and T. H. Courtney, *Metall and Mat Trans A*, 1990, **21**(1), 289.
- G. Zhan and H. C. Zeng, *Chemical communications (Cambridge, England)*, 2016.
- A. Stolle, R. Schmidt and K. Jacob, *Faraday discussions*, 2014, **170**, 267.
- C. F. Burmeister, A. Stolle, R. Schmidt, K. Jacob, S. Breitung-Faes and A. Kwade, *Chem. Eng. Technol.*, 2014, **37**(5), 857.
- G. Kaupp, M. Reza Naimi-Jamal and J. Schmeyers, *Tetrahedron*, 2003, **59**(21), 3753.
- V. P. Balema, J. W. Wiench, M. Pruski and V. K. Pecharsky, *J. Am. Chem. Soc.*, 2002, **124**(22), 6244.
- G.-W. Wang, *Chemical Society reviews*, 2013, **42**(18), 7668.
- L. Takacs and J. S. McHenry, *J Mater Sci*, 2006, **41**(16), 5246.
- G. Le Caër, P. Delcroix, S. Bégin-Colin and T. Ziller, *Hyperfine Interactions*, 2002, **141/142**(1/4), 63.
- D. E. Crawford and J. Casaban, *Advanced materials (Deerfield Beach, Fla.)*, 2016, **28**(27), 5747.
- H. F. Giles, J. R. Wagner and E. M. Mount, *Extrusion: The definitive processing guide and handbook*, William Andrew an imprint of Elsevier, Amsterdam, 2014.
- C. L. Raston and J. L. Scott, *Green Chem.*, 2000, **2**(2), 49.
- F. Ravalico, S. L. James and J. S. Vyle, *Green Chem.*, 2011, **13**(7), 1778.
- J. Clayden, N. Greeves, S. G. Warren and P. Wothers, *Organic chemistry*.
- Ben Hutchings, *Feedback kinetics in a mechanochemical reaction*, Masters, Belfast, 2015.
- A. Pichon and S. L. James, *CrystEngComm*, 2008, **10**(12), 1839.
- M. Kolahdozan, R. J. Kalbasi, Z. S. Shahzeidi and F. Zamani, *Journal of Chemistry*, 2013, **2013**(1), 1.
- [Cannot display reference #23, because the template "Bibliography - Internet Document - (Default template)" contains only fields that are empty in this reference.]
- Ratan Chaudhuri, *Photostable organic sunscreen composition*(US 20070059258 A1), 2004.
- P. Cucos, F. Tuna, L. Sorace, I. Matei, C. Maxim, S. Shova, R. Gheorghe, A. Caneschi, M. Hillebrand and M. Andruh, *Inorganic chemistry*, 2014, **53**(14), 7738.
- B. Maleki, M. Raei, E. Akbarzadeh, H. Ghasemnejad-Bosra, A. Sedrpoushan, S. S. Ashrafi and M. N. Dehdashti, *Organic Preparations and Procedures International*, 2016, **48**(1), 62.
- A. Ilangovan, S. Muralidharan, P. Sakthivel, S. Malayappasamy, S. Karuppusamy and M. P. Kaushik, *Tetrahedron Letters*, 2013, **54**(6), 491.
- G. Kaupp, M. R. Naimi-Jamal and J. Schmeyers, *Chemistry (Weinheim an der Bergstrasse, Germany)*, 2002, **8**(3), 594.
- N. P. Peet, E. W. Huber and J. C. Huffman, *Journal of Heterocyclic Chemistry*, 1995, **32**(1), 33.
- G. Cravotto, A. Demetri, G. M. Nano, G. Palmisano, A. Penoni and S. Tagliapietra, *Eur. J. Org. Chem.*, 2003, **2003**(22), 4438.