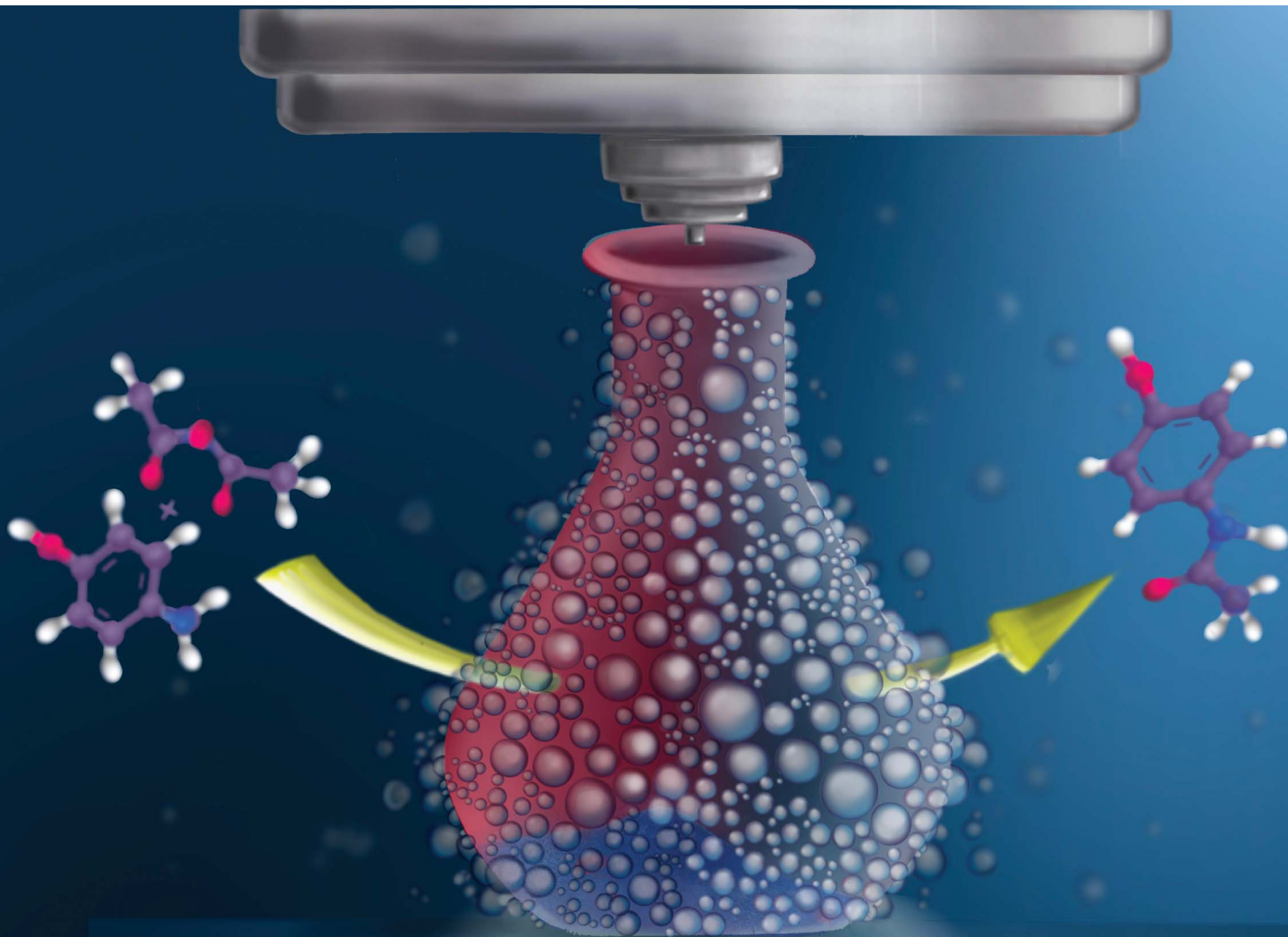


# Chemical Science


Volume 16  
Number 14  
14 April 2025  
Pages 5757–6122

[rsc.li/chemical-science](https://rsc.li/chemical-science)



ISSN 2041-6539

Synthesis of organic molecules *via* spray-drying†Cite this: *Chem. Sci.*, 2025, 16, 5770Gerard Pena, <sup>ab</sup> Jorge Albalad, <sup>ab</sup> Daniel Maspocho <sup>\*abc</sup> and Inhar Imaz <sup>\*ab</sup>

 All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 7th January 2025  
Accepted 20th February 2025DOI: 10.1039/d5sc00126a  
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Confining chemical reactions within microdroplets has attracted significant attention from chemists due to the accelerated reaction rates resulting from the drastically smaller reaction volumes than in standard solutions. Herein we report that, beyond its widespread use for producing dry-powder formulations for industries (e.g. pharmaceuticals and food) *via* the atomization of microdroplets followed by drying in a hot gas stream, spray-drying can also be employed in organic synthesis. Specifically, we used spray-drying to run three model reactions: a Schiff-base condensation, a Claisen–Schmidt reaction, and acylation of amines, for synthesizing small organic molecules. Our results showcase that, compared to traditional methods, spray-drying can reduce reaction times without compromising (high) yields, paving the way for its use as a scalable method for industrial-scale organic synthesis.

## Introduction

Synthetic organic chemistry is a perpetual wellspring of discovery and synthesis of small molecules, macromolecules, and polymers, all of which are subject to further exploration and application across myriad uses. Progress in this field is linked to development of novel reactions, synthesis of new compounds, as well as method and fabrication technology development for known syntheses.

Since the 2010s, a few studies have demonstrated the enormous potential of using aerosols as microscale reactors for conducting organic reactions. Initially, aerosols were primarily important within the context of environmental chemistry, as many atmospheric reactions occur within microdroplets,<sup>1</sup> such as the atmospheric oxidation of SO<sub>2</sub>, which leads to acid rain.<sup>2</sup> Soon after, several studies revealed that charged aqueous aerosols could spontaneously generate nucleosides and peptides from their constituents (e.g. natural amino acids, monosaccharides, or nitrogenous bases),<sup>3</sup> even though these reactions are typically slow in bulk and require a constant energy supply. More recently, important advances on the use of aerosol-based technologies in synthetic organic chemistry have been reported by Cooks *et al.* and Zare *et al.*, who have demonstrated its utility to run and accelerate<sup>4–6</sup> several reactions, such as epoxy ring-opening,<sup>7</sup> amination of benzylic sp<sup>3</sup> carbon atoms,<sup>8</sup> and aza-Michael additions,<sup>9</sup> as well as to enable

unusual transformations<sup>10</sup> by employing electrospray ionization coupled to mass spectrometry (ESI-MS). Using this technique, multiple groups have expanded the scope of organic reactions that can be performed using aerosols.<sup>11–16</sup> Additionally, other techniques, such as the microdroplet/thin film method, have also proven effective for aerosol-based organic reactions, enabling processes like two-phase oxidations,<sup>17</sup> phosphorylations,<sup>18</sup> and more.<sup>19–22</sup> Most recently, Zare's and Cooks' groups have also begun the first efforts to scale up these aerosol technologies (on the order of a few grams per hour),<sup>23,24</sup> utilizing either a heated ultrasonic-nebulization device (Zare *et al.*) or a custom-built atomic sprayer apparatus with a solvent-recirculation system (Cooks *et al.*). Remarkably, these set-ups have been used to test various organic reactions, including Claisen–Schmidt condensations, Schiff-base formation, Katritzky salt reactions, and Suzuki couplings.

Building on these pioneering efforts, a next step is to make aerosol technologies more universally accessible for synthetic organic chemistry, both in academia and industry. This means developing and utilizing systems that are readily available in laboratories and industry, user-friendly, scalable, and ideally, commercially viable. A promising technology that meets these criteria is spray-drying,<sup>25</sup> which is already widely applied in various industrial processes, especially for drying and encapsulation.<sup>26,27</sup> Recently, spray-drying has also begun to be used for synthesizing inorganic materials and related composites in remarkably short synthetic times.<sup>28</sup> For instance, our group pioneered its use for porous metal–organic frameworks (MOFs)<sup>29</sup> and related composites.<sup>30–32</sup> Nonetheless, an important question remains: can spray-drying facilitate the synthesis of small organic compounds? Such an approach could shorten reaction times and enable continuous organic reactions with the potential for solvent-recycling. In fact, as early as 2017, in our attempts to covalently post-synthesize MOFs by spray-drying, we observed such potential in control Schiff-base

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† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d5sc00126a>

condensation reactions of small aldehydes and amines.<sup>33</sup> Herein, we describe the value of spray-drying in synthetic organic chemistry.

## Results and discussion

In our spray-drying process, all chemistry begins with the atomization of a solution of reagents, into a spray of micro-droplets, which is facilitated by a two-fluid nozzle (Fig. 1). This involves simultaneous injection of the solution, at a specified feed rate, and nitrogen gas, at another specified flow rate. In our reactions, the flow rate was maintained at 357 L h<sup>-1</sup> and the feed rate, at 3.0 mL min<sup>-1</sup>. Consequently, each precursor droplet comes into contact with — and is suspended by — a gas stream heated to a designated temperature (the inlet temperature), thereby initiating the evaporation of the solvent. This in

turn leads to the formation of a dried micro-structured powder, which is then directed through a cyclone, separated from the gas stream, and finally, collected inside a vessel. In this study, after each spray-drying synthesis, the powder is collected from the vessel and characterized using <sup>1</sup>H NMR to determine its purity. At this stage, the reaction was deemed complete for products with purities equal to or above 95%, while products with purities below 95% underwent further purification using standard work-up processes.

To confirm our previously reported observations, we first extended the use of spray-drying to conduct Schiff-base condensations. We examined the formation of (*E*)-4-((pyridin-4-ylmethylene)amino)phenol (**3a**) using 4-aminophenol (**1**) and 4-pyridinecarboxaldehyde (**2a**) as reagents (Fig. 1b(i)). The synthesis began with the dissolution of both reagents (1 : 1 molar ratio) in 25 mL of ethanol. The resultant solution was

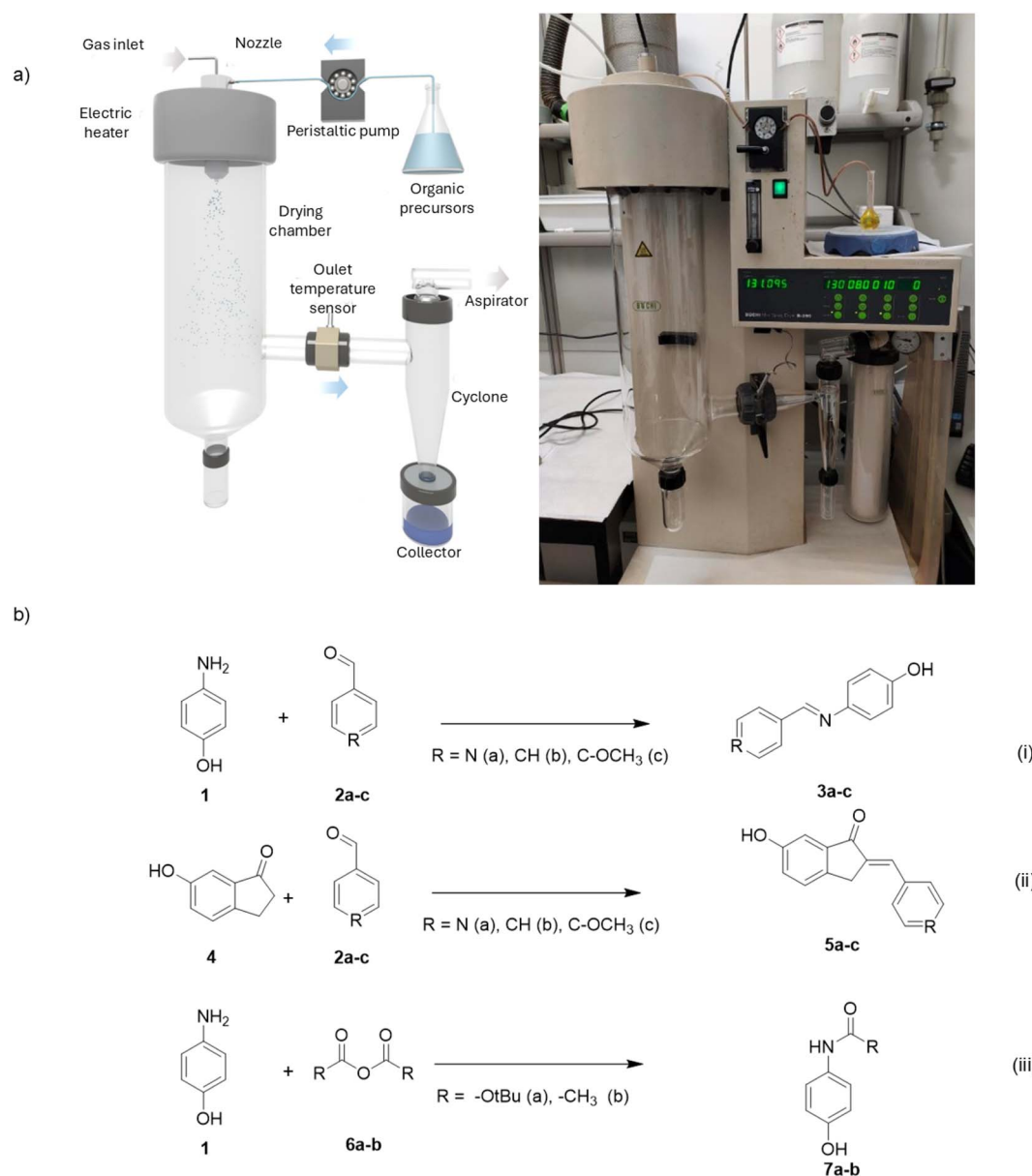


Fig. 1 (a) Schematic (left) and photo (right) of the lab-scale spray-dryer used for the organic reactions. (b) The reactions run with spray-drying.

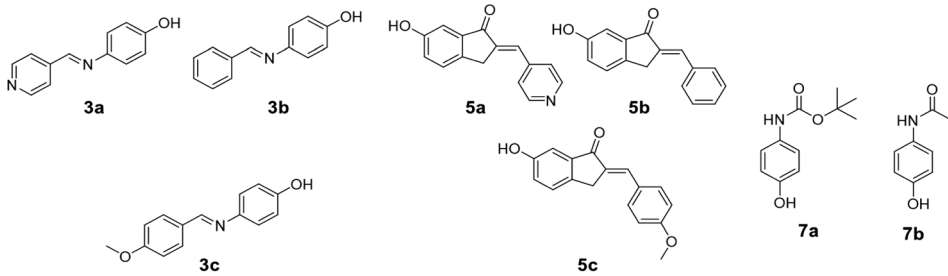


then spray-dried at an inlet temperature of 130 °C for 8.33 min, using a Mini Spray Dryer (Buchi, model B-290). The inlet temperature was selected to ensure evaporation of both the ethanol and the water generated during the reaction, as a way to facilitate the formation of imines according to Le Chatelier's principle. The reaction afforded a powder structured in the form of microspheres that was analyzed by  $^1\text{H}$  NMR without any further purification, which confirmed the formation of **3a** (Fig. S1–S5†) at a purity of 98% (0.917 g, yield: 90%; Table 1). Remarkably, comparing these results to the reported values for batch synthesis, the reaction time was 88% shorter, yet the yield was comparable (yield: 93%, reaction time: 240 min).<sup>34</sup>

Next, to study how the spray-dryer circumvents the effects of neutral or electron-donor substituents at the electrophile moiety, we expanded our chemistry to two other Schiff-base condensations: that of **1** and benzaldehyde (**2b**) to produce (*E*)-4-(*N*-benzylidene)aminophenol (**3b**); and that of **1** and 4-methoxybenzaldehyde (**2c**) to give (*E*)-4-[*N*-(4-methoxybenzylidene)amino]phenol (**3c**). Under stoichiometric synthetic conditions, we collected both imines (**3b** and **3c**) from the spray-drier with purities of 90% and 44%, respectively, and then purified each one by liquid/liquid extraction to get **3b** and **3c** in yields of 62% and 16%, respectively. Although these yields were low compared to those reported for the corresponding batch syntheses (91% for **3b**,<sup>35</sup> and 97% for **3c**<sup>36</sup>), we were able to increase the purity and yield for each one by tuning the molar ratio of the reagents. Thus, we reproduced the spray-drying protocols using molars of 1 : 1.3 (**1** : **2b**), which afforded **3b** in 85% yield, and of 1 : 3 (**1** : **2c**), which afforded **3c** in 80% yield (Tables 1, S1 and S2, and Fig. S6–S19†). Crucially, use of excess aldehyde in each case favored purity of the corresponding crude product (97%), thus obviating the need for any tedious and solvent-consuming additional purification.

Having demonstrated the efficacy of spray-drying in Schiff-base condensations, we next applied it to a second reaction: the Claisen–Schmidt reaction, an aldol condensation variant that involves a ketone and a non-enolizable aldehyde and is widely used in medicinal chemistry (Fig. 1b(ii)). Moreover, the Claisen–Schmidt reaction has been widely used as a model reaction in many microdroplet chemistry studies.<sup>23,24,37–42</sup> As in Schiff-based condensations, in Claisen–Schmidt condensations spray-drying can facilitate formation of the desired products by forcing evaporation of the water generated during the reaction. We tested this by separately reacting 6-hydroxy-1-indanone (**4**) with each of the same three aldehydes that we had previously used (**2a–c**). The condensations were run in methanol in the presence of two equivalents of KOH as base, using similar spray-drying conditions as in the Schiff-base reactions, except that the inlet temperature was lowered to 80 °C to avoid formation of by-products.<sup>43</sup> After spray-drying, the collected solids were treated with aqueous HCl because of their ionic character, and re-collected by filtration. All three isolated condensation adducts **5a–c** had purities below 95% (Tables S3–S5†). After purification, the products were obtained in yields of 55% (**5a**), 41% (**5b**) and 78% (**5c**). However, similarly to the Schiff-based condensation reactions, increasing the molar ratios to 1 : 1.7 (**4** : **2a**), 1 : 2 (**4** : **2b**) and 1 : 1.3 (**4** : **2c**) enabled spray-drying synthesis of **5a–c** without the need for any further purification (Fig. S20–S39†). Thus, **5a** was obtained at 96% purity (79% yield); **5b**, at 95% purity (67% yield); and **5c**, at 97% purity (93% yield) (Table 1). These values are comparable or superior to those obtained from batch procedures,<sup>44–46</sup> while offering much shorter reaction times and requiring far less of the (catalytic) base. Moreover, compared to the initial works by Cooks and co-workers,<sup>38–40</sup> we were able to eliminate the need for high voltage while maintaining high yields. Additionally, our final observations suggest

Table 1 Conditions used for the spray-drying synthesis of various small organic compounds



Reagent A	Reagent B	Product	Reagent ratio (A : B)	Inlet temperature (°C)	Purity <sup>a</sup> (%)	Yield (%)
1	<b>2a</b>	<b>3a</b>	1 : 1	130	98	90
1	<b>2b</b>	<b>3b</b>	1 : 1.3	130	97	85
1	<b>2c</b>	<b>3c</b>	1 : 3	130	97	80
4	<b>2a</b>	<b>5a</b>	1 : 1.7	80	96 <sup>b</sup>	79 <sup>b</sup>
4	<b>2b</b>	<b>5b</b>	1 : 2	80	95 <sup>b</sup>	67 <sup>b</sup>
4	<b>2c</b>	<b>5c</b>	1 : 1.3	80	97 <sup>b</sup>	93 <sup>b</sup>
1	<b>6a</b>	<b>7a</b>	1 : 1.3	100	91	81 <sup>c</sup>
1	<b>6b</b>	<b>7b</b>	1 : 1.3	80	97	83

<sup>a</sup> After collecting the product from the spray-drier. <sup>b</sup> Measured after acidifying the crude and isolating the solid. <sup>c</sup> After purification.





that electron-rich aldehydes facilitate the formation of relatively pure unsaturated products when Claisen–Schmidt reactions are performed *via* spray-drying.

Having validated spray-drying in both condensations, we then extended its scope to include acylation of a primary amine — namely, *N*-Boc protection of 4-aminophenol (Fig. 1b(iii)). Accordingly, an equimolar mixture of amine **1** and Boc<sub>2</sub>O (**6a**) in

methanol, containing 1.5 equivalents of TEA, was spray-dried for form carbamate **7a**.<sup>47</sup> These conditions proved successful, affording the protected product at a purity of 88%, which, after purification, gave **7a** in 66% yield (Table S6, and Fig. S40–S44†). Consistent with the previous reactions, spraying **1** with excess Boc<sub>2</sub>O (1.3 mol eq.) streamlined the process, giving the protected carbamate at 91% purity, and in 81% yield after purification (Table 1).

As acylation of amines to obtain amides is among the most frequent reactions in medicinal chemistry, we assessed our spray-drying approach in the synthesis of *N*-acetyl-*para*-aminophenol (the analgesic known as paracetamol or acetaminophen) (**8a**). It is considered an Essential Medicine by the World Health Organization<sup>48</sup> and is widely used as a synthetic intermediate.<sup>49</sup> Thus, a solution containing 4-aminophenol and acetic anhydride (molar ratio: 1 : 1.3) in 25 mL of THF was spray-dried at an inlet temperature of 80 °C for 8.33 min. Next, a solid was collected from the spray-drier, and then analyzed by <sup>1</sup>H NMR (Fig. S45 and S46†), HPLC (Fig. S49†) and X-ray powder diffraction (XRPD, Fig. S50†), which together confirmed the direct formation of crystalline paracetamol (in its monoclinic form)<sup>50</sup> at 97% purity and in 83% yield. Importantly, spray-drying not only enables continuous synthesis of paracetamol at shorter-than-standard reaction times, it also does so at high purity, without the need for any work-up, because the by-product, acetic acid, is volatile and therefore, evaporates off with the solvent. Another interesting observation is that our spray-drying reaction provides chemoselective *N*-acylation of 4-aminophenol: <sup>1</sup>H NMR analysis did not reveal the possible *O*-acylated derivative.

Finally, having synthesized paracetamol as a powder in a single, continuous step, without the need for isolation from the solvent, motivated us to explore the scalability of this process (×10 relative to the first reaction) using our lab-scale spray-drier (Fig. 2). To achieve this, we reproduced the above-mentioned spray-drying synthesis, increasing the amount of reagents with a precursor solution of 250 mL of THF containing 4-aminophenol (5.45 g) and acetic anhydride (6.63 g). Remarkably, after spray-drying the solution for 83.3 minutes, we were able to directly collect paracetamol as a white powder (6.60 g) at the same purity (98%) and in the same yield (85%) as in the milligram-scale synthesis, as confirmed by <sup>1</sup>H NMR and HPLC (Fig. 2).

## Conclusions

In summary, we have shown that spray-drying can be an interesting method for the continuous synthesis of small organic compounds. We have demonstrated its utility in three different reactions (Schiff-base condensations, Claisen–Schmidt reactions, and acylation of amines), to synthesize a total of eight such compounds. In these reactions, spray-drying allows the fast synthesis of these molecules with high purities and yields. Moreover, in some cases, spray-drying bypasses the need of purification protocols, further simplifying the production of these molecules. We believe that, as spray-drying is a widely available technique in industry allowing the processability of

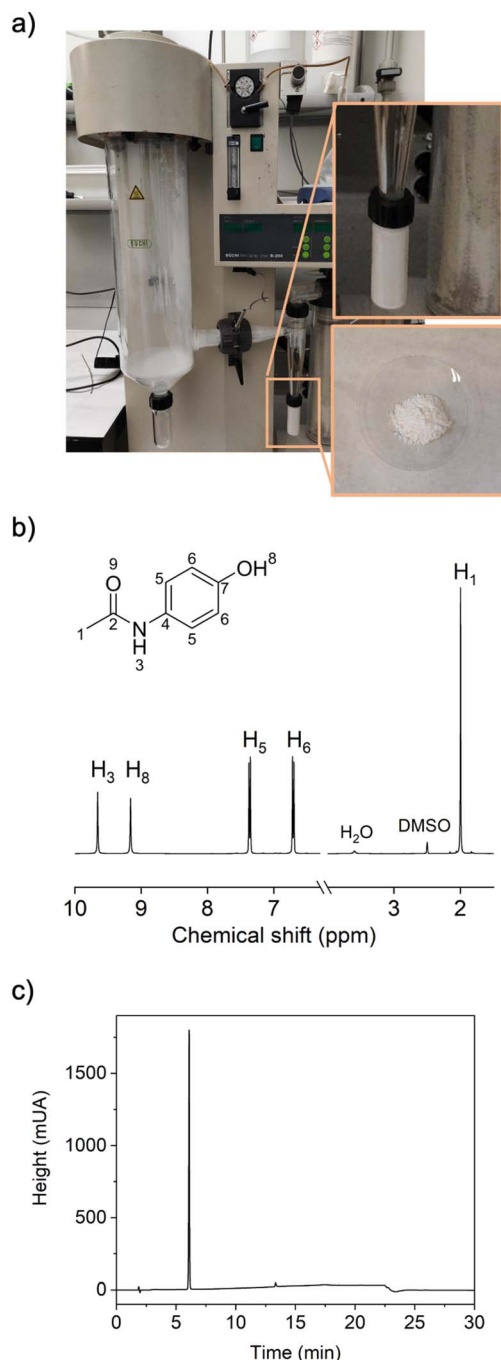


Fig. 2 (a) Photograph of the spray-drier after the gram-scale synthesis of paracetamol. (Insets) Photos of the collector after the spray-drying synthesis (top) and of the synthesized paracetamol (bottom). (b) <sup>1</sup>H NMR spectrum of the synthesized paracetamol, corroborating its structure. (c) HPLC chromatogram of the synthesized paracetamol, confirming its purity.



liters of solutions within minutes, the results shown herein will contribute to easily scale-up aerosol technologies to produce small organic molecules in a continuous and fast way.

## Data availability

The data supporting this article have been included as part of the ESI.†

## Author contributions

G. P.: methodology, investigation, and writing-original draft. J. A.: validation and investigation. D. M.: funding acquisition, conceptualization, supervision and writing-review and editing. I. I.: funding acquisition, conceptualization, supervision and writing-review and editing.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work has received funding from the Catalan AGAUR (project 2021 SGR 00458). It was also funded by the CERCA Programme/Generalitat de Catalunya. ICN2 is supported by the Severo Ochoa Centres of Excellence programme, Grant CEX2021-001214-S, funded by MCIN/AEI/10.13039.501100011033. G. P. acknowledges funding from the Spanish Research Agency (PID2021-123265NB-I00).

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