Reaction Chemistry & Engineering

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
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Cite this: *React. Chem. Eng.*, 2023, **8**, 482

# Upgrading furanic platforms to α-enaminones: tunable continuous flow hydrogenation of bio-based cyclopentenones†

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Received 21st July 2022,
Accepted 8th September 2022

DOI: 10.1039/d2re00292b

rsc.li/reaction-engineering

Here we describe a tunable continuous flow hydrogenation of *trans*-4,5-diamino cyclopentenones (DCPs) allowing the selective stepwise synthesis of novel bifunctionalized cyclopentanones (up to 96% yield and >92% selectivity). Stability studies of the diamino cyclopentanone motif led to the development of an elimination procedure yielding the corresponding α-enaminones in good yields. Deuteration of the cyclopentene scaffold can also be performed using $D_2O$ as a source of $D_2$. A sequential process for the synthesis of α-enaminones directly from furfural is also described. The methodology allows the preparation of a previously reported ATP-sensitive potassium channel agonist in 71% yield.

## Introduction

α-Enaminones are versatile synthons exhibiting dual electronic properties.[1] The enamine nucleophilic character and enone electrophilic nature of these compounds attracted particular interest as intermediates for the construction of heterocyclic compounds (*e.g.* tetrahydro-1*H*-carbazol-1-ones,[2] pyrroles,[3] quinolones[4]). Examples of pharmaceutically relevant α-enaminones are dehydro-benzoxazine and dehydro-benzothiazine derivatives, which exhibit activity as ATP-sensitive potassium ($K_{ATP}$) channel agonists (Fig. 1a)[5–9] and precursors of imino 1,2,3,4-tetrahydrocyclopent[*b*]indoles, known to inhibit acetylcholinesterase and monoamine oxidase (Fig. 1a).[10]

The extensive utility of this synthon promotes the development of new methods for the assembly of α-enaminones, constituting a topic of ongoing interest.

Over the years, different protocols have been developed for the synthesis of α-enaminones (Fig. 1b): (1) the conventional multistep synthesis from diketones;[11–16] (2) cyclic ketone oxidative coupling with anilines or *O*-benzoylhydroxylamines under mild conditions, including electrochemical methods;[17–21] more recently, (3) a three-component gold-catalysed coupling/cyclization reaction.[22]

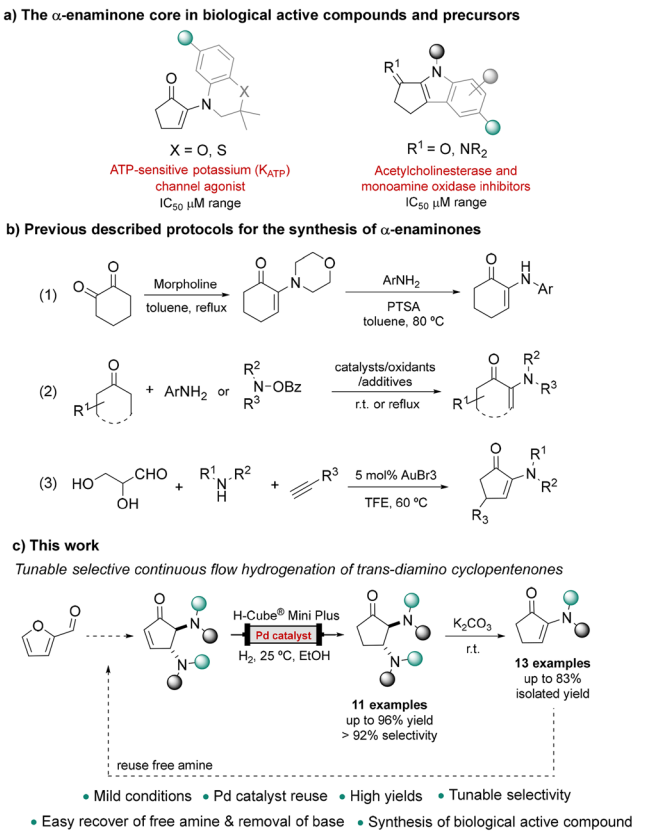


**Fig. 1** a) Importance of the α-enaminone core in biological active compounds and precursors; b) reported methods for the synthesis of α-enaminones; and c) proposed work towards the preparation of α-enaminones from furfural applying a more sustainable continuous flow hydrogenation of DCPs.

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† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d2re00292b

Despite all the progress, these elegant methods have some limitations, as they require pre-functionalised amination reagents (*i.e.* *o*-benzoylhydroxylamines) and use of stoichiometric amounts of additives and/or oxidants and are often limited to the use of aromatic amines.

In view of these limitations, the design of new protocols that improve the sustainability of the existing methods bypassing the use of high amounts of additives/oxidants and tolerating a broad range of amination reagents would be highly desirable.

Following the "12 Principles of Green Chemistry", we are contributing to sustainability, where the use of renewable feedstocks (*i.e.* biomass) is a prevalent trend to reduce the chemical impact of a process.[23,24] In this sense, furfural is a renewable raw material included in the U.S. Department of Energy top "10 + 4" list of bio-based materials.[25] The discovery of novel methods to prepare added value compounds from bio-based synthons, including furanic platforms such as furfural and 5-hydroxymethylfurfural (HMF), has attracted the attention of researchers over the years.[26,27]

Our group has been involved in the valorisation of furfurals,[28,29] in particular for the preparation of functionalized cyclopentenones.[11,30,31] Previous reports show that biomass derived *trans*-4,5-diamino-cyclopentenones (DCPs) undergo base catalysed β-amine elimination upon thiol 1,4-addition, yielding the corresponding enaminone.[11,32,33] Hence we envisioned that hydrogenation of the DCP olefin may lead to similar behaviour under basic conditions, therefore forming the desired scaffold under mild conditions from cheap biomass furanic platforms. Furthermore, the use of continuous flow conditions will allow fine-tuning of the reaction selectivity to obtain either the cyclopentanone or the enaminone, facilitate scale-up/scale-out processes and reduce the reaction waste by reusing heterogeneous catalysts.

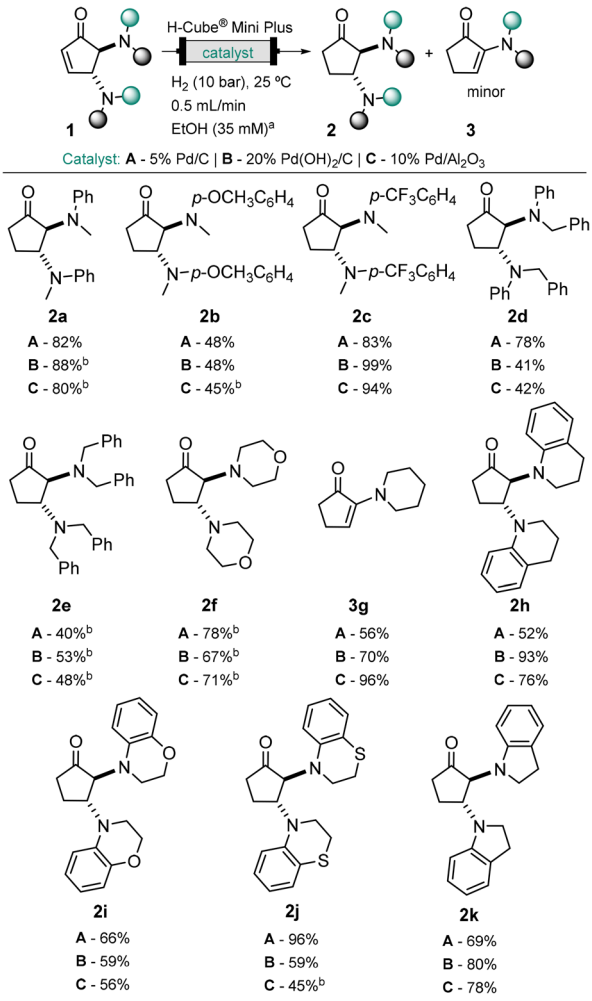
## Results and discussion

### Continuous flow hydrogenation of DCP using an H-Cube® Mini Plus for the selective formation of cyclopentanones 2

Aiming at cascade hydrogenation/elimination of DCP, **1a** underwent hydrogenation under batch conditions. However, the reaction yielded a mixture of products corresponding to the hydrogenated cyclopentanone **2a** and the desired enaminone **3a** (see ESI,† Scheme S1). Highlighting the challenges of preparing 4,5-substituted cyclopentanones, we optimised the hydrogenation selectivity towards the formation of cyclopentanone **2a** which we could also use to explore the elimination conditions towards enaminones.

An emerging strategy to increase reaction selectivity, hence decreasing the formation of side products, is the use of continuous flow. This methodology tends to increase the selectivity due to the higher catalyst/substrate ratio and shorter reaction times.[34] Focusing on the hydrogenated product **2a**, the reaction was performed under continuous flow using H-Cube® Mini Plus apparatus in order to increase both the selectivity and safety of the hydrogenation reaction. After screening several parameters (see ESI,† Scheme S2) the optimal conditions were selected as 10 bar of $H_2$ pressure, 0.5 mL $min^{-1}$ flow rate, 7.8 seconds residence time, 65 μL reactor volume, 25 °C and 35 mM substrate concentration.

The scope of the hydrogenation reaction to cyclopentanones **2** was extended to a variety of previously described DCPs,[30,35] promoted by three different catalysts. Cyclopentanones **2a–2f** and **2h–2k** were obtained in high yield and selectivity, with minor formation of the α-enaminone product (Scheme 1). All the three palladium catalysts (5% Pd/C, 20% $Pd(OH)_2/C$ and 10% $Pd/Al_2O_3$) tested were suitable for this transformation. Each cartridge allowed the running of more than 40 reactions and tolerated different substrates without cross-contamination or loss of efficiency. Overall, 5% Pd/C afforded higher yields (up to 96%) and selectivity (>92%).




**Scheme 1** Scope of functionalized cyclopentanones **2a–2k** from continuous flow hydrogenation of DCPs **1a–1k**. DCPs (20 mg, 1 equiv.) in EtOH (35 mM), 5% Pd/C, 20% $Pd(OH)_2/C$ or 10% $Pd/Al_2O_3$, $H_2$ (10 bar), 25 °C, 0.5 mL $min^{-1}$. [a]Concentration adjusted according to the type of substrate. [b]Obtained as a mixture of DCPs containing α-enaminone as a minor product (<10%, see ESI,† Table S1).

It is noteworthy that despite the 10 bar system pressure, the deprotection of benzylamines in DCPs **1d** and **1e** was not observed. This selectivity for the hydrogenation of the enone may be due to the short residence time (7.8 s). In most cases, amine elimination with formation of α-enaminone was not observed when arylamine-DCPs were employed. The small extent of elimination observed for **2a** explains the sensitivity of these compounds to temperature (40 °C) during solvent evaporation. In the case of alkyl amines (**2e**–**2g**), we observed the elimination to enaminones **3** to some extent, most pronounced in the case of piperidine DCP **1g**, which afforded solely the α-enaminone product **3g**.

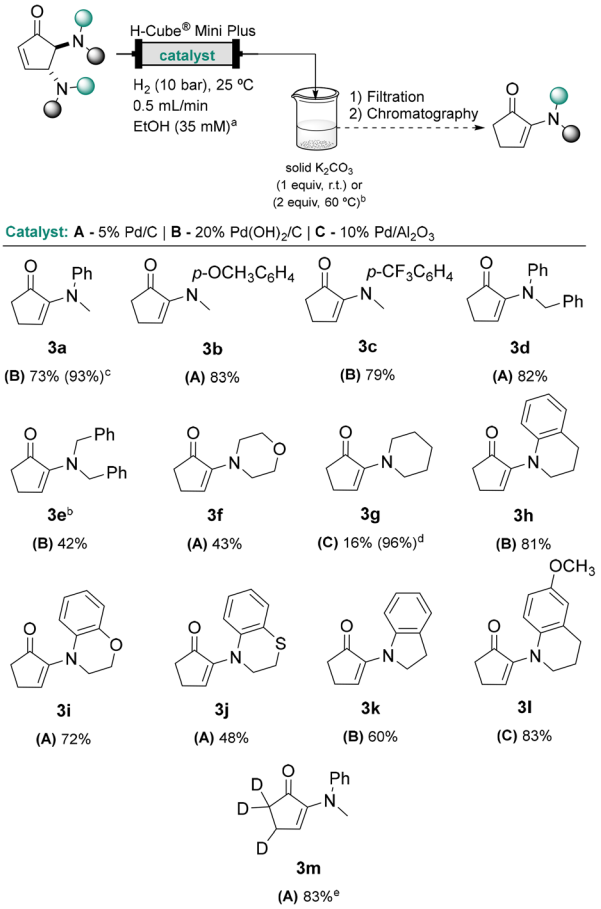
To better understand the α-enaminone product **3a** formation, the stability of cyclopentanone form **2a** was initially assessed by exposing the reaction crude mixture to different deuterated solvents (see ESI,† Fig. S2) and additives with acidic or basic properties (see ESI,† Fig. S3 and S4). The studies suggested that β-amine elimination was inhibited under slightly acidic conditions (*i.e.* in non-neutralized $CDCl_3$ and with $NaH_2PO_4$). On the other hand, a base catalysed elimination of the amine in the presence of $K_2CO_3$ and possibility of an autocatalytic mechanism by *N*-methyl aniline were observed.

### Continuous flow hydrogenation of DCPs using an H-Cube® Mini Plus for the selective formation of α-enaminones 3

Based on these results, we envisioned that a simple treatment of the crude reaction mixture, rich in cyclopentanone **2**, with $K_2CO_3$ would promote the elimination, therefore converting the cyclopentenones **1** to the corresponding α-enaminones **3**. We started the elimination studies by i) employing a sequential HPLC column filled with $K_2CO_3$ connected to the H-Cube® apparatus outlet; ii) stirring the output of the hydrogenation reaction with a $K_2CO_3$ saturated aqueous solution; iii) stirring with solid $K_2CO_3$ under heterogeneous conditions (see ESI,† section 6). The simple use of solid $K_2CO_3$ afforded the desired product in high yields and the base could be easily removed by filtration. By using this methodology, α-enaminone **3a** was obtained in 73% yield using 5% Pd/C, with the recovery of the free *N*-methyl aniline by column chromatography in neutral alumina (81% yield).

The scope of α-enaminones was extended to various DCPs by selecting the most appropriate palladium catalyst. The desired compounds were obtained in up to 83% isolated yield (Scheme 2). Despite most DCPs affording the desired product at room temperature, dibenzylamine cyclopentanone derivative **2e** was an exception, requiring higher temperatures (60 °C) and 2 equivalents of $K_2CO_3$ to yield 42% of **3e**.

A single cartridge of 5% Pd/C containing 150 mg of catalyst allowed full conversion in gram scale reaction using **1a** for the preparation of **3a**. To this end, solutions of DCP (200 mg, 35 mM) were fed to the reactor in a series of 4 sequential injections (each injection corresponds to an average of 310 reactor volumes). The yields were consistent in all cycles (see ESI,† Fig. S5 and Table S2) and overall, the




**Scheme 2** Scope of α-enaminones **3a**–**3m** obtained after basic treatment of the continuous flow hydrogenation crude mixture obtained using the corresponding Pd catalyst A, B or C. [a]Concentration adjusted according to the type of substrate (see ESI† for detailed information). [b]Obtained only by treatment with 2 equivalents of $K_2CO_3$ at 60 °C. [c]Isolated yield in gram scale reaction (**1g**). [d]Obtained directly from hydrogenation reaction, without requiring treatment with $K_2CO_3$; the yield without chromatographic purification is given in parentheses. [e]Obtained using $D_2O$ as a source of $D_2$ under reported conditions and followed by in acetone-$d_6$/$D_2O$ (1 : 1) and $K_2CO_3$ after 3 days.

desired α-enaminone was obtained in 93% isolated yield and a productivity of 1.7 g $L^{-1}$ $h^{-1}$. To further improve the metrics of the reaction, significantly more concentrated solutions (173 mM) were fed to the reactor in a series of 3 sequential injections which allowed the production of a similar amount of product with only a fraction of the solvent, equivalent to 231 reactor volumes (see ESI,† Fig. S6 and Table S3). The productivity was significantly increased at this concentration, achieving 53.6 g $L^{-1}$ $h^{-1}$, despite a decrease in yield to 76%.

The importance of labelling scaffolds with hydrogen isotopes, in conjunction with the ease of forming $D_2$ using the H-Cube® Mini Plus apparatus, led us to study the incorporation of deuterium in our cyclopentane scaffolds. Compounds labelled with hydrogen isotopes (*i.e.* deuterium and tritium) are of extreme utility in mechanistic, spectroscopic and tracer studies.[36] Isotope labelled compounds prove to have additional uses in medicinal

chemistry, such as slowing the metabolism of drug candidates.[37] The insertion of deuterium at $C_4$ and at enolizable $C_5$ positions was possible affording α-enaminone **3m** in 83% yield (Scheme 2 and ESI,† Scheme S3).

### Sequential continuous flow process by tandem hydrogenation/elimination

At this stage, α-enaminones were obtained from furfural in a stepwise manner. In order to avoid intermediate isolation and purification, we developed a sequential continuous flow process to obtain α-enaminones directly from furfural.

A previously described continuous flow system for the preparation of DCPs from furfural[38] was coupled with the herein described hydrogenation setup (see ESI,† Scheme S4). The sequential reaction was able to afford α-enaminone **3a** directly from furfural in 1 g $L^{-1}$ $h^{-1}$ productivity (Scheme 3).

Catalyst leaching measurement of Cu and Pd was conducted through ICP-AES analyses using the crude sample obtained from this flow process (see ESI,† section 10). The results indicated leaching of Cu in 679 ppm $mg^{-1}$ of sample, while the amount of Pd was below the limit of detection (<0.16 ppm for hydrogenation reaction). The amount of Cu detected in the sample was consistent with previous work,[38] although a simple washing of the crude sample with water after redissolution in EtOAc was enough to reduce the amount of Cu to 83.5 ppm $mg^{-1}$ of sample.

### Synthesis of ATP-sensitive potassium channel agonist 3n

To showcase the versatility of the method, a model ATP-sensitive potassium ($K_{ATP}$) channel agonist was selected as the target molecule. The active dehydro-benzoxazine α-enaminone scaffold has been previously reported, and the selected derivative exhibits $IC_{50}$ in the μM range.[9]

The original total synthesis of this compound comprises two steps from cyclopentanone, affording the desired α-enaminone **3n** in 50% global yield. Despite the straightforward process, the procedure requires harsh conditions and sensitive reagents.[9]

In order to improve the existing method in terms of sustainability and easier handling of materials, the synthesis of α-enaminone **3n** is proposed applying the described continuous flow process.

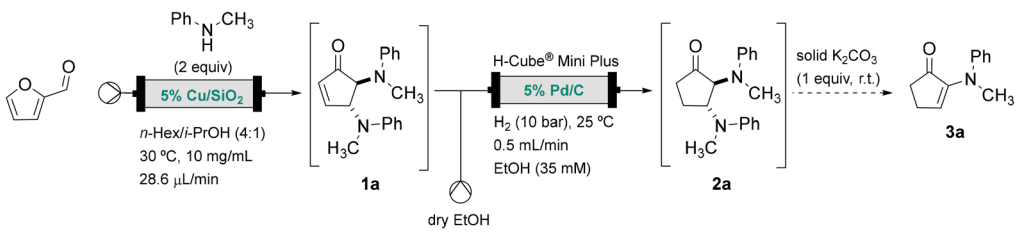
The hydrogenation conditions described above were employed to yield a different product than the expected. Preliminary characterization by $^1$H NMR and HRMS suggests the formation of an α-enaminone resulting from additional reduction of the aromatic nitro group (see ESI,† Scheme S5). Adjustment of the original conditions to 2 mL $min^{-1}$ flow rate and change to ACN/EtOH (1 : 1) to increase the substrate concentration inhibited the reduction of the nitro group, hence yielding the desired product **3n** in 71% yield from the corresponding cyclopentenone (Scheme 4).

This new approach overcomes price, raw material availability and sustainability limitations of the original total synthesis. The sustainability of the process was enhanced not only by the use of furfural but also by the implementation of a continuous flow process that allowed catalyst reuse. The increased safety and the use of milder conditions in all steps are also advantages.

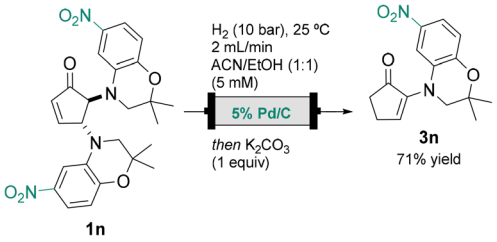
### Quantitative and qualitative green metrics of the process

We compared the quantitative and qualitative green metrics of the continuous flow hydrogenation/elimination of DCP **1a** and reported batch procedures in the preparation of α-enaminones according to the CHEM21 toolkit (Table 1).[39] The reported procedures were selected in a way to encompass current different approaches, including 1) an electrochemical procedure (method 1),[18] 2) a method using hydroxylamines as amine sources (method 2)[20] and 3) a procedure using $TEMPO^+$ $PF_6^-$ as an oxidant (method 3).[17] Since it was not possible to compare substrate **1a** to methods 2 and 3, the calculations were conducted with similar derivatives (*i.e. N*-benzylaniline for method 2 and 4-chloro-*N*-methylaniline for method 3). The yields and the "reaction mass efficiency (RME)" are comparable between the procedures, except for the hydroxylamine method that presents a low RME value. Regarding the "optimum efficiency (OE)", it is significantly better in the hydrogenation/elimination process. Although the "atom economy (AE)" is expectedly lower than that of the other procedures due to free amine elimination, the AE metric value is compensated by RME.

The "process mass intensity" (PMI) values were calculated taking into account the workup and chromatographic procedures whenever experimental information was available. The herein described method has a PMI value of 386, significantly lower than the value of 403 observed for method 3. It is noteworthy that methods 1–3 use commercially available cyclopentanone as the substrate, known to be




Scheme 3 Sequential continuous flow process for the direct synthesis of α-enaminone **3a** from furfural, integrating the *in situ* preparation of DCP **1a** and the herein described hydrogenation setup.




**Scheme 4** Synthesis of biologically active α-enaminone **3n** applying the presented continuous flow hydrogenation methodology.

prepared from furfural upon the Piancatelli rearrangement and hydrogenation.[40,41] Despite DCPs not being commercially available, they can be easily obtained in a single step from furfural in quantitative yields.[30] Nevertheless, the quantitative green metrics of the process starting from furfural were assessed (Table 1). For that, the synthesis of DCPs from furfural **1a**[30] was accounted in the overall process, including work-up and chromatographic solvents (see ESI,† Table S11). No significant changes were observed in the PMI value of 388.

The PMI values for comparison with methods 1 and 2 are given in parenthesis (Table 1). This is due to the lack of information concerning the chromatographic procedure of the reported methods. Thus, the PMI used for comparison was calculated after excluding the chromatographic solvents parameter. The PMI values of 56 and 61, respectively, are slightly higher than the corresponding values calculated for our method, including for the synthesis from furfural.

Qualitative analysis of the processes was performed based on the aforementioned toolkit, and to each criterion was attributed a colored flag concerning the sustainability of the process (Table 2). Despite these methodologies receiving a green flag for being catalytic and conducted at room temperature, only the new procedure receives a green flag for being performed under flow conditions. A single red flag is attributed to our method regarding the use of chromatographic purification, which is common to all methods. Concerning solvents, ethanol is considered a preferred solvent, conferring an advantage compared to methods 2 and 3 which were attributed with a red flag for using hazardous solvents. All the four methods used a critical element in the process. Nevertheless, a yellow flag is attributed to Pd, as well as to Cu and Sc used in method 2. Ag, Pt and Sb are considered very critical elements receiving a red flag.

In a global consideration, the described method is comparable to recent reported procedures in terms of quantitative metrics. Regarding qualitative measures, the most advantageous criterion is the use of continuous flow. A clear advantage of this method is the use of biomass feedstocks such as furfural and bioethanol which is in accordance with the 12 principles of green chemistry.

## NMR kinetic studies and DFT calculations for mechanism elucidation

To elucidate the elimination reaction mechanism, both quantitative $^1$H-NMR kinetics and computation studies were performed.

Firstly, the relevance of electronic effects of the aryl amine substituent on the elimination reaction was evaluated (see ESI,† section 13). To this end, competitive experiments were conducted using cyclopentanones **2a**, **2b** and **2c**. Stoichiometric mixtures of **2a**/**2b** and **2a**/**2c** were treated with $K_2CO_3$ and the profile of elimination was followed over time by $^1$H NMR experiments in $CDCl_3$ (see ESI,† Fig. S10 and S11). These results suggest a high dependence of the elimination reaction with the electronic character of the arylamine substituent. The order of stability is then proposed to be **2b** (OMe) > **2a** (H)> **2c** ($CF_3$).

Finally, quantitative $^1$H NMR kinetic experiments were performed to study the reaction kinetics (see ESI,† section 14). The elimination of cyclopentanone **2a** in the corresponding α-enaminone **3a** was assessed by $^1$H NMR experiments over time in methanol-$d_4$, promoted by $K_2CO_3$. A pseudo zero-order kinetics in solution was observed (see ESI,† Fig. S12 and S13).

To further understand the mechanism of the elimination reaction, density functional theory (DFT) calculations were performed at the ωB97X-D/Def2-TZVPP/PCM(SMD, ethanol)//B3LYP/6-31G(d) level of theory. Aniline-substituted cyclopentanones **2a**, **2b** and **2c** and bis-dimethylamino-cyclopentanone were selected as model substrates (see ESI,† section 15). Calculations suggest that the β-amine elimination reaction proceeds through the enolate intermediate *via* protonation by EtOH (solvent of the reaction, see ESI,† Fig. S14 and S15). Calculations also support that a second molecule of the substrate in its enol form could participate as a proton donor (see ESI,† Fig. S16), explaining the occurrence of the neat reaction.

The calculated activation barriers corroborate the observed competitive experiments where the elimination rate follows

**Table 1** Comparison of quantitative green metrics between the developed hydrogenation/elimination flow procedure and three reported procedures

| Metric | This work | This work, from furfural | Method 1 | Method 2 | Method 3 |
|---|---|---|---|---|---|
| Yield (%) | 76 | 76 | 79 | 71 | 62 |
| RME | 49 | 46 | 54 | 22 | 51 |
| OE | 76 | 50 | 55 | 34 | 52 |
| PMI | 386 (36[a]) | 388 (38[a]) | 56[a] | 61[a] | 403 (67[a]) |

[a] PMI values not counting chromatographic procedures. "Reaction mass efficiency (RME)" is the division of the product and reactant mass. "Optimum efficiency (OE)" is the ratio of RME and "atom economy (AE)".

**Table 2** Comparison of qualitative green metrics between the developed hydrogenation/elimination flow procedure and three reported procedures

| Criterion | *This work* | *Method 1* | *Method 2* | *Method 3* |
|---|---|---|---|---|
| Reactor | Flow | Batch | Batch | Batch |
| *T* (°C) | 25 | 26 | 25 | 25 |
| Workup | Filtration/evaporation/ chromatography | Evaporation/chromatography | Evaporation/chromatography | Filtration/evaporation/ chromatography |
| Solvent | EtOH | MeOH | ACN | DCE |
| Critical element | Pd | Pt | Cu, Sc | Ag, Sb |

Green flag represents "preferred". Yellow flag represents "acceptable". Red flag represents "undesirable".

the following trend: dialkylamine > aniline (*p*-$CF_3$ > H > *p*-OMe).

# Conclusions

A continuous flow approach is described for the stepwise synthesis of a series of previously inaccessible 2,3-diamino-cyclopentanones in high yield and selectivity through a tunable hydrogenation of 4,5-*trans*-diamino-cyclopent-2-enones under mild conditions. Studies on the stability of diamino cyclopentanones led to the development of a procedure to selectively obtain α-enaminones under basic conditions. Preparation of α-enaminones directly from biomass derived furfural was accomplished by a sequential continuous flow process that first yielded the corresponding diamino cyclopentenone followed by tandem hydrogenation/elimination. Incorporation of deuterium in high extent on the diamino cyclopentenone $C_4$ and $C_5$ was accomplished by employing deuterated water on the H-Cube® Mini Plus apparatus. The flow process was used to prepare a previously reported ATP-sensitive potassium channel agonist.

Mechanistic highlights revealed the influence of the electronic features of aniline substituents as well as a pseudo zero-order reaction kinetics in solution.

On a final note, this method is a new green methodology for the synthesis of α-enaminones. It encompasses several principles among the "12 Principles of Green Chemistry", by making use of biorenewable raw materials, avoiding the use of oxidants and additives, allowing catalyst reuse, and easy free amine recovery.

# Experimental

## Materials and methods

All solvents were of analytical grade and distilled prior to use. Unless otherwise stated, all reagents were used as received from commercial suppliers. Continuous flow hydrogenation reactions were conducted in an H-Cube® Mini Plus from ThalesNano® using ThalesNano CatCart® cartridge systems (30 mm L, 0.226 mL dead volume). NMR spectra were recorded in a Bruker Fourier 300 spectrometer. High resolution mass spectrometry (HRMS) results were recorded in a Thermo Scientific Q Exactive hybrid quadrupole-Orbitrap mass spectrometer (Thermo Scientific™ Q Exactive™ Plus). Infrared spectra were recorded in a Bruker Alpha II FT-IR spectrometer. Inductively coupled-plasma atomic emission spectroscopy (ICP-AES) analyses were carried out on a Horiba Jobin Yvon ULTIMA sequential ICP, using the Horiba Jobin Yvon ICP Analyst 5.4 software. A monochromator with a Czerny Turner spectrometer was used. The gas used was argon.

## Synthetic procedures

**General procedure for batch hydrogenation of DCP.** DCP **1** (1 equiv.) was dissolved in distilled EtOH (0.1 M) and placed in a Schlenk flask with 10% w/w Pd/C (0.2 equiv.). After purging with argon, the reaction was stirred at room temperature in the presence of $H_2$ (1 bar) for 30 min. The reaction mixture was filtered through celite, followed by several washes with EtOH and evaporation under reduced pressure at 40 °C. The specific hydrogenation of 4,5-*trans*-bis(methyl(phenyl)amino)cyclopent-2-en-1-one **1a** afforded a crude mixture (38.4 mg) containing *trans*-2,3-bis(methyl(phenyl)amino)cyclopentan-1-one **2a** and 2-(methyl(phenyl)amino)cyclopent-2-en-1-one **3a** which was analysed by NMR in $CDCl_3$. Cyclopentanone **2a** was obtained in 51% NMR yield with a selectivity of 65%. 2-(Methyl(phenyl)amino)cyclopent-2-en-1-one **3a** was obtained in 27% yield.

**General procedure for continuous flow hydrogenation of DCPs into cyclopentanones 2a–2l.** The hydrogenations were performed using a Thales Nano H-Cube® Mini Plus reactor equipped with a Thales Nano 30 mm CatCart® (5% Pd/C, 20% $Pd(OH)_2$/C or 10% $Pd/Al_2O_3$). Before each experiment, the catalysts were pre-treated for 10 min at full $H_2$ mode and 0.5 mL $min^{-1}$ pure solvent. Then, a 5–35 mM (concentration according to the substrate, see ESI† for detailed information) solution of DCP **1** in EtOH was passed through the cartridge at full $H_2$ mode (10 bar) and 0.5 mL $min^{-1}$ flow rate at 25 °C. The ethanolic solution was evaporated under reduced pressure at 30 °C in the presence of $Na_2HPO_4{\cdot}2H_2O$ (0.5 equiv.) as an additive, which was further removed by filtration. The crude reaction mixtures, containing cyclopentanone **2** or a mixture of cyclopentanone **2** and α-enaminone **3**, were analysed by NMR in $CDCl_3$.

**General procedure for continuous flow hydrogenation of DCPs into α-enaminones 3a–3l.** The hydrogenations were performed using a Thales Nano H-Cube® Mini Plus reactor equipped with a Thales Nano 30 mm CatCart®. The appropriate cartridge was selected from the previous hydrogenation reaction results (see ESI†). Before each experiment, the catalysts were pre-treated for 10 min at full $H_2$ mode and 0.5 mL $min^{-1}$ pure solvent. Then, a 5–35 mM (concentration adjustments according to the substrate, see ESI† for detailed information) solution of DCP **1** in EtOH was passed through the cartridge at full $H_2$ mode (10 bar) and 0.5 mL $min^{-1}$ flow rate at 25 °C. The reaction solution was collected in a flask containing

solid $K_2CO_3$ (1 equiv., unless otherwise specified) with constant stirring for 40 minutes at room temperature. After filtration through a cotton pipette, EtOH was evaporated under reduced pressure at 40 °C and the crude mixture was analysed by $^1$H NMR in $CDCl_3$. The crude mixture was redissolved in DCM (1 mL) and a second filtration was performed, followed by evaporation and crude analysis by $^1$H NMR in $CDCl_3$. α-Enaminones were obtained upon purification by column chromatography in neutral alumina (*n*-hexane/EtOAc – 9 : 1).

**Optimized general procedure for continuous flow hydrogenation of DCP 1a into α-enaminone 3a.** The hydrogenation was performed using a Thales Nano H-Cube® Mini Plus reactor equipped with a 20% $Pd(OH)_2$/C Thales Nano 30 mm CatCart®. Before the experiment, the catalyst was pre-treated for 10 min at full $H_2$ mode and 0.5 mL min$^{-1}$ pure solvent. Then, a 35 mM solution of DCP **1a** in EtOH was passed through the cartridge at full $H_2$ mode (10 bar) and 0.5 mL min$^{-1}$ flow rate at 25 °C. The reaction solution was collected into a flask containing solid $K_2CO_3$ (1 equiv.) with constant stirring for 40 minutes at room temperature. After filtration through a cotton pipette, EtOH was evaporated under reduced pressure at 40 °C and the crude mixture was analysed by $^1$H NMR in $CDCl_3$. The crude mixture was further purified by column chromatography in neutral alumina (*n*-hexane/EtOAc – 9 : 1). α-Enaminone **3a** was obtained as a yellow oil (9 mg, 65% yield). *N*-Methyl aniline was recovered (6.8 mg, 81% yield).

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

The authors acknowledge the Fundação para a Ciência e Tecnologia (FCT) for financial support (PD/BD/143127/2019, PTDC/QUI-QOR/32008/2017, UIDB/04138/2020, UIDP/04138/2020 UIDB/00100/2020, UIDP/00100/2020 and LA/P/0056/2020). J. A. S. C. thanks the FCT for Scientific Employment Stimulus 2020/02383/CEECIND. The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 951996. The NMR spectrometers are part of the National NMR Network (PTNMR) partially supported by Infrastructure Project No. 022161 (co-financed by FEDER through COMPETE 2020, POCI and PORL and FCT through PIDDAC).

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