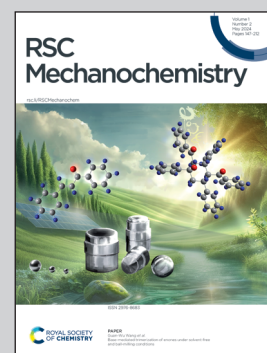


Showcasing research from Dr Jean-Marc Sotiropoulos, IPREM-CNRS, France and Dr Michel Baltas, Laboratoire de Chimie de Coordination du CNRS, France.

Unprecedented linear products by a mechanochemically activated Biginelli reaction using lawsone

Here, we present our findings regarding the unique outcome of a Biginelli MCR involving lawsone, benzaldehydes, and ureas under mechanochemical conditions. The study describes the unprecedented high-yield formation, isolation, characterization and X-Ray determination of a three-component non-cyclized Biginelli-linear compounds. They are assumed to be the last intermediate before cyclisation in the classical Biginelli reaction affording dihydropyrimidones (DHPMs) that were never observed under mechanochemical conditions. The theoretical DFT study supported the experimental results. Further research involving in this reaction can pave the way for the elaboration of new important building blocks.

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Unprecedented linear products by a mechanochemically activated Biginelli reaction using lawsone†

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The Biginelli reaction, a crucial multicomponent reaction, was investigated involving 2-hydroxy-1,4-naphthoquinone (lawsone), *p*-substituted benzaldehydes, and ureas. Surprisingly, the classic Biginelli cyclized DHPM was not observed under various experimental conditions. Mechanochemical conditions, unlike traditional liquid phase conditions, led to the unprecedented formation of a series of 'Biginelli-linear' lawsone derivatives with high yields. The observed outcomes were consistent with DFT theoretical predictions, highlighting the preference for the Michael adduct under liquid conditions and the energetically implausible cyclization pathway for the classic DHPM compound. Additionally, the study achieved the novel cyclization of a 'Biginelli-linear' lawsone derivative into a cyclic carbamate for the first time.

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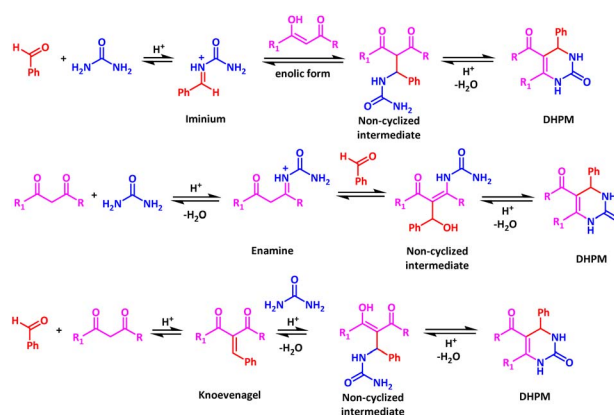
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Introduction

Multicomponent reactions (MCRs) are defined as those employing three or more reagents in a one-pot reaction to form a single product that essentially contains all the reactants.^{1–4} Due to the simple experimental procedures and one-pot character the MCRs have become excellent tools for the elaboration of libraries of small (essentially heterocyclic) derivatives. In the past decades, several novel and old MCRs have been further developed and nowadays they are widely used in natural product synthesis and drug discovery.^{5–8}

Biginelli reaction is a classic amongst the MCRs. Discovered in 1893, this reaction results in the condensation of three components: a β -ketoester, a urea, and an aldehyde to form the 4-aryl-3,4-dihydropyrimidin-2(1*H*)-one (DHPM). This one-pot multicomponent reaction stands out due to the pharmacological functionality of the produced dihydropyrimidine derivatives,⁹ showcasing notable biological activities including anticancer,¹⁰ antimalarial,¹¹ anti-HIV agents¹² and others.^{13,14} In the last few decades, different variations of the experimental conditions have been proposed for the Biginelli reaction: use of Brønsted or Lewis acid catalysts,¹⁵ ionic

liquids,¹⁶ or excess of one reactant.^{17,18} After extensive efforts by many groups based on computational studies involving β -ketoesters, urea, and benzaldehyde, three mechanisms with many different intermediates are proposed for the classical Biginelli reaction (Scheme 1): (i) the so-called iminium route,¹⁹ implying first condensation of the aldehyde and urea to form a C–N iminium bond, followed by nucleophilic addition of the β -ketoester; (ii) the so-called enamine route,²⁰ implying first reaction of the urea and β -ketoester to form an enamine C–N bond, which consecutively reacts with the aldehyde and (iii) mechanism based on the synthesis of the Knoevenagel intermediate²¹ where first the aldehyde and the β -ketoester form a C–C bond before reacting with urea (Scheme 1).



Scheme 1 Three proposed mechanisms for the Biginelli reaction.

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In 2015, Puripat *et al.*²² after using an Artificial Force Induced Reaction (AFIR) calculation scheme concluded that: (1) a second urea molecule can be beneficial in catalysing nearly every step of the reaction; (2) the substitution pattern on the aryl ring of the aldehyde has little influence on the reaction, and (3) the rate determining step (RDS) is the C–N bond formation during the final intramolecular cyclisation step for mechanisms (i) and (ii), and the C–O bond cleavage during the Knoevenagel reaction of the proposed mechanism (iii). The authors concluded that, while these three mechanisms remain the major ones, one could modify the RDS by varying the substitution patterns of the reactants and the acid catalysts.

Similar to most MCRs, the Biginelli reaction is well-suited for the principles of “green chemistry”.^{23–25} Mal *et al.*²⁶ reported the first solvent-free ball-milling Biginelli reaction between the classical ethyl-acetoacetate, urea and substituted benzaldehydes. Very recently, Bolm *et al.* reported the synthesis of cyclic 2,3-dihydro-1,2,6-thiadiazine-1-oxides when NH-free sulfonimidamides react with ethyl acetoacetate and benzaldehydes under mechanochemical conditions.²⁷

The interesting natural product lawsone (2-hydroxy-1,4-naphthoquinone) is unprecedented as a substrate in the Biginelli reaction. In addition, lawsone is an important scaffold in many biologically active compounds and drugs. For example, atovaquone is reported to be a leading drug targeting specifically the mitochondrion of *P. falciparum* parasite. Many research groups are studying the reactivity of lawsone and potential modifications of atovaquone that could lead to compounds overcoming the strong resistance of *Plasmodium* to this drug.²⁸ In this field, we have recently reported a domino reaction between lawsone, aldehydes and isocyanides, affording naphthofuroquinones and naphtho-enaminodiones under microwave irradiation. These new series of molecules exhibited interesting activities against both parasites *P. falciparum* and *L. donovani*.²⁹

One of the main goals in the area of organic synthesis oriented towards biologically active compounds is the research and development of environmentally safe methods in terms of efficiency, waste management and energy input, issues now addressed and termed “Green Chemistry”.³⁰ Mechanochemistry fulfils this portfolio. According to IUPAC, a mechanochemical reaction is a “Chemical reaction that is induced by the direct absorption of mechanical energy”. Mechanochemistry for organic compounds started to be developed after the pioneering work reported by Toda in the 1980s³¹ and Kaupp.³² Mechanochemical synthesis has emerged as an efficient approach applicable in different fields,³³ and particularly for biologically active molecules. This rapidly increasing field includes nowadays preparation of biologically active compounds,^{34,35} of Active Pharmaceutical Ingredients (APIs),³⁶ cocrystals and many other aspects that can be entitled “medicinal mechanochemistry”.³⁷

Here, we wish to share our discoveries regarding the unique outcome of a Biginelli MCR involving lawsone, diverse benzaldehydes, and ureas under mechanochemical conditions. Our investigation outlines the unprecedented formation of a “Biginelli-type” reaction resulting in non-cyclized three-component products, termed here ‘Biginelli-linear’.

Results and discussion

To set up efficient conditions, lawsone (**4**) was reacted with 4-chlorobenzaldehyde (**5**) and urea (**6**) under conventional conditions in common solvents, then in ionic liquids (ILs) and deep eutectic solvents (DES). Next, the reaction was explored by using microwave irradiation and mechanochemical activation. The expected cyclized DHPM Biginelli product was not observed under any of the above conditions. Instead, compound **7** (Biginelli-linear) and the Michael adduct **8** were exclusively observed. The results of the optimization of the reaction conditions are summarized in Table 1.

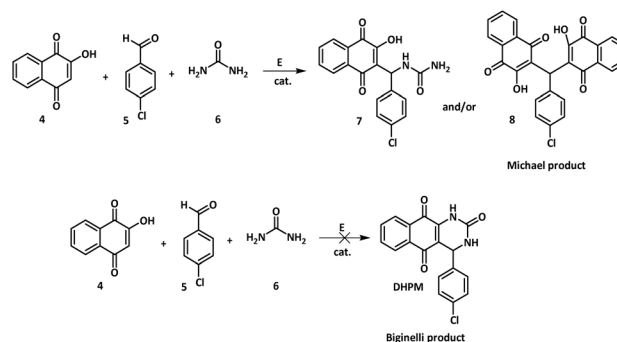
Our initial efforts were focused on the conventional synthetic protocols according to literature procedures reported previously. When the reaction was carried out in EtOH catalysed by 5 mol% Zn(OAc)₂ at r.t. overnight, in contrast to the results published by Patel,³⁸ only the Michael adduct **8** (entry 1, Table 1) was obtained as a major product in 45% yield after purification (4-Cl-benzaldehyde conversion: 50%).

Surprisingly, no traces of any compound integrating all three Biginelli reactants (DHPM or **7**) were found in the crude reaction mixture analysed by ¹H NMR and mass spectrometry. The reaction between 2 eq. of lawsone and 1 eq. of 4-chlorobenzaldehyde under the same reaction conditions (entry 3, Table 1) expectedly afforded the Michael adduct **8**. Under refluxing conditions in EtOH and catalysed by 10 mol% hypophosphorous acid³⁹ the three-component reaction led to a mixture which upon purification afforded **8** in 15% yield and compound **7** in 35% yield (entry 4, Table 1). Again, no Biginelli-cyclized compound DHPM was observed.

Faced with these surprising results, we turned to ionic liquids (ILs) and deep eutectic solvents (DESS), as multicomponent Biginelli reactions have also been reported in such a medium. Among various possible ionic liquids, the home-made 1-methyl-2-pyrrolidonium hydrogen sulfate {[HNMP] HSO₄} and the commercially available 1-butyl-3-methylimidazolium bis (trifluoro-methanesulfonyl) imide {BMIM-NTF₂} were chosen.^{40,41} Reactions in these ILs, frequently used in the literature for a classical Biginelli reaction (entries 5 and 6, Table 1), did not afford any Biginelli-type compound. Instead, the Michael adduct **8** was found to be the major product, obtained in 46–47% yield in both cases. Two DES media were also selected and prepared according to literature procedures. When the reaction was carried out in choline chloride/urea,⁴² the linear Biginelli-type compound **7** was obtained along with compound **8** in 20% and 30% yields respectively (entry 7, Table 1). When choline chloride/chloroacetic acid was used as DES (entry 8, Table 1),⁴³ only compound **8** was obtained in 35% yield. The reaction was also tested under microwave irradiation (two examples presented in entries 9 and 10, Table 1) but disappointingly no meaningful reaction occurred as there was only 2% and 8% of aldehyde conversion and only traces (entry 9, Table 1) and <5% (entry 10, Table 1) of compound **7** were detected. Many modifications of the reaction conditions, including the catalyst variation (CH₃COOH, *p*-TSA, H₃PO₂), the reaction time and solvent (EtOH, CH₃CN, IL), failed



Table 1 Study of the Biginelli-type reaction between lawsone, urea and 4-chlorobenzaldehyde



Entry	Activation/catalyst/temperature	Eq. 4/6/5	Reaction time	Conversion 5 (%)	Yield 7 (%)	Yield 8 (%)
1	EtOH/5% Zn(OAc) ₂	1 : 1 : 1	15 h	50	—	45
2	EtOH/20% <i>p</i> TSA	1 : 1 : 1	15 h	50	Trace	41
3	EtOH/5% Zn(OAc) ₂	2 : 1 : 0	15 h	70	—	55
4	EtOH (reflux)/10% H ₃ PO ₂	1.2 : 1.2 : 1	15 h	50	35	15
5	[HNMP]HSO ₄ (80 °C)	1 : 1 : 1	120 min	60	Trace	47
6	BMIM·NTF ₂ (80 °C)	1 : 1 : 1	300 min	84	Trace	46
7	Choline chloride/urea (80 °C)	1 : 2 : 1	60 min	40	20	30
8	Choline chloride/chloro-acetic acid (70 °C)	1 : 1 : 1	60 min	35	—	30
9	μw-irradiation EtOH/10% H ₃ PO ₂	1.2 : 1.2 : 1	120 min	2	Trace	—
10	μw-irradiation CH ₃ CN/20% <i>p</i> TSA	1 : 1 : 1.1	60 min	8	5	—
11	MM400 (30 Hz)/10% H ₃ PO ₂	1 : 1 : 1	2 × 40 min	50	30	—
12	MM400 (30 Hz)/20% <i>p</i> TSA	1 : 1 : 1	2 × 40 min	50	45	—
13	MM400 (30 Hz)/20% <i>p</i> TSA	1 : 1.5 : 1	2 × 40 min	70	55	—
14	P7 (800 rpm)/20% <i>p</i> TSA	1 : 1.5 : 1	2 × 40 min	95	90	—
15	P7 (800 rpm)/20% <i>p</i> TSA	2 : 1 : 0	2 × 40 min	95	—	91

to improve the reaction, all leading to compound 7 at a maximum of 5% yield.

Finally, the reaction was performed under mechanochemical activation. When operating an equimolar mixture of all three components with 10% of H₃PO₂ as the catalyst in a vibrator ball mill (MM400) working at frequency 30 Hz, for 2 successive runs of 40 min each, compound 7 was obtained in 30% yield, along with the non-reacted starting material (entry 11, Table 1). Modification of the catalyst to *p*-TSA (20%)⁴⁴ or increase of the urea amount (1.5 equiv. instead of 1 equiv.) afforded compound 7 in 55% or 45% yield respectively (entries 12 and 13, Table 1) which was obtained by precipitation in a mixture of dichloromethane/diethyl ether (1 : 2). Gratifyingly, when operating with the planetary ball mill Pulverisette 7 (P7), and under the same conditions (entry 14, Table 1), compound 7 was obtained with an excellent 90% yield. Noteworthy, compound 7 was conveniently obtained by a simple wash with water to remove the urea excess and the catalyst. Surprisingly, under mechanochemical activation, the Michael adduct 8 was not formed, and the linear Biginelli-type compound 7 was in all cases the unique product of the multicomponent reaction. This result was further investigated by two additional experiments. The three-component reaction in solution (entry 2, Table 1) afforded only the Michael adduct 8 with 41% yield. The reaction between 2 eq. of lawsone and 1 eq. of 4-chlorobenzaldehyde

under mechanochemical activation (entry 15, Table 1) afforded the Michael adduct 8 with an excellent 91% yield.

Scope of the mechanochemical activation when using different aldehydes and ureas

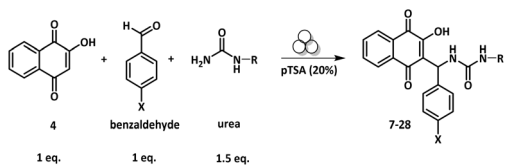
Having in hand the optimal reaction conditions to obtain compound 7 in high yield (entry 12, Table 1), we explored the substrate scope of this reaction, by modifying the *para*-benzaldehyde substituent and by using *N*-mono substituted urea derivatives. The results are summarized in Table 2.

All reactions were conducted in a P7 planetary ball mill (the number of runs was studied and optimized for each reaction) catalysed by 20 mol% *p*TSA, while the ratio of the three reactants was lawsone/urea/aldehyde 1 : 1.5 : 1.

First, *N*-ethylurea was chosen to undergo the reaction with lawsone and various *para*-substituted benzaldehydes (entries 2–8, Table 2). In all cases where the benzaldehyde was substituted by a halogen atom (entries 2–5, Table 2) or a methyl group (entry 8, Table 2), the non-cyclized target products 9, 10, 11, 12 and 15 were obtained in a good range of 62–70% yields.

When using electron withdrawing *p*-nitrobenzaldehyde or *p*-trifluoromethylbenzaldehyde, the yields of the expected products 13 and 14 rose up to 85–90% (entries 6 and 7, respectively, Table 2). For all cases studied, no side-products were observed and the selectivity of the reaction to provide the Biginelli-linear



Table 2 Substrate scope of the reaction between lawsone, (alkyl)ureas and *para*-substituted benzaldehydes


Entry	Compound	X	R	Yield ^a (%)
1	7	Cl	H	90
2	9	F	Et	63
3	10	Cl	Et	62
4	11	Br	Et	70
5	12	I	Et	70
6	13	NO ₂	Et	85
7	14	CF ₃	Et	90
8	15	CH ₃	Et	70
9	16	F	<i>n</i> -Bu	81
10	17	Cl	<i>n</i> -Bu	85
11	18	Br	<i>n</i> -Bu	95
12	19	NO ₂	<i>n</i> -Bu	90
13	20	CF ₃	<i>n</i> -Bu	80
14	21	F	CH ₂ C≡CH	83
15	22	Cl	CH ₂ C≡CH	73
16	23	Br	CH ₂ C≡CH	88
17	24	NO ₂	CH ₂ C≡CH	70
18	25	CF ₃	CH ₂ C≡CH	82
19	26	Cl	(CH ₂) ₂ OH	80
20	27	NO ₂	(CH ₂) ₂ OH	82
21	28	CF ₃	(CH ₂) ₂ OH	80

^a Isolated yield after filtration and isolation of the target product.

derivative was over 97%. The target products were conveniently isolated from the reaction mixtures as powders, by simply washing with water and crystallizing in the minimum volume of dichloromethane/diethyl ether. No column chromatography was used for purifications of any reaction mixture mentioned herein.

When *N*-ethylurea was changed to *N*-butylurea the conversion of both starting materials in deficit (benzaldehyde and lawsone) was complete under the same mechanochemical conditions. All target compounds **16**, **17**, **18**, **19** and **20** (entries 9–13, Table 2) were obtained with excellent yields ranging from 80 to 95%. Analogous to *N*-ethylurea, a unique major product was obtained, and no side-products were formed. Similar results were obtained with *N*-propargylurea affording compounds **21–25** with yields in the range of 73–88% (entries 14–18, Table 2). Finally, 2-hydroxyethylurea was also chosen to undergo this three-component reaction. The expected products **26–28** were obtained in 80–82% yield, whatever the benzaldehyde substituent was, –Cl, –NO₂ or –CF₃ (entries 19–20, Table 2). Together, a series of 20 Biginelli-linear derivatives were obtained in isolated yields varying between a good value of 62% and an excellent value of 95%. While there are no other side products and the aldehyde conversion is complete, the discrepancies in yields might result from the solubility

differences of the formed compounds in the mixture of organic solvents used during the crystallization process.

Among all compounds, **22** was crystallized and used for X-ray diffraction analysis also confirming our structure proposal. Crystallization was achieved in the solvent mixture of dichloromethane/methanol (3 : 1). The obtained single crystals appeared as yellow platelets.

The compound exhibited a triclinic $P\bar{1}$ space group (find crystallographic data in the ESI†) under Mo-K α radiation ($\lambda = 0.71073$ Å). Inspection of the structure exhibited dihedral angles of 19.7° for O₃/O₂/C₃/C₁₁, of 9.2° for C₂/C₃/C₁₁/N₁, of 83.6° for C₄/C₃/C₁₁/N₁ and of 79.5° for C₃/C₁₁/N₁/C₁₂, indicating that none of the three pi system components of the molecule (urea, naphthoquinone and 4-chlorophenyl rings) share coplanarity. All hydrogen bonds N₁–H₁, N₂–H₂, O₃–H₃ and C₁₁–H₁₁ had consistent values. Finally, it's noteworthy to highlight the significance of the very long distance between the atoms N₂–C₂ ($d = 5.3$ Å) and N₂–O₃ ($d = 5.8$ Å) for assessing any potential interactions that might favor the formation of the cyclized Biginelli DHPM (Fig. 1). Considering all experimental data, we conclude that when reacting under mechanochemical conditions, lawsone with aryl aldehydes and ureas, the unique 'Biginelli-linear' compounds containing all three starting reagents were obtained in good to excellent yields. To the best of our knowledge, this is the first time that a linear Biginelli compound is isolated. Considering the three routes proposed for a classical Biginelli reaction (Scheme 1), two of them, namely the iminium and the Knoevenagel ones, go through a Biginelli-linear intermediate before cyclizing.

Without having the aim to undergo an extensive theoretical study concerning all possible mechanisms and potential intermediates that could be in equilibrium, we envisaged to consider only the fact that we obtain either starting compounds, either the Michael adduct or the Biginelli-linear derivative.

In that respect, in order to compare our findings regarding Michael adduct vs. Biginelli-linear we considered the reaction mechanism starting from the addition of lawsone to the aldehyde.

A preliminary modelling in the gas phase, using the B3LYP functional coupled with a 6-31+G(d,p) Gaussian basis set and

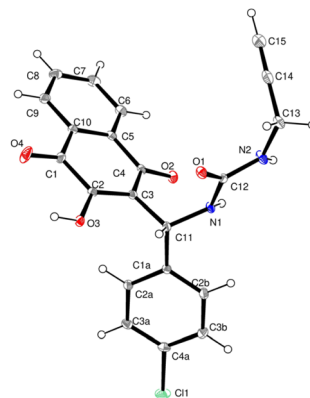
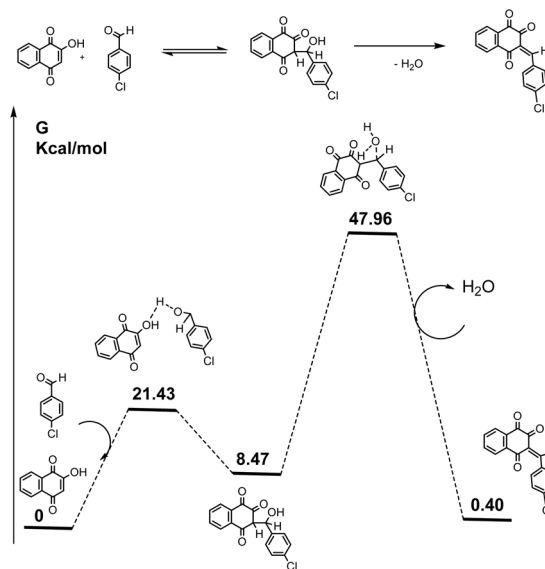


Fig. 1 X-ray structure of compound **22**.

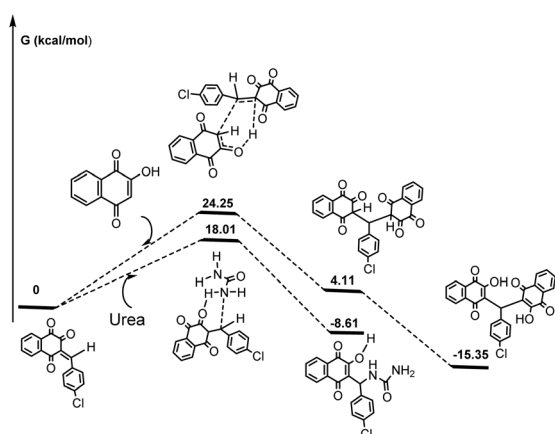




Scheme 2 Calculation of the Knoevenagel intermediate pathway (B3LYP/6-31+G(d,p) D3).

accounting for dispersion (D3), when using *p*-chlorobenzaldehyde, revealed the energy profile shown in Scheme 2. The nucleophilic attack of lawsone to the carbonyl group of the aldehyde, led to the formation of an initial adduct with rapid kinetics. Specifically, the calculated activation energy for the intermediate formation was 21.43 kcal mol⁻¹, while the energy level of the intermediate is situated at 8.47 kcal mol⁻¹. At this stage, a slower elimination of a water molecule with an energy barrier of 47.96 kcal mol⁻¹ and an energy difference from the first intermediate of 39.49 kcal mol⁻¹, can lead to formation of the Knoevenagel intermediate.

Two pathways emerged starting from the Knoevenagel intermediate (Scheme 3). The first one involved a Michael addition between the Knoevenagel intermediate and lawsone, with an activation energy of 24.25 kcal mol⁻¹. This resulted in the formation of a significantly stable enolic derivative through



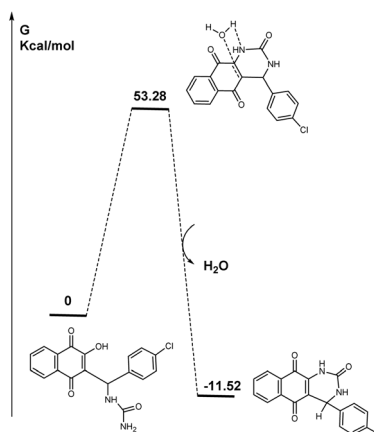
Scheme 3 Calculation of the Michael and urea addition pathways (B3LYP/6-31+G(d,p) D3).

a keto form. This process represented the driving force of this step. Next, we looked on the reaction coordinates when a urea was present along with the Knoevenagel intermediate, leading to the formation of a three-component Biginelli-linear adduct. This reaction exhibited a more favorable energy profile compared to the previous Michael one. Its activation energy was at least 6.24 kcal lower than that leading to the Michael adduct (Scheme 3).

In addition, the Michael triketone derivative was energetically less favorable than the final linear adduct by 12.72 kcal. It is the dienolic form of the Michael adduct that can be extremely stable, this presumably mostly occurring under protic conditions.

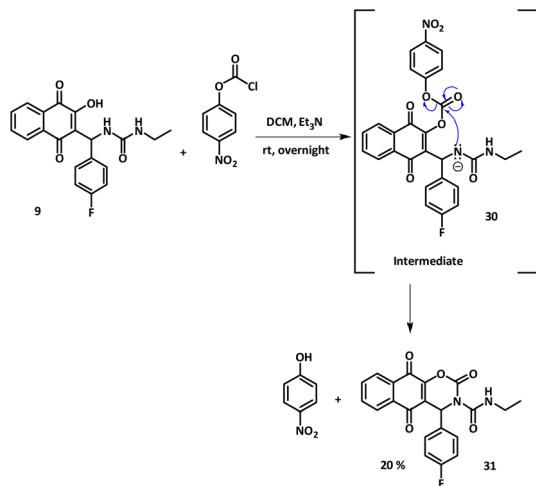
It should be noted that calculations considering ethanol as the solvent (solvent effects were taken into account using the conductor-like polarizable continuum model (CPCM)) did not modify in a significant manner both barriers leading to a Michael adduct (around 25 kcal mol⁻¹) and to a Biginelli-linear derivative (around 20 kcal mol⁻¹). This could be probably more pronounced when using catalysts like Zn(OAc)₂, ILs or DES (choline chloride/chloroacetic acid) leading more favourably to the Michael adduct, than when using H₃PO₂ which was a weak monobasic acid or DES choline chloride/urea where the Biginelli linear compound can also be obtained. We believe that these findings were in complete agreement with our experimental results and the consequent observations.

Finally, concerning the cyclization impossibility for the DHPM obtention in the solid-state reaction, it is interesting to note two points. The first one relates to the activation energy required to cyclize the compound. In fact, it is necessary to overcome a barrier of 53.28 kcal mol⁻¹, which was not at all favourable. The second point concerns the structure. In fact, the calculated structure aligns with the resulting structure obtained from X-ray resolution. Here, we have a geometric structure where the “amido” part is positioned opposite to the carbon it is supposed to attack. As a result, even if we can consider that by mechanochemical friction we can transfer energy to the Biginelli-linear derivative, the amount is not sufficient for the cyclization process to take place even if the cyclized structure is thermodynamically favoured (-11.52 kcal mol⁻¹) (Scheme 4).

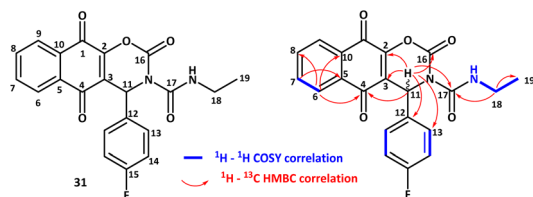


Scheme 4 Cyclization pathway (B3LYP/6-31+G(d,p) D3).





Scheme 5 Cyclization attempt for compound 9.

Scheme 6 ^1H and ^{13}C NMR data assignments of compound 31 in CDCl_3 at 298 K.

Interestingly, protons H_a -18 and H_b -18 appeared as diastereotopic because of structure rigidity and they exhibited coupling with both neighbouring CH_3 , and NH . The ^{13}C resonance data revealed 19 signals in total for each type of carbon, permitting the non-ambiguous structural identification of 31. Among them, the signals at 176.3 and 180.9 ppm were attributed to the two carbonyl groups of the naphthoquinone system while the urea carbon C-17 resonated at 151.3 ppm and the newly formed carbamate carbonyl C-16 signal appeared at 148.5 ppm. Finally, the ^{13}C - ^1H HMBC experiment allowed the identification of all long-range couplings between protons and carbons: the most important ones are depicted in Scheme 6. In addition, the fact that H-11 was correlated with all carbons C-2, C-3, C-4, C-16, C-12, C-13, C-14 and C-17 and that H-11 and C-11 chemical shifts were found dislocated compared to the starting compound 9 confirmed that the cyclization occurred, leading to the formation of a stable carbamate ring.

Conclusion

Our investigation focused on the three-component Biginelli-type reaction utilizing the 2-hydroxy-1,4-naphthoquinone compound (lawsone) 4 as the active methylene system in conjunction with aryl aldehydes and ureas. Notably, classical Biginelli cyclized DHPM was consistently elusive under all explored experimental conditions. While “liquid conditions,” particularly under weak acid catalysis, predominantly yielded the Michael adduct, successful isolation of ‘Biginelli-linear’ derivatives was achieved

under mechanochemical conditions with good to excellent yields. This marks the first instance where a three-component Biginelli reaction resulted in Biginelli-type linear adducts, assumed to be intermediates in the classical reaction rather than cyclized DHPMs. All attempts to cyclize the latter Biginelli-linear compound in a final step proved unsuccessful, aligning with both experimental and theoretical results highlighting the energetically improbable pathway for final cyclization. The formation of Biginelli-linear products is attributed to the iminium and/or Knoevenagel mechanisms.

Remarkably, we achieved the novel cyclization of a Biginelli-linear derivative into a cyclic carbamate, presenting an innovative development. We believe that our findings have opened new and promising perspectives.

Perspectives

Under the reaction conditions examined here, two out of three classical Biginelli mechanisms are apparently operating with the lawsone reagent. In future work it is important to explore ways to selectively conduce the reaction through the enamine-mechanism. It is noteworthy to point out the work of Cook and Clemmer⁴⁷ concerning a microdroplet-accelerated Biginelli reaction providing evidence for two competing pathways, the enamine and the Knoevenagel one. The scope of the carbamate cyclisation reaction is underway in order to find the optimal conditions and the scope of the Biginelli-linear derivatives that can efficiently undergo cyclization. Finally, the outcome of this multicomponent reaction with other cyclic β -dicarbonyl systems (dimedone, syncarpic acid...) will be investigated.

Data availability

Data for the crystal structure reported in this paper have been deposited at the Cambridge Crystallographic Centre (CCDC) under the deposition 2268819. All other data supporting the findings of this study, including experimental procedures, characterization of compounds and computational data are available within the paper and its ESI files.†

Author contributions

C. L. K. performed all experiments and analysed data, prepared the experimental part of the ESI file and was implicated in all draft changes. C. B. supervised all 2D NMR analyses. L. V. performed the X-ray structure and analysis. A. R. was implicated for initial discussions on the project and for draft ameliorations. P. C. performed the computational study. J. M. S. performed the computational data, wrote the computational part of the manuscript and prepared the corresponding ESI. M. B. conceived, led the project, analysed all data and prepared the final draft along with C. L. K. and J. M. S. All authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.



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