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First mechanosynthesis of piperlotines A, C, and derivatives through solvent-free Horner–Wadsworth–Emmons reaction

Oscar Abelardo Ramírez-Marroquín[a], Flavio Manzano-Pérez[a], Adolfo López-Torres[a], Alejandro Hernández-López[b], Abimelek Cortés-Pacheco[a], and Miguel Angel Reyes-González[c]

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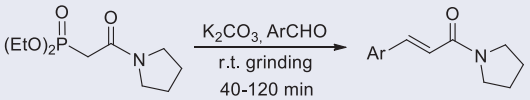
ABSTRACT

Piperlotines are natural products characterized by an α,β-unsaturated amide moiety. These compounds found wide applications in Medicinal Chemistry like antibacterials, cytotoxic agents, anticoagulants, among others. To date, diverse methods of synthesis have been reported for piperlotines, but involving the use of catalysts, hazard reagents, anhydrous media or coupling reagents. Thus, in this work, we developed a greener method of synthesis of piperlotines A, C, and derivatives, through mechanochemical activation under solvent-free conditions. The reaction of a β-amidophosphonate, K_2CO_3, and an aromatic aldehyde afforded target compounds in moderate to good yields (46–77%), in an open atmosphere by grinding. It is worth to mention that this mechanochemical process was under thermodynamic control because just *E* isomer was isolated for every reaction. Moreover, synthesized piperlotines have been predicted by means of chemoinformatic analysis as potential therapeutic agents for the treatment of arthritis or cancer.

GRAPHICAL ABSTRACT



Solvent-free and open atmosphere HWE reaction

8 examples (3 natural products)
Only *E* isomer isolated

ARTICLE HISTORY
Received 31 October 2018

KEYWORDS
Green chemistry; mechanochemistry; Horner–Wadsworth–Emmons reaction; *Piper* genus; arthritis

Introduction

Piperlotines are secondary metabolites isolated from *Piper* genus plants[1]. An example of this is black pepper (*Piper nigrum*), that has very important applications in medicinal chemistry like antibacterial[2–4], antiplatelet aggregation[5–7], cytotoxic[8–10], and biopesticide activities[11]. Despite its broad pharmacological application, the most of studies on

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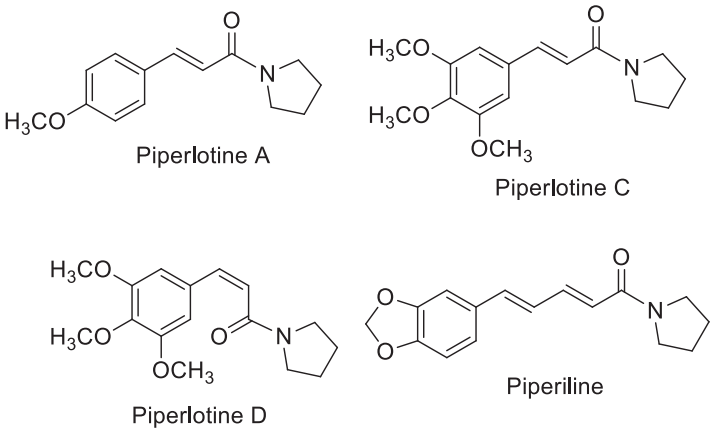


Figure 1. Some natural α,β-unsaturated amides present in *Piper* genus plants.

Piper species have been done using extracts or fractions from plants, instead of pure compounds[12, 13]. Therefore, the structure-activity relationships are unknown or incomplete in most of cases.

Nonetheless, piperlotine A, piperlotine C, piperlotine D, and piperiline among others, have been isolated from *Piper* genus species (Figure 1).

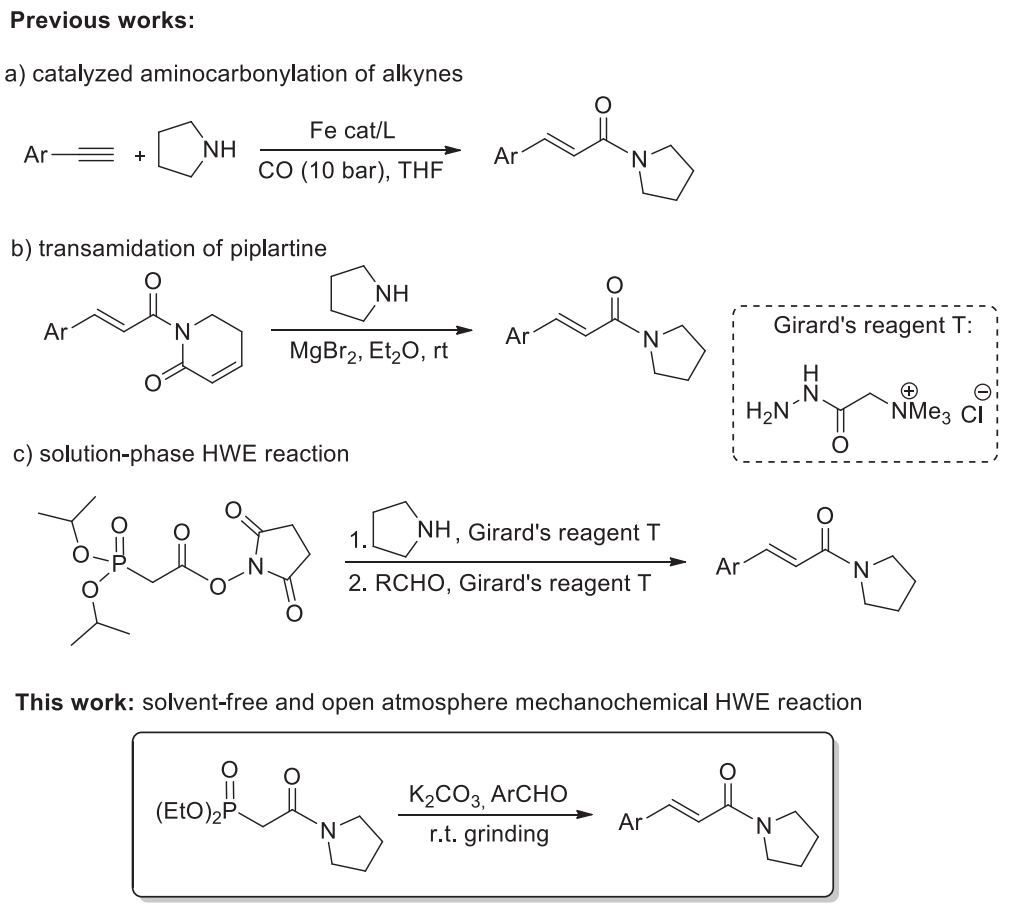
These natural products are characterized by an α,β-unsaturated amide moiety and have been synthesized through solution-phase Horner–Wadsworth–Emmons (HWE) reaction[14], catalyzed aminocarbonylation of alkynes[15], transamidation reaction[16], amidation from cinnamic acids[17–21], in addition to others[22] (Scheme 1). In this respect, to the best of our knowledge, piperlotines have not been prepared by means of mechanochemical HWE reaction.

Mechanosynthesis is a greener approach to prepare a broad range of organic compounds including drugs, secondary metabolites, catalysts, fine chemicals, etc., and it has been gaining attention because of its interesting advantages over solution-phase synthesis: solvents could be avoided, mechanochemical processes lower reaction times and sometimes change selectivity[23, 24]. To the best of our knowledge, there are just few reports on mechanochemical Wittig reaction[25–27] (limited to the synthesis of stilbenes) and a smaller amount on mechanochemical HWE reactions[28, 29] limited to the synthesis of α,β-unsaturated esters. In view of all above mentioned, in this work, we report the first mechanosynthesis of piperlotines A, C, and derivatives through an operationally simple and stereoselective HWE reaction, under solvent-free conditions by grinding (Scheme 1).

Results and discussion

Synthesis

The key step in the synthesis of piperlotines is the stereoselective formation of alkene group. Therefore, we envisaged the synthesis of target compounds **3a–i** trough the HWE reaction of an aromatic aldehyde and key β-amidophosphonate **2** under thermodynamic control, by means of a highly stabilized carbanion. Phosphonate **2** could be



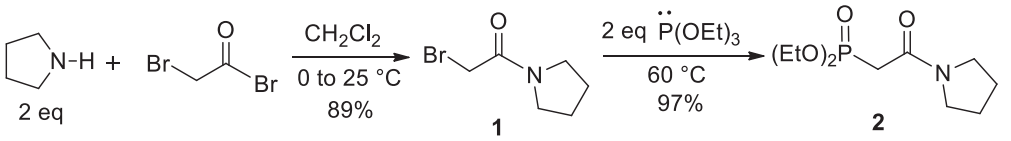
Scheme 1. Syntheses of piperlotines previously reported and our green HWE approach.

easily prepared from *N*-(bromoacetyl)pyrrolidine **1** and triethyl phosphite through Michaelis-Arbuzov reaction.

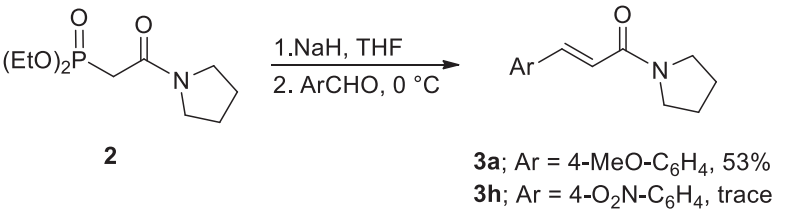
Hence, the reaction of pyrrolidine and bromoacetyl bromide provided *N*-(bromoacetyl)pyrrolidine **1** in 89% yield, without chromatographic purification. Next, treatment of **1** with triethyl phosphite under solvent-free conditions afforded key *β*-amidophosphonate **2** in 97% yield (Scheme 2).

Then, we carried out HWE process starting from classical reaction conditions: the mixture of **2**, NaH and *p*-anisaldehyde in anhydrous THF at 0 °C afforded Piperlotine A **3a** in 53% yield; but just trace amount of product **3 h** was obtained when using *p*-nitrobenzaldehyde, observing a complex reaction mixture (Scheme 3).

Because of lack of selectivity, in addition to previous reports of HWE reactions in non-anhydrous media using mild bases[30], we changed reaction conditions. This time, the use of K_2CO_3 as base in reflux of CH_3CN afforded desired *α*,*β*-unsaturated amides **3a–i** in moderate to good yields (39–92%) and just *E* isomer was isolated in every reaction (Table 1). It is worth to mention that *E* configuration prevails in the most of biologically active *α*,*β*-unsaturated amides of *Piper* species[1]. Additionally, to the best of our knowledge, derivative **3e** has not been previously reported in the literature.

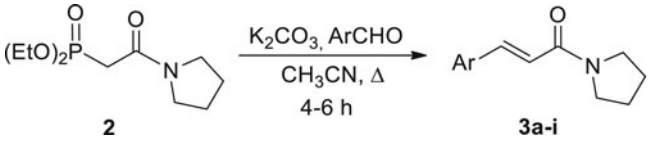


Scheme 2. Synthesis of key intermediate **2**.



Scheme 3. Classical HWE conditions for the synthesis of **3a** and **3h**.

Table 1. Synthesis of **3a–i** trough solution-phase HWE reaction.

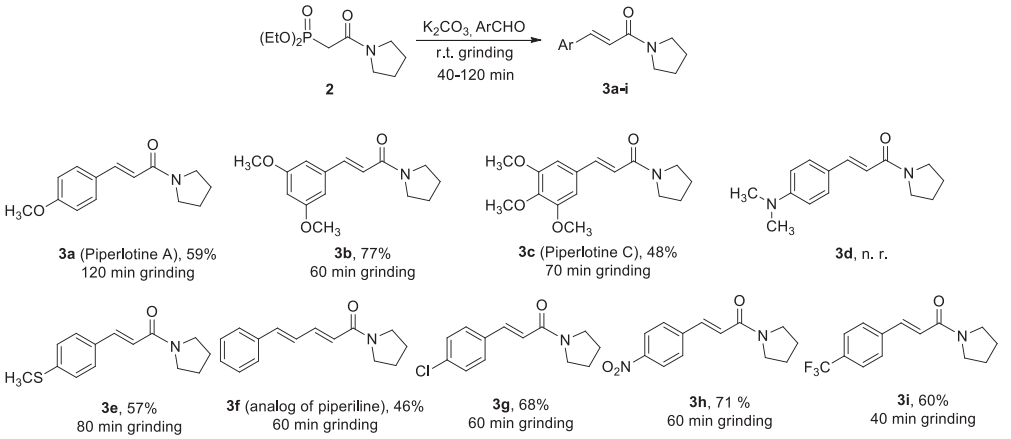


Entry	Product	Yield/%
1	**3a**, Ar = 4-MeOC$_6$H$_4$	60
2	**3b**, Ar = 3,5-(MeO)$_2$C$_6$H$_3$	77
3	**3c**, Ar = 3,4,5-(MeO)$_3$C$_6$H$_2$	56
4	**3d**, Ar = 4-(Me)$_2$NC$_6$H$_4$	49
5	**3e**, Ar = 4-MeSC$_6$H$_4$	46
6	**3f**, Ar = cinnamoyl	61
7	**3g**, Ar = 4-ClC$_6$H$_4$	39
8	**3h**, Ar = 4-O$_2$NC$_6$H$_4$	92
9	**3i**, Ar = 4-F$_3$CC$_6$H$_4$	70
9	**3i**, Ar = 4-F$_3$CC$_6$H$_4$	70

Configuration of obtained alkenes was unambiguously assigned through ^{1}H NMR spectrometry; specifically in order to $^3J_{H\text{-}H}$ vinylic coupling constant of ~15 Hz.

Encouraged with these results and according to preliminary observations (HWE reaction of **2**, an aldehyde and K_2CO_3 in CH_3CN proceeded at room temperature), we decided to carry out this HWE process at room temperature and avoiding CH_3CN, a carcinogenic solvent. In consequence, the reaction of *β*-amidophosphonate **2**, K_2CO_3 and an aromatic aldehyde (solid or liquid) in absence of solvent was carried out in a mortar and pestle by grinding, affording target products **3a–i** in moderate to good yields (46–77%). Astonishingly, shorter reaction times than reflux conditions were observed (40–120 min *vs.* 4–6 h, respectively); thus, grinding process accelerated formation of desired compounds (Scheme 4).

In this context, it is important to mention that previously reported mechanochemical HWE processes required 2–7 h in a ball mill to obtain desired products and use of solvent or a resin[28, 29]. Under our solvent-free conditions, just *E* isomer was isolated in



Scheme 4. Synthesis of **3a–i** trough mechanochemical HWE reaction.

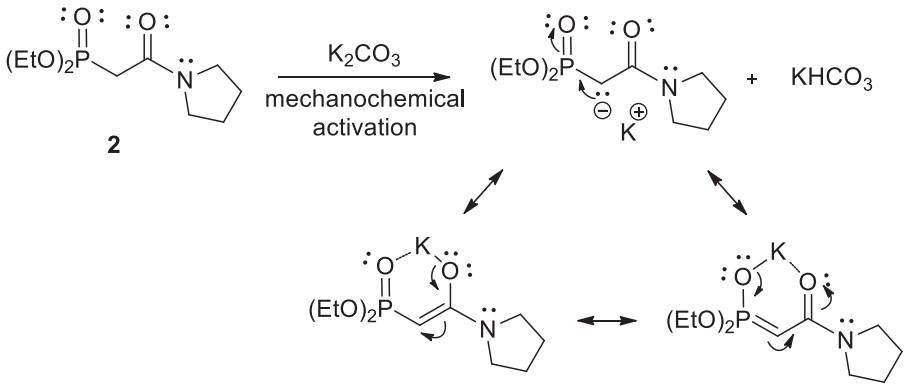


Figure 2. Resonance stabilization of carbanion **2**.

every reaction, despite temperature change from previous reflux conditions. We suggest that reaction is under thermodynamic control due to the high stability of β-amido-phosphonate carbanion which is stabilized by resonance. Evidence in this respect is that all mechanochemical HWE reactions were carried out under open atmosphere with a relative humidity >50%, suggesting significant stability of carbanion **2** (Figure 2).

Among studied reactions, only compound **3d** could not be obtained by grinding (90% aldehyde was recovered). To date, we can preliminary argument electrodonating effect of dimethylamino substituent is decreasing the reactivity of aldehyde, but further research is needed to have a clear explanation.

Design and prediction of biological activity

In other instance, as part of our ongoing interest in developing anti-inflammatory agents[31], we started from piperine, which is contained in black pepper and has been recognized by its anti-inflammatory activity[32, 33]. Synthesized compounds **3a–i** are structurally related with piperine. Both are characterized by a conjugated α,β-unsaturated amide with a substituted benzene ring (Figure 3).

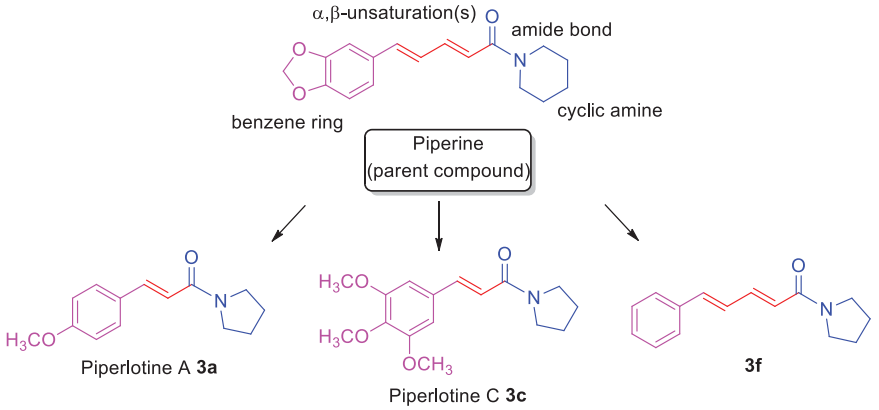


Figure 3. Rational design of novel anti-inflammatory agents.

Table 2. Prediction of pharmacological activity of products **3a–i**.

Product	Activity	Pa[a]:Pi[b]
3a	MMP9 expression inhibitor	0.805 : 0.003
3b	MMP9 expression inhibitor	0.820 : 0.003
3c	MMP9 expression inhibitor	0.791 : 0.003
3d	MMP9 expression inhibitor	0.650 : 0.011
3e	Other activities	–
3f	MMP9 expression inhibitor	0.823 : 0.003
3g	Other activities	–
3h	MMP9 expression inhibitor	0.592 : 0.016
3i	MMP9 expression inhibitor	0.617 : 0.014

[a]Pa: Probability to be active.
[b]Pi: probability to be inactive.
Prediction values are normalized to 1 (being 1 the maximal probability to be active/inactive).

In addition to the structural relationship between piperine and **3a–i**, these compounds were predicted as matrix metalloproteinase-9 (MMP-9) expression inhibitors, according to Prediction of Activity Spectra for Substances (PASS Online) database[34] (Table 2). PASS Online predicts more than 7000 types of biological activity with an average accuracy >95%[35] and has been used successfully to predict *in vitro* and *in vivo* diverse pharmacological activities of new compounds[36–38]. It is known that MMP-9 is mainly expressed in inflammatory cells during diseases as rheumatoid arthritis and cancer[39]. Furthermore, other studies demonstrated a relationship between high circulating MMP-9 in those patients with osteoporosis[40]. In this respect, we considered synthesized compounds **3a–i** as potential therapeutic agents for treatment of rheumatoid arthritis or cancer. Moreover, all synthesized amides **3a–i** agreed with Lipinski's rules, thus would have good absorption (by passive diffusion) in biologic systems due to their appropriate lipophilicity, molecular weight, and hydrogen-bonding capacity[41].

Consequently, compounds **3a–i** emerged as promising bioactive compounds for the treatment of some important diseases as arthritis or cancer. Lastly, all above discussed opens an opportunity to scale HWE reaction of *β*-amidophosphonate **2** and aromatic aldehydes under ball milling conditions in search of better yields and even shorter reaction times for obtaining such valuable natural products and derivatives.

Conclusions

In this work, we developed a practical and operationally simple method of mechanosynthesis of natural products: Piperlotine A **3a**, **3b,** Piperlotine C **3c**, and derivatives, which have proved its pharmacological value in previous reports. The synthesis of compounds **3a–i** was carried out through the HWE reaction as key step of synthesis under solvent-free conditions and in an open atmosphere, yielding desired products in moderate to good yields with short reaction times as compared with those reported. In this respect, it is important to mention that reported yields were the best obtained under manual grinding reactions. These yields correlated better with applied pressure than grinding speed or reaction time. It is needed a study of this HWE process under controlled conditions (i.e., in a ball mill) to ensure a better reproducibility.

In other instance, we did not need to use solvents or resins as in previous works. Also, it is important to mention that this method tolerated well the introduction of electrowithdrawing groups, electrodonating groups, and unsaturations in the utilized aldehydes, both in solid or liquid state. Additionally, our mechanochemical HWE reaction afforded stereoselectively *E* isomer in shorter reaction times than solution-phase process. It is worth to mentioning that an in-depth mechanochemical study of the synthesis of biologically relevant α,β-unsaturated amides (including synthesized products **3a–i**) and its pharmacological applications are under current research and will be published elsewhere.

Experimental

All commercial materials were used as received from Sigma-Aldrich® without further purification. Flash chromatography was performed using 230–400 mesh Silica Flash 60® silica gel. Thin layer chromatography was performed with pre-coated TLC sheets of silica gel (60F254, Merck). NMR spectra were recorded in a Varian System instrument (400 MHz for ^{1}H, 100 MHz for ^{13}C, and 161.9 MHz for ^{31}P) and calibrated with $CDCl_3$ as the solvent and TMS as the internal standard signal. Chemical shifts (d) are reported in parts per million. Multiplicities are recorded like: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, td = triplet of doublets, bs = broad singlet, q = quartet, and m = multiplet. Coupling constants (*J*) are given in Hz. High resolution mass spectra (HRMS) were obtained by direct infusion in a Synapt G2-Si Q-TOF system (Waters) equipped with an electrospray (ESI) probe, and the following conditions were used: flow rate, 10 μL/min; ionization mode, positive; capillary voltage, 3000 V; cone voltage, 40 V; capillary temperature, 100 °C; desolvation temperature, 200 °C; desolvation gas flow, 800 L/h, cone gas, 50 L/h; Nebulizer pressure; 6 Bar. Data were acquired in the MS Full Scan mode and centroid mode. Spectra were corrected infusing simultaneously the lockmass Leucine Enkephaline (556.2771). Data analysis was conducted using MassLynx software version 4.1 (Waters).

Synthesis of N*-(bromoacetyl)pyrrolidine* (1)

To an ice bath, cooled solution of bromoacetyl bromide (1.2 mL, 2.78 g, 13.78 mmol) in 20 cm^3 of CH_2Cl_2 was added dropwise *via* addition funnel a solution of pyrrolidine

(2.4 mL, 2.4 g, 28.75 mmol) in 30 cm^3 of CH_2Cl_2, and the reaction mixture was stirred overnight. Then, reaction mixture was quenched by the addition of 20 $cm^3$of distilled water and extracted with CH_2Cl_2 (3 × 20 cm^3). Then, 30 cm^3 of HCl 2.0 N was added to the combined organic extracts. After partition, the final organic extract was dried over Na_2SO_4, filtered, and evaporated under reduced pressure, yielding 2.416 g (92%) of a white solid that melts at room temperature. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.87–1.94$ (m, 2H, CH_2), 1.98–2.05 (m, 2H, CH2), 3.50 (t, $J = 6.9$ Hz, 2H, CH_2N), 3.54 (t, $J = 6.8$ Hz, 2H, CH_2N), 3.82 (AB system, $J = 20.0$ Hz, 2H, CH_2Br) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 24.31$ (CH_2), 26.15 (CH_2), 27.39 (CH_2Br), 46.43 (CH_2N), 47.06 (CH_2N), 165.07 (C = O) ppm; HRMS [ESI]: *m/z* calculated for $C_6H_{11}BrNO$ [M + H] + 192.0024, found 192.0095.

Synthesis of diethyl (2-oxo-2-(pyrrolidin-1-yl)ethyl)phosphonate (2, $C_{10}H_{20}NO_4P$)

A mixture of 298 mg (1.55 mmol) of **1** and 543 mg (3.27 mmol) of triethyl phosphite was stirred at 60 °C for 4.5 h. Then, crude product was purified using flash chromatography AcoEt:MeOH (90:10), yielding 377 mg (97%) of a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.34$ (t, $J = 7.1$ Hz, 6 H, CH_3), 1.83–2.01 (m, 4 H, CH_2–CH_2), 3.01 (d, $J = 22.1$ Hz, 2H, CH_2P), 3.49 (td, $J = 6.9$, 2.0 Hz, 2H, CH_2N), 3.60 (t, $J = 6.8$ Hz, 2H, CH_2N), 4.11–4.26 (m, 4 H, $(CH_2O)_2P$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 16.28$ (d, $J = 6.4$ Hz, CH_3), 24.47, 25.99, 34.64 (d, $J = 133.6$ Hz, CH_2P), 47.00, 47.59, 62.63 (d, $J = 6.4$ Hz), 163.16 (d, $J = 5.7$ Hz, C = O) ppm; ^{31}P NMR (161.9 MHz, $CDCl_3$): δ 22.01 ppm; HRMS [ESI]: *m/z* calculated for $C_{10}H_{21}NO_4P$ $[M + H]^+$ 250.1208, found 250.1214.

General procedure for the synthesis of α,β-unsaturated amides 3a–i

Method A: A mixture of β-amidophosphonate **2** (1.0 equiv), K_2CO_3 (1.5 equiv) and the corresponding aldehyde (1.1 equiv) was refluxed in 5 cm^3 CH_3CN during 4–6 h. After this time, reaction mixture was filtered, eliminating excess of K_2CO_3, then concentrated under reduced pressure and finally, crude product was purified using flash column chromatography AcOEt 100%, yielding corresponding products **3a–i**.

Method B: A mixture of β-amidophosphonate **2** (1.0 equiv), K_2CO_3 (1.5 equiv) and the corresponding aldehyde (1.1 equiv) was grinded homogenously for 40–120 min in periods of 10 min in a porcelain mortar and pestle. It was observed an optimum grinding speed of 100 compressions/min. Then, reaction mixture was suspended in a minimum of CH_2Cl_2, filtered and concentrated under reduced pressure. The crude product was purified using flash column chromatography AcOEt 100%, obtaining corresponding compounds **3a–i**.

(E)-3-(4-methoxyphenyl)-1-(pyrrolidin-1-yl)prop-2-en-1-one (3a)

Yield: 67 mg (59%) as a white solid; m.p.: 115.8–116.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.86–1.93$ (m, 2H, CH_2–CH_2), 1.97–2.03 (m, 2H, CH_2–CH_2), 3.59 (t, $J = 6.1$ Hz, 2H, CH_2N), 3.62 (t, $J = 6.0$ Hz, 2H, CH_2N), 3.83 (s, 3 H, CH_3O), 6.60 (d, $J = 15.5$ Hz, 1 H,

CH), 6.89 (AA' BB' system, $J = 8.8$ Hz, 2H, H_{arom}), 7.48 (AA' BB' system, $J = 8.7$ Hz, 2H, H_{arom}), 7.66 (d, $J = 15.5$ Hz, 1 H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 24.55$ (CH_2–CH_2), 26.33 (CH_2–CH_2), 46.18 (CH_2N), 46.72 (CH_2N), 55.52 (OCH_3), 114.35, 116.65, 128.26, 129.54, 141.46, 160.94, 165.21 (C = O) ppm; HRMS [ESI]: *m/z* calculated for $C_{14}H_{18}NO_2$ $[M + H]^+$ 232.1338, found 232.1335.

(E)-3-(3,5-dimethoxyphenyl)-1-(pyrrolidin-1-yl)prop-2-en-1-one (3b)

Yield: 123 mg (77%) as a white solid; m.p.: 117.1–117.9 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.87$–1.94 (m, 2H, CH_2–CH_2), 1.97–2.04 (m, 2H, CH_2–CH_2), 3.61 (dt, $J = 13.7$, 6.8 Hz, 4 H, CH_2N), 3.81 (bs, 6 H, CH_3O), 6.46 (t, $J = 2$. 2H z, 1 H, H_{arom}), 6.67 (d, $J = 2.4$ Hz, 2H, H_{arom}), 6.69 (d, $J = 15.7$ Hz, 1 H, CH), 7.61 (d, $J = 15.4$ Hz, 1 H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 24.53$ (CH_2–CH_2), 26.33 (CH_2–CH_2), 46.26 (CH_2N), 46.79 (CH_2N), 55.60 (OCH_3), 101.74, 106.06, 119.58, 137.48, 141.84, 161.13, 164.76 (C = O) ppm; HRMS [ESI]: *m/z* calculated for $C_{15}H_{20}NO_3$ $[M + H]^+$ 262.1443, found 262.1439.

(E)-1-(pyrrolidin-1-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (3c)

Yield: 89 mg (48%) as a white solid; m.p.: 156.3–157.4 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.88$–1.95 (m, 2H, CH_2–CH_2), 1.99–2.05 (m, 2H, CH_2–CH_2), 3.60 (t, $J = 6.9$ Hz, 2H, CH_2N), 3.65 (t, $J = 6.8$ Hz, 2H, CH_2N), 3.87 (bs, 3 H, OCH_3), 3.90 (bs, 3 H, OCH_3), 6.62 (d, $J = 15.4$ Hz, 1 H, CH), 6.75 (bs, 2H, H_{arom}), 7.62 (d, $J = 15.4$ Hz, 1 H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 24.53$ (CH_2–CH_2), 26.32 (CH_2–CH_2), 46.26 (CH_2N), 46.81 (CH_2N), 56.37 (OCH_3), 61.12 (OCH_3), 105.25, 118.25, 131.09, 139.71, 141.96, 153.55, 164.83 (C = O) ppm; HRMS [ESI]: *m/z* calculated for $C_{16}H_{22}NO_4$ $[M + H]^+$ 292.1549, found 292.1544

(E)-3-(4-(dimethylamino)phenyl)-1-(pyrrolidin-1-yl)prop-2-en-1-one (3d)

Yield: 96 mg (49%) as a pale yellow solid (reflux conditions); m.p.: 151.9–152.9 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.85$–1.92 (m, 2H, CH_2–CH_2), 1.96–2.02 (m, 2H, CH_2–CH_2), 3.00 (s, 6 H, $(CH_3)_2N$), 3.58 (t, $J = 5.5$ Hz, 2H, CH_2N), 3.62 (t, $J = 5.5$ Hz, 2H, CH_2N), 6.52 (d, $J = 15.4$ Hz, 1 H, CH), 6.67 (AA' BB' system, $J = 8.9$ Hz, 2H, H_{arom}), 7.43 (AA' BB' system, $J = 8.9$ Hz, 2H, H_{arom}), 7.64 (d, $J = 15.4$ Hz, 1 H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 24.59$ (CH_2–CH_2), 26.34 (CH_2–CH_2), 40.39 ($(CH_3)_2N$), 46.13 (CH_2N), 46.68 (CH_2N), 112.06, 113.79, 123.45, 129.51, 142.24, 151.47, 165.79 (C = O) ppm; HRMS [ESI]: *m/z* calculated for $C_{15}H_{21}N_2O$ $[M + H]^+$ 245.1654, found 245.1651.

(E)-3-(4-(methylthio)phenyl)-1-(pyrrolidin-1-yl)prop-2-en-1-one (3e, $C_{14}H_{17}NOS$)

Yield: 88 mg (57%) as a white solid; m.p.: 102.2–102.9 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.86$–1.93 (m, 2H, CH_2–CH_2), 1.97–2.04 (m, 2H, CH_2–CH_2), 2.50 (s, 3 H, SCH_3), 3.61 (dt, $J = 13.4$, 6.8 Hz, 4 H, CH_2N), 6.68 (d, $J = 15.5$ Hz, 1 H, CH), 7.22 (AA' BB'

system, $J = 8.4$ Hz, 2H, H_{arom}), 7.45 (AA' BB' system, $J = 8.6$ Hz, 2H, H_{arom}), 7.65 (d, $J = 15.5$ Hz, 1 H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 15.53$ (SCH_3), 24.54 (CH_2–CH_2), 26.34 (CH_2–CH_2), 46.24 (CH_2N), 46.76 (CH_2N), 118.08, 126.31, 128.39, 132.16, 140.89, 141.25, 164.95 (C = O) ppm; HRMS [ESI]: *m/z* calculated for $C_{14}H_{18}NOS$ $[M + H]^+$ 248.1109, found 248.1107.

(2E,4E)-5-phenyl-1-(pyrrolidin-1-yl)penta-2,4-dien-1-one (3f)

Yield: 63 mg (46%) as a white solid; m.p.: 122.5–123.7 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.85$–1.92 (m, 2H, CH_2–CH_2), 1.95–2.02 (m, 2H, CH_2–CH_2), 3.56 (td, $J = 6.8$, 3.3 Hz, 4 H, CH_2N), 6.31 (d, $J = 14.7$ Hz, 1 H, CH), 6.84–6.95 (m, 2H), 7.26–7.36 (m, 3H), 7.44–7.50 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 24.53$ (CH_2–CH_2), 26.31 (CH_2–CH_2), 46.13 (CH_2N)), 46.68 (CH_2N), 122.36, 127.02, 127.13, 128.78, 128.90, 136.57, 139.14, 141.83, 165.01 (C = O) ppm; HRMS [ESI]: *m/z* calculated for $C_{15}H_{18}NO$ $[M + H]^+$ 228.1388, found 228.1386.

(E)-3-(4-chlorophenyl)-1-(pyrrolidin-1-yl)prop-2-en-1-one (3g)

Yield: 101 mg (68%) as a white solid; m.p.: 154.1–155.4 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.88$–1.94 (m, 2H, CH_2–CH_2), 1.98–2.05 (m, 2H, CH_2–CH_2), 3.59 (t, $J = 7$. 2H z, 2H, CH_2N), 3.63 (t, $J = 6.8$ Hz, 2H, CH_2N), 6.71 (d, $J = 15.5$ Hz, 1 H, CH), 7.34 (AA' BB' system, $J = 8.5$ Hz, 2H, H_{arom}), 7.47(AA' BB' system, $J = 8.4$ Hz, 2H, H_{arom}), 7.65 (d, $J = 15.5$ Hz, 1 H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 24.53$ (CH_2–CH_2), 26.33 (CH_2–CH_2), 46.29 (CH_2N), 46.80 (CH_2N), 119.53, 129.18, 129.20, 133.99, 135.48, 140.50, 164.58 (C = O) ppm; HRMS [ESI]: *m/z* calculated for $C_{13}H_{15}ClNO$ $[M + H]^+$ 236.0842, found 236.0840.

(E)-3-(4-nitrophenyl)-1-(pyrrolidin-1-yl)prop-2-en-1-one (3h)

Yield: 106 mg (71%) as a white solid; m.p.: 207.8–208.9 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.90$–1.97 (m, 2H, CH_2–CH_2), 2.01–2.08 (m, 2H, CH_2–CH_2), 3.61 (t, $J = 6.9$ Hz, 2H, CH_2N), 3.67 (t, $J = 6.8$ Hz, 2H, CH_2N), 6.88 (d, $J = 15.5$ Hz, 1 H, CH), 7.68 (AA' BB' system, $J = 8.9$ Hz, 2H, H_{arom}), 7.73 (d, $J = 15.5$ Hz, 1 H, CH), 8.23 (AA' BB' system, $J = 8.9$ Hz, 2H, H_{arom}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 24.49$ (CH_2–CH_2), 26.32 (CH_2–CH_2), 46.43 (CH_2N), 46.89 (CH_2N), 123.20, 124.27, 128.57, 139.16, 141.77, 148.19, 163.79 (C = O) ppm; HRMS [ESI]: *m/z* calculated for $C_{13}H_{15}N_2O_3$ $[M + H]^+$ 247.1083, found 247.1079.

(E)-1-(pyrrolidin-1-yl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (3i)

Yield: 100 mg (60%) as a white solid; m.p.: 131.7–133.8 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.89$–1.95 (m, 2H, CH_2–CH_2), 2.00–2.06 (m, 2H, CH_2–CH_2), 3.60 (t, $J = 6.9$ Hz, 2H, CH_2N), 3.65 (t, $J = 6.8$ Hz, 2H, CH_2N) 6.81 (d, $J = 15.5$ Hz, 1 H, CH), 7.62 (AA'BB' system, 4 H, H_{arom}), 7.71 (d, $J = 15.5$ Hz, 1 H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 24.51$ (CH_2–CH_2), 26.33 (CH_2–CH_2), 46.37 (CH_2N), 46.86 (CH_2N), 121.44, 124.10

(q, $J = 270.7$ Hz, CF_3), 125.91 (q, $J = 3.8$ Hz), 128.14, 131.23 (q, $J = 32.6$ Hz), 138.92, 140.19, 164.26 (C = O) ppm; HRMS [ESI]: *m/z* calculated for $C_{14}H_{15}F_3NO$ $[M + H]^+$ 270.1106, found 270.1101.

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