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A versatile domino process for the synthesis of substituted 3-aminomethylene-chromanones and 2-pyridones catalyzed by CsF

Catalin Pintiala, Ata Martin Lawson *, Sébastien Comesse, Adam Daïch *

URCOM, EA 3221, INC3M CNRS FR-3038, UFR des Sciences et Techniques de l'Université du Havre, 25 Rue Philippe Lebon, B.P. 540, F-76058 Le Havre Cedex, France

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ABSTRACT

The addition of various primary amines onto 3-α,β-unsaturated diester chromone derivative was studied under mild conditions. Basically, this reaction provided 2-pyridone-based compounds through an interesting domino 'Addition/Ring Opening/Ring Closure' process (ARORC). In this study, aniline and tryptamine series exhibited different reactivity profiles leading unexpectedly to 3-aminomethylene chromanones with or without the 2-pyridone derivatives. This constitutes the first description and study of 3-aminomethylene chromanone formation that is supposed to follow a domino process combining 'Addition/Ring Opening/Ring Closure by Oxa-Michael addition' (ARORCOM).

A high number of biologically active compounds bear the 2-pyridone ring system.[1] This scaffold is an interesting key intermediate which can easily provide complex heterocyclic compounds that exhibit important biological properties. For example, these compounds turn out to be potent anti-hepatitis B,[2] MEK-1 inhibitors,[3] Receptor Tyrosine Kinase c-Kit inhibitors,[4] Anaplastic Lymphoma Kinase inhibitors,[5] and they also show marked anti Pim-1 kinase activities.[6] For many years our research group has been interested in pyridone-based compounds such as the natural topoisomerase-I poison rosettacin and its derivatives.[7] One of our ongoing research activities is focused on the synthesis of simple heterocyclic compounds bearing a pyridone skeleton starting from cheap chromone derivatives (Fig. 1).

Moreover, the presence of a chromone ring in many biologically active compounds[8] and various natural flavonoids[9,10] represents an interest for their use as new synthetic scaffolds. Especially, the 3-vinylchromone derivative and the more explored 3-formyl-chromone are now proven to be useful building blocks in organic and medicinal chemistry.[11–15] The chemical importance of these electron-deficient-fused dienes is due to their reactivity through four potential electrophilic sites: C-2, C-4, C-1′ and the carbonyl moieties from ester groups (Fig. 1, substrate **1**). The α,β-unsaturated chromone can also be involved in Diels–Alder reactions as described recently by Bodwell group.[16]

To reach the targeted 3-ethoxycarbonyl-2-pyridone derivatives of type **2** (Fig. 1), the simple and efficient route that gives priority to aza-Michael addition on α,β-unsaturated chromone as the main starting material[17–19] has held our attention. Surprisingly, the use of α,β-unsaturated chromone to provide compounds bearing a pyridone core is not widely described in the literature as shown by the fact that there are very few studies related to this reaction.[2,11,12,19] Most of these publications reported on the different sites of reactivity of this substrate in relation to the nucleophilicity of the nitrogen atom of amines, hydrazines, hydroxylamines, and *para*-toluidine. Recently, different alkylamines and substituted anilines were used on a monoester derivative of α,β-unsaturated chromone in the presence of Et_3N in refluxing MeOH. This reaction led to pyridone compounds only and no other compounds are mentioned in this Letter.[2]

We report herein a simple, fast and broadly tolerable protocol for the synthesis of benzoyl-substituted 2-pyridone derivatives **2** (Scheme 1). Compared to the existing methods, which are limited in terms of amines diversity,[2,11,12,18,19] our approach has proven to be efficient with a wide range of either sterically hindered or poorly nucleophilic amines. Another significant aspect of our methodology is the access, in some cases, to 3-aminomethylene-chromanone compounds **3** never described before. In fact, our methodology allowed the formation of **2** or **3** independently or together. It also gave the possibility to modulate in some cases the formation of both products according to reaction conditions. In addition, the possible synthetic usefulness of 3-aminomethylene-chromanones **3** and their formation provide some insights into the plausible mechanism of the domino reaction.

* Corresponding authors. Tel.: +33 02 32 74 44 00; fax: +33 02 32 74 43 91 (A.M.L.); tel.: +33 02 32 74 44 03; fax: +33 02 32 74 43 91 (A.D.).

E-mail addresses: lawsona@univ-lehavre.fr (A.M. Lawson), adam.daich@univ-lehavre.fr (A. Daïch).

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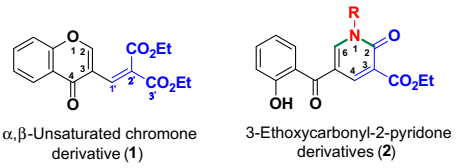
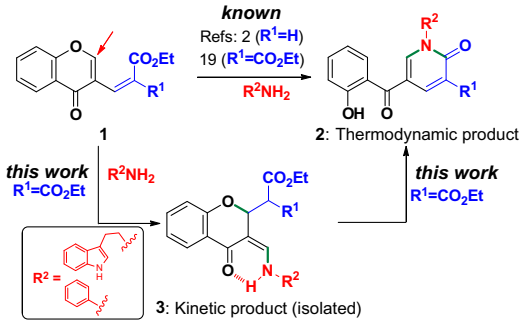


Figure 1. Unsaturated chromone and 2-pyridones structures.



Scheme 1. Synthesis of pyridones **2** and/or 3-aminomethylene-chromanones **3** under mild conditions via a domino process.

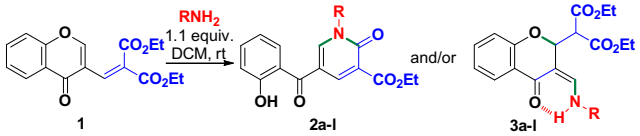
Besides the originality of the kinetic intermediate **3**, it is very important to underline the attractiveness of the system regarding its versatility. Indeed, it is possible to stop the process in some cases at the isolable enaminochromanones **3** stage or let it evolve in order to ultimately provide 2-pyridone compounds **2**.

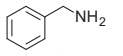
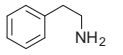
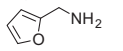
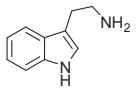
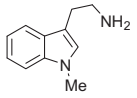
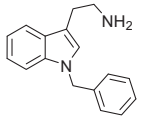
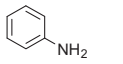
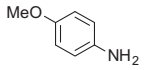
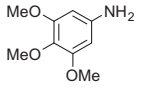
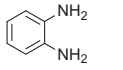
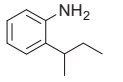
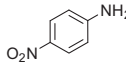
Treatment of substrate **1** with different primary amines afforded the corresponding pyridone **2** in good yields through a domino process including three reactions: aza-Michael addition, then chromone ring opening followed by ring closure. As shown in Table 1, the expected pyridones **2** were obtained through this approach in excellent yields (92–95%) when benzylamine (entry 1), phenethylamine (entry 2), and furfurylamine (entry 3) were used. Surprisingly, different results were observed when starting from other amines (Table 1, entries 4–10).

In tryptamine series (entries 4–6) both products **2** and **3** were obtained at room temperature in DCM. When tryptamine was used, **2d**[20] and **3d**[20] were formed in the same proportion and in a good yield (88%). Moreover, substitution of the indolic nitrogen atom with a methyl (entry 5) or benzyl (entry 6) group promoted the formation of compounds **3e** and **3f**, since the ratio increased from 1:1 up to 3:5 and 3:7, respectively, in favor of compound **3**. In aniline series, the course of the reaction was different according to the nucleophilicity of amine function. In fact, only 30% of isolated compound **3g** (entry 7) was obtained after 24 h of reaction with aniline. Conducted with an aniline bearing electron donating group such as *p*-methoxyaniline (entry 8), the reaction provided the desired pyridone **2h** accompanied by bicyclic enaminone **3h** (Table 1) in 64% isolated yield and 1:5 ratio. Additional methoxy groups on aromatic ring (entry 9) enhanced the nucleophilicity and **3i** was exclusively obtained in 84% yield. Contrary to aniline, the presence of another NH_2 group in *ortho*-position of aniline (entry 10) favored the formation of both compounds **2j** and **3j** in 54% yield and 1:2 ratio to the detriment of pyridone **2**. Nevertheless, in the case of the sterically hindered aniline and aniline bearing electron withdrawing group, limitations of the reaction appeared. Indeed, the use of 2-(*sec*-butyl)aniline (entry 11) and *para*-nitroaniline (entry 12) resulted in total inhibition of the reaction.

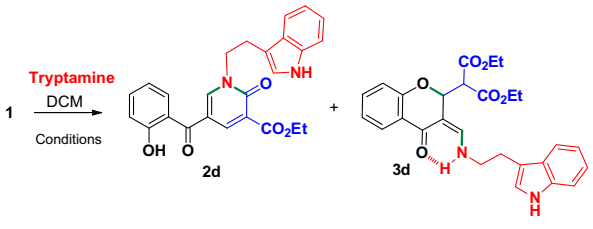
From these results, it seemed that the reaction was very sensitive to the electronic and steric effects of amine derivatives. In this context we decided to extend the experimental conditions by test-

Table 1
Benzoyl-substituted pyridones **2a–1** synthesis accompanied by the unexpected enaminochromanone **3a–1**



Entry/ Product	RNH_2	Time (h)	Yield[a] (%)	Ratio[b] Products **2**:**3**
1/**a**		3	95	1:0
2/**b**		3	92	1:0
3/**c**		3	95	1:0
4/**d**		1	88	1:1
5/**e**		3	76	3:5
6/**f**		6	85	3:7
7/**g**		24	30	0:1
8/**h**		16	64	1:5
9/**i**		16	84	0:1
10/**j**		48	54	1:2
11/**k**		24	0	–[c]
12/**l**		24	0	–[c]

[a] The yields were reported for the isolated products after separation by silica gel column chromatography.
[b] The ratios were calculated for the pure isolated products.
[c] Recovery of starting materials.



Scheme 2. Synthesis of pyridone derivative **2d** and corresponding enaminochromanone product **3d**.

ing the influence of other parameters such as catalysts and solvents to overcome the limitations of the process. Depending on the conditions used, we were hoping to tune the reactivity in order to form pyridone product **2d** or 3-aminomethylene-chromanone compounds **3** exclusively. As a 1:1 ratio of **2d** and **3d** was observed in the tryptamine case, the impact of these parameters was investigated by using this amine as model substrate (Scheme 2).

Different catalysts were then tested for the reaction between tryptamine and α,β-unsaturated chromone diester **1** at room temperature or heating at 40 °C. The results are highlighted in Table 2.

This study showed in all cases a slight or significant enhancement of 2-pyridone compound ratio in the mixture.[21] At room temperature, by using $ZnCl_2$ or CuI as the catalyst, the amount of **2d** was improved from 1:1 ratio (entry 1), to respectively 5:4 and 4:3 ratios with an overall yield of 80%. A 2:1 ratio (**2d**:**3d**) was obtained in the case of $LiClO_4$. Better results were achieved with $Bi(OTf)_3$ and $Ti(OiPr)_4$ where more than 80% yield for both products was obtained in a 4:1 ratio.

After reaction screening (Table 2), the best catalysts to promote the formation of pyridone **2d** (ratio 1:0) remarkably at ambient temperature were CsF (entry 4) and TFA (entry 8). Carrying out the reactions at 40 °C in DCM in the presence of the mentioned catalysts clearly showed that the conversion of the starting substrate **1** into pyridone **2d** was significantly improved compared to the non-catalyzed domino reaction (entry 1). Comparable or slightly improved results were observed in the case of $LiClO_4$ and $Bi(OTf)_3$ (entries 5 and 6). These results proved that catalysts and temperature influenced considerably the formation of the expected pyridone **2d**.

To improve the yield of pyridone **2d** and understand the formation of enaminone **3d**, we then studied the potential effects of solvent and temperature (Table 3). As previously mentioned, using DCM as solvent and carrying out the reactions at ambient temperature or at 40 °C without catalyst, both products (**2d** and **3d**) were obtained in 1:1 and 4:3 ratios, respectively. Additionally, we assumed that increasing the reaction temperature could be a strategic parameter in order to form the pyridone product **2d** selectively or more challengingly to reverse the proportion of **2d** versus **3d**.

The reactions were then conducted at low temperature and as described in Table 3 at 0 °C (entry 2), the usual 1:1 ratio obtained at room temperature did not really change in favor of **3d**. Surprisingly, at −78 °C (entry 1) the same result was obtained. At 40 °C (entry 4), formation of pyridone **2d** was slightly favored (ratio **2d**:**3d** = 4:3). These results evidenced the existence of a possible equilibrium between two intermediate compounds governed by the reaction temperature (Scheme 3). To ascertain this hypothesis,

Table 2
Impact of the temperature and/or catalyst on the domino course

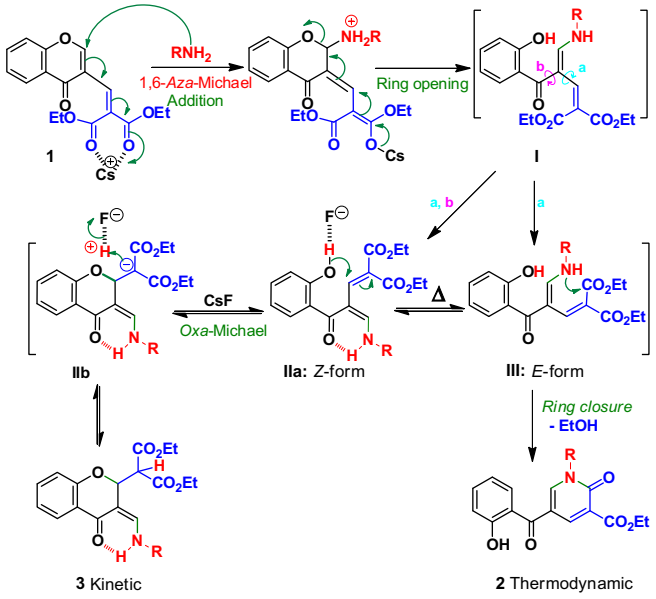
Entry	Catalyst (mol %)	Yield[a] (%)		Ratio[b] (**2d**:**3d**)	
		rt	40 °C	rt	40 °C
1	No catalyst	88	98	1:1	4:3
2	$ZnCl_2$ (10)	80	89	5:4	2:1
3	CuI (10)	78	82	4:3	2:1
4	CsF (5)	93	nr[c]	1:0	nr[c]
5	$LiClO_4$ (10)	82	93	2:1	7:3
6	$Bi(OTf)_3$ (5)	88	90	4:1	4:1
7	$Ti(OiPr)_4$ (10)	85	96	4:1	1:0
8	TFA (10)	70	nr[c]	1:0	nr[c]

[a] The yields were reported for the isolated products after separation by silica gel column chromatography or filtration. In all cases full conversion of starting materials was observed after 30 min of the reaction.
[b] The ratios were calculated from ^1H NMR spectra of crude mixture. (integration of H-2 proton for enaminochromanone derivative and H-4 proton for 2-pyridone compound).
[c] Not realized.

Table 3
Solvent and temperature effects on the reaction

Entry	Solvent	Temperature (°C)	Yield[a] (%)	Ratio[b](**2d**:**3d**)
1	DCM	−78	88	1:1
2	DCM	0	75	1:1
3	DCM	rt	88	1:1
4	DCM	40	98	4:3
5	Toluene	115[c]	99	1:0
6	EtOH	rt	88	1:0
7	THF	rt	80	1:0

[a] The yields of isolated products were reported after separation by silica gel column chromatography or filtration.
[b] The ratios were calculated from ^1H NMR spectra of crude mixture. (integration of H-2 proton for enaminochromanone derivative and H-4 proton for 2-pyridone compound)
[c] Reaction time = 1 h.

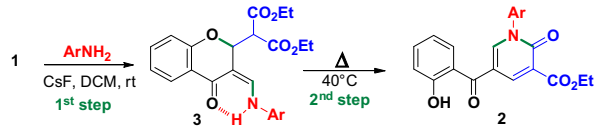


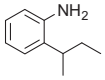
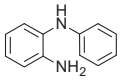
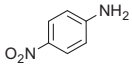
Scheme 3. Mechanistic proposal.

we then decided to perform the reaction under high boiling point solvents such as toluene. As expected, only pyridone derivative **2d** (entry 5) was obtained as a thermodynamic compound. Furthermore, we noticed that the nature of the solvent also influenced the domino reaction ratio. Indeed, pyridone **2d** could be exclusively obtained when the reaction was conducted at room temperature in protic solvents such as EtOH. Based on these studies, the most successful conditions to reach the 2-pyridone compound exclusively starting from tryptamine were: 5 mol % of CsF in DCM at room temperature, 10 mol % of $Ti(OiPr)_4$ at reflux in DCM and refluxing reaction in toluene.

The selected three conditions providing the best results with tryptamine were then tested with aniline as a starting amine. Among them, only CsF at room temperature in DCM appeared to be very efficient and was applied to aniline derivatives that did not previously react as outlined in Table 1. As shown in Table 4, application of these previously well-established conditions provided interesting and promising results. In this case, it was possible to reach kinetic compound **3** selectively in the first step. The latter was then converted into thermodynamic compound **2** by refluxing the reaction mixture in the second step. In fact, aniline and 2-(*sec*-butyl)aniline[22] led to a total conversion of the substrate **1** into corresponding 3-aminomethylene-chromanone **3** after 8 or 24 h of reaction, respectively. Moreover, refluxing the reaction mixture

Table 4
Kinetic and thermodynamic products after treatment of diester **1** with aniline derivatives



Entry/product	$ArNH_2$	% of conversion[a] (Time in hours)	
		Enaminochromanone **3**	Pyridone **2**
1/**g**		100 (8 h)	100 (3 h)
2/**k**		100 (24 h)	100 (3 h)
3/**m**		33[b] (24 h)	100 (3 h)
4/**n**		33 (24 h)	15[c] (3 h)
5/**l**		45 (30 h)	no[d] (3 h)

[a] The reaction conversions were based on the consumption of **1** and were calculated from ^{1}H NMR spectra of crude mixture.
[b] Mixture of **3m** and **2m** (ratio 1:1) was observed in 66% conversion.
[c] Mixture of **3n** and **2n** (ratio 5:2) was observed in 52% conversion.
[d] No = not observed.

containing exclusively the formed 3-amino-methylene-chromanone, provided the corresponding pyridone compounds **2** in nearly quantitative yield after 3 h.

According to the results summarized in Table 4, when *ortho*-*N*-phenylaminoaniline (entry 3) was used only 67% conversion into aminomethylene-chromanone **3m** and pyridone **2m** was obtained in a 1:1 ratio. Even in the case of sterically hindered amine such as 2-(*tert*-butyl)aniline (entry 4) or very weak nucleophile amine such as *para*-nitro-aniline (entry 5), 3-amino-methylene-chromanone **3** was obtained in 33% and 45% conversion, respectively. Satisfactorily, 2-(*tert*-butyl)aniline and *para*-nitro-aniline provided **2** and **3** in 100% conversion in 1:0 ratio and 1:3 ratio, respectively, by refluxing (56 h) the reaction in DCM in the presence of **1** and 10 mol % of CsF. The purification by column chromatography using silica gel led to the isolation of **2n** (46% yield) and **2l** (15% yield).

Interestingly, pyridone **2** or enamino-chromanone **3** could be obtained conveniently according to the reaction conditions and nucleophilicity of the employed amines. Positively, the use of CsF as catalyst has helped to enlarge the application area of this domino process even on hindered or weak nucleophilic anilines which did not react under classical conditions. Based on all these observations, the mechanism presented in Scheme 3 was proposed.

The addition of primary amines onto diester **1** occurred in the first step at position 2 followed by chromone ring opening to generate a non-isolated intermediate **I**. After possible internal rotations, *Z*-form **II** and *E*-form **III** were envisioned. According to the reaction conditions these isomers could be in equilibrium or in favor of the intermediate *E* to the detriment of *Z* and vice versa. At this stage, two possible routes can be considered: (1) *Z*-isomer could lead directly to the kinetic product **3** while (2) *E*-isomer could afford pyridone **2** as the thermodynamic product via an intramolecular peptidic coupling. In aniline series, when the reaction proceeded at room temperature in the presence of CsF, the 1,6-aza-Michael addition was promoted by the Cs coordination with diester groups. After the ring-opening step, fluoride ion probably acted as a base.[23] In this way it promoted an intramolecular 1,4-oxa-Michael addition leading to enamino-chromanone **3** ring closure. Under heating, CsF catalyzed the aminomethylene-chromanone ring opening leading to pyridone ring closure *via* a second nucleophilic attack between the secondary amine group and one of the carboxyl moieties. In tryptamine series where the nitrogen atom is more nucleophile, one possible explanation could be that the equilibrium between *Z* and *E*-forms was very rapid even at low temperature providing a mixture of kinetic and thermodynamic products. Activation of 4-carbonyl group from chromone moiety by Lewis acids, metallic ions, Brønsted acids, or hydrogen bonds[24,25] (EtOH) reversed the equilibrium in favor of *E*-isomer giving access to pyridone derivatives **2** exclusively.[26]

In summary, in this study, we report a convenient and versatile domino process leading to a wide variety of 2-pyridone compounds or 3-aminomethylene-chromanones. These compounds can be obtained together or independently according to reaction conditions. Their syntheses were based on a domino process involving the 1,6-aza-Michael addition on α,β-unsaturated chromone derivative/pyran ring opening followed by pyridone or chromanone ring closure. During these investigations, we checked different parameters to yield exclusively the desired 2-pyridones as thermodynamic products or the kinetic ones; aminomethylene-chromanones. According to reaction conditions, a plausible mechanism providing both compounds was proposed.

Finally, the domino reaction studied in this Letter constitutes a versatile route to provide new synthetic intermediates to reach polysubstituted pyridones. A large library of polyheterocyclic compounds with promising biological properties based on 2-pyridone scaffold is now under construction. The biological results and chemical synthesis applications will be published in due course.

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References and notes

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20. Typical procedure for the synthesis of **2d** and **3d** These compounds were prepared by treating 3-α,β-unsaturated chromone (1 equiv) with the corresponding amine (1.1 equiv) in DCM (Scheme 2.). The reaction was stirred at room temperature for the required time (monitored by TLC). At the end of the reaction the mixture was evaporated under vacuum and purified by column chromatography (gradient of hexane and ethyl acetate) to afford the desired products **2d** and **3d** in 88% and 1:1 ratio. Ethyl 5-(*o*-hydroxybenzoyl)-1-(indol-3′-yl-ethyl)pyridin-2(1*H*)-one-3-carboxylate (**2d**). Yellow solid mp: 237–239 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.41 (t, J = 7.1 Hz, 3H), 3.34 (t, J = 6.3 Hz, 2H), 4.31 (t, J = 6.3 Hz, 2H), 4.42 (q, J = 7.1 Hz), 6.52–6.53 (m, 2H), 6.96–6.98 (m, 2H), 7.10 (t, J = 7.4 Hz, 2H), 7.21 (t, J = 7.5 Hz, 1H), 7.37–7.43 (m, 2H), 7.49–7.52 (m, 2H), 8.30 (s, 1H, N*H*), 8.52 (d, J = 2.4 Hz, 1H), 11.22 (s, 1H, O*H*); ^{1}H NMR (75 MHz, $CDCl_3$) δ (ppm) 14.3, 24.1, 53.1, 61.6, 111.2, 111.6, 114.9, 118.2, 118.3, 118.6, 119.0, 120.1, 120.2, 122.7, 123.0, 127.0, 130.9, 136.1, 136.4, 143.9, 147.2, 158.8, 162.2, 164.2, 193.9; HRMS of [$C_{25}H_{22}N_2O_5$+H^+]: calcd: 431.1618; found: 431.1607 (*Z*)-2-Diethoxycarbonyl-3-(indol-3′-yl-ethyl)aminomethylene-benzochroman-4-one (**3d**). Orange amorphous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.13 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 3.01 (t, J = 6.6 Hz, 2H), 3.53 (m, 2H), 3.91 (d, J = 10.3 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 4.24 (m, 2H), 5.45 (d, J = 10.3 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.94 (d, J = 13.2 Hz, 1H), 6.96–7.06 (m, 2H), 7.11 (d, J = 7.5 Hz, 1H), 7.17 (t, J = 7.3 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.36 (t, J = 7.4 Hz, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.89 (d, J = 7.5 Hz, 1H), 8.52 (br s, 1H, –NH), 10.20 (m, 1H, –NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.0, 14.1, 27.2, 49.8, 57.2, 61.6, 61.7, 77.6, 97.2, 111.4, 111.5, 117.9, 118.3, 119.4, 121.9, 122.1, 122.6, 123.2, 126.2, 126.9, 133.9, 136.4, 153.3, 156.4, 166.6, 166.7, 180.1; HRMS of [$C_{27}H_{28}N_2O_6$+H^+]: calcd: 477.2025; found: 477.2027.
21. The ratios were calculated from ^{1}H NMR spectra of crude product obtained after full conversion (integration of H-2 proton for enaminochromanone derivative and H-4 proton for 2-pyridone compound). The reaction yields in Table 2 were calculated by referring to the isolated quantity of each compound.
22. Typical procedure for the synthesis of products **2k** and **3k**. These compounds were prepared by treating 3-α,β-unsaturated chromone (1 equiv) with the corresponding amine (1.1 equiv) and 10 mol % of CsF in DCM (Scheme 2). The reaction was stirred at room temperature for the required time (monitored by TLC). At the end of the reaction the mixture was evaporated under vacuum and purified by column chromatography (gradient of hexane and ethyl acetate) to afford the desired products. Ethyl 5-(*o*-hydroxybenzoyl)-1-(2′-*sec*-butylphenyl)pyridin-2(1*H*)-one-3-carboxylate (**2k**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.75–0.84 (m, 3H), 1.19–1.27 (m, 3H), 1.37 (t, J = 7.2 Hz, 3H), 1.54–1.64 (m, 2H), 2.43–2.50 (m, 1H), 4.38 (q, J = 6.7 Hz, 2H), 6.88–6.94 (dd, J = 7.0, 7.3 Hz, 1H), 7.07 (d, J = 8.3 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.41–7.54 (m, 3H), 7.57 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 1.8 Hz, 1H), 8.63 (d, J = 1.8 Hz, 1H), 11.35 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 12.5, 14.2, 21.6, 31.0, 35.8, 61.7, 115.5, 118.6, 118.9, 119.1, 121.3, 127.0, 127.2, 127.3, 130.4, 131.3, 136.6, 138.4, 144.1, 144.2, 147.4, 158.5, 162.6, 164.2, 194.4; HRMS of [$C_{25}H_{25}NO_5$+H^+]: calcd: 420.1811; found: 420.1802 (*Z*)-2-Diethoxycarbonyl-3-(2′-*sec*-butylphenyl)aminomethylene-benzochroman-4-one (**3k**). Orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.80 (m, 3H), 1.07 (d, J = 7.1 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H), 1.60 (m, 2H), 2.93 (m, 1H), 3.91 (d, J = 10.4 Hz, 1H), 4.01 (q, J = 7.0 Hz, 2H), 4.19 (q, J = 7.0 Hz, 2H), 5.58 (d, J = 10.4 Hz, 1H), 6.80(d, J = 8.2 Hz, 1H), 7.00 (d, J = 7.4 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 8.3 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 7.34 (t, J = 7.2 Hz, 1H), 7.52 (d, J = 12.2 Hz, 1H), 7.90 (d, J = 7.7 Hz, 1H), 12.13 (d, J = 12 Hz, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 12.0, 14.0, 14.1, 20.8, 30.3, 34.7, 57.1, 61.7, 61.8, 77.6, 100.8, 116.3, 118.2, 122.1, 122.9, 124.9, 126.5, 126.9, 127.1, 134.6, 136.5, 137.8, 145.7, 156.7, 166.4, 166.5, 181.2; HRMS of [$C_{27}H_{31}NO_6$+H^+]: calcd: 466.2230; found: 466.2230.
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26. We supposed that the hydrogen bonds between the amino group and 4-carbonyl moiety of *Z*-intermediate (**II**) were cleaved under these conditions promoting the *E*-isomer (**III**) quite exclusively. These suppositions were confirmed by carrying out two complementary reactions: (1) the pure isolated product **3l** was refluxed in DCM for 2 h; and (2) 5 mol % of CsF were added at room temperature to the reaction mixture. As expected, total conversions into pyridone **2l** were achieved. In agreement with our hypothesis, we proved in this series also that the isolable 3-aminomethylene-chromanone **3l** as the kinetic product can be easily transformed into pyridone **2l** as the thermodynamic derivative.