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Synthesis of 5*H*-chromeno[3,4-*b*]pyridines via DABCO-catalyzed [3+3] annulation of 3-nitro-2*H*-chromenes and allenoates

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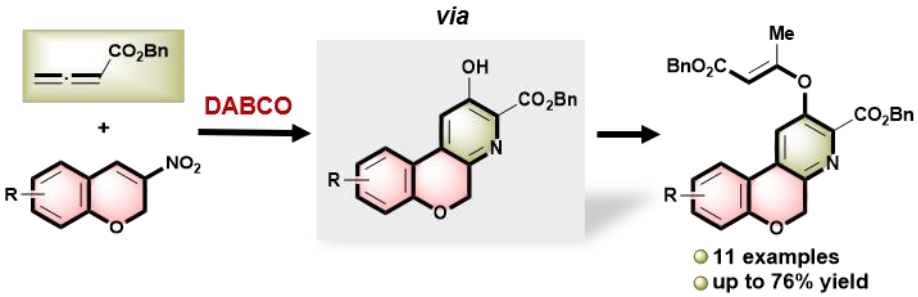
Abstract:

The DABCO-catalyzed [3+3] annulation between 3-nitro-2*H*-chromenes and benzyl 2,3-butadienoate has been developed as a route to 5*H*-chromeno[3,4-*b*]pyridine derivatives. Under optimal reaction conditions, 5*H*-chromeno[3,4-*b*]pyridines incorporating two allenoate units were obtained in moderate to good yields (30-76%). The same type of transformation could be carried out using butynoates as allene surrogates. Mechanistic studies by mass spectrometry allowed the identification of the key intermediates involved in the reaction mechanism. The reported synthetic methodology represents an entirely

new approach for the synthesis of the 5*H*-chromeno[3,4-*b*]pyridine core structure based on allene chemistry.

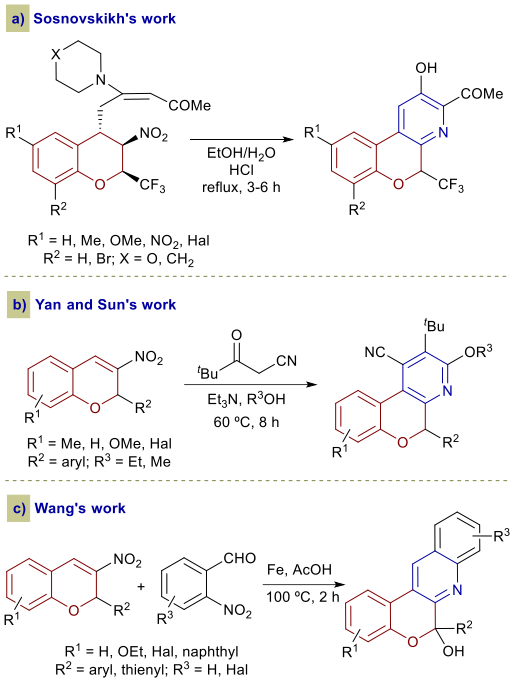


Introduction

Chromeno-fused heterocycle framework is found in several natural products and biologically active molecules.[1] Among them, molecules embodying the chromeno-pyridine core structure are well-known for their pharmacological activities, namely as antimicrobial,[2] anti-inflammatory,[2b,3] antitumoral,[4] and topoisomerase targeting antiproliferative agents,[5] and as estrogen receptor ligands.[6]

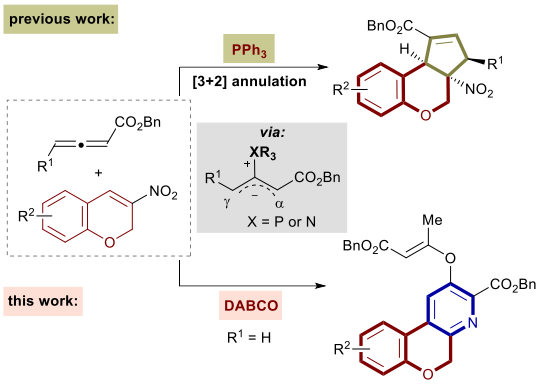
Several strategies for the synthesis of chromeno[4,3-*b*]pyridine derivatives are known,[7] in contrast with the quite scarce available approaches for the construction of systems containing the isomeric chromeno[3,4-*b*]pyridine core. Sosnovskikh *et al.* reported the synthesis of 5-(trifluoromethyl)-5*H*-chromeno[3,4-*b*]pyridines under acid-catalyzed hydrolysis of 3-nitrochromanes bearing an enaminone group at position 4 (Scheme 1a).[8] The cyclization protocol is compatible with both electron-donating and electron-withdrawing substituents at the benzene ring, but limited to 3-nitrochromanes bearing a trifluoromethyl substituent at position 2. Yan, Sun and co-workers described the synthesis of alkoxy-substituted chromeno[3,4-*b*]pyridines via a NEt_3-mediated cascade annulation reaction of 2-aryl-3-nitro-2*H*-chromenes with pivaloylacetronitriles (Scheme 1b).[9] The process involves the reaction of two molecules of pivaloylacetronitrile with one molecule of 2-aryl-3-nitro-2*H*-chromene and the most likely mechanism involves an imino-substituted dihydrofuro[2,3-*c*]chromene derivative intermediate. Wangs' group reported the synthesis of 6*H*-chromeno[3,4-*b*]quinolin-6-ol derivatives by a reductive cyclization reaction between 2-aryl-3-nitro-2*H*-chromenes and substituted 2-nitrobenzaldehydes mediated by a Fe/AcOH-system (Scheme 1c).[10] 6*H*-Chromeno[3,4-*b*]quinolin-6-ols were obtained as major products by a one-step protocol involving sequential reduction,

hydrolysis, aldol condensation, intramolecular addition and nucleophilic addition. It is noteworthy that, among the limited number of examples, all protocols share the use of 2*H*-chromenes or chromanes bearing a nitro group at position 3 as starting material.



Scheme 1. Different known approaches for the synthesis of 5*H*-chromeno[3,4-*b*]pyridine derivatives.

The versatility of 3-nitro-2*H*-chromenes as building blocks is due to their easy accessibility, but mainly to their rich and high reactivity pattern. These reactive starting materials can behave as Michael acceptors in the reaction with nucleophiles or as a 2π component in cycloaddition reactions.[11,12] The use of allenes as building blocks has been one of the research topics of our group.[13] We have described the phosphine-catalyzed formal [3+2] cycloaddition between allenic esters (allenoates) and 3-nitro-2*H*-chromenes for the synthesis of novel carbocyclic-fused chromane systems (Scheme 2).[13d] The strategy allowed the synthesis of a range of tetrahydrocyclopenta[*c*]chromenes in good yields with high stereo- and regioselectivity. Thus, having access to these two classes of reactive and versatile building blocks, allenoates and 3-nitrochromenes, we envisaged that nitrogen-containing Lewis base catalysts would induce different allenoate activation resulting in a different reactivity towards 3-nitrochromenes.



Scheme 2. Phosphine- and DABCO-catalyzed reactions between 3-nitro-2*H*-chromenes and allenoates.

In fact, allenoates are very attractive substrates for catalysis with Lewis bases. The zwitterionic intermediate generated by addition of a Lewis base to the β-carbon of an allenoate can react differently with electrophiles depending on the nature of the catalyst. Under phosphine catalysis [3+2] annulation products are obtained,[13d-g, 14] whereas in the presence of tertiary amines, conjugate addition may be observed for activated alkenes. In 2003, the synthesis of acyclic products by quinuclidine-catalyzed coupling of allenoates and α,β-unsaturated carbonyls was disclosed.[15] Later, the enantioselective Rauhut-Currier (RC) reaction of allenoates catalyzed by a chiral amine,[16] and an asymmetric intramolecular version of this reaction[17] were described. Alternatively, allenoates participate as 2C synthon in formal [4+2] cycloadditions in the presence of α,β-unsaturated carbonyl compounds that can behave as formal (hetero)dienes. In this context, the [4+2] annulation of allenoates and enones using DABCO[18] or a chiral tertiary amine[19] as catalysts was reported, paving the way for the development of a useful strategy for the synthesis of dihydopyrans.[20]

Unlike phosphine-catalyzed reactions, in the amine-catalyzed reactions, the intermediate generated from the initial conjugate addition of the zwitterionic enolate to the electrophilic partner does not undergo a second carbon-carbon bond-forming step to generate a cyclic ylide-like structure. This divergent behaviour was rationalized by DFT calculations. Yu's group observed that, under phosphine catalysis, the ring-closing step is more favourable due to the exergonic formation of phosphorus-ylides and [3+2] annulation prevails, whereas amine catalysts do not stabilize [3+2] ammonium-ylides.[21]

In this case, RC or [4+2] annulation products were observed. Nevertheless, all these advances were focused in the reactions of allenoates with α,β-unsaturated carbonyl compounds.

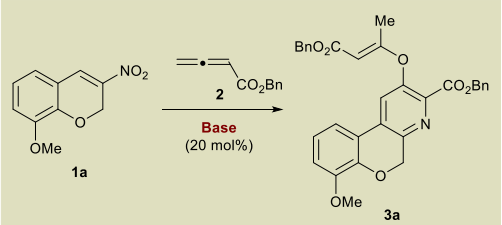
Herein, we wish to report a novel approach to pyridine-fused chromeno derivatives based on a DABCO-catalyzed [3+3] annulation between benzyl allenoate and 3-nitro-2*H*-chromenes (Scheme 2).

Results and discussion

Initially, the reaction of 8-methoxy-3-nitro-2*H*-chromene (**1a**) (1 equiv) and benzyl 2,3-butadienoate (**2**) (1.2 equiv) was carried out in toluene with DABCO as the base catalyst (20 mol%). The reaction, carried out at room temperature for 16 h, unexpectedly afforded 5*H*-chromeno[3,4-*b*]pyridine **3a** in 34% yield, in which two allene moieties were incorporated in the final product (Table 1, entry 1). This interesting result prompted us to investigate the influence of the substrate ratio in the reaction outcome. Surprisingly, it was observed that when using 2 equiv of allenoate **2**, the yield decreased to 26% (entry 2). Thus, other reaction conditions were studied, namely by changing the reaction time, solvent and additives (Table 1). The reaction of **1a** with 1.2 equiv of allenoate and 1.2 equiv of K_2CO_3 additive for 16 h afforded compound **3a** in 46% when performed in toluene, and in 40% when performed in dioxane (entries 3 and 4). The combination of 1.2 equiv of allenoate and 1.2 equiv of K_2CO_3 and 4 Å molecular sieves (MS) in toluene for 24 h proved to be the best choice, giving product **3a** in 54% yield (entry 5). The advantage of using 4 Å MS and K_2CO_3 additive was confirmed when reproducing the best conditions in their absence, since the yield decreased to 44% and 43%, respectively (entries 6 and 7). Additionally, lower yields were obtained when using DABCO pre-heated at 40 ºC for 24 h (entry 8), longer reaction times (entry 9) or using THF as solvent (entry 10). No products were isolated when performing the reaction in ethanol or acetonitrile (entries 11 and 12). Thus, with the best conditions in hand, we look again into the required amount of allenoate. Unfortunately, all attempts proved to be unsuccessful, either by using 2 (added at once or in two portions), 2.5 or 3 equiv of allenoate, leading to compound **3a** in only 9-26% yield (entries 13-16). The reaction was also carried out under microwave (MW) irradiation at 80 ºC for 25 min affording 5*H*-chromeno[3,4-*b*]pyridine **3a** in modest yield (entry 17). The influence of water has also been explored. It was observed that when water (1 equiv) was added to the reaction medium, the reaction yield dropped from

46% to 39% (Table 1, cf. entries 3 and 18). The same trend was also observed when the reaction was carried out in the absence of K_2CO_3 additive (Table 1, cf. entries 2 and 19). The use of Cs_2CO_3 instead of K_2CO_3 as additive under the best reaction conditions did not lead to an improvement, affording the target compound **3a** in 23% yield (entry 20). Finally, the use of other base catalysts was investigated. When performing the reaction in the presence DMAP, DIPEA, triethylamine or pyridine, no reaction was observed even after 48 h (Table 1, entries 21-24). On the other hand, the reaction in the presence of DBU led to the consumption of the reactants, however only a trace amount of an unidentified compound was detected (Table 1, entry 25).

Table 1. Optimization of the reaction conditions.



Entry	Allene [equiv]	Base	Additive ([equiv])	Reaction Conditions	Yield [%][a]
1	1.2	DABCO	-	toluene, rt, 16 h	34
2	2	DABCO	-	toluene, rt, 16 h	26
3	1.2	DABCO	K_2CO_3 (1.2)	toluene, rt, 16 h	46
4	1.2	DABCO	K_2CO_3 (1.2)	dioxane, rt, 16 h	40
5	**1.2**	**DABCO**	**K_2CO_3 (1.2)**	**toluene, rt, 24 h, MS 4 Å**	**54**
6	1.2	DABCO	K_2CO_3 (1.2)	toluene, rt, 24 h	44
7	1.2	DABCO	-	toluene, rt, 24 h, MS 4 Å	43
8	1.2	DABCO	K_2CO_3 (1.2)	toluene, rt, 24 h, MS 4 Å[b]	36
9	1.2	DABCO	K_2CO_3 (1.2)	toluene, rt, 48 h, MS 4 Å	44
10	1.2	DABCO	K_2CO_3 (1.2)	THF, rt, 24 h, MS 4 Å	44
11	1.2	DABCO	K_2CO_3 (1.2)	EtOH, rt, 1.5 h, MS 4 Å	-
12	1.2	DABCO	K_2CO_3 (1.2)	MeCN, rt, 1.5 h, MS 4 Å	Trace amount
13	2	DABCO	K_2CO_3 (1.2)	toluene, rt, 24 h, MS 4 Å	26
14	2[c]	DABCO	K_2CO_3 (1.2)	toluene, rt, 24 h, MS 4 Å	9
15	2.5	DABCO	K_2CO_3 (1.2)	toluene, rt, 24 h, MS 4 Å	24
16	3	DABCO	K_2CO_3 (1.2)	toluene, rt, 24 h, MS 4 Å	21
17	1.2	DABCO	-	toluene, MW, 80 ºC, 25 min	29
18	1.2	DABCO	K_2CO_3 (1.2)	toluene, H_2O (1 equiv), rt, 16 h	39
19	1.2	DABCO	-	toluene, H_2O (1 equiv), rt, 16 h	21

20	1.2	DABCO	Cs_2CO_3 (1.2)	toluene, rt, 24 h, MS 4Å	23
21	1.2	DMAP	K_2CO_3 (1.2)	toluene, rt, 48 h, MS 4 Å	- [d]
22	1.2	DIPEA	K_2CO_3 (1.2)	toluene, rt, 48 h, MS 4 Å	- [d]
23	1.2	NEt_3	K_2CO_3 (1.2)	toluene, rt, 48 h, MS 4 Å	- [d]
24	1.2	Py	K_2CO_3 (1.2)	toluene, rt, 48 h, MS 4 Å	- [d]
25	1.2	DBU	K_2CO_3 (1.2)	toluene, rt, 24 h, MS 4 Å	-

[a] Isolated yields; [b] DABCO heated at 40 ºC for 24 h; [c] 1 equiv added at the beginning of the reaction and another equiv after 7 h; [d] no reaction.

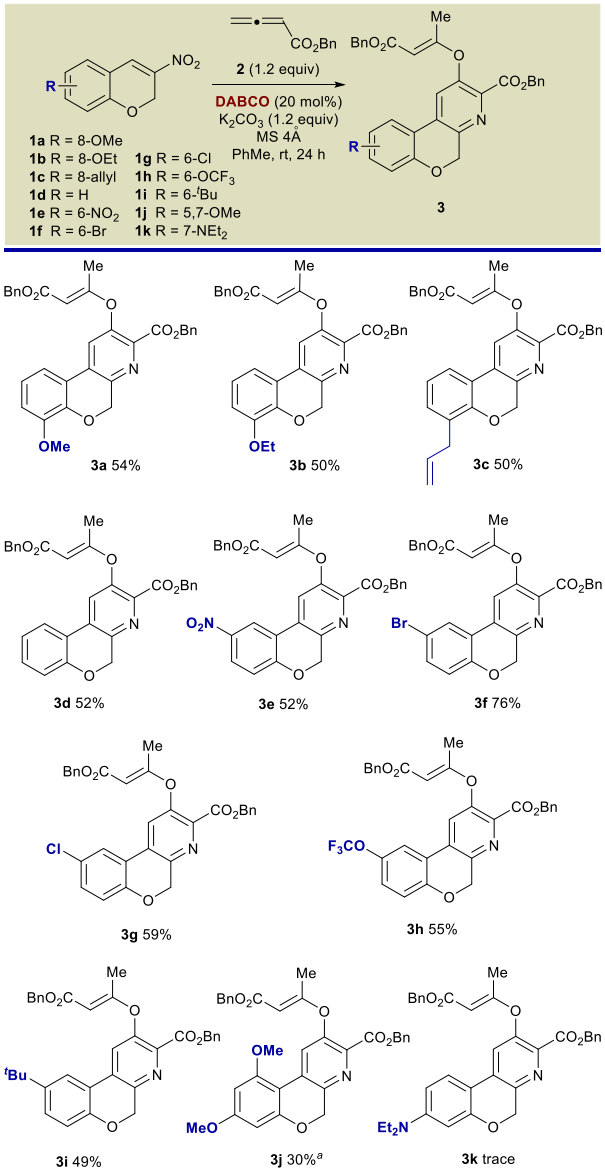
The optimized reaction conditions were applied to the reaction of allenoate **2** with other substituted 3-nitro-2*H*-chromenes **1**. The results are summarized in Scheme 3. The reaction of allenoate **2** with 8-ethoxy-3-nitro-2*H*-chromene (**1b**) afforded 7-ethoxy-5*H*-chromeno[3,4-*b*]pyridine **3b** in 50% yield. The molecular structure of compound **3b** was unambiguously established by single-crystal X-ray diffraction. Figure 1 depicts its ORTEP diagram, the most relevant bond distances (Å) and angles (º) being reported in the corresponding Figure caption. The molecular structure of compound **3b** features three almost coplanar fused rings, with substituents on the C2 and C3 atoms of the pyridine ring, and on C7 of the 5*H*-chromene moiety. The dihedral angle between the chromeno and pyridine rings is 18.04(5)º. All distances and angles are within the expected values for similar compounds.[22]

The target chromeno[3,4-*b*]pyridines **3c** and **3d** were also obtained in good yields from 7-allyl- and unsubstituted 3-nitro-2*H*-chromenes **1c** and **1d**, respectively. The reaction of allenoate **2** with 3-nitro-2*H*-chromenes bearing electron-withdrawing and electron-donating substituents at position 6 afforded chromeno[3,4-*b*]pyridines **3e-i** in yields ranging from 49% to 76%, with the best result observed starting from the nitrochromene bearing a bromine substituent.

The reaction of disubstituted nitrochromene **1j**, carried out at under the optimized conditions (rt, 24 h) led to the formation of chromeno[3,4-*b*]pyridine **3j** in only 4% together with 2-hydroxy-8,10-dimethoxy-5*H*-chromeno[3,4-*b*]pyridine **4** (Scheme 4). Under these conditions, about half of the initial quantity of 3-nitro-2*H*-chromene **1j** was recovered. The structure of compound **4** was determined by single-crystal X-ray diffraction (Scheme 4). In this case, the dihedral angle between the chromeno and pyridine rings is smaller than that observed for compound **3b**, being of 6.85(13)º and

5.53(14)º for the two molecules in the asymmetric unit. The difference observed between the two derivatives is mainly due to the existence of π-π interactions with parallel displaced geometry between the two molecules in the asymmetric unit. These interactions are inexistent in **3b** because of the bulky substituents present at C2 and C3 of the pyridine moiety that prevents π-stacking. Moreover, in the case of compound **4**, it was also possible to observe O−H···O interactions that lead to dimerization through the formation of $R_2^2(12)$ synthons. All bond lengths and angles are consistent with the values reported in the literature.[22]

In order to improve the synthesis of compound **3j**, the reaction was carried out at higher temperature, 60 ºC for 30 h, affording compound **3j** as the sole product in 30% yield (Scheme 3). Attempts to carry out the reaction at higher temperatures (*e.g.* 80 ºC) were unsuccessful, giving compound **3j** in lower yield. The lower efficiency observed in the synthesis of compound **3j** may be explained considering the higher steric hindrance in the vicinity of the activated carbon-carbon double bond. Finally, the reactivity of 3-nitro-2*H*-chromene **1k** bearing a diethylamino group at position 7 with allenoate **2** was examined. The reaction performed under the optimized conditions led to the formation of the target product **3k** in trace amount and in a very impure form and could only be detected by ^{1}H NMR spectroscopy.



Scheme 3. DABCO-catalyzed reaction of benzyl 2,3-butadienoate (**2**) with 3-nitro-2*H*-chromenes **1**. [a] The reaction was performed at 60 ºC for 30 h.

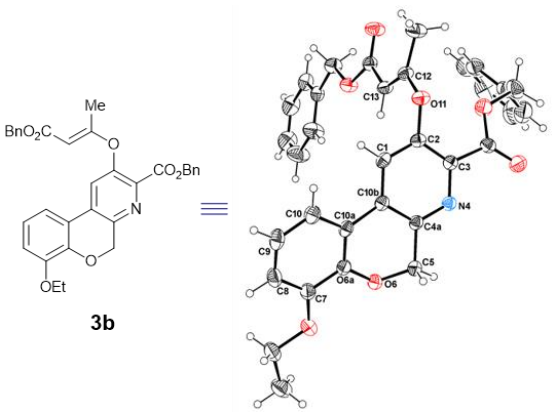
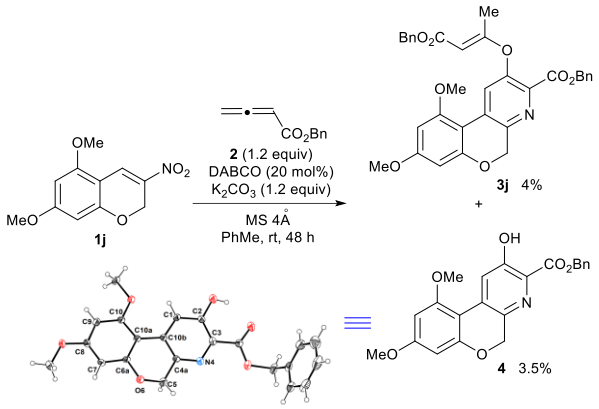
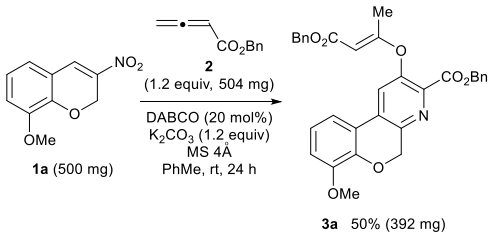


Figure 1. ORTEP representation of compound **3b**, using 30% level ellipsoids. Selected bond lengths: C1–C2 1.387(2) Å, C2–C3 1.403(2) Å, C3–N4 1.3492(19) Å, N4–C4a 1.329(2) Å, C4a–C5 1.508(2) Å, C5–O6 1.445(2) Å, O6–C6A 1.3771(19) Å, C4a–C10b 1.410(2) Å. Selected bond angles: C3–N4–C4a 118.76(13)º, C4a–C5–O6 111.09(13)º, C5–O6–C6a 113.81(12)º.



Scheme 4. DABCO-catalyzed reaction of benzyl 2,3-butadienoate (**2**) with 3-nitro-2*H*-chromene **1j** carried out at rt for 48 h and ORTEP representation of compound **4**, using 30% level ellipsoids. One independent molecule was omitted for clarity. Selected bond lengths: C1–C2 1.389(6) Å, C2–C3 1.388(6) Å, C3–N4 1.340(5) Å, N4–C4a 1.324(5) Å, C4a–C5 1.486(6) Å, C5–O6 1.405(5) Å, O6–C6A 1.385(5) Å, C4a–C10b 1.396(5) Å. Selected bond angles: C3–N4–C4a 118.0(4)º, C4a–C5–O6 114.3(4)º, C5–O6–C6a 116.6(3)º.

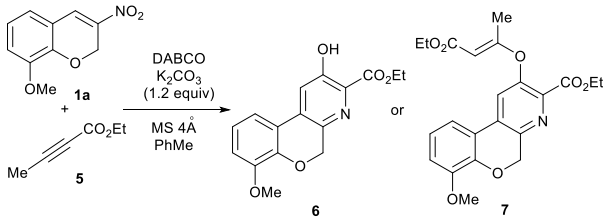
To demonstrate the practicability of our protocol, a scale-up experiment was carried out, wherein 500 mg of **1a** was reacted with 504 mg of allenoate **2** under the optimized conditions to give 392 mg of **3a** in 50% yield (Scheme 5).



Scheme 5. Scale-up reaction of benzyl 2,3-butadienoate (**2**) with 3-nitro-2*H*-chromene **1a**.

The DABCO-catalyzed reaction of benzyl γ-methyl- and γ-phenylallenoates, with 3-nitro-2*H*-chromene **1a** in the presence of K_2CO_3 was also examined. However, although some evidence of the formation of the corresponding chromeno[3,4-*b*]pyridines by ^{1}H NMR spectroscopy was observed, it was not possible to isolate any products in pure form. Then, we evaluated the scope of allenoate with different ester moieties. Due to its volatility, monosubstituted 2,3-butadienoates, such as methyl and ethyl 2,3-butadienoate, are very difficult to handle. Thus, the use of ethyl 2-butynoate (**5**) as 1,3-dipole precursor was investigated as an alternative to ethyl allenoate. Phosphines have been used to generate formal 1,3-dipoles from 2-butynoates,[23,13f] however the use of DABCO to catalyse the generation of these zwitterionic species is less common.[24] Initially, the reaction of 3-nitro-2*H*-chromene **1a** with ethyl 2-butynoate (**5**) was attempted under the reaction conditions optimized for the reaction with allenoate **2** (Table 2, entry 1). However, no products were observed even after 48 h. Next, we attempted to use the conditions recently described by us for the phosphine-catalyzed [3+2] annulation between 6-alkyllidenepenicillanates and 2-butynoates.[13f] However, the reaction 3-nitro-2*H*-chromene **1a** with 2-butynoate **5** (6 equiv) and DABCO (2.4 equiv) at room temperature only showed evidence of a product after 120 h. Thus, a second portion of **5** (6 equiv) was added and the reaction was stirred for more 48 h, affording 2-hydroxy-5*H*-chromeno[3,4-*b*]pyridine **6** in low yield (6%) together with starting material, 3-nitrochromene **1a** (75%) (Table 3, entry 2). When the reaction was carried out at 60 ºC, the reaction was completed over 120 h and chromeno[3,4-*b*]pyridine **7** was obtained as single product in 21% yield (Table 3, entry 3). By carrying out the reaction at higher temperatures, the reaction was completed with shorter reaction time, while the yield remained relatively low (Table 3, entries 4 and 5). A 2D NOE experiment confirmed the *E* configuration of the side chain of compound **7**. From the analysis of the NOESY spectrum no cross-peaks were observed between the methyl protons (δ = 2.56 ppm) and vinyl proton (δ = 4.79 ppm) of the double bond in the side-chain.

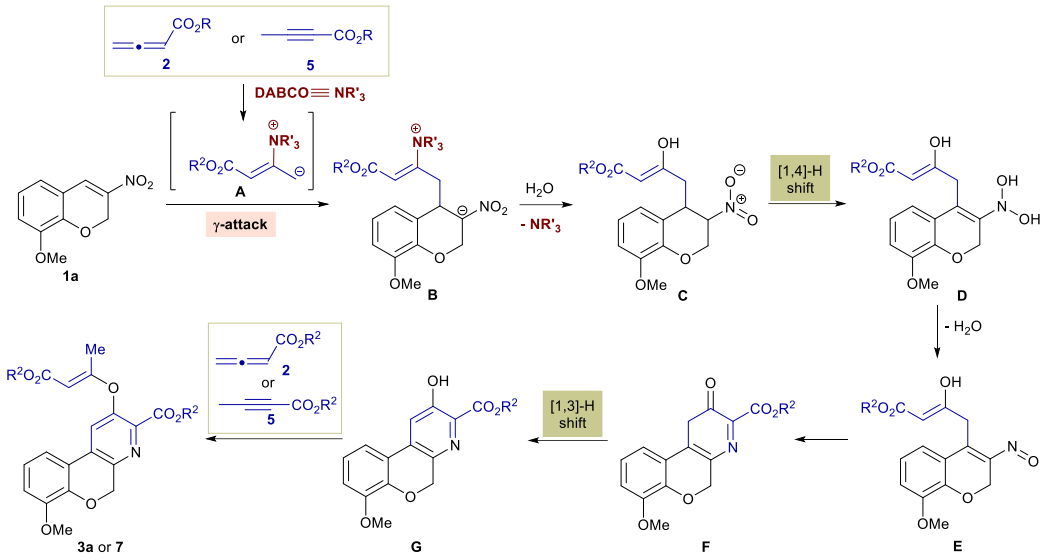
Table 2. DABCO-mediated reaction of ethyl 2-butynoate (**5**) with 3-nitro-2*H*-chromene **1a**



Entry	**5** (equiv)	DABCO (equiv)	Reaction Conditions	Yield (%)[a]	
				6	**7**
1	1.2	0.2	rt, 48 h	- [b]	
2	12[c]	2.4	rt, 168 h	6[d]	-
3	6	2.4	60 ºC, 120 h	-	21
4	6	2.4	80 ºC, 72 h	-	18
5	6	2.4	100 ºC, 24 h	-	15

[a] Isolated yields; [b] no reaction; [c] 6 equiv added at the beginning of the reaction and 6 equiv after 120 h; [d] isolated with nitrochromene **1a** (75%).

Based on the amine-catalyzed allenoate reactivity, a plausible reaction mechanism for the synthesis of chromeno[3,4-*b*]pyridines is depicted in Scheme 6. Initial conjugate addition of the γ-position of the allenoate/alkyne-derived zwitterionic species **A** to the activated alkenes **1** generates intermediates **B**. Due to the hygroscopic properties of DABCO, we can assume that water could be present in the reaction medium. Thus, intermediates **B** undergo a nucleophilic attack by water to give enol intermediates **C** with elimination of DABCO. Subsequent [1,4]-H shift and dehydration leads to nitroso alkene intermediates **E**. Intramolecular nucleophilic attack of the enol on the nitroso group followed by dehydration and rearrangement through a [1,3]-H shift gives 2-hydroxy-5*H*-chromeno[3,4-*b*]pyridines **G**. Nucleophilic addition of **G** to a second allenoate, or alkyne, molecule furnishes chromeno[3,4-*b*]pyridine derivatives containing a double bond with *E* configuration in the side chain. The selective formation of enamines with *E* configuration in the reaction of allenoates with nitrogen nucleophiles (aziridines) has been previously reported for the synthesis of *N*-vinylaziridines.[25]



Scheme 6. Proposed mechanism for the synthesis of 5*H*-chromeno[3,4-*b*]pyridines.

This proposal is consistent with the work reported by the Sosnovskikh group, in which the formation of a nitroso alkene intermediate analogous to **E** was invoked to rationalize the synthesis of 2-hydroxy-5-(trifluoromethyl)-5*H*-chromeno[3,4-*b*]pyridines from aminoenone-substituted 3-nitrochromanes under acid-catalyzed conditions (see Scheme 1a).[8] The authors proposed the generation of a nitroso alkene intermediate via an initial nucleophilic substitution of the cyclic amine moiety by water, [1,4]-H shift and dehydration. Cyclization of the nitroso alkene intermediate followed by a second dehydration and a double [1,3]-H shift provided the final products.

The formation of 2-hydroxy-5*H*-chromeno[3,4-*b*]pyridines **4** and **6** (intermediates **G** in the mechanistic proposal) in the DABCO-catalyzed reaction of allenoate **2** or butynoate **5** with 3-nitro-2*H*-chromenes **1j** and **1a**, respectively, strongly supports this proposal (see Scheme 4 and Table 2). Regarding water involvement in the proposed mechanism, it was observed that when pre-heated DABCO was used, the reaction yield dropped from 54% to 36% (see Table 1, entry 8). On the other hand, the reaction yields also decreased when water was added to the reaction (Table 1, entries 18 and 19). Thus, the presence of a small amount of water seems to be crucial, however, the excess of water does not favour the efficiency of the overall synthesis.

In order to validate our proposal, the reaction mechanism was investigated by mass spectrometry. The [3+3] annulation of allene **2** with nitrochromene **1a** was chosen as the model reaction. The full mass spectrum of the reaction mixture obtained in the ESI

positive mode, at 60 min, allowed the identification of a peak attributed to the protonated form of intermediate **B** (*m/z* 494) (Fig. S26 in ESI). The ESI/MS spectrum obtained in the negative mode, at the same reaction time, showed three peaks which were assigned to the deprotonated forms of intermediates **C/D** (*m/z* 398), **E** (*m/z* 380) and **F/G** (*m/z* 362) (Fig. S27 in ESI). MS^2 spectra obtained by collision induced dissociations (CID) of these precursor ions in the ion trap analyser, allowed the characterization of the intermediates **B**, **C/D**, **E** and **F/G** based on the corresponding fragmentation patterns (see the MS^2 spectra and proposed fragmentation pathways, Figs. S28-35 in ESI). Subsequently, the identification of all intermediates was achieved by high-resolution mass spectrometry (HRMS). The high-resolution full scan mass spectrum, obtained in the ESI positive mode for the reactional mixture at 20 min, showed the presence of a small peak at *m/z* 494.2299 which was assigned to the protonated form of intermediate **B** (Figure 2a). The deprotonated forms of intermediates **C/D** (*m/z* 398.1243), **E** (*m/z* 380.1142) and **F/G** (362.1038) were identified in the high-resolution full scan mass spectrum obtained in the ESI negative mode at the same reaction time (Figure 2b). Thus, the identification and characterization of all intermediates by HRMS combined with MS^2 experiments, strongly supports the proposed reaction mechanism.

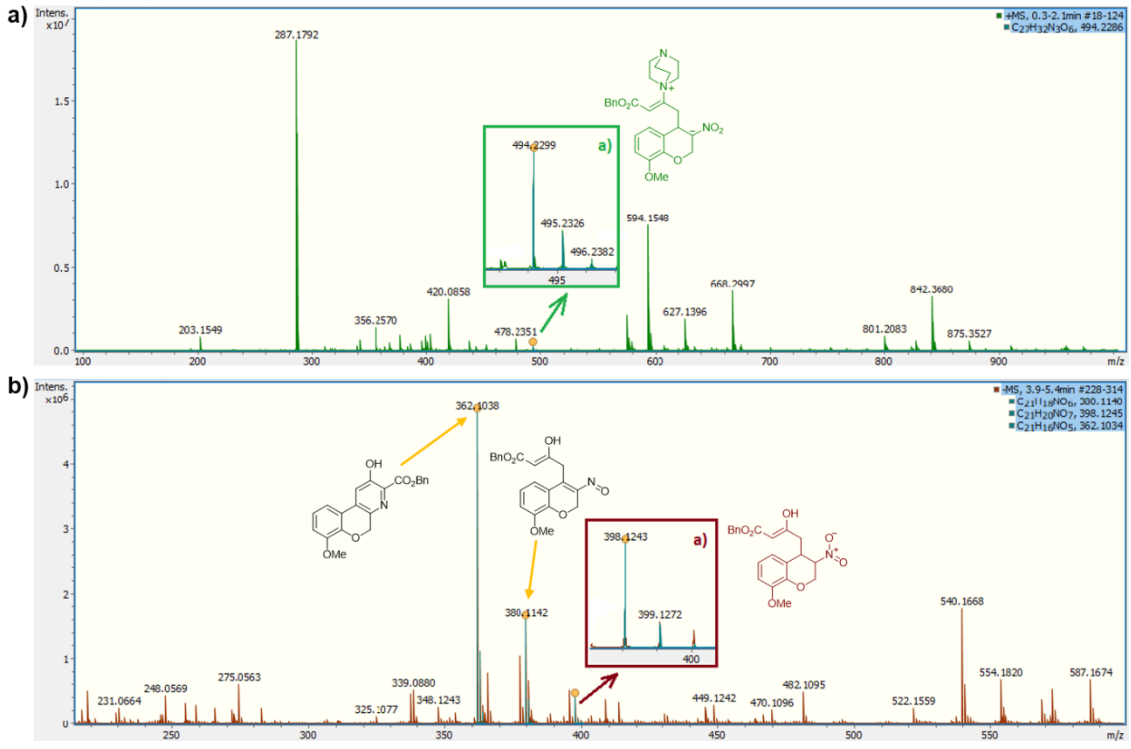


Figure 2. a) High-resolution full scan mass spectrum obtained in the ESI positive mode for the reactional mixture, at 20 min. The small peak at *m/z* 494.2299 (insert a) was assigned to the protonated molecule of intermediate **B** ($C_{27}H_{32}N_3O_6^+$, -2.8 ppm); b) High-resolution full scan mass spectrum obtained in the ESI negative mode for the reactional mixture, at 20 min. Peaks at *m/z* 398.1243 (insert a), 380.1142 and 362.1038 were attributed to the deprotonated molecules of the intermediates **C/D** ($C_{21}H_{20}NO_7^-$, +0.5 ppm), **E** ($C_{21}H_{18}NO_6^-$, +0.9 ppm), **F/G** ($C_{21}H_{16}NO_5^-$, -3.3 ppm), respectively.

Conclusions

In summary, we have disclosed a novel [3+3] annulation protocol for the preparation of new chromeno[3,4-*b*]pyridines using 3-nitro-2*H*-chromenes and benzyl 2,3-butadienoate in the presence of DABCO. The synthetic procedure requires mild reaction conditions and is compatible with several electron-donating and electron-withdrawing substituted 3-nitro-2*H*-chromenes. Additionally, we have demonstrated that chromeno[3,4-*b*]pyridines can also be obtained using alkynes as allene surrogates. The identification of the reaction intermediates by mass spectrometry validated the proposed reaction mechanism. The reported methodology represents an alternative route for the synthesis of biologically relevant chromeno[3,4-*b*]pyridine systems based on allenoate chemistry.

Experimental section

General remarks

Thin-layer chromatography (TLC) analyses were performed using precoated silica gel plates. Flash column chromatography was performed with silica gel 60 as the stationary phase. The ^{1}H NMR spectra were recorded on an instrument operating at 400 MHz, the ^{13}C NMR spectra were recorded on an instrument operating at 100 MHz. and the ^{19}F NMR spectra were recorded with an instrument operating at 376 MHz. Chemical shifts are expressed in parts per million relatively to internal tetramethylsilane (TMS), and coupling constants (*J*) are in hertz. Infrared spectra (IR) were recorded in a Fourier Transform spectrometer. Elemental analyses were carried out with an Elemental Vario Micro Cube analyser. High-resolution mass spectra (HRMS) were obtained on a TOF VG Autospect M spectrometer or on a Thermo Orbitrap Q-Exactive Focus spectrometer with electrospray ionization (ESI). Melting points were determined in open glass capillaries.

3-Nitro-2*H*-chromenes **1a**, **b**, **d-h** and **j**,[26,13d] and allenoate **2**[27] were prepared as described in the literature.

8-Allyl-3-nitro-2*H*-chromene (1c): In accordance with the general procedure described elsewhere for the synthesis of 3-nitro-2*H*-chromenes,[1] 3-allyl-2-hydroxy-benzaldehyde (1.05 g, 6.47 mmol) afforded **1c** (0.61 g, 43%) as a yellow solid. M.p. 77-78 ºC (from petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.36 (d, J = 6.5 Hz, 2H), 5.04-5.09 (m, 2H), 5.27 (pseudo-d, J = 0.9 Hz, 2H), 5.89-5.99 (m, 1H), 6.96 (pseudo-t, J = 7.6 Hz, 1H), 7.14 (dd, J = 1.5 and 7.6 Hz, 1H), 7.23 (dd, J = 1.3 and 7.6 Hz, 1H), 7.79 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 33.6, 62.9, 116.2, 118.2, 122.4, 128.3, 128.8, 129.6, 134.7, 135.8, 139.0, 152.5 ppm. IR (ATR): ν = 1654, 1595, 1517, 1459, 1322, 1237, 1198, 1051 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{11}NO_3$ $[M+H]^+$ 218.0812; found 218.0815.

6-(*tert*-Butyl)-3-nitro-2*H*-chromene (1i): In accordance with the general procedure described elsewhere for the synthesis of 3-nitro-2*H*-chromenes,[1] 5-*tert*-butyl-2-hydroxy-benzaldehyde (1.00 g, 5.61 mmol) afforded **1i** (0.33 g, 25%) as a yellow solid. M.p. 114-115 ºC (from petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.30 (s, 9H), 5.23 (pseudo-d, J = 0.8 Hz, 2H), 6.86 (d, J = 8.6 Hz, 1H), 7.24 (d, J = 2.4 Hz, 1H), 7.38 (dd, J = 2.4 and 8.6 Hz, 1H), 7.81 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 31.3, 34.2, 63.0, 116.1, 117.8, 127.2, 129.9, 131.3, 139.0, 145.8, 152.8 ppm. IR (ATR): ν = 1654, 1546, 1503, 1324, 1268, 1231, 1196, 1140 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{16}NO_3$ $[M+H]^+$ 234.1125; found 234.1122.

***N*,*N*-Diethyl-3-nitro-2*H*-chromen-7-amine (1k):** In accordance with the general procedure described elsewhere for the synthesis of 3-nitro-2*H*-chromenes,[1] 4-(diethylamino)salicylaldehyde (1.05 g, 5.43 mmol) afforded **1k** (0.100 g, 7%) as a purple solid. M.p. 109-110 ºC (from petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.20 (t, J = 7.1 Hz, 6H), 3.39 (q, J = 7.1 Hz, 4H), 5.21-5.22 (m, 2H), 6.14 (d, J = 2.2 Hz, 1H), 6.31 (dd, J = 2.5 and 8.8 Hz, 1H), 7.06 (d, J = 8.7 Hz, 1H), 7.81 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.6, 44.9, 63.4, 97.8, 106.6, 106.8, 131.3, 132.4, 132.5, 153.0, 157.6 ppm. IR (ATR): ν = 1604, 1526, 1472, 1443, 1307, 1195, 1133, 1072 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{17}N_2O_3$ $[M+H]^+$ 249.1234; found 249.1238.

General procedure for the DABCO-catalyzed reaction of allenoate 2 with 3-nitrochromenes 1. To a suspension of 3-nitro-2*H*-chromene **1** (0.66 mmol), DABCO (0.13 mmol), K_2CO_3 (0.79 mmol) and 4 Å molecular sieves (1 g) in toluene (6 mL), a solution of benzyl 2,3-butadienoate (**2**) (0.79 mmol) in toluene (4 mL) was added. The reaction mixture was stirred at room temperature under nitrogen for 24 h. After completion of the reaction, the mixture was filtered through a pad of celite and washed with ethyl acetate. The solvent was evaporated, and the products were purified by flash chromatography.

Benzyl (*E*)-2-((4-(benzyloxy)-4-oxobut-2-en-2-yl)oxy)-7-methoxy-5*H*-chromeno[3,4-*b*]pyridine-3-carboxylate (3a): Obtained from chromene **1a** (47 mg, 0.23 mmol) and allene **2** (47 mg, 0.27 mmol). Purification by flash chromatography [hexane/EtOAc (3:1), then [1:1]) gave compound **3a** as solid (39 mg, 54%). Crystallization from EtOAc/petroleum ether gave the compound as a white solid. M.p. 153-155 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.32 (s, 3H), 3.93 (s, 3H), 4.78 (s, 1H), 5.05 (s, 2H), 5.38 (s, 4H), 6.96 (dd, *J* = 1.1 and 8.1 Hz, 1H), 7.04 (pseudo-t, *J* = 8.0 Hz, 1H), 7.20 (dd, *J* = 1.2 and 7.9 Hz, 1H), 7.28-7.33 (m, 8H), 7.38-7.40 (m, 2H), 7.62 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.1, 56.2, 65.8, 67.8, 69.7, 96.5, 113.9, 116.0, 119.9, 122.6, 125.0, 128.2, 128.3, 128.5, 128.6, 128.7, 130.7, 135.1, 136.1, 139.6, 144.4, 148.7, 149.4, 150.0, 163.2, 166.6, 173.0 ppm. IR (ATR): ν = 1704, 1641, 1426, 1396, 1255, 1226, 1141, 1116 cm^{-1}. HRMS (ESI): calcd for $C_{32}H_{28}NO_7$ $[M+H]^+$ 538.1860; found 538.1863.

Benzyl (*E*)-2-((4-(benzyloxy)-4-oxobut-2-en-2-yl)oxy)-7-ethoxy-5*H*-chromeno[3,4-*b*]pyridine-3-carboxylate (3b): Obtained from chromene **1b** (145 mg, 0.66 mmol) and allene **2** (137 mg, 0.79 mmol). Purification by flash chromatography [hexane/EtOAc (3:1), then [1:2]) gave compound **3b** as solid (110 mg, 50%). Crystallization from EtOAc/petroleum ether gave the compound as a yellow solid. M.p. 141-142 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.48 (t, *J* = 7.0 Hz, 3H), 2.32 (s, 3H), 4.15 (q, *J* = 7.0 Hz, 2H), 4.78 (s, 1H), 5.05 (s, 2H), 5.37 (s, 2H), 5.38 (s, 2H), 6.94-7.03 (m, 2H), 7.19 (dd, *J* = 1.5 and 7.7 Hz, 1H), 7.28-7.33 (m, 8H), 7.38-7.40 (m, 2H), 7.61 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.8, 18.1, 64.8, 65.8, 67.8, 69.7, 96.4, 115.4, 116.0, 120.0, 122.5, 124.9, 128.2, 128.3, 128.5, 128.6, 128.7, 130.8, 135.1, 136.1, 139.5, 144.7, 148.7, 148.8,

150.0, 163.2, 166.6, 173.0 ppm. IR (ATR): ν = 1727, 1705, 1638, 1390, 1252, 1219, 1123 cm^{-1}. HRMS (ESI): calcd for $C_{33}H_{30}NO_7$ $[M+H]^+$ 552.2017; found 552.2010.

Benzyl (*E*)-7-allyl-2-((4-(benzyloxy)-4-oxobut-2-en-2-yl)oxy)-5*H*-chromeno[3,4-*b*]pyridine-3-carboxylate (3c): Obtained from chromene **1c** (87 mg, 0.40 mmol) and allene **2** (84 mg, 0.48 mmol). Purification by flash chromatography [hexane/EtOAc (3:1)] gave compound **3c** as solid (66 mg, 50%). Crystallization from EtOAc/petroleum ether gave the compound as a white solid. M.p. 110-111 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.32 (s, 3H), 3.43 (d, *J* = 6.4 Hz, 2H), 4.77 (s, 1H), 5.05 (s, 2H), 5.05-5.09 (m, 2H), 5.29 (s, 2H), 5.38 (s, 2H), 5.94-6.04 (m, 1H), 7.03 (pseudo-t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.3 Hz, 1H), 7.44-7.27 (m, 10H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.62 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.1, 33.9, 65.8, 67.8, 69.4, 96.4, 116.0, 119.0, 122.4, 122.5, 124.8, 128.2, 128.3, 128.5, 128.6, 128.6, 129.7, 131.1, 132.7, 135.2, 136.1, 136.2, 139.3, 148.9, 150.0, 152.8, 163.2, 166.6, 173.0 ppm. IR (ATR): ν = 1704, 1647, 1253, 1213, 1141, 1104 cm^{-1}. HRMS (ESI): calcd for $C_{34}H_{30}NO_6$ $[M+H]^+$ 548.2068; found 548.2061.

Benzyl (*E*)-2-((4-(benzyloxy)-4-oxobut-2-en-2-yl)oxy)-5*H*-chromeno[3,4-*b*]pyridine-3-carboxylate (3d): Obtained from chromene **1d** (135 mg, 0.76 mmol) and allene **2** (159 mg, 0.91 mmol). Purification by flash chromatography [hexane/EtOAc (3:1)] gave compound **3d** as solid (122 mg, 52%). Crystallization from EtOAc/petroleum ether gave the compound as a white solid. M.p. 124-125 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.33 (s, 3H), 4.78 (s, 1H), 5.06 (s, 2H), 5.31 (s, 2H), 5.38 (s, 2H), 7.03-7.10 (m, 2H), 7.28-7.40 (m, 11H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.63 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.1, 65.8, 67.8, 69.4, 96.4, 118.1, 119.1, 122.7, 124.4, 124.6, 128.2, 128.3, 128.5, 128.6, 128.7, 130.7, 132.2, 135.1, 136.1, 139.5, 148.8, 150.0, 155.0, 163.2, 166.6, 173.0 ppm. IR (ATR): ν = 1704, 1643, 1255, 1238, 1192, 1140, 1114 cm^{-1}. HRMS (ESI): calcd for $C_{31}H_{26}NO_6$ $[M+H]^+$ 508.1755; found 508.1752.

Benzyl (*E*)-2-((4-(benzyloxy)-4-oxobut-2-en-2-yl)oxy)-9-nitro-5*H*-chromeno[3,4-*b*]pyridine-3-carboxylate (3e): Obtained from chromene **1e** (130 mg, 0.58 mmol) and allene **2** (122 mg, 0.70 mmol). Purification by flash chromatography [hexane/EtOAc (3:1)] gave compound **3e** as solid (101 mg, 52%). Crystallization from EtOAc/petroleum ether gave the compound as a pale-yellow solid. M.p. 120-121 ºC. ^{1}H NMR ($CDCl_3$, 400

MHz): δ = 2.35 (s, 3H), 4.77 (s, 1H), 5.06 (s, 2H), 5.39 (s, 2H), 5.44 (s, 2H), 7.14 (d, *J* = 9.0 Hz, 1H), 7.29-7.39 (m, 10H), 7.77 (s, 1H), 8.23 (dd, *J* = 2.5 and 9.0 Hz, 1H), 8.52 (d, *J* = 2.5 Hz, 1H), ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.0, 65.9, 68.0, 69.8, 96.9, 118.9, 119.2, 120.5, 125.4, 127.3, 128.3, 128.4, 128.6, 128.67, 128.70, 134.9, 136.0, 141.4, 142.9, 147.5, 150.0, 159.6, 162.8, 166.3, 172.9 ppm. IR (ATR): ν = 1713, 1637, 1520, 1340, 1236, 1199, 1111 cm^{-1}. HRMS (ESI): calcd for $C_{31}H_{25}N_2O_8$ $[M+H]^+$ 555.1605; found 555.1608.

Benzyl (*E*)-2-((4-(benzyloxy)-4-oxobut-2-en-2-yl)oxy)-9-bromo-5*H*-chromeno[3,4-*b*]pyridine-3-carboxylate (3f): Obtained from chromene **1f** (155 mg, 0.61 mmol) and allene **2** (127 mg, 0.73 mmol). Purification by flash chromatography [hexane/EtOAc (3:1)] gave compound **3f** as solid (163 mg, 76%). Crystallization from EtOAc/petroleum ether gave the compound as a pale-yellow solid. M.p. 127-128 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.33 (s, 3H), 4.76 (s, 1H), 5.06 (s, 2H), 5.30 (s, 2H), 5.38 (s, 2H), 6.93 (d, *J* = 8.7 Hz, 1H), 7.29-7.33 (m, 8H), 7.38-7.40 (m, 2H),7.43 (dd, *J* = 2.2 and 8.7 Hz, 1H), 7.61 (s, 1H), 7.70 (d, *J* = 2.2 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.0, 65.8, 67.9, 69.4, 96.6, 115.1, 119.9, 121.0, 124.8, 127.0, 128.2, 128.4, 128.5, 128.6, 128.7, 129.4, 134.8, 135.0, 136.1, 140.3, 148.4, 150.0, 154.0, 163.0, 166.4, 172.9 ppm. IR (ATR): ν = 1706, 1647, 1389, 1237, 1184, 1139 cm^{-1}. HRMS (ESI): calcd for $C_{31}H_{25}NO_6$ $[M+H]^+$ 586.0860; found 586.0863.

Benzyl (*E*)-2-((4-(benzyloxy)-4-oxobut-2-en-2-yl)oxy)-9-chloro-5*H*-chromeno[3,4-*b*]pyridine-3-carboxylate (3g): Obtained from chromene **1g** (144 mg, 0.68 mmol) and allene **2** (142 mg, 0.82 mmol). Purification by flash chromatography [hexane/EtOAc (4:1)] gave compound **3g** as solid (131 mg, 59%). Crystallization from EtOAc/petroleum ether gave the compound as a white solid. M.p. 119 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.33 (s, 3H), 4.76 (s, 1H), 5.06 (s, 2H), 5.30 (s, 2H), 5.38 (s, 2H), 6.98 (d, *J* = 8.7 Hz, 1H), 7.28-7.33 (m, 9H), 7.38-7.39 (m, 2H),7.56 (d, *J* = 2.4 Hz, 1H), 7.61 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.0, 65.8, 67.9, 69.5, 96.6, 119.5, 120.5, 124.1, 124.8, 127.9, 128.2, 128.4, 128.5, 128.6, 128.7, 129.6, 131.9, 135.0, 136.1, 140.3, 148.5, 150.0, 153.5, 163.0, 166.4, 172.9 ppm. IR (ATR): ν = 1709, 1638, 1392, 1238, 1183, 1133, 1122 cm^{-1}. Anal. Calcd for $C_{31}H_{24}ClNO_6$: C, 68.70; H, 4.46; N, 2.58. Found: C, 68.76; H, 4.37; N, 2.61.

Benzyl (*E*)-2-((4-(benzyloxy)-4-oxobut-2-en-2-yl)oxy)-9-(trifluoromethoxy)-5*H*-chromeno[3,4-*b*]pyridine-3-carboxylate (3h): Obtained from chromene **1h** (122 mg, 0.47 mmol) and allene **2** (98 mg, 0.56 mmol). Purification by flash chromatography [hexane/EtOAc (3:1)] gave compound **3h** as solid (92 mg, 55%). Crystallization from EtOAc/petroleum ether gave the compound as a white solid. M.p. 129-131 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.33 (s, 3H), 4.76 (s, 1H), 5.06 (s, 2H), 5.32 (s, 2H), 5.38 (s, 2H), 7.06 (d, *J* = 8.9 Hz, 1H), 7.21 (dd, *J* = 8.8 and 2.0 Hz, 1H), 7.29-7.33 (m, 8H), 7.38-7.40 (m, 2H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.60 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.0, 65.8, 67.9, 69.5, 96.6, 117.2, 119.4, 120.1, 120.5 (q, $J_{C\text{-}F_3}$ = 255.7 Hz), 125.3, 128.2, 128.4, 128.5, 128.58, 128.65, 128.7, 129.5, 135.0, 136.0, 140.5, 144.2 (d, $J_{C\text{-}O\text{-}CF_3}$ = 1.8 Hz), 148.5, 150.0, 153.4, 163.0, 166.4, 172.9 ppm. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -58.25 ppm. IR (KBr): ν = 1726, 1707, 1645, 1396, 1246, 1223, 1198, 1169, 1136 cm^{-1}. HRMS (ESI): calcd for $C_{33}H_{25}F_3NO_7$ $[M+H]^+$ 592.1578; found 592.1587.

Benzyl (*E*)-2-((4-(benzyloxy)-4-oxobut-2-en-2-yl)oxy)-9-(*tert*-butyl)-5*H*-chromeno[3,4-*b*]pyridine-3-carboxylate (3i): Obtained from chromene **1i** (148 mg, 0.63 mmol) and allene **2** (133 mg, 0.76 mmol). Purification by flash chromatography [hexane/EtOAc (3:1)] gave compound **3i** as solid (105 mg, 49%). Crystallization from EtOAc/petroleum ether gave the compound as a pale-yellow solid. M.p. 159-160 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (s, 9H), 2.34 (s, 3H), 4.78 (s, 1H), 5.06 (s, 2H), 5.27 (s, 2H), 5.38 (s, 2H), 6.98 (d, *J* = 8.6 Hz, 1H), 7.28-7.33 (m, 8H), 7.38-7.41 (m, 3H), 7.56 (d, *J* = 2.3 Hz, 1H), 7.63 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.1, 31.4, 34.5, 65.8, 67.8, 69.5, 96.4, 117.6, 118.3, 120.7, 124.4, 128.2, 128.3, 128.5, 128.5, 128.6, 128.7, 129.7, 131.3, 135.2, 136.1, 139.1, 145.7, 149.1, 150.0, 152.8, 163.2, 166.6, 173.1 ppm. IR (ATR): ν = 1734, 1701, 1636, 1393, 1239, 1190, 1130 cm^{-1}. HRMS (ESI): calcd for $C_{35}H_{34}NO_6$ $[M+H]^+$ 564.2381; found 564.2376.

Benzyl (*E*)-2-((4-(benzyloxy)-4-oxobut-2-en-2-yl)oxy)-8,10-dimethoxy-5*H*-chromeno[3,4-*b*]pyridine-3-carboxylate (3j): Obtained from chromene **1j** (75 mg, 0.32 mmol) and allene **2** (66 mg, 0.38 mmol). The reaction mixture was stirred at 60 ºC for 30 h. Purification by flash chromatography [hexane/EtOAc (3:1)1] gave compound **3j** as a solid (32 mg, 30%). Crystallization from EtOAc/petroleum ether gave the compound as

a pale-yellow solid. M.p. 143-145 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.32 (s, 3H), 3.82 (s, 3H), 3.88 (s, 3H), 4.79 (s, 1H), 5.06 (s, 2H), 5.19 (s, 2H), 5.37 (s, 2H), 6.20 (d, *J* = 2.2 Hz, 1H), 6.24 (d, *J* = 2.2 Hz, 1H), 7.28-7.34 (m, 8H), 7.38-7.40 (m, 2H), 8.19 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.2, 55.6, 55.8, 65.6, 67.6, 69.9, 93.8, 94.5, 95.9, 102.7, 127.7, 128.1, 128.3, 128.4, 128.5, 128.57, 128.61, 130.2, 135.3, 136.2, 136.8, 147.6, 149.8, 158.1, 159.9, 163.0, 163.4, 166.9, 173.2 ppm. IR (ATR): ν = 1725, 1712, 1613, 1575, 1329, 1253, 1205, 1130, 1104, 10044 cm^{-1}. HRMS (ESI): calcd for $C_{33}H_{30}NO_8$ $[M+H]^+$ 568.1966; found 568.1957.

Benzyl (*E*)-2-((4-(benzyloxy)-4-oxobut-2-en-2-yl)oxy)-8-(diethylamino)-5*H*-chromeno[3,4-*b*]pyridine-3-carboxylate (3k): Obtained from chromene **1i** (40 mg, 0.16 mmol) and allene **2** (34 mg, 0.19 mmol). Purification by flash chromatography [hexane/EtOAc (3:1)] gave compound **3i** in trace amount and in a very impure form.

Benzyl 2-hydroxy-8,10-dimethoxy-5*H*-chromeno[3,4-*b*]pyridine-3-carboxylate (4) and Benzyl (*E*)-2-((4-(benzyloxy)-4-oxobut-2-en-2-yl)oxy)-8,10-dimethoxy-5*H*-chromeno[3,4-*b*]pyridine-3-carboxylate (3j): To a suspension of 3-nitro-2*H*-chromene **1j** (65 mg, 0.27 mmol), DABCO (6 mg, 0.055 mmol), K_2CO_3 (45 mg, 0.33 mmol) and 4 Å molecular sieves (0.40 g) in toluene (3 mL), a solution of benzyl 2,3-butadienoate (**2**) (57 mg, 0.33 mmol) in toluene (2 mL) was added. The reaction mixture was stirred at room temperature under nitrogen for 48 h. After completion of the reaction, the mixture was filtered through a celite pad, washed with ethyl acetate, and the solvent was evaporated. Purification of the crude product by flash chromatography [hexane/EtOAc (3:1)] gave, in order of elution, 3-nitro-2*H*-chromene **1j** (28 mg), 5*H*-chromeno[3,4-*b*]pyridine **4** (3 mg, 3.5%) and 5*H*-chromeno[3,4-*b*]pyridine **3j** (4 mg, 4%).

*Data for 5H-chromeno[3,4-b]pyridine **4***: Crystallization from EtOAc/petroleum ether gave the compound as a pale-yellow solid. M.p. 171-173 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.82 (s, 3H), 3.92 (s, 3H), 5.09 (s, 2H), 5.51 (s, 2H), 6.22 (s, 2H), 7.34-7.40 (m, 3H), 7.51 (d, *J* = 7.2 Hz, 2H), 8.18 (s, 1H), 10.68 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 55.5, 55.7, 67.5, 70.0, 93.7, 94.5, 103.3, 121.3, 125.6, 128.5, 128.6, 131.4, 135.4, 142.7, 158.4, 159.2, 160.2, 162.8, 169.4 ppm. IR (KBr): ν = 1709, 1664, 1618, 1591, 1456, 1412, 1209, 1157, 1105 cm^{-1}. HRMS (ESI): calcd for $C_{22}H_{20}NO_6$ $[M+H]^+$ 394.1285; found 394.1281.

Ethyl 2-hydroxy-7-methoxy-5*H*-chromeno[3,4-*b*]pyridine-3-carboxylate (6): To a suspension of 3-nitro-2*H*-chromene **1a** (300 mg, 1.45 mmol), K_2CO_3 (240 mg, 1.74 mmol), DABCO (390 mg, 3.48 mmol) and 4 Å molecular sieves (2.00 g) in toluene (14 mL), a solution of ethyl 2-butynoate (**5**) (974 mg, 8.69 mmol) in toluene (8 mL) was added. After stirring at room temperature under nitrogen for 120 h, a second portion of **5** (974 mg, 8.69 mmol) was added and the reaction mixture was stirred another 48 h. The reaction mixture was filtered through a celite pad, washed with ethyl acetate, and the solvent was evaporated. Purification of the crude product by flash chromatography [hexane/EtOAc (3:1), then (2:1)] gave, in order of elution, 3-nitro-2*H*-chromene **1a** (224 mg, 75%) and compound **6** in impure form (25 mg, 6%). Recrystallization of **6** from petroleum ether/ethyl acetate furnished a purer sample which was used to obtain the NMR spectrum. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.49 (t, J = 7.1 Hz, 3H), 3.93 (s, 3H), 4.56 (q, J = 7.1 Hz, 2H), 5.30 (s, 2H), 6.96 (dd, J = 1.1 and 8.1 Hz, 1H), 7.05 (pseudo-t, J = 8.0 Hz, 1H), 7.29 (dd, J = 1.3 and 7.9 Hz, 1H), 7.58 (s, 1H), 10.91 (s, 1H) ppm. HRMS (ESI): calcd for $C_{16}H_{16}NO_5$ $[M+H]^+$ 302.1023; found 302.1022.

Ethyl (*E*)-2-((4-ethoxy-4-oxobut-2-en-2-yl)oxy)-7-methoxy-5*H*-chromeno[3,4-*b*]pyridine-3-carboxylate (7): To a suspension of 3-nitro-2*H*-chromene **1a** (65 mg, 0.31 mmol), K_2CO_3 (52 mg, 0.38 mmol), DABCO (84 mg, 0.75 mmol) and 4 Å molecular sieves (0.50 g) in toluene (3 mL), a solution of ethyl but-2-ynoate (**5**) (209 mg, 1.86 mmol) in toluene (2 mL) was added. The reaction mixture was stirred at 60 ºC under nitrogen for 120 h. After completion of the reaction, the mixture was filtered through a celite pad, washed with ethyl acetate, and the solvent was evaporated. Purification of the crude product by flash chromatography [hexane/EtOAc (3:1), then (2:1)] gave compound **7** (27 mg, 21%). Crystallization from EtOAc/petroleum ether gave the compound as a pale-yellow solid. M.p. 153-155 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.20 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 2.56 (s, 3H), 3.94 (s, 3H), 4.09 (q, J = 7.1 Hz, 2H), 4.43 (q, J = 7.1 Hz, 2H), 4.79 (s, 1H), 5.40 (s, 2H), 6.98 (dd, J = 1.1 and 8.1 Hz, 1H), 7.06 (pseudo-t, J = 8.0 Hz, 1H), 7.23 (dd, J = 1.2 and 7.9 Hz, 1H), 7.67 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.2, 14.2, 18.2, 56.2, 59.8, 62.1, 69.7, 96.8, 113.8, 116.0, 120.0, 122.6, 125.0, 130.5, 139.6, 144.3, 148.5, 149.4, 150.0, 163.2, 166.9, 172.3 ppm. IR (ATR): ν = 1727, 1705, 1640, 1416, 1255, 1224, 1138, 1129 cm^{-1}. HRMS (ESI): calcd for $C_{22}H_{24}NO_7$ $[M+H]^+$ 414.1547; found 414.1543.

X-ray diffraction

Crystals suitable for single-crystal X-ray analysis of compounds **3b** and **4** were selected, covered with Fomblin (polyfluoro ether oil) and mounted on a nylon loop. The data were collected at room temperature on a Bruker D8 Venture diffractometer equipped with a Photon 100 CMOS detector, using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The data was processed using the APEX3 suite software package, which includes integration and scaling (SAINT), absorption corrections (SADABS)[28] and space group determination (XPREP). Structure solution and refinement were done using direct methods with the programs SHELXT 2014/5 and SHELXL (version 2018/3)[29] inbuilt in APEX and WinGX-Version 2020.1[30] software packages. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were inserted in idealized positions and allowed to refine riding on the parent carbon or oxygen atom with C−H distances of 0.95 Å and 0.98 Å, for aromatic and methyl H atoms, respectively. Although compound **3b** showed a high R_{int} (22%), it refined to convergence and all results were consistent with the model reported herein. The molecular diagrams were drawn with ORTEP3 (version 2020.1)[30] included in the software package. The data was deposited in CCDC under the deposit numbers 2079932 for **3b** and 2079933 for **4**.

Mass spectrometry studies

Characterization of allene 2, intermediates and compound 3a by HRMS: Samples were analyzed by direct infusion on a QqTOF Impact II^{TM} mass spectrometer operating in the ESI positive and negative modes. Internal calibration was achieved with a solution of ammonium formate 10 mM over a mass range of 100-1000 *m/z* at a spectra rate of 1Hz. Data acquisition and processing were performed using the Data Analysis 4.2 software. HRMS spectra are available in Electronic Supplementary Information.

Compound 2: HRMS (ESI): calcd for $C_{11}H_{11}O_2$ $[M+H]^+$ 175.0765; found 175.0767.

***Intermediate A*:** HRMS (ESI): calcd. for $C_{17}H_{23}N_2O_2$ $[M+H]^+$ 287.1754; found 287.1764.

Intermediate B: HRMS (ESI): calcd. for $C_{27}H_{32}N_3O_6$ $[M+H]^+$ 494.2286; found 494.2300.

Intermediate C/D: HRMS (ESI): calcd. for $C_{21}H_{20}NO_7$ $[M-H]^-$ 398.1245; found 398.1243.

Intermediate E: HRMS (ESI): calcd. for $C_{21}H_{18}NO_6$ $[M-H]^-$ 380.1140; found 380.1136.

Intermediate F/G: HRMS (ESI): calcd. for $C_{21}H_{16}NO_5$ $[M-H]^-$ 362.1034; found 362.1046

Compound 3a: HRMS (ESI): calcd. for $C_{32}H_{27}KNO_7$ $[M+K]^+$ 576.1419; found 576.1439.

Structural Characterization of the reaction intermediates: The MS^2 spectra were obtained in a Bruker HCT QIT mass spectrometer equipped with an ESI source operating in the positive and negative mode. Full scan mass spectra, MS^2 spectra and proposed fragmentation pathways are available in Electronic Supplementary Information.

Conflicts of interest

There are no conflicts to declare.

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