Tetrahedron 66 (2010) 4542–4550

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

One-pot approach to the synthesis of novel 12*H*-chromeno[2′,3′:4,5]imidazo-[1,2-*a*]pyridines in aqueous media

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ARTICLE INFO

Article history:
Received 11 March 2010
Received in revised form 12 April 2010
Accepted 13 April 2010
Available online 24 April 2010

Keywords:
Salicylaldehyde
Pyridinium chloride
Chromene
Imidazo[1,2-*a*]pyridine
Cascade reaction

ABSTRACT

The chromeno-imidazo[1,2-*a*]pyridine scaffold was generated in an one pot condensation/cyclization reaction involving a salicylaldehyde and 1-(cyanomethyl)pyridinium chloride, in aqueous sodium carbonate solution. These novel compounds were isolated in 47–71% yield. The reaction pathway was followed by ^{1}H NMR spectroscopy allowing a clear understanding of the side reactions involved in the process.

Different mono-substituted pyridinium chlorides were synthesized and reacted with mono-substituted salicylaldehydes and a detailed discussion of the scope of the synthetic method is also presented.

1. Introduction

Chromene derivatives are an important class of compounds, considering their diverse biological properties and therapeutic applications.[1] Structural modifications of this core unit led to new drug candidates for the treatment of psychiatric and neurological disorders, a research area of recent interest for our research group. Substituted chromenes can bind to 5HT receptors, acting as antagonists,[2] and were also reported as MAO inhibitors[3] and human β-secretase inhibitors.[4] The imidazo[1,2-*a*]pyridine nucleus is also an important scaffold in the preparation of a diversity of biologically active compounds. Molecules incorporating this core unit showed antibacterial,[5] *anti*-inflammatory,[6,7] analgesic,[6,7] antipyretic,[6] anticonvulsant,[6] hypnoselective,[8] and anxioselective[8] activities. The antiulcer agent zolimidine and the hypnotic drug zolpidem are bioactive molecules already on the market (Fig. 1).

Different synthetic pathways have been used to prepare substituted imidazo[1,2-*a*]pyridines, either from the imidazole or from the pyridine nucleus.[9] To the best of our knowledge, the association of this moiety with the chromene unit has never been reported. The combination of these two important scaffolds may lead to new and alternative drug candidates with improved pharmacological profile.

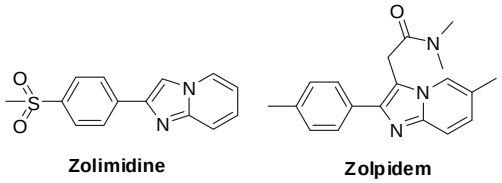

Figure 1. Representative examples of bioactive molecules containing the imidazo[1,2-*a*]pyridine scaffold.

2. Results and discussion

Our previous studies on the synthesis of chromene derivatives by the Knoevenagel condensation of salicylaldehydes with *N*-substituted cyanoacetamides showed that the reaction occurs in aqueous base, under mild conditions, leading to 2-imino and 2-oxo-3-carboxamido-chromenes in excellent yield.[10] The substituent in position 3 of the chromene ring is a crucial element for biological activity[3d] and the present work was initially aimed at the synthesis of 2-imino and 2-oxo-chromenes bearing a good leaving-group in the 3-position. The pyridinium ion was considered a good candidate and the commercially available 1-(cyanomethyl)pyridinium chloride **1a** was reacted with salicylaldehyde **2a** using a similar synthetic approach.

Compound **4a** was expected as the major product, from the Knoevenagel condensation of carbon acid **1** with the aldehyde,

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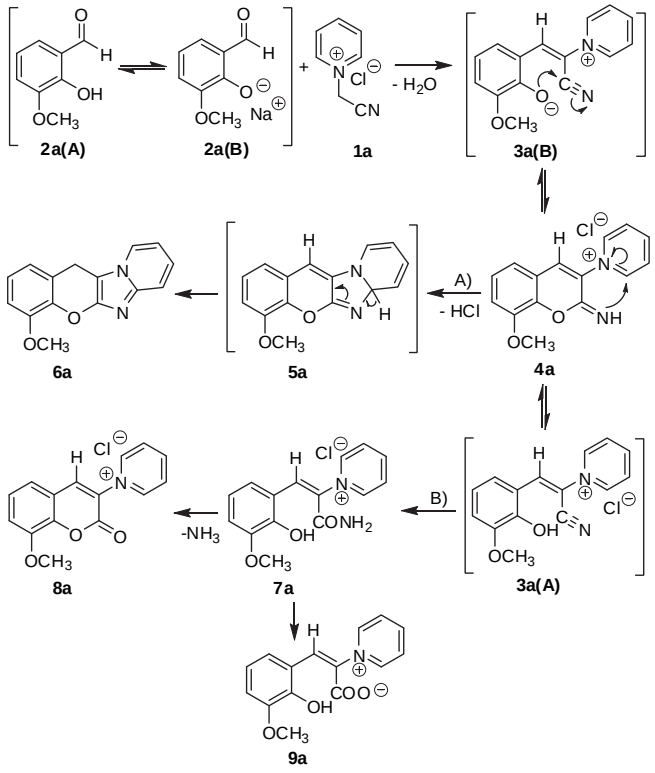
doi:10.1016/j.tet.2010.04.059

followed by intramolecular cyclization of intermediate **3a**, as is represented in Scheme 1. When a 1.1:1 M ratio of reagents **1a** and **2a** were combined in an aqueous 0.05 M sodium carbonate solution, and stirred in a water bath at 60 °C for 16 h, the solid that precipitated from the reaction mixture was fully characterized and identified as the tetracyclic product **6a** (Scheme 1). In aqueous base, the reaction of **4a** proceeds with nucleophilic attack of the imine nitrogen to C-2 of the activated pyridinium ring. The neutral species **5a** rapidly tautomerizes to the isolated product **6a**.



Scheme 1. Proposed mechanism for the reaction of 1-(cyanomethyl)pyridinium chloride **1a** with 3-methoxysalicylaldehyde **2a**. (A) Intramolecular cyclization by nucleophilic substitution on the pyridinium ring. (B) Hydrolysis of the cyano group due to a prolonged contact with the aqueous basic medium.

The ^{1}H NMR spectrum of this compound showed a singlet at δ 4.28 ppm integrating for two protons assigned to C-11 (δ 22.4 ppm). The HMBC and HMQC spectra confirmed the neighboring carbon atoms through the two- three- and four-bonds correlations (Fig. 2). A doublet at δ 8.31 ppm, assigned to the proton on C-10 (δ 124.6 ppm), allowed the identification of C-10b (δ 98.5 ppm), C-6a (δ 139.0 ppm), C-7 (δ 114.9 ppm), C-8 (δ 125.0 ppm), and C-9 (δ 112.8 ppm). Elemental analysis confirmed the empirical formula and IR spectroscopy showed the absence of OH/NH signals, supporting the novel structure assigned to the compound.

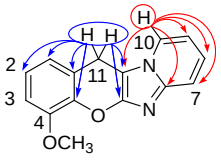


Figure 2. Structural information obtained by NMR correlation studies (HMBC and HMQC) on a DMSO-d_6 solution of compound **6a**.

Nucleophilic attack of a primary amine to C-2 of a *N*-aryl pyridinium salt, known as the Zincke reaction[11] leads to ring opening of the pyridinium moiety followed by ring closure to generate a new pyridinium salt incorporating the primary amine.[12] In this work, the unprecedented evolution of the *N*-heteroaryl pyridinium chloride is primarily due to the presence of a nucleophilic imino nitrogen in the chromene moiety, conveniently located in the vicinity of the pyridinium ring. The evolution of intermediate **5a** to generate the stable tautomer **6a** was considered a key feature for the success of this cascade reaction. The aldehyde was combined with the pyridinium salt under different temperature conditions (rt, 60 and 80 °C) using aqueous 0.05 M sodium carbonate or sodium hydrogen carbonate solution and varying the reaction time. Compound **6a** was always the only product isolated in a yield that never exceeded 62% (Table 1).

Table 1
Synthesis of substituted 1-(cyanomethyl)pyridinium chlorides **1**

Compd	Reaction conditions	Yield (%)
1a	**10a**+**11** (2 equiv), CH_3CN, reflux, 7.5 h	85[a]
1b	**10b**+**11** (2 equiv), CH_3CN, reflux, 7 h	95[a]
1c	**10c**+**11** (1 equiv), rt, 1 day	5
	10c+bromoacetonitrile (1 equiv) rt, 17.5 h	58[b]
1d	**10d**+**11** (2 equiv), CH_3CN, reflux, 1.5 h	93
1e	**10e**+**11** (2 equiv), CH_3CN, reflux, 40 min	95
1f	**10f**+**11** (3.2 equiv), CH_3CN, reflux, 6 h	92[c]
1g	**10g**+**11** (4.5 equiv), CH_3CN, reflux, 3 days	77
1h	**10h**+**11** (4 equiv), CH_3CN, reflux, 1 day	77
1i	**10c**+**11** (6.2 equiv), CH_3CN, reflux, 3 days	89

[a] Commercially available.
[b] Isolated as the bromide salt.
[c] Ref. 13.

Although the reaction of salicylaldehyde **2a** with the pyridinium chloride **1a** in aqueous sodium carbonate proceeds directly to the tetracyclic product **6**, the use of ethanol/acetone (1:3 volume ratio) and one molar equivalent of *N*-methylpiperazine allowed the isolation of the intermediate 2-iminochromene **4a**. The product precipitated from solution and was isolated in 78% yield after 30 min in an ice bath. A similar synthetic approach was used to prepare compounds **4b**–**d**, isolated in 45–86% yield and fully characterized. When **4a** was solubilized in aqueous 0.05 M sodium hydrogen carbonate, and the mixture was stirred at 60 °C for 5 h, the same product **6a** was isolated in 54% yield, supporting the proposed reaction pathway.

This reaction was also followed by ^{1}H NMR, at room temperature. Salicylaldehyde **2a**, pyridinium salt **1a** and sodium carbonate were combined in D_2O, inside the NMR tube. The first spectrum, registered immediately after addition of the solvent, shows that 2-iminochromene **4a** is the only new compound present in solution (34%) besides the aldehyde (26%) and the pyridinium chloride (40%). The aldehyde proton, around δ 9.9 ppm, confirms the presence of this functional group, but the aromatic protons are considerably shifted to higher field. This indicates that the shielding effect of the electron-donating oxygen atom is enhanced by the formation of the anion (**2a**(**B**)). The chemical shift of the adjacent methoxyl group is also affected, shifting from δ 3.89 ppm (in the phenolic aldehyde) to δ 3.69 ppm. The concentration of compound **4a** gradually increases in solution. This study indicates that only part of the iminochromene **4a** evolves to **6a**. The presence of base facilitates ring opening to generate the anion **3a**(**B**) or the corresponding phenolic species **3a**(**A**), where the cyano group is susceptible to hydrolysis (Scheme 1). The extent of this process increases with time and temperature and a delicate balance is required to optimize the yield of the chromeno-imidazo[1,2-*a*] pyridine **6**.

After approximately 2 h at room temperature, traces of a compound identified as **7a** were detected in solution. The signals for **6a** were always absent in the spectrum, as this compound is completely insoluble in water and gradually precipitates from solution. The solid suspension was not visible during the first eight hours at room temperature. After 12 days, no noticeable evolution was detected in the reaction mixture and the solid was separated from solution. Both crops were studied by ^{1}H and ^{13}C NMR using correlation techniques (HMBC and HMQC). The major product in solution was compound **7a**, generated by hydrolysis of the cyano group due to a long contact with aqueous base. The solid, solubilized in deuterated DMSO, was a mixture of compounds **6a** and **9a** (1:1.6 M ratio).

Compound **8a** was always isolated from the mother liquor, in the synthesis of compound **6a**, and probably arises from intramolecular cyclization of **7a**, with elimination of ammonia, also identified in the NMR spectrum. Compound **8a** could be generated directly from **4a** in ethanol and aqueous HCl solution. The product precipitated from solution and was isolated in 64% yield after two days at room temperature and a further four days standing at 0 °C.

Other substituted pyridines were converted to *N*-cyanomethyl pyridinium chlorides **1b**–**i** upon reaction with chloroacetonitrile (Table 1). The reaction usually requires reflux conditions in acetonitrile and the use of an excess of alkyl halide (2–6.2 M equiv).

Pyridine **10c** (R=3-$COOCH_3$) is unstable at temperatures above 40 °C, and the neat liquid reagents were combined at room temperature. The reaction was very slow, and only 5% of the solid product was isolated after one day. The use of bromoacetonitrile under similar experimental conditions (neat mixture, at room temperature) led to the corresponding pyridinium bromide in 58% yield.

Aldehydes **2b**–**d** were reacted with the pyridinium salt **1b**, **1g**, and **1i** under similar reaction conditions as those used for the preparation of compound **6a** (Table 2).

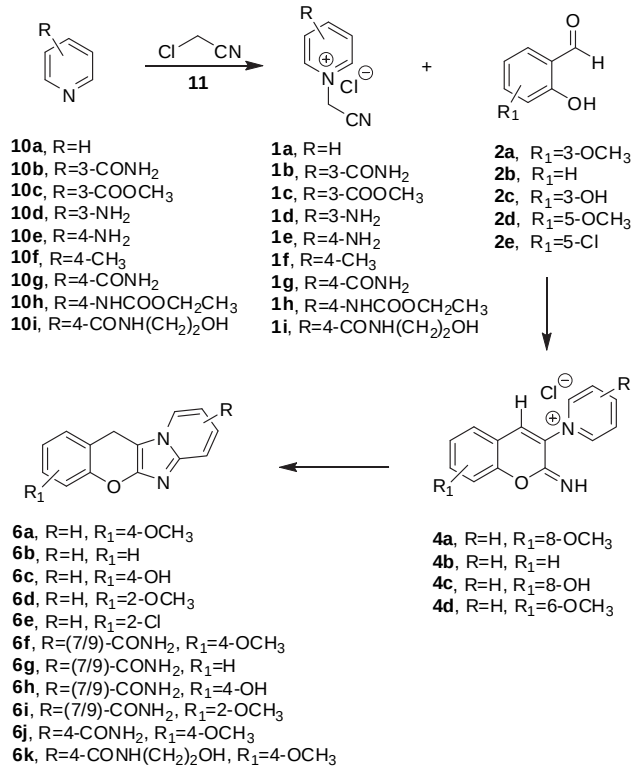
Table 2
Synthesis of chromeno-imidazo[1,2-*a*]pyridines **6**

Compd	Reaction conditions[a]	Yield (%)
6a	**2a**+**1a** (1.1 equiv), 60 °C, 16 h	62
6b	**2b**+**1a** (1.1 equiv), 80 °C, 7 h	49
6c	**2c**+**1a** (1.1 equiv), 80 °C, 14.5 h	58
6d	**2d**+**1a** (1.1 equiv), 80 °C, 13.5 h and 60 °C 19 h	47
6e	**2e**+**1a** (1.1 equiv), reflux, 1 h 40 min	50[b]
6f	**2a**+**1b** (1 equiv), 60 °C, 16 h	55[c]
6g	**2b**+**1b** (1.1 equiv), 60 °C, 16 h	61[c]
6h	**2c**+**1b** (1.1 equiv), 60 °C, 16 h	71[c]
6i	**2d**+**1b** (1.1 equiv), 60 °C, 16 h	52[c]
6j	**2a**+**1g** (1.1 equiv), 60 °C, 19 h	67
6k	**2a**+**1i** (1.1 equiv), 60 °C, 19 h	58

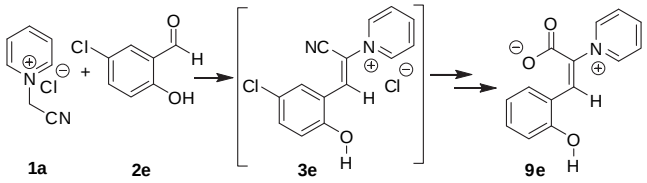
[a] All reactions were carried out in aqueous 0.05 M Na_2CO_3 or $NaHCO_3$ solution.
[b] The product was slightly contaminated with **9e**.
[c] Yield of the isolated mixture of **6f**–**i**(**A**) and **6f**–**i**(**B**) (approximately 1:1.6 ratio by ^{1}H NMR).

The corresponding chromeno-imidazo[1,2-*a*]pyridines **6** were isolated after 24–29 h at room temperature (**6b**–**d** and **f**) or in a water bath (60/80 °C) for 7–19 h (**6b**–**k**). The yellow solid precipitates from the reaction medium on cooling and requires no further purification (Scheme 2).

The low solubility of aldehyde **2e** (R=5-Cl) in aqueous base, at room temperature, resulted in a very slow reaction with **1a**. The suspension was heated at 40 °C for 11 h, followed by 18 h at 80 °C, leading to a solid product identified as a mixture of **6e** and **9e** (1:1.3 ratio by ^{1}H NMR) (Scheme 3). A second crop was isolated, corresponding to the pure compound **9e** (23%).



Scheme 2. Reaction sequence for the preparation of chromeno-imidazo[1,2-*a*]pyridines **6**.



Scheme 3. Proposed mechanism for the formation of compound **9e**.

The reaction was repeated using reflux conditions, leading to compound **6e** (50%) after 1 h 40 min. Prolonged heating in aqueous base leads to hydrolysis of the cyano group in intermediate **3e**, preventing intramolecular cyclization to **4e**. The formation of a carboxylate function and the vicinity of the acidic proton to the chlorine atom on C-5 of the aromatic ring constitute a plausible driving force for nucleophilic substitution of the halogen, under the experimental conditions that were used (Scheme 3).

The new pyridinium chlorides prepared, with electron donating (NH_2, $NHCOOCH_2CH_3$, CH_3) and electron withdrawing ($CONH_2$, $COOCH_3$, $CONH(CH_2)_2OH$) substituents in the 3- and 4- position of the heteroaromatic ring, were reacted with 3-methoxysalicylaldehyde **2a**. Compounds **1b**, **1g**, and **1i** were combined with **2a** in aqueous base and heated at 60 °C for 16–19 h leading to the corresponding chromeno-imidazo[1,2-*a*]pyridines **6f**, **6j**, and **6k** in 55–67% yield (Table 2). The 3-substituted pyridinium chloride **1b** generated a mixture of isomers **6f**(**A**) and **6f**(**B**) in a 1:1.9 M ratio, by ^{1}H NMR (Fig. 3). This indicates that the steric hindrance of the carbamoyl substituent has a moderate effect on the final cyclization step, resulting from nucleophilic attack of the imine nitrogen to the pyridinium ring.

Attempts to improve selectivity by performing the reaction at room temperature (17.5 h) led to a similar isomer ratio by ^{1}H NMR (**6f**(**A**)/**6f**(**B**), 1:1.5). These two compounds could be separated using

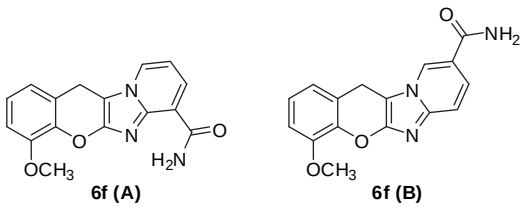


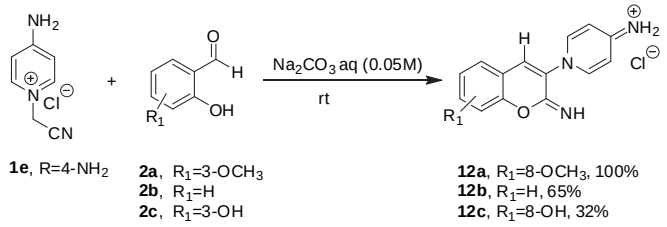
Figure 3. Isomers formed in the reaction of 1-(cyanomethyl)pyridinium chloride **1b** with 3-methoxysalicylaldehyde **2a**.

preparative chromatography and a mixture of dichloromethane and ethanol (9:1 ratio) as eluent.

No further reactions were carried out using 3-substituted pyridinium salts due to the absence of selectivity in the formation of the tetracyclic product.

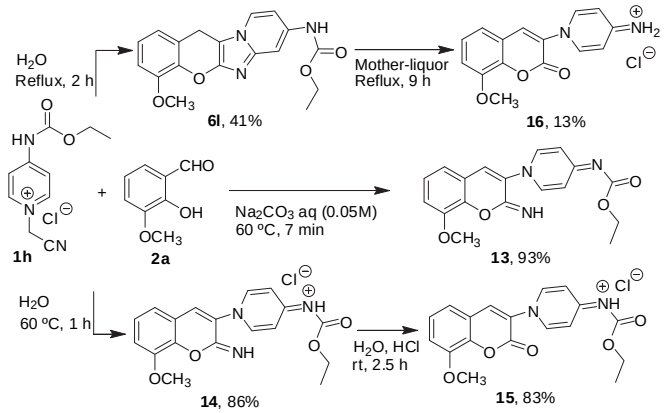
Reaction of salicylaldehyde **2a** with pyridinium salt **1f** (R=4-CH_3) in aqueous solution resulted in extensive degradation, with the formation of dark polymeric materials and was not investigated further.

The reaction of pyridinium salt **1e** (R=4-NH_2) with salicylaldehydes **2a**–**c** (Scheme 4), led to the formation of imino-chromenes **12a**–**c**, insoluble in aqueous base at room temperature.



Scheme 4. Reaction of 4-amino-1-(cyanomethyl)pyridinium chloride **1e** with salicylaldehydes **2a**–**c**.

Under these experimental conditions, intramolecular cyclization was never observed. The formation of isomer **12** was associated with the basicity of the amino substituent in the 4-position of the pyridine moiety. Protection of the amino group as a carbamate and synthesis of the corresponding pyridinium chloride **1h** allowed studies on the reaction with salicylaldehyde **2a**, in aqueous media (Scheme 5).



Scheme 5. Isomers formed in the reaction of pyridinium chloride **1h** with 3-methoxysalicylaldehyde **2a**.

In aqueous base (Na_2CO_3, 0.05 M), product **13** was isolated in 93% yield after 7 min at 60 °C. When the reagents were combined in water, at 60 °C, the same 2-iminochromene was formed, isolated as the hydrochloride salt **14** (86%). Addition of concentrated HCl (3 M equiv) at room temperature resulted in hydrolysis of the imine to generate the 2-oxochromene **15** (83%). The tetracyclic product **6l** was isolated in 41% yield after refluxing the reagents in water for 2 h. Compound **16** (13%) was collected from the mother liquor, after a further 9 h of reflux.

3. Conclusions

In conclusion, we developed an environmentally benign one-pot procedure for the synthesis of 12*H*-chromeno[2′,3′:4,5]imidazo[1,2-*a*]pyridines **6**, through an unprecedented cascade condensation/cyclisation approach from a salicylaldehyde and 1-(cyanomethyl)pyridinium chloride. The products are isolated in a high purity form by simple filtration from the aqueous solution. Following the reaction by ^{1}H NMR allowed a clear understanding of the major pathway and of the side-reactions that are responsible for a product yield that never exceeded 70%. 4-Substituted pyridinium chlorides were also used in this reaction. The presence of an amine substituent prevents the imidazo-pyridine formation, as the positive charge of the imino-chromene intermediate is preferentially transferred to the exocyclic nitrogen atom. The presence of an acidic N–H in the 4-position of the pyridinium chloride moiety was also a source of alternative pathways, but refluxing the reagents in water proved to be the appropriate medium for the formation of the tetracyclic product. 3-Substituted pyridinium chlorides present no such problems, but no selectivity was achieved in the final intramolecular cyclization step. A mixture of two isomeric tetracyclic products was formed, but they can easily be separated by chromatographic techniques. 12*H*-Chromeno[2′,3′:4,5]imidazo[1,2-*a*] pyridines **6**, prepared in aqueous base from simple starting materials, can be considered important new scaffolds for the preparation of biologically significant molecules.

4. Experimental section

4.1. General

All compounds were fully characterized by elemental analysis and spectroscopic data. The NMR spectra were recorded at room temperature, on a Varian Unity Plus (^{1}H: 300 MHz, ^{13}C: 75 MHz) and Bruker Avance 3400 (^{1}H: 400 MHz, ^{13}C: 100 MHz), including the ^{1}H–^{13}C correlation spectra (HMQC and HMBC) and deuterated DMSO was used as solvent. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet and br, broad. The coupling constants, *J*, are reported in hertz (Hz). IR spectra were recorded on a FT-IR Bomem MB 104 using Nujol mulls and NaCl cells. The reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F_{254} (Merck). The melting points were determined on a Stuart SMP3 melting point apparatus and are uncorrected. Elemental analysis were performed on a LECO CHNS-932 instrument. High resolution mass spectra (HRMS) were obtained from the C.A.C.T.I.—Universidade de Vigo.

4.2. General procedure for the synthesis of 1-(cyanomethyl) pyridinium chlorides 1

2-Chloroacetonitrile **11** (5.0–31.0 mmol) was added to a solution of pyridine **10** (5.0 mmol) in acetonitrile (6 mL) and the reaction mixture was refluxed (40 min to 3 days). After a few minutes the solid started to precipitate from solution. The solid was filtered and washed with acetonitrile leading to the pure product **1**.

*4.2.1. 1-(Cyanomethyl)pyridinium chloride (**1a**).* Brown solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.07 (s, 2H), 8.26 (td, J=6.9, 1.8 Hz, 2H), 8.73 (td, J=1.5, 1.2 Hz, 1H), 9.24 (d, J=6.2, 2H) ppm.

*4.2.2. 3-Carbamoyl-1-(cyanomethyl)pyridinium chloride (**1b**).* Yellow solid: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.10 (s, 2H), 8.22 (s, 1H), 8.36 (t, J=7.2 Hz, 1H), 8.86 (s, 1H), 9.17 (d, J=8.1 Hz, 1H), 9.36 (d, J=6.6 Hz, 1H), 9.73 (s, 1H) ppm.

*4.2.3. 1-(Cyanomethyl)-3-(methoxycarbonyl)pyridinium bromide (**1c**).* Yellow solid. Mp 146–148 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.99 (s, 3H), 6.12 (s, 2H), 8.40 (td, J=6.9, 1.5 Hz, 1H), 9.10 (dt, J=8.1, 2.1 Hz, 1H), 9.45 (dt, J=6.0, 1.5 Hz, 1H), 9.78 (t, J=1.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 47.9, 53.7, 114.1, 128.8, 129.9, 146.97, 147.04, 148.5, 161.8 ppm; IR (Nujol mull): ν 3500–1800 (br, fringed), 1749, 1730, 1691, 1641, 1588, 1498, 1463, 1443, 1411, 1400 cm^{-1}. Anal. Calcd for $C_9H_9N_2O_2Br\cdot 0.2H_2O$: C, 41.44; H, 3.61; N, 10.74, found: C, 41.45; H, 3.53; N, 10.80.

*4.2.4. 3-Amino-1-(cyanomethyl)pyridinium chloride (**1d**).* White solid. Mp 163–165 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.04 (s, 2H); 7.16 (s, 2H); 7.72–7.80 (m, 2H); 8.28–8.32 (m, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 47.2, 114.6, 127.8, 128.3, 128.8, 131.4, 149.2 ppm; IR (Nujol mull): ν 3500–1700 (br, fringed), 1640, 1618, 1585, 1502, 1459 cm^{-1}. Anal. Calcd for $C_7H_8N_3Cl\cdot 0.2H_2O$: C, 48.53; H, 4.85; N, 24.26, found: C, 48.42; H, 4.74; N, 24.39.

*4.2.5. 4-Amino-1-(cyanomethyl)pyridinium chloride (**1e**).* Yellow solid. Mp 270–272 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.59 (s, 2H), 6.98 (d, J=7.5 Hz, 2H), 8.29 (d, J=7.5 Hz, 2H), 8.86 (s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.8, 109.7 (2C), 115.4, 142.8 (2C), 159.4 ppm; IR (Nujol mull): ν 3500–1800 (br, fringed), 1727, 1706, 1667, 1644, 1544, 1519, 1463, 1410 cm^{-1}. Anal. Calcd for $C_7H_8N_3Cl$: C, 49.56; H, 4.72; N, 24.78, found: C, 49.48; H, 4.75; N, 24.86.

*4.2.6. 1-(Cyanomethyl)-4-methylpyridinium chloride (**1f**).* Brown solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.64 (s, 3H), 6.02 (s, 2H), 8.08 (d, J=6.6 Hz, 2H), 9.09 (d, J=6.9 Hz, 2H).

*4.2.7. 4-Carbamoyl-1-(cyanomethyl)pyridinium chloride (**1g**).* Yellow solid. Mp 218–220 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.24 (s, 2H), 8.35 (s, 1H), 8.62 (d, J=7.2 Hz, 2H), 9.06 (s, 1H), 9.46 (d, J=7.2 Hz, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 47.5, 114.2, 126.4 (2C), 146.5 (2C), 149.7, 163.1 ppm; IR (Nujol mull): ν 3400–1800 (br, fringed), 1693, 1675, 1627, 1568, 1459, 1422 cm^{-1}. Anal. Calcd for $C_8H_8N_3OCl.0.3H_2O$ contaminated with 5% of $C_6H_7N_2OCl$: C, 47.16; H, 4.25; N, 20.54, found: C, 47.43; H, 4.04; N, 20.14.

*4.2.8. 1-(Cyanomethyl)-4-(ethoxycarbonylamino)pyridinium chloride (**1h**).* Protection of the amino group in 4-amino-1-(cyanomethyl) pyridinium chloride **1e** was carried out in two steps. First, ethyl chloroformate (0.80 g, 7.41 mmol, 720 μL) and DBU (0.94 g, 6.16 mmol, 930 μL) were added to a solution of pyridin-4-amine (0.58 g, 6.17 mmol) in acetonitrile (3 mL). The reaction mixture was refluxed for 1 h and then the solvent was removed under reduced pressure. The reaction mixture was purified by flash chromatography, using dichloromethane (15 mL+10 mL) as eluent. The yellow solution was concentrated to dryness under reduced pressure and then acetonitrile (4 mL) was added to the oil. 2-Chloroacetonitrile **11** (1.86 g, 24.70 mmol, 1600 μL) was added to the solution and the reaction mixture was refluxed for 1 day and then concentrated under reduced pressure and kept at 0 °C for 2 days. A white solid started to precipitate from solution. The solid was filtered and washed with acetonitrile leading to the pure product **1h** (1.14 g, 4.71 mmol). Mp 186–188 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (t, J=6.9 Hz, 3H), 4.24 (q, J=7.2 Hz, 2H), 5.90 (s, 2H), 8.08 (d, J=7.5 Hz, 2H), 8.90 (d, J=7.8 Hz, 2H), 11.86 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.1, 45.6, 62.3, 114.2 (2C), 114.8, 145.4 (2C), 154.3, 152.7 ppm; IR (Nujol mull): ν 3470–1800 (br, fringed), 1743, 1638, 1590, 1532, 1519, 1467 cm^{-1}. Anal. Calcd for $C_{10}H_{12}N_3O_2Cl$: C, 49.67; H, 4.97; N, 17.39, found: C, 49.40; H, 5.10; N, 17.38.

*4.2.9. 1-(Cyanomethyl)-4-(2-hydroxyethylcarbamoyl)pyridinium chloride (**1i**).* Yellow solid. Mp 211–213 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.38 (q, J=5.7 Hz, 2H), 3.56 (t, J=6.3 Hz, 2H), 3.60–4.80 (br s, 1H), 6.14 (s, 2H), 8.63 (d, J=6.6 Hz, 2H), 9.40 (d, J=6.9 Hz, 2H), 9.67 (t, J=5.4 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.0, 47.6, 59.1, 114.2, 126.3 (2C), 146.4 (2C), 149.7, 161.6 ppm; IR (Nujol mull): ν 3310–1740 (br, fringed), 1662, 1606, 1550, 1462, 1409, 1330, 1313, 1283, 1236, 1223, 1154, 1094, 1055, 1040, 1002 cm^{-1}. Anal. Calcd for $C_{10}H_{11}N_3O_2Cl$: C, 49.69; H, 4.97; N, 17.39, found: C, 49.34; H, 4.96; N, 17.60.

4.3. General procedure for the synthesis of 1-(2-Imino-2*H*-chromen-3-yl)pyridinium chlorides 4

1-(Cyanomethyl)pyridinium chloride **1** (1.0 mmol) was added to a yellow solution of salicylaldehyde **2** (1.0 mmol) and 1-methylpiperazine (0.90 mmol) in EtOH/acetone (0.4 mL:1.2 mL). The reaction mixture was stirred in an ice bath (30 min to 1 h). A solid started to precipitate after 15 min. The solid was filtered and washed with acetone leading to the pure product **4**.

*4.3.1. 1-(2-Imino-8-methoxy-2H-chromen-3-yl)pyridinium chloride (**4a**).* Yellow solid, 78%. Mp 132–134 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.91 (s, 3H), 7.21 (dd, J=7.8, 2.1 Hz, 1H), 7.27 (t, J=7.8 Hz, 1H), 7.36 (dd, J=7.8, 1.8 Hz, 1H), 8.23 (s, 1H), 8.34 (td, J=7.5, 0.9 Hz, 2H), 8.82 (td, J=7.5, 1.8 Hz, 1H), 9.12 (s, 1H), 9.30 (dd, J=6.8, 1.2 Hz, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.2, 115.8, 118.2, 120.8, 124.5, 127.8 (2C), 131.1, 134.3, 142.4, 146.1 (2C), 146.2, 148.0, 151.0 ppm; IR (Nujol mull): ν 3600–1700 (br, fringed), 1663, 1626, 1605, 1580, 1482 cm^{-1}. Anal. Calcd for $C_{15}H_{13}N_2O_2Cl.H_2O.0.2NH_4Cl$: C, 56.74; H, 4.98; N, 9.71, found: C, 57.10; H, 4.98; N, 9.79.

*4.3.2. 1-(2-Imino-2H-chromen-3-yl)pyridinium chloride (**4b**).* Yellow solid, 45%. Mp 251–253 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30–7.35 (m, 2H), 7.63 (td, J=6, 1.6 Hz, 1H), 7.68 (dd, J=7.6, 1.6 Hz 1H), 8.28 (s, 1H), 8.35 (td, J=6.4, 1.6 Hz, 2H), 8.83 (tt, J=7.6, 1.6 Hz, 1H), 9.02 (br s, 1H), 9.32 (dt, J=5.6, 1.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 115.4, 117.6, 124.5, 127.8 (2C), 129.8, 130.9, 133.2, 134.2, 146.1 (2C), 148.0, 151.5, 153.2 ppm; IR (Nujol mull): ν 3600–1700 (br, fringed), 1673, 1620, 1600, 1568, 1462 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_2OCl\cdot 1.2H_2O.0.2NH_4Cl$: C, 57.77; H, 4.88; N, 10.59, found: C, 57.77; H, 4.69; N, 10.50.

*4.3.3. 1-(8-Hydroxy-2-imino-2H-chromen-3-yl)pyridinium chloride (**4c**).* Yellow solid, 86%. Mp 242–244 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.05 (dd, J=7.6, 1.6 Hz, 1H), 7.11 (t, J=7.6 Hz, 1H), 7.27 (dd, J=8.0, 1.6 Hz 1H), 8.19 (s, 1H), 8.33 (td, J=6.4, 1.6 Hz, 2H), 8.82 (tt, J=7.6, 1.6 Hz, 1H), 8.87 (s, 1H), 9.30 (dt, J=6.0, 1.6 Hz, 2H), 10.59 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 118.4, 119.4, 119.7, 124.3, 127.7 (2C), 130.9, 134.6, 141.6, 144.6, 146.2 (2C), 147.9, 151.5 ppm; IR (Nujol mull): ν 3500–1700 (br, fringed), 1665, 1628, 1615, 1580, 1519, 1480, 1466 cm^{-1}. Anal. Calcd for $C_{14}H_{11}N_2O_2Cl.0.75H_2O.0.1NH_4Cl$: C, 57.27; H, 4.40; N, 10.02, found: C, 56.93; H, 4.62; N, 10.00.

*4.3.4. 1-(2-Imino-6-methoxy-2H-chromen-3-yl)pyridinium chloride (**4d**).* Yellow solid, 46%. Mp 177–179 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.80 (s, 3H), 7.21 (dd, J=9.0, 2.8 Hz, 1H), 7.24 (d, J=2.8 Hz, 1H),

7.27 (d, *J*=8.8 Hz, 1H), 8.21 (s, 1H), 8.34 (td, *J*=6.6, 1.6 Hz, 2H), 8.83 (tt, *J*=7.6, 1.6 Hz, 1H), 8.91 (s, 1H), 9.31 (dd, *J*=6.8, 1.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.8, 112.7, 116.5, 118.1, 119.6, 127.8 (2C), 131.3, 134.1, 146.1 (2C), 147.5, 148.0, 151.8, 155.4 ppm; IR (Nujol mull): ν 3600–1700 (br, fringed), 1667, 1627, 1581, 1493, 1460, 1432 cm^{-1}. Anal. Calcd for $C_{15}H_{13}N_2O_2Cl.2H_2O\cdot0.2NH_4Cl$: C, 53.70; H, 5.31; N, 9.19, found: C, 53.77; H, 5.34; N, 9.12.

4.4. General procedure for the synthesis of 12*H*-chromeno [2′,3′:4,5]imidazo[1,2-*a*]pyridines 6

1-(Cyanomethyl)pyridinium chloride **1** (0.81 mmol) was added to a yellow solution of salicylaldehyde **2** (0.75 mmol) in aqueous Na_2CO_3 (0.05 M, 2 mL) or $NaHCO_3$ (0.05 M, 2 mL). The reaction mixture was stirred at 60/80 °C (1 h and 40 min to 19 h). A solid started to precipitate after a few minutes. The suspension was cooled to room temperature in an ice bath and the yellow solid was filtered and washed with water leading to the pure product **6**.

*4.4.1. 4-Methoxy-12H-chromeno[2′,3′:4,5]imidazo[1,2-a]pyridine (**6a**).* Yellow solid. Mp 155–157 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.85 (s, 3H), 4.28 (s, 2H), 6.92 (dd, *J*=7.0, 1.2 Hz, 1H), 6.99 (dd, *J*=7.4, 1.2 Hz, 1H), 7.05–7.10 (m, 2H), 7.36 (td, *J*=7.6, 0.8 Hz, 1H), 7.56 (d, *J*=8.8 Hz, 1H), 8.31 (d, *J*=6.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.4, 55.8, 98.5, 110.8, 112.8, 114.9, 119.0, 121.7, 123.6, 124.6, 125.0, 139.0, 140.6, 148.4, 149.6 ppm; IR (Nujol mull): ν 1652, 1604, 1501, 1573, 1480, 1465, 1431 cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_2O_2.0.4H_2O$: C, 69.44; H, 4.94; N, 10.80, found: C, 69.48; H, 4.67; N, 10.46.

*4.4.2. 12H-Chromeno[2′,3′:4,5]imidazo[1,2-a]pyridine (**6b**).* Yellow solid. Mp 211–213 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.29 (s, 2H), 6.96 (td, *J*=5.8, 0.8 Hz, 1H), 7.14 (td, *J*=7.6, 0.9 Hz, 1H), 7.19 (dd, *J*=8.0, 1.2 Hz, 1H), 7.24–7.32 (m, 2H), 7.38 (d, *J*=7.6 Hz, 1H), 7.51 (d, *J*=8.8 Hz, 1H), 8.26 (d, *J*=6.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.4, 98.1, 112.0, 115.4, 117.5, 118.4, 123.6, 123.8, 124.2, 128.1, 130.7, 139.8, 151.0, 151.2 ppm; IR (Nujol mull): ν 1651, 1606, 1570, 1504, 1484, 1465, 1456 cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.68; H, 4.50; N, 12.61, found: C, 75.53; H, 4.20; N, 12.31.

*4.4.3. 4-Hydroxy-12H-chromeno[2′,3′:4,5]imidazo[1,2-a]pyridine (**6c**).* Yellow solid. Mp 279–281 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.26 (s, 2H), 6.77 (dd, *J*=8.0, 1.5 Hz, 1H), 6.81 (dd, *J*=8.1, 1.5 Hz, 1H), 6.92 (t, *J*=7.8 Hz, 1H), 6.98 (td, *J*=6.8, 1.2 Hz, 1H), 7.26 (td, *J*=7.2, 1.2 Hz, 1H), 7.51 (d, *J*=9.0 Hz, 1H), 8.25 (d, *J*=6.6 Hz, 1H), 9.64 (br s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.5, 98.2, 112.0, 114.8, 115.5, 119.2, 120.2, 123.3, 123.8, 124.2, 139.8, 140.2, 146.3, 151.1 ppm; IR (Nujol mull): ν 3181 (br), 1650, 1612, 1583, 1503, 1470, 1432 cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_2O_2.0.4H_2O$: C, 68.52; H, 4.40; N, 11.42, found: C, 68.65; H, 4.30; N, 11.05.

*4.4.4. 2-Methoxy-12H-chromeno[2′,3′:4,5]imidazo[1,2-a]pyridine (**6d**).* Yellow solid. Mp 176–178 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.75 (s, 3H), 4.25 (s, 2H), 6.84–6.92 (m, 2H), 6.98 (td, *J*=6.9, 0.9 Hz, 1H), 7.13 (d, *J*=8.7 Hz, 1H), 7.26 (t, *J*=7.5 Hz, 1H), 7.49 (d, *J*=8.7 Hz, 1H), 8.23 (d, *J*=6.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.7, 55.4, 97.7, 112.0, 114.1, 114.5, 115.4, 118.3, 119.0, 123.7, 124.1, 139.8, 145.1, 151.3, 155.1 ppm; IR (Nujol mull): ν 1650, 1610, 1581, 1493, 1466 cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_2O_2.0.25H_2O$: C, 70.18; H, 4.87; N, 10.92, found: C, 70.19; H, 4.61; N, 10.59.

*4.4.5. 2-Chloro-12H-chromeno[2′,3′:4,5]imidazo[1,2-a]pyridine (**6e**).* Yellow solid. Mp 222–224 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.31 (s, 2H), 7.01 (td, *J*=6.6, 0.9 Hz, 1H), 7.24 (d, *J*=8.7 Hz, 1H), 7.28 (t, *J*=7.2 Hz, 1H), 7.35 (dd, *J*=9.0 Hz, 2.4 Hz, 1H), 7.47 (d, *J*=2.4 Hz, 1H), 7.51 (d, *J*=9.3 Hz, 1H), 8.26 (d, *J*=6.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.4, 97.7, 112.2, 115.6, 119.3, 120.7, 124.1, 124.3, 127.1, 128.0, 130.1, 139.9, 150.1, 150.8 ppm; IR (Nujol mull): ν 1648, 1630, 1603, 1566, 1504, 1465, 1434 cm^{-1}. Anal. Calcd for $C_{14}H_9N_2OCl.0.8H_2O$: C, 62.02; H, 3.91; N, 10.34, found: C, 62.02; H, 3.57; N, 10.20.

*4.4.6. 4-Methoxy-12H-chromeno[2′,3′:4,5]imidazo[1,2-a]pyridine-7-carboxamide (**6f**(**A**)).* Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.86 (s, 3H), 4.34 (s, 2H), 6.95 (d, *J*=7.6 Hz, 1H), 7.02 (d, *J*=7.6 Hz, 1H), 7.11 (t, *J*=8.0 Hz, 1H), 7.19 (t, *J*=6.8 Hz, 1H), 7.98 (s, 1H), 8.02 (dd, *J*=7.4, 1.2 Hz, 1H), 8.50 (dd, *J*=5.4, 1.2 Hz, 1H), 9.02 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.50, 55.82, 99.18, 110.92, 111.94, 119.00, 119.19, 121.71, 123.70, 126.70, 127.52, 138.06, 140.57, 148.45, 150.21, 163.72 ppm.

*4.4.7. 4-Methoxy-12H-chromeno[2′,3′:4,5]imidazo[1,2-a]pyridine-9-carboxamide (**6f**(**B**)).* Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.86 (s, 3H), 4.34 (s, 2H), 6.95 (d, *J*=7.6 Hz, 1H), 7.01 (d, *J*=7.4 Hz, 1H), 7.10 (t, *J*=8.0 Hz, 1H), 7.52 (s, 1H), 7.55 (dd, *J*=9.6, 0.4 Hz, 1H), 7.72 (dd, *J*=9.2, 1.6 Hz, 1H), 8.07 (s, 1H), 8.84 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.44, 55.80, 99.16, 110.85, 114.49, 118.98, 119.33, 121.78, 122.69, 123.50, 125.49, 140.26, 140.70, 148.44, 151.83, 165.68 ppm. Anal. Calcd for $C_{16}H_{13}N_3O_3.0,75H_2O$: C, 62.24; H, 4.70; N, 13.61, found: C, 62.19; H, 4.32; N, 13.70.

*4.4.8. Mixture of 12H-chromeno[2′,3′:4,5]imidazo[1,2-a]pyridine-7-carboxamide (**6g**(**A**)) and 12H-chromeno[2′,3′:4,5]imidazo[1,2-a]-pyridine-9-carboxamide (**6g**(**B**)).* Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.33 (s, 2H), 4.35 (s, 2H), 7.16–7.19 (m, 3H), 7.21 (dd, *J*=8.2, 1.2 Hz, 1H), 7.28–7.32 (m, 2H), 7.41 (d, *J*=7.6 Hz, 2H), 7.54 (dd, *J*=9.6, 0.8 Hz, 2H), 7.73 (dd, *J*=9.4, 1.6 Hz, 1H), 7.98 (br s, 1H), 8.02 (dd, *J*=7.6, 1.2 Hz, 1H), 8.08 (s, 1H), 8.43 (dd, *J*=6.8, 1.2 Hz, 1H), 8.84 (s, 1H), 9.01 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.31, 22.36, 99.20 (2C), 111.97, 114.49, 117.53, 117.58, 118.29 (2C), 119.19, 119.39, 122.72, 123.80, 123.98, 125.46, 126.67, 127.48, 128.20, 128.26, 130.72, 130.77, 138.04, 140.26 (2C), 150.25, 150.89, 151.03, 151.88, 163.74, 165.71 ppm. Anal. Calcd for $C_{15}H_{11}N_3O_2.0.4H_2O$: C, 66.13; H, 4.34; N, 15.43, found: C, 66.17; H, 4.18; N, 15.30.

*4.4.9. Mixture of 4-hydroxy-12H-chromeno[2′,3′:4,5]imidazo[1,2-a]pyridine-7-carboxamide (**6h**(**A**)) and 4-hydroxy-12H-chromeno[2′,3′:4,5]imidazo[1,2-a]pyridine-9-carboxamide (**6h**(**B**)).* Yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.30 (s, 2H), 4.32 (s, 2H), 6.80 (dd, *J*=8.6, 1.5 Hz, 2H), 6.82 (dd, *J*=8.4, 1.2 Hz, 2H), 6.95 (t, *J*=7.5 Hz, 1H), 6.97 (t, *J*=7.5 Hz, 1H), 7.18 (t, *J*=6.6 Hz, 1H), 7.55 (dd, *J*=9.4, 0.9 Hz, 2H), 7.73 (dd, *J*=9.6, 1.8 Hz, 1H), 8.02 (dd, *J*=7.5, 1.2 Hz, 2H), 8.09 (s, 1H), 8.49 (dd, *J*=6.9, 1.2 Hz, 1H), 8.85 (d, *J*=0.6 Hz, 1H), 9.06 (d, *J*=2.1 Hz, 1H), 9.20–10.20 (br s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.45 (2C), 99.35, 99.37, 111.94, 114.44, 114.94 (2C), 119.13 (2C), 119.39 (2C), 120.22, 120.29 (2C), 122.82, 123.56, 123.72, 125.53, 126.64, 127.53, 138.04, 139.90, 140.03, 140.17, 146.37 (2C), 150.30, 151.81, 163.83, 165.75 ppm. Anal. Calcd for $C_{15}H_{11}N_3O_3.1.3H_2O$: C, 59.13; H, 4.47; N, 13.80, found: C, 59.11; H, 4.38; N, 13.40.

*4.4.10. Mixture of 2-methoxy-12H-chromeno[2′,3′:4,5]imidazo[1,2-a]-pyridine-7-carboxamide (**6i**(**A**)) and 2-methoxy-12H-chromeno[2′,3′:-4,5]imidazo[1,2-a]pyridine-9-carboxamide (**6i**(**B**)).* Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.77 (s, 6H), 4.31 (s, 2H), 4.32 (s, 2H), 6.88–6.92 (m, 2H), 6.94 (d, *J*=2.8 Hz, 2H), 7.17 (d, *J*=8.8 Hz, 2H), 7.18 (t, *J*=6.8 Hz, 1H), 7.53 (dd, *J*=9.2, 0.8 Hz, 2H), 7.72 (dd, *J*=9.2, 2.0 Hz, 1H), 7.97 (d, *J*=1.6 Hz, 1H), 8.02 (dd, *J*=7.2, 1.2 Hz, 1H), 8.08 (s, 1H), 8.48 (dd, *J*=6.8, 1.2 Hz, 1H), 8.81 (dd, *J*=1.4, 0.8 Hz, 1H), 9.02 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.60, 22.65, 55.48 (2C), 98.77 (2C), 111.88, 114.10, 114.21, 114.36, 114.58, 114.68, 118.31, 118.34, 119.00 (2C), 119.08, 119.29, 122.63, 125.39, 126.58, 127.41, 138.05, 140.26, 144.77, 144.92, 150.55, 152.17, 155.21, 155.32, 163.75,

165.72 ppm. Anal. Calcd for $C_{16}H_{13}N_3O_3.0.3H_2O$: C, 63.92; H, 4.53; N, 13.98, found: C, 64.06; H, 4.51; N, 13.59.

*4.4.11. 4-Methoxy-12H-chromeno[2′,3′:4,5]imidazo[1,2-a]pyridine-8-carboxamide (**6j**).* Cream solid. Mp higher than 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.85 (s, 3H), 4.35 (s, 2H), 6.93 (d, J=7.6 Hz, 1H), 7.01 (dd, J=8.0, 1.2 Hz, 1H), 7.09 (t, J=8.0 Hz, 1H), 7.45 (dd, J=7.0, 2.0 Hz, 1H), 7.51 (s, 1H), 8.11 (s, 1H), 8.12 (d, J=0.8 Hz, 1H), 8.33 (d, J=7.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.5, 55.8, 100.0, 110.6, 110.9, 114.6, 118.9, 121.7, 123.5, 123.7, 128.8, 138.9, 140.6, 148.4, 152.2, 166.3 ppm; IR (Nujol mull): ν 3386, 3177, 1675, 1652, 1625, 1601, 1569, 1513, 1458 cm^{-1}; HRMS–FAB (m/z): [M+H]$^+$ calcd for $C_{16}H_{14}N_3O_3$ 296.10362, found: 296.10297.

*4.4.12. N-(2-Hydroxyethyl)-4-methoxy-12H-chromeno[2′,3′:4,5]imidazo[1,2-a]pyridine-8-carboxamide (**6k**).* Cream solid. Mp 251–252 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.32–3.38 (m, 2H), 3.53 (t, J=6.0 Hz, 2H), 3.86 (s, 3H), 4.30–4.70 (br s, 1H), 4.33 (s, 2H), 6.93 (dd, J=7.8, 1.2 Hz, 1H), 7.01 (dd, J=8.2, 1.6 Hz, 1H), 7.09 (t, J=8.0 Hz, 1H), 7.44 (dd, J=7.0, 1.6 Hz, 1H), 8.08 (dd, J=0.8 Hz, 1H), 8.33 (d, J=6.6 Hz, 1H), 8.61 (t, J=5.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.6, 42.4, 55.8, 59.7, 100.0, 110.5, 110.9, 114.3, 118.9, 121.7, 123.5, 123.8, 129.0, 138.9, 140.7, 148.4, 152.2, 164.7 ppm; IR (Nujol mull): ν 3500–3200 (br), 1633, 1604, 1573, 1547, 1515, 1481, 1458 cm^{-1}; HRMS–FAB (m/z): [M+H]$^+$ calcd for $C_{18}H_{18}N_3O_4$ 340.12984, found: 340.12918.

4.5. 2-[3-Amino-3-oxo-2-pyridinium-1-ylprop-1-en-1-yl]-6-methoxybenzenolate 7a

^{1}H NMR (400 MHz, D_2O): δ 3.87 (s, 3H), 6.85 (t, J=8.0 Hz, 1H), 7.04 (dd, J=8.0, 1.2 Hz, 1H), 7.11 (dd, J=8.0, 1.2 Hz, 1H), 7.38 (s, 1H), 8.15 (t, J=7.2 Hz, 2H), 8.66 (td, J=6.6, 1.2 Hz, 1H), 8.93 (dd, J=6.6, 1.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, D_2O): δ 56.1, 113.7, 118.7, 120.1, 122.0, 127.8 (2C), 131.0, 138.9, 144.3 (2C), 146.4, 147.4, 148.4, 167.2 ppm.

4.6. Procedure for the synthesis of 1-(8-Methoxy-2-oxo-2*H*-chromen-3-yl)pyridinium chloride 8a

Concentrated HCl (0.05 g, 1.50 mmol, 124 μL) was added to a yellow suspension of 1-(2-imino-8-methoxy-2*H*-chromen-3-yl) pyridinium chloride **4a** (0.14 g, 0.50 mmol) in EtOH (2 mL). The reaction mixture was stirred at room temperature for 49 h and then kept at 0 °C for 4 days. A yellow solid precipitated from solution and was filtered and washed with EtOH (cold) leading to the pure product **8a** (0.05 g, 0.17 mmol). The mother liquor was kept at 0 °C for 14 days and the yellow solid was filtered (0.04 g, 0.15 mmol). This product was identified by ^{1}H NMR as a second crop of the pure compound **8a** (0.09 g, 0.32 mmol). Mp 132–134 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.91 (s, 3H), 7.21 (dd, J=7.8, 2.1 Hz, 1H), 7.27 (t, J=7.8 Hz, 1H), 7.36 (dd, J=7.8, 1.8 Hz, 1H), 8.23 (s, 1H), 8.34 (td, J=7.5, 0.9 Hz, 2H), 8.82 (td, J=7.5, 1.8 Hz, 1H), 9.12 (s, 1H), 9.30 (dd, J=6.8, 1.2 Hz, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.2, 115.8, 118.2, 120.8, 124.5, 127.8 (2C), 131.1, 134.3, 142.4, 146.1 (2C), 146.2, 148.0, 151.0 ppm; IR (Nujol mull): ν 3600–1700 (br, fringed), 1663, 1626, 1605, 1580, 1482 cm^{-1}. Anal. Calcd for $C_{15}H_{13}N_2O_2Cl.H_2O.0.2NH_4Cl$: C, 56.74; H, 4.98; N, 9.71, found: C, 57.10; H, 4.98; N, 9.79.

4.7. 3-(2-Hydroxy-3-methoxyphenyl)-2-(pyridinium-1-yl) prop-2-enoate 9a

Identified in the mixture with **6a** in a ratio of **9a**/**6a**=1:1.6 by ^{1}H NMR. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.75 (s, 3H), 6.78 (t, J=8.0 Hz, 1H), 6.94–7.02 (m*, 1H), 7.10 (dd, J=7.8, 1.2 Hz, 1H), 7.14 (s, 1H), 8.09 (td, J=6.4, 1.6 Hz, 2H), 8.60 (td, J=7.6, 1.2 Hz, 1H), 9.05 (dd, J=6.8, 1.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.1, 113.5, 119.0, 121.8, 124.4, 127.4 (2C), 130.0, 140.8, 145.4 (2C), 146.0, 146.8, 150.0, 163.5 ppm (*under the signal for compound **6a**).

4.8. Procedure for the synthesis of 3-(2-hydroxyphenyl)-2-(pyridinium-1-yl)prop-2-enoate 9e

1-(Cyanomethyl)pyridinium chloride **1a** (0.12 g, 0.76 mmol) was added to a white suspension of 5-chlorosalicylaldehyde **2e** (0.11 g, 0.70 mmol) in aqueous Na_2CO_3 (0.05 M, 3 mL). The reaction mixture was heated at 40 °C for 11 h, followed by 18 h at 80 °C. The yellow suspension was cooled to room temperature in an ice bath and the yellow solid (0.08 g) was filtered and washed with water. The solid product was identified as a mixture of **6e** and **9e** (1:1.3 ratio by ^{1}H NMR). A second crop was isolated from the mother liquor. The yellow-brownish solid was filtered and washed with water leading to the pure product **9e** (0.02 g, 0.17 mmol). Mp 180–182 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.83 (td, J=7.2, 1.2 Hz, 1H), 6.87 (d, J=7.6 Hz, 1H), 7.22 (s, 1H), 7.26 (td, J=7.8, 1.6 Hz, 1H), 7.42 (dd, J=7.6, 1.6 Hz, 1H), 8.12 (t, J=5.1 Hz, 2H), 8.62 (t, J=6.0 Hz, 1H), 9.12 (d, J=4.2 Hz, 2H), 13.25 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 118.6, 119.6, 121.4, 126.9 (2C), 131.3, 131.7, 133.4, 140.0, 145.5 (2C), 145.6, 157.8, 162.8 ppm; IR (Nujol mull): ν 3536, 3403, 1638, 1610, 1572, 1460 cm^{-1}. HRMS–FAB (m/z): [M+H]$^+$ calcd for $C_{14}H_{12}NO_3$ 242.08176, found: 242.08117.

4.9. General procedure for the synthesis of 1-(2-imino-2*H*-chromen-3-yl)pyridin-4(1*H*)-iminium chloride 12

4-Amino-1-(cyanomethyl)pyridinium chloride **1e** (0.69 mmol) was added to a yellow solution of salicylaldehyde **2** (0.59 mmol) in aqueous Na_2CO_3 (0.05 M, 4 mL). The reaction mixture was stirred at room temperature (1 h and 30 min to 17 h and 30 min). A yellow solid started to precipitate after a few minutes. The solid was filtered and washed with water leading to the pure product **12**. For **12a** and **b**: the mother liquor was stirred at 10 °C for 16 h and a solid was filtered. This product was identified by ^{1}H NMR as a second crop of pure compound **12**.

*4.9.1. 1-(2-Imino-8-methoxy-2H-chromen-3-yl)pyridin-4(1H)-iminium chloride (**12a**).* Green solid. Mp 276–278 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.88 (s, 3H), 6.98 (d, J=7.8 Hz, 2H), 7.14 (dd, J=7.8, 1.5 Hz, 1H), 7.21 (t, J=7.8 Hz, 1H), 7.27 (dd, J=8.1, 1.8 Hz, 1H), 7.94 (d, J=1.8 Hz, 1H), 8.29 (d, J=7.2 Hz, 2H), 8.82 (s, 2H), 8.96 (d, J=1.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.1, 108.6 (2C), 115.0, 118.7, 120.4, 124.2, 130.6, 132.4, 142.0, 143.4 (2C), 146.1, 151.5, 159.6 ppm; IR (Nujol mull): ν 3347, 3267, 3227, 2726, 1661, 1608, 1581, 1522, 1479, 1462 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_3O_2Cl.2H_2O$: C, 53.02; H, 5.30; N, 12.37, found: C, 52.80; H, 5.37; N, 12.46.

*4.9.2. 1-(2-Imino-2H-chromen-3-yl)pyridin-4(1H)-iminium chloride (**12b**).* White solid. Mp 293–295 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.96 (d, J=7.5 Hz, 2H), 7.22–7.31 (m, 2H), 7.51–7.62 (m, 2H), 7.96 (d, J=1.5 Hz, 1H), 8.30 (d, J=7.2 Hz, 2H), 8.72 (s, 2H), 8.88 (d, J=1.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 108.6 (2C), 115.2, 118.1, 124.2, 129.2, 130.4, 132.3 (2C), 143.4 (2C), 151.9, 152.9, 159.6 ppm; IR (Nujol mull): ν 3449, 3318, 3288, 3268, 1657, 1624, 1598, 1539, 1458 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_3OCl$: C, 61.43; H, 4.39; N, 15.36, found: C, 61.10; H, 4.44; N, 15.15.

*4.9.3. 1-(8-Hydroxy-2-Imino-2H-chromen-3-yl)pyridin-4(1H)-iminium chloride (**12c**).* Cream solid. Mp 270–272 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.00–6.00 (br s, 3H), 6.92–6.97 (m, 3H), 7.04 (t, J=7.6 Hz, 1H), 7.10 (dd, J=8.0, 1.6 Hz, 1H), 7.87 (s, 1H), 8.29

(d, J=7.6 Hz, 2H), 8.64 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 108.6, 108.9, 118.5, 118.8, 119.0, 124.1, 130.2, 132.8, 141.4, 143.2, 143.5, 144.9, 152.1, 159.5 ppm; IR (Nujol mull): ν 3375, 3291, 3234, 3188, 3078, 1682, 1657, 1649, 1628, 1615, 1580, 1546, 1528, 1475, 1463 cm^{-1}; HRMS–FAB (m/z): $[M+H]^+$ calcd for $C_{14}H_{12}N_3O_2$ 254.09306, found: 254.09240.

4.10. Procedure for the synthesis of ethyl [1-(2-imino-8-methoxy-2*H*-chromen-3-yl)pyridin-4(1*H*)-ylidene]carbamate 13

1-(Cyanomethyl)-4-(ethoxycarbonylamino)pyridinium chloride **1h** (0.13 g, 0.55 mmol) was added to a yellow solution of 3-methoxysalicylaldehyde **2a** (0.09 g, 0.56 mmol) in aqueous Na_2CO_3 (0.05 M, 5 mL). The reaction mixture was stirred at 60 °C for 7 min. A yellow solid started to precipitate after 2 min. The solid was filtered and washed with water leading to the pure product **13** (0.16 g, 0.49 mmol). Mp 134–136 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.21 (t, J=7.2 Hz, 3H), 3.82 (s, 3H), 4.07 (q, J=7.2 Hz, 2H), 7.14 (dd, J=7.6, 1.6 Hz, 1H), 7.20 (t, J=7.6 Hz, 1H), 7.26 (dd, J=8.0, 1.6 Hz, 1H), 7.35 (d, J=7.6 Hz, 2H), 7.90 (s, 1H), 8.26 (d, J=7.2 Hz, 2H), 8.94 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.4, 56.0, 60.4, 114.0 (2C), 114.9, 118.8, 120.3, 124.2, 130.7, 132.0, 142.0, 142.3 (2C), 146.0, 151.4, 159.3, 161.2 ppm; IR (Nujol mull): ν 3575, 3320, 3272, 3220, 1676, 1657, 1631, 1623, 1607, 1578, 1538, 1526, 1464, 1411, 1405 cm^{-1}. Anal. Calcd for $C_{18}H_{17}N_3O_4.1.4H_2O$: C, 59.31; H, 5.44; N, 11.53, found: C, 59.41; H, 5.25; N, 11.25.

4.11. Procedure for the synthesis of ethoxy-*N*-[1-(2-imino-8-methoxy-2*H*-chromen-3-yl)pyridin-4(1*H*)-ylidene] oxomethanaminium chloride 14

1-(Cyanomethyl)-4-(ethoxycarbonylamino)pyridinium chloride **1h** (0.29 g, 1.19 mmol) was added to a yellow solution of 3-methoxysalicylaldehyde **2a** (0.17 g, 1.12 mmol) in water (5 mL). The reaction mixture was stirred at 60 °C for 1 h. A yellow solid started to precipitate after 25 min. The solid was filtered and washed with water leading to the pure product **14** (0.36 g, 0.95 mmol). Mp 172–173 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.28 (t, J=7.2 Hz, 3H), 3.89 (s, 3H), 4.25 (q, J=7.2 Hz, 2H), 7.16–7.26 (m, 2H), 7.31 (dd, J=7.8, 1.8 Hz, 1H), 8.09 (d, J=7.5 Hz, 2H), 8.90 (d, J=7.5 Hz, 2H), 9.05 (s, 1H), 11.20–12.40 (br s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.3, 56.1, 62.3, 113.2 (2C), 115.5, 118.4, 120.7, 124.4, 130.5, 133.5, 142.3, 145.8 (2C), 146.1, 151.1, 152.9, 154.8 ppm; IR (Nujol mull): ν 3400–1700 (br, fringed), 1656, 1641, 1605, 1578, 1530, 1462 cm^{-1}. Anal. Calcd for $C_{18}H_{18}N_3O_4Cl\cdot 2.2H_2O$: C, 52.03; H, 5.39; N, 10.12, found: C, 52.05; H, 5.08; N, 10.11.

4.12. Procedure for the synthesis of ethoxy-*N*-[1-(8-methoxy-2-oxo-2*H*-chromen-3-yl)pyridin-4(1*H*)-ylidene] oxomethanaminium chloride 15

Concentrated HCl (0.04 g, 1.05 mmol, 187 μL) was added to a yellow suspension of ethoxy-*N*-[1-(2-imino-8-methoxy-2*H*-chromen-3-yl)pyridin-4(1*H*)-ylidene]oxomethanaminium chloride **14** (0.13 g, 0.34 mmol) in water (1.6 mL). The reaction mixture was stirred at room temperature and after 2 min a homogeneous solution was obtained. A yellow solid started to precipitate after 3 min. The suspension was kept stirring for a further 2 h and 25 min. The yellow solid was filtered and washed with water leading to the pure product **15** (0.10 g, 0.26 mmol). Mp 241–243 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.31 (t, J=7.2 Hz, 3H), 3.97 (s, 3H), 4.28 (q, J=6.9 Hz, 2H), 7.40 (dd, J=7.6, 1.8 Hz, 1H), 7.45 (t, J=7.8 Hz, 1H), 7.50 (dd, J=8.0, 1.8 Hz, 1H), 8.14 (d, J=7.2 Hz, 2H), 8.69 (s, 1H), 8.89 (d, J=7.2 Hz, 2H), 11.89 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.1, 56.4, 62.4, 113.4 (2C), 116.1, 118.4, 120.7, 125.7, 128.6, 140.0, 142.3, 145.6 (2C), 146.6, 152.6, 154.7, 156.4 ppm; IR (Nujol mull): ν 3700–1800 (br, fringed), 1748, 1717, 1682, 1643, 1611, 1581, 1525, 1483, 1469 cm^{-1}. Anal. Calcd for $C_{18}H_{17}N_2O_5Cl.0.8H_2O$: C, 55.26; H, 4.76; N, 7.16, found: C, 55.25; H, 4.62; N, 7.35.

4.13. Procedure for the synthesis of ethyl (4-methoxy-12*H*-chromeno[2′,3′:4,5]imidazo[1,2-*a*]pyridin-8-yl)carbamate 6l and 1-(8-methoxy-2-oxo-2*H*-chromen-3-yl)pyridin-4(1*H*)-iminium chloride 16

1-(Cyanomethyl)-4-(ethoxycarbonylamino)pyridinium chloride **1h** (0.40 g, 1.64 mmol) was added to a yellow solution of 3-methoxysalicylaldehyde **2a** (0.23 g, 1.51 mmol) in water (2.5 mL). The reaction mixture was refluxed for 2 h. A yellow solid started to precipitate after 20 min. The yellow solid was filtered and washed with water leading to the pure product **6l** (0.21 g, 0.62 mmol). Mp 282–284 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.26 (t, J=5.4 Hz, 3H), 3.84 (s, 3H), 4.16 (q, J=5.4 Hz, 2H), 4.23 (s, 2H), 6.90 (dd, J=7.6, 1.6 Hz, 1H), 6.98 (dd, J=7.6, 1.6 Hz, 1H), 7.05 (d, J=7.6 Hz, 1H), 7.06 (t, J=7.2 Hz, 1H), 7.63 (d, J=1.6 Hz, 1H), 8.15 (dd, J=7.2, 0.4 Hz, 1H), 9.93 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.4, 22.53, 55.8, 60.6, 96.5, 100.5, 105.6, 110.7, 119.1, 121.8, 123.2, 124.5, 136.1, 140.6, 140.9, 148.4, 151.1, 153.4 ppm; IR (Nujol mull): ν 3220, 3122, 1721, 1660, 1609, 1592, 1573, 1508, 1491, 1482, 1456, 1426 cm^{-1}. Anal. Calcd for $C_{18}H_{17}N_3O_4\cdot 0.2H_2O$: C, 63.05; H, 5.08; N, 12.26, found: C, 62.87; H, 4.80; N, 12.17.

The mother liquor was refluxed for a further 9 h. After cooling the yellow-greenish solution in an ice-bath, a yellow solid started to precipitate. The solid was filtered and washed with water leading to the pure product **16** (0.05 g, 0.18 mmol). Mp higher than 300 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.95 (s, 3H), 7.01 (d, J=7.2 Hz, 2H), 7.35 (dd, J=7.4, 2.1 Hz, 1H), 7.41 (t, J=8.1 Hz, 1H), 7.46 (d, J=6.3 Hz, 1H), 8.28 (d, J=7.2 Hz, 2H), 8.53 (s, 1H), 8.84 (s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.5, 109.0 (2C), 115.5, 118.7, 120.4, 125.5, 128.5, 138.9, 142.0, 143.1 (2C), 146.5, 156.8, 159.6 ppm; IR (Nujol mull): ν 3800–2000 (br, fringed), 1707, 1681, 1664, 1609, 1580, 1548, 1531, 1465, 1481, 1442 cm^{-1}. Anal. Calcd for $C_{15}H_{13}N_2O_3Cl.0.5H_2O$: C, 57.42; H, 4.46; N, 8.93, found: C, 57.43; H, 4.32; N, 8.73.

Acknowledgements

We gratefully acknowledge the financial support from Fundação para a Ciência e a Tecnologia through project PPCDT/QUI/59356/2004 and a Ph.D. grant awarded to M.C. (SFRH/BD/31531/2006). We also thank Dr. Elisa Pinto for careful NMR studies.

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.059.

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