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Switching the reactivity of cyanomethylpyridinium salts in the 1,3-cycloaddition conditions with alkyl propiolates to cyanoindolizines or cyanoazaindoliziny-indolizines

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Abstract

A particular reactivity of 1-cyanomethylpyridinium salts was revealed in the [3+2] cycloaddition conditions with alkyl propiolates. Cycloadducts **3** were obtained in reactions carried out at room temperature while refluxing in CH₃CN provided unexpected ethyl or methyl 3-(3-cyanoimidazo[1,2- α]pyridin-2-yl)indolizine-1-carboxylates **4**. The structure of the new 2:1 azaindolizine-indolizine adducts was secured by X-ray analysis. Methodological efforts have enabled the adjustment of the reactivity towards the formation of 3-cyanoindolizines **3** or cyanoazaindolizine-indolizines **4**. A mechanism for the formation of azaindolizine-indolizines was proposed. A portfolio of rare cyanoindolizines and cyanoazaindolizine-indolizines has been successfully obtained.

1. Introduction

Only few representatives of cyanoindolizines were reported in the literature and they demonstrated very diverse and promising therapeutic potential. The main active derivatives are regrouped in Figure 1. 1-Cyanoindolizine **A** displayed *in vitro* antiproliferative activity on Hep-G2 cell lines¹ (Figure 1). Derivative **B**,² decorated in the same way, disrupted the migration and proliferation of PC3 prostate tumor cells by preventing protein-protein interaction in which the endothelial vascular growth factor (VEGF) is involved (Figure 1). Indolizine **C** incorporating a cyano group at position 7 is a potential anti-inflammatory agent, cyclooxygenase (COX)-2 inhibitor³ (Figure 1). 2-Cyanoindolizine **D** is effective against Gram-positive and Gram-negative bacterial strains, with increased potency on *Bacillus subtilis* UC564 and *Vibrio cholera* 7201 (Figure 1).⁴ Antibacterial activity has also been reported for 3-cyanoindolizine **E** on *Mycobacterium tuberculosis* (Figure 1).⁵ 2-Cyanoindolizine **F** was reported as non-nucleoside inhibitor of HIV-1 reverse transcriptase (NNRTI).^{6,7} The indolizine showed very strong picomolar inhibitory activity toward wild-type HIV-1 (EC₅₀ (WT HIV1) = 0.38 nM,⁶ Figure 1) and excellent low nanomolar enzymatic activity against HIV with reverse transcriptase (RT) variants containing the K101P mutation (enzyme EC₅₀ (RT (K101P)) = 1.9 nM,⁷ Figure 1). 3-Cyanoindolizine **G** decorated with a salicylic acid moiety is a xanthine oxidase inhibitor in

the nanomolar range (Figure 1) with potential application to reduce the production of uric acid (gouty tophus, gout arthritis or other diseases caused by hyperuricemia).⁸

Our group recently discovered 3-acetylindolizine derivative **H** with excellent potential to inhibit the cell growth of cancer cell lines, especially MDA-MB-435 melanoma cells ($GI_{50} = 1.8$ nM).⁹ In an endeavor to enrich the structure-activity relationships information in this series and to provide additional insights into their anticancer potential, we were interested in the synthesis of a portfolio of compounds bearing a cyano group in position 3 of the indolizine as a withdrawing isostere of the acetyl unit (Figure 1). The new study mainly focused on the synthesis of key intermediates 3-cyanoindolizines **3** (target compounds, Figure 1), essential for a future access to the designed phenothiazine-indolizine hybrids. Unexpectedly, some by-products were detected in the crude of this traditional [3+2] cycloaddition of cyanomethylpyridinium salt with alkyl propiolate. These new compounds have been isolated and their structure elucidated as cyanoazaindoliziny-indolizines. A straightforward synthetic pathway was developed which allowed to tune the reactivity and obtain either classical cyanoindolizines or the cyanoazaindoliziny-indolizines.

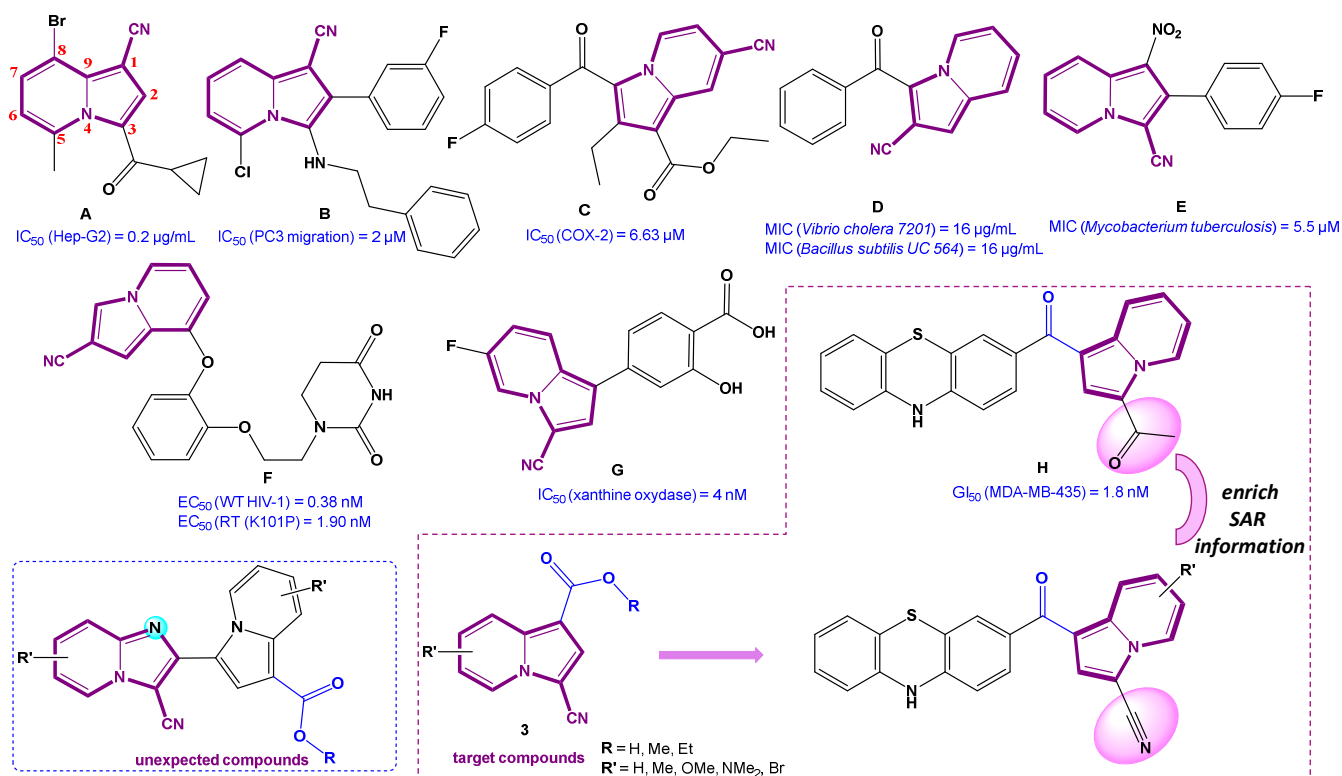
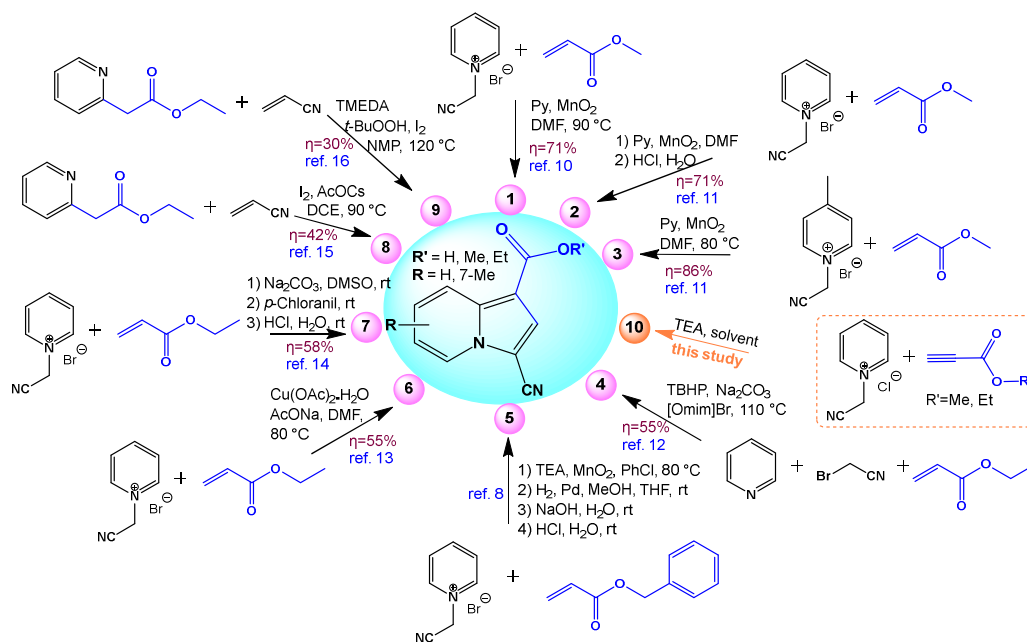


Figure 1. Structure of main bioactive cyanoindolizines **A-G**,¹⁻⁸ indolizine **H**⁹ and of target and unexpected compounds investigated in this study.

Analysis of the literature revealed that only four 3-cyanoindolizines derivatives of interest (methyl 3-cyanoindolizine-1-carboxylate, methyl 3-cyano-7-methylindolizine-1-carboxylate, ethyl 3-cyanoindolizine-1-carboxylate and 3-cyanoindolizine-1-carboxylic acid) have been described *via* diverse procedures. Their syntheses are mainly based on [3+2] cycloadditions and presented in Scheme 1. Methyl 3-cyanoindolizine-1-carboxylate has been obtained in 71% yield from the cycloaddition reaction of ylide generated *in situ* from 1-(cyanomethyl)pyridinium bromide with methyl acrylate in the presence of MnO₂ used as dehydrogenation agent in DMF at 90 °C (pathway 1, Scheme 1).¹⁰ The same 3-cyanoindolizine has been constructed in the same way and in the same yield by Wang and co-workers¹¹ with a modified final workup

using aqueous HCl (pathway 2, Scheme 1). The methyl 3-cyano-7-methylindolizine-1-carboxylate has also been isolated in 86% yield by 1,3-dipolar cycloaddition of pyridinium *N*-ylide to methyl acrylate, followed by internal aromatization mediated by MnO₂ (pathway 3, Scheme 1). Now, the ethyl 3-cyanoindolizine-1-carboxylate has also been synthesized mainly through 1,3-cycloaddition reaction but using different catalysts and conditions (pathways 4, 6-9, Scheme 1): i) one-pot reaction of pyridine, bromoacetonitrile and ethyl acrylate in imidazolium-based ionic liquid [O_{mim}]Br used to reinforce the final cycloaddition reaction by the noncovalent interactions between the ionic liquid and substrates at 110 °C (55% yield, pathway 4);¹² ii) reaction of pyridinium salt with ethyl acrylate in the presence of copper acetate monohydrate and sodium acetate in DMF at 80 °C (55% yield, pathway 6);¹³ iii) reaction of pyridinium salt with ethyl acrylate in the presence of Na₂CO₃ in DMSO at rt, followed by the oxidation of the intermediate with chloranil and final acid treatment (58%, pathway 7);¹⁴ iv) iodine-mediated cesium acetate-controlled annulation of ethyl 2-(pyridin-2-yl)acetate with acrylonitrile in DCE at 90 °C (42%, pathway 8);¹⁵ and v) iodine-catalyzed cesium acetate-controlled annulation of ethyl 2-(pyridin-2-yl)acetate with acrylonitrile in DCE at 90 °C (42%, pathway 8);¹⁵ and v) iodine-catalyzed intermolecular oxidative tandem cyclization reaction of acrylonitrile and ethyl 2-(pyridin-2-yl)acetate under metal-free conditions in the presence of TMEDA and TBHP in NMP at 120 °C (30%, pathway 9).¹⁶ The only free carboxylic acid in the series of 3-cyanopyridine described in the literature is 3-cyanoindolizine-1-carboxylic acid.⁸ The acid has been also obtained by cycloaddition reaction of the same ylide with benzyl acrylate operated in chlorobenzene, followed by internal aromatization induced by MnO₂. Resulting benzyl ester was next deprotected to generate free carboxylic acid in reductive conditions (pathway 5, Scheme 1).

Herein we report the synthesis of target 3-cyanoindolizines *via* oxidant free [3+2] cycloaddition reaction between pyridinium *N*-ylides generated *in situ* from cyanomethylpyridinium salts and triethylamine, and alkyl propiolates (pathway 10, Scheme 1), in the same way as some reactions of other cycloimmonium salts.^{17,18}

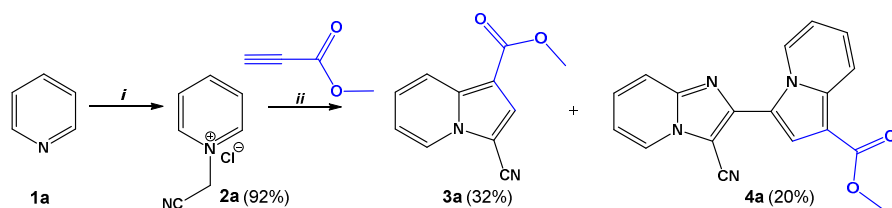


Scheme 1. Synthetic entries to target 3-cyanoindolizine derivatives reported in the literature^{8,10-16} and strategy applied in this study.

2. Results/discussion

In the first attempt to obtain methyl 3-cyanoindolizine-1-carboxylate **3a**, a [3+2] cycloaddition of the dipolarophile methyl propiolate with the pyridinium *N*-ylide formed *in situ* from 1-(cyanomethyl)pyridinium chloride **2a** was performed. The target indolizine **3a** was obtained in modest 32% yield. A supplementary unexpected product was detected in the crude, purified and corresponded

to methyl 3-(3-cyanoimidazo[1,2-*a*]pyridin-2-yl)indolizine-1-carboxylate **4a**, isolated in 20% yield (Scheme 2 and entry 1, Table 1).



Scheme 2. First attempt to synthesize methyl 3-cyanoindolizine-1-carboxylate **3a**. *Reagents and conditions:* (i) chloroacetonitrile (1.3 equiv.), CH₃CN, rt, 48h; (ii) TEA (1.4 equiv.), methyl propiolate (1.5 equiv.), CH₃CN, rt, 24h.

Different operatory conditions were next selected and tested for the 1,3-cycloaddition starting from 1-cyanomethylpyridinium chloride and methyl propiolate (Table 1).

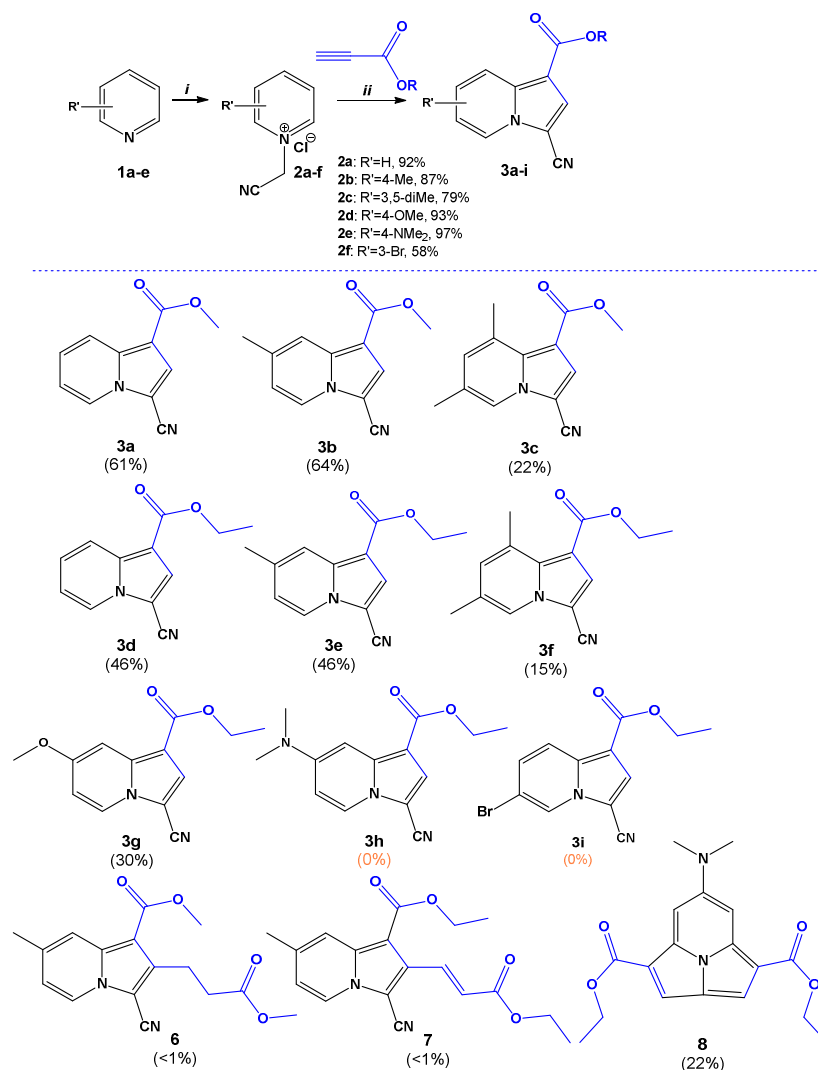
First, the doubling of the reaction time did not lead to yield improvement (entry 2, Table 1). The heating of the reaction mixture at 80 °C resulted in a drastic decrease in the yield of the target 3-cyanoindolizine **3a** and the formation of the cyanoazaindolizine-indolizine **4a** was preferred (entry 3, Table 1). Next, diminishing the amount of TEA from 1.4 equiv. to 1.2 equiv. while heating at 80 °C, very slightly increased the yield of **3a** from 13% to 16%, cyanoazaindolizine-indolizine **4a** being the major product (entry 4, Table 1). On the contrary, increasing the amount of base from 1.4 equiv. to 1.6 equiv. while performing the reaction at rt was more favourable to the formation of the expected product **3a** (entry 5, Table 1). A screening of different solvents was next performed. The reaction performed at rt in equivolumic mixture of acetonitrile and DMF increased the yield of **3a** to 46% (entry 6, Table 1). We next envisaged to associate the diminishing of the amount of TEA revealed in entry 4 as slightly reaction promoter with the latter mixture of solvents. These conditions were the most efficient in our hands and allowed to obtain the target 3-cyanoindolizine **3a** in 61% and traces of the by-product (entry 7, Table 1). The same conditions under heating at 80 °C favored the formation of the azaindolizino-indolizine product **4a** and considerably inhibited the formation of cyanoindolizine **3a** (entry 8, Table 1). Next, the use of potassium carbonate instead of TEA in the initial conditions (1.4 equiv. of base in acetonitrile at rt) was less tolerated and target indolizine **3a** was isolated in 25% yield along with 8% of cyanoazaindolizine-indolizine **4a** (entry 9, Table 1). Increasing the amount of K₂CO₃ to 2.0 equiv. gave similar result as 1.4 equiv. of TEA (compare entries 1 and 10, Table 1). The heating of the mixture at 80 °C favored once again the formation of **4a** compared to target **3a** (entry 11, Table 1). The combinations K₂CO₃-DMF and K₂CO₃-toluene were also favorable for the studied cycloadditions, but not considerably better than TEA-acetonitrile/DMF (compare entries 6, 12 and 13, Table 1). As expected, although a good solvent for pyridinium salts, water was not a favorable solvent for this type of reaction and allowed the partial hydration of the cyano group to amide (entry 14, Table 1). Ethanol did not favor either the formation of indolizine **3a** (entry 15, Table 1), but its use under heating resulted in the formation of the azaindolizine-indolizine by-product **4a** (entry 16, Table 1).

Table 1 Optimization of reaction conditions of the [3+2] cycloaddition of cyanomethylpyridinium salt **2a** with methyl propiolate.^a

Entry	Base	Solvent	Time (h)	T (°C)	Yield (%) ^b 3a/4a
1	Et ₃ N (1.4 eq.)	CH ₃ CN	24	20	32/20
2	Et ₃ N (1.4 eq.)	CH ₃ CN	48	20	35/22
3	Et ₃ N (1.4 eq.)	CH ₃ CN	24	80	13/54
4	Et ₃ N (1.2 eq.)	CH ₃ CN	24	80	16/50
5	Et ₃ N (1.6 eq.)	CH ₃ CN	24	20	41/18
6	Et ₃ N (1.4 eq.)	CH ₃ CN+DMF	24	20	46/22
7	Et₃N (1.2 eq.)	CH₃CN+DMF	24	20	61/traces
8	Et ₃ N (1.2 eq.)	CH ₃ CN+DMF	24	80	19/54
9	K ₂ CO ₃ (1.4 eq.)	CH ₃ CN	24	20	25/8
10	K ₂ CO ₃ (2.0 eq.)	CH ₃ CN	24	20	34/20
11	K ₂ CO ₃ (2.0 eq.)	CH ₃ CN	24	80	13/30
12	K ₂ CO ₃ (1.4 eq.)	DMF	24	20	46/5
13	K ₂ CO ₃ (1.4 eq.)	toluene	24	20	36/traces
14	K ₂ CO ₃ (1.4 eq.)	H ₂ O	24	20	10/0 ^c
15	K ₂ CO ₃ (1.4 eq.)	EtOH	24	20	15/0
16	K ₂ CO ₃ (1.4 eq.)	EtOH	24	78	9/35

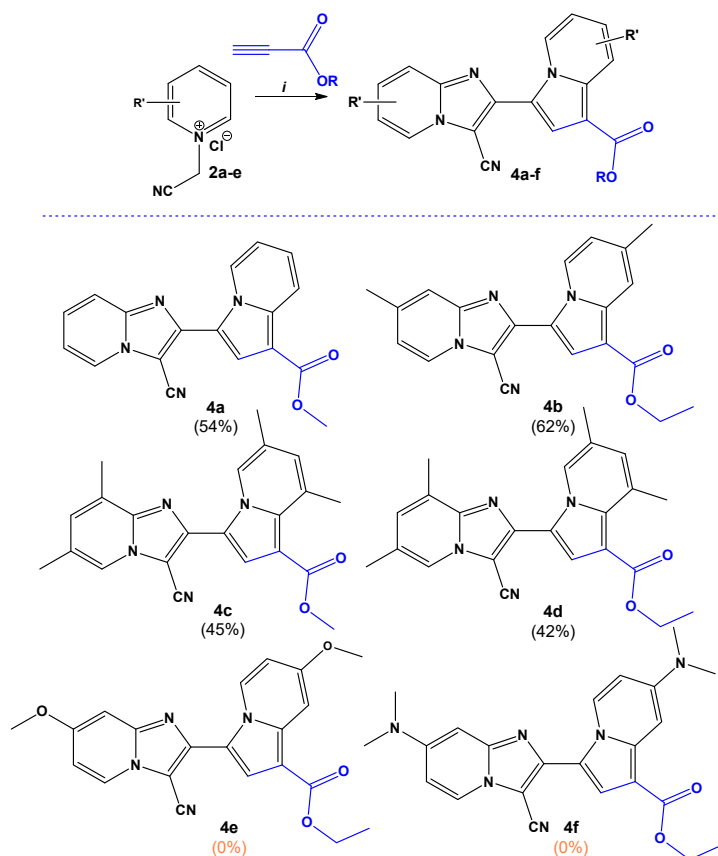
^a 1 g of salt **2a** and 1.5 equiv. methyl propiolate were used in all experiments. ^b Isolated yield. ^c By-product corresponding to the amide analogue of **3a** was obtained in 8% yield.

Using the optimized conditions (Table 1, entry 7), the scope and versatility of the 1,3-cycloaddition were explored to access the target cyanoindolizines. First, cycloimmonium salts **2a-f** were easily prepared in good to excellent yields (58-97%) by reaction of pyridines **1a-f** with chloroacetonitrile in acetonitrile at rt (Scheme 3). Salts **2a-c** and **2e** were previously reported¹⁹⁻²² while salts **2d** and **2f** are newly synthesized compounds. Next, salts **2a-f** were treated with TEA in acetonitrile/DMF mixture and alkyl propiolate to construct the 3-cyanoindolizines **3a-f** (Scheme 3). Three reactions were performed with methyl propiolate and three methyl esters were thus obtained **3a-c** in moderate to good yields (22-64%) (Scheme 3). It is to be noted that in the case of cyanoindolizine **3b** isolated herein in the best yield, traces of a by-product **6** were also obtained (Scheme 3). Bis methyl ester **6** issued from an additional reaction of the dipolarophile with the indolizine ring intermediate. Six transformations were performed with ethyl propiolate. Only four indolizines **3d-g** were obtained in moderate yields. A bis ethyl ester **7** formed by additional attack of ethyl propiolate was again detected and isolated in the synthesis of indolizine **3e** (Scheme 3). The mechanisms proposed for the formation of unexpected compounds **6** and **7** are presented in the Supplementary data section (Scheme S1). The 4-dimethylamino substituted salt **2e** behave completely different and underwent double cycloaddition reaction and cyano group elimination upon TEA treatment to provide tricyclic by-product **8** in 22% yield (Scheme 3). The ability of *p*-(dimethylamino)pyridinium ylides to undergo a double dipolar cycloaddition and generate tricyclic systems was already documented using olefinic dipolarophiles.²³ On the contrary, the 3-bromo substituted salt **2f** was stable in the tested conditions and did not allow the formation of the target indolizine **3i**. We also observed that the quality of the alkyl propiolate used was very important. The time elapsed from the degassing of the vial with the reagent to its effective use had an influence on the final yield. A reaction with freshly opened ethyl propiolate provided the product of interest in a higher yield under the same reaction conditions (64% versus 33% for **3b**, and 46% versus 25% for **3e**).



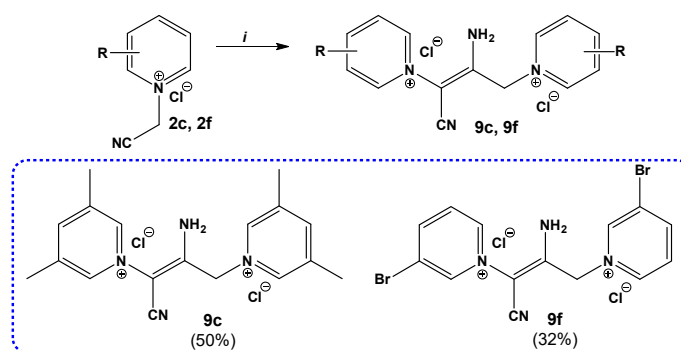
Scheme 3. Synthesis of cyanoindolizines **3a-i**. *Reagents and conditions:* (i) chloroacetonitrile (1.3 equiv.), CH₃CN, rt, 48h; (ii) TEA (1.2 equiv.), ethyl or methyl propiolate (1.5 equiv.), CH₃CN+DMF, rt, 24h.

Next, the reactions performed under heating at 80 °C allowed the tuning of the reactivity and the construction of cyanoazaindolizine-indolizines **4** to the detriment of the classical cycloaddition expected products (Scheme 4). Cyanomethylpyridinium salts **2a-c** reacted easily with methyl and ethylpropiolate in the presence of TEA under heating and generated cyanoazaindolizine-indolizines **4a-d** in good yields (Scheme 4). The *p*-methoxy and *p*-dimethylamino-substitutions in salts **2d** and **2e** were very reactive and generated a complex mixture of inseparable chemical entities. The structure of the resulting adducts **4** as well as the positioning of the cyano and ester groups were secured by X-ray analysis of **4c**²⁴ (Schemes 4 and 6). This compound crystallizes in *P*-1 space group of monoclinic system. It exhibits a molecular crystal structure which is built up from the neutral entities of **4c** and co-crystallized chloroform molecules in 3:2 ratio. The asymmetric unit comprises three crystallographic independent but chemically identical molecules of **4c** (denoted as **A**, **B** and **C**) and two solvate molecules of CHCl₃ (see Figure S1 and Table S1 in the Supplementary information section for full characterization).



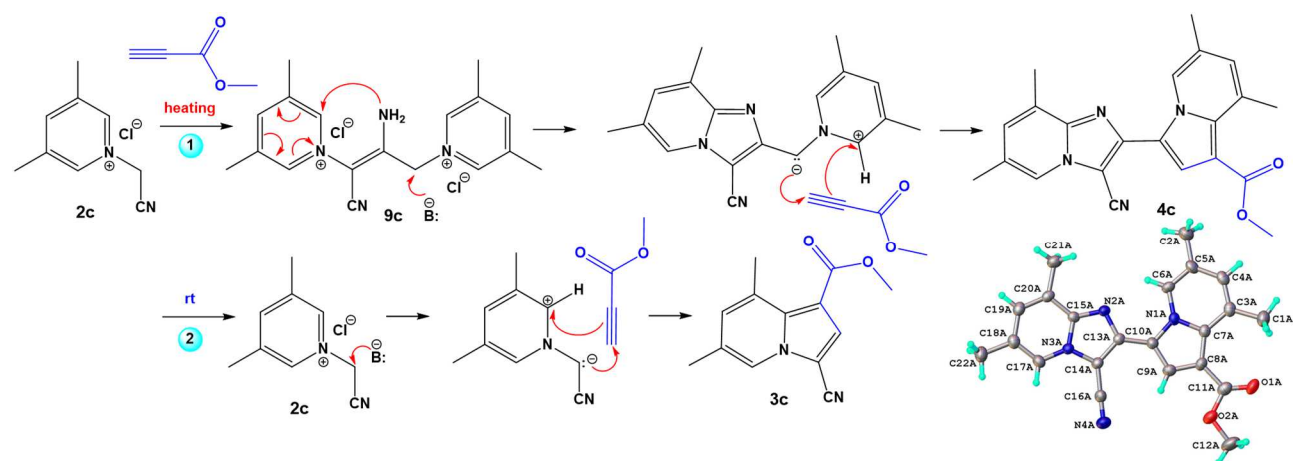
Scheme 4. Synthesis of cyanoazaindolizine-indolizine **4a-f**. Reagents and conditions: (i) TEA (1.2 equiv.), ethyl or methyl propiolate (1.5 equiv.), CH₃CN+DMF, 80 °C, 24h.

The previous studies on 1-(cyanomethyl)pyridinium chlorides **2a** and **2b** revealed the formation of corresponding bispyridinium salts under reflux in acetonitrile for several days.^{22, 25} The reaction of these bispyridinium salts with α,β -unsaturated carbonyl compounds resulted in the formation of pyrido[2,3-*b*]indolizine-10-carbonitriles through intramolecular cyclization of bispyridinium salts.²² In order to explain the mechanism of the formation of azaindolizine-indolizines **4**, we hypothesized that these bispyridinium salts formed in the medium and underwent tandem cyclization. This side-reaction seemed favored by the heating of the medium. The least reactive 1-cyanomethylpyridinium salts in the cycloaddition reaction **2c** and **2f** were next heated in acetonitrile for 4 days in the absence of dipolarophile. Two dimers of the cycloimmonium salts **9c** and **9f** have been isolated in 50% and 32% yield, respectively (Scheme 5).



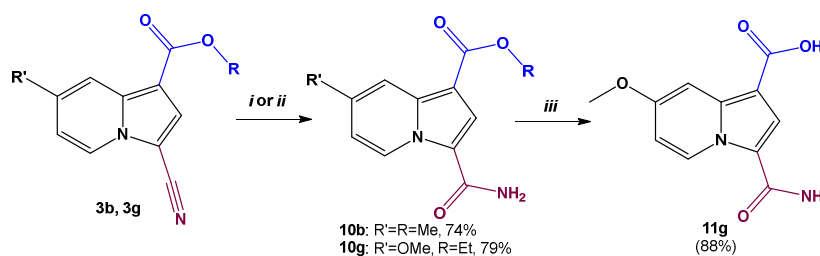
Scheme 5. Dimerization of 1-cyanomethylpyridinium salts **2c** and **2f**. Reagents and conditions: (i) CH₃CN, reflux, 96h.

These dimers reacted next with ethyl or methyl propiolate to create the indolizine ring while the free amino group of the dimer attacked the alpha position of the left pyridinium cycle to generate the azaindolizine unit. This was illustrated with dimer **9c** and salt **2c** in Scheme 6. A competition of reactivity between the initial salt and the dimer formed *in situ* with the dipolarophile established in the medium. The competition was gained by the dimer when the medium was heated (route 1, Scheme 6) and by conventional salt at low temperature (route 2, Scheme 6) thus generating either azaindolizine-indolizine or indolizine. Isolated salt **9c** was next reacted with methyl propiolate and TEA under heating at 80 °C in a mixture CH₃CN/DMF and signals of compound **4c** have been identified in the ¹H NMR spectrum of the crude, confirming the mechanism.



Scheme 6. Proposed mechanism of the formation of indolizine **3c** and azaindolizine-indolizine **4c** and X-ray molecular structure of **4c** (molecule A) with atom labelling and thermal ellipsoids at 50% level.

Finally, 3-cyanoindolizines **3b** and **3g** were submitted to saponification conditions. Reaction occurred at the CN group generating the amides **10b** and **10g** in good yields without impact on the methyl or ethyl ester group (Scheme 7). The reaction was therefore tested with a weaker base (LiOH) and resulted in an inseparable mixture of products. Cesium carbonate was next tested, but also provided amides as unique reaction products. The cyano group was more reactive compared to the ester group in all tested conditions. The acid **11g** could be obtained by successive saponification of the amide **10g** (Scheme 7).



Scheme 7. Hydrolysis of 3-cyanoindolizines **3b** and **3g**. Reagents and conditions: (i) NaOH (1.3 equiv.), EtOH, reflux, 2h; (ii) Cs₂CO₃ (1.3 equiv.), EtOH, rt, 5h; (iii) NaOH (2.0 equiv.), EtOH, 80 °C, 24h.

3. Conclusion

In summary, the investigation of the [3+2] cycloaddition of pyridinium *N*-ylides obtained from 1-cyanomethylpyridinium salts with alkyl propiolates revealed the formation of expected 3-cyanoindolizines along with original by-products. The structure of these by-products was elucidated and secured by X-Ray analysis as ethyl or methyl 3-(3-cyanoimidazo[1,2-*a*]pyridin-2-yl)indolizine-1-carboxylates. Experiments were next designed to access either the expected 3-cyanoindolizines **3** or the cyanoazaindolizine-indolizines

adducts **4**. The performing of the reactions at room temperature were favorable for the classical reactivity and construction of cyanoindolizines **3** while heating induced the formation of cyanoazaindolizine-indolizines **4**. The protocol described herein to access 3-cyanoindolizines **3** is simple, does not require the use of an oxidant (copper acetate, MnO₂ or chloranil) or special solvents such as ionic liquids like many processes described previously (Scheme 1). Also, it is interesting to note that the [3+2] cycloaddition reaction described in this study takes places at rt and is therefore advantageous from an energetic point of view. Investigation of the mechanism of the formation of cyanoazaindolizine-indolizines revealed heating-facilitated 1-cyanomethylpyridinium salt dimerization followed by internal cyclization and [3+2] cycloaddition. The saponification in classical basic conditions (NaOH, LiOH or Cs₂CO₃) did not allow to obtain the free carboxylic acids from 3-cyanoindolizines but induced partial hydrolysis of the nitrile group to produce amides **10**. A portfolio of rare compounds bearing a cyano or amide group in position 3 of the indolizine or azaindolizine ring has been successfully obtained in this study. These functionalized compounds constitute interesting building blocks for organic and medicinal chemists to access bioactive molecules.

4. Experimental section

Starting materials are commercially available and were used without further purification (suppliers: Carlo Erba Reagents S.A.S., Tokyo Chemical Industry Co. Ltd. and Acros Organics). Melting points were measured on an MPA 100 OptiMelt[®] apparatus and are uncorrected. Nuclear Resonance Magnetic (NMR) were acquired at 400 MHz for ¹H NMR and at 100 MHz for ¹³C NMR, on a Varian 400-MR spectrometer or at 500 MHz for ¹H NMR and at 125 MHz for ¹³C NMR, on a Bruker Avance III 500 MHz spectrometer with tetramethylsilane (TMS) as internal standard, at 25 °C. Chemical shifts (δ) are expressed in ppm relative to TMS. Splitting patterns are designed: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; quint, quintuplet; br s, broaden singlet; br t, broaden triplet. Coupling constants (*J*) are reported in Hertz (Hz). Thin layer chromatography (TLC) was realized on Macherey Nagel silica gel plates with fluorescent indicator and were visualized under a UV-lamp at 254 nm and 365 nm. Flash chromatography was performed with a CombiFlash Rf Companion (Teledyne-Isco System) using RediSep packed columns. IR spectra were recorded on a Varian 640-IR FT-IR or on a FTIR Bruker Tensor 27 spectrometer. Elemental analyses (C, H, N) of new compounds were determined on a Thermo Electron apparatus by "Pole Chimie Moleculaire-Welience", Faculte des Sciences Mirande, Dijon, France.

General procedure A for the synthesis of 1-(cyanomethyl)pyridinium salts 2a-f: Chloroacetonitrile (1.3 equiv.) has been added to a solution of pyridine **1a-f** (1.0 equiv.) in acetonitrile. The mixture was magnetically stirred at rt for 48 h. The precipitate formed has been filtered, washed with acetone and dried to provide the pure 1-(cyanomethyl)pyridinium salt **2a-f**. Salts **2a-c** and **2e** had the same physico-chemical characteristics as previously reported.¹⁹⁻²²

1-(Cyanomethyl)-4-methoxypyridinium chloride (2d). The general procedure A was used with 3.22 g (29.5 mmol) of 4-methoxypyridine and 2.42 mL (38.3 mmol) chloroacetonitrile in 40 mL acetonitrile. Beige solid; 5.06 g (93% yield); ¹H NMR (DMSO-*d*₆, 400 MHz) δ (ppm): 4.14 (s, 3H, CH₃), 5.91 (s, 2H, CH₂), 7.75 (dd, *J* = 7.6, 2.4 Hz, 2H, ArH), 9.06 (dd, *J* = 7.6, 2.4 Hz, 2H, ArH). ¹³C NMR (DMSO-*d*₆, 100 MHz) δ (ppm): 46.1 (CH₃), 58.9 (CH₂), 113.9 (C), 114.4 (2CH), 147.1 (2CH), 172.3 (C). IR ν (cm⁻¹): 3001, 2176, 1637, 1566, 1521, 1437, 1313, 1185, 999, 931, 845, 771, 722, 656, 580, 522, 469, 415.

1-(Cyanomethyl)-3-bromopyridinium chloride (2f). The general procedure A was used with 8.0 g (50.63 mmol) of 3-bromopyridine and 4.17 mL (65.82 mmol) chloroacetonitrile in 70 mL acetonitrile. Brown solid; 5.80 g (58% yield); ¹H NMR (DMSO-*d*₆, 500 MHz) δ (ppm): 6.35 (s, 2H, CH₂), 8.25 (dd, *J* = 8.5, 2.5 Hz, 1H, ArH), 9.03 (d, *J* = 8.5 Hz, 1H, ArH), 9.46 (d, *J* = 6.0 Hz, 1H, ArH), 9.92 (s, 1H, ArH). ¹³C NMR (DMSO-*d*₆, 125 MHz) δ (ppm): 47.2 (CH₂), 114.0 (C), 122.2 (C), 129.2 (CH), 144.5 (CH), 146.9 (CH), 149.8 (CH). IR ν (cm⁻¹): 3442, 3378, 3110, 3059,

2963, 2891, 2189, 1984, 1649, 1637, 1620, 1476, 1453, 1415, 1348, 1251, 1191, 1171, 1111, 1099, 1032, 916, 861, 804, 685, 610, 542, 420.

General procedure B for the synthesis of 3-cyanoindolizines 3: 1-(Cyanomethyl)pyridinium salt **2a-e** (1.0 equiv.) was suspended in a mixture of CH₃CN and DMF (1/1 vol/vol). Triethylamine (1.2 equiv.) was next added to the mixture, then the methyl or ethyl propiolate (1.5 equiv.). The resulting medium was stirred at rt for 24 hours, then concentrated *in vacuo*. The crude was washed with distilled water and extracted with ethyl acetate or dichloromethane. The organic phase was dried over Na₂SO₄, concentrated, then purified by flash chromatography (mobile phase: gradient cyclohexane/EtOAc 100/0 to 0/100) on silica (40-60 μm) pre-packed column to afford pure 3-cyanoindolizines **3a-g**.

Methyl 3-cyanoindolizine-1-carboxylate (3a). The general procedure **B** was used with 4.0 g (25.87 mmol) of 1-(cyanomethyl)pyridinium chloride **2a** to obtain pure indolizine **3a** with the same physico-chemical as previously reported.²³ White solid; 3.16 g (61% yield); mp (EtOAc/cyclohexane) = 119-121 °C; R_f (EtOAc/cyclohexane 5/5) = 0.66. ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 3.92 (s, 3H, CH₃), 7.05 (t, *J* = 7.5 Hz, 1H, ArH), 7.35 (t, *J* = 8.0 Hz, 1H, ArH), 7.78 (s, 1H, ArH), 8.34 (t, *J* = 8.5 Hz, 2H, ArH). ¹³C NMR (CDCl₃, 125 MHz) δ (ppm): 51.4 (CH₃), 96.7 (C), 105.7 (C), 112.6 (C), 115.1 (CH), 120.4 (CH), 125.2 (CH), 125.7 (CH), 126.1 (CH), 137.8 (C), 163.7 (C). IR ν (cm⁻¹): 3121, 2950, 2922, 2851, 2211, 1697, 1632, 1518, 1444, 1366, 1265, 1240, 1220, 1152, 1071, 1028, 930, 776, 741, 625, 565, 482, 445, 417.

Methyl 3-cyano-7-methylindolizine-1-carboxylate (3b). The general procedure **B** was used with 2.0 g (11.86 mmol) of 1-(cyanomethyl)-4-methylpyridinium chloride **2b** to obtain pure indolizine **3b** with the same physico-chemical as previously reported.^{26,27} Yellow solid; 1.62 g (64% yield); mp (EtOAc/cyclohexane): 132-135 °C; R_f (EtOAc/cyclohexane 5/5) = 0.66. ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 2.46 (s, 3H, CH₃), 3.90 (s, 3H, CH₃), 6.87 (dd, *J* = 7.0, 1.5 Hz, 1H, ArH), 7.72 (s, 1H, ArH), 8.11 (t, *J* = 1.0 Hz, 1H, ArH), 8.21 (d, *J* = 7.0 Hz, 1H, ArH). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 21.5 (CH₃), 51.3 (CH₃), 96.1 (C), 104.3 (C), 112.9 (C), 117.6 (CH), 119.0 (CH), 125.1 (CH), 125.3 (CH), 137.7 (C), 138.3 (C), 163.8 (C). IR ν (cm⁻¹): 3121, 2948, 2210, 1696, 1632, 1518, 1488, 1443, 1412, 1365, 1334, 1306, 1262, 1239, 1219, 1152, 1126, 1070, 1028, 1011, 966, 930, 890, 863, 842, 805, 775, 740, 625, 566, 482, 443, 418.

Methyl 3-cyano-2-(3-methoxy-3-oxopropyl)-7-methylindolizine-1-carboxylate (6). By-product obtained from the synthesis of indolizine **3b**. Yellow solid; 0.03 g (traces); mp (EtOH): 113-116 °C; R_f (EtOAc/cyclohexane 5/5) = 0.60. ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 2.39 (s, 3H, CH₃), 2.67 (t, *J* = 7.5 Hz, 2H, CH₂), 3.30 (t, *J* = 7.5 Hz, 2H, CH₂), 3.63 (s, 3H, CH₃), 3.97 (s, 3H, CH₃), 6.76 (d, *J* = 7.5 Hz, 1H, ArH), 7.41 (s, 1H, ArH), 8.14 (d, *J* = 7.0 Hz, 1H, ArH). ¹³C NMR (CDCl₃, 125 MHz) δ (ppm): 19.9 (CH₂), 21.4 (CH₃), 34.9 (CH₂), 51.7 (CH₃), 52.1 (CH₃), 96.1 (C), 113.4 (C), 115.8 (C), 117.4 (CH), 118.3 (CH), 123.3 (C), 124.6 (CH), 133.1 (C), 135.0 (C), 163.4 (C), 173.6 (C). IR ν (cm⁻¹): 2953, 2916, 2850, 2201, 1734, 1709, 1647, 1530, 1486, 1359, 1302, 1263, 1196, 1152, 1116, 1018, 992, 967, 951, 857, 777, 666, 483, 449, 427. Elem. Analysis calcd. for C₁₆H₁₆N₂O₄: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.26; H, 5.57; N, 9.52%.

Methyl 3-cyano-6,8-dimethylindolizine-1-carboxylate (3c). The general procedure **B** was used with 5.43 g (29.73 mmol) of 1-(cyanomethyl)-3,5-dimethylpyridinium chloride **2c** to obtain pure indolizine **3c**. White solid; 1.58 g (22% yield); mp (EtOAc/cyclohexane): 147-149 °C; R_f (EtOAc/cyclohexane 5/5) = 0.76. ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 2.34 (s, 3H, CH₃), 2.76 (s, 3H, CH₃), 3.85 (s, 3H, CH₃), 6.93 (s, 1H, ArH), 7.34 (s, 1H, ArH), 8.01 (s, 1H, ArH). ¹³C NMR (CDCl₃, 125 MHz) δ (ppm): 17.9 (CH₃), 21.7 (CH₃), 51.6 (CH₃), 95.9 (C), 107.0 (C), 113.1 (C), 121.8 (CH), 124.9 (C), 126.4 (CH), 130.4 (CH), 130.5 (C), 135.9 (C), 163.5 (C). IR ν (cm⁻¹): 2218, 1717, 1520, 1486, 1432, 1388, 1354, 1270, 1213, 1187, 1127, 1049, 983, 944, 842, 772, 660, 624, 575, 518, 488, 442. Elem. Analysis calcd. for C₁₃H₁₂N₂O₂: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.18; H, 5.13; N, 12.15%.

Ethyl 3-cyanoindolizine-1-carboxylate (3d). The general procedure **B** was used with 1.0 g (6.47 mmol) of 1-(cyanomethyl)pyridinium chloride **2a** to obtain pure indolizine **3d** with the same physico-chemical as previously reported.²⁸ White solid; 0.64 g (46% yield); mp (EtOAc/cyclohexane): 100-103 °C; R_f

(EtOAc/cyclohexane 5/5) = 0.72. ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 1.38 (t, J = 7.0 Hz, 3H, CH_3), 4.35 (q, J = 7.0 Hz, 2H, CH_2), 7.00 (t, J = 7.0 Hz, 1H, ArH), 7.30 (td, J = 8.0, 1.0 Hz, 1H, ArH), 7.72 (s, 1H, ArH), 8.25-8.29 (m, 2H, ArH). ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 14.5 (CH_3), 60.3 (CH_2), 96.6 (C), 106.0 (C), 112.6 (C), 115.0 (CH), 120.4 (CH), 125.1 (CH), 125.7 (CH), 126.0 (CH), 137.7 (C), 163.2 (C). IR ν (cm^{-1}): 3120, 2210, 1692, 1517, 1433, 1304, 1262, 1207, 1071, 1029, 773, 752, 628, 564.

Ethyl 3-cyano-7-methylindolizine-1-carboxylate (3e). The general procedure B was used with 1.0 g (5.93 mmol) of 1-(cyanomethyl)-4-methylpyridinium chloride **2b** to obtain pure indolizine **3e**. Yellow solid; 0.63 g (46%); mp (EtOAc/cyclohexane) = 100-101 °C; R_f (EtOAc/cyclohexane 5/5) = 0.72. ^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 1.41 (t, J = 7.2 Hz, 3H, CH_3), 2.46 (s, 3H, CH_3), 4.37 (q, J = 7.2 Hz, 2H, CH_2), 6.87 (dd, J = 6.8, 1.2 Hz, 1H, ArH), 7.74 (s, 1H, ArH), 8.12 (s, 1H, ArH), 8.22 (d, J = 7.2 Hz, 1H, ArH). ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 14.5 (CH_3), 21.5 (CH_3), 60.1 (CH_2), 95.9 (C), 104.6 (C), 112.9 (C), 117.5 (CH), 119.0 (CH), 125.1 (CH), 125.4 (CH), 137.6 (C), 138.3 (C), 163.5 (C). IR ν (cm^{-1}): 3115, 2988, 2911, 2207, 2168, 1680, 1640, 1518, 1487, 1465, 1424, 1382, 1341, 1294, 1259, 1229, 1179, 1168, 1128, 1062, 892, 872, 777, 729, 676, 615, 487, 412. Elem. Analysis calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.69; H, 5.56; N, 12.48%.

Ethyl 3-cyano-6,8-dimethylindolizine-1-carboxylate (3f). The general procedure B was used with 3.00 g (16.42 mmol) of 1-(cyanomethyl)-3,5-dimethylpyridinium chloride **2c** to obtain pure indolizine **3f**. Yellow solid; 0.6 g (15% yield); mp (EtOAc/cyclohexane): 103-106 °C; R_f (EtOAc/cyclohexane 5/5) = 0.76. ^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 1.40 (t, J = 7.2 Hz, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 4.36 (q, J = 7.2 Hz, 2H, CH_2), 6.95 (s, 1H, ArH), 7.32 (s, 1H, ArH), 8.16 (s, 1H, ArH). ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 14.4 (CH_3), 16.8 (CH_3), 21.6 (CH_3), 59.6 (CH_2), 95.9 (C), 107.2 (C), 111.9 (C), 116.5 (CH), 126.4 (C), 127.0 (CH), 131.0 (C), 133.6 (C), 141.0 (C), 163.4 (C). IR ν (cm^{-1}): 2232, 1717, 1505, 1438, 1352, 1210, 1179, 1124, 986, 853, 774, 660, 618, 522, 486, 441. Elem. Analysis calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.78; H, 6.01; N, 11.68%.

Ethyl 3-cyano-7-methoxyindolizine-1-carboxylate (3g). The general procedure B was used with 2.0 g (10.83 mmol) of 1-(cyanomethyl)-4-methoxypyridinium chloride **2d** to obtain pure indolizine **3g**. Yellow solid; 0.8 g (30%); mp (EtOAc/cyclohexane): 129-131 °C; R_f (EtOAc/cyclohexane 5/5) = 0.76. ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 1.38 (t, J = 7.0 Hz, 3H, CH_3), 3.93 (s, 3H, CH_3), 4.35 (q, J = 7.0 Hz, 2H, CH_2), 6.72 (dd, J = 7.5, 2.5 Hz, 1H, ArH), 7.65 (d, J = 2.0 Hz, 1H, ArH), 7.69 (s, 1H, ArH), 8.15 (d, J = 7.5 Hz, 1H, ArH). ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 14.5 (CH_3), 55.9 (CH_3), 60.2 (CH_2), 95.4 (C), 97.8 (CH), 103.9 (C), 109.8 (CH), 113.1 (C), 125.7 (CH), 126.7 (CH), 140.3 (C), 158.8 (C), 163.7 (C). IR ν (cm^{-1}): 2207, 1681, 1647, 1525, 1475, 1430, 1275, 1236, 1204, 1174, 1136, 1067, 1017, 903, 840, 772, 675, 618, 604, 491, 445, 423. Elem. Analysis calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.14; H, 5.20; N, 11.65%.

Diethyl 6-(dimethylamino)pyrrolo[2,1,5-cd]-indolizine-1,4-dicarboxylate (8). The general procedure B was used with 2.0 g (10.12 mmol) of 1-(cyanomethyl)-4-dimethylaminopyridinium chloride **2e** to obtain pure tricycle **8**. Orange solid; 0.46 g (22%); mp (EtOAc/cyclohexane): 158-159 °C; R_f (EtOAc/cyclohexane 5/5) = 0.80. ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 1.47 (t, J = 7.0 Hz, 6H, 2CH_3), 3.24 (s, 6H, 2CH_3), 4.45 (q, J = 7.0 Hz, 4H, 2CH_2), 7.68 (s, 2H, ArH), 7.98 (s, 2H, ArH). ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 14.7 (2CH_3), 41.4 (2CH_3), 60.3 (2CH_2), 99.9 (2CH), 116.0 (2C), 122.9 (2CH), 123.4 (C), 132.0 (2C), 151.2 (C), 165.0 (2C). IR ν (cm^{-1}): 2980, 2902, 2803, 1687, 1625, 1522, 1508, 1424, 1384, 1342, 1238, 1150, 1120, 1019, 967, 864, 815, 774, 724, 690, 634, 490, 450. Elem. Analysis calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 66.10; H, 6.36; N, 8.84%.

General procedure C for the synthesis of cyanoazaindoliziny-indolizines 4: 1-(Cyanomethyl)pyridinium salt **2a-e** (1.0 equiv.) was suspended in a mixture of CH_3CN and DMF (1/1 vol/vol). Triethylamine (1.2 equiv.) was next added to the mixture, then the methyl or ethyl propiolate (1.5 equiv.). The resulting medium was stirred for 24 hours under heating at 80 °C. After cooling to rt, the volatiles have been removed *in vacuo*. The crude was washed with distilled water and extracted with ethyl acetate or dichloromethane. The organic phase was

dried with Na₂SO₄, concentrated, then purified by flash chromatography (mobile phase: gradient cyclohexane/EtOAc 100/0 to 0/100) on silica (40-60 μm) pre-packed column to afford pure cyanoazaindolizine-indolizines **4a-d**.

Methyl 3-(3-cyanoimidazo[1,2-a]pyridin-2-yl)-indolizine-1-carboxylate (4a). The general procedure **C** was used with 1.0 g (6.47 mmol, 1.0 equiv.) of 1-(cyanomethyl)-pyridinium chloride **2a** and methyl propiolate (0.82 g, 0.86 mL, 9.70 mmol, 1.5 equiv.) to obtain pure azaindolizine-indolizine **4a**. Brown solid; 0.56g (54%); mp (EtOAc/cyclohexane) = 254-256 °C; R_f (EtOAc/cyclohexane 5/5) = 0.52. ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 3.93 (s, 3H, CH₃), 6.94 (t, *J* = 7.0 Hz, 1H, ArH), 7.10 (t, *J* = 7.0 Hz, 1H, ArH), 7.24 (d, *J* = 8.0 Hz, 1H, ArH), 7.47 (t, *J* = 8.0 Hz, 1H, ArH), 7.73 (d, *J* = 8.5 Hz, 1H, ArH), 8.10 (s, 1H, ArH), 8.35 (m, 2H, ArH), 10.00 (d, *J* = 7.0 Hz, 1H, ArH). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 51.1 (CH₃), 92.8 (C), 105.1 (C), 112.7 (C), 113.7 (CH), 114.8 (CH), 116.0 (C), 117.6 (CH), 118.8 (CH), 119.5 (CH), 124.4 (CH), 125.4 (CH), 127.7 (CH), 128.7 (CH), 137.8 (C), 146.5 (C), 146.7 (C), 164.8 (C). IR ν (cm⁻¹): 2204, 2008, 1697, 1688, 1632, 1557, 1517, 1487, 1449, 1316, 1295, 1245, 1216, 1056, 777, 759, 741, 437, 425. Elem. Analysis calcd. for C₁₈H₁₂N₄O₂: C, 68.35; H, 3.82; N, 17.71. Found: C, 68.46; H, 4.13; N, 18.09%.

Ethyl 3-(3-cyano-7-methylimidazo[1,2-a]pyridin-2-yl)-7-methylindolizine-1-carboxylate (4b). The general procedure **C** was used with 1.0 g (5.93 mmol, 1.0 equiv.) of 1-(cyanomethyl)-4-methylpyridinium chloride **2b** and ethyl propiolate (0.87 g, 0.90 mL, 8.89 mmol, 1.5 equiv.) to obtain pure azaindolizine-indolizine **4b**. Yellow solid; 0.66 g (62%); mp (EtOAc/cyclohexane) > 230 °C; R_f (EtOAc/cyclohexane 5/5) = 0.56. ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 1.34 (t, *J* = 7.0 Hz, 3H, CH₃), 2.45 (s, 3H, CH₃), 2.50 (s, 3H, CH₃), 4.40 (q, *J* = 7.0 Hz, 2H, CH₂), 6.77 (d, *J* = 7.0 Hz, 1H, ArH), 6.93 (d, *J* = 6.5 Hz, 1H, ArH), 7.51 (s, 1H, ArH), 8.05 (s, 1H, ArH), 8.15 (s, 1H, ArH), 8.23 (d, *J* = 6.5 Hz, 1H, ArH), 8.87 (d, *J* = 7.0 Hz, 1H, ArH). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 14.7 (CH₃), 21.4 (CH₃), 21.6 (CH₃), 59.7 (CH₂), 92.0 (C), 104.1 (C), 113.1 (C), 115.6 (C), 116.1 (CH), 116.3 (CH), 117.2 (CH), 118.1 (CH), 118.7 (CH), 124.6 (CH), 127.2 (CH), 135.4 (C), 138.3 (C), 140.3 (C), 146.9 (C), 147.0 (C), 164.7 (C). IR ν (cm⁻¹): 2355, 2339, 2193, 1680, 1642, 1562, 1515, 1481, 1463, 1346, 1315, 1247, 1223, 1193, 1159, 1102, 1048, 875, 793, 776, 702, 667, 608, 523, 504, 459, 437. Elem. Analysis calcd. for C₂₁H₁₈N₄O₂: C, 70.38; H, 5.06; N, 15.63. Found: C, 70.77; H, 5.20; N, 15.81%.

Methyl 3-(3-cyano-6,8-dimethylimidazo[1,2-a]pyridin-2-yl)-6,8-dimethylindolizine-1-carboxylate (4c). The general procedure **C** was used with 1.0 g (5.47 mmol, 1.0 equiv.) of 1-(cyanomethyl)-3,5-dimethylpyridinium chloride **2c** and methyl propiolate (0.69 g, 0.73 mL, 8.21 mmol, 1.5 equiv.) to obtain pure azaindolizine-indolizine **4c**. Yellow solid; 0.46 g (45%); mp (CHCl₃): 231-233 °C; R_f (EtOAc/cyclohexane 5/5) = 0.70. ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 2.34 (s, 3H, CH₃), 2.39 (s, 3H, CH₃), 2.67 (s, 3H, CH₃), 2.79 (s, 3H, CH₃), 3.88 (s, 3H, CH₃), 6.84 (s, 1H, ArH), 7.10 (s, 1H, ArH), 8.00 (s, 1H, ArH), 8.03 (s, 1H, ArH), 9.75 (s, 1H, ArH). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 16.8 (CH₃), 18.3 (CH₃), 18.6 (CH₃), 22.1 (CH₃), 51.5 (CH₃), 93.3 (C), 106.4 (C), 113.4 (C), 115.6 (C), 120.3 (CH), 121.2 (CH), 122.9 (C), 123.4 (CH), 125.0 (C), 127.2 (C), 128.6 (CH), 129.3 (C), 130.7 (CH), 135.6 (C), 145.8 (C), 146.0 (C), 165.0 (C). IR ν (cm⁻¹): 3091, 2941, 2920, 2209, 1707, 1556, 1492, 1446, 1359, 1333, 1282, 1263, 1202, 1060, 988, 943, 840, 771, 710, 582, 543, 487. Elem. Analysis calcd. for C₂₂H₂₀N₄O₂: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.32; H, 5.70; N, 15.37%.

Ethyl 3-(3-cyano-6,8-dimethylimidazo[1,2-a]pyridin-2-yl)-6,8-dimethylindolizine-1-carboxylate (4d). The general procedure **C** was used with 1.0 g (5.47 mmol, 1.0 equiv.) of 1-(cyanomethyl)-3,5-dimethylpyridinium chloride **2c** and ethyl propiolate (0.805 g, 0.832 mL, 8.21 mmol, 1.5 equiv.) to obtain pure azaindolizine-indolizine **4d**. White solid; 0.45 g (42%); mp (EtOAc/cyclohexane): 221-224 °C; R_f (EtOAc/cyclohexane 5/5) = 0.80; ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 1.43 (t, *J* = 7.0 Hz, 3H, CH₃), 2.34 (s, 3H, CH₃), 2.36 (s, 3H, CH₃), 2.64 (s, 3H, CH₃), 2.77 (s, 3H, CH₃), 4.35 (q, *J* = 7.0 Hz, 2H, CH₂), 6.81 (s, 1H, ArH), 7.07 (s, 1H, ArH), 7.95 (s, 1H, ArH), 8.01 (s, 1H, ArH), 9.73 (s, 1H, ArH). ¹³C NMR (CDCl₃, 125 MHz) δ (ppm): 16.7 (CH₃), 18.5 (CH₃), 18.7 (CH₃), 22.2 (CH₃), 51.7 (CH₃), 59.6 (CH₂), 93.5 (C), 106.5 (C), 113.2 (C), 115.6 (C), 120.8 (CH), 121.1 (CH), 123.1

(C), 123.4 (CH), 125.1 (C), 127.4 (C), 128.8 (CH), 129.4 (C), 130.9 (CH), 135.7 (C), 145.9 (C), 146.1 (C), 164.8 (C). Elem. Analysis calcd. for C₂₃H₂₂N₄O₂: C, 71.48; H, 5.74; N, 14.50. Found: C, 71.89; H, 5.99; N, 14.83%.

1,1'-[2-Amino-1-cyanoprop-1-ene-1,3-diyl]bis(3,5-dimethylpyridin-1-ium)chloride (9c). 1-(Cyanomethyl)-3,5-dimethylpyridinium chloride **2c** (2.0 g, 10.9 mmol) have been added in 30 mL of CH₃CN and stirred under reflux for 96 hours. The precipitate formed in the medium was filtered, washed with absolute ethanol to provide dipyridinium dichloride **9c** as a brown solid; 1.0 g (50%); mp (EtOH): 245-247 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ (ppm): 2.48 (s, 6H, 2CH₃), 2.53 (s, 6H, 2CH₃), 5.82 (s, 2H, CH₂), 8.35 (br s, 1H, NH), 8.44 (s, 1H, ArH), 8.47 (s, 1H, ArH), 8.85 (br s, 1H, NH), 9.18 (s, 4H, ArH). ¹³C NMR (DMSO-*d*₆, 125 MHz) δ (ppm): 17.7 (2CH₃), 17.8 (2CH₃), 58.3 (CH₂), 87.6 (C), 116.6 (C), 138.0 (2C), 139.8 (2C), 142.6 (2CH), 144.8 (2CH), 147.6 (CH), 148.5 (CH), 153.0 (C). IR ν (cm⁻¹): 3455, 3396, 3006, 2193, 1664, 1600, 1473, 1300, 1202, 672, 634, 562, 468.

1,1'-[2-Amino-1-cyanoprop-1-ene-1,3-diyl]bis(3-bromopyridin-1-ium)chloride (9f). 1-(Cyanomethyl)-3-bromopyridinium chloride **2f** (3.2 g, 13.7 mmol) have been added in 40 mL of CH₃CN and stirred under reflux for 96 hours. The precipitate formed in the medium was filtered, washed with absolute ethanol to provide dipyridinium dichloride **9f** as a brown solid; 1.02 g (32%); mp (EtOH) > 300 °C; ¹H NMR (DMSO-*d*₆, 400 MHz) δ (ppm): 5.87 (s, 2H, CH₂), 8.27 (dd, *J* = 8.4, 2.0 Hz, 1H, ArH), 8.31 (dd, *J* = 8.4, 2.4 Hz, 1H, ArH), 8.46 (br s, 1H, NH), 8.84 (br s, 1H, NH), 9.05 (t, *J* = 7.6 Hz, 2H, ArH), 9.32 (d, *J* = 6.0 Hz, 1H, ArH), 9.39 (d, *J* = 6.4 Hz, 1H, ArH), 9.77 (d, *J* = 5.2 Hz, 2H, ArH). ¹³C NMR (DMSO-*d*₆, 100 MHz) δ (ppm): 58.6 (CH₂), 87.8 (C), 116.2 (C), 122.0 (C), 124.2 (C), 128.9 (CH), 130.7 (CH), 144.9 (CH), 147.4 (2CH), 149.3 (CH), 149.5 (CH), 150.2 (CH), 153.1 (C). IR ν (cm⁻¹): 3045, 2988, 2971, 2203, 1653, 1613, 1563, 1491, 1442, 1341, 1288, 1261, 1204, 1180, 876, 806, 785, 675, 610, 506, 412.

General procedure D for the synthesis of amides 10b and 10g: 3-Cyanoindolizine **3b** or **3g** (1.0 equiv.) was mixed with absolute ethanol. In the case of 3-cyanoindolizine **3b**, NaOH (1.3 equiv.) dissolved in water (2 mL) was next added and the mixture was stirred under reflux for 2 hours. In the case of 3-cyanoindolizine **3g**, Cs₂CO₃ (1.3 equiv.) was used as base and dissolved in water (4 mL), then added to the mixture and stirred at rt for 5 hours. In both cases, a neutralization was operated by adding conc. HCl dropwise. The formed precipitate was filtered, washed with water and then with absolute ethanol and finally dried to provide pure amides **10b** or **10g**.

Methyl 3-carbamoyl-7-methylindolizine-1-carboxylate (10b). The general procedure **D** was used with 1.0 g (4.67 mmol, 1.0 equiv.) of methyl 3-cyano-7-methylindolizine-1-carboxylate (**3b**) and 0.243 g (6.07 mmol, 1.3 equiv.) of NaOH. White solid; 0.79 g (74%); mp (EtOH) 261-263 °C; R_f (EtOAc/cyclohexane 5/5) = 0.26; ¹H NMR (DMSO-*d*₆, 500 MHz) δ (ppm): 2.39 (s, 3H, CH₃), 3.81 (s, 3H, CH₃), 6.91 (dd, *J* = 7.0, 1.5 Hz, 1H, ArH), 7.19 (br s, 1H, NH), 7.87 (br s, 1H, NH), 7.95 (s, 1H, ArH), 8.03 (s, 1H, ArH), 9.63 (d, *J* = 7.0 Hz, 1H, ArH). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 20.9 (CH₃), 50.8 (CH₃), 101.5 (C), 116.5 (CH), 116.9 (C), 117.0 (CH), 120.1 (CH), 127.4 (CH), 136.2 (C), 137.7 (C), 162.8 (C), 163.9 (C). IR ν (cm⁻¹): 3394, 3164, 3112, 1661, 1614, 1522, 1490, 1467, 1392, 1302, 1283, 1218, 1197, 1129, 1093, 1046, 995, 871, 797, 768, 696, 666, 619, 566, 533, 436, 409. Elem. Analysis calcd. for C₁₂H₁₂N₂O₃: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.18; H, 5.41; N, 12.12%.

Ethyl 3-carbamoyl-7-methoxyindolizine-1-carboxylate (10g). The general procedure **D** was used with 0.16 g (0.66 mmol, 1.0 equiv.) of ethyl 3-cyano-7-methoxyindolizine-1-carboxylate (**3g**) and 0.277 g (0.85 mmol, 1.3 equiv.) of Cs₂CO₃. White solid; 0.13 g (79%); mp (EtOH) >230 °C; R_f (EtOAc/cyclohexane 5/5) = 0.28. ¹H NMR (DMSO-*d*₆, 400 MHz) δ (ppm): 1.34 (t, *J* = 7.2 Hz, 3H, CH₃), 3.89 (s, 3H, CH₃), 4.28 (q, *J* = 7.2 Hz, 2H, CH₂), 6.80 (dd, *J* = 7.6, 2.4 Hz, 1H, ArH), 7.14 (br s, 1H, NH), 7.54 (d, *J* = 2.8 Hz, 1H, ArH), 7.84 (br s, 1H, NH), 7.98 (s, 1H, ArH), 9.62 (d, *J* = 7.6 Hz, 1H, ArH). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 14.5 (CH₃), 55.4 (CH₃), 59.1 (CH₂), 96.4 (CH), 101.0 (C), 107.8 (CH), 116.3 (C), 120.1 (CH), 129.4 (CH), 139.7 (C), 157.3 (C), 162.8 (C), 163.6 (C). IR ν (cm⁻¹): 3423, 2361, 1665, 1643, 1595, 1536, 1475, 1456, 1382, 1285, 1263, 1214, 1091, 1051, 1021, 911, 869, 858, 848, 835, 759, 662, 546, 520, 459, 425, 415. Elem. Analysis calcd. for C₁₃H₁₄N₂O₄: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.72; H, 5.55; N, 10.81%.

3-Carbamoyl-7-methoxyindolizine-1-carboxylic acid (11g). Ethyl 3-carbamoyl-7-methoxyindolizine-1-carboxylate **10g** (80 mg, **3.1 mmol**) was dissolved in absolute ethanol. Aqueous 2N NaOH solution (**0.248 g, 6.2 mmol**, 2 equiv.) was next added to the solution and the medium was heated to reflux for 24h. After cooling to rt, concentrated aqueous 2N HCl has been added dropwise and the precipitate formed has been filtered, washed with water, then with cold ethanol and dried to obtain pure carboxylic acid **11g** as a white solid; 0.065 g (88%); mp (EtOH) > 230 °C. ¹H NMR (DMSO-*d*₆, 500 MHz) δ (ppm): 3.86 (s, 3H, CH₃), 6.77 (dd, *J* = 8.0, 2.5 Hz, 1H, ArH), 7.11 (br s, 1H, NH), 7.52 (d, *J* = 2.5 Hz, 1H, ArH), 7.81 (br s, 1H, NH), 7.93 (s, 1H, ArH), 9.59 (d, *J* = 7.5 Hz, 1H, ArH), 12.08 (br s, 1H, COOH). ¹³C NMR (DMSO-*d*₆, 125 MHz) δ (ppm): 55.5 (CH₃), 96.5 (CH), 102.0 (C), 107.8(CH), 116.1 (C), 120.8 (C), 129.4 (CH), 139.7 (C), 157.1 (C), 163.0 (C), 165.4 (C). IR ν (cm⁻¹): 1659, 1614, 1602, 1530, 1507, 1471, 1429, 1407, 1350, 1306, 1283, 1239, 1182, 1120, 1085, 1044, 1020, 893, 881, 836, 800, 778, 756, 669, 585, 561, 549, 516, 425. Elem. Analysis calcd. for C₁₁H₁₀N₂O₄: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.64; H, 4.49; N, 12.08%.

Acknowledgements

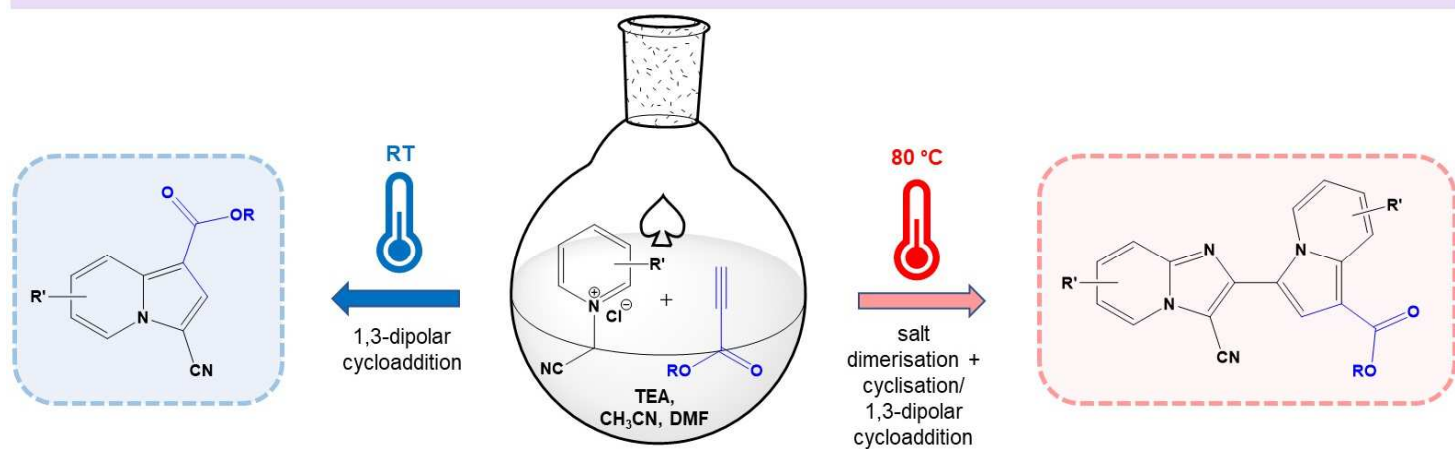
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5. References

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24. *Crystal data for 4c*. C₆₈H₆₂Cl₆N₁₂O₆ ($M_r = 1355.99 \text{ g}\cdot\text{mol}^{-1}$), triclinic, $a = 10.8362(7) \text{ \AA}$, $b = 17.3969(8) \text{ \AA}$, $c = 18.7086(10) \text{ \AA}$, $\alpha = 81.045(4)^\circ$, $\beta = 76.765(5)^\circ$, $\gamma = 74.166(5)^\circ$, $V = 3286.5(3) \text{ \AA}^3$, $Z = 2$, $\rho_{\text{calcd}} = 1.370 \text{ g cm}^{-3}$, $\mu(\text{MoK}\alpha) = 0.324 \text{ mm}^{-1}$, $F(000) = 1408$, 24287 reflections in $h(-12/12)$, $k(-20/20)$, $l(-22/19)$, measured in the range $3.152 \leq 2\theta \leq 50.052$, $T = 173 \text{ K}$, completeness $\Theta_{\text{max}}=99.97\%$, 11598 independent reflections, $R_{\text{int}} = 0.0607$, 844 parameters, 0 restraints, $R_{1\text{obs}}=0.0708$, $wR_{2\text{obs}} = 0.1242$, $R_{1\text{all}} = 0.1521$, $wR_{2\text{all}} = 0.1570$, GoF = 1.004, largest difference peak and hole: 0.31/-0.33 e \AA^{-3} . CCDC 1999585. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.ca.ac.uk).
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- 29.

Cyanoindolizine or cyanoazaindolizine-indolizine?



3-cyano-pyrrolo[1,2-a]pyridine
(3)



3-(3-cyano-imidazo[1,2-a]pyridin-2-yl)indolizine
(4)