Pergamon

Tetrahedron 58 (2002) 5747–5754

TETRAHEDRON

Conformationally constrained 1,4-DHPs. A convenient route to bis-1,4-DHPs as a novel class of nitrogen compounds

Štefan Marchalín,[a] Miloslav Chudík,[a] Katarína Cvopová,[a] Jozef Kozíšek,[b] Ján Leško[c] and Adam Daïch[d,*]

[a]*Department of Organic Chemistry, Faculty of Chemical Technology, Slovak University of Technology, SK-812 37 Bratislava, Slovak Republic*

[b]*Department of Physical Chemistry and Central Laboratory, Faculty of Chemical Technology, Slovak University of Technology, SK-812 37 Bratislava, Slovak Republic*

[c]*Central Laboratory, Faculty of Chemical Technology, Slovak University of Technology, SK-812 37 Bratislava, Slovak Republic*

[d]*Laboratoire de Chimie de l'Université du Havre, Faculté des Sciences and Techniques, URCOM, EA 3221, 25 rue Philippe Lebon, B.P: 540, F-76058 Le Havre Cedex, France*

Received 10 December 2001; revised 21 January 2002; accepted 5 February 2002

Abstract—2-Formyl-1,4-DHP derivatives **2** undergo the tandem Knoevenagel condensation/amino-nitrile cyclisation with activated methylene reagents to afford high functionalised indolizines. However, in the absence of this tandem, the Knoevenagel condensation intermediate leads to bis-1,4-DHPs as a new class of nitrogen compounds.

1. Introduction

As a part of our research program directed towards the synthesis and the biological evaluation of the 1,4-dihydropyridines (1,4-DHPs) polyheterocycles,[1] we have recently explored the utility of 2-formyl-1,4-DHP derivatives **2**[2,3] as remarkable synthons for the synthesis of various pyrrolo-[3,4-*b*]-1,4-DHPs,[3] high functionalised indolizines,[2,4] and corresponding dihydroindolizines and tetrahydroindolizines.[4] These last compounds **2** are obtained by basic amino-ester cyclisation,[2] thermal amino-ester cyclisation[3] or by the tandem Knoevenagel condensation/amino-nitrile cyclisation in alkaline conditions,[4] respectively.

This tandem, which uses 2-formyl-1,4-DHP substrates and activated methylene reagents in a basic medium, constitutes a new and competitive methodology to access efficiently to indolizines with different degrees of unsaturation.[5] Because of the exceptional biological potential of theses species allied with our great interest to develop this chemistry fully, we decided to investigate, evaluate and compare the regiocontrol features of this process in acidic conditions.

2. Results and discussion

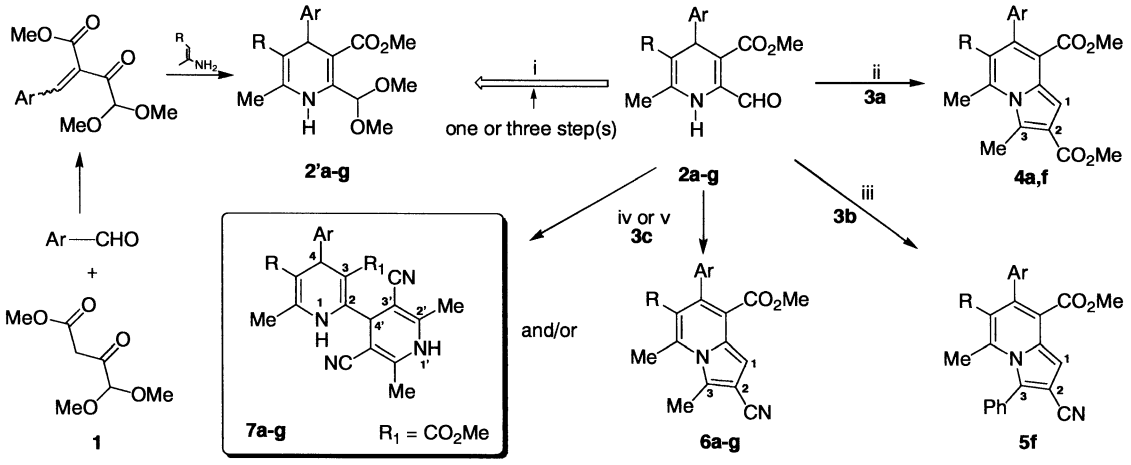
To begin our study, a series of 2-formyl-1,4-DHP reagents **2a–g** with substituents of different bulk at C_4 and C_5 DHP positions was easily prepared in a three-step sequence according to our reported procedure. In fact, this synthetic scheme starts with condensation of aromatic carboxaldehyde with methyl 4,4-dimethoxy-3-oxo-butanoate **1** followed by thermal cyclisation in the presence of enamine derivatives and acidic hydrolysis (Scheme 1). In all cases the resulting 2-formyl-1,4-DHP derivatives **2a–g** were solids and isolated in a range of 63–95% yields after recrystallisation from absolute ethanol.[6]

In the first set of our Knoevenagel condensation experiments (Scheme 1), a 2-formyl-1,4-DHP **2a** was subjected to 1 equiv. of methyl acetoacetate (**3a**) in acetic acid at reflux for 30 min. The ^{1}H NMR and GC–MS analysis of crude reaction products indicated the presence of one single compound. This compound was then isolated by recrystallisation from ethanol in 65% yield, and its structure was established as **4a** by an array of classical monodimensional NMR experiments including ^{1}H NMR, ^{13}C NMR and DEPT program as well as by its elemental analysis and by comparison to related structures described earlier.[7] In the same manner as above, 2-formyl-1,4-DHP **2f** with 1 equiv. of freshly distilled methyl acetoacetate (**3a**) or benzoylacetonitrile (**3b**), led to indolizine **4f** or **5f** as a sole reaction product in 79 and 88% yields, respectively (see Table 1).

Keywords: 1,4-DHP; bis-1,4-DHP; tandem; Knoevenagel; indolizine; intramolecular cyclisation; [1,3]-hydrogen transfer.

* Corresponding author. Tel.: +33-2-32-74-44-03; fax: +33-2-32-74-43-91; e-mail: adam.daich@univ-lehavre.fr

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00542-2



Scheme 1. Key: (i) See Refs. 2,3; (ii) 1 equiv. of methyl acetoacetate (**3a**), AcOH; (iii) 1 equiv. of benzoylacetonitrile (**3b**), AcOH; (iv) 1 equiv. of 3-aminocrotonitrile (**3c**), AcOH; (v) 2 equiv. of 3-aminocrotonitrile (**3c**), AcOH. See Tables 1 and 2 for aryl and R groups.

Table 1. Synthesis of functionalised indolizines **4**–**6** in a one-pot procedure from 2-formyl-1,4-DHP derivatives **2**

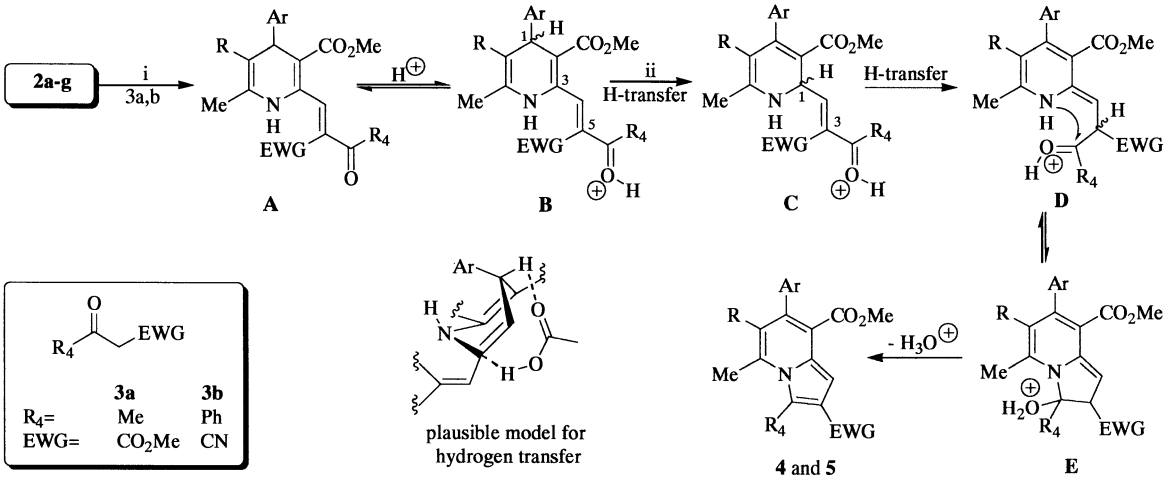
Entry[a]	Aryl group	R group	Product	Yield (%)[b]	Mp (°C)
1	5-NO_2-2-C_4H_2O	Ac	**4a**	65	192–199
2	3-NO_2-C_6H_4	CO_2iPr	**4f**	79	174–177
3	3-NO_2-C_6H_4	CO_2iPr	**5f**	88	146–148
4	2-C_4H_3S	CO_2Me	**6**,**7g**[c]	–	–
5	2-C_4H_3S	CO_2Me	–[d]	–	–

[a] The reactions were performed in equimolar amount.
[b] The indicated yields were obtained after recrystallisation from ethanol.
[c] Under conditions iv cited above (Scheme 1), a mixture of indolizine **6g** and bis-1,4-DHP **7g** was obtained.
[d] See Table 2 for bis-1,4-DHPs **7a**–**g**.

Interestingly, the 2-enone-1,4-DHP **A** (Scheme 2) as the Knoevenagel condensation intermediate[8] was protonated in acetic medium to give the oxonium ion **B**. This ion, under an acidic catalysis (AcOH), underwent two consecutive [1,3]-hydrogen transfer reactions[9] to produce the dihydro-pyridinium salt **C** then **D**. In fact, because the proton at C_4 position of the intermediate **B** is acid and taking into account that the DHP nucleus could take a chairlike conformation,[1] the migration of the proton H_4 could be performed with acetic acid assistance as indicated in the plausible model depicted in Scheme 2. Furthermore, during the course of this migration process, the transferring proton remains associated with the same face of the π-system. This phenomenon is similar to that commonly known as a suprafacial process. At this present time, the resulting ion **C** is converted to **D** in the same manner by proton transfer.

This ion **D** was, in turn, capable of an intramolecular aminoketone cyclisation with a nitrogen atom as an internal nucleophile into **E**. Under this sequential set, followed by departure of one molecule of water, the reaction produced azabicyclic systems **4** and **5**. In our conditions, it is worth mentioning that:

1°—the regioselectivity was inverted in comparison with earlier study using basic conditions from 2-formyl-1,4-DHPs,[10] and Lewis acids as catalysts from 3-(2-pyridyl)-2-propenols;[11] and finally
2°—the reaction proceeded cleanly and selectively in a one-pot procedure.



Scheme 2. Plausible mechanism leading to functionalised indolizines **4** and **5**. Key: (i) Knoevenagel condensation;[8] (ii) Two consecutive acid catalysed proton transfer reactions were required, see also Refs. 4,9.

Table 2. Bis-1,4-DHPs **7a–g** obtained in a one-pot procedure by reaction of 2-formyl-1,4-DHPs **2a–g** with enamine derivatives

Entry	Aryl group	R group	Product	Yield (%)[a]	Mp (°C)[b]
1	5-NO_2-2-C_4H_2O	Ac	**7a**	79	293–295
2	5-NO_2-2-C_4H_2O	CN	**7b**	53	335–338
3	5-CN-2-C_4H_2O	Ac	**7c**	50	296–299
4	5-CN-2-C_4H_2O	CN	**7d**	82	298–300
5	5-CO_2Me-2-C_4H_2O	CN	**7e**	80	255–258
6	3-NO_2-C_6H_4	CO_2iPr	**7f**	73	176–178
7	2-C_4H_3S	CO_2Me	**7g**	56	159–160

The reactions were performed on 1–3 mmol using 2 equiv. of enamine derivative.

[a] The indicated yields were obtained after recrystallisation from ethanol.

[b] In general, the mp measurements were accompanied with the decomposition of the products.

On the other hand, when the 2-formyl-1,4-DHP **2g** interacted with 3-aminocrotonitrile **3c**[12] (entry 4, Table 1) in equimolar amount under acidic conditions as underlined above, the reaction after 30 min to 1 h of reflux produced three compounds: 1°—the unreacted starting material **2g**; 2°—the indolizine **6g**; and 3°—the azabicyclic structure **7g** as the main component. The both unexpected and new products were separated by chromatography on a silica gel column (dichloromethane/ethyl acetate (9.5/0.5)), and their structure was identified as **6g** and **7g** by spectroscopic analyses. In the case of **7g**, monodimensional and bidimensional NMR experiments including techniques like homocorrelation $^1H-^1H$ and $^{13}C-^{13}C$, heterocorrelation $^1H-^{13}C$, DEPT, HMQC, and HMBC were necessary.

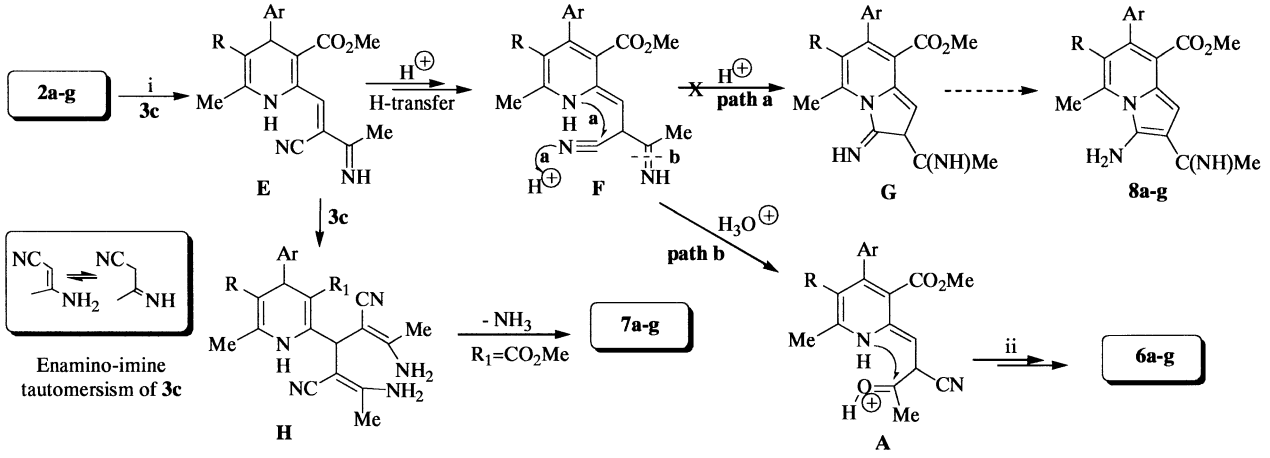
In view of the fact that reaction of arylcarboxaldehyde with enamine derivatives could bring about the formation of 1,4-DHP nucleus by a modified Hantzsch type reaction, we anticipated the subjection of 2-formyl-1,4-DHP derivative **2g** to 2 equiv. of **3c** under same conditions as outlined (entry 5, Table 1). In this case, interestingly, all starting material was consumed after 30 min of reaction and the novel bis-1,4-DHP component **7g** was obtained in 56% yield after filtration off followed by recrystallisation from absolute ethanol.[13]

We then examined the generalisation of this reaction by evaluation of the effect of the substituent R and aryl groups at C_4 and C_5 positions of the 1,4-DHP ring in the cyclisation step. So, in a similar manner as above (i.e. 2 equiv. of **3c**, AcOH, reflux, 30 min) 2-formyl-1,4-DHPs **2a–f** prepared as outlined in Scheme 1 (conditions i),[6] afforded the bis-1,4-DHP products **7a–f** in a range of 50–82% yields (see Table 2). It is important to notice that there was no discernible preference for the nature and the range of the substituents R and aryl groups since the indolizine skeletons **6a–f** were observed in comparable yields, as indicated above.[13,14]

As shown in Scheme 3, the described transformations could possibly be rationalised by two consecutive [1,3]-hydrogen transfer processes as outlined above in Scheme 2 from the common intermediates **E**. This was obtained by the Knoevenagel condensation of formyl derivatives **2a–g** with activated methylene **3c** (conditions i, Scheme 3). At this stage, the resulting non-isolated imino-nitrile **F** could be protonated at cyano group (path a) followed by the favoured intramolecular amino-nitrile cyclisation into **G**. This latter, in the final imino-amine tautomerism, could furnish indolizines **8a–g**. Because we have never detected the formation of these species in the reaction medium, combined with the fact that the imino function of the imino-nitrile **F** could be hydrolysed easily (path b),[15] the resulting keto-nitrile **A** similar to that proposed as intermediate in Scheme 2 (with R_4=Me and EWG=CN) might open up an efficient entry to indolizines **6a–g** as discussed above for related products **4** and **5**.

Otherwise, predominant production of **7** could be explained by assuming that the condensation product **E** takes another course with a more reactive **3c** involving initial C-alkylation to form the dienamino-derivative **H**. This latter, after an intramolecular cyclisation with elimination of ammonia, would afford the corresponding bis-1,4-DHPs **7a–g**. This process also appears to follow the Hantzsch type reaction pattern leading to 1,4-DHP systems.

The structure elucidation of bis-1,4-DHPs **7a–g** was established by spectroscopic analyses. By comparison of ^1H NMR spectra of **7a–g** with that of their 2-formyl congeners **2a–g**, we found that protons H_4 and NH signals are shifted to upfield ($\Delta\delta$=0.19–0.54 ppm) and to downfield ($\Delta\delta$=0.43–1.35 ppm), respectively. For other signals, no



Scheme 3. Probable mechanism leading to bis-1,4-DHPs **7a–g**. Key: (i) Knoevenagel condensation with 3-aminocrotonitrile **3c** as active methylene;[8] (ii) See also Scheme 2 for the proposed mechanism leading to indolizines related to **6a–g**.

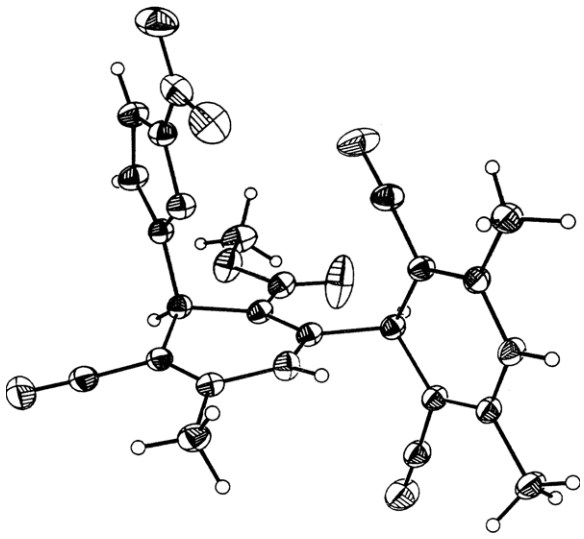


Figure 1. ORTEP view of the molecular structure of the bis-1,4-DHP **7b**. Thermal ellipsoids are at 50% probability level.

significant alterations were observed. Furthermore, the ^{13}C NMR spectra of bis-1,4-DHPs **7a–g** showed typical signals for C_2–C_6 and for nitrile groups at δ=111.8–119.3 ppm.[16] Their distribution was also unambiguously performed by off-resonance, DEPT, HMQC, and HMBC techniques. From these experiments it should be pointed out that:

1°—only C_2 signal did not show any interaction;
2°—the $H_{4'}$ signal appears as broadband at δ=5.88–5.94 ppm; and finally
3°—the ^{13}C NMR spectra showed broadband signals with low intensity. These facts were the consequence of the slow rotation around the C_2–$C_{4'}$ bond (see also Fig. 1).

These data, the microanalyses and the coupling GC–MS clearly confirm the proposed structure of products **7a–g** and suggest the existence of the bis-1,4-DHP system in constrained conformation. Finally, the identity of these non symmetrical bis-1,4-DHP components **7a–g** was secured through an X-ray crystallographic determination. In fact, an ORTEP view of representative derivative **7b**, namely methyl 5,3′,5′-tricyano-6,2′,6′-trimethyl-4-(5-nitrofuran-2-yl)-1,4,1′,4′-tetrahydro[2,4′]bipyridinyl-3-carboxylate is shown in Fig. 1.[17,18]

3. Conclusion

In conclusion, the synthesis in one step of polysubstituted indolizines **4** and **5** by ring transformation of the formyl containing 1,4-DHPs **2** by reaction with two active methylene reactants in acidic medium has been reported. These 1,4-DHPs **2** have also been allowed to react with 3-aminocrotonitrile and, to our surprise, afforded bis-1,4-DHPs **7** accompanied with indolizines **6** as minor products. A mechanism performing these transformations was proposed and discussed. Finally, because of the novelty and potential of these tandem reactions, extension to other activated methylene reactants is possible. Investigation in this way is underway.

4. Experimental

4.1. General

All melting points were measured on a Boetius micro hot-stage and are uncorrected. The infrared spectra of solids (potassium bromide) were recorded on a Perkin–Elmer FT-IR paragon 1000 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 MHz and 300 MHz instruments in deuteriochloroform unless other indicated solvent and chemical shifts (δ) are expressed in ppm relative to TMS as internal standard. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualised using an ultraviolet lamp or iodine vapor. Mass spectral measurements were recorded on a AEI MS 902 S spectrophotometer. The elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 Mt St Aignan, France.

4.2. General procedure for preparation of 1,4-DHP derivatives 2a–g

A mixture of arylcarboxaldehyde (10 mmol), methyl 4,4-dimethoxy-3-oxo-butanoate **1** (1.76 g, 10 mmol) and piperidine (90 mg, 1 mmol) in benzene (10 ml) was refluxed with a Dean–Stark for 5 h. The solvent was evaporated under reduced pressure to give an oil olefin, which was used for the next step without any additional purification. To this oily residue, enamine derivative (4-aminopent-3-en-2-one, 3-aminocrotonitrile or alkyl 3-aminocrotonate) (10 mmol) was added and the resulting mixture was stirred at 100–120° for 3 h. After cooling, viscous oil was dissolved in acetone (37 ml) and 6N hydrochloric acid (6.5 ml) was added dropwise. The solution was stirred at room temperature for 3 h. The organic solvent was removed under vacuo and the residue was poured onto water (10 ml) and neutralised with 10% solution of $NaHCO_3$. After classical workup, the solid residue was purified by recrystallisation from ethanol and gave suitable 2-formyl-1,4-DHPs **2a–g** in 63–95% yield.

4.2.1. Methyl 5-acetyl-2-formyl-6-methyl-4-(5-nitrofuran-2-yl)-1,4-dihydropyridine-3-carboxylate (2a). Yield=65%; mp 156–157°C; IR ν/cm^{-1}: 3321 (NH), 2953 (CH), 1707 (C=O), 1506 (NO_2); ^1H NMR (300 MHz): δ 2.38 (s, 3H, Ac), 2.53 (s, 3H, Me), 3.86 (s, 3H, OMe), 5.49 (s, 1H, H_4), 6.50 (d, 1H, $H_{3'}$, $J_{3',4'}$=3.5 Hz), 7.38 (d, 1H, $H_{4'}$, $J_{3',4'}$=3.5 Hz), 8.47 (s, 1H, NH), 10.43 (s, 1H, CHO); ^{13}C NMR (80 MHz): δ 20.5 (Me), 30.2 (Ac), 35.1 (C_4), 52.6 (OMe), 107.2 (C_5), 109.6 ($C_{3'}$), 110.0 (C_3), 112.7 ($C_{4'}$), 139.7 (C_2), 145.7 (C_6), 151.9 ($C_{5'}$), 159.2 ($C_{2'}$), 165.1 (CO_2), 185.8 (CHO), 195.7 (CO); EIMS *m*/*z* (%): 334 ($M^{\cdot+}$, 14), 317 (43), 285 (22), 275 (12), 244 (27), 190 (12), 43 (100); Anal. Calcd for $C_{15}H_{14}N_2O_7$ (334.08): C, 53.88; H, 4.22; N, 8.38. Found: C, 53.99; H, 4.31; N, 8.34%.

4.2.2. Methyl 5-cyano-2-formyl-6-methyl-4-(5-nitrofuran-2-yl)-1,4-dihydropyridine-3-carboxylate (2b). Yield=63%; mp 160–161°C; IR ν/cm^{-1}: 3330 (NH), 2958 (CH), 2201 (CN), 1718 (C=O), 1512 (NO_2); ^1H NMR (300 MHz): δ 2.29 (s, 3H, Me), 3.97 (s, 3H, OMe), 5.06 (s, 1H, H_4), 6.72 (d, 1H, $H_{3'}$, $J_{3',4'}$=3.9 Hz), 7.48 (d, 1H,

$H_{4'}$, $J_{3',4'}$=3.9 Hz), 8.83 (s, 1H, NH), 10.41 (s, 1H, CHO); ^{13}C NMR (80 MHz): δ 18.5 (Me), 36.3 (C_4), 52.8 (OMe), 81.2 (C_5), 108.1 (C_3), 110.2 ($C_{3'}$), 112.6 ($C_{4'}$), 117.8 (CN), 139.4 (C_2), 147.6 (C_6), 152.0 ($C_{5'}$), 157.3 ($C_{2'}$), 164.8 (CO_2), 185.7 (CHO); EIMS *m/z* (%): 317 ($M^{\cdot+}$, 51), 300 (77), 298 (22), 288 (33), 272 (27), 268 (100), 258 (27), 255 (40), 227 (22), 214 (22), 211 (17), 205 (22), 199 (16), 184 (33), 177 (17), 173 (79), 155 (42), 145 (58), 118 (26), 117 (55), 101 (16), 91 (37), 77 (19), 76 (19), 75 (16), 63 (35), 59 (30), 51 (30), 45 (66), 42 (63), 39 (43), 38 (31); Anal. Calcd for $C_{14}H_{11}N_3O_6$ (317.06): C, 53.00; H, 3.49; N, 13.24. Found: C, 53.41; H, 3.76; N, 12.96%.

4.2.3. Methyl 5-acetyl-4-(5-cyanofuran-2-yl)-2-formyl-6-methyl-1,4-dihydropyridine-3-carboxylate (2c). Yield=80%; mp 140–142°C; IR ν/cm^{-1}: 3351 (NH), 2959 (CH), 2227 (CN), 1702 (C=O); ^{1}H NMR (300 MHz): δ 2.33 (s, 3H, Ac), 2.51 (s, 3H, Me), 3.85 (s, 3H, OMe), 5.45 (s, 1H, H_4), 6.36 (d, 1H, $H_{3'}$, $J_{3',4'}$=3.1 Hz), 7.27 (d, 1H, $H_{4'}$, $J_{3',4'}$=3.1 Hz), 8.40 (s, 1H, NH), 10.42 (s, 1H, CHO); ^{13}C NMR (80 MHz): δ 20.4 (Me), 30.0 (Ac), 35.0 (C_4), 52.5 (OMe), 107.4 (C_5), 107.8 ($C_{3'}$), 110.4 (C_3), 111.5 (CN), 123.1 ($C_{4'}$), 125.1 ($C_{5'}$), 139.5 (C_2), 145.4 (C_6), 161.3 ($C_{2'}$), 165.2 (CO_2), 185.9 (CHO), 195.9 (CO); EIMS *m/z* (%): 314 ($M^{\cdot+}$, 80), 282 (18), 271 (24), 260 (30), 255 (22), 254 (34), 240 (35), 239 (57), 212 (23), 211 (29), 190 (17), 45 (75), 43 (100); Anal. Calcd for $C_{16}H_{14}N_2O_5$ (314.09): C, 61.14; H, 4.49; N, 8.91. Found: C, 61.46; H, 4.62; N, 8.88%.

4.2.4. Methyl 5-cyano-4-(5-cyanofuran-2-yl)-2-formyl-6-methyl-1,4-dihydropyridine-3-carboxylate (2d). Yield=73%; mp 169–171°C; IR ν/cm^{-1}: 3291 (NH), 2962 (CH), 2229, 2201 (CN), 1709 (C=O); ^{1}H NMR (300 MHz): δ 2.27 (s, 3H, Me), 3.80 (s, 3H, OMe), 5.01 (s, 1H, H_4), 6.57 (d, 1H, $H_{3'}$, $J_{3',4'}$=3.7 Hz), 7.38 (d, 1H, $H_{4'}$, $J_{3',4'}$=3.7 Hz), 8.75 (s, 1H, NH), 10.40 (s, 1H, CHO); ^{13}C NMR (80 MHz): δ 18.4 (Me), 35.9 (C_4), 52.5 (OMe), 81.5 (C_5), 108.3 ($C_{3'}$), 108.4 (C_3), 111.3 (CN), 118.0 (CN), 123.2 ($C_{4'}$), 125.9 ($C_{5'}$), 139.3 (C_2), 147.3 (C_6), 159.5 ($C_{2'}$), 164.8 (CO_2), 185.8 (CHO); EIMS *m/z* (%): 297 ($M^{\cdot+}$, 88), 268 (39), 265 (49), 254 (25), 236 (71), 237 (100), 211 (20), 210 (34), 209 (53), 205 (18), 177 (16), 173 (51), 155 (17), 145 (34), 118 (17), 117 (29), 90 (20), 64 (20), 63 (20), 59 (14), 53 (13), 52 (13), 42 (29), 39 (18); Anal. Calcd for $C_{15}H_{11}N_3O_4$ (297.07): C, 60.61; H, 3.73; N, 14.14. Found: C, 60.38; H, 3.77; N, 14.11%.

4.2.5. Methyl 5-cyano-2-formyl-4-(5-methoxycarbonylfuran-2-yl)-6-methyl-1,4-dihydropyridine-3-carboxylate (2e). Yield=79%; mp 156–158°C; IR ν/cm^{-1}: 3325 (NH), 2952 (CH), 2200 (CN), 1712 (C=O); ^{1}H NMR (300 MHz): δ 2.27 (s, 3H, Me), 3.78 (s, 3H, OMe), 3.81 (s, 3H, OMe), 4.98 (s, 1H, H_4), 6.47 (d, 1H, $H_{3'}$, $J_{3',4'}$=3.2 Hz), 7.16 (d, 1H, $H_{4'}$, $J_{3',4'}$=3.2 Hz), 8.66 (s, 1H, NH), 10.39 (s, 1H, CHO); ^{13}C NMR (80 MHz): δ 18.2 (Me), 35.8 (C_4), 51.7 (OMe), 52.5 (OMe), 81.7 (C_5), 108.9 ($C_{3'}$), 109.2 (C_3), 118.2 (CN), 119.0 ($C_{4'}$), 139.2 (C_2), 144.2 ($C_{5'}$), 147.1 (C_6), 158.5 ($C_{2'}$), 158.5 (CO_2), 165.1 (CO_2), 185.9 (CHO); EIMS *m/z* (%): 330 ($M^{\cdot+}$, 22), 298 (43), 271 (31), 270 (36), 255 (31), 239 (36), 184 (11), 183 (19), 173 (24), 155 (22), 149 (21), 145 (17), 45 (100), 43 (21); Anal. Calcd for $C_{16}H_{12}N_2O_6$ (330.09): C, 58.18; H, 4.27; N, 8.48. Found: C, 58.09; H, 4.12; N, 8.25%.

4.2.6. Methyl-isopropyl 2-formyl-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2f). Yield=91%; mp 147–149°C; IR ν/cm^{-1}: 3366 (NH), 2963 (CH), 1701 (C=O), 1518 (NO_2); ^{1}H NMR (300 MHz): δ 1.27 (d, 6H, Me_2CH, J=6.7 Hz), 2.44 (s, 3H, Me), 3.78 (s, 3H, OMe), 4.98 (sept, 1H, Me_2CH, J=6.7 Hz), 5.23 (s, 1H, H_4), 7.43–8.12 (m, 4H, H-aromatic), 7.00 (s, 1H, NH), 10.49 (s, 1H, CHO); ^{13}C NMR (80 MHz): δ 19.6 (Me), 22.1 (Me), 22.8 (Me), 40.9 (C_4), 52.4 (OMe), 67.8 ($OCHMe_2$), 102.5 (C_5), 114.5 (C_3), 122.1 ($C_{4'}$), 123.1 ($C_{2'}$), 129.2 ($C_{5'}$), 134.3 ($C_{6'}$), 139.1 (C_2), 144.6 (C_6), 147.9 ($C_{1'}$), 148.3 ($C_{3'}$), 165.8 (CO_2), 166.1 (CO_2), 186.5 (CHO); EIMS *m/z* (%): 388 ($M^{\cdot+}$, 14), 371 (18), 359 (7), 345 (20), 329 (16), 313 (18), 301 (18), 280 (64), 266 (100), 238 (16), 234 (11), 224 (64), 196 (11), 192 (77), 164 (32), 75 (14), 44 (32), 32 (20), 28 (70); Anal. Calcd for $C_{19}H_{20}N_2O_7$ (388.13): C, 58.76; H, 5.19; N, 7.21. Found: C, 58.78; H, 5.11; N, 7.15%.

4.2.7. Dimethyl 2-formyl-6-methyl-4-thiophen-2-yl-1,4-dihydropyridine-3,5-dicarboxylate (2g). Yield=95%; mp 152–154°C; IR ν/cm^{-1}: 3344 (NH), 2952 (CH), 1705 (C=O); ^{1}H NMR (300 MHz): δ 2.44 (s, 3H, Me), 3.72 (s, 3H, OMe), 3.85 (s, 3H, OMe), 5.45 (s, 1H, H_4), 6.81–7.14 (m, 3H, $H_{3'}$, $H_{4'}$ and $H_{5'}$, $J_{3'',5''}$=1.3 Hz, $J_{3'',4''}$=3.3 Hz and $J_{4'',5''}$=5.2 Hz), 7.18 (s, 1H, NH), 10.50 (s, 1H, CHO); ^{13}C NMR (80 MHz): δ 19.3 (Me), 35.1 (C_4), 51.3 (OMe), 52.2 (OMe), 102.0 (C_5), 114.5 (C_3), 124.0 ($C_{4'}$), 124.3 ($C_{5'}$), 126.8 ($C_{3'}$), 138.6 (C_2), 144.9 (C_6), 148.4 ($C_{2'}$), 165.9 (CO_2), 167.0 (CO_2), 186.6 (CHO); EIMS *m/z* (%): 321 ($M^{\cdot+}$, 34), 292 (16), 289 (10), 262 (100), 246 (28), 238 (16), 230 (28), 206 (30), 202 (15), 178 (24), 172 (15), 147 (14), 111 (10), 75 (16), 59 (12), 44 (10), 43 (26), 38 (14), 28 (15); Anal. Calcd for $C_{15}H_{15}NO_5S$ (321.07): C, 56.06; H, 4.70; N, 4.36; S, 9.98. Found: C, 56.01; H, 4.76; N, 4.33; S, 10.01%.

4.3. General procedure for synthesis of indolizines 4a, 4f and 5f

A solution of 2-formyl-1,4-DHP derivative **2a** or **2f** (3 mmol) and methyl acetoacetate (**3a**, 0.35 g, 3 mmol) or benzoylacetonitrile (**3b**, 0.44 g, 3 mmol) in glacial acetic acid (15 ml) was refluxed for 30 min. After cooling, 10 ml of water was added and the solid material which began to precipitate was collected by suction washed with water and air dried. An analytical sample of **4a**, **4f** or **5f** was obtained after recrystallisation from ethanol.

4.3.1. Dimethyl 6-acetyl-3,5-dimethyl-7-(5-nitrofuryl)-indolizin-2,8-dicarboxylate (4a). Yield=65% (0.80 g); mp 169–172°C; IR ν/cm^{-1}: 3136, 2953 (CH), 1732 (C=O), 1508, 1473 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.41 (s, 3H, Ac), 2.88 (s, 3H, Me_5), 3.16 (s, 3H, Me_3), 3.82–3.83 (s-board, 3H, OMe), 6.74 (d, 1H, $H_{3'}$, $J_{3',4'}$=3.9 Hz), 7.03 (s, 1H, H_1), 7.77 (d, 1H, $H_{4'}$, $J_{3',4'}$=3.9 Hz); ^{13}C NMR (80 MHz, DMSO-d_6): δ 14.4 (Me_3), 18.5 (Me_3), 32.7 (Ac), 51.6–53.2 (OMe), 105.0 (C_1), 113.2 (C_6), 114.0 ($C_{3'}$), 114.6 ($C_{4'}$), 119.4 (C_2), 123.8 (C_8), 125.2 (C_3), 127.9 (C_7), 132.1 (C_5), 135.3 (C_{8a}), 150.9 ($C_{2'}$), 151.3 ($C_{5'}$), 165.3–164.6 (CO_2Me), 203.3 (Ac); EIMS *m/z* (%): 414 ($M^{\cdot+}$, 92), 399 (5), 383 (15), 368 (35), 353 (5), 336 (10), 324 (12), 309 (100), 308 (33), 294 (15), 250 (10), 184 (8), 45

(17), 44 (13), 43 (23), 31 (31), 28 (23); Anal. Calcd for $C_{20}H_{18}N_2O_8$ (414.37): C, 57.97; H, 4.38; N, 6.76. Found: C, 58.03; H, 4.45; N, 6.59%.

4.3.2. Dimethyl-2-propyl 3,5-dimethyl-7-(3-nitrophenyl)-indolizin-2,6,8-tricarboxylate (4f). Yield=79% (1.11 g); mp 174–177°C; IR ν/cm^{-1}: 2988, 2951 (CH), 1713 (C=O), 1533, 1450 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.90 (d, 6H, Me_2CH, J=6.3 Hz), 2.91 (s, 3H, Me_5), 3.17 (s, 3H, Me_3), 3.57–3.81 (s-board, 3H, OMe), 4.74 (sept, 1H, Me_2CH, J=6.3 Hz), 6.97 (s, 1H, H_1), 7.64 (d, 1H, $H_{6'}$, $J_{5',6'}$=8.1 Hz), 7.73 (dd, 1H, $H_{5'}$, and $J_{4',5'}$ and $J_{5',6'}$=8.1 Hz), 7.98 (s, 1H, $H_{2'}$), 8.28 (d, 1H, $H_{4'}$, $J_{4',5'}$= 8.1 Hz); ^{13}C NMR (80 MHz, DMSO-d_6): δ 14.3 (Me_3), 18.8 (Me_5), 20.8 (Me_2CH), 51.5–52.5 (OMe), 69.4 (Me_2CH), 103.3 (C_1), 118.7 (C_2), 120.5 (C_6), 121.8 (C_8), 122.9 ($C_{4'}$), 123.0 ($C_{2'}$), 126.7 (C_3), 128.3 (C_7), 130.0 ($C_{5'}$), 130.7 (C_5), 135.3 ($C_{6'}$), 137.2 (C_{8a}), 138.5 ($C_{1'}$), 147.3 ($C_{3'}$), 164.9–165.3 (CO_2Me), 166.6 (CO_2iPr); EIMS m/z (%): 468 ($M^{\cdot+}$, 96), 438 (11), 437 (10), 426 (100), 411 (34), 409 (18), 379 (18), 45 (14), 44 (14), 31 (21), 28 (36); Anal. Calcd for $C_{24}H_{24}N_2O_8$ (468.46): C, 61.53; H, 5.16; N, 5.98. Found: C, 61.43; H, 5.09; N, 6.05%.

4.3.3. Dimethyl-2-propyl 2-cyano-5-methyl-3-phenyl-7-(3-nitrophenyl)indolizin-6,8-dicarboxylate (5f). Yield= 88% (1.31 g); mp 146–148°C (decomposition); IR ν/cm^{-1}: 2984, 2949 (CH), 2231 (CN), 1722 (C=O), 1527 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (d, 6H, Me_2CH, J=6.3 Hz), 2.08 (s, 3H, Me_5), 3.65 (s, 3H, OMe), 4.71 (sept, 1H, Me_2CH, J=6.3 Hz), 7.35 (s, 1H, H_1), 7.51–7.66 (m, 5H, H-aromatic), 7.68 (d, 1H, $H_{6'}$, $J_{5',6'}$=7.8 Hz), 7.76 (dd, 1H, $H_{5'}$, $J_{4',5'}$ and $J_{5',6'}$=8.1 Hz), 8.03 (s, 1H, $H_{2'}$), 8.31 (d, 1H, $H_{4'}$, $J_{4',5'}$=7.8 Hz); ^{13}C NMR (80 MHz, DMSO-d_6): δ 19.8 (Me_5), 20.7 (Me_2CH), 52.7 (OMe), 69.6 (Me_2CH), 101.8 (C_2), 105.0 (C_1), 115.6 (CN), 121.5 (C_6), 121.6 (C_8), 122.9 ($C_{4'}$), 123.2 ($C_{2'}$), 127.9 ($C_{2''}$), 128.7 (C_3), 129.6 (C_7), 129.8 ($C_{4''}$), 130.0 ($C_{5'}$), 130.9 (C_5), 131.3 ($C_{3''}$), 134.2 ($C_{1''}$), 135.3 ($C_{6'}$), 136.2 (C_{8a}), 138.1 ($C_{1'}$), 147.3 ($C_{3'}$), 164.7 (CO_2Me), 165.3 (CO_2iPr); EIMS m/z (%): 497 ($M^{\cdot+}$, 100), 467 (11), 455 (98), 438 (15), 408 (22), 303 (9), 45 (9), 44 (13), 28 (44); Anal. Calcd for $C_{28}H_{23}N_3O_6$ (497.50): C, 67.60; H, 4.66; N, 8.45. Found: C, 67.48; H, 4.59; N, 8.63%.

4.4. General procedure for synthesis of indolizines 6 and bis-1,4-DHPs 7

A solution of 2-formyl-1,4-DHP derivatives **2a**–**g** (3 mmol) and 3-aminocrotonitrile **3c** (0.5 g, 6 mmol) in glacial acetic acid (10 ml) was refluxed under magnetical stirring for 30 min (the reaction was monitored by TLC). After cooling, the solid material which began to precipitate was collected by suction washed with water and air dried. An analytical analysis of bis-1,4-DHPs **7a**–**g** was obtained after recrystallisation from ethanol. For example, in the case of the substrate **2g**, the resulting mother liquor obtained after filtration of the solid **7g**, after concentration, classical workup and purification by flash chromatography on silica gel column, gave the indolizine **6g** as colourless solid.

4.4.1. Dimethyl 2-cyano-3,5-dimethyl-7-thiophen-2-yl-indolizine-6,8-dicarboxylate (6g). 5%; mp 190–193°C (decomposition); IR ν/cm^{-1}: 3009, 2987 (CH), 2221 (CN), 1726 (C=O); ^{1}H NMR (300 MHz): δ 2.85 (s, 3H, Me), 3.01 (s, 3H, Me), 3.60 (s, 3H, OMe), 3.69 (s, 3H, OMe), 6,83 (s, 1H, H_1), 6.97 (dd, 1H, $H_{3'}$, $J_{3',5'}$=1.2 Hz and $J_{3',4'}$=3.6 Hz), 7.02 (dd, 1H, $H_{4'}$, $J_{3',4'}$=3.6 Hz and $J_{4',5'}$=5.1 Hz), 7.36 (dd, 1H, $H_{5'}$, $J_{3',5'}$=1.2 Hz and $J_{4',5'}$= 5.1 Hz); ^{1}H NMR (80 MHz): δ 16.3, 18.8, 52.5, 52.6, 101.9, 103.9, 115.9, 122.5, 123.0, 123.8, 126.9, 127.0, 128.0, 130.6, 131.1, 134.8, 136.8, 165.9, 167.6; EIMS m/z 368 ($M^{\cdot+}$, 15); Anal. Calcd for $C_{19}H_{16}N_2O_4S$ (368.41): C, 61.94; H, 4.38; N, 7.60; S, 8.70. Found: C, 61.87; H, 4.19; N, 7.55; S, 8.61%.

4.4.2. Methyl 5-acetyl-3′,5′-dicyano-6,2′,6′-trimethyl-4-(5-nitrofuran-2-yl)-1,4,1′,4′-tetrahydro[2,4′]bipyridinyl-3-carboxylate (7a). Yield=79%; mp 293–295°C (decomposition); IR ν/cm^{-1}: 3321 (NH), 3009, 2953 (CH), 2204 (CN), 1701, 1662 (C=O), 1508 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.98 (s, 3H, Me), 1.99 (s, 3H, Me), 2.34 (s, 3H, Ac), 2.42 (s, 3H, Me), 3.68 (s, 3H, OMe), 5.30 (s, 1H, H_4), 5.90 (s, 1H, $H_{4'}$ 6.43 (d, 1H, $H_{3''}$, $J_{3'',4''}$=3.3 Hz), 7.50 (d, 1H, $H_{4''}$, $J_{3'',4''}$=3.3 Hz), 8.90 (s, 1H, NH), 9.52 (s, 1H, NH); ^{1}H NMR (80 MHz, DMSO-d_6): δ 18.0 (Me), 18.1 (Me), 19.0 (Me), 30.2 (Ac), 34.1 ($C_{4'}$), 34.1 (C_4), 51.5 (OMe), 78.3 ($C_{3'}$), 78.6 ($C_{5'}$), 99.3 (C_3), 107.3 (C_5), 109.2 ($C_{3''}$), 113.9 ($C_{4''}$), 118.2 (CN), 118.3 (CN), 147.7 (C_2), 147.7 (C_6), 148.8 ($C_{5''}$), 149.5 ($C_{2'}$), 149.5 ($C_{6'}$), 161.7 ($C_{2''}$), 165.9 (CO_2), 195.3 (CO); EIMS m/z 463 ($M^{\cdot+}$,12); Anal. Calcd for $C_{23}H_{21}N_5O_6$ (463.15): C, 59.61; H, 4.57; N, 15.11. Found: C, 59.73; H, 4.61; N, 15.20%.

4.4.3. Methyl 5,3′,5′-tricyano-6,2′,6′-trimethyl-4-(5-nitrofuran-2-yl)-1,4,1′,4′-tetrahydro[2,4′]bipyridinyl-3-carboxylate (7b). Yield=53%; mp 335–338°C (decomposition); IR ν/cm^{-1}: 3301 (NH), 3000, 2954 (CH), 2203 (CN), 1715, 1666 (C=O), 1506 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.01 (s, 6H, 2xMe), 2.18 (s, 3H, Me), 3.61 (s, 3H, OMe), 4.89 (s, 1H, H_4), 5.94 (s, 1H, $H_{4'}$), 6.62 (d, 1H, $H_{3''}$, $J_{3'',4''}$=3.5 Hz), 7.63 (d, 1H, $H_{4''}$, $J_{3'',4''}$= 3.5 Hz), 9.39 (s, 1H, NH), 9.60 (s, 1H, NH); ^{1}H NMR (80 MHz, DMSO-d_6): δ 17.8 (Me), 18.2 (Me), 18.2 (Me), 35.2 ($C_{4'}$), 35.2 (C_4), 51.8 (OMe), 78.2 ($C_{3'}$), 78.3 ($C_{5'}$), 79.9 (C_5), 97.9 (C_3), 110.0 ($C_{3''}$), 114.2 ($C_{4''}$), 118.3 (CN), 118.5 (CN), 118.9 (CN), 148.7 ($C_{5''}$), 149.9 ($C_{2'}$), 149.9 ($C_{6'}$), 150.1 (C_2), 150.1 (C_6), 160.5 ($C_{2''}$), 165.7 (CO_2); EIMS m/z 446 ($M^{\cdot+}$,12) 429 (26), 334 (12), 333 (53), 274 (18), 273 (12), 177 (14), 159 (11), 158 (100), 157 (13), 73 (11); Anal. Calcd for $C_{22}H_{18}N_6O_5$ (446.13): C, 59.19; H, 4.06; N, 18.83. Found: C, 58.98; H, 3.99; N, 18.71%.

4.4.4. Methyl 5-acetyl-3′,5′-dicyano-4-(5-cyanofuran-2-yl)-6,2′,6′-trimethyl-1,4,1′,4′-tetrahydro[2,4′]bipyridinyl-3-carboxylate (7c). Yield=50%; mp 296–299°C (decomposition); IR ν/cm^{-1}: 3323 (NH), 3012, 2956 (CH), 2233, 2204 (CN), 1666 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.98 (s, 3H, Me), 2.00 (s, 3H, Me), 2.31 (s, 3H, Ac), 2.40 (s, 3H, Me), 3.66 (s, 3H, OMe), 5.27 (s, 1H, H_4), 5.89 (s, 1H, $H_{4'}$), 6.30 (d, 1H, $H_{3''}$, $J_{3'',4''}$=3.6 Hz), 7.37 (d, 1H, $H_{4''}$, $J_{3'',4''}$=3.6 Hz), 8.75 (s, 1H, NH), 9.51 (s, 1H, NH); ^{1}H NMR (80 MHz, DMSO-d_6): δ 18.0 (Me), 18.2 (Me), 19.0 (Me), 30.2 (Ac), 33.8 ($C_{4'}$), 33.8 (C_4), 51.5 (OMe), 78.5 ($C_{3'}$), 78.5 ($C_{5'}$), 100.4 (C_3), 107.9 (C_5), 107.1 ($C_{3''}$), 112.1 (CN), 118.3 (CN), 118.3 (CN), 123.4 ($C_{5''}$), 124.2 ($C_{4''}$), 147.5 (C_6), 148.3 (C_2), 149.4 ($C_{2'}$), 149.4 ($C_{6'}$), 163.6

($C_{2''}$), 166.0 (CO_2), 195.3 (CO); EIMS *m/z* 443 ($M^{\cdot+}$,18), 412 (21), 411 (66), 400 (21), 384 (24), 368 (32), 350 (19), 194 (20), 158 (100), 43 (49); Anal. Calcd for $C_{24}H_{21}N_5O_4$ (443.16): C, 65.00; H, 4.77; N, 15.79. Found: C, 64.79; H, 4.63; N, 15.61%.

4.4.5. Methyl 5,3′,5′-tricyano-4-(5-cyanofuran-2-yl)-6,2′,6′-trimethyl-1,4,1′,4′-tetrahydro[2,4′]bipyridinyl-3-carboxylate (7d). Yield=82%; mp 298–300°C (decomposition); IR ν/cm^{-1}: 3311 (NH), 3009, 2953 (CH), 2235, 2202 (CN), 1698 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.00 (s, 3H, Me), 2.01 (s, 3H, Me), 2.16 (s, 3H, Me), 3.59 (s, 3H, OMe), 4.83 (s, 1H, H_4), 5.91 (s, 1H, $H_{4'}$), 6.48 (d, 1H, $H_{3''}$, $J_{3'',4''}$=3.4 Hz), 7.49 (d, 1H, $H_{4''}$, $J_{3'',4''}$=3.4 Hz), 9.25 (s, 1H, NH), 9.55 (s, 1H, NH); ^{1}H NMR (80 MHz, DMSO-d_6): δ 17.7 (Me), 18.1 (Me), 18.1 (Me), 35.1 ($C_{4'}$), 35.1 (C_4), 51.6 (OMe), 78.3 ($C_{3'}$), 78.3 ($C_{5'}$), 80.2 (C_5), 98.3 (C_3), 107.8 ($C_{3''}$), 111.8 (CN), 118.0 (CN), 118.4 (CN), 119.0 (CN), 124.0 ($C_{5''}$), 124.5 ($C_{4''}$); 148.3 (C_2), 149.5 ($C_{2'}$), 149.5 ($C_{6'}$), 149.6 (C_6), 162.5 ($C_{2''}$), 165.7 (CO_2); EIMS *m/z* 426 ($M^{\cdot+}$,20), 394 (13), 368 (17), 367 (64), 365 (14), 333 (13), 274 (24), 177 (14), 158 (100), 42 (23); Anal. Calcd for $C_{23}H_{18}N_6O_3$ (426.14): C, 64.78; H, 4.25; N, 19.71. Found: C, 64.63; H, 4.24; N, 19.83%.

4.4.6. Methyl 5,3′,5′-tricyano-4-(5-methoxycarbonylfuran-2-yl)-6,2′,6′-trimethyl-1,4,1′,4′-tetrahydro[2,4′]-bipyridinyl-3-carboxylate (7e). Yield=80%; mp 255–258°C (decomposition); IR ν/cm^{-1}: 3457 (NH), 3011, 2954 (CH), 2228, 2202 (CN), 1683, 1663 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.00 (s, 3H, Me), 2.02 (s, 3H, Me), 2.13 (s, 3H, Me), 3.57 (s, 3H, OMe), 3.78 (s, 3H, OMe), 4.80 (s, 1H, H_4), 5.92 (s, 1H, $H_{4'}$), 6.41 (d, 1H, $H_{3''}$, $J_{3'',4''}$=3.7 Hz), 7.21 (d, 1H, $H_{4''}$, $J_{3'',4''}$=3.7 Hz), 9.20 (s, 1H, NH), 9.58 (s, 1H, NH); ^{1}H NMR (80 MHz, DMSO-d_6): δ 17.8 (Me), 18.1 (Me), 18.2 (Me), 35.2 ($C_{4'}$), 35.2 (C_4), 51.7 (OMe), 51.8 (OMe), 78.1 ($C_{3'}$), 78.5 ($C_{5'}$), 80.9 (C_5), 98.8 (C_3), 108.4 ($C_{3''}$), 118.3 (CN), 118.8 (CN), 119.3 (CN), 119.7 ($C_{4''}$), 142.9 ($C_{5''}$), 148.1 (C_2), 149.2 ($C_{2'}$), 149.6 ($C_{6'}$), 149.8 (C_6), 158.4 (CO_2), 161.8 ($C_{2''}$), 166.0 (CO_2); EIMS *m/z* 459 ($M^{\cdot+}$, 46), 427 (24), 401 (19), 400 (68), 340 (22), 333 (17), 320 (32), 312 (21), 274 (29), 158 (100); Anal. Calcd for $C_{24}H_{21}N_5O_5$ (459.15): C, 62.74; H, 4.61; N, 15.24. Found: C, 62.69; H, 4.72; N, 15.28%.

4.4.7. Methyl-isopropyl 3′,5′-dicyano-6,2′,6′-trimethyl-4-(3-nitrophenyl)-1,4,1′,4′-tetrahydro[2,4′]bipyridinyl-3,5-dicarboxylate (7f). Yield=73%; mp 176–178°C (decomposition); IR ν/cm^{-1}: 3369 (NH), 3015, 2989 (CH), 2206 (CN), 1681, 1669 (C=O), 1553 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.61 (d, 6H, Me_2CH, J=6.5 Hz), 2.02 (s, 3H, Me), 2.10 (s, 3H, Me), 2.15 (s, 3H, Me), 3.61 (s, 3H, OMe), 4.19 (sept, 1H, Me_2CH, J=6.5 Hz), 4.69 (s, 1H, H_4), 5.72 (s, 1H, $H_{4'}$), 7.99 (s, 1H, NH), 7.15–7.45 (m, 3H, $H_{2''}$, $H_{5''}$ and $H_{6''}$), 8.01–8.15 (dd, 1H, $H_{4''}$, $J_{4',5'}$=7.8 Hz and $J_{4',6'}$= 1.9 Hz), 8.98 (s, 1H, NH); ^{1}H NMR (80 MHz, DMSO-d_6): δ 18.0 (Me), 18.1 (Me), 18.6 (Me), 21.5 (Me), 21.5 (Me), 32.2 ($C_{4'}$), 33.9 (C_4), 51.4 (OMe), 68.5 ($OCHMe_2$), 78.4 ($C_{3'}$), 78.6 ($C_{5'}$), 98.6 (C_3), 101.5 (C_5), 118.1 (CN), 118.9 (CN), 119.8 ($C_{4''}$), 122.3 ($C_{2''}$), 131.5 ($C_{5''}$), 135.1 ($C_{6''}$), 138.1 ($C_{1''}$), 147.6 (C_2), 148.6 (C_6), 148.9 ($C_{2'}$), 149.1 ($C_{6'}$), 149.2 ($C_{2''}$), 164.6 (CO_2), 165.8 (CO_2); EIMS *m/z* 517 ($M^{\cdot+}$, 10), 486 (28), 485 (70), 474 (22), 458 (47), 457 (39), 395 (32), 393 (40), 351 (32), 196 (100), 158 (68); Anal. Calcd for $C_{27}H_{27}N_5O_6$ (517.53): C, 62.66; H, 5.26; N, 13.53. Found: C, 62.54; H, 5.16; N, 13.36%.

4.4.8. Dimethyl 3′,5′-dicyano-6,2′,6′-trimethyl-4-thiophen-2-yl-1,4,1′,4′-tetrahydro[2,4′]bipyridinyl-3,5-dicarboxylate (7g). Yield=56%; mp 159–160°C (decomposition); IR ν/cm^{-1}: 3300, 3226 (NH), 3012, 2990 (CH), 2210, 2197 (CN), 1683, 1668 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.00 (s, 3H, Me), 2.02 (s, 3H, Me), 2.34 (s, 3H, Me), 3.62 (s, 3H, OMe), 3.66 (s, 3H, OMe), 5.27 (s, 1H, H_4), 5.90 (s, 1H, $H_{4'}$), 6.79–6.82 (m, 2H, $H_{3''}$ and $H_{4''}$, $J_{3'',5''}$=1.2 Hz and $J_{3'',4''}$=3.8 Hz), 7.22 (d, 1H, $H_{5''}$, $J_{4'',5''}$=5.1 Hz), 8.55 (s, 1H, NH), 9.50 (s, 1H, NH); ^{1}H NMR (80 MHz, DMSO-d_6): δ 18.1 (Me), 18.2 (Me), 18.3 (Me), 34.5 (C_4), 34.5 ($C_{4'}$), 50.9 (OMe), 51.4 (OMe), 78.1 ($C_{3'}$), 79.3 ($C_{5'}$), 101.7 (C_3), 103.7 (C_5), 118.3 (CN), 118.7 (CN), 123.3 ($C_{2''}$), 124.0 ($C_{4''}$), 126.3 ($C_{3''}$), 147.2 ($C_{5''}$), 148.3 (C_2), 149.1 (C_6), 149.8 ($C_{2''}$), 149.8 ($C_{6''}$), 166.6 (CO_2), 166.9 (CO); EIMS *m/z* 450 ($M^{\cdot+}$, 12); Anal. Calcd for $C_{23}H_{22}N_4O_4S$ (450.51): C, 61.17; H, 4.77; N, 12.40; S, 7.06. Found: C, 61.32; H, 4.92; N, 12.44; S, 7.11%.

Acknowledgements

The authors thank the Grant Agency of Slovak Republic, Grant No.1/9249/2002 and the Scientific Council of University of Le Havre, France, for their financial support for this research. We also thank Professor Bernard Decroix for helpful comments and discussions made during the course of this work.

References

1. (a) Bossert, F.; Vater, W. *Med. Res. Rev.* **1989**, *9*, 291. (b) Goldmann, S.; Stoltefuss, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1559. (c) Sausins, A.; Duburs, G. *Khim. Geterotsikl. Soedin.* **1992**, *4*, 435. (d) Marchalín, Š.; Chudík, M.; Mastihuba, V.; Decroix, B. *Heterocycles* **1998**, *48*, 1943 and references therein.
2. (a) Chudík, M.; Marchalín, Š.; Havrilová, K. *Collect. Czech. Chem. Commun.* **1998**, *63*, 826. (b) Chudík, M.; Marchalín, Š.; Pham-Huu, D.-P.; Humpa, O.; Friedl, Z. *Monatsh. Chem.* **1999**, *130*, 1241.
3. (a) Chudík, M.; Marchalín, Š.; Knesl, P.; Daïch, A.; Decroix, B. *J. Heterocycl. Chem.* **2000**, *37*, 1549. (b) Chudík, M.; Marchalín, Š.; Daïch, A.; Decroix, B. *Res. Adv. Synth. Org. Chem.* **2000**, *1*, 1.
4. Marchalín, Š.; Cvopová, K.; Pham-Huu, D.-P.; Chudík, M.; Kožíšek, J.; Svoboda, I.; Daïch, A. *Tetrahedron Lett.* **2001**, *42*, 5663.
5. Only three general methods have been reported for the preparation of indolizines and in all these cases, substituted pyridine was used as a starting material. For recent article see the following reference: Katritzky, A. R.; Qiu, G.; Yang, B.; He, H. Y. *J. Org. Chem.* **1999**, *64*, 7618 and most references therein.
6. (a) The oily residue used as intermediates during the synthesis of 2-formyl-1,4-DHPs **2a**–**g**, was isolated and identified as the 2-dimethylacetal-1,4-DHPs **2′a**–**g**. (b) See in the following,

selected data for 2-dimethylacetal **2′a**: *methyl 5-acetyl-2-dimethoxymethyl-6-methyl-4-(5-nitrofuran-2-yl)-1,4-dihydropyridine-3-carboxylate (**2′a**)*. Yield=70%; mp 120–122°C; IR (KBr), ν/cm^{-1}: 3353 (NH), 2960 (CH), 1682 (C=O), 1512 (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3H, Ac), 2.39 (s, 3H, Me), 3.44 (s, 3H, OMe), 3.51 (s, 3H, OMe), 3.77 (s, 3H, CO_2Me), 5.36 (s, 1H, H_4), 6.00 (s, 1H, CH), 6.31 (d, 1H, $H_{3'}$, $J_{3',4'}$=4.0 Hz), 7.17 (s, 1H, NH), 7.20 (d, 1H, $H_{4'}$, $J_{3',4'}$= 4.0 Hz); ^{13}C NMR (80 MHz, $CDCl_3$): δ 20.6 (Me), 30.1 (Ac), 34.1 (C_4), 51.7 (CO_2Me), 54.4 (OMe), 55.8 (OMe), 98.1 (CH), 100.1 (C_5), 108.0 (C_3), 108.9 ($C_{3'}$), 112.9 ($C_{4'}$), 145.5 (C_2), 145.5 (C_6), 151.1 ($C_{5'}$), 161.0 ($C_{2'}$), 165.7 (CO_2), 195.9 (CO); EIMS *m/z* (%): 380 ($M^{\cdot+}$, 17), 363 (15), 348 (31), 331 (100), 321 (10), 317 (17), 305 (46), 301 (26), 289 (54), 275 (10), 274 (13), 260 (26), 255 (17), 241 (23), 236 (44), 228 (28), 208 (28), 198 (18), 75 (96), 59 (23), 43 (94); Anal. Calcd for $C_{17}H_{20}N_2O_8$ (380.12): C, 53.68; H, 5.30; N, 7.37. Found: C, 53.79; H, 5.14; N, 7.44%. (c) All other acetals **2′b–g**, have similar characteristics.

7. A few analogous types of products were described in poor to moderate yields (9–58%) by another pathway, see for example: (a) Uchida, T.; Matsumoto, K. *Synthesis* **1972**, 209 and references therein. (b) Hurst, J.; Melton, T.; Wibberley, D. G. *J. Chem. Soc.* **1965**, 2948. (c) Pohjala, E. K. *J. Heterocycl. Chem.* **1977**, *14*, 273 and references therein.
8. For more details of the Knoevenagel condensation mechanism, see the following reference: Jones, G. *Org. React.* **1967**, *15*, 204.
9. For recent advances in the [1,*n*]-hydrogen transfer study, see: (a) Jensen, F. *J. Am. Chem. Soc.* **1995**, *117*, 7487. (b) Hussénius, A.; Matsson, O.; Bergson, G. *Chem. Commun.* **1998**, 2693.
10. Using same 2-formyl-1,4-DHP precursors **2** but under basic conditions, only the formation of 3-amino-2-alkyl(aryl, alkoyl, or aroyl)indolizines were observed. See also Refs. 2,4 for this end.
11. Abe, Y.; Ohsawa, A.; Igeta, H. *Chem. Pharm. Bull.* **1982**, *30*, 881.
12. The 3-aminocrotonitrile reagent constitutes an activated methylene after an enamino-imine tautomerism.
13. Since our first attention was focused on the bis-1,4-DHP systems, indolizines **6a–f** were not systematically isolated and identified. For clarity, only indolizine **6g** was isolated but its yield did not exceed 5%.
14. The reaction was monitored by TLC (silica gel, dichloromethane/ethyl acetate: 9.5/0.5) and the ratios of products **6a–f** and **7a–f** were determined by the coupling GC–MS analyses.
15. Water was liberated in the medium during the Knoevenagel condensation between 2-formyl-1,4-DHPs **2** and 3-aminocrotonitrile **3c**.
16. Kurfürt, A.; Trska, P.; Goljer, I. *Collect. Czech. Chem. Commun.* **1984**, *49*, 2393.
17. Crystallographic structure of methyl 5,3′,5′-tricyano-6,2′,6′-trimethyl-4-(5-nitrofuran-2-yl)-1,4,1′,4′-tetrahydro[2,4′]bipyridinyl-3-carboxylate (**7b**): colourless, 0.80×0.40×0.06 mm^3 block, $C_{25}H_{25}N_7O_6$, triclinic, *P*-1, a=9.0170(1) Å, b= 11.4599(2) Å, c=12.8268(1) Å, α=93.87(1)°, β= 102.640(1)°, γ=96.040(1)°, Z=2. Stoe Stadi-4 diffractometer using Mo Kα radiation, T=183(2) K, 19715 reflections measured up to $2\theta = 65.62°$, 8770 independent data (R_{int}= 1.93%) for 374 refined parameters. The structure was refined on the basis of absorption-corrected data (T_{min}=0.9248, T_{max}=0.9941), using standard methods[18] with constraints for hydrogen atoms. Final R indices: R_1=4.51% for 6945 data having $I > 2\sigma(I)$ and wR_2=12.08% for all data.
18. Sheldrick, G. N. *SHELX-97 User's Manual*; University of Göttingen: Germany, 1997.