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Synthesis of Indolizine Derivatives by the Reaction of 2-(2′-Pyridyl)-Pyridinium Ylides with Ethylenic Dipolarophiles

Ioan I. Druța*, Mioara A. Andrei, Cristian I. Ganj, Pompiliu S. Aburel

"Al. I. Cuza" University, Organic Chemistry Departament, B-dul Copou, Nr. 11, Iași-6600, Romania.

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Abstract : The reaction of 2-(2′-pyridyl)-pyridinium N-ylides with substituted ethylenes such as acrylonitrile and ethyl acrylate gave the corresponding tetrahydroindolizine derivatives in high yields. Tetrahydroindolizine derivatives were dehydrogenated by treating with tetrapyridinecobalt(II) bichromate [$CoPy_4(HCrO_4)_2$] to give aromatic indolizines bearing cyano, aroyl, 2′-pyridyl, ester group at the different positions. Seventeen new indolizine derivatives were prepared. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Key words: 2,2′-Bipyridyl, 2-(2′-pyridyl)-piridinium ylides, indolizines, cycloaddition reaction

Introduction

In view of the practical and theoretical importance of indolizine compounds[1,2] we considered it of interest to make an addition to the synthetic methods for their preparation. Indolizines are important intermediates for drugs, dyestuffs and light-screening agents in photographic emulsions.

Several methods are available for the synthesis of indolizines. The most important of them, although usually low yielding, is the 3+2 dipolar cycloaddition of cycloimmonium-ylides to activated acetylenes.[3-9]

In an our previous paper[10] we have reported, for the first time in the class of 2,2′-bipyridyls, the synthesis of 5-(2′-pyridyl)-indolizine derivatives by 3+2 dipolar cycloaddition of 2-(2′-pyridyl)-pyridinium ylides with ethyl propiolate and dimethyl acetylenedicarboxylate.

In an extension of our work on the 2,2′-bipyridyl compounds, we here report the synthesis of indolizine derivatives, in good to high yields, by 3+2 dipolar cycloaddition of 2-(2′-pyridyl)-pyridinium ylides with substituted ethylenes such as acrylonitrile and ethyl acrylate. The advantage of this method is the easy availability of the olefinic dipolarophiles which can successfully replace acetylenes, much less accessible reagents.

Tetrahydroindolizine derivatives, obtained in the first step, are then dehydrogenated in the presence of the TPCB [tetrapyridynecobalt(II) bichromate, $CoPy_4(HCrO_4)_2$] as an oxidant. This has been found of value in the synthesis of aromatic ring nitrogen heterocycles.[11-14]

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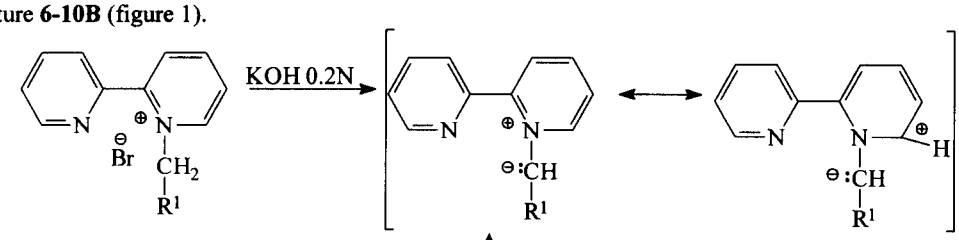
Results and Discussion

2-(2′-Pyridyl)-pyridinium salts **1-5** were synthesized by reaction of 2,2-bipyridyl with reactive halide derivatives, as previously reported.[15] The 2-(2′-pyridyl)-pyridinium ylides **6-10**, obtained *in situ* have a dipolar structure and can react in 3+2 dipolar cycloaddition reactions, as a 1,3-dipole, according to the structure **6-10B** (figure 1).



1 R^1= COC_6H_5
2 R^1= $COC_6H_4NO_2$
3 R^1=$COC_6H_4OCH_3$
4 R^1= COC_6H_4Br
5 R^1=COC_6H_4Cl

6 R^1= COC_6H_5
7 R^1= $COC_6H_4NO_2$
8 R^1=$COC_6H_4OCH_3$
9 R^1= COC_6H_4Br
10 R^1=COC_6H_4Cl

Fig. 1. Dipolar structure of the 2–(2′–pyridyl)–pyridinium ylides.

The reaction of **1-5** with acrylonitrile or ethyl acrylate in the presence of KOH 0.2 N in water:ethanol (5:1), at room temperature, under nitrogen, gave the tetrahydroindolizines **14-23**, in good to high yields. The reaction is regioselective and is in a agreement with the electronic effects in molecule of acrylonitrile and ethyl acrylate. The adducts **14-23** could possibly be formed by a concerted cycloaddition , but it is more probable that the cycloimmonium ylides **6-10** undergo a Michael addition to the dipolarophile, giving a reactive enolate **13** which rapidly ring-closes into the heterocyclic ring to give the bicyclic adducts (figure 2).

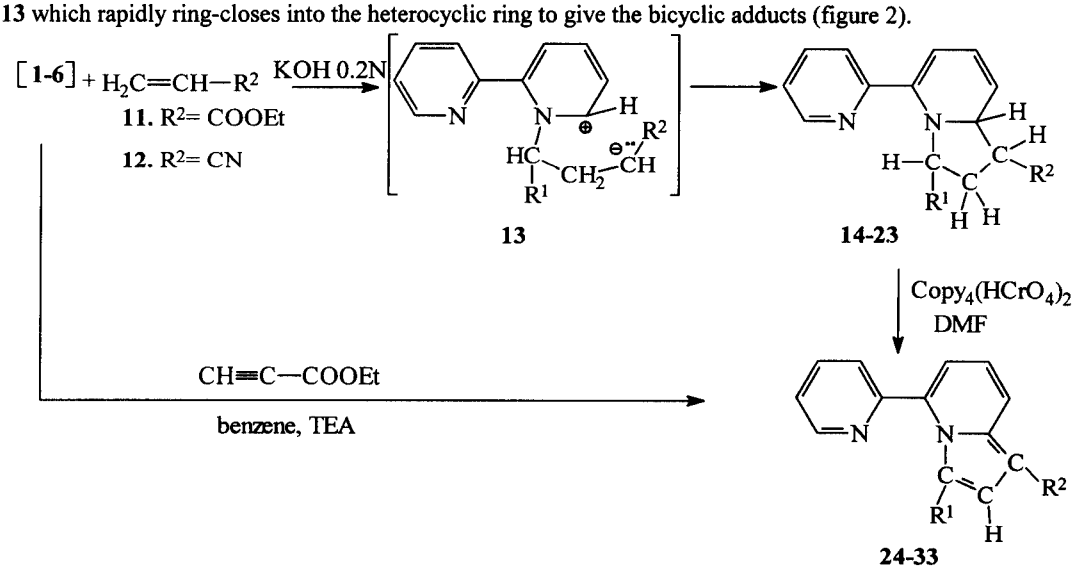
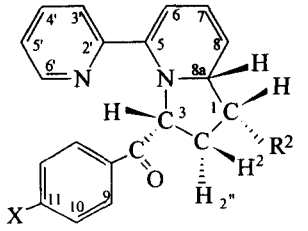


Fig. 2. Reaction between cycloimmonium ylides and ethylenic dipolarophiles

Table 1. IR (ν, cm^{-1}) and ^{1}H-NMR (δ, ppm) spectra of tetrahydroindolizines **14-23** derived from 2-(2'-pyridyl)-pyridinium salts

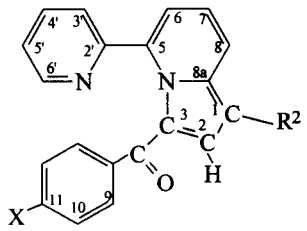


14 X = H, R^2 = $COOC_2H_5$ **19** X = H, R^2 = CN
15 X = NO_2, R^2 = $COOC_2H_5$ **20** X = NO_2, R^2 = CN
16 X = OCH_3, R^2 = $COOC_2H_5$ **21** X = OCH_3, R^2 = CN
17 X = Br, R^2 = $COOC_2H_5$ **22** X = Br, R^2 = CN
18 X = Cl, R^2 = $COOC_2H_5$ **23** X = Cl, R^2 = CN

Compd.	H-1	H-2	H-2''	H-3	H-6	H-7
14	3.68[a]	2.45[b]	1.9[c]	5.31[d]	5.62[e]	6.1[c]
15	3.67[a]	2.4[b]	1.89[c]	5.29[d]	5.6[e]	6.08[c]
16	3.68[a]	2.4[b]	1.89[c]	5.27[d]	5.6[e]	6.08[c]
17	3.65[a]	2.4[b]	1.85[c]	5.27[d]	5.62[e]	6.08[c]
18	3.65[a]	2.38[b]	1.85[c]	5.27[d]	5.6[e]	6.08[c]
19	3.75[a]	2.38[b]	2.2[c]	5.4[f,k]	5.72[e]	6.25[c]
20	3.75[a]	2.38[b]	2.18[c]	5.4[f,k]	5.72[e]	6.25[c]
21	3.75[a]	2.38[b]	2.18[c]	5.38[f,k]	5.7[e]	6.23[c]
22	3.75[a]	2.38[b]	2.18[c]	5.4[f,k]	5.75[e]	6.25[c]
23	3.75[a]	2.38[b]	2.18[c]	5.4[f,k]	5.72[e]	6.23[c]
Compd.	**H-8**	**H-8a**	**H-aromatic**	**Other**	**ν C=O**	**ν CN**
14	5.05[d]	5.2[b]	6.9-7.9[f,g]	1.29[h] (CH_3) 4.22[a] (CH_2)	1735 1670	-
15	5.05[d]	5.2[b]	6.9-8.4[f,j]	1.29[h] (CH_3) 4.22[a] (CH_2)	1735 1695	-
16	5.02[d]	5.18[b]	6.8-7.9[f,j]	1.29[h] (CH_3) 4.22[a] (CH_2) 3.85[i] (CH_3)	1735 1670	-
17	5.05[d]	5.18[b]	6.9-7.8[f,j]	1.29[h] (CH_3) 4.22[a] (CH_2)	1735 1690	-
18	5.05[d]	5.18[b]	6.9-7.9[f,j]	1.29[h] (CH_3) 4.22[a] (CH_2)	1735 1690	-
19	5.4[f,k]	5.17[b]	6.9-7.9[f,g]	-	1680	2250
20	5.4[f,k]	5.15[b]	6.9-8.4[f,j]	-	1710	2255
21	5.38[f,k]	5.12[b]	6.8-7.9[f,j]	3.89[i] (CH_3)	1675	2250
22	5.4[f,k]	5.12[b]	6.9-7.8[f,j]	-	1710	2250
23	5.4[f,k]	5.12[b]	6.9-7.9[f,j]	-	1710	2250

[a]-quartet; [b]-doublet of triplets; [c]-quartet of doublets; [d]-doublet of doublets; [e]-doublet; [f]-multiplet; [g]-signals overlap, 9H; [h]-triplet; [i]-singlet; [j]-signals overlap, 8H; [k]-signals overlap;

Table 2. IR (ν, cm^{-1}) and ^{1}H-NMR (δ, ppm) spectra of indolizines **26, 28-33**



24 X = H, R^2 = $COOC_2H_5$
25 X = NO_2, R^2 = $COOC_2H_5$
26 X = OCH_3, R^2 = $COOC_2H_5$
27 X = Br, R^2 = $COOC_2H_5$
28 X = Cl, R^2 = $COOC_2H_5$

29 X = H, R^2 = CN
30 X = NO_2, R^2 = CN
31 X = OCH_3, R^2 = CN
32 X = Br, R^2 = CN
33 X = Cl, R^2 = CN

Compd	H-2	H-6	H-7	H-8	H-3'	H-4'
26	7.55[a]	7.08[b]	7.53[b]	8.48[b]	7.70[b]	7.83[c]
28	7.42[a]	7.35[b]	7.67[b]	8.38[b]	7.80[b]	7.92[c]
29	7.36[a]	7.08-7.18[b,h]	7.45[b]	7.81-7.91[j,i]	7.69[b]	7.81-7.91[j,i]
30	7.34[a]	7.10-7.21[b,h]	7.54[b]	7.84-7.96[j,i]	7.72[b]	7.84-7.96[c,h]
31	7.33[a]	7.06-7.17[b,h]	7.43[b]	7.78-7.90[j,i]	7.66[b]	7.78-7.90[j,i]
32	7.33[a]	7.08-7.18[b,h]	7.44[b]	7.79-7.91[j,i]	7.68[b]	7.79-7.91[c,h]
33	7.32[a]	7.08-7.18[b,h]	7.44[b]	7.80-7.91[j,i]	7.68[b]	7.80-7.91[c,h]
Compd	**H-5'**	**H-6'**	**H-aromatic**	**Other**	**ν C=O**	**ν CN**
26	7.10[d]	8.23[b]	7.61[e](H-9) 6.8[e](H-10)	1.39[f](CH_3); 3.85[a](CH_3) 4.38[q](CH_2)	1700 1650	-
28	7.24[d]	8.12[b]	7.75[e](H-9) 7.59[e](H-10)	1.31[f](CH_3) 4.30[q](CH_2)	1700 1645	-
29	7.08-7.18[d,h]	8.16[b]	7.81-7.91[j,i] (H-9,10,11)	-	1655	2235
30	7.10-7.21[d,h]	8.16[b]	8.01[e](H-9) 8.30[e](H-10)	-	1660	2235
31	7.06-7.17[d,h]	8.13[b]	7.82[e](H-9) 6.95[e](H-10)	3.87[a](CH_3)	1650	2235
32	7.08-7.18[d,h]	8.14[b]	7.76[e](H-9) 7.61[e](H-10)	-	1660	2235
33	7.08-7.18[d,h]	8.14[b]	7.75[e](H-9) 7.59[e](H-10)	-	1660	2235

[a]-singlet; [b]-doublet of doublets; [c]- triplet of doublets; [d]-quartet of doublets; [e]-doublet; [f]- triplet; [g]-quartet; [h]- signals overlap but distinguishable; [i]- signals overlap, not distinguishable; [j]- multiplet.

The initially formed tetrahydroindolizines are then dehydrogenated by treatment with TPCB, in DMF (dimethylformamide), at 90°C , under nitrogen, for 2h, after which the reaction mixture was worked up to give yellow crystals. The compounds **24, 25, 27** are identicaly (IR, ^{1}H-NMR, m.p.) with indolizine derivatives obtained by the reaction between salts **1-5** with ethyl propiolate.[10]

The structure of **14-23** and **24-33** compounds were proved by elemental and spectral methods.

Spectra of the tetrahydroindolizines. The IR and ^{1}H-NMR spectra of the adducts **14-23** derived from 2-(2'-pyridyl)-pyridinium salts are given in Table 1 and Table 3. All adducts had a strong absorption band between 1670 cm^{-1} and 1710 cm^{-1} which are characteristic for the ketonic carbonyl groups. The ester carbonyl groups of **14-18** absorb at 1735 cm^{-1} and the nitrile groups of **19-23** absorb at 2250 cm^{-1}. The ^{1}H-NMR provide essential data concerning the structure of compounds **14-23**. Analysis of the spectra, such as that of product **15**, a representative of the series, reveals the following data. The H-6 proton having only one CH neighbour gave doublet at 5.6 ppm. The H-2 and H-2'' protons are two non-equivalent protons. Their signals appears as a doublet of triplets (H-2) at 2.4 ppm and a quartet of doublets (H-2'') at 1.89 ppm. Their coupling constant is $J_{2,2''}$= 12.6 Hz.

Table 3. Coupling constants[a] (J, Hz) of compounds **14-23** and **24,28-33**

Cmpd.	$J_{1,2}$	$J_{1,2''}$	$J_{1,8a}$	$J_{2,2''}$	$J_{2,3}$	$J_{2'',3}$	$J_{6,7}$	$J_{7,8}$	$J_{7,8a}$	$J_{8,8a}$
14	9	6.8	7.6	12.6	9	2.6	5.8	9.4	2.2	2.2
15	9	6.8	7.6	12.6	9	2.6	5.8	9.4	2.2	2.2
16	9	6.8	7.6	12.6	9	2.6	5.8	9.4	2.2	2.2
17	9	6.8	7.6	12.6	9	2.6	5.8	9.4	2.2	2.2
18	9	6.8	7.6	12.6	9	2.6	5.8	9.4	2.2	2.2
19	9	7.2	7.2	12.4	9	2.6	6	9.3	2.2	2.2
20	9	7.2	7.2	12.4	9	2.6	6	9.3	2.2	2.2
21	9	7.2	7.2	12.4	9	2.6	6	9.3	2.2	2.2
22	9	7.2	7.2	12.4	9	2.6	6	9.3	2.2	2.2
23	9	7.2	7.2	12.4	9	2.6	6	9.3	2.2	2.2
	$J_{7,8}$	J_{68}	$J_{6,7}$	$J_{3',4'}$	$J_{4',5'}$	$J_{3',5'}$	$J_{4',6'}$	$J_{5',6'}$	$J_{9,10}$	$J_{12,13}$
26	9	1.3	7	7.6	7.8	1.1	1.6	4.3	8.5	7.2
28	8.8	1.3	7	7.6	7.6	1.1	1.5	4.3	8.5	7.2
29	8.8	1.2	7.1	7.9	7.8	1.1	1.6	4.7	-	-
30	8.8	1.2	7.1	7.9	7.9	-	1.7	4.7	8.8	-
31	8.8	1.2	7.2	7.9	7.9	-	1.6	4.7	8.8	-
32	8.8	1.2	7.1	7.9	7.9	-	1.7	4.7	8.8	-
33	8.8	1.2	7.1	7.9	7.9	-	1.7	4.7	8.6	-

[a]The couplings were confirmed by double irradiation experiments

The aromatic protons gave a 8H multiplet at 6.9-8.4 ppm. On the basis of these data and of the data available in the cited literature[16,17] , we propose tetrahydroindolizine structures for compounds **14-23**. Cis-orientation of benzoyl and R^2 substituients can be provided by coupling constants for the vicinal protons. According with the literature data[18-20] for the similar structures, the coupling constants for cis-orientations are higher than

those for trans-orientation. The chemical shifts and coupling constants in the pyrrolidine ring of **14, 16-23** are very similar to those of adduct **15.**

Spectra of the aromatic indolizines. The IR spectra for compounds **24-33** show absorption bands between 1645-1660 cm^{-1}, characteristic for diaryl ketones. The esteric carbonyl groups absorb at lower wave number (1700 cm^{-1}) than in the adducts **14-18** due to the conjugation with double bonds in the indolizine ring. The conjugation appears in the adducts **29-33**, too. Their spectra show nitrile absorption at 2235 cm^{-1}. The ^{1}H-NMR spectra for the **24-33** adducts contain only the aromatic, ethylene (-CH_2-) and methyl (-CH_3) protons; no signals for the H-1, H-2″, H-3 and H-8. We have established that the doublet of doublets which appears at 8.38-8.48 ppm for the compounds **24-28** and at 7.81-7.91 ppm for compounds **29-33** is assigned to H-8. This signal appeared at low field for compounds **24-28** due to the ethoxycarbonyl group nearby. There is a clear singlet for H-2 in the aromatic region, namely 7.32-7.55 ppm, in all compounds.

Experimental

The ^{1}H-NMR spectra were recorded on a VARIAN-GEMINI-200 spectrometer, in ppm downfield from an internal standard, TMS in $CDCl_3$.

The IR spectra were recorded with a SPECORD-71 spectrometer in KBr pellets.

All melting points were measured with a MEL-TEMP capillary apparatus.

TPCB was obtained easily by adding pyridine (4 equiv.) to aqueous chromium trioxide (2 equiv.) and cobalt(II) acetate (1 equiv.).[14]

2-(2′-Pyridyl)-pyridinium salts **1-5** were synthesized by reaction of 2,2′-bipyridyl with reactive halide derivatives, as previously reported.[15]

General procedure for preparation of the tetrahydroindolizines 14-23. 1 Mmol cycloimmonium salt **1-5** , 1.1 mmol olefinic dipolarophile **11-12** and 15 ml water:ethanol (5:1) were stirred together at room temperature. Then 6 ml 0.2N aqueous KOH was added dropwise and the resulting solution stirred for 20 min. (2h, at 30-35°C for salt **2**). The solution became yellow-orange and the product crystallized rapidly. The adduct was filtered off to give yellow microcrystals which were washed with 10 ml water: ethanol (5:1).

General procedure for preparation of the indolizines 24-33. 1 Mmol tetrahydroindolizine **14-23** (freshly prepared), 0.65 mmol TPCB in 5 ml DMF was stirred at 90°C for 2h. The mixture was then cooled to room temperature and the solvent evaporated. The residue was dissolved in 3 ml benzene and was chromatographed on a short column of neutral alumina using a mixture of benzene: ethyl acetate (4:1) as an eluent. The fluorescent part was kept. After removal of the solvent the crude product was recrystallized from methanol to give yellow crystals.

Ethyl 3-benzoyl-5-(2′-pyridyl)-1,2,3,8a-tetrahydroindolizine-1-carboxylate (14). Yellow crystals. Yield 80 %, mp 120-122 °C. Anal. $C_{23}H_{22}N_2O_3$. Calcd. C 73.79; H 5.88; N 7.48. Found C 73.86; H 5.80; N 7.31.

Ethyl 3-(p-nitro-benzoyl)-5-(2′-pyridyl)-1,2,3,8a-tetrahydroindolizine-1-carboxylate (15). Orange crystals. Yield 75 %, mp 145-146 °C. Anal. $C_{23}H_{21}N_3O_5$. Calcd. C 65.87; H 5.01; N 10.02. Found C 65.63; H 4.95; N 10.14.

Ethyl 3-(p-methoxy-benzoyl)-5-(2′-pyridyl)-1,2,3,8a-tetrahydroindolizine-1-carboxylate (16). Yellow crystals. Yield 80 %, mp 98-100 °C. Anal. $C_{24}H_{24}N_2O_4$. Calcd. C 71.28; H 5.94; N 6.93. Found C 72.05; H 5.81; N 7.08.

Ethyl 3-(p-bromo-benzoyl)-5-(2′-pyridyl)-1,2,3,8a-tetrahydroindolizine-1-carboxylate (17). Yellow crystals. Yield 87 %, mp 135-136 °C. Anal. $C_{23}H_{21}Br\ N_2O_3$. Calcd. C 60.92; H 4.63; N 6.18. Found C 60.75; H 4.69; N 6.3.

Ethyl 3-(p-chloro-benzoyl)-5-(2′-pyridyl)-1,2,3,8a-tetrahydroindolizine-1-carboxylate (18). Yellow crystals. Yield 85 %, mp 140-142 °C. Anal. $C_{23}H_{21}Cl\ N_2O_3$. Calcd. C 67.56; H 5.14; N 6.85. Found C 67.84; H 5.03; N 6.78.

3-(Benzoyl)-5-(2′-pyridyl)-1,2,3,8a-tetrahydroindolizine-1-carbonitrile (19). Yellow crystals. Yield 87 %, mp. 124-125 °C. Anal. $C_{21}H_{17}N_3O$. Calcd. C 77.06; H 5.19; N 12.84. Found C 76.83; H 5.08; N 12.93.

3-(p-Nitro-benzoyl)-5-(2′-pyridyl)-1,2,3,8a-tetrahydroindolizine-1-carbonitrile (20). Orange crystals. Yield 78 %, mp 135-137 °C. Anal. $C_{21}H_{16}N_4O_3$. Calcd. C 67.74; H 4.30; N 15.05. Found C 67.30; H 4.19; N 15.23.

3-(p-Methoxy-benzoyl)-5-(2′-pyridyl)-1,2,3,8a-tetrahydroindolizine-1-carbonitrile (21). Yellow crystals. Yield 80 %, mp 123-125 °C. Anal. $C_{22}H_{19}N_3O_2$. Calcd. C 73.93; H 5.36; N 11.73. Found C 74.14; H 5.15; N 11.50.

3-(p-Bromo-benzoyl)-5-(2′-pyridyl)-1,2,3,8a-tetrahydroindolizine-1-carbonitrile (22). Yellow crystals. Yield 82 %, mp 115-117 °C. Anal. $C_{21}H_{16}BrN_3O$. Calcd. C 62.06; H 3.94; N 10.34. Found C 61.88; H 3.88; N 10.63.

3-(p-Chloro-benzoyl)-5-(2′-pyridyl)-1,2,3,8a-tetrahydroindolizine-1-carbonitrile (23). Yellow crystals. Yield 80 %, mp 118-120 °C. Anal. $C_{21}H_{16}ClN_3O$. Calcd. C 69.70; H 4.42; N 11.61. Found C 70.01; H 4.45; N 11.42.

Ethyl 3-benzoyl-5-(2′-pyridyl)-indolizine-1-carboxylate (24). Lemon yellow crystals. Yield 50 %, mp 155 °C(ref.[10] 155°C).

Ethyl 3-(p-nitro-benzoyl)-5-(2′-pyridyl)-indolizine-1-carboxylate (25). Yellow crystals. Yield 55 %, mp 227 °C (ref.[10] 227°C).

Ethyl 3-(p-methoxy-benzoyl)-5-(2′-pyridyl)-indolizine-1-carboxylate (26). Yellow crystals. Yield 50 %, mp 184-185 °C. Anal. $C_{24}H_{20}N_2O_4$. Calcd. C 72.00; H 5.00; N 7.00. Found C 72.35; H 5.16; N 6.83.

Ethyl 3-(p-bromo-benzoyl)-5-(2′-pyridyl)-indolizine-1-carboxylate (27). Yellow crystals. Yield 60 %, mp. 233-235 °C (ref.[10] 233-235°C).

Ethyl 3-(p-chloro-benzoyl)-5-(2′-pyridyl)-indolizine-1-carboxylate (28). Yellow crystals. Yield 45 %, mp 213-214 °C. Anal. $C_{23}H_{17}N_2O_3Cl$. Calcd. C 68.23; H 4.20; N 6.92. Found C 67.93; H 4.12; N 7.12.

3-(Benzoyl)-5-(2′-pyridyl)-1,2,3,8a-indolizine-1-carbonitrile (29). Yellow crystals. Yield 53 %, mp 239-240 °C. Anal. $C_{21}H_{13}N_3O$. Calcd. C 78.01; H 4.02; N 13.00. Found C 77.85; H 4.11; N 12.83.

3-(p-Nitro-benzoyl)-5-(2′-pyridyl)-indolizine-1-carbonitrile (30). Yellow crystals. Yield 60 %, mp. 288-289°C. Anal. $C_{21}H_{12}N_4O_3$. Calcd. C 68.47; H 3.26; N 15.21. Found C 68.70; H 3.33; N 15.55.

3-(p-Methoxy-benzoyl)-5-(2′-pyridyl)-indolizine-1-carbonitrile (31). Yellow crystals. Yield 58%, mp 206-208 °C. Anal. $C_{22}H_{15}N_3O_2$. Calcd. C 74.78; H 4.24; N 11.89. Found C 75.47; H 4.10; N 11.73.

3-(p-Bromo-benzoyl)-5-(2′-pyridyl)-indolizine-1-carbonitrile(32). Yellow crystals. Yield 40 %, mp 220-221 °C. Anal. $C_{21}H_{12}BrN_3O$. Calcd. C 62.68; H 2.98; N 10.44. Found C 62.35; H 3.03; N 10.76.

3-(p-Chloro-benzoyl)-5-(2′-pyridyl)-indolizine-1-carbonitrile (33). Yellow crystals. Yield 45 %,

mp 218-219 °C. Anal. $C_{21}H_{12}ClN_3O$. Calcd. C 70.48; H 3.35; N 11.74. Found C 70.55; H 3.22; N 11.53.

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