HETEROCYCLES, Vol. 77, No. 1, 2009, pp. 471 - 481. © The Japan Institute of Heterocyclic Chemistry
Received, 11th July, 2008, Accepted, 22nd August, 2008, Published online, 25th August, 2008.
DOI: 10.3987/COM-08-S(F)44

PREPARATION OF NEW NITROGEN-BRIDGED HETEROCYCLES. 64.[1] A SMOOTH FORMATION OF 2,4-DIARYLPYRIDO[2,3-*b*]INDOLIZINE-10-CARBONITRILE DERIVATIVES

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Abstract – The syntheses of the title compounds from the reactions of 2-amino-3-(arylcarbonyl)indolizine-1-carbonitriles with various acetophenones in the presence of strong base were investigated. When the reactions were carried out between 2-aminoindolizines and 1.2-equimolar amounts of acetophenones, the yields for the target molecules were low or very low. However, when a large excess of acetophenones were used without any solvent or in as small as amount of solvent as possible, their yields were considerably improved. The smooth hydrolysis of the 10-cyano group to the carbamoyl one was also observed.

Previously we reported a first construction method for pyrido[2,3-*b*]indolizine ring system starting from some 3-acetyl-2-(alkylamino)indolizine derivatives.[2] We particularly noticed during the reaction that, in contrast with the 2-thiol group,[3] the 2-alkylamino group on the indolizine ring was scarcely reactive to various electrophiles even under more drastic conditions. The extremely lowered reactivity of the 2-alkylamino group is maybe due to the severe steric congestion caused by the shorter carbon-nitrogen bond and to the tight hydrogen-bonding between the 2-alkylamino proton and the 3-acyl carbonyl group. Hence, the only group which we could introduce at that time was the smallest functional group, formyl, and the intramolecular dehydration reaction between the resulting 2-formamide and the 3-acetyl group on the indolizine ring afforded the corresponding 1,4-dihydropyrido[2,3-*b*]indolizin-4-one derivative. Recently two groups have reported the formation of pyrido[2,3-*b*]indolizines and pyrimido[4,5-*b*]-indolizines in the reactions of 2-(*N*-unsubstituted amino)indolizines with some electrophiles.[4,5] They have also described that these products have an antimicrobial activity and are selective partial agonists or

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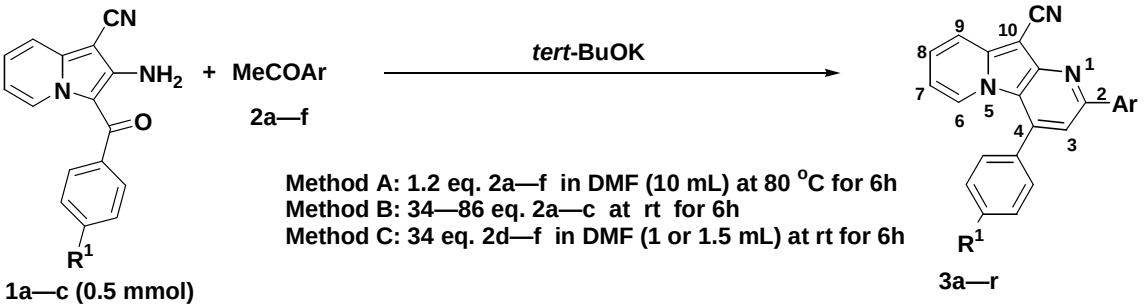
Dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

antagonists of human CRF1 receptor. In the continuation of our effort for nitrogen-bridged heterocycle synthesis, we are very interested in the use of 2-(*N*-unsubstituted amino)indolizines as a starting material because of their ready availability[6,7] and their expected increased reactivity due to the relief of steric congestion. To the best of my knowledge, pyrido[2,3-*b*]indolizine derivatives functionalized at the 4-position have been prepared from the alkyl 2-amino-1-arylindolizine-3-carboxylates,[4] but those functionalized at the 10-position are unknown until now. We selected a cyano group as a functional one at the 10-position in the target molecules because of the less steric hindrance and of the ready convertibility to other functional groups. In this paper we report the synthesis of the title compounds from the reaction of the 2-amino-3-(arylcarbonyl)indolizine-3-carbonitriles and some acetophenones in the presence of a base.

RESULTS AND DISCUSSION

We first examined the *N*-alkylation of 2-amino-3-benzoylindolizine-1-carbonitriles (**1a**—**c**) with electrophilic agents such as ethyl bromoacetate and phenacyl bromide under various conditions, but no significant products could be obtained at all. So, we turned our attention to the dehydration between the 2-amino group on the indolizine ring and the ketone carbonyl one in the acetophenone compound. When the mixture of 2-amino-3-benzoylindolizine-1-carbonitrile (**1a**) and a 1.2-equivalent of acetophenone (**2a**) was allowed to react in chloroform or ethanol in the presence of a base such as triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene, the direct formation of 2,4-diphenylpyrido[2,3-*b*]indolizine-10-carbonitrile (**3a**) with very strong fluorescence was observed, though the yield was very low (<3%). After numerous modifications of the reaction conditions, we found a little improvement (13%) for the yield of **3a** when the *N*,*N*-dimethylformamide (DMF) solution of **1a** and **2a** was treated with potassium *tert*-butoxide at 80 ^{o}C in a water bath for 6h (Method A). The results of the reactions of 2-amino-3-benzoyl- (**1a**), 2-amino-3-(*p*-chlorobenzoyl)- (**1b**) or 2-amino-3-(*p*-bromobenzoyl)indolizine-1-carbonitirile (**1c**) with acetophenone (**2a**), *p*-chloroacetophenone (**2b**), *p*-methylacetophenone (**2c**), *p*-bromoacetophenone (**2d**), *p*-methoxyacetophenone (**2e**), and methyl 2-naphthyl ketone (**2f**) under the conditions of Method A are shown in Scheme 1, but their yields were not be satisfactory (<24%). To improve further these yields we next examined the amounts of acetophenone and solvent and the reaction temperature which is employed. The reactions of 2-aminoindolizines **1a**—**c** with a large excess of liquid acetophenones **2a**—**c** (34—86 equivalents) without any solvent in the presence of potassium *tert*-butoxide at room temperature (Method B) and similar treatment of **1a**—**c** and solid acetophenones **2d**—**f** (34 equivalents) dissolved in small amount of DMF as possible (Method C) provided the corresponding 2,4-diarylpyrido[2,3-*b*]indolizine-10-carbonitrile derivatives **3a**—**r** in 27—68% yields. The decrease of

the mole number of **2a** used gave the decreased yield of product (**3a**) and the increase did not lead to the improvement in the yield. In addition, the reaction at a higher temperature (80 °C) was accompanied with a small amount of hydrolytic product **4a** (see below) together with the expected compound **3a**. In these reactions primary imine intermediates such as **8** (see Scheme 3) were not detected at all. These results are exhibited in Scheme 1.



1	R^1
a	H
b	Cl
c	Br

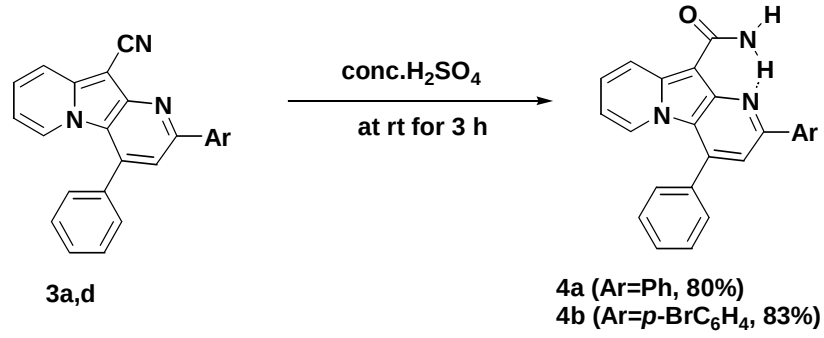
2	Ar
a	Ph
b	*p*-ClC_6H_4
c	*p*-MeC_6H_4
d	*p*-BrC_6H_4
e	*p*-$MeOC_6H_4$
f	2-naphthyl

3	R^1	Ar	Yield (%) A	B	C
a	H	Ph	13	48	--
b	H	*p*-ClC_6H_4	20	33	--
c	H	*p*-MeC_6H_4	17	29	--
d	H	*p*-BrC_6H_4	16	--	58
e	H	*p*-$MeOC_6H_4$	13	--	34
f	H	2-naphthyl	24	--	46
g	Cl	Ph	5	61	--
h	Cl	*p*-ClC_6H_4	7	29	--
i	Cl	*p*-MeC_6H_4	5	27	--
j	Cl	*p*-BrC_6H_4	5	--	61
k	Cl	*p*-$MeOC_6H_4$	6	--	68
l	Cl	2-naphthyl	3	--	48
m	Br	Ph	8	55	--
n	Br	*p*-ClC_6H_4	8	30	--
o	Br	*p*-MeC_6H_4	a)	35	--
p	Br	*p*-BrC_6H_4	6	--	65
q	Br	*p*-$MeOC_6H_4$	11	--	52
r	Br	2-naphthyl	5	--	47

a) Trace.

Scheme 1

When pyrido[2,3-*b*]indolizine-10-carbonitriles **3a**,**d** thus obtained were treated with conc. sulfuric acid at room temperature for 3h, the corresponding 10-carboxamides **4a**,**b** were obtained in 80 and 83% yields, respectively (Scheme 2).



3a,d

4a (Ar=Ph, 80%)
4b (Ar=*p*-BrC_6H_4, 83%)

Scheme 2

The structural assignments for products **3a**—**r** and **4a**,**b** were performed mainly by elemental and IR and ^{1}H-NMR spectral analyses. The elemental analyses for **3a**—**r** were in good accord with our proposed compositions and the IR spectra showed a cyano absorption band in the range of 2205—2213 cm^{-1} for **3a**—**r** and carbonyl and amino bands at 1647, 3156, and 3366 cm^{-1} for **4a** and at 1642, 3192, and 3382 cm^{-1} for **4b**, respectively. In the ^{1}H-NMR spectra (see Table 1) of **3a**—**r** and **4a**,**b** the chemical shifts and signal patterns of the pyrido[2,3-*b*]indolizine ring protons were very similar to each other except for the 9-H signal. The 9-H signal for **4a**,**b** was shifted considerably to the lower magnetic region by the deshielding effect of the 10-carbamoyl group. In addition, one of the amide protons resonated at the low field (δ 9.46 for **4a** and δ 9.35 for **4b**) attributable to a hydrogen-bonding between it and the nitrogen atom on the newly constructed pyridine ring. The final structural confirmation of products **3a**—**r** and **4a**,**b** was carried out by X-ray analyses of the compounds (**3c** and **4b**). The ORTEP drawing[8] of **3c** and **4a** is showed in Figure 1.[9]

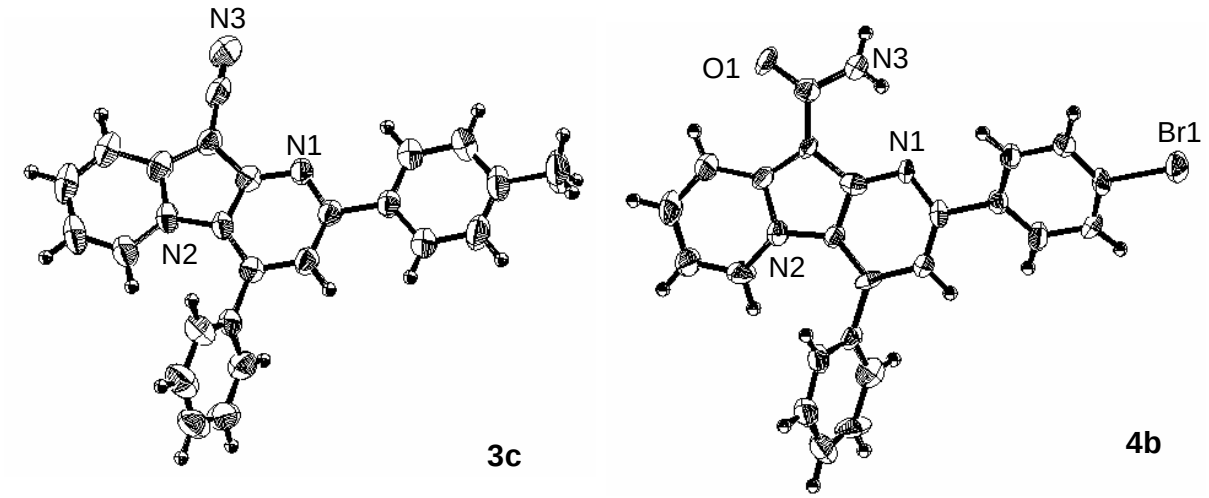


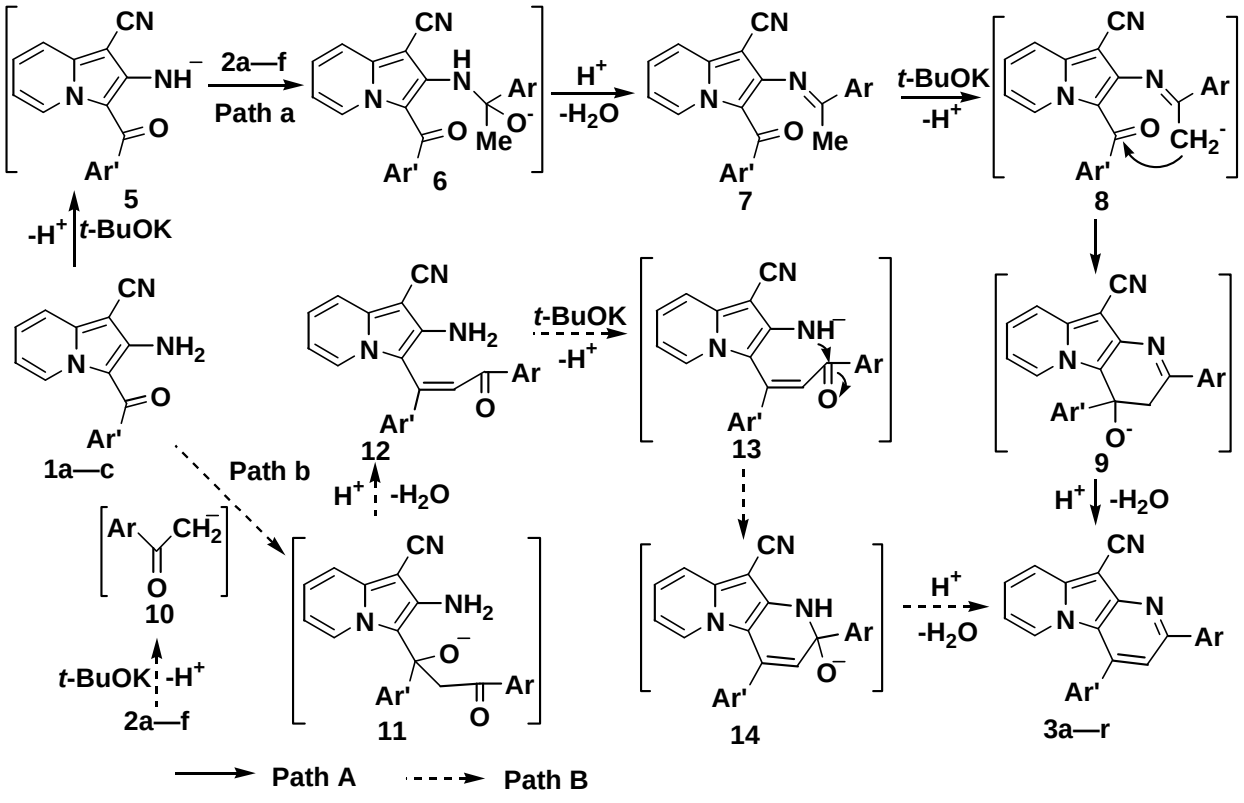
Figure 1. ORTEP drawings of compounds **3c** and **4b**.

Table 1. ^{1}H-NMR spectral data for the ring protons of **3a**—**r** and **4a**,**b**

No[a)]	C-3	C-6	C-7	C-8	C-9		No[a)]	C-3	C-6	C-7	C-8	C-9
3a	7.59	7.84	6.54	7.29	7.78		**3k**	7.48	7.83	6.59	7.30	7.78
3b	7.54	7.83	6.55	7.30	7.77		**3l**	7.67	7.84	6.58	7.29	7.78
3c	7.54	7.81	6.52	7.26	7.75		**3m**	7.56	7.86	6.61	7.33	7.82
3d	7.51	7.81	6.54	7.29	7.74		**3n**	7.49	7.85	6.62	7.33	7.80
3e	7.52	7.81	6.52	7.27	7.77		**3o**	7.54	7.85	6.60	7.31	7.80
3f	7.75	7.84	6.54	7.30	7.81		**3p**	7.51	7.85	6.62	7.34	7.81
3g	7.53	7.86	6.61	7.30	7.79		**3q**	7.46	7.83	6.59	7.30	7.77
3h	7.47	7.83	6.60	7.32	7.76		**3r**	7.70	7.86	6.61	7.32	7.81
3i	7.52	7.83	6.59	7.39	7.79		**4a**	7.54	7.81	6.49	7.26	8.78
3j	7.47	7.83	6.60	7.32	7.76		**4b**	7.50	7.82	6.51	7.29	8.80

a) $J_{6,7}$=6.9-7.1 Hz, $J_{6,8}$=0.9-1.0 Hz, $J_{7,8}$=6.9-7.1 Hz, $J_{7,9}$=1.1-1.2 Hz, $J_{8,9}$=8.9-9.1 Hz.

Mechanistically, the formation of the title compounds **3a**—**r** may be as shown in Scheme 3. The deprotonation from the 2-amino group of **1a**—**c** by a strong base followed by the nucleophilic addition of the resulting amide **5** onto the carbonyl carbon of acetophenones **2a**—**f** may provide the alkoxide ion **6**. The proton abstraction of the alkoxide ion **6** and subsequent dehydration should afford the imine intermediate **7**. The base-catalized dehydration between the active methyl and the 3-acyl carbonyl group in **7** can lead to the pyrido[2,3-*b*]indolizine derivatives (**3a**—**r**) via the corresponding intermediates **8** and **9** (Path A). There is an alternative route (Path B) in which the nucleophilic addition of the arylcarbonylmethanide **10**, generated from the deprotonation of **2a**—**f**, to the 2-arylcarbonyl carbon followed by the protonation and dehydration of the adduct **11** may provide 2-amino-3-(2-arylcarbonylvinyl)indolizines **12** and subsequent base catalyzed intramolecular dehydration should form the same products **3a**—**r**. However, we could not determine whether these reactions proceed through Path A or Path B, because intermediates such as **7** and **12** could not be detected during these reactions.



Scheme 3

EXPERIMENTAL

Melting points were measured with a Yanagimoto micromelting point apparatus and were not corrected. Microanalyses were carried out on a Perkin-Elmer 2400 elemental analyzer. The ^{1}H-NMR and ^{13}C-NMR spectra were determined with a JEOL JNM-LA400 (^{1}H: 400 MHz) spectrometer in

deuteriochloroform with tetramethylsilane used as the internal standard; the chemical shifts are expressed in δ values. The IR spectra were taken with JASCO FT/IR-5300 IR spectrophotometers.

Reactions of 2-aminoindolizines (1) with acetophenones (2). General method A. A mixture of 2-amino-3-arylcarbonylindolizine-1-carbonitirile (**1**, 0.5 mmol), acetophenone derivative (**2**, 0.6 mmol), and potassium *tert*-butoxide (1.1 mmol) was dissolved in DMF (10 mL) and the resulting solution was heated in a water bath (80 ^{o}C) for 6 h. After the removal of potassium *tert*-butoxide by filterating the resulting solution through the thin layer of alumina, the filtrate was concentrated at reduced pressure. The residue was separated by column chromatography on alumina using hexane, Et_2O, and $CHCl_3$ as an eluent. The fractions involving the desired pyrido[2,3-*b*]indolizine (**3**), which has very strong fluorescence, were combined and concentrated at reduced pressure. The crude product (**3**) was purified by recrystallization from $CHCl_3$-hexane. The respective yields for these compounds (**3a**—**r**) in method A are shown in Scheme 1. The changes (temperature, solvents (DMSO, acetic acid, and benzene), and base (NaH, Et_3N, and DBU)) of the reaction conditions in this method did not provide good results.

General method B. To a solution of 2-amino-3-arylcarbonylindolizine-1-carbonitirile (**1**, 0.5 mmol) dissolved in liquid acetophenone derivative (**2a**—**c**, 17—43 mmol), potassium *tert*-butoxide (1.1 mmol) was added and the resulting mixture was stirred at room temperature for 6h. The reaction mixture was treated according to the procedure described in method A. The yields for compounds (**3a**—**c**,**g**—**i**,**m**—**o**) obtained by this method are shown in Scheme 1, and the amounts of **2a**—**c** used to dissolve 2-aminoindolizines (**1a**—**c**) are shown in each description for products (**3a**—**c**,**g**—**i**,**m**—**o**)**.** When these reactions were performed at a higher temperature (80 ^{o}C), the improvement in the yields for pyridoindolizines (**3**) were not observed and, in addition, the concomitant formation of 10-carboxamide derivative (**4**) was confirmed.

General method C. A solution of 2-amino-3-arylcarbonylindolizine-1-carbonitirile (**1**, 0.5 mmol), solid acetophenone derivative (**2d**—**f**, 17 mmol), potassium *tert*-butoxide (1.1 mmol), and DMF (1 or 1.5 mL) was allowed to react at room temperature for 6h. Similar work-ups of the reaction mixtures provided the corresponding pyrido[2,3-*b*]indolizines (**3d**—**f**,**j**—**l**,**p**—**r**) in the yields indicated in Scheme 1. The amount of the DMF used to dissolve **1a**—**c** and **2d**—**f** are indicated in each description for products (**3d**—**f**,**j**—**l**,**p**—**r**).

The ^{1}H-NMR spectral data for the ring protons of the pyrido[2,3-*b*]indolizine skeleton are listed in Table 1, and other spectral and analytical data and some reaction conditions are shown below.

2,4-Diphenylpyrido[2,3-*b*]indolizine-10-carbonitrile (**3a**): from **1a** and **2a** (17 mmol for method B),

yellow prisms, mp 246—247 °C. IR (KBr): ν 2207 cm^{-1}. ^{1}H-NMR δ: 7.40—7.56 (5H, m, Ar-H), 7.59—7.66 (3H, m, Ar-H), 8.19—8.25 (2H, m, Ar-H). ^{13}C-NMR δ: 111.1, 115.1, 116.0, 117.7, 119.3, 127.2, 127.6, 127.6, 128.3, 128.4, 128.9, 129.1, 135.9, 136.8, 138.5, 143.4, 146.1, 155.4 (two carbon are overlapping). *Anal.* Calcd for $C_{24}H_{15}N_3$: C, 83.46; H, 4.38; N, 12.17. Found: C, 83.54; H, 4.33; N, 12.14.

2-(*p*-Chlorophenyl)-4-phenylpyrido[2,3-*b*]indolizine-10-carbonitrile (**3b**): from **1a** and **2b** (17 mmol for method B), yellow needles, mp 259—260 °C. IR (KBr): ν 2207 cm^{-1}. ^{1}H-NMR δ: 7.41—7.46 (2H, m, Ar-H), 7.50—7.55 (2H, m, Ar-H), 7.60—7.65 (3H, m, Ar-H), 8.13—8.18 (2H, m, Ar-H). *Anal.* Calcd for $C_{24}H_{14}ClN_3$: C, 75.89; H, 3.72; N, 11.06. Found: C, 76.12; H, 3.53; N, 11.02.

2-(*p*-Methylphenyl)-4-phenylpyrido[2,3-*b*]indolizine-10-carbonitrile (**3c**): from **1a** and **2c** (17 mmol for method B), yellow prisms, mp 281—282 °C. IR (KBr): ν 2203 cm^{-1}. ^{1}H-NMR δ: 2.41 (3H, s, Me), 7.25—7.30 (2H, m, Ar-H), 7.50—7.56 (2H, m, Ar-H), 7.58—7.65 (3H, m, Ar-H), 8.08—8.14 (2H, m, Ar-H). ^{13}C-NMR δ: 21.4, 111.2, 115.4, 115.9, 117.8, 119.3, 127.2, 127.6, 127.8, 128.5, 129.2, 129.2, 129.3, 135.9, 136.2, 136.9, 139.2, 143.5, 146.3, 155.6 (two carbon are overlapping). *Anal.* Calcd for $C_{25}H_{17}N_3$: C, 83.54; H, 4.77; N, 11.69. Found: C, 83.59; H, 4.71; N, 11.70.

2-(*p*-Bromophenyl)-4-phenylpyrido[2,3-*b*]indolizine-10-carbonitrile (**3d**): from **1a** and **2d** (DMF (1 mL) for method C), yellow needles, mp 281—283 °C. IR (KBr): ν 2207 cm^{-1}. ^{1}H-NMR δ: 7.52—7.59 (4H, m, Ar-H), 7.60—7.67 (3H, m, Ar-H), 8.03—8.10 (2H, m, Ar-H). *Anal.* Calcd for $C_{24}H_{14}BrN_3$: C, 67.94; H, 3.33; N, 9.90. Found: C, 68.17; H, 3.13; N, 9.87.

2-(*p*-Methoxyphenyl)-4-phenylpyrido[2,3-*b*]indolizine-10-carbonitrile (**3e**): from **1a** and **2e** (DMF (1 ml) for method C), yellow needles, mp 291—292 °C. IR (KBr) cm^{-1}: 2207. ^{1}H-NMR δ: 3.88 (3H, s, OMe), 6.97—7.02 (2H, m, Ar-H), 7.50—7.54 (2H, m, Ar-H), 7.58—7.63 (3H, m, Ar-H), 8.16—8.21 (2H, m, Ar-H). *Anal.* Calcd for $C_{25}H_{17}N_3O$: C, 79.98; H, 4.56; N, 11.19. Found: C, 80.00; H, 4.64; N, 11.10.

2-(2-Naphthyl)-4-phenylpyrido[2,3-*b*]indolizine-10-carbonitrile (**3f**): from **1a** and **2f** (DMF (1.5 mL) for method C), yellow needles, mp 296—297 °C. IR (KBr) cm^{-1}: 2205. ^{1}H-NMR δ: 7.48—7.59 (4H, m, Ar-H), 7.60—7.67 (3H, m, Ar-H), 7.86—7.91 (1H, m, Ar-H), 7.94—8.00 (2H, m, Ar-H), 8.43 (1H, dd, *J*=8.8, 2.0 Hz, Ar-H), 8.69 (1H, d, *J*=2.0 Hz, Ar-H). *Anal.* Calcd for $C_{28}H_{17}N_3$: C, 85.04; H, 4.33; N, 10.63. Found: C, 85.17; H, 4.22; N, 10.61.

4-(*p*-Chlorophenyl)-2-phenylpyrido[2,3-*b*]indolizine-10-carbonitrile (**3g**): From **1b** and **2a** (43 mmol for

method B), yellow prisms, mp 292 °C. IR (KBr) cm^{-1}: 2213. ^{1}H-NMR δ: 7.41—7.52 (5H, m, Ar-H), 7.74—7.79 (2H, m, Ar-H), 8.17—8.22 (2H, m, Ar-H). ^{13}C-NMR δ: 111.6, 115.1, 116.1, 118.0, 119.2, 127.4, 127.6, 127.9, 128.6, 129.3, 129.6, 129.9, 134.6, 135.6, 135.7, 138.5, 143.6, 146.4, 155.7 (one carbon is overlapping). *Anal.* Calcd for $C_{24}H_{14}ClN_3$: C, 75.89; H, 3.72; N, 11.06. Found: C, 75.74; H, 3.90; N, 11.02.

2,4-Bis(*p*-chlorophenyl)pyrido[2,3-*b*]indolizine-10-carbonitrile (**3h**): From **1b** and **2b** (33 mmol for method B), yellow prisms, mp >300 °C. IR (KBr) cm^{-1}: 2211. ^{1}H-NMR δ: 7.39—7.44 (2H, m, Ar-H), 7.47—7.52 (2H, m, Ar-H), 7.58—7.64 (2H, m, Ar-H), 8.10—8.15 (2H, m, Ar-H). ^{13}C-NMR δ: 111.7, 115.0, 115.7, 118.0, 119.2, 127.6, 128.0, 128.5, 128.7, 129.6, 129.9, 134.4, 135.4, 135.7, 135.9, 136.9, 143.7, 146.3, 154.2 (one carbon is overlapping). *Anal.* Calcd for $C_{24}H_{13}Cl_2N_3$: C, 69.58; H, 3.16; N, 10.14. Found: C, 69.85; H, 2.98; N, 10.06.

4-(*p*-Chlorophenyl)-2-(*p*-methylphenyl)pyrido[2,3-*b*]indolizine-10-carbonitrile (**3i**): From **1b** and **2c** (38 mmol for method B), yellow needles, mp 295—298 °C. IR (KBr) cm^{-1}: 2205. ^{1}H-NMR δ: 2.42 (3H, s, Me), 7.27—7.31 (2H, m, Ar-H), 7.45—7.50 (2H, m, Ar-H), 7.57—7.62 (2H, m, Ar-H), 8.08—8.13 (2H, m, Ar-H). ^{13}C-NMR δ: 21.4, 111.5, 115.2, 115.8, 117.8, 119.0, 127.1, 127.6, 127.7, 129.3, 129.5, 129.9, 134.6, 135.4, 135.6, 135.6, 139.3, 143.4, 146.2, 155.5 (one carbon is overlapping). *Anal.* Calcd for $C_{25}H_{16}ClN_3$: C, 76.24; H, 4.09; N, 10.67. Found: C, 76.45; H, 3.89; N, 10.65.

2-(*p*-Bromophenyl)-4-(*p*-chlorophenyl)pyrido[2,3-*b*]indolizine-10-carbonitrile (**3j**): From **1b** and **2d** (DMF (1 mL) for method C), yellow needles, mp >300 °C. IR (KBr) cm^{-1}: 2209. ^{1}H-NMR δ: 7.47—7.52 (2H, m, Ar-H), 7.54—7.64 (4H, m, Ar-H), 8.03—8.07 (2H, m, Ar-H). *Anal.* Calcd for $C_{24}H_{13}BrClN_3$: C, 62.84; H, 2.86; N, 9.16. Found: C, 62.94; H, 2.74; N, 9.17.

4-(*p*-Chlorophenyl)-2-(*p*-methoxyphenyl)pyrido[2,3-*b*]indolizine-10-carbonitrile (**3k**): From **1b** and **2e** (DMF (1 mL) for method C), yellow needles, mp 290—292 °C. IR (KBr) cm^{-1}: 2207. ^{1}H-NMR δ: 3.88 (3H, s, OMe), 6.98—7.03 (2H, m, Ar-H), 7.45—7.51 (2H, m, Ar-H), 7.57—7.63 (2H, m, Ar-H), 8.14—8.21 (2H, m, Ar-H). *Anal.* Calcd for $C_{25}H_{16}ClN_3O$: C, 73.26; H, 3.93; N, 10.25. Found: C, 73.52; H, 3.72; N, 10.20.

4-(*p*-Chlorophenyl)-2-(2-naphthyl)pyrido[2,3-*b*]indolizine-10-carbonitrile (**3l**): From **1b** and **2f** (DMF (1.5 mL) for method C), yellow needles, mp >300 °C. IR (KBr) cm^{-1}: 2207. ^{1}H-NMR δ: 7.47—7.57 (4H, m, Ar-H), 7.60—7.65 (2H, m, Ar-H), 7.84—7.89 (1H, m, Ar-H), 7.90—7.96 (2H, m, Ar-H), 8.38 (1H, dd, *J*=8.8, 2.0 Hz, Ar-H), 8.62 (1H, d, *J*=2.0 Hz, Ar-H). *Anal.* Calcd for $C_{28}H_{16}ClN_3$: C, 78.23; H,

3.75; N, 9.77. Found: C, 78.38; H, 3.60; N, 9.77.

4-(*p*-Bromophenyl)-2-phenylpyrido[2,3-*b*]indolizine-10-carbonitrile (**3m**): From **1c** and **2a** (35 mmol for method B), yellow prisms, mp 292—294 °C. IR (KBr) cm^{-1}: 2211. ^{1}H-NMR δ: 7.40—7.54 (5H, m, Ar-H), 7.74—7.79 (2H, m, Ar-H), 8.19—8.25 (2H, m, Ar-H). *Anal.* Calcd for $C_{24}H_{14}BrN_3$: C, 67.94; H, 3.33; N, 9.90. Found: C, 68.22; H, 3.06; N, 9.89.

4-(*p*-Bromophenyl)-2-(*p*-chlorophenyl)pyrido[2,3-*b*]indolizine-10-carbonitrile (**3n**): From **1c** and **2b** (25 mmol for method B), yellow prisms, mp >300 °C. IR (KBr) cm^{-1}: 2211. ^{1}H-NMR δ: 7.41—7.47 (4H, m, Ar-H), 7.75—7.79 (2H, m, Ar-H), 8.12— 8.17 (2H, m, Ar-H). *Anal.* Calcd for $C_{24}H_{13}BrClN_3$: C, 62.84; H, 2.86; N, 9.16 Found: C, 62.49; H, 3.10; N, 9.27.

4-(*p*-Bromophenyl)-2-(*p*-methylphenyl)pyrido[2,3-*b*]indolizine-10-carbonitrile (**3o**): From **1c** and **2c** (33 mmol for method B), yellow prisms, mp >300 °C. IR (KBr) cm^{-1}: 2205. ^{1}H-NMR δ: 2.42 (3H, s, Me), 7.27—7.31 (2H, m, Ar-H), 7.38—7.44 (2H, m, Ar-H), 7.72—7.77 (2H, m, Ar-H), 8.09—8.14 (2H, m, Ar-H). *Anal.* Calcd for $C_{25}H_{16}BrN_3$: C, 68.50; H, 3.68; N, 9.59. Found: C, 68.74; H, 3.52; N, 9.51.

2,4-Bis(*p*-bromophenyl)pyrido[2,3-*b*]indolizine-10-carbonitrile (**3p**): From **1c** and **2d** (DMF (1 mL) for method C), yellow prisms, mp >300 °C. IR (KBr) cm^{-1}: 2209. ^{1}H-NMR δ: 7.40—7.44 (2H, m, Ar-H), 7.59—7.64 (2H, m, Ar-H), 7.75—7.79 (2H, m, Ar-H), 8.07—8.12 (2H, m, Ar-H). *Anal.* Calcd for $C_{24}H_{13}Br_2N_3$: C, 57.29; H, 2.60; N, 8.19. Found: C, 57.63; H, 2.42; N, 8.19.

4-(*p*-Bromophenyl)-2-(*p*-methoxyphenyl)pyrido[2,3-*b*]indolizine-10-carbonitrile (**3q**): From **1c** and **2e** (DMF (1 mL) for method C), yellow prisms, mp 292 °C. IR (KBr) cm^{-1}: 2205. ^{1}H-NMR δ: 3.88 (3H, s, OMe), 6.97—7.03 (2H, m, Ar-H), 7.39—7.45 (2H, m, Ar-H), 7.73—7.78 (2H, m, Ar-H), 8.13—8.19 (2H, m, Ar-H). *Anal.* Calcd for $C_{25}H_{16}BrN_3O$: C, 66.09; H, 3.55; N, 9.25. Found: C, 65.96; H, 3.63; N, 9.30.

4-(*p*-Bromophenyl)-2-(2-naphthyl)pyrido[2,3-*b*]indolizine-10-carbonitrile (**3r**): From **1c** and **2f** (DMF (1.5 mL) for method C), yellow prisms, mp >300 °C. IR (KBr) cm^{-1}: 2207. ^{1}H-NMR δ: 7.44—7.55 (4H, m, Ar-H), 7.75—7.81 (2H, m, Ar-H), 7.85—7.90 (1H, m, Ar-H), 7.92—7.98 (2H, m, Ar-H), 8.39 (1H, dd, *J*=8.8, 2.0 Hz, Ar-H), 8.65 (1H, d, *J*=2.0 Hz, Ar-H). *Anal.* Calcd for $C_{28}H_{16}BrN_3$: C, 70.90; H, 3.40; N, 8.86. Found: C, 71.12; H, 3.25; N, 8.78.

Acid hydrolyses of pyrido[2,3-*b*]indolizine-10-carbonitiriles. A mixture of 2,4-diarylpyrido[2,3-*b*]indolizine-10-carbonitirile (**3a** or **3d**, 0.3 mmol) and conc. sulfuric acid (3 g) was

stirred at rt for 3h. The mixture was poured into cold water (70 mL) and the crystalline products which were separated were collected by suction. The aqueous filtrate was then neutralized by 1N sodium hydroxide and the resulting solution was extracted twice with 30 mL of $CHCl_3$. The residue from the chloroform layers and the crystalline product were combined and separated by column chromatography on alumina using $CHCl_3$ and $CHCl_3$-EtOH (10:1) as an eluent. The recrystallization form $CHCl_3$ afforded the corresponding 10-carboxamide derivative (**4a** or **4b**). The ^{1}H-NMR spectral data for the ring protons of the pyrido[2,3-*b*]indolizine skeleton are listed in Table 1, and other spectral and analytical data are shown below.

2,4-Diphenylpyrido[2,3-*b*]indolizine-10-carboxamide (**4a**): From **3a**, yellow prisms, mp 284—286 ^{o}C. IR (KBr) cm^{-1}: 1647, 3156, 3366. ^{1}H-NMR δ: 5.69 (1H, br s, NH), 7.41—7.67 (8H, m, Ar-H), 8.07—8.19 (2H, m, Ar-H), 9.46 (1H, br s, NH). *Anal.* Calcd for $C_{24}H_{17}N_3O$: C, 79.32; H, 4.72; N, 11.56. Found: C, 79.52; H, 4.64; N, 11.44.

2-(*p*-Bromophenyl)-4-phenylpyrido[2,3-*b*]indolizine-10-carboxamide (**4b**): From **3d**, yellow prisms, mp >300 ^{o}C. IR (KBr) cm^{-1}: 1642, 3192, 3382. ^{1}H-NMR δ: 5.68 (1H, br s, NH), 7.51—7.56 (2H, m, Ar-H), 7.59—7.67 (5H, m, Ar-H), 7.98—8.02 (2H, m, Ar-H), 9.35 (1H, br s, NH). *Anal.* Calcd for $C_{24}H_{16}BrN_3O$: C, 65.17; H, 3.65; N, 9.50. Found: C, 65.32; H, 3.80; N, 9.19.

Crystallography of 2-(*p*-methylphenyl)-4-phenylpyrido[2,3-*b*]indolizine-10-carbonitrile (3c) A yellow prismatic single crystal (0.62x0.38x0.06mm) grown from chloroform was used for the unit-cell determinations and data was collected using a Rigaku AFC5S four-circle diffractometer with graphite-monochromated MoK_α radiation (λ=0.71069 Å). The crystal data of this compound are as follows: **3c**: $C_{25}H_{17}N_3$; *M*=352.47; monoclinic, space group $P2_1/n$ (#14), *Z*=4 with *a*=7.293 (9) Å, *b*=13.172 (13) Å, *c*=19.901 (11) Å, β=98.18 (8)^o,*V*=1892.5 (30) Å^3 and $D_{calc.}$=1.261 g/cm^3. All calculations were performed using CrystalStructure.[10] The structure was solved by a direct method (SIR).[11] The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were attached at the idealized position and not refined. The final *R*- and R_w-factors after full-matrix least-squares refinements were 0.055 and 0.040 respectively for 1898 ($I>2.00\sigma(I)$) observed reflections.

Crystallography of 2-(*p*-Bromophenyl)-4-phenylpyrido[2,3-*b*]indolizine-10-carboxamide (4b) A yellow prismatic single crystal (0.58x0.52x0.16mm) grown from $CHCl_3$ was used for the unit-cell determinations and data was collected using a Rigaku AFC5S four-circle diffractometer with graphite-monochromated MoK_α radiation (λ=0.71069 Å). The crystal data of this compound are as follows: **3c**: $C_{24}H_{16}BrN_3O$-$CHCl_3$; *M*=561.69; triclinic, space group *P*-1(#2), *Z*=2 with *a*=10.491 (11) Å,

b=11.856 (15) Å, *c*=10.30 (2) Å, α=110.11 (15)°, β=98.18 (8)°, γ=97.46 (9), *V*=1159.6 (33) Å^3 and $D_{calc.}$=1.609 g/cm^3. All calculations were performed using CrystalStructure.[10] The structure was solved by a direct method (SIR).[11] The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were attached at the idealized position and not refined. The final *R*- and R_w-factors after full-matrix least-squares refinements were 0.083 and 0.062 respectively for 2621 (I>2.00σ(I)) observed reflections.

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