PREPARATION OF NEW NITROGEN-BRIDGED HETEROCYCLES. 64.1
A SMOOTH FORMATION OF 2,4-DIARYLPYRIDO[2,3-b]INDOLIZINE-
10-CARBONITRILE DERIVATIVES

Akikazu Kakehi, * Hiroyuki Suga, and Shuichi Sato

Department of Chemistry and Material Engineering, Faculty of Engineering,
Shinshu University, Wakasato, Nagano 380-8553.  E-Mail:
akakehi@shinshu-u.ac.jp

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-acetyl 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]-

Dedicated to Dr. Keiichiro Fukumoto on the occasion of his 75th birthday.
indolizines in the reactions of 2-(N-unsubstituted amino)indolizines with some electrophiles. They have also described that these products have an antimicrobial activity and are selective partial agonists or 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 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, 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 °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-carbonitrile (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-diarylpseudo[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.

When pyrido[2,3-b]indolizine-10-carbonitiles 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).
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.](image)

Table 1. \(^1\)H-NMR spectral data for the ring protons of \(3a-r\) and \(4a, b\)

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\(^a\) \(J_{6,7}=6.9-7.1\) 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-catalyzed 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 ¹H-NMR and
$^{13}$C-NMR spectra were determined with a JEOL JNM-LA400 (¹H: 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 °C) for 6 h. After the removal of potassium tert-butoxide by filtering 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, Et₂O, and CHCl₃ 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 CHCl₃-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, Et₃N, 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 °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): v 2207 cm⁻¹. ¹H-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). ¹³C-NMR δ: 111.1, 115.1, 116.0, 117.7, 119.3, 127.2, 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 C₂₄H₁₅N₃: 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): v 2207 cm⁻¹. ¹H-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 C₂₄H₁₄ClN₃: 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): v 2203 cm⁻¹. ¹H-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). ¹³C-NMR δ: 21.4, 111.2, 115.4, 115.9, 117.8, 119.3, 127.2, 127.6, 128.5, 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 C₂₅H₁₇N₃: 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): v 2207 cm⁻¹. ¹H-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 C₂₄H₁₄BrN₃: 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. ¹H-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 C₂₅H₁₇N₃O: 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. ¹H-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,
\( J=8.8, 2.0 \text{ Hz, Ar-H}, 8.69 (1\text{H, d, } J=2.0 \text{ Hz, Ar-H}) \).  

**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.  
\( ^1\text{H-NMR} \delta: 7.41—7.52 (5\text{H, m, Ar-H}), 7.74—7.79 (2\text{H, m, Ar-H}), 8.17—8.22 (2\text{H, m, Ar-H}) \).  
\( ^{13}\text{C-NMR} \delta: 111.6, 115.1, 116.1, 118.0, 119.2, 127.4, 127.6, 127.9, 128.6, 129.3, 129.6, 129.9, 134.6, 135.6, 135.7, 138.5, 143.6, 146.4, 155.7 \) (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.  
\( ^1\text{H-NMR} \delta: 7.39—7.44 (2\text{H, m, Ar-H}), 7.47—7.52 (2\text{H, m, Ar-H}), 7.58—7.64 (2\text{H, m, Ar-H}), 8.10—8.15 (2\text{H, m, Ar-H}) \).  
\( ^{13}\text{C-NMR} \delta: 111.7, 115.0, 115.7, 118.0, 119.2, 127.6, 128.0, 128.5, 128.7, 129.6, 129.9, 134.4, 135.4, 135.7, 135.9, 136.9, 143.7, 146.3, 154.2 \) (one carbon is overlapping).  
**Anal.** Calcd for \( C_{24}H_{13}Cl_{2}N_{3} \): 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.  
\( ^1\text{H-NMR} \delta: 2.42 (3\text{H, s, Me}), 7.27—7.31 (2\text{H, m, Ar-H}), 7.45—7.50 (2\text{H, m, Ar-H}), 7.57—7.62 (2\text{H, m, Ar-H}), 8.08—8.13 (2\text{H, m, Ar-H}) \).  
\( ^{13}\text{C-NMR} \delta: 21.4, 111.5, 115.2, 115.8, 117.8, 119.0, 127.1, 127.6, 127.7, 129.3, 129.5, 129.9, 134.6, 135.4, 135.6, 139.3, 143.4, 146.2, 155.5 \) (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.  
\( ^1\text{H-NMR} \delta: 7.47—7.52 (2\text{H, m, Ar-H}), 7.54—7.64 (4\text{H, m, Ar-H}), 8.03—8.07 (2\text{H, m, Ar-H}) \).  
**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.  
\( ^1\text{H-NMR} \delta: 3.88 (3\text{H, s, OMe}), 6.98—7.03 (2\text{H, m, Ar-H}), 7.45—7.51 (2\text{H, m, Ar-H}), 7.57—7.63 (2\text{H, m, Ar-H}), \)
8.14—8.21 (2H, m, Ar-H).  Anal. Calcd for C_{25}H_{16}ClN_{3}O: 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 \(\delta\): 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-(2-naphthyl)pyrido[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 \(\delta\): 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 \(\delta\): 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 \(\delta\): 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 \(\delta\): 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}BrN_{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 \(\delta\): 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,

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. ¹H-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-carbonitriles. A mixture of 2,4-diarylpyrido[2,3-b]indolizine-10-carbonitrile (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 CHCl₃. The residue from the chloroform layers and the crystalline product were combined and separated by column chromatography on alumina using CHCl₃ and CHCl₃-EtOH (10:1) as an eluent. The recrystallization form CHCl₃ afforded the corresponding 10-carboxamide derivative (4a or 4b). The ¹H-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 °C. IR (KBr) cm⁻¹: 1647, 3156, 3366. ¹H-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_{3}O: 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 °C. IR (KBr) cm⁻¹: 1642, 3192, 3382. ¹H-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_{3}O: 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 MoKα radiation (λ=0.71069 Å). The crystal data of this compound are as
follows: 3c: C_{25}H_{17}N_{3}; \text{ } M=352.47; \text{ } \text{monoclinic, space group } P2_1/n (\#14), \text{ } Z=4 \text{ with } a=7.293 (9) \text{ Å}, \text{ } b=13.172 (13) \text{ Å}, \text{ } \text{c}=19.901 (11) \text{ Å}, \text{ } \text{ } \beta=98.18 (8)^\circ, \text{ } V=1892.5 (30) \text{ Å}^3 \text{ and } D_{\text{calc}}=1.261 \text{ g/cm}^3. \text{ All calculations were performed using CrystalStructure.}^{10} \text{ The structure was solved by a direct method (SIR).}^{11} \text{ The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were attached at the idealized position and not refined. The final } R \text{- and } R_w\text{-factors after full-matrix least-squares refinements were 0.055 and 0.040 respectively for 1898 } (\text{ } I>2.00\sigma(I)) \text{ 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$_\alpha$ radiation ($\lambda=0.71069$ Å). The crystal data of this compound are as follows: 3c: C$_{24}$H$_{16}$BrN$_3$O-CHCl$_3$; M=561.69; \text{ triclinic, space group } P-1(\#2), \text{ } Z=2 \text{ with } a=10.491 (11) \text{ Å}, \text{ } b=11.856 (15) \text{ Å}, \text{ } \text{c}=10.30 (2) \text{ Å}, \text{ } \alpha=110.11 (15)^\circ, \text{ } \beta=98.18 (8)^\circ, \text{ } \gamma=97.46 (9), \text{ } V=1159.6 (33) \text{ Å}^3 \text{ and } D_{\text{calc}}=1.609 \text{ g/cm}^3. \text{ All calculations were performed using CrystalStructure.}^{10} \text{ The structure was solved by a direct method (SIR).}^{11} \text{ The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were attached at the idealized position and not refined. The final } R \text{- and } R_w\text{-factors after full-matrix least-squares refinements were 0.083 and 0.062 respectively for 2621 } (\text{ } I>2.00\sigma(I)) \text{ observed reflections.}

REFERENCES

1. For part 63 of this series, see A. Kakehi, H. Suga, A. Izumita, and T. Abe, Heterocycles, 2008, 76, 391.
9. The chloroform molecule involved in the crystal lattice of compound 4b is omitted.
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