A New Synthetic Approach to Pyrrolo[3,4-*a*]indolizines

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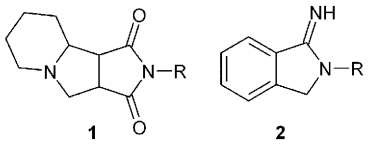
Abstract: 2-Pyridineacetonitrile was found to react with 1,3-dichloro-2-propanone in the presence of chlorotrimethylsilane yielding 2-chloromethyl-1-indolizinecarbonitrile. The chlorine atom in the prepared indolizine was replaced by various nucleophiles including substituted anilines. Treatment of 2-(arylamino)methyl-1-indolizinecarbonitriles with hydrochloric acid resulted in 2-aryl-2,3-dihydro-1*H*-pyrrolo[3,4-*a*]indolizine-1-iminium chlorides.

Key words: alkylations, amidines, chlorotrimethylsilane, nitriles, ultrasound

Pyrrolo[3,4-*a*]indolizine chemistry was developed intensively in the 1980s as a part of general investigations on ylide cycloaddition reactions. Thus, maleimides were found to be suitable traps for ylides and, as the result, various pyrrolo[3,4-*a*]indolizines were obtained by addition of pyridinium ylides to maleimides.[1] Moreover, a number of hydrogenated pyrroloindolizines was prepared nearly at the same time by reaction of certain piperidine-derived azomethine ylides with maleimides.[2] Along with the synthesis some properties of pyrroloindolizines were also studied.[3] In particular, potent thrombin inhibitors with high selectivity for thrombin over trypsin have been discovered recently among pyrrolo[3,4-*a*]indolizines.[4] This finding stimulated new researches on their synthesis.[5] However, all further investigations[5] exploited the old cycloaddition strategy for pyrroloindolizine skeleton construction and were rather devoted to novel ylides and methods of their generation, whereas the trapping agents remained to be maleimides. As the result a curious situation appeared when almost all pyrrolo[3,4-*a*]indolizines known to date are 1,3-dioxo derivatives of type **1** (Figure 1). A few compounds with another substitution pattern of the pyrrole moiety exhibiting the highest biological activity[4b] were obtained by further transformations of dioxo derivatives **1**. Hence, elaboration of an alternative approach to pyrrolo[3,4-*a*]indolizines providing another substitution pattern at positions 1 and 3 is of great interest.

A well-known method of pyrrole ring annulation is the reaction of vicinal halomethyl-substituted nitriles with primary amines. Thus, amination of 2-(chloromethyl)benzonitrile and related compounds has shown to give cyclic amidines **2** (Figure 1) or their salts.[6] Recently, a similar pyrrole annulation has been reported by us for fused pyridine derivatives.[7] Continuing our investigations[7,8] on the amination of heterocycles containing a 4-halonitrile moiety, we were interested to prepare 2-(chloromethyl)indolizine-1-carbonitrile (**4**) as a precursor of target pyrroloindolizines. Since certain amidines derived from structure **2** were claimed as anesthetic, antiarrhythmic, antihypertensive, and antiinflammatory agents,[9] the synthesis of pyrroloindolizine amidines on the basis of compound **4** leads to the combination of the active fragments[4,9] and, therefore, is promising from a biological viewpoint.



1 2

Figure 1

Pyridin-2-ylacetonitrile (**3**) was described to react with α-haloketones yielding indolizine-1-carbonitriles.[10] The use of 1,3-dichloroacetone in this reaction should afford chloromethyl derivative **4** (Scheme 1). However, attempts to perform the condensation of compound **3** with 1,3-dichloroacetone under the conditions reported[10] for other haloketones gave unsatisfactory results. According to the literature,[10] the indolizine formation occurs via initial N-alkylation of pyridine **3** with haloketone and further intramolecular condensation. In the case of 1,3-dichloroacetone there are two pathways for further transformations of the appropriate alkylated intermediate, namely the intramolecular condensation with the carbonyl group and the intramolecular alkylation with the second CH_2Cl group. This vague behavior is believed to be a reason of the failure. Therefore, inversion of the reaction sequence during the indolizine synthesis was assumed to facilitate the preparation of compound **4**. Indeed, if the reaction starts from a Knoevenagel-type condensation of pyridine **3** with 1,3-dichloroacetone, the following intramolecular alkylation should proceed clearly because of the absence of any alternative. Hence, the problem was to achieve firstly condensation and to suppress initial alkylation. It was solved using chlorotrimethylsilane (TMSCl) as condensing agent. Thus, TMSCl and related halosilanes were reported to promote certain condensation reactions including those with unusual methylene and carbonyl com-

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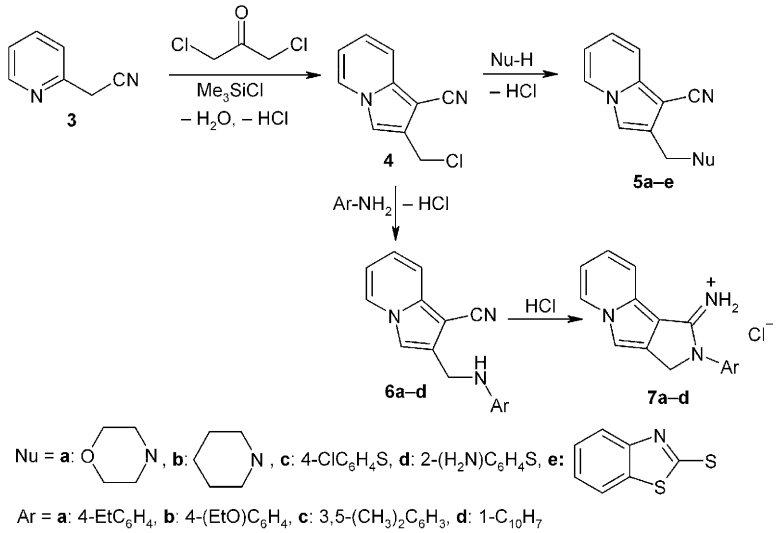

Scheme 1

ponents.[11] Treatment of pyridine **3** with 1,3-dichloroacetone in the presence of an excess of TMSCl allowed to obtain the desired indolizine **4** in 65% isolated yield.

As expected, a nucleophilic substitution of the chlorine in compound **4** proceeded smoothly yielding the corresponding derivatives **5a–e**. When anilines were employed as nucleophiles a concomitant bis-alkylation process was observed. Therefore, the reaction conditions were optimized in order to obtain pure mono-alkylated products **6a–d**. Aprotic solvents were found to facilitate bis-alkylation, whereas the starting chloride **4** was less soluble in alcohols. Nevertheless, compounds **6a–d** were obtained in 50–80% yields when the reaction was carried out heterogeneously in *i*-PrOH in the presence of triethylamine and using ultrasonic irradiation[12] as a high effective stirring equivalent. Application of these conditions to the preparation of derivatives **5a–e** also gave better results and, hence, we accepted it as the standard for chlorine substitution in compound **4**.

Upon reflux in ethanol in the presence of aqueous hydrochloric acid, compounds **6a–d** underwent cyclization to form the target pyrrolo[3,4-*a*]indolizine amidinium salts **7a–d**. It should be noted that, during amination of the 2-(chloromethyl)benzonitrile, amidinium salts **2** were always formed directly without isolation of the alkylated intermediate.[6] Probably, the ring closure was accomplished at the expense of HCl liberated during the alkylation step. In the present case we failed to achieve a direct conversion of the indolizine **4** into derivatives **7a–d**. Furthermore, the cyclization reaction of compounds **6a–d** hardly proceeded and the yields of salts **7a–d** were only moderate (~50%). Perhaps this could be explained by the lower reactivity of the nitrile group in compound **4** compared to the corresponding benzonitrile analogue.

The structures of the prepared compounds **4–7** were confirmed by ^{1}H and ^{13}C NMR spectroscopic data. Thus, absence of the nitrile absorption both in IR and ^{13}C NMR spectra of compounds **7** clearly indicated the ring closure with its participation. A very characteristic signal of the amidinium carbon atom appeared in the ^{13}C NMR spectra of derivatives **7** at 156–158 ppm. The signals of the immonium group hydrogen atoms were observed as two broad one-proton singlets at 9.6–9.7 and 8.4–8.6 ppm. The one-proton doublet of 9-H of compounds **7** was present in the spectra at 8.5–8.6 ppm, whereas for their precursors **6** the same atom (8-H) signal was observed at 7.5–7.6 ppm. This 1 ppm shift is the remarkable attribute of the cyclization and is explained by deshielding of 9-H by the neighboring magnetically anisotropic immonium group in derivatives **7**, which is absent for compounds **6**. In addition, it is interesting to note that for the naphthyl-substituted derivative **7d** the signal of the methylene hydrogen atoms appeared as two one-proton doublets at 4.75 ppm and 4.68 ppm with a geminal coupling constant of J = 15.3 Hz. It is probably the restricted rotation of the naphthyl moiety around the C–N bond that brings in an axial chirality to molecule **7d** and makes the hydrogen atoms of the methylene group magnetically non-equivalent. A similar effect was reported previously for certain *N*-(1-naphthyl)-substituted pyrrole derivatives.[13]

To resume, the present investigation has resulted in a new approach to pyrrolo[3,4-*a*]indolizine framework construction. It includes pyrrole annulation to the indolizine nucleus whereas the previously reported methods[1–5] are based on formation of the central ring of the system by means of cycloaddition reactions. Thus, this work extends the scope of available pyrroloindolizines and diversifies the substitution pattern at positions 1 and 3, which hitherto has been limited to 1,3-dioxo compounds **1**.

All starting materials were commercially available. Melting points were determined in open capillary tubes in a *Thiele* apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian UNITY*plus* 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer in DMSO-d_6 solutions. Chemical shifts (δ) are given in ppm downfield from internal Me_4Si. The purity of all compounds pre-

pared was verified by ^{1}H NMR spectroscopy and LC/MS on an Agilent 1100 instrument.

2-(Chloromethyl)indolizine-1-carbonitrile (4)
TMSCl (1.09 g, 100 mmol) was added to a solution of pyridin-2-ylacetonitrile (**3**, 3.00 g, 25.4 mmol) and 1,3-dichloroacetone (3.87 g, 30.5 mmol) in anhyd DMF (10 mL) in a 50 mL flask. The flask was sealed thoroughly with a rubber stopper and heated in a boiling water bath for 4 h. After cooling it was opened (*Caution! There is excessive pressure inside!*) and the reaction mixture was poured into H_2O (100 mL). The solid formed was filtered off, washed with H_2O, dried, and recrystallized from *i*-PrOH to give 3.15 g (65%) of compound **4** as colorless crystals.

Mp 140 °C.

^{1}H NMR: δ = 4.82 (s, 2 H, CH_2), 6.83 (t, *J* = 9.0 Hz, 1 H, 6-H), 7.15 (t, *J* = 9.0 Hz, 1 H, 7-H), 7.56 (d, *J* = 9.0 Hz, 1 H, 8-H), 7.74 (s, 1 H, 3-H), 8.42 (d, *J* = 9.0 Hz, 1 H, 5-H).

^{13}C NMR: δ = 37.9 (CH_2), 80.6 (1-C), 113.9 (6-C), 115.5 (8-C), 115.9 (CN), 117.2 (3-C), 124.7 (7-C), 127.9 (2-C), 128.3 (5-C), 138.1 (8a-C).

Anal. Calcd for $C_{10}H_7ClN_2$: C, 63.01; H, 3.70; N, 14.69; Cl 18.60. Found: C, 63.15; H, 3.81; N, 14.72; Cl 18.70.

Indolizine-1-carbonitriles 5a–e; General Procedure
An appropriate amine or thiol (8.92 mmol) and Et_3N (0.91 g, 9.0 mmol) were added to a suspension of compound **4** (1.7 g, 8.92 mmol) in *i*-PrOH (10 mL). The resulting mixture was heated at 60–70 °C with simultaneous ultrasonic irradiation for 7 h. Then the mixture was cooled to 4 °C, the solid was filtered off and washed with cold *i*-PrOH and H_2O. Recrystallization from *i*-PrOH afforded derivatives **5a**–**e** as white powders.

2-(Morpholin-4-ylmethyl)indolizine-1-carbonitrile (5a)
Yield: 1.66 g (77%); mp 76 °C.

^{1}H NMR: δ = 2.95 (m, 4 H, NCH_2), 3.61 (m, 6 H, 2-CH_2, OCH_2), 6.75 (t, *J* = 6.9 Hz, 1 H, 6-H), 7.05 (t, *J* = 6.9 Hz, 1 H, 7-H), 7.48 (s, 1 H, 3-H), 7.51 (d, *J* = 6.9 Hz, 1 H, 8-H), 8.31 (d, *J* = 6.9 Hz, 1 H, 5-H).

^{13}C NMR: δ = 42.8 (CH_2), 54.1 (NCH_2), 68.2 (OCH_2), 79.5 (1-C), 113.6 (6-C), 115.2 (3-C), 117.6 (8-C), 117.8 (CN), 125.6 (7-C), 126.1 (2-C), 127.3 (5-C), 136.4 (8a-C).

Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.67; H, 6.15; N, 17.47.

2-(Piperidin-1-ylmethyl)indolizine-1-carbonitrile (5b)
Yield: 1.47 g (69%); mp 68 °C.

^{1}H NMR: δ = 1.41 (m, 2 H, 4-H_{Nu}), 1.54 (m, 4 H, 3,5-H_{Nu}), 2.40 (m, 4 H, 2,6-H_{Nu}), 3.57 (s, 2 H, 2-CH_2), 6.74 (dd, *J* = 6.9, 7.8 Hz, 1 H, 6-H), 7.04 (dd, *J* = 9.0, 7.8 Hz, 1 H, 7-H), 7.44 (s, 1 H, 3-H), 7.50 (d, *J* = 9.0 Hz, 1 H, 8-H), 8.30 (d, *J* = 6.9 Hz, 1 H, 5-H).

^{13}C NMR: δ = 23.9 (CH_2), 29.3 (2 CH_2), 47.9 (2-CH_2), 58.6 (NCH_2), 79.6 (1-C), 114.0 (8-C), 115.9 (6-C), 116.0 (CN), 116.1 (3-C), 122.7 (7-C), 126.8 (2-C), 128.0 (5-C), 139.4 (8a-C).

Anal. Calcd for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56. Found: C, 75.39; H, 7.37; N, 17.49.

2-{[(4-Chlorophenyl)thio]methyl}indolizine-1-carbonitrile (5c)
Yield: 2.29 g (86%); mp 88 °C.

^{1}H NMR: δ = 4.33 (s, 2 H, CH_2), 6.84 (dd, *J* = 6.9, 7.8 Hz, 1 H, 6-H), 7.14 (dd, *J* = 9.0, 7.8 Hz, 1 H, 7-H), 7.37 (m, 4 H, H_{Nu}), 7.54 (d, *J* = 9.0 Hz, 1 H, 8-H), 7.58 (s, 1 H, 3-H), 8.41 (d, *J* = 6.9 Hz, 1 H, 5-H).

^{13}C NMR: δ = 28.1 (CH_2), 80.2 (1-C), 113.0 (6-C), 114.4 (8-C), 115.7 (CN), 116.5 (3-C), 123.6 (7-C), 127.2 (1-C_{Nu}), 127.5 (2-C), 128.9 (3,5-C_{Nu}), 130.2 (2,6-C_{Nu}), 130.8 (5-C), 134.7 (4-C_{Nu}), 137.3 (8a-C).

Anal. Calcd for $C_{16}H_{11}ClN_2S$: C, 64.32; H, 3.71; N, 9.38; Cl, 11.87; S, 10.73. Found: C, 64.39; H, 3.73; N, 9.49; Cl, 11.92; S, 10.87.

2-{[(2-Aminophenyl)thio]methyl}indolizine-1-carbonitrile (5d)
Yield: 2.02 g (81%); mp 60 °C.

^{1}H NMR: δ = 4.05 (s, 2 H, CH_2), 5.35 (s, 2 H, NH_2), 6.45 (t, *J* = 7.6 Hz, 1 H, 5-H_{Nu}), 6.71 (d, *J* = 7.6 Hz, 1 H, 3-H_{Nu}), 6.85 (dd, *J* = 6.8, 7.2 Hz, 1 H, 6-H), 7.02 (dd, *J* = 6.8, 9.2 Hz, 1 H, 7-H), 7.15 (m, 2 H, 4,6-H_{Nu}), 7.47 (s, 1 H, 3-H), 7.55 (d, *J* = 9.2 Hz, 1 H, 8-H), 8.40 (d, *J* = 7.2 Hz, 1 H, 5-H).

^{13}C NMR: δ = 29.8 (CH_2), 81.0 (1-C), 111.5 (6-C), 112.2 (8-C), 112.7 (3-C_{Nu}), 115.0 (CN), 116.0 (3-C), 117.2 (5-C_{Nu}), 118.5 (1-C_{Nu}), 124.7 (7-C), 128.2 (2-C), 129.1 (5-C), 129.9 (6-C_{Nu}), 131.6 (4-C_{Nu}), 135.4 (8a-C), 154.7 (2-C_{Nu}).

Anal. Calcd for $C_{16}H_{13}N_3S$: C, 68.79; H, 4.69; N, 15.04; S, 11.48. Found: C, 68.93; H, 4.73; N, 14.94; S, 11.40.

2-[(1,3-Benzothiazol-2-ylthio)methyl]indolizine-1-carbonitrile (5e)
Yield: 2.26 g (79%); mp 125 °C.

^{1}H NMR: δ = 4.77 (s, 2 H, CH_2), 6.88 (dd, *J* = 6.8, 7.8 Hz, 1 H, 6-H), 7.18 (dd, *J* = 8.8, 7.8 Hz, 1 H, 7-H), 7.36 (t, *J* = 7.6 Hz, 1 H, 5-H_{Nu}), 7.48 (t, *J* = 7.6 Hz, 1 H, 6-H_{Nu}), 7.59 (d, *J* = 8.8 Hz, 1 H, 8-H), 7.79 (s, 1 H, 3-H), 7.91 (d, *J* = 7.6 Hz, 1 H, 7-H_{Nu}), 8.01 (d, *J* = 7.6 Hz, 1 H, 4-H_{Nu}), 8.47 (d, *J* = 6.8 Hz, 1 H, 5-H).

^{13}C NMR: δ = 29.9 (CH_2), 77.3 (1-C), 114.0 (6-C), 114.7 (8-C), 115.2 (CN), 117.4 (3-C), 118.6 (7-C_{Nu}), 119.2 (4-C_{Nu}), 122.8 (7-C), 124.8 (5-C_{Nu}), 125.7 (2-C), 126.6 (6-C_{Nu}), 131.0 (5-C), 134.8 (7a-C_{Nu}), 138.4 (8a-C), 152.0 (3a-C_{Nu}), 164.3 (2-C_{Nu}).

Anal. Calcd for $C_{17}H_{11}N_3S_2$: C, 63.53; H, 3.45; N, 13.07; S, 19.95. Found: C, 63.60; H, 3.61; N, 13.16; S, 20.06.

2-Anilinomethylindolizine-1-carbonitriles 6a–d; General Procedure
An appropriate aniline (10.7 mmol) and Et_3N (0.91 g, 9.0 mmol) were added to a suspension of compound **4** (1.7 g, 8.92 mmol) in *i*-PrOH (10 mL). The resulting mixture was heated at 60–70 °C with simultaneous ultrasonic irradiation for 7 h and then was cooled to 4 °C. The precipitate was filtered off, washed with cold *i*-PrOH and H_2O, and recrystallized from *i*-PrOH to yield derivatives **6a**–**d** as white powders.

2-{[(4-Ethylphenyl)amino]methyl}indolizine-1-carbonitrile (6a)
Yield: 1.77 g (72%); mp 105 °C.

^{1}H NMR: δ = 1.09 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.42 (q, *J* = 7.2 Hz, 2 H, CH_2), 4.35 (s, 2 H, 2-CH_2), 5.98 (br s, 1 H, NH), 6.55 (d, *J* = 8.0 Hz, 2 H, 2,6-H_{Ar}), 6.85 (dd, *J* = 6.8, 7.2 Hz, 1 H, 6-H), 6.90 (d, *J* = 8.0 Hz, 2 H, 3,5-H_{Ar}), 7.15 (dd, *J* = 8.0, 7.2 Hz, 1 H, 7-H), 7.57 (m, 2 H, 3-H, 8-H), 8.45 (d, *J* = 6.8 Hz, 1 H, 5-H).

^{13}C NMR: δ = 8.4 (CH_3), 27.3 (CH_2), 45.2 (2-CH_2), 79.5 (1-C), 112.4 (2,6-C_{Ar}), 112.8 (6-C), 113.5 (8-C), 116.1 (CN), 116.4 (3-C), 123.2 (7-C), 127.5 (2-C), 128.1 (3,5-C_{Ar}), 131.0 (5-C), 131.3 (4-C_{Ar}), 137.2 (8a-C), 146.4 (1-C_{Ar}).

Anal. Calcd for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26. Found: C, 78.39; H, 6.30; N, 15.30.

2-{[(4-Ethoxyphenyl)amino]methyl}indolizine-1-carbonitrile (6b)
Yield: 1.77 g (68%); mp 109 °C.

^{1}H NMR: δ = 1.25 (t, *J* = 6.8 Hz, 3 H, CH_3), 3.86 (q, *J* = 6.8 Hz, 2 H, OCH_2), 4.32 (s, 2 H, 2-CH_2), 5.76 (br s, 1 H, NH), 6.56 (d, *J* = 8.8 Hz, 2 H, 2,6-H_{Ar}), 6.69 (d, *J* = 8.8 Hz, 2 H, 3,5-H_{Ar}), 6.85 (dd, *J* = 6.8, 7.2 Hz, 1 H, 6-H), 7.15 (dd, *J* = 8.0, 7.2 Hz, 1 H, 7-H), 7.58 (m, 2 H, 3-H, 8-H), 8.47 (d, *J* = 6.8 Hz, 1 H, 5-H).

^{13}C NMR: δ = 14.1 (CH_3), 44.2 (2-CH_2), 64.0 (OCH_2), 78.7 (1-C), 112.7 (8-C), 113.0 (6-C), 116.3 (3-C), 118.9 (3,5-C_{Ar}), 119.1 (CN), 119.2 (2,6-C_{Ar}), 124.9 (7-C), 127.9 (2-C), 131.0 (5-C), 137.5 (8a-C), 142.4 (1-C_{Ar}), 156.7 (4-C_{Ar}).

Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.21; H, 5.88; N, 14.42. Found: C, 73.99; H, 5.80; N, 14.40.

2-{[(3,5-Dimethylphenyl)amino]methyl}indolizine-1-carbonitrile (6c)
Yield: 2.04 g (83%); mp 133 °C.

^{1}H NMR: δ = 2.08 (s, 6 H, 2 CH_3), 4.34 (d, *J* = 6.0 Hz, 2 H, CH_2), 5.98 (t, *J* = 6.0 Hz, 1 H, NH), 6.19 (s, 1 H, 4-H_{Ar}), 6.25 (s, 2 H, 2,6-H_{Ar}), 6.85 (dd, *J* = 6.8, 7.2 Hz, 1 H, 6-H), 7.15 (dd, *J* = 7.6, 7.2 Hz, 1 H, 7-H), 7.57 (m, 2 H, 3-H, 8-H), 8.48 (d, *J* = 6.8 Hz, 1 H, 5-H).

^{13}C NMR: δ = 21.3 (2 CH_3), 45.3 (CH_2), 79.6 (1-C), 110.3 (2,6-C_{Ar}), 112.8 (6-C), 113.5 (8-C), 116.1 (CN), 116.4 (3-C), 118.2 (4-C_{Ar}), 123.2 (7-C), 127.5 (2-C), 130.9 (5-C), 137.2 (8a-C), 137.6 (3,5-C_{Ar}), 148.5 (1-C_{Ar}).

Anal. Calcd for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26. Found: C, 78.60; H, 6.32; N, 15.05.

2-[(1-Naphthylamino)methyl]indolizine-1-carbonitrile (6d)
Yield: 1.38 g (52%); mp 160 °C.

^{1}H NMR: δ = 4.62 (d, *J* = 5.6 Hz, 2 H, CH_2), 6.48 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 6.86 (m, 2 H, NH, 6-H), 7.10–7.23 (m, 3 H, 7-H, 2 H_{Ar}), 7.43 (m, 2 H, H_{Ar}), 7.58 (d. *J* = 9.2 Hz, 1 H, 8-H), 7.61 (s, 1 H, 3-H), 7.76 (d, *J* = 8.8 Hz, 1 H, H_{Ar}), 8.22 (d, *J* = 7.7 Hz, 1 H, H_{Ar}), 8.44 (d, *J* = 6.9 Hz, 1 H, 5-H).

^{13}C NMR: δ = 39.0 (CH_2), 79.5 (1-C), 103.5 (4-C_{Ar}), 112.8 (6-C), 113.4 (8-C), 115.9 (2-C_{Ar}), 116.2 (CN), 116.4 (3-C), 121.8 (3-C_{Ar}), 123.1 (8a-C_{Ar}), 123.2 (7-C), 124.1 (7-C_{Ar}), 125.7 (6-C_{Ar}), 126.7 (8-C_{Ar}), 127.5 (2-C), 128.0 (5-C_{Ar}), 130.7 (5-C), 134.1 (4a-C_{Ar}), 137.3 (8a-C), 143.5 (1-C_{Ar}).

Anal. Calcd for $C_{20}H_{15}N_3$: C, 80.78; H, 5.08; N, 14.13. Found: C, 80.89; H, 4.91; N, 13.97.

Pyrrolo[3,4-*a*]indolizines 7a–d; General Procedure
Concd aq HCl (0.5 mL) was added to a solution of compounds **6a–d** (1.5 mmol) in EtOH (15 mL) and the mixture was refluxed for 7 h. The solvent was removed in vacuo, the residue was treated with acetone, filtered off, washed with Et_2O and dried to give analytically pure salts **7a–d** as yellowish powders. If necessary, compounds **7a–d** can be purified by recrystallization from a small amount of *i*-PrOH.

2-(4-Ethylphenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*a*]indolizin-1-iminium Chloride (7a)
Yield: 0.23 g (50%); mp 242 °C.

^{1}H NMR: δ = 1.24 (t, *J* = 7.6 Hz, 3 H, CH_3), 2.71 (q, *J* = 7.6 Hz, 2 H, CH_2), 5.11 (s, 2 H, CH_2), 7.07 (dd, *J* = 6.8, 8.8 Hz, 1 H, 7-H), 7.34 (dd, *J* = 6.8, 7.2 Hz, 1 H, 8-H), 7.45 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.53 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.83 (s, 1 H, 4-H), 8.53 (d, *J* = 8.8 Hz, 1 H, 9-H), 8.58 (br s, 1 H, NH), 8.71 (d, *J* = 7.2 Hz, 1 H, 6-H), 9.64 (br s, 1 H, NH).

^{13}C NMR: δ = 8.3 (CH_3), 27.8 (CH_2), 45.1 (3-C), 105.4 (9b-C), 107.4 (9-C), 113.9 (7-C), 118.4 (4-C), 123.6 (8-C), 126.3 (2,6-C_{Ar}), 128.2 (6-C), 128.3 (3a-C), 129.3 (3,5-C_{Ar}), 132.4 (4-C_{Ar}), 134.2 (9a-C), 144.4 (1-C_{Ar}), 157.0 (1-C).

Anal. Calcd for $C_{18}H_{18}ClN_3$: C, 69.34; H, 5.82; N, 13.48; Cl, 11.37. Found: C, 69.25; H, 5.83; N, 13.61; Cl, 11.31.

2-(4-Ethoxyphenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*a*]indolizin-1-iminium Chloride (7b)
Yield: 0.28 g (57%); mp 254 °C.

^{1}H NMR: δ = 1.37 (t, *J* = 6.9 Hz, 3 H, CH_3), 4.12 (q, *J* = 6.9 Hz, 2 H, CH_2), 5.06 (s, 2 H, CH_2), 7.05 (dd, *J* = 6.9, 7.8 Hz, 1 H, 7-H), 7.13 (d, *J* = 8.7 Hz, 2 H, H_{Ar}), 7.32 (dd, *J* = 9.0, 7.8 Hz, 1 H, 8-H), 7.52 (d, *J* = 8.7 Hz, 2 H, H_{Ar}), 7.81 (s, 1 H, 4-H), 8.41 (br s, 1 H, NH), 8.53 (d, *J* = 9.0 Hz, 1 H, 9-H), 8.70 (d, *J* = 6.9 Hz, 1 H, 6-H), 9.58 (br s, 1 H, NH).

^{13}C NMR: δ = 13.7 (CH_3), 43.9 (3-C), 59.7 (OCH_2), 106.1 (9b-C), 107.0 (9-C), 114.7 (7-C), 118.2 (4-C), 121.2 (3,5-C_{Ar}), 124.6 (8-C), 127.3 (6-C), 129.2 (3a-C), 130.5 (2,6-C_{Ar}), 133.8 (9a-C), 134.4 (1-C_{Ar}), 156.0 (4-C_{Ar}), 157.2 (1-C).

Anal. Calcd for $C_{18}H_{18}ClN_3O$: C, 65.95; H, 5.53; N, 12.82; Cl, 10.81. Found: C, 65.74; H, 5.55; N, 12.70; Cl, 10.63.

2-(3,5-Dimethylphenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*a*]indolizin-1-iminium Chloride (7c)
Yield: 0.33 g (71%); mp 187 °C.

^{1}H NMR: δ = 2.36 (s, 6 H, 2 CH_3), 5.11 (s, 2 H, CH_2), 7.07 (dd, *J* = 6.8, 8.4 Hz, 1 H, 7-H), 7.15 (s, 1 H, 4-H_{Ar}), 7.23 (s, 2 H, 2,6-H_{Ar}), 7.34 (dd, *J* = 8.8, 8.4 Hz, 1 H, 8-H), 7.82 (s, 1 H, 4-H), 8.54 (d, *J* = 8.8 Hz, 1 H, 9-H), 8.57 (br s, 1 H, NH), 8.70 (d, *J* = 6.8 Hz, 1 H, 6-H), 9.62 (br s, 1 H, NH).

^{13}C NMR: δ = 20.9 (2 CH_3), 53.8 (CH_2), 105.4 (9b-C), 107.4 (9-C), 113.9 (7-C), 118.5 (4-C), 123.6 (2,6-C_{Ar}), 126.0 (8-C), 128.2 (6-C), 128.3 (3a-C), 129.9 (4-C_{Ar}), 132.3 (9a-C), 136.4 (1-C_{Ar}), 139.4 (3,5-C_{Ar}), 156.8 (1-C).

Anal. Calcd. for $C_{18}H_{18}ClN_3$: C, 69.34; H, 5.82; N, 13.48; Cl, 11.37. Found: C, 69.52; H, 5.63; N, 13.69; Cl, 11.27.

2-(1-Naphthyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*a*]indolizin-1-iminium Chloride (7d)
Yield: 0.24 g (47%); mp 301 °C.

^{1}H NMR: δ = 4.68 (d, *J* = 15.3 Hz, 1 H, 3-H), 4.75 (d, *J* = 15.3 Hz, 1 H, 3-H), 6.95 (m, 1 H, H_{Ar}), 7.10 (dd, *J* = 6.8, 7.2 Hz, 1 H, 7-H), 7.27–7.39 (m, 2 H, 8-H, H_{Ar}), 7.63–7.75 (m, 3 H, H_{Ar}), 7.87 (s, 1 H, 4-H), 8.16 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 8.20 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 8.42 (br s, 1 H, NH), 8.59 (d, *J* = 8.8 Hz, 1 H, 9-H), 8.77 (d, *J* = 6.8 Hz, 1 H, 6-H), 9.73 (br s, 1 H, NH).

^{13}C NMR: δ = 54.7 (CH_2), 104.9 (9b-C), 107.6 (9-C), 114.0 (7-C), 118.4 (4-C), 121.8 (2-C_{Ar}), 123.8 (8-C), 126.2 (7-C_{Ar}), 127.0 (6-C_{Ar}), 127.4 (3-C_{Ar}), 127.9 (4-C_{Ar}), 128.4 (6-C), 128.5 (3a-C), 128.9 (5-C_{Ar}), 129.5 (8-C_{Ar}), 130.3 (8a-C_{Ar}), 132.4 (9a-C), 133.0 (4a-C_{Ar}), 134.4 (1-C_{Ar}), 158.4 (1-C).

Anal. Calcd for $C_{20}H_{16}ClN_3$: C, 71.96; H, 4.83; N, 12.59; Cl, 10.62. Found: C, 72.03; H, 4.80; N, 12.68; Cl, 10.67.

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