DOI 10.1007/s10593-020-02754-w

Chemistry of Heterocyclic Compounds **2020**, *56*(7), 942–948

Synthesis of antiaromatic thiazinoindolizines based on electrophilic cyclizations of indolizine-5-thione

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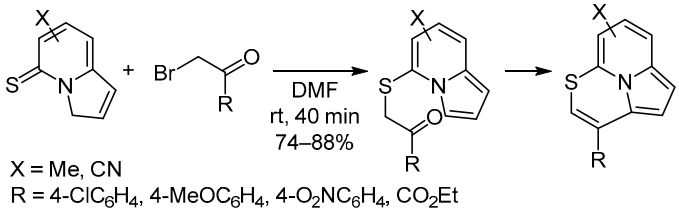
Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2020, *56*(7), 942–948

Submitted May 13, 2020
Accepted after revision July 20, 2020



Alkylation of indolizinethione at the sulfur atom by the action of $RCOCH_2Br$ (R = Me, Ar, CO_2Me, OEt) leads to thioethers, and subsequent closure of the thiazine ring of which leads to the formation of stable antiaromatic thiazino[4,3,2-*cd*]indolizines.

Keywords: thiazino[4,3,2-*cd*]indolizine, thioethers, 5-thioxo-3,5-dihydroindolizine, alkylation, cyclization, X-ray structural analysis.

Indolizines annulated at *peri* positions 3 and 5 with the thiazine ring (Fig. 1) are very interesting from the point of view of theory. Although they do not meet the aromaticity criteria due to the *peri* structure of the entire π-system,[1] these heterocycles nevertheless should be antiaromatic along the perimeter, decaying into a 12π-electron thiopentadiene fragment and a lone pair of the nodal nitrogen atom, which is not conjugated with the perimeter.

The literature describes two examples of the synthesis of these tricycles,[2] and both approaches included path *a* (Fig. 1) of constructing the 5+6+6 system, that is, the attachment of a five-membered fragment. Relatively recently, we proposed a simple method for the synthesis of indolizine-5-thiols, which proved to be stable in the form of 3*H*-indolizyl-5-thiones.[3] Such thiones were capable of *S*-alkylation by the action of MeI. The indicated type of tautomerism made it possible to expect the manifestation of binucleophilic properties by these thiones in reactions with α-halogencarbonyl compounds (across the S atom and the C-3 position), and therefore, suggested the possibility of an alternative cyclization of the thiazinoindolizine system with the closure of the six-membered ring *via* path *b* (Fig. 1). This work is devoted to the study of this approach.

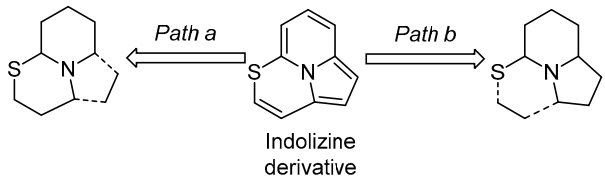
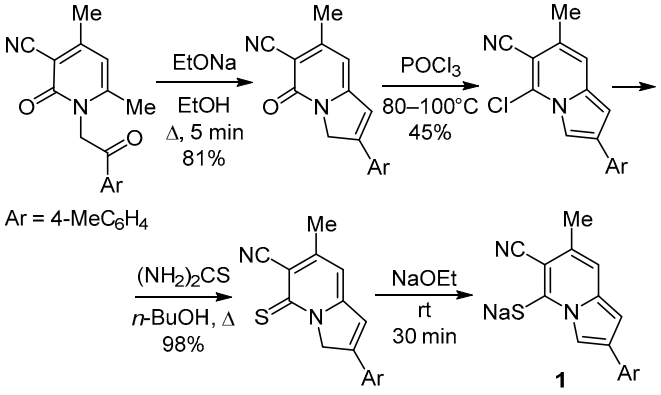


Figure 1. Possible routes for the synthesis of indolizines annulated at *peri* positions 3 and 5 with the thiazine ring.

The target 7-methyl-5-thioxo-3,5-dihydroindolizine-6-carbonitrile was synthesized in three steps from the available *N*-phenacyl derivative of pyridin-2-one, easily obtained by phenacylation of the Guareschi pyridone (Scheme 1). All steps – the closure of the 7-methyl-5-oxo-3,5-dihydroindolizine-6-carbonitrile ring, its conversion to 5-chloro-7-methylindolizine-6-carbonitrile by the action of $POCl_3$, and the conversion of the latter into 7-methyl-5-thioxo-3,5-dihydroindolizine-6-carbonitrile by the action of thiourea in 98% yield – proceeded smoothly according to the described procedure.[3] To study the subsequent reactions, 7-methyl-5-thioxo-3,5-dihydroindolizine-6-carbonitrile was converted into sodium salt **1**.

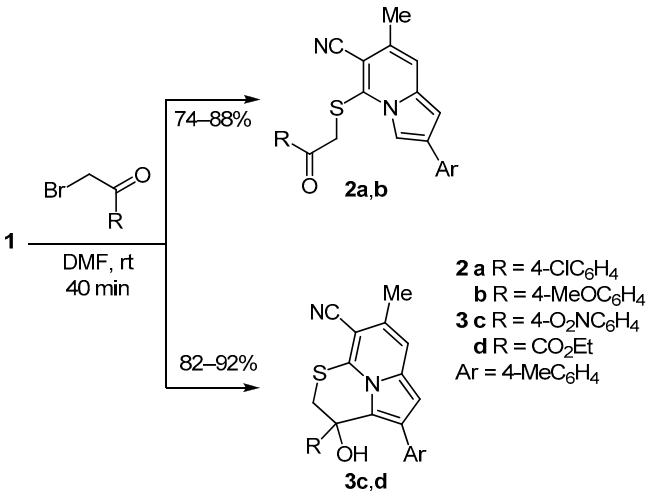
It turned out that the reaction of the sodium salt of thione **1** with 4-chloro- and 4-methoxyphenacyl bromides gave the expected products of *S*-alkylation **2a**,**b**, respectively (Scheme 2). Their ^{1}H NMR spectra contain singlet signals of the SCH_2 group protons at 4.44 and

Scheme 1



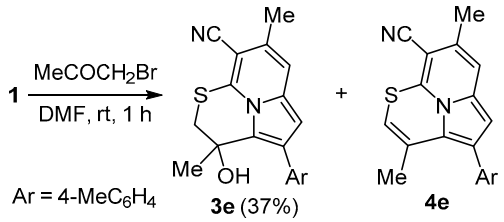
4.47 ppm, respectively, and the IR spectra contain an absorption band of the CO group at 1680 cm^{-1}. The reaction of salt **1** with 4-nitrophenacyl bromide was unusual. Under the same conditions, a new compound **3c** was isolated, which is not an analog of compounds **2a**,**b**. The ^{1}H NMR spectrum of compound **3c** contained only two signals of the protons of the indolizine ring. The signals of the protons of the 4-nitrophenyl ring and the signal of the CH_2 group protons at 3.17 ppm, which, however, was not a singlet, but a doublet of doublets, corresponded to the fragment of the added phenacyl bromide. In addition, a new signal with an intensity of 1H was observed at 3.49 ppm. In the IR spectrum of compound **3c**, the absorption band of the carbonyl group was absent, and an absorption band was observed at 3460 cm^{-1}, which corresponded to the OH group. Based on the obtained data, we concluded that the structure of this compound corresponds to the structure of tricyclic hydrate **3c** (Scheme 2). The reaction of salt **1** with ethyl bromopyruvate under similar conditions led to the formation of adduct **3d**.

Scheme 2



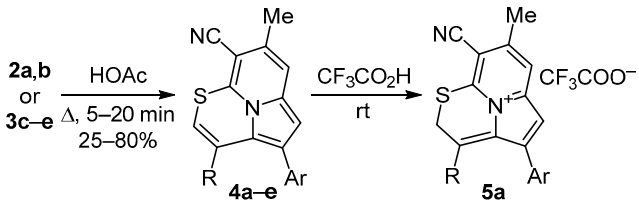
The reaction of salt **1** with bromoacetone proceeded rather unexpectedly: after 30 min, according to TLC data, two new compounds were present in the reaction mixture, giving a blue color with the Ehrlich reagent (which is typical for 1- and/or 3-unsubstituted indolizines). The products were separated by column chromatography. Their ^{1}H NMR and IR spectra unambiguously prove the structure of hydroxy adduct **3e**. The minor component of the mixture could not be isolated individually. According to LC/MS data, the isolated sample contains 78% of a compound with a molecular ion mass of 316, which corresponds to compound **4e**, that is, the product of dehydration of molecule **3e** (Scheme 3).

Scheme 3



We found that the action of acetic acid on compounds **2a**,**b** resulted in cyclodehydration (Scheme 4). It was complete within 5 min of heating, and the resulting products **4a**,**b** precipitated. No further purification was required; the yields of the obtained compounds were 75–80%. The obtained products **4a**,**b** were stable bright-red crystals. Cycloadducts **3c**–**e** were easily dehydrated under the same conditions, leading to analogous compounds **4c**–**e**. Only in the case of carbethoxy derivative **3d** was more prolonged heating (20 min) and chromatographic purification of product **4d** necessary; its yield was low (25%).

Scheme 4



4 a R = 4-ClC_6H_4, **b** R = 4-$MeOC_6H_4$, **c** R = 4-$O_2NC_6H_4$, **d** R = CO_2Et, **e** R = Me; Ar = 4-MeC_6H_4

In the ^{1}H NMR spectra of the obtained compounds **4a**–**e**, an unusual position of the proton signals was observed. Both signals of the protons of the indolizine ring are shifted upfield to 5.91–6.28 ppm, and the signal of the 2-CH proton of the new tricyclic system was in the region of 4.71–5.76 ppm, which is atypical for aromatic systems. This position of the signals is consistent with the data obtained earlier for the homolog of these systems.[2] An explanation of this phenomenon can also be found in the literature.[4] As applied to the systems under investigation, it condenses into the following: the structure of a new class of thiazinoindolizines contains 12 π-electrons along the perimeter, therefore, it should be antiaromatic. Due to the small energy difference between HOMO and LUMO, the triplet level of antiaromatic compounds is located very low, which leads to the appearance of a strong paramagnetic

current and a shift of signals to the region of a stronger field. The same probably explains the bright color usually inherent in antiaromatic compounds. On the other hand, the thiazinoindolizines obtained by us exhibited high stability, which is not typical for antiaromatic compounds (although exceptions are known, for example, cycl[3.3.3]azine).[5] We recorded ^{13}C NMR spectra for thiazinoindolizines **4a**–**e**. The purity of all compounds has been proven by elemental analysis.

The structure of compound **4a** was investigated by X-ray structural analysis (Fig. 2). All three rings of the molecule are located in the same plane, which is typical for the entire class of cyclazines. The length of the C(11)–C(12) bond is 1.34 Å, which indicates its pronounced "double" character.

We studied the protonation of thiazinoindolizines using the example of compound **4a** in a $CDCl_3$ solution by the action of CF_3CO_2H (Scheme 4, Fig. 3). In the ^1H NMR spectrum of the resulting product, a singlet signal with an intensity of 2H appeared at 4.64 ppm, which apparently corresponds to the 2-CH_2 group in cation **5a** that appeared upon protonation. The signals of the H-5 and H-6 protons, in comparison with the spectrum of the starting compound **4a** shifted downfield and had the usual values characteristic of aromatic indolizines. Most probably the obtained cation has structure **5a**. Note that the aza analogs of salt **5a** obtained earlier by us were rather unstable cations.[6] Apparently, the sulfur atom introduces additional stabilization into the antiaromatic system.

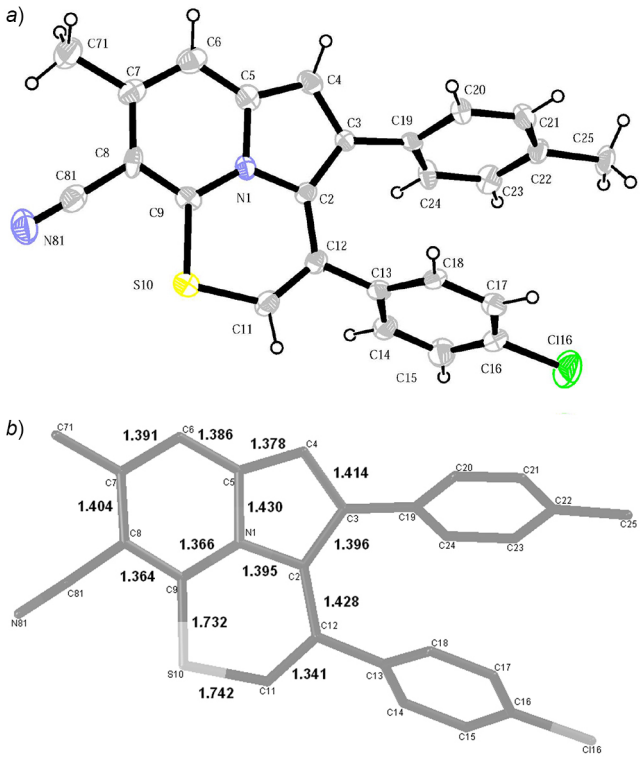


Figure 2. *a*) Molecular structure of compound **4a** with atoms represented as thermal vibration ellipsoids of 50% probability. *b*) Selected bond lengths in the structure of compound **4a** (indicated in Å).

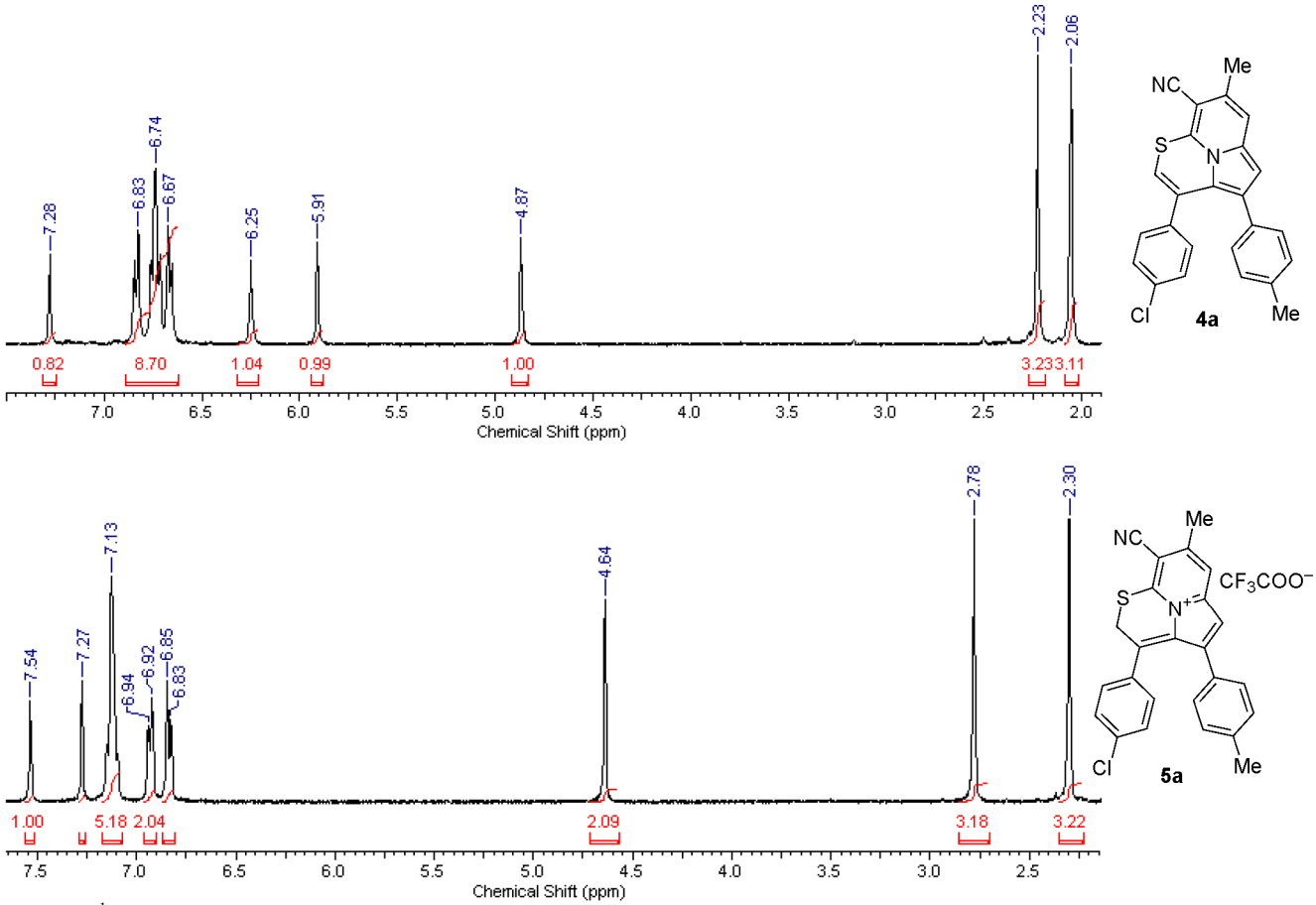
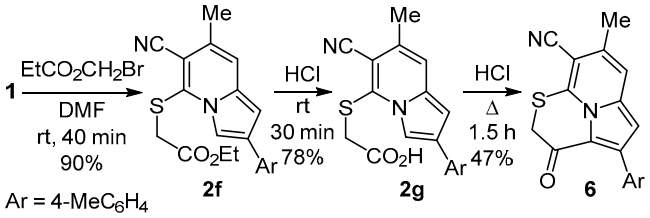


Figure 3. ^1H NMR spectrum of starting compound **4a** in $CDCl_3$ (top); spectrum of compound **5a** in CF_3CO_2H (bottom).

In order to expand the range of bielectrophiles, ethyl bromoacetate was introduced into the reaction with salt **1**. The reaction was carried out at room temperature in DMF. After 30 min, a precipitate of alkylation product, compound **2f**, formed in 90% yield (Scheme 5). In the ^{1}H NMR spectrum of the obtained product, all signals of the protons of the indolizine fragment, as well as the CH_2 group (at 3.75 ppm) and the carbethoxy group were observed.

Scheme 5

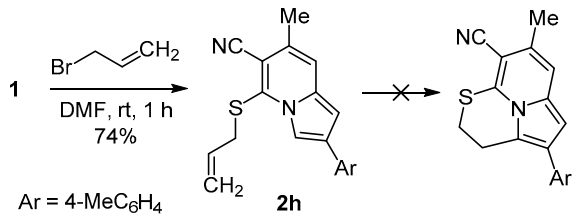


Acid-catalyzed cyclization of ethyl mercaptoacetate **2f** was carried out in HCl. At room temperature, a new compound **2g** was formed, the ^{1}H NMR spectrum of which differs from the spectrum of compound **2f** only by the absence of the signals of the protons of the ester group. The IR spectrum contained absorption bands of the carboxyl group (1720 cm^{-1}) and the OH group (3200 cm^{-1}). The absorption band of the cyano group remained unchanged (2235 cm^{-1}). Obviously, hydrolysis of the ester group to acid **2g** occurred. Further heating of this compound with concentrated HCl under reflux led to its cyclization to the corresponding oxothiazinoindolizine **6**. Its structure was unambiguously established by IR and ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of this compound contains only two signals of indolizine (7.27 and 6.67 ppm), the signal of the H-3 proton (the most downfield one) is absent. The IR spectrum of compound **6** contains an absorption band of the carbonyl group in the 1650 cm^{-1} region. Even with such prolonged heating under reflux in HCl, no hydrolysis of the cyano group occurred, which follows from the IR spectrum of compound **6** (ν_{CN} 2230 cm^{-1}). It should be noted that intramolecular acylation in the mercaptoacetic derivative of indolizine **2g** proceeds easily and does not require preliminary activation of the acid group in the molecule (for example, by conversion to the corresponding anhydride or acid chloride). In this case, hydrolysis of the nitrile substituent does not occur.

In order to obtain a saturated analog of thiazinoindolizine, the synthesis of indolizine 5-allylthio derivative **2h** was carried out (Scheme 6). However, we failed to carry out its subsequent cyclization. By the action of various acidic agents (HCl, H_2SO_4, $BF_3{\cdot}Et_2O$, TfOH, HCl in 1,4-dioxane, $TiCl_4$), there was either no conversion of compound **2h** (at low temperatures) or decomposition of compound **2h** (upon heating).

We have developed a simple and convenient method for the alkylation of an indolizinethione salt, which was used to obtain 5-alkylthio derivatives of indolizine containing carbonyl, carboxyl, and allyl groups in the side chain. In the case of some α-halo ketones, alkylation was accompanied by spontaneous cyclization of the carbonyl group at

Scheme 6



position 3 of indolizine to form hydroxy adducts. By the action of acetic acid on the alkylation products of 7-methyl-2-(4-methylphenyl)-5-sulfanylindolizine-6-carbonitrile representatives of the thiazinoindolizine class, including those containing a functional group (carboxyethyl), were successfully obtained. The structure of thiazinoindolizines was studied by X-ray structural analysis, and their protonation was studied by ^{1}H NMR spectroscopy. We found that the cyclization of ethyl [6-cyano-7-methyl-2-(4-methylphenyl)indolizin-5-yl]sulfanylacetate into the oxo derivative of thiazinoindolizine occurs upon heating under reflux in an aqueous solution of a mineral acid and includes the step of hydrolysis of the ester group.

Experimental

IR spectra were registered on a UR-20 spectrometer in petroleum jelly. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker AM 400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ or DMSO-d_6, with TMS as internal standard. Liquid chromato-mass spectrometry (LC/MS) analysis was performed by the chemical ionization method on an Agilent Technologies 11000 LCMSD system equipped with an ELSD (PL-ELS-1000) mass detector. Elemental analysis was performed on an Elementar vario MICRO cube CHN-analyzer. Melting points were determined on an Electrothermal IA910 apparatus. Monitoring of the reaction progress and assessment of the purity of synthesized compounds were done by TLC on Silufol UV-254 plates. Visualization under UV light (at 254 and 365 nm), in some cases also with Ehrlich reagent, ninhydrin, iodine vapor, or potassium permanganate sulfuric acid solution. Chromatographic separation was carried out on columns using Merck silica gel (40–60, 60–100 μm). In some cases, a Büchi Sepacor preparative chromatograph was used for separation.

All solvents used in the work were purified by distillation.

4,6-Dimethyl-1-[2-(4-methylphenyl)-2-oxoethyl]-2-oxo-1,2-dihydropyridine-3-carbonitrile (42%),[7] **7-methyl-2-(4-methylphenyl)-5-oxo-3,2-dihydroindolizine-6-carbonitrile** (81%), **5-chloro-7-methyl-2-(4-methylphenyl)-indolizine-6-carbonitrile** (45%), **7-methyl-2-(4-methylphenyl)-5-thioxo-3,5-dihydroindolizine-6-carbonitrile** (98%) were obtained by known procedures.[3]

Synthesis of 7-methyl-2-(4-methylphenyl)-5-thioxo-3,5-dihydroindolizine-6-carbonitrile sodium salt (1). 7-Methyl-5-thioxo-3,5-dihydroindolizine-6-carbonitrile was added to a solution of EtONa, prepared from NaH (1 equiv) and EtOH. The mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced

pressure to obtain dry sodium salt **1**, which was used for further conversions without purification.

Synthesis of compounds 2a,b, 3c (General method). Anhydrous DMF (10 ml) and phenacyl bromide (0.79 mmol, 1.1 equiv) were added to sodium salt **1**. The mixture was stirred at room temperature for 40 min, then poured into H_2O and left overnight. The yellow precipitate that formed the next day was filtered off, washed with a small amount of petroleum ether, and air-dried.

5-{[2-(4-Chlorophenyl)-2-oxoethyl]sulfanyl}-7-methyl-2-(4-methylphenyl)indolizine-6-carbonitrile (2a). Yield 0.23 g (74%). Mp 143–144°C. IR spectrum, ν, cm^{-1}: 2235 (CN), 1680 (CO), 1615 (Ar). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 8.00 (1H, s, H-3); 7.79–7.77 (2H, m, H Ar); 7.53–7.51 (2H, m, H Ar); 7.40–7.38 (2H, m, H Ar); 7.22–7.24 (3H, m, H Ar, H-8); 6.78 (1H, s, H-1); 4.44 (2H, s, SCH_2); 2.42 (3H, s, CH_3); 2.40 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.2; 21.2; 39.3; 96.3; 106.9; 110.2; 113.0; 114.3; 118.0; 127.5; 127.8; 128.1; 129.9; 130.9; 132.5; 133.2; 135.5; 137.8; 141.9; 158.3; 193.0. Found, %: C 69.45; H 4.38; N 6.70. $C_{25}H_{19}ClN_2OS$. Calculated, %: C 69.68; H 4.44; N 6.50.

5-{[2-(4-Methoxyphenyl)-2-oxoethyl]sulfanyl}-7-methyl-2-(4-methylphenyl)indolizine-6-carbonitrile (2b). Yield 0.45 g (88%). Mp 149–150°C. IR spectrum, ν, cm^{-1}: 2235 (CN), 1680 (CO), 1600 (Ar). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 8.04 (1H, s, H-3); 7.87–7.85 (2H, m, H Ar); 7.54–7.52 (2H, m, H Ar); 7.22–7.24 (3H, m, H Ar, H-8); 6.91–6.89 (2H, m, H Ar); 6.78 (1H, s, H-1); 4.47 (2H, s, SCH_2); 3.86 (3H, s, OCH_3); 2.43 (3H, s, CH_3); 2.39 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.2; 21.2; 39.8; 55.6; 99.6; 107.4; 110.5; 114.0; 116.6; 118.9; 126.3; 127.9; 129.6; 130.9; 131.1; 132.3; 133.6; 135.2; 137.3; 157.1; 164.2; 191.4. Found, %: C 73.40; H 5.17; N 6.75. $C_{26}H_{22}N_2O_2S$. Calculated, %: C 73.21; H 5.20; N 6.57.

3-Hydroxy-7-methyl-4-(4-methylphenyl)-3-(4-nitrophenyl)-2,3-dihydro[1,3]thiazino[4,3,2-*cd*]indolizine-8-carbonitrile (3c). Yield 0.49 g (92%). Mp 139–140°C. IR spectrum, ν, cm^{-1}: 3460 (OH), 2240 (CN), 1620, 1535, 1360. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.91–7.89 (2H, m, H Ar); 7.43–7.41 (2H, m, H Ar); 7.22 (1H, s, H-6); 7.12–7.10 (2H, m, H Ar); 6.89–6.87 (2H, m, H Ar); 6.59 (1H, s, H-5); 3.49 (1H, s, OH); 3.17 (2H, dd, J = 13.1, J = 11.3, SCH_2); 2.51 (3H, s, CH_3); 2.20 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.3; 21.2; 39.6; 63.8; 90.4; 96.5; 105.4; 111.7; 114.5; 123.6; 125.4; 127.6; 128.3; 133.8; 134.4; 135.0; 138.7; 148.2; 151.9; 155.8. Found, %: C 68.13; H 4.39; N 9.52. $C_{25}H_{19}N_3O_3S$. Calculated, %: C 68.01; H 4.34; N 9.52.

Ethyl 8-cyano-3-hydroxy-7-methyl-4-(4-methylphenyl)-2,3-dihydro[1,3]thiazino[4,3,2-*cd*]indolizine-3-carboxylate (3d). DMF (10 ml) and ethyl bromopyruvate (0.3 ml, 2.4 mmol) were added to salt **1** prepared from 7-methyl-5-thioxo-3,5-dihydroindolizine-6-carbonitrile (0.33 g, 1.2 mmol). The mixture was stirred at room temperature for 30 min. Then it was poured into H_2O, the formed yellow precipitate was filtered off, washed with H_2O followed by a small amount of petroleum ether, and air-dried. Yield 0.39 g (82%). Mp 111–112°C. IR spectrum, ν, cm^{-1}: 3465 (OH), 2230, 1720, 1620. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.43–7.41 (2H, m, H Ar); 7.23–7.21 (2H, m, H Ar); 7.16 (1H, s, H-6); 6.57 (1H, s, H-5); 4.38 (1H, s, OH); 3.76–3.78 (1H, m, $C\underline{H}_2CH_3$); 3.40–3.42 (1H, m, $C\underline{H}_2CH_3$); 3.29 (1H, d, J = 13.1, SCH_2); 3.05 (1H, d, J = 13.1, SCH_2); 2.48 (3H, s, CH_3); 2.40 (3H, s, CH_3); 0.86–0.88 (3H, m, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.4; 20.0; 21.2; 38.9; 61.5; 65.7; 90.7; 96.5; 106.8; 111.6; 114.3; 125.2; 128.7; 130.98; 132.0; 133.9; 135.4; 138.8; 155.5; 169.2. Found, %: C 67.22; H 5.32; N 7.25. $C_{22}H_{20}N_2O_3S$. Calculated, %: C 67.33; H 5.14; N 7.14.

3-Hydroxy-3,7-dimethyl-4-(4-methylphenyl)-2,3-dihydro[1,3]thiazino[4,3,2-*cd*]indolizine-8-carbonitrile (3e). Anhydrous DMF (15 ml) and bromoacetone (0.3 ml, 3.6 mmol) were added to salt **1** prepared from 7-methyl-5-thioxo-3,5-dihydroindolizine-6-carbonitrile (0.5 g, 1.8 mmol). The mixture was stirred at room temperature for 1 h, then poured into H_2O. The formed yellow precipitate was filtered off, washed with H_2O, and air-dried. The product was isolated by column chromatography on silica gel using gradient elution, eluent petroleum ether – EtOAc. Yield 0.22 g (37%). Mp 135–136°C (decomp.). IR spectrum, ν, cm^{-1}: 3380 (OH), 2225 (CN), 1620 (Ar). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.55–7.53 (2H, m, H Ar); 7.11 (1H, s, H-6); 7.28–7.26 (2H, m, H Ar); 6.48 (1H, s, H-5); 3.06–3.08 (2H, m, SCH_2); 2.87 (1H, s, OH); 2.47 (3H, s, CH_3); 2.45 (3H, s, CH_3); 1.60 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 19.9; 21.3; 26.7; 38.3; 67.1; 103.0; 103.7; 114.6; 121.6; 126.5; 129.0; 129.9; 131.1; 133.5; 132.9; 137.3; 137.4; 144.5. Found, %: C 72.00; H 5.30; N 8.18. $C_{20}H_{18}N_2OS$. Calculated, %: C 71.83; H 5.43; N 8.38.

Synthesis of compounds 4a–e (General method). AcOH (3 ml) was added to compound **2a**,**b** or **3c**–**e**. The mixture was brought to a boil. After cooling to room temperature, the red precipitate was filtered off, washed with H_2O, and air-dried.

3-(4-Chlorophenyl)-7-methyl-4-(4-methylphenyl)[1,3]-thiazino[4,3,2-*cd*]indolizine-8-carbonitrile (4a) was obtained from compound **2a** (50 mg, 0.12 mmol). Yield 40 mg (80%). Mp 254–255°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.84–6.82 (2H, m, H Ar); 6.72–6.76 (4H, m, H Ar); 6.66–6.64 (2H, m, H Ar); 6.25 (1H, s, H-6); 5.91 (1H, s, H-5); 4.87 (1H, s, 2-CH); 2.23 (3H, s, CH_3); 2.05 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 18.8; 21.2; 92.6; 102.8; 113.8; 114.4; 115.4; 121.2; 127.9; 128.8; 129.1; 129.7; 130.1; 131.4; 132.9; 135.0; 136.0; 138.4; 141.0. Found, %: C 72.58; H 3.99; N 6.82. $C_{25}H_{17}ClN_2S$. Calculated, %: C 72.72; H 4.15; N 6.78.

3-(4-Methoxyphenyl)-7-methyl-4-(4-methylphenyl)[1,3]-thiazino[4,3,2-*cd*]indolizine-8-carbonitrile (4b) was obtained from compound **2b** (300 mg, 0.7 mmol). Yield 0.21 g (75%). Mp 190°C (decomp.). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.72–6.70 (6H, m, H Ar); 6.35–6.33 (2H, m, H Ar); 6.24 (1H, s, H-6); 5.92 (1H, s, H-5); 4.83 (1H, s, 2-CH); 3.65 (3H, s, OCH_3); 2.19 (3H, s, CH_3); 2.05 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 19.7; 21.0; 55.3; 92.5; 102.9; 104.3; 113.1; 114.8; 115.5; 120.4; 127.9; 128.9; 131.6; 132.2; 134.7; 135.9; 143.5; 159.3. Found, %:

C 76.50; H 4.99; N 6.70. $C_{26}H_{20}N_2OS$. Calculated, %: C 76.44; H 4.93; N 6.86.

7-Methyl-4-(4-methylphenyl)-3-(4-nitrophenyl)[1,3]-thiazino[4,3,2-*cd*]indolizine-8-carbonitrile (4c) was obtained from compound **3c** (0.3 g, 0.7 mmol). Yield 0.23 g (76%). Mp 235–236°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.74–7.72 (2H, m, H Ar); 6.98–6.97 (2H, m, H Ar); 6.71–6.69 (4H, m, H Ar); 6.28 (1H, s, H-6); 5.93 (1H, s, H-5); 5.00 (1H, s, 2-CH); 2.14 (3H, s, CH_3); 2.10 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 18.9; 21.3; 92.7; 102.8; 113.9; 114.4; 115.1; 122.4; 123.5; 127.9; 129.0; 130.4; 130.1; 131.8; 135.9; 136.2; 138.2; 138.6; 141.1; 143.6; 147.6. Found, %: C 70.83; H 4.02; N 9.80. $C_{25}H_{17}N_3O_2S$. Calculated, %: C 70.90; H 4.05; N 9.92.

Ethyl 8-cyano-7-methyl-4-(4-methylphenyl)[1,3]thiazino-[4,3,2-*cd*]indolizine-3-carboxylate (4d) was obtained from compound **3d** (0.25 g, 0.64 mmol) (heating under reflux for 20 min, purification by column chromatography on silica gel, eluent petroleum ether – EtOAc, 10:1). Yield 60 mg (25%). Mp 116–117°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.16–7.14 (2H, m, H Ar); 7.11–7.09 (2H, m, H Ar); 6.25 (1H, s, H-6); 5.97 (1H, s, H-5); 5.76 (1H, s, 2-CH); 3.49 (2H, q, *J* = 7.0, CH_2); 2.35 (3H, s, CH_3); 2.04 (3H, s, CH_3); 0.83 (3H, t, *J* = 7.2, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.1; 17.6; 21.2; 60.5; 92.4; 102.9; 113.5; 114.9; 116.9; 121.9; 127.7; 128.7; 129.3; 131.8; 135.1; 136.8; 137.0; 139.6; 161.9. Found, %: C 70.38; H 4.91; N 7.35. $C_{22}H_{18}N_2O_2S$. Calculated, %: C 70.57; H 4.85; N 7.48.

3,7-Dimethyl-4-(4-methylphenyl)[1,3]thiazino[4,3,2-*cd*]-indolizine-8-carbonitrile (4e) was obtained from compound **3e** (0.1 g, 0.3 mmol). Yield 62 mg (69%). Mp 183–184°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.16–7.14 (4H, m, H Ar); 6.16 (1H, s, H-6); 5.77 (1H, s, H-5); 4.71 (1H, s, 2-CH); 2.38 (3H, s, CH_3); 2.00 (3H, s, CH_3); 1.39 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.9; 17.8; 21.2; 92.0; 101.7; 113.6; 113.9; 114.5; 122.9; 127.8; 129.3; 131.4; 134.9; 135.3; 136.0; 136.0; 137.2; 138.7. Found, %: C 75.95; H 5.02; N 8.70. $C_{20}H_{16}N_2S$. Calculated, %: C 75.92; H 5.10; N 8.85.

3-(4-Chlorophenyl)-8-cyano-7-methyl-4-(4-methyl-phenyl)-2*H*-[1,3]thiazino[4,3,2-*cd*]indolizin-9-ium trifluoroacetate (5a). Compound **4a** (9 mg) was dissolved in $CDCl_3$ in an NMR vial, and CF_3CO_2H (1 drop) was added. The orange color of the solution changes to bright-red. ^{1}H NMR spectrum (CF_3CO_2H), δ, ppm: 7.54 (1H, s, H-6); 7.14–7.12 (5H, m, H Ar, H-5); 6.93–6.91 (2H, m, H Ar); 6.85–6.83 (2H, m, H Ar); 4.64 (2H, s, SCH_2); 2.78 (3H, s, CH_3); 2.30 (3H, s, CH_3).

Ethyl {[6-cyano-7-methyl-2-(4-methylphenyl)indolizin-5-yl]sulfanyl}acetate hemihydrate (2f). Anhydrous DMF (10 ml) and ethyl bromoacetate (0.32 ml, 2.9 mmol) were added to salt **1** prepared from 7-methyl-5-thioxo-3,5-dihydroindolizine-6-carbonitrile (0.4 g, 1.4 mmol). The mixture was stirred at room temperature for 40 min, then poured into H_2O. The formed yellow precipitate was filtered off, washed with H_2O followed by a small amount of petroleum ether, and air-dried. Yield 0.46 g (90%). Mp 115–116°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.07 (1H, s, H-3); 7.59–7.57 (2H, m, H Ar); 7.27 (1H, s, H-8); 7.25–7.23 (2H, m, H Ar); 6.80 (1H, s, H-1); 4.10 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 3.75 (2H, s, SCH_2); 2.46 (3H, s, CH_3); 2.41 (3H, s, CH_3); 1.14 (3H, t, *J* = 7.2, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.0; 18.4; 21.2; 36.2; 61.2; 93.7; 105.8; 112.5; 114.5; 118.6; 127.5; 129.8; 129.9; 133.1; 135.4; 137.7; 157.1; 169.4. Found, %: C 67.50; H 5.69; N 7.45. $C_{21}H_{20}N_2O_2S\cdot0.5H_2O$. Calculated, %: 67.54; H 5.67; N 7.50.

{6-Cyano-[7-methyl-2-(4-methylphenyl)indolizin-5-yl]sulfanyl}acetic acid (2g). HCl (2 ml) was added to compound **2f** (0.1 g, 0.3 mmol). The mixture was stirred at room temperature for 30 min. Compound **2f** gradually dissolved, and a precipitate formed. The mixture was poured into H_2O. The formed yellow precipitate was filtered off, washed with H_2O, and air-dried. Yield 70 mg (78%). Mp 145–146°C. IR spectrum, ν, cm^{-1}: 3200 (OH), 2235 (CN), 1720, 1620. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.26 (1H, s, H-3); 7.50 (1H, s, H-8); 7.12–7.10 (2H, m, H Ar); 7.10–7.08 (2H, m, H Ar); 6.99 (1H, s, H-1); 3.92 (2H, s, CH_2); 2.52 (3H, s, CH_3); 2.36 (3H, s, CH_3). Found, %: C 68.10; H 4.95; N 8.44. $C_{19}H_{16}N_2O_2S$. Calculated, %: C 67.84; H 4.79; N 8.33.

7-Methyl-4-(4-methylphenyl)-3-oxo-2,3-dihydro[1,3]-thiazino[4,3,2-*cd*]indolizine-8-carbonitrile hydrate (6). HCl (5 ml) was added to indolizine **2g** (0.2 g, 0.5 mmol), and the mixture was heated under reflux for 1.5 h. The mixture was cooled to room temperature and poured into H_2O. The formed precipitate was filtered off, washed with H_2O, and air-dried. The product was chromatographed twice on silica gel, eluent petroleum ether–EtOAc, 1:1. Yield 80 mg (47%). Mp 175–176°C. IR spectrum, ν, cm^{-1}: 1615, 1650, 2230. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.69–7.67 (2H, m, H Ar); 7.28–7.26 (3H, m, H Ar, H-6); 6.67 (1H, s, H-5); 3.71 (2H, s, CH_2); 2.55 (3H, s, CH_3); 2.43 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 19.1; 21.2; 40.0; 97.9; 113.0; 114.8; 119.2; 123.3; 126.8; 127.2; 131.9; 136.6; 153.0; 181.4. Found, %: C 67.81; H 4.69; N 8.35. $C_{19}H_{14}N_2OS\cdot H_2O$. Calculated, %: 67.84; H 4.79; N 8.33.

7-Methyl-2-(4-methylphenyl)-5-(prop-2-en-1-yl-sulfanyl)indolizine-6-carbonitrile (2h). Anhydrous DMF (10 ml) and allyl bromide (0.12 ml, 1.4 mmol) were added to salt **1** prepared from 7-methyl-5-thioxo-3,5-dihydroindolizine-6-carbonitrile (0.2 g, 0.7 mmol). The mixture was stirred at room temperature for 1 h, then worked up as in the case of compound **2f**. Yield 0.17 g (74%). Yellow powder. Mp 115–116°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.13 (1H, s, H-3); 7.65–7.64 (2H, m, H Ar); 7.31–7.29 (3H, m, H Ar, H-8); 6.83 (1H, s, H-1); 5.97–5.95 (1H, m, CH); 5.01–4.99 (2H, m, CH_2); 3.77 (2H, d, *J* = 7.2, CH_2); 2.50 (3H, s, CH_3); 2.45 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 19.1; 21.2; 40.0; 97.9 (2C); 113.0; 114.8; 119.2; 123.3; 126.8; 127.2; 131.9; 132.5; 136.6; 153.0; 181.4. According to elemental analysis data, contains *N*,*N*-dimethylformamide. Found, %: C 73.60; H 6.00; N 9.50. $3C_{20}H_{18}N_2S\cdot C_3H_7NO$. Calculated, %: 73.58; H 5.98; N 9.53.

X-ray structural analysis of compound 4a. Single crystals of compound **4a** grown from MeCN were selected using a microscope. Experimental intensities of diffraction reflections were obtained at room temperature on a CAD-4

automatic diffractometer (CuKα radiation, graphite monochromator, ω-scanning). The unit cell parameters were determined and refined from 25 reflections in the range of θ angles of 30–35°. The primary processing of the experimental data array was carried out using the WinGX software package;[8a] all subsequent calculations were performed within the SHELX software package.[8b] The crystal structure was solved by the direct methods with subsequent refinement of the positional and thermal parameters in the anisotropic approximation for all non-hydrogen atoms. The full set of X-ray structural data for compound **4a** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1988864).

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