Received: 7 June 2018 | Revised: 16 October 2018 | Accepted: 17 October 2018

DOI: 10.1002/hc.21451

RESEARCH ARTICLE

WILEY Heteroatom Chemistry

Condensations based on 5-(indol-3-yl)-pyrrolidin-2-thiones

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Funding information
Russian Foundation for Basic Research, Grant/Award Number: 18-03-00703a. and project 15-29-05785 ofi_m

Abstract

New activated indolylpyrrolidones—their methylthiopyrrolinium salts—in the reactions with several CH-acids were studied. 2-Nitromethylene- and 2-dicyanomethyle neindolylpyrrolidines were obtained from 5-indolyl-2-methylthiopyrrolinium salts with good yields. The reduction in these nitro compounds yields the respective aminomethylpyrolidines. The rigid structure of the starting compounds has significant stereoelectronic requirements of nucleophilic agents.

1 | INTRODUCTION

Functional derivatives of known heterocyclic compounds such as pyrroles and indoles are of interest as a promising biologically active substance. Their skeleton is represented in a number of natural compounds such as proline, tryptophan, nicotine, and rozevin.[1] Most of these derivatives are found to bear diverse biological properties including nootropic (Nootropil[2]), analgetic and anti-inflammatory (Indomethacin[3]), and antihypertensive and antianginal (Pinadol, Sandonorm[4]) activities. In recent years, demand for modification of these biologically significant molecules has increased.[5–7]

Previously, we found a convenient method of preparative synthesis of 5-(indolyl-3)-pyrrolidones[8] and showed reduced reactivity of the carbonyl group of these compounds in organic synthesis.[9] Synthesized derivatives of indole were of interest in terms of pharmacology, by analogy with the known structures.[10,11]

Taking into account the weakness of the reported methods for the preparation of the derivatives of 5-(indolyl-3)-pyrrolidones, we have studied the reactivity of thioiminium salts obtained by us from basis of indolylpyrrolidones **1** as their activated derivatives and developed the useful protocol for efficient synthesis of several new N-containing functional derivatives in the side chain. Previously, such activated derivatives (thioiminium salts) were commonly used in the chemistry of amides and lactams.[12,13]

2 | RESULT AND DISCUSSIONS

5-Indolylpyrrolidinethiones **2** were obtained by thionation of indolylpyrrolidones **1** with Lawesson's reagent or phosphorus

Contract grant sponsor: Russian Foundation for Basic Research.

Contract grant number: 18-03-00703a.

Contract grant number: 15-29-05785.

pentasulfide freshly prepared. In the latter case, we have developed a simple convenient method for isolation of pyrrolidinethiones **2**, which gives good yields (60%-80%). Spectral characteristics of thions **2** (namely, shift of the signals in the ^{1}H NMR spectra of pyrrolidine ring protons was downfield) indicate a significant contribution of iminothiolate mesomeric structure in indolylpyrrolidinethiones **2** system. Alkylation of thiones **2** was performed with triethyloxonium borofluoride or methyl iodide; moreover, the latter method is preferable because of isolation and purification simplicity. Thioiminium derivatives **3** obtained were used without further purification.

Reduction in thioiminium salts obtained **3** with sodium borohydride affords indolylpyrrolidines **4** with good yields (at least 60%) unlike most cases of the corresponding pyrrolidone reductions described by us previously.[9] Compounds **4a-c** obtained by this method are identical to the previously synthesized ones in.[9] Thus, indolylpyrrolidines obtained by reduction in pyrrolidone thioiminium derivatives are preparatively useful (Scheme 1).

Interaction thioiminium salts **3** with *p*-toluidine, contrary to expectations, do not lead to the corresponding amidines: During reaction with salt **3f** in alcohol, only corresponding pyrrolidone **1f** and dealkylation product thione **2f** are formed in tetrahydrofuran. The latter process is the same as known[14,15] intramolecular rearrangement of S-alkylthioiminium salts into N-alkylthioamides.

Interaction of salts **3** with nitromethane has proceeded more successfully. The reaction easily proceeds both in excess of nitromethane and methylene chloride in the presence of triethylamine. Despite the fact that small amount of thioiminium salt decomposition occurs with formation of indolylpyrrolidones **1**, indolylpyrrolidone nitrometylene derivatives **5a-f** are obtained in good yields as yellow crystalline substances are stable enough and have characteristic absorption of the nitro group in the IR spectra (~1575, 1355 cm^{-1}) and their NMR spectra correspond to the structure.

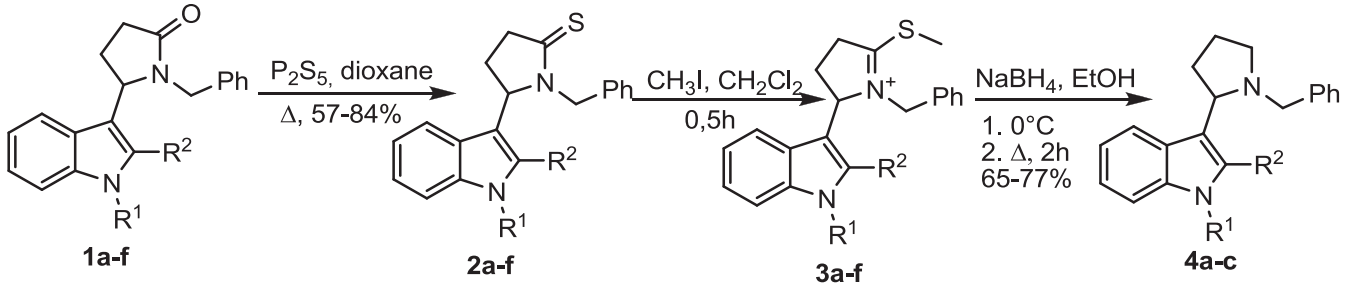
Reduction in nitrovinyl derivatives **5** with lithium aluminum hydride according to[16] yields the corresponding 5-aminomethyl-2-indolylpyrrolidines **6a,f**, identified as hydrochlorides, as well as **6e** identified as phenylthiocarbamoyl derivative because the amine hydrochloride one is very hygroscopic. Attempts at selective reduction in nitrovinyl group with sodium borohydride under various conditions[17] were unsuccessful. No reduction occurred, and starting compounds **5** and their decomposition products (the corresponding indolylpyrrolidones **1**) were identified.

Interaction of the thioiminium salt **3f** with nitroacetic ester both in the presence of triethylamine and with the KF catalysis (herein after under nonaqueous environment), despite its high CH-acidity in accordance with the special stereoelectronic effects,[18] has proceeded ambiguously: Along with a minor amount of the expected nitrovinyl product **7f**, preferential formation of the corresponding indolylpyrrolidone **1f** was observed. The spectral characteristics of the compound **7f** correspond to its structure (Scheme 2).

Conversely, reaction of thioiminium salt **3** with malononitrile under KF catalysis proceeds easily with good yields (up to 70%), as in the case of 5-unsubstituted pyrrolidones,[19] and gives the corresponding methylendinitriles **8a**,**c**,**e**,**f**. The IR spectra of compounds **8** have CN absorption bands of medium intensity at 2240-2260 cm^{-1} and NMR spectra correspond to the structures of dicyanometylenepyrrolidines.

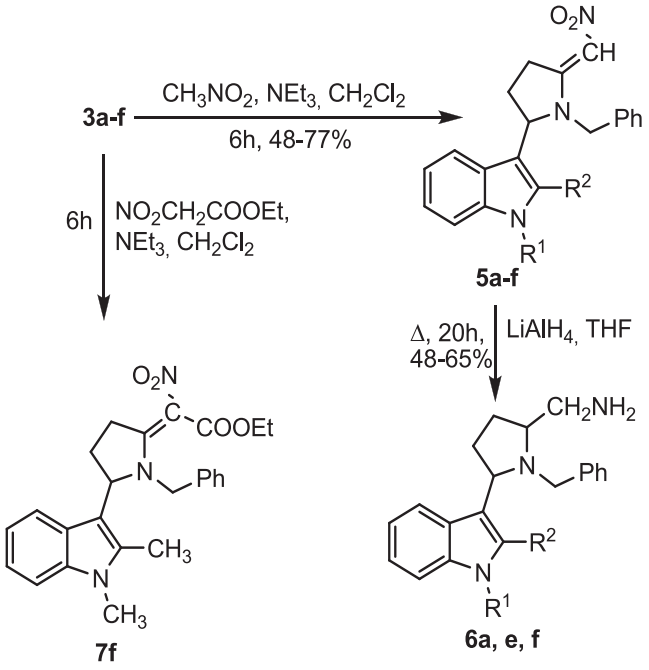
Interaction of the thioiminium salt **3f** with cyanoacetic ester under KF catalysis leads to the corresponding pyrrolidone **1f** formation, along with the expected product **9f** in trace amounts. We have conducted this transformation more successfully in the presence of triethylamine, from which cyanoacetate **9f** and pyrrolidone **1f** are formed in approximately equal amounts. Ester **9f** was isolated by chromatography, and its IR spectrum has absorption bands as the CN- (2250 cm^{-1}) and COOEt-groups (1760 cm^{-1}); ^{1}H NMR spectrum corresponds to the structure of cyanoacetate **9f** (Scheme 3).

Attempts to perform thioiminium salts **3e** and **3f** reactions with other active C-nucleophilic compounds containing two large volume O-containing groups (malonic and acetoacetic esters) were unsuccessful. In various reaction conditions, such as KF and triethylamine catalysis, immobilization on the surface of adsorbents-catalysts (Al_2O_3, Al_2O_3/KF; Al_2O_3/NaOH, without a solvent or in an inert solvent) led only to the formation of the corresponding indolylpyrrolidones **1**. Attempts to react salts **3e** and **3f** with other easily enolizated CH-acidic compounds such as 3-methyl-1-phenylpyrazol-5-one and

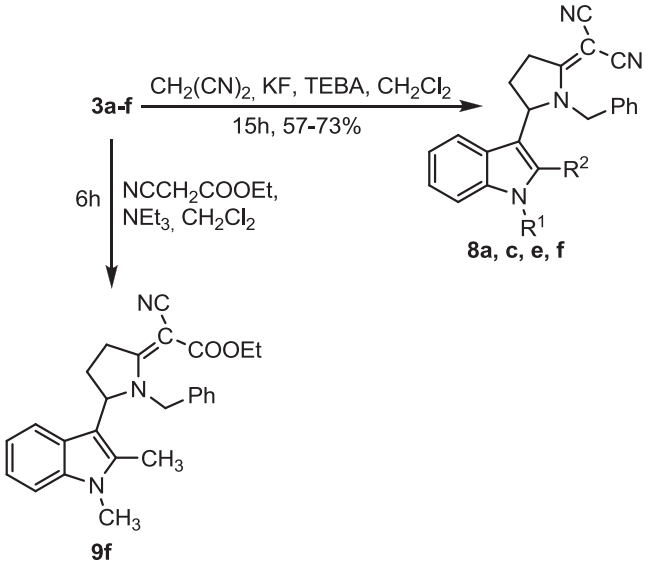


a-c R^1=H; **d-f** R^1=Me; **a,d** R^2=H; **b,e** R^2=*p*-Tol; **c,f** R^2=Me

SCHEME 1 Preparation of indolylpyrrolidines



SCHEME 2 Interaction of the thioiminium salts with nitrocompounds



SCHEME 3 Preparation of cyanoderivatives

oxyindole were unsuccessful as well. In all cases, only pyrrolidones **1** were isolated and the isolated samples of compounds **1** were identical to samples with known structure according to IR and NMR spectra and the absence of the melting point depression.

3 | SUMMARY

Thus, there are significant stereoelectronic effects of the CH-acid agents and the initial compounds structures on the possibility of nucleophilic attack on the "carbonyl" atom of pyrrolidone (in the case of its reduced reactivity). Indeed, only agents that have significant CH-acidity and a small volume, for example, nitromethane and malononitrile, react relatively easily with the thioiminium salt as activated form of pyrrolidone. At the same time, during the attack of oxygen-containing enolizable agents, esters, and similar compounds, the transformation takes place through the oxygen center of the agent and stable pyrrolidone is formed. Its stability is confirmed by the high intensity (more than 90%) of the molecular ion in the mass spectrum of **1f**.[20]

The decrease in the reactivity of both indolylpyrrolidones and their activated derivatives is likely to be in large part due to a set of effects of the benzene nucleus of indole spatially close to the carbonyl or thioiminium center of pyrrolidone, the large size of the S-center, and the influence of the benzyl fragment. This assumption was made on the basis of the X-ray diffraction data (Figures 1 and 2).

4 | EXPERIMENTAL

4.1 | General methods

IR spectra were recorded for Nujol mulls on a UR-20 instrument. ^{1}H and ^{13}C NMR spectra were acquired for $CDCl_3$ solutions at room temperature on Bruker Avance-400 (400 MHz) and Agilent 400-MR (100 MHz) spectrometers, respectively; the internal standard was TMS. Mass spectra were recorded on a Bruker Autoflex II instrument, EI ionization (70 eV). Elemental analysis was performed on a Carlo Erba ER-20 CHN-analyser. Melting points were determined on a Elecrothermal IA9100 apparatus.

4.2 | Materials

Common solvents and reagents were obtained from the Aldrich Chemical Company. Tetrahydrofuran (THF) was distilled from

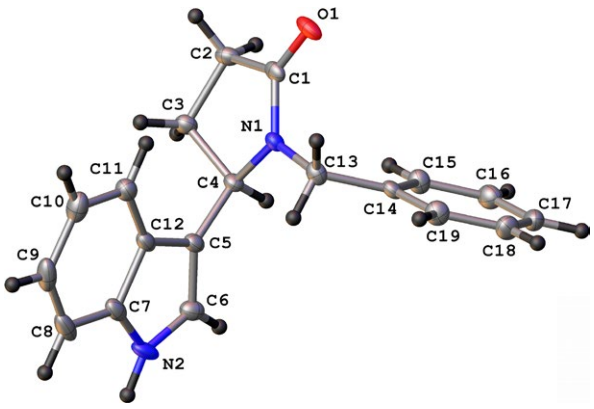


FIGURE 1 General view of 1-benzyl-5-(1*H*-indol-3-yl) pyrrolidin-2-one **1a** in representation of atoms by thermal ellipsoids ($P = 50\%$)

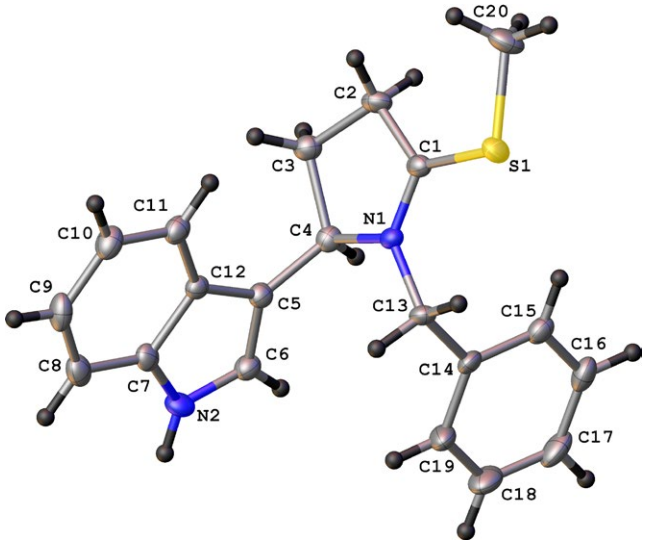


FIGURE 2 General view of cation in 1-benzyl-5-(1*H*-indol-3-yl)-5-(methylthio)-3,4-dihydropyrrolidinium iodide **3a** (obtained as a crystalosolvate with ethanol in the ratio 1:1) in the representation of atoms by thermal ellipsoids ($P = 50\%$)

lithium aluminum hydride in a nitrogen atmosphere prior to use; methylene chloride from calcium hydride. The starting indolylpyrrolidones **1a-f** were synthesized according to method.[8] The reaction mixtures were separated by flash chromatography on a dry column with L grade (5/40) silica gel according to[21]; the eluent was benzene. The reaction progress, column chromatography fractions, and the purity of compounds were controlled by TLC on Silufol UV-254 plates, eluent benzene—EtOAc, 10:1 and 2:1, visualization with iodine vapor or UV light.

4.3 | Synthesis

4.3.1 | 1-Benzyl-5-(1*H*-indol-3-yl) pyrrolidine-2-thiones (general methods)

Method A. 0.35 mmol of Lawesson's reagent was added to a solution of 0.7 mmol 1-benzyl-5-(indol-3-yl)pyrrolidine-2-one (**1**) in 15 mL anhydrous CH_2Cl_2. The reaction was mixed for 1 hour, then was boiled until the starting substance disappeared (TLC control). The reaction mixture was treated with saturated aqueous K_2CO_3 solution during half an hour, the organic layer was decanted and washed with water, and the aqueous layer was extracted with methylene chloride. The organic extracts were combined and dried over anhydrous Na_2SO_4, then were evaporated in vacuum and separated by dry-column flash chromatography (eluent benzene). Substances were obtained as white powders.

Method B. 1.5 mmol of fresh prepared P_2S_5 was added to a solution of 0.7 mmol 1-benzyl-5-(indol-3-yl)pyrrolidine-2-one (**1**) in 15 mL anhydrous dioxane, then was boiled until the starting substance disappeared (TLC control). The liquid layer was decanted, and the P_2S_5 residue was washed with hot dioxane, and then, the solvent was removed by evaporation. Benzene was added to the residue, and the mixture was flowed through a silica gel thin layer, washed several times with water, and dried over anhydrous Na_2SO_4. The benzene was removed by evaporation, and then, ~5 mL ether was added to the oil formed and pulverized until fine-crystalline precipitate was obtained. The precipitate was filtered, washed several times with ether, and dried in a desiccator, and then, the substances were purified by recrystallization from a benzene-petroleum ether, 4:1 mixture.

1-Benzyl-5-(1*H*-indol-3-yl)pyrrolidine-2-thione (2a)
Yield: 62% (method A), 72% (method B), mp 119-121°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.15-2.18; 2.31-2.33 (2H, two m, H-4); 2.54-2.57; 2.64-2.67 (2H, two m, H3); 3.76 (1H, d, $J = 14$, C$\underline{H}_2$Ph); 5.01 (1H, dd, $^1J = 7$, $^2J = 9$, H5); 5.79 (1H, d, $J = 14$, C$\underline{H}_2$Ph); 6.02-7.37 (10H, m, Ar.), 8.50 (1H, wide s, NH). ^{13}C NMR spectrum, δ, ppm: 28.05; 44.2; 48.8; 62.5; 111.9; 113.5; 118.8; 120.4; 122.9; 123.4; 125.0; 127.8; 128.4(2C); 128.6(2C); 135.4; 136.9; 201.6. Found, %: C 74.25, H 5.95, N 8.87, S 10.29. $C_{19}H_{18}N_2S$. Calculated, %: C 74.47, H 5.92, N 9.14, S 10.46.

1-Benzyl-5-(2-*p*-tolyl-1*H*-indol-3-yl)pyrrolidine-2-thione (2b)
Yield: 86% (method A), 64% (method B), mp 213-214°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.40 (3H, s, ArC$\underline{H}_3$); 2.38-2.42 (2H, m, H-4), 3.16-3.19; 3.40-3.42 (2H, two m, H3); 3.83 (1H, d, $J = 14$, C$\underline{H}_2$Ph); 5.22 (1H, dd, $^1J = 8$, $^2J = 9$, H5); 5.93 (1H, d, $J = 14$, C$\underline{H}_2$Ph); 7.02-7.48 (13H, m, Ar); 8.30 (1H, wide s, NH). ^{13}C NMR spectrum, δ, ppm: 21.2; 27.8; 44.4; 48.7; 62.0; 111.3(2C); 113.8; 119.1; 120.9(2C); 122.9(2C); 124.6; 127.5(2C); 128.3(3C); 129.6(2C); 135.2(2C); 138.5; 164.1; 201.7. Found, %: C 78.36, H 5.92, N 6.72, S 7.76. $C_{26}H_{24}N_2S$. Calculated, %: C 78.75, H 6.10, N 7.06, S 8.09.

1-Benzyl-5-(2-methyl-1*H*-indol-3-yl)pyrrolidine-2-thione (2c)
Yield: 68% (method A), 57% (method B), mp 189-191°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.04 (3H, s, 2C$\underline{H}_3$); 2.35-2.38 (2H, m, H-4); 3.21-3.33; 3.41-3.43 (2H, two m, H3); 3.70 (1H, d. $J = 14$, C$\underline{H}_2$Ph); 4.98 (1H, m, H5); 5.98 (1H, d, $J = 14$, C$\underline{H}_2$Ph); 7.11-7.39 (9H, m, Ar); 7.96 (1H, wide s, NH). Found, %: C 74.77, H 6.19, N 8.60, S 9.81. $C_{20}H_{20}N_2S$. Calculated, %: C 74.96, H 6.29, N 8.74, S 10.01.

1-Benzyl-5-(1-methyl-1*H*-indol-3-yl)pyrrolidine-2-thione (2d)
Yield: 56% (method A), mp 102-103°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.24-2.26, 2.44-2.46 (2H, two m, H-4); 3.20-3.22; 3.37-3.39 (2H, two m, H3); 3.81 (3H, s, NC$\underline{H}_3$) 3.93 (1H, d, $J = 14$, C$\underline{H}_2$Ph); 5.11 (1H, dd, $^1J = 6$, $^2J = 9$, H5);

5.88 (1H, d, $J = 14$, C$\underline{H}_2$Ph); 6.91 (1H, s, H-2); 7.14-7.41 (9H, m, Ar.). Found, %: C 74.67, H 6.23, N 8.50, S 9.79. $C_{20}H_{20}N_2S$. Calculated, %: C 74.96, H 6.29, N 8.74, S 10.01.

1-Benzyl-5-(1-methyl-2-*p*-tolylindol-3-yl)pyrrolidine-2-thione (2e)

Yield: 79% (method A), 82% (method B), mp 212-214°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32-2.34 (2H, m, H-4); 2.41 (3H, s, ArC$\underline{H}_3$); 3.11-3.13; 3.35-3.37 (2H, two m, H3); 3.61 (3H, s, NC$\underline{H}_3$) 3.89 (1H, d, $J = 14$, C$\underline{H}_2$Ph); 4.96-4.98 (1H, m, H5); 5.91 (1H, d, $J = 14$, C$\underline{H}_2$Ph); 6.90-7.44 (13H, m, Ar). Found, %: C 78.91, H 6.04, N 6.44, S 7.56. $C_{27}H_{26}N_2S$. Calculated, %: C 78.98, H 6.38, N 6.82, S 7.81.

1-Benzyl-5-(1,2-dimethylindol-3-yl)pyrrolidine-2-thione (2f)

Yield: 72% (method A), 84% (method B), mp 147-149°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.02 (3H, s, IndC$\underline{H}_3$); 2.35-2.37 (2H, m, H-4); 3.20-3.22, 3.41-3.44 (2H, two m, H3); 3.70 (3H, s, NC$\underline{H}_3$), 3.69 (1H, d, $J = 14$, C$\underline{H}_2$Ph); 5.00-5.02 (1H, m, H5); 5.96 (1H, d, $J = 14$, C$\underline{H}_2$Ph); 7.13-7.39 (9H, m, Ar). ^{13}C NMR spectrum, δ, ppm: 9.9; 27.3; 29.6; 44.5; 48.7; 61.6; 107.7; 109.2; 118.3; 120.1; 121.5; 127.7(2C); 128.3(2C); 128.5(2C); 135.1; 135.6; 137.2; 199.2. Found, %: C 75.25 H 6.95, N 7.98, S 9.58. $C_{21}H_{22}N_2S$. Calculated, %: C 75.41, H 6.63, N 8.38, S 9.59.

4.3.2 | 1-Benzyl-2-(1*H*-indol-3-yl)-5-(methylthio)-3,4-dihydro-2*H*-pyrrolidinium iodide (3a)

2.2 mL (0.3 mmol) of methyl iodide was added to a solution of 0.83 g (0.3 mmol) of indolylpyrrolidine-2-thione **2a** in 15 mL anhydrous methylenechloride. The reaction mixture was stirred for 30 minutes before the start of precipitation. The precipitate was filtered, washed with ether and several times with benzene, and then was dried in air. Yield 120 mg (99%). IR spectrum, ν, cm^{-1}: 1580 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.34-2.36, 2.46-2.48 (2H, two m, H-3); 2.70 (3H, s, SC$\underline{H}_3$); 3.43-3.45, 3.54-3.56 (2H, two m, H-4); 4.06 (1H, d, $J = 13$, C$\underline{H}_2$Ph); 4.44 (1H, d, $J = 13$, C$\underline{H}_2$Ph); 5.40 (1H, m, H2); 6.74-7.14 (10H, m, Ar); 10.78 (1H, wide s, NH).

Thioiminium salts **3b-f** were obtained in a similar way with quantitative yield as light yellow powders, and the salts were used in subsequent reactions without further purification.

4.3.3 | 3-(1-Benzylpyrrolidin-2-yl)-1*H*-indoles 4 (general methods)

Method A. 0.5 g (1.3 mmol) $NaBH_4$ was added in portions to a solution of 0.18 g (0.53 mmol) thioiminium salt **3a** in 15 mL anhydrous ethanol at 0°C. The mixture was stirred for another half an hour while maintaining the temperature at approximately 0°C, then was boiled for 2 hour. The reaction mixture was treated with 10% aqueous HCl solution until pH ~2, stirred for 15 minutes, and treated with 10% aqueous NaOH solution until pH ~10; then, the mixture was extracted with ether, and the extracts were combined, washed with saturated NaCl solution, and dried over anhydrous Na_2SO_4. The ether was removed by vacuum distillation, and indolylpirrolidine **4a** was isolated as a yellow oil and purified by SiO_2 dry-column chromatography.

Method B. 1 mmol of 1-benzyl-5-(indol-3-yl)pyrrolidine-2-thione **2b,c** was added to solution of triethyloxonium borofluoride, taken in 1.3-fold excess in anhydrous methylene chloride, and the mixture was stirred for 1 hour until the starting thioamide disappeared (TLC control, benzene-ethylacetate, 10:1). The reaction mixture was evaporated, and intermediate formed was solved in abs. ethanol and was cooled to 0°C. Then $NaBH_4$ 2.5-fold excess was added in portions maintaining the temperature ~0°C, and the mixture was stirred another half an hour with cooling and was boiled additional 2 hour. The reaction mixture was worked up in the same way as in method A; the corresponding tertiary amines **4a-c** were obtained as a yellow oil. The substances were purified by SiO_2 dry-column chromatography.

Chromatographic mobility of indolylpyrrolidines **4a-c** obtained corresponds with data for compounds obtained according to[9] by pyrrolidones **1a-c** reduction. The IR spectra of compounds **4a-c** and the compounds according to[9] by reduction in pyrrolidones **1a-c** are the same in the fingerprints area.

3-(1-Benzylpyrrolidin-2-yl)-1*H*-indole (4a). Yield: 62% (method A), 66% (method B)

3-(1-Benzylpyrrolidin-2-yl)-2-*p*-tolyl-1*H*-indole (4b). Yield: 77% (method B)

3-(1-Benzylpyrrolidin-2-yl)-2-methyl-1*H*-indole (4c). Yield: 60% (method B)

4.3.4 | 3-(1-Benzyl-5-(nitromethylene) pyrrolidine-2-yl)-indoles, 5 (general methods)

Tenfold excess of nitromethane and 2 eq. of triethylamine were added to the salt **3** (which was obtained from (1 mmol) of 1-benzyl-5-(indol-3-yl)pyrrolidine-2-thion **2**) in 15 mL of absolute methylene chloride. The mixture was stirred for 6 hour (TLC control, benzene-ethylacetate, 3:1) and poured into water. The precipitate formed was filtered off, washed with water several times, then with an ether. For thioiminium salts **3a-c** with NH-unsubstituted in the indole nucleus, the reaction was carried out in nitromethane with the addition of several (2-3) mL of DMF. The solvent excess was evaporated, and the mixture obtained was poured into water. The precipitate formed was filtered off and washed

with water. The crystalline substances obtained were dried in a desiccator over P_2O_5 and recrystallized from MeOH-ether, 5:1.

(E)-1-Benzyl-5-(1*H*-indol-3-yl)-2-nitromethylenepyrrolidine (5a)

Yellow crystals. Yield: 52%, mp 183-184°C. IR spectrum: 3280 (NH), 1580, 1370 cm^{-1} (NO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.37-2.39, 2.55-2.57 (2H, two m, H-4); 3.60-3.62, 3.92-3.94 (2H, two m, H3); 4.17 (1H, d, $J = 16$, C$\underline{H}_2$Ph); 4.39 (1H, d, $J = 16$, C$\underline{H}_2$Ph); 5.17 (1H, dd, $^1J = 8$, $^2J = 9$, H2); 6.97 (1H, s, C$\underline{H}$NO$_2$); 7.06-7.49 (10H, m, Ar); 8.42 (1H, wide s, NH). ^{13}C NMR spectrum, δ, ppm: 28.7; 33,6; 48.2; 62.5; 110.1; 112.0; 118.6; 120.5; 123.0; 123.7; 127.0(2C); 128.1; 129.0; 131.4; 134.3; 137.0; 146.6; 153.3; 181.2. Found, %: C 71.79, H 5.73, N 12.43. $C_{20}H_{19}N_3O_2$. Calculated, %: C 72.05, H 5.74, N 12.60.

(E)-1-Benzyl-5-(2-(*p*-tolyl)-1*H*-indol-3-yl)-2-nitromethylenepyrrolidine (5b)

Yield: 62%, mp 211-213°C. Orange crystals. IR spectrum: 3300 (NH), 1570 cm^{-1}, 1370 cm^{-1} (NO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.43 (3H, s, Ar-C$\underline{H}_3$); 2.42-2.44 (1H, m, H-4); 2.54-2.56 (1H, m, H-4); 3.55-3.57, 4.03-4.05 (2H, two m, H-3); 4.12 (1H, d, $J = 16$, C$\underline{H}_2$-Ph); 4.37 (1H, d, $J = 16$, C$\underline{H}_2$-Ph); 5.24-5.26 (1H, m, H-5); 6.95 (1H, s, C$\underline{H}$NO$_2$); 7.00-7.48 (13H, m, Ar); 8.22 (1H, wide s, NH). Found, %: C 76.35, H 6.11 N 9.52. $C_{27}H_{25}N_3O_2$. Calculated, %: C 76.59, H 5.91, N 9.92.

(E)-1-Benzyl-5-(2-methyl-1*H*-indol-3-yl)-2-nitromethylenepyrrolidine (5c)

Yield: 48%, mp 197-199°C. Yellow crystals. IR spectrum: 3290 (NH), 1580, 1370 cm^{-1} (NO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2,20 (3H, s, Ind-C$\underline{H}_3$); 2.36-2.38, 2.60-2.62 (2H, two m, H-4); 3.61-3.63, 3.92-3.94 (2H, two m, H-3); 4.01 (1H, d, $J = 16$, C$\underline{H}_2$-Ph); 4.41 (1H, d, $J = 16$, C$\underline{H}_2$-Ph); 5.06-5.08 (1H, m, H-5); 7.01 (1H, s, C$\underline{H}$NO$_2$); 7.05-7.46 (9H, m, Ar); 8.25 (1H, wide s, NH). Found, %: C 72.50, H 6.28, N 11.78. $C_{21}H_{21}N_3O_2$. Calculated, %: C 72.62, H 6.05, N 12.10.

(E)-1-Benzyl-5-(1-methylindol-3-yl)-2-nitromethylenepyrrolidine (5d)

Yield: 69%, mp 124-125°C. Light yellow crystals. IR spectrum: 1580, 1360 cm^{-1} (NO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.38-2.40, 2.56-2.58 (2H, two m, H-4); 3.60-3.62 (1H, m, H3); 3.81 (3H, s, N-C$\underline{H}_3$); 3.90-3.92 (1H, m, H3); 4.19 (1H, d, $J = 16$, C$\underline{H}_2$Ph); 4.37 (1H, d, $J = 16$, C$\underline{H}_2$Ph); 5.14-5.16 (1H, m, H2); 6.93-6.95 (1H, m, Ar); 6.98 (1H, s, C$\underline{H}$NO$_2$); 6.99-7.43 (10H, m, Ar). Found, %: C 72.39, H 6.17, N 11.83. $C_{21}H_{21}N_3O_2$. Calculated, %: C 72.62, H 6.05, N 12.10.

(E)-1-Benzyl-5-(1-methyl-(2-*p*-tolyl)indol-3-yl)-2-nitromethylenepyrrolidine (5e)

Yield: 62%, mp 191-193°C. Yellow crystals. IR spectrum: 1580, 1350 cm^{-1} (NO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.41-2.44 (2H, m, H-4); 2.43 (3H, s, Ar-C$\underline{H}_3$,); 3.41-3.43 (1H, m, H3); 3.60 (3H, s, N-C$\underline{H}_3$); 3.96-3.98 (1H, m, H3); 4.16 (1H, d, $J = 16$, C$\underline{H}_2$Ph); 4.31 (1H, d, $J = 17$, C$\underline{H}_2$Ph); 5.01-5.03 (1H, m, H2); 6.98 (1H, s, C$\underline{H}$-NO$_2$); 6.90-7.44 (13H, m, Ar). Found, %: C 76.94, H 6.39, N 9.48. $C_{28}H_{27}N_3O_2$. Calculated, %: C 76.86, H 6.22, N 9.60.

(E)-1-Benzyl-5-(1,2-dimethylindol-3-yl)-2-nitromethylenepyrrolidine (5f)

Yield: 77%, mp 198-200°C. Yellow crystals. IR spectrum: 1570, 1360 cm^{-1} (NO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2,17 (3H, s, Ind-C$\underline{H}_3$); 2.37-2.39, 2.47-2.49 (2H, m, H-4); 3.52-3.54 (1H, m, H3); 3.70 (3H, s, N-C$\underline{H}_3$); 4.00-4.03 (1H, m, H3); 4.02 (1H, d, $J = 16$, C$\underline{H}_2$Ph); 4.37 (1H, d, $J = 16$, C$\underline{H}_2$Ph); 5.09 (1H, m, H2); 6.93-6.94 (1H, m, Ar); 7.03 (1H, s, C$\underline{H}$-NO$_2$); 7.12-7.43 (9H, m, Ar). ^{13}C NMR spectrum, δ, ppm: 8.8; 29.7; 33.8; 46.1; 47.9; 61.9; 107.2; 109.4; 110.0; 120.1; 121.6; 127.3(2C); 127.8; 128.3; 128.9(2C); 134.3; 136.9; 140.5; 154.8; 164.3. Mass spectrum, m/z (I_{rel}, %); 361$[M]^+$ (80), 331(13), 315(67), 255(20), 236(34), 224(33), 223(27), 211(13), 209(13), 184(45), 171(89), 170(65), 160(50), 158(78), 145(29), 144(38), 128(12), 115(15), 91(100). Found, %: C 72.96, H 6.59, N 11.33. $C_{22}H_{23}N_3O_2$. Calculated, %: C 73.13, H 6.41, N 11.63.

1-Benzyl-5-(1,2-dimethylindol-3-yl)-2-ethoxycarbonyl-nitromethylenepyrrolidine (7f)

Two equivalents (0.2 mL) of trimethylamine were added to a solution of 350 mg (0.7 mmol) of 1-benzyl-2-(1,2-di methylindol-3-yl)-5-(methylthio)-3,4-dihydro-2*H*-pyrrolid inium iodide **3f** and an equimolar amount (98 mg) of nitroacetic ester in 15 mL of anhydrous methylene chloride and were stirred for ~6 hour. After the reaction complete (TLC control, benzene-ethylacetate, 3:1), the reaction mixture was washed with water several times and dried over sodium sulfate. The solvent was removed by evaporation, and the further purification from indolylpyrrolidone was carried out by dry-column flash chromatography (eluent benzene). 1-Benzyl-5-(1,2-dimethylindol-3-yl)-2-ethox ycarbonyl-nitromethylenepyrrolidine **7f** was obtained in small amounts.

IR spectrum: 1767(COOEt), 1579, 1360 (NO_2) cm^{-1}. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.35 (3H, t, $J = 7$, O-CH$_2$C$\underline{H}_3$); 2,35 (3H, s, Ind-C$\underline{H}_3$); 2.40-2.42, 3.18-3.20 (2H, m, H-3); 3.43-3.45 (H, m, H-4); 3.70 (3H, s, N-C$\underline{H}_3$); 4.24 (2H, q, $J = 7$, O-C$\underline{H}_2$CH$_3$), 4.34-4.35 (1H, m, H-4), 4.36 (1H, d, $J = 16$, C$\underline{H}_2$-Ph); 5.97 (1H, d, $J = 16$, C$\underline{H}_2$-Ph); 5.00-5.02 (1H, m, H-5); 7.15-7.54 (9H, m, Ar).

The major product isolated from the reaction mixture as a white precipitate with mp 187°C. The IR and NMR spectra of the compound obtained are identical to 1-benzyl-5-(1,2-dimethylindol-3-yl)pyrrolidin-2-one **1f**. A mixed sample of melting with a sample of known structure does not give a depression of the melting point.

4.3.5 | 2-(Aminomethyl)-1-benzyl-5-(1*H*-indol-3-yl)-2-pyrrolidines 6 (general methods)

A solution of ~1 mmol indolylnitromethylenepyrrolidine **5** in 10 mL of tetrahydrofuran was added by portions with vigorous stirring to the excess (6 eq) of lithium aluminum hydride in 15 mL of anhydrous tetrahydrofuran, and then, the mixture was boiled for 20 hour on a water bath. Then, with vigorous stirring and cooling with ice, the calculated amount of water was added dropwise to decompose the complex, and the precipitate obtained was filtered and washed with ether several times. The combined extracts were washed with an aqueous solution of oxalic acid (pH = 5.5-6) and water. The aqueous layer was basified with a saturated solution of potassium carbonate and extracted with ether. The extracts were dried over sodium sulfate, filtered, and treated with an alcoholic solution of hydrogen chloride until an acidic reaction occurs. The solvents are distilled off, and the precipitate formed is washed on the filter with absolute ether several times, dried in a desiccator. Recrystallization was made from absolute alcohol.

2-(Aminomethyl)-1-benzyl-5-(1*H*-indol-3-yl)-2-pyrrolidine hydrochloride (6a)

Yield 48%, mp 143-145°C. Light orange crystals. IR spectrum: 2600-3000 cm^{-1} (NH_3^+). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.95-1.97 (2H, m, H-4); 2.07-2.10, 2.51-2.53 (2H, two m, H-3); 2.60-2.61 (1H, m, $C\underline{H}_2NH_3^+$); 2.73-2.75 (1H, m, $C\underline{H}_2NH_3^+$); 3.06 (1H, d, *J* = 15, $C\underline{H}_2$-Ph); 3.50-3.52 (1H, m. H-2); 3.97 (1H, d, *J* = 15, $C\underline{H}_2$-Ph); 4.06-4.08 (1H, m, H-5); 5.31 (wide s, NH_3^+), 7.18-7.57 (10H, m, Ar); 8.18 (1H, wide s, NH). Found, %: C 70.20, H 7.28, N 12.12. $C_{20}H_{24}ClN_3$. Calculated, %: C 70.28, H 7.03, N 12.30.

2-(Aminomethyl)-1-benzyl-5-(1,2-dimethylindol-3-yl) pyrrolidine hydrochloride (6f)

Yield: 65%, mp 136-138°C. Light orange crystals. IR spectrum: 2600-3000 cm^{-1} (NH_3^+). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.93-1.95 (2H, m, H-4); 2.07-2.09, 2.21-2.23 (2H, two m, H-3); 2.42 (3H, s, Ind-$C\underline{H}_3$); 2.74-2.76 (1H, m, $C\underline{H}_2NH_3^+$); 2.86-2.88 (1H, m, $C\underline{H}_2NH_3^+$); 3.39 (1H, d, *J* = 15, $C\underline{H}_2$-Ph); 3.65 (3H, s, N-$C\underline{H}_3$); 3.66-3.68 (1H, m, H-2); 3.85 (1H, d, *J* = 15, $C\underline{H}_2$-Ph); 3.96-3.98 (1H, m, H-5); 6.05 (wide s, NH_3^+); 7.07-7.26 (9H, m, Ar). ^{13}C NMR spectrum, δ, ppm: 9.8; 28.6; 29.1; 38.8; 39.2; 42.3; 54.9; 61.2; 107.9; 113.1; 117.9; 118.5; 119.7; 125.5; 126.2; 127.4(2C); 128.5(2C); 133.9; 136.1; 137.5. Found, %: C 71.20, H 7.74, N 11.12. $C_{22}H_{28}ClN_3$. Calculated, %: C 71.45, H 7.58, N 11.37.

1-Benzyl-2-(phenylthiocarbamoylaminometyl)-5-(1-metyl-2-*p*-tolylindol-3-yl)pyrrolidine (6e)

69.5 Ml (0.55 mmol) of phenyl isothiocyanate was added to a solution of 200 mg (0.5 mmol) of crude amine **6e** in 5 mL of benzene and left for 24 hour. Then, benzene was removed by evaporation, the residue obtained washed with ether and dried in a desiccator. 130 Mg (yield 62%) as a white powder was obtained, mp 185-186°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.87-1.90 (2H, m, H-4); 2.07-2.09, 2.16-2.18 (2H, two m, H-3); 2.48 (3H, s, Ar-$C\underline{H}_3$); 2.70-2.72 (1H, m, $C\underline{H}_2NH$); 3.05 (1H, d, *J* = 15, $C\underline{H}_2$-Ph); 3.22-3.24 (1H, m, $C\underline{H}_2NH$); 3.54 (3H, s, N-$C\underline{H}_3$); 3.57-3.59 (1H, m, H-2); 3.81 (1H, d, *J* = 15, $C\underline{H}_2$-Ph); 4.08-4.10 (1H, m, H-5); 6.41 (1H, wide s, $CH_2N\underline{H}$); 6.85-7.40 (18H, m, Ar); 7.42 (1H, wide s, N$\underline{H}$-Ph). Found, %: C 77.22, H 6.98, N 10.06, S 6.15. $C_{35}H_{36}N_4S$. Calculated, %: C 77.21, H 6.62, N 10.29, S 5.88.

4.3.6 | 1-Benzyl-2-(dicyanomethylene)-5-(indol-3-yl)pyrrolidines 8 (general methods)

Equimolar amounts of 1-benzyl-2-(indol-3-yl)-5-(methylthio)-3,4-dihydro-2*H*-pyrrolidinium iodide **3**, malononitrile, and potassium fluoride in 15 mL of absolute methylene chloride in the presence of catalytic amount of triethylbenzylammonium chloride (10 mol. %) were stirred at room temperature for 15 hour and left overnight. Next day, the reaction mixture was washed with water several times and dried over Na_2SO_4. The solvent was removed by distillation and rubbed the oil formed with a drop of ether, achieving crystallization of the precipitate. The precipitate was purified by recrystallization from ethyl alcohol. The substances were obtained as white powders.

1-Benzyl-2-(dicyanomethylene)-5-(1H-indol-3-yl) pyrrolidine (8a)

Yield: 57%, mp 154-156°C. White crystals. IR spectrum: 3400 (NH), 2250 cm^{-1} (CN). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.36-2.38 (2H, m, H-4); 3.15-3.17, 3.34-3.36 (2H, two m, H-3); 3.94 (1H, d, *J* = 15, $C\underline{H}_2$-Ph); 5.04-5.06 (1H, m, H-5) 5.56 (1H, d, *J* = 15, $C\underline{H}_2$-Ph); 7.03-7.77 (10H, m, Ar); 8.23 (1H, wide s, NH). Found, %: C 78.28, H 5.46, N 16.79. $C_{22}H_{18}N_4$. Calculated, %: C 78.11, H 5.33, N 16.57.

1-Benzyl-2-(dicyanomethylene)-5-(2-methyl-1*H*-indol-3-yl)pyrrolidine (8c)

Yield 68%, mp 146-148°C. White crystals. IR spectrum: 3450 (NH), 2250 cm^{-1} (CN). ^1H NMR spectrum, δ, ppm, (*J*, Hz): 2.11 (3H, s, Ind-$C\underline{H}_3$); 2.43-2.45 (2H, m, H-4); 3.14-3.16, 3.33-3.35 (2H, two m, H-3); 4.06 (1H, d, *J* = 15, $C\underline{H}_2$-Ph);

5.15-5.17 (1H, m, H-5); 5.46 (1H, d, J = 15, C$\underline{H}_2$-Ph); 7.11-7.47 (9H, m, Ar); 8.53 (1H, wide s, NH). Found, %: C 78.22, H 5.36, N 16.09. $C_{23}H_{20}N_4$. Calculated, %: C 78.41, H 5.68, N 15.91.

1-Benzyl-2-(dicyanomethylene)-5-(1-methyl-2-*p*-tolyl) indol-3-yl)pyrrolidine (8e)

Yield: 68%, mp 159-162°C. White crystals. IR spectrum: 2260 cm^{-1} (CN). ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.35-2.37 (2H, m, H-4); 2.44 (3H, s, Ar-C$\underline{H}_3$); 3.04-3.06, 3.20-3.22 (2H, two m, H-3); 3.61 (3H, s, N-C$\underline{H}_3$); 4.12 (1H, d, J = 15, C$\underline{H}_2$-Ph); 5.05-5.07 (1H, m, H-5); 5.46 (1H, d, J = 15, C$\underline{H}_2$-Ph); 7.05-7.39 (13H, m, Ar). ^{13}C NMR spectrum, δ, ppm: 21.3; 27.7; 30.8; 35.3; 47.8; 65.2; 108.1; 110.2; 118.3; 120.9; 122.7; 126.1; 127.1; 127.5(2C); 127.9; 128.9(2C); 129.4(2C); 130.1; 130.4; 134.4; 139.2; 140.1; 145.1; 169.9. Found, %: C 81.19, H 6.18, N 12.46. $C_{30}H_{26}N_4$. Calculated, %: C81.45, H 5.88, N 12.67.

1-Benzyl-2-(dicyanomethylene)-5-(1,2-dimethylindol-3-yl)pyrrolidine (8f)

Yield: 73%, mp 137-139°C. White crystals. IR spectrum: 2260 cm^{-1} (CN). ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.07 (3H, s, Ind-C$\underline{H}_3$); 2.38-2.40 (2H, m, H-4); 3.14-3.16 (2H, two m, H-3); 3.71 (3H, s, N-C$\underline{H}_3$); 3.96 (1H, d, J = 15, C$\underline{H}_2$-Ph); 5.10-5.11 (1H, m, H-5); 5.55 (1H, d, J = 15, C$\underline{H}_2$-Ph); 7.05-7.39 (9H, m, Ar). Found, %: C 78.71, H 6.26, N 15.09. $C_{24}H_{22}N_4$. Calculated, %: C 78.69, H 6.01, N 15.30.

1-Benzyl-5-(1,2-dimethylindol-3-yl)-2-ethoxycarbonylcyanomethylenepyrrolidine (9f)

2 Equivalents (0.2 mL) of triethylamine were added to a solution of 350 mg (0.73 mmol) of 1-benzyl-2-(1,2-dimethylindol-3-yl)-5-(methylthio)-3,4-dihydro-2*H*-pyrrolidinium iodide **3f** and 83 mg (0.73 mmol) of cyanoacetic ester in 15 mL absolute methylene chloride and were stirred for ~6 hour. After the reaction complete (TLC control, benzene-ethylacetate, 3:1), the reaction mixture was washed with water several times and dried over sodium sulfate. The solvent was removed by evaporation and the further purification was carried out by dry-column flash chromatography (eluent benzene). 85 Mg (yield 45%) of 1-benzyl-5-(1,2-dimethylindol-3-yl)-2-ethoxycarbonylcyanomethylenepyrrolidine was obtained, mp 176-178°C. IR spectrum: 2250 cm^{-1} (CN); 1760 cm^{-1} (COOEt). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.38 (3H, t, J = 7, O-CH$_2$C$\underline{H}_3$); 2.06 (3H, s, Ind-C$\underline{H}_3$); 2.34-2.36 (2H, m, H-4); 3.36-3.38 (1H, m, H-3); 3.69 (3H, s, N-C$\underline{H}_3$); 3.84-3.86 (1H, m, H-3); 3.98 (1H, d, J = 15, C$\underline{H}_2$-Ph); 4.24 (2H, q, J = 7, OC$\underline{H}_2$CH$_3$); 5.00-5.02 (1H, m, H-5); 5.89 (1H, d, J = 15, C$\underline{H}_2$-Ph); 7.06-7.36 (9H, m, Ar). Found, %: C 75.46, H 6.74, N 9.89. $C_{26}H_{27}N_3O_2$. Calculated, %: C 75.54, H 6.55, N 10.19.

4.4 | X-ray diffraction for compounds 1a and 3a

Crystals of **1a** ($C_8H_5ClFN_3$, M = 197.60) ($C_{19}H_{18}N_2O$, M = 290.35) are orthorhombic, space group Pbca, at 120 K: a = 10.4956(9), b = 15.4215(13), c = 18.9714(16) Å, V = 3070.7(5) Å^3, Z = 8, d_{calc} = 1.256 g cm^{-3}, μ(MoKα) = 0.79 cm^{-1}, F(000) = 1232. Crystals of **3a** ($C_{22}H_{27}IN_2OS$, M = 494.41) are monoclinic, space group C2/c, at 120 K: a = 26.488(2), b = 9.4478(8), c = 20.6351(17) Å, β = 122.598(2)°, V = 4350.6(6) Å^3, Z = 8, d_{calc} = 1.510 g cm^{-3}, μ(MoKα) = 15.82 cm^{-1}, F(000) = 2000. Intensities of 32 303 and 25 487 reflections for **1a** and **3a**, respectively, were measured with a Bruker APEX2 DUO CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 56°$ and 58°]; 3708 and 5773 independent reflections [R_{int} 0.0343 and 0.0480] were used in further refinement. The structures were solved by the direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. Hydrogen atoms of the NH groups in **1a** and **3a** and of the OH group of the solvate ethanol molecule in **3a** were found in difference Fourier synthesis; H(C) atom positions were calculated. All hydrogen atoms were refined in the isotropic approximation within the riding model. For **1a**, the refinement converged to wR2 = 0.1485 and GOF = 1.007 for all the independent reflections (R1 = 0.0451 was calculated against F for 2806 observed reflections with I > 2σ(I)). For **3a**, the refinement converged to wR2 = 0.0925 and GOF = 1.019 for all the independent reflections (R1 = 0.0405 was calculated against F for 4349 observed reflections with I > 2σ(I)). All calculations were performed using SHELXTL PLUS 5.0.[22] CCDC 1470858 and 1470857 contain the supplementary crystallographic information for **1a** and **3a**, respectively. Supplementary information files containing X-ray structural analysis data for compounds **1a** and **3a** are also available online: http://hgs.osi.lv.

ACKNOWLEDGMENTS

This work was financially supported by the Russian Foundation for Basic Research (projects 15-29-05785 ofi_m; 18-03-00703a. The contribution of Center for molecule composition studies of INEOS RAS is gratefully acknowledged.

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How to cite this article: Sadovoy AV, Kattsyna VV, Protopopova PS, et al. Condensations based on 5-(indol-3-yl)-pyrrolidin-2-thiones. *Heteroatom Chem*. 2018;e21451. https://doi.org/10.1002/hc.21451