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N-Substituted cyanacetohydrazides in the synthesis of 3,3-dialkyl-1,2,3,4-tetrahydroisoquinolines by Ritter reaction

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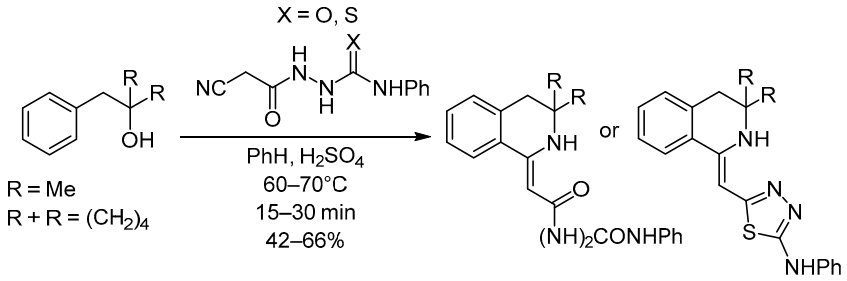


Cyanacetohydrazide, protected at the nitrogen atom of hydrazide group, underwent cyclocondensation by Ritter reaction with 3,3-dialkylbenzylcarbinols, forming 3,3-dialkyl-1,2,3,4-tetrahydroisoquinolines. The reagents used for the protection of hydrazide group were benzaldehyde, benzoyl chloride, phenyl isocyanate, and phenyl isothiocyanate. As a result, *N*-substituted derivatives of 2-(3,3-dialkyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene)acetohydrazide were obtained – *N*-phenylmethylidene ethanehydrazide, acetylbenzohydrazide, and *N*-phenylhydrazinecarboxamide. Cyanacetohydrazide that was acylated with phenyl isothiocyanate gave a heterocyclization product – 1,3,4-thiadiazole under these conditions.

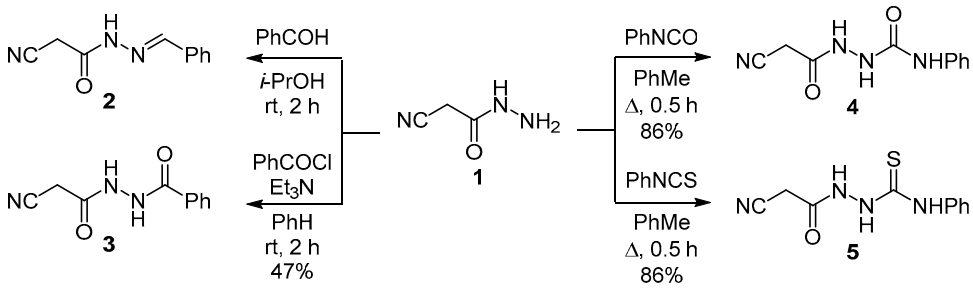
Keywords: cyanacetohydrazide, 2-(3,3-dialkyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene)acetohydrazide, 1,3,4-thiadiazole, heterocyclization, Ritter cyclization.

Enamines derived from 1,2,3,4-tetrahydroisoquinoline have shown considerable reactivity. The presence of an electron-withdrawing group (EWG) – an ester,[1,2] amide,[3–8] thioamide,[9] nitrile,[10–12] or ketone[13] – in the structure of these compounds at the β-carbon atom of the enamine moiety facilitates the stabilization of the enamine form. The obtained isoquinoline derivatives include compounds that have exhibited strong biological activity.[6–8] At the same time, practically no data are available in the literature on enaminohydrazides of this series. This fact is probably associated with the difficulties encountered during the hydrazinolysis of enaminoesters. The nucleophilic site is deactivated due to the shift of electron density from the nitrogen atom of heterocycle along the chain of conjugation to the carbonyl carbon atom of the ester group[14]. When the preparation of enaminohydrazides of 1,2,3,4-tetrahydroisoquinoline derivatives was attempted by direct Ritter cyclocondensation[15] between dialkylbenzylcarbinols and cyanacetohydrazide, no product could be isolated, which can be explained by the anomalous instability of the starting hydrazide. Cyanacetohydrazide (cyazid) is a drug that has been used against tuberculosis.[16] The colorless crystals of this compound turned red upon exposure to air under the illumination with sunlight for 3–4 h, demonstrating its instability and showing the need for protection of nitrogen atom. The possible methods of protection include the preparation of hydrazone, acylation with acyl chlorides, carbamoylation with isocyanates, or thiocarbamoylation with isothiocyanates.

The goal of this work was to synthesize enaminohydrazides derived from 1,2,3,4-tetrahydroisoquinoline, substituted at the nitrogen atom of hydrazide group.

The starting nitriles were obtained by mixing of cyanacetohydrazide **1** with the appropriate reagents (Scheme 1).

Scheme 1



The obtained hydrazone **2** was sufficiently pure (control by TLC) and therefore could be used immediately after the reaction, without recrystallization. The rest of the nitriles were recrystallized. Acylation was accomplished by treatment with benzoyl chloride in benzene and produced the diacyl hydrazine derivative **3**. Carbamoylation of hydrazide **1** by the action of phenyl isocyanate led to the formation of compound **4**, while the reaction with phenyl isothiocyanate provided the respective thio analog **5**.

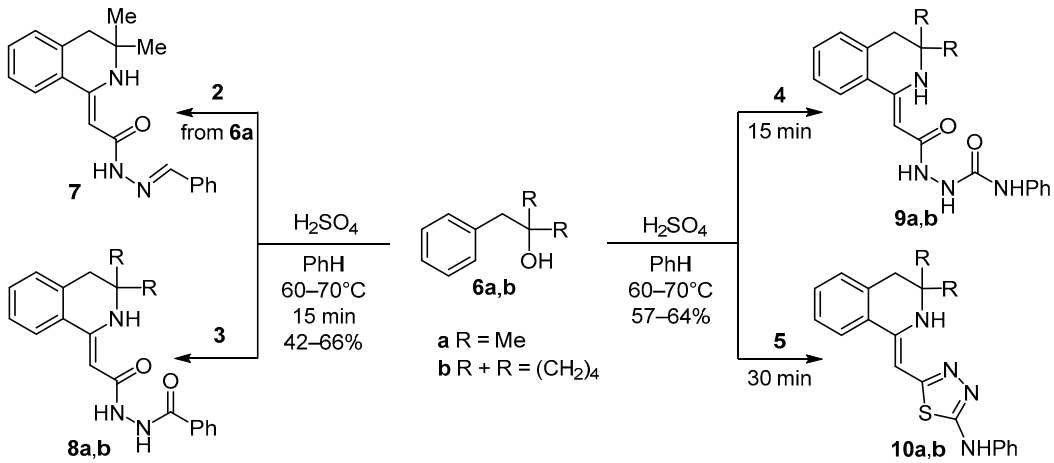
Compounds **6a**,**b** were selected as the starting carbinols. The studies showed that all 4 variants for the protection of nitrogen atom in the hydrazide group gave the desired result. Cyclocondensation of carbinol **6a** with hydrazone **2** gave isoquinoline **7**, while the reactions of carbinols **6a**,**b** with *N*-benzoylcyanoacetylhydrazine **3** led to the *N*-benzoylated enaminohydrazides **8a**,**b** (Scheme 2).

The reaction of carbinols **6a**,**b** with amide **4** resulted in isoquinolines **9a**,**b** (Scheme 2). A different structure was formed under these conditions when thioamide **5** was used as the nitrile component. In that case, the reaction products were 1,3,4-thiadiazole derivatives **10a**,**b**. Heterocyclization leading to a 1,3,4-thiadiazole can be explained by the known readily occurring isomerization of thioamide derivatives to a thioimidol form. Additional facilitating factors for this reaction are the preferred protonation of oxygen atom compared to sulfur atom, the energetically favored formation of aromatic system, and the role of water molecule as a good leaving group (Scheme 3).

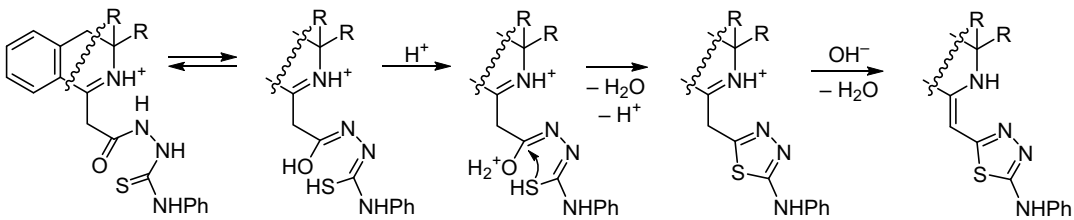
IR spectra of the obtained compounds featured absorption bands of the respective functional groups. Thus, the spectra of the starting nitriles **3**–**5** contained bands in the ranges of 2215–2240, 1640–1680, and 3240–3380 cm^{-1}, corresponding to the absorption by C≡N, C=O, and NH groups. The spectra of enamines **7**–**10** showed a broadened band of chelated NH group (3100–3150 cm^{-1}), while the spectra of carbonyl compounds **7**–**9** contained a band of chelated C=O group at 1610 cm^{-1}, pointing to a *Z*-configuration of the enaminohydrazide moiety.

^{1}H NMR spectra of carbonyl compounds **7**–**9** contained singlets of the vinyl proton (5.08–5.31 ppm) and the NH group of the ring (9.30–10.67 ppm), corresponding to a *Z*-configuration of enamine, which was stabilized by H-chelation. Analogous configuration was also confirmed for enamines **10a**,**b** (singlets of HC= proton at 5.97 and 5.98 ppm) and singlets of the ring NH proton at 10.07 and 10.08 ppm. The spectra also contained proton signals of the respective substituent groups. All of the synthesized isoquinoline bases formed stable hydrochlorides. During the salt formation, the enamine form was converted to the imino form (Scheme 4).

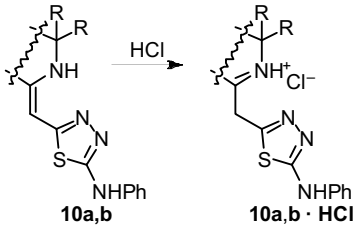
Scheme 2



Scheme 3



Scheme 4



This transformation resulted in the disappearance of vinyl proton singlet in ^{1}H NMR spectrum at 5.97 ppm, while a singlet of two protons appeared at 4.90 ppm. Analogous transformation was observed for all of the obtained enamines, as described in earlier publications.[6–10]

^{13}C NMR spectra of compounds **7**–**9** contained signals in the range of 23.0–28.4 ppm (alkyl groups at the 3-C atom), in the range of 38.5–41.4 ppm (4-CH_2 group), in the range of 48.6–59.6 ppm (a weak signal of quaternary 3-C atom), in the range of 78.5–78.9 ppm (the HC= group), and in the range of 118.4–135.8 ppm (carbon atoms of aromatic rings). Besides that, the spectra of compounds **7**–**9** contained signals of carbonyl groups in the region downfield from 140.0 ppm. The spectra of 1,3,4-thiadiazole derivatives contained signals of C=N groups that were part of the 1,3,4-thiadiazole ring (152.3 and 158.0 ppm).

Mass spectra of all synthesized compounds contained the molecular ion peaks with intensities between 9 and 100%. In the mass spectra of compounds **7**–**9**, which contained an enaminocarbonyl fragment in their structure, the peak with 100% intensity was assigned to the 3,3-dialkyl-3,4-dihydroisoquinolin-1(2*H*)-ylideneacetyl fragment (*m*/*z* 200 and 226, which corresponded to structures containing two methyl groups or a cyclopentane ring at position 3). Mass spectra of the same compounds featured a signal of low intensity (3–7%) that was assigned to 3,3-dialkyl-1,2,3,4-tetrahydroisoquinolin-1-idene fragment (*m*/*z* 159 for R = CH_3 and *m*/*z* 184 for R + R = $(CH_2)_4$). The spectra of 1,3,4-thiadiazole derivatives **10a**,**b** showed molecular ion peaks with the intensity of 100 and 92%, respectively. The spectrum of the molecule containing 2 methyl groups (compound **10a**) contained a strong peak (56% intensity) corresponding to the loss of CH_3 fragment. In the case of cyclopentane ring at position 3 (compound **10b**), the peak with 100% intensity was assigned to the 1,3,4-thiadiazole fragment.

On the basis of IR and NMR spectra, as well as mass spectrometry, the structure **A** was initially proposed for compounds **10a**,**b** (Fig. 1), analogously to compounds **9a**,**b**. The overall appearance of ^{1}H and ^{13}C NMR spectra for compounds **9** and **10** was very similar, while the strongest peak in mass spectra of compound **10** can be interpreted as due to elimination of water molecule from the structure **A**, analogously to the structure of compounds **9a**,**b**. In this case, besides the aforementioned structures **A** and **B**, there is another possible structure (compound **C**). The determination of structure is also complicated by the fact that the latter two molecules have identical mass values.

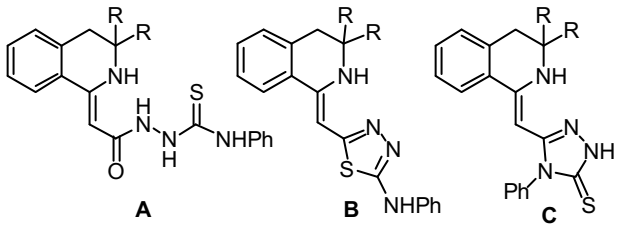


Figure 1. The possible structures of compounds **10a**,**b**.

For the purpose of obtaining unequivocal proof of structure, X-ray structural analysis was performed for compound **10b**, using a monocrystal obtained *via* slow crystallization from 2-propanol.

The bond lengths and valence angles in the molecules of compound **10b** were in a good agreement with the values typical for analogous atoms in related compounds. The molecule was nonplanar, and besides the presence of a spiro-fusion angle at the C(22) carbon atom, the angle between the phenyl (C(3)–C(8)) and thiadiazole ring planes was approximately 37.1°, with the N(1) and C(9) atoms situated in the plane of thiadiazole ring (Fig. 2).

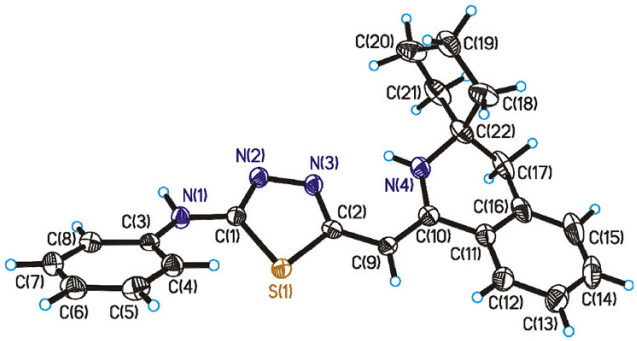


Figure 2. The molecular structure of compound **10b** with atoms represented by thermal vibration ellipsoids of 50% probability.

The molecules of compound **10b** formed centro-symmetric dimers in the crystal structure, linked by intermolecular N(1)–H···N(2A) and N(1A)–H···N(2) hydrogen bonds (Fig. 3). An intramolecular N(4)–H···N(3) hydrogen bond was also present.

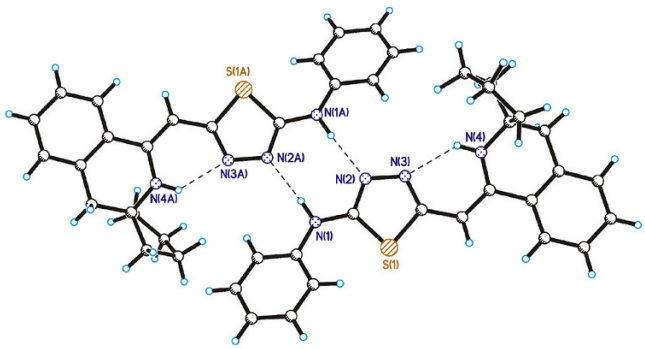


Figure 3. Centrosymmetric dimer in the crystal structure of compound **10b**. The intra- and intermolecular hydrogen bonds are shown by dashed lines.

The formation of such centrosymmetric dimer apparently led to the stabilization of the less common molecular conformation of compound **10b**, in which the phenyl substituent was *syn*-oriented to the sulfur atom relative to the C(1)–N(1) bond, in contrast to other structures containing the same moiety,[17] where the molecular packing in crystal was different. Indeed, only in two structures[18,19] out of the 17 relevant records in the Cambridge Structural Database an analogous conformation was observed for a thiadiazolylaminophenyl moiety, which was in complete agreement with the presence of dimers formed by intermolecular hydrogen bonds.

Thus, the protection of nitrogen atom in hydrazide moiety of cyanacetohydrazide by the preparation of hydrazone, acylation with benzoyl chloride, carbamoylation with isocyanate, or thiocarbamoylation with phenyl isothiocyanate prior to cyclization by Ritter reaction served its purpose: the respective *N*-substituted derivatives of enaminohydrazides belonging to 3,3-dialkyl-1,2,3,4-tetrahydroisoquinoline series were successfully obtained. As a result of these reactions, the thiocarbamoyl fragment cyclized to 1,3,4-thiadiazole, thus a sequence of two processes (a domino reaction) occurred. The obtained *N*,*N*'-diacyl derivatives of isoquinoline, as well as isoquinolines containing a 1,3,4-thiadiazole moiety and reactive enamine group in the side chain can be further used as synthetic intermediates and also in the role of biologically active compounds.

Experimental

IR spectra were recorded on a Specord M-80 spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker AMX 500 spectrometer (500 and 125 MHz, respectively) in DMSO-d_6, with TMS as internal standard. Mass spectra were recorded on a Finnigan MAT INCOS-50 instrument (EI ionization, 70 eV). Elemental analysis was performed on a Leco 932 CHNS analyzer. The purity of the obtained compounds was controlled by TLC using Silufol UV-254 plates with 1:3:6 mixture of Me_2CO–EtOH–$CHCl_3$ as the mobile phase, visualization under UV light or with bromine vapor.

The starting compounds **2**–**5** were obtained according to previously described procedures.[20–23] The melting points of amides **3** and **4** were higher compared to the literature data,[21,22] probably due to the fact that the authors of those studies used acylation in aqueous medium and in methanol – solvents that cause rapid decomposition of acyl chlorides and isocyanates, leading to the presence of impurities in the products and the formation of solvates.

***N*'-(2-Cyanoacetyl)benzohydrazide (3)**. A suspension of cyanacetohydrazide **1** (9.9 g, 0.1 mol) in anhydrous benzene (200 ml) was treated by the addition of Et_3N (15.5 ml, 0.11 mol), followed by dropwise addition of benzoyl chloride (11.5 ml, 0.1 mol), while maintaining the temperature at or below 20°C by cooling with ice water. The solution was left for 2 h at 20°C. The obtained precipitate was filtered off, carefully washed with water in order to remove Et_3N·HCl, dried, and recrystallized. Yield 9.54 g (47%), colorless crystals, mp 230–232°C (2-propanol) (mp 178–180°C[21]). IR spectrum, ν, cm^{-1}: 1640–1680 (2C=O), 2240 (C≡N), 3240–3310 (2NH). ^{1}H NMR spectrum, δ, ppm: 3.85 (2H, s, CH_2); 7.52–7.95 (5H, m, H Ph); 10.10 (2H, s, 2NH). ^{13}C NMR spectrum, δ, ppm: 32.1; 120.9; 126.2 (2C); 127.2; 128.4 (2C); 135.2; 147.5; 173.4. Mass spectrum, *m*/*z* (I_{rel}, %): 105 (100), 77 (45). Found, %: C 59.03; H 4.28; N 20.92. $C_{10}H_9N_3O_2$. Calculated, %: C 59.11; H 4.46; N 20.68.

2-(2-Cyanoacetyl)-*N*-phenylhydrazine-1-carboxamide (4). A mixture of cyanacetohydrazide **1** (9.9 g, 0.1 mol) with phenyl isocyanate (10.8 ml, 0.1 mol) was refluxed while stirring in toluene (150 ml) for 30 min. Initially, the formation of an oily liquid was observed (cyanacetohydrazide **1**, mp 107°C), which was not miscible with the solvent. Its volume decreased over the course of refluxing and the crystallization of product started. After cooling to room temperature, the obtained amide **4** was filtered off, dried, and recrystallized. Yield 18.7 g (86%), colorless crystals, mp 210–211°C (2-propanol) (mp 165–167°C[22]). IR spectrum, ν, cm^{-1}: 1640–1680 (2C=O), 2230 (C≡N), 3280–3380 (2NH). ^{1}H NMR spectrum, δ, ppm: 3.73 (2H, s, CH_2); 6.98–7.48 (5H, m, H Ph); 8.24 (1H, s, NH); 8.75 (1H, s, NH); 10.04 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 31.7; 121.2; 124.7 (2C); 126.2 (2C); 127.1; 131.6; 162.2; 175.1. Mass spectrum, *m*/*z* (I_{rel}, %): 218 $[M]^+$ (26), 120 (24), 119 (100), 105 (5), 99 (40), 91 (26), 77 (24). Found, %: C 54.87; H 4.47; N 25.76. $C_{10}H_{10}N_4O_2$. Calculated, %: C 55.04; H 4.62; N 25.68.

2-(2-Cyanoacetyl)-*N*-phenylhydrazine-1-carbothioamide (5) was obtained analogously to the procedure for preparation of amide **4** from cyanacetohydrazide **1** (9.9 g, 0.1 mol) and phenyl isothiocyanate (12.0 ml, 0.1 mol). Yield 19.7 g (86%), colorless crystals, mp 201–202°C (2-propanol). IR spectrum, ν, cm^{-1}: 1210 (C=S); 1670 (C=O), 2215 (C≡N), 3280–3370 (2NH). ^{1}H NMR spectrum, δ, ppm: 3.72 (2H, s, CH_2); 7.33–7.38 (5H, m, H Ph); 8.81 (1H, s, NH); 9.28 (2H, s, 2NH). ^{13}C NMR spectrum, δ, ppm: 32.0; 122.4; 125.0 (2C); 126.3 (2C); 127.2; 132.0; 163.0; 203.2. Mass spectrum, *m*/*z* (I_{rel}, %): 234 $[M]^+$ (20), 218 (2), 136 (29), 135 (100), 99 (23), 77 (48), 68 (13). Found, %: C 51.18; H 4.23; N 24.03; S 13.57. $C_{10}H_{10}N_4OS$. Calculated, %: C 51.27; H 4.30; N 23.92; S 13.68.

***N*'-((*E*)-Benzylidene)-2-((*Z*)-3,3-dimethyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene)acetohydrazide (7)**. Cyanacetohydrazide **1** (9.9 g, 0.1 mol) was dissolved in 2-propanol (150 ml) while heating to 60–70°C, and benzaldehyde (10.6 ml, 0.11 mol) was added. Precipitate of *N*'-benzylidene-2-cyanacetohydrazide **2** started to form after 5–10 min as large, colorless crystals. The solution was left for 2 h at room temperature and then cooled to 0°C. The product was filtered off and washed with anhydrous ether (20 ml). The hydrazone was obtained in quantitative yield and after drying for 1 h, was used in the next step without additional purification. A mixture of hydrazone **2** (3.74 g, 21 mmol) and carbinol **6a** (3 ml, 20 mmol) in anhydrous benzene (50 ml) was vigorously stirred and treated by dropwise addition of concd H_2SO_4 (8 ml). The stirring was continued for 15 min at 60–70°C, the reaction mixture was cooled to 20°C, poured into ice water (200 ml), while keeping the

temperature at or below 25°C. The benzene layer was separated, the aqueous phase was neutralized with aqueous 25% ammonia solution while cooling with ice and maintaining the mixture at 20°C. The precipitate that formed was filtered off, dried, and recrystallized. Yield 2.68 g (42%), colorless crystals, mp 169–170°C (2-propanol). IR spectrum, ν, cm^{-1}: 1640 (C=N), 1610 (C=O of chelate), 3150–3300 (NH of chelate and NH of hydrazone). ^{1}H NMR spectrum, δ, ppm: 1.22 (6H, s, $2CH_3$); 2.86 (2H, s, 4-CH_2); 8.02 (1H, s, HC=N); 7.28–7.78 (9H, m, H Ph); 9.83 (1H, s, NH); 10.67 (1H, s, NH of ring). ^{13}C NMR spectrum, δ, ppm: 28.4 (2C); 41.3; 48.7; 76.6; 124.6; 126.5 (2C); 127.0; 127.8; 128.6; 128.8 (2C); 129.1; 129.2; 130.6; 135.0 (2C); 140.1; 153.1. Mass spectrum, *m*/*z* (I_{rel}, %): 319 $[M]^+$ (14), 200 (100), 159 (5), 158 (15), 119 (9). Found, %: C 75.08; H 6.52; N 13.23. $C_{20}H_{21}N_3O$. Calculated, %: C 75.21; H 6.63; N 13.16.

(*Z*)-*N*'-[2-(3,3-dimethyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene)acetyl]benzohydrazide (8a) was obtained analogously to the procedure for preparation of compound **7** from nitrile **3** (4.06 g, 20 mmol) and carbinol **6a** (3.0 g, 20 mmol). Yield 4.08 g (61%), colorless crystals, mp 169–170°C (2-propanol). IR spectrum, ν, cm^{-1}: 1610 (C=O of chelate), 1670 (C=O), 3100–3380 (NH of chelate and free NH). ^{1}H NMR spectrum, δ, ppm: 1.18 (6H, s, $2CH_3$); 2.82 (2H, s, 4-CH_2); 5.29 (1H, s, HC=); 7.26–7.90 (9H, m, H Ph); 9.21 (1H, s, NH); 9.33 (1H, s, 1NH); 10.10 (1H, s, NH of ring). ^{13}C NMR spectrum, δ, ppm: 28.4 (2C); 41.3; 49.0; 78.5; 118.4; 121.8; 124.1; 126.9; 128.6; 128.7 (2C); 129.4 (2C); 130.4; 135.4; 140.0; 152.1; 156.4; 171.0. Mass spectrum, *m*/*z* (I_{rel}, %): 335 $[M]^+$ (12), 200 (100), 159 (7), 158 (12), 105 (80), 77 (63). Found, %: C 71.57; H 6.18; N 12.61. $C_{20}H_{21}N_3O_2$. Calculated, %: C 71.62; H 6.31; N 12.53.

(*Z*)-*N*'-[2-(2'*H*-Spiro[cyclopentane-1,3'-isoquinolin]-1'(4'H)-ylidene)acetyl]benzohydrazide (8b) was obtained analogously to the procedure for preparation of compound **7** from nitrile **3** (4.06 g, 20 mmol) and carbinol **6b** (3.52 g, 20 mmol). Yield 4.77 g (66%), colorless crystals, mp 213–214°C (2-propanol). IR spectrum, ν, cm^{-1}: 1610 (C=O of chelate), 1670 (C=O), 3100–3380 (NH of chelate and free NH). ^{1}H NMR spectrum, δ, ppm: 1.52–1.69 (8H, m, $4CH_2$); 2.91 (2H, s, 4-CH_2); 5.31 (1H, s, HC=); 7.28–7.90 (9H, m, H Ph); 9.24 (1H, s, NH); 9.52 (1H, s, NH); 10.13 (1H, s, NH of ring). ^{13}C NMR spectrum, δ, ppm: 23.0 (4C); 38.5; 59.6; 78.9; 124.1; 126,9; 127.5 (3C); 128.4 (2C); 129.1 (2C); 130.2; 131.7; 132.9; 135.8; 166.0; 170.2. Mass spectrum, *m*/*z* (I_{rel}, %): 361 $[M]^+$ (9), 226 (100), 105 (39), 77 (32). Found, %: C 73.04; H 6.28; N 11.74. $C_{22}H_{23}N_3O_2$. Calculated, %: C 73.11; H 6.41; N 11.63.

(*Z*)-2-[2-(3,3-Dimethyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene)acetyl]-*N*-phenylhydrazine-1-carboxamide (9a) was obtained analogously to the procedure for preparation of compound **7** from nitrile **4** (4.36 g, 20 mmol) and carbinol **6a** (3.0 g, 20 mmol). Yield 4.35 g (62%), colorless crystals, mp 183–184°C (2-propanol). IR spectrum, ν, cm^{-1}: 1610 (C=O of chelate), 1670 (C=O), 3120–3380 (NH of chelate and free NH). ^{1}H NMR spectrum, δ, ppm: 1.18 (6H, s, $2CH_3$); 2.81 (2H, s, 4-CH_2); 5.24 (1H, s, HC=); 6.92–7.61 (9H, m, H Ph); 7.75 (1H, s, NHPh); 8.69 (1H, s, NH); 8.97 (1H, s, NH); 9.30 (1H, s, NH of ring). ^{13}C NMR spectrum, δ, ppm: 28.4 (2C); 41.40; 48.6; 78.6; 118.4; 121.8; 124.1; 126.9; 128.6; 128.7 (2C); 129.2 (2C); 130.3; 135.2; 139.9; 152.0; 156.2; 170.8. Mass spectrum, *m*/*z* (I_{rel}, %): 350 $[M]^+$ (9), 200 (100), 15 (3), 158 (19), 143 (7), 120 (6), 119 (18), 91 (6). Found, %: C 68.43; H 6.21; N 16.07. $C_{20}H_{22}N_4O_2$. Calculated, %: C 68.55; H 6.33; N 15.99.

(*Z*)-2-[2-(2'*H*-Spiro[cyclopentane-1,3'-isoquinolin]-1'(4'H)-ylidene)acetyl]-*N*-phenylhydrazine-1-carboxamide (9b) was obtained analogously to the procedure for preparation of compound **7** from nitrile **4** (4.36 g, 20 mmol) and carbinol **6b** (3.52 g, 20 mmol). Yield 4.29 g (57%), colorless crystals, mp 127–128°C (2-propanol). IR spectrum, ν, cm^{-1}: 1610 (C=O of chelate), 1670 (C=O), 3100–3370 (NH of chelate and free NH). ^{1}H NMR spectrum, δ, ppm: 1.50–1.67 (8H, m, $4CH_2$); 2.90 (2H, s, 4-CH_2); 5.25 (1H, s, HC=); 6.92–7.59 (9H, m, H Ph); 7.78 (1H, s, NHPh); 8.68 (1H, s, NH); 9.02 (1H, s, NH); 9.51 (1H, s, NH of ring). ^{13}C NMR spectrum, δ, ppm: 23.0 (4C); 40.9; 48.6; 78.6; 118.4; 122.0; 124.1; 126.9; 128.7; 128.8 (2C); 129.3(2C); 130.5; 135.3; 140.0; 152.0; 156.2; 170.4. Mass spectrum, *m*/*z* (I_{rel}, %): 376 $[M]^+$ (9), 226 (100), 184 (5), 120 (8), 119 (37), 92 (8). Found, %: C 70.07; H 6.35; N 15.02. $C_{22}H_{24}N_4O_2$. Calculated, %: C 70.19; H 6.43; N 14.88.

(*Z*)-5-[(3,3-Dimethyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene)methyl]-*N*-phenyl-1,3,4-thiadiazol-2-amine (10a) was obtained analogously to the procedure for preparation of compound **7** from nitrile **5** (4.68 g, 20 mmol) and carbinol **6a** (3.0 g, 20 mmol) by stirring for 0.5 h. Yield 2.23 g (64%), yellow crystals, mp 190°C (decomp.). IR spectrum, ν, cm^{-1}: 1640 (C=C), 3100–3270 (NH of chelate and NHPh). ^{1}H NMR spectrum, δ, ppm: 1.26 (6H, s, $2CH_3$); 2.86 (2H, s, 4-CH_2); 5.97 (1H, s, HC=); 6.96–7.81 (9H, m, H Ph); 8.78 (1H, s, NHPh); 10.07 (1H, s, NH of ring). ^{13}C NMR spectrum, δ, ppm: 28.3 (2C); 41.7; 49.1; 77.4; 119.0; 123.2; 124.2 (2C); 124.3; 125.7 (2C); 126.1; 128.5 (2C); 130.7; 132.0; 136.5; 152.3; 157.5. Mass spectrum, *m*/*z* (I_{rel}, %): 348 $[M]^+$ (100), 347 (41), 333 (56), 91 (8), 77 (27). Found, %: C 68.85; H 5.61; N 16.15; S 9.03. $C_{20}H_{20}N_4S$. Calculated, %: C 68.94; H 5.79; N 16.08; S 9.20.

(*Z*)-5-((2'*H*-Spiro[cyclopentane-1,3'-isoquinolin]-1'(4'*H*)-ylidene)methyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (10b) was obtained analogously to the procedure for preparation of compound **10a** from nitrile **5** (4.68 g, 20 mmol) and carbinol **6b** (3.52 g, 20 mmol). Yield 2.28 g (61%), yellow crystals, mp 218°C (decomp.). IR spectrum, ν, cm^{-1}: 1640 (C=C), 3100–3270 (NH of chelate and NHPh). ^{1}H NMR spectrum, δ, ppm: 1.58–1.78 (8H, m, $4CH_2$); 2.94 (2H, s, 4-CH_2); 5.98 (1H, s, HC=); 6.97–7.80 (9H, m, H Ph); 8.95 (1H, s, NHPh); 10.08 (1H, s, NH of ring). ^{13}C NMR spectrum, δ, ppm: 23.1 (4C); 41.8; 49.1; 77.5; 119.0; 123.2; 124.2 (2C); 124.4; 125.8 (2C); 126.2; 128.5 (2C); 131.1; 132.1; 137.2; 152.4; 158.0. Mass spectrum, *m*/*z* (I_{rel}, %): 374 $[M]^+$ (92), 373 (37), 84 (100), 77 (13). Found, %: C 70.47; H 5.86; N 15.11; S 8.47. $C_{22}H_{22}N_4S$. Calculated, %: C 70.56; H 5.92; N 14.96; S 8.56.

X-ray structural analysis of compound 10b was performed on an Agilent XCalibur automatic diffractometer with Agilent EOS two-dimensional CCD detector. The

recording of reflections, determination and refinement of unit cell parameters were performed by using the CrysAlis PRO software suite.[24] The X-ray diffraction data were obtained at sample temperature of 150.0(1) K by using MoKα radiation (λ 0.71073 Å). The structure was solved by direct methods. The full-matrix refinement of non-hydrogen atom positions and temperature parameters was performed in anisotropic approximation. The hydrogen atom positions were revealed from differential synthesis of electron density. All calculations were performed by using the SHELXTL software suite.[25] The key crystallographic parameters and structural refinement parameters for compound **10b** ($C_{22}H_{22}N_4S$, *M* 374.5): monoclinic syngony; space group $P2_1/c$; *a* 7.9313(3), *b* 21.8407(7), *c* 11.2891(4) Å; β 109.892(4)°; *V* 1838.9(1) Å^3; *Z* 4; d_{calc} 1.353 g/cm^3; μ(MoKα) 0.191 mm^{-1}. A pale-yellow monocrystal with the dimensions of 0.1 × 0.15 × 0.3 mm^3 was used to collect the intensities of 8114 reflections (2θ < 52.62°), of which 3711 independent reflections (R_{int} 0.0371) were used for the further refinement. The final values of probability factors: R_1 0.0440 for 2628 observed reflections with $I > 2\sigma(I)$, wR_2 0.0742 for all independent reflections, the number of refined parameters 332, *GOF* 0.949. The complete crystallographic data set was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1553133).

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