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Intramolecular Cyclization of 4-Amino-3-alkylsulfanyl-1,2,4-triazoles as a Method for Annelation of Thiadiazine and Thiadiazole Rings

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Abstract—4-Amino-5-(pyridin-4-yl)-4*H*-1,2,4-triazole-3-thiols reacted with N-substituted isatins to give 2-oxo-3-[5-(pyridin-4-yl)-3-sulfanyl-4*H*-1,2,4-triazole-4-ylimino]-2,3-dihydro-1*H*-indoles which were treated with phenacyl bromides to obtain the corresponding S-phenacyl derivatives. The latter underwent base-catalyzed intramolecular cyclization with formation of 6,7-dihydro-5*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines spiro-fused to 2-oxo-2,3-dihydro-1*H*-indole fragment at C^3. Analogous cyclization of 2,6-di-*tert*-butyl-4-[5-hetaryl-3-(2-aryl-2-oxoethylsulfanyl)-4*H*-1,2,4-triazole-4-ylimino]cyclohexa-2,5-dienones involved the imino nitrogen atom to produce the corresponding 6-aroyl-5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-hetaryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles.

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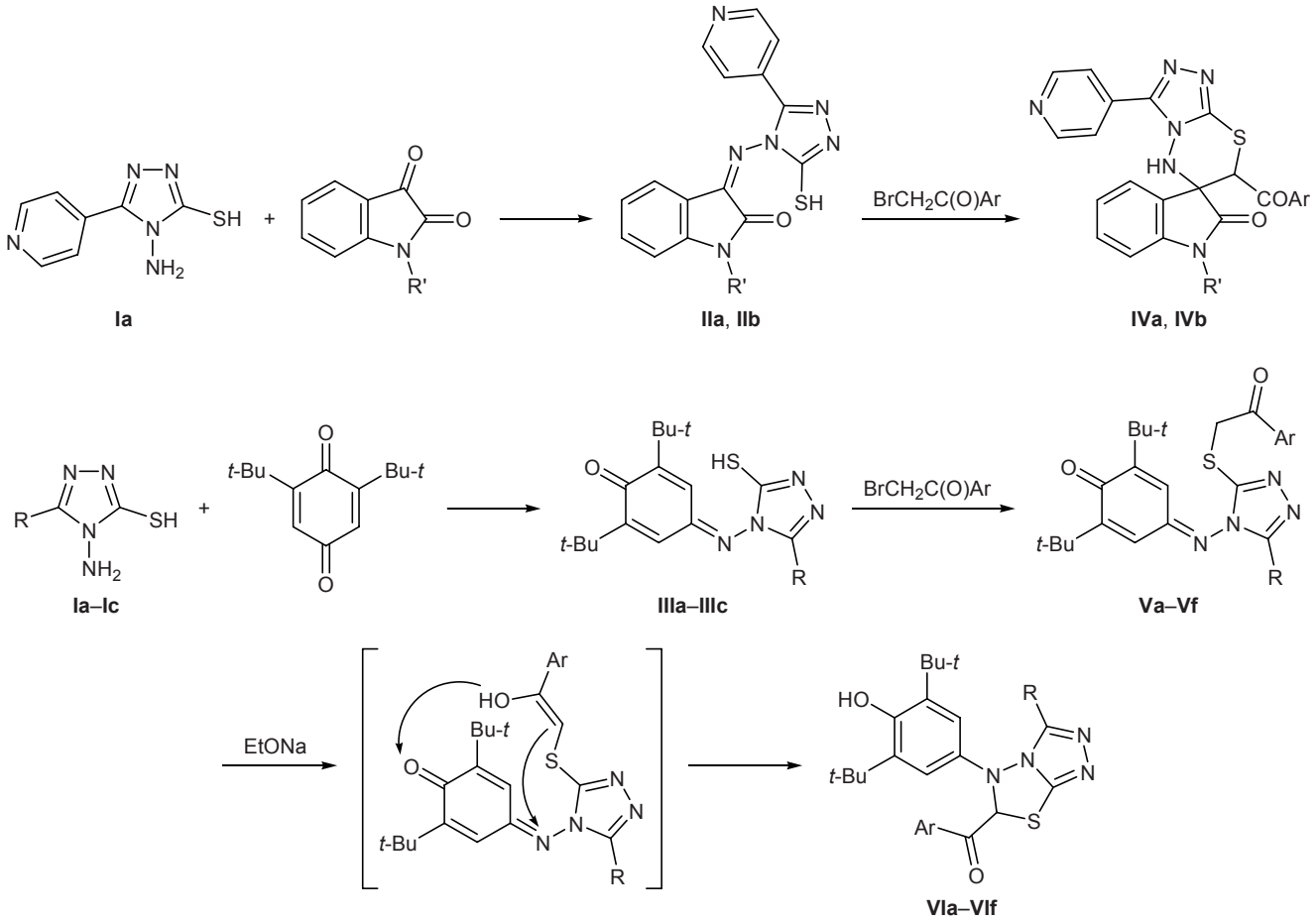
We previously showed that intramolecular cyclization of S-methylene derivatives of imidazolyl imines into 3,4-dihydro-2*H*-imidazo[2,1-*b*][1,3,4]thiadiazines provides a new convenient method for fusion of a dihydrothiadiazine ring to an imidazole fragment via formation of a new C–C bond [1]. In the present work we examined intramolecular cyclization of S-phenacyl derivatives of aminoazolethiols using 4-amino-5-hetaryl-4*H*-1,2,4-triazole-3-thiols as examples with a view to obtain new fused heterocycles, including spiro-fused systems. Despite numerous publications on the synthesis of fused heterocyclic systems containing a 1,2,4-triazole fragment, we have found only two examples of preparation of 6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazines, namely reduction of triazolothiadiazines [2, 3] and reaction of arylmethylideneamino-1,2,4-triazoles with phenacyl bromide and ethyl bromoacetate [4, 5].

By condensation of 4-amino-5-hetaryl-4*H*-1,2,4-triazole-3-thiols **Ia**–**Ic** with N-substituted isatins and 2,6-di-*tert*-butyl-1,4-benzoquinone we obtained the corresponding Schiff bases **IIa**, **IIb**, and **IIIa**–**IIIc**. Alkylation of the sulfanyl group in **II** with phenacyl bromides resulted in the formation of spiro-fused 6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **IVa** and **IVb**. Thus the reaction did not stop at the stage of formation of S-phenacyl-substituted triazole, but the latter rapidly underwent intramolecular cyclization to triazolothiadiazine **IV** (Scheme 1).

The spirocyclic structure of compounds **IV** follows from the presence in their ^{1}H NMR spectra of two one-proton singlets at δ 6.0–6.2 (SCH) and 7.8–8.0 ppm (NH), whereas no two-proton singlet typical of SCH_2 group was observed. Compound **IVb** displayed in the ^{1}H NMR spectrum an *AB* quartet from protons in the prochiral NCH_2Ph methylene group at δ 4.4–5.0 ppm, indicating formation of diastereoisomers. In addition, some signals in the spectra of compounds **IVa** and **IVb** were doubled at ratios of 40 : 60 and 50 : 50, respectively. Thus these compounds are formed as mixtures of diastereoisomers due to the presence in their molecules of two asymmetric carbon atoms.

The structure of triazolothiadiazine derivative **IVb** was unambiguously proved by X-ray analysis (Fig. 1). The thiadiazine ring in molecule **IVb** is flattened ($C^2S^1C^3N^2N^1$ fragment); only the S^1 atom considerably deviates from the plane of the triazolothiadiazine system. The deviations amount to 0.584 Å for C^1, 0.023 Å for C^2, and 0.058 Å for S^1 to the same side of the triazole ring plane, while the N^1 atom deviates by 0.084 Å from the same plane to the opposite side. The H^{1A} and H^{2A} atoms in the thiadiazine ring are arranged *cis* with respect to each other and *trans* with respect to the C^1–C^5 bond in the indole fragment: the torsion

Scheme 1.



I, **III**, R = pyridin-4-yl (**a**), pyridin-3-yl (**b**), 2-furyl (**c**); **II**, R′ = Me (**a**), $PhCH_2$ (**b**); **IV**, Ar = Ph, R′ = Me (**a**); Ar = 4-BrC_6H_4, R′ = $PhCH_2$ (**b**); **V**, **VI**, R = pyridin-4-yl, Ar = 4-BrC_6H_4 (**a**), Ph (**b**); R = pyridin-3-yl, Ar = 4-BrC_6H_4 (**c**), Ph (**d**), 3-$O_2NC_6H_4$ (**e**); R = 2-furyl, Ar = 4-BrC_6H_4 (**f**).

angles $H^{2A}C^2C^1C^5$ and $H^{1A}N^1C^1C^5$ are 171.3(1) and 109.2(3)°, respectively. The C^2–H^{2A} and C^1–C^5 bonds are axial, while C^2–C^{13} and C^1–C^{11} are equatorial. The indole fragment is almost orthogonal to the triazolothiadiazine plane, and the dihedral angle between the $C^2S^1C^3N^2N^1$ and $C^1C^5N^6C^6C^{11}$ planes is 79.80°. The pyridine ring is turned with respect to the triazole ring through an angle of 5°: the torsion angles $C^{17}C^{16}C^4N^2$ and $C^{15}C^{16}C^4N^3$ are 5.1(4) and 4.5(4)°, respectively. The aromatic rings in the *N*-benzyl and *para*-bromobenzoyl fragments are almost coplanar (the dihedral angle between the corresponding planes is 10.30°) but are located at opposite sides with respect to the indole ring system which is orthogonal to the phenyl rings: the corresponding dihedral angles are 79.27 (benzyl) and 83.99° (*para*-bromobenzoyl).

Both asymmetric C^1 and C^2 atoms in the molecule shown in Fig. 1 have *S* configuration according to Cahn–Ingold–Prelog. Monoclinic crystal lattice of compound **IVb** consists of a racemic mixture of (*S*,*S*)- and (*R*,*R*)-diastereoisomers. Molecules **IVb** with the same configuration in crystal give rise to zigzag chains through intermolecular NH···N hydrogen bonds (d = 2.844 Å) between their thiadiazine and triazole fragments (Fig. 2).

In the reactions of quinone imines **III** with phenacyl bromides we isolated only compounds **Va**–**Vf** which underwent intramolecular ring closure by the action of sodium ethoxide in ethanol. However, unlike Schiff bases derived from isatins, the products had the structure of 5,6-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazoles **VI** (Scheme 2). The ^{1}H NMR spectra of compounds **VIa**–**VIf** lacked two-proton singlet typical of SCH_2 methylene protons in initial quinone imines **V**, while signals from CH and OH protons appeared. In addition, two protons in the phenol fragment gave

a two-proton singlet at δ 6.9–7.5 ppm, and protons in the *tert*-butyl groups resonated as a 18H-singlet at δ 1.3–1.4 ppm.

Presumably, closure of thiadiazole ring in compounds **V** is favored by facile enolization of the phenacyl fragment due to enhanced acidity of the methylene group, and the subsequent intramolecular attack by the electrophilic CH carbon atom on the imino nitrogen atom is followed by aromatization of the quinone imine fragment.

To conclude, it should be noted that intramolecular cyclization of phenacylsulfanyl derivatives of *N*-triazolyl imines makes it possible to obtain spirocyclic dihydrotriazolothiadiazines that are inaccessible by other methods via formation of new C–C bond at the last heterocyclization stage. Analogous C–C bonding in the final stage of heterocyclization of quinone imine derivatives **V** is hampered by facile aromatization of the quinone imine fragment, which leads to the formation of dihydrotriazolothiadiazoles **VI**.

EXPERIMENTAL

The ^{1}H NMR spectra were measured at 25°C on Varian Unity-300 (300 MHz) and Bruker DPX-250 (250 MHz) spectrometers using tetramethylsilane as internal reference. The mass spectra were recorded on a Finnigan MAT INCOS-50 mass spectrometer.

A 0.25×0.35×0.40-mm single crystal of compound **IVb** suitable for X-ray analysis was obtained by crystallization from acetonitrile. The X-ray diffraction data (an experimental set of 22445 reflections) were acquired at 120 K on a Bruker SMART 1000 CCD diffractometer (graphite monochromator, λMoK_α irradiation, $2\theta_{max}$ = 58°). Averaging of equivalent reflections gave 7641 independent reflections with R_{int} = 0.0444, which were used in the structure solution and refinement. Colorless needles, $C_{32}H_{24}BrN_7O_2S$, *M* 650.55, monoclinic crystals. Unit cell parameters (120 K): *a* = 14.3376(18), *b* = 7.7669(10), *c* = 26.417(3) Å; β = 101.086(3); *V* = 2886.9(6) Å^3; space group *P*2(1)/*c*; *Z* = 4; d_{calc} = 1.497 g/cm^3; μ = 15.4 cm^{-1}. The structure was solved by the direct method; all non-hydrogen atoms were localized by difference syntheses of electron density, and their positions were refined by F^2_{hkl} in anisotropic approximation. The positions of hydrogen atoms were determined from the geometry considerations and were involved in the refinement procedure using the riding model, *U*(H) = *nU*(C), where *U*(C) is the equivalent temperature factor of the corresponding carbon atom; *n* = 1.2 and 1.5 for sp^2- and sp^3-carbon atoms, respectively. The final divergence factors were R_1 = 0.0532 [for 4587 reflections with $I > 2\sigma(I)$] and wR_2 = 0.1386 (for all 7641 independent reflections); goodness of fit 0.991; 388 refined parameters. All cal-

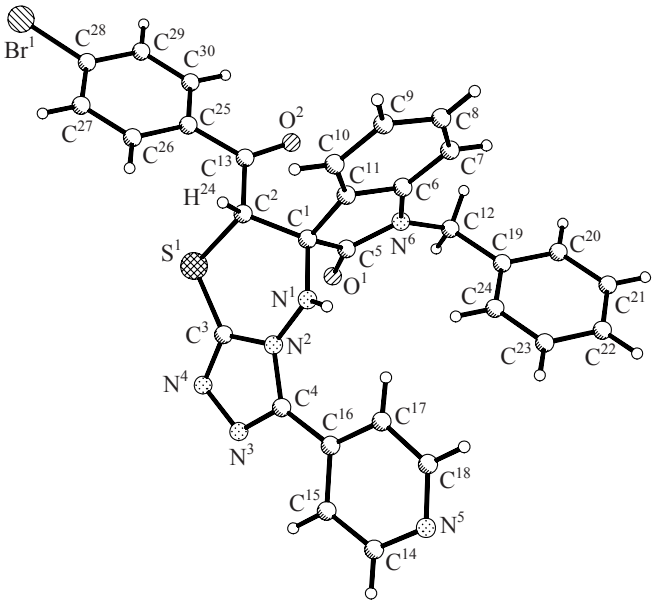


Fig. 1. Structure of the molecule of 1-benzyl-7′-(4-bromobenzoyl)-3′-(pyridin-4-yl)-5′,7′-dihydrospiro[indole-3,6′-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin]-2(1*H*)-one (**IVb**) according to the X-ray diffraction data.

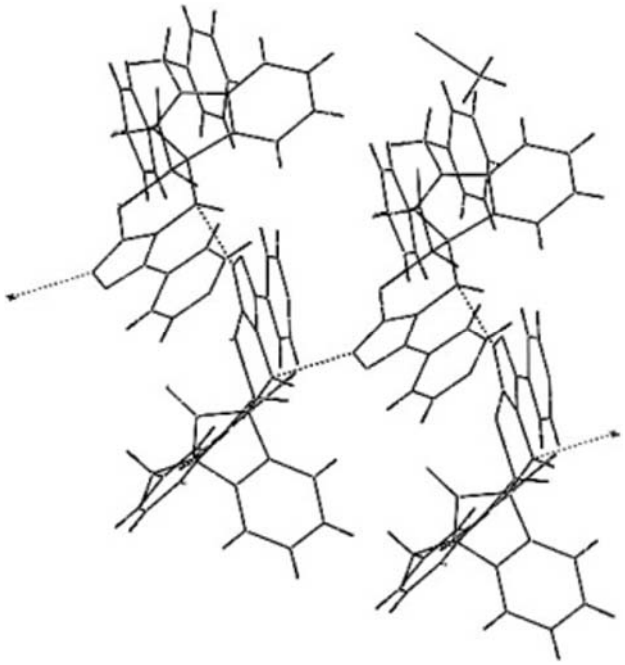


Fig. 2. A fragment of intermolecular hydrogen bond chain in the crystalline structure of 1-benzyl-7′-(4-bromobenzoyl)-3′-(pyridin-4-yl)-5′,7′-dihydrospiro[indole-3,6′-[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazin]-2(1*H*)-one (**IVb**) according to the X-ray diffraction data.

culations were performed using SHELXTL PLUS 5 software package [6]. The complete set of crystallographic data for compound **IVb** was deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 677672).

Initial 4-amino-5-hetaryl-4*H*-1,2,4-triazole-3-thiols were synthesized according to the procedure described previously [7].

3-[5-(Pyridin-4-yl)-3-sulfanyl-4*H*-1,2,4-triazole-4-ylimino]-2,3-dihydro-1*H*-indol-2-ones IIa and IIb (*general procedure***).** A mixture of 20 mmol of aminotriazole **Ia**, 20 mmol of the corresponding N-substituted isatin, and 20 ml of glacial acetic acid was heated for 4 h under reflux. The mixture was cooled and diluted with water, and the precipitate was filtered off and recrystallized from ethanol.

1-Methyl-3-[5-(pyridin-4-yl)-3-sulfanyl-4*H*-1,2,4-triazole-4-ylimino]-2,3-dihydro-1*H*-indol-2-one (IIa). Yield 2.352 g (35%), orange crystals, mp 230°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.08 s (3H, CH_3), 6.85 d (1H, H_{arom}, J = 7.77 Hz), 7.02 t (1H, H_{arom}, J = 7.45 Hz), 7.56 t (1H, H_{arom}, J = 7.45 Hz), 7.81–7.86 m (3H, 1H_{arom}, 2H, pyridine), 8.73 d (2H, pyridine, J = 4.53 Hz), 14.51 s (1H, SH). Mass spectrum, m/z (I_{rel}, %): 336 (60.0) $[M]^+$, 308 (100), 232 (10.1), 193 (13.4), 178 (20.0), 160 (37.8), 131 (76.7), 104 (99.0), 77 (95.0). Found, %: C 57.36; H 3.42; N 25.13. $C_{16}H_{12}N_6OS$. Calculated, %: C 57.13; H 3.60; N 24.98. M 336.38.

1-Benzyl-3-[5-(pyridin-4-yl)-3-sulfanyl-4*H*-1,2,4-triazole-4-ylimino]-2,3-dihydro-1*H*-indol-2-one (IIb). Yield 3.131 g (38%), orange crystals, mp 234°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.72 d and 5.03 d (1H each, NCH_2, J = 15.86 Hz), 6.9 d (1H, H_{arom}, J = 7.44 Hz), 7.02 m (1H, H_{arom}), 7.18 t (1H, H_{arom}, J = 7.44 Hz), 7.33–7.43 m (5H, Ph), 7.58 m (1H, H_{arom}), 7.89 d (2H, pyridine, J = 6.15 Hz), 8.76 d (2H, pyridine, J = 6.15 Hz), 14.51 s (1H, SH). Mass spectrum, m/z (I_{rel}, %): 412 (0.9) $[M]^+$, 384 (1.6), 321 (0.7), 193 (100), 178 (2.1), 162 (6.3), 122 (13.2), 105 (32.5), 78 (39.2). Found, %: C 63.93; H 3.75; N 20.80. $C_{22}H_{16}N_6OS$. Calculated, %: C 64.06; H 3.91; N 20.37. M 412.48.

2,6-Di-*tert*-butyl-4-(5-hetaryl-3-sulfanyl-4*H*-1,2,4-triazole-4-ylimino)cyclohexa-2,5-dienones IIIa–IIIc (*general procedure***).** Aminotriazole **Ia**–**Ic**, 20 mmol, was dissolved in a solution of 20 mmol of sodium hydroxide in 50 ml of methanol, 20 mmol of 2,6-di-*tert*-butyl-1,4-benzoquinone was added, and the mixture was heated for 30–60 min under reflux. The mixture was cooled, diluted with water, and neutralized to pH 7.0–7.5 with dilute hydrochloric acid, and the precipitate was filtered off and recrystallized from benzene–hexane (1 : 1).

2,6-Di-*tert*-butyl-4-[5-(pyridin-4-yl)-3-sulfanyl-4*H*-1,2,4-triazole-4-ylimino]cyclohexa-2,5-dienone (IIIa). Yield 4.345 g (55%), orange crystals, mp 234°C. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 1.25 s and 1.38 s (9H each, *t*-Bu), 7.18 d and 7.26 d (1H each, 3-H, 5-H, J = 2.63 Hz), 7.85 d and 8.74 d (2H each, pyridine, J = 6.13 Hz). Mass spectrum, m/z (I_{rel}, %): 395 (55.0) $[M]^+$, 338 (100), 294 (5.1), 250 (3.2), 218 (65.0), 202 (22.9), 178 (24.2), 105 (22.6), 77 (22.3). Found, %: C 63.83; H 6.35; N 17.80. $C_{21}H_{25}N_5OS$. Calculated, %: C 63.79; H 6.33; N 17.72. M 395.53.

2,6-Di-*tert*-butyl-4-[5-(pyridin-3-yl)-3-sulfanyl-4*H*-1,2,4-triazole-4-ylimino]cyclohexa-2,5-dienone (IIIb). Yield 4.976 g (63%), red crystals, mp 224°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.22 s and 1.31 s (9H each, *t*-Bu), 6.79 d and 7.11 d (1H each, 3-H, 5-H, J = 2.71 Hz), 7.43 d.d (1H, pyridine, J = 4.84, 8.07 Hz), 8.18 d (1H, pyridine, J = 8.20 Hz), 8.73 d (1H, pyridine, J = 4.84 Hz), 9.07 s (1H, pyridine), 11.42 br.s (1H, SH). Mass spectrum, m/z (I_{rel}, %): 395 (10.3) $[M]^+$, 338 (26.9), 294 (2.1), 250 (2.3), 218 (27.0), 202 (9.3), 193 (100), 178 (26.2), 105 (57.5), 78 (43.6). Found, %: C 63.91; H 6.44; N 17.79. $C_{21}H_{25}N_5OS$. Calculated, %: C 63.79; H 6.33; N 17.72. M 395.53.

2,6-Di-*tert*-butyl-4-[5-(furan-2-yl)-3-sulfanyl-4*H*-1,2,4-triazole-4-ylimino]cyclohexa-2,5-dienone (IIIc). Yield 5.143 g (67%), yellow crystals, mp 197°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.21 s and 1.33 s (9H each, *t*-Bu), 6.55 m (1H, furan), 6.76 d (1H, 3-H, J = 2.68 Hz), 6.97 d (1H, furan, J = 3.60 Hz), 7.18 d (1H, 5-H, J = 2.66 Hz), 7.61 s (1H, furan), 11.56 br.s (1H, SH). Mass spectrum, m/z (I_{rel}, %): 384 (15.1) $[M]^+$, 369 (6.1), 327 (25.0), 263 (2.2), 218 (24.9), 202 (11.8), 167 (18.0), 93 (32.6), 41 (100). Found, %: C 62.62; H 6.48; N 14.37. $C_{20}H_{24}N_4O_2S$. Calculated, %: C 62.50; H 6.25; N 14.58. M 384.50.

Triazolo[3,4-*b*][1,3,4]thiadiazines IVa and IVb (*general procedure***).** Compound **IIa** or **IIb**, 5 mmol, and phenacyl or 4-bromophenacyl bromide, 5 mmol, were added to a solution of 5 mmol of sodium hydroxide in 10 ml of alcohol. The mixture was heated to the boiling point, cooled, and diluted with 50 ml of water, and the precipitate was filtered off and recrystallized from acetonitrile.

7′-Benzoyl-1-methyl-3′-(pyridin-4-yl)-5′,7′-dihydrospiro[indole-3,6′-[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazin]-2(1*H*)-one (IVa). Yield 0.272 g (12%), colorless crystals, mp 211°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.82 s (1.8H) and 3.09 s (1.2H) (CH_3), 5.98 s (0.6H) and 6.11 s (0.4H) (7′-H), 6.85 d (0.4H, H_{arom}, J = 8.02 Hz), 6.96–7.14 m (1.2H, H_{arom}), 7.3–7.45 m (5H, H_{arom}), 7.57 m (1.6H, H_{arom}), 7.72 t (0.4H, H_{arom}, J = 6.87 Hz), 7.84 d (2H, pyridine, J = 5.72 Hz), 7.95 m (1.4H, NH, H_{arom}), 8.65 d (2H, pyridine, J = 5.72 Hz). Mass spectrum, m/z (I_{rel}, %): 454 (0.16) $[M]^+$, 308 (2.6), 277 (8.2), 173 (8.7), 160 (6.6), 131 (17.1), 105 (100), 77 (96.0). Found, %: C 63.62; H 3.48; N 19.07. $C_{24}H_{18}N_6O_2S$. Calculated, %: C 63.42; H 3.99; N 18.49. M 454.51.

1-Benzyl-7′-(4-bromobenzoyl)-3′-(pyridin-4-yl)-5′,7′-dihydrospiro[indole-3,6′-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazin]-2(1*H*)-one (IVb). Yield 0.344 g (11%), colorless crystals, mp 214°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.39 d and 4.83 d (0.5H each, NCH_2, J = 15.82 Hz), 4.75 d and 4.93 d (0.5H, NCH_2, J = 15.89 Hz), 6.05 s and 6.22 s (0.5H each, 7′-H), 6.82 d (0.5H, H_{arom}, J = 7.91 Hz), 6.94–7.12 m (4H, H_{arom}), 7.15–7.34 m (4H, H_{arom}), 7.37 d (1H, H_{arom}, J = 8.57 Hz), 7.45 d (0.5H, H_{arom}, J = 7.32 Hz), 7.62 d (1H, H_{arom}, J = 8.49 Hz), 7.78–7.86 m (3H, NH, H_{arom}), 7.9 d (1H, H_{arom}, J = 8.64 Hz), 8.04 d (1H, H_{arom}, J = 2.05 Hz), 8.59 d (1H, H_{arom}, J = 6.01 Hz), 8.65 d (1H, H_{arom}, J = 5.93 Hz). Mass spectrum, m/z (I_{rel}, %): 236 (36.5), 208 (19.3), 185 (19.5), 183 (19.5), 157 (7.3), 155 (7.3), 145 (34.2), 117 (13.5), 91 (100). Found, %: C 60.62; H 3.48; N 14.37. $C_{30}H_{21}BrN_6O_2S$. Calculated, %: C 59.12; H 3.47; N 13.79.

2,6-Di-*tert*-butyl-4-[5-hetaryl-3-(2-aryl-2-oxoethylsulfanyl)-4*H*-1,2,4-triazol-4-ylimino]cyclohexa-2,5-dienones Va–Vf (*general procedure*). Compound **IIIa–IIIc**, 3 mmol, was added to a solution of 3 mmol of sodium hydroxide in 10 ml of methanol, the mixture was stirred until it turned homogeneous, 3 mmol of the phenacyl bromide or 4-bromophenacyl bromide was added, and the mixture was stirred for 15 min on slight heating and evaporated. The residue was treated with 50 ml of water, and the precipitate was filtered off and recrystallized from benzene–hexane (1:3).

4-{3-[2-(4-Bromophenyl)-2-oxoethylsulfanyl]-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-4-ylimino}-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (Va). Yield 1.456 g (82%), yellow crystals, mp 207–208°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.11 s and 1.33 s (9H each, *t*-Bu), 4.90 s (2H, SCH_2), 6.45 d and 7.13 d (1H, 3-H, 5-H, J = 2.71 Hz), 7.63 d (2H, H_{arom}, J = 8.59 Hz), 7.69 d (2H, pyridine, J = 6.14 Hz), 7.87 d (2H, H_{arom}, J = 8.60 Hz), 8.69 d (2H, pyridine, J = 6.13 Hz). Found, %: C 58.84; H 5.11; N 11.71. $C_{29}H_{30}BrN_5O_2S$. Calculated, %: C 58.78; H 5.07; N 11.82.

2,6-Di-*tert*-butyl-4-[3-(2-oxo-2-phenylethylsulfanyl)-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-4-ylimino]-cyclohexa-2,5-dien-1-one (Vb). Yield 1.197 g (78%), yellow crystals, mp 186°C. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 1.20 s and 1.35 s (9H each, *t*-Bu), 5.05 s (2H, SCH_2), 6.82 d and 7.31 d (1H each, 3-H, 5-H, J = 2.69 Hz), 7.58 t (2H, Ph, J = 7.12 Hz), 7.71 t (1H, Ph, J = 7.27 Hz), 7.78 d (2H, pyridine, J = 6.19 Hz), 8.11 d (2H, Ph, J = 7.02 Hz), 8.69 d (2H, pyridine, J = 6.16 Hz). Mass spectrum, m/z (I_{rel}, %): 513 (7.0) $[M]^+$, 471 (67.5), 456 (17.5), 380 (6.7), 338 (20.0), 232 (29.6), 202 (19.8), 176 (17.6), 105 (100), 77 (51.1). Found, %: C 67.99; H 5.91; N 13.77. $C_{29}H_{31}N_5O_2S$. Calculated, %: C 67.84; H 6.04; N 13.65. M 513.67.

4-{3-[2-(4-Bromophenyl)-2-oxoethylsulfanyl]-5-(pyridin-3-yl)-4*H*-1,2,4-triazol-4-ylimino}-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (Vc). Yield 1.434 g (81%), yellow crystals, mp 194°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.09 s and 1.29 s (9H each, *t*-Bu), 4.86 s (2H, SCH_2), 6.49 d and 7.10 d (1H each, 3-H, 5-H, J = 2.73 Hz), 7.36 d.d (1H, pyridine, J = 4.84, 8.15 Hz), 7.61 d and 7.86 d (2H each, H_{arom}, J = 8.58 Hz), 8.13 d (1H, pyridine, J = 7.99 Hz), 8.61 d (1H, pyridine, J = 4.87 Hz), 8.94 s (1H, pyridine). Mass spectrum, m/z (I_{rel}, %): 591 (0.6) $[M]^+$, 552 (2.8), 494 (5.1), 492 (5.1), 232 (58.0), 218 (22.3), 202 (27.9), 185 (97.0), 183 (100). Found, %: C 58.88; H 5.16; N 11.92. $C_{29}H_{30}BrN_5O_2S$. Calculated, %: C 58.78; H 5.07; N 11.82. M 592.56.

2,6-Di-*tert*-butyl-4-[3-(2-oxo-2-phenylethylsulfanyl)-5-(pyridin-3-yl)-4*H*-1,2,4-triazol-4-ylimino]-cyclohexa-2,5-dien-1-one (Vd). Yield 1.250 g (81%), yellow crystals, mp 88°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.12 s and 1.31 s (9H, *t*-Bu), 4.95 s (2H, SCH_2), 6.50 d and 7.12 d (1H, 3-H, 5-H, J = 2.69 Hz), 7.39 d.d (1H, pyridine, J = 4.84, 8.13 Hz), 7.48 t (2H, Ph, J = 7.21 Hz), 7.60 t (1H, Ph, J = 7.26 Hz), 8.02 d (2H, Ph, J = 7.27 Hz), 8.16 d.d (1H, pyridine, J = 8.12, 3.57 Hz), 8.64 d.d (1H, pyridine, J = 4.72, 1.31 Hz), 8.94 d (1H, pyridine, J = 1.31 Hz). Mass spectrum, m/z (I_{rel}, %): 513 (4.0) $[M]^+$, 471 (7.9), 414 (15.2), 336 (2.5), 232 (42.3), 218 (14.9), 202 (22.0), 176 (31.4), 105 (100). Found, %: C 68.18; H 5.66; N 12.94.

$C_{29}H_{31}N_5O_2S$. Calculated, %: C 67.81; H 6.08; N 13.63. *M* 513.67.

2,6-Di-*tert*-butyl-4-{3-[2-(3-nitrophenyl)-2-oxoethylsulfanyl]-5-(pyridin-3-yl)-4*H*-1,2,4-triazol-4-ylimino}cyclohexa-2,5-dien-1-one (Ve). Yield 1.411 g (84%), yellow crystals, mp 117°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.12 s and 1.31 s (9H each, *t*-Bu), 4.92 s (2H, SCH_2), 6.52 d and 7.13 d (1H, 3-H, 5-H, *J* = 2.63 Hz), 7.39 d.d (1H, pyridine, *J* = 4.88, 8.38 Hz), 7.72 t (1H, H_{arom}, *J* = 8.05 Hz), 8.16 d.d (1H, pyridine, *J* = 8.02, 3.70 Hz), 8.36 d (1H, H_{arom}, *J* = 7.78 Hz), 8.45 d (1H, H_{arom}, *J* = 7.42 Hz), 8.64 d (1H, pyridine, *J* = 4.80 Hz), 8.84 d (1H, H_{arom}, *J* = 1.80 Hz), 8.94 s (1H, pyridine). Mass spectrum, *m*/*z* (I_{rel}, %): 559 (4.1) $[M]^+$, 459 (20), 395 (12.5), 338 (30.0), 232 (45.2), 216 (75.0), 202 (23.8), 178 (46.1), 150 (100). Found, %: C 62.18; H 5.74; N 14.64. $C_{29}H_{30}N_6O_4S$. Calculated, %: C 62.35; H 5.41; N 15.04. *M* 558.66.

4-{3-[2-(4-Bromophenyl)-2-oxoethylsulfanyl]-5-(furan-2-yl)-4*H*-1,2,4-triazol-4-ylimino}-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (Vf). Yield 1.327 g (76%), yellow crystals, mp 180°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.11 s and 1.33 s (9H each, *t*-Bu), 4.87 s (2H, SCH_2), 6.49 d.d (1H, furan, *J* = 3.48, 1.77 Hz), 6.51 d (1H, 3-H, *J* = 2.64 Hz), 6.85 d (1H, furan, *J* = 3.26 Hz), 7.14 d (1H, 5-H, *J* = 2.67 Hz), 7.48 s (1H, furan), 7.62 d and 7.88 d (2H each, H_{arom}, *J* = 8.51 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 583 (15) $[M + 1]^+$, 581 (14.5) $[M - 1]^+$, 483 (22.2), 481 (21.6), 232 (41.7), 218 (22.0), 202 (35.9), 185 (87.5), 183 (100). Found, %: C 57.91; H 5.06; N 9.71. $C_{28}H_{29}BrN_4O_3S$. Calculated, %: C 57.83; H 4.99; N 9.64. *M* 581.54.

1,2,4-Triazolo[3,4-*b*][1,3,4]thiadiazoles VIa–VIf (*general procedure*). Compound **Va**–**Vf**, 2 mmol, was added to 10 ml of a solution of excess sodium ethoxide in ethanol on cooling with an ice bath. The mixture was kept for 15 min, diluted with 50 ml of water, and neutralized with dilute acetic acid to pH 7.0–7.5. The precipitate was filtered off and recrystallized from benzene–hexane (3 : 1).

(4-Bromophenyl){5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(pyridin-4-yl)-5,6-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl}methanone (VIa). Yield 0.600 g (51%), light yellow crystals, mp 154°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.40 s (18H, *t*-Bu), 5.31 s (1H, 6-H), 6.89 s (2H, 2′-H, 6′-H), 7.35 d and 7.51 d (2H each, H_{arom}, *J* = 8.53 Hz), 7.90 d and 8.51 d (2H each, pyridine, *J* = 4.80 Hz). Found, %: C 58.91; H 5.24; N 12.11. $C_{29}H_{30}BrN_5O_2S$. Calculated, %: C 58.78; H 5.07; N 11.82.

5-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(pyridin-4-yl)-5,6-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl(phenyl)methanone (VIb). Yield 0.470 g (46%), light yellow crystals, mp 232°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.35 s (18H, *t*-Bu), 6.79 s (1H, 6-H), 7.44 s (2H, 2′-H, 6′-H), 7.85 d (2H, pyridine, *J* = 4.89 Hz), 7.92 m (3H, Ph), 8.71 m (2H, Ph), 8.74 d (2H, pyridine, *J* = 5.08 Hz), 13.91 s (1H, OH). Mass spectrum, *m*/*z* (I_{rel}, %): 513 (0.7) $[M]^+$, 336 (6.3), 282 (3.8), 216 (11.2), 178 (13.8), 105 (100), 77 (74.9). Found, %: C 68.03; H 6.21; N 13.82. $C_{29}H_{31}N_5O_2S$. Calculated, %: C 67.84; H 6.04; N 13.65. *M* 513.67.

(4-Bromophenyl){5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(pyridin-3-yl)-5,6-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl}methanone (VIc). Yield 0.517 g (44%), colorless crystals, mp 214–216°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.35 s (18H, *t*-Bu), 5.26 s (1H, 6-H), 6.90 s (2H, 2′-H, 6′-H), 7.34 m (1H, pyridine), 7.35 d and 7.44 d (2H each, H_{arom}, *J* = 8.63 Hz), 8.45 m (2H, pyridine), 9.61 s (1H, pyridine). Mass spectrum, *m*/*z* (I_{rel}, %): 593 (12.4) $[M + 1]^+$, 591 (12.4) $[M - 1]^+$, 575 (1.8), 416 (0.8), 362 (0.6), 263 (0.5), 216 (17.1), 178 (100), 105 (23.2), 78 (15.9). Found, %: C 58.91; H 5.24; N 12.03. $C_{29}H_{30}BrN_5O_2S$. Calculated, %: C 58.78; H 5.07; N 11.82. *M* 592.56.

5-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(pyridin-3-yl)-5,6-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl(phenyl)methanone (VId). Yield 0.386 g (38%), colorless crystals, mp 192°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.31 s (18H, *t*-Bu), 6.75 s (1H, 6-H), 7.39 m (1H, pyridine), 7.41 s (2H, 2′-H, 6′-H), 7.55 m (3H, Ph), 8.22 m (1H, pyridine), 8.61 m (3H, Ph, pyridine), 9.06 s (1H, pyridine). Mass spectrum, *m*/*z* (I_{rel}, %): 513 (1.9) $[M]^+$, 497 (0.6), 452 (1.2), 336 (4.2), 282 (77.3), 263 (38.1), 178 (76.2), 105 (100), 77 (18.4). Found, %: C 67.18; H 6.16; N 13.24. $C_{29}H_{31}N_5O_2S$. Calculated, %: C 67.81; H 6.08; N 13.63. *M* 513.67.

5-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(pyridin-3-yl)-5,6-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl(3-nitrophenyl)methanone (VIe). Yield 0.400 g (36%), colorless crystals, mp 195°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.34 s (18H, *t*-Bu), 6.81 s (1H, 6-H), 7.42 m (1H, pyridine), 7.45 s (2H, 2′-H, 6′-H), 7.79 m (1H, H_{arom}), 8.26–8.41 m (2H, H_{arom}, pyridine), 8.63 m (2H, H_{arom}, pyridine), 9.12 m (2H, H_{arom}, pyridine). Mass spectrum, *m*/*z* (I_{rel}, %): 540 (0.5), 525 (0.8), 493 (1.2), 446 (1.1), 370 (1.8), 325 (2.2), 248 (4.3), 216 (7.5), 178 (27.3), 150 (72.4), 104

(100), 76 (91.1). Found, %: C 62.88; H 5.84; N 15.67. $C_{29}H_{30}N_6O_4S$. Calculated, %: C 62.35; H 5.41; N 15.04.

(4-Bromophenyl){5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(furan-2-yl)-5,6-dihydro[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazol-6-yl}methanone (VIf). Yield 0.546 g (47%), colorless crystals, mp 151°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.35 s (18H, *t*-Bu), 5.29 s (1H, 6-H), 6.87 s (2H, 2′-H, 6′-H), 7.37 m (4H, H_{arom}), 7.90 d (1H, furan, J = 5.90 Hz), 8.33 m (1H, furan), 8.60 d (1H, furan, J = 5.74 Hz). Mass spectrum, m/z (I_{rel}, %): 397 (0.7), 216 (8.0), 185 (94.2), 183 (100), 167 (23.1), 157 (25.0), 155 (25.0), 109 (16.1), 76 (23.3). Found, %: C 58.04; H 5.11; N 9.81. $C_{28}H_{29}BrN_4O_3S$. Calculated, %: C 57.83; H 4.99; N 9.64.

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