Synthesis of bis-spirofused thiapyrrolizidinooxindoles by 1,3-dipolar cycloaddition

A. A. Shvets,[a] Yu. V. Nelyubina,[b] K. A. Lyssenko,[b] and S. V. Kurbatov[a]*

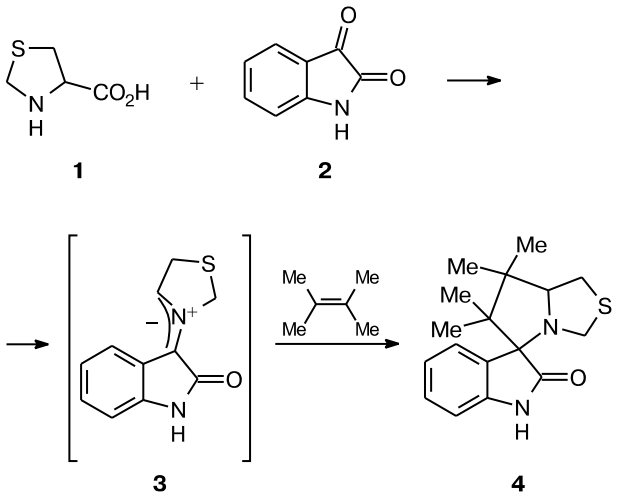
[a]*Department of Chemistry, Southern Federal University, 7 ul. Zorge, 344090 Rostov-on-Don, Russian Federation. Fax: +7 (863) 297 5267. E-mail: shvets@sfedu.ru*
[b]*A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 119991 Moscow, Russian Federation. Fax: +7 (499) 135 5085. E-mail: kostya@xray.ineos.ac.ru*

The 1,3-dipolar cycloaddition of unstabilized azomethine ylide, which is generated *in situ* from isatin and thiaproline, to arylidene derivatives of rhodanine affords bis-spirofused thiapyrrolizidinooxindoles. The 1,3-dipolar addition reactions under consideration are fully regio- and diastereoselective.

Key words: isatin, thiaproline, spiroheterocycles, spirothiapyrrolizidinooxindole, azomethine ylides, 1,3-dipolar cycloaddition.

It is known[1] that α-amino acids (for example, thiaproline **1**) react with isatin **2** to form *in situ* unstable azomethine ylides **3**, and the latter readily undergo addition to C=C dipolarophiles to give thiapyrrolizidinooxindoles **4**. In recent years, the literature has seen an explosion of interest in compounds, which contain substructure **4** (see Ref. 2) and exhibit antidiabetic[3] and antituberculosis[3—5] activity.

Scheme 1



We studied for the first time the 1,3-dipolar cycloaddition of azomethine ylide **3** to arylidene and heteroarylidene rhodanines **5**. We chose compounds **5** as dipolarophiles for the following reasons. Firstly, arylidene rhodanines exhibit antiviral,[6] antileukemic,[7] and antidiabetic[8] properties. Secondly, these compounds additionally include two diversification points, which allows one to change the pharmacodynamic and pharmacokinetic activity of the target compounds by varying the substituent at the nitrogen atom and the arylidene moiety. Earlier, arylidene and heteroarylidene derivatives of rhodanine have been synthesized either by heating the corresponding aldehyde and rhodanine in acetic acid under prolonged reflux[9] or under microwave radiation.[10] The method developed in the present study is suitable for the preparation of rhodanine derivatives **5**, without additional purification, in high yields at room temperature within a few minutes (Scheme 2).

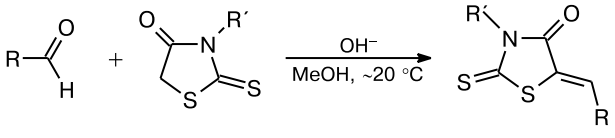
The heating of a mixture of compounds **1**, **2**, and **5** under reflux in methanol for 3 h results in the *in situ* formation of azomethine ylide **3**, which undergoes addition to the asymmetric C=C bond of compounds **5** exclusively *via* the path *B* to form vicinally fused bis-spirocycles **6a—c** (Scheme 3).

This is evidenced by the characteristic spin-spin interactions between the hydrogen atoms at the C(3′a) and C(4′) atoms. The COSY spectra of **6a—c** are also indicative of the vicinal positions of the spiro units in molecules **6a—c**, because they show correlations between the signal of the proton at the C(3′a) atom observed at δ 4.75 and the signals of the hydrogen atoms at the C(4′) atom and the protons of the methylene unit $C(3')H_2$.

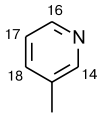
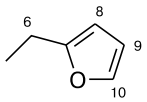
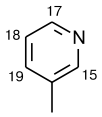
The structure of compound **6a** was established by X-ray diffraction (Fig. 1). It should be noted that the carbonyl groups of the 2-oxindole and rhodanine moieties are in

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1642—1645, August, 2012.

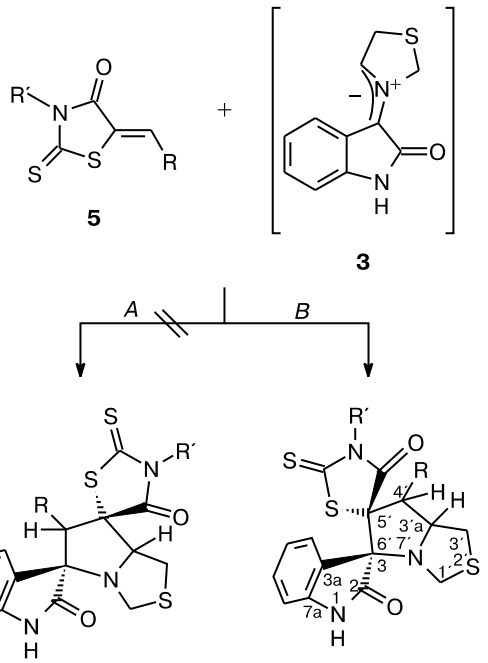
Scheme 2



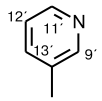
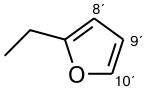
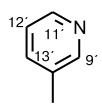
5a—c

Compound	R	R´
5a		
5b		Bn
5c	Ph	Bn

Scheme 3



6a—c

6	R	R´
a		
b		Bn
c	Ph	Bn

a transoid configuration. This is apparently due to the intramolecular O(14)...S(1´) interaction accompanied by the charge transfer from the lone pair of the oxygen atom to the σ* orbital of the S(1´)—C(2´) bond (S...O, 3.060(2) Å; C—S—O, 148.9(1)°). The cycloaddition results in the formation of four chiral centers, thus indicating that formally 16 stereoisomers of compound **6** can be formed. However, since the addition of azomethine ylide **3** takes place *via* the equally probable attack from above or below of the enantiotropic plane of dipolarophile **5** accompanied by the formation of spiro units, only two stereoisomers (enantiomers) are produced, and they were isolated from the reaction as a racemate. The absence of even trace amounts of other possible stereoisomers in the ^{1}H NMR spectra confirms the full diastereoselectivity of the cycloaddition. According to the X-ray diffraction data, molecules **6a** in

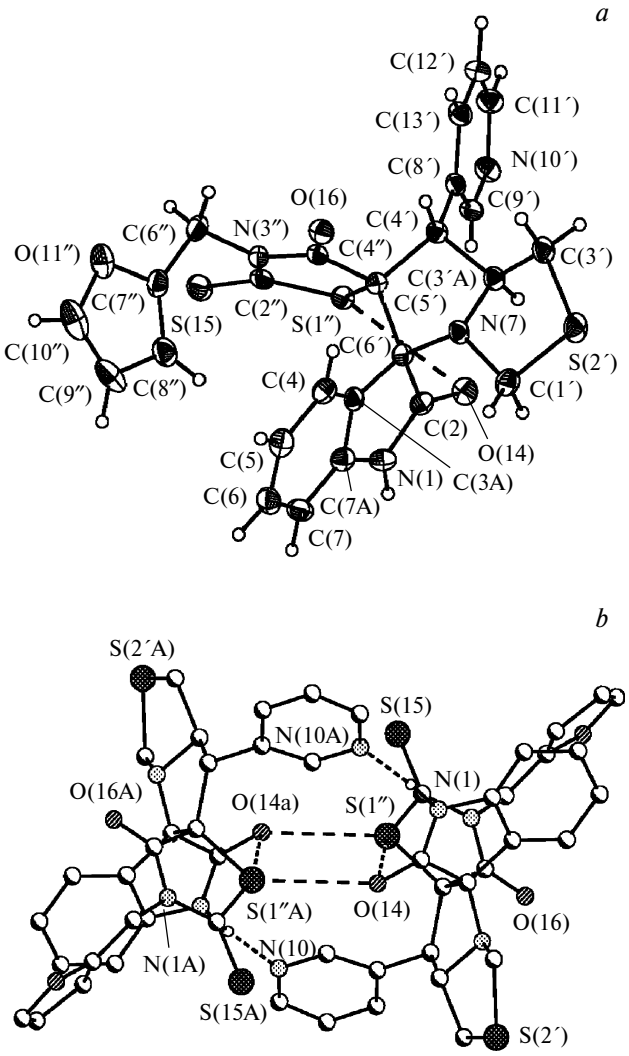


Fig. 1. Molecular structure of compound **6a** with thermal ellipsoids ($p = 50\%$) (*a*) and the centrosymmetric dimer in the crystal structure (*b*) (hydrogen atoms, except for H(1N), are not shown).

the crystal structure are packed as a racemic mixture (space group $P2_1/c$) through the N(1)—H(1N)...N(10′) hydrogen bond (N...N, 2.825(2) Å; N—H—N, 165°) and the intermolecular O(14)...S(1′) interaction (S...O, 3.279(2) Å; C—S—O, 132.7(1)°), resulting in the formation of centrosymmetric dimers (see Fig. 1). The supramolecular associates are linked to each other by a number of weak contacts (C—H...S, C—H...O, C=S...π, and C—H...π) to form a three-dimensional framework.

Therefore, due to the full regio- and diastereoselectivity combined with the possibility of varying substituents both in the oxindole core and the rhodanine moiety, these methods can be used for the synthesis of wide series of potent biologically active bis-spirofused heterocycles.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker DPX-250 instrument (250 MHz, 60 MHz) in $CDCl_3$ and DMSO-d_6 using Me_4Si as the internal standard. Single crystals of compound **6a** were obtained by the crystallization from methanol.

X-ray diffraction study. Crystals of **6a** ($C_{25}H_{20}N_4O_3S_3$, M = 520.63) are monoclinic, space group $P2_1/c$ at 120 K: a = 12.9604(8) Å, b = 17.8710(11) Å, c = 10.0603(7) Å, β = 95.0370(10)°, V = 2321.1(3) Å^3, Z = 4 (Z' = 1), d_{calc} = = 1.490 g cm^{-3}, μ(MoKα) = 3.57 cm^{-1}, F(000) = 1080. The intensities of 14973 reflections were measured on a Bruker SMART 1000 CCD diffractometer (λ(MoKα) = 0.71072 Å, ω-scanning technique, 2θ < 58°), and 6131 unique reflections (R_{int} = 0.0217) were used in the subsequent refinement. The structure was solved by direct methods and refined by the full-matrix least-squares method based on F^2 with anisotropic and isotropic displacement parameters. The hydrogen atoms were positioned geometrically and refined isotropically using a riding model. The final R factors for compound **6a** were wR_2 = 0.1187, GOOF = 1.018 for all unique reflections (R_1 = 0.0484 was calculated based on F for 4611 observed reflections with $I > 2\sigma(I)$). All calculations were carried out using the SHELXTL PLUS 5.0 program package.[11]

N-Benzylrhodanine[12] and *N*-furfurylrhodanine[9] were synthesized according to known procedures.

Synthesis of arylidene or heteroarylidene derivatives of rhodanine 5a—c (general procedure). A 40% KOH aqueous solution (0.1 mL) was added to a solution of equimolar amounts of the corresponding aldehyde (1 mol) and N-substituted rhodanine (1 mol) in methanol (30 mL). After 20 min, the precipitate that formed was filtered off and washed with methanol.

3-(Furan-2-ylmethyl)-5-(pyridin-3-ylmethylene)-2-thioxo-1,3-thiazolidin-4-one (5a). Yellow crystals. Yield 82%, m.p. 179 °C. Found (%): C, 55.59; H, 3.45; N, 8.95. $C_{14}H_{10}N_2O_2S_2$. Calculated (%): C, 55.61; H, 3.33; N, 9.26. ^{1}H NMR ($CDCl_3$), δ: 5.32 (s, 2 H, H(6)): 6.31 (dd, 1 H, H(9), J = 3.2 Hz, J = 1.9 Hz); 6.43 (d, 1 H, H(8), J = 3.2 Hz); 7.34 (dd, 1 H, H(10), J = 1.9 Hz, J = 0.9 Hz); 7.43 (dd, 1 H, H(17), J = 8.1 Hz, J = 4.9 Hz); 7.72 (s, 1 H, =CH); 7.76 (m, 1 H, H(18)); 8.63 (dd, 1 H, H(16), J = 4.9 Hz, J = 1.5 Hz); 8.76 (d, 1 H, H(14), J = 2.1 Hz).

3-Benzyl-5-(pyridin-3-ylmethylene)-2-thioxo-1,3-thiazolidin-4-one (5b). Yellow crystals. Yield 76%, m.p. 182 °C. Found (%): C, 61.38; H, 3.71; N, 9.17. $C_{16}H_{12}N_2OS_2$. Calculated (%): C, 61.51; H, 3.87; N, 8.97. ^{1}H NMR ($CDCl_3$), δ: 5.32 (s, 2 H, H(6)); 7.26—7.52 (m, 6 H, Ph, H(18)); 7.70 (s, 1 H, =CH); 7.75 (dd, 1 H, H(19), J = 8.1 Hz, J = 2.2 Hz); 8.63 (dd, 1 H, H(17), J = 4.7 Hz, J = 1.6 Hz); 8.76 (d, 1 H, H(15), J = 2.2 Hz).

3-Benzyl-5-benzylidene-2-thioxo-1,3-thiazolidin-4-one (5c). Yield 63%, m.p. 155 °C (*cf.* lit. data[12]: m.p. 157—159 °C). Found (%): C, 64.93; H, 4.80; N, 4.39. $C_{17}H_{13}NOS_2$. Calculated (%): C, 65.57; H, 4.21; N, 4.50. ^{1}H NMR ($CDCl_3$), δ: 5.32 (s, 2 H, H(6)); 7.26 (m, 3 H, Bn); 7.42—7.58 (m, 7 H, Bn, Ph); 7.74 (s, 1 H, =CH).

Synthesis of bis-spirothiapyrrolizidinooxindoles 6a—c (general procedure). A mixture of dipolarophile **5** (1 mmol), isatin **6** (1 mmol, 147 mg), and thiaproline **1** (1 mmol, 133 mg) was suspended in methanol (30 mL). The reaction mixture was refluxed for 3 h. The course of the reaction was monitored by TLC on Silufol 245 plates in AcOEt; the spots were visualized with iodine vapor. The reaction mixture was cooled, methanol was distilled off under reduced pressure, and the residue was recrystallized from methanol.

3″-(2-Furylmethyl)-4′I-(pyridin-3-yl)-2″-thioxo-4′,3a′-dihydro-3′*H*,4″*H*-dispiro[indole-3,6′-pyrrolo[1,2-*c*][1,3]thiazole-5′,5″-[1,3]thiazolidine]-2,4″(1*H*)-dione (6a). Pale-yellow crystals. Yield 40%, m.p. 190 °C (MeOH). Found (%): C, 57.83; H, 3.99; N, 10.65. $C_{25}H_{20}N_4O_3S_3$. Calculated (%): C, 57.67; H, 3.87; N, 10.76. ^{1}H NMR ($CDCl_3$), δ: 2.88 (dd, 1 H, C(3′)H$_2$, J = 9.6 Hz, J = 7.0 Hz); 3.01 (dd, 1 H, C(3′)H$_2$, J = 9.6 Hz, J = 7.0 Hz); 3.63 (d, 1 H, C(1′)H$_2$, J = 6.0 Hz); 4.02 (d, 1 H, C(1′)H$_2$, J = 6.0 Hz); 4.21 (d, 1 H, H(4′), J = 9.6 Hz); 4.81—5.07 (m, 3 H, H(3′a), NC(6″)H$_2$Furyl); 6.10 (d, 1 H, H(8″), J = 3.5 Hz); 6.22 (dd, 1 H, H(9″), J = 3.5 Hz, J = 2.8 Hz); 6.70 (d, 1 H, H(7), J = 7.9 Hz); 6.90 (dd, 1 H, H(1), J = 7.9 Hz, J = 7.9 Hz); 7.18—7.24 (m, 1 H, H(10″)); 7.23—7.29 (m, 1 H, H(5)); 7.32 (dd, 1 H, H(12′), J = 7.9 Hz, J = 4.7 Hz); 7.39 (d, 1 H, H(4), J = 7.9 Hz); 7.88 (d, 1 H, H(13′), J = 7.9 Hz); 7.96 (s, 1 H, N(1)H); 8.43 (d, 1 H, H(9′), J = 1.2 Hz); 8.56 (dd, 1 H, H(11′), J = 4.7, J = 1.2 Hz).

3″-Benzyl-(4′-pyridin-3-yl)-2″-thioxo-4′,3a′-dihydro-3′*H*, 4″*H*-dispiro[indole-3,6′-pyrrolo[1,2-*c*][1,3]thiazole-5′,5″-[1,3]-thiazolidine]-2,4″(1*H*)-dione (6b). Pale-yellow crystals. Yield 45%, m.p. 195 °C (MeOH). Found (%):C, 61.05; H, 4.26; N, 10.43. $C_{27}H_{22}N_4O_2S_3$. Calculated (%): C, 61.11; H, 4.18; N, 10.56. ^{1}H NMR ($CDCl_3$), δ: 2.91 (dd, 1 H, C(3′)H$_2$, J = 9.5 Hz, J = 7.0 Hz); 3.04 (dd, 1 H, C(3′)H$_2$, J = 9.5 Hz, J = 7.0 Hz); 3.66 (d, 1 H, C(1′)H$_2$, J = 6.0 Hz); 4.05 (d, 1 H, C(1′)H$_2$, J = 6.0 Hz); 4.24 (d, 1 H, H(4′), J = 9.2 Hz); 4.83—5.23 (m, 3 H, H(3′a), NCH$_2$Ph); 6.75 (dd, 1 H, H(6), J = 7.6 Hz, J = 7.6 Hz); 6.84 (d, 1 H, H(7), J = 7.6 Hz); 7.00—7.12 (m, 2 H, H(4), H(5)); 7.16—7.35 (m, 5 H, Ph); 7.40 (dd, 1 H, H(12′), J = 7.6 Hz, J = 4.7 Hz); 7.90 (d, 1 H, H(13′), J = 7.9 Hz); 8.51 (s, 1 H, 1-NH); 8.55—8.80 (m, 2 H, H(9′), H(11′)). ^{13}C NMR (DMSO-d_6), δ: 38.1 (C (3′)), 47.0 (C(6″)), 47.5 (C(4′)), 55.2 (C(3′a)), 69.9 (C(1′)), 75.6 (C(5′)), 76.1 (C(6′)), 110.5 (C(7)), 121.5 (C(3a)), 122.5 (C(5)), 123.7 (C(12′)), 127.1 (C(8″), C(12″), Bn), 127.4 (C(4)), 127.5 (C(10″)), 128.4(C(9″), C(11″), Bn), 130.9 (C(6)), 131.7 (C(8′)), 134.1 (C(7″)), 137.3 (C(13′)), 143.1 (C(7a)), 149.3 (C(9′)), 150.2 (C(11″)), 175.8 (C(2)), 175.9(C(4″)), 197.7 (C(2″)).

3″-Benzyl-4′-phenyl-2″-thioxo-4′,3a′-dihydro-3′*H*,4″*H*-dispiro[indole-3,6′-pyrrolo[1,2-*c*][1,3]thiazole-5′,5″-[1,3]thiazolidine]-2,4″(1*H*)-dione (6c). Pale-yellow crystals. Yield 44%, m.p. 172 °C (MeOH). Found (%): C, 63.55; H, 4.33; N, 7.91.

$C_{28}H_{23}N_3O_2S_3$. Calculated (%): C, 63.49; H, 4.38; N, 7.93. ^{1}H NMR ($CDCl_3$), δ: 2.84 (dd, 1 H, C(3′)H_2, J = 9.6 Hz, J = 7.1 Hz); 3.02 (dd, 1 H, C(3′)H_2, J = 9.6 Hz, J = 7.1 Hz); 3.62 (d, 1 H, C(1′)H_2, J = 6.0 Hz); 3.97 (d, 1 H, C(1′)H_2, J = 6.0 Hz); 4.19 (d, 1 H, H(4′), J = 9.6 Hz); 4.85—5.09 (m, 3 H, H(3′a), CH_2Ph); 6.65—6.85 (m, 2 H, H(7), H(6)); 6.95—7.40 (m, 12 H, H(4), H(5), Ph^1, Ph^2); 7.78 (s, 1 H, N(1)H). ^{13}C NMR (DMSO-d_6), δ: 38.8 (C (3′)), 47.0 (C(6″)), 47.3 (C(4′)), 57.9 (C(3′a)), 69.7 (C(1′)), 75.6 (C(5′)), 76.9 (C(6′)), 110.4 (C(7)), 121.9 (C(3a)), 122.4 (C(5)), 126.9 (C(8″), C(12″), Bn), 127.3 (C(4)), 127.5 (C(10″)), 128.2 (C(11″)), 128.4 (C(9″), C(11″), Bn), 128.9 (C(9′), C(13′), Ph), 129.6 (C(12′), C(10′), Ph), 130.9 (C(6)), 134.1 (C(7″), 135.5 (C(8′)), 143.1 (C(7a)), 175.7 (C(2)), 176.2 (C(4″)), 198.4 (C(2″)).

This study was financially supported by the Russian Foundation for Basic Research (Project No. 09-03-00726-a), the Foundation for Facilitation of Development of Small Businesses in the Field of Science and Technology (Project No. 9653/10), and the Ministry of Education and Science of the Russian Federation (Project AVTsP RNP VSh 3.6.11).

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Received August 18, 2011;
in revised form April 9, 2012