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[3 + 2]-Cycloaddition of azomethine ylide at 1,3-dimethyl-6-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)-3a,9a-diphenyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*][1,3]thiazolo[3,2-*b*][1,2,4]triazine-2,7(1*H*,6*H*)-diones

Angelina N. Kravchenko,*[a] Pavel A. Poluboyarov,[a] Sergei V. Vasilevskii,[a] Galina A. Gazieva[a] and Yulia V. Nelyubina[b]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: kani@server.ioc.ac.ru*
[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 495 135 5085; e-mail:unelya@xrlab.ineos.ac.ru*

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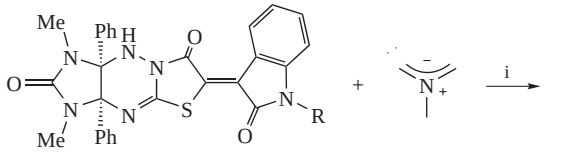
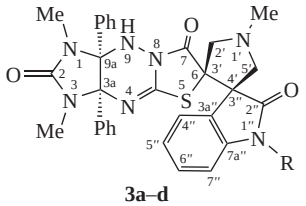
[3 + 2]-Cycloaddition of azomethine ylide generated from formaldehyde and sarcosine at the double bond of 1,3-dimethyl-6-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)-3a,9a-diphenyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*][1,3]thiazolo[3,2-*b*][1,2,4]triazine-2,7(1*H*,6*H*)-diones occurs stereospecifically at the face opposite to the phenyl substituents. Product **3a** crystallizes as a conglomerate.

Isatins are often coupled with various reactants thus providing formation of alkaloid-like fragments in molecules. For instance, azomethine ylides generated *in situ* from formaldehyde and sarcosine were reacted with indolyl-containing heterocycles.[1–4]

Herein, according to a recently developed procedure,[2] we succeeded in using of 1,3-dimethyl-6-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)-3a,9a-diphenyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*][1,3]thiazolo[3,2-*b*][1,2,4]triazine-2,7(1*H*,6*H*)-diones **1a–d** in such a transformation. The reaction was performed by refluxing **1a–d** in toluene for 2.5–10 h with a four-fold excess of sarcosine and formaldehyde (generating *in situ* azomethine ylide **2**) which was necessary to provide its completion. The reaction time was monitored both by the discolouration of the mixture (solutions of **1a–d** in toluene were originally yellow-orange) and by the precipitation of the products **3a–d**, which were isolated in 52–69% yields (Scheme 1).†



1a–d **2**



3a–d

1a R = Me
1b R = Et
1c R = Bu
1d R = H

3a R = Me
3b R = Et
3c R = Bu
3d R = CH_2NMe_2

Scheme 1 *Reagents and conditions*: i, toluene, reflux, 2.5 h (for **1a**), 3 h (for **1b**,**c**), 10 h (for **1d**).

The unexpected product **3d** resulted from the reaction of sarcosine and formaldehyde with N-unsubstituted derivative **1d**. In this case, not only [3 + 2]-cycloaddition at the C=C bond but also the replacement of hydrogen atom in the indole fragment by CH_2NMe_2 group occurred. The ^{1}H NMR spectrum of product **3d** does not contain the signal for the NH proton but contains a singlet for the NMe_2 protons at δ 2.29 ppm and two doublets (AB system) for NCH_2 fragment protons at 4.36 and 4.45 ppm (the integrated intensity ratio is 6 : 1 : 1). The ^{13}C NMR spectrum exhibits signals for C atoms of NCH_2NMe_2 fragment at δ 62.5 ppm and at δ 42.1 ppm. Evidently, compound **1d** underwent NH-aminomethylation with formaldehyde and sarcosine followed by decarboxylation.

No doubling of proton and carbon atoms signals was observed in the ^{1}H and ^{13}C NMR spectra of compounds **3a–d**, which was

† The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 or 75.47 MHz for ^{1}H or ^{13}C, respectively). Chemical shifts were measured with reference to the residual protons of a DMSO-d_6 solvent (δ 2.50 ppm). HRMS (ESI) were measured on a MicrOTOF II (Bruker Daltonics) instrument. Melting points were determined with a GALLENKAMP instrument (Sanyo).

Starting compounds **1a–c** were synthesized by condensation of 1,3-dimethyl-3a,9a-diphenyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*][1,3]thiazolo[3,2-*b*][1,2,4]triazine-2,7(1*H*,6*H*)-dione with isatins as described.[5] For the synthesis of 1,3-dimethyl-3a,9a-diphenyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*][1,3]thiazolo[3,2-*b*][1,2,4]triazine-2,7(1*H*,6*H*)-dione, see refs. 6–8.

*(3a*R*,*4'*R*,*6*S*,*9a*S*)*-1,1',1'',3-Tetramethyl-3a,9a-diphenyl-3,3a,9,9a-tetrahydrodispiro(imidazo[4,5-e][1,3]thiazolo[3,2-*b*][1,2,4]triazine-6,3'-pyrrolidine-4',3''-indole)-2,2'',7(1*H*,1''*H*)-trione* **3a**: yield 67%, mp 280–282 °C. ^{1}H NMR, δ: 2.47 (s, 3H, MeN), 2.56 (s, 3H, MeN), 2.63 (s, 3H, MeN), 3.21 (br. s, 4H, MeN, NCH_2), 3.48–3.57 (m, 2H, CH_2), 3.78 (d, 1H, NCH_2, *J* 10.5 Hz), 6.08 (d, 2H, Ph, *J* 7.6 Hz), 6.62 (d, 2H, Ph, *J* 7.5 Hz), 6.91 (t, 2H, Ph, *J* 7.7 Hz), 7.04–7.22 (m, 6H, Ph, Indole), 7.35 (d, 1H, Indole, *J* 7.5 Hz), 7.62 (m, 1H, Indole), 8.05 (s, 1H, NH). ^{13}C{^{1}H} NMR, δ: 25.3 (MeN), 25.9 (MeN), 26.1 (MeN), 42.1 (MeN), 60.3, 60.8, 61.0, 61.8 (NCH_2, C_{spiro}), 78.9, 83.1 (*C*Ph), 109.0, 122.6, 124.2, 126.9, 127.0, 127.2, 127.6, 128.1, 129.8, 133.7, 134.5, 144.9 (Indole, Ph), 145.9 (C=N), 159.3, 166.1, 176.0 (C=O). HRMS, *m/z*: 594.2278 $[M + H]^+$ ($C_{32}H_{31}N_7O_3S$, Δ = 0.7 ppm).

*(3a*R*,*4'*R*,*6*S*,*9a*S*)*-1''-Ethyl-1,1',3-trimethyl-3a,9a-diphenyl-3,3a,9,9a-tetrahydrodispiro(imidazo[4,5-e][1,3]thiazolo[3,2-*b*][1,2,4]triazine-6,3'-pyrrolidine-4',3''-indole)-2,2'',7(1*H*,1''*H*)-trione* **3b**: yield 52%, mp 180–182 °C. ^{1}H NMR, δ: 1.20 (t, 3H, Me, *J* 7.0 Hz), 2.47 (s, 3H, MeN), 2.55 (s, 3H, MeN), 2.62 (s, 3H, MeN), 3.19 (d, 1H, NCH_2, *J* 10.2 Hz), 3.47–3.56 (m, 2H, NCH_2), 3.72–3.84 (m, 3H, NCH_2), 6.08 (d, 2H, Ph, *J* 7.7 Hz), 6.62 (d, 2H, Ph, *J* 7.5 Hz), 6.93 (t, 2H, Ph, *J* 7.6 Hz), 7.06–7.27 (m, 6H, Ph, Indole), 7.31–7.36 (m, 1H, Indole), 7.60 (m, 1H, Indole), 8.03 (s, 1H, NH). ^{13}C{^{1}H} NMR, δ: 12.5 (Me), 25.4 (MeN), 26.0 (MeN), 34.4 (NCH_2), 42.1 (MeN), 60.8, 62.0 (NCH_2), 79.0, 83.1 (*C*Ph), 109.1, 122.6, 122.9, 124.5, 126.9, 127.1, 127.3, 127.6, 128.2, 128.9, 129.9, 133.8, 134.6, 143.9 (Indole, Ph), 146.0 (C=N), 159.3, 166.1, 176.0 (C=O). HRMS, *m/z*: 608.2437 $[M + H]^+$ ($C_{33}H_{33}N_7O_3S$, Δ = 0.2 ppm).

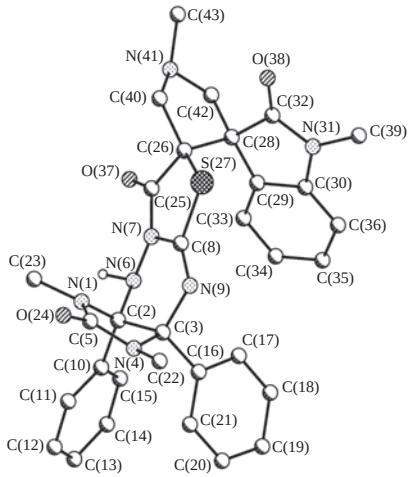


Figure 1 General view of the molecule of **3a**. Hydrogen atoms except that of the NH group are omitted for clarity.

indicative of the azomethine ylide addition to the molecules of heterocycles **1a**–**d** merely on one side of the double bond and of the diastereospecific formation of a single product. Protons signals similar to those for **3a**–**d** were absent in the spectra of mother liquors evaporated to dryness (these spectra displayed signals of protons belonging to unreacted sarcosine). This provides more evidence of the stereospecificity of the studied reactions.

This statement was ultimately supported by the X-ray diffraction investigation of compound **3a**, which crystallized from toluene in the non-centrosymmetric spatial group $P2_1$ and was a conglomerate (a mechanical mixture of enantiomers) (Figure 1).‡ According to the X-ray data, the conformation of the imidazolidine and thiazolidine moieties in a crystal is an envelope with the atoms C(3) and S(27) (hereafter the labeling scheme used is one from Figure 1) deviated by 0.55(1) and 0.32(1) Å, respectively. The conformation of the triazine cycle is a half-chair; the atoms C(2) and N(6) deviate from the plane of others by 0.40(1) and 0.29(1) Å. The triazine and indole fragments are turned relative to the pyrrole one with the corresponding dihedral angles between their mean square planes equal to 87.6(3) and 33.7(3)°, respectively. The absolute configuration of the chiral carbon atoms C(2), C(3), C(26) and C(28) in a crystal **3a** is (*R*), (*R*), (*S*) and (*R*), respectively.§

Thus, we have extended the use of [3 + 2]-cycloaddition of azomethine ylide at complex isatin-derived compounds **1a**–**d** which turned to occur stereospecifically. We believe that the presence of alkaloid-like spiro(indole-3,3′-pyrrolidine) fragment will provide the use of similar compounds. It has been revealed that compound **3a** crystallizes as a conglomerate and the absolute configuration of its enantiomer has been established.

*(3a*R*,*4′*R*,*6*S*,*9a*S*)-*1′′-Butyl-1,1′,3-trimethyl-3a,9a-diphenyl-3,3a,9,9a-tetrahydrodispiro(imidazo[4,5-*e*][1,3]thiazolo[3,2-*b*][1,2,4]triazine-6,3′-pyrrolidine-4′,3′′-indole)-2,2′′,7(1*H*,1′′*H*)-trione* **3c**: yield 59%, mp 240–242 °C. ^{1}H NMR, δ: 0.90 (t, 3H, Me_{Bu}, J 7.3 Hz), 1.32–1.39 (m, 2H, $CH_{2\,Bu}$), 1.57–1.64 (m, 2H, $CH_{2\,Bu}$), 2.47 (s, 3H, MeN), 2.54 (s, 3H, MeN), 2.62 (s, 3H, MeN), 3.18 (d, 1H, NCH_2, J 10.2 Hz), 3.47–3.55 (m, 2H, $NCH_{2\,Bu}$), 3.66–3.79 (m, 3H, NCH_2), 6.09 (d, 2H, Ph, J 7.7 Hz), 6.62 (d, 2H, Ph, J 7.6 Hz), 6.90 (t, 2H, Ph, J 7.6 Hz), 7.05–7.17 (m, 5H, Ph, Indole), 7.23 (d, 1H, Indole, J 7.9 Hz), 7.34 (d, 1H, Indole, J 7.5 Hz), 7.58 (m, 1H, Indole), 8.04 (s, 1H, NH). ^{13}C{^{1}H} NMR, δ: 13.6 (Me_{Bu}), 19.5 (CH_2), 25.3 (MeN), 25.9 (MeN), 28.9 (CH_2), 42.1 (MeN), 60.8, 61.2, 61.8 (NCH_2), 78.9, 83.0 (*C*Ph), 109.2, 122.5, 122.8, 124.5, 126.9, 127.0, 127.2, 127.6, 128.2, 128.9, 129.8, 133.8, 134.6, 144.3 (Indole, Ph), 146.0 (C=N), 159.3, 166.1, 176.0 (C=O). HRMS, *m*/*z*: 636.2755 [M + H]$^+$ ($C_{35}H_{37}N_7O_3S$, Δ = 1.2 ppm).

*(3a*R*,*4′*R*,*6*S*,*9a*S*)-*1′′-Dimethylaminomethyl-1,1′,3-trimethyl-3a,9a-diphenyl-3,3a,9,9a-tetrahydrodispiro(imidazo[4,5-*e*][1,3]thiazolo-[3,2-*b*][1,2,4]triazine-6,3′-pyrrolidine-4′,3′′-indole)-2,2′′,7(1*H*,1′′*H*)-trione* **3d**: yield 69%, mp 249–251 °C. ^{1}H NMR, δ: 2.29 (s, 6H, NMe_2), 2.46 (s, 3H, MeN), 2.55 (s, 3H, MeN), 2.63 (s, 3H, MeN), 3.21 (d, 1H, NCH_2, J 10.2 Hz), 3.43–3.55 (m, 2H, CH_2), 3.78 (d, 1H, NCH_2, J 10.7 Hz), 4.36, 4.45 (2d, 1H, NCH_2N, J 12.7 Hz), 6.10 (d, 2H, Ph, J 7.4 Hz), 6.62 (d, 2H, Ph, J 7.3 Hz), 6.90 (t, 2H, Ph, J 7.4 Hz), 7.01–7.20 (m, 6H, Ph, Indole), 7.29–7.35 (m, 1H, Indole), 7.57 (m, 1H, Indole), 8.04 (s, 1H, NH). ^{13}C{^{1}H} NMR, δ: 25.4 (MeN), 26.0 (MeN), 42.1 (MeN), 42.8 (Me_2N), 61.3, 61.6, 62.5 (NCH_2), 79.0, 83.1 (*C*Ph), 110.6, 122.5, 122.8, 124.3, 126.9, 127.1, 127.3, 127.7, 128.3, 129.8, 133.8, 134.6, 144.9 (Indole, Ph), 146.1 (C=N), 159.4, 166.2, 177.1 (C=O). HRMS, *m*/*z*: 637.2703 [M + H]$^+$ ($C_{34}H_{36}N_8O_3S$, Δ = 0.2 ppm).

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‡ *Crystal data*. Crystals of **3a** ($C_{32}H_{31}N_7O_3S$, M = 593.70) are monoclinic, space group $P2_1$, at 100 K: a = 10.5934(6), b = 11.3079(7) and c = = 12.4658(7) Å, β = 98.5530(10)°, V = 1476.66(15) Å^3, Z = 2 (Z' = 1), d_{calc} = 1.335 g cm^{-3}, μ(MoKα) = 1.56 cm^{-1}, F(000) = 624. Intensities of 21 874 reflections were measured with a Bruker SMART 1000 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, 2θ < 58°], and 7793 independent reflections (R_{int} = 0.0573) were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The hydrogen atom of NH group was located from the Fourier density synthesis. The H(C) atom positions were calculated. All hydrogen atoms were refined in the isotropic approximation witin riding model. The refinement converged to wR_2 = 0.1000 and GOF = 1.002 for all independent reflections [R_1 = 0.0457 was calculated against F for 6475 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.[9]

CCDC 867346 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2012.

§ X-Ray program gave for compound **3a** (3a*R**,4′*R**,6*S**,9a*R**)-configuration.