ISSN 1070-4280, Russian Journal of Organic Chemistry, 2010, Vol. 46, No. 2, pp. 306–308. © Pleiades Publishing, Ltd., 2010.
Original Russian Text © A.A. Shvets, S.V. Kurbatov, 2009, published in Zhurnal Organicheskoi Khimii, 2010, Vol. 46, No. 2, pp. 309–310.

SHORT COMMUNICATIONS

New Method of Synthesis of β,β'-Spiropyrrolidinooxindoles

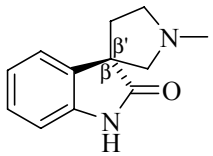
A. A. Shvets and S. V. Kurbatov

Southern Federal University, Rostov-on-Don, 344090 Russia
e-mail: kurbatov@rsu.ru

Received August 1, 2009

DOI: 10.1134/S1070428009020296

Natural alkaloids containing spiroheterocyclic fragment A (horsfiline, spirotryprostatin, pteropodin etc.) exhibit a pronounced biological activity, in particular, immunomodulating, antitumor, and antibacterial action [1, 2].



A

One of the promising approaches to the designing of this β,β'-spiro joint structure is the reaction of [3+2]-dipolar cycloaddition of azomethine ylides to 3-ylidene isatin derivatives [2].

We developed a new method of the synthesis of heterocycles with bis-spiro junction using as dipolarophiles condensation products of isatins **Ia–Ic** with the methylene-active heterocycles **IIa–IIc**: rhodanine, pseudothiohydantoin, and thiazolidine-2,4-dione. The reaction proceeded at room temperature with nearly quantitative yields. Isatin derivatives **IIIa–IIIc** formed quickly as brightly colored crystals not requiring further purification (Scheme 1).

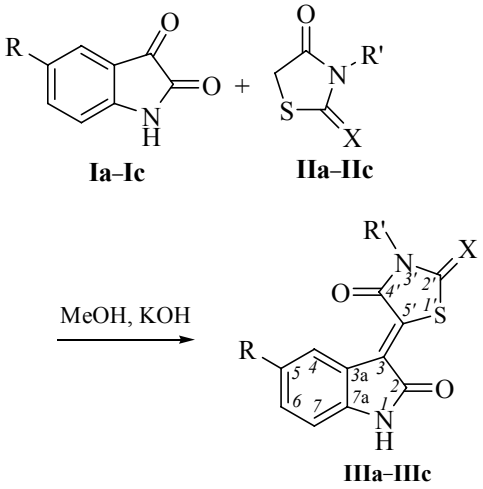
In all events formed exclusively *E*-stereoisomer with the trans-location of the carbonyl groups, the signal of the H^4 proton of the isatylidene fragment suffered a considerable downfield shift in the ^1H NMR spectra under the influence of the carbonyl group.

The azomethine ylide was generated *in situ* by the standard method from paraformaldehyde and sarcosine [3]. A visual criterion of the reaction completion was the total decoloration of the reaction mixture.

Most probably compounds **IVa–IVc** formed as racemic mixture of two enantiomers **IVa–IVc** and **IV'a–IV'c** resulting from the addition of azomethine ylide from above and from below of the plane of isatylidenes **IIIa–IIIc** (Scheme 2).

The cycloaddition reaction proceeded absolutely diastereoselectively as showed the absence in the NMR spectra even minor signals of other possible diastereomers. The bis-spiroheterocycles synthesized in this way contain a labile hydrogen in the oxindole fragment

Scheme 1.

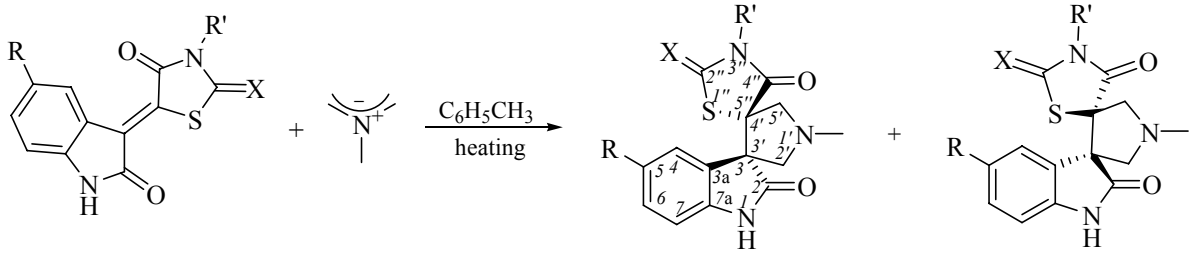


Ia–Ic **IIa–IIc**

IIIa–IIIc

III, R = Cl, R' = H, X = S (**a**); R = OEt, R' = Ph, X = NPh (**b**); R = Br, R' = H, X = O (**c**).

Scheme 2.



IIIa–IIIc **IVa–IVc** **IV'a–IV'c**

and can be subjected to further functionalization by alkylation, acylation, and aminomethylation.

The successful replacement of heterocycles at the 2-oxindolin-3-ylidene fragment makes it possible to state that the described approach can be applied to sufficiently numerous sterically overloaded systems analogous to compounds **IIIa–IIIc**, and this opens wide opportunities for the preparation of new bis-spirooxindole derivatives.

Dipolarophiles IIIa–IIIc. To a solution of equimolar amounts (0.01 mol each) of isatin and an appropriate methylene-active heterocycle in 30 ml of methanol was added 0.001 ml of 40% aqueous KOH. After 20 min the separated precipitate was filtered off and washed with methanol.

Bisspirooxindoles IVa–IVc. In 40 ml of toluene was dispersed an appropriate dipolarophile, sarcosine, and paraform aldehyde in the molar ratio 1:4:4. The reaction mixture was boiled for 7 h. After 30–40 min the reaction mixture started to loose color and completely decolorized to the end of the process. The reaction mixture was cooled, toluene was distilled off at a reduced pressure, and the residue was recrystallized from methanol (**IVa**, **IVb**) or butanol (**IVc**).

(3Z)-3-(4-Oxo-2-thioxo-1,3-thiazolidin-5-ylidene)-5-chloro-1,3-dihydro-2H-indol-2-one (IIIa). Yield 91%, mp 344°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 6.89 s (1H, H^7, *J* 7.9 Hz), 7.37 m (1H, H^6), 8.71 C (1H, H^4), 11.30 s (1H, NH^1), 14.02 br.s (1H, NH^3). Found, %: C 44.62; H 1.64; Cl 11.67; N 9.30. $C_{11}H_5ClN_2O_2S_2$. Calculated, %: C 44.52; H 1.70; Cl 11.95; N 9.44.

(3Z)-3-[(2E)-4-Oxo-3-phenyl-2-(phenylimino)-5-ethoxy-1,3-thiazolidin-5-ylidene]-1,3-dihydro-2*H*-indol-2-one (IIIb). Yield 90%, mp 314°C. ^{1}H NMR spectrum, δ, ppm: 1.28 t (3H, OCH_2CH_3, J 7.0 Hz), 3.93 q (2H, OCH_2CH_3, *J* 7.0 Hz), 6.82 d (1H, H^7, *J* 8.8 Hz), 6.90–7.00 m (3H$_{arom}$, H^6), 7.10–7.25 m (1H$_{arom}$), 7.30–7.45 m (2H$_{arom}$), 7.45–7.7 m (5H$_{arom}$), 8.44 d (1H, H^4, *J* 2.5 Hz), 11.00 br.s (1H, NH^1). Found, %: C 68.19; H 4.43; N 9.89. $C_{25}H_{19}N_3O_3S$. Calculated, %: C 68.01; H 4.34; N 9.52.

(5Z)-5-(5-Bromo-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1,3-thiazolidin-2,4-dione (IIIc). Yield 93%, mp 406°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 6.90 d (1H, H^7, J 8.8 Hz), 7.55 d.d (1H, H^6, *J* 8.8, *J* 2.3 Hz), 8.92 d (1H, H^4, J 2.3 Hz), 11.35 s (1H, NH^1), 12.91 br.s (1H, NH^3). Found, %: C 40.87; H 1.61; Br 24.61; N 8.59. $C_{11}H_5BrN_2O_3S$. Calculated, %: C 40.64; H 1.55; Br 24.58; N 8.62.

1'-Methyl-2"-thioxo-5-chloro-4"H-dispiro-[indole-3,3'-pyrrolidine-4',5'-[1,3]thiazolidine]-2,4"(1H)-dione (IVa). Yield 10%, mp 328°C. ^{1}H NMR spectrum, δ, ppm: 2.72 s (3H, NCH_3), 3.46 d (1H, H$^{2'}$, *J* 10.2 Hz), 3.80 d (1H, H$^{5'}$, J 10.6 Hz), 3.89 d (1H, H$^{2'}$, *J* 10.2 Hz), 4.18 d (1H, H$^{5'}$, J 10.6 Hz), 6.96 d (1H, H^7, *J* 8.3 Hz), 7.14–7.25 m (1H, H^6), 7.74 s (1H, H^4), 12.43 (1H, NH^1). Found, %: C 47.73; H 3.51; Cl 9.68; N 11.84. $C_{14}H_{12}ClN_3O_2S_2$. Calculated, %: C 47.52; H 3.42; Cl 10.02; N 11.88.

1'-Methyl-3"-phenyl-2"-(phenylimino)-5-ethoxy-4"H-dispiro[indole-3,3'-pyrrolidine-4',5"-[1,3]thiazolidine]-2,4"(1H)-dione (IVb). Yield 50%, mp 166°C. ^{1}H NMR spectrum, δ, ppm: 1.40 t (3H, OCH_2CH_3, *J* 6.8 Hz), 3.38 d (1H, H$^{2'}$, J 10.4 Hz), 3.55–3.72 m (2H, H$^{2'}$, H$^{5'}$), 3.75–3.97 m (2H, OCH_2CH_3), 4.01 d (1H, H$^{5'}$, J 10.9 Hz), 6.65–8.82 m (2H), 6.83–7.00 m (3H), 7.02–7.15 m (1H$_{arom}$), 7.18–7.37 m (4H$_{arom}$), 7.40–7.65 m (3H$_{arom}$), 8.44 s (1H, NH^1). Found, %: C 67.53; H 5.31; N 11.12. $C_{28}H_{26}N_4O_3S$. Calculated, %: C 67.45; H 5.26; N 11.24.

5-Bromo-1'-methyl-2"*H*,4"*H*-dispiro[indole-3,3'-pyrrolidine-4',5"-[1,3]thiazolidine]-2,2",4"(1*H*)-trione (IVc). Yield 12%, mp 320°C. ^{1}H NMR spectrum, δ, ppm: 2.71 s (3H, NCH_3), 3.44 d (1H, H$^{2'}$, *J* 10.1 Hz), 3.79 d (1H, H$^{5'}$, J 10.7 Hz), 3.86 d (1H, H$^{2'}$, *J* 10.1 Hz),

4.21 d (1H, $H^{5'}$, J 10.7 Hz), 6.98 d (1H, H^7, J 8.5 Hz), 7.41 d (1H, H^6, J 8.5 Hz), 7.86 s (1H, H^4), 12.47 s (1H, NH^1). Found, %: C 43.81; H 3.07; Br 20.65; N 11.15. $C_{14}H_{12}BrN_3O_3S$. Calculated, %: C 43.99; H 3.16; Br 20.90; N 10.99.

^1H NMR spectra were registered on spectrometers Bruker DPX-250 (250 MHz) and Varian Unity VXR-300 (300 MHz) in DMSO-d_6 and pyridine-d_5 with respect to TMS.

The study was carried out under a financial support of the Russian Foundation for Basic Research (grant no. 09-03-00726-a) and project RNP 2.2.1.1/2348.

REFERENCES

1. Christiane M. and Carreira M., *Eur. J. Org. Chem.* 2003, vol. 46, p. 2209.
2. Chris V. and Scheidt A., *Angew. Chem., Int. Ed.* 2007, vol. 46, p. 8748.
3. Nair V., Sheela K.C., and Rath N.P., *Chem. Lett.* 2000, vol. 29, p. 980.