ISSN 1070-3632, Russian Journal of General Chemistry, 2008, Vol. 78, No. 10, pp. 1977–1979. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © A.V. Bogdanov, V.F. Mironov, L.I. Musin, B.I. Buzykin, A.I. Konovalov, 2008, published in Zhurnal Obshchei Khimii, 2008, Vol. 78, No. 10, pp. 1741–1743.

LETTERS TO THE EDITOR

Isatin Derivatives in the Reaction with Phosphorous Hexaethyltriamide. A New Approach to the Synthesis of Isoindigo Derivatives

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Received June 18, 2008

DOI: 10.1134/S1070363208100277

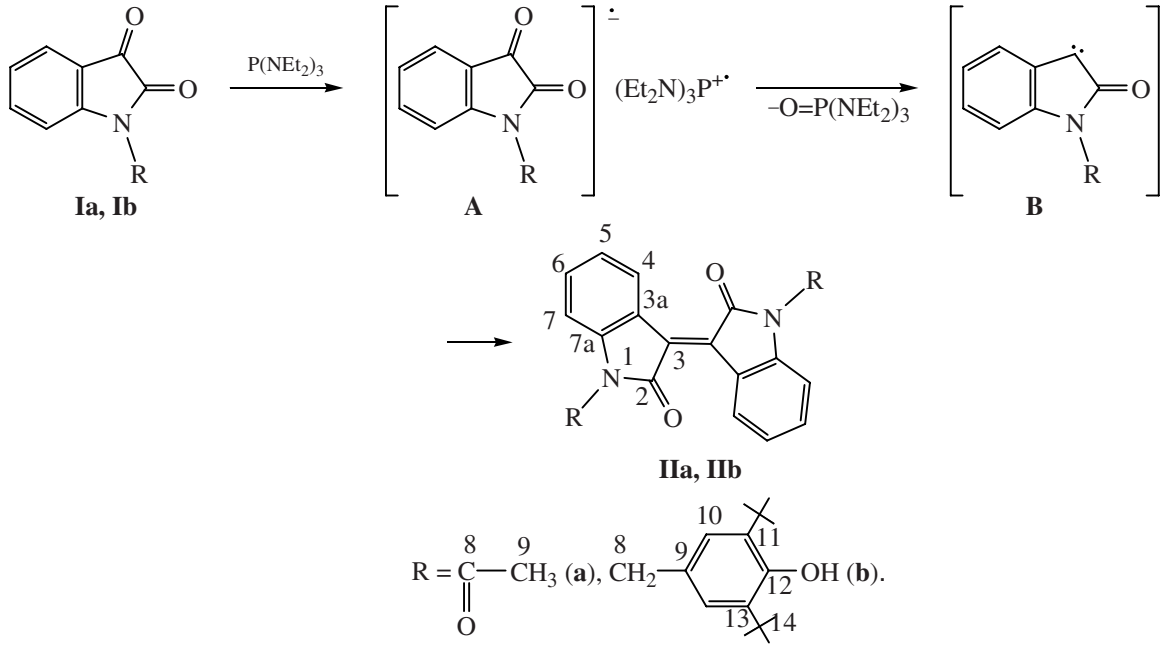
Isoindigo [1*H*,1'*H*-bis(indolyl-3-indeno)-2,2'-dione] and its 1- and 1,1'-substituted derivatives in the recent years attract attention of researchers not only as dyes, but also as the substances with specific biological activity (antileukemic, enterohemorragic, proliferative, antiinflammation and others), inhibiting ortho-monooxygenases or kinases and possessing other related properties [1–4]. 1-(β-*D*-glucopyranosyl) isoindigo and isoindigo glycoside have been proposed as antileilkemia means [2, 3].

Synthesis of 1-substituted isoindigo, including isoindigo glycoside [4], often is a multistep process. The most prospective pathway for the synthesis of isoindigo derivatives seems to be the dimerization of ketocarbenes generated from derivatives of isatin. Isatin and its derivatives **Ia, Ib** relate to the highly reactive cyclic α-diketones that are used in the syntheses of various heterocyclic compounds such as 1,2,4-triazines, quinolines and others. In [5] has been assumed that 3-(triphenylphosphoranylidene)-2,3-dihydro-1*H*-indol-2-one mixed with isoindigo (**II**, R = H, Me) is formed at the reaction of triphenylphosphine with isatin and 1-methylisatin in a moderate yield (44 and 49%) via a step of intermediate formation of carbene (B, R = H, Me). Generation of carbines from heterocyclic α-diketones at the action of trico-ordinated phosphorus derivatives has not been studied sufficiently [6, 7]. Unlike triphenylphosphine, dialkyl phosphites and chlorophosphites do not generate ketocarbenes but are added to isatin forming dioxindolephosphonates and 3-(3-chlorooxindolyl) phosphine oxides, respectively. Dioxaphospholanes, phosphites and trialkyl phosphites react also at the 3 position of isatin affording dimeric spirophospholanes [6, 8, 9 and refs.].

Recently on an example of acetophenone we have shown that phosphorous hexaehyltriamide is more conventional reagent for the generation of keto-carbenes and related dimers from cyclic α-diketones [10]; the fact of formation of respective carbenes was confirmed by trapping them with an active dipolarophile fullerene C_{60} [11].

Now we for first time studied reaction of phosphorous hexamethyltriamide with isatin substituted at 1 position (**Ia, Ib**). Reaction proceeds selectively under mild conditions (CH_2Cl_2, –60°C) for 5–10 min and leads to formation in almost quantitative yield of 1,1'-R,R-3,3'-bis(indolin-3-ylidene)-2,2'-diones (**IIa, IIb**). Regiochemistry of the desoxy-genation just at the C^3 carbon atom is revealed unambiguously by means of NMR spectroscopy. In the not decoupled ^{13}C NMR spectrum of **IIb** a singlet at 167.13 ppm corresponding to atom C^2 is converted into a triplet with spin-spin coupling constant $^3J_{HCNC}$ 3.5 Hz due to coupling with methylene group protons. The C^3 carbon atom induces a doublet with the constant $^3J_{HCCC}$ 2.4 Hz due to coupling with the proton at the C^4 atom.

Taking into account typical change of color in time we suggest that the first step includes single electron transfer from phosphorus atom onto isatin heterocyclic system with formation of ion-radical pair (**A**) that then through several intermediate steps generates ketocarbene (**B**) with liberation of phosphoric hexaethyltriamide. Then under the reaction conditions



the ketocarbene (B) exerts dimerization with formation of respective isoindigo derivative **IIa** and **IIb**.

Structures of compounds **IIa** and **IIb** were confirmed by the methods of NMR and IR spectroscopy.

1,1'-Diacetylbis (indolin-3-ylidene)-2,2'-dione (IIa). To a solution of 0.5 g of 1-acetylisatin **Ia** in 10 ml of methylene chloride at –60°C and at bubbling of argon was added dropwise 0.69 ml of phosphorous hexaethyltriamide. Color of reaction mixture sharply changed from light brown to dark green, and after adding whole amount of phosphorous amide to red. Then the reaction mixture was allowed to warm to 20°C and the crimson colored precipitate formed was filtered off and dried in a vacuum 12 mm Hg. 0.4 g (89%) of compound **IIa** was obtained, mp 260–263°C (published 258°C [12]). IR spectrum, cm^{-1}: 1712, 1596, 1548, 1415, 1331, 1290, 1183, 1152, 1104, 1022, 916, 776, 744, 671, 639, 581, 461. The ^1H NMR spectrum ($CDCl_3$, δ, ppm, *J,* Hz): 8.32 d.d (H^4, $^3J_{HCCH}$ 8.2, $^4J_{HCCCH}$ 0.6), 7.25 d.t (H^5, $^3J_{HCCH}$ 8.2, $^4J_{HCCCH}$ 0.9), 7.48 d.t (H^6, $^3J_{HCCH}$ 8.2, $^4J_{HCCCH}$ 0.9), 8.86 d.d (H^7, $^3J_{HCCH}$ 8.2, $^4J_{HCCCH}$ 0.6), 2.77 s (H^9). The ЯМР ^{13}C NMR spectrum ($CDCl_3$, δ_C, ppm, *J*, Hz) (here and hereinafter in parentheses is given appearance of the signal under conditions of $^{13}C–\{^1H\}$ decoupling): 167.98 s (s) (C^2), 132.98 s (overlapping with a component of C^6) (C^3), 122.36 m (s) (C^{3a}), 128.82 d.d (s) (C^4, $^1J_{HC}$ 167.4, $^3J_{HCCC}$ 7.9), 124.96 d.d.d (s) (C^5, $^1J_{HC}$ 161.7–161.0, $^3J_{HCCC}$ 8.4, $^2J_{HCC}$ 2.2), 133.82 d.d.d (s) (C^6, $^1J_{HC}$ 160.6, $^3J_{HCCC}$ 7.3–8.4, $^2J_{HCC}$ 2.2–2.9), 116.30 d.d (s) (C^7, $^1J_{HC}$ 170.9, $^3J_{HCCC}$ 7.7), 141.90 br.d.d (s) (C^{7a}, $^3J_{HCCC}$ 8.8), 170.54 q (s) (C^8, $^2J_{HCC}$ 7.1), 27.31 q (s) (C^9, $^1J_{HC}$ 130.9).

1,1'-[3,5-Di(*tert*-butyl)-4-hydroxyphenylmethyl] bis(indolin-3-ylidene)-2,2'-dione (IIb). To a suspendsion of 1 g of benzylisatin **Ib** in 20 ml of methylene chloride at –60°C and at bubbling of argon was added dropwise 0.72 ml of phosphorous hexaethyltriamide. The reaction mixture becomes dark qoickly. After complete adding of the phosphorous amide the reaction mixture was allowed to warm to 20°C. After removing of solvent in a vacuum (0.1 mm Hg) a viscous dark red mass was obtained that was triturated in dry hexane, filtered off and dried in vacuum (12 mm Hg) 0.9 g (95%) of compound **IIb** was isolated, red substance, mp 266–267°C. The IR sectrum, cm^{-1}: 3634, 1701, 1606, 1578, 1468, 1435, 1382, 1237, 1187, 1155, 1104, 1077, 1040, 1023, 919, 870, 773, 748, 677, 658, 559, 460. The ^1H NMR spectrum (DMSO-d_6, δ, ppm, *J,* Hz): 7.09 d (H^4, $^3J_{HCCH}$ 7.6), 7.03 d.d (H^5, $^3J_{HCCH}$ 7.6, $^3J_{HCCH}$ 7.3), 7.41 d.d (H^6, $^3J_{HCCH}$ 7.9, $^3J_{HCCH}$ 7.9), 9.12 d (H^7, $^3J_{HCCH}$ 7.9), 4.89 s (H^8), 7.15 br.s (H^{10}), 1.32 s (H^{14}). ^{13}C NMR spectrum (DMSO-d_6, δ_C, ppm, *J* Hz): 167.13 s (t) (C^2, $^3J_{HCNC}$ 3.5), 132.75 s (d) (C^3, $^3J_{HCCC}$ 2.4), 120.80 s (m) (C^{3a}, $^3J_{HCCC}$ 6.8–7.2), 129.46 d.d (s) (C^4, $^1J_{HC}$ 166.9, $^3J_{HCCC}$ 8.9), 121.84 d.d (s) (C^5, $^1J_{HC}$ 162.1, $^3J_{HCCC}$ 6.8), 132.75

d.d (s) (C^6, $^1J_{HC}$ 161.4, $^3J_{HCCC}$ 8.1), 109.16 d.d (s) (C^7, $^1J_{HC}$ 162.2–162.7, $^3J_{HCCC}$ 7.8–8.2), 144.43 m (s) (C^{7a}), 66.30 t.m (s) (C^8, $^1J_{HC}$ 144.4, $^3J_{HCCC}$ 1.9–2.0), 127.18 m (s) (C^9, $^2J_{HCC}$ 3.5–4.2), 123.79 d.m (s) (C^{10}, $^1J_{HC}$ 154.7), 139.34 m (s) (C^{11}), 153.11 т (s) (C^{12}, $^3J_{HCCC}$ 8.6–9.0), 34.37 br.m (s) (C^{13}), 30.73 q.m (s) (C^{13}, $^1J_{HC}$ 125.7, $^3J_{HCCC}$ 4.4).

The ^1H (400 MHz), ^{13}C (100.6 MHz) and ^{31}P (162.0 MHz) NMR spectra were taken on a Bruker Avance-400. The IR spectra were registered from the suspensions of substances in Vaseline oil in a Bruker Vector-22 instrument.

ACKNOWLEDGMENTS

This work was carried out in the framework of the Program no. 1 of Chemistry Division and Material Science of Russian Academy of Sciences and at the support of the Concil on the Grants of the President of Russian Federation (grant MK-2444.2007.3).

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