Monatsh Chem (2011) 142:81–85
DOI 10.1007/s00706-010-0416-z

ORIGINAL PAPER

A convenient synthetic route from isatin N-Mannich bases to nitrogen-containing derivatives of isoindigo

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Received: 14 May 2010 / Accepted: 1 November 2010 / Published online: 8 December 2010
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Abstract The reaction of aminomethylisatins (isatin N-Mannich bases) with hexaethylphosphorous triamide leads to the formation of 1,1′-bis(dialkylaminomethyl)-3,3′-bis(indolin-3-ylidene)-2,2′-diones and 1,1′-bis(1,3-dioxo-1,3-dihydroisoindol-2-ylmethyl)-1*H*,1′*H*-[3,3′]bisindolylidene-2,2′-dione.

Keywords Carbenes · Isatin · Isoindigo · Mannich bases · Phosphorus compounds

Introduction

Isatin (indole-2,3-dione) and its derivatives play an important role in the pharmaceutical and dye industries. Drug substances containing an isatin moiety may cure diseases such as epilepsy [1], tuberculosis [2], and bulimia [3]. 1-Aminomethyl derivatives of isatin (so-called isatin N-Mannich bases) are particularly important among the wide variety of such compounds [4, 5], and isatin N-Mannich bases containing morpholine and piperidine groups possess moderate activity against certain Gram-negative bacteria [6].

These compounds are also widely used in the synthesis of a number of heterocycles, in particular isoindigo [7, 8]. Derivatives of isoindigo (1*H*,1′*H*-bis(indolin-3-yliden)-2,2′-dione) attract great attention mostly as substances which show a specific biological activity (anti-leukemia, antiproliferative, anti-inflammatory, etc.) [9–12]. For example, 1-(β-D-glucopyranosyl)isoindigo [10–12] and 1-methylisoindigo are anti-leukemia drugs, the latter of which has been applied in China since the 1980s [13, 14].

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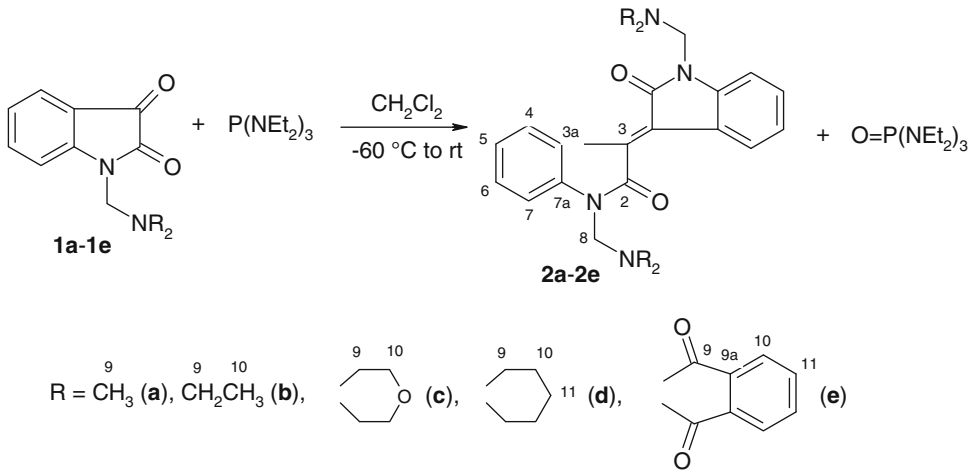
Results and discussion

Herein we describe a novel synthetic approach to the synthesis of 1,1′-bis(dialkylaminomethyl)isoindigo derivatives. 1,1′-Bis(*N*-phthalimidomethyl)isoindigo (**2e**) was also obtained. This method is based on our recent work [15, 16] and concludes in a very simple and easy procedure which involves a novel deoxygenation reaction of the corresponding isatins **1a**–**1e** with hexaethylphosphorous triamide (HEPTA). The title reaction proceeds under mild conditions (dichloromethane, −60 °C) for 10 min to give 1,1′-bis(aminomethyl)isoindigos **2a**–**2e** in 75–91% yield (Scheme 1). The regiochemistry of deoxygenation at the C^3 atom in all cases was unequivocally established by using ^{13}C NMR spectroscopy. The ^{13}C NMR spectra of compounds **2a**–**2e** displayed signals at 167.67–168.84 ppm as triplets with spin–spin coupling constants $^3J_{HCNC} = 2.2–3.5$ Hz due to two methylene protons, indicating the presence of one carbonyl group. The signals of C^3 appeared at 133.38–133.59 ppm as doublets with $^3J_{HCCC} = 1.9–2.6$ Hz due to the proton at C^4. Assignment of signals in ^1H NMR spectra was made on the basis of signal multiplicities and is in good agreement with data published earlier [17]. In addition, the ^{31}P NMR spectra of the reaction mixtures in all cases showed complete conversion of starting phosphite ($\delta_P = 118$ ppm) to corresponding phosphate (24 ppm).

Unambiguous evidence for the structure of **2b** was obtained from single-crystal X-ray analysis. The Oak

Scheme 1



Ridge thermal ellipsoid plot (ORTEP) drawing of **2b** is shown in Fig. 1.

Molecule **2b** occupies a special position in the crystal (in the center of symmetry). The indole fragment is planar within 0.016(2) Å. Since molecule **2b** is in the center of symmetry two indole fragments are in the same plane. The deviation of the O^2 atom from this plane is 0.091(2) Å and that of the C^8 atom −0.083(2) Å. The bond length distribution in the indole moiety indicates the conjugation of the nitrogen lone pair with the C=O bond, and the planarity of the pyrrolidinone ring also indicates some conjugation of the C^3=$C^{3'}$ bond with the benzene fragment. Selected geometrical parameters are presented in Table 1.

Probably owing to steric factors caused by the proximity of the O^2 atom and the hydrogen at $C^{4'}$, the C^2–C^3 bond length is somewhat increased. At the same time the C^3=$C^{3'}$ bond length corresponds to a standard double bond length in alkenes.

A plausible mechanism of the reaction is shown in Scheme 2. It is reasonable to assume that the first step includes a one-electron transfer from phosphorus to the heterocyclic system to form ion–radical pair **3**. The next step is likely to include the formation of the phosphonium salt **4**. Then this intermediate eliminates hexaethyltriaminophosphine oxide to give carbene **5**, which under the reaction conditions undergoes a dimerization to form the final product **2**.

Experimental

Melting points were measured with a Stuart digital SMP10 apparatus. Mass spectra were recorded on a DFS Thermo Electron Corporation (USA) mass spectrometer operating at an ionization potential of 70 eV. The mass spectrometric data were processed by using the Xcalibur program. Elemental analyses for C, H, and N were performed by using a CHNS-3 analyzer and were found to be in accord with the calculated values. IR spectra were measured with a Bruker Vector-22 spectrometer as suspensions in Nujol. NMR spectra were recorded with a Bruker Avance-400 instrument (400 MHz for ^{1}H and 100.6 MHz for ^{13}C) with $CDCl_3$ or DMSO-d_6 as solvents. Chemical shifts are given in ppm (δ) relative to residual $CHCl_3$ or DMSO signals,

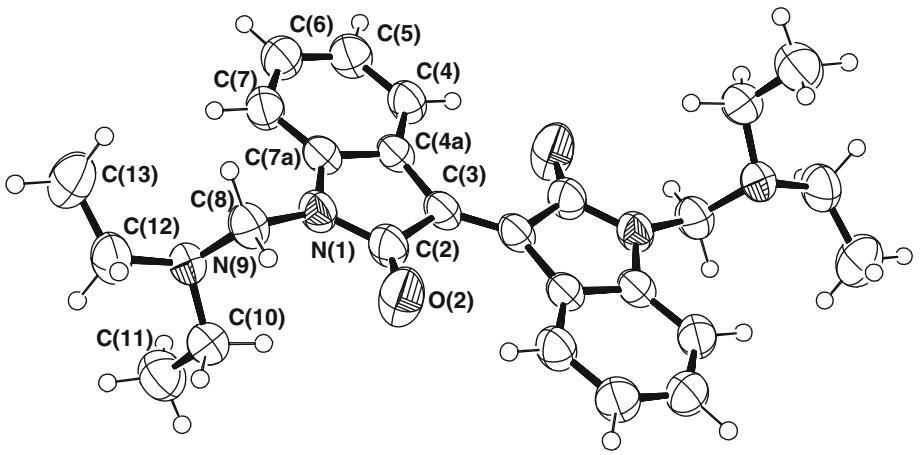


Fig. 1 ORTEP drawing of compound **2b**, with 50% probability displacement ellipsoids

Table 1 Selected geometrical parameters: bond distances *d*, bond angles φ, and torsion angles τ

	d (Å)		*d* (Å)
O^2–C^2	1.213(3)	C^3–$C^{3'}$	1.364(3)
N^1–C^2	1.361(3)	N^1–C^8	1.454(3)
N^1–C^{7a}	1.399(2)	C^2–C^3	1.519(3)
C^3–C^{4a}	1.477(3)	N^1–C^8	1.454(3)
N^9–C^8	1.449(2)	N^9–C^{10}	1.459(3)
N^9–C^{12}	1.469(3)		
	φ (°)		φ (°)
C^2–N^1–C^{7a}	110.59(15)	C^2–N^1–C^8	124.47(16)
C^{7a}–N^1–C^8	124.59(18)	O^2–C^2–N^1	123.01(19)
O^2–C^2–C^3	129.0(2)	N^1–C^2–C^3	107.95(16)
C^2–C^3–C^{4a}	103.83(17)	C^2–C^3–$C^{3'}$	122.96(18)
$C^{3'}$–C^3–C^{4a}	133.21(16)	N^1–C^{7a}–C^{4a}	110.00(18)
N^1–C^{7a}–C^7	126.30(17)	N^1–C^8–N^9	112.14(17)
C^8–N^9–C^{10}	111.04(16)	C^8–N^9–C^{12}	109.20(18)
C^{10}–N^9–C^{12}	111.57(18)		
	τ (°)		τ (°)
C^{7a}–N^1–C^2–O^2	177.4(2)	C^8–N^1–C^2–O^2	4.1(3)
C^{7a}–N^1–C^2–C^3	−2.2(2)	C^8–N^1–C^2–C^3	−175.55(16)
C^2–N^1–C^{7a}–C^7	−177.01(19)	C^2–N^1–C^{7a}–C^{4a}	1.9(2)
C^8–N^1–C^{7a}–C^{4a}	175.20(16)	C^{7a}–N^1–C^8–N^9	73.8(2)
C^2–N^1–C^8–N^9	−113.8(2)	N^1–C^2–C^3–C^{4a}	1.7(2)
O^2–C^2–C^3–C^{4a}	−177.9(2)	O^2–C^2–C^3–$C^{3'}$	1.6(3)
N^1–C^2–C^3–$C^{3'}$	−178.80(17)	C^2–C^3–$C^{3'}$–$C^{4a'}$	0.7(3)
C^2–C^3–$C^{3'}$–$C^{2'}$	−180.00(17)	C^{4a}–C^3–$C^{3'}$–$C^{2'}$	−0.7(3)
C^{4a}–C^3–$C^{3'}$–$C^{4a'}$	180.00(19)	$C^{3'}$–C^3–C^{4a}–C^{7a}	180.0(2)

Primes (′) indicate translation of symmetry code to equiv. pos (1 − *x*, 1 − *y*, 1 − *z*)

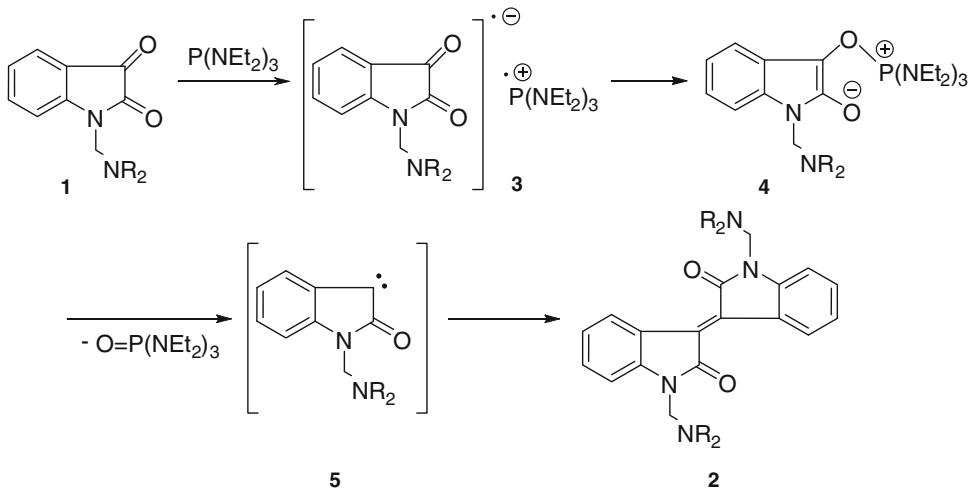
and coupling constants (*J*) are reported in hertz (Hz). 1-Aminomethylisatins and HEPTA were prepared by known methods [4, 18].

General procedure for preparation of compounds ***2a–2e*** *(exemplified by* ***2a****)*

A solution of 0.32 cm^3 hexaethylphosphorous triamide (1.23 mmol) in 3 cm^3 dichloromethane was added dropwise to a solution of 0.30 g 1-(dimethylaminomethyl)isatin (**1a**, (1.23 mmol) in dichloromethane (10 cm^3) at −60 °C with bubbling of dry argon for 2 min. The reaction mixture was then allowed to warm up to room temperature. The solid was filtered, washed with dry *n*-hexane, and dried in vacuo (16 mbar) to give pure **2a**. If the above procedure did not give any solid, the reaction mixture was evaporated in vacuo (16 mbar) to dryness and the residue was treated with 10 cm^3 of dry *n*-hexane to give a precipitate, which was separated as described above.

1,1′-Bis[(dimethylamino)methyl]-3,3′-bis-3H-indolylidene-2,2′(1H,1′H)-dione (**2a**, $C_{22}H_{24}N_4O_2$)
Dark-red crystals, yield 91%; m.p.: 152–154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 6H, H-9), 4.43 (s, 2H, H-8), 6.96 (d, 1H, $^3J_{HH}$ = 7.3 Hz, H-7), 7.04 (m, 1H, H-5), 7.34 (m, 1H, H-6), 9.11 (m, 1H, H-4) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 43.05 (C-9), 62.93 (C-8), 109.19 (C-7), 121.51 (C-3a), 122.40 (C-5), 129.61 (C-4), 132.50 (C-6), 133.43 (C-3), 145.18 (N–C-7a), 168.67 (O=C-2) ppm; IR (Nujol): $\bar{\nu}$ = 1,727 (C=O), 1,703 (C=O), 1,608 (C=C) cm^{-1}; UV–Vis (CH_2Cl_2, $c = 2.0 \times 10^{-4}$ mol dm^{-3}): λ_{max} (log ε) = 269 (4.65), 397 (4.38) nm (mol^{-1} dm^3 cm^{-1}); MS: *m/z* (%) = 376 [$(M)^{+\cdot}$, 3], 331 [$(M - C_2H_7N)^+$, 2], 262

Scheme 2



[(M − $C_6H_{14}N_2$)$^+$, 16], 234 [(M − $C_6H_{14}N_2$ − CO)$^+$, 18], 205 [(M − $C_6H_{14}N_2$ − CO − CON)$^+$, 7], 177 (3), 151 (2), 103 (3), 73 (9), 77 (3), 58 (100).

1,1′-Bis[(diethylamino)methyl]-3,3′-bis-3H-indolylidene-2,2′(1H,1′H)-dione (**2b**, $C_{26}H_{32}N_4O_2$)

Red crystals, yield 80%; m.p.: 166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.09$ (t, 6H, $^3J_{HH} = 7.3$ Hz, H-10), 2.69 (q, 4H, $^3J_{HH} = 7.3$ Hz, H-9), 4.56 (s, 2H, H-8), 7.02 (d, 1H, $^3J_{HH} = 7.9$ Hz, H-7), 7.05 (dt, 1H, $^3J_{HH} = 7.6$, 7.9 Hz, $^4J_{HH} = 1.0$ Hz, H-5), 7.34 (dt, 1H, $^3J_{HH} = 7.6$, 7.6 Hz, $^4J_{HH} = 1.3$ Hz, H-6), 9.11 (dd, 1H, $^3J_{HH} = 7.9$, $^4J_{HH} = 1.0$ Hz, H-4) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 11.86$ (C-10), 44.75 (C-9), 59.12 (C-8), 109.62 (C-7), 121.60 (C-3a), 122.27 (C-5), 129.40 (C-4), 132.36 (C-6), 133.59 (C-3), 145.20 (C-7a), 168.71 (C-2) ppm; IR (Nujol): $\bar{\nu} = 1{,}695$ (C=O), 1,609 (C=C) cm^{-1}; UV–Vis (CH_2Cl_2, $c = 7.1 \times 10^{-5}$ mol dm^{-3}): λ_{max} (log ε) = 267 (5.15), 406 (4.83) nm (mol^{-1} dm^3 cm^{-1}); MS: *m/z* (%) = 432 [(M)$^{+\cdot}$, 1], 262 [(M − $C_6H_{11}N$ − $C_6H_{11}N$)$^+$, 50], 248 [(M − C_6H_{11} N − $C_6H_{10}N$ − CH_3N)$^+$, 2], 234 [(M − $C_6H_{11}N$ − C_6H_{11} N − CO)$^+$, 53], 220 (7), 205 (13), 177 (4), 151 (3), 117 (4), 103 (6), 86 (100), 77 (3), 70 (27), 58 (11); selected X-ray crystallographic data: triclinic, space group = *P*-1 (molecule in special position), $a = 7.487(3)$ Å, $b = 9.043(3)$ Å, $c = 9.837(3)$ Å, $\alpha = 99.618(4)°$, $\beta = 99.355(4)°$, $\gamma = 113.863(3)°$, $V = 580.6(3)$ Å^3, $T = 293$ (2) K, $Z = 1$, $d_{calc} = 1.237$ g cm^{-3}; CCDC 774581 contains the supplementary crystallographic data for this paper.

1,1′-Bis(morpholin-4-ylmethyl)-3,3′-bis-3H-indolylidene-2,2′(1H,1′H)-dione (**2c**, $C_{26}H_{28}N_4O_4$)

Crimson powder, yield 77%; m.p.: 191 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.66$ (m, 4H, H-9), 3.70 (m, 4H, H-10), 4.52 (s, 2H, H-8), 6.98 (d, 1H, $^3J_{HH} = 7.9$ Hz, H-7), 7.09 (t, 1H, $^3J_{HH} = 7.6$ Hz, H-5), 7.38 (t, 1H, $^3J_{HH} = 7.6$ Hz, H-6), 9.11 (d, 1H, $^3J_{HH} = 7.9$ Hz, H-4) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 51.16$ (C-9), 62.22 (C-8), 66.75 (C-10), 109.27 (C-7), 121.49 (C-3a), 122.54 (C-5), 129.65 (C-4), 132.27 (C-6), 133.38 (C-3), 145.09 (C-7a), 168.74 (C-2) ppm; IR (Nujol): $\bar{\nu} = 1{,}693$ (C=O), 1,606 (C=C) cm^{-1}; UV–Vis (EtOH, $c = 8.5 \times 10^{-5}$ mol dm^{-3}): λ_{max} (log ε) = 242 (4.62), 270 (4.21) nm (mol^{-1} dm^3 cm^{-1}); MS: *m/z* (%) = 460 [(M)$^{+\cdot}$, 2], 375 [(M − C_4H_7ON)$^+$, 1], 373 [(M − C_4H_9 ON)$^+$, 1], 262 [(M − $C_{10}H_{18}O_2N_2$)$^+$, 16], 234 [(M − C_{10} $H_{18}O_2N_2$ − CO)$^+$, 18], 205 [(M − $C_{10}H_{19}O_2N_2$ − CO − CO)$^+$, 6], 177 (2), 147 (3), 119 (8), 100 (100), 73 (4), 77 (6), 58 (100).

1,1′-Bis(piperidin-4ylmethyl)-3,3′-bis-3H-indolylidene-2,2′(1H,1′H)-dione (**2d**, $C_{28}H_{32}N_4O_2$)

Red crystals, yield 75%; m.p.: 178–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.39$ (m, 2H, H-11), 1.55 (m, 4H, H-10), 2.59 (m, 4H, H-9), 4.50 (s, 2H, H-8), 6.97 (d, 1H, $^3J_{HH} = 7.9$ Hz, H-7), 7.03 (t, 1H, $^3J_{HH} = 7.9$ Hz, H-6), 7.33 (dt, 1H, $^3J_{HH} = 7.3$ Hz, $^4J_{HH} = 0.6$ Hz, H-5), 9.08 (d, 1H, $^3J_{HH} = 8.3$ Hz, H-4) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 23.97$ (C-9), 25.75 (C-10), 52.09 (C-9), 62.77 (C-8), 109.37 (C-7), 121.48 (C-3a), 122.21 (C-5), 129.43 (C-4), 132.30 (C-6), 133.41 (C-3), 145.53 (C-7a), 168.84 (C-2) ppm; IR (Nujol): $\bar{\nu} = 1{,}717$ (C=O), 1,697 (C=O), 1,609 (C=C) cm^{-1}; UV–Vis (CH_2Cl_2, $c = 2.0 \times 10^{-4}$ mol dm^{-3}): λ_{max} (log ε) = 265 (4.57), 405 (4.20) nm (mol^{-1} dm^3 cm^{-1}); MS: *m/z* (%) = 456 [(M)$^{+\cdot}$, 1], 359 [(M − $C_6H_{11}N$)$^+$, 0.5], 262 [(M − $C_6H_{11}N$ − $C_6H_{11}N$)$^+$, 20], 234 [(M − $C_6H_{11}N$ − $C_6H_{11}N$ − CO)$^+$, 23], 205 (5), 191 [($C_{12}H_{19}N_2$)$^+$, 38], 163 (7), 135 (8), 119 (15), 98 [($C_6H_{12}N$)$^+$, 100], 97 (57), 96 (55), 77 (9), 72 (36), 60 (98).

1,1′-Bis(1,3-dihydro-1,3-dioxoisoindol-2-ylmethyl)-3,3′-bis-3H-indolylidene-2,2′(1H,1′H)-dione (**2e**, $C_{34}H_{20}N_4O_6$)

Red powder, yield 90%; m.p.: 111 °C; due to the very low solubility of this compound in a wide range of organic solvents NMR spectra could not be recorded; IR (Nujol): $\bar{\nu} = 1{,}774$ (C=O), 1,726 (C=O), 1,711 (C=O), 1,609 (C=C) cm^{-1}; MS: *m/z* (%) = 580 [(M)$^{+\cdot}$, 10], 538 [(M − CON)$^+$, 0.2], 500 (4), 478 (1), 420 [(M − $C_9H_6NO_2$)$^+$, 1], 405 [(M − $C_9H_6NO_2$ − CH_3)$^+$, 1], 392 [(M − C_9H_6 NO_2 − CO)$^+$, 3], 335 [(M − $C_{15}H_5N_2$ − 2O)$^+$, 15], 313 (5), 285 (9), 235 (5), 169 (100), 160 (37), 147 (50), 119 (20), 97 (28), 77 (12), 69 (96).

Acknowledgments We are grateful to Prof. B.I. Buzykin for discussions and to the Russian Foundation for Basic Research (grant No. 09-03-00933) and the Council on Grants of the President of the Russian Federation (grant MK-1670.2010.3) for financial support.

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