Synthesis and study of 3-(triphenylphosphoranylidene)-2,3-dihydro-1*H*-indol-2-one

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The reaction of isatin 1 (2,3-dihydroindole-2,3-dione) and triphenylphosphine 2 afforded the new title compound 6 and isoindigo 7 and not the earlier proposed indirubin 3. Wittig reactions of 6 with the benzaldehydes 8a–c gave the corresponding (*Z*-)- and (*E*)-3-(arylmethylidene)-2,3-dihydro-1*H*-indol-2-ones 9a–c and 10a–c, respectively, in moderate yields.

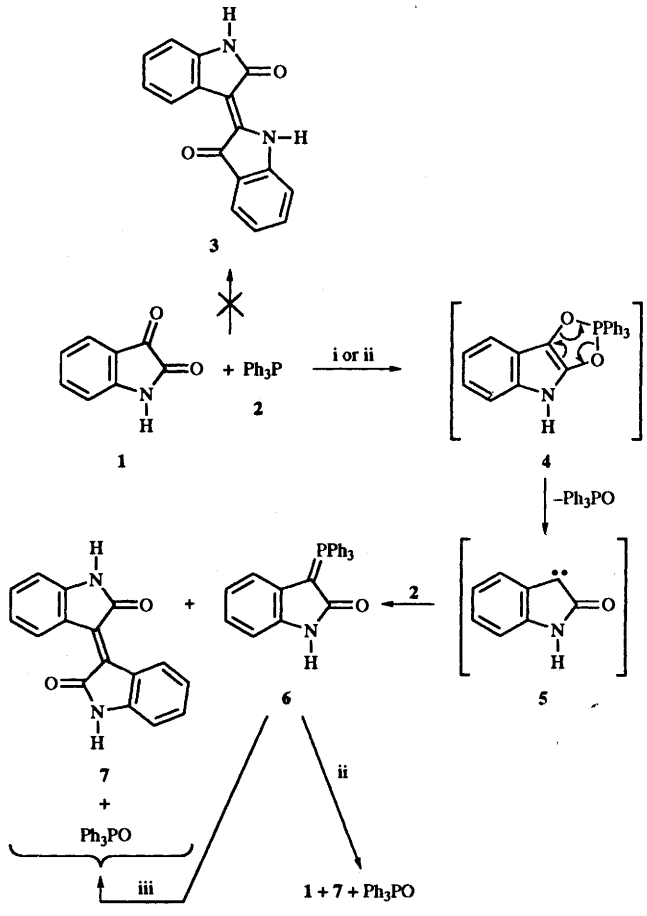
Boulos and El-Kateb reported[1] in 1983 that the reaction of isatin **1** with triphenylphosphine **2** in toluene afforded indirubin **3**, while earlier[2] Sidky *et al.* reported that the same reactants in refluxing benzene remain unchanged. In continuation of our interest[3] in the reactions of *ortho*-quinones with phosphorus ylides both in the presence and absence of **2**, and in order to extend[4] these reactions to the synthesis of natural products and/or biologically active molecules, we decided to study the reaction of **1** with **2** in different solvents in order to find out if an unknown phosphorane is formed initially and by further reaction with **1** gave **3**. If this proved correct we planned to use this new phosphorane as a synthetic intermediate.

Results and discussion

A mixture of isatin **1** (1 mol equiv.) and triphenylphosphine **2** (2 mol equiv.) in dichloromethane was stirred at room temperature for 20 d to give as a precipitate 3-triphenylphosphoranylidene-2,3-dihydro-1*H*-indole-2-one **6** (74%) (see Scheme 1). Column chromatography of the filtrate afforded isoindigo **7** (3%), unchanged isatin **1** (5%), triphenylphosphine oxide (92%) and additional **6** (8%; total yield 82%). The same reaction of **1** and **2** (in a molar ratio 2:3) in refluxing toluene for 20 h gave the same products: **6** (44%), **7** (49%), unchanged **1** (7%) and Ph_3PO (72%). Although the expected[1] indirubin **3** was not detected in the reaction products, isoindigo **7** was isolated and identified from its spectral characteristics. IR absorption for C=O occurred at 1695 cm^{-1} and not 1730 cm^{-1} as was expected[5] for indirubin. The mass spectral pattern for **7** is different from that of indirubin.[6] The UV–VIS spectrum of **7** in 1,1,2,2 tetrachloroethane (λ_{max} 485, 397 and 269 nm) is different from that of **3** (λ_{max} 550, 367 and 296 nm) and resembles closely that of isoindigo.[7]

The MS characteristics and analyses for the new phosphorane were in accord with structure **6** whilst the CO absorption in its IR spectrum was at 1600 cm^{-1}, similar to that for $Ph_3P{=}CHCONPh_2$ (1570 cm^{-1}).[8] Compound **6** in Wittig reactions with benzaldehydes **8a–c** also gave the expected products **9a–c** and **10a–c**. Attempted preparation of the *N*-methyl analogue of **6** by pyrolysis of the corresponding 3-triphenylphosphazene derivative[9] had failed earlier and gave dimers such as **7**, nitrogen and triphenylphosphine **2**.

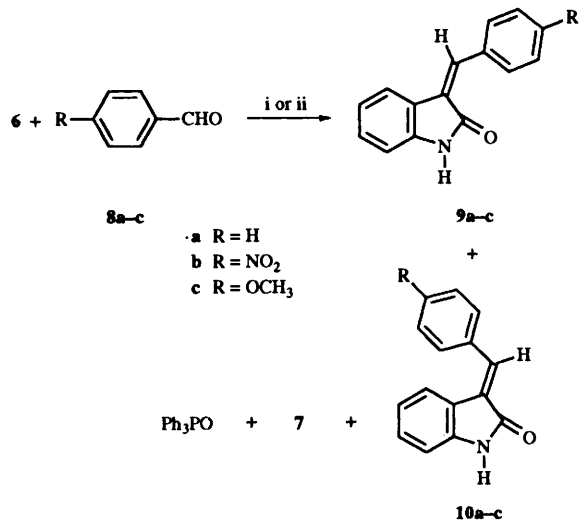
Formation of **7** is understandable in terms of initial formation of the dioxaphospholane **4** by a [4+2] cycloaddition of Ph_3P to isatin, followed by Ph_3PO abstraction to give the intermediate carbene **5**, the reaction of which with Ph_3P gives the ylide **6**. Dimerization of indermediate carbene **5** and/or Wittig reaction of the ylide **6** with isatin **1** afforded isoindigo **7**. In a control experiment, the heating of **6** and **1** in refluxing toluene for 48 h gave **7** (25%), Ph_3PO (21%), unchanged **6** (55%) and **1** (70%).



Scheme 1 *Reagents and conditions:* i, CH_2Cl_2, room temp., ii, toluene, reflux, iii, 1, toluene, reflux

Scheme 2 depicts the reactions of the ylide **6** with the benzaldehydes **8a–c**. A mixture of **6** and **8a** (1:1) in toluene heated under reflux for 10 d gave, after cooling, removal of the unchanged ylide **6** (14%) by filtration, evaporation of the filtrate and column chromatography of the residue, the *Z* isomer[10] **9a** (16%), the *E* isomer[10,11] **10a** (37%), isoindigo **7** (12%), unchanged **1** (7%) and Ph_3PO. The UV and ^1H NMR spectra of the products **9a** and **10a** were in agreement with literature data.[10,11]

Reaction of **6** with **8b** under the same conditions resulted in (*Z*-) indol-2-one[10] **9b** (14%), the (*E*-) indol-2-one[11] **10b** (31%), **7** (16%), Ph_3PO, unchanged **6** (38%) and the aldehyde **8b** (54%). A reaction in the absence of solvent at 150 °C for 3 d gave **9b** (7%), **10b** (15%), **7** (55%), **1** (traces), Ph_3PO and unchanged **6** (22%) and **8b** (75%). The reaction of **6** and **8c** in



Scheme 2 *Reagents and conditions:* i, toluene, reflux, ii, neat, 150 °C

refluxing toluene for 10 d gave the (*Z*)-indol-2-one[11] **9c** (12%), the (*E*-) indol-2-one[10] **10c** (27%), **7** (8%), Ph_3PO and unchanged **6** (51%) and **8c** (54%).

In these reactions the Wittig products were obtained in moderate yields owing to the stability of the ylide **6**. Compound **7** was also obtained as a by-product in yields which increased with the temperature, possibly as a result of the decomposition of **6**. In order to check this, we performed a control experiment by refluxing a dispersion of **6** in toluene for 5 d. Unchanged **6** (36%) was precipitated and filtered off, and PTLC separation of the filtrate gave isoindigo **7** (15%), isatin **1** (27%), Ph_3PO (45%) and further **6** (4%; total 40%). The formation of **7** may be attributed to oxidation of **6** under the reaction conditions to **1** and Ph_3PO and further reaction of **1** with the starting material **6**.

In conclusion, indirubin **3** was not detected in the reaction of isatin with Ph_3P; rather, isoindigo **7** and the new ylide **6** were isolated. The latter can be used to obtain Wittig products with a variety of carbonyl compounds in spite its stability at lower temperatures and its oxidation at higher.

Experimental

Mps were determined on a Kofler hot-stage apparatus and are uncorrected. UV–VIS spectra were obtained with a Shimadzu UV-210A spectrophotometer. IR spectra were run on a Perkin-Elmer 1310 spectrophotometer. ^1H NMR spectra were recorded on a Bruker AW80 (80 MHz) spectrometer with $SiMe_4$ as internal standard. *J* Values are given in Hz. Mass spectra were determined on a VG-250 spectrometer with ionization energy maintained at 70 eV.

Reactions of isatin 1 with triphenylphosphine 2

(a) A mixture of **1** (0.735 g, 5 mmol) and **2** (2.6 g, 10 mmol) in dichloromethane (50 cm^3) was stirred at room temperature for 20 days and then evaporated. The residue was treated with dichloromethane–ether to give 3-(triphenylphosphoranylidene)-2,3-dihydro-1*H*-indol-2-one **6**, as red-brown crystals (1.451 g, 74%), mp 320–322 °C (decomp.) (from ethanol, in a sealed tube) (Found: C, 79.2; H, 5.4; N, 3.7. $C_{26}H_{20}NOP$ requires C, 79.4; H, 5.1; N, 3.55%); ν_{max}(Nujol)/cm^{-1} 3050, 1600 and 1105; λ_{max}(EtOH)/nm 238 (ε/dm^3 mol^{-1} cm^{-1} 23.300), 260 (16.100) and 297 (9.800); δ_H($CDCl_3$–[$^2H_6$]-DMSO) 6.6–7.8 (m); *m*/*z* 394 (22%), 393 (M^+, 100), 392 (23), 208 (12), 185 (13), 183 (62) and 77 (10). The filtrate was evaporated and the residue was separated by column chromatography on silica gel with ethyl acetate–hexane (1:1) as eluent to give (i) unchanged triphenylphosphine **2** (0.34 g, 13%), (ii) isoindigo **7** (21 mg, 3%), mp > 325 °C (ether–hexane) (lit.,[12] mp 364 °C); ν_{max}(Nujol)/cm^{-1} 3190, 3130, 3060, 1695 and 1600; λ_{max}($C_2H_2Cl_4$)/nm 396 (ε/dm^3 mol^{-1} cm^{-1} 10.900) and 483 (5.100); δ_H($CDCl_3$–[$^2H_6$]-DMSO) 6.6–8.0 (8 H, m), 9.08 (1 H, s) and 10.47 (1 H, s); *m*/*z* 263 (20%), 262 (M^+, 100), 261 (6), 235 (13), 234 (83), 206 (7), 205 (18), 151 (4), 131 (6) and 109 (9), (iii) unchanged isatin **1** (34 mg, 5%), (iv) triphenylphosphine oxide (1.273 g, 92%) and (v) the ylide **6** (0.157 g, 8%; total yield 82%).

(b) A mixture of **1** (0.147 g, 1 mmol) and **2** (0.393 g, 1.5 mmol) in toluene (10 cm^3) was heated under reflux for 20 h. After cooling, evaporation of the reaction mixture and treatment of the residue with dichloromethane–ether gave the ylide **6** (0.163 g, 41%) as a precipitate. Evaporation of the filtrate and separation of the residue by PTLC [ethyl acetate–hexane (1:1)] gave isoindigo **7** (64 mg, 49%) from the faster moving band, followed by unchanged isatin **1** (9 mg, 7%), Ph_3PO (0.202 g, 72%) and then compound **6** (11 mg, 3%; total yield 44%).

Reaction of the ylide 6 with isatin 1

A mixture of **6** (55 mg, 0.14 mmol) and **1** (20 mg, 0.14 mmol) in toluene (8 cm^3) was refluxed for 48 h after which it was cooled and filtered to give unchanged **6** (22 mg, 40%). Evaporation of the filtrate and separation of the residue by PTLC [silica gel, hexane–ethyl acetate (2:1)] gave from the faster moving band **7** (9 mg, 25%), and then **1** (14 mg, 70%), Ph_3PO (8 mg, 21%) and the ylide **6** (8 mg; 15%; total yield 55%).

Reaction of the ylide 6 with benzaldehyde 8a

A mixture of **6** (0.393 g, 1 mmol) and **8a** (0.106 g, 1 mmol) in toluene (20 cm^3) was heated under reflux for 10 d after which it was cooled and filtered to give unchanged **6** (56 mg, 14%). The filtrate was evaporated and the residue subjected to column chromatography on silica gel [ethyl acetate–hexane (1:3)] to give (*Z*-) 3-benzylidene-2,3-dihydro-1*H*-indol-2-one **9a** (35 mg, 16%), mp 180–181 °C (from dichloromethane) (lit.,[10] mp 180–181 °C); δ_H($CDCl_3$) 6.72–7.16 (2 H, m), 7.18–7.70 (6 H, m) and 8.14–8.53 (2 H, m). Further elution afforded (*E*-) 3-benzylidene-2,3-dihydro-1*H*-indol-2-one **10a** (82 mg, 37%), mp 174–176 °C (from dichloromethane) (lit.,[10,11] 175–176 °C); δ_H($CDCl_3$) 6.70–6.99 (2 H, m), 7.07–7.78 (7 H, m), 7.84 (1 H, s) and 9.23 (1 H, br s). Isoindigo **7** (16 mg, 12%) and isatin **1** (11 mg, 7%) were also eluted, followed by triphenylphosphine oxide.

Reactions of the ylide 6 with 4-nitrobenzaldehyde 8b

(a) A stirred mixture of **6** (0.393 g, 1 mmol) and **8b** (0.151 g, 1 mmol) in toluene (20 cm^3) was refluxed for 10 d after which it was cooled and filtered to remove unchanged **6** (0.15 g, 38%). The filtrate was evaporated and the residue chromatographed on silica gel (dichloromethane) to give unchanged aldehyde **8b** (82 mg, 54%) followed by (*Z*-) 3-(4-nitrobenzylidene)-2,3-dihydro-1*H*-indol-2-one **9b** (38 mg, 14%), mp 222–224 °C (from dichloromethane) (lit.,[10] mp 224–225 °C); δ_H($CDCl_3$ + [$^2H_6$]-DMSO) 6.78–7.65 (5 H, m), 8.23 (2 H, d, *J* 8.5), 8.37 (2 H, d, *J* 8.5) and 10.13 (1 H, br s). Next eluted was (*E*-) 3-(4-nitrobenzylidene)-2,3-dihydro-1*H*-indol-2-one **10b** (82 mg, 31%), mp 240–242 °C (from ethanol) (lit.,[11] 240–243 °C); δ_H($CDCl_3$) 6.73–7.05 (2 H, m), 7.12–7.55 (2 H, m), 7.78 (1 H, s), 7.80 (2 H, d, *J* 8) and 8.22 (2 H, d, *J* 8) followed by isoindigo **7** (21 mg, 16%).

(b) A mixture of **6** (0.196 g, 0.5 mmol) and **8b** (75 mg, 0.5 mmol) was heated at ~150 °C for 3 d and then cooled and treated with toluene to give unchanged ylide **6** (44 mg, 22%). Column chromatography of the residue on silica gel [ethyl acetate–hexane (1:3)] afforded, after unchanged aldehyde **8b** (56 mg, 75%), compounds **9b** (9 mg, 7%), **10b** (20 mg, 15%), isoindigo **7** (36 mg, 55%) and isatin **1** (traces).

Reaction of the ylide 6 with 4-methoxybenzaldehyde 8c

A stirred mixture of **6** (0.393 g, 1 mmol) and **8c** (0.136 g, 1 mmol) in toluene (20 cm^3) was boiled for 10 d, after which it was cooled and filtered to give unchanged **6** (0.2 g, 51%). The filtrate was concentrated and separated by column chromatography on silica gel (dichloromethane) to give unchanged aldehyde **8c** (73 mg, 54%), followed by (*Z*)-3-(4-methoxybenzylidene)-2,3-dihydro-1*H*-indol-2-one **9c** (31 mg, 12%), mp 174–176 °C (from dichloromethane) (lit.,[10] 175–176 °C); $\delta_H(CDCl_3)$ 3.83 (3 H, s), 6.77–7.90 (7 H, m) and 8.35 (2 H, d, *J* 8). Next eluted was (*E*)-3-(4-methoxybenzylidene)-2,3-dihydro-1*H*-indol-2-one **10c** (68 mg, 27%), mp 156–158 °C (from dichloromethane) (lit.,[10] 156–157 °C) followed by isoindigo **7** (11 mg, 8%).

Decomposition of the ylide 6

A mixture of the ylide **6** (98 mg, 0.25 mmol) in toluene (5 cm^3) was refluxed for 5 d and then cooled and evaporated. The residue was treated with ether to give unchanged ylide **6** (35 mg, 36%) as a precipitate which was filtered off. Separation of the filtrate with PTLC on silica gel [ethyl acetate–hexane (1:2)] gave from the faster moving band isoindigo **7** (10 mg, 15%), followed by isatin **1** (10 mg, 27%), triphenylphosphine oxide (31 mg, 45%) and unchanged ylide **6** (4 mg, 4%; total yield 40%).

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