Synthesis of 3,4,6-trisubstituted Cinnolines by Intramolecular Wittig Reaction of *ortho*-Carbonyl Substituted Arylazomethylenetriphenylphosphoranes

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This paper reports the first example of Wittig reaction on arylazomethylenetriphenylphosphoranes, producing the new cinnolines **6** and **7**. A new unexpected rearrangement reaction producing quinoline **8** is also reported. The structure of compound **8** was determined by X-ray analysis.

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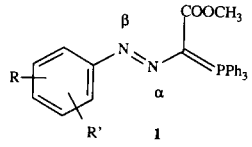
During our work on the chemical behaviour of arylazomethylenetriphenylphosphoranes **1**, aimed at the synthesis of heterocyclic compounds, we showed that their reactivity was strictly tied to the ability of delocalizing the negative charge from the ylidic carbon atom on the azo group; as a consequence, electrophilic functions (*e.g.* alkyl halides, formyl group, *etc.*) attack the α- or β-nitrogen atoms rather than the ylidic carbon atom [1-3]. Moreover we did not observe any products arising from a Wittig reaction between the ylidic function and a carbonyl group [2].

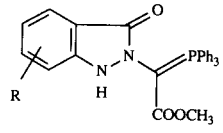
Formula 1



a: R = H R' = o-COCOOH
b: R = p-Br R' = o-COCOOH
c: R = p-Br R' = o-COCOOCH$_3$

In previous work we reported the synthesis of phosphoranes **1a-c** from isatic acid [4] with the aim of utilizing suitable *ortho*-functionalized arylazomethylenetriphenylphosphoranes for the synthesis of cinnoline rings through an intramolecular Wittig reaction. In fact we discussed that the presence of an electron-withdrawing group (COOH or COOR) could make the carbonyl function more susceptible to electrophilic attack than the formyl group. However compounds **1a,b** were highly reactive and not isolable compounds which, as soon as formed, underwent an intramolecular cyclization reaction with loss of carbon dioxide and formation of compounds **2a,b**.

Formula 2



a: R = H
b: R = 5-Br

At this point we thought that compounds **1c** and **5** should have been more suitable substrates than **1a,b** because they could not undergo an easy decarboxylation reaction.

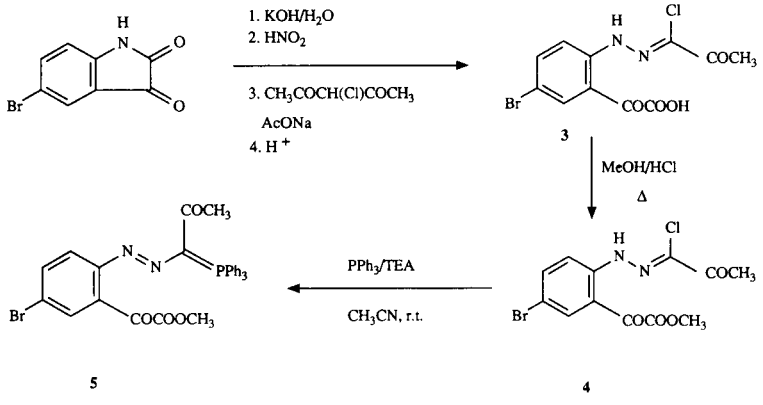
We wish now to report the synthesis of the new azophosphorane **5** and the results of the thermal reaction of compounds **1c** and **5**. Compound **5** was prepared following the reactions sequence reported in Scheme 1, which was the same already utilized for the synthesis of compounds **1a-c** [4] (Scheme 1).

Treatment with aqueous potassium hydroxide of the 5-bromoisatin, diazotization, copulation with 3-chloro-2,4-pentandione and esterification afforded the ester **4** in 13% overall yield.

Treatment of compound **4** with triphenylphosphine and triethylamine in acetonitrile solution at room temperature for 3 hours, gave the arylazophosphorane **5** in a 80% yield. Both compounds **1c** and **5** were submitted to thermal treatment: when refluxed in toluene for 48 hours, compound **1c** furnished the 6-bromo-3,4-dimethoxycarbonylcinnoline **6** in a 45% yield of the isolated product, other than triphenylphosphine oxide and unidentified black by-products (Scheme 2). Compound **6**, previously not described in the literature, arises from an intramolecular Wittig reaction between the phosphorane group and the *ortho*-carbonyl function, activated by the presence of the ester moiety.

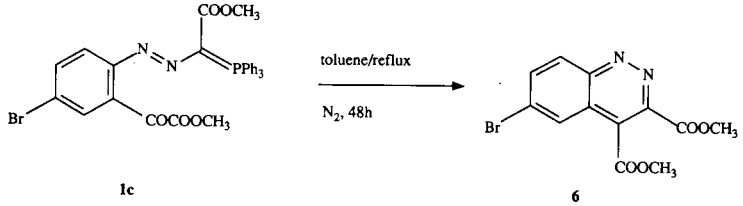
Analogously, compound **5** was refluxed in xylene under nitrogen for 48 hours: after purification of the reaction mixture by flash chromatography, two main products were recovered: the 6-bromo-3-acetyl-4- methoxycarbonylcinnoline **7** in a 20% yield and a small amount of 6-bromo-2-cyano-4-methoxycarbonylquinoline **8** (Scheme 3). Both compounds **7** and **8** were unknown (Scheme 3). The structure of compounds **6** and **7** was assigned on the basis of analytical and spectroscopic data (See Experimental).

Scheme 1



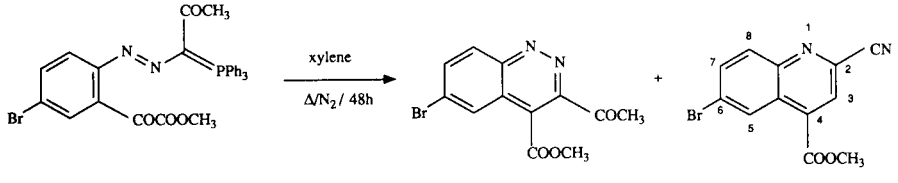
5 4

Scheme 2



1c 6

Scheme 3



5 7 8

Analogously to compound **6**, the cinnoline **7** resulted from an intramolecular Wittig reaction.

The obtaining of cinnolines **6** and **7** represents the first example of a Wittig reaction in azophosphoranes **1** and demonstrates that the regiochemistry of the electrophilic attack on the azophosphorane moiety is dependent on the nature of the electrophile [5].

6-Bromo-2-cyano-4-methoxycarbonylquinoline **8** was a quite unexpected product, whose structure was assigned by the X-ray analysis of a single crystal.

Fractional atomic coordinates for the non-hydrogen are given in Table 1. Tables 2 and 3 list the bond lengths and valence angles. The molecule (Figure 1) is planar with a maximum deviation from the least squares plane of 0.07 Å, for C(11). There is a noticeable degree of bond ordering about N(1) with the N(1)-C(2) length (1.310(5) Å) significantly shorter than that for N(1)-C(8a), (1.357(5) Å). Despite an absence of any significant conjugative shortening of the C(4)-C(10) bond the ester is coplanar with the

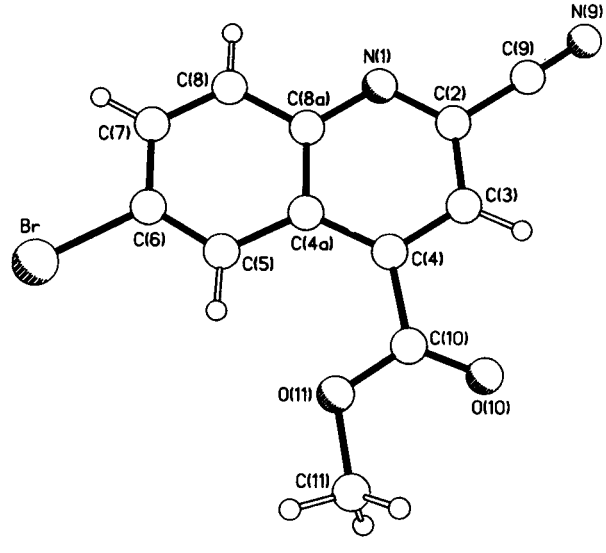


Figure 1. The molecular structure of **8** showing atom numbering.

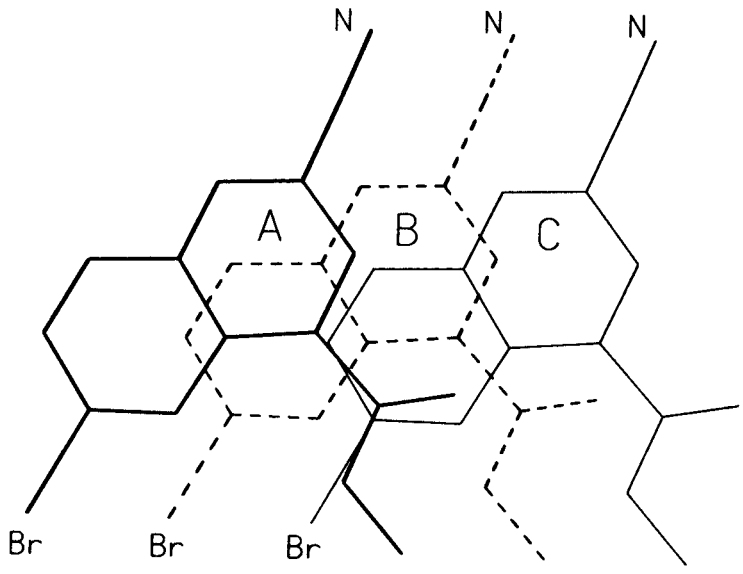


Figure 2a. Plan view of the stacking of the molecules in the crystal, in the order A→B→C.

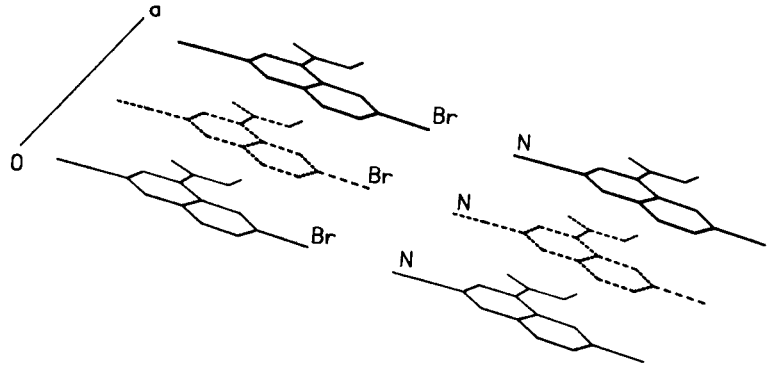


Figure 2b. Elevation illustrating the linear alignment of the cyano groups and Br atoms in adjacent stacks.

rest of the molecule, and gives rise to a short intramolecular contact (2.19 Å) between H(5) and the methoxy oxygen O(11). This may indicate the presence of a weak C-H-O hydrogen bond, though the enlargement of the C(4a)C(4)-C(10) angle 127.1(3)° *cf* C(3)C(4)C(10), 113.7(3)° may argue against this.

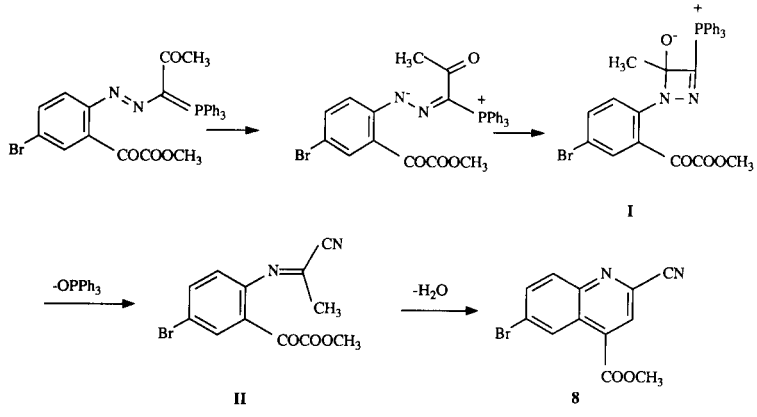
Investigation of the packing of the molecules in the crystal reveals two major intermolecular packing interactions. 1) The molecules form continuous parallel stacks in the crystallographic *a* direction (Figure 2a) with an interplanar separation of 3.4 Å. 2) There is a short inter-stack contact of 3.18 Å between the cyano nitrogen N(9) and the bromine atom with the bromine atoms of the molecules in one stack aligned along the axis of the cyano groups in the adjacent stack (the C(9)-N(9)...Br′ angle is 178°) (Figure 2b).

Even if compound **8** was not expected, its formation could be interpreted once more as an attack of the carbonyl group on the nitrogen atom, as depicted in Scheme 4.

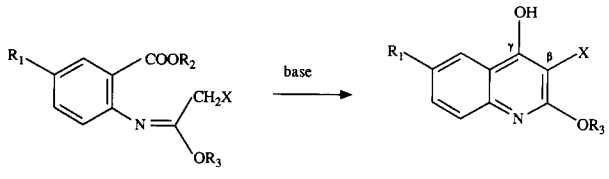
The intermediate bi-cycle **I** thus formed could lose triphenylphosphine oxide and give the 1-cyanoimine **II**; the methyl substituent of such a product is acidic enough to react with the *ortho*-carbonyl group, giving the quinoline **8**.

The transformation of intermediate **II** into quinoline **8** bears some resemblance to the modification of the Camps quinoline synthesis, in which an activated methyl group reacts with an alkoxycarbonyl moiety with the bond formation between the β and γ-carbons of the ring (Scheme 5) [6].

Scheme 4



Scheme 5



EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer X98 spectrophotometer. The ^{1}H nmr were recorded on a Varian EM-390 spectrometer operating at 90 MHz. The ^{13}C nmr spectra were recorded on a Varian XL-300 MHz. Mass Spectra were taken with a Varian MAT 311-A spectrometer equipped with a combined EI-FI-FD ion source. The tlc analyses were performed on Merck precoated silica gel 60F-254 plates.

Synthesis of Compound **3**.

An aqueous solution of potassium salt of 5-bromoisatic acid (from 0.076 mole of 5-bromoisation and 0.076 moles of potassium hydroxide in 100 ml of water [3]) was added dropwise into a 20% aqueous solution of sulfuric acid (135 g) and sodium nitrite (0.16 mole), kept at 0°. Then, the solution of the diazonium salt was added dropwise into a solution of 3-chloro-2,4-pentandione (0.076 mole) in methanol (30 ml) at 0°. Simultaneously solid sodium acetate was added at the reaction mixture, to *p*H = 5. After 1 hour at 0°, the yellow precipitate was filtered off and used as such for the esterification. The mother liquors were acidified with 10% aqueous hydrochloric acid and extracted with dichloromethane. The organic layer was separated, dried over sodium sulfate and the solvent was distilled off under reduced pressure. The brown solid residue thus obtained was used as such for the esterification.

Esterification of Compound **3**.

The crude products obtained from the above reaction were dissolved in methanol (200 ml), a dry hydrochloric acid saturated methanol solution (12 ml) was added and the solution refluxed for two hours. After cooling of the reaction mixture, the yellow precipitate, consisting of pure ester **4**, was filtered off. The overall yield from 5-bromoisatin was 12%, mp 174°; ir (nujol): cm^{-1} 3210 (NH), 1760, 1680, 1650 (3 CO); ^{1}H nmr (deuteriochloroform): δ 2.5 (s, 3H, $COCH_3$), 3.9 (s, 3H, $COCOOCH_3$), 7.6-7.9 (m, 3H, aromatic), 11.8 (s, 1H, NH).

Anal. Calcd. for $C_{12}H_{10}BrClN_2O_4$: C, 39.8; H, 2.8; N, 7.7. Found: C, 40.0; H, 2.6: N, 8.0.

Synthesis of Compound **5**.

Compound **5** was prepared starting from compound **4** with triphenylphosphine and triethylamine in acetonitrile, as already reported for analogous substrates [3], yield 77%, mp 159° (washed with diethyl ether); ir (nujol): cm^{-1} 1740, 1680, 1620 (3 CO); ^{1}H nmr (deuteriochloroform): δ 2.3 (s, 3H, $COCH_3$), 3.6 (s, 3H, $COCOOCH_3$), 6.4 (d, 1H, H-6 J_{ortho} = 9 Hz), 7-7.6 (m, 17H, aromatic).

Anal. Calcd. for $C_{30}H_{24}BrN_2O_4P$: C, 61.33; H, 4.08; N, 4.77. Found: C, 61.51; H, 4.09; N, 4.78.

Thermal Treatment of Phosphorane **1c**.

A solution of compound **1c** (1.7 mmoles) in toluene (25 ml) was refluxed for 48 hours under nitrogen. The black precipitate obtained by cooling the reaction mixture was filtered off and eliminated. The toluene was evaporated at reduced pressure and the oil residue was purified by flash chromatography (eluant: light petroleum/ethyl acetate 7:3). 6-Bromo-3,4-dimethoxycarbonylcinnoline **7** was recovered as a pure product, yield 46%, mp 147-149° (ethanol); ir (nujol): cm^{-1} 1730, 1720 (2 $COOCH_3$); ^{1}H nmr (deuteriochloroform): δ 4.2 (s, 6H, 2 CH_3), 8-8.13 (m, 2H, H_5 + H_7, J_{5-7} = 2 Hz), 8.56 (dd, 1H, H_8, J_{7-8} = 9 Hz, J_{5-8} = 0.6 Hz); ^{13}C nmr (deuteriochloroform): δ 53.6 (C_{11}, C_{12}), 122.6 (C_{4a}), 127 (C_5), 127.7 (C_4), 128.6 (C_6), 131.8 (C_8), 136.6 (C_7), 141.2 (C_3), 149.5 (C_{8a}), 164.35 (C_9), 165.06 (C_{10}).

Anal. Calcd. for $C_{12}H_9BrN_2O_4$: C, 44.5; H, 2.78; N, 8.57. Found: C, 44.1; H, 2.81; N, 8.56.

The triphenylphosphine oxide was recovered, from the flash chromatography, as a second fraction, yield 34%.

Thermal Treatment of Phosphorane **5**.

A solution of compound **5** (6 mmoles) in xylene (70 ml) was refluxed for 48 hours under nitrogen. The solvent was then evaporated at reduced pressure and the residue purified by flash chromatography (eluant: light petroleum/ethyl acetate 9:1). The quin-

oline **8** was recovered as the first product, in 8% yield, mp 181° (chloroform); ir (nujol): cm^{-1} 2220 (CN), 1720 (CO); ^1H nmr (deuteriochloroform): δ 4.08 (s, 3H, CH_3), 7.96 (dd, 1H, H_7), 8.09 (d, 1H, H_8), 8.24 (s, 1H, H_3), 9.14 (d, 1H, H_5); ^{13}C nmr (deuteriochloroform): δ 53.30 (OCH_3), 116.67 (CN), 125.34 (C_3), 126.59 (C_{4a}), 126.64 (C_6), 128.19 (C_5), 131.97 (C_8), 133.58 (C_2), 134.95 (C_4), 135.15 (C_7), 147.91 (C_{8a}), 164.43 (CO).

The 3-acetyl-6-bromo-4-methoxycarbonylcinnoline **7** was recovered in 15% yield as a second product; mp 176° (methanol), ir (nujol): cm^{-1} 1730, 1690 (2 CO); ms: m/e 308 (M^+); ^1H nmr (deuteriochloroform): δ 3 (s, 3H, $COCH_3$), 4 (s, 3H, $COOCH_3$), 7.8-8.6 (m, 3H, aromatic); ^{13}C nmr (deuteriochloroform): δ 27.1 (C_{11}), 53.4 (C_{12}), 122.8 (C_{4a}), 125.77 (C_4), 127.14 (C_5), 128.21 (C_6), 131.4 (C_8), 136.58 (C_7), 145.27 (C_3), 149.44 (C_{8a}), 165.63 (C_{10}).

Anal. Calcd. for $C_{12}H_9BrN_2O_3$: C, 46.6; H, 2.9; N, 9.06. Found: C, 46.5; H, 2.87; N, 9.02.

X-Ray structural determination of compound **8**. Crystal data: $C_{12}H_7N_2O_2Br$, M = 291.1, triclinic, a = 4.070(1), b = 11.192(3), c = 11.979(4) Å, α = 90.05(2), β = 93.05(2), γ = 94.22(2)°, U = 543 $Å^3$, space group P$\bar{1}$, Z = 2, D_c = 1.78 g cm^{-3}, Cu radiation, $\bar{\lambda}$ = 1.54178 Å, μ (Cu-K_α) = 51 cm^{-1}, F(000) = 288. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. A crystal of dimensions 0.05 x 0.06 x 0.33 mm was used; 1470 independent reflections were measured ($2\theta \leq 116°$), of which 1361 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarization factors; a numerical absorption correction (face-indexed crystal) was applied. Maximum and minimum transmission factors .781 and .613. The structure was solved by the heavy atom method. The non-hydrogen atoms were refined anisotropically. The positions of the hydrogen atoms were idealised, C-H = 0.96 Å, assigned isotropic thermal parameters, U(H) = 1.2 U_g (C), and allowed to ride on their parent carbon atoms. The methyl group was refined as a rigid body. Refinement was by block-cascade, full-matrix least squares to R = 0.038, R_w = 0.039 [$w^{-1} = \sigma^2(F) + 0.00128F^2$]. The maximum and minimum residual electron densities in the final △F map were 0.84 and −0.73 e $Å^{-3}$ respectively. The mean and maximum shift/error in the final refinement were 0.004 and 0.043 respectively.

Computations were carried out on an Eclipse S140 computer using the SHELXTL program system [7].

Acknowledgments.

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