Study of Insertion Reactions with Phosphorus Ylides − On Reactions between 4-(4-Methylphenyl)-2,3-benzoxazin-1-one and Alkylidene Phosphoranes

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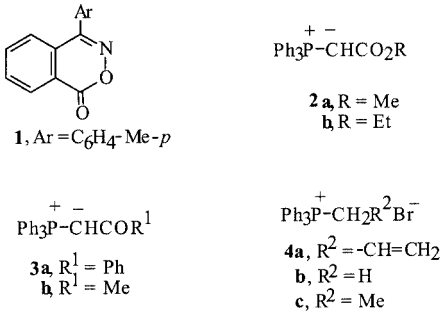
4-(4-Methylphenyl)-2,3-benzoxazin-1-one (**1**) reacts thermally with a series of alkylidene phosphoranes and the relevant salts to give mainly substituted isoquinolines. Thus, compound **1** reacts with ester ylides **2a** and **2b** to give isoquinolones **7a** and **7b**, whereas with benzoylmethylenetriphenylphosphorane (**3a**), compound **7c** was obtained together with the corresponding ylide **9a**. The latter compound was treated with K_2CO_3 and then with polyphosphoric acid to give the isoquinolone **7c**. With acetyl ylide **3b**, *o*-diacetyl-α-naphthol **13** and cycloheptenone **14** were also obtained, in addition to **7d**. On the other hand, isoquinolone derivatives **18**, **21a**, and **21b** were successfully prepared by treatment of **1** with moderately (**4a**) and more reactive (**4b**, **4c**) phosphonium salts.

Introduction

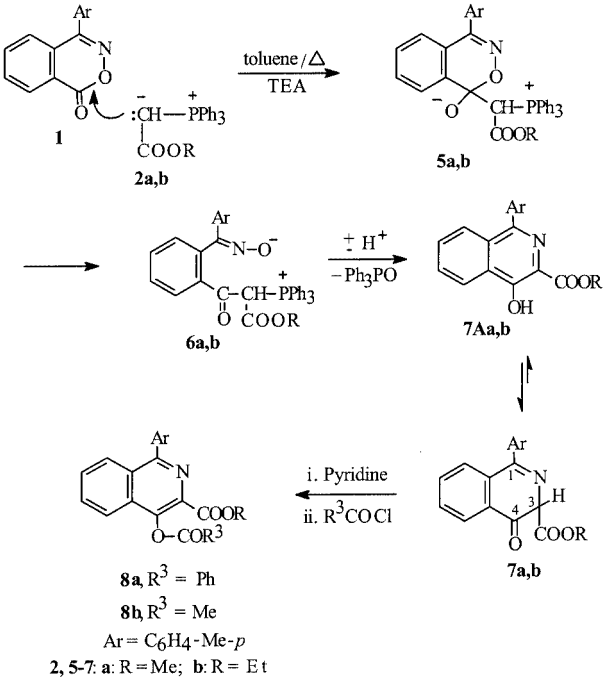
In a continuing exploration of the attack of alkylidene phosphoranes on carbon-nitrogen systems,[1] we became interested in reactions between 4-(4-methylphenyl)-2,3-benzoxazin-1-one (**1**) and ester- (**2a**, **2b**) and keto- (**3a**, **3b**) ylide phosphoranes, as well as the relevant phosphonium salts **4a−c**. The reactions studied and the products obtained are depicted in Schemes 1−6.



Results and Discussion

When a solution of equimolar amounts of **1** and (methoxycarbonyl)methylenetriphenylphosphorane (**2a**) in toluene was heated under reflux, the reaction did not proceed to any appreciable extent, and the starting materials were recovered practically unchanged even after three days.

In boiling toluene containing triethylamine, the reaction afforded methyl 1-(4-methylphenyl)-4-oxo-3*H*-isoquinoline-3-carboxylate (**7a**) as the sole reaction product in 74% yield. Similar treatment of **1** with ylide **2b** afforded the isoquinolone **7b** in 68% yield (Scheme 1). Isoquinolones **7a** and **7b** were weakly soluble in dilute alkali and gave no colour with alcoholic ferric chloride solution. Compounds **7a** and **7b** displayed strong absorptions at 1763 and 1772 cm^{-1}, re-



Scheme 1

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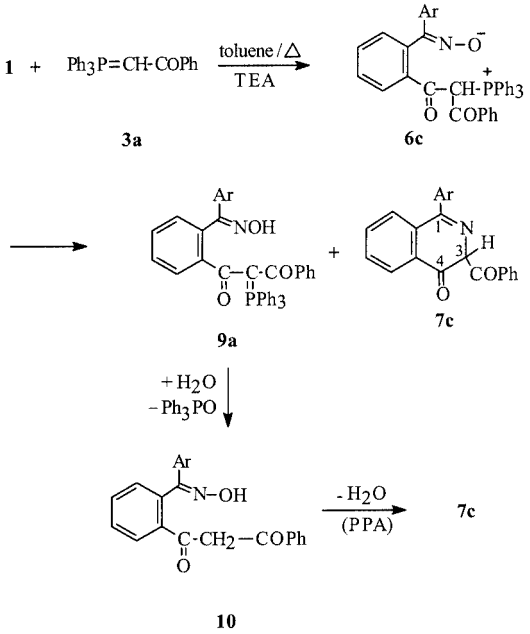
spectively, characteristic of carbonyl groups comprising part of the ring in similar six-member heterocyclic compounds.[2−4] Other bands appeared at about 1730 (C=O, ester) and at about 1595 cm^{-1} (C=N). The ^1H NMR spectra of compounds **7a** and **7b** each showed a singlet for the C(3)-methine proton around $\delta \approx 3.5$. Furthermore, the distinguishing features in the ^{13}C NMR spectra of **7a** and **7b** were the presence of signals at $\delta \approx 42$ (*C*H−CO_2R), about 163 [(*C*=O), ester] and at about 175 [*C*(4)=O].

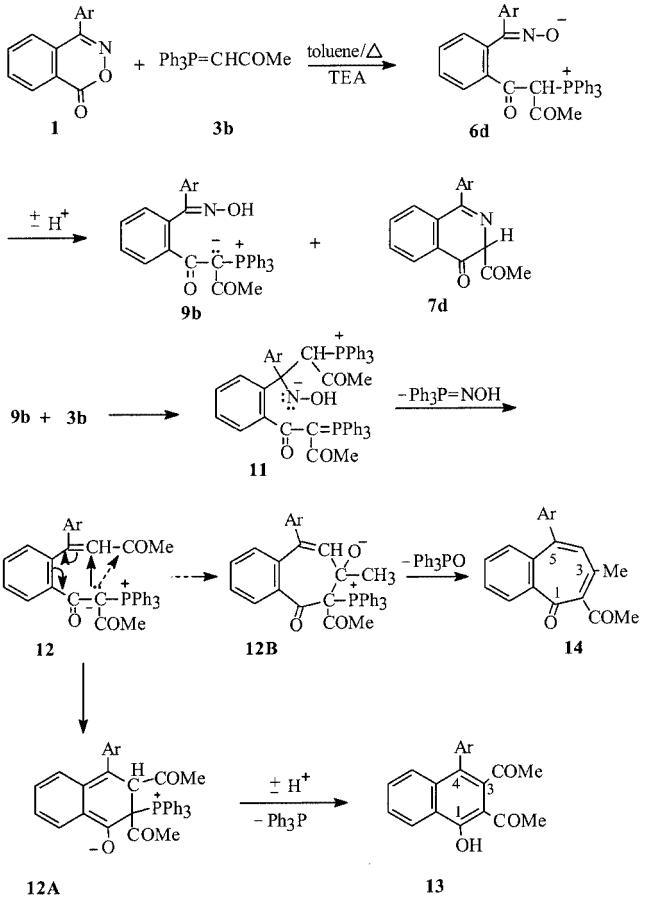
A reasonable mechanistic explanation for these transformations involves an initial attack[3,4] of the ylide carbon in **2a** and **2b** on the C(1)=O group, with subsequent ring-opening of **1** to afford **6** via the intermediate **5**. Under thermal conditions and in the presence of a base (TEA) the zwitterion **6** is presumably formed. A one-step [σ2 + σ2] reaction of the intermediate **6** with concomitant elimination of triphenylphosphane oxide would produce the final products **7**. Notwithstanding that the physical and spectroscopic data indicated that **7** existed in the keto form, the more stable hydroxy structures **7a** and **7b** clearly cannot be overlooked.[5] Treatment of **7a** with either benzoyl chloride or acetic anhydride in pyridine gave the expected *O*-benzoylated and *O*-acetylated products **8a** and **8b** in 72 and 75% yields, respectively.

Treatment of oxazinone **1** with an equimolar amount of keto ylide **3a** in refluxing toluene containing TEA for 3 days gave, in addition to isoquinolone derivative **7c** (38%), a new ylide **9a** (22%) (Scheme 2). The formation of **7c** and **9a** resulted from the initial production of the parallel betaine intermediate analogue **6c**. Migration of the methine proton to the electron-rich oxygen would give the ylide **9a**. The reactions described in Schemes 1 and 2 parallel the reactions of the substrate **1** with amines and hydrazones.[3,4] The ^1H, ^{13}C, and ^{31}P (δ = 15.98) NMR characteristics for **9a** were consistent with the assigned structure. Ylide **9a**, however, failed to undergo a Wittig reaction when it was heated with aromatic aldehydes, and instead cyclized to isoquinolone **7c** in 40% yield. Furthermore, when an ethyl acetate solution of ylide **9a** was heated under reflux for 30 h, compound **7c** was isolated in 40% yield. On the other hand, treatment of **9a** with Na_2CO_3 (15%) yielded the expected compound **10** (55% yield), from which compound **7c** could be obtained by cyclization with polyphosphoric acid (Scheme 2). The analytical and spectroscopic data for the products **9a**, **10** and **7c** were in good agreement with the proposed structures.



Scheme 2

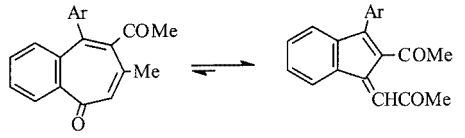
In contrast, when a toluene solution of an equimolar amount of **1** and the keto ylide **3b** containing TEA was heated under reflux, the reaction was not complete even after 4 days. On repetition of the reaction between **1** and 2 equiv. of ylide **3b** in refluxing toluene containing TEA for 3 days (TLC), the isoquinolone **7d** was obtained in only 12% yield; instead, 2,3-diacetyl-4-(4-methylphenyl)-α-naphthol (**13**) (33%) and 2-acetyl-3-methyl-5-(4-methylphenyl)-benzocyclohepten-1-one (**14**) (22%) were the major products (Scheme 3).



Scheme 3

Obviously, the expected initially formed zwitterion intermediate **6d** would give rise to **7d** and the oxime analogue **9b**. An addition of a second ylide species **3b** to **9b** would afford the diylide intermediate **11**,[4] followed by a "Wittig-type" reaction of the second ylide group with the hydroxyi-

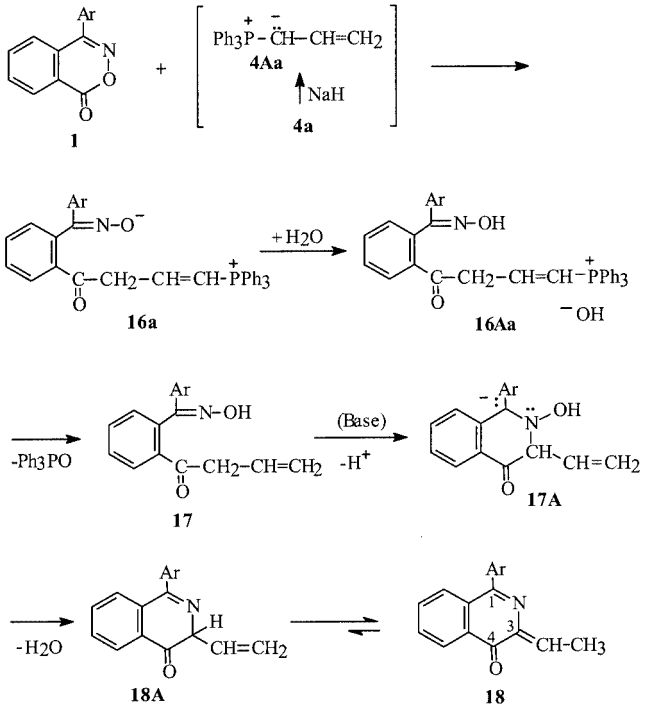
mino group and elimination of (hydroxyimino)triphenylphosphorane species to afford the arylidene intermediate **12**. Formation of an intermediate of this type and its transformation into **12** has, however, been reported for the reaction between **1** and phenylhydrazine.[4] Moreover, an analogous "Wittig-type" reaction has been reported to proceed between phosphorus ylides and Schiff bases, with elimination of the triphenyl(phenylimino)phosphorane moiety.[1b][1e,6] The formation of **13** and **14** from the intermediate **12** could be explained (as suggested by one of the referees of this article) by an electrocyclic reaction involving the ylide carbon atom with subsequent loss of Ph_3P or Ph_3PO, respectively. Although an intramolecular cyclization of the intermediate **12** with elimination of triphenylphosphane oxide might also result in products such as **14A** or **15**, the IR and ^1H NMR spectra of the compound in question correspond better to structure **14**. Thus, IR absorption maxima at 1725 and 1656 cm^{-1}, indicating two types of carbonyl group, and two signals for the carbonyl carbons in the ^{13}C NMR, at $\delta = 163.5$ [*C*-1-(O)] and 206.7 [*C*(O), acetyl], are in better agreement with cycloheptatrienone **14**.[7]



14A **15**

Treatment of **1** with a moderately reactive ylide phosphorane was next investigated. Treatment of **1** with 4 equiv. of sodium hydride (NaH) in ethyl methyl ketone (EMK), followed by 1.2 equiv. of allyltriphenylphosphonium bromide (**4a**), yielded 3-ethylidene-1-(4-methylphenyl)-isoquinolin-4-one (**18**) (62%) and unidentified products with high melting points. The reaction mechanism for the formation of **18** can be interpreted in terms of an initial addition reaction between the ylide generated in situ (from **4a**) and the carbonyl carbon of the oxazinone **1**, affording the intermediate **16a**. Subsequent hydrolysis, electrocyclic ring-closure and loss of a molecule of H_2O could result directly in the observed equilibrium **18** ⇄ **18A** (Scheme 4). A similar elimination of a molecule of water was also found to proceed in reactions between oximes and Wittig reagents.[6b,8] The spectroscopic data (IR, ^1H and ^{13}C, see Exp. Sect.) for **18** indicated that the initially formed product **18A** made only a minor contribution to the structure of the molecule and that it had undergone prototropic rearrangement to the tautomeric form **18**.

We have also studied the behaviour of **1** toward reactive phosphonium salts **4b** and **4c**. When a solution of **1** and 2 equiv. of **4b** or **4c** in EMK was treated with NaH, the 4-alkoxy-1-(4-methylphenyl)isoquinolines **21a** or **21b** (≈50%), respectively, were produced. As shown in Scheme 5 (and as suggested by one of the referees of this article), addition of a second phosphorane species (from **4b** or **4c**) to the initially formed **16b** or **16c**[5a,8,9] (**16b,c** ↔ **16Bb,c**) afforded the



Scheme 4

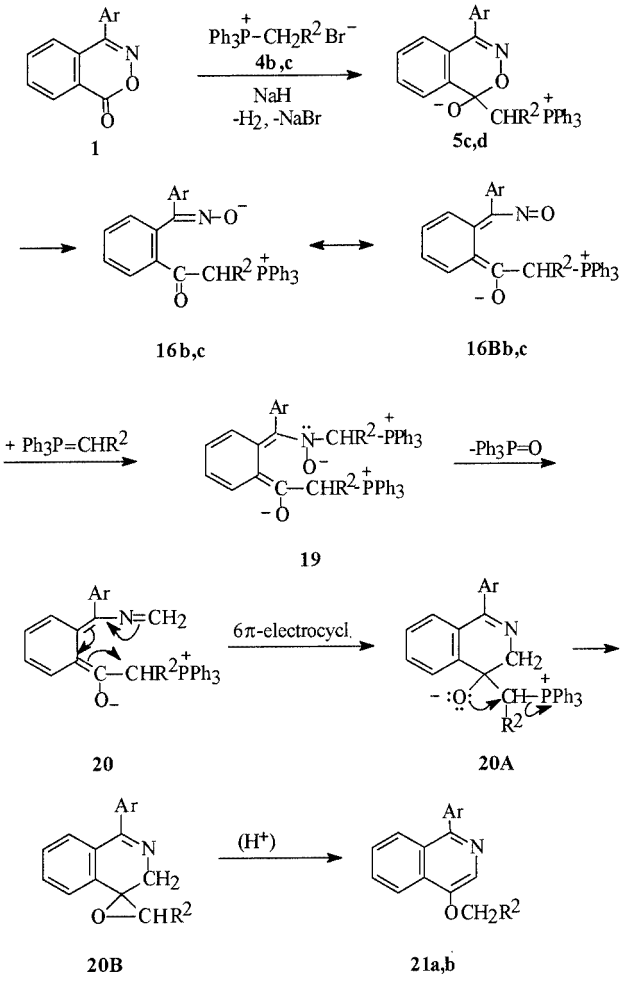
di-ylide **19**, which was followed by the loss of Ph_3PO. An electrocyclic ring-closure of **20** affords **20A**, and subsequent formation of an oxirane **20B** (and loss of Ph_3P) and proton migration could account for the formation of **21a** and **21b**.[11] Compounds **21a** and **21b** were obtained equally, irrespective of whether one or two molar equivalents of the phosphonium salts **4b** or **4c** were used.

In order to support the mechanism outlined in Scheme 5, compound **21a** was synthesised independently (see Exp. Sect.). The route involved alkaline hydrolysis and decarboxylation of **7a** or **7b** to give **22**. Further methylation of **22** by the usual method gave the required product **21a** according to Scheme 6.

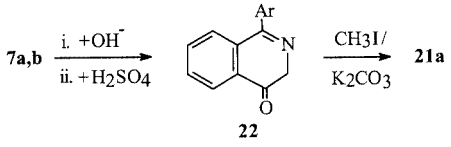
In conclusion, reactions between oxazinones and alkylidene phosphoranes are of significant value from the synthetic and applied points of view. Thus, the title reactions provide an easy route to isoquinoline derivatives, in good yields. Quinolines or isoquinolines, however, also constitute a class of organic compounds of considerable medicinal interest since a wide range of these compounds have shown therapeutic activity, against malaria, cancer, and micro-organisms.[12,13]

Experimental Section

All melting points are uncorrected. IR spectra were recorded on a Perkin−Elmer spectrophotometer model 297 with KBr discs. The ^1H and ^{13}C NMR spectra were run on a Varian Gemini 200 (200 MHz) instrument, with TMS as an internal reference. The ^{31}P NMR spectra were recorded relative to external H_3PO_4 (85%) with a Varian CFT-80 instrument. The mass spectra were performed at



Scheme 5



Scheme 6

70 eV on an MS-50 Kratos (A.E.I.) spectrometer provided with a data system. The appropriate precautions in handling moisture-sensitive compounds were observed. Materials and reagents were purchased from Aldrich Company.

Treatment of 4-(4-Methylphenyl)-2,3-benzoxazin-1-one (1) with Ylides 2a and 2b. (A) Preparation of Compound 7a: No reaction was observed when equimolar amounts of **1**[14] and **2a** or **2b** were heated under reflux in toluene even after 3 days, after which compounds **1** and **2** were recovered practically unchanged in ≈85% yield. A stirred solution of oxazinone **1** (1 g, 4.22 mmol) and methoxycarbonylmethylenetriphenylphosphorane **(2a)** (1.44 g, 4.3 mmol) in dry toluene (25 mL) containing TEA (0.3 mL) was therefore boiled under reflux for two days. After removal of the solvent, the residue was chromatographed on silica gel. Elution with hexane/$CHCl_3$ (7:3, v/v) afforded colourless crystals of **methyl 1-(4-methylphenyl)-4-oxo-3*H*-isoquinoline-3-carboxylate** (**7a**) (0.9 g, 74%), m.p. 142−144 °C (pentane). [$C_{18}H_{15}NO_3$ (293.33): calcd.C 73.71, H 5.15, N 4.77; found C 73.63, H 5.06, N 4.62%]. IR (KBr): $\tilde{\nu}$ = 1763 (4-C=O), 1731 (C=O, ester), 1595 (C=N), 1536 (C=C) cm^{-1}; NMR: δ_H ($CDCl_3$) = 2.42 (s, 3 H, Ph−C*H*$_3$), 3.53 (s, 1 H, 3-C-*H*), 3.76 [s, 3 H, C(O)OC*H*$_3$], 7.39−8.35 (m, 8 H, Ph-*H*); δ_c ($CDCl_3$) = 21.9 (Ph-*C*H$_3$), 42.3 (3-*C*−H), 55.7 (O*C*H$_3$), 163.2 (C=O, ester), 175.1 (4-C=O); MS *m/z* (EI) (%): 293 [M^+] (100), 278 (7), 262 (60), 234 (28), 142 (16).

(B) Preparation of 7b: A stirred solution of **1** (1 g, 4.22 mmol) and ethoxycarbonylmethylenetriphenylphosphorane (**2b**) (1.5 g, 4.3 mmol) in dry toluene (25 mL) containing TEA (0.3 mL) was heated at reflux for 2 days. The product mixture was worked up according to the procedure described above for ylide **2a**. Elution with hexane/$CHCl_3$ (7:3, *v*/*v*) yielded colourless crystals of **methyl 1-(4-methylphenyl)-4-oxo-3*H*-isoquinoline-3-carboxylate** (**7b**) (880 mg, 68%), m.p. 135−137 °C (cyclohexane). [$C_{19}H_{17}NO_3$ (307.35): calcd. C 74.25, H 5.57, N 4.56; found C 74.34, H 5.43, N 4.47%]; IR (KBr): $\tilde{\nu}$ = 1772 (4-C=O), 1730 (C=O, ester), 1596 (C=N), 1545 (C=C) cm^{-1}; NMR: δ_H ($CDCl_3$) = 0.83 (t, 3 H, $J_{H,H}$ = 7.1 Hz, OCH_2-CH_3), 2.58 (s, 3 H, Ph−C*H*$_3$), 3.47 (s, 1 H, 3-C-*H*), 4.18 (q, $J_{H,H}$= 7.1 Hz, 2 H, O*CH*$_2$CH$_3$), 7.15−8.34 (m, 8 H, Ph-*H*); δ_C ($CDCl_3$) = 18.2 (OCH_2-*C*H$_3$), 22.2 (Ph-*C*H$_3$), 41.8 (3-*C*−H), 62.3 (O*C*H$_2$CH$_3$), 162.7 (*C*=O, ester), 176.5 (4-*C*=O); *m/z* (EI) (%): 307 [M^+] (66), 279 (13), 234 (100), 262 (60), 233 (21), 143 (48). Compounds **7a** and **7b** are partially soluble in 10% aq. NaOH and give no colour reaction with 1% alcoholic $FeCl_3$ solution.

Acylation of 7a with Benzoyl Chloride or Acetic Anhydride. Preparation of 8a and 8b: Benzoyl chloride (or acetic anhydride) (1.1 mmol) was added to a solution of **7a** (0.3 g, 1.0 mmol) in dry pyridine (5 mL). The reaction mixture was allowed to stand for 2 days at room temp. The product mixture, with a small amount of pyridine hydrochloride present, was poured onto 40 g of crushed ice. Stirring and scratching afforded a white solid, which was filtered and washed with 20 mL of ice water, air-dried, and recrystallised from a small amount of CH_2Cl_2 to give a pure sample.

Compound **8a** (*O*-benzoyl) was obtained in 72% yield: m.p. 158−158.5 °C. [$C_{25}H_{19}NO_4$ (397.43): calcd. C 75.55, H 4.82, N 3.52; found C 75.67, H 4.74, N 3.46%]; IR (KBr): $\tilde{\nu}$ = 1728 (C=O, ester), 1686 (C=O, benzoyl), 1597 (C=N) cm^{-1}; NMR: δ_H ($CDCl_3$) = 2.44 (s, 3 H, Ph−C*H*$_3$), 3.76 [s, 3 H, C(O)OC*H*$_3$], 7.18−8.32 (m, 13 H, Ph-*H*); *m/z* (EI) (%): 397 [M^+] (100), 382 (56), 379 (20), 338 (14), 320 (19), 292 (28), 193 (11).

Compound **8b** (*O*-acetyl) was obtained in 75% yield: m.p. 172−173 °C. [$C_{20}H_{17}NO_4$ (335.36): calcd. C 71.63, H 5.12, N 4.17; found C 71.69, H 5.25, N 4.04%]; IR (KBr): $\tilde{\nu}$ = 1730 (C=O, ester), 1663 (C=O, acetyl), 1592 (C=N), 1545 (C=C) cm^{-1}; NMR: δ_H ($CDCl_3$) = 2.11 (s, 3 H, C*H*$_3$, acetyl), 2.58 (s, 3 H, Ph−C*H*$_3$), 3.88 [s, 3 H, C(O)OC*H*$_3$], 7.13−8.33 (m, 8 H, Ph-*H*); *m/z* (EI) (%): 335 [M^+] (100), 330 (65), 292 (23), 276 (6), 261 (16), 223 (33).

Treatment of 1 with Keto Ylides 3a and 3b. (A) Preparation of Compounds 7c, 9a, and 10: (i) A stirred solution of **1** (1 g, 4.22 mmol) and benzoylmethylenetriphenylphosphorane (**3a**) (1.63 g, 4.3 mmol) in dry toluene (30 mL) containing TEA (0.5 mL) was heated under reflux for 3 days. The product mixture was chromatographed on silica gel (hexane/$CHCl_3$) to give two fractions.

The first fraction (3:7, v/v) yielded colourless crystals of **3-benzoyl-1-(4-methylphenyl)-3*H*-isoquinolin-4-one** (**7c**) (540 mg, 38%), m.p. 144−147 °C (CH_2Cl_2). [$C_{23}H_{17}NO_2$ (339.4): calcd. C 81.39, H 5.05, N 4.13; found C 81.44, H 5.13, N 4.07%]; IR (KBr): $\tilde{\nu}$ = 1765 (4-C=O), 1682 (C=O, benzoyl), 1605 (C=N) cm^{-1}; NMR: δ_H ($CDCl_3$) = 2.43 (s, 3 H, Ph−C*H*$_3$), 3.46 (s, 1 H, 3-C-*H*), 7.35−8.45

(m, 13 H, Ph-*H*); δ_C ($CDCl_3$) = 21.9 (Ph-*C*H_3), 39.8 (3-*C*−H), 174.3 (4-C=O), 195.2 (C=O, benzoyl); *m*/*z* (EI) (%): 339 [M^+] (100), 311 (33), 262 (12), 234 (25). Compound **7c** is partially soluble in 10% aq. NaOH, and gives no colour reaction with 1% alcoholic $FeCl_3$ solution.

The second fraction (7:3, v/v) was triturated with a small volume of cyclohexane to give yellow crystals of **(2-benzoylmethylenetriphenylphosphorane) *o*-(4-methylphenyl)benzophenone oxime (9a)** (570 mg, 22%), m.p. 193−195 °C (benzene) [$C_{41}H_{32}NO_3P$ (617.69): calcd. C 79.72, H 5.22, N 2.27, P 5.01; found C 79.64, H 5.15, N 2.13, P 5.07%]; IR (KBr): $\tilde{\nu}$ = 3419 (NOH), 1750 [C-7−(O)], 1682 [C-9−(O)], 1610 (C=N), 1478 (C=P), 976 (P−Ph) cm^{-1}; NMR: δ_H ($CDCl_3$) = 2.41 (s, 3 H, Ph−CH_3), 7.24−8.46 (m, 28 H, Ph-*H*), 8.78 (s, 1 H, NO*H*); δ_C ($CDCl_3$) = 22.2 (Ph-*C*H_3), 87.6 (d, $J_{C,P}$= 96.8 Hz, *C*−P), 154.5 (*C*=NOH), 192.8 (*C*=O, benzoyl), 196.3 (7-*C*=O); δ_P ([D_6]DMSO) = 15.98; *m*/*z* (EI) (%): 617 [M^+] (20), 589 (8), 511 (29), 478 (26), 301 (100).

(ii) Conversion of 9a into Isoquinolone 7c: The ylide **9a** (0.3 g) was heated under reflux in ethyl acetate (10 mL) for 30 h. After evaporation of the solvent in vacuo, the pale yellow solid (66 mg, 40%) was collected in a small amount of chloroform and shown to be identical with **7c** (TLC, and comparative IR and mass spectra).

The reaction between the ylide **9** (0.3 g) and benzaldehyde (0.1 mL) in boiling toluene (or EtOAc) (10 mL) for 45 h, was carried out and the product mixture was worked up as above to give the isoquinolone **7c** (61 mg, 35%).

(iii) Alkaline Treatment of the Ylide 9a. Preparation of Compound 10: A mixture of **9a** (0.3 g, 0.49 mmol) and Na_2CO_3 (15% aq., 20 mL) was heated under reflux for 10 h. The mixture was cooled, diluted with water (5 mL), and extracted with $CHCl_3$. The residue obtained on removal of the solvent was boiled with light petroleum ether (40−60 °C) to afford on concentration 0.13 g of a compound, m.p. 155 °C, shown to be Ph_3PO. The insoluble portion (167 mg, 58%) was recrystallised to give the corresponding benzoylacetophenone **10**, m.p. 161−163 °C (CH_2Cl_2). [$C_{23}H_{19}NO_3$ (357.41): calcd. C 77.29, H 5.36, N 3.92; found C 77.36, H 5.42, N 3.88%]; IR (KBr): $\tilde{\nu}$ = 3424 (OH), 1731 [C-7−(O)], 1678 [C(O)Ph], 1609 (C=N) cm^{-1}; NMR: δ_H ($CDCl_3$) = 2.42 (s, 3 H, Ph−CH_3), 2.84 (s, 2 H, CH_2) 7.24−8.44 (m, 13 H, Ph-*H*), 8.73 (br, 1 H, NO*H*); δ_c ($CDCl_3$) = 21.6 (Ph-*C*H_3), 38.3 (*C*H_2), 153.7 (*C*=NOH), 166.5 [*C*-7-(O)], 188.4 [*C*(O)Ph]; *m*/*z* (%) = 357 [M^+] (100), 329 (13), 253 (21), 237 (100).

(iv) Cyclization of Compound 10 to 7c: Compound **10** (0.13 g) in polyphosphoric acid (5.0 g) was heated at 140−150 °C for 4 h. The cooled reaction product was poured into ice-water (20 mL) and then extracted with $CHCl_3$. After evaporation of the dried $CHCl_3$ solution, the residual solid was recrystallised from CH_2Cl_2 to give 0.05 g (49%) of colourless crystals, shown to be identical with **7c** (TLC, and comparative IR and mass spectra).

(B) Preparation of Compounds 7d, 13, and 14: A stirred mixture of **1** (1 g, 4.22 mmol) and acetylmethylenetriphenylphosphorane (**3b**) (2.78 g, 8.5 mmol) in dry toluene (30 mL) containing TEA (0.5 mL) was heated under reflux for 3 days. The product mixture was worked up as above and gave compounds **7d**, **13**, and **14**.

3-Acetyl-1-(4-methylphenyl)-3*H*-isoquinolin-4-one (7d): This compound was obtained (hexane/ethyl acetate, 3:7, v/v) as colourless crystals (140 mg, 12%), m.p. 156−158 °C (acetonitrile). [$C_{18}H_{15}NO_2$ (277.39): calcd. C 77.94, H 5.45, N 5.07; found C 77.99, H 5.48, N 5.02%]; IR (KBr): $\tilde{\nu}$ = 1762 (4-C=O), 1675 (C=O, acetyl]; NMR: δ_H ($CDCl_3$) = 2.36 (s, 3 H, Ph−CH_3), 2.43 [s, 3 H, C(O)CH_3], 3.66 (s, 1 H, 3-C-*H*), 6.85−7.78 (m, 13 H, Ph-*H*); *m*/*z* (EI) (%): 277 [M^+] (100), 249 (34), 144 (58). Compound **7d** is partially soluble in 10% NaOH aq., and gives no colour reaction with 1% alcoholic $FeCl_3$ solution.

2-Acetyl-3-methyl-5-(4-methylphenyl)benzocyclohepten-1-one (14): This compound was obtained (hexane/EtOAc, 4:6, v/v) as colourless crystals (280 mg, 22%), m.p. 175−177 °C (MeCN). [$C_{21}H_{18}O_2$ (302.37): calcd. C 83.42, H 6.00; found C 83.32, H 5.87%]; IR (KBr): $\tilde{\nu}$ = 1725 (1-C=O), 1656 cm^{-1} (C=O, acetyl); NMR: δ_H ($CDCl_3$) = 2.18, 2.47 (2s, 2 × 3 H, 3-C−CH_3 and Ph−CH_3), 2.55 [s, 3 H, C(O)CH_3], 6.67 (s, 1 H, 4-C-*H*), 7.46−8.23 (m, 8 H, Ph-*H*); δ_C ($CDCl_3$) = 13.8 (3-C-*C*H_3), 21.8 (Ph-*C*H_3), 28.65 [C(O)*C*H_3), 111.4 (2-*C*), 144.6 (4-*C*), 163.5 (1-*C*=O), 206.7 (*C*=O, acetyl); *m*/*z* (EI) (%): [M^+], 302 (18), 274 (25), 259 (55), 231 (100), 216 (12), 201 (31).

2,3-Diacetyl-4-(4-methylphenyl)-α-naphthol (13): This compound was obtained (hexane/EtOAc, 2:8 v/v) as colourless crystals (440 mg, 33%), m.p. 185−187 °C (C_2H_5OH). [$C_{21}H_{18}O_3$ (318.37): calcd. C 79.22, H 5.70; found C 79.36, H 5.62%]; IR (KBr): $\tilde{\nu}$ = 3430 (OH), 1662 (br., 2 × C=O, acetyl) cm^{-1}; NMR: δ_H ($CDCl_3$) = 2.43 (s, 3 H, Ph−CH_3), 2.55, 2.57 (2s, 2 × 3 H, 2 × C(O)CH_3), 10.36 (s, 1 H, O*H*); δ_C ($CDCl_3$) = 22.4 (Ph-*C*H_3), 28.51, 28.83 [2 × C(O)*C*H_3], 153.7 (*C*-1-OH), 202.7, 206.6 (2 × *C*=O, acetyl); *m*/*z* (EI) (%): [M^+], 318 (38), 257 (18), 231 (100), 204 (50).

The reaction between equimolar amounts of **1** and **3b** under the same conditions again afforded **7d** (10%), **13** (14%), and **14** (11%) along with **1** (28%).

Treatment of 1 with Allyltriphenylphosphonium Bromide (4a). Preparation of Compound 18: The oxazinone **1** (1 g, 4.22 mmol) in ethyl methyl ketone (EMK, 20 mL) was added dropwise to a slurry of sodium hydride (NaH) dispersion (60% in paraffin oil, 200 mg) in the same solvent (10 mL). The reaction mixture was stirred at room temperature until all hydrogen evolution had ceased, and the salt **4a** (1.7 g, 4.5 mmol) was introduced all at once. The reaction mixture was allowed to remain at room temp. for further two hours and was then heated under reflux for 24 h. The product mixture was concentrated to 10 mL, diluted with 30 mL of dist. H_2O, acidified with conc. HCl, and then extracted with two portions of $CHCl_3$. The $CHCl_3$ extracts were combined, back-washed with 100 mL of H_2O and dried with anhydrous $MgSO_4$, and the solvents were evaporated to dryness. The residue was chromatographed on silica gel with hexane/chloroform (3:7, v/v) and afforded colourless crystals of **3-ethylidene-1-(4-methylphenyl)isoquinolin-4-one (18)** (680 mg, 62%), m.p. 132−133 °C (CH_2Cl_2). [$C_{18}H_{15}NO$ (261.33): calcd. C 82.73, H 5.78, N 5.36; found C 82.81, H 5.74, N 5.23%]; IR (KBr): $\tilde{\nu}$ = 1740 (4-C=O), 1627 (C=C, ethylidene), 1600 (C=N) cm^{-1}; NMR: δ_H ($CDCl_3$) = 1.85 (d, 3 H, $J_{H,H}$= 7.2 Hz, = CH−CH_3), 2.43 (s, 3 H, Ph−CH_3), 7.55 (q, 1 H, $J_{H,H}$ = 7.2 Hz, = C*H*−CH$_3$), 7.34−8.42 (m, 8 H, Ph-*H*); δ_C ($CDCl_3$) = 17.6 (=CH-*C*H_3), 21.9 (Ph-*C*H_3), 133.5 (=*C*H−CH$_3$), 145.3 (3-*C*), 192.2 (4-*C*=O); *m*/*z* (EI) (%): [M^+], 261 (75), 247(30), 219 (100).

Treatment of 1 with Phosphonium Salts 4b and 4c. Preparation of Compounds 21a and 21b: A solution of the appropriate salt **4b** (3 g, 8.5 mmol) or **4c** (3.2 g, 8.5 mmol) and **1** (1 g, 4.22 mmol) in EMK (30 mL) was treated with NaH under the experimental conditions described for the salt **4a**. The reaction mixture was heated under reflux for ca. 18 h (TLC) and then worked up as described for **4a** and chromatographed with hexane/$CHCl_3$ to give **21a** (3:7, v/v) or **21b** (2:8, v/v), respectively.

4-Methoxy-1-(4-methylphenyl)isoquinoline (21a) was obtained in 53% yield (560 mg), m.p. 138−140 °C (cyclohexane). [$C_{17}H_{15}NO$ (249.32): calcd. C 81.90, H 6.06, N 5.62; found C 82.54, H 6.13, N 5.47%]; IR (KBr): $\tilde{\nu}$ = 1605 (C=N) cm^{-1}; NMR: δ_H ($CDCl_3$) = 2.53 (s, 3 H, Ph−CH_3), 3.83 (s, 3 H, OCH_3), 7.36−8.43 (m, 9 H, Ph-*H* and 3-C-*H*); δ_C ($CDCl_3$) = 22.4 (Ph-*C*H_3), 55.7 (O*C*H_3), 150.4 (4-*C*), 154.1 (3-*C*); *m*/*z* (EI) (%): [M^+], 249 (28), 219 (100).

4-Ethoxy-3-methyl-1-(4-methylphenyl)isoquinoline (21b) was obtained in 48% yield (560 mg), m.p. 125−127 °C (cyclohexane). [$C_{19}H_{19}NO$ (277.37): calcd. C 82.28, H 6.90, N 5.05; found C 82.41, H 6.78, N 4.97%]; IR (KBr): $\tilde{\nu}$ = 1596 (C=N) cm^{-1}; NMR: δ_H ($CDCl_3$) = 1.18 (t, 3 H, $J_{H,H}$ = 6.7 Hz, OCH_2CH_3), 2.15 (s, 3 H, het.-CH_3), 2.42 (s, 3 H, Ph−CH_3), 4.16 (q, 2 H, $J_{H,H}$ = 6.7 Hz, OCH_2CH_3), 7.33−8.45 (m, 8 H, Ph-*H*); δ_C ($CDCl_3$) = 14.3 (OCH_2CH_3), 18.6 (het.-*C*H_3), 22.6 (Ph-*C*H_3), 60.3 (OCH_2CH_3), 149.3 (4-*C*); *m*/*z* (EI) (%): [M^+], 277 (33), 233 (100).

The reaction between equimolar amounts of compounds **1** and **4b** and **4c** under the conditions described above again afforded the same products **21a** (28%) or **21b** (22%) along with the substrate **1** (≈ 38%).

Unequivocal Method for Preparation of 21a: A solution of **7a** (0.5 g) and NaOH (5 g) in H_2O (15 mL) was heated to boiling for 10−15 minutes (until the ester had disappeared). The reaction mixture was diluted with an equal volume of H_2O and stirred vigorously, and sulfuric acid (3 parts of conc. acid to 1 part of H_2O, 50 mL) was added. The mixture was cooled to 15 °C in an ice bath, and compound **22** was collected by filtration, washed with a small amount of H_2O and dried at 100 °C to give **1-(4-methylphenyl)-2*H*-isoquinolin-4-one** (**22**) (33%) as white leaflets, m.p. 161−162 °C (benzene). [$C_{16}H_{13}NO$ (235.29): calcd. C 81.68, H 5.57, N 5.95; found C 81.51, H 5.73, N 5.99%]; IR (KBr): $\tilde{\nu}$ = 1760 (4-C=O), 1594 (C=N) cm^{-1}; NMR: δ_H ($CDCl_3$) = 2.44 (s, 3 H, Ph−CH_3), 3.16 (br., 2 H, het.-H_2), 7.35−8.35 (m, 8 H, Ph-*H*); *m*/*z* (EI) (%): M^+, found 235 (100).

Methylation of 22. Preparation of 21a: Anhydrous K_2CO_3 (5 g) was added to a stirred solution of **22** (1.5 g, 6.38 mmol) in dry acetone (50 mL) and stirring was continued at room temperature for 1 h. Freshly distilled CH_3I (2.1 g, 15 mmol) was added, and the mixture was gently heated under reflux for 6 h. The inorganic and volatile materials were removed to give a semi-solid substance (820 mg, 52%), which recrystallised from CH_2Cl_2 to give colourless crystals, shown to be identical with **21a** (TLC, and comparative IR and mass spectra).

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