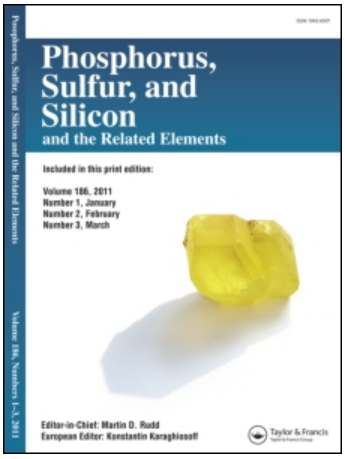

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An Efficient Route to Phosphono-Substituted-Indoles and Quinolines from the Condensation Of 2,3-and 2,4-Benzoxazin-1-Ones with α-Phosphonyl Carbanions

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An Efficient Route to Phosphono-Substituted Indoles and Quinolines from the Condensation of 2,3- and 2,4-Benzoxazin-1-ones with α-Phosphonyl Carbanions

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*A series of phosphono-substituted indoles, quinolines, and isoquinolines were prepared in reasonable yields from the reactions of 2,3-(**1**) and 2,4-benzoxazinones (**2**) with different types of the Wittig-Horner reagents, **13a**, **13b**, **13c**, and **20**, in the presence of a base. The products were rationalized as proceeding via 1:1 intermediates, which can be envisaged as having the anionic forms **15** or **25**, and in turn were relevant to the overall products.*

Keywords α-Phosphonyl carbanions; benzoxazinones; phosphono-substituted indoles; quinolines and isoquinolines

INTRODUCTION

In a previous study, it was reported[1] that 2,3-benzoxazin-1-one (**1**) underwent an insertion reaction when it was allowed to react with Wittig reagents (e.g., **3a**, **3b**, or **6**), in the presence of a base, to give mainly isoquinolone derivatives **5a**, **5b**, or **8** (Scheme 1).

On the other hand, 2,4-benzoxazin-1-one (**2**) yielded the quinoline derivatives **9**, **10**, and **12** when it was allowed to react with the same reagents **3a**, **3b**, or **6** under basic catalysis conditions (Scheme 2).[2] Nevertheless, a ring contraction was observed when the same oxazinones were treated with phosphite esters,[3] giving mainly the phosphono-substituted isoindoles and indoles.

In a series of articles from this laboratory, we reported[4] on the synthesis and reactions of new phosphono-substituted heterocycles starting from the inexpensive and easily accessible α-phosphonyl carbanions. This article describes an efficient route to the synthesis of phosphono-substituted indoles, quinolines, and isoquinolines of potential interest to biochemistry and pharmaceutical chemistry. The methodology was

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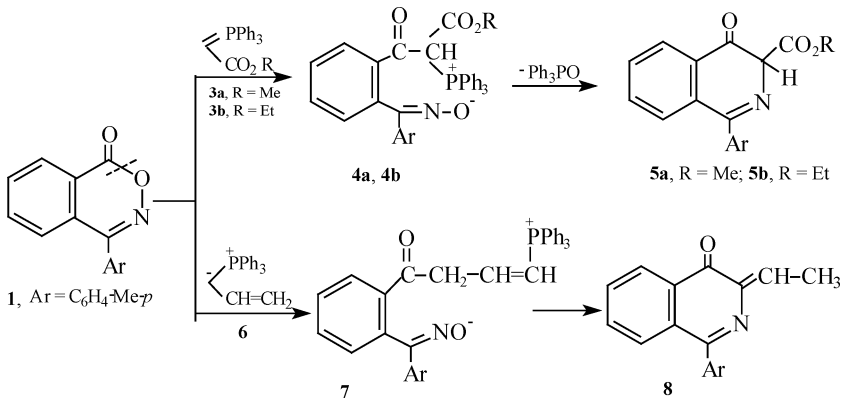
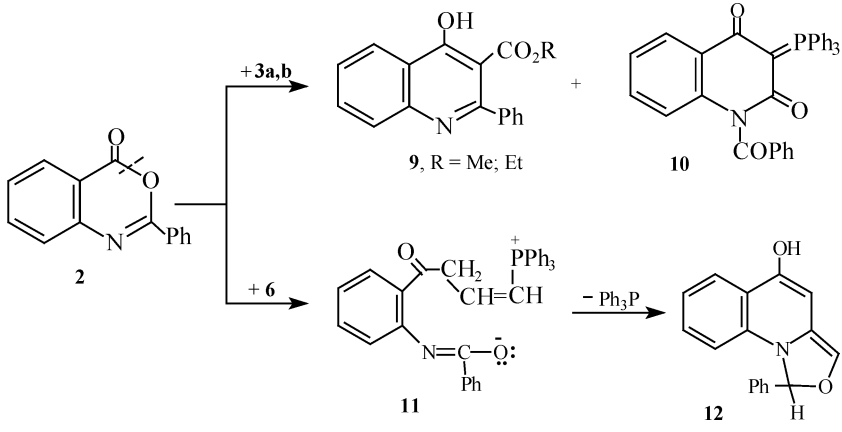


SCHEME 1

based on the reactions of 2,3-(**1**) and 2,4-benzoxazin-1-ones (**2**) with different types of α-phosphonyl carbanions, **13a**, **13b**, **13c** and **20**. However, in view of the interesting parallelism between the reactions of phosphonium and phosphonate carbanions toward electrophiles, the reactions of α-phosphonyl carbanions **13a**, **13b**, **13c**, and **20** with benzoxazinones **1** and **2** might be expected to proceed analogous to the reactions of Wittig reagents with the same substrates.[1,2] In reality, the reactions are not straightforward as implied in Schemes 1 and 2. The mode of transformations depends on the nature of the reactants and the conditions of the experiments. However, this is not surprising since phosphonate-stabilized carbanions are more basic than



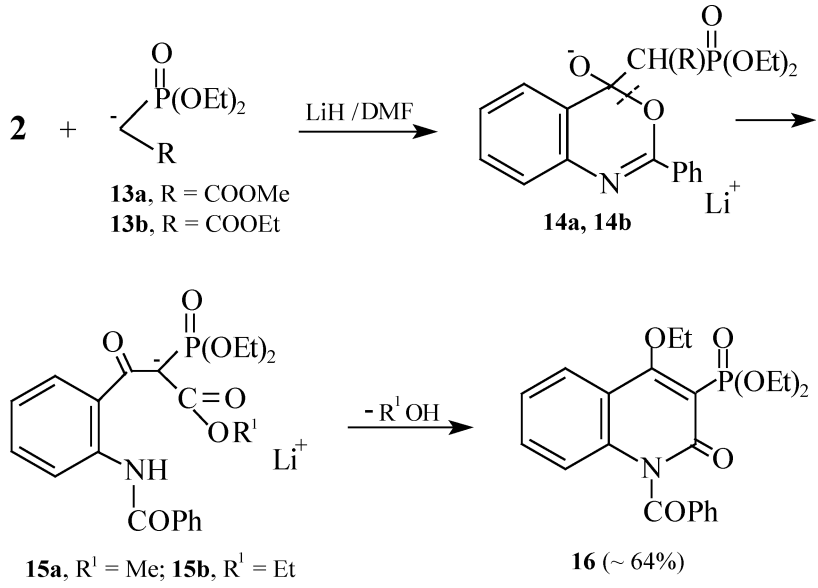
SCHEME 2

their phosphorane counterparts, and there are instances where they are incompatible with sensitive substrates.[5–7]

RESULTS AND DISCUSSION

Treatment of 3-phenyl 2,4-benzoxazin-1-one (**2**) with diethyl phosphonoacetates **13a** or **13b** (three-fold molar excess compared with **2**) in boiling Dimethylformamide (DMF) containing excess LiH (2 equivalents of **13**) afforded the phosphono substituted-quinoline **16** in ~64% yields (Scheme 3).

The chemical structure of **16** (δp = 17.2 ppm) was in accord with elemental analysis, molecular weight determination (MS), and spectroscopic data. The IR spectrum of **16** showed absorption bands at 1635 (C=O, benzoyl), 1750 (2-C=O), and 1269 (P=O, free); its ^{1}H NMR revealed the presence of two types of ethoxy group protons with different chemical shifts. The two equivalent OC_2H_5 protons coupled with phosphorus appeared as a doublet of a triplet (6H, J_{H-H} 7.2 Hz, $^4J_{H-P}$ = 2.8 Hz) at δ_H 0.99 ppm and as a doublet of a quartet (4H, J_{H-H} = 6.6 Hz, $^3J_{H-P}$ = 4.4 Hz) at 4.09 ppm, whereas 4-OC_2H_5 protons displayed as a triplet (3H, J_{H-H} = 7.5 Hz) at δ_H 1.22 and a quartet (2H, J_{H-H} = 7.2 Hz) at 3.87 ppm. The ^{13}C NMR[8] spectrum of **16** revealed a doublet at 84.8 ppm (d, $^1Jc\text{-}p$ = 183.7 Hz), which was attributed to the



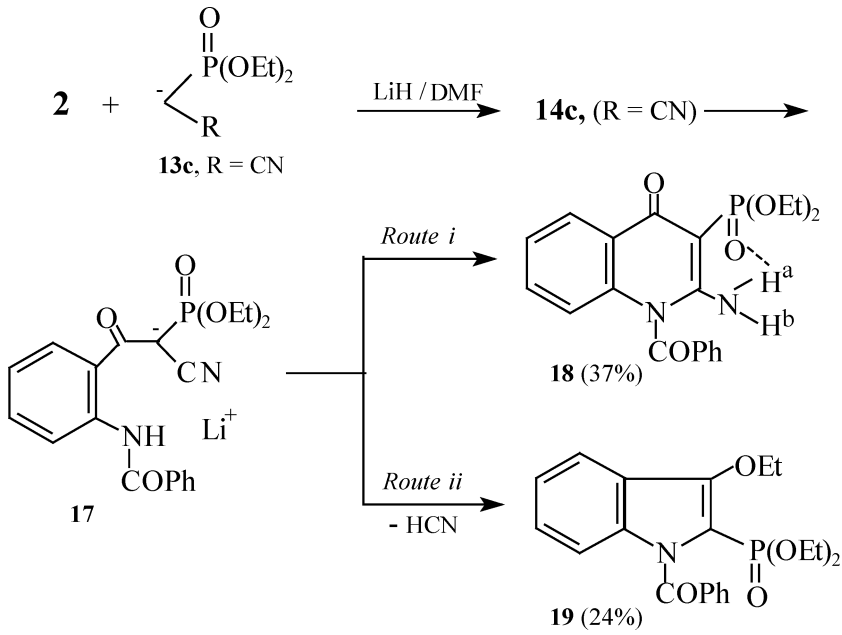
SCHEME 3

unsaturated carbon bearing no hydrogen and was attached to phosphorus as indicated from the large coupling constant.

A reasonable mechanism of the condensation of **2** with α-phosphonyl carbanions **13a** and **13b** involves an initial nucleophilic attack[9–12] of the carbanion center in **13** onto the C(1)=O group, with a subsequent ring opening of **2** to afford **15** via intermediates **14**. Under thermal conditions and the presence of a base, **15** is presumably formed. Furthermore, direct alkylation[13,14] using ethyl phosphonate as an alkylating agent on the carbanion intermediate **15** and further intramolecular cyclization would produce the phosphono-substituted quinolinone **16**, with concomitant elimination of the appropriate alcohol moiety.

Next, the reaction of **2** with diethyl α-cyanomethylphosphonate (**13c**) was studied. In contrast to the transformations previously described, when **2** was treated with **13c** (three-fold molar excess compared to **2**) in boiling DMF containing LiH (2 equivs., based on **13c**), phosphonates **18** and **19** were obtained in 37% and 24% yields, respectively (Scheme 4).

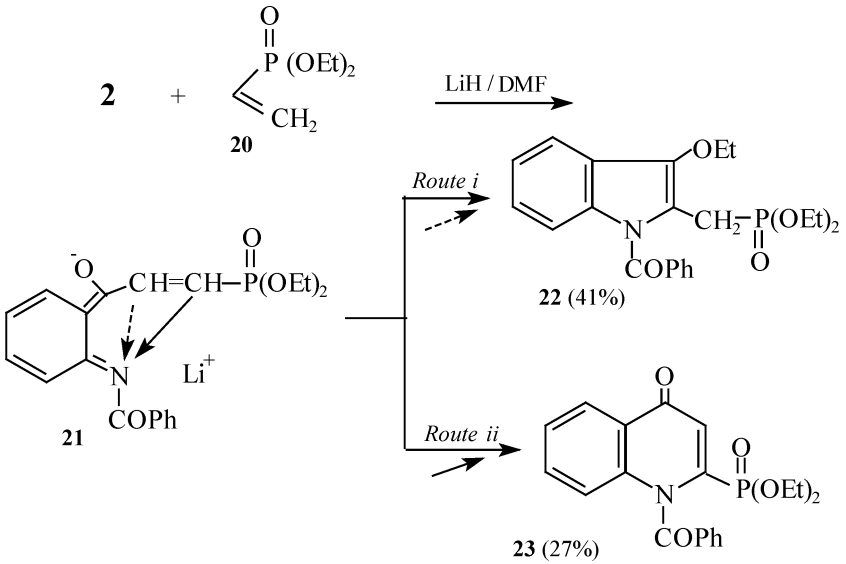
The constitution of the isolated products **18** and **19** were in accord with elemental analyses and spectroscopic properties. The structure of phosphono substituted-aminoquinoline **18** was based on the following reasons: the IR spectrum showed absorption bands at 3324 (NH_2), 1225 (P=O, bonded), 1050 (P-O-C), and 1740 cm^{-1} (4-C=O). The ^1H NMR



SCHEME 4

exhibited two types of NH protons with different chemical shifts at δ_H= 6.05 (NH^a, HNH) and 9.74 (NH^b, HNH), based upon intramolecular hydrogen-bond formation between one of the hydrogens of the NH_2 group and the oxygen atom of the P=O bonding in the phosphonate moiety. The two-ethoxy groups were non-equivalent, whereupon the OC_2H_5 protons coupled with phosphorus were split into two doublet of triplets at δ_H 1.05 and 1.09 and two doublet of quartets at 4.08 and 4.12 ppm. In the ^{13}C NMR, the C-P carbon was given as a doublet at δc 92.08 ppm (J_{C-P} = 197 Hz), and the ^{31}P NMR showed a signal at δp = 18.6 ppm corresponding to the phosphonate moiety. The formation of **18** and **19** resulted from the initial production of the intermediate **17** (an analog to intermediate **15**), which was followed by two separate routes for completion: (a) hydrolysis of the nitril group[15] and further intramolecular cyclisation led to the formation of the aminoquinoline phosphonate **18**; and (b) the nitril function was acting as a good leaving group,[16] and the zwitterionic intermediate **17** eliminated HCN to form a more stable phosphono substituted-indole **19**, via readily alkylation with the phosphonate reagent.

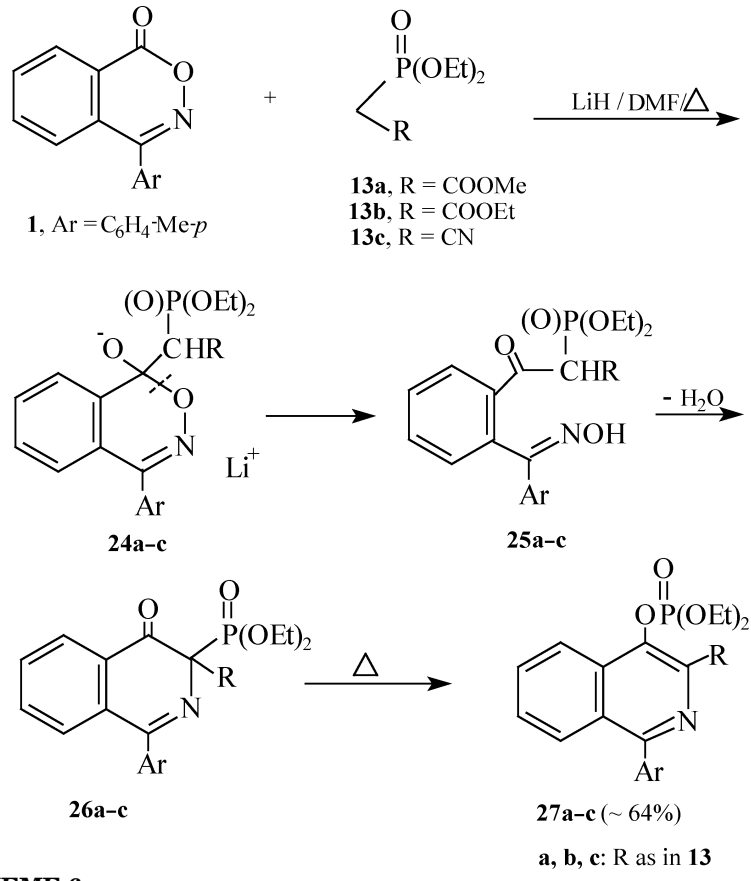
When **2** was allowed to react with diethyl vinylphosphonate (**20**) under the same experimental conditions as in (**2** + **13**), the phosphono substituted-indole **22** together with the phosphono substituted-quinoline **23** were isolated in 41% and 27% yields, respectively (Scheme 5).



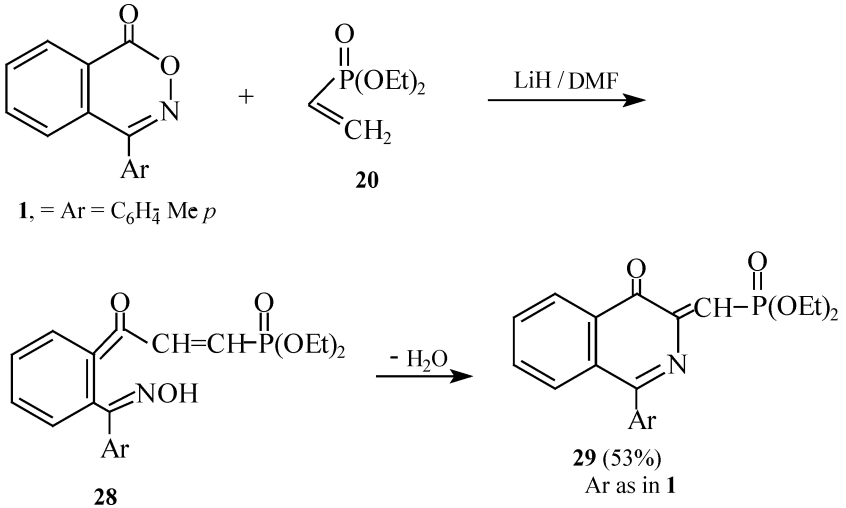
SCHEME 5

The respective mechanism for the formation of **22** and **23** might involve an initial generation of the vinylphosphonate intermediate **21** via electrophilic attack of 1-C=O in oxazinone **2** on the β-carbon of the unsaturated phosphonate**20**;[17] this was followed by two different routes to electrocyclic ring-closure furnishing products **22** and **23** according to Scheme 5.

Next, in a systematic study, the reactions of 4-(4-methylphenyl)-2,3-benzoxazin-1-one (**1**) with the same Wittig-Horner reagents **13a**, **13b**, **13c**, and **20** were studied, and the products obtained are depicted in Schemes 6 and 7. Thus, when oxazinone **1** and phosphonate reagents **13a**, **13b**, and **13c** (3 molar amounts) were refluxed in DMF and in the presence of LiH (2 equivalents of **13**) for 16–20 h (TLC), they gave the corresponding phosphate **27a** (60% yield), **27b** (64% yield), or **27c** (66% yield) (Scheme 6).



SCHEME 6



SCHEME 7

The formation of **27a**, **27b**, and **27c** resulted from the initial production of the corresponding intermediate **25** as it is previously discussed in Scheme 3. A one-step ($\sigma^2+\sigma^2$) reaction of intermediate **25** with concomitant loss of a molecule of water afforded the alkyl phosphonate **26** that underwent thermal rearrangement for the phosphorus moiety to oxygen yielding the substituted enol phosphates **27a–c**. Analogous thermal rearrangement was previously observed during the reaction of α,β-cycloalkenones with cyanophosphonate synthon in the presence of a catalyst.[18a,b]

Finally, treatment of **1** with diethyl vinylphosphonate **20**, under the same experimental conditions, afforded the vinylphosphonate **29** (53% yield) as the sole reaction product (Scheme 7). Obviously, compound **29** is the product of the initial addition of **1** to the beta-carbon in **20**, followed by elimination of H_2O molecule.[19]

It is noteworthy to mention that the previously discussed reactions of **1** and **2** with α-phosphonyl carbanions **13** or **20** were carried out in ethanol-containing sodium ethoxide, whereupon the same products that are depicted in Schemes 3, 4, 5, 6, and 7 were isolated and identified, otherwise in lower yields.

CONCLUSION

The results of the previous[1,2] and the present work point out the variety of the reaction pathways, which can follow an initial attack of

phosphorus carbanions onto the C=O group in oxazinones **1** and **2** with a subsequent ring opening. However, the transformations are quite different. The main difference between the present work and the corresponding work[1,2] of the Wittig reagents with the same substrates **1** and **2** is that, in the latter case, the transformation of the products is accompanied by elimination of the phosphorus moiety. This is because Ph_3P species is a much better leaving group than $[(EtO)_2PO^-]$. There is much precedence for this difference.[20] Finally, the present work describes an efficient and simple approach to the synthesis of a variety of condensed phosphono substituted 5- and 6-*N*-heterocycles in reasonable yields. This is achieved by application of the appropriate α-phosphonyl carbanion to oxazinones **1** and **2**. Data on the pharmaceutical potency of the new phosphorylated compounds will be published elsewhere.

EXPERIMENTAL

Melting points (m.p.) are uncorrected. Infrared spectra were measured with a Perkin-Elmer IR-spectrometer model 597 using KBr discs. ^1H and ^{13}C NMR spectra were recorded by a Bruker Model WH-300 MHz spectrometer, using TMS as an internal reference. Chemical shifts are given in the δ-scale (ppm), coupling constants J are given in Hz. ^{31}P NMR spectra were run on a Varian CFT-20 relative to external H_3PO_4. Mass spectra were run at 70 eV on a Schimatzu GCS-QPEX spectrometer provided with a data system. The appropriate precautions in handling moisture-sensitive compounds were observed. The silica gel used for column chromatography was Kieselgel 60, particle size 0.2–0.5 mm (E. Merck, Darmstadt).

Treatment of 3-Phenyl-2,4-benzoxazin-1-one (2) with α-Phosphonyl Carbanions 13 and 20

General Procedure

To a slurry of $\sim$ 1 g of LiH (60% in mineral oil, washed with pentane) in a stirred solution of DMF (20 mL) was added dropwise three-molar solution of the appropriate Wittig-Horner reagents **13a**, **13b**, **13c**, or **20** in 10 mL DMF. After the evolution of H_2 had ceased, the suspension was stirred at r.t., for further 20 min and then refluxed for 1 h. The reaction mixture was cooled to r.t., the substrate 1 g of **2**[21] (4.48 mmol) was introduced all at once, and the reaction mixture was refluxed for 12–36 h (TLC). The product mixture was then concentrated, and the excess LiH was quenched carefully with 30 mL of ice water followed by acidification with conc. HCl, and solvent extraction. After evaporation of the dried $CHCl_3$ solution, the residue was chromatographed on silica

gel/*n*-hexane with increasing amounts of AcOEt as eluents, whereupon compounds **16**, **18**, **19**, **22**, and **23** were isolated.

Preparation of 16

A solution of 2.8 g of methyl diethylphosphonoacetate (**13a**) (13.44 mmol) or 3.0 g of triethylphosphonoacetate (**13b**) (13.44 mmol) and 1.0 g of**2** (4.48 mmol) in 30 mL dry DMF was treated with ~1 g LiH at r.t., and the system was further refluxed for 24 h. Working up the product mixture as described in the general procedure and column chromatography furnished compound **16**.

Diethyl N-benzoyl-4-ethoxy-2-oxo-(2H)-quinolin-3-yl-phosphonate (**16**) was obtained (1:1, v/v) as yellow crystals (1.2 g, 62% with **13a**) or (1.3 g, 66% with **13b**), m.p., 142–144°C (from benzene). (Found: C, 61.60; H, 5.72; N, 3.31; P, 7.15. $C_{22}H_{24}NO_6P$ (429.41), requires C, 61.53; H, 5.63; N, 3.26; P, 7.21); ν_{max} (KBr)/cm^{-1}1635 (N-C=O, benzoyl), 1750 (2-C=O), 1269 (P=O, free), 1035 (P-O-C); δ_H (270 MHz; $CDCl_3$): 0.99 (6H, dt, J_{H-H} 7.2, $^4J_{H-P}$ 2.8, P-O-C-CH_3), 1.22 (3H, t, J_{H-H} 7.5, 4-C-O.C.CH_3), 3.87 (2H, q, J_{H-H} 7.2, 4-C-O-CH_2,), 4.09 (4H, dq, J_{H-H} 6.6, $^3J_{H-P}$ 4.4, P-O-CH_2), 7.48–8.15 (9H, m, Ph-*H*);δ_c (270 MHz; $CDCl_3$): 14.27 (4-C.O-C-*C*H$_3$), 16.27 (d, P-O-C-*C*H$_3$), 58.27(d, P-O-*C*H$_2$), 62.26 (4-C.O-*C*H$_2$), 84.8 (d, ^1Jc-*p* 183.7, 3-*C*-P), 122.50, 124.79, 128.37, 128.03, 130.15, 135. 89, 135.54 (*C*=*C*, phenyl), 148.87 (4-*C*-O), 170.00 (2-*C*=O), 183.4 (*C*=O, benzoyl); δ_p ($CDCl_3$): 17.2 ppm; *m/z* (EI): 429 [M$^+$] (13).

Preparation of 18 and 19

A solution of 2.45 g diethyl α-cyanomethylphosphonate (**13c**) (13.44 mmol) and 1.0 g of **2** (4.48 mmol) in 30 mL dry DMF was treated with ~1 g LiH at r.t., and the reaction mixture was further refluxed for 36 h. Working up the product mixture as described in the general procedure and column chromatography afforded compounds **19** and **18**, respectively.

Diethyl N-benzoyl-3-ethoxy-indol-2-yl-phosphonate (**19**) was obtained (4:6, v/v) as yellow crystals (430 mg, 24%), m.p., 133–136°C (from acetone). (Found: C, 62.92; H, 6.09; N, 3.41; P, 7.75. $C_{21}H_{24}NO_5P$ (401.4), requires C, 62.84; H, 6.03; N, 3.49; P, 7.72); ν_{max} (KBr)/cm^{-1}1632 (N-C=O), 1258 (P=O), 1065 (P-O-C); δ_H (270 MHz; $CDCl_3$): 0.98 (6H, dt, J_{H-H} 7.1, $^4J_{H-P}$ 2.7, P-O-C-CH_3), 1.26 (3H, t, J_{H-H} 7.2, 3-C.O.C-CH_3), 3.68 (2H, q, J_{H-H} 7.5, 3-C-O-CH_2), 4.11 (4H, dq, J_{H-H} 6.5, $^3J_{H-P}$ 4.3, P-O-CH_2), 7.4–8.86 (9H, m, Ph-*H*);δ_c (270 MHz; $CDCl_3$): 13.95 (3-C-O-C-*C*H$_3$), 16.04 (d, P-O-C-*C*H$_3$), 57.46 (3-C-O-*C*H$_2$), 63.34 (d, P-O-*C*H$_2$), 107.02 (d, ^1Jc-*p* 178, 2-C-P), 119.01, 121.7, 127.7, 127.85, 128.13, 128.99,

137.57 (*C*=*C*, phenyl), 147.91 (3-C), 179.65 (*C*=O, benzoyl); δ_p ($CDCl_3$): 19.7 ppm; *m/z* (EI): 401 [M^+] (19).

Diethyl N-benzoyl-2-amino-4-oxo(4H)-quinolin-3-yl-phosphonate (**18**) was obtained (2:8, v/v) as orange crystals (665 mg, 37%), m.p., 162–163°C (from EtOH). (Found: C, 60.08; H, 5.33; N, 6.92; P, 7.68. $C_{20}H_{21}N_2O_5P$ (400.37), requires C, 60.00; H, 5.29; N, 7.00; P, 7.74); ν_{max} (KBr)/cm^{-1} 3324 (HNH), 1225 (P=O, bonded), 1050 (P-O-C), 1740(4-C=O), 1638 (N-C=O, benzoyl); δ_H (270 MHz; d_6-DMSO): 1.05, 1.09 (6H, 2dt, J_{H-H} 7.1, $^4J_{H-P}$ 2.6, P-O-C.CH_3), 4.08, 4.12 (4H, 2dq, J_{H-H} 6.8, $^3J_{H-P}$ 3.8, P-O-CH_2), 6.05 (1H, br. NH^a, HNH), 7.43–8.11 (9H, m, *H*-Ph), 9.74 (1H, br. NH^b, HNH);δ_c (270 MHz; d_6-DMSO): 16.65 (d, P-O-C-CH_3), 64.27(d, P-O-CH_2), 92.08 (d, ^1Jc-*p* 197, 3-*C*-P), 122.1, 124.19, 125.94, 126.0, 129.24, 129.26, 134.20, 135.2, 143.53 (*C*=*C*, phenyl), 141.33 (2-*C*), 172.3 (4-*C*=O), 185.2 (*C*=O, benzoyl); δ_p (d_6-DMSO): 18.6 ppm; *m/z* (EI): 400 [M^+] (15).

Preparation of 22 and 23

A solution of 2.11 g diethyl vinylphosphonate (**20**) (13.44 mmol) and 1.0 g of **2** (4.48 mmol) in 30 mL dry DMF was treated with ~1 g LiH at r.t., and the reaction mixture was further refluxed for 12 h, Working up the product mixture as described in the general procedure and column chromatography yielded compounds **22** and **23**, respectively.

Diethyl N-benzoyl-3-ethoxyindole-2-methylphosphonate **(22)** was obtained (7:3, v/v) as yellow crystals (730 mg, 41%), m.p. 139–141°C (from CH_2Cl_2). (Found: C, 63.68; H, 6.34; N, 3.43; P, 7.39. $C_{22}H_{26}NO_5P$ (415.43), requires C, 63.61; H, 6.31; N, 3.37; P, 7.45); ν_{max} (KBr)/cm^{-1}1638 (N-C=O), 1255 (P=O), 1040 (P-O-C); δ_H (270 MHz; $CDCl_3$): 1.01(6H, dt, J_{H-H} 7.2, $^4J_{H-P}$ 2.7, P-O-C-CH_3), 1.25 (3H, t, J_{H-H} 7.2, 3-C-O.C-CH_3), 3.28 (2H, d, J_{H-P} 18.2, 2-C.CH_2-P), 3.67 (2H, q, J_{H-H} 7.2, 3-C-O-CH_2), 3.99 (4H, dq, J_{H-H} 6.8, $^3J_{H-P}$ 3.8, P-O-CH_2), 7.35–8.28 (9H, m, *H*−Ph); δ_c (270 MHz; $CDCl_3$): 14.27 (3-C-O-C-CH_3), 16.18 (d, P-O-C-CH_3), 26.43 (d, J_{C-P} 137, CH_2-P), 60.98 (d, P-O-CH_2), 63.89 (3-C-O-CH_2), 109.91 (2-*C*), 120.27, 122.59, 123.19, 125.29, 128.34, 128.49, 135.42, 136.21 (*C*=*C*, phenyl), 168.77 (*C*=O, benzoyl); δ_p ($CDCl_3$): 24.7 ppm; *m/z* (EI): 415 [M^+](13).

Diethyl N-benzoyl-4-oxo-(4H)-quinolin-2-ylphosphonate (**23**) was obtained (1:1, v/v) as yellow crystals (470 mg, 27%), m.p. 153–155°C (from benzene). (Found: C, 62.38; H, 5.27; N, 3.71; P, 8.13. $C_{20}H_{20}NO_5P$ (385.36), requires C, 62.30; H, 5.23; N, 3.64; P, 8.04); ν_{max} (KBr)/cm^{-1}1630 (N-C=O), 1755 (4-C=O), 1265 (P=O), 1033 (P-O-C); δ_H (270 MHz; $CDCl_3$): 1.06 (6H, dt, J_{H-H} 7.5, $^4J_{H-P}$ 2.5, P-O-C-CH_3), 3.99 (4H, dq, J_{H-H} 6.6, $^3J_{H-P}$ 4.4, P-O-CH_2), 6.79 (1H, d, $^3J_{H-P}$ 4.8, 3-C*H*), 7.62–8.63 (9H,m, Ph-*H*); δ_c (270 MHz; $CDCl_3$): 16.04 (d, P-O-C-CH_3),

59.66 (d, P-O-*C*H_2), 115.38 (d, 3-*C*), 127.45, 128.67, 129.05, 129.58, 138.2 (*C*=*C*, phenyl), 145.45 (d, ^1Jc-*p*187, 2-*C*-P), 169.3 (4-*C*=O), 184.03 (*C*=O, benzoyl); δ_p ($CDCl_3$): 18.7 ppm; *m/z* (EI): 385 [M^+] (20).

When **2** (4.48 mmol) was allowed to react with **13a**, **13b**, **13c,** or **20** (13.4 mmol) in absolute ethanol, containing NaOEt (2 molar equivalents of **13** or **20**) under the previously discussed above same conditions and work-up, compounds **16** (~ 48%), **18** (25%), **19** (18%), **22** (32%), and **23** (16%) were isolated and identified.

Reaction of 4-(4-Methylphenyl)-2,3-benzoxazin-1-one (1) with α-Phosphonyl Carbanions 13a–c and 20

Preparation of 27a, 27b, and 27c

A solution of 12.6 mmol of Wittig–Horner reagent **13a**, **13b**, or **13c** and 1g of **1**[22] (4.2 mmol) in 30 mL dry DMF was treated with ~1 g LiH at r.t., and the system was further refluxed for 16–20 h (TLC). The product mixture was worked up in the usual manner, and then subjected to column chromatography to give **27a**, **27b**, or **27c**.

Diethyl 1-(4-methylphenyl)-3-methylcarboxylate isoquinolin-4-yl-phosphate **(27a)** was obtained (4:6, v/v) as yellow crystals (1 g, 60%), m.p. 126–128°C (from CH_2Cl_2). (Found: C, 61.62; H, 5.70; N, 3.22; P, 7.28. $C_{22}H_{24}NO_6P$ (429.41): requires C, 61.53; H, 5.63; N, 3.26; P, 7.21); ν_{max} (KBr)/cm^{-1} 1730 (C=O, ester), 1596 (C=N), 1586 (C=C), 1262 (P=O), 1041 (P-O-C); δ_H (270 MHz; $CDCl_3$): 0.97 (6H, dt, J_{H-H} 7.5, $^4J_{H-P}$ 2.6, P-O-C.CH_3), 2.28 (3H, s, CH_3-Ar), 3.69 (3H, s, OCH_3, ester), 4.08 (4H, dq, J_{H-H} 6.5, $^3J_{HP}$ 5.8, P-O-CH_2), 7.42–8.62 (8H, m, *H*-Ar); δ_c (270 MHz; $CDCl_3$): 15.6 (d, P-O-C.*C*H_3), 21.80 (*C*H_3-Ar), 54.75 (O*C*H_3, ester), 61.4 (d, P-O-*C*H_2), 122.23, 123.24, 125.0, 129.2, 130.0, 131.43, 132.25, 134.8, 141.23 (*C*=*C*, Ar), 145.03 (d, 4-*C*-O-P), 150.88 (*C*=N), 163.34 (*C*=O, ester); δ_p ($CDCl_3$): −4.02 ppm; *m/z* (EI): 429 [M^+] (20).

Diethyl 3-ethylcarboxylate-1-(4-methylphenyl) isoquinolin-4-yl-phosphate (**27b**) was obtained (1:1, v/v) as yellow crystals (1.2 g, 64%), m.p. 148–150°C (from EtOH). (Found: C, 63.38; H, 5.97; N, 3.09; P, 6.89. $C_{23}H_{26}NO_6P$ (443.44): requires C, 63.30; H, 5.91; N, 3.16; P, 6.98); ν_{max} (KBr)/cm^{-1} 1720 (C=O, ester), 1590 (C=N), 1537 (C=C), 1263 (P=O), 1043 (P-O-C); δ_H (270 MHz; $CDCl_3$): 0.99 (3H, t, J_{H-H} 7.1, O-C.CH_3, ester), 1.08 (6H, dt, J_{H-H} 7.5, $^4J_{H-P}$ 2.8, P-O-C-CH_3), 2.28 (3H, s, CH_3-Ar), 4.12 (4H, dq, J_{H-H} 6.7, $^3J_{HP}$ 4.9, P-O-CH_2), 4.34 (2H, q, $^3J_{H-P}$ 11.6, OCH_2, ester), 7.42–8.62 (8H, m, *H*-Ar); δ_c (270 MHz; $CDCl_3$): 14.02 (C.*C*H_3, ester), 16.18 (d, P-OC·*C*H_3), 21.80 (*C*H_3-Ar), 61.65 (O*C*H_2, ester), 63.75 (d, P-O-*C*H_2), 122.23, 123.24, 125.01, 128.9, 129.5, 130.0, 131.43, 132.25, 134.8, 135.2,141.32 (*C*=*C*, Ar), 144.7 (d,

4-*C*-O-P), 149.8 (*C*=N), 161.65 (*C*=O, ester); δ_p ($CDCl_3$): -3.96 ppm; *m/z* (EI): 443 [M^+] (24).

Diethyl 3-cyano-1-(4-methylphenyl)isoquinolin-4-yl-phosphate (**27c**) was obtained (2:8 v/v) as brown crystals (1.1 g, 66%), m.p. 181–182°C (from $CHCl_3$). (Found: C, 63.70; H, 5.38; N, 7.00; P, 7.75. $C_{21}H_{21}N_2O_4P$ (396.39): requires C, 63.63; H, 5.34; N, 7.07; P, 7.81); ν_{max} (KBr)/cm^{-1} 2222 (CN), 1586 (C=N), 1530 (C=C), 1258 (P=O), 1043 (P-O-C); δ_H (270 MHz; d_6-DMSO): 1.41 (6H, dt, J_{H-H} 7.3, $^4J_{H-P}$ 2.91, P-O-C.CH_3), 2.28 (3H, s, CH_3_Ar), 4.06 (4H, dq, J_{H-H} 6.5, $^3J_{HP}$ 5.2, P-O-CH_2), 7.38–8.75 (8H, m, *H*-Ar);δ_c (270 MHz; d_6-DMSO): 16.25 (d, P-O-C.*C*H_3), 21.80 (Ar-*C*H_3), 64.75 (d, P-O*C*H_2), 111.7 (*C*-CN), 118.3 (*C*N), 123.9, 124.5, 124.9, 125.2, 125.3, 131.2, 132.1, 135.1, 141.3 (*C*=*C*, Ar), 143.2 (d, 4-*C*-O-P), 161.7 (*C*=N); δ_p (DMSO): −4.28 ppm; *m/z* (EI): 396 [M^+] (22).

Preparation of 29

A solution of 1.98 g diethyl vinylphosphonate (**20**) (12.6 mmol) and 1.0 g of**1** (4.2 mmol) in 30 mL dry DMF was treated with ∼1 g LiH at r.t., and the reaction mixture was further refluxed for 8 h. The product mixture was worked up in the usual manner and chromatographed to afford compound **29** as the sole reaction product.

Diethyl [1-(4-methylphenyl)-(4H)-4-oxo-isoquinolin-3-ylidene]methylphosphonate (**29**) was obtained (1:1, v/v) as colorless crystals (860 mg, 53%), m.p. 188–191°C (from $CHCl_3$). (Found: C, 65.83; H, 5.87; N, 3.60; P, 8.14. $C_{21}H_{22}NO_4P$ (383.38): requires C, 65.79; H, 5.78; N, 3.65; P, 8.08); ν_{max} (KBr)/cm^{-1} 1772 (4-C=O), 1585 (C=N), 1577 (C=C), 1253 (P=O), 1057 (P-O-C); δ_H (270 MHz; d_6-DMSO): 1.31 (6H, dt, J_{H-H} 7.5, $^4J_{H-P}$ 2.8, P-O-C-CH_3), 2.34 (3H, s, CH_3-Ar), 4.02 (4H, dq, J_{H-H} 6.8, $^3J_{H-P}$ 4.6, P-O-CH_2), 6.14 (1H, d, $^2J_{H-P}$ 21.8.5, 3-C=C*H*), 7.42–8.28 (8H,m, Ar-*H*); δ_c (270 MHz; d_6-DMSO): 16.38 (d, P-O-C.*C*H_3), 21.30 (*C*H_3-Ar), 60.57 (d, P-O-*C*H_2), 91.47 (d, J_{C-P} 198, 3-C=*C*-P), 125.05, 127.97, 130.0, 131.82, 133.38, 135.67, 135.69, 142.6, 168.0, 169.1 (*C*=*C*, Ar), 151.55 (d, 3-*C*), 164.06 (*C*=N), 188.02 (4-*C*=O); δ_p (d_6-DMSO): 21.7 ppm; *m/z* (EI): 383 [M^+] (26).

Similarly, **27a** (48%), **27b** (53%), **27c** (55%), and **29** (46%) were obtained and identified when NaOEt replaced LiH in the previously discussed reactions.

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