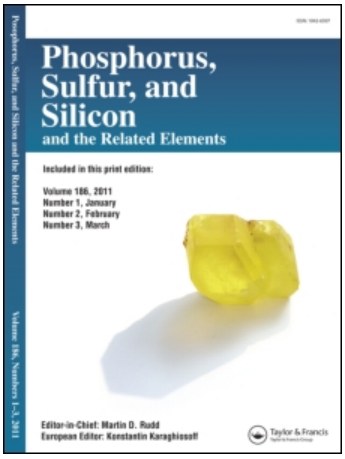

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Regioselective Condensation of Alkylidenephosphoranes with Bifunctionalized Compounds: New Approach to the Synthesis of Fused *O*- and *N*-Heterocycles

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Regioselective Condensation of Alkylidenephosphoranes with Bifunctionalized Compounds: New Approach to the Synthesis of Fused *O*- and *N*-Heterocycles

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A series of fused pyran- (~40% yield) and furan- (~20% yield) derivatives were regioselectively prepared from the reactions of 5,6-difur-2′yl-3-oxo-2,3-dihydropyridazin-4-carbonitrile with ester- and keto phosphorus ylides, whereas new ylides were obtained, in addition to fused furans, in almost equal yields (33%) from the reaction of the same substrate with cyanomethylene(triphenyl)phosphorane. However, application of such Wittig reagents on 2-[(benzylidene)amino]-benzonitrile afforded, in all cases, 4-hydroxyquinolines in a ~42% yield as major products. Moreover, 2-[(triphenylphosphoranylidene)amino] benzonitrile, with the corresponding alkene, was also isolated a side products.

Keywords Alkylidenephosphoranes; *N*-Heterocycles; nitriles; Shiff's base

Many pyridazine derivatives[1] are reported as insecticides, miticides, nematocides,[1a] acaricides, fungicides,[1b] and cardiotonics.[1c] In addition, many substituted benzofurans show marked pharmacological activity, e.g., 2-(4-hydroxybenzoyl)benzofuran exhibits a relaxant effect on histamine and an acetylcholine spasm.[2] This has been the main impetus behind growth of research in new derivatives of these substrates during the last four decades.

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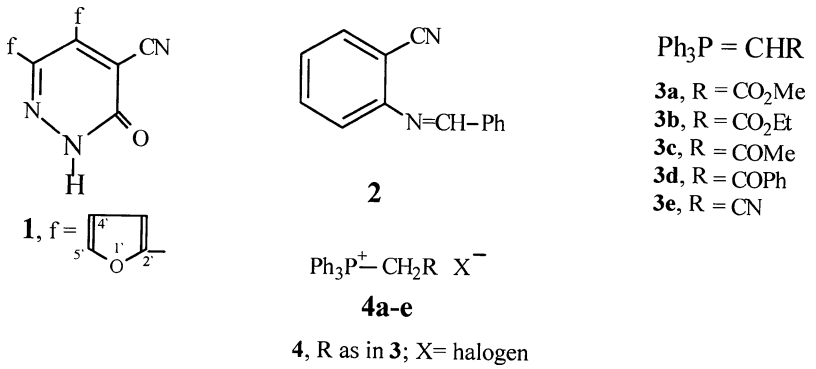
Over the past decade, we have investigated the synthetic utility of phosphorus ylides. We also have illustrated the usefulness of such reagents for the synthesis of heterocycles with numerous examples.[3] Consequently, in the present work, we describe the use of alkylidenephosphoranes **3** for building fused heterocyclic systems that are condensed with pyridazine and phenyl species. Target compounds were achieved from the reactions of **3a**, **3b**, **3c**, **3d**, and **3e** with 5,6-difur-2′yl-3-oxo-1,3-dihydropyridazin-4-carbonitrile (**1**) and 2-[(benzylidene)amino]benzonitile (**2**) (Scheme 2).

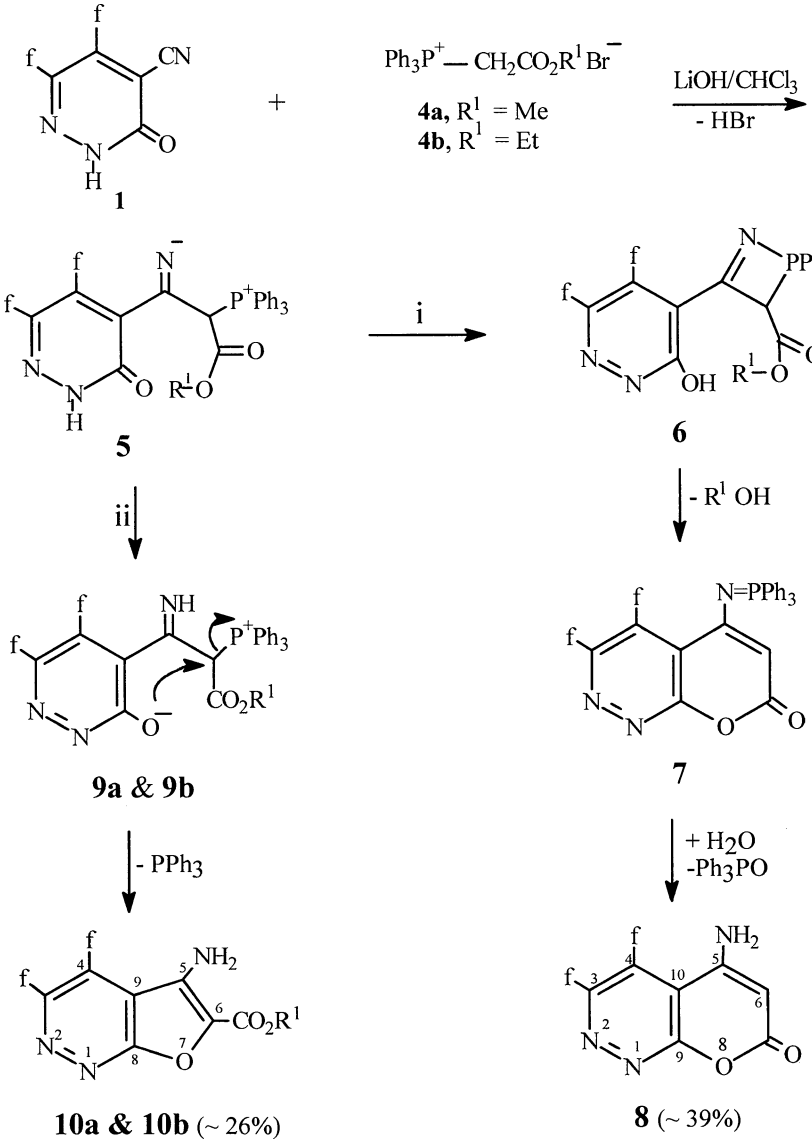
The investigation also highlighted the influence of replacing the carbonyl group with a Schiff's base (anil) moiety at the *ortho*-position with respect to the nitrile group in the behavior toward phosphorus ylides. The reactions studied and the products obtained are depicted in Schemes 2, 4, 5, and 7.



SCHEME 1

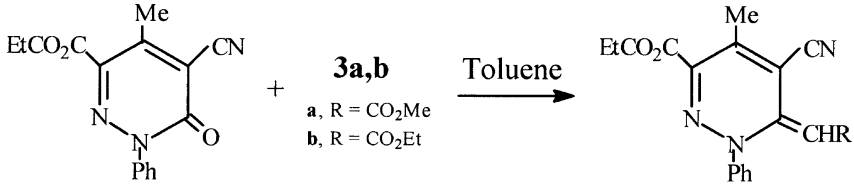
RESULTS AND DISCUSSION

The required carbonitrile **1** was prepared according to the literature[4] by ternary condensation of 2-furaldehyde, ethylcyanoacetate, and hydrazine hydrate in an alcoholic sodium ethoxide solution. No reaction was observed when equimolar amounts of **1** and ester-**3a** and **3b**, keto ylides **3c** and **3d**, or cyanomethylene(triphenyl)phosphorane (**3e**) were refluxed in dry toluene (or dry ethyl acetate), even after 3 days. However, treatment of **1** with ylide **3a** or **3b**, generated in situ from the corresponding phosphonium bromide **4a** or **4b** by addition of aqueous lithium hydroxide in chloroform, yielded 5-amino-3,4-difur-2′yl-7H-7-oxopyran[2,3-*c*]pyridazine (**8**) (~39% yield) and alkyl 5-amino-3,4-difur-2′ylfuro[2,3-*c*]pyridazine-6-carboxylates (**10a** and **10b**) (~26% yield) (Scheme 2).

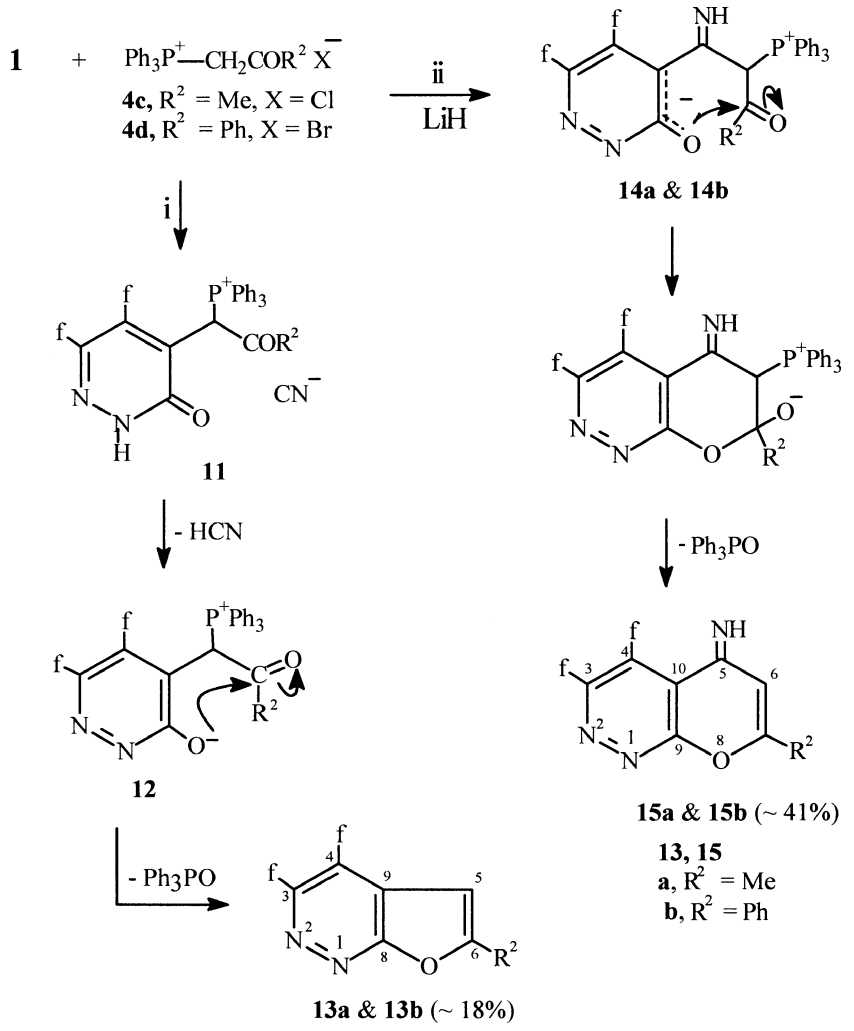


SCHEME 2

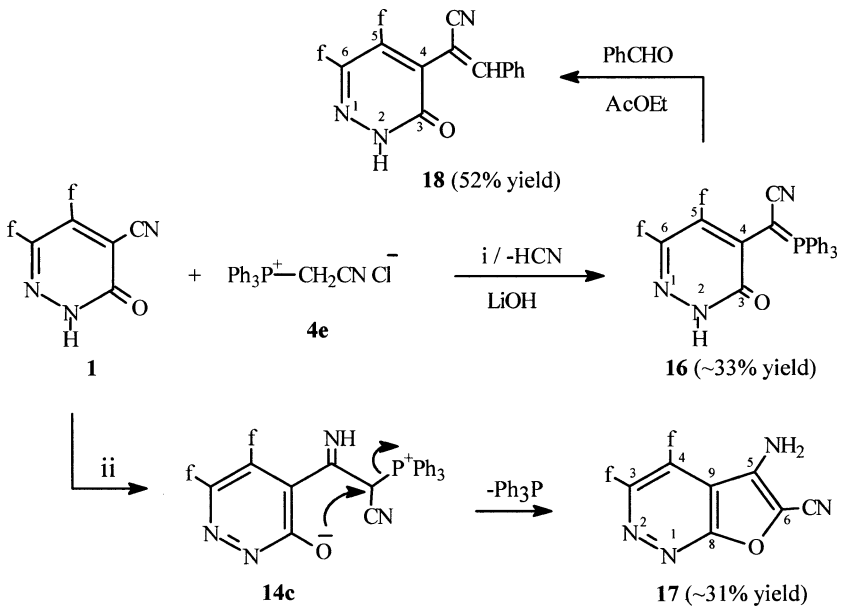
The mechanism of condensation of the nitrile **1** with ylides **3a** and **3b** probably involved the initial formation of an intermediate of type **5** with a subsequent ring closure to afford dihydroazaphosphete **6**.[5,6] Under thermal conditions, and in the presence of a base (LiOH), the



SCHEME 3

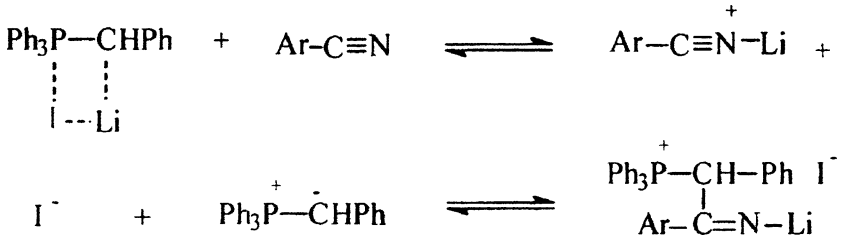


SCHEME 4

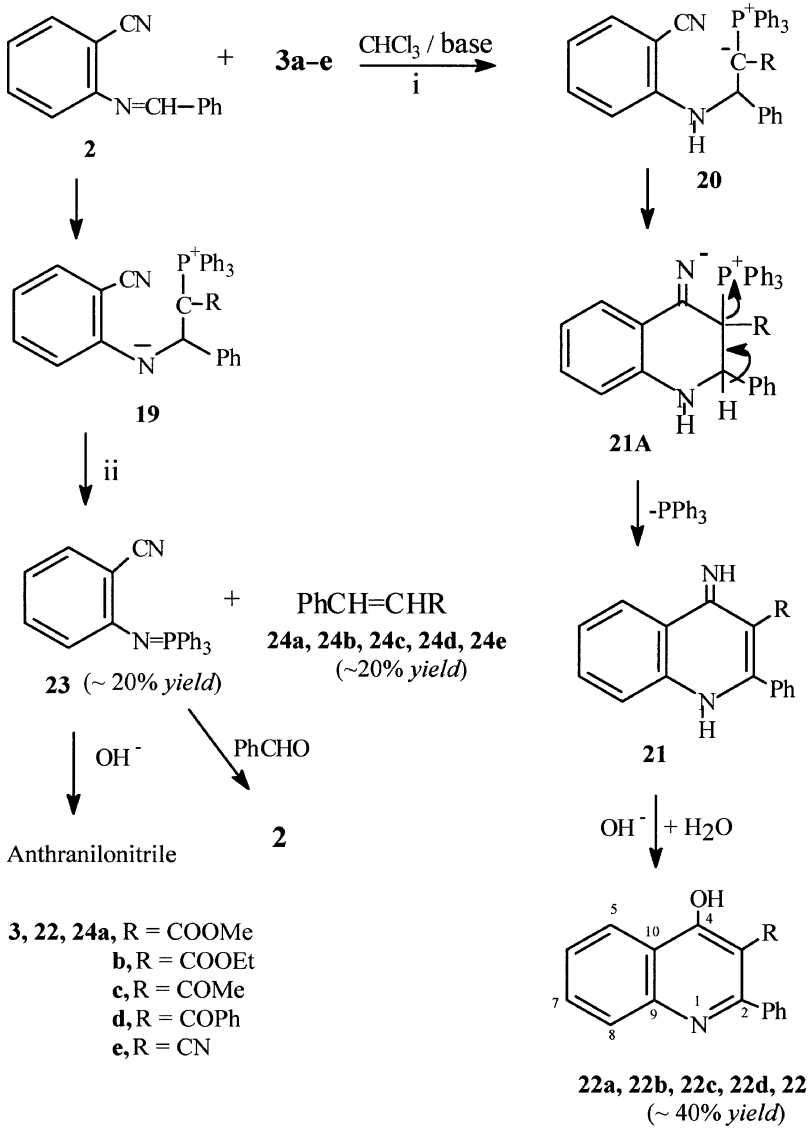


SCHEME 5

zwitterion **5** presumably was formed. The iminophosphorane **7** then resulted from the opening of the four membered ring, lactonization, and extrusion of the appropriate alcohol moiety. Further hydrolysis of **7** yielded the final product **8** and triphenylphosphine oxide (Scheme 2(i)). On the other hand, rearrangement[6,7] of **5** to the imino intermediate **9**, followed by the attack of anionic oxygen on the ylidic carbon, led to the furopyridazines **10a** or **10b** via elimination of triphenylphosphine and prototropic rearrangement (Scheme 2(ii)). An analogous mechanism has been reported previously by Barnhardt[6a] and recently by Vicente[5a] for the reactions of phosphonium salts with nitriles.



SCHEME 6



3, 22, 24a, R = COOMe
b, R = COOEt
c, R = COMe
d, R = COPh
e, R = CN

SCHEME 7

In contrast to these findings that were obtained from the reaction of pyridizanone **1** with **3a** and **3b**, Wittig olefination occurred when **3a** and **3b** were allowed to react with ethyl 2-phenyl-5-methyl-3-oxo-2, 3-dihydropyridazine-6-carboxylate (**A**) in dry toluene to give the

corresponding olefin **Ba** and **Bb**[8] ('Scheme 3'). Considering the latter reaction of pyridazine **A** with **3a** and **3b**, the ylide's attack of the carbonyl-carbon in **A** and not of the nitrile moiety as it took place in the reactions of pyridazinone **1** with **3a** and **3b** could be attributed to the lack of a mobile hydrogen in **A**. However, it seemed necessary to extend this investigation to optimize the conditions that control the selectivity of the nucleophilic attack toward substituted pyridazines of type **1**. Variation of the type of the pyrimidine substituent, the reaction solvent, the temperature, and the base used, will be addressed in a forthcoming communication.

When a mixture of an equimolar amount of **1** and 2-oxopropyl (triphenyl)phosphonium chloride (**4c**) or (2-oxo-2-phenylethyl)(triphenyl)phosphonium bromide (**4d**) in dimethylformamide was treated with LiH or $CHCl_3/H_2O$/LiOH (best yields with LiH/DMF), the substituted furopyridazines **13a** and **13b** (~18% yield) and pyranopyridazines **15a** and **15b** (~41% yield) were isolated (Scheme 4).

Obviously, the reaction of **1** with **4c** and **4d** proceeds under more drastic conditions (a higher temperature [DMF] and stronger base [LiH]) than that used for **1** with **4a** (or **4b**). Scheme 4 shows that **3c** and **3d** can affect a replacement[9] of the nitrile group, forming the phosphonium intermediate **11**, which loses HCN, giving the phosphorane **12**. Hydrolysis of **12**, followed by internal hemi-acetalization,[10] yielded **13a** and **13b** (Scheme 4(i)). On the other hand (parallel to **9**, Scheme 2), the expected initially formed zwitterion intermediates **14a** and **14b**, which would give rise to the iminopyrans **15a** and **15b** through intramolecular cyclization and the elimination of triphenylphosphine oxide (Scheme 4(ii)). The formation of an intermediate of type **14**[11,12] and its transformation into imines has, however, been reported for the reaction of alkylidenephosphoranes and nitriles.[6a] Following this, Schemes 2 and 4 point out a variety of reaction pathways, which can follow an initial attack of phosphorus ylides **3a**, **3b**, **3c**, and **3d** to *CN* moiety.

On treating pyridizanone **1** with cyanomethylene (triphenyl)phosphonium chloride (**4e**), in CH_3/H_2OLiOH, (5,6-difur-2′yl-3-oxo-1,3-dihydropyridazin-4-yl) (triphenyl)phospharylideneacetonitrile (**16**, 33% yield) along with the substituted furopyridazine **17** (~30% yield) were obtained according to Scheme 5. On heating the complex ylide **16** under reflux, in ethyl acetate containing a catalytic amount of triethylamine with benzaldehyde for 10 h, the Wittig-reaction readily occurred yielding 2-(5,6-difur-2′yl-3-oxo-1,3-dihydropyridazin-4-yl)-3-phenylacrylonitrile (**18**, 52% yield). Only one isomer of **18** was isolated and it was suggested that it may have a *syn*-configuration (based on NMR investigation of the CH resonance). Thus, the exocyclic

methine proton appeared as a singlet at δ 5.85 ppm in the ^{1}H NMR spectrum of **18**, which is in accordance with a chemical shift expected for the *Z*-configuration and readily eliminates the *E* isomer. The latter would predict a singlet at a more downfield resonance in the range δ 6.5–7.6 ppm. Furthermore, it is reported[13] that the presence of the two higher-ranking groups on the same side of the double bond is in favor of the assigned *Z* structure.

The results presented in Schemes 2, 4, and 5 make it likely that resonance-stabilized phosphoranes **3** attack **1** only at the nitrile group, instead of the amidic carbonyl function, whereby the betaine intermediates corresponding to **5** are formed in all the reactions of **3a**, **3b**, **3c**, **3d**, and **3e** with the nitrile **1**. However, perusal of the literature indicated that attempts to add nitriles to resonance-stabilized ylides, i.e., those carrying electron-withdrawing groups on the ylide carbon, were unsuccessful.[5b] The findings also reflect the inertness of molecule **1**. This is probably due to the low reactivity of the nitrile function and the carbonyl group of amides toward nucleophilic attack.[14] The thermal conditions, coupled with the presence of an excess of a strong base (LiOH or LiH) used for the generation of a ylide, however, deprotonate either the ylide or the pyridazinone promoting thus a further reaction. The attack at the nitrile-carbon, in these cases, could be attributed to the formation of lithium ion complexes with the nitrile and, thereby, increase the electrophilic reactivity of the carbon atom of the cyano group in the condensation reactions under consideration. Furthermore, the adjacent carbonyl group reinforces the electrophilic character of the nitrile moiety. The probable mechanism of the condensation step in the reaction of the ylide, derived from phosphonium salt with arylnitriles, in the presence of lithium ion, was previously discussed by Barnhardt and colleagues[6a] (Scheme 6).

The reactions of alkylidenephosphoranes **3a**, **3b**, **3c**, and **3d** with 2-[(benzylidene)amino]benzonitrile (**2**) were investigated next in an effort to search for possible dissimilarities that might occur when another electronegative species (−N=C) was introduced, in lieu of the amidic carbonyl group, at the *ortho*-position to the nitrile moiety. The required Schiff-base **2** was prepared in a reasonable yield (88%) from the condensation of the parent *o*-aminobenzonitrile with benzaldehyde.[15] Treatment of anil **2** with ester ylide **3a** (one equivalent) in boiling chloroform containing a trace amount of piperidine for 60 h afforded 4-hydroxyquinoline **22a** (42% yield), 2-[(triphenylphosphoranylidene)amino]benzonitrile (**23**)[16] (22%) and methyl cinnamate (**24a**) (20% yield). Similarly, **2** reacted with **3b**, **3c**, **3d**, and **3e** to give **22b**[17,18] or **22c**, **22d**, and **22e** (~40% yield) together

with **23** (~20% yield) and the corresponding olefin **24b**, **24c 24d**, and **24e** (~20% yield). When **23** was allowed to react with benzaldehyde, the Wittig reaction readily occurred and yielded the expected product **2**, whereas *o*-aminobenzonitrile was obtained by alkali-hydrolysis of **23** (or by standing at room temperature for few days). Benzylidine derivatives **24** were verified by m.p. and mixed m.p., as well as comparative spectra with reference samples.

Scheme 7 shows a working hypothesis for the formation of the isolated products **22**, **23**, and **24**. Wittig reagent **3** adds to the imine linkage of **2**, giving the intermediate **19**. The further collapse[11] of **19**, by the transfer of nitrogen from carbon to phosphorus (Wittig-type reaction), yields the iminophosphorane **23** and the respective alkene **24**. On the other hand, the prototropic rearrangement of **19** results in the intermediates **20**. Next, internal Hofmann elimination of Ph_3P and intramolecular cyclization leads to 4-imino-quinolines **21**, which affords 4-hydroxyquinolines **22** by hydrolysis. A similar transformation, i.e., an imino group to a hydroxyl moiety, is known for the imino intermediates to the corresponding hydroxyl compounds or the keto-structure.[5,6,19] It also is worthy to note that the IR and ^{1}H NMR spectra of **22** indicated the presence of **22** only in the enol form, which is the more stable structure.[20] Furthermore, the formed alkenes **24** did not have any further reaction with Wittig reagents. This finding is along the line, which has been previously pointed out, that such reagents do not react with the isolated alkenes from Wittig reactions.[11]

Finally, the methods previously described for the preparation of quinoline **22b** are lengthy and indirect.[17,18] For example, **22b** was synthesized from the condensation of ethyl benzoylmalonates and aniline. The acrylates, unstable under normal conditions, was cyclized to **22b** (~27% yield) using acetic anhydride and sulfuric acid. In the present context, **22a–e** (~ 42% yield) could be available by a one-step synthesis from the reaction of the proper anilide with resonance-stabilized phosphorus ylides.

CONCLUSION

In summary, the present investigation clearly shows that the phosphoranes **3a**, **3b**, **3c**, **3d**, and **3e** behave toward the nitriles **1** and **2** in different manners. The nature of the α-substituent to the nitrile group in **1** and **2** plays, however, a decisive role in their reactions with the Wittig reagents of type **3** . Thus, **3** exclusively attacks the nitrile group in **1**, whereas the imino function **2** is the reactive one. Finally, the *O*- and *N*-heterocycles prepared in the present work might be biologically active compounds based on known drug skeletons.

EXPERIMENTAL

Melting points (m.p.) are uncorrected. Infrared spectra were measured with a Perkin-Elmer IR-spectrometer model 597 using KBr discs. The ^{1}H 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 in Hz. The ^{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. Light petroleum refers to the fraction 40–60°C. Methyl *trans*-cinnamate (**24a**) and the ethyl analog (**24b**) are available from Aldrich Company.

Reactions of 5,6-di-2-furyl-3-oxo-2,3-dihydropyridazin-4-carbonitrile (1) with Ester Ylides 3a and 3b

Preparation of Compounds 8 and 10a and 10b

General Method. A solution of 4.5 mmol alkoxycarbonylmethylene (triphenyl)phosphonium bromide **4a** or **4b** and 1 g (3.95 mmol) pyridazine **1**[4] in 30 mL $CHCl_3$ was stirred at room temperature up to the dissolution of the starting materials (~1 h). Freshly prepared 15 mL aqueous LiOH (0.5 *M*) was added in one portion to the mixture, and the two-phase system was stirred at the reflux temperature up to the consumption of the starting pyridazinone (~40 h, TLC). After concentration of the solvent, 20 mL distilled water was added and the solution was acidified with concentrated HCl. The resulting solution was extracted with (3 × 50 mL) chloroform. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel by using *n*-hexane/$CHCl_3$ as the eluents whereupon compounds **10a** and **8** or **10b** and **8** were isolated, respectively.

With 4a

Methyl 5-amino-3,4-difur-2′-ylfuro[2,3-c]pyridazine-6-carboxylate (**10a**) was obtained (8:2, v/v) as pale yellow crystals (300 mg, 24% yield), m.p. 158–160°C (EtOH). Anal. calcd. for $C_{16}H_{11}N_3O_5$ (325.29): C, 59.08; H, 3.41; N, 12.92. Found: C, 59.14; H, 3.33; N, 12.86%. IR: 3458, 3355 (NH_2), 1695 (C=O, ester). ^{1}H NMR (d_6-DMSO): δ 3.39 (s, 3H,H_3CO, ester), 5.91 (s, 2H,H_2N), 6.73, 7.16 (2d, $J_{HH} = 4.7$, 4H, 2 × $H^{3'}$, $H^{4'}$, furans), 7.31, 7.57 (2d, $J_{HH} = 4$, 2H, 2 × $H^{5'}$, furans); ^{13}C NMR (d_6-DMSO): δ 55.3 (OCH_3, ester), 106.2, 106.8, 110.2, 110.9 (2 × (3′-*C*

& 4′-*C*), furans), 127.6 (9-*C*), 140.8, 141.3, 144.5, 144.7, 147.4 (2 × 5′-*C*-furans, 5-*C*, 4-*C*, 3-*C*), 151.3, 151.9 (2′-*C*-furans), 153.3 (6-*C*), 155.1 (8-*C*), 161.4 (*C*=O, ester); MS: *m/z* (EI) (%): 325 (100) [M^+], 310 (7), 294 (11), 266 (22), 258 (18), 191 (46), 199 (27), 132 (64), 67 (30).

5-amino-3,4-difur-2′-yl-7H-7-oxopyran[2,3-c]pyridazine (**8**) was obtained (2:8, v/v) as greenish-yellow crystals (430 mg, 37% yield), m.p. 305–307°C (EtOH). Anal. calcd. for $C_{15}H_9N_3O_4$ (295.26): C, 61.02; H, 3.07; N, 14.23. Found: C, 61.08; H, 3.01; N, 14.15%. IR: 3435, 3268 (NH_2), 1685 (C=O, lactone), 1610 (C=C, furans). δ_H NMR (d_6-DMSO): δ 5.93 (s, 2H, H_2N), 6.42 (s, 1H, 6-C*H*), 6.71, 7.27 (2d, $J_{HH} = 4.7$, 4H, 2 × $H^{3'}$ & $H^{4'}$, furans), 7.63, 7.88 (2d, $J_{HH} = 4$, 2H, 2 × $H^{5'}$-furyl rings); ^{13}C NMR (d_6-DMSO): δ 106.2, 106.7, 110.2, 110.6 (2 × (3′*C* & 4′*C*), furans), 118.5 (6-*C*), 127.6 (10-*C*), 140.7, 141.4, 143.6 (5-*C*, 4-*C*, 3-*C*), 147.1, 148.1 (2 × 5′-*C*, furans), 151.6, 152.5 (2′-*C*, furans), 155.4 (9-*C*), 174.6 (*C* =O, lactone); MS: *m/z* (EI) (%): 295 (100) [M^+], 279 (14), 267 (18), 251 (35), 229 (41), 185 (52), 163 (70), 67 (26).

With 4b

Ethyl 5-amino-3,4-difur-2′-ylfuro[2,3-c]pyridazine-6-carboxylate (**10b**) was obtained (8:2, v/v) as pale-yellow crystals (375 mg, 28% yield), m.p. 132–134°C (CH_2Cl_2). Anal. calcd. for $C_{17}H_{13}N_3O_5$ (339.32): C, 60.18; H, 3.86; N, 12.38. Found: C, 60.25; H, 3.78; N, 12.26%. IR: 3463, 3364 (NH_2), 1695 (C=O, ester). ^{1}H NMR (d_6-DMSO): δ 0.92 (t, J_{HH} =7, 3H, OCH_2CH_3), 3.70 (q, $J_{HH} = 7.2$, 2H, OCH_2), 5.92 (s, 2H, H_2N), 6.77, 7.16 (2d, $J_{HH} = 4.8$, 4H, 2 × $H^{3'}$-, $H^{4'}$-furans), 7.27, 7.58 (2d, $J_{HH} = 4$, 2H, 2 × $H^{5'}$, furans); ^{13}C NMR (d_6-DMSO): δ 15.6 (O.C.CH_3, ester), 61.8 (OCH_2), 106.6, 106.8, 110.1, 111.2 (2 × (3′-*C*, 4′-*C*), furans), 129.3 (9-*C*), 140.7, 142.1, 144.5, 144.4, 147.8 (2 × 5′-*C*-furans & 5-*C*, 4-*C*, 3-*C*), 150.6, 151.4 (2′-*C*-furans), 153.3 (6-*C*), 155.1 (8-*C*), 162.2 (C=O, ester); MS: *m/z* (EI) (%): 339 (100) [M^+], 323 (10), 310 (16), 272 (26), 266 (27), 206 (38), 199 (36), 132 (58), 67 (31).

Compound **8** also was obtained (2:8, v/v) in 41% yield (m.p., mixed m.p., and IR as previously described, *see supra*).

No reaction was observed when equimolar amounts of **1** and **3a** (or **3b**) were refluxed in dry toluene (or dry ethyl acetate), even after 3 days.

Reaction of 1 with Keto Ylides 3c and 3d

Preparation of Compounds 13a, 13b, 15a and 15b

General Method. A solution of 1.77 g (2-oxopropyl)(triphenyl)phosphonium chloride (**4c**) (5 mmol) or 2.3 g (2-oxo-2-phenylethyl)-(triphenyl)phosphonium bromide (**4d**) (5 mmol) in 25 mL DMF was added dropwise to 200 mg slurry of LiH dispersion (60% in paraffin

oil) in 15 mL DMF. The reaction mixture was stirred at room temperature, until all hydrogen evolution had ceased, and 1 g pyridazinone **1** (3.95 mmol) was introduced together. The reaction mixture was allowed to remain at room temperature for another 2 h, and was then heated under reflux for ~3 days (TLC). The product mixture was concentrated to 10 mL, diluted with 30 mL distilled. H_2O, acidified with conc. HCl, and then extracted with two portions (100 mL) of ethyl acetate. The AcOEt extracts were combined, back-washed with 100 mL H_2O, and dried, and the solvents were evaporated to dryness. The residue was chromatographed on silica gel with n-hexane/$CHCl_3$ as the eluent whereupon compounds **13a** and **15a** or **13b** and **15b** were isolated.

3,4-Difur-2′-yl-6-methylfuro[2,3-c]pyridazine (**13a**) was obtained (1:1, v/v) as yellow leaflets (158 mg, 15% yield), m.p. 123–125°C (MeCN). Anal. calcd. for $C_{15}H_{10}N_2O_3$ (266.26): C, 67.66; H, 3.78; N, 10.52. Found: C, 67.77; H, 3.72; N, 10.45%. IR: 1598, 1610 (C=C, furans). ^{1}H NMR ($CDCl_3$): δ 2.21 (s, 3H, -CH_3), 6.42–6.73 (m, 5H, 5-CH & 2 × ($H^{3'}$, $H^{4'}$) furans), 7.36, 7.82 (2d, J_{HH} = 4, 2H, 2 × H^5, furans); ^{13}C NMR ($CDCl_3$/d_6-DMSO): δ 22.6 (6-C.CH$_3$), 104.4 (5-C), 106.77, 106.8, 110.1, 111.2 (2 × (3′-C, 4′-C), furans), 129.3 (9-C), 140.7, 142.1, 144.5, 147.8 (2 × 5′-C, furans & 4-C, 3-C), 150.6, 151.4 (2′-C, furans), 152.3 (6-C), 155.1 (8-C); MS: m/z (EI) (%): 266 (55) [M$^+$], 251 (14), 200 (23), 185 (37), 134 (18), 119 (100), 66 (22).

3,4-Difur-2′-yl-7-methyl-5H-pyrano[2,3-c]pyridazine-5-imine (**15a**) was obtained ($CHCl_3$) as orange crystals (485 mg, 42% yield), m.p. 166–168°C (benzene). Anal. calcd. for $C_{16}H_{11}N_3O_3$ (293.29): C, 65.52; H, 3.78; N, 14.33. Found: C, 65.61; H, 3.74; N, 14.26%. IR: 3330 (NH, weak), 1622 (C=NH). ^{1}H NMR ($CDCl_3$/d_6-DMSO): 2.24 (s, 3H -CH_3), 6.08 (s, 1H, 6-CH-pyran), 6.42–6.73 (2d (m), 2 × 4H, ($H^{3'}$, $H^{4'}$), furans), 7.28, 7.89 (2d, J_{HH} = 4, 2H 2 × $H^{5'}$, furans), 8.99 (s br, 1H, =NH); ^{13}C NMR ($CDCl_3$/d_6-DMSO): δ 13.8 (CH$_3$), 106.3, 106.8, 108.2, 110.3, 110.7 (6-C & 2 × (3′-C, 4′-C),furans), 128.1 (10-C), 141.2, 141.6, 144.4, 146.1 (2 × 5′-C-furans & 4-C, and 3-C), 151.5, 152.3, 152.8 (7-C and 2 × 2′-C-furans), 154.3 (9-C), 158.8 (5-C); MS: m/z (EI) (%): 293 (21) [M$^+$], 292 (32), 278 (17), 263 (44), 197 (11), 131 (100), 67 (26).

3,4-Difur-2′-yl-6-phenylfuro[2,3-c]pyridazine (**13b**) was obtained (3:7, v/v) as yellow crystals (270 mg, 21% yield), m.p. 148–150°C (acetone). Anal. calcd. for $C_{20}H_{12}N_2O_3$ (328.33): C, 73.16; H, 3.68; N, 8.53. Found: C, 73.23; H, 3.61; N, 8.42%. IR: 1595, 1610 (C=C, furans). ^{1}H NMR (d_6-DMSO): δ 6.42–6.78 (m, 5H, 5-CH & 2 × ($H^{3'}$, $H^{4'}$), furans), 7.28–8.24 (m, 7H, 2 × $H^{5'}$, furans & H-phenyl); ^{13}C NMR ($CDCl_3$/d_6-DMSO): δ 106.4 (5-C), 106.77, 106.8, 110.5, 110.9 (2 ×

(3′-*C*& 4′-*C*), furans), 117.8, 120.8, 129.2, 134.6 (*C*=*C*, Ph), 128.8 (9-*C*), 140.6, 142.4, 143.4, 144.1, 147.6 (2 × 5′-*C*-furans & 4-*C*, 3-*C*), 150.7, 151.4 (2′-*C*-furans), 153.6 (6-*C*), 155.1 (8-*C*); MS: *m/z* (EI) (%): 328 (55) [M^+], 327 (33), 262 (27), 196 (100), 67 (35).

3,4-Difur-2′-yl-7-phenyl-5H-pyrano[2,3-c]pyridazine-5-imine (**15b**) was obtained (AcOEt) as brown needles (560 mg, 40% yield), m.p. 285–287°C ($CHCl_3$). Anal. calcd. for $C_{21}H_{13}N_3O_3$ (355.36): C, 70.98; H, 3.69; N, 11.82. Found: C, 71.08; H, 3.63; N, 11.71%. IR: 3325 (NH, weak), 1618 (C=NH). ^{1}H NMR ($CDCl_3$/d_6-DMSO): δ 6.03 (s, 1H, 6-C*H*-pyran), 6.42–6.73 (2d(m),2 × 4H, $H^{3'}$, $H^{4'}$, furans), 7.24–8.13 (m, 7H, 2 × $H^{5'}$-furans and *H*-phenyl), 8.74 (s br, 1H, =N*H*); ^{13}C NMR ($CDCl_3$/d_6-DMSO): δ 106.3, 106.8, 108.2, 110.3, 110.7 (6-*C* & 2 × (3′-*C*, 4′-*C*), furans), 118.7, 121.0, 129.3, 135.4 (*C*=*C*, Ph), 128.1 (10-*C*), 141.2, 141.6, 144.3, 144.8 (2 × 5′-*C*, furans, 4-*C*, and 3-*C*), 148.9, 151.5 (2 × 2′-*C*-furans), 153.6 (7-*C*), 155.2 (9-*C*), 158.8 (5-*C*); MS: *m/z* (EI) (%): 355 (17) [M^+], 354 (26), 353 (29), 340 (22), 274 (31), 208 (100), 67 (24).

When the above reactions, between **1** and **4c** (or **4d**), using the same amounts, was refluxed in $CHCl_3$/H_2O/LiOH solution for 100 h under the same conditions and working up previously described for the reaction **1** with **4a** (and **4b**), compounds **13a** (100 mg, 10% yield) and **15a** (265 mg, 23% yield) or **13b** (167 mg, 13% yield) and **15b** (265 mg, 23% yield) were isolated and characterized (m.p., mixed m.p., and comparative spectra).

No reaction was observed when equimolar amounts of **1** and **3a** (or **3b**) were refluxed in dry toluene (or dry ethyl acetate), even after 3 days.

Reaction of 1 with Cyanomethylene(triphenyl)phosphorane (3e)

A solution of 1.52 g phosphonium chloride **4e** (4.5 mmol) and 1 g of pyridazine **1** (3.95 mmol) in 30 mL $CHCl_3$ was treated with 12 mL LiOH (0.5 M) for 1 h at room temperature, and then refluxed for 24 h. The mixture was worked up as described for the reactions **4a** (or **4b**) and separated by column chromatography using AcOEt and then EtOH as the eluents.

5-Amino-3,4-difur-2-ylfuro[2,3-c]pyridazine-6-carbonitrile (**17**) was obtained (AcOEt) as pale-brown crystals (340 mg, 30% yield), m.p. 198–200°C ($CHCl_3$). Anal. calcd. for $C_{15}H_{18}N_4O_3$ (292.26): C, 61.64; H, 2.76; N, 19.17. Found: C, 61.68; H, 2.70, N, 19.07%. IR: 3459, 3342 (NH_2), 2212 (CN). ^{1}H NMR (d_6-DMSO): δ 5.94, 5.95 (2d, J_{HH} = 6.5, 2 × 1H, NH_2), 6.48, 6.70 (2d, J_{HH} = 3.5, 4H, 2 × ($H^{3'}$, $H^{4'}$), furans), 7.41, 7.95 (2d, J_{HH} = 3.5, 2H, 2 × $H^{5'}$-furans); ^{13}C NMR ($CDCl_3$/d_6-DMSO): δ 106.3,

106.8, 110.3, 110.7 (2 × (3′-*C*, 4′-*C*), furans), 117.4 (*C*N), 128.1 (9-*C*), 140.7 (5-*C*), 141.2, 143.4, 144.1, 144.5 (2 × 5′-*C*, furans, 4-*C*, and 3-*C*), 150.2, 151.5 (2 × 2′-*C*,furans), 153.6 (6-*C*), 155.2 (8-*C*); MS: *m/z* (EI) (%): 292 (23) [M^+], 276 (27), 241 (44), 250 (11), 184 (36), 160 (14), 118 (55), 67 (30).

(5,6-difur-2-yl-3-oxo-2,3-dihydropyridazin-4-yl)(triphenylphosphanylidene) acetonitrile (**16**) was obtained (ethyl alcohol) as brown powder (680 mg, 33% yield), m.p. 289–291°C (EtOH). Anal. calcd. for $C_{32}H_{22}N_3O_3P$ (527.53): C, 72.86; H, 4.20; N, 7.97; P, 5.87. Found: C, 72.74; H, 4.13; N, 7.88; P, 5.93%. IR: 3360 (NH), 2212 (CN), 1654 (C=O, amide), 1682, 1505 (C=P). ^{1}H NMR (d_6-DMSO): δ 6.46, 6.76 (2d, J_{HH} = 3.5, 4H (2 × $H^{3'}$ & $H^{4'}$), furans), 7.36–7.95 (m, 17H, 2 × $H^{5'}$-furans & *H*-phenyl), 12.98 (br, 1H, N*H*); ^{13}C NMR ($CDCl_3$/d_6-DMSO): δ 88.7 (d, $^1J_{CP}$ = 104.6, *C*=PPH_3), 106.3, 107.6, 110.6, 110.5 (2 × (3′-*C* & 4′-*C*), furans), 117.4, 118.3, 118.7, 121.0, 122.4, 123.6, 129.3, 133.2, 133.8, 135.4 (*C*N, *C*=*C*, Ph & 4-*C*), 141.4, 144.9 (5-*C*, and 6-*C*), 146.9, 150.7 (2 × 5′-*C*-furans), 172.4 (3-*C* =O); ^{31}P NMR (d_6-DMSO): δ 14.88 ppm; MS: *m/z* (EI) (%): 527 (9) [M^+], 501 (14), 265 (38), 239 (100), 199 (26), 133 (42), 67 (27).

No reaction was observed when equimolar amounts of **1** and **3e** were refluxed in dry toluene (or dry ethyl acetate), even after 3 days.

Wittig Reaction of the Produced Ylide 16

To a solution of 0.5g **16** (0.95 mmol) in 15 mL ethyl acetate containing 0.3 mL TEA (1.3 mmol), 160 mg benzaldehyde (1.5 mol) was added. The reaction mixture was refluxed for 10 h and then the volatile materials were removed under the reduced pressure. Extraction of the residual substance with hot petroleum (*boiling range*, 60–80°C) gave on cooling Ph_3PO, m.p. 155–156°C. Crystallization of the residue from acetone yielded *2-(5,6-difur-2′-yl-3-oxo-1,3-dihydropyridazin-4-yl)-3-phenylacrylonitrile* (**18**) (175 mg, 52% yield), m.p. 212–214°C. Anal. calcd. for $C_{21}H_{13}N_3O_3$ (355.36): C, 70.98; H, 3.69; N, 11.82. Found: C, 70.92; H, 3.64; N, 11.71%. IR: 3360 (NH), 2219 (CN), 1654 (C=O, amide), 1613 (C=C, exocyclic); ^{1}H NMR (d_6-DMSO): δ 5.85 (s, 1H, =C*H*, exocyclic), 6.35–6.90 (m, 4H, 2 × ($H^{3'}$-, $H^{4'}$), furans), 7.36–8.14 (m, 7H, 2 × $H^{5'}$-furans and *H*-phenyl), 12.85 (br, 1H, N*H*); ^{13}C NMR ($CDCl_3$/d_6-DMSO): δ 98.8 (*C*-CN), 106.3, 108.6, 110.6, 110.5 (2 × 3′-*C*, 4′*C*, furans), 117.7 (*C*N), 118.7, 122.4, 133.7, 135.4 (*C*=*C*, Ph & 4-*C*), 141.4, 142.4, 144.6, 144.9 (2 × 5′-*C*, furans, 5-*C*, and 6-*C*), 146.9, 148.9, 150.7 (*C*HPh & 2 × 2′-*C*-furans), 174.2 (3-*C*=O); MS: *m/z* (EI) (%): 355 (25) [M^+], 329 (33), 327 (7), 301 (16), 265 (100), 223 (60), 67 (18).

Reactions of 2-[(Benzylidene)amino]benzonitrile (2) with ylides 3a, 3b, 3c, 3d, and 3e

Preparation of Compounds 22, 23, and 24

A stirred solution of 0.8g **2**[15] (3.88 mmol) and the appropriate ylide **3a**, **3b**, **3c**, **3d**, and **3e** (4.1 mmol) in 20 mL $CHCl_3$ containing 0.5 mL piperidine was boiled under reflux for 40–60 h (TLC). The pale-yellow material that precipitated was collected, crystallized from EtOH, and identified as 2-*[(triphenylphosphoranylidene)amino]benzonitrile* (**23**) (~ 20% yield), m.p. 149–151°C (lit.,[16] m.p. 149–151°C).

The filtrate was evaporated under reduced pressure and the residue was separated by column chromatography on silica gel. Elution with n-hexane yielded the corresponding known *E*-olefin **24a**, **24b**, **24c**, **24d**, and **24e**.

Methyl trans-cinnamate (**24a**) was obtained as colorless liquid, b.p. 260–262°C (lit.,[21a] b.p. 260–262°C).

Ethyl trans-cinnamate (**24b**) was obtained as colorless liquid, b.p. 126–130°C/6 m (lit.,[21b] b.p. 126–131°C/6 mm).

Benzylidene-acetone (**24c**) was dissolved in 95% EtOH and the solution was treated with an aqueous solution of 2,4-dinitrophenylhydrazinium sulfate. The precipitate was recrystallized, m.p. 218–220°C (EtOH) and was identified as benzalacetone-2,4-dinitrophenylhydrazone [lit.,[22] m.p. 218–220°C, (EtOH)].

Benzylidene-acetophenone (**24d**) was obtained as pale-yellow crystals, m.p. 55–57°C (dilute EtOH) [lit.,[23a] m.p. 55–56°C (dilute EtOH].

Cinnamonitrile (**24e**) was obtained as a colorless liquid, TLC, comparative IR, and mass spectra with a commercial sample (lit.[23] b.p. 137–138°C/19 mm).

-Elution with *n*-hexane/$CHCl_3$ (~2:8 v/v) yielded 4-hydroxyquinolines **22a**, **22b**, **22c**, **22d**, and **22e**.

Methyl 4-hydroxy-2-phenylquinoline-3-carboxylate (**22a**) was obtained as pale yellow crystals (454 mg, 42% yield), m.p. 276–278°C (MeOH). Anal. calcd. for $C_{17}H_{13}NO_3$ (279.30): C, 73.11; H, 4.69; N, 5.01. Found: C, 73.03; H, 4.62; N, 5.11%. IR(KBr)/cm^{-1}: 3248 (NH), 1712 (C=O, ester), 1645 (C=O, quinolinone). ^1H NMR ($CDCl_3$): δ 3.72 (s, 3H, OCH_3), 7.28–7.74 (m, 5H), 8.34–8.47 (m, 4H), 10.29 (s br, 1H, O*H*); MS: *m/z* (EI) (%): 279 (77) [M^+], 278 (100), 263 (14), 219 (29), 200 (15), 77 (18).

Ethyl 4-hydroxy-2-phenylquinoline-3-carboxylate (**22b**) was obtained as pale-yellow crystals (510 mg, 45% yield), m.p. 260–262°C from MeOH (lit.,[18] m.p. 260–261°C).

3-Acetyl-4-hydroxy-2-phenylquinoline (**22c**) was obtained as yellow needles (378 mg, 37% yield), m.p. 292–294°C (EtOH). Anal. calcd. for

$C_{17}H_{13}NO_2$ (263.30): C, 77.55; H, 4.98; N, 5.32. Found: C, 77.63; H, 4.88; N, 5.28%. IR: 3437 (OH), 1672 (C=O, acetyl); ^{1}H NMR ($CDCl_3$): δ 2.25 (s, 3H, C*H*$_3$, acetyl), 7.31–7.79 (m, 5H, *H*-Ph), 8.27–8.44 (m, 4H, *H*-Ph), 10.84 (br, 1H, O*H*); ^{13}C NMR ($CDCl_3$): δ 26.3 (C(O)*C*H$_3$), 101.4 (5-*C*), 119.7, 121.4, 125.2, 126.4, 128.3, 133.4 (7-*C*, 10-*C*, 6-*C* & *C*=*C*, Ph), 137.3 (3-*C*), 143.7 (9-*C*), 151.2 (4-*C*), 169.6 (2-*C*), 197.4 (*C*(O)Me); MS: *m/z* (EI) (%): 263 (87) [M$^+$], 262 (100), 235 (23), 220 (31), 143 (48), 77 (25).

3-Benzoyl-4-hydroxy-2-phenylquinoline (**22d**) was obtained as pale-yellow crystals (500 mg, 40% yield), m.p. 240–242°C (benzene). Anal. calcd. for $C_{22}H_{15}NO_2$ (325.37): C, 81.21; H, 4.65; N, 4.31. Found: C, 81.28; H, 4.57; N, 4.24%. IR: 3462 (OH), 1654 (C=O, benzoyl). ^{1}H NMR ($CDCl_3$): δ 7.25–7.82 (m, 9H, *H*-Ph), 8.07–8.33 (m, 5H, *H*-Ph), 9.97 (s br, 1H, O*H*);^{13}C NMR ($CDCl_3$): δ 26.3 (C(O)*C*H$_3$), 108.5 (5-*C*), 119.2, 121.4, 122.8, 123.4, 125.4, 126.7, 129.8, 133.4, 134.4 (6-*C*, 7-*C*, 10-*C* & *C*=*C*, Ph), 133.7 (3-*C*), 144.6 (9-*C*), 150.3 (4-*C*), 166.3 (2-*C*), 178.7 (*C*(O)Ph); MS: *m/z* (EI) (%): 325 (100) [M$^+$], 326 (55), 297 (36), 248 (9), 210 (45), 77 (22).

3-Cyano-4-hydroxy-2-phenylquinoline (**22e**) was obtained as yellow crystals (360 mg, 38% yield), m.p. 223–225°C ($CHCl_3$). Anal. calcd. for $C_{16}H_{10}N_2O$ (246.27): C, 78.03; H, 4.09; N, 11.38. Found: C, 78.09; H, 4.01; N, 11.30%. IR: 3450 (OH), 2212 (CN), ^{1}H NMR ($CDCl_3$): δ 7.25–8.34 (m, 9H,*H*-Ar and *H*-Ph), 11.42 (s br, 1H, O*H*); ^{13}C NMR ($CDCl_3$): δ 110.2 (5-*C*), 112.3 (3-*C*), 117.9 (*C*N), 119.6, 121.8, 124.1, 125.6, 128.5, 134.7, (6-*C*, 7-*C*, 10-*C* & *C*=*C*, Ph), 144.6 (9-*C*), 153.3 (4-*C*), 167.6 (2-*C*); MS: *m/z* (EI) (%): 246 (52) [M$^+$], 221 (100).

B-Wittig Reaction of Iminophosphorane 23

To a solution of 0.5 g **23** (1.32 mmol) in 20 mL AcOEt containing 0.3 mL TEA, 160 mg benzaldehyde (1.5 mmol) was added, and the mixture was refluxed for 10 h. After the removal of the volatile materials under reduced pressure, the residual substance was extracted with hot petroleum ether (b.r. 60–80°C). Concentration of the extracts and cooling afforded Ph_3PO. Crystallization of the residue from pentane afforded yellow crystals of 2-(benzylideneamino)benzonitrile (**2**) (114 mg, 42% yield), m.p. 109–111°C (hexane); [lit.,[15] m.p. 109–111°C (hexane)].

C-Alkaline Treatment of 23

A mixture of 0.5 g **23** and 20 mL Na_2CO_3 (15% *aqueous*) was heated under reflux for 1 h. The mixture was cooled, diluted with distilled H_2O (5 mL), and extracted with $CHCl_3$. The residue that was obtained, on removal of chloroform, was boiled with light petroleum ether to give

anthranilonitrile as yellow crystals, m.p. 47–49°C (light petroleum); [lit.,[24] m.p. 46–48°C (light petroleum)].

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