

Synthetic Studies Using Unsaturated and Active Phosphonium Salts. A Convenient Preparation of Furano- and Pyrano[2,3-*c*]pyridazines and Substituted Quinolines

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Received 3 March 2004; revised 15 September 2004

ABSTRACT: By applying vinyl- (**3**) and allyltriphenylphosphonium bromides (**9**) to 4-cyano-5,6-difur-2'yl-2*H*-pyridazin-3-one (**1**) the corresponding fused 5,8-oxazolo- **6**, **12** (~37%) and pyrano- **8**, **13**, **14** (~20%) derivatives are isolated whereas with alkylphosphonium bromides **15a,b** fused furans **17a,b** (22%) and isopyrroles **18a,b** (~45%) are obtained. On the other hand, the reaction of 2-[(benzylidene)amino]benzonitrile (**2**) with **3** and **9** yielded benzoazepines **20** and **21** (~56%). With **15a,b**, quinolines **23a,b** (~46%) and quinazoline **25** (~24%) are obtained.
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INTRODUCTION

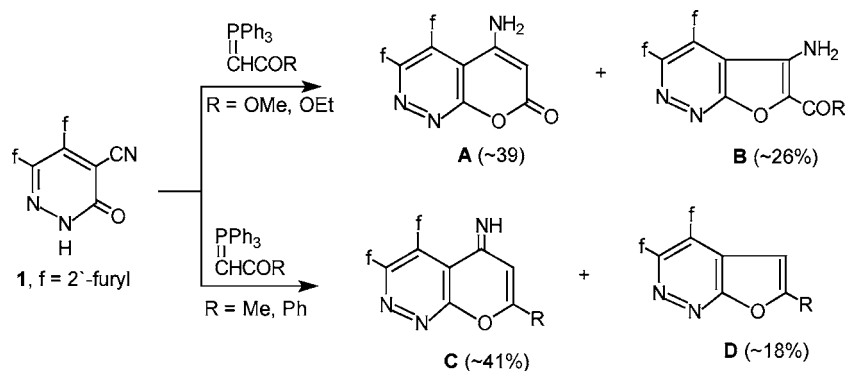
In one of our previous studies [1] on the synthesis of new biologically active heterocycles based on known drug skeletons from alkylidenephosphoranes as starting synthons and substrates that bear carbon–

nitrogen multiple bonds, we reported that the reaction of 4-cyano-5,6-difur-2'yl-2*H*-pyridazin-3-one (**1**) with resonance-stabilized ylides resulted in the formation of a series of fused pyrano and furano [2,3-*c*]pyridazine derivatives [2] (Scheme 1).

On contrary, application of such reagents to 2-[(benzylidene)amino]benzonitrile (**2**) afforded, in all cases, quinoline derivatives in reasonable yields as the major products [2] (Scheme 2).

It has been pointed out [2] that the reaction of **1** with such ylides proceeded only when the latter were generated in situ from the corresponding phosphonium salts in the presence of ~4 excess LiOH or LiH. The findings highlighted the inertness of molecule **1**, which was attributed to the low reactivity of the nitrile function and the amidic carbonyl group toward nucleophilic attack. The thermal condition, coupled with the presence of an excess of a strong base, used for the generation of ylide, however, deprotonates either the ylide or the pyridazinone promoting thus a further reaction. Such interesting results encouraged us to examine the reaction of unsaturated- **3**, **9**, and active phosphonium bromides **15a,b** with these two nitriles **1** and **2**. The program aimed at synthesizing heterocycle patterns condensed with pyridazine or phenyl moieties required for a biological chemistry program.

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SCHEME 1

RESULTS AND DISCUSSION

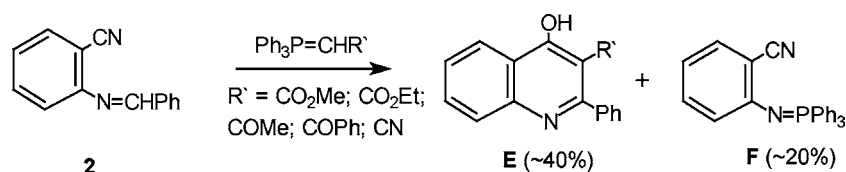
Treatment of **1** with an equimolar amount of vinyltriphenylphosphonium bromide (**3**) in a mixture of $\text{LiOH}/\text{H}_2\text{O}/\text{EtOH}$ yielded 2,3-difur-2'-yl-4-cyano-5,8-oxazolo[2,3-*b*]-1,2-dihydropyridazine (**6**, 36%) and 5-amino-3,4-difur-2'-ylpyrano[2,3-*c*]-1,2-dihydropyridazine (**8**, 23%).

Structures **6** and **8** were assigned to the isolated products on the basis of their elemental analyses, IR, ^1H , ^{13}C NMR, and mass spectral data. Thus, the ^1H NMR spectrum of **6** exhibited the characteristic resonances for the oxazole ring system (δ_{H} 6.57 and 7.79) along with resonances corresponding to the furan rings and NH (δ 5.23). Its ^{13}C NMR spectrum displayed the oxazole carbon resonances at δ 118.8 (7-*C*), 145.4 (6-*C*), 154.8 (9-*C*) and the cyano group at 100.6 (4-*C*), 117.7 (CN). The MS spectrum of **6**, as expected, confirms its molecular weight. Initial fragmentation involves loss of C_2H_2 and scission of the rings. On the other hand, the IR spectrum of **8** showed strong broad bands at 3366, 3253 cm^{-1} due to free NH_2 and the nearly complete disappearance of nitrile and carbonyl bands; its ^1H NMR spectrum showed a singlet at δ 5.78 due to the amino protons. The methylene protons in **8** are nonequivalent, and the shift between them is small compared with geminal coupling constant. Thus, the *AB* system pattern is quite distorted, and the net result is three peaks in the range δ 4.25–4.38. The methine proton on 6-*C* appeared as an ill defined two pairs ($J = 1.8$ Hz)

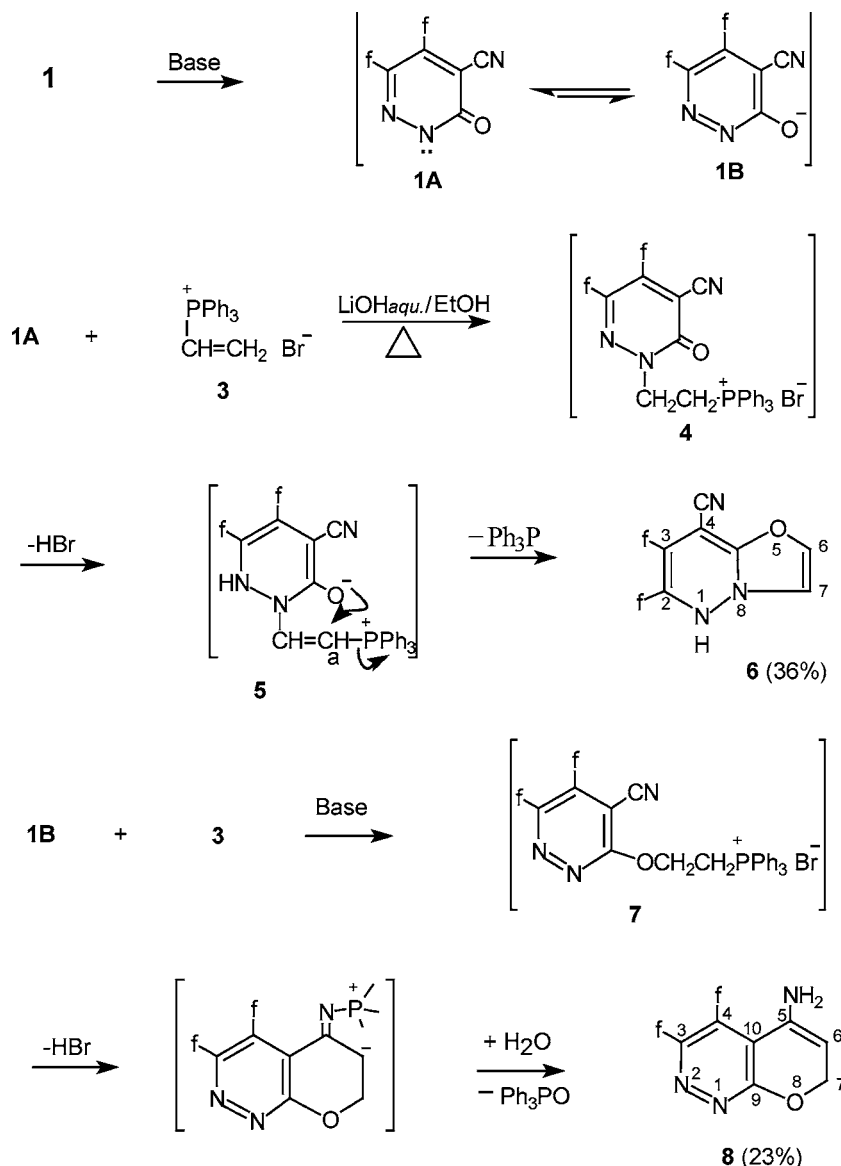
in the range δ 6.18–6.23. Further evidence was obtained from the ^{13}C NMR spectrum, which displayed the methylene carbon resonance at δ_{C} 68.7 and 6-*C* at 133.2 ppm.

Obviously, the product **6** is produced via the corresponding intermediate **4**, suggested by Yavari et al. [3] for the synthesis of 1*H*-pyrrolizines by treating pyrrole-2-carbaldehyde with vinylphosphonium salts. Then, extrusion of hydrogen bromide from **4** and prototropic rearrangement, phosphonium ylide **5** occurs. This is followed by an attack of the enolate oxygen on α -carbon [4] with the simultaneous expulsion of triphenylphosphine yielding **6** (Scheme 3). Synthesis of the nitrogen bridgehead heterocycles is of interest because they constitute an important class of natural and nonnatural products, many of which exhibit useful biological activity [5]. In contrast, the fused pyran **8** resulted from an initial addition of the anion **1B** [6] to **3** to form the phosphonium salt **7**. Further attack of the ylide on the carbon–nitrogen triple bond [7] and hydrolysis leads to the formation of **8** (Scheme 3). An analogous mechanism has been previously reported by Schweizer et al. [8] for the reaction of vinylphosphonium bromide **3** with anthranilonitrile.

A similar treatment of **1** with one equivalent of allyltriphenylphosphonium bromide (**9**) afforded 2,3-difur-2'-yl-4-cyano-7-methyl-5,8-oxazolo[2,3-*b*]-pyridazine (**12**, 39%) along with 3,4-difur-2'-yl-7-methyl-5*H*-5-iminopyrano[2,3-*c*]-1,2-dihydropyridazine (**13**, 13%) and its oxidation form, pyranone



SCHEME 2

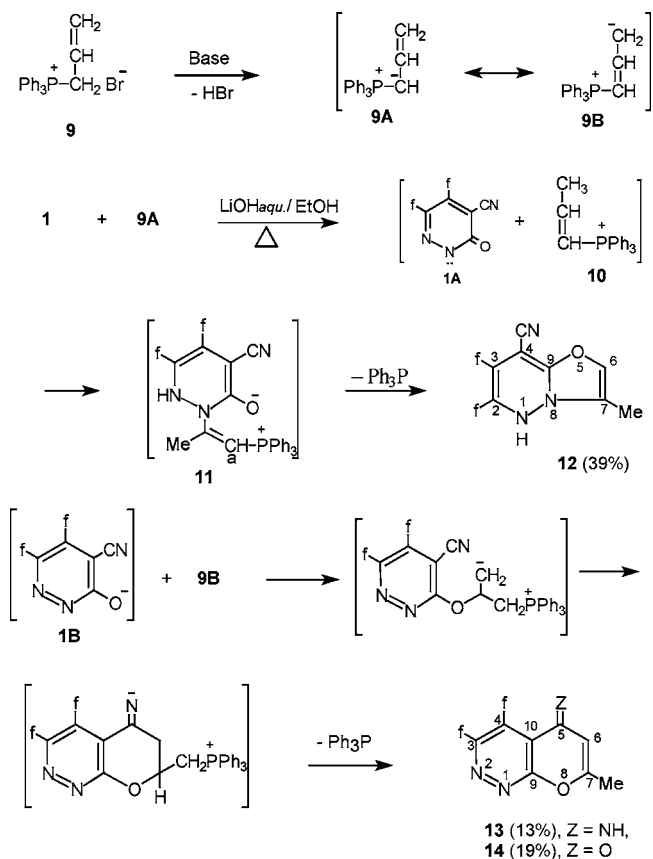


SCHEME 3

14 (19%) (Scheme 4). Iminopyran **13** was identical in all aspects with material previously obtained from the reaction of **1** with 2-(oxopropyl)-(triphenyl)phosphorane (C-Scheme 2 [2]). Further treatment of **13** with alkali afforded **14** in 72% yield. The formation of **12** can be rationalized, as with the reaction between **1** and **3**, through the attack of the initially formed nitrogen anion **1A** on the β -carbon atom in **10**, to generate the phosphorane **11**. Further attack of the enolate oxygen on α -carbon [4] with concomitant elimination of triphenylphosphine would produce the final product **12**. The electrophilic attack of an electrophile at the central atom of the allyl group in **10** is a documented process [9]. Meanwhile, iminopyran

13, most probably, derived from the attack of the parallelly formed oxygen anion **1B** on the β -carbon atom of **9B** to form the phosphorane, which is converted into **13** via an intramolecular cyclization [1f, 8], according to Scheme 4. Finally **14** is regarded as the oxidized form of **13** through the hydrolysis. A similar transformation is known for the imino function to the keto-structure [10].

In contrast, when a DMF solution of an equimolar amount of **1** and methylenetriphenylphosphorane, prepared in situ from its bromide salt **15a**, in the presence of lithium hydride, was heated under reflux, the reaction was not complete, even after 2 days. On repetition of the reaction between **1** and an excess (up to 2 equiv.) of **15a** in refluxing DMF,



SCHEME 4

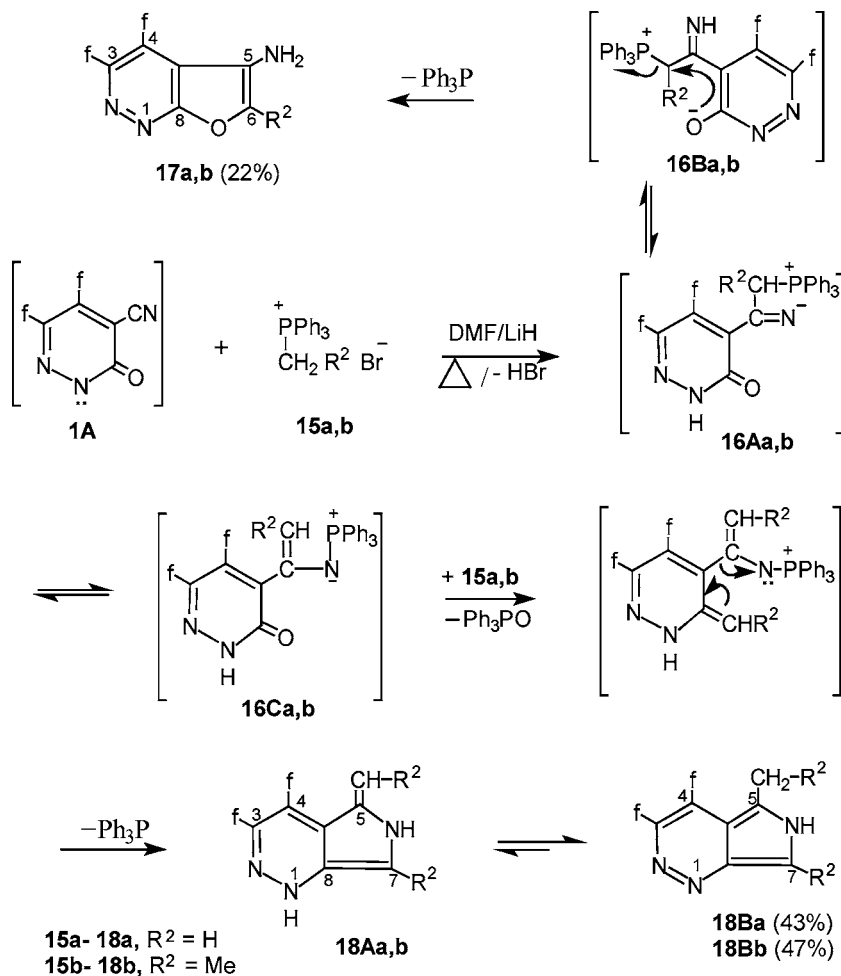
containing LiH, for 30 h afforded 5-amino-3,4-difur-2-ylfurano[2,3-*c*]-1,2-dihydropyridazine (**17a**, 22%) and 5-methyl-3,4-difur-2-yl-6*H*-isopyrrolo[2,3-*c*]-1,2-dihydropyridazine (**18a**, 43%) (Scheme 5).

The reaction products of **1** with ethyltriphenylphosphonium bromide (**15b**) under the same conditions were assigned analogous structures **17b** (22%) and **18b** (47%) on the basis of comparable spectroscopic arguments. The chemical structures of **17** and **18** were delineated from their spectroscopic properties. Thus, the IR spectrum of **17a** showed the characteristic band due to the amino group at 3054 and 2853 cm^{-1} and the disappearance of the bands at ~ 2230 and ~ 1650 cm^{-1} corresponding to CN and C=O groups in **1** [6]. On the other hand, the spectroscopic data indicated that **18b** is tautomeric with **18A**, since its IR spectrum revealed two strong broad bands at 2922 and 2854 cm^{-1} due to 1- and 6-NH groups in **18Aa**. A sharp and strong band also appeared at 1619 cm^{-1} due to the exocyclic double bond in **18Aa**. The ^1H NMR spectrum showed two signals at 1.95 (s, 3H) and 4.87 (s, 2H) ppm due to the methyl in **18Ba** and the methyldene protons in **18Aa**. Two broad signals appeared at 4.57 (br, 1H) and at 5.25

(br, 1H) due to the two NH in **18Aa**. However, the structure of **18Ba** is confirmed from ^{13}C NMR data, which is consistent with the equilibrium **18Aa** $\rightleftharpoons$ **18Ba** and showed signals among others, at 13.7 (CH_3), 112.2 ($=\text{CH}_2$). However, the results of the spectroscopic interpretation for **18Ba** indicate that both isopyrrolidene form **18A** and its isopyrrole tautomer **18B** present in equilibrium although structure **18B** should be more stable and in turn more preferable on steric hindrance reasons. The formation of the products **17** and **18** may be envisaged as occurring via the previous workers [2,7b,10,11] suggested structure **16** for the intermediate of the reaction between nitriles and ylides. Further intramolecular attack of the anionic oxygen on the ylidic carbon in **16B** afforded the fused furan **17**. On the other hand, Wittig olefination of **16C** with a second ylide species, followed by intramolecular cyclization and the loss of Ph_3P , led to the formation of **18A** $\rightleftharpoons$ **18B**. Olefination of the amidic carbonyl group in **1** with active ylides ($\text{Ph}_3\text{P}=\text{CHR}^2$) is not surprising since it has been reported that *N*-phenyl substituted pyridazinone derivative undergoes olefination reaction with resonance-stabilized phosphorus ylides [12].

In summary, the findings from the reactions of pyridazinone carbonitrile **1** with unsaturated- and nonstabilized ylides, which have been reported in the present investigation, or with stable ylides that are reported in the earlier work [2], highlight the initial attack by alkylidenephosphoranes would vary with the electronic characteristics of the phosphorus reagent. Considering the previous report [2], the common feature of the reactions of ester and keto ylides with **1** seemed to be proceeding via the initial attack on the nitrile group (Scheme 1). Conversely, the involvement of pyridazine portion (Schemes 3, 4) and the amidic carbonyl group (Scheme 5) in the reactions of **1** with unsaturated and active ylides have also been observed.

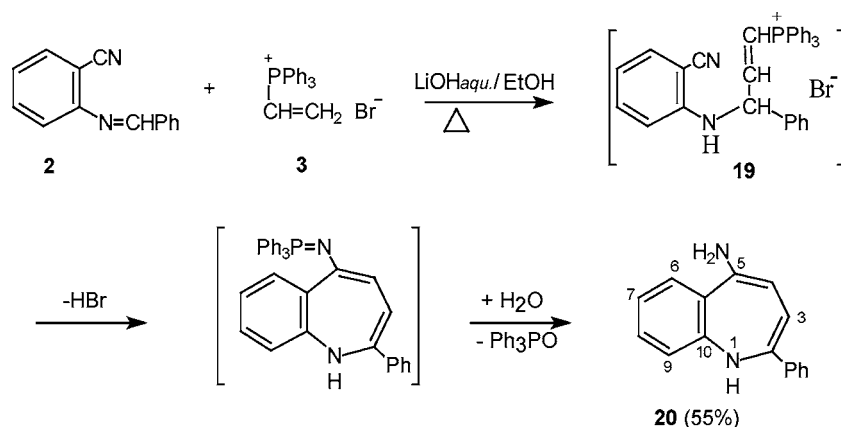
Next, the behavior of 2-[(benzylidene)amino]-benzonitrile (**2**) toward the same unsaturated- and nonstabilized ylides was investigated (Schemes 6–8). When **2** was caused to react with one equivalent of the phosphonium bromide **3** in a mixture of $\text{LiOH}/\text{H}_2\text{O}/\text{EtOH}$ yielded 5-amino-2-phenylbenzoazepine (**20**), advantageously, in 55% yield (see Scheme 6). Compound **20** may be regarded as a product of an intramolecular Wittig-type reaction [7]. Such an addition-cyclization product apparently results from the initial addition of **3** to the azomethine portion of **2**, giving the ylide **19**. Further attack of the ylidic carbon on the nitrile group and hydrolysis would lead to the formation of **20** [7], as it is discussed for the formation of **8** from the reaction of **1** with **3**.



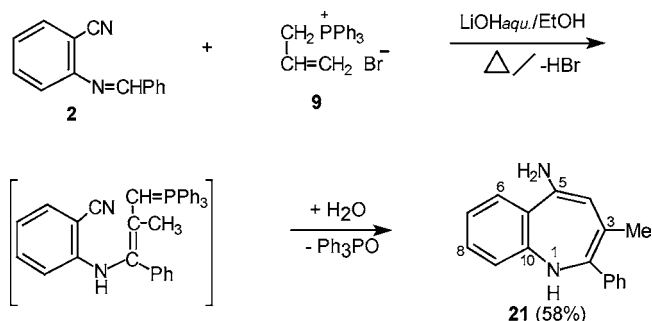
SCHEME 5

Similar to **20**, this synthesis was extended to 5-amino-3-methyl-2-phenylbenzazepine (**21**, 58%), which was readily obtained by allowing anil **2** to react with **9** in ethanol containing LiOH solution (0.5 M) according to Scheme 7.

Finally, the heating of **2** with one equivalent alkyltriphenylphosphonium bromides **15a,b** in DMF under reflux with a catalytic amount of LiH gave the known substituted quinolines **23a** [13] or **23b** [14](~43%) along with 4-amino-3-(2-benzonitrile)-



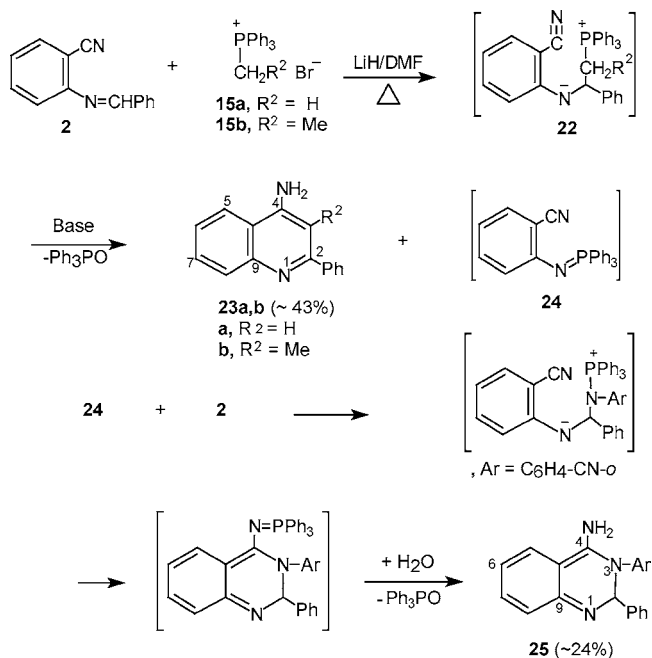
SCHEME 6



SCHEME 7

2-phenyl-1-hydroquinazoline (**25**) (~24%). A reasonable mechanistic explanation of these transformations involves the expected initially formed zwitterion **22**, which leads to **23a,b**, in the usual pathway, and 2-[(triphenylphosphorylidene)amino]-benzonitrile, which resulted from partial collapse of **22** [2]. In contrast to the reaction between **2** and resonance-stabilized ylides (Scheme 2), the iminophosphorane **24** could not be isolated. Instead, it underwent an addition-cyclization reaction with the Schiff's base **2** to give the final adduct **25** as shown in Scheme 8.

Summarizing, although the initial step in all of the present (Schemes 6–8) and previous work (Scheme 2 in [2]) is nucleophilic attack by the carbanions at the azomethine portion in **2**, the consequences of the initial step vary markedly according



SCHEME 8

to the structure of the phosphoranes. It is worth mentioning here that the methods previously described for the preparation of substituted quinolines **23a** [13] and **23b** [14] are lengthy and indirect. For example compound **23b**, which is patented as new type calcium channel antagonist for the treatment of pain, was synthesized by the condensation of isatin and propiophenone in ethanol containing KOH pellets to give 3-methyl-2-phenyl-4-quinolinecarboxylic acid. The latter could be converted to the corresponding amine **23b** after multistep synthesis [14]. In the present context, **23b** (45%) could be available by a one step synthesis from the reaction of the proper anilide with **15b**.

CONCLUSION

The previously noted observations show that the earlier [2] studied reactions of **1** and **2** with resonance-stabilized ylides can be considerably extended. Moreover, application of alkylidene-phosphoranes to the substrates **1** and **2** provide an easy route, not only for the expected fused O- and N-heterocycles, but also for N-bridgehead nitrogen heterocycles, for example, **6** and **12** and quinazoline **25**. Data on the pharmaceutical potency of the new compounds will be published elsewhere.

EXPERIMENTAL SECTION

The melting points are uncorrected. The IR spectra were recorded on a Perkin Elmer spectrophotometer model 297 (Grating) using KBr disks. The ¹H and ¹³C NMR spectra were run in CDCl₃ or d₆-DMSO as solvents on a Jeol-270 MHz instrument, using SiMe₄ as an internal reference. The ³¹P NMR spectra were recorded relative to external H₃PO₄ (85%) with a Varian CFT-20 instrument. The mass spectra were performed at 70 eV on a Shimadzu GCS-QP 1000 EX spectrometer provided with a data system. The appropriate precautions in handling moisture-sensitive compounds were observed. Solvents were dried by standard techniques. Light petroleum refers to the fraction 40–60°C.

Reaction of 4-Cyano-5,6-difur-2'-yl-2H-pyridazin-3-one (**1**) with Vinyltriphenylphosphonium Bromide (**3**): Preparation of Compounds **6** and **8**

To a stirred solution of 1 g (3.95 mmol) **1** [6] and 1.6 g (4.4 mmol) **3** in 30 mL EtOH, freshly prepared 20 mL LiOH solution (0.5 M) was added in one portion. The reaction mixture was stirred at r.t. for 2 h and then heated under reflux for 36 h (TLC). After removing the solvent, 20 mL of dist. H₂O was added and then extracted with CHCl₃. After evaporation

of the dried CHCl_3 solution, the residue was chromatographed on silica gel using *n*-hexane/ CHCl_3 as the eluents whereupon compounds **6** and **8** were isolated.

2,3-Difur-2'-yl-4-cyano-5,8-oxazolo[2,3-*b*]pyridazine (**6**) was obtained (1:1, v/v) as yellow crystals (395 mg, 36%), mp 144–146°C (from MeCN) (found: C, 64.44; H, 3.17; N, 14.96. $\text{C}_{15}\text{H}_9\text{N}_3\text{O}_3$ (279.26) requires: C, 64.51; H, 3.25; N, 15.05%); ν_{max} (KBr)/ cm^{-1} 3224_w(NH), 2225 (CN), 1610 (C=C, furans); δ_{H} (d_6 -DMSO); 5.23 (s, 1H, NH), 6.57 (d, J_{HH} 4.6 Hz, 1H, 7-CH), 6.77, 7.15 (2d, J_{HH} 4.3 Hz, 4H, 2 × ($H^{3'}$, $H^{4'}$), furans), 7.27, 7.58 (2d, J_{HH} 4.2 Hz, 2H, 2 × $H^{5'}$, furans), 7.79 (d, J_{HH} 3.6 Hz, 1H, 6-CH); δ_{C} (d_6 -DMSO); 100.6 (4-C), 106.6, 106.8, 110.1, 111.2 (2 × (3'-C, 4'-C), furans), 117.7 (CN), 118.8 (7-C), 140.7, 142.1, 144.4, 144.6 (2 × 5'-C, furans and 3-C, 2-C), 145.4 (6-C), 151.8, 152.7 (2'-C, furans), 154.8 (9-C); MS: m/z (EI) (%): 279 (18) [M^+], 278 (13), 253 (100), 227 (42), 160 (24), 83 (56), 67 (28).

5-Amino-3,4-difur-2'-ylpyrano[2,3-*c*]-1,2-hydropyridazine (**8**) was isolated (2:8, v/v) as dark yellow crystals (255 mg, 23%), mp 190–192°C (from EtOH) (found: C, 64.11; H, 3.88; N, 14.86. $\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_3$ (281.27) requires: C, 64.05; H, 3.94; N, 14.94%); ν_{max} (KBr)/ cm^{-1} 3366, 3253 (NH_2), 1610 (C=C, furans); δ_{H} (d_6 -DMSO); 4.25–4.38 (2d, distorted, 2H, 7- CH_2), 5.78 (s_w , 2H, NH_2), 6.18–6.23 (two pairs, J_{HH} 1.8 Hz, 6-CH), 6.71, 7.27 (2d, J_{HH} 4.3 Hz, 4H, 2 × ($H^{3'}$ and $H^{4'}$), furans), 7.63, 7.88 (2d, J_{HH} 4 Hz, 2H, 2 × $H^{5'}$, furyl rings); δ_{C} (d_6 -DMSO); 68.7 (7- CH_2), 106.2, 106.7, 110.2, 110.6 (2 × (3'-C and 4'-C), furans), 128.1 (10-C), 133.2 (6-C), 141.4, 143.6, 145.8 (4-C, 3-C, and 5-C), 151.6, 152.5 (2'-C, furans), 156.6 (9-C); MS: m/z (EI) (%): 281 (100) [M^+], 264 (51), 248 (11), 236 (22), 197 (18), 130 (28), 67 (32).

Reaction of **1** with Allyltriphenylphosphonium Bromide (**9**): A Preparation of Compounds **12**, **13**, and **14**

A stirred solution of 1 g (3.95 mmol) **1** and 1.66 g (4.34 mmol) of **9** in 30 mL EtOH was treated with 10 mL of aqueous LiOH solution (0.5 M). The reaction mixture was heated under reflux for 2 days, and then was worked up as described for the reaction of **1** with **3**. The residue was chromatographed using *n*-hexane/ CHCl_3 as the eluents to give compounds **12**, **13**, and **14**, respectively.

2,3-Difur-2'-yl-4-cyano-7-methyl-5,8-oxazolo[2,3-*b*]pyridazine (**12**) was obtained (1:1, v/v) as yellow crystals (452 mg, 39%), mp 157–159°C (from CH_2Cl_2) (found: C, 65.57; H, 3.72; N, 14.24. $\text{C}_{16}\text{H}_{11}\text{N}_3\text{O}_3$ (293.28) requires: C, 65.52; H, 3.78; N, 14.33%); ν_{max} (KBr)/ cm^{-1} 3205, (NH), 2236 (CN); δ_{H} 1.97 (s, 3H,

CH_3), 5.47 (s, 1H, NH), 6.75, 7.18 (2d, J_{HH} 4.8 Hz, 4H, 2 × $H^{3'}$, $H^{4'}$ -furans), 7.25, 7.58 (2d, J_{HH} 4.4 Hz, 2H, 2 × $H^{5'}$, furans), 7.83 (s, 1H, 6-CH); δ_{C} (CDCl_3); 13.8 (CH_3), 98.6 (4-C), 106.4, 106.7, 110.2, 111.4 (2 × (3'-C, 4'-C), furans), 118.2 (CN), 131.2 (7-C), 142.4, 144.1, 145.8 (3-C, 2-C, 6-C), 147.1, 147.8 (2 × 5'-C, furans), 154.3, 154.9 (2 × 2'-C, furans), 156.7 (9-C); MS: m/z (EI) (%): 293 (47) [M^+], 292 (33), 277 (20), 251 (24), 249 (36), 184 (15), 117 (28), 67 (31).

3,4-Difur-2'-yl-7-methyl-5H-5-iminopyrano[2,3-*c*]-1,2-dihydropyridazine (**13**) was obtained (2:8, v/v) as orange crystals (150 mg, 13%), mp 166–168°C (from benzene) [lit. [2], mp 166–168°C (from benzene)].

3,4-Difur-2'-yl-7-methyl-5H-5-oxopyrano[2,3-*c*]-1,2-dihydropyridazine (**14**) was obtained (CHCl_3 , v/v) as pale yellow needles (220 mg, 19%), mp 186–188°C (from CH_2Cl_2) (found: C, 65.37; H, 3.46; N, 9.55. $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_4$ (294.27) requires: C, 65.31; H, 3.42; N, 9.52%); ν_{max} (KBr)/ cm^{-1} 1728 (C=O), 1610, 1598 (C=C, furyl); δ_{H} (CDCl_3) 2.22 (s, 3H, CH_3), 6.21 (s, 1H, 6-CH), 6.53, 6.85 (2d, J_{HH} 3.6 Hz, 4H, 2 × ($H^{3'}$, $H^{4'}$)-furans), 7.28, 7.89 (2d, J_{HH} 3.8 Hz, 2H, 2 × $H^{5'}$, furans); δ_{C} (CDCl_3) 13.8 (CH_3), 106.6, 107.1, 110.5, 111.2 (2 × (3'-C, 4'-C), 117.3 (6-C), 127.5 (10-C), 140.8, 141.6 (4-C, 3-C), 146.8, 147.3 (2 × 5'-C, furans), 151.4, 152.6, 152.9 (7-C and 2 × 2'-C-furans), 156.3 (9-C), 178.2 (5-C=O); MS: m/z (EI) (%): 294 (100) [M^+], 279 (17), 263 (42), 235 (18), 196 (14), 130 (54), 67 (26).

Oxidation of 13. A mixture of 0.3 g (1.02 mmol) **13** and 20 mL NaOH (15% aq.) was heated under reflux for 3 h. The mixture was cooled, diluted with 5 mL water and extracted with CHCl_3 . After evaporation of the solvent in vacuo, the residual yellow solid was taken up (72%) with a small amount of CH_2Cl_2 and shown to be identical with **14** (TLC, IR, and mass spectra).

Reaction of **1** with Alkylidenetriphenylphosphonium Bromides **15a,b**: Preparation of Compounds **17a,b** and **18a,b**

To a solution of 7.4 mmol of the appropriate salt **15a** (or **15b**) and 1 g (3.95 mmol) of **1** in 30 mL dry DMF, a solution of a slurry of 250 mg of LiH dispersion (57% dispersion in mineral oil) in 10 mL dry DMF was added in one portion. The system was stirred at room temperature for 2 h and was further refluxed for 30 h (TLC). The product mixture was poured into 300 mL distilled water, and extracted with 2 × 100 mL portion of chloroform. The combined organic extracts were backwashed with distd. water (50 mL), dried with Na_2SO_4 and the

solvent was removed under reduced pressure. The residue was chromatographed on silica gel by using *n*-hexane/EtOAc as the eluents whereupon **17a** and **18a** (or **17b** and **18b**) were isolated, respectively.

With 15a. 5-Amino-3,4-difur-2'ylfurano[2,3-*c*]-1,2-dihydropyridazine (**17a**) was obtained (8:2, v/v) as orange crystals (232 mg, 22%), mp 137–139°C (from cyclohexane) (found: C, 62.86; H, 3.35; N, 15.78. $C_{14}H_9N_3O_3$ (267.24) requires: C, 62.92; H, 3.39; N, 15.72%; $\nu_{\max}$ (KBr) cm^{-1} 3054, 2853 (NH₂); δ_H (CDCl₃) 5.78 (s br, 2H, NH₂), 6.68, 6.89 (2d, J_{HH} 3.5 Hz, 4H, 2 × ($H^{3'}$, $H^{4'}$), furans), 7.45, 7.69 (2d, J_{HH} 3.5 Hz, 2H, 2 × $H^{5'}$, furans), 7.74 (s, 1H, 6-CH); δ_C (CDCl₃) 106.3, 106.8, 110.3, 110.7 (2 × (3'-C and 4'-C), furans), 127.2 (9-C), 141.4, 144.6, 145.5 (4-C, 3-C, and 5-C), 147.2 (6-C), 150.6, 151.6 (2 × 2'-C), 154.5 (8-C); MS: m/z (EI) (%): 267 (37) [M^+], 252 (100), 239 (66), 224 (17), 157 (28), 67 (33).

3,4-Difur-2'yl-5-methylisopyrrolo[2,3-*c*]-1,2-dihydropyridazine (**18a**) was obtained (1:1, v/v) as pale brown crystals (450 mg, 43%), mp 175–177°C (from CHCl₃) (found: C, 67.86; H, 4.11; N, 15.75. $C_{15}H_{11}N_3O_2$ (265.27) requires: C, 67.92; H, 4.18; N, 15.84%; $\nu_{\max}$ (KBr) cm^{-1} 2922, 2854 (2 × NH); 1619 (=CH₂, exocyclic); NMR (DMSO): **18Aa** δ_H 4.57, 5.25 (2s, 2 × 1H, 2NH), 4.87 (s, 2H, =CH₂); **18Ba** δ_H 1.95 (s, 3H, CH₃), 6.66–7.89 (m, 7H, 6-CH and *H*-furans); δ_C (CDCl₃) 13.7 (CH₃), 112.2 (=CH₂), 106.4, 106.8, 110.5, 110.9 (2 × (3'-C and 4'-C), furans), 118.5 (7-C), 122.5, 130.6 (8-C and 9-C), 141.1, 141.8, 144.6, 145.2 (2 × 5'-C, furans, 4-C, 3-C), 151.3, 151.6 (2 × 2'-C, furans); MS: m/z (EI) (%): 265 (55) [M^+], 264 (100), 250 (18), 249 (26), 235 (31), 207 (9), 198 (17), 121 (28), 67 (31).

With 15b. The first fraction (8:2, v/v) afforded orange crystals of 5-amino-3,4-difur-2'yl-6-methylfurano[2,3-*c*]-1,2-dihydropyridazine (**17b**) (244 mg, 22%), mp 151–153°C (from MeCN) (found: C, 64.11; H, 3.99; N, 14.86. $C_{15}H_{11}N_3O_3$ (281.27) requires: C, 64.05; H, 3.94; N, 14.94%; $\nu_{\max}$ (KBr) cm^{-1} 3057, 2925 (NH₂); δ_H (CDCl₃) 1.32 (s, 3H, CH₃), 5.75 (s br, 2H, NH₂), 6.66, 6.87 (2d, J_{HH} = 3.5 Hz, 4H, 2 × ($H^{3'}$, $H^{4'}$), furans), 7.46, 7.71 (2d, J_{HH} = 3.5 Hz, 2H, 2 × $H^{5'}$ -furans); δ_C (CDCl₃) 14.2 (CH₃), 106.4, 106.8, 110.2, 110.5 (2 × (3'-C and 4'-C), furans), 127.6 (9-C), 141.6, 143.8, 146.2 (4-C, 3-C, and 5-C), 151.6, 152.2, 154.7, 155.3 (2 × 2'-C, furans, 6-C, 8-C); MS: m/z (EI) (%): 281 (41) [M^+], 266 (41), 253 (33), 252 (100), 224 (16), 157 (21), 137 (31), 90 (29), 67 (36).

The second fraction (1:1, v/v) yielded orange crystals of 3,4-difur-2'yl-6H-5-ethyl-7-methylisopyrrolo[2,3-*c*]-1,2-dihydropyridazine (**18b**) (544 mg, 47%), mp 195–197°C (CHCl₃) (found: C, 69.66; H,

5.22; N, 14.42. $C_{17}H_{15}N_3O_2$ (293.33) requires: C, 69.61; H, 5.15; N, 14.32%; $\nu_{\max}$ (KBr) cm^{-1} 2922, 2852 (2 × NH), 1627 (=CH₂, exocyclic); δ_H (CDCl₃) 0.97–1.32 (m, 2 × 3H, CH₃, **18Ab** and **18Bb**), 2.38 (q, J_{HH} = 6.8 Hz, 2H, CH₂CH₃, **18Bb**), 4.18 (q (ill), 1H, =CHCH₃, **18Ab**), 4.56, 4.68 (2s, br, 2 × 1H, 2NH), 6.64–7.78 (m, 6H, *H*-furans); δ_C (CDCl₃) 14.1, 15.3, 18.2 (2 × CH₃, **18Ab** and **18Bb**) 28.8 (CH₂, **18Bb**) 106.3, 106.8, 110.4, 110.7 (2 × (3'-C and 4'-C), furans), 127.9, 128.3, 129, 130.6, 140.6, 141.6, 143.2, 145.7, 151.2, 152.6, 154.1, 155.8; MS: m/z (EI) (%): 293 (41) [M^+], 292 (100), 278 (10), 263 (19), 248 (35), 232 (16), 220 (45), 149 (24), 67 (33).

The reaction of equimolar amounts of **1** and **15a** (or **15b**) under the same condition, again afforded **17a** (or **17b**) (~14%) and **18a** (or **18b**) (~28%) along with **1** (~20%).

Reaction of 2-[(Benzylidene)amino]benzonitrile (**2**) with Vinyl- (**3**) and Allyltriphenylphosphonium Bromide (**9**): Preparation of Compounds **20** and **21**

A solution of the appropriate salt **3** or **9** (4.1 mmol) and 0.8 g (3.88 mmol) Schiff's base **2** [15] in 30 mL EtOH was treated with 15 mL, and the mixture was heated under reflux for 15 (with **3**), or 20 h (with **9**). The reaction mixture was worked up as described for the reaction of **1** + **3**, and separated by column chromatography, using *n*-hexane-EtOAc yielding compound **20** (from **3**) or **21** (from **9**) and unidentified products.

5-Amino-2-phenylbenzoazepine (**20**) was obtained (6:4, v/v) as yellow prisms (500 mg, 55%), mp 180–182°C (from acetone) (found: C, 82.11; H, 6.09; N, 11.9. $C_{16}H_{14}N_2$ (234.3) requires: C, 82.02; H, 6.02; N, 11.96%; $\nu_{\max}$ cm^{-1} 3446–3255 (NH and NH₂); δ_H (CDCl₃) 5.49 (s br, 1H, NH), 5.77 (s br, 2H, NH₂), 6.23, 6.79 (2d, J_{HH} 4.4 Hz, 3-CH and 4-CH), 7.25–8.13 (m, 9H, *H*-Ph); δ_C (CDCl₃) 111.3 (3-C), 130.78 (4-C), 135.2 (2-C), 121.3, 124.4, 124.9, 126.1, 127.9, 129.6, 131.5 (C=C, Ph), 148.2 (5-C); MS: m/z (EI) (%): 234 (18) [M^+], 233 (22), 219 (40), 193 (100), 77 (55).

5-Amino-3-methyl-2-phenylbenzoazepine (**21**) was obtained (6:4, v/v) as yellow prisms (558 mg, 58%), mp 208–210°C (from EtOH) (found: C, 82.28; H, 6.42; N, 11.34. $C_{17}H_{16}N_2$ (248.33) requires: C, 82.22; H, 6.49; N, 11.28%; $\nu_{\max}$ cm^{-1} 3302, 3061 (NH and NH₂); δ_H (CDCl₃) 1.45 (s, 3H, CH₃) 4.41 (s, 1H, NH), 5.86 (s br, 2H, NH₂), 6.67 (s, 1H, 4-CH), 6.94–7.97 (m, 9H, *H*-Ph); δ_C (CDCl₃) 14.7 (CH₃), 114.6 (4-C), 133.6 (3-C), 136.4 (2-C), 121.6, 122.7, 124.5, 124.9, 126.7, 127.5, 129.8, 131.3 (C=C, Ph), 147.2 (5-C); MS: m/z (EI) (%): 248 (14) [M^+], 249 (19), 233 (52), 218 (27), 193 (100), 77 (62).

Reaction of **2 with Alkyltriphenylphosphonium Bromides **15a,b**: Preparation of Compounds **23a, 23b**, and **25****

A DMF solution of the appropriate salt **15a** or **15b** (4.1 mmol) and the Schiff's base **2** (0.8 g, 3.88 mmol) was treated with LiH under the experimental conditions described above for the reaction of **1** and **15a,b**. The reaction mixture was heated under reflux for 15 h (with **15a**) or 22 h (with **15b**), followed by the usual working up. The product residue was then separated by column chromatography using *n*-hexane-CHCl₃ as the eluents.

*The Reaction of 0.8 g (3.88 mmol) **2** with 1.46 g (4.1 mmol) **15a** Afforded **23a** and **25**.* 4-Amino-2-phenylquinoline (**23a**) was obtained (8:2, v/v) as yellow crystals (358, 42%), mp 164–166°C (from MeCN) [lit. [13c], mp 164°C (from C₆H₆)].

4-Amino-3-(2-benzonitrile)-2-phenyl-1*H*-hydroquinazoline (**25**) was obtained (1:1, v/v) as green crystals (327 mg, 26%), mp 136–138°C (from cyclohexane) (found: C, 77.71; H, 4.86; N, 17.34. C₂₁H₁₆N₄ (324.39) requires: C, 77.76; H, 4.97; N, 17.27%); $\nu_{\max}$ cm⁻¹ 3058–3168 (br NH₂), 2218 (CN); δ_{H} (CDCl₃) 5.87 (s, 2H, NH₂), 7.39–7.69 (m, 13H, *H*-Ph); δ_{C} (CDCl₃) 112.2 (C-CN), 118.5 (CN), 120.2, 121.3, 124.6, 124.7, 125.6, 126.6, 128.1, 128.5, 131.6, 132.3 (C=C, Ph), 148.3 (4-C), 151.6 (9-C); MS: *m/z* (EI) (%): 324 (35) [M⁺], 310 (21), 284 (22), 233 (9), 221 (27), 181 (100), 103 (40), 77 (56).

*The Reaction of 0.8 g **2** (3.88 mmol) with 1.52 g **15b** (4.1 mmol) Afforded **23b** and **25**.* 4-Amino-3-methyl-2-phenylquinoline (**23b**) was obtained (8:2, v/v) as yellow crystals (408 mg, 45%), mp 192–194°C (from CHCl₃) (lit. [14], mp or spectral data were not cited) (found: C, 82.09; H, 5.94; N, 11.88. C₁₆H₁₄N₂ (234.3) requires: C, 82.02; H, 6.02; N, 11.96%); $\nu_{\max}$ cm⁻¹ 2255–3346 (NH₂); δ_{H} (CDCl₃) 2.24 (s, 3H, CH₃), 5.77 (s br, 2H, NH₂), 7.36–7.56.13 (m, 3H, *H*-Ph), 7.58–7.74 (m, 3H, *H*-Ph), 7.77–7.86 (m, 2H, *H*-Ph), 8.08 (d, *J*_{HH} 8.2 Hz, 1H, *H*-Ph); δ_{C} (CDCl₃) 18.2 (CH₃), 120.6, 122.4, 124.2, 126.5, 127.1, 129.4, 131.6 (C=C, Ph), 133.7 (3-C), 143.7 (9-C), 144.3 (4-C), 148.2 (5-C), 153.8 (2-C); MS: *m/z* (EI) (%): 234 (38) [M⁺], 233 (42), 219 (22), 218 (100), 193 (65), 77 (55).

Compound **25** was obtained (1:1, v/v) as green crystals (289 mg, 23%), and shown to be identical with the material, previously described.

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