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A New, General Approach for the Synthesis of Heteroannulated 3,1-Oxazin-4-ones [1]

Heinrich Wamhoff[a]*, Stefan Herrmann[a], Stephan Stölben[a] and Martin Nieger[b]

a) Institut für Organische Chemie und Biochemie der Universität, Gerhard-Domagk-Str. 1, D-5300 Bonn, Germany
b) Institut für Anorganische Chemie der Universität, Gerhard-Domagk-Str. 1, D-5300 Bonn, Germany

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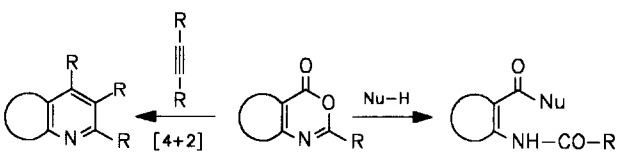
Abstract: *β-(N-Triphenylphosphoranyliden)-enamino esters afford the synthetically useful heteroannulated 3,1-oxazin-4-ones with aroyl chlorides in different solvents. The reaction proceeds in one step and in high yields and appears to be independent of the reactivity of the heterocyclic substrate.*

Heteroannulated 3,1-oxazine-4-ones are of increasing preparative interest due to their reactivity toward nucleophiles on the one hand and toward electron-rich dienophiles on the other.
Nucleophilic attack at the carbonyl function of the oxazinones results in ring cleaved amides which may be recyclized to form heterocondensed pyrimidines and pyridines depending on the nature of the nucleophile.[2] Diels-Alder reactions with inverse electron demand employing electron-rich dienophiles provide access to polyfunctionalized pyridines,[3] quinolines [4] and other fused pyridines.[5]



Besides these valuable synthetic utilities, the ease of nucleophilic ring cleavage is responsible for the biological activities of several oxazinones. Especially the benzoxazinones have been shown to be potent serine protease inhibitors.[6] Oxanosine, an oxa-analogue of guanosine, shows immunotherapeutical activities comparable with those of the parent compound.[7]

A common approach to annulated oxazinones is the reaction of β-enamino carboxylic acids with acid chlorides.[6] However, this method is limited to readily accessible precursors bearing amino groups which are sufficiently nucleophilic for a smooth reaction with the acid chlorides. As we have shown previously [8], oxazine-4-ones can also be prepared easily from β-amido esters by condensation with *in situ* generated diha-

logentriphenylphosphoranes. The yields are higher compared with the previous method and even less reactive β-enamino esters can often be converted into amides using bases. Still the ester group has to be sufficiently electrophilic to enable the cyclization step. On the other hand highly nucleophilic amines are doubly acylated, the resulting bis-amides not being suitable for cyclization.

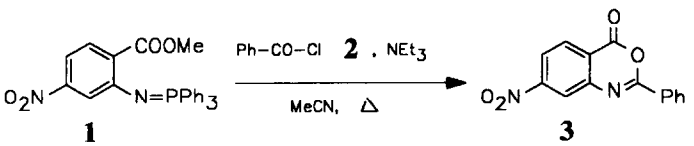
In the course of our "building-kit"-chemistry for the synthesis of tailor-made condensed heterocyclic systems we got interested in a more general method for the annulation of 3,1-oxazinone rings to various heteroaromatic systems of different reactivity such as thiophene or pyridazine. Because of the disadvantages mentioned for the syntheses above, we developed a novel strategy which enables adaption to the different substrate reactivity.

The iminophosphoranes of heterocyclic and heteroaromatic β-enamino esters have proved to be very versatile synthons for the construction of manifold heterocondensed systems.[9] They are readily available from amines with dihalogen triphenylphosphorane or via the Staudinger reaction from azides and triphenylphosphine. As we have shown, with isocyanates condensed pyrimidinones are formed,[9b] the mechanism of the formation being different for aromatic and nonaromatic substrates.[9b,9k] This reaction principle was furthermore successfully transferred to other activated carbonyl compounds such as ketenes.[10]

The treatment of the iminophosphoranes of (hetero-)aromatic β-enamino esters with aroyl chlorides leads to the formation of the condensed 1,3-oxazine-4-ones in good to excellent yields avoiding all problems mentioned for the previously known methods. The reaction conditions have to be adapted to fit the requirements of the substrate heterocycle.

Results and discussion

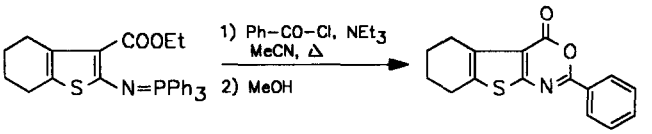
Benzoxazinones such as **3**, previously prepared by the methods mentioned above,[6] are smoothly obtained on heating the iminophosphorane **1** with benzoyl chloride **2** in acetonitrile in the presence of a small excess of triethylamine. Here, the tertiary amine seems to be essential for the reaction as is demonstrated for an example without Et_3N: Only 13 % product are obtained.



1 **3**

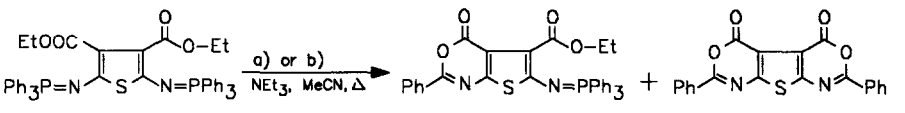
2-Nitrobenzoyl chloride is not suitable to convert **1** into an oxazinone. Obviously, the sterically demanding triphenylphosphoranylidenamino group is not able to attack the carbonyl group of the 2-substituted benzoyl chloride.

π-Excess heteroaromatic substrates react as well. The tetrahydrobenzo[b]thiophene **4** is converted into the oxazinone **5** in excellent yield on the action of benzoyl chloride.



4 **5**

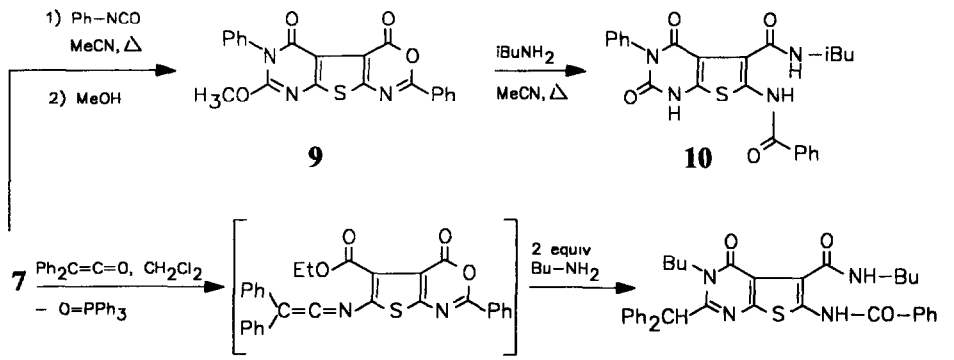
Employing the thiophene bis-iminophosphorane **6**, a differentiation between the two β-enaminocarbonyl functions is possible: With equimolar amounts of benzoyl chloride, only the thieno[2,3-d]oxazinone imino-phosphorane **7** is generated. On treatment with a fourfold excess of the aroyl chloride, the bis-oxazinone **8** is obtained together with the mono-oxazinone **7**. In this case, the electron-deficient oxazinone ring appears to decrease the basicity of the second triphenylphosphoranylidenamino group so that its reaction is somewhat handicapped.



6 **7** **8**

a) 4 equiv PhCOCl :	21%	15%
b) 1 equiv. PhCOCl :	82%	0%

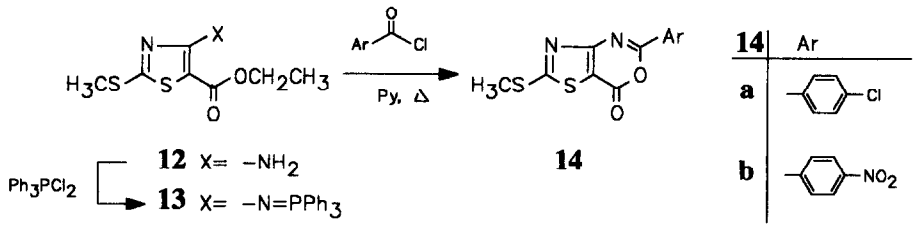
However, **7**, still possessing a β-enaminocarbonyl site, can undergo further aza-Wittig type reactions. Thus, with diphenyl ketene and butylamine, a thieno[2,3-d]pyrimidinone **11b** is obtained under cleavage of the oxazinone ring. The reaction with phenylisocyanate proceeds under preservation of the oxazinone ring and affords the heterotricycle **9** after pyrimidine annulation. Subsequent reaction with isobutylamine produces the thieno-pyrimidinedione bisamide **10**.



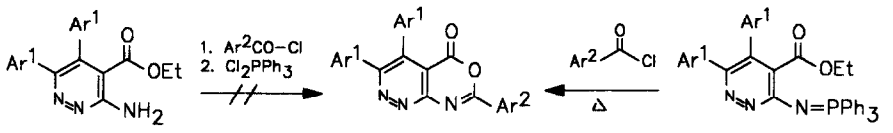
9 **10**

11a **11b**

The amines of π-excess-heteroaromates such as thiazole are nucleophilic enough to undergo a double-acylation on treatment with aroyl chlorides.[11] Even if the acid chloride is employed in less than equimolar amounts, the bisacylated amide is obtained besides the desired monoacylated product in some cases which hampers the purification. On the other hand, conversion into an iminophosphorane is facilitated. Thus, the thiazole **12** is transformed into the thiazolo[4,5-d]oxazinone **14** by reaction with dichlorotriphenylphosphorane and subsequent treatment of the resulting iminophosphorane **13** with aroyl chlorides. The solvent pyridine acts as a base and at the same time allows a sufficient reaction temperature.



This method proves to be especially useful with the β-enamino esters of π-deficient heteroaromates, where the electron withdrawing effect of the heterocycle decreases the nucleophilicity of amino groups in such a way, that acylation becomes extremely difficult. Even if the acylation succeeded subsequent cyclization may be impossible. This is the case for the pyridazines **15**. Furthermore, the corresponding β-enamino acids do not react completely with aroyl chlorides and the separation of polar by-products is difficult. On the other hand, simple heating of the iminophosphoranes **17** *in* aroyl chlorides yields the pyridazino[3,4-d]oxazinones **16** almost pure.



16	Ar^1:	16	Ar^1:
a	Ar^2:	d	Ar^2:
b	Ar^2:	e	Ar^2:
c	Ar^2:	f	Ar^2:
		g	Ar^2:

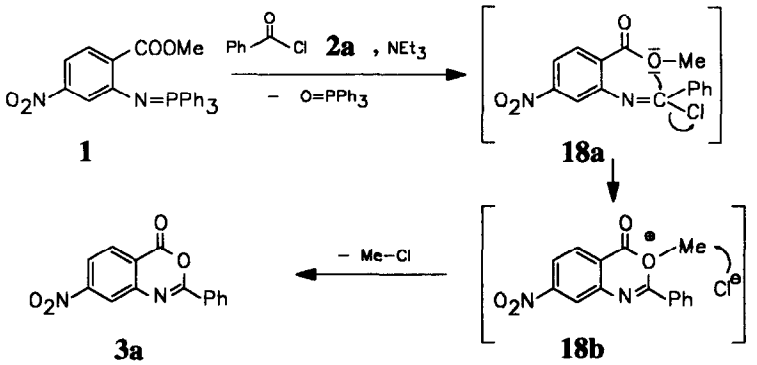
The by-product triphenylphosphine oxide is removed by crystallization from acetonitrile in which the oxazinones are only moderately soluble. Although forcing conditions are necessary, the method is also advantageous

with respect to the fact that the iminophosphoranes **17** are precursors for the aminopyridazines **15** employed in the classical methods.

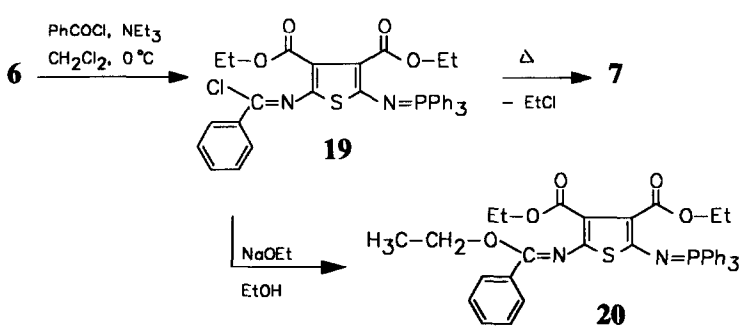
Mechanism

The reaction of iminophosphoranes with carboxylic acid chlorides was intensively examined by Zbiral, who showed that upon warming or in the presence of tertiary amines imidoyl chlorides are obtained [12] which react with nucleophiles to yield various products. The reaction with internal nucleophiles leads to the formation of some heterocyclic systems.[12,13] 1,4-, 1,5- and 1,6-dicarboxylic acid dichlorides are transformed into five- to seven-membered cyclic imides in a related reaction.[14]

For the iminophosphoranes of the β-enamino esters, the pathway of the reaction can be discussed as follows: First, an iminophosphorane such as **1** undergoes an aza-Wittig type reaction with the aroyl chloride **2a** yielding an imidoyl chloride **18a**. The newly generated electrophilic carbon center is then attacked by the ester alkoxy group forming a thermodynamically favoured six-membered ring intermediate **18b**. Elimination of alkylhalide affords the stable oxazinone **3a**.



This mechanism is supported by the isolation of the imidoyl chloride **19**, prepared from **6** on treatment with benzoyl chloride at low temperature. Upon heating it cyclizes spontaneously to afford the oxazinone **7**. The addition of nucleophiles such as ethoxide leads to the formation of the stable imino ester **20**.



Mass spectrometric proof of **19** is possible only with FAB ionization; the EI ionization results in formation of the oxazinone **7** with lower mass.

As we have shown, this new oxazinone annulation is almost independent of the substrate heterocycle. Nevertheless, a certain limitation follows from the nature of the carboxylic acid chloride. As a base is necessary in most reactions, only acid chlorides without α-hydrogens can be used because competing ketene formation would otherwise lead to side reactions. In an experiment with the pyridazine iminophosphorane **17**, trichloroacetyl chloride was tried as the acyl halide component. In this case, only an amide could be obtained. Aroyl chlorides seem to be the best choice.

One reason for this observation follows from the X-ray analysis of a single crystal obtained from **16b**: The aryl substituent of the oxazinone ring - originating from the aroyl chloride - is virtually in plane with the bicyclic pyridazino-oxazinone system. The C-8 to C-24 bond is relatively short. Hence, the aryl group is in conjugation with the bicyclic system forming an extended π-system which is thermodynamically favoured.

The possibility of an extension of this reaction to nonaromatic substrates is currently investigated.

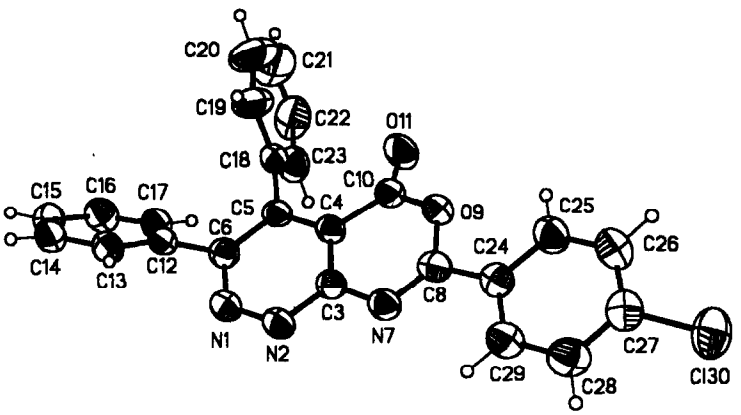


Fig.: X-ray analysis of ***16b*** *(for details see experimental section).*

Selected bond lengths (Å):

N1-N2	*1.330(4)*	*N2-C3*	*1.341(4)*	*C3-C4*	*1.405(4)*
C4-C5	*1.375(4)*	*C5-C6*	*1.419(4)*	*C6-N1*	*1.344(4)*
C3-N7	*1.378(4)*	*N7-C8*	*1.277(4)*	*C8-O9*	*1.370(4)*
O9-C10	*1.378(4)*	*C10-C4*	*1.481(4)*	*C10-O11*	*1.190(4)*
C5-C18	*1.493(4)*	*C6-C12*	*1.486(4)*	*C8-C24*	*1.460(4)*

Selected bond angles (°):

N1-N2-C3	*119.1(3)*	*N2-C3-C4*	*121.8(3)*	*C3-C4-C5*	*119.8(3)*
C4-C5-C6	*115.5(3)*	*C5-C6-N1*	*122.1(3)*	*C6-N1-N2*	*121.6(2)*
C3-C4-C10	*116.7(3)*	*C4-C10-O9*	*114.4(2)*	*C10-O9-C8*	*122.0(2)*
N7-C8-O9	*124.8(3)*	*C3-N7-C8*	*117.2(3)*	*C4-C3-N7*	*123.5(3)*
C4-C5-C18	*122.7(3)*	*C5-C6-C12*	*124.3(3)*	*C4-C10-O11*	*128.1(3)*
N7-C8-C24	*122.9(3)*				

Selected torsion angles (°)

N1-C6-C12-C13	*44.9(4)*	*C6-C5-C18-C19*	*84.9(4)*
O9-C8-C24-C25	*1.3(4)*		

EXPERIMENTAL SECTION

IR Spectra were recorded on a Perkin-Elmer 157-G.- ^{1}H and ^{13}C NMR-Spectra were measured with the Bruker WP-60, WH-90, AC-200, WM-250 and AM-400 spectrometers. Chemical shifts δ are reported downfield in ppm from TMS as internal standard, for ^{1}H with multiplicity and coupling constants in Hz. MS data were obtained with the A.E.I. Kratos instruments MS-30, MS-50 and Concept 1H (for FAB-MS). Melting points were taken on a Büchi SMP-20 and are not corrected.
All new compounds gave satisfactory microanalyses:[15] C +0.38 -0.47; H +0.16 -0.09; N +0.23 -0.32.

7-Nitro-2-phenyl-4H-3,1-benzoxazin-4-one (3): 4.56 g (10 mmol) of the iminophosphorane **1**[9b] are suspended in dry acetonitrile. Consecutively, 2.02 g (20 mmol) triethylamine and 1.69 g (12 mmol) benzoyl chloride are added. After 4 h of reflux and standing overnight, the resulting precipitate is filtered off and washed with 100 ml dry acetonitrile. Recrystallization from acetonitrile yields 1.13 g (42 %) of colourless needles.
Mp.: 175-176 °C.- IR: 1760, 1630, 1610, 1530, 1355 cm^{-1}.- ^{1}H NMR: ($CDCl_3$): δ = 7.28-7.73 (m), 8.03-8.34 (m), 8.42 (m).- ^{13}C NMR(d_6-dMSO): δ = 121.46, 121.96, 122.15, 128.09, 129.11, 129.40, 130.02, 133.34 , 147.05, 152.22, 157.74, 158.01 ppm. - MS (70 eV): *m/z* (%) = 268 [M^+] (81), 224 [$M^+ - CO_2$] (13), 105 [$M^+ - C_7H_3N_2O_3$] (100); $C_{14}H_8N_2O_4$ calc. 268.0484, found 268.0485.

5,6,7,8-Tetrahydro-2-phenyl-4H-benzo[4,5]thieno[2,3-d][3,1]-oxazin-4-one (5): 12.14 g (25 mmol) of the iminophosphorane **4** [9d] are suspended in dry acetonitrile and treated with 6.07 g (60 mmol) triethylamine. 4.22 g (30 mmol) benzoyl chloride are added dropwise. After 5 h at reflux, the solvent is evaporated and the residue is taken up in boiling methanol. Cooling to 5 °C results in precipitation of the product **5**. It is filtered off and washed with 200 ml of methanol to yield 6.25 g (88 %) of light yellow needles.
Mp.: 138-139.5 °C.- IR (KBr): ν = 1760, 1555 cm^{-1}.- ^{13}C NMR ($CDCl_3$): δ = 21.98, 22.88, 25.15, 25.21, 116.56, 128.21, 128.79, 129.99, 132.32, 132.51, 134.97 , 155.24, 158.60, 162.26 ppm.

Diethyl 2,5-bis(triphenylphosphoranylideneamino)thiophen-3,4-dicarboxylate (6) :[16a] 15.5 g (60 mmol) of diethyl 2,5-diaminothiophene-3,4-dicarboxylate [16b] are suspended in 350 ml of dry acetonitrile. Consecutively, 37.77 g (144 mmol) triphenylphosphine, 24.30 g (240 mmol) triethylamine and 28.41 g (120 mmol) hexachloroethane are added. At the end of the exothermic reaction the mixture is stirred at ambient temp. for 4 h. The precipitate is filtered and stirred in boiling ethanol for 1 h. After filtration and washing with 150 ml of ethanol, recrystallization from acetonitrile yields 33.7 g (72 %) of orange-red needles.
Mp.: 201-203 °C.- IR (KBr): ν = 1695, 1585, 1440, 1330 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 1.20 (t, 7.0), 4.16 (q, 7.0), 7.16-7.87 (m). - ^{13}C NMR ($CDCl_3$): δ = 14.40, 59.39, 114.28 (d, J_{CP}=19.8), 128.42 (d, J_{CP}=12.4), 130.93 (d, J_{CP}=101.1), 131.76 (d, J_{CP}=2.9), 132.97 (d, J_{CP}= 10.4), 146.82 (d, J_{CP}=5.9), 165.76. - MS (70 eV): *m/z* (%) = 778 [M^+] (100).

Ethyl 4-oxo-2-phenyl-6-(triphenylphosphoranylideneamino)-4H-thieno[2,3-d][3,1]oxazin-5-carboxylate (7) and 2,7-diphenyl-4H,5H-thieno[2,3-d:5,4-d']bis[3,1]oxazin-4,5-dione (8)
Method A: 4.04 g (40 mmol) Triethylamine and 2.81 g (20 mmol) benzoyl chloride are subsequently added to a solution of 3.89 g (5 mmol) of **6** in 150 ml dry acetonitrile. After 6 h reflux, the solvent is evaporated and the residue is taken up in hot ethanol. The precipitate obtained on cooling is stirred in boiling chloroform. The insoluble bisoxazinone **8** is filtered from the hot mixture. Removal of some of the solvent and depolarization with petrol ether yields **7** from the filtrate. Yields: 612 mg (21 %) of **7** and 280 mg (15 %) of **8**.
Method B: 15.58 g (20 mmol) of **6** are suspended in 120 ml of dry acetonitrile and 4.04 g (40 mmol) of triethylamine are added. At reflux temperature, a solution of 3.37 g (24 mmol) benzoyl chloride in 30 ml dry acetonitrile is added dropwise. After 4 h at 80 °C the solution is allowed to cool. The resulting precipitate is filtered off, washed with 200 ml ethanol and recrystallized from ethanol to yield 9.4 g (82 %) yellow crystals of **7**. No **8** is formed under this conditions.

7: Mp.: 203-205 °C.- - UV (CH_3CN): λ_{max} (lg ε) = 538, 408, 312, 256 nm (2.61, 4.14, 3.89, 4.31). - IR (KBr): ν = 1755, 1700, 1440 cm^{-1} . - ^1H NMR ($CDCl_3$): δ = 1.36 (t, 7.0), 4.39 (q, 7.0), 7.24-8.20 (m). - ^{13}C NMR ($CDCl_3$): δ = 14.24, 60.57, 110.18 (d, J_{CP}=19.7), 115.78, 127.29, 127.66 (d, J_{CP}=102.5), 128.47, 128.93 (d, J_{CP}=12.6), 129.96, 131.67, 132.74 (d, J_{CP}=10.3), 132.76 (d, J_{CP}=2.8), 151.97, 152.95, 157.25 (d, J_{CP}=4.7), 157.44, 164.31. - MS (70 eV): *m/z* (%) = 576 [M^+] (100); $C_{33}H_{25}N_2O_4PS$ calc. 576.1273, found 576.1278.

8: Mp.: 345-350 °C (Lit.:[5] 332 °C).-- IR (KBr): ν = 1810, 1790 , 1585 cm^{-1}. - MS (FAB): *m/z* (%) = 374 [M^+] (95).

3,4-Dihydro-2-methoxy-3,7-diphenyl-5H-1,3-oxazino[5',4':4,5]-thieno[2,3-d]pyrimidin-4,5-dione (9): To a solution of 1.79 g (15 mmol) phenylisocyanate in 100 ml dichloromethane is added dropwise a solution of 1.73 g (3 mmol) of the iminophosphorane **7** in 50 ml dichloromethane. After 4 h stirring at ambient temp. the solvent is removed and the residue is treated with dry, boiling methanol. The resulting precipitate is filtered off, washed with 150 ml of methanol and recrystallized twice from dichloromethane/n-hexane. Yield: 518 mg (43 %) of light yellow needles.

Mp.: >250 °C.- UV (CH_3CN): λ_{max} (lg ε) = 392, 368, 352, 319, 303, 256, 221, 202 nm (4.03, 4.31, 4.33, 4.05, 3.98, 4.45, 4.47, 4.52). - IR (KBr): ν = 1785, 1695, 1565, 1500 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 3.93 (s), 7.11-7.69 (m), 8.16-8.37 (m). - ^{13}C NMR ($CDCl_3$ + TFA): δ =57.77, 111.55, 112.05, 127.59, 128.15, 129.02, 129.38, 130.16, 130.45, 133.07, 134.61, 155.95, 156.10, 159.43, 161.96, 164.06, 165.46. - MS (70 eV): *m/z* (%) = 403 [M^+] (36), 105 [M^+ - $C_{14}H_8N_3O_3S$] (100); $C_{21}H_{13}N_3O_4S$ calc. 403.0627, found 403.0629.

6-Benzoylamino-1,2,3,4-tetrahydro-2,4-dioxo-3-phenylthieno-[2,3-d]pyrimidin-5-carbox-N-(2-methylpropyl)amide (10): 1.41 g of **9** and 10 ml isobutylamine are refluxed in 100 ml dry acetonitrile. The almost insoluble product is removed by filtration, washed with acetonitrile and treated twice with 100 ml of boiling ethanol to obtain 1.24 g (77 %) fine, colourless needles melting above 400 °C.- IR (KBr): ν = 3240, 3160, 3050, 1715, 1640, 1620, 1590, 1570, 1540 cm^{-1}. - ^1H NMR ([D_6]-DMSO): δ = 0.85 (d, 6.0), 1.70 (m), 3.16 (m), 7.13-8.00 (m), 11.05 (t, 6.0, broad), 12.45 (s, broad), 14.50 (s, broad). - MS (70 eV): *m/z* (%) = 462 [M^+] (34), 390 [M^+ - $C_4H_{10}N$] (30); $C_{24}H_{22}N_4O_4S$ calc. 462.1362, found 462.1366.

6-Benzoylamino-3-butyl-3,4-dihydro-2-diphenylmethyl-4-oxothieno[2,3-d]pyrimidin-5-carbox-N-butylamide (11a): A solution of 1.73 g (3 mmol) of the iminophosphorane **7** in 50 ml dichloromethane is treated with 0.68 g (3.5 mmol) of diphenylketene and stirred for 3 h at ambient temp. under argon. 0.73 g (10 mmol) n-Butylamine are added and the stirring is continued for 2 h. The solvent is evaporated and the residue taken up in hot ethanol. After filtering hot and removal of part of the solvent, the product precipitates. It is recrystallized from dichloromethane/n-pentane to yield 1.42 g (80 %) fine, light yellow needles.
Mp.: 280 °C.- UV (CH_3CN): λ_{max} (lg ε) = 349, 327, 239, 221 nm (2.95, 3.01, 3.15, 3.06). - IR (KBr): ν = 3230, 1660, 1645, 1600 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 0.98 (t, 7.0), 1.00 (t, 7.0), 1.47 (sext., 7.0), 1.71 (quint., 7.0), 3.48 (q, 7.0), 4.18 (t, 7.0), 5.86 (s), 7.09-7.23 (m), 7.32-7.47 (m), 7.55 (td, 7.5, 1.5), 7.67 (tt, 7.5, 1.5), 7.98 (dd, 7.5, 1.5), 11.50 (t, 7.0, broad), 14.68 (s, broad). - ^{13}C NMR ($CDCl_3$): δ = 13.82, 13.92, 20.42, 31.20, 31.36, 39.55, 44.41, 55.32, 109.47, 115.88, 127.66, 127.95, 128.86, 129.02, 129.34, 132.32, 132.74, 139.47, 147.14, 156.50, 158.25, 160.12, 164.56, 165.92. - MS (70 eV): *m/z* (%) = 592 [M^+] (100), 520 [M^+ - $C_4H_{10}N$] (28), 105 [M^+ - $C_{28}H_{31}N_4O_2S$] (96); $C_{35}H_{36}N_4O_3S$ calc. 592.2508, found 592.2519.

Ethyl 2-methylthio-4-(triphenylphosphoranylideneamino)thiazol-5-carboxylate (13): To a solution of 6.54 g (30 mmol) of ethyl 4-amino-2-methylthiothiazol-5-carboxylate **12** [17] in 120 ml dry acetonitrile under argon are added consecutively 8.3 ml triethylamine, 9.43 g (36 mmol) triphenylphosphine and 7.11 g hexachloroethane. After 5 h reflux the solution is cooled with stirring, the solvent is removed and the residue is recrystallized twice from ethanol to yield 9.05 g (63 %) of greenish yellow crystals.
Mp.: 148 °C. - IR (KBr): ν = 1685, 1490 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 1.1 (t, 7.0), 2.17 (s), 4.20 (q, 7.0), 7.2- 7.9 (m). - ^{13}C NMR($CDCl_3$): δ = 14.73, 15.28, 59.75, 90.30 (d, J_{CP}=24.1), 128.45 (d, J_{CP}=12.5), 129.96 (d, J_{CP}=101.1), 131.90 (d, J_{CP}=2.9), 133.23 (d, J_{CP}=10.3), 163.52, 163.94, 166.92. - MS (70 eV): *m/z* (%) = 478 [M+] (80), 262 [M^+ - $C_7H_8N_2O_2S_2$] (100).

Preparation of the thiazolo[4,5-d]oxazinones 14a,b: A solution of 4.4 mmol aroyl chloride in 4 ml dry acetonitrile is added dropwise to a suspension of 1.91 g (4 mmol) of the iminophosphorane **13** in 10 ml of dry pyridine under argon. After 1 h at reflux the solution is allowed to cool and the resulting precipitate is filtered off and recrystallized twice from acetonitrile.

6-Methylthio-2-(4-nitrophenyl)thiazolo[4,5-d][3,1]oxazin-4-one (14a): From 1.91 g (4 mmol) of **13** and 0.82 g (4.4 mmol) of 4-nitrobenzoyl chloride. Yield: 0.55 g (43 %). Mp.: 228 °C.- IR (KBr): ν= 1745, 1580, 1520 cm^{-1}. - ^{1}H NMR ([D$_6$]DMSO): δ = 2.87 (s), 8.22 (d, 9.0), 8.40 (d, 9.0). - MS (70 eV): *m/z* (%) = 321 [M+] (100).

2-(4-Chlorophenyl)-6-methylthiothiazolo[4,5-d][3,1]oxazin-4-one (14b): From 1.91 g (4 mmol) of **13** and 0.77 g of 4-chlorobenzoyl chloride. Yield: 0.86 g (69 %). Mp.: 214 °C.- IR (KBr): ν = 1755, 1595, 1370 cm^{-1}. - ^{1}H NMR ([D$_6$]DMSO): δ = 2.80 (s), 7.67 (d, 9.0), 8.17 (d, 9.0). - MS (70 eV): *m/z* (%) = 310 [M+] (96), 139 [M$^+$ - $C_5H_3N_2OS_2$] (100). (Due to the low solubility of **14a** and **14b**, no ^{13}C NMR spectra were obtained.)

Preparation of the pyridazine iminophosphoranes (17) :[18] 30 mmol of the corresponding 3-chloropyridazine-4-carboxylate [19] and 6.5 g (100 mmol) sodium azide are suspended in 200 ml DMF and warmed to 80 °C until TLC-monitoring indicates complete conversion (ca. 14 h). After cooling to ambient temp., the solution is poured into 1.6 l of water, stirred for 30 min. and the precipitate is filtered and dried. The intermediate is refluxed in 300 ml xylene with 10 g (38 mmol) triphenylphosphine for 12 h. After evaporation of the solvent, the residue is stirred with 250 ml of diethyl ether and filtered. The pure products are obtained after recrystallization from ethanol.

Ethyl 5,6-diphenyl-3-(triphenylphosphoranylideneamino)pyridazin-4-carboxylate (17a): From 10.36 g (30 mmol) of ethyl 3-chloro-5,6-diphenylpyridazin-4-carboxylate. Yield: 10.3 g (59 %). Mp.: 225 °C.- IR (KBr): ν = 3058, 1725, 1430 cm^{-1}.- ^{1}H NMR ([D$_6$]DMSO): δ = 1.05 (t, 7.0), 4.14 (q, 7.0), 7.0-7.3 (m), 7.5-7.9 (m).- MS (70 eV): *m/z* (%) = 579 [M+] (2), 550 [M$^+$ - C_2H_5] (100); $C_{37}H_{30}N_3O_2P$ calc. 579.2075 found 579.2080.

Ethyl 5,6-bis(4-methoxyphenyl)-3-(triphenylphosphoranylideneamino)pyridazin-4-carboxylate (17b): From 12.16 g (30 mmol) of ethyl 3-chloro-5,6-bis(4-methoxyphenyl)pyridazin-4-carboxylate. Yield: 11.2 g (60 %). Mp.: 223-225 °C. - IR (KBr): ν = 2830, 1720, 1605, 1425 cm^{-1}.- ^{1}H NMR ([D$_6$]DMSO): δ = 1.1 (t, 7.0), 3.65 (s), 3.70 (s), 4.20 (q, 7.0), 6.73 (d, 8.4), 6.86 (d, 8.4), 7.05 (d, 8.4), 7.07 (d, 8.4), 7.45-7.7 (m), 7.75-7.95 (m). - MS (70 eV): *m/z* (%) = 639 [M+] (28), 610 [M$^+$ - C_2H_5] (100); $C_{39}H_{34}N_3O_4P$ calc. 639.2287 found 639.2296.

Preparation of the pyridazino[3,4-d]oxazinones 16a-g:

Method A (16a,b,d-g): 5 mmol of the iminophosphorane **17a** or **17b**, resp., are heated in an oil bath with 14 ml of the aroyl chloride after addition of some crystals of DMAP for the time noted below. The temperature

of the oil bath should not exceed 120 °C. After cooling the solid is immediately removed by filtration, washed twice with icecold diethyl ether and dried for 8 h in high vacuum. The crude product is recrystallized two times from acetonitrile and dried again as described above.

Method B (16c): 2.90 g (5 mmol) of the iminophosphorane **17a** and 1.86 g (10 mmol) 4-nitrobenzoyl chloride are mixed in a mortar under argon. The mixture is heated to 100 °C (bath temp.) under argon. A viscous, brown melt results which becomes almost solid to the end of the reaction (ca. 4 h). After cooling, 40 ml dry acetonitrile are added and the mixture is refluxed for 0.5 h. The precipitated, yellow solid is filtered off and purified as described under *method A*. (Analytical data see below).

2,5,6-Triphenylpyridazino[3,4-d][3,1]oxazin-4-one (16a): From 2.90 g (5 mmol) **17a**; reaction time 8 h. Yield: 1.59 g (85 %). Mp.: 263 °C. - UV (CH_3CN): λ_{max} (lg ε) = 296 nm (4.45). - IR (KBr): ν = 1770, 1620 cm^{-1} . - ^1H NMR ([D_6]DMSO): δ = 7.2-7.4 (m), 7.6-7.8 (m), 8.3 (dd, 7.0, 6.0).- ^{13}C NMR ([D_6]DMSO): δ= 113.9, 127.7, 127.8, 128.4, 128.5, 128.9, 129.3 ,129.34, 129.7, 133.8, 133.86, 136.3, 138.7, 156.8, 157.09, 159.99, 160.5. - MS (70 eV): *m/z* (%) = 377 [M+] (46), 105 [M^+ - $C_{17}H_{10}N_3O$] (100); $C_{24}H_{15}N_3O_2$ calc. 377.1161, found 377.1165.

2-(4-Chlorphenyl)-5,6-diphenylpyridazino[3,4-d][3,1]oxazin-4-one (16b): From 2.90 g (5 mmol) **17a**, reaction time 3 h. Yield 1.56 g (76 %). Mp.: 266 °C. - UV (CH_3CN): λ_{max} (lg ε) = 301 nm (4.51). - IR (KBr): ν = 1778, 1640 cm^{-1}. - ^1H NMR ([D_6]DMSO): δ = 7.1 - 7.4 (m), 7.72 (dd, 9.0, 2.0), 8.26 (dd, 9.0, 2.0). - ^{13}C NMR ([D_6]DMSO): δ = 114.0, 127.84, 127.88, 128.2, 128.5, 128.6, 129.0, 129.5, 129.8, 130.2, 133.8, 136.2, 138.74, 138.76, 156.7, 157.0, 159.6, 160.2. - MS (70 eV): *m/z* (%) = 411 [M+] (85), 139 [M^+ - $C_{17}H_{10}N_3O$] (100).

5,6-Diphenyl-2-(4-nitrophenyl)pyridazino[3,4-d][3,1]oxazin-4-one (16c): Yield 1.22 g (58 %), reaction time ca. 4 h. Mp.: 262 °C. - IR (KBr): ν = 1782, 1625 cm^{-1}. - ^1H NMR ([D_6]DMSO): δ = 7.2-7.4 (m), 8.47 (dd, 9.2, 2.3), 8.53 (dd, 9.2, 2.3). -^{13}C NMR ([D_6]DMSO): δ = 114.4, 124.4, 127.9, 128.54, 128.67, 129.0, 129.8, 133.7, 135.0, 136.13, 138.8, 150.3, 156.4, 156.8, 158.8, 160.5. -MS (70 eV): *m/z* (%) = 422 [M+] (67), 150 [M^+ - $C_{17}H_{10}N_3O$] (100); $C_{24}H_{14}N_4O_4$ calc. 422.1012, found 422.1012.

5,6-Bis(4-methoxyphenyl)-2-phenylpyridazino[3,4-d][3,1]oxazin-4-one (16d): From 3.20 g **17b**, reaction time 9 h. Yield 0.56 g (26 %). Mp.: 220 °C. - UV (CH_3CN): λ_{max} (lg ε) = 308 nm (4.40). - IR (KBr): ν = 2830, 1782, 1618 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 3.78 (s), 3.82 (s), 6.79 (dd, 8.0, 2.0), 6.90 (dd, 8.0, 2.0), 7.10 (dd, 8.0, 2.0), 7.27 (dd, 8.0, 2.0), 7.5 - 7.7 (m), 8.4 (m). - ^{13}C NMR ($CDCl_3$): δ = 55.21, 112.1, 113.6, 113.9, 125.4, 128.4, 128.9, 129.1, 130.6, 131.6, 133.9, 139.4, 156.7, 156.9, 160.1, 160.2, 160.9, 161.0. - MS (70 eV): *m/z* (%) = 437 [M+] (100), 105 [M^+ - $C_{19}H_{14}N_3O_3$] (70); $C_{26}H_{19}N_3O_4$ calc. 437.1371, found 437.1369.

2-(4-Chlorphenyl)-5,6-bis(4-methoxyphenyl)-pyridazino[3,4-d][3,1]-oxazin-4-one (16e): From 3.20 g (5 mmol) **17b**, reaction time 4 h. Yield 1.75 g (74 %). Mp.: 218 °C. - UV (CH_3CN): λ_{max} (lg ε) = 309, 220 nm (4.46, 4.44). - IR (KBr): ν = 2830, 1780, 1610 cm^{-1}. - ^1H NMR ($CDCl_3$ + [D_6]DMSO): δ = 3.70 (s), 3.78

(s), 6.68 (dd, 8.0, 2.0), 6.82 (dd, 8.0, 2.0), 7.05 (dd, 8.0, 2.0), 7.15 (dd, 8.0, 2.0), 7.47 (dd, 9.0, 2.0), 8.22 (dd, 9.0, 2.0). - ^{13}C NMR ($CDCl_3$ + [D_6]DMSO): δ = 54.7, 112.2, 113.0, 113.2, 124.9, 127.2, 127.8, 128.8, 129.7, 130.21, 131.0, 138.8, 139.4, 155.95, 155.99, 159.31, 159.40, 159.44, 160.1. - MS (70 eV): *m/z* (%) = 471 [M+] (100), 139 [M^+ - $C_{19}H_{14}N_3O_3$] (95).

2-(3-Chlorphenyl)-5,6-bis(4-methoxyphenyl)-pyridazino[3,4-d][3,1]-oxazin-4-one (16f): From 3.20 g (5 mmol) **17b**, reaction time 12 h. Yield 1.28 g (54 %), Mp.: 186 °C. - IR (KBr): ν = 2830, 1782, 1620 cm^{-1}. - ^{1}H NMR ([D_6]DMSO): δ = 3.74 (s), 3.78 (s), 6.86 (d, 8.8), 6.93 (d, 8.8), 7.16 (d, 8.8), 7.21 (d, 8.8), 7.69 (dd, 8.2, 8.2), 7.82 (ddd, 8.2, 1.5, 1.5), 8.20 (m). - ^{13}C NMR ([D_6]DMSO): δ = 55.08, 55.12, 113.43, 113.49, 114.1, 125.8, 127.0, 127.6, 128.5, 130.7, 131.3, 131.5, 133.4, 134.0, 138.5, 156.4, 156.6, 158.9, 159.4, 159.5, 160.1. - MS (70 eV): *m/z* (%) = 471 [M+] (100); $C_{26}H_{18}ClN_3O_4$ calc. 471.0982, found 471.0993.

5,6-Bis(4-methoxyphenyl)-2-(4-methylphenyl)pyridazino[3,4-d][3,1]-oxazin-4-one (16g): From 3.20 g (5 mmol) **17b**, reaction time 10 h. Yield 255 mg (11 %). Mp.: 213 °C. - UV (CH_3CN): λ_{max} (lg ε) = 313, 222 nm (4.45, 4.39). - IR (KBr): ν = 3830, 1768, 1610 cm-1. - ^{1}H NMR($CDCl_3$): δ = 2.45 (s), 3.67 (s), 3.72 (s), 6.75 (dd, 8.4, 2.0), 6.87 (dd, 8.4, 2.0), 7.10 (dd, 8.4, 2.0), 7.27 (dd, 8.4, 2.0), 7.32 (d, 8.0), 8.29 (d, 8.0). - ^{13}C NMR ($CDCl_3$): δ = 21.8, 55.2, 112.0, 113.56, 113.89, 125.4, 126.2, 128.4, 129.2, 129.7, 130.6, 131.6, 139.4, 145.1, 156.9, 157.0, 160.03, 160.13, 160.54, 161.13. - MS (70eV): *m/z* (%) = 451 [M+] (31), 119 [M^+ - $C_{19}H_{14}N_3O_3$] (100); $C_{27}H_{21}N_3O_4$ calc. 451.1527, found 451.1549.

Diethyl 5-(1-chlor-1-phenylmethylenamino)-2-(triphenylphosphoranylideneamino)thiophen-3,4-dicarboxylate (19): 15.58 g (20 mmol) of **6** and 4.05 g (40 mmol) triethylamine are dissolved in 150 ml dry dichloromethane. At 0 °C, a solution of 3.37 g (24 mmol) benzoyl chloride in 20 ml dichloromethane is added dropwise and the solution is stirred for additional 4 h at this temperature. The solvent is evaporated and the residue is taken up in dry ethanol. The product is filtered off, washed with cold ethanol and recrystallized twice from dichloromethane/n-hexane. Yield: 8.66 g (68 %) of yellow platlets. Mp.: 171 °C (on measuring in an apparatus preheated to 160 °C; if the warming is too slow, thermal decay into the oxazinone **7** occurs and most of the solid melts at 203-205 °C). - UV (CH_3CN): λ_{max} (lg ε) = 542, 424, 334, 250, 232, 222 nm (2.52, 3.78, 3.22, 3.64, 3.76, 3.83). - IR (KBr): ν = 1730, 1700, 1440 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 1.32 (t, 7.5), 1.35 (t, 7.5), 4.29 (q, 7.5), 4.39 (q, 7.5), 7.22-8.04 (m). - ^{13}C NMR ($CDCl_3$): δ = 14.35, 14.42, 59.65, 61.19, 111.28 (d, J_{CP}=19.5), 125.92 , 127.51 (d, J_{CP}=102.2), 128.12, 128.38, 128.88 (d, J_{CP}=12.4), 130.32, 131.32, 132.71 (d, J_{CP}=2.8), 132.99 (d, J_{CP}=10.4), 135.68, 136.16, 163.43, 163.74 (d, J_{CP}=4.0), 166.68. - MS (70 eV): *m/z* (%) = 576 [M^+ - C_2H_5Cl] (100); under usual EI conditions the fast ethyl chloride separation prevents an observation of M^+;. - MS (FAB, matrix MNBA): *m/z* (%) = 640 [M^+] (4), 576 [M^+ - C_2H_5Cl] (1).

Diethyl 5-(1-ethoxy-1-phenylmethyleneamino)-2-(triphenylphosphoranylidenamino)thiophen-3,4-dicarboxylate (20): 1 g (1.56 mmol) of the imidoyl chloride **19** is added to a solution of 0.1 g sodium in 50 ml of dry ethanol under argon. The solution is stirred for 12 h at ambient temp after 2 h of reflux. The solvent is evaporated and the residue is taken up in 100 ml of dichloromethane. The solution is washed with four por-

tions of 200 ml of water and dried with sodium sulfate. The residue obtained after removal of the dichloromethane is solved in ethanol. The solution is filtered from small amounts of insoluble impurities and part of the filtrate is distilled off. The resulting precipitate is recrystallized twice from ethanol. Yield: 700 mg (69 %) of yellow crystals.

Mp.: 143-144°C. - UV (CH_3CN): λ_{max} (lg ε) = 543, 357 nm (2.62, 4.02). - IR (KBr): ν = 1730, 1695, 1440 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 1.12 - 1.43 (m), 3.95 - 4.37 (m), 7.03 - 7.87 (m). - ^{13}C NMR ($CDCl_3$): δ = 14.27, 14.47, 14.60, 59.52, 60.53, 63.99, 128.11, 128.76, 128.78 (d, J_{CP}=12.5), 128.78 (d, J_{CP}=101.8), 129.99, 132.13, 132.32 (d, J_{CP}=2.9), 133.03 (d, J_{CP}=10.3), 164.37, 166.07. - MS (70 eV): *m/z* (%) = 650 [M^+] (100), 621 [$M^+ - C_2H_5$] (45); $C_{37}H_{35}N_2O_5PS$ calc. 650.2004, found 650.2004.

X-ray analysis of 16b: A single crystal of **16b** (0.20 × 0.35 × 0.60 mm^3) was obtained by sublimation of some mg of amorphous **16b** in a Kugelrohr distillation apparatus at 250 °C and 1 mbar. Diffraction data were collected on a Siemens R3m/V diffractometer at 293 K with graphite monochromated MoKα radiation (λ = 0.71073 Å). The unit cell parameters were determined with 48 reflections (20°<2Θ<25°). The crystals are monoclinic, space group $P2_1/c$ with 4 formula units $C_{24}H_{14}ClN_3O_2$ in the unit cell: a = 19.598(6) Å, b = 10.318(4) Å, c = 9.535(3) Å, β = 92.75(2) °, V = 1926(1) $Å^3$, $\rho_{calc.}$ = 1.420 g cm^{-3}, μ(MoKα) = 0.23 mm^{-1}, F(000) = 848. 3721 reflections (ω-scan, scan range Δω = 1.20°) were collected with 3396 independent reflections and 2313 observed reflections (F>3.0σ(F)). The structure was solved with Siemens SHELXTL PLUS (VMS) by direct methods and refined with full matrix-least-squares technique (271 parameters) to R = 0.050, R_w = 0.054 ($w^{-1}=\sigma^2(F)+ 0.0013F^2$). H-atoms were located by difference fourier synthesis and refined with fixed isotropic U using a "riding" model. All other atoms were refined anisotropically, with a data-to-parameter ratio of 8.5 : 1. The complete data has been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für Wissenschaftlich-Technische Information mbH, W-7514 Eggenstein, Leopoldstraße 2 under the deposition number CSD 56693.

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