Versatile Synthesis of 4-Methylidenepyrazolidin-3-ones Using a Horner–Wadsworth–Emmons Approach

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Abstract: A new, versatile method for the synthesis of, so far unknown, variously substituted 4-methylidenepyrazolidin-3-ones as potential cytotoxic agents is described. Target compounds were synthesized from the corresponding 4-diethoxyphosphorylpyrazolidin-3-ones which were used as Horner–Wadsworth–Emmons reagents for the olefination of formaldehyde. 4-Phosphorylpyrazolidin-3-ones were, in turn, obtained starting from the sodium salt of ethyl 2-diethoxyphosphoryl-3-hydroxy-2-propenoate, ethyl 2-acyl-2-diethoxyphosphorylacetates, or 3-methoxy-2-diethoxyphosphorylacrylate and monosubstituted or 1,2-disubstituted hydrazines.

Key words: alkylation, antitumor agents, heterocycles, lactams, Michael addition, olefination

Carbo- and heterocycles containing an exo-methylidene moiety conjugated with a carbonyl group constitute a large class of natural and synthetic compounds which display a broad spectrum of biological properties, ranging from cytotoxic/anticancer, allergenic, anti-inflammatory, and cardiovascular to antibacterial, antifungal, and phytotoxic activities. These classes of compounds include α-methylidenecyclopentanones **1**,[1] and α-alkylidene-γ- and δ-lactones **2** and **3** as well as α-alkylidene-γ- and δ-lactams **4** and **5** (Figure 1)[2] It is believed that the Michael acceptor functionality, which is present in all these compounds, can effectively react with various bionucleophiles and therefore is crucial for their biological activities.[3]

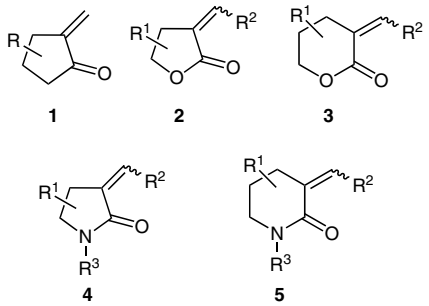

Figure 1

In a search for new, biologically promising analogues we have developed syntheses of several classes of α-alkylidene-γ- and δ-lactones, as well as α-methylidene-γ-lactams, by applying a Horner–Wadsworth–Emmons approach to the construction of the exo-alkylidene bond.[2b,4] Many of the compounds obtained in our laboratory turned out to be highly potent against several cancer cell lines as well as against nosocomial and community-associated staphylococci (MRSA) which are resistant to most or all available therapeutic classes of antimicrobial drugs.[5] Recently, we envisaged that introduction of an additional heteroatom to the lactone or lactam ring might be beneficial for biological activity. Consequently, a series of 4-methylideneisoxazolidin-5-ones **6** (Figure 2) containing an additional nitrogen atom in the lactone ring, has been synthesized in our laboratory and, to our satisfaction, certain isoxazolidinones **6** proved to be very potent against HL-60, NALM-6, MCF-7, and MDA-MB-231 cancer cells.[6] The most active compounds have been subjected to extended biological studies which have shed light on their mode of action at the molecular level.[7]

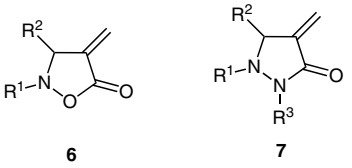

Figure 2

Encouraged by these results we decided to develop the synthesis of, so far unknown, 4-methylidenepyrazolidin-3-ones **7** which have an additional nitrogen atom in the lactam ring. Although it is well established that α-alkylidene-γ-lactams usually display lower cytotoxic activity than α-alkylidene-γ-lactones,[5a–c] on the other hand, these species are considered as particularly promising because the γ-lactam moiety can help to mitigate the biological toxicity often observed for γ-lactones.[8] Therefore, synthesis of α-methylidene-γ-lactams with potentially enhanced cytotoxicity profile seemed an attractive goal. In this paper we describe our preliminary results concerning a convenient and versatile Horner–Wadsworth–Emmons approach to variously substituted 4-methylidenepyrazolidin-3-ones **7**.

Synthesis of 2-aryl-1-methyl-4-methylidenepyrazolidin-3-ones **14a**–**e** substituted with various aryl groups in position 2 was accomplished as shown in Scheme 1. 1-Aryl-4-diethoxyphosphoryl-1*H*-pyrazol-5-ols **11a**–**e** were prepared by adapting the literature procedure described for

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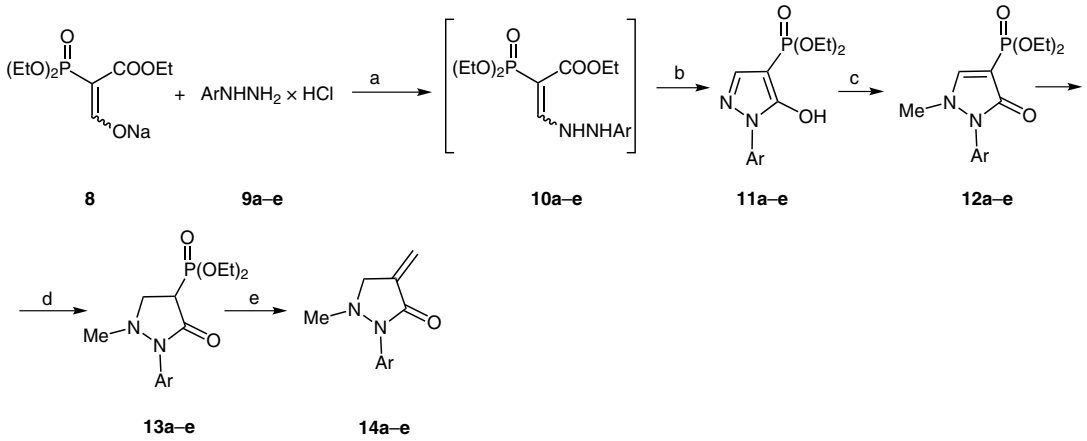


Scheme 1 *Reagents and conditions*: (a) H_2O, reflux, 10 min; (b) K_2CO_3 (1.1 equiv), H_2O, reflux, 10 min; (c) Me_2SO_4 (1.2 equiv), DCE, 80 °C, 18 h; (d) L-Selectride (1.25 equiv), THF, –78 °C, 1 h, then r.t., 18 h; (e) $(CH_2O)_n$ (5 equiv), NaH (1.2 equiv), THF, r.t., 2 h.

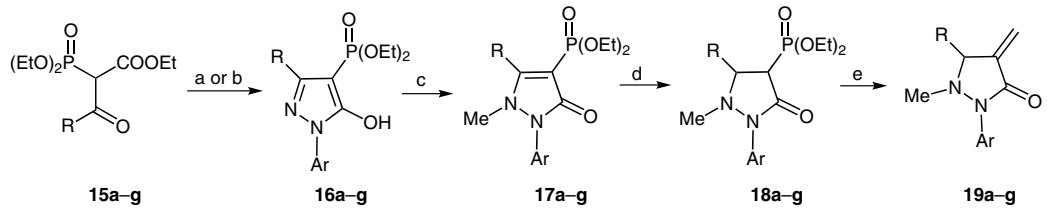
the corresponding 4-dimethoxyphosphorylpyrazol-5-ols.[9] The sodium salt of ethyl 2-diethoxyphosphoryl-3-hydroxy-2-propenoate **8** was treated with arylhydrazine hydrochlorides **9a–e** followed by addition of potassium carbonate (Table 1). This one-pot, two-step reaction obviously proceeds via an addition–elimination sequence to give substitution products **10a–e** followed by intramolecular cyclization. Pyrazoles **11a–e** obtained in this fashion were next N-methylated with dimethyl sulfate to give 2-aryl-1-methyl-4-diethoxyphosphorylpyrazol-3-ones **12a–e** in satisfactory yields (Table 1).[10] Unfortunately, all attempts to introduce various substituents into position 5 of the pyrazolone ring, by executing Michael addition of Grignard reagents to **12**, failed. Therefore, we decided to perform the reduction of the double bond in pyrazolones **12** to provide access to Horner–Wadsworth–Emmons reagents **13**. Standard hydrogenation of **12a** in the presence of palladium or platinum catalysts gave only starting material. However, application of L-Selectride as a reducing agent furnished the expected pyrazolidinones **13a–e** in good yields (Table 1).[11] Finally, reaction of **13a–e** with paraformaldehyde in the presence of sodium hydride gave the targeted 4-methylidenepyrazolidin-3-ones **14a–e** in good to excellent yields (Table 1).[12]

To gain access to 5-substituted 2-aryl-1-methyl-4-methylidenepyrazolidin-3-ones **19a–g** we decided to prepare substituted 1-aryl-4-diethoxyphosphoryl-1*H*-pyrazol-5-ols **16a–g** from various ethyl 2-acyl-2-diethoxyphosphorylacetates **15a–g** and arylhydrazine hydrochlorides by applying a modified literature procedure[13] (Scheme 2,

Table 1 Preparation of 1-Aryl-4-diethoxyphosphoryl-1*H*-pyrazol-5-ols **11a–e**, 2-Aryl-4-diethoxyphosphoryl-1-methyl-1,2-dihydro-3*H*-pyrazol-3-ones **12a–e**, 2-Aryl-4-diethoxyphosphoryl-1-methylpyrazolidin-3-ones **13a–e**, and 2-Aryl-1-methyl-4-methylidenepyrazolidin-3-ones **14a–e**

Entry	Compd	Ar	Yield of **11** (%)[a]	Yield of **12** (%)[a]	Yield of **13** (%)[a]	Yield of **14** (%)[a]
1	**a**	Ph	79	54	86	91
2	**b**	2-MeC_6H_4	86	72	77	68
3	**c**	4-MeC_6H_4	87	67	82	68
4	**d**	4-ClC_6H_4	85	46	80	84
5	**e**	4-BrC_6H_4	81	63	79	61

[a] Yield of purified, isolated products based on **8**, **11**, **12**, or **13**, respectively.



Scheme 2 *Reagents and conditions*: (a) 1. $H_2NNHAr{\cdot}HCl$, H_2O, reflux, 2 h; 2. K_2CO_3 (2 equiv), reflux, 2 h, then r.t., 18 h; (b) H_2NNHPh, AcOH (2 equiv), H_2O, reflux, 3 h; (c) CF_3SO_3Me (2 equiv), DCE, 80 °C, 2 h; (d) L-Selectride (1.25 equiv), THF, –78 °C, 1 h, then r.t., 18 h; (e) $(CH_2O)_n$ (5 equiv), NaH (1.2 equiv), THF, r.t., 2 h.

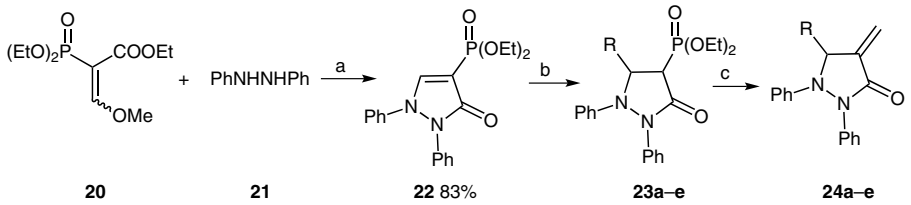
procedure a). This procedure worked well for alkyl-substituted acetates **15a–e** (R = Alk) but aryl-substituted acetates **15f**,**g** (R = Ar) gave low yield of the expected pyrazoles. Pleasingly, heating aryl-substituted acetates **15f**,**g** and phenylhydrazine with acetic acid in water (procedure b) furnished 1,3-diarylpyrazolols **16f**,**g** in good yields (Table 2).[14] N-Methylation of pyrazolols **16a–g**[10] using methyl triflate followed by reduction of 2-aryl-1-methylpyrazol-3-ones **17a–g**[11] with L-Selectride gave Horner–Wadsworth–Emmons reagents **18a–g**, which were obtained as single isomers or mixtures of *trans* and *cis* diastereoisomers in the ratio shown in Table 2. Due to highly basic conditions employed during the reduction one could expect thermodynamic control within the reaction and the preferential formation of the *trans* isomers. Unfortunately, resonances for the H-4 and H-5 protons in the ^{1}H NMR spectra of pyrazolidiones **18** were not sufficiently resolved to determine $J_{H4–H5}$ coupling constants and to confirm the assumed *trans* configuration of these compounds. In view of the planned transformation of pyrazolidinones **18** into methylidenepyrazolidinones **19** no efforts were undertaken to separate the diastereoisomers. In the final step, pyrazolidinones **18a–g** were used for the olefination with formaldehyde to provide final 5-substituted pyrazolidinones **19a–g** in good yields (Table 2).[12]

Having accomplished the synthesis of 3-methylidene-1-methyl-2-arylpyrazolidin-3-ones **14a–e** and **19a–g** we turned our attention to the reaction of the sodium salt of 3-hydroxy-2-propenoate **8** with disubstituted hydrazines. To our disappointment the reaction of **8** with 1,2-diphenylhydrazine hydrochloride did not occur. Pleasingly, replacement of **8** by 3-methoxy-2-diethoxyphosphoryl-acrylate (**20**)[15] proved to be successful. When acrylate **20** and 1,2-diphenylhydrazine (**21**) were heated in refluxing toluene for 80 hours the expected 4-diethoxyphosphoryl-1,2-diphenyl-1,2-dihydro-3*H*-pyrazol-3-one (**22**) was obtained in 83% yield (Scheme 3). In the next step we examined the addition of Grignard reagents to pyrazolone **22**. Unfortunately, all attempts to perform the addition of methylmagnesium chloride to **22** under standard conditions (0 °C to r.t., THF or Et_2O as solvent, addition of CuI) failed. However, performing this reaction in boiling THF for two hours with 1.2 equivalents of MeMgCl gave, after purification by column chromatography, the expected 5-methyl-4-diethoxyphosphoryl-1,2-diphenylpyrazolidin-3-one (**23a**) in a reasonable 52% yield. Applying these optimized conditions we performed the reaction of several Grignard reagents with pyrazolone **22** and obtained the expected adducts **23b–e**, usually as mixtures of *trans* and *cis* isomers (Table 3).[16] Contrary to pyrazolidinones **18**, in the ^{1}H NMR spectra of **23** all signals were resolved and $J_{H4–H5}$ coupling constants could be easily determined. For example, for the major and minor diastereoisomer of **23a** $J_{H4–H5}$ coupling constants were 2.8 Hz and 6.7 Hz, respectively, confirming the *trans* configuration of the latter if pseudoaxial positions of phosphoryl and methyl groups are assumed. To unequivocally confirm the *trans* configuration of the major isomer of pyrazolidinone **23a**, a NOE experiment was performed, showing 13% enhancement in the signal of the H-4 proton when protons of the methyl group in position 5 were irradiated. Because of similar coupling constant patterns in all major isomers of pyr-

Table 2 Preparation of 1-Aryl-4-diethoxyphosphoryl-1*H*-pyrazol-5-ols **16a–g**, 2-Aryl-4-diethoxyphosphoryl-1-methylpyrazol-3-ones **17a–g**, 2-Aryl-4-diethoxyphosphoryl-1-methypyrazolidin-3-ones **18a–g**, and 2-Aryl-1-methyl-4-methylidenepyrazolidin-3-ones **19a–g**

Entry	Compd	R	Ar	Yield of **16** (%)[a]	Yield of **17** (%)[a]	Yield of **18** (%)[a] (*trans*/*cis* ratio)	Yield of **19** (%)[a]
1	**a**	Me	Ph	86	61	75 (85:15)	72
2	**b**	Et	Ph	64	60	75 (90:10)	61
3	**c**	*i*-Pr	Ph	41	51	41 (65:35)	70
4	**d**	*n*-Bu	Ph	72	57	88 (90:10)	58
5	**e**	Et	3-ClC_6H_4	72	75	70 (90:10)	79
6	**f**	Ph	Ph	75	65	84 (100:0)	63
7	**g**	4-MeOC_6H_4	Ph	72	61	51 (100:0)	85

[a] Yield of purified, isolated products based on **15**, **16**, **17**, or **18**, respectively.



Scheme 3 *Reagents and conditions*: (a) toluene, reflux, 80 h; (b) RMgX (1.2 equiv), THF, reflux, 2 h; (c) NaH (1.2 equiv), $(CH_2O)_n$ (5 equiv), THF, r.t., 2 h.

Table 3 Synthesis of 4-Diethoxyphosphoryl-1,2-diphenylpyrazolidin-3-ones **23a–e** and 4-Methylidene-1,2-diphenylpyrazolidin-3-ones **24a–e**

Entry	Compd	RMgX	Yield of **23** (%)[a] (*trans*/*cis* ratio)	Yield of **24** (%)[a]
1	**a**	MeMgCl	52 (85:15)	87
2	**b**	EtMgCl	42 (90:10)	92
3	**c**	*n*-BuMgCl	56 (95:5)	92
4	**d**	vinylMgBr	83 (90:10)	85
5	**e**	PhMgBr	35 (100:0)	89

[a] Yield of purified, isolated product based on **22** or **23**, respectively.

azolidinones **23a–e**, we construe that all major isomers have the *trans* configuration. Phosphorylated pyrazolidinones **23a–e** were next used as Horner–Wadsworth–Emmons reagents for the olefination with formaldehyde to furnish the targeted 4-methylidene-1,2-diphenylpyrazolidin-3-ones **24a–e** in excellent yields (Table 3).[12]

In summary, as a part of an ongoing program in our laboratory focused on the application of Horner–Wadsworth–Emmons approaches in the synthesis of biologically important 2-alkylidene-1-oxoheterocyles, we have developed a simple, effective, and general methodology for the synthesis of novel 4-methylidenepyrazolidin-3-ones. As disclosed, three complementary methods enable the introduction of various alkyl or aryl substituents at positions 1, 2, and/or 5 on the pyrazolidinone ring and open access to a new class of α-alkylidene-γ-lactams with potential cytotoxic activity. Further studies to extend the presented methodology and to test the obtained compounds for their cytotoxic activity are under way.

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(10) **General Procedure for the N-Methylation: Synthesis of 2-Aryl-4-diethoxyphosphoryl-1-methyl-1,2-dihydro-3*H*-pyrazol-3-ones 12a–e and 2-Aryl-4-diethoxyphosphoryl-1-methyl-1,2-dihydro-3*H*-pyrazol-3-ones 17a–g**
A solution of the corresponding pyrazolol **11a–e** (5 mmol) and $(MeO)_2SO_2$ (0.57 mL, 6 mmol) in DCE (50 mL) was heated at 80 °C for 18 h. The solvent was evaporated, and the crude product was purified by column chromatography (eluent: EtOAc–MeOH, 9:1). With the pyrazolols **16a–g** the reaction was performed with CF_3SO_3Me (1.64 g, 10 mmol) at 80 °C for 2 h.
Diethyl [1-Methyl-3-oxo-2-(*p*-tolyl)-2,3-dihydro-1*H*-pyrazol-4-yl]phosphonate (12c)
Pale-yellow oil. IR (film): 3035, 1655, 1509, 1258, 1029, 758, 542 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.25 [t, $^3J_{H–H}$ = 7.1 Hz, 6 H, $(CH_3CH_2O)_2P(O)$], 2.28 (s, 3 H, CH_3), 3.27 (s, 3 H, CH_3), 4.06–4.14 [m, 4 H, $(CH_3CH_2O)_2P(O)$], 7.09 (d, $^3J_{H–H}$ = 8.2 Hz, 2 H, 2 × HAr), 7.18 (d, $^3J_{H–H}$ = 8.2 Hz, 2 H, 2 × HAr), 7.84 (d, $^3J_{H–P}$ = 4.4 Hz, 1 H, H-5). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.0 [d, $^3J_{C–P}$ = 6.9 Hz, $(CH_3CH_2O)_2P(O)$], 20.8 (s, CH_3), 36.9 (s, CH_3), 62.0 [d, $^2J_{C–P}$ = 5.6 Hz, $(CH_3CH_2O)_2P(O)$], 93.8 (d, $^1J_{C–P}$ = 222.2 Hz, C-4), 126.3 (s, 2 × CAr), 129.8 (s, 2 × CAr), 130.0 (s, CAr), 138.6 (s, CAr), 147.1 (d, $^2J_{C–P}$ = 18.8 Hz, C5), 162.9 (d, $^2J_{C–P}$ = 14.0 Hz, C3). ^{31}P NMR (101 MHz, $CDCl_3$): δ = 12.51. Anal. Calcd for $C_{15}H_{21}N_2O_4P$: C, 55.55; H, 6.53. Found: C, 55.42; H, 6.60.
(11) **General Procedure for L-Selectride Reduction: Synthesis of 2-Aryl-4-diethoxyphosphoryl-1-methylpyrazolidin-3-ones 13a–e and 2-Aryl-4-diethoxyphosphoryl-1-methylpyrazolidin-3-ones 18a–g**
To a cooled (–78 °C) solution of the corresponding pyrazolone **12a–e** or **17a–g** (1 mmol) in THF (15 mL) was added dropwise a THF solution of L-Selectride (1.25 mmol) under an argon atmosphere, and the mixture was stirred at this temperature for 1 h. Then, the mixture was allowed to slowly warm to r.t. and was stirred at r.t. overnight. The reaction mixture was concentrated to half the initial volume and quenched with 10% aq NH_4Cl. After extraction with CH_2Cl_2 (3 × 15 mL), the combined organic layers were washed with brine and dried over $MgSO_4$. After filtration and evaporation, the crude product was purified by column chromatography (eluent: EtOAc–MeOH, 9:1).

Diethyl [1-Methyl-3-oxo-2-(*p*-tolyl)pyrazolidin-4-yl]phosphonate (13c)

Pale-yellow oil. IR (film): 2982, 1689, 1614, 1508, 1354 1248, 1018, 963 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 1.24 [t, $^3J_{H–H}$ = 7.0 Hz, 3 H, (CH_3CH_2O)P(O)], 1.27 [t, $^3J_{H–H}$ = 7.0 Hz, 3 H, (CH_3CH_2O)P(O)], 2.25 (s, 3 H, CH_3), 2.57 (s, 3 H, CH_3), 3.56 (dd, $^3J_{H–H}$ = 9.2 Hz, $^3J_{H–P}$ = 14.5 Hz, 2 H, 2 × H-5), 3.84 (dt, $^3J_{H–H}$ = 9.2 Hz, $^2J_{H–P}$ = 21.5 Hz, 1 H, H-4), 4.05–4.20 [m, 4 H, (CH_3CH_2O)$_2$P(O)], 7.13–7.20 (m, 2 H, 2 × HAr), 7.48–7.55 (m, 2 H, 2 × HAr). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 15.5 [d, $^3J_{C–P}$ = 5.6 Hz, (CH_3CH_2O)$_2$P(O)], 19.8 (s, CH_3), 40.4 (d, $^1J_{C–P}$ = 146.9 Hz, C-4), 42.9 (s, CH_3), 51.7 (d, $^2J_{C–P}$ = 1.8 Hz, C-5), 61.5 [d, $^2J_{C–P}$ = 6.7 Hz, (CH_3CH_2O)P(O)], 61.9 [d, $^2J_{C–P}$ = 6.4 Hz, (CH_3CH_2O)P(O)], 119.7 (s, 2 × CAr), 128.7 (s, 2 × CAr), 133.7 (s, CAr), 134.1 (s, CAr), 164.9 (d, $^2J_{C–P}$ = 2.3 Hz, C-3). ^{31}P NMR (101 MHz, DMSO-d_6): δ = 23.13. Anal. Calcd for $C_{15}H_{23}N_2O_4P$: C, 55.21; H, 7.10. Found: C, 55.11; H, 7.23.

(12) **General Procedure for Methylidenation: Synthesis of 2-Aryl-1-methyl-4-methylidenepyrazolidin-3-ones 14a–e, 2-Aryl-1-methyl-4-methylidenepyrazolidin-3-ones 19a–g, and 4-Methylidene-1,2-diphenylpyrazolidin-3-ones 24a–e**

To a solution of the corresponding pyrazolidinone **13a–e**, **18a–g**, or **23a–e** (0.5 mmol) in THF (5 mL), NaH (14 mg, 0.6 mmol) was added, and the resulting mixture was stirred at r.t. for 30 min. Then, paraformaldehyde (75 mg, 2.5 mmol) was added in one portion. After 2 h the reaction mixture was quenched with brine (5 mL), the solvent was evaporated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were dried over $MgSO_4$, filtered, and the solvent was evaporated. The crude product was purified by column chromatography (eluent: CH_2Cl_2).

1-Methyl-4-methylene-2-(*p*-tolyl)pyrazolidin-3-one (14c)

Pale-yellow oil. IR (film): 2960, 2858, 1693, 1662, 1492, 1348, 822 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.32 (s, 3 H, CH_3), 2.56 (s, 3 H, CH_3), 3.52–3.88 (m, 1 H, 1 × H-5), 4.06–4.40 (m, 1 H, 1 × H-5), 5.49–5.51 (m, 1 H, *H*CH=), 6.14–6.16 (m, 1 H, *H*CH=), 7.15–7.20 (m, 2 H, 2 × HAr), 7.70–7.79 (m, 2 H, 2 × HAr). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 19.5 (s, CH_3), 45.9 (s, CH_3), 55.8 (s, C-5), 117.9 (s, CH_2=), 119.3 (s, 2 × CAr), 127.9 (s, 2 × CAr), 134.3 (s, CAr), 134.8 (s, CAr), 139.2 (s, C-4), 165.2 (s, C-3). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98. Found: C, 71.09; H, 7.12.

(13) Miller, P. C.; Curtis, J. M.; Molyneaux, J. M.; Owen, T. J. US 6,297,194 B1, **2001**.

(14) **General Procedure for the Synthesis of 1-Aryl-4-diethoxyphosphoryl-1*H*-pyrazol-5-ols 16f,g**

A mixture of ethyl 2-aroyl-2-diethoxyphosphorylacetate **15f**,**g** (10 mmol), phenylhydrazine (11 mmol), and AcOH (0.6 g, 20 mmol) was refluxed in H_2O (50 mL) for 3 h. The reaction mixture was cooled and extracted with EtOAc (2 × 30 mL). The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography (eluent: EtOAc–hexane, 1:1).

(15) Janecki, T.; Albrecht, A.; Koszuk, J. K.; Modranka, J.; Słowak, D. *Tetrahedron Lett.* **2010**, *51*, 2274.

(16) **General Procedure for the Synthesis of 4-Diethoxyphosphoryl-1,2-diphenylpyrazolidin-3-ones 23a–e**

To a solution of the 4-diethoxyphosphoryl-1,2-diphenylpyrazol-3-one **22** (2 mmol) in THF (15 mL) a solution of the corresponding Grignard reagent (2.4 mmol) was added dropwise, under an argon atmosphere at r.t., and the resulting mixture was refluxed for 2 h. After this time the reaction mixture was quenched with H_2O (5 mL), acidified to pH ca. 3 with 10% aq HCl solution, and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were dried over $MgSO_4$, filtered, and the solvent was evaporated. The crude product was purified by column chromatography (eluent: $CHCl_3$–MeOH, 98:2).

4-Diethoxyphosphoryl-1,2,5-triphenylpyrazolidin-3-one (23e)

Pale-yellow oil. IR (film): 2981, 1703, 1593, 1489, 1391, 1250, 1014, 964 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.07 [t, $^3J_{H–H}$ = 7.1 Hz, 3 H, (CH_3CH_2O)P(O)], 1.30 [t, $^3J_{H–H}$ = 7.0 Hz, 3 H, (CH_3CH_2O)P(O)], 3.30 (dd, $^2J_{H–P}$ = 23.4 Hz, $^3J_{H–H}$ = 3.0 Hz, 1 H, *H*-4), 3.67–3.84 [m, 1 H, (CH_3CHO)P(O)], 3.91–4.04 [m, 1 H, (CH_3CHO)P(O)], 4.08–4.22 [m, 2 H, (CH_3CH_2O)P(O)], 5.39 (dd, $^3J_{H–P}$ = 19.1 Hz, $^3J_{H–H}$ = 3.0 Hz, 1 H, H-5), 6.81–6.98 (m, 4 H, 4 × HAr), 7.10–7.24 (m, 3 H, 3 × HAr), 7.31–7.43 (m, 4 H, 4 × HAr), 7.50–7.53 (m, 2 H, 2 × HAr), 7.83–7.87 (m, 2 H, 2 × HAr). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.9 [d, $^3J_{C–P}$ = 5.4 Hz, (CH_3CH_2O)P(O)], 16.1 [d, $^3J_{C–P}$ = 6.1 Hz, (CH_3CH_2O)P(O)], 46.7 (d, $^1J_{C–P}$ = 137.2 Hz, *C*-4), 62.9 [d, $^2J_{C–P}$ = 6.9 Hz, (CH_3CH_2O)P(O)], 63.3 [d, $^2J_{C–P}$ = 6.6 Hz, (CH_3CH_2O)P(O)], 68.6 (d, $^2J_{C–P}$ = 0.9 Hz, C-5), 117.4 (s, 2 × CAr), 118.9 (s, 2 × CAr), 123.1 (s, CAr), 125.0 (s, CAr), 125.2 (s, 2 × CAr), 128.1 (s, CAr), 128.7 (s, 2 × CAr), 128.9 (s, 2 × CAr), 129.1 (s, 2 × CAr), 137.7 (s, CAr), 142.1 (d, $^3J_{C–P}$ = 12.1 Hz, CAr), 149.4 (s, CAr), 164.6 (d, $^2J_{C–P}$ = 5.7 Hz, C-3). ^{31}P NMR (101 MHz, $CDCl_3$): δ = 19.60. Anal. Calcd for $C_{25}H_{27}N_2O_4P$: C, 66.66; H, 6.04. Found: 66.49; H, 5.97.