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-diethoxyphosphorylactates, or 3-methoxy-2-diethoxyphosphoryl acrylate 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

In a search for new, biologically promising analogues we have developed syntheses of several classes of α-alkyldene-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

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,5b,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-1H-pyrazol-5-ols 11a–e were prepared by adapting the literature procedure described for
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). 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). 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).

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-1H-pyrazol-3-ones 16a–g from various ethyl 2-acyl-2-diethoxyphosphorylacettes 15a–g and arylhydrazine hydrochlorides by applying a modified literature procedure (Scheme 2).
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-diarylpazolidinol 16f–g in good yields (Table 2).14 N-Methylation of pyrazolones 16a–g10 using methyl triflate followed by reduction of 2-aryl-1-methylpyrazol-3-ones 17a–g11 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 1H NMR spectra of pyrazolidinones 18 were not sufficiently resolved to determine JH4-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-dioethoxophosphoryl-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-dioethoxophosphoryl-1,2-diphenyl-1,2-dihydro-3H-pyrazol-3-one (22) was obtained in 83% yield (Scheme 3). In the next step we examined the addition of Grignard reagents to pyrazoline 22. Unfortunately, all attempts to perform the addition of methylmagnesium chloride to 22 under standard conditions (0 °C to r.t., THF or Et2O 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-dioethoxophosphoryl-1,2-diphenylpyrazolidin-3-one (23a) in a reasonable 52% yield. Applying these optimized conditions we performed the reaction of several Grignard reagents with pyrazoline 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 1H NMR spectra of 23 all signals were resolved and JH4-H5 coupling constants could be easily determined. For example, for the major and minor diastereoisomer of 23a JH4-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 pyrazolidinones 18a–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-dioethoxophosphoryl-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-dioethoxophosphoryl-1,2-diphenyl-1,2-dihydro-3H-pyrazol-3-one (22) was obtained in 83% yield (Scheme 3). In the next step we examined the addition of Grignard reagents to pyrazoline 22. Unfortunately, all attempts to perform the addition of methylmagnesium chloride to 22 under standard conditions (0 °C to r.t., THF or Et2O 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-dioethoxophosphoryl-1,2-diphenylpyrazolidin-3-one (23a) in a reasonable 52% yield. Applying these optimized conditions we performed the reaction of several Grignard reagents with pyrazoline 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 1H NMR spectra of 23 all signals were resolved and JH4-H5 coupling constants could be easily determined. For example, for the major and minor diastereoisomer of 23a JH4-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 pyrazolidinones 18a–g

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

<table>
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<th>Ar</th>
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<th>Yield of 18 (%)</th>
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<td>51 (100:0)</td>
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*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), (CH2O)n (5 equiv), THF, r.t., 2 h.

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azolidinones 23a–e, we conclude 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-oxoheterocycles, we have developed a simple, effective, and general methodology for the synthesis of novel 4-methylidene-1,2-dihydro-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.

Acknowledgement

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References and Notes

(10) General Procedure for the N-Methylation: Synthesis of 2-Aryl-4-dioxyphosphoryl-1-methyl-1,2-dihydro-3H-pyrazol-3-ones 12a–e and 2-Aryl-4-dioxyphosphoryl-1-methyl-1,2-dihydro-3H-pyrazol-3-ones 17a–g

A solution of the corresponding pyrazolone 11a–e (5 mmol) and (MeO)2SO2 (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 (elucent: EtOAc–MeOH, 9:1). With the pyrazolones 16a–g the reaction was performed with CF3SO2Me (1.6 g, 10 mmol) at 80 °C for 2 h.

Diethyl [1-Methyl-3-oxo-2-(p-tolyl)-3,2-dihydro-1H-pyrazol-4-yl]phosphonate (12c)

Pale-yellow oil. IR (film): 3035, 1655, 1509, 1258, 1029, 758, 542 cm–1. 1H NMR (250 MHz, CDCl3): δ = 1.25 [t, JH–H = 7.1 Hz, 6 H, (CH3CH2O)2P(O)], 2.28 (s, 3 H, CH3), 3.27 (s, 3 H, CH3), 4.06–4.14 [m, 4 H, (CH3C=O)2P(O)], 4.07 (d, JH–H = 8.2 Hz, 2 H, 2 × HAr), 7.18 (d, JH–H = 8.2 Hz, 2 H, 2 × HAr), 7.84 (d, JH–H = 4.4 Hz, 1 H, H-5). 13C NMR (62.9 MHz, CDCl3): δ = 66.0 [d, Jc–H = 6.9 Hz, (CH3CH2O)2P(O)], 20.5 (s, CH3), 36.9 (s, CH2O), 62.0 [d, Jc–C = 5.6 Hz, (CH3CH2O)2P(O)], 93.8 (s, Jc–C = 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, Jc–C = 18.8 Hz, C5), 162.9 (d, Jc–C = 14.0 Hz, C3). 31P NMR (101 MHz, CDCl3): δ = -12.51. Anal. Calcd for C19H18N2O4P: 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-dioxyphosphoryl-1-methylpyrazolidin-3-ones 13a–e and 2-Aryl-4-dioxyphosphoryl-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 NH4Cl. After extraction with CH2Cl2 (3 × 15 mL), the combined organic layers were washed with brine and dried over MgSO4. After filtration and evaporation, the crude product was purified by column chromatography (elucent: EtOAc–MeOH, 9:1).
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Synthesis of 4-Methylidenepyrazolidin-3-ones

Diethyl [1-Methyl-3-oxo-2-(p-toly1)pyrazolidin-4-yl]phosphonate (10c)

Pale-yellow oil. IR (film): 2982, 1699, 1614, 1508, 1248, 1018, 963 cm−1. 1H NMR (250 MHz, CDCl3): δ = 2.32 (3 H, CH3), 2.56 (3 H, CH3), 3.52–3.88 (m, 1 H, 1 × H-5), 3.84 (dt, 3 JH–H = 9.2 Hz, 3 H, CH3), 4.05–4.20 [m, 4 H, (CH3C=CH2O)2P(O)], 7.12. 13C NMR (62.9 MHz, CDCl3): δ = 31.6, 33.9, 45.9 (s, CH3), 55.8 (s, C-5), 117.9 (s, CH-3, 2 × CH3C=CH2O)P(O), 127.9 (s, 2 × CH3C=CH2O)P(O), 134.3 (s, CAr), 134.8 (s, CAr), 139.2 (s, C-4), 165.2 (s, C-3). Anal. Calcd for C15H23N2O4P: C, 55.21; H, 7.10. Found: C, 55.11; H, 7.23.

(12) General Procedure for Methylenation: Synthesis of 2-Aryl-1-methyl-4-methylidene-1,2-diphenylpyrazolidin-3-ones 14a–e, 2-Aryl-1-methyl-4-methylidene-1,2-diphenylpyrazolidin-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 CH2Cl2 (2 × 30 mL). The organic extracts were washed with brine, dried over Na2SO4, and concentrated. The crude product was purified by column chromatography (eluent: CHCl3–MeOH, 98:2). (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-dietoxyphosphoryl-1H-pyrazol-5-ols 16f,g

A mixture of ethyl 2-aryl-2-dietoxyphosphorylacetate (15f,g (10 mmol), phenylhydrazine (11 mmol), and AcOH (0.6 g, 20 mmol) was refluxed in H2O (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 Na2SO4, and concentrated. The crude product was purified by column chromatography (eluent: EtOAc–hexane, 1:1).


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

To a solution of the 4-dietoxyphosphoryl-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 H2O (5 mL), acidified to pH ca. 3 with 10% aq HCl solution, and extracted with CH2Cl2 (3 × 10 mL). The organic extracts were dried over MgSO4, filtered, and the solvent was evaporated. The crude product was purified by column chromatography (eluent: CHCl3–MeOH, 98:2). (16) 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, CDCl3): δ = 1.07 [t, 3 JH–H = 7.1 Hz, 3 H, (CH3CH2O)2P(O)], 1.39 [t, 3 JH–H = 7.0 Hz, 3 H, (CH3CH2O)2P(O)], 3.30 (dd, 3 JPC = 23.4 Hz, 3 JH–H = 3.0 Hz, H–H = 7.0 Hz, 3 H, (CH3CH2O)2P(O)], 5.39 (dd, 3 JPC = 19.1 Hz, 3 JH–H = 3.0 Hz, H–H = 7.0 Hz, 3 H, (CH3CH2O)2P(O)], 6.81–6.98 (m, 4 H, 4 × CHAr), 7.10–7.24 (m, 3 H, 3 × CHAr), 7.31–7.43 (m, 4 H, 4 × CHAr), 7.50–7.53 (m, 2 H, 2 × CHAr), 7.83–7.87 (m, 2 H, 2 × CHAr). 13C NMR (62.9 MHz, CDCl3): δ = 15.9 [d, 3 JPC = 5.4 Hz, (CH3CH2O)2P(O)], 16.1 [d, 3 JPC = 6.1 Hz, (CH3CH2O)2P(O)], 46.7 (d, 3 JPC = 137.2 Hz, C-4), 62.9 [d, 3 JPC = 6.9 Hz, (CH3CH2O)2P(O)], 63.3 (d, 3 JPC = 6.6 Hz, (CH3CH2O)2P(O)], 68.6 (d, 3 JPC = 0.9 Hz, C-5), 117.4 (s, 2 × CHAr), 118.9 (s, 2 × CHAr), 121.3 (s, CHAr), 125.0 (s, CHAr), 125.2 (s, 2 × CHAr), 128.1 (s, CHAr), 128.7 (s, 2 × CHAr), 128.9 (s, 2 × CHAr), 129.1 (s, 2 × CHAr), 137.3 (s, CHAr), 142.1 (d, 3 JPC = 12.1 Hz, CAr), 149.4 (s, CHAr), 164.6 (d, 3 JPC = 5.7 Hz, C-3). 31P NMR (101 MHz, CDCl3): δ = 19.60. Anal. Calcd for C25H27N2O8P: C, 66.66; H, 6.04. Found: 66.49; H, 5.97.