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New, diastereoselective synthesis of 1-alkyl-5-alkylidene-3-methylidenepyrrolidin-2-ones

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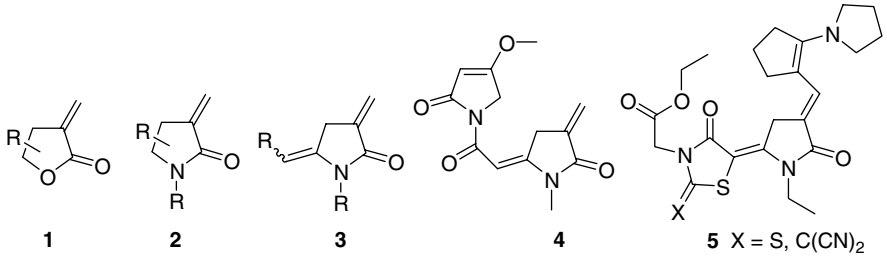
Abstract—The diastereoselective synthesis of 1-alkyl-5-alkylidene-3-methylidenepyrrolidin-2-ones was readily accomplished in a two-step reaction sequence consisting of the reaction of 2-diethoxyphosphoryl-4-oxoalkanoates with amines followed by Horner–Wadsworth–Emmons olefination of formaldehyde using the intermediate 1-alkyl-5-alkylidene-3-diethoxyphosphorylpyrrolidin-2-ones.

α-Methylidene-γ-lactones **1** and γ-lactams **2** are a well-known group of natural compounds possessing a wide spectrum of biological activities.[1,2] Much less recognized are 5-alkylidene-3-methylidenepyrrolidin-2-ones (γ-alkylidene-α-methylidene-γ-lactams) **3**. A natural product possessing this structure, pukeleimid E **4**, was isolated from a shallow-water variety of the marine blue-green alga, *Lyngbya majuscula*.[3] Compounds containing moiety **3** were also found to be intermediates in the reduction of biliverdin to phycocyanobilin, a key step in the biosynthesis of the linear tetrapyrrole prosthetic groups of cyanobacterial phytochromes and the light-harvesting phycobiliproteins.[4] However, to the best of our knowledge, there are no reports on the synthesis of pyrrolidinones **3**. The only compounds of related structure described in the literature are sensitizing dyes **5**, which can be used to sensitize Ag halide emulsions.[5]

Our research focused on the synthesis of α-methylidene-γ-lactones and γ-lactams exhibiting cytotoxic activity[6–8] has recently led to the development of a simple and efficient route to 2-diethoxyphosphoryl-4-oxoalkanoates **6**, based on a Michael addition of the sodium derivatives of nitroalkanes to (2-diethoxyphosphoryl)acrylate and a Nef reaction of the intermediate 3-diethoxyphosphoryl-4-nitroalkanoates.[9]

In this letter, we describe an interesting and rather unexpected application of oxoalkanoates **6** in the synthesis of 1-alkyl-5-alkylidene-3-methylidenepyrrolidin-2-ones **10**.

The reaction of **6** with hexyl- or benzylamine in the presence of *p*-toluenesulfonic acid (*p*-TSA) in boiling toluene gave 1-alkyl-5-alkylidene-3-diethoxyphosphoryl-pyrrolidin-2-ones **9a**–**g** (Scheme 1), which were purified by column chromatography on silica gel enriched with



Keywords: Pyrrolidinones; Horner–Wadsworth–Emmons olefination; α-Methylidene-γ-lactams.
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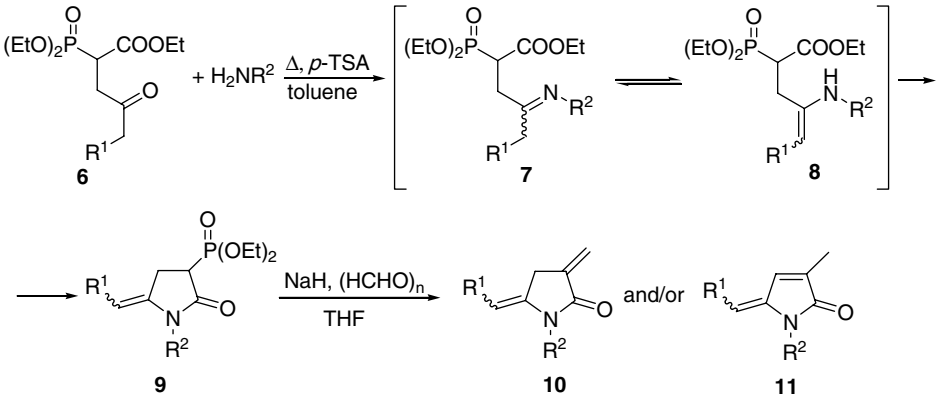


Scheme 1.

0.1% Ca (Fluka®). It is worth stressing that the use of regular silica gel caused decomposition of the obtained products and substantially decreased the yields. Pyrrolidinones **9** were formed in good to excellent yields as single diastereoisomers of *E* configuration. Only **9d** was obtained as a mixture of *E* and *Z* isomers in a 95:5 ratio (Table 1).[10] Careful analysis of the ^{1}H, ^{13}C and ^{31}P NMR spectra fully confirmed the structure and configuration of compounds **9**. The most characteristic signals were those of the vinyl protons. For example, in the proton spectrum of **9f**, the vinyl proton appeared as a singlet with a chemical shift $\delta = 5.76$ ppm, whereas calculated values[11] for (*E*)-**9f** and (*Z*)-**9f** are 5.73 and 5.55 ppm, respectively. Formation of pyrrolidinones **9** can be easily rationalized assuming that there is an equilibrium between imines **7** and enamines **8**. Lactamization of enamines **8** gives pyrrolidinones **9**.

A Horner–Wadsworth–Emmons olefination of paraformaldehyde using pyrrolidinones **9a**–**g** performed in boiling THF in the presence of NaH as a base gave, after purification by column chromatography on silica gel enriched with 0.1% Ca, pure 1-alkyl-5-alkylidene-3-methylidenepyrrolidin-2-ones **10** and/or their rearrangement products 1-alkyl-5-alkylidene-3-methylpyrrol-2-ones **11**, usually in moderate yields (Table 1).[12] The *E*/*Z* diastereoisomer ratios in products **10** and **11** were the same as in the starting pyrrolidinones **9**. Also, chemical shifts of the corresponding vinyl protons in **10** or **11** indicated that the geometry of the alkylidene double bond did not change in the reaction process. The correctness of the configurational assignments was further confirmed by a NOE experiment performed on the major diastereoisomer of pyrrolidinone **10d** (Fig. 1).

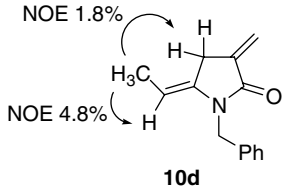
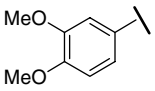
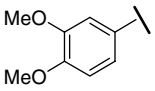


Figure 1.

Table 1. Diastereoselective synthesis of 5-alkylidene-3-diethoxyphosphorylpyrrolidin-2-ones **9** and 5-alkylidene-3-methylidenepyrrolidin-2-ones **10** or 5-alkylidene-3-methylpyrrol-2-ones **11**

Compound	R^1	R^2	**9**		**10** and/or **11**		
			Yield[a] [%]	*E*/*Z*[b]	Yield[a] [%]	*E*/*Z*[b]	**10**/**11**[b]
a	Me	*n*-C_6H_{13}	60	>99/1	54	>99/1	>99/1
b	Ph	*n*-C_6H_{13}	65	>99/1	70	>99/1	>99/1
c		*n*-C_6H_{13}	50	>99/1	27	>99/1	>99/1
d	Me	$PhCH_2$	68	>95/5	45	95/5	>99/1
e	*n*-Bu	$PhCH_2$	95	>99/1	42	>99/1	>99/1
f	Ph	$PhCH_2$	85	>99/1	50	>99/1	>1/99
g		$PhCH_2$	88	>99/1	48[c]	>99/1	35/65

[a] All yields refer to pure, isolated products based on **6** or **9**, respectively. All new compounds were fully characterized by IR, ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and elemental analysis.

[b] Ratio determined from the ^{1}H NMR spectrum of the crude product.

[c] Combined yield of **10g** and **11g**.

In summary, we have developed a new, simple and general route to biologically important 5-alkylidene-3-methylidenepyrrolidin-2-ones **10** starting from easily available 2-diethoxyphosphoryl-4-oxoalkanoates **6**. Further synthetic efforts will be undertaken to improve the yield of the olefination step and to broaden the scope of the method by using more elaborate oxoalkanoates **6**. Moreover, pyrrolidinones **10** and pyrrolone **11f** are currently being tested for their cytotoxic activity.

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10. General procedure for the synthesis of 1-alkyl-5-alkylidene-3-diethoxyphosphorylpyrrolidin-2-ones **9a**–**g**: A mixture of 2-diethoxyphosphoryl-4-oxoalkanoate **6** (1.7 mmol), corresponding amine (2.04 mmol) and *p*-toluenesulfonic acid (0.016 g, 0.085 mmol) in toluene (25 mL) was refluxed with azeotropic removal of water. The progress of the reaction was occasionally monitored by ^{31}P NMR. After oxoalkanoate **6** had been completely consumed (approximately 23 h) the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography ($CHCl_3$ as eluent) on silica gel 60 (SiO_2 + 0.1% Ca, 230–400 mesh, FLUKA®) affording pure **9**. Sample data: (E)-1-Benzyl-5-benzylidene-3-diethoxyphosphorylpyrrolidin-2-one **9f**: (0.577 g, 85%); colourless oil; IR (film, cm^{-1}): ν 1712, 1656, 1248; ^{31}P NMR (101 MHz, $CDCl_3$): δ 22.96; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.30 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.38 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 3.20–3.45 (m, 3H), 4.10–4.32 (m, 4H), 4.69 (d, $^2J_{HH}$ = 15.5 Hz, 1H), 4.99 (d, $^2J_{HH}$ = 15.5 Hz, 1H), 5.76 (s, 1H), 7.24–7.37 (m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.62 (d, $^3J_{PC}$ = 6.0 Hz), 24.54 (d, $^2J_{PC}$ = 3.1 Hz), 37.86 (d, $^1J_{PC}$ = 143.8 Hz), 42.60 (s), 61.04 (d, $^2J_{PC}$ = 6.6 Hz), 61.52 (d, $^2J_{PC}$ = 6.6 Hz), 102.98 (s), 124.01 (s), 125.22 (s), 125.69 (s), 125.95 (s), 126.70 (s), 126.87 (s), 133.70 (s), 134.25 (s), 137.00 (d, $^3J_{PC}$ = 4.6 Hz), 168.21 (d, $^2J_{PC}$ = 4.9 Hz); Anal. Calcd for $C_{22}H_{26}NPO_4$: C, 66.16; H, 6.56; N, 3.51. Found: C, 66.31; H, 6.63; N, 3.63.
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12. General procedure for the synthesis of 1-alkyl-5-alkylidene-3-methylidenepyrrolidin-2-ones **10a**–**e**,**g** and 1-alkyl-5-alkylidene-3-methylpyrrol-2-ones **11f**,**g**: A solution of 1-alkyl-5-alkylidene-3-diethoxyphosphorylpyrrolidin-2-one **9** (1.0 mmol) in THF (3 mL) was added at room temperature to a stirred suspension of NaH (0.025 g, 1.05 mmol) in THF (5 mL) under an argon atmosphere. The reaction mixture was stirred at room temperature for 30 min. Next, paraformaldehyde (0.033 g, 2.0 mmol) was added in one portion and the reaction mixture was refluxed for 1 h, cooled to 0 °C and water (10 mL) was added. The solvent was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure affording the crude product, which was purified by column chromatography ($CHCl_3$ as eluent) on silica gel 60 (SiO_2 + 0.1% Ca, 230–400 mesh, FLUKA®) to give **10** or **11**. Sample data: (E)-1-Benzyl-3-methylidene-5-pentylidenepyrrolidin-2-one **10e**: (0.107 g, 42%); pale-yellow oil; IR (film, cm^{-1}): ν 1708, 1680; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.85 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.18–1.38 (m, 4H), 1.94 (q, $^3J_{HH}$ = 7.5 Hz, 2H), 3.50 (dt, $^4J_{HH}$ = 2.8 Hz, $^4J_{HH}$ = 2.5 Hz, 2H), 4.62 (tt, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 2.8 Hz, 1H), 4.77 (s, 2H), 5.45 (t, $^4J_{HH}$ = 2.5 Hz, 1H), 6.14 (t, $^4J_{HH}$ = 2.5 Hz, 1H), 7.20–7.36 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.86 (s), 22.07 (s), 26.49 (s), 28.04 (s), 32.04 (s), 43.98 (s), 102.45 (s), 116.48 (s), 126.78 (s), 127.17 (s), 128.45 (s), 134.90 (s), 136.16 (s), 136.62 (s), 168.15 (s); Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 80.14; H, 8.26; N, 5.56; (E)-1-Benzyl-5-benzylidene-3-methyl-1H-pyrrol-2(5H)-one **11f**: (0.138 g, 50%); pale-yellow oil; IR (film, cm^{-1}): ν 1684, 1624; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.08 (s, 3H), 4.95 (s, 2H), 6.26 (s, 1H), 7.12 (s, 1H), 7.20–7.54 (m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 11.21 (s), 43.06 (s), 112.51 (s), 124.87 (s), 127.24 (s), 127.45 (s), 127.92 (s), 128.57 (s), 128.63 (s), 129.19 (s), 134.97 (s), 135.18 (s), 137.30 (s), 138.96 (s), 170.38 (s); Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.69; H, 6.17; N, 5.30.