2-Diethoxyphosphoryl-4-nitroalkanoates – Versatile Intermediates in the Synthesis of α-Alkylidene-γ-lactones and Lactams

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Abstract: Michael addition of various nitroalkanes **7a–f** to ethyl (2-diethoxyphosphoryl)acrylate (**6**) gave 2-diethoxyphosphoryl-4-nitroalkanoates **8a–f**. Transformation of the nitro functionality into hydroxy or amino group and cyclization yielded 3-(diethoxyphosphoryl)tetrahydro-2-furanones **11a–e** or 3-(diethoxyphosphoryl)pyrrolidin-2-ones **14a–e**, respectively. These compounds were then used in Horner–Wadsworth–Emmons olefinations of aldehydes to give 3-alkylidenedihydrofuran-2-ones **12a–e** or **17a–c** and 3-methylidenepyrrolidin-2-ones **15a–e**.

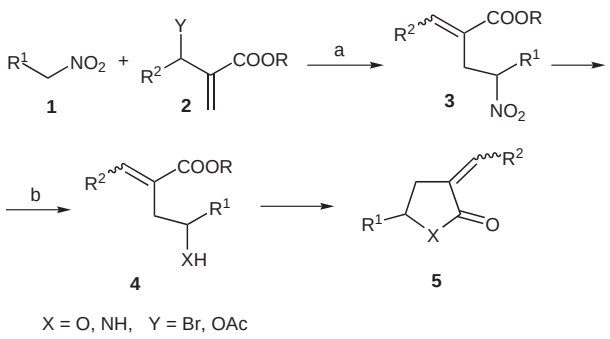
Key words: Michael addition, nitroalkanoates, Wittig type olefination, α-alkylidenelactones, α-methylidenelactams

α-Alkylidene-γ-lactone and lactam framework can be found in many natural compounds exhibiting wide and usually strong biological activity.[1] As a consequence, many synthetic routes for the construction of this skeleton have been developed.[1–4]

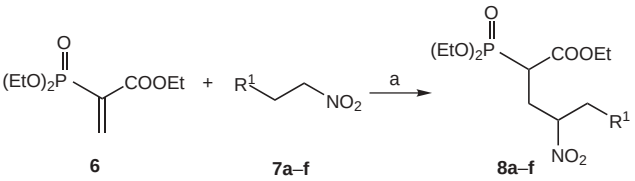
One of very attractive but little explored approaches employs functionalized nitroalkanes for the construction of lactone or lactam ring. This method utilizes 2-alkylidene-4-nitroalkanoates **3** which can be prepared in base-promoted S_N2' reaction of nitroalkanes **1** with acrylates **2** easily accessible from Baylis–Hillman adducts[5] (Scheme 1). Transformation of **3** into 4-hydroxy- or 4-aminoalkanoates **4** can be accomplished via Nef reaction followed by reduction of the carbonyl group or simple reduction of nitro group, respectively. Depicted reaction sequence has been successfully used in the preparation of γ-lactones **5** (X = O)[6,7] and, very recently, γ-lactams **5** (X = NH).[8] These syntheses, although convenient, are however restricted to α-arylmethylidene-γ-lactones,[6] α-methylidene-γ-lactones[7] or α-arylmethylidene-γ-lactams.[8]

In this communication we report that nitroalkanoate approach combined with Horner–Wadsworth–Emmons technique for the construction of alkylidene bond[9] establishes a novel, general and convenient method for the synthesis of α-alkylidene-γ-lactones **12** or **17** and α-methylidene-γ-lactams **15**.

2-Diethoxyphosphoryl-4-nitroalkanoates **8a–f**, which are the key intermediates in our method, were readily obtained in Michael addition of nitroalkanes **7a–f** to ethyl (2-diethoxyphosphoryl)acrylate (**6**)[10] in THF, in the presence of NaH as a base (Scheme 2). Initially, we used equimolar amounts of nitroalkane and acrylate (**6**:**7**:NaH = 1:1:1.1). However, yields of nitroalkanoates **8** were only moderate (40–50%) under these conditions. We found out that yield can be improved significantly when two-fold excess of nitroalkane (**6**:**7**:NaH = 1:2:1.1) was used. Crude products were purified by column chromatography to give alkanoates **8a–f**[11] as mixtures of diastereoisomers with close to a 3:2 ratio (Table 1).



Scheme 1 (a) Base; (b) Nef reaction and reduction of carbonyl group (X = O) or reduction of nitro group (X = NH).



Scheme 2 *Reagents and conditions*: (a) NaH, THF, r.t., 24 h.

4-Nitroalkanoates **8a–e** were then used in two independent synthetic protocols for the preparation of 3-alkylidenedihydrofuran-2-ones **12a–e** or **17a–c** and 3-methylidenepyrrolidin-2-ones **15a–e**.

In the first protocol nitro functionality was converted into carbonyl group (Nef reaction) using mild oxidative conditions to give 2-diethoxyphosphoryl-4-oxoalkanoates **9a–e**, usually in excellent yields (Scheme 3, Table 1). Chemoselective reduction of the carbonyl group in alkanoates **9** using $NaBH_4$ gave 4-hydroxyalkanoates **10a–e** which, after acidic work up, lactonized spontaneously to 3-(diethoxyphosphoryl)tetrahydrofuran-2-ones **11a–e**. These compounds were obtained as mixtures of diastereoisomers with close to a 1:1 ratio. Finally, furanones

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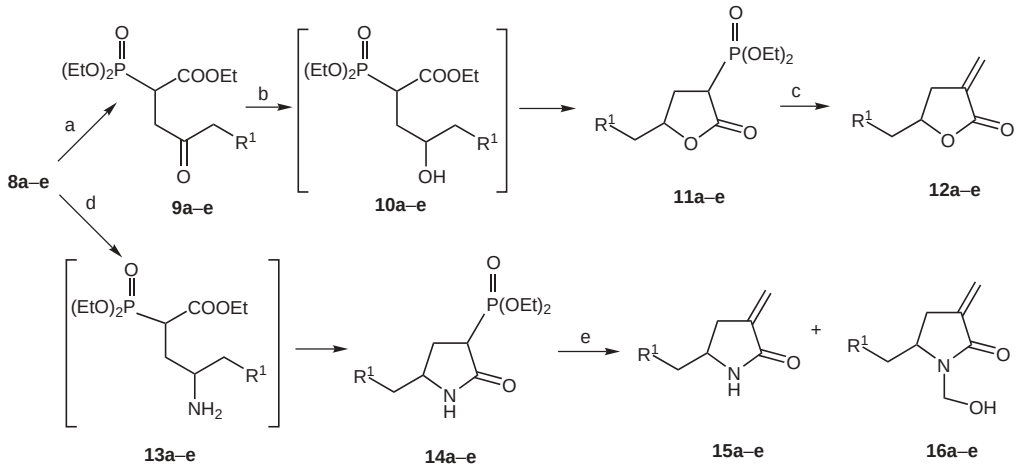


Scheme 3 *Reagents and conditions*: (a) 1. MeONa/MeOH, r.t., 0.5 h; 2. conc. H_2SO_4, MeOH, –60 °C, 2 h; (b) 1. $NaBH_4$, MeOH, NaOH, H_2O, r.t, 20 h; 2. 1 N $HCl_{(aq)}$; (c) K_2CO_3, 36% formalin, 0–5 °C, 15 min; (d) NH_4HCO_2, 10% Pd/C, MeOH–THF, 0 °C to r.t., 24 h; (e) 1. NaH, THF; 2. $(CH_2O)_n$, reflux, 1 h.

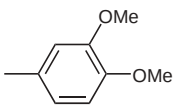
11a–e treated with formalin in the presence of K_2CO_3 at 0–5 °C (Villieras procedure)[12] yielded expected 3-methylidenedihydrofuran-2-ones **12a–e**.[13] All obtained compounds were purified by column chromatography on silica gel; yields are given in Table 1.

The second protocol starts with palladium-catalyzed ammonium formate reduction of nitro group in 4-nitroalkanoates **8a–e** to give, after spontaneous lactamization, 3-(diethoxyphosphoryl)pyrrolidin-2-ones **14a–e** as mixtures of diastereoisomers with close to a 3:2 ratio (Scheme 3, Table 1). Disappointingly, application of the Villieras procedure to pyrrolidinones **14a–e** was unsuccessful with substrates recovered after standard work-up. However, we were pleased to observe that olefination of formaldehyde using **14a–e** can be effectively accomplished when sodium hydride with paraformaldehyde in boiling THF was used. Under these conditions expected 3-methylidenepyrrolidin-2-ones **15a–e** were formed along with various amounts (6–26%) of 1-hydroxymethyl-3-methylidenepyrrolidin-2-ones **16a–e** as by-products. Purification and separation of these mixtures using column chromatography on silica gel afforded pure pyrrolidinones **15a–e**[14] in good to moderate yields (Table 1).

Unfortunately, neither of these protocols proved effective toward nitroalkanoate **8f**. In both cases complex mixtures of products, difficult to identify, were obtained.

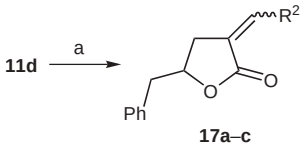
Extension of our method on the synthesis of 3-alkylidenedihydrofuran-2-ones was fully successful. Aliphatic as well as aromatic aldehydes reacted efficiently with sodium derivatives of furanone **11d** in boiling benzene to give, after standard work-up and purification by column chromatography, 3-alkylidenedihydrofuran-2-ones **17a–c** (Scheme 4). Compounds **17a**,**b** were obtained as mixtures of *E*- and *Z*-isomers, whereas compound **17c** was formed as a single *E*-isomer (Table 2).

Table 1 Synthesis of 3-Methylidenedihydrofuran-2-ones **12** and 3-Methylidenepyrrolidin-2-ones **15**

		Yield (%)[a,b]						Ratio[c]
	R^1	**8**	**9**	**11**	**12**	**14**	**15**	**15:16**
a	H	95	95	70	67	88	58	93:7
b	Me	95	96	72	67	84	63	74:26
c	*n*-Bu	98	92	72	76	69	60	86:14
d	Ph	68	83	83	56	60	76	82:18
e		85	62	70	48	70	40	94:6
f	*p*-$NO_2C_6H_4$	40	–	–	–	–	–	–

[a] Yield of isolated, purified product.
[b] All new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectroscopy and gave satisfactory elemental analyses.
[c] Ratio determined from ^{1}H NMR of the crude product.

Configurational assignments were made using diagnostic deshielding effect of the carbonyl group exerted on the *cis*-oriented vinyl proton,[15] e.g., in **17a** vinyl protons with chemical shift δ = 6.51 ppm and δ = 5.90 ppm were attributed to (*E*)-**17a** and (*Z*)-**17a**, respectively. Disappointingly, reaction of the sodium salt of pyrrolidinone **14d** with *iso*butyraldehyde in boiling benzene gave (*E*)-3-(2′-methylpropylidene)-5-benzylpyrrolidin-2-one in low, 6% yield after purification by column chromatography. In the similar reaction performed with benzaldehyde we were unable to isolate a pure product.



17a–c

Scheme 4 *Reagents and conditions*: (a) 1. NaH, benzene, r.t., 0.5 h; 2. R^2CHO, benzene, reflux, 4 h.

Table 2 Synthesis of 3-Alkylidenedihydrofuran-2-ones **17a–c**

17	R^2	*E*:*Z*[a]	Yield (%)[b,c]
a	*i*-Pr	30:70	78
b	Ph	85:15	90
c	1-naphtyl	>99:1	82

[a] Taken from ^{1}H NMR of the crude product.
[b] Yield of isolated, purified product based on **11d**.
[c] All new compounds were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and gave satisfactory elemental analyses.

In summary, we have developed a novel, facile and general approach to 3-alkylidenedihydrofuran-2-ones **12** or **17** and 3-methylidenepyrrolidin-2-ones **15** starting from common intermediates – 2-diethoxyphosphoryl-4-nitroalkanoates **8**.

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(10) (a) Prepared in 73% yield by modified literature procedure.[10b] A mixture of 36% formaline (28 mL, 0,30 mol), piperidine (1 mL) and MeOH (450 mL) was refluxed for 0.5 h. To this mixture was added triethyl phosphonoacetate (30.0 g 0.13 mol) in one portion at 25 °C and the mixture was heated at reflux for 70 h. After 20 h and 48 h additional portions of piperidine (0.5 mL) were added. Progress of the reaction was monitored by ^{31}P NMR. The solution was cooled and concentrated by rotatory evaporation, the residue was extracted with CCl_4 (3 × 100 mL), combined extracts were dried ($MgSO_4$), evaporated and 85% H_3PO_4 (3 mL) was added to the residue which was distilled in high vacuum (85–87 °C/0.4 Torr) to give pure ethyl 2-(diethoxyphosphory)lacrylate (**6**, 22.4 g; 73%).
(b) Semmelhack, M. F.; Tomesh, J. C.; Czarny, M.; Boettger, S. *J. Org. Chem.* **1978**, *43*, 1259.
(11) **General Procedure for the Preparation of Ethyl 2-diethoxyphosphoryl-4-nitroalkanoates 8a–f**. A solution of nitroalkane **7** (17.0 mmol) in THF (10 mL) was added to a stirred suspension of NaH (0.213 g; 8.9 mmol) in THF (40 mL) under argon atmosphere at 0–4 °C. The reaction mixture was stirred for 40 min at r.t., cooled to 0–4 °C, and a solution of ethyl 2-diethoxyphosphorylacrylate (**6**) (2.000 g; 8.5 mmol) in THF (10 mL) was added. The mixture was then stirred for 24 h at r.t., THF was evaporated off at r.t. and the residue was quenched with H_2O (15 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The organic extracts were dried ($MgSO_4$) and evaporated at r.t., to give a crude product, which was purified by column chromatography (silica gel, eluent $CHCl_3$–acetone = 90:10 for **8a–c**, $CHCl_3$–acetone = 95:5 for **8d**,**e** and EtOAc–hexane = 95:5 for **8f**). Spectroscopic data for ethyl 2-diethoxyphosphoryl-5-(3,4-dimethoxyphenyl)-4-nitropentanoate (**8e**); dr 65:35. IR (film): 1732, 1552, 1260 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.28 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, major + minor), 1.31 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, major), 1.32 (td, $^3J_{HH}$ = 7.2 Hz, $^4J_{PH}$ = 0.5 Hz, 3 H, minor), 1.33 (td, $^3J_{HH}$ = 7.5 Hz, $^4J_{PH}$ = 0.5 Hz, 3 H, major), 1.34 (td, $^3J_{HH}$ = 7.0 Hz, $^4J_{PH}$ = 0.5 Hz, 3 H, minor), 2.28–2.75 (m, 2 H, major + minor), 2.84 (m, 1 H, major + minor), 3.02 (dd, $^2J_{HH}$ = 14.5 Hz, $^3J_{HH}$ = 7.2 Hz, 1 H, minor), 3.03 (dd, $^2J_{HH}$ = 14.5, $^3J_{HH}$ = 5.5 Hz, 1 H, major), 3.22 (dd, $^2J_{HH}$ = 14.5 Hz, $^3J_{HH}$ = 8.8 Hz, 1 H, major), 3.23 (dd, $^2J_{HH}$ = 14.5 Hz, $^3J_{HH}$ = 7.5 Hz, 1 H, minor), 3.85 (s, 3 H, major + minor), 3.86 (s, 3 H, major + minor), 4.02–4.28 (m, 4 H, major + minor), 4.67–4.81 (m, 1 H, major), 4.90–5.03 (m, 1 H, minor), 6.62–6.82 (m, 3 H, major + minor). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.82 (s), 16.07 (d, $^3J_{PC}$ = 6.0 Hz), 30.04 (d, $^2J_{PC}$ = 4.5 Hz), 30.26 (d, $^2J_{PC}$ = 3.5 Hz), 39.46 (s), 39.60 (s), 41.77 (d, $^1J_{PC}$ = 130.2 Hz), 42.06 (d, $^1J_{PC}$ = 130.6 Hz), 55.67 (s), 55.70 (s), 61.76 (s), 61.82 (s), 62.99 (d, $^2J_{PC}$ = 6.5 Hz), 87.39 (d, $^3J_{PC}$ = 8.4 Hz), 87.67 (d, $^3J_{PC}$ = 15.0 Hz), 111.26 (s), 111.73 (s), 111.81 (s), 120.88 (s), 121.02 (s), 127.10 (s), 148.28 (s), 148.93 (s), 167.58 (d, $^2J_{PC}$ = 5.7 Hz), 167.73 (d, $^2J_{PC}$ = 6.3 Hz). ^{31}P NMR (101 MHz, $CDCl_3$): δ = 20.46 (major), 21.12 (minor). Anal. Calcd for $C_{19}H_{30}NO_9P$: C, 51.00; H, 6.76; N, 3.13; P, 6.92. Found: C, 51.12; H, 6.69; N, 3.20; P, 6.80.
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(13) **General Procedure for the Preparation of 3-Methylidenedihydrofuran-2-ones 12a–e**. A mixture of 3-(diethoxyphosphoryl)tetrahydrofuran-2-one **11** (1.0 mmol), K_2CO_3 (0.415 g; 3.0 mmol) and 36% formaline (0.54 mL; 7.0 mmol) was stirred at 0–4 °C for 15 min. The mixture was extracted with Et_2O (4 × 15 mL), dried ($MgSO_4$) and evaporated. Residue was purified by column chromatography (silica gel, eluent $CHCl_3$) to give **12**. Spectroscopic data for 5-(3,4-dimethoxyphenylmethyl)-3-methylidenedihydrofuran-2-one (**12e**). IR (film): 1772, 1664 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.59 (ddt, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 6.0 Hz, $^4J_{HH}$ = 2.8 Hz, 1 H), 2.81 (dd, $^2J_{HH}$ = 14.3 Hz, $^3J_{HH}$ = 6.0 Hz, 1 H), 2.89 (ddt, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 2.8 Hz, 1 H), 2.95 (dd, $^2J_{HH}$ = 14.3 Hz, $^3J_{HH}$ = 6.0 Hz, 1 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 4.69 (dq, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 6.0 Hz, 1 H), 5.49 (t, $^4J_{HH}$ = 2.8 Hz, 1 H), 6.10 (t, $^4J_{HH}$ = 2.8 Hz, 1 H), 6.65–6.78 (m, 3 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 32.50 (s), 41.27 (s), 55.90 (s), 55.92 (s), 77.21 (s), 111.32 (s), 112.74 (s), 121.68 (s), 127.89 (s), 148.14 (s), 149.02 (s), 121.98 (s), 134.37 (s), 170.13 (s). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.88; H, 6.41.

(14) **General Procedure for the Preparation of 3-Methylidenepyrrolidin-2-ones 15a–e.** A solution of 3-(diethoxyphosphoryl)pyrrolidin-2-one **14** (1.00 mmol) in THF (7.0 mL) was added to a suspension of NaH (0.025 g; 1.05 mmol) in THF (3 mL) and the reaction mixture was stirred at r.t. for 30 min. Next, paraformaldehyde (0.033 g, 1.10 mmol) was added in one portion, the mixture was refluxed for 1 h and cooled to 0–4 °C. Then H_2O (3 mL) was added, THF was evaporated under reduced pressure and the residue was extracted with CH_2Cl_2 (3 × 15 mL). Combined organic extracts were washed with H_2O (5 mL), dried ($MgSO_4$) and evaporated to give crude **15**, which were purified by column chromatography (silica gel, eluent $CHCl_3$). Spectroscopic data for 5-(3,4-dimethoxyphenylmethyl)-3-methylidenepyrrolidin-2-one (**15e**). IR (film): 3100, 1684, 1662 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.45 (ddt, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 4.0 Hz, $^4J_{HH}$ = 2.2 Hz, 1 H), 2.73 (ddt, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 2.2 Hz, 1 H), 2.82 (dd, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 7.6 Hz, 1 H), 3.15 (dd, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 3.4 Hz, 1 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.02–4.20 (m, 1 H), 5.18 (t, $^4J_{HH}$ = 2.2 Hz, 1 H), 5.83 (t, $^4J_{HH}$ = 2.2 Hz, 1 H), 6.53–6.57 (m, 3 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.13 (s), 37.41 (s), 55.81 (s), 58.20 (s), 115.92 (s), 111.14 (s), 112.69 (s), 121.72 (s), 128.17 (s), 147.89 (s), 148.93 (s), 135.58 (s), 163.89 (s). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.09; H, 6.57, N, 5.83.

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