A Convenient Synthesis of Dialkyl 3-Alkoxy-, 3-Aryloxy-, and 3-Arylthio-2-oxoalkanephosphonates

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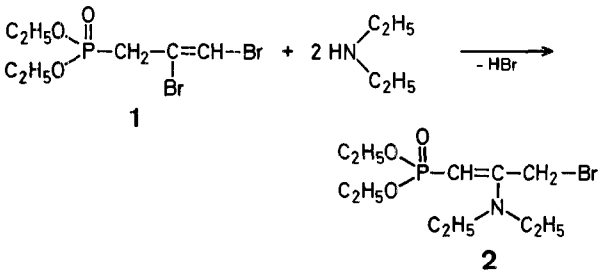
Our interest in some 3-alkoxy-2-oxoalkanephosphonic acid esters, in particular in connection with the synthesis of modified prostaglandins[1], led us to elaborate new synthetic routes to this class of compounds.

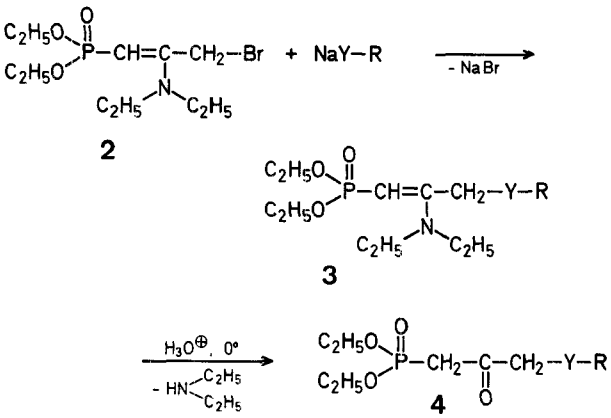
A few years ago, we described the preparation of dialkyl 3-amino-2-oxoalkanephosphonates[2] and the one-step synthesis of α-amino-α'-cyclopropyl ketones[3] and of some 1-(4-alkylhexahydropyrazino)-3-alken-2-ones[4]. We have now prepared diethyl 3-bromo-2-diethylamino-1-propenephosphonate (**2**) from diethyl 2,3-dibromo-1-propenephosphonate (**1**) and diethylamine by an elimination-addition reaction.



1

2

The bromine atom in compound **2** may be easily replaced by phenoxy groups, the phenylthio group, or by saturated or unsaturated alkoxy and alkylthio groups, depending on the reaction conditions, to give compounds of the type **3** (Y = O, S) in 70–90% yields of crude oily product. In general, the enamines **3** can only be purified with difficulty by distillation, due to thermal decomposition. The structures of the crude compounds **3** thus obtained were established by I.R. and ^{1}H-N.M.R. spectrometry (Table 2). We used the crude compounds **3** directly in the next step; acid hydrolysis at room temperature afforded the corresponding diethyl 2-oxoalkanephosphonates **4**, some of which are distillable without decomposition (Table 1).



2

3

4

Our present method for the preparation of compounds **4** seems to be more general than that employed by Corey et al.[5] which consists of the condensation of diethyl lithiomethanephosphonate with an appropriate carboxylic ester, even though in this latter reaction the yield may be improved by the *in situ* conversion of the organolithium compound into an organocopper(I) compound which is then subjected to the condensation[6].

The structures of all products obtained were established by I.R. and N.M.R. spectrometry. The I.R. spectra were recorded on a Perkin Elmer model, type 257. The ^{1}H-N.M.R. spectra were recorded on a JEOL C 60 HL model, using 30% solutions in $CDCl_3$ and TMS as internal standard. Melting points were determined on a Kofler block. Melting and boiling points are uncorrected.

Diethyl 3-Bromo-2-diethylamino-1-propenephosphonate (2):
A solution of diethyl 2,3-dibromo-1-propenephosphonate[2] (**1**; 33.6 g, 0.1 mol) in dry ether (200 ml) is placed in a three-necked flask equipped with a mechanical stirrer, a thermometer, and a dropping funnel. The flask is cooled to 0° and a solution of diethylamine (14.6 g, 0.2 mol) in dry ether (100 ml) is added dropwise with stirring. Diethylamine hydrobromide precipitates from the solution. After the addition is complete, the mixture is allowed

Table 1. Diethyl 3-Alkoxy-, 3-Aryloxy-, and 3-Arylthio-2-oxopropanephosphonates (**4**) prepared from **2** via the Corresponding 2-Diethylamino-1-propenephosphonates (**3**)

			Preparation of **3**		Compounds **4**			
	Y	R	Solvent	Reflux time [h]	Yield[a] [%]	b.p./torr	n_D/t	Molecular formula[b]
a	O		THF	0.5	85	163°/0.02	1.5021/17°	$C_{13}H_{19}O_5P$ (285.3)
b	O		THF	4	80	166°/0.01	1.5142/23°	$C_{13}H_{18}ClO_5P$ (320.7)
c	O		THF	4	75	184°/0.01	1.5199/23°	$C_{13}H_{18}BrO_5P$ (365.2)
d	O		ethanol	3	75	decomposes	—	$C_{13}H_{17}Cl_2O_5P$ (355.2)
e	O		THF/ethanol	1	60	decomposes	—	*no analysis*
f	O		THF/ethanol	1	52	decomposes	—	no analysis
g	O		ethanol	2	60	121°/0.01 (dec)	1.4562/17°	$C_{15}H_{21}O_7P$ (344.3)
h	O		THF	3	60	decomposes	—	$C_{13}H_{18}NO_7P$ (331.3)
i	S		ethanol	2	82	156°/0.01 (dec)	1.5334/21°	$C_{13}H_{19}O_4PS$ (302.3)
j	O	$-CH_2-C\equiv CH$	THF	3	82	137°/0.1	1.4580/20°	$C_{10}H_{17}O_5P$ (248.2)
k	O	$-CH_2-C\equiv C-$ 	THF	3	70	160°/0.02 (dec)	1.5488/20°	$C_{16}H_{21}O_5P$ (324.3)
l	O	$-CH_2-\overset{O}{\overset{\|}{C}}-CH_3$	(from **4j**)		85	152°/0.01 (dec)	1.4662/20°	$C_{10}H_{19}O_6P$ (265.2)
m	O	$-CH_2-CH=CH_2$	THF	0.5	83	120°/0.08	1.4546/20°	$C_{10}H_{19}O_5P$ (249.2)
n	O	$-CH_2-CH=CH-$ 	THF	0.5	70	144°/0.03 (dec)	1.5435/20°	$C_{16}H_{23}O_5P$ (326.3)

[a] Based on **2**.

[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.24; H, ±0.18. We thank the C.N.R.S. Laboratories for performance of the microanalyses.

to stand at 0° for 2 h. It is then filtered and the ether is removed from the filtrate at reduced pressure. The residual liquid is washed with slightly basified water (50 ml). The aqueous solution is extracted with chloroform, the organic phases are combined and dried with sodium sulfate, and the solution is evaporated to give pale-yellow viscous liquid; *yield: 29.5 g (90%); purity: 98% (by* N.M.R.).

$C_{11}H_{23}BrNO_3P$	calc.	C 40.24	H 7.01	Br 24.39
(328.2)	found	40.02	7.16	24.11

I.R. (film): ν_{max} = 1580 (s, C=C—N); 1230 (s, P=O); 1040, 970 cm^{-1} (P—O—C).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.27 (m, 12H, $-CH_2-C\underline{H}_3$); 3.35 [m, 4H, (N)—$C\underline{H}_2-CH_3$]; 3.75 (s, —CH=); 3.97 (m, 4H, O—$C\underline{H}_2-CH_3$); 4.67 ppm (s, —$C\underline{H}_2$—Br).

Preparation of Diethyl 3-Alkoxy-, 3-Aryloxy-, and 3-Arylthio-2-diethylamino-1-propenephosphonates (3); General Procedure:
To a solution of diethyl 3-bromo-2-diethylamino-1-propenephosphonate (**2**; 16.4 g, 0.05 mol) in the solvent (80 ml) indicated in Table 1, a solution of the appropriate sodium alkoxide, phenoxide, or phenylthiolate (0.05 mol) in the same solvent (50 ml) is added with stirring at 20°. In most cases, a precipitate forms. After the addition is complete the mixture is refluxed for the time indicated in Table 1. The mixture is then allowed to cool, the salt is filtered off, and the solvent evaporated from the filtrate at reduced pressure. The residue is washed with water and the aqueous washings are extracted with chloroform. The organic phases are combined, dried with sodium sulfate, and reduced in volume to give a viscous oil which may be colored depending on the reagents employed. The crude product **3** is used in the next step.

Preparation of Diethyl 3-Alkoxy-, 3-Aryloxy-, and 3-Arylthio-2-oxopropanephosphonates (4); General Procedure:
To the 2-amino-1-propenephosphonate **3** obtained as described above, an aqueous solution of 10% hydrochloric acid (pH ~ 1) is added with stirring at 0°. The mixture is then allowed to warm to room temperature within a 2 h period with stirring. The aqueous phase is extracted with chloroform, the organic phase is combined with the extract, and the solution is dried with sodium sulfate. The solvent is removed at reduced pressure to give an oil which is distillable in some cases.

Diethyl 2,6-Dioxo-4-oxaheptanephosphonate (4l):
Diethyl 2-oxo-3-(2-propynyloxy)-propanephosphonate (**4j**; 2.48 g, 0.01 mol) is refluxed for 2.5 h in a solution of mercury(II) sulfate (0.1 g) and sulfuric acid (0.07 g) in 30% aqueous methanol (80 ml). The mixture is then extracted with chloroform. The yellow oil obtained is distilled in vacuo; yield: 85%; b.p. 152°/0.01 torr; n_D^{20}: 1.4662.

$C_{10}H_{19}O_6P$	calc.	C 45.11	H 7.14
(265.2)	found	44.93	7.31

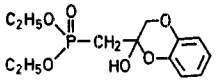
I.R. (film): ν_{max} = 1730 (very st, C=O); 1620 cm^{-1} (P=O).

^{1}H-N.M.R. ($CDCl_3$): δ = 4.17 (m, 4H, $-OC\underline{H}_2-CH_3$); 4.20, 4.06

Table 2. Spectral Data of Compounds **3** and **4**

Compounds 3 or 4	Compounds 3			Compounds 4				
	I.R. (film) [cm^{-1}]		^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	^{1}H-N.M.R. δ [ppm]				
	$\nu_{P=O}$	$\nu_{enamine}$	P—CH=C	—O—CH_2—CH_3	—O—CH_2—CH_3	P—CH_2—CO—	—CO—CH_2—OR	R
a	1225	1575	3.95 (m)	1.28 (t)	4.03 (m)	3.13 (d)	4.60 (s)	7.32–6.62 (m)
b	1255	1575	4.13 (m)	1.35 (t)	4.16 (m)	3.35 (d)	4.78 (s)	7.57–6.68 (m)
c	1250	1578	4.07 (m)	1.36 (t)	4.15 (m)	3.38 (d)	4.71 (s)	7.52–6.5 (m)
d	1225	1575	3.87 (m)	1.33 (t)	4.10 (m)	3.21 (d)	4.78 (s)	7.6–6.7 (m)
e	1225	1580	4.03 (m)	1.31 (t)	4.08 (m)	3.23 (d)	4.12 (s)	6.75 (m), 4.75 (s)[a]
f	1230	1580	4.03 (m)	1.36 (t)	4.20 (m)	3.28 (d)	4.98 (s)	7.92–6.83 (m), 10.51 (s)
g	1255	1580	3.90 (m)	1.33 (t)	4.08 (m)	3.08 (d)	4.03 (s)	3.38 (s), 7.7–6.7 (m)
h	1235	1575	3.92 (m)	1.35 (t)	4.10 (m)	3.20 (d)	4.98 (s)	8.03 (m), 6.92 (m)
i	1220	1570	3.87 (m)	1.32 (t)	4.15 (m)	3.28 (d)	3.91 (s)	7.32 (m)
j	1235	1580	3.96 (m)	1.35 (t)	4.18 (m)	3.16 (d)	4.21 (m)	2.60 (m)
k	1225	1575	4.02 (m)	1.37 (t)	4.21 (m)	3.18 (d)	4.42 (m)	7.35 (m)
m	1235	1575	3.93 (m)	1.37 (t)	4.22 (m)	3.20 (d)	4.18 (s)	6.25–5.65 (m), 5.5–5.13 (m)
n	1230	1580	4.06 (m)	1.38 (t)	4.18 (m)	3.16 (d)	4.15 (m)	6.72–6.32 (m), 7.23 (m)

[a] This compound exists to 50% in a cyclic semiacetal form:



δ = 2.26 ppm [d, P—CH_2—C(OH)].

(s, 4H, CH_2—O—CH_2); 3.15 (d, P—CH_2—CO—, J_{H-P} = 22.5 Hz); 1.35 (s, 6H, —O—CH_2—CH_3); 1.16 ppm (s, —CO—CH_3).

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Eine einfache Synthese von Pyridinalkaloiden

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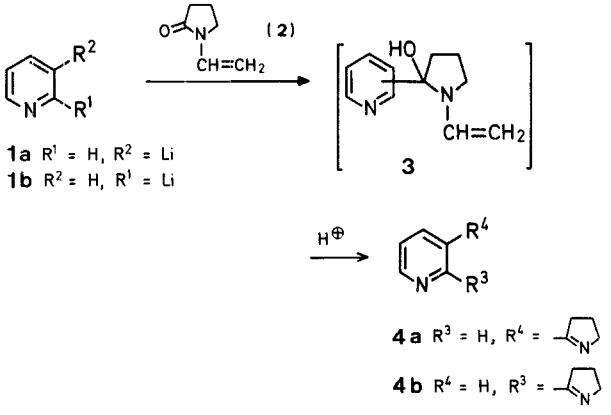
Das Tabak(rauch)alkaloid Myosmin (**4a**) und das Abbauprodukt Apoferrorosamin (**4b**) von Ferrorosamin A[1] (aus *Pseudomonas roseus fluoreszens*) sind Vertreter aus der Reihe der einfachen Pyridinalkaloide, für deren Herstellung verschiedene mehrstufige Synthesen bekannt sind[2]. Kürzlich wurde die Darstellung von **4a** mit 2-Oxo-*N*-vinyltetrahydropyrrol (**2**) als Synthon beschrieben[3].

Wie wir fanden, eignet sich die *N*-Vinyl-Gruppe als Schutzgruppe bei der Umsetzung von Grignard- oder Lithium-Verbindungen mit Lactamen. Verbindungen **4a** und **4b** lassen sich so in befriedigender Ausbeute durch Addition des entsprechenden Lithiumpyridyls **1a** bzw. **1b** an 2-Oxo-*N*-vinyltetrahydropyrrol (**2**) und anschließender saurer Aufarbeitung synthetisieren.



Dabei wird das nicht isolierte Enamin **3** protoniert und anschließend leicht zu Acetaldehyd auf der einen und dem 4,5-Dihydro-pyrrol **4a** bzw. **4b** auf der anderen Seite hydrolysiert.

Ob sich die *N*-Vinyl-Gruppe als Schutzgruppe bei anderen Amiden bewährt, ist Gegenstand weiterer Experimente.