Synthesis of Some 4-Chloro-5-cyano-2-dialkylamino-6*H*-1,3-oxazin-6-ones and their Reactions with Trialkyl Phosphites to Give Dialkyl (5-Cyano-2-dialkylamino-6-oxo-6*H*-1,3-oxazin-4-yl)phosphonates

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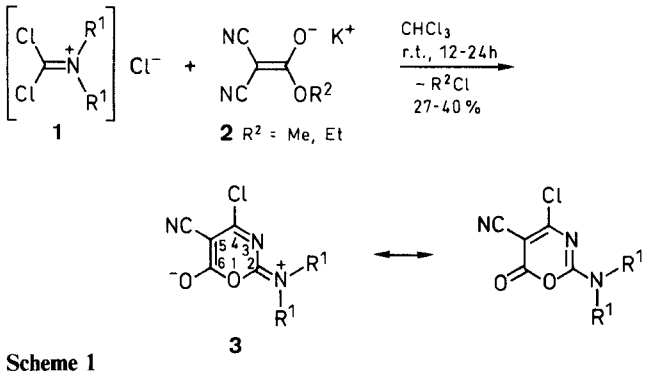
The reaction of the salts of alkyl dicyanoacetates and *N*-(dichloromethylene)dialkylammonium chlorides in chloroform leads to 4-chloro-5-cyano-2-dialkylamino-6*H*-1,3-oxazin-6-ones. The chloro atom of these compounds can be easily substituted in a Michaelis–Arbuzov reaction with trialkyl phosphites, giving dialkyl (5-cyano-2-dialkylamino-6-oxo-6-*H*-1,3-oxazin-4-yl)phosphonates in good yields.

Recently we reported that reaction of alkyl dicyanoacetates[1-9] with *N*-(dichloromethylene)dialkylammonium chlorides gives 4-chloro-5-cyano-2-dialkylamino-6*H*-1,3-oxazin-6-ones.[10] Since this class of compounds shows high synthetic potential in heterocyclic chemistry,[11] and appears important from a biological point of view, we were interested in generalising the reaction and in the investigation of further transformations based on the Michaelis–Arbuzov reaction.

We varied the substituents R of the *N*-(dichloromethylene)dialkylammonium chlorides **1** (which were prepared by passing chlorine gas through a solution of bis(dialkylthiocarbamoyl)disulfide in chloroform[12]) and found that they react completely in chloroform at room temperature with alkyl dicyanoacetates[13] **2** to give the corresponding 1,3-oxazinones **3** (Scheme 1, Table 1).



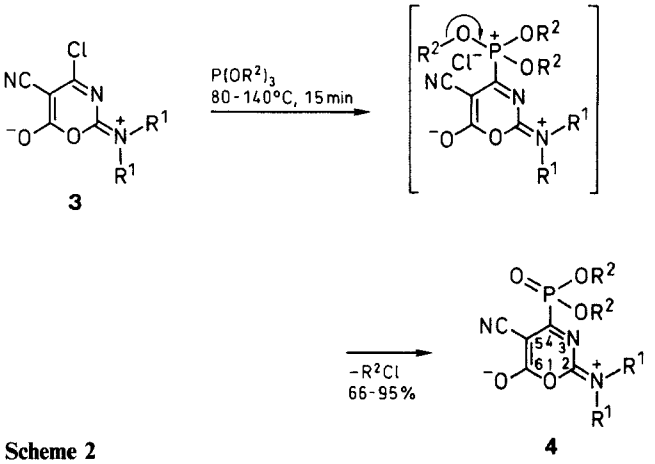
Scheme 1

Table 1. 4-Chloro-5-cyano-2-dialkylamino-6*H*-1,3-oxazin-6-ones **3** Prepared

Product	R^1_2N	Time (h)	Yield (%)[a]	mp (°C)[b]
3a	*i*-Pr_2N	24	30	176
3a		24	35[c]	
3b	Bn_2N	12	40	134
3c	piperidino	16	33	149
3d	(*c*-$C_6H_{11})_2N$	24	27	213–214
3d		24	32[c]	

[a] Based upon bis(dialkylthiocarbamoyl) disulfide.
[b] Recrystallized from EtOAc.
[c] The higher yields of the compounds **3a** and **3d** were obtained when R^2 in substrate **2** is Et instead of Me.

The zwitterionic structure of **3**, which is strongly suggested by ^{13}C NMR and ^1H NMR spectroscopy gave two signals for the substituents R in accord with the presence of an chloroimine structure element. Therefore, it seemed to be of interest to see if the reaction of **3** with trialkyl phosphites would lead to the expected dialkyl oxazinyl-substituted phosphonates.[14] We employed trimethyl and triethyl phosphite and showed that the 4-chloro-5-cyano-2-dialkylamino-6*H*-1,3-oxazin-6-ones **3** react under mild conditions in high yields according to Michaelis–Arbuzov[15] to give the corresponding dialkyl (5-cyano-2-dialkylamino-6-oxo-6*H*-1,3-oxazin-4-yl)phosphonates **4** (Scheme 2, Table 2).



Scheme 2

Table 2. Dialkyl (5-Cyano-2-dialkylamino-6-oxo-6*H*-1,3-oxazin-4-yl)phosphonates **4** Prepared

Product	R^1_2N	R^2	Temp. (°C)	Yield (%)	mp (°C)[a]
4a	Me_2N	Me	80–90	92	159–161
4b	Me_2N	Et	80–90	95	98–99
4c	*i*-Pr_2N	Me	80–90	84	124
4d	*i*-Pr_2N	Et	110–115	79	84
4e	Bn_2N	Me	110–120	76	115
4f	piperidino	Me	70–80	70	181
4g	piperidino	Et	70–80	83	102
4h	(*c*-$C_6H_{11})_2N$	Me	125–130	71	195
4i	(*c*-$C_6H_{11})_2N$	Et	130–140	66	155–156

[a] Recrystallized from EtOAc except: **4d**, pentane; **4e**, pentane/EtOAc (3 : 1).

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Microanalyses were performed on a Heraeus automatical analyser. UV spectra were recorded on a Carl Zeiss DMR 10 spectrophotometer and IR spectra on a Perkin-Elmer 325

spectrophotometer. NMR spectra were recorded on a Bruker WM-250 spectrometer (for ^1H NMR at 250.13 MHz, for ^{13}C NMR at 62.89 MHz). Mass spectra were obtained on a Varian MAT 311A instrument.

4-Chloro-5-cyano-2-dialkylamino-6*H*-1,3-oxazin-6-ones (3); General Procedure:

A suspension of potassium alkyl dicyanoacetate[13] **2** (10 mmol) and *N*-(dichloromethylene)dialkylammonium chloride[12] (**1**; 10 mmol) in

Table 3. Compounds **3a–d** Prepared

Product	Molecular[a] Formula	UV (MeCN) λ_{max} nm (logε)	IR (KBr) ν (cm^{-1})	^1HNMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}CNMR ($CDCl_3$/TMS)[b] δ	MS (80 eV) *m/z* (%)
3a	$C_{11}H_{14}ClN_3O_2$ (255.7)	229 (4.425), 332 (4.515)	2230, 1770, 1600, 1535	1.35 (d, 6H, CH_3, ^3J = 6.8), 1.43 (d, 6H, CH_3, ^3J = 6.8), 4.09 (sept, 1H, CH, ^3J = 6.8), 4.69 (sept, 1H, CH, ^3J = 6.8)	19.6 (−, CH_3), 20.2 (−, CH_3), 48.4 (−, CH), 50.0 (−, CH), 81.1 (+, C-5), 113.0 (+, CN), 155.2 (+, C-2), 156.8 (+, C-6), 168.1 (+, C-4)	257 (M^+ + 2, 3), 255 (M^+, 16), 43 (100)
3b	$C_{19}H_{14}ClN_3O_2$ (351.8)	222 (4.302), 325 (4.330)	2230, 1780, 1760, 1610, 1540, 1520	4.62 (s, 2H, NCH_2), 4.82 (s, 2H, NCH_2), 7.20–7.44 (m, $10H_{arom}$)	49.9 (+, CH_2), 51.0 (+, CH_2), 82.6 (+, C-5), 112.6 (+, CN), 128.2 (−, Ph), 128.5 (−, Ph), 128.8 (−, Ph), 129.1 (−, Ph), 129.2 (−, Ph), 133.1 (+, Ph), 133.5 (+, Ph), 154.6 (+, C-2), 158.0 (+, C-6), 169.1 (+, C-4)	353 (M^+ + 2, 2), 351 (M^+, 7), 91 (100)
3c	$C_{10}]_{10}ClN_3O_2$ (299.7)	222 (4.907), 321 (4.941)	2220, 1775, 1620, 1530	1.65–1.82 (m, 6H), 3.74 (m, 2H, NCH_2), 3.87 (m, 2H, NCH_2)	23.4 (+, C-4′), 25.3 (+, C-3′), 25.5 (+, C-5′), 46.0 (+, C-3′), 47.0 (+, C-6′), 80.8 (+, C-5), 112.9 (+, CN), 155.1 (+, C-2), 168.8 (+, C-6), 171.8 (+, C-4)	241 (M^+ + 2, 30), 239 (M^+, 100), 155 (73)
3d	$C_{17}H_{22}ClN_3O_2$ (335.8)	227 (4.153), 326 (4.285)	2220, 1775, 1595, 1525	1.00–2.15 (m, $20H_{c\text{-}hexyl}$), 3.50–3.75 (m, 1H, NCH), 4.05–4.35 (m, 1H, NCH)	24.7 (+, C-4′), 24.9 (+, C-4″), 25.5 (+, C-3′, C-5′), 25.8 (+, C-3″, C-5″), 29.6 (+, C-2′, C-6′), 30.0 (+, C-2″, C-6″), 57.9 (−, C-1′), 58.7 (−, C-1″), 81.1 (+, C-5), 113.1 (+, CN), 155.3 (+, C-2), 156.9 (+, C-6), 168.0 (+, C-4)	337 (M^+ + 2, 1), 335 (M^+, 12), 55 (100)

[a] Satisfactory microanylysis obtained: C ± 0.27, H ± 0.14, N ± 0.29, except **3d:** N ± 0.39.
[b] ^{13}CNMR: spin-echo.

Table 4. Compounds **4a–i** Prepared

Product	Molecular[a] Formula	UV (MeCN) λ_{max} nm (logε)	IR (KBr) ν (cm^{-1})	^1HNMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}CNMR ($CDCl_3$/TMS)[b] δ, J (Hz)	MS (80 eV) *m/z* (%)
4a	$C_9H_{12}N_3O_5P$ (273.2)	224 (4.221), 348 (4.210)	2220, 1755, 1630, 1510	3.22 (s, 3H, NCH_3), 3.30 (s, 3H, NCH_3), 3.92 (d, 6H, OCH_3, ^3J = 10.7)	36.9 (−, NCH_3), 38.3 (−, NCH_3), 54.6 (−, OCH_3, ^2J = 6.7), 85.3 (+, C-5, ^2J = 19.0), 112.9 (+, CN, ^3J = 2.7), 155.6 (+, C-2, ^3J = 15.8), 159.0 (+, C-6, ^3J = 32.2), 168.4 (+, C-4, ^1J = 217.0)	273 (M^+, 17), 229 (28), 72 (100)
4b	$C_{11}H_{16}N_3O_5P$ (301.25)	225 (4.230), 349 (4.203)	2220, 1765, 1630, 1510	1.43 (t, 6H, CH_2CH_3, ^3J = 6.5), 3.26 (s, 3H, NCH_3), 3.36 (s, 3H, NCH_3), 4.28–4.45 (m, 4H, OCH_3)	16.1 (−, CH_2CH_3, ^3J = 5.4), 36.8 (−, NCH_3), 38.1 (−, NCH_3), 64.4 (+, OCH_2, ^2J = 6.0), 85.0 (+, C-5, ^2J = 18.6), 112.8 (+, CN, ^3J = 2.8), 155.7 (+, C-2, ^3J = 15.3), 158.9 (+, C-6, ^3J = 32.0), 168.7 (+, C-4, ^1J = 215.4)	301 (M^+, 10), 201 (20), 72 (100)
4c	$C_{13}H_{20}N_3O_5P$ (329.3)	230 (3.802), 353 (4.154)	2230, 1760, 1595, 1510	1.37 (d, 6H, CH_3, ^3J = 6.7), 1.43 (d, 6H, CH_3, ^3J = 6.7), 3.98 (d, 6H, OCH_3, ^3J = 11), 4.11 (sept, 1H, CH, ^3J = 6.7), 4.72 (sept, 1H, CH, ^3J = 6.7)	19.6 (−, CH_3), 20.2 (−, CH_3), 48.2 (−, CH), 49.9 (−, CH), 54.4 (−, OCH_3, ^2J = 6.6), 85.3 (+, C-5, ^2J = 19.8), 113.0 (+, CN, ^3J = 2.9), 155.7 (+, C-2, ^3J = 15.6), 158.4 (+, C-6, ^3J = 32.7), 168.0 (+, C-4, ^1J = 218.7)	329 (M^+, 26), 286 (53), 100 (67), 43 (100)
4d	$C_{15}H_{24}N_3O_5P$ (357.3)	228 (4.088), 353 (4.136)	2230, 1770, 1775, 1590, 1580, 1510	1.37 (d, 6H, CH_3, ^3J = 6.7), 1.43 (d, 6H, CH_3, ^3J = 6.7), 1.40–1.48 (m, 6H, CH_2CH_3), 4.10 (sept, 1H, CH, ^3J = 6.7), 4.27–4.44 (m, 4H, OCH_2), 4.72 (sept, 1H, CH, ^3J = 6.7)	16.2 (−, CH_2CH_3, ^3J = 6.0), 19.6 (−, CH_3), 20.2 (−, CH_3), 48.1 (−, CH), 49.8 (−, CH), 64.3 (+, OCH_2, ^2J = 6.5), 85.3 (+, C-5, ^3J = 18.8), 113.0 (+, CN, ^3J = 3.0), 159.9 (+, C-2, ^3J = 15.4), 158.4 (+, C-6, ^3J = 32.3), 168.4 (+, C-4, ^1J = 217.5)	357 (M^+, 18), 314 (25), 201 (31), 100 (100)

Table 4. (continued)

Product	Molecular[a] Formula	UV (MeCN) λ_{max} nm (logε)	IR (KBr) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS)[b] δ, J (Hz)	MS (80 eV) m/z (%)
4e	$C_{21}H_{20}N_3O_5P$ (425.4)	228 (3.899), 350 (4.226)	2230, 1770, 1600, 1575, 1510	3.92 (d, 6H, OCH_3, ^3J = 10.7), 4.66 (s, 2H, NCH_2), 4.87 (s, 2H, NCH_2), 7.15–7.50 (m, 10H_{arom})	50.0 (+, NCH_2), 51.1 (+, NCH_2), 54.6 (−, OCH_3, ^2J = 6.8), 87.0 (+, C-5, ^2J = 18.3), 112.6 (+, CN, ^3J = 2.5), 128.10 (−, Ph), 128.13 (−, Ph), 128.70 (−, Ph), 128.73 (−, Ph), 129.11 (−, Ph), 129.15 (−, Ph), 133.26 (+, Ph), 133.8 (+, Ph), 155.1 (+, C-2, ^3J = 15.7), 159.5 (+, C-6, ^3J = 31.6), 168.0 (+, C-4, ^1J = 217.8)	425 (M^+, 6), 334 (56), 132 (60), 91 (100)
4f	$C_{12}H_{16}N_3O_5P$ (313.25)	234 (4.831), 357 (4.828)	2230, 1765, 1605, 1505	1.75 (m, 6H_{piper}), 3.74 (m, 2H, NCH_2), 3.89 (m, 2H, NCH_2), 3.96 (d, 6H, ^3J = 10.0)	23.4 (+, C-4′), 25.2 (+, C-3′), 25.5 (+, C-5′), 45.7 (+, C-2′), 46.9 (+, C-6′), 54.5 (−, CH_3, ^2J = 6.5), 85.0 (+, C-5, ^2J = 19.0), 112.9 (+, CN, ^3J = 3.0), 155.7 (+, C-2, ^3J = 15.5), 157.6 (+, C-6, ^3J = 32.3), 168.5 (+, C-4, ^1J = 218.0)	313 (M^+, 19), 229 (19), 84 (100)
4g	$C_{14}H_{20}N_3O_5P$ (341.3)	228 (4.195), 352 (4.176)	2220, 1765, 1600, 1505	1.42 (t, 6H, CH_2CH_3), 1.75 (m, 6H_{piper}), 3.75 (m, 2H, C-1′), 3.91 (m, 2H, C-5′), 4.34 (m, 4H, OCH_2)	16.0 (−, CH_3, ^3J = 6.0), 23.3 (+, C-4′), 25.1 (+, C-3′), 25.4 (+, C-5′), 45.6 (+, C-2′), 46.7 (+, C-6′), 64.3 (+, OCH_2, ^2J = 6.4), 84.7 (+, C-5, ^2J = 19.2), 112.8 (+, CN, ^3J = 2.8), 155.8 (+, C-2, ^3J = 15.2), 157.4 (+, C-6, ^3J = 32.3), 168.8 (+, C-4, ^1J = 216.3)	341 (M^+, 22), 233 (23), 112 (56), 82 (100)
4h	$C_{19}H_{28}N_3O_5P$ (409.4)	230 (4.262), 356 (4.259)	2230, 1770, 1575, 1505	1.08–2.10 (m, 20$H_{c\text{-}hexyl}$), 3.52–3.72 (m, 1H, C-1′), 3.99 (d, 6H, CH_3, ^3J = 11.0), 4.15–4.40 (m, 1H, C-1″)	24.7 (+, C-4′), 24.8 (+, C-4″), 25.6 (+, C-3′, C-5′), 25.7 (+, C-3″, C-5″), 29.5 (+, C-2′, C-6′), 30.0 (+, C-2″, C-6″), 54.5 (−, OCH_2, ^2J = 6.3), 57.8 (−, C-1′), 58.8 (−, C-1″), 85.1 (+, C-5, ^2J = 18.5), 113.0 (+, CN, ^3J = 2.8), 155.7 (+, C-2, ^3J = 16.0), 158.6 (+, C-6, ^3J = 23.0), 168.1 (+, C-4, ^1J = 219.5)	409 (M^+, 20), 328 (56), 246 (100)
4i	$C_{21}H_{32}N_3O_5P$ (437.5)	230 (4.691), 356 (4.680)	2230, 1760, 1580, 1505	1.10–2.10 (m, 20$H_{c\text{-}hexyl}$), 1.42–1.50 (m, 6H, CH_3), 3.50–3.70 (m, 5H, 2OCH_2, NCH)	16.3 (−, CH_3, ^3J = 6.0), 24.7 (+, C-4′), 24.9 (+, C-4″), 25.6 (+, C-3′, C-5′), 25.8 (+, C-3″, C-5″), 29.6 (+, C-2′, C-6′), 30.0 (+, C-2″, C-6″), 57.7 (−, C-1′), 58.7 (−, C-1″), 64.3 (+, OCH_2, ^2J = 6.5), 85.2 (+, C-5, ^2J = 19.0), 113.0 (+, CN, ^3J = 3.0), 155.9 (+, C-2, ^3J = 15.4), 158.7 (+, C-6, ^3J = 33.5), 168.4 (+, C-4, ^1J = 218.2)	437 (M^+, 13), 201 (63), 126 (91), 55 (100)

[a] Satisfactory microanalysis obtained: C ± 0.20, H ± 0.13, N ± 0.21.
[b] ^{13}C NMR: spin-echo.

abs. $CHCl_3$ (30 mL) was stirred under Ar at r.t. for 12–24 h and then filtered. The solvent was removed under reduced pressure. The solid residue was washed with cold abs. EtOH and recrystallized from EtOAc, giving colorless crystals. For yields and physical data see Scheme 1 and Table 1.

Dialkyl (5-Cyano-2-dialkylamino-6-oxo-6*H*-1,3-oxazin-4-yl)phosphonates (4); General Procedure:

A mixture of compound **3** (2 mmol) and trialkyl phosphite (2.4 mmol, 1.2 equiv) was heated to 80–120 °C until the evolution of gas was finished. After 15 min the excess of trialkyl phosphite and the remaining alkyl chloride were removed under reduced pressure. The residue was recrystallized from EtOAc or pentane.

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