SYNTHESES OF NEW HETEROCYCLES STARTING FROM DICYANO-ACETATES

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Abstract - The reactions of 4-chloro-2-dialkylamino-6-oxo-6H-1,3-oxazine-5-carbonitriles (3) with C-, N- and S-nucleophiles are reported. The chloro atom can also be substituted in a Michaelis-Arbuzov reaction giving the corresponding 1,3-oxazinyl phosphinates and phosphin-oxides.

INTRODUCTION

In continuation of using dicyanoacetates as simple and inexpensively accessible synthetic starting materials for a lot of different heterocycles,1-11 we reported syntheses of 4-chloro-2-dialkylamino-6-oxo-6H-1,3-oxazine-5-carbonitriles12,13 (3) from the salts of alkyl dicyanoacetates13,14 (1) and N-dichloromethylenedialkyliminium chlorides (2). Since this class of compounds show high synthetic potential in heterocyclic chemistry15 and appear important from a biological point of view we were interested in the investigation of further transformations.

The present paper describes the results of our studies concerning the reactions of 4-chloro-2-dialkylamino-6-oxo-6H-1,3-oxazine-5-carbonitriles with C-, N- and S-nucleophiles and also the Michaelis-Arbuzov reactions with diethoxyphosphines and methoxydiphenylphosphine.
RESULTS AND DISCUSSION

The chloro atom of 4-chloro-2-dialkylamino-6-oxo-6H-1,3-oxazine-5-carbonitriles can be easily substituted with O-nucleophiles. While the reaction with alcohols proceeds by heating the components for some time, we found that thiols, such as methanethiol and ethanethiol, didn’t react. From these reactions starting material was recovered. To remedy this problem it was necessary to employ a more reactive salt such as sodium methanethiolate. With the sodium salt the 1,3-oxazine-carbonitriles (3) reacted at room temperature to form 2-dialkylamino-4-methylthio-6-oxo-6H-1,3-oxazine-5-carbonitriles (4a-c) (Scheme 1).

Amines are stronger nucleophiles than alcohols and reacted under milder conditions and in better yields with the 1,3-oxazine-5-carbonitriles. The amino group of ethyl glycinates (5a, b) was so reactive that the reaction started at room temperature and was quite exothermic. We also found that the reaction with a bulky amine, diisopropylamine, similarly proceeded to give the corresponding product (6f). Due to the sensitivity of the 1,3-oxazines to basic conditions and the presence of the stabilized conjugated electronic system a cyclization couldn’t be achieved. For example, treatment of the 2-dialkylamino-(2-hydroxypropylamino)-6-oxo-6H-1,3-oxazine-5-carbonitrile (6c) with phosphoryl chloride gave (7), no cyclic product (8) being formed (Scheme 2).
Under mild conditions we treated 1,3-oxazine-5-carbonitriles bearing an imidechloride in one of its mesomeric structures with cyanoacetic acid ester (9a) and malonic esters (9b-d). After deprotonation with NaH the resulting carbanions displaced the chloro atom in position 4 of the
heterocycle to yield 2-(1,3-oxazin-4-yl)acetates (10) (Scheme 3).

Recently we reported the Michaelis-Arbusov reaction$^{17}$ with the 1,3-oxazine-5-carbonitriles.$^{12}$ In continuing of these studies we have now employed diethoxyphosphines (11a, b) and methoxy-diphenylphosphine (13) in order to obtain phosphinates (12a, b) and diphenylphosphinoxides (14 a-c). The reactions were carried out by heating without a solvent. The 4-chloro-2-dialkylamino-6H-1,3-oxazine-5-carbonitriles yield the 1,3-oxazin-4-yl-phosphinates (12) and diphenylphosphinoxides (14) accompanied by the loss of alkyl chloride (Scheme 4).
**EXPERIMENTAL**

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer ir spectrophotometer 283 using potassium bromide and are given as cm$^{-1}$. $^1$H- and $^{13}$C-Nmr spectra were recorded on either a Bruker WM-250 ($^1$H-nmr: 250.13 MHz, $^{13}$C-nmr: 62.89 MHz) or a Varian XL 300 ($^1$H-nmr: 299.95 MHz, $^{13}$C-nmr: 75.43 MHz) spectrometer in CDCl$_3$ or DMSO-d$_6$. The chemical shifts are reported in ppm downfield from internal tetramethylsilane; coupling constants J are given in Hz. Ultraviolet spectra were measured with a Perkin-Elmer 320 uv spectrophotometer in acetonitrile and are given as $\lambda_{max}$ (lg $\varepsilon$) in nm. Electron impact mass spectra were obtained on a Varian MAT 311A instrument. Element analyses were performed on a Heraeus Vario EL CHNS apparatus. P-analyses were conducted by the Department of Chemistry of the University of Heidelberg.

**General procedure for preparation of 2-dialkylamino-4-methylthio-6-oxo-6H-1,3-oxazine-5-carbonitriles (4):**

To a solution of 2 mmol of 4-chloro-2-dialkylamino-6-oxo-6H-1,3-oxazine-5-carbonitrile$^1$ (3) (3a: 400 mg, 3b: 511 mg, 3c: 670 mg) in 10 ml of dimethylformamide (3b in 5 ml of tetrahydrofuran) was added 210 mg (3 mmol) of sodium methanethiolate under cooling with ice. After stirring at room temperature for 40 h, threefold volume of ice-water was added. The resulting precipitate was washed with water and dried. Recrystallisation from ethyl acetate gave light yellow crystals.

Scheme 4
2-Dimethylamino-4-methylthio-6-oxo-6H-1,3-oxazine-5-carbonitrile (4a) - 267 mg (63.2%), mp 203 °C (subl.). H-Nmr (250.13 MHz, CD3CN) δ = 2.57 (s, 3H, SCH3), 3.13 (s, 3H, NCH3), 3.26 (s, 3H, NCH3). 13C-Nmr (62.89 MHz, CF3COOD, [1H]) δ = 14.2 (s, CH3), 37.9 (s, NCH3), 75.5 (s, C-5), 158.3 (s, C-2), 163.5 (s, C-6), 187.1 (s, C-4).

IR (KBr) ν = 2960, 2220 (C=S), 1760 (C=O), 1630, 1490, 1425, 1415, 1305, 1290, 1220, 1200, 1055, 1010, 990, 920, 840, 745. UV (CH3CN) λmax (Ige) = 233 (4.241), 272 (4.301), 324 (4.228). Anal. Calcd for C8HgN3O2S: C, 45.49; H, 4.29; N, 19.89; S, 15.17. Found: C, 45.61; H, 4.27; N, 19.68; S, 14.92.

2-Diisopropylamino-4-methylthio-6-oxo-6H-1,3-oxazine-5-carbonitrile (4b) - 187 mg (35.0%), mp 185 °C. H-Nmr (250.13 MHz, CDCl3) δ = 1.40 (d, JHH=6.9 Hz, 6H, CHCH3), 2.57 (s, 3H, SCH3), 4.04-4.25 (m, 1H, CH), 4.50-4.70 (m, 1H, CH). 13C-Nmr (62.89 MHz, CDCl3, [1H]) δ = 13.6 (-, s, SCH3), 19.7 (-, s, CHCH3), 48.0 (-, s, CH), 49.1 (-, s, CH), 76.2 (+, s, C-5), 114.2 (+, s, CN), 155.4 (+, s, C-6), 156.3 (+, s, C-4), 180.7 (+, s, C-4). IR (KBr) ν = 2990, 2970, 2945, 2880, 2220 (C=S), 1740 (C=O), 1595, 1500 (C-N), 1455, 1445, 1370, 1300, 1260, 1195, 1185, 1155, 1140, 1045, 1005, 920, 890, 865, 790, 760. UV (CH3CN) λmax (Ige) = 231 (4.201), 271 (4.289), 324 (4.257). Anal. Calcd for C12H17N3O2S: C, 53.91; H, 6.41; N, 15.72; S, 11.99. Found: C, 54.07; H, 6.60; N, 15.58; S, 11.77.

2-Dicyclohexylamino-4-methylthio-6-oxo-6H-1,3-oxazine-5-carbonitrile (4c) - 360 mg (51.9%), mp 267-268 °C. H-Nmr (250.13 MHz, CDCl3) δ = 1.08 - 1.47 (m, 6Hcyclohex.), 1.60 - 2.15 (m, 14Hcyclohex.), 2.57 (s, 3H, CH3), 3.63 - 3.85 (m, 1H, CH), 3.99 - 4.17 (m, 1H, CH). 13C-Nmr (62.89 MHz, CDCl3, [1H]) δ = 13.7 (-, s, CH3), 24.8 (+, s, C-4), 25.2 (+, s, C-4'), 25.8 (+, s, C-3'), 25.9 (+, s, C-3') 29.6 (+, s, C-2'), 30.3 (+, s, C-2'), 57.5 (-, s, C-1'), 58.2 (-, s, C-1'), 76.1 (+, s, C-5), 114.3 (+, s, CN), 155.5 (+, s, C-6), 156.4 (+, s, C-2), 180.4 (+, s, C-4). IR (KBr) ν = 2930, 2860, 2220 (C≡N), 1760 (C=O), 1580, 1490, 1455, 1385, 1335, 1300, 1260, 1160, 1050, 1035, 1000, 890, 750. UV (CH3CN) λmax (Ige) = 234 (4.195), 275 (4.264), 326 (4.268). Anal. Calcd for C18H25N3O2S: C, 62.22; H, 7.25; N 12.09. Found: C, 61.93; H, 7.19; N 11.71.

Ethyl N-(5-Cyano-2-dimethylaminoo-6-oxo-6H-1,3-oxazine-4-yl)glycinate (6a)

To a solution of 200 mg (1 mmol) of 4-chloro-2-dimethylamino-6-oxo-6H-1,3-oxazine-5-carbonitrile (3a) in 10 ml of CH2Cl2 was added 0.2 ml (2 mmol) of ethyl glycinate in 3 ml of CH2Cl2.
After stirring for 16 h the solution was filtered and the solvent was removed under reduced pressure. The residue was recrystallised from ethyl acetate to give 157 mg (58.9%) of white crystals, mp 181°C. 1H-Nmr (250.13 MHz, CDCl₃) δ = 1.29 (t, 3J_HH=7.3 Hz, 3H, CH₃), 3.16 (s, 6H, NCH₃), 4.18 (d, 3J_HH=6.1 Hz, 2H, NCH₂), 4.24 (q, 3J_HH=6.8 Hz, 2H, OCH₂), 6.52 (br, 1H, NH). 13C-Nmr (62.89 MHz, DMSO-d₆, {1H}) δ = 14.0 (-, s, CH₃), 35.9 (-, s, NCH₃), 36.9 (-, s, NCH₃), 43.0 (+, s, C-7), 57.5 (+, s, C-5), 60.5 (+, s, OCH₂), 115.9 (+, s, CN), 157.5 (+, s, C-6), 158.2 (+, s, C-2), 164.0 (+, s, C-4), 169.1 (+, s, C-8). IR (KBr) ν = 3305 (N-H), 3150 (N-H), 2990, 2960, 2210 (CGN), 1770 (C=O), 1745 (C=O), 1635, 1590 (C-O), 1535, 1410, 1315, 1300, 1275, 1260, 1205, 1190, 1015, 990, 960, 885, 865, 765. UV (CH₃CN) λ_max (lge) = 229 (4.596), 285 (4.287). Anal. Calcd for C₁₁H₁₅N₄O₄: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.61; H, 5.38; N, 21.03.

Ethyl N-(5-Cyano-2-dicyclohexylamino-6-oxo-6H-1,3-oxazin-4-yl)glycinate (6b)

Similarly prepared from 335 mg (1 mmol) of 4-chloro-2-dicyclohexylamino-6-oxo-6H-1,3-oxazine-5-carbonitrile (3c) and 0.2 ml (2 mmol) of ethyl glycinate in 10 ml of CHCl₃. Recrystallisation from hexane/ethyl acetate (2:1) yielded 202 mg (50.2%) of white crystals, mp 226°C. 1H-Nmr (250.13 MHz, CDCl₃) δ = 1.05-2.30 (m, 20Hcyclohexyl), 1.29 (t, 3J_HH=6.8 Hz, 3H, CH₂CH₂), 3.50- 4.00 (m, 2H, NCH), 4.15 (d, 3J_HH=6.4 Hz, 2H, NCH₂), 4.21 (q, 3J_HH=7.3 Hz, 2H, OCH₂), 6.70 (t, 3J_HH=5.4 Hz, 1H, NH). 13C-Nmr (62.89 MHz, CDCl₃, {1H}) δ = 14.1 (-, s, CH₃), 24.9 (+, s, C-a'), 25.1 (+, s, C-4'), 25.7 (+, s, C-3'), 25.9 (+, s, C-3'), 29.5 (+, s, C-2'), 30.4 (+, s, C-2), 43.1 (+, s, C-7), 56.9 (-, s, CH), 57.4 (-, s, CH), 59.6 (+, s, C-5), 61.5 (+, s, OCH₂), 116.0 (+, s, CN), 157.5 (+, s, C-6), 158.3 (+, s, C-2), 164.8 (+, s, C-4), 168.9 (+, s, C-8). IR (KBr) ν = 3290 (N-H), 3140 (N-H), 2930, 2850, 2220 (C≡N), 1760 (C≡O), 1745 (C≡O), 1580, 1525 (C≡N), 1445, 1415, 1385, 1355, 1336, 1250, 1200, 1020, 950, 765. UV (CH₃CN) λ_max (lge) = 229 (4.593), 289 (4.381). Anal. Calcd for C₁₁H₃₀N₄O₄: C, 62.67; H, 7.51; N, 13.92. Found: C, 62.49; H, 7.47; N, 13.76.

2-Dimethylamino-4-(2-hydroxypropylamino)-6-oxo-6H-1,3-oxazine-5-carbonitrile (6c) - To a solution of 400 mg (1 mmol) of 3a in 10 ml of CHCl₃ was added 0.3 ml (4 mmol) of 1-aminopropanol in 3 ml of CHCl₃. After stirring for 16 h the precipitate was filtered, washed with water and recrystallised from CHCl₃/CH₃CN (3:1) to give 254 mg (53.4%) of white crystals, mp 196°C. 1H-Nmr (250.13 MHz, DMSO-d₆) δ = 1.04 (d, 3J_HH=6.4 Hz, 3H, CHCH₃), 3.06 (s, 3H, NCH₃), 3.12 (s, 3H, NCH₃), 3.24 - 3.43 (m, 2H, CH₂), 3.75 - 3.92 (m, 1H, CH), 4.78 (d, 3J_HH=4.4 Hz, 1H,
OH), 7.81 (br, 1H, NH). $^{13}$C-Nmr (62.89 MHz, Acetone-d$_6$, ($^1$H)) $\delta$ = 21.3 (-, s, CCH$_3$), 36.5 (-, s, NCH$_3$), 37.7 (-, s, NCH$_3$), 49.5 (+, s, CH$_2$), 58.7 (+, s, C-5), 66.6 (-, s, CH), 116.5 (+, s, CN), 158.7 (+, s, C-6), 159.7 (+, s, C-2), 165.9 (+, s, C-4). Ir (KBr) $\nu$ = 3450 (O-H), 3310 (N-H), 3260 (N-H), 2970, 2930, 2210 (C-N), 1765 (C-O), 1620, 1580 (C-N), 1530, 1475, 1410, 1250, 1205, 1125, 1070, 1030, 980, 920, 880, 760. Uv (CH$_3$CN) $\lambda_{max}$ (lg$e$) = 231 (4.577), 284 (4.229). Anal. Calcd for C$_{10}$H$_{14}$N$_4$O$_3$: C, 50.41; H, 5.92; N, 23.52. Found: C, 50.30; H, 5.69; N, 23.54.

4-(2-Aminophenylamino)-2-dimethylamino-6-oxo-6H-1,3-oxazine-5-carbonitrile (6d)

A suspension of 400 mg (2 mmol) of 3a and 432 mg (4 mmol) of o-phenylenediamine in 10 ml of ethanol was refluxed for 5 h. After cooling to room temperature the precipitate was filtered and washed with 0.1N NaOH and water. Recrystallisation from CHCl$_3$/CH$_3$CN (3:1) yielded 456 mg (84.0%) of 6d, mp 209°C.

IH-Nmr (250.13 MHz, DMSO-d$_6$) $\delta$ = 2.90 (s, 3H, CH$_3$), 3.02 (s, 3H, CH$_3$), 4.58 - 5.25 (br, 2H, NH$_2$), 6.50 - 7.05 (4H arom.), 8.90 - 9.60 (br, 1H, NH). $^{13}$C-Nmr (62.89 MHz, DMSO-d$_6$, ($^1$H)) $\delta$ = 35.8 (-, s, CH$_3$), 36.9 (-, s, CH$_3$), 58.5 (+, s, C-5), 115.6 (-, s, CAr), 115.8 (+, s, CN), 122.0 (+, s, C-1'), 127.5, 127.9 (-, s, CAr), 144.2 (+, s, C-2'), 157.4 (+, s, C-6), 159.0 (+, s, C-2), 163.1 (+, s, C-4). Ir (KBr) $\nu$ = 3180 (N-H), 3080, 2950, 2820, 2620, 2220 (C-N), 1720 (C-O), 1640, 1560 (C=N), 1535, 1465, 1415, 1400, 1315, 1290, 1275, 1200, 1170, 1080, 895, 770, 750. Uv (CH$_3$CN) $\lambda_{max}$ (lg$e$) = 233 (4.583), 290 (4.287). Anal. Calcd for C$_{13}$H$_{13}$N$_5$O$_2$: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.42; H, 4.70; N, 25.75.

N-(5-Cyano-2-dimethylamino-6-oxo-6H-1,3-oxazin-4-yl)-2-aminobenzoic acid (6e)

A mixture of 300 mg (1.5 mmol) of 3a and 400 mg (3 mmol) of anthranilic acid was refluxed in n-butanol for 6 h. The precipitate was filtered and washed with water, recrystallised from CH$_3$CN to give 295 mg (65.6%) of white crystals, mp 260°C (decomp.). $^1$H-Nmr (250.13 MHz, DMSO-d$_6$) $\delta$ = 3.10 (s, 3H, NCH$_3$), 3.15 (s, 3H, NCH$_3$), 7.16 - 7.28 (m, 1H arom.), 7.52-7.66 (m, 1H arom.), 7.90-8.04 (m, 1H$_{arom}$), 8.32-8.44 (m, 1H$_{arom}$), 11.45 (br, 1H, NH). $^{13}$C-Nmr (62.89 MHz, DMSO-d$_6$, ($^1$H)) $\delta$ = 36.4 (-, s, NCH$_3$), 37.6 (-, s, NCH$_3$), 60.6 (+, s, C-5), 115.2 (+, s, CN), 118.5 (+, s, C-1'), 122.2, 123.6, 130.8, 133.5 (-, s, CAr), 139.4 (+, s, C-2'), 157.9 (+, s, C-6*), 158.0 (+, s, C-2*), 162.3 (+, s, C-4), 169.4 (+, s, COOH). * = attachment changeable. Ir (KBr) $\nu$ = 3200 - 2600, 2210 (C=N), 1740 (C=O), 1690, 1620 (C=N), 1540, 1505, 1445, 1405,1290, 1210, 1150, 1080, 885, 790, 760, 750. Uv (CH$_3$CN) $\lambda_{max}$ (lg$e$) = 204 (4.382), 237 (4.289), 286 (4.328), 304 (4.340), 320 sh (4.268).
Anal. Calcd for C₁₄H₁₂N₄O₄: C, 56.00; H, 4.03; N, 18.66. Found: C, 55.83; H, 4.00; N, 18.56.

2-Dicyclohexylamino-4-diisopropylamino-6-oxo-6H-1,3-oxazine-5-carbonitrile (6f)

A mixture of 335 mg (1 mmol) of 3c and 1 ml (7.2 mmol) of diisopropylamine were refluxed in 5 ml of CHCl₃ for 4 h. The cooled solution was filtered, the solvent removed under reduced pressure and the residue was washed with water, dried and recrystallised from ethyl acetate/CHCl₃ to give 274 mg (68.5%) of white crystals, mp 218 °C. 

1H-Nmr (250.13 MHz, CDCl₃) δ = 1.05 - 1.95 (m, 20H cyclohex), 1.41 (d, JHH=6.4 Hz, 6H, CHCH₃), 1.49 (d, JHH=6.4 Hz, 6H, CHCH₃), 2.15 - 2.35 (m, 2H cyclohex). 3.06 - 3.49 (m, 2H, CHisoprop), 4.44 -4.61 (m, 1H, CHcyclohex).

13C-Nmr (62.89 MHz, CDCl₃, {1H}) δ = 19.2 (-, s, CH₃), 21.4 (-, s, CH₃), 24.8 (+, s, C-4'), 25.1 (+, s, C-4'), 25.6 (+, s, C-3'), 26.4 (+, s, C-3'), 30.1 (+, s, C-2'), 31.0 (+, s, C-2'), 47.4 (-, s, CHCH₃), 56.5 (-, s, C-1'), 57.3 (-, s, C-1'), 59.7 (+, s, C-5), 118.1 (+, s, CN), 155.6 (+, s, C-6), 161.1 (+, s, C-2), 163.1 (+, s, C-4). 

IR (KBr) ν = 2960, 2940, 2860, 2210 (C-N), 1740 (C=O), 1575, 1525 (C=N), 1460, 1445, 1400, 1385, 1350, 1350, 1270, 1230, 1200, 1145, 1040, 1000, 920, 900, 760, 725. UV (CH₃CN) λmax (lge) = 239 (4.392), 261 (4.415). Anal. Calcd for C₂₃H₂₆N₄O₂: C, 68.97; H, 9.06; N, 13.99. Found: C, 69.05; H, 9.19; N, 14.05.

4-(2-Chloropropylamino)-2-dimethylamino-6-oxo-6H-1,3-oxazine-5-carbonitrile (7)

To 180 mg (0.76 mmol) of 6c was added 1 ml (10.7 mmol) of phosphoryl chloride. The resulting clear solution was heated to 90 °C for 5 h, cooled down and poured into ice-water. The light green precipitate was filtered, washed with water and recrystallised from hexane to give 134 mg (68.7%) of yellow crystals, mp 187 °C. 1H-Nmr (250.13 MHz, CDCl₃) δ = 1.54 (d, 3JHH= 6.9 Hz, 3H, CHCH₃), 3.18 (s, 3H, NCH₃), 3.19 (s, 3H, NCH₃), 3.58 - 3.70 (m, 1H, CH₂), 3.75 - 3.87 (m, 1H, CH₂), 4.14 - 4.24 (m, 1H, CH), 6.06 - 6.18 (m, 1H, NH). 13C-Nmr (62.89 MHz, CDCl₃, {1H}) δ = 22.5 (-, s, CCH₃), 36.6 (-, s, NCH₃), 37.7 (-, s, NCH₃), 48.9 (+, s, CH₂), 55.8 (-, s, CH), 59.3 (+, s, C-5), 115.7 (+, s, CN), 158.1 (+, s, C-6), 158.7 (+, s, C-2), 165.1 (+, s, C-4). IR (KBr) ν = 3300 (N-H), 3140 (N-H), 2970, 2940, 2210 (C≡N), 1760 (C=O), 1625, 1595 (C≡N), 1530, 1410, 1230, 1205, 1060, 1010, 965, 920, 870, 760. UV (CH₃CN) λmax (lge) = 230 (4.535), 285 (4.203). Anal. Calcd for C₁₀H₁₃N₄O₂Cl: C, 46.79; H, 5.10; N, 21.83. Found: C, 46.09; H, 5.00; N, 21.19. HRms: 256.0729, calcd. 256.0728.
Ethyl 2-Cyano-2-(5-cyano-2-dilsopropylamlno-6-oxo-6H-1,3-oxazln-4-yl)-2-phenyl-acetate (10a) - To a suspension of 60 mg (2 mmol) of (80%) sodium hydride in 10 ml of abs. THF was added a solution of 380 mg (2 mmol) of ethyl 2-cyano-2-phenylacetate (9a) in 10 ml of abs. THF at 0 °C under argon. After stirring for 1 h at room temperature 511 mg (2 mmol) of 3b in 5 ml of abs. THF was added and stirred for 16 h. On addition of water a white precipitate was formed. Recrystallisation from ethyl acetate gave 530 mg (65.0%) of white crystals, mp 186 °C. ¹H-Nmr (250.13 MHz, CDCl₃) δ = 1.22 (d, J HH= 6.8 Hz, 3H, CHCH₃), 1.36 (d, J HH=6.4 Hz, 6H, CHCH₃), 1.37 (t, J HH=7.1 Hz, 3H, CH₂CH₃), 4.09 - 4.39 (m, 2H, CH), 4.410 (q, J HH=7.1 Hz, 1H, OCH₂), 4.415 (q, J HH=7.1 Hz, 1H, OCH₂), 7.57-7.66 (m, 2Har), 7.43-7.50 (m, 3Har). ¹³C-Nmr (62.89 MHz, CDCl₃, [¹H]) δ = 13.7 (-, s, CH₂CH₃), 19.7 (-, s, CHCH₃), 20.1 (-, s, CHCH₃), 48.9 (-, s, CH), 61.0 (+, s, C-7), 64.6 (+, s, OCH₂), 81.7 (+, s, C-5), 112.2 (+, s, CN), 115.1 (+, s, CN), 128.2, 129.0, 129.7 (-, s, C₆H₅), 156.4 (+, s, C-6), 157.2 (+, s, C-2), 163.9 (+, s, C-8), 171.0 (+, s, C-4). Ir (KBr) ν = 2980, 2940, 2220 (C≡N), 1755 (C=O), 1600, 1535 (C=O), 1490, 1370, 1340, 1240, 1140, 1050, 1015, 910, 790, 775, 740, 695. Uv (CH₃CN) λmax (Ige) = 228 (4.292), 337 (4.280). Anal. Calcd for C₂₂H₂₄N₄O₄: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.53; H, 6.02; N, 13.44.

Diethyl 5-Cyano-2-dilsopropylamlno-6-oxo-6H-1,3-oxazln-4-ylethylmalonate (10b) - To a suspension of 60 mg (2 mmol) of (80%) sodium hydride in 15 ml of ether under argon was added a solution of 376 mg (2 mmol) of diethyl ethylmalonate (9b) in 10 ml of ether. After 1 h at room temperature 511 mg (2 mmol) of 3b were added. After stirring over night the solution was filtered. The solvent was removed under reduced pressure and the solid residue was recrystallised from pentane to give 423 mg (52.1%) of colourless crystals, mp 115 °C. ¹H-Nmr (250.13 MHz, CDCl₃) δ = 1.07 (t, J = 7.5 Hz, 3H, CCH₂CH₃), 1.31 (t, J =7.1 Hz, 6H, OCH₂CH₃), 1.33 (d, J =6.8 Hz, 6H, CHCH₃), 1.38 (d, J =7.1 Hz, 6H, CHCH₃), 2.43 (q, J =7.5 Hz, 2H, CCH₂), 4.17 - 4.41 (m, 6H, 2xOCH₂, 2xCH). ¹³C-Nmr (62.89 MHz, CDCl₃, [¹H]) δ = 9.7 (-, s, CH₂CH₃), 13.9 (-, s, OCH₂CH₃), 19.8 (-, s, CHCH₃), 20.3 (-, s, CHCH₃), 27.4 (+, s, CCH₂), 48.4 (-, s, CH), 49.2 (-, s, CH), 62.3 (+, s, OCH₂), 66.7 (+, s, C-7), 82.0 (+, s, C-5), 114.0 (+, s, CN), 156.9 (+, s, C-6), 157.0 (+, s, C-2), 167.2 (+, s, C-8), 174.4 (+, s, C-4). Ir (KBr) ν = 2990, 2950, 2230 (C=N), 1770 (C=O), 1750 (C=O), 1725, 1590 (C=N), 1515, 1505, 1490, 1480, 1390, 1370, 1265, 1205, 1160, 1140, 1130, 1115,
1095, 1065, 1030, 960, 910, 870, 860, 790, 760. \textit{UV} (CH$_3$CN) $\lambda_{\text{max}}$ (lge) = 228 (4.168), 337 (4.263).

\textit{Anal. Calcd for C$_{20}$H$_{29}$N$_3$O$_6$:} C, 58.95; H, 7.17; N, 10.31. Found: C, 58.93; H, 7.21; N, 10.28.

\textbf{Diethyl 5-Cyano-6-oxo-2-piperidino-6H-1,3-oxazin-4-ylethylmalonate (10c)}

A similar reaction using 60 mg of (80%) sodium hydride, 376 mg (2 mmol) of 9b and 480 mg (2 mmol) of 4-chloro-6-oxo-2-piperidino-6H-1,3-oxazine-5-carbonitrile (3) in 25 ml of ether gave 352 mg (45.0%) of (10c), mp 102°C (pentane). $^{1}$$\text{H-Nmr}$ (250.13 MHz, CDCl$_3$) $\delta$ =1.06 (t, $J_{HH}$= 7.4 Hz, 3H, CCH$_2$CH$_3$), 1.31 (t, $J_{HH}$=7.4 Hz, 6H, OCH$_2$CH$_3$), 1.60 - 1.80 (m, 6H, piper.), 2.40 (q, $J_{HH}$=7.4 Hz, 2H, CCH$_2$CH$_3$), 3.66-3.81(m, 4H, NCH$_2$), 4.18-4.38 (m, 4H, OCH$_2$). $^{13}$$\text{C-Nmr}$ (62.89 MHz, CDCl$_3$, $^{1}$$\text{H})$ $\delta$ = 9.5 (-, s, CCH$_2$CH$_3$), 13.8 (-, s, OCH$_2$CH$_3$), 23.5 (+, s, C-3'), 25.2 (+, s, C-2'), 25.5 (+, s, C-2'), 27.1 (+, s, CCH$_2$CH$_3$), 45.5 (+, s, C-1'), 46.6 (+, s, C-1'), 62.2 (+, s, OCH$_2$), 66.5 (+, s, C-7), 81.8 (+, s, C-5), 114.0 (+, s, CN), 156.6 (+, s, C-6), 157.0 (+, s, C-2), 167.2 (+, s, C-8), 174.9 (+, s, C-4). \textit{Ir} (KBr) $\nu$ = 2960, 2940, 2860, 2220 (C=N), 1750 (C-O), 1730 (C=O), 1610, 1510 (C=N), 1485, 1465, 1450, 1370, 1300, 1260, 1200, 1095, 1020, 855, 755. \textit{UV} (CH$_3$CN) $\lambda_{\text{max}}$ (lge) = 226 (4.223), 334 (4.268). \textit{Anal. Calcd for C$_{19}$H$_{25}$N$_3$O$_6$:} C, 58.30; H, 6.44; N; 10.74: Found: C, 58.17; H, 6.56; N, 10.70.

\textbf{Dimethyl 5-Cyano-2-diisopropylamino-6-oxo-6H-1,3-oxazin-4-ylmalonate (10d)}

To a suspension of 120 mg (4 mmol) of (80%) sodium hydride in 15 ml of abs. THF under argon was added a solution of 522 mg (4 mmol) of dimethyl malonate (9d) in 10 ml of THF at -20°C. After stirring for 1 h at room temperature 510 mg (2 mmol) of 3c in 5 ml of THF were added and 1 h later the solution was filtered and double the volume of water was added. With conc. HCl the solution was acidified to pH 1 and cooled to -20°C. A solid residue was obtained. Recrystallisation from C$_2$H$_5$OAc yielded 220 mg (31.3%) of yellow crystals, mp 153°C. $^{1}$$\text{H-Nmr}$ (250.13 MHz, CDCl$_3$) $\delta$ = 1.36 (d, $^2$$J_{HH}$= 6.7 Hz, 6H, CHCH$_3$), 1.37 (d, $^2$$J_{HH}$=6.7 Hz, 6H, CHCH$_3$), 3.86 (s, 6H, OCH$_3$), 4.21 - 4.44 (m, 2H, NCH), 4.91 (s, 1H, CH). $^{13}$$\text{C-Nmr}$ (62.89 MHz, CDCl$_3$, $^{1}$$\text{H})$ $\delta$ = 19.8 (-, s, CCH$_3$), 20.2 (-, s, CCH$_3$), 48.8 (-, s, NCH), 49.4 (-, s, NCH), 53.4 (-, s, OCH$_3$), 58.0 (-, s, C-7), 82.5 (+, s, C-5), 113.7 (+, s, CN), 156.1 (+, s, C-6), 157.9 (+, s, C-2), 165.0 (+, s, C-8), 170.1 (+, s, C-4). \textit{Ir} (KBr) $\nu$ = 3000, 2980, 2960, 2940, 2220 (C=≡N), 1760 (C=O), 1750 (C=O), 1595, 1540 (C=N), 1525, 1460, 1440, 1390, 1370, 1340, 1310, 1260, 1210, 1190, 1180, 1150, 1050, 1010, 980, 910, 770, 750. \textit{UV} (CH$_3$CN) $\lambda_{\text{max}}$ (lge) = 227 (4.176), 331 (4.296). \textit{Anal. Calcd for
Ethyl 5-Cyano-2-dicyclohexylamino-6-oxo-6H-1,3-oxazin-4-yl-methylphosphinate (12a) - A mixture of 670 mg (2 mmol) of 3c and 340 mg (2.5 mmol) of diethoxymethylphosphine (11a) was heated to 100 °C until the evolution of gas was completed. After 30 min the solution was cooled and 15 ml of hexane/ethyl acetate (2:1) was added. A precipitate was obtained. Recrystallisation from hexane/ethyl acetate (1:1) yielded 390 mg (40.2 %) of white crystals, mp 167 °C.

1H-Nmr (250.13 MHz, CDC13) δ = 0.96 - 1.45 (m, 6Hcyclohex.), 1.42 (t, J=6.8 Hz, 3H, CH2CH3), 1.51-2.05 (m, 14Hcyclohex.), 1.79 (d, 2JPH=15.6 Hz, 3H, PCH3), 3.57 - 3.83 (m, 1H, NCH), 3.88 - 4.45 (m, 3H, NCH, OCH2). 13C-Nmr (62.89 MHz, CDC13, {1H}) δ = 13.8 (-, d, 1JPC= 106.6 Hz, PCH3), 16.5 (-, d, 3JPC=5.9 Hz, CH2CH3), 24.9 (+, s, C-4'), 25.1 (+, s, C-4'), 25.8 (+, s, C-3'), 29.7 (+, s, C-2'), 30.1 (+, s, C-2'), 57.9 (-, s, C-1'), 58.8 (-, s, C-1'), 62.4 (+, d, 2JPC=6.6 Hz, OCH2), 84.4 (+, d, 2JPC=15.8 Hz, C-5), 113.2 (+, d, 3JPC=2.5 Hz, CN), 156.1 (+, d, 3JPC=11.6 Hz, C-6), 158.6 (+, d, 3JPC=29.9 Hz, C-2), 171.5 (+, d, 1JPC=143.4 Hz, C-4). Ir (KBr) ν = 2930, 2860, 2210 (C-N), 1765 (CPO), 1575, 1500 (CPN), 1475, 1460, 1390, 1300, 1240 (P-O), 1160, 1020 (P-O-Alk.), 930, 875, 780, 755. UV (CH3CN) λmax (lge) = 230 (4.276), 354 (4.272). Anal. Calcd for C20H30N3O4P: C, 58.96; H, 7.42; N, 10.31; P, 7.60. Found: C, 59.06; H, 7.52; N, 10.29; P, 7.36.

Ethyl 5-Cyano-2-dimethylamino-6-oxo-6H-1,3-oxazin-4-yl-phenylphosphinate (12b) - A mixture of 400 mg (2 mmol) of 3a and 0.5 ml (2.5 mmol) of diethoxyphenylphosphine (11b) was heated to 80 °C until the evolution of gas was completed. After 15 min the solution was cooled and 20 ml of hexane was added. The residue was recrystallised from hexane/ethyl acetate (1:1) to give 512 mg (76.9%) of 12b, mp 145 °C. 1H-Nmr (250.13 MHz, CDC13) δ = 1.46 (t, J=7.0 Hz, 3H, CH2CH3), 3.17 (s, 3H, NCH3), 3.19 (s, 3H, NCH3), 4.34 (virt. quin. J=7.1 Hz, 2H, OCH2), 7.46 - 7.66 (m, 3Har), 7.88 - 8.00 (m, 2Har). 13C-Nmr (62.89 MHz, CDC13, {1H}) δ = 16.4 (-, d, 3JPC=6.2 Hz, CH2CH3), 36.9 (-, s, NCH3), 38.2 (-, s, NCH3), 63.1 (+, d, 2JPC=6.5 Hz, OCH2), 85.6 (+, d, 2JPC=16.5 Hz, C-5), 113.1 (+, s, CN), 127.9 (+, d, 1JPC=145.5 Hz, C-1'), 128.6 (-, d, 3JPC=14.0 Hz, C-3'), 132.7 (-, d, 2JPC=9.6 Hz, C-2'), 133.5 (-, s, C-4'), 156.1 (+, d, 3JPC=12.1 Hz, C-6), 159.0 (+, d, 3JPC=28.7 Hz, C-2), 171.8 (+, d, 1JPC=149.6 Hz, C-4). Ir (KBr) ν = 2990, 2940, 2220 (C=N), 1755 (C=O), 1630, 1510 (C=N), 1475, 1415, 1340, 1270, 1240 (P=O), 1120, 1010 (P-O-Alk.), 955, 925, 830, 780, 760, 750, 710, 695. UV (CH3CN) λmax (lge) = 229 (4.334), 352 (4.207). Anal.
Calcd for C\textsubscript{15}H\textsubscript{16}N\textsubscript{3}O\textsubscript{4}P: C, 54.06; H, 4.84; N, 12.61. Found: C, 54.11; H, 4.88; N, 12.63.

**General procedure for preparation of 5-cyano-2-dialkylamino-6-oxo-6H-1,3-oxazin-4-yl-diphenylphosphinoxides (14):**

A mixture of compound (3)\textsuperscript{11} (1 mmol) and 0.34 ml (1.5 mmol) of methoxydiphenylphosphine (13) was heated to 80 °C until the evolution of gas was finished. After 15 min the solution was cooled and 10 ml of ethyl acetate (14b,c) or ethyl acetate/pentane (1:1) (14a) was added. The residue was recrystallised giving white crystals.

**5-Cyano-2-dicyclohexylamino-6-oxo-6H-1,3-oxazin-4-yl-diphenylphosphinoxide (14a)** - 203 mg (81.0%) from ethyl acetate/pentane (1:1), mp 120-122 °C. \(^1\)H-Nmr (299.95 MHz, CDCl\textsubscript{3}) \(\delta = 1.00 - 2.05\) (m, 20Hcyclohex), 3.40 - 4.00 (m, 2H, NCH), 7.45 - 7.70 (m, 6Haromat), 7.81 - 7.95 (m, 4Haromat). \(^1^3\)C-Nmr (62.89 MHz, CDCl\textsubscript{3}, \(^1\)H) \(\delta = 24.6 (+, s, C-4')\), 24.7 (+, s, C-4''), 25.5 (+, s, C-3''), 25.8 (+, s, C-3''), 29.5 (+, s, C-2''), 30.1 (+, s, C-2''), 57.8 (-, s, NCH), 58.6 (-, s, NCH), 87.0 (+, d, \(^2\)J\textsubscript{PC}=16.8 Hz, C-5), 112.3 (+, s, CN), 128.5 (-, d, \(^3\)J\textsubscript{PC}=12.5 Hz, C-3'), 129.2 (+, d, \(^1\)J\textsubscript{PC}=107.2 Hz, C-1'), 132.1 (+, d, \(^2\)J\textsubscript{PC}=9.6 Hz, C-2'), 132.7 (+, d, \(^4\)J\textsubscript{PC}=2.5 Hz, C-4''), 156.0 (+, d, \(^3\)J\textsubscript{PC}=10.7 Hz, C-6), 158.0 (+, d, \(^3\)J\textsubscript{PC}=24.4 Hz, C-2), 173.4 (+, d, \(^1\)J\textsubscript{PC}=112.5 Hz, C-4). IR (KBr) \(v = 2930, 2855, 2220\) (C=N), 1765 (C=O), 1570, 1495, 1455, 1435 (P-Ar), 1385, 1305, 1255 (P=O), 1225, 1205, 1115, 1100, 1010, 995, 895, 830, 790, 760, 750, 725, 690. UV (CH\textsubscript{3}CN) \(\lambda_{\text{max}}\) (lgc) = 226 (4.499), 358 (4.263). Anal. Calcd for C\textsubscript{29}H\textsubscript{32}N\textsubscript{3}O\textsubscript{3}P: C, 69.44; H, 6.43; N, 8.38. Found: C, 68.79; H, 6.50; N, 8.26. HRMS: 501.2181, calcd: 501.2182.

**5-Cyano-6-oxo-2-piperidino-6H-1,3-oxazin-4-yl-diphenylphosphinoxide (14b)** - 175 mg (86.4%) from ethyl acetate/CH\textsubscript{3}Cl\textsubscript{3} (3:1), mp 183 °C. \(^1\)H-Nmr (250.13 MHz, CDCl\textsubscript{3}) \(\delta = 1.45 - 1.75\) (m, 6Hpiper.), 3.50 - 3.70 (m, 4H, NCH\textsubscript{2}), 7.42 - 7.67 (m, 6Haromat), 7.80 - 7.97 (m, 4Haromat). \(^1^3\)C-Nmr (62.89 MHz, CDCl\textsubscript{3}, \(^1\)H) \(\delta = 23.4 (+, s, C-3'')\), 25.1 (+, s, C-2''), 25.5 (+, s, C-2''), 45.7 (+, s, C-1''), 46.8 (+, s, C-1''), 86.8 (+, d, \(^2\)J\textsubscript{PC}=15.3 Hz, C-5), 112.3 (+, d, \(^3\)J\textsubscript{PC}=2.7 Hz, CN), 128.4 (-, d, \(^3\)J\textsubscript{PC}=12.9 Hz, C-3'), 129.2 (+, d, \(^1\)J\textsubscript{PC}=107.1 Hz, C-1''), 132.2 (-, d, \(^2\)J\textsubscript{PC}=9.8 Hz, C-2), 132.7 (-, s, C-4'), 156.0 (+, d, \(^3\)J\textsubscript{PC}=11.3 Hz, C-6), 156.8 (+, d, \(^3\)J\textsubscript{PC}=25.5 Hz, C-2), 173.5 (+, d, \(^1\)J\textsubscript{PC}=110.3 Hz, C-4). IR (KBr) \(v = 3060, 3020, 2960, 2940, 2870, 2230\) (C=N), 1760 (C=O), 1615, 1515 (C=N), 1505, 1475, 1465, 1450, 1435 (P-Aryl), 1370, 1330, 1300, 1235 (P=O), 1220, 1200, 1120, 1105, 1020, 855, 835, 800, 765, 755, 750, 730, 700. UV (CH\textsubscript{3}CN) \(\lambda_{\text{max}}\) (lgc) = 226 (4.452), 354
Anal. Calcd for C_{22}H_{20}N_{3}O_{3}P: C, 65.18; H, 4.97; N, 10.37; P, 7.64. Found: C, 65.16; H, 5.07; N, 10.24; P, 7.56.

5-Cyano-2-dibenzylamino-6-oxo-6H-1,3-oxazin-4-yl-diphenylphosphinoxide (14c) - 202 mg (78.1%) from C_2H_5OAc/CHCl_3 (1:1), mp 187 °C. ¹H-Nmr (250.13 MHz, CDCl₃) δ = 4.57 (s, 2H, CH₂), 4.62 (s, 2H, CH₂), 6.84 - 7.00 (m, 2H_arom.), 7.16 - 7.61 (m, 14H_arom.), 7.73 - 7.92 (m, 4H_arom.). ¹³C-Nmr (62.89 MHz, CDCl₃, {¹H}) δ = 50.3 (+, s, CH₂), 51.1 (+, s, CH₂), 88.8 (+, d, ²J_pC=14.6 Hz, C-5), 111.9 (+, s, CN), 127.7, 128.3, 128.7, 128.9, 129.1 (-, s, C_Ar), 128.5 (-, d, ³J_pC=12.2 Hz, C-3'), 128.5 (+, d, ¹J_pC=107.2 Hz, C-1'), 132.1 (-, d, ²J_pC=10.0 Hz, C-2'), 132.8 (-, d, ⁴J_pC=2.4 Hz, C-4'), 133.3, 133.8 (+, s, NCC_Ar), 155.3 (+, d, ³J_pC=10.5 Hz, C-6), 158.6 (+, d, ³J_pC=25.7 Hz, C-2), 173.8 (+, d, ¹J_pC=109.5 Hz, C-4). IR (KBr) ν = 3060, 3040, 3010, 2980, 2940, 2225 (C≡N), 1765 (C=O), 1605, 1585 (C≡N), 1505, 1500, 1475, 1455, 1440 (P-Aryl), 1430, 1375, 1295 (P=O), 1205, 1115, 930, 840, 800, 765, 750, 720, 690. UV (CH₃CN) λ_max (lgɛ) = 224 sh (4.429), 350 (4.224). Anal. Calcd for C_{31}H_{24}N_{3}O_{3}P: C, 71.95; H, 4.67; N, 8.12; P, 5.99. Found: C, 71.87; H, 4.63; N, 7.99; P, 5.91.

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REFERENCES AND NOTES


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