A General Synthesis of 3,5-Dihalo-2*H*-1,4-oxazin-2-ones from Cyanohydrins

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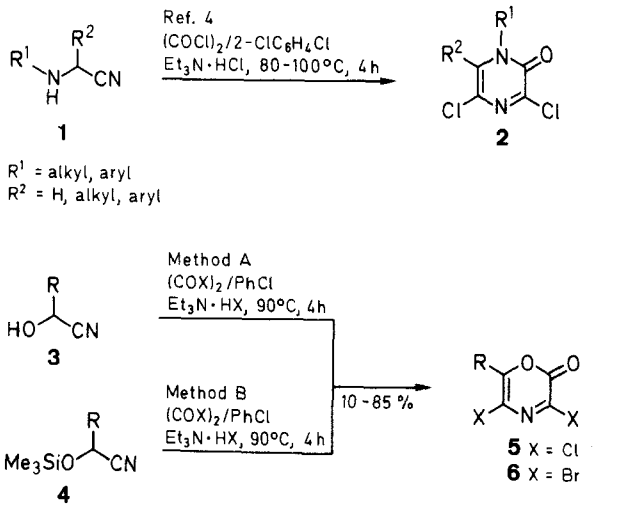
In a novel approach starting from *O*-trimethylsilyl protected or unprotected cyanohydrins and oxalyl chloride or bromide, a series of unknown 6-substituted 3,5-dihalo-2*H*-1,4-oxazin-2-ones were prepared. The method was shown to be efficient for various types of cyanohydrins; however cyclization was not obtained with cyanohydrins containing bulky substituents, electron-rich aryl or heteroaryl groups. A mechanism is proposed.

2*H*-1,4-Oxazin-2-ones are scarcely described in the literature.[1-3] The oxidation of 5,6-dihydro-1,4-oxazin-2-one systems with several oxidation agents gives only a very poor yield of 2*H*-1,4-oxazin-2-ones.[1] Another method is the cyclization of the hydrobromides from α-amino acid acetonyl (or phenylacyl) esters to form the 3,6-dihydro-2*H*-1,4-oxazin-2-ones, which were then converted into 2*H*-1,4-oxazin-2-ones by bromination followed by dehydrobromination. This method needs several steps and does not allow further functionalization. A third method[3] mentioned one example of a chloro(ethoxycarbonyl)methyleneiminium salt as precursor for 2*H*-1,4-oxazin-2-ones. A few years ago we described[4] the synthesis of 3,5-dichloro-2(1*H*)-pyrazinones **2** starting from α-amino nitriles **1** and oxalyl chloride in 1,2-dichlorobenzene at 80–100 °C. Considering the structural analogy between 2(1*H*)-pyrazinones and 2*H*-1,4-oxazin-2-ones **5**, we tried[5] the cyclization of cyanohydrins **3** and **4** with oxalyl halide (Scheme **A**). Compounds **5** and **6** are of interest because of the Diels–Alder activity of their azadiene system that can be functionalized variably.



3–6	R	3–6	R	3–6	R
a	H	**h**	Ph	**o**	$MeOCH_2$
b	Me	**i**	$4\text{-}MeC_6H_4$	**p**	$ClCH_2$
c	Et	**j**	$4\text{-}ClC_6H_4$	**q**	Cl_2CH
d	*i*-Pr	**k**	$3,4\text{-}(MeO)_2C_6H_3$	**r**	Cl_3C
e	*c*-C_6H_{11}	**l**	$4\text{-}MeO_2CC_6H_4$	**s**	MeO_2C
f	*t*-Bu	**m**	$3\text{-}MeOC_6H_4$	**t**	2-furyl
g	CH_2Ph	**n**	$EtOCH_2CH_2$	**u**	3-pyridyl

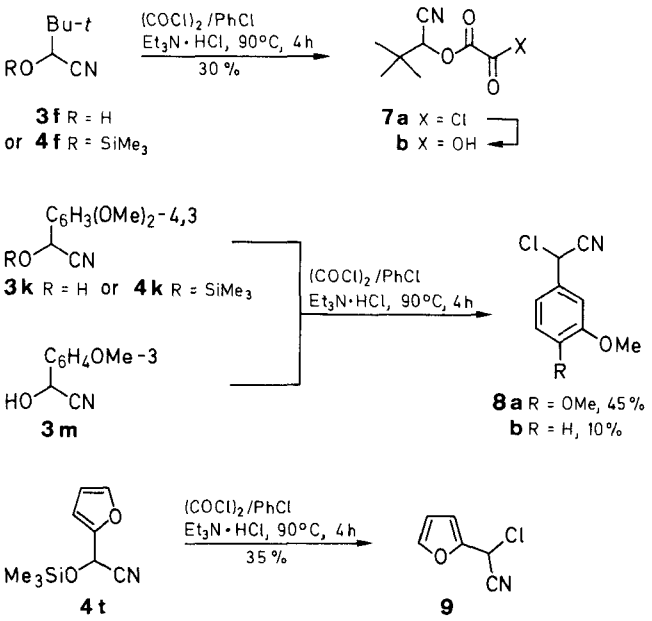
Scheme A

The cyanohydrins **3**, easily accessible by known methods,[6-14] were prepared by a general procedure described in the experimental section. In the cases of unstable α-hydroxy nitriles or the aldehydes, only the corresponding trimethylsilyl derivatives[15-21] were used. For the synthesis of compound **5a** we reported[5] a method starting from **4a**. (For safety reasons[6] we did not use the hydroxyacetonitrile in pure form). We have now prepared a chloroacetic acid stabilized diethyl ether solution of the cyanohydrin **3a**, obtained from formaldehyde sodium bisulfite adduct and potassium cyanide, which was used as such.

In a series of alkyl, cyclohexyl, phenylmethyl and aryl cyanohydrins **3a–m** and **4a,c,f,k** only two cyanohydrins, the bulky 3,3-dimethyl-2-hydroxybutanenitriles **3f, 4f** and the cyanohydrins **3k, 4k** with electron rich aryl group, failed to cyclize with oxalyl chloride. In the cases of **3f, 4f** the ester **7a** was formed and isolated as the acid **7b**. The cyanohydrins **3k, 4k** gave as main product the α-chloronitrile **8a**, also obtained by Katamna[12] by treatment of **3k** with thionyl chloride (Scheme **B**). The chlorinated compound **8b** was formed as a side product in the reaction of oxalyl chloride with *m*-methoxy derivative **3m** along with the oxazinone **5m**, which was obtained in 47% yield.

The cyanohydrin **3b** was also treated with oxalyl bromide in the presence of triethylammonium bromide. Due to its instability, oxazinone **6b** was obtained only in moderate yield.

To prove the versatility of this method we used also some functionalized cyanohydrins. Compounds **3n,o** gave moderate to good yield of the corresponding oxazinones **5n** and **5o**, respectively. For R = halomethyl or carbomethoxy, the silylated derivatives **4p-s** had to be used. Deprotection, *in situ* as described above, and reaction with oxalyl chloride gave the oxazonones **5p,q** in good yield; however **5s** was obtained in poor yield. The cyanohydrin **4r** of trichloroacetaldehyde did not undergo cyclization with oxalyl chloride probably due to the bulkiness of the trichloromethyl group.



Scheme **B**

Table 1. Oxazinones **5** and **6b** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b,c]	IR (KBr) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
5a	30 (25)	53–54	$C_4HCl_2NO_2$ (164.9)	1600, 1770	7.63 (s, H)
5b	72	74–75	$C_5H_3Cl_2NO_2$ (178.9)	1600, 1760	2.34 (s, CH_3)
5c	61 (61)	oil	$C_6H_5Cl_2NO_2$ (192.9)	1595, 1750	1.30 (t, 3H, CH_3), 2.73 (q, 2H, J = 7.5, CH_2)
5d	38	57–58	$C_6H_5Cl_2NO_2$ (206.9)	1600, 1750	1.29 (d, 6H, J = 7.5, CH_3), 3.19 (sept, 1H, J = 7.5, CH)
5e	59	123–124	$C_{10}H_{11}Cl_2NO_2$ (247.0)	1600, 1765	1.56–1.95 (m, 10H, CH_2), 2.85 (tt, 1H, $J_{a,a}$ = 12, $J_{a,e}$ = 4, CH)
5g	40	65–66	$C_{11}H_7Cl_2NO_2$ (254.9)	1610, 1755	3.92 (s, 2H, CH_2), 7.31 (s, 5H$_{arom}$)
5h	85	65–67	$C_{10}H_5Cl_2NO_2$ (240.9)	1610, 1770	7.43 (m, 3H$_{arom}$), 7.83 (m, 2H$_{arom}$)
5i	63	124–125	$C_{11}H_7Cl_2NO_2$ (254.9)	1605, 1765	2.49 (s, 3H, CH_3), 7.18 (d, 2H$_{arom}$, J = 8.0), 7.72 (d, 2H$_{arom}$, J = 8.0)
5j	59	99–100	$C_{10}H_4Cl_3NO_2$ (274.9)	1590, 1770	7.47 (d, 2H$_{arom}$, J = 8.0), 7.85 (d, 2H$_{arom}$, J = 8.0)
5l	39	111–113 (dec)	$C_{12}H_7Cl_2NO_3$ (298.9)	1590, 1770	4.0 (s, 3H, CH_3), 7.90 (d, 2H$_{arom}$, J = 7.5), 8.10 (d, 2H$_{arom}$, J = 7.5)
5m	47	78–79	$C_{11}H_7Cl_2NO_3$ (270.9)	1580, 1750	3.84 (s, 3H, CH_3), 7.03 (m, 1H$_{arom}$), 7.38 (m, 3H$_{arom}$)
5n	51	oil[e]	$C_8H_9Cl_2NO_3$ (236.9)	1600, 1770	1.19 (t, 3H, J = 6.5, CH_3), 2.96 (t, 2H, J = 6.2, OCH_2CH_2), 3.57 (q, 2H, J = 6.5, $-CH_2O$), 3.78 (t, 2H, J = 6.2, OCH_2CH_2)
5o	75[d]	oil[e]	$C_6H_5Cl_2NO_3$ (208.9)	1605, 1760	3.43 (s, 3H, CH_3), 4.37 (s, 2H, CH_2)
5p	73[d]	75–76	$C_5H_2Cl_3NO_3$ (212.9)	1615, 1765	4.47 (s, CH_2)
5q	52[d]	39–40	$C_6HCl_4NO_2$ (246.8)	1610, 1780	6.77 (s, CH)
5s	10[d]	133–134	$C_6H_3Cl_3NO_4$ (222.9)	1595, 1725, 1770	3.96 (s, CH_3)
6b	25 (49)[d]	129 (oil)	$C_5H_3Br_2NO_2$ (269.1)	1600, 1740	2.43 (s, CH_3)

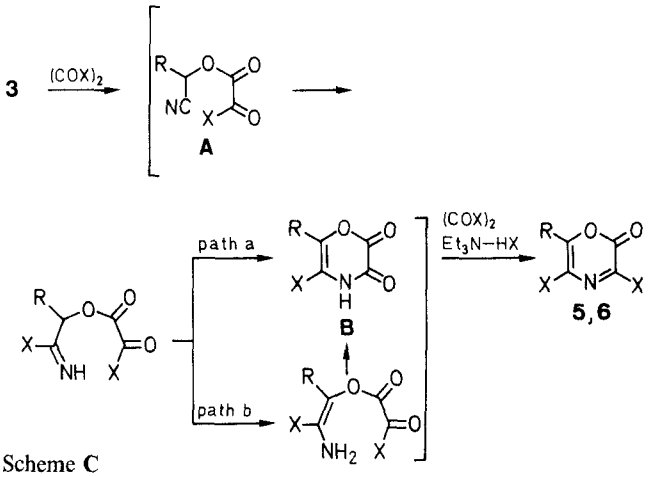
[a] Yield of recrystallized product, except oils.
[b] Satisfactory microanalyses obtained: C ±0.13, H ±0.06, N ±0.11; exception **5a**, C −0.84.
[c] HRMS data are in agreement with required values.
[d] Yield of the oxazinone starting from **4** (Method B).
[e] Oxazinones obtained as oils with low stability.

Two types of heteroaryl substituted cyanohydrins were tested. With the 2-furyl substituted compound **4t**, 2-(chlorocyanomethyl)furan (**9**) was isolated among a number of unidentified products. This behaviour, which is comparable with the results from **3k, 4k**, could be due to the electron donor capacities of the furan moiety. The 3-pyridyl substituted cyanohydrin **4u** gave only tarry products.

All compounds **5** and **6** show IR absorptions (Table 1) at approximately $\nu = 1760\ cm^{-1}$ and $1600\ cm^{-1}$, which can be ascribed to the conjugated six membered lactone ring and the imidoyl halide function. The mass spectra of **5** and **6** with relative abundances of M^+, M^{+2} and M^{+4} ions point out to the presence of two chlorine or bromine atoms in **5** and **6**, respectively. Insufficient structural information was obtained from the ^{1}H-NMR spectra; however their ^{13}C-NMR absorptions at about $\delta = 150$ (C-2), 142 (C-3), 122 (C-5) and the variable (C-6) absorption at $\delta = 137-156$ are in good agreement with the proposed structures. The long range coupled ^{13}C-NMR of some model compounds **5a,b,h** and **6b** are given in Table 2.

Regarding the reaction path followed, we propose a mechanism (Scheme **C**) comparable to that postulated for the reaction of α-aminonitriles with oxalyl chloride.[4] Acylation of the α-hydroxynitrile would give the ester **A**, which cyclizes into **B** by acid catalyzed intramolecular acylation of the nitrile function along path a or b. The excess of oxalyl halide and triethylammonium halide converts the lactam into an imidoyl halide.

The procedure described constitutes a convenient method for the preparation of 6-substituted 3,5-dihalo-2*H*-1,4-oxazin-2-ones **5** or **6** derived from the corresponding cyanohydrins **3** or **4** and oxalyl halide. Only



Scheme **C**

cyanohydrins with bulky substituents, electron rich aryl or heteroaryl cyanohydrins failed to cyclize with oxalyl halogenide. By the versatility of this method and possible modes for functionalization of the title compounds, a way is opened for the study of a multifunctionalized 2-azadiene system.

All reagent were of commercial quality. Most starting aldehydes are commercially available. 2-Ethoxyacetaldehyde,[13] 2-methoxyacetalaldehyde,[22] 2-chloroacetaldehyde,[23] and methylglyoxalate[24] were prepared according to literature. The cyanohydrins **3b,h** are commercial products. The silylated cyanohydrins **4** were prepared according to literature.[15–21]

The oxalyl halides were used as such, whereas the ammonium salts were predried as follows. A $CHCl_3$ solution of the ammonium salts was treated with $MgSO_4$, filtered and evaporated. KF was predried in an vacuum desiccator with P_2O_5 at r.t. Reagent quality chlorobenzene was dried over P_2O_5 and distilled before use. Analytical TLC plates (Sil G/UV 254) and silica gel (70–230 mesh) were

Table 2. ^{13}C-NMR Data of Oxazinones **5** and **6b** [$CDCl_3$/TMS; δ, $J_{C,H}$(Hz)]

Compound	C-2	C-3	C-5	C-6	Others
5a	148.9 (d, $^3J = 6$)	145.5 (d, $^4J = 2$)	126.3 (d, $^2J = 7$)	137.9 (d, $^1J = 211$)	
5b	150.0 (s)	141.3 (q, $^5J = 1.5$)	123.7 (q, $^3J = 5$)	149.7 (q, $^2J = 8$)	16.7 (CH_3) (q, $^1J = 120$)
5c	149.9	141.1	122.1	153.6	10.1 (CH_3), 23.8 (CH_2)
5d	150.4	141.5	121.7	156.5	19 (CH_3), 29.7 (CH)
5e	150.4	141.1	121.8	156	25.2, 25.6, 28.8 (CH_2), 39.2 (CH)
5g	150	142.3	123.8	150.2	36.5 (CH_2), 127.9, 129, 133.8 (C_{arom})
5h	149.7 (s)	141.5 (s)	122.5 (s)	148.4 (t, $^3J = 3.6$)	127.5 (m, $C_{arom\text{-}m}$), 127.9 (t, $C_{arom\text{-}ipso}$), 128.6 (m, $C_{arom\text{-}o}$), 130.4 (m, $C_{arom\text{-}p}$)
5i	149.9	140.9	122	148.8	21.6 (CH_3), 125.1, 128.6, 129.4, 142.6 (C_{arom})
5j	149.5	142	122.5	147	126, 129, 138 (C_{arom})
5l	149.4	142.8	124	147.4	52.5 (OCH_3), 128.7, 129.8, 132, 132.7 (C_{arom}), 165.8 (CO)
5m	148	141.5	122	149.5	55 (OCH_3), 114, 117, 121, 129, 130, 159 (C_{arom})
5n	149.9	141.8	123.9	150.5	14.8 (CH_3), 31 ($\underline{C}H_2CH_2O$), 65.6, 66.1 ($\underline{C}H_2O\underline{C}H_2$)
5o	149.5	144.6	124.9	147.3	59.3 (CH_2), 67.4 (CH_3)
5p	149	145.4	124.7	145.9	38 (CH_2Cl)
5q	147.8	146.7	121.3	143.7	61.4 (CH)
5s	148.7	147.7	129.4	136.9	53.7 (CH_3), 158 (CO)
6b	149.5 (s, br)	133.6 (s, br)	111 (m)	150.8 (q, $^2J = 7.5$)	17.6 (CH_3) (q, $^1J = 130$)

purchased from Macherey-Nagel. Melting points were taken using a Reichert-Jung Thermovar apparatus and are uncorrected. Microanalyses were performed by Janssen Pharmaceutica on a Carlo Erba elemental analyser type 1106.

IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer. NMR spectra were obtained on a Bruker Cryospec FT-250 spectrometer and HRMS on a Kratos MS 50 TC apparatus at 70 eV.

Note: Because of the instability of oxazinones **5** and **6** (up to 50% decomposition) towards silica gel, normal column chromatography is not recommended. Chromatography on alumina led to complete decomposition. Further purification was performed by recrystallization from mixtures of hexane/Et_2O unless otherwise mentioned.

Formaldehyde Cyanohydrin (3a):
A solution KCN (43.6 g, 0.67 mol) in water (80 mL) is added dropwise to a vigorously stirred solution of formaldehyde $NaHSO_3$ adduct (30 g, 0.22 mol) in water (80 mL) at 0–10 °C. After stirring for 1 h in an ice bath, water (50 mL) is added and the mixture is extracted with Et_2O (10 × 200 mL). The combined Et_2O extracts are dried (2 × $MgSO_4$), a catalytic amount of chloroacetic acid is added and the solution is concentrated under vacuum at r.t. till a volume of 50–100 mL is obtained. This pale yellow solution is used for the synthesis of **5a**.

Alkyl and Aryl Cyanohydrins 3c–g, i–o; General Procedure:
The purified aldehyde (0.2 mol) is added at once to a vigorously stirred ice cooled solution of $NaHSO_3$ (76 g, 0.4 mol) in water (200 mL) (in the case of **3i–m** the temperature of the solution is kept at 40 °C and cooled after a period of 30 min). After stirring for 0.5 h a solution of KCN (52 g, 0.8 mol) in water (100 mL) is added dropwise to the cooled mixture. After stirring for 1 h in an ice bath, water (100 mL) is added. Then the mixture is extracted with $CHCl_3$ (3 × 250 mL, in the case of **3o**, 5 × 250 mL) the combined organic extracts are dried ($MgSO_4$) and evaporated under vacuum. The cyanohydrins are used as such and are known in the literature, except **3l**.

3l; yield: 84%; mp 70–72 °C (Et_2O/Hexane).

IR (KBr): ν = 1740 (C=O), 2250 cm^{-1} (CN).

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.90 (s, 3H, OCH_3), 4.13 (s, 1H, OH), 5.56 (s, 1H, CH), 7.53 (d, 2 H_{arom}, J = 8.0 Hz), 8.03 (d, 2 H_{arom}, J = 8.0).

MS: m/z (%) = 191 (5), 164 (60), 133 (100), 105 (30), 77 (24).

3,5-Dichloro-2*H*-1,4-oxazin-2-ones 5a–o and Compounds 7b and 8a,b from Cyanohydrins 3a–o; General Procedure:

Method A: A solution of cyanohydrin **3a–o** (0.2 mol) in chlorobenzene (200 mL) is added dropwise to a stirred solution of oxalyl chloride (100.8 g, 0.8 mol) in chlorobenzene (600 mL) at 0 °C under N_2 atmosphere. After 30 min, the solution is slowly heated to 90 °C in an oil bath and $Et_3N \cdot HCl$ (13.7 g, 0.1 mol) [$Me_3N \cdot HCl$ (9.5 g, 0.1 mol) in the case of **3a**] is added. After 4 h the mixture is cooled and evaporated under vacuum at 60 °C. The dark oil or crystal mass is treated with Et_2O (~ 700 mL, pro analysis). The suspension is filtered and the residue is washed with Et_2O (3 × 100 mL). After evaporation of the combined filtrates, further purification is done by flash column chromatography (~ 300 g silica gel, eluent: 50% hexane/$CHCl_3$ to 100% $CHCl_3$). Evaporation and recrystallization (Et_2O/hexane or CCl_4 in the case of **5a**) gives pure oxazinone **5a–o** (Tables 1 and 2). Spectral data for compounds **7b**, **8a,b** obtained from reactions with cyanohydrins **3f,k,m** are given below.

7b; yield: 30%; mp 63–64 °C (hexane).

IR (KBr): ν = 3400 (OH), 1770 cm^{-1} (CO).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.16 (s, 9H, CH_3), 5.13 (s, 1H, CH).

MS: m/z (%): 170 (2), 96 (24), 69 (19), 57 (100).

8a: yield: 45%; oil (Lit.[12] oil).

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.93 (s, 6H, MeO), 5.56 (s, 1H, CH), 7.1 (m, 3 H_{arom}).

MS: m/z (%): 211 (61), 176 (100).

8b: yield: 10%; oil.

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.76 (s, 3H, OCH_3), 5.53 (s, 1H, CH), 7.89, 8.40 (m, 4 H_{arom}).

MS: m/z (%): 181 (28), 146 (100).

3,5-Dichloro-2*H*-1,4-oxazin-2-ones 5a,c,p–s and Compounds 8a and 9 from Cyanohydrins 4a,c,k,p–t; General Procedure:

Method B: The same procedure and amounts as described above in Method A are used; however dry KF (26.7 g, 0.46 mol) and a catalytic amount of 18-crown-6 ether are present in the initial solution of oxalyl chloride (100.8 g, 0.8 mol) in chlorobenzene (600 mL). In the case of **4k** compound **8a** and **4t** compound **9** is isolated respectively:

9: yield: 35%; oil.

^{1}H-NMR ($CDCl_3$/TMS): δ = 4.72 (s, 1H, CH), 6.51, 6.78, 6.97 (m, 3 H_{furyl}).

MS: m/z (%): 141 (3), 106 (100), 67 (9).

3,5-Dibromo-2*H*-1,4-oxazin-2-one (6b) from 3b:
The reaction is performed using the same procedure as described in Method A but with reduced amounts (1/10). Oxalyl bromide (17.28 g, 0.08 mol) and dry $Et_3N \cdot HBr$ (1.82 g, 0.01 mol) are used instead of the chloro derivatives. After work up as described in Method A, the product is recrystallized from CCl_4; yield: 25% (Tables 1 and 2).

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