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SYNTHESIS OF 3,5-DIHALOGENO-2H-1,4-OXAZIN-2-ONES FROM CYANOHYDRINES

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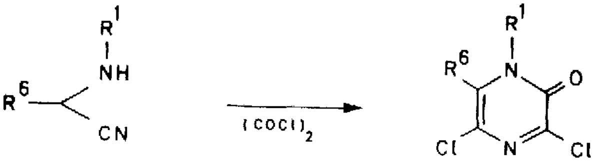
Summary : The title compounds 4 were obtained on treatment of cyanohydrines 3 of aliphatic and aryl aldehydes with oxalyl chloride or bromide in chlorobenzene at 90°C. Evidence for their structure is given by their spectroscopic data and by the Diels Alder reaction of 4a and 4g with acetylenic dienophiles to yield substituted pyridines. Cycloaddition was also observed with ethene.

In previous work[1] we investigated the reaction between α-aminonitriles 1 and oxalyl chloride in 1,2-dichlorobenzene at 80-100°C; they gave 6-substituted 3,5-dichloro-2(1H)-pyrazinones 2 in good yield.

Now we wish to describe a comparative synthetic method for 3,5-dihalogeno-2H-1,4-oxazin-2-ones 4, starting from the appropriate cyanohydrines 3 and oxalyl chloride or bromide. Synthetic methods for 2H-1,4-oxazin-2-ones are scarcely described in the literature[2]. Furthermore their access needs several steps, which give in most cases rather poor yield and do not allow to generate a variable substitution pattern.

The cyanohydrines 3a needed in our method are mostly easily accessible by known methods[3] starting from the corresponding aryl or aliphatic aldehydes. Compounds 3a ($R^6 = CH_3$, CH_2CH_3, C_6H_{11}, C_6H_5 and p-ClC_6H_4) were brought into reaction with excess oxalyl chloride in chlorobenzene at 90°C in the presence of triethylammonium chloride. Evaporation of the reaction mixture and filtration over silica gel (20% hexane-chloroform) yielded the 3,5-dichloro-2H-1,4-oxazin-2-ones 4a-e, which were recrystallized from diethyl ether/hexane (table 1). When oxalyl bromide was reacted with 2-hydroxy-propane nitrile the corresponding 3,5-dibromo derivative 4g was obtained in moderate yield, even after careful recrystallization from carbon tetrachloride, due to its decomposition .



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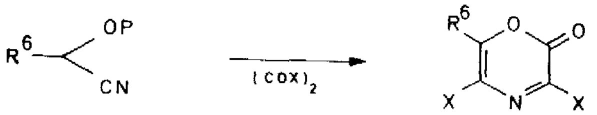
R^1 = alkyl, aryl

R^6 = H, alkyl, aryl



X = Cl, Br

4

3a : P = H

3b : P = $SiMe_3$

R^6 = H, alkyl, aryl

X = Cl, Br

The method was also shown to be valuable when the corresponding α-hydroxynitrile is not easily available by direct methods as in the case of 3a (R^6=H). We prepared the trimethylsilyl protected cyanohydrine 3b (R^6=H, Et) by reaction of the corresponding aldehyde with trimethyl silyl cyanide in the presence of zinc iodide[4]. After purification by distillation these silyl derivatives were deprotected in situ with tetrabutylammonium fluoride[5] or potassium fluoride in the presence of 18-crown-6 ether[4a]. Subsequent reaction with oxalyl chloride gave the 1,4-oxazin-2-one 4b in a comparable yield as with the unprotected cyanohydrine. A rather poor yield of 4f was realized with 3b (R^6=H).

All compounds 4 show IR-absorptions around 1760 cm^{-1} and 1600 cm^{-1} (KBr-pellet), which can be ascribed to the conjugated six membered lactone ring and the imidoyl halogenide function. The mass spectra of 4 with the relative abundances of M, M+2, M+4 ions point out to the presence of two chlorine or bromine atoms. Unsufficient structural information is obtained from the ^1H-NMR spectra; however their ^{13}C-NMR absorptions at about 150 ppm (C-2), 142 ppm (C-3) and 122 ppm (C-5) and the variable C-6 absorption (138-156 ppm) are in good agreement with the proposed structures.

Table 1 : 2H-1,4-oxazin-2-ones 4 from cyanohydrines:
substitution pattern, yield and melting points.

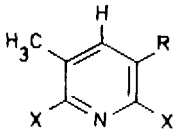
Comp.	R^6	X	yield (%)	mp.(°C)
4a	Me	Cl	72	70
4b	Et(1,2)	Cl	65	oil
4c	C_6H_{11}	Cl	59	128
4d	C_6H_5	Cl	85	81
4e	pCl-C_6H_4	Cl	58	102
4f	H(1)	Cl	25	57
4g	Me	Br	49(3)	128

(1) the trimethylsilyl protected cyanohydrine was used
(2) comparable yield was obtained with the unprotected cyanohydrine
(3) decomposition

Furthermore we proved the oxazinone structure by reacting model compounds 4a and 4g (unpurified) with acetylenic compounds in toluene at 80°C. As we are dealing with a similar dihalogeno-2-azadiëne system as in the 2(1H)-pyrazinones[6], we expected easy Diels Alder reaction of the 2H-1,4-oxazin-2-ones. As far as we know only a few suggestions about their Diels Alder activity has been made in the literature[7]. In contrast with the 2(1H)-pyrazinones, which yielded 2(1H)-pyridinones and/or pyridines after spontaneous decomposition of the initial adduct with acetylenes, we always obtained substituted 2,6-dihalogenopyridines. The regiochemistry of the 2,6-dihalogeno pyridines was deduced from their off-resonance and gated decoupled ^{13}C-NMR spectra. A C_4-H absorption was observed at about 140 ppm for compounds 5 and a C_3-H absorption at about 120 ppm for compound 6. Regioselective formation of compounds 5 was observed with phenyl acetylene and propyne as shown in table 2. However reaction seems to be more difficult and less regioselective (mixture of 5 + 6) when electron deficient acetylenes as methyl propynoate are used.

Not only acetylenic compounds but also alkenes do react : with ethylene and 4a the adduct was isolated in high yield after heating in toluene at 80°C (^1H-NMR ($CDCl_3$) : 1.79 ppm, s, CH_3; 1.93-2.50 ppm, m, $(CH_2)_2$; IR(oil) : 1790 cm^{-1}(lactone); 1605 cm^{-1} (imidoyl function). In contrast with 1,3-oxazin-6-ones easy loss of CO_2 upon heating could not be observed even with temperatures up to 160°C (decomposition of the adduct).

The synthesis of other substituted 2H-1,4-oxazin-2-ones and their Diels Alder reactivities are under current investigation.



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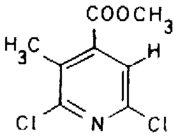

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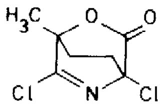

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X = Cl, Br

R = CH_3, Ph or $COOCH_3$

Table 2. Yields of pyridines 5-6 in the reaction of oxazinones 4a, g with acetylenes in toluene at 80°C for 20 hours

R	X	%5	mp.(°C)	%6
CH_3	Cl	95	98	/
C_6H_5	Cl	95	94	/
$COOCH_3$*	Cl	54	77	40(oil)
C_6H_5	Br	65	92	/

* : reaction time was 120 hours

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