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The Synthesis of 3-Functionalized 5-Chloro-6-methyl-2*H*-1,4-oxazin-2-ones and of Pyridines from Cycloaddition-elimination Reactions with Substituted Acetylenic Compounds.

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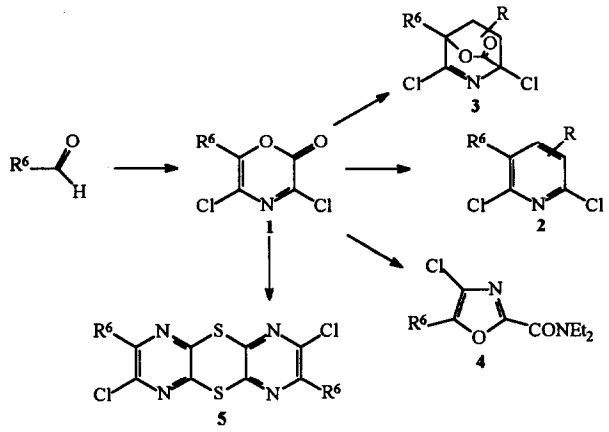
Abstract: Selective functionalisation of the chlorimine group in 3,5-dichloro-6-methyl-2*H*-1,4-oxazin-2-one is usually realised in appropriate conditions, by electrophilic catalysis avoiding reaction of the lactone function. The azadiene system in the 3-substituted 5-chloro-6-methyl-2*H*-1,4-oxazin-2-ones is shown to react easily with monosubstituted acetylenic compounds yielding polyfunctionalized pyridines in excellent yield via a cycloaddition-elimination process. The usually high regioselectivity and its dependence on the nature of the 3-substituent is discussed.

The synthetic potential of the 2*H*-1,4-oxazin-2-one skeleton was unexplored for a long time, probably due to the lack of efficient synthetic methods for variably substituted derivatives.[1] Recently the easy one pot synthesis and subsequent study of 6-substituted 3,5-dichloro-2*H*-1,4-oxazin-2-ones **1**[2] opened some promising applications in heterocyclic synthesis. Their 2-azadiene system turned out to be an efficient Diels-Alder partner towards alkynes[3] and alkenes[4] giving high yields of pyridines **2** or thermally stable bicyclic adducts **3**, respectively. Furthermore, on treatment with specific nucleophiles ($HNEt_2$, ^-SCN) polyfunctionalized oxazoles **4**[5] or polycyclic compounds of type **5**[6] were isolated (scheme 1). This behaviour shows the peculiar characteristics of this skeleton which contains an azadiene system, lactone and chlorimine function. In this report, methods for the introduction of a variety of substituents in position 3 are described; the reactivity and regioselectivity in cycloadditions of the 3-substituted 2*H*-1,4-oxazin-2-ones with acetylenic compounds yielding variably substituted pyridines is also discussed.

RESULTS AND DISCUSSION

As shown in a preliminary communication[6], the easily accessible 3,5-dichloro-6-methyl-2*H*-1,4-oxazin-2-one **6a** has bielectrophilic character with the lactone function being more sensitive to nucleophiles than the chlorimine group. Activation of the latter group is usually required for selective nucleophilic attack of position 3. Working under acidic conditions or with Lewis acids proved to be extremely useful: the nucleophilic reagents now preferentially attack the imidoyl chloride function which is more reactive due to protonation or complexation. Typical reaction conditions (hydrogen halogenide, Lewis acid, solvent) are presented in table 1a.



Scheme 1

Surprisingly, secondary amines reacted exclusively with the chlorimine function in refluxing $CHCl_3$ whereas reaction at -78°C exclusively yielded oxazoles of type **4** originating from an initial C-2 attack.[5] Furthermore, reactions of the chlorimine with organometallic compounds was investigated. Reactions of 3,5-dichlorooxazinones with Grignard reagents, which were used in the functionalisation of the position 3 in 3,5-dichloro-2(1*H*)-pyrazin-2-ones,[7] were unsuccessful. In the case of alkyllithium reagents, only *tert*-butyllithium yielded the corresponding 3-alkyl substituted 2*H*-1,4-oxazin-2-one **6s**. The reaction of lithium diorganocopper[8] and organocadmium[9] reagents with the 3,5-dichloro-2*H*-1,4-oxazin-2-one was not successful. However the method for carbon-carbon bond formation using a organotin compound and a palladium catalyst,[10] gave satisfying results with the oxazinone. (table 1b)

The mentioned smooth reaction conditions gave 2*H*-1,4-oxazin-2-ones with electron-donating and conjugated groups in position 3. The introduction of electron-withdrawing substituents (e.g. CN) via classical substitution methods[11] or via palladium catalysed cross-coupling reactions[12], was unsuccessful. However, sulfinyl or sulfonyl groups could be introduced via sulfur oxidation[13] of **6i**. (table 1b)

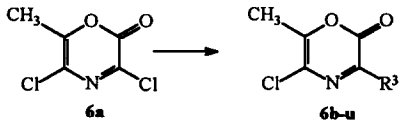
The 3-substituted 5-chloro-6-methyl-2*H*-1,4-oxazin-2-ones are crystalline in most cases and show a typical dark violet color under UV light (366 nm). IR absorptions for the carbonyl group and for the 2-azadiene system are observed around 1740 and 1600 cm^{-1}, respectively; the mass spectral data show an intense signal at M^+-28, due to easy CO loss. The NMR data are taken up in tables 2 and 3. The methyl group absorbs around 2.35 (± 0.15) ppm (^1H NMR) and 17 (± 2.5) ppm (^{13}C NMR). The ^{13}C NMR values for C-5 about 125 and C-2 about 150 are little affected by the nature of the R^3, but the C-3 and C-6 signals can be found in a wide range (135-150 ppm and 140-155 ppm, respectively).

The pyridine nucleus is a structural unit appearing in many natural products. Because of the pharmacological importance of functionalized pyridines, a lot of synthetical pathways have been developed[14] including [4+2] cycloaddition reactions on cyclic 2-azadienes systems as oxazoles, 1,2,4-triazines, thiazoles, pyrimidines, pyrazines,[15] 2(1*H*)-pyrazin-2-ones[16] and 6*H*-1,3-oxazin-6-ones.[17] General synthetical applications of cycloadditions with many of these systems encounter one or more of the following disadvantages: low reactivity or yield, limited substitution pattern, low regio or site selectivity and substituent dependent reaction route.

Recently, the striking high reactivity of 3,5-dichloro-2*H*-1,4-oxazin-2-ones towards acetylenic compounds, revealed a new versatile method towards polyfunctionalized pyridines. In this context, we have studied the behaviour of a selection of 3-substituted 5-chloro-6-methyl-2*H*-oxazin-2-ones (R^3 = OMe, SCH_2Ph, 2-thienyl, 4-tolyl, $SO_{(2)}CH_2Ph$, Et, *tert*-Bu) towards four model acetylenic compounds (methyl propiolate, phenyl acetylene, propargyl chloride and ethoxyethyne) under comparable reaction conditions.

The experimental results summarized in table 4 show the excellent yields of pyridines in the reaction of 3-substituted oxazinones with all kinds of acetylenic compounds (electron-deficient, conjugated, non-conjugated).

Table 1. 5-Chloro-6-methyl-2*H*-1,4-oxazin-2-ones generated from 6a.



6a **6b-u**

a. by Electrophilic Catalysis at room temperature

Compd.	R^3	reaction conditions (reagent, solvent, time)*	yield (%)
6b	Br	HBr, $CHCl_3$, 15 min	93
6c	OMe	MeOH (HCl sat.), 15 min	91
6d	OEt	EtOH (HCl sat.), 2 h	41
6e	2-pyrrolyl	1.1 equiv pyrrole, EtOAc (HBr sat.), 10 min	81
6f	3-indolyl	1.1 equiv indole, EtOAc (HBr sat.), 10 min	85
6g	3-(N-methyl-indolyl)	1.1 equiv N-methylindole, EtOAc (HBr sat.), 10 min	87
6h	SPr	1.1 equiv 1-propanethiol, 1.1 equiv $AlCl_3$, CH_2Cl_2, 30 min	82
6i	SBn	1.1 equiv thiobenzyl alcohol, 1.1 equiv $AlCl_3$, CH_2Cl_2, 30 min	71
6j	SPh	1.1 equiv thiophenol, 1.1 equiv $AlCl_3$, CH_2Cl_2, 2 h	73
6k	4-MeOPh	4 equiv methoxybenzene, 4 equiv $AlCl_3$, CH_2Cl_2, 2 h	91
6l	Ph	benzene, 4 equiv $AlCl_3$, 2 h	85
6m	4-MePh	toluene, 4 equiv $AlCl_3$, 2 h	89
6n	2-thienyl	1.1 equiv thiophene, 2.1 equiv $SnCl_4$, CH_2Cl_2, overnight	71
		b. by other methods.	
6o	NEt_2	2.1 equiv diethylamine, $CHCl_3$ reflux, 10 min	88
6p	1-piperidinyl	2.1 equiv piperidine, $CHCl_3$ reflux, 10 min	84
6q	4-Bn-piperazin-1-yl	2.1 equiv N-(phenylmethyl)piperazine, $CHCl_3$ reflux, 10 min	88
6r	Et	1.1 equiv $SnEt_4$, 0.001 equiv $Pd(PPh_3)_4$, toluene reflux, 8 days	80
6s	*tert*-Bu	8 equiv *tert*-BuLi, CH_2Cl_2, -78°C, 3 h	45
6t	SOBn	**6i**, 1.3 equiv MCPBA, CH_2Cl_2, rt, 30 min	*
6u	SO_2Bn	**6i**, 3 equiv MCPBA, CH_2Cl_2, rt, 12 h	*

* Purification led to a considerable product loss.

The ratio of both regioisomers could be obtained from the integration of both pyridine hydrogens (or two other appropriate signals) in the ^1H NMR spectrum of the reaction mixture. Not only the ^1H NMR absorptions for the hydrogens but also the ^{13}C NMR absorptions for the carbon atoms in both 3(5)- and 4-position of the pyridine nucleus appear in different regions and show a different coupling pattern (Table 5).

The ratio of regioisomers seems to be determined by the nature of the substituent in position 3: electron-releasing or (hetero)aryl groups led mainly to 2,3,5,6-substituted derivatives whereas the other regioisomers predominate with electron-withdrawing or steric groups in the position 3. Surprisingly, both reactivity and regioselectivity of ethoxyethyne towards this electron-deficient 2-azadiene system was lower than expected.

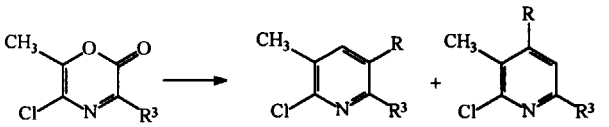
Table 2. ^1H NMR data of 3-substituted 5-chloro-6-methyl-2*H*-1,4-oxazin-2-ones ($CDCl_3$/ppm).

	R^6 (3H, s)	R^3
6b	2.36	
6c	2.29	4.00 (s, 3H, OCH_3)
6d	2.29	1.45 (t, 3H, OCH_2CH_3), 4.42 (q, 2H, OCH_2CH_3)
6e	2.37	6.40 (m, 1H, 4'-H), 7.10 (m, 1H, 3'-H), 7.45 (m, 1H, 5'-H), 9.90 (s (br), 1H, NH)
6f	2.29	7.20-7.32 (m, 2H, 5'- and 6'-H), 7.59 (d, 1H, 7'-H), 8.42 (d, 1H, 4'-H), 8.63 (s, 1H, 2'-H), 12.11 (br s, 1H, NH)
6g	2.39	3.88 (s, 3H, NCH_3), 7.37 (m, 3H, 5'-, 6'- and 7'-H), 8.53 (s, 1H, 2'-H), 8.61 (m, 1H, 4'-H)
6h	2.31	1.06 (t, 3H, $SCH_2CH_2CH_3$), 1.75 (sextet, 2H, $SCH_2CH_2CH_3$), 3.05 (t, 2H, $SCH_2CH_2CH_3$)
6i	2.29	4.27 (s, 2H, CH_2Ph), 7.20-7.45 (m, 5H, Ph)
6j	2.28	7.40-7.60 (m, 5H, Ph)
6k	2.39	3.88 (s, 3H, OCH_3), 6.93 (d, 2H, 3'- and 5'-H), 8.33 (d, 2H, 2'- and 6'-H)
6l	2.30	7.30-7.45 (m, 3H, 3'-, 5'- and 4'-H), 8.20 (d, 2H, 2'- and 6'-H)
6m	2.35	2.35 (s, 3H, $PhCH_3$), 7.30 (d, 2H, 3'- and 5'-H), 8.30 (d, 2H, 2'- and 6'-H)
6n	2.39	7.12 (t, 1H, 4'-H), 7.57 (d, 1H, 5'-H), 8.23 (d, 1H, 3'-H)
6o	2.20	1.22 (t, 6H, NCH_2CH_3), 3.70 (q, 4H, NCH_2)
6p	2.23	1.62-1.72 (m, 6H, CH_2), 3.78-3.68 (m, 4H, NCH_2-)
6q	2.24	2.58 (m, 4H, CH_2NBn), 3.57 (s, 2H, CH_2Ph), 3.94 (m, 4H, NCH_2), 7.25-7.40 (m, 5H, Ph)
6r	2.34	1.25 (t, 3H, CH_2CH_3), 2.78 (q, 2H, CH_2CH_3)
6s	2.33	1.36 (s, 9H, $C(CH_3)_3$)
6t	2.41	4.35 (d, 1H, CH_2Ph), 4.50 (d, 1H, CH_2Ph), 7.20-7.40 (m, 5H, Ph)
6u	2.49	4.78 (s, 2H, CH_2Ph), 7.30-7.50 (m, 5H, Ph)

Table 3. ^{13}C NMR-data of 3-substituted 5-chloro-6-methyl-2*H*-1,4-oxazinones ($CDCl_3$ /ppm).

	ring carbon atoms				substituent carbon atoms	
	C-2	C-3	C-5	C-6	6-CH_3	R^3
6b	150.1	134.3	123.9	149.8	16.9	
6c	150.2	149.7	121.5	142.0	16.1	55.6 (OCH_3)
6d	150.3	149.3	121.6	141.7	16.1	13.7 (CH_3), 64.9 (CH_2)
6e	153.1	144.4	125.8	142.4	16.9	112.0 (4'-C), 117.2 (3'-C), 124.5 (5'-C), 139.3 (2'-C)
6f	153.1	144.6	124.7	143.1	16.5	109.8 (3'-C), 112.4 (7'-C), 121.6 122.2 123.2 (4'-, 5'- and 6'-C), 125.6 (7a'-C), 133.2 (2'-C), 136.8 (7a'-C)
6g	153.6	144.3	126.6	142.6	16.8	35.5 (NCH_3), 109.6 (7'-C), 109.7 (3'-C), 122.3 123.2 123.6 (4'-, 5'- en 6'-C), 126.0 (3a'-C), 136.5 (2'-C), 137.4 (7a'-C)
6h	152.4	154.6	125.5	142.9	16.4	13.4 (CH_3), 21.4 (CH_2CH_3), 32.1 (SCH_2)
6i	152.1	153.6	125.4	143.5	16.3	34.6 (CH_2Ph), 127.6 (4'-C), 128.5 (2'-C), 129.3 (3'-C), 135.6 (1'-C)
6j	152.0	153.8	125.5	144.2	16.4	126.2 (1'-C), 129.3 (2'-C), 129.8 (4'-C), 134.9 (3'-C)
6k	153.0	145.8	125.6	147.1	16.9	55.3 (OCH_3), 113.8 (3'- and 5'-C), 125.5 (1'-C), 130.9 (2'- and 6'-C), 162.4 (4'-C)
6l	152.8	146.4	125.7	148.4	17.1	128.3 (3'- and 5'-C), 128.9 (2'- and 6'-C), 131.5 (4'-C), 132.7 (1'-C)
6m	152.6	146.1	125.5	147.8	16.6	21.3 (CH_3), 128.8 and 128.9 (2'-, 3'-, 5'- and 6'-C), 130.0 (1'-C), 142.0 (4'-C)
6n	151.9	146.9	125.4	142.4	17.0	128.5 132.7 132.8 137.1 (2'-, 3'-, 4'- and 5'-C)
6o	151.2	143.6	124.1	135.7	15.4	13.2 (CH_3), 44.5 (CH_2)
6p	151.6	144.8	124.0	137.1	15.8	24.5 ($NCH_2CH_2CH_2$-), 26.0 (NCH_2CH_2-), 47.8 (NCH_2-)
6q	151.4	144.6	123.9	137.8	15.7	46.3 (CH_2NCH_2Ph), 52.7 (NCH_2CH_2), 62.7 (CH_2Ph), 127.3 (4'-C_{Ph}), 128.3 129.2 (2'- and 3'-C_{Ph}), 137.2 (1'-C_{Ph})
6r	153.8	156.0	125.1	147.2	16.9	10.0 (CH_2CH_3), 26.9 (CH_2CH_3)
6s	151.7	159.6	124.5	147.7	16.8	27.2 (CH_3), 38.6 ($C(CH_3)_3$)
6t	150.2	154.7	126.9	152.1	17.2	58.0 (CH_2), 128.7 129.0 129.8 (1'-, 2'-, 3'- and 4'-C_{Ph})
6u	148.4	145.5	124.9	157.2	18.1	59.0 (CH_2), 125.7 (1'-C_{Ph}), 129.0 (3'-C_{Ph}), 129.4 (4'-C_{Ph}), 131.3 (2'-C_{Ph})

Table 4. Pyridines from reaction of some 3-substituted 2*H*-1,4-oxazin-2-ones with monosubstituted alkynes: reaction time and isomer distribution.



R = COOMe	**7**	**8**
R = Ph	**9**	**10**
R = CH_2Cl	**11**	**12**
R = OEt	**13**	**14**

	A. Methyl propiolate (neat, 80°C)			B. Phenyl acetylene (neat, 80°C)			C. Propargyl chloride (neat, reflux°)			D. Ethoxyethyne (50 w% in hexane, 80°C, sealed tube)		
	time	yield	ratio	time	yield	ratio	time	yield	ratio	time	yield	ratio
6		**% 7+8**	**7/8**		**% 9+10**	**9/10**		**% 11+12**	**11/12**		**% 13+14**	**13/14**
6c	2 h	92	95:5	1 day	83	95:5	12 h	85	100:0	< 1 week	72	40:60
6i	< 1 h	95	95:5	1.5 h	78	100:0	/	/	/	/	/	/
6m	1 h	90	90:10	1 h	81	95:5	19 h	95	100:0	/	/	/
6n	1 h	92	95:5	1 h	80	100:0	14 h	95	100:0	/	/	/
6r	33 h[a]	73	60:40	6 days[a]	90	65:35	/	/	/	/	/	/
6s	1 day	90	15:85	12 h	84	10:90	36 h	60	0:100	< 1 week	90	0:100
6t	/	/	/	1 h	> 80	40:60	/	/	/	/	/	/
6u	2 h	> 80	10:90	/	/	/	4 h	>80	50:50	/	/	/

(a) 1 mmol oxazinone, 3 equiv dienophile, 5 ml acetonitrile, 80°C

In conclusion, 3-substitution of 2*H*-1,4-oxazin-2-ones and subsequent cycloaddition-elimination provides an efficient and general method for the synthesis of polyfunctionalyzed pyridines. The smooth reaction conditions and high yield, the regioselectivity and the broad substitution pattern at position 3 are the great values of this method.

Table 5. Typical NMR data of the regioisomers.

	Compds. **6, 8, 10, 12**		Compds. **7, 9, 11, 13**	
^{1}H NMR	4-H	7.50-7.80	5-H	7.00-7.50
^{13}C NMR	C-4	± 140 (d x q)*	C-5	± 120 (d)*
		$^1J_{C-H}$ = 160 Hz, $^3J_{C-H}$ = 5 Hz		$^1J_{C-H}$ = 160 Hz
	CH_3	q x d*	CH_3	q*
		$^1J_{C-H}$ = 130 Hz, $^3J_{C-H}$ = 5 Hz		$^1J_{C-H}$ = 130 Hz

* additional coupling with other substituents (e.g. R) are not presented.

EXPERIMENTAL PART

IR spectra were recorded as thin films between NaCl plates or as solids in KBr pellets on a Perkin-Elmer 297 grating IR spectrophotometer and a Perkin-Elmer 1720 infrared Fourier transform spectrometer. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker WM 250 instrument operating at 250 MHz for ^{1}H and 63 MHz for ^{13}C measurements. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane or the deuterated solvent as an internal reference. Mass spectra were run by using a Kratos MS50TC instrument and a DS90 data system. Exact mass measurements were performed at a resolution of 10,000. For the chromatography analytical TLC plates (Alugram Sil G/UV$_{254}$) and silica gel (70-230 mesh) from Macherey Nagel were used. 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. The preparation of all compounds except **6c**[18] is described below.

A. Synthesis of the 3-functionalized-5-chloro-6-methyl-2*H*-1,4-oxazin-2-ones.

3-bromo- and 3-alkoxy-5-chloro-6-methyl-2*H*-1,4-oxazin-2-ones 6b-d. General procedure.
Dry hydrogen bromide (**6b**) or dry hydrogen chloride (**6c,d**) was led for 15 minutes through a solution of **6a** (1 g, 5.6 mmol) in 50 ml $CHCl_3$ (**6b**) or 20 ml dry (m)ethanol (**6c,d**) at 0°C. The mixture was then stirred for 15 minutes (**6b,c**) or 2 h (**6d**) at room temperature. After evaporation, flash chromatography ($CHCl_3$/EtOAc) yielded the crude product which was recrystallised from hexane.

3-bromo-5-chloro-6-methyl-2*H*-1,4-oxazin-2-one 6b.
Yield: 93%; m.p. 83°C; IR (KBr) cm^{-1}: 1740, 1605; MS m/z : 223 (40, M$^+$), 195 (54), 43 (100); exact mass calcd for $C_5H_3BrClNO_2$: 222.9035; found: 222.9028; anal calcd for $C_5H_3BrClNO_2$: C 26.76, H 1.35, N 6.24; found: C 26.54, H 1.30, N 6.19.

5-chloro-3-ethoxy-6-methyl-2*H*-1,4-oxazin-2-one 6d.
Yield: 41%; m.p. 64°C; IR (KBr) cm^{-1}: 1762, 1623; MS m/z : 189 (17, M$^+$), 133 (49), 43 (100); exact mass calcd for $C_7H_8ClNO_3$: 189.0193; found: 189.0210.

Synthesis of the 5-chloro-3-heteroaryl-6-methyl-2*H*-1,4-oxazin-2-ones 6e-f. General procedure.
Compound **6a** (1 g, 5.6 mmol) was dissolved in 50 ml of a hydrogen bromide saturated EtOAc solution. Then 1.1 equiv of the heteroaromatic compound (pyrrole, indole, 1-methylindole) was added to the solution.

This mixture was stirred for 10 minutes at room temperature. Evaporation of the solvent followed by recrystallisation of the crude product using a EtOAc/$CHCl_3$ mixture yielded the pure yellow crystals of compounds **6e-f**.

5-chloro-6-methyl-3-(2-pyrrolyl)-2*H*-1,4-oxazin-2-one 6e.

Yield: 81%; m.p. 152°C; IR (KBr) cm^{-1}: 1740, 1600; MS m/z : 210 (60, M^+), 182 (39), 94 (100); exact mass calcd for $C_9H_7ClN_2O_2$: 210.0196; found: 210.0212.

5-chloro-3-(3-indolyl)-6-methyl-2*H*-1,4-oxazin-2-one 6f.

Yield: 85%; m.p. 268°C; IR (KBr) cm^{-1}: 1720, 1600; MS m/z : 260 (65, M^+), 232 (100); exact mass calcd for $C_{13}H_9ClN_2O_2$: 260.0352; found: 260.0347.

5-chloro-6-methyl-3-(1-methyl-3-indolyl)-2*H*-1,4-oxazin-2-one 6g.

Yield: 87%; m.p. 226°C; IR (KBr) cm^{-1}: 1720, 1600; MS m/z : 274 (73, M^+), 246 (100); exact mass calcd for $C_{14}H_{11}C_lN_2O_2$: 274.0509; found: 274.0506.

Synthesis of the 5-chloro-6-methyl-3-alkylthio- and the corresponding 3-arylthio-2*H*-1,4-oxazin-2-ones 6h-j. General procedure.

A mixture of **6a** (1 g, 5.6 mmol), 1.1 equiv $AlCl_3$ and 50 ml CH_2Cl_2 was stirred at room temperature. After 15 minutes 1.1 equiv of the thioreagent (1-propanethiol, thiobenzyl alcohol, thiophenol) was added. This mixture was stirred at room temperature for 30 minutes (**6h,i**) or 2 h (**6j**). The mixture was poured in an ice bath and extracted with $CHCl_3$ The combined $CHCl_3$ portions were dried with $MgSO_4$. Evaporation of the solvent yielded the crude products **6h-j**, which were further purified by recrystallisation from a hexane/$CHCl_3$ mixture giving yellow crystals.

5-chloro-6-methyl-3-(propylthio)-2*H*-1,4-oxazin-2-one 6h.

Yield: 82%; oil; IR (NaCl plates) cm^{-1}: 1750, 1610; MS m/z : 219 (32, M^+), 191 (11), 148 (99), 43 (100); exact mass calcd for $C_8H_{10}ClNO_2S$: 219.0121; found: 219.0124.

5-chloro-6-methyl-3-(phenylmethylthio)-2*H*-1,4-oxazin-2-one 6i.

Yield: 71%; m.p. 93°C; IR (KBr) cm^{-1}: 1740, 1605; MS m/z : 267 (21, M^+), 91 (100); exact mass calcd for $C_{12}H_{10}ClNO_2S$: 267.0120; found: 267.0121.

5-chloro-6-methyl-3-(phenylthio)-2*H*-1,4-oxazin-2-one 6j.

Yield: 73%; m.p. 114°C; IR (KBr) cm^{-1}: 1735, 1605; MS m/z : 253 (31, M^+), 225 (23), 121 (100); exact mass calcd for $C_{11}H_8ClNO_2S$: 252.9964; found: 252.9969.

Synthesis of the 3-(hetero)aryl-5-chloro-6-methyl-2*H*-1,4-oxazin-2-ones 6k-n. General procedure.

A mixture of **6a** (1 g, 5.6 mmol) and 4.0 equiv $AlCl_3$ (**6k-m**) or 2.1 equiv $SnCl_4$ (**6n**) in 50 ml CH_2Cl_2 (**6k,n**) or 50 ml benzene (**6l**) or toluene (**6m**) was stirred during 30 minutes at room temperature. After addition of 4.0 equiv methoxybenzene (**6k**) or 1.1 equiv thiophene (**6n**) the mixtures were stirred for another 2 hours (**6k-m**) or overnight (**6n**) and poured into a ice bath. The water layer was extracted with 3 portions $CHCl_3$ (3x50 ml) and the combined fractions were dried with $MgSO_4$. Evaporation of the solvent gave the crude product, which was further purified by recrystallisation from a CH_2Cl_2/hexane mixture.

5-chloro-3-(4-methoxyphenyl)-6-methyl-2*H*-1,4-oxazin-2-one 6k.

Yield: 91%; m.p. 63°C; IR (KBr) cm^{-1}: 1760, 1730; MS m/z : 251 (100, M^+), 223 (84); exact mass calcd for $C_{12}H_{10}ClNO_3$: 251.0349; found: 251.0366; anal calcd for $C_{12}H_{10}ClNO_3$: C 57.27, H 4.01, N 5.57; found: C 57.00,H 3.92, N 5.48.

5-chloro-6-methyl-3-phenyl-2*H*-1,4-oxazin-2-one 6l.

Yield: 85%; m.p. 95°C; IR (KBr) cm^{-1}: 1730, 1600; MS m/z : 221 (51, M^+), 193(100); exact mass calcd for $C_{11}H_8ClNO_2$: 221.0243; found: 221.0243.

5-chloro-6-methyl-3-(4-methylphenyl)-2*H*-1,4-oxazin-2-one 6m.

Yield: 89%; m.p. 112°C; IR (KBr) cm^{-1}: 1755, 1605; MS m/z : 235 (41, M^+), 207 (100); exact mass calcd for $C_{12}H_{10}ClNO_2$: 235.0400; found: 235.0403; anal calcd for $C_{12}H_{10}ClNO_2$: C 61.16, H 4.28, N 5.94; found: C 60.87, H 4.17, N 5.83.

5-chloro-6-methyl-2-(2-thienyl)-2*H*-1,4-oxazin-2-one 6n.
Yield: 71%; oil; IR (NaCl plates) cm^{-1}: 1730, 1590; MS m/z : 227 (98, M^+), 199 (100); exact mass calcd for $C_9H_6ClNO_2S$: 226.9808; found: 226.9817.

Synthesis of 5-chloro-3-alkylamino-6-methyl-2*H*-1,4-oxazin-2-ones 6o-q. General procedure.
A mixture of the amine (2.1 equiv, diethylamine, piperidine, 1-benzylpiperazine) and $CHCl_3$ was added dropwise to a refluxing mixture of **6a** (1 g, 5.6 mmol) in 50 ml $CHCl_3$. The solvent was evaporated after 10 minutes and the residue was purified by flash chromatography ($CHCl_3$). The obtained crude materials **6o-q** were further purified by recrystallisation from a hexane solution yielding yellow crystals.
5-chloro-3-diethylamino-6-methyl-2*H*-1,4-oxazin-2-one 6o.
Yield: 88%; oil; IR (NaCl plates) cm^{-1}: 1736, 1624; MS m/z : 216 (30, M^+), 188 (39), 43 (100); exact mass calcd for $C_9H_{13}ClN_2O_2$: 216.0666; found: 216.0666.
5-chloro-6-methyl-3-(1-piperidinyl)-2*H*-1,4-oxazin-2-one 6p.
Yield: 84%; m.p. 42°C; IR (KBr) cm^{-1}: 1730, 1620; MS m/z : 228 (60, M^+), 200 (100); exact mass calcd for $C_{10}H_{13}ClN_2O_2$: 228.0665; found: 228.0666; anal calcd for $C_{10}H_{13}ClN_2O_2$: C 61.97, H 5.20, N 9.63; found: C 61.71, H 5.09, N 9.56.
5-chloro-6-methyl-3-(4-(phenylmethyl)piperazin-1-yl)-2*H*-1,4-oxazin-2-one 6q.
Yield: 88%; m.p. 216°C; IR (KBr) cm^{-1}: 1730, 1620; MS m/z : 319 (50, M^+), 146 (100), 99 (88); exact mass calcd for $C_{16}H_{18}ClN_3O_2$: 319.1086; found: 319.1091.

Synthesis of the 3-alkyl-5-chloro-6-methyl-2*H*-1,4-oxazin-2-ones 6r,s.

5-chloro-3-ethyl-6-methyl-2*H*-1,4-oxazin-2-one 6r.
A mixture of **6a** (0.54 g, 3 mmol), 1.2 equiv tetraethyltin and 0.001 equiv $Pd(PPh_3)_4$ in 6 ml toluene was refluxed for 8 days. The solvent was evaporated and the residue was treated for 12 hours with KF in EtOAc. This mixture was filtrated and evaporated. The crude material was dissolved in CH_3CN and extracted with pentane. The CH_3CN layer was evaporated yielding the crude product **6r**, which was further purified by flash chromatography (hexane/EtOAc) and recrystallisation (diisopropylether/CH_2Cl_2). The oxazinone **6r** was isolated in a 80% yield.
Yield: 80%; m.p. 68°C; IR (KBr) cm^{-1}: 1732, 1617; MS m/z : 173 (12, M^+), 144 (28), 130 (29), 43 (100); exact mass calcd for $C_7H_8ClNO_2$: 173.0244; found: 173.0244.

3-*tert*-butyl-5-chloro-6-methyl-2*H*-1,4-oxazin-2-one 6s.
Tert-BuLi (13 ml, 1.5 M solution in hexane) was added at -78°C to a solution of **6a** (3 g, 16.7 mmol) in dry CH_2Cl_2. This mixture was stirred for 3 hours at -78°C and evaporated. The crude material was purified by chromatography (hexane/$CHCl_3$) yielding 1.51 g (45%) **6s**.
Yield: 45%; oil; IR (NaCl plates) cm^{-1}: 1745, 1615; MS m/z : 201 (10, M^+), 173 (14); exact mass calcd for $C_9H_{12}ClNO_2$: 201.0557; found: 201.0557.

Oxidation of the 5-chloro-6-methyl-3-(phenylmethylthio)-2*H*-1,4-oxazin-2-one 6i.
A mixture of **6i** (0.4 g, 1.5 mmol) and 3-chloroperbenzoic acid 70-75% 0.4 g for **6t** or 1.65 g for **6u** in 20 (40) ml CH_2Cl_2 was stirred at room temperature for 30 minutes (**6t**) or 12 h (**6u**). Flash chromatography and recrystallisation (pentane) of the crude material yielded **6t** or **6u** as light yellow and unstable crystals.
The corresponding 3-(phenylmethylsulfi(o)nyl)-2H-1,4-oxazin-2-ones **6t,u** were used as such in cycloaddition-elimination reactions with acetylenic compounds.

B. Cycloaddition-elimination reactions of the 3-substituted oxazinones.

Pyridines 7-8 from the reaction of the oxazinones 6c,i,m,n,r,s,u with methyl propiolate. General procedure.

Compound **6c,i,m,n,r,s,u** (0.20 g) and 3 ml methyl propiolate were stirred at 80°C. Evaporation of the dienophile yielded a mixture of the two regioisomers, which were separated by chromatography or by crystallisation. (yields are given in table 4)

methyl 6-chloro-2-methoxy-5-methyl-3-pyridinecarboxylate 7c.

m.p. 98°C; IR (KBr) cm^{-1}: 1710; ^1H NMR ($CDCl_3$) δ: 2.34 (s, 3H, CH_3), 3.94 (s, 3H, $COOCH_3$), 4.06 (s,3H,OCH_3), 8.07 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 18.1 (CH_3), 52.3 ($COOCH_3$), 54.7 (OCH_3), 112.1 (C-3), 124.0 (C-5), 144.3 (C-4), 151.7 (C-6), 160.3 (C-2), 164.6 (*C*OOCH$_3$); MS m/z : 215 (65, M^+), 184 (100); exact mass calcd for $C_9H_{10}ClNO_3$: 215.0347; found: 215.0356; anal calcd for $C_9H_{10}ClNO_3$: C 50.13, H 4.67, N 6.50; found: C 50.00, H 4.60, N 6.45.

methyl 6-chloro-5-methyl-2-(phenylmethylthio)-3-pyridinecarboxylate 7i.

m.p. 100°C; IR (KBr) cm^{-1}: 1713; ^1H NMR ($CDCl_3$) δ: 2.33 (s, 3H, CH_3), 3.90 (s, 3H, $COOCH_3$), 4.38 (s, 2H, CH_2Ph), 7.10-7.50 (m, 5H, Ph), 8.05 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 18.6 (CH_3), 35.2 (CH_2Ph), 52.3 (OCH_3), 121.3 (C-3), 126.7 (C-5), 127.0 (4'-C_{Ph}), 128.3 (2'-C_{Ph}), 129.6 (3'-C_{Ph}), 137.7 (1'-C_{Ph}), 141.8 (C-4), 153.8 (C-6), 159.5 (C-2), 165.1 ($COOCH_3$); MS m/z : 307 (64, M^+), 91 (100); exact mass calcd for $C_{15}H_{14}ClNO_2S$: 307.0434; found: 307.0435.

methyl 6-chloro-5-methyl-2-(4-methylphenyl)-3-pyridinecarboxylate 7m.

m.p. 91°C; IR (KBr) cm^{-1}: 1720; ^1H NMR ($CDCl_3$) δ: 2.38 (s, 6H, CH_3 and $ArCH_3$), 3.67 (s, 3H, $COOCH_3$), 7.18 (d, 2H, 3'- and 5'-H_{Ar}); 7,42 (d, 2H, 2'- and 6'- H_{Ar}), 7.90 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 18.8 (CH_3), 21.3 ($ArCH_3$), 52.1 (OCH_3), 125.2 (C-3), 128.3 128.6 (2'-, 3'-, 5'- and 6'-C_{Ar}), 130.1 (C-5), 135.5 (1'-C_{Ar}), 138.7 (4'-C_{Ar}), 140.6 (C-4), 152.6 (C-6), 156.3 (C-2), 167.6 ($COOCH_3$); MS m/z : 275 (54,M^+), 260 (100); exact mass calcd for $C_{15}H_{14}ClNO_2$: 275.0713; found: 275.0713.

methyl 6-chloro-5-methyl-2-(2-thienyl)-3-pyridinecarboxylate 7n.

m.p. 84°C; IR (KBr) cm^{-1}: 1730; ^1H NMR ($CDCl_3$) δ: 2.35 (s, 3H, CH_3), 3.88 (s, 3H, $COOCH_3$), 7.11 (dxd, 1H, 4' H_{HetAr}); 7.51 (s, 2H, 3' and 5' H_{HetAr}), 7.88 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 18.8 (CH_3), 52.3 (OCH_3), 123.9 (C-3), 127.3, 127.8 128.4 (3'-, 4'- and 5'-C_{HetAr}), 129.9 (C-5), 140.2 (C-4), 140.7 (2'-C_{HetAr}), 148.3 (C-6), 151.9 (C-2), 167.3 ($COOCH_3$); MS m/z : 267 (100, M^+), 236 (44); exact mass calcd for $C_{12}H_{10}ClNO_2S$: 267.0120; found: 267.0120.

methyl 6-chloro-2-ethyl-5-methyl-3-pyridinecarboxylate 7r.

oil; IR (NaCl plates) cm^{-1}: 1725; ^1H NMR ($CDCl_3$) δ: 1.28 (t, 3H, C*H*$_3$CH$_2$), 2.38 (s, 3H, CH_3), 3.11 (q, 2H, CH_3CH_2), 3.92 (s, 3H, OCH_3), 8.00 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ:13.7 (CH_2CH_3), 18.8 (CH_3), 29.5 (*C*H$_2$CH$_3$), 52.2 (COO*C*H$_3$), 123.6 (C-3), 129.3 (C-5), 141.4 (C-4), 153.5 (C-6), 162.9 (C-2), 166.1 (*C*OOCH$_3$); MS m/z : 213 (34, M^+), 198 (100), 182 (21), 154 (18), 91 (30); exact mass calcd for $C_{10}H_{12}ClNO_2$: 213.0557; found: 213.0559.

methyl 2-chloro-6-ethyl-3-methyl-4-pyridinecarboxylate 8r.

oil; IR (NaCl plates) cm^{-1}: 1741; ^1H NMR ($CDCl_3$) δ: 1.30 (t, 3H, C*H*$_3$CH$_2$), 2.54 (s, 3H, CH_3), 2.80 (q, 2H, CH_3CH_2), 3.93 (s, 3H, OCH_3), 7.40 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 13.6 (CH_2CH_3), 16.6 (CH_3), 30.5 (*C*H$_2$CH$_3$), 52.6 (COO*C*H$_3$), 120.5 (C-5), 128.8 (C-3), 140.8 (C-4), 152.7 (C-2), 161.6 (C-6), 166.6 (*C*OOCH$_3$); MS m/z :213 (71, M^+), 212 (100), 182 (16); exact mass calcd for $C_{10}H_{12}ClNO_2$: 213.0557; found: 213.0557.

methyl 6-(*tert*-butyl)-2-chloro-3-methyl-4-pyridinecarboxylate 8s.

oil; IR (NaCl plates) cm^{-1}: 1740; ^1H NMR ($CDCl_3$) δ: 1.35 (s, 9H, $C(CH_3)_3$), 2.52 (s, 3H, CH_3), 3.93 (s, 3H, $COOCH_3$), 7.53 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 16.4 (CH_3), 29.2 ($C(CH_3)_3$), 37.1 ($C(CH_3)_3$), 52.3 (OCH_3), 117.3 (C-5), 128.2 (C-3), 140.1 (C-4), 152.2 (C-2), 166.4 (C-6), 167.3 ($COOCH_3$); MS m/z : 241 (44, M^+), 226 (100); exact mass calcd for $C_{12}H_{16}ClNO_2$: 241.0869; found: 241.0859.

methyl 6-chloro-5-methyl-2-(phenylmethylsulfonyl)-3-pyridinecarboxylate 7u.
m.p. 121°C; IR (KBr) cm^{-1}: 1742; ^1H NMR ($CDCl_3$) δ: 2.48 (s, 3H, CH_3), 3.93 (s, 3H, $COOCH_3$), 4.78 (s, 2H, CH_2Ph); 7.20-7.50 (m, 5H, Ph), 7.86 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 19.5 (CH_3), 53.5 (OCH_3), 59.0 (CH_2Ph), 126.7 (1'-C_{Ph}), 127.8 (C-3), 128.6 (3'-C_{Ph}), 128.8 (4'-C_{Ph}), 131.5 (2'-C_{Ph}), 137.4 (C-5), 140.8 (C-4), 152.0 (C-2), 152.1 (C-6), 165.0 ($COOCH_3$); MS m/z : 339 (8, M^+), 91 (100); exact mass calcd for $C_{15}H_{14}ClNO_4S$: 339.0330; found: 339.0332.

methyl 2-chloro-3-methyl-6-(phenylmethylsulfonyl)-4-pyridinecarboxylate 8u.
m.p. 121°C; IR (KBr) cm^{-1}: 1735; ^1H NMR ($CDCl_3$) δ: 2.62 (s, 3H, CH_3), 3.87 (s, 3H, $COOCH_3$), 4.60 (s, 2H, CH_2Ph); 7.15-7.30 (m, 5H, Ph), 8.02 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 17.1 (CH_3), 52.9 (OCH_3), 57.8 (CH_2Ph), 121.3 (C-5), 126.6 (1'-C_{Ph}), 128.5 (3'-C_{Ph}), 128.6 (4'-C_{Ph}), 130.8 (2'-C_{Ph}), 137.7 (C-3), 141.2 (C-4), 153.3 (C-6), 153.7 (C-2), 164.2 ($COOCH_3$); MS m/z : 339 (9, M^+), 91 (100); exact mass calcd for $C_{15}H_{14}ClNO_4S$: 339.0330; found: 339.0344.

Pyridines 9-10 from the reaction of the oxazinones 6c,i,m,n,r-t with phenylacetylene. General procedure.
Compound **6c,i,m,n,r-t** (0.20 g) and 3 ml phenyl acetylene were stirred at 80°C. The dienophile was evaporated and the two regioisomers were separated by chromatography or by crystallisation. (yields are given in table 4)

2-chloro-6-methoxy-3-methyl-5-phenylpyridine 9c.
oil; IR (NaCl plates) cm^{-1}: 1610, 1590; ^1H NMR ($CDCl_3$) δ: 2.27 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 7.25-7.55 (m, 6H, Ph and PyH); ^{13}C NMR ($CDCl_3$) δ: 18.1 (CH_3), 53.9 (OCH_3), 122.8 (C-5), 123.9 (C-3), 127.5 (4'-C_{Ph}), 128.1 128.8 (2'-, 3'-, 5'- and 6'-C_{Ph}), 135.5 (1'-C_{Ph}), 141.7 (C-4), 145.9 (C-2), 158.2 (C-6); MS m/z : 233 (100, M^+); 232 (72); exact mass calcd for $C_{13}H_{12}ClNO$: 233.0607; found: 233.0605.

2-chloro-6-methoxy-3-methyl-4-phenylpyridine 10c.
oil; IR (NaCl plates) cm^{-1}: 1610, 1600; ^1H NMR ($CDCl_3$) δ: 2.19 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 6.56 (s, 1H, PyH), 7.30-7.50 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ: 16.4 (CH_3), 53.9 (OCH_3), 109.9 (C-5), 121.9 (C-3), 128.1 (4'-C_{Ph}), 128.4 (2'-, 3'-, 5'- and 6'-C_{Ph}), 139.2 (1'-C_{Ph}), 148.7 (C-2), 154.9 (C-4), 161.2 (C-6); MS m/z :233 (96, M^+), 232 (100); exact mass calcd for $C_{13}H_{12}ClNO$: 233.0607; found: 233.0600.

2-chloro-3-methyl-5-phenyl-6-(phenylmethylthio)pyridine 9i.
m.p. 85°C; IR (KBr) cm^{-1}: 1602, 1587; ^1H NMR ($CDCl_3$) δ: 2.25 (s, 3H, CH_3), 4.32 (s, 2H, CH_2Ph), 7.10-7.50 (m, 11H, PyH and Ph); ^{13}C NMR ($CDCl_3$) δ: 18.6 (CH_3), 35.2 (CH_2Ph), 126.9 (4'-C_{Ph}), 127.0 (C-3), 128.2 128.4 128.9 129.3 (2'-, 3'-, 5'-, 6'-C_{Ph} and 2"-, 3"-, 4"-, 5"-, 6"-C_{Bn}), 134.3 (C-5), 136.8 (1'-C_{Ph}), 137.7 (1"-C_{Bn}), 140.0 (C-4), 149.1 (C-2), 154.0 (C-6);MS m/z : 325 (63, M^+); 91 (100); exact mass calcd for $C_{19}H_{16}ClNS$: 325.0692; found: 325.0695.

2-chloro-3-methyl-6-(4-methylphenyl)-5-phenylpyridine 9m.
m.p. 93°C; IR (KBr) cm^{-1}: 1610, 1590; ^1H NMR ($CDCl_3$) δ: 2.26 (s, 3H, CH_3), 2.40 (s, 3H, $ArCH_3$), 7.00-7.40 (m, 9H, Ph and H_{Ar}), 7.51 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 18.9 (CH_3), 21.0 ($ArCH_3$), 127.3 (4'-C_{Ph}), 128.3 128.5 129.3 129.7 (2'-, 3'-, 5'-, 6'-C_{Ph} and 2"-, 3"-, 5"-, 6"-C_{Ar}), 130.2 (C-3), 134.7 (C-5), 135.8 (1"-C_{Ar}), 137.7 (4"-C_{Ar}), 139.0 (1'-C_{Ph}), 141.8 (C-4), 149.7 (C-2), 154.7 (C-6); MS m/z : 293 (69, M^+), 292 (100); exact mass calcd for $C_{19}H_{16}ClN$: 293.0969; found: 293.0971.

2-chloro-3-methyl-6-(2-thienyl)-5-phenylpyridine 9n.
m.p. 93°C; IR (KBr) cm^{-1}: 1590, 1540; ^1H NMR ($CDCl_3$) δ: 2.33 (s, 3H, CH_3), 6.40-6.85 (m, 2H, H_{HetAr}), 7.20-7.30 (m, 7H, PyH, H_{HetAr} and Ph); ^{13}C NMR ($CDCl_3$) δ: 18.9 (CH_3), 127.1 127.5 128.0 (3"-, 4"- and 5"-C_{HetAr} and 4'-C_{Ph}), 128.6 129.0 (2'-, 3'-, 5'- and 6'-C_{Ph}), 129.7 (C-3), 133.3 (C-5), 138.7 (1'-C_{Ph}), 141.9 (C-4), 142.5 (2"-C_{HetAr}), 147.9 (C-6), 149.3 (C-2); MS m/z : 285 (100, M^+), 270 (3); exact mass calcd for $C_{16}H_{12}ClNS$: 285.0379; found: 285.0372.

2-choro-6-ethyl-3-methyl-5-phenylpyridine 9r.
oil; IR (NaCl plates) cm^{-1}: 2874-3083; ^1H NMR ($CDCl_3$) δ: 1.16 (t, 3H, CH_2CH_3), 2.34 (s, 3H, CH_3),

2.70 (q, 2H, CH_2CH_3), 7.2-7.5 (m, 6H, Ph and PyH); ^{13}C NMR ($CDCl_3$) δ: 13.9 (CH_2CH_3), 18.9 (CH_3), 27.9 (CH_2CH_3), 127.5 (4'-C_{Ph}), 128.2 128.8 (C-3, 2'-, 3'-, 5'- and 6'-C_{Ph}), 135.4 (1'-C_{Ph}), 138.7 (C-5), 140.7 (C-4), 149.6 (C-2), 158.6 (C-6); MS m/z : 231 (30, M^+), 230 (100); exact mass calcd for $C_{14}H_{14}ClN$: 213.0815; found: 231.0790.

2-chloro-6-ethyl-3-methyl-4-phenylpyridine 10r.

oil; IR (NaCl plates) cm^{-1}: 2871-3060; ^1H NMR ($CDCl_3$) δ: 1.30 (t, 3H, CH_2CH_3), 2.26 (s, 3H, CH_3), 2.78 (q, 2H, CH_2CH_3), 7.2-7.4 (m, 5H, Ph), 6.96 (PyH); ^{13}C NMR ($CDCl_3$) δ: 13.7 (CH_2CH_3), 16.7 (CH_3), 30.5 (CH_2CH_3), 121.8 (C-5); 126.7 (C-3), 128.0 (4'-C_{Ph}), 128.3 128.4 (2'-, 3'-, 5'- and 6'-C_{Ph}), 139.2 (1'-C_{Ph}), 151.7 (C-4), 152.6 (C-2), 160.7 (C-6); MS m/z : 231 (81, M^+), 230 (100); exact mass calcd for $C_{14}H_{14}ClN$: 213.0815; found: 231.0804.

6-(*tert*-butyl)-2-chloro-3-methyl-4-phenylpyridine 10s.

oil; IR (NaCl plates) cm^{-1}: 1588, 1531; ^1H NMR ($CDCl_3$) δ: 1.36 (s, 9H, $C(CH_3)_3$), 2.26 (s, 3H, CH_3), 7.10 (s, 1H, PyH), 7.20-7.50 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ: 16.8 (CH_3), 30.0 ($C(CH_3)_3$), 37.0 ($C(CH_3)_3$), 118.9 (C-5), 126.3 (C-3), 127.9 (4'-C_{Ph}), 128.3 128.5 (2'-, 3'-, 5'- and 6'-C_{Ph}), 139.6 (1'-C_{Ph}), 151.4 (C-2), 152.2 (C-4), 166.7 (C-6); MS m/z : 259 (52, M^+), 244 (100); exact mass calcd for $C_{16}H_{18}ClN$: 259.1125; found: 259.1133.

2-chloro-3-methyl-5-phenyl-6-(phenylmethylsulfinyl)pyridine 9t.

oil; IR (NaCl plates) cm^{-1}: 1580, 1535; ^1H NMR ($CDCl_3$) δ: 2.48 (s, 3H, CH_3), 4.20 (d, 1H, CH_2Ph), 4.50 (d, 1H, CH_2Ph), 6.70-7.40 (m, 10H, Ph), 7.48 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 19.6 (CH_3), 59.2 (CH_2Ph), 128.2 (4'-C_{Ph}), 128.4 128.7 (2"-, 3", 4"-, 5"- and 6"-C_{Bn}), 129.4 130.3 (2'-, 3'-, 5'- and 6'-C_{Ph}), 129.5 (1"-C_{Bn}) , 134.4 (C-5), 135.6 (C-3), 138.3 (1'-C_{Ph}), 141.3 (C-4), 151.9 (C-2), 155.3 (C-6); MS m/z : 341 (13, M^+), 91 (100); exact mass calcd for $C_{19}H_{16}ClNOS$: 341.0640; found: 341.0651.

2-chloro-3-methyl-4-phenyl-6-(phenylmethylsulfinyl)pyridine 10t.

oil; IR (NaCl plates) cm^{-1}: 1575, 1525; ^1H NMR ($CDCl_3$) δ: 2.36 (s, 3H, CH_3), 4.17 (d, 1H, CH_2Ph), 4.40 (d, 1H, CH_2Ph), 7.00-7.50 (m, 11H, Ph and PyH); ^{13}C NMR ($CDCl_3$) δ: 17.3 (CH_3), 51.8 (CH_2Ph), 120.4 (C-5), 128.2, 128.1 128.2 (2"-, 3"-, 5"-, 6"-C_{Bn} and 4'-C_{Ph})), 128.4 130.2 (2'-, 3'-, 5'- and 6'-C_{Ph}), 128.6 (4"-C_{Bn}), 129.0 (1"-C_{Bn}), 131.3 (C-3), 137.6 (1'-C_{Ph}), 152.1 (C-6), 153.6 (C-4), 160.0 (C-2); MS m/z : 341 (12, M^+), 91 (100); exact mass calcd for $C_{19}H_{16}ClNOS$: 341.0640; found: 341.0641.

Pyridines 11-12 from the reaction of the oxazinones 6c,m,n,s,u with propargyl chloride. General procedure.

Compound **6c,m,n,s,u** (0.20 g) and 3 ml propargyl chloride were stirred at 60°C. The dienophile was evaporated and the two regioisomers were separated by chromatography or by crystallisation. (yields are given in table 4)

2-chloro-5-chloromethyl-6-methoxy-3-methylpyridine 11c.

m.p. 61°C; IR (KBr) cm^{-1}: 1610, 1567; ^1H NMR ($CDCl_3$) δ: 2.29 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.52 (s, 2H, CH_2Cl), 7.50 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 18.3 (CH_3), 40.0 (CH_2Cl), 54.2 (OCH_3), 118.5 (C-5), 124.1 (C-3), 141.9 (C-4), 147.5 (C-2), 159.0 (C-6); MS m/z : 205 (23, M^+), 170 (100); exact mass calcd for $C_8H_9Cl_2NO$: 205.0061; found: 205.0066.

2-chloro-5-chloromethyl-3-methyl-6-(4-methylphenyl)pyridine 11m.

m.p. 94°C; IR (KBr) cm^{-1}: 1610, 1590; ^1H NMR ($CDCl_3$) δ: 2.36 (s, 6H, CH_3 and $ArCH_3$), 2.38 (s, 3H, CH_3), 4.50 (s, 2H, CH_2Cl), 7.23 (d, 2H, 3'- and 5'-H_{Ar}), 7.48 (d, 2H, 2'- and 6'-H_{Ar}), 7.67 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 19.0 (CH_3), 21.2 ($ArCH_3$), 42.9 (CH_2Cl), 128.8 129.0 (2'-, 3'-, 5'- and 6'-C_{Ar}), 129.5 (C-5), 131.1 (C-3), 134.8 (1'-C_{Ar}), 138.7 (4'-C_{Ar}), 141.7 (C-4), 150.7 (C-2), 156.0 (C-6); MS m/z : 265 (73, M^+), 230 (100); exact mass calcd for $C_{14}H_{13}Cl_2N$: 265.0425; found: 265.0424.

2-chloro-5-chloromethyl-3-methyl-6-(2-thienyl)pyridine 11n.

m.p. 87°C; IR (KBr) cm^{-1}: 1590, 1540; ^1H NMR ($CDCl_3$) δ: 2.35 (s, 3H, CH_3), 4.70 (s, 2H, CH_2Cl), 7.15 (dxd, 1H, 4' H_{HetAr}), 7.40-7.70 (m, 2H, 3'- and 5' H_{HetAr}); ^{13}C NMR ($CDCl_3$) δ: 18.9 (CH_3), 43.3 (CH_2Cl), 127.5 127.7 128.4 (3'-,4'- and 5'-C_{HetAr}), 128.0 (C-5), 131.0 (C-3), 140.9 (2'-C_{HetAr}), 142.1

(C-4), 149.1 (C-6), 150.4 (C-2); MS m/z : 257 (14, M^+); 222 (100); exact mass calcd for $C_{11}H_9Cl_2NS$: 256.9832; found: 256.9834.

6-(*tert*-butyl)-2-chloro-4-chloromethyl-3-methylpyridine 12s.

oil; IR (NaCl plates) cm^{-1}: 1590, 1550; ^1H NMR ($CDCl_3$) δ: 1.33 (s, 9H, $C(CH_3)_3$), 2.40 (s, 3H, CH_3), 4.52 (s, 2H, CH_2Cl), 7.22 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 14.8 (CH_3), 29.8 ($C(CH_3)_3$), 37.1 ($C(CH_3)_3$), 43.3 (CH_2Cl), 118.4 (C-5), 127.4 (C-3), 146.3 (C-4), 151.4 (C-2), 167.7 (C-6); MS m/z : 231 (27, M^+), 216 (100); exact mass calcd for $C_{11}H_{15}Cl_2N$: 231.0581; found: 231.0570.

2-chloro-3-chloromethyl-5-methyl-6-(phenylmethylsulfonyl)pyridine 11u.

oil; IR (NaCl plates) cm^{-1}: 1587, 1542; ^1H NMR ($CDCl_3$) δ: 2.45 (s, 3H, CH_3), 4.76 (s, 2H, CH_2Ph), 4.85 (s, 2H, CH_2Cl), 7.20-7.40 (m, 5H, Ph), 7.82 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 19.4 (CH_3), 39.2 (CH_2Cl), 58.7 (CH_2Ph), 126.9 (1'-C_{Ph}), 128.5 (3'- and 5'-C_{Ph}), 128.7 (4'-C_{Ph}), 131.3 (2'- and 6'-C_{Ph}), 132.2 (C-5), 137.7 (C-3), 142.9 (C-4), 149.8 (C-2), 150.7 (C-6); MS m/z : 329 (8, M^+); 91 (100); exact mass calcd for $C_{14}H_{13}Cl_2O_2S$: 329.0044; found: 329.0048.

2-chloro-4-chloromethyl-3-methyl-6-(phenylmethylsulfonyl)pyridine 12u.

m.p. 117°C; IR (KBr) cm^{-1}: 1570, 1550; ^1H NMR ($CDCl_3$) δ: 2.52 (s, 3H, CH_3), 4.50 (s, 2H, CH_2Cl), 4.60 (s, 2H, CH_2Ph), 7.20-7.40 (m, 5H, Ph), 7.72 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 15.7 (CH_3), 41.9 (CH_2Cl), 58.2 (CH_2Ph), 121.9 (C-5), 126.9 (1'-C_{Ph}), 128.6 (3'- and 5'-C_{Ph}), 128.7 (4'-C_{Ph}), 131.0 (2'- and 6'-C_{Ph}), 136.3 (C-5), 148.5 (C-4), 152.3 (C-2), 153.6 (C-6); MS m/z : 329 (8, M^+), 91 (100); exact mass calcd for $C_{14}H_{13}Cl_2O_2S$: 329.0044; found: 329.0061.

Pyridines 13-14 from the reaction of the oxazinones 6c,s with ethoxyethyne. General procedure.

Compound **6c,s** (0.20 g) and 50% ethoxyethyne/hexane were heated at 80°C in a sealed tube. The dienophile was evaporated and the two regioisomers were separated by chromatography. (yields are given in table 4)

2-chloro-5-ethoxy-3-methyl-6-methoxypyridine 13c.

oil; ^1H NMR ($CDCl_3$) δ: 1.43 (t, 3H, OCH_2CH_3), 2.28 (s, 3H, CH_3), 4.00 (s,3H,OCH_3), 4.03 (q, 2H, OCH_2CH_3), 6.98 (s, 1H, PyH); MS m/z : 201 (100, M^+),172 (66), 143 (49); exact mass calcd for $C_9H_{12}ClNO_2$: 201.0556; found: 201.0571.

2-chloro-4-ethoxy-3-methyl-6-methoxypyridine 14c.

oil; ^1H NMR ($CDCl_3$) δ: 1.43 (t, 3H, OCH_2CH_3), 2.15 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.03 (q, 2H, OCH_2), 6.09 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 11.7 (CH_3), 14.4 (OCH_2CH_3), 53.7 (OCH_3), 64.3 (OCH_2CH_3), 91.5 (C-5), 114.1 (C-3), 147.9 (C-2), 162.6 (C-4), 166.4 (C-6) MS m/z : 201 (23, M^+), 172 (22), 44 (100); exact mass calcd for $C_9H_{12}ClNO_2$: 201.0557; found: 201.0553.

6-(*tert*-butyl)-2-chloro-4-ethoxy-3-methylpyridine 14s.

oil; IR (NaCl plates) cm^{-1}: 1590, 1550; ^1H NMR ($CDCl_3$) δ: 1.32 (s, 9H, $C(CH_3)_3$), 1.42 (t, 3H, OCH_2CH_3), 2.20 (s, 3H, CH_3), 4.15 (q, 2H, OCH_2), 6.73 (s, 1H, PyH); ^{13}C NMR ($CDCl_3$) δ: 11.8 (CH_3), 14.5 (OCH_2CH_3), 29.9 ($C(CH_3)_3$), 37.3 ($C(CH_3)_3$), 64.0 (OCH_2CH_3), 101.1 (C-5), 117.3 (C-3), 150.9 (C-2), 164.5 (C-4), 168.1 (C-6); MS m/z : 227 (70, M^+), 212 (100); exact mass calcd for $C_{12}H_{18}ClNO$: 227.1077; found: 227.1070.

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