Diels–Alder Reactions of 6-Alkyl-3,5-dichloro-2*H*-1,4-oxazin-2-ones with Alkynes: Synthesis of 3,5-Disubstituted 2,6-Dichloropyridines

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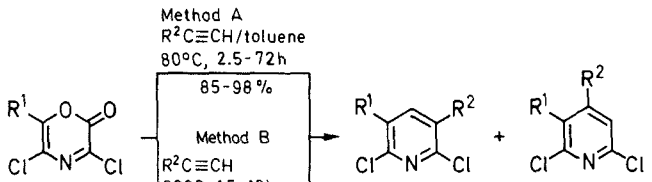
The Diels–Alder reaction of 6-alkyl-3,5-dichloro-2*H*-1,4-oxazin-2-ones **1** with different types of acetylenic compounds **2** is shown to be a versatile method for the generation of variously substituted 2,6-dichloropyridines. In most cases a high degree of regioselectivity and a high yield of 3,5-disubstituted 2,6-dichloropyridines **3** is obtained.

Inter- and intramolecular Diels–Alder reactions on 2-azadiene systems[1] and accompanying ring transformations are used by many chemists interested in the synthesis of heterocycles and natural products. Some time ago we described the Diels–Alder reaction of variously substituted 2(1*H*)-pyrazinones[2,3] with acetylenes giving specifically substituted pyridinones or pyridines. In this paper we would like to discuss the addition of alkynes on the easily accessible 2-azadiene system of recently described 6-alkyl-3,5-dichloro-2*H*-1,4-oxazin-2-ones,[4,5] synthesized from cyanohydrins and oxalyl chloride. To our knowledge, cycloadditions on 2*H*-1,4-oxazin-2-ones were not described; only some predictions about the reactivity of their 2-azadiene system in comparison to that of 1,3-oxazin-6-ones were made.[6] Via Diels–Alder addition followed by extrusion of carbon dioxide new 2,6-dichloropyridines could be reached. Such compounds, not easily accessible via known mostly multistep approaches,[7–13] could be of interest because of their potential biocide characteristics.



1	R^1	1	R^1	2	R^2	2	R^2
a	H	**e**	Bn	**a**	CH_2Br	**e**	CO_2Et
b	Me	**f**	CH_2Cl	**b**	Me	**f**	OEt
c	Et	**g**	$CHCl_2$	**c**	CH_2CH_2Ph	**g**	Ph
d	*i*-Pr	**h**	CO_2Me	**d**	*t*-Bu	**h**	3,4,5-$(MeO)_3C_6H_2$

Scheme 1

The regioselectivity, scope and limitations of the method for the generation of substituted 2,6-dichloropyridines were first examined for the cycloaddition of 3-bromopropyne (**2a**); six equivalents from a 80 w% solution of 3-bromopropyne in toluene were reacted with a series of 6-alkyl-3,5-dichloro-2*H*-1,4-oxazin-2-ones **1a–g**. As shown in Table 1 the expected pyridines **3a–g/4a–g** are obtained in high yield with compound **3** predominating. These pyridines can be easily isolated from the reaction mixture by flash chromatography. Further purification of solid pyridines **3** can be performed by recrystallization from hexane/diethyl ether mixtures; separation by HPLC is needed for the oily mixtures **3q/4q** and **3t/4t**.

Table 1. Pyridines **3, 4** Prepared

3, 4	R^1	R^2	Method	Yield (%)[a]	Ratio **3/4**[b]	Time (h)
a	H	CH_2Br	A	97	>20:1	3
b	Me	CH_2Br	A	97	20:1	6
c	Et	CH_2Br	A	95	>20:1	7
d	*i*-Pr	CH_2Br	A	85	>20:1	9
e	Bn	CH_2Br	A	98	20:1	6
f	CH_2Cl	CH_2Br	A	93	7:2	3
g	$CHCl_2$	CH_2Br	A	95	20:1	2.5
h	Me	Me	A	95	>20:1	14
i	Me	CH_2CH_2Ph	A	95	20:1	15
j	Me	*t*-Bu	A	91	>20:1	72
k	Me	CO_2Et	A	94	≈1:1	24
			B	95	4:1	3
l	Me	OEt		90	2:1	16[d]
m	Me	Ph	A	95	4:1	18
			B	95	6:1	2
n	Me	3,4,5-$(MeO)_3C_6H_2$	A	95	10:1	4
o	H	Ph	B	95	>20:1	1.5
p	Bn	Ph	B	94	>20:1	7
q	CH_2Cl	Ph	B	95	10:1	7
r	$CHCl_2$	Ph	B	92	>20:1	7
s	H	CO_2Et	B	92	3:1	1.5
t	$CHCl_2$	CO_2Et	B	95	4:1	3
u	CO_2Me	CO_2Et	B	89	4:1	16

[a] Total yield of chromatographed **3/4**.
[b] Ratio calculated via ^{1}H-NMR integration; the value >20:1 means that absorptions for the isomer **4** are not observed.
[c] 6 Equivalents of acetylene **2a** or 3 Equivalents of acetylenes **2b–h** are used.
[d] 3 Equivalents from a commercial 50 w% solution in hexane is used and reacted at 60°C.

Table 2. Concentration and Temperature Effect on the Diels–Alder Reaction of **1b** with **2e, g**

Reaction Conditions	Time (h)	Total Yield (%)	Ratio	**3/4**
2e; 3 equiv, toluene, 80°C	24	94	≈1:1	**k**
2e; neat, 80°C	4	96	4:1	**k**
2e; neat, r.t.	96	95	9:1	**k**
2g; 3 equiv, toluene, 80°C	18	95	4:1	**m**
2g; neat, 80°C	2	95	6:1	**m**
2g; neat, r.t.	84	95	9:1	**m**

From the time needed for complete reaction it appears that electron-attracting groups in position-6 of the oxazinone enhance the rate. The isomer ratio suggests that the regiochemistry is influenced by both electronic and steric effects. The cycloaddition is further shown to be useful for other substituted acetylenes **2b–h** (three equivalents) reacting with oxazinone **1b**. However, for acetylenes with electron-donating, **2f**, or aryl groups, **2g, h**, and especially with electron-attracting groups, **2e**, the regioselectivity is lowered. This lack of regioselectiv-

Table 3. NMR data of Pyridines **3**

Compound	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C-NMR ($CDCl_3$/TMS) δ				
		C-2	C-3	C-4	C-5	C-6
3b	2.40 (s, 3H, CH_3), 4.53 (s, 2H, CH_2Br), 7.73 (s, 1H, PyH)	146.5	130.9	142.3	132.2	149.6
3c	1.23 (t, 3H, J = 7.5, CH_3), 2.70 (q, 2H, J = 7.5, CH_2), 4.53 (s, 2H, CH_2Br), 7.66 (s, 1H, PyH)	146.5	131.1	140.9	137.5	149.3
3d	1.21 (d, 6H, J = 7, CH_3), 3.2 (sept, 1H, J = 7, CH), 4.47 (s, 2H, CH_2Br), 7.61 (s, 1H, PyH)	146.4	131.8	138.6	141.8	149.0
3e	4.10 (s, 2H, CH_2Br), 4.47 (s, 2H, CH_2Ph), 7.23 (m, 5H, Ph), 7.50 (s, 1H, PyH)	147.2	131.2	142.1	137.2	149.6
3f	4.55 (s, 2H, CH_2Br), 4.69 (s, 2H, CH_2Cl), 7.95 (s, 1H, PyH)	148.7	131.3	141.9	131.7	149.0
3g	4.6 (s, 2H, CH_2Br), 7.02 (s, 1H, CH), 8.34 (s, 1H, PyH)	150.5	133.9	140.5	132.6	145.6
3h	2.30 (s, 6H, CH_3), 7.43 (s, 1H, PyH)	147.1	131.1	142.3	131.1	147.1
3i	2.27 (s, 3H, CH_3), 2.93 (s, 4H, CH_2CH_2), 7.2 (m, 6H, Ph + PyH)	140.4	126.3	141.9	126.3	131.2
3j	1.46 (s, 9H, *t*-Bu), 2.4 (s, 3H, CH_3), 7.7 (s, 1H, PyH)	146.0	130.7	139.7	141.9	146.5
3k	1.40 (t, 3H, J = 7.5, CH_3), 2.41 (s, 3H, CH_3), 4.43 (q, 2H, J = 7.5, CH_2), 8.10 (s, 1H, PyH)	146.2	125.2	142.7	131.4	152.4
3l	1.5 (t, 3H, J = 7.5, CH_3), 2.4 (s, 3H, CH_3), 4.2 (q, 2H, J = 7.5, CH_2), 7.1 (s, 1H, PyH)	136.8	150.3	124.1	132.0	139.8
3m	2.36 (s, 3H, CH_3), 7.43 (m, 5H, Ph), 7.53 (s, 1H, PyH)	145.3	136.2	142.5	135.5	148.6
3n	2.43 (s, 3H, CH_3), 3.97 (s, 9H, OCH_3), 6.67 (s, 2H, Ph), 7.6 (s, 1H, PyH)	145.3	138.4	142.3	135.5	148.6
3p	4.1 (s, 2H, CH_2), 7.5 (m, 11H, Ph + PyH)	146.1	136.3	142.4	135.9	148.5
3q	4.68 (s, 2H, CH_2), 7.43 (m, 5H, Ph), 7.8 (s, 1H, PyH)	147.6	136.3	142.0	135.6	147.9
3r	7.1 (s, 1H, CH), 7.5 (s, 5H, Ph), 8.3 (s, 1H, PyH)	144.3	135.4	140.5	133.4	149.7
3t	1.4 (t, 3H, J = 7.5), 4.5 (q, 2H, J = 7.5, CH_2), 7.1 (s, 1H, CH), 8.7 (s, 1H, PyH)	147.8	126.8	141.3	133.3	149.9
3u	1.43 (t, 3H, J = 7.5, CH_3), 4.03 (s, 3H, OCH_3), 4.5 (q, 2H, J = 7.5, OCH_2), 8.77 (s, 1H, PyH)	151.1	125.3	144.1	124.8	151.2

ity can be improved by performing the reaction at room temperature as demonstrated in Table 2. The Diels–Alder reaction of ethyl propynoate (**2e**) (3 equivalents in toluene at 80 °C) with oxazinone **1b** shows to be a nonselective reaction (**3k/4k**, ≈ 1:1). In neat ethyl propynoate (**2e**) at 80 °C and at room temperature a higher regioselectivity (4:1 and 9:1, respectively) is

Table 4. ^{1}H-NMR Data of Isolated Pyridines **4**

Compound	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
4f	4.56 (s, 2H, CH_2Br), 4.68 (s, 2H, CH_2Cl), 7.90 (s, 1H, PyH)
4k[a]	1.47 (t, 3H, J = 7.5, CH_2CH_3), 2.63 (s, 3H, CH_3), 4.47 (q, 2H, J = 7.5, CH_2), 7.67 (s, 1H, PyH)
4l	1.5 (t, 3H, J = 7.5, CH_3), 2.2 (s, 3H, CH_3), 4.1 (q, 2H, CH_2), 6.7 (s, 1H, PyH)
4m	2.23 (s, 3H, CH_3), 7.1 (s, 1H, PyH), 7.43 (m, 5H, Ph)
4q	4.53 (s, 2H, CH_2), 7.21 (s, 1H, PyH), 7.43 (m, 5H, Ph)
4t	1.4 (t, 3H, J = 7.5, CH_3), 4.5 (q, 2H, J = 7.5, CH_2), 7.6 (s, 2H, CH + PyH)
4u	1.43 (t, 3H, J = 7.5, CH_3), 3.9 (s, 3H, OCH_3), 4.5 (q, 2H, J = 7.5, CH_2O), 7.87 (s, 1H, PyH)

[a] mp 46 °C.

Table 5. Physical Data of Pyridines **3**

Product[a]	Yield (%)	mp (°C)	Molecular Formula or Lit. mp (°C)	MS (70 eV) m/z (%)	IR (KBr) ν (cm^{-1})
3a	94	86–87	88–90[8]	239 (M^+, 6), 160 (100)	1585, 1550
3b	92	56	$C_7H_6BrCl_2N$ (254.9)	253 (M^+, 5), 174 (100)	1590, 1550
3c	90	82	$C_8H_7BrCl_2N$ (267.9)	267 (M^+, 2), 178 (100)	1580, 1540
3d	85	oil	$C_9H_{10}BrCl_2N$ (282.9)	281 (M^+, 6), 202 (100)	1585, 1540
3e	93	73–74	$C_{13}H_{10}BrCl_2N$ (330.9)	329 (M^+, 9), 214 (100)	1585, 1540
3f	72	89–90	$C_7H_5BrCl_3N$ (289.4)	287 (M^+, 5), 208 (100)	1590, 1550
3g	89	oil	$C_7H_4BrCl_4N$ (323.9)	321 (M^+, 4), 244 (100)	1590, 1545
3h	90	98	$C_7H_7Cl_2N$ (176.0)	175 (M^+, 100)	1590, 1550
3i	90	66	$C_{14}H_{13}Cl_2N$ (266.0)	265 (M^+, 10), 91 (100)	1590, 1550
3j	88	38	$C_{10}H_{13}Cl_2N$ (218.0)	217 (M^+, 33), 202 (100)	1590, 1550
3k	70[b]	50–51	$C_9H_9Cl_2NO_2$ (234.0)	233 (M^+, 28), 188 (100)	1710, 1590, 1540
3l	60	78	$C_8H_9Cl_2NO$ (206.0)	205 (M^+, 43), 177 (100)	1582
3m	80[b]	93–94	$C_{12}H_9Cl_2N$ (238.0)	237 (M^+, 100)	1570, 1540
3n	95	105	$C_{15}H_{15}Cl_2NO_3$ (328.0)	327 (M^+, 100)	1580, 1540
3o	87	92	92[3]	223 (M^+, 100)	1575, 1545
3p	89	118	$C_{18}H_{13}Cl_2N$ (314.0)	313 (M^+, 100)	1580, 1540
3q	86	oil	$C_{12}H_8Cl_3N$ (272.5)	271 (M^+, 45), 236 (100)	1585, 1530
3r	92	oil	$C_{12}H_7Cl_4N$ (307.0)	305 (M^+, 24)	1585, 1530
3s	68	49	49[10]	219 (M^+, 5), 173 (100)	1710, 1590, 1540
3t	74	oil	$C_9H_7Cl_4NO_2$ (303.0)	300 (M^+, 9), 266 (100)	1740, 1595, 1540
3u	70	49–50	$C_{10}H_9Cl_2NO_4$ (278.0)	277 (M^+, 35), 218 (100)	1740, 1585, 1535

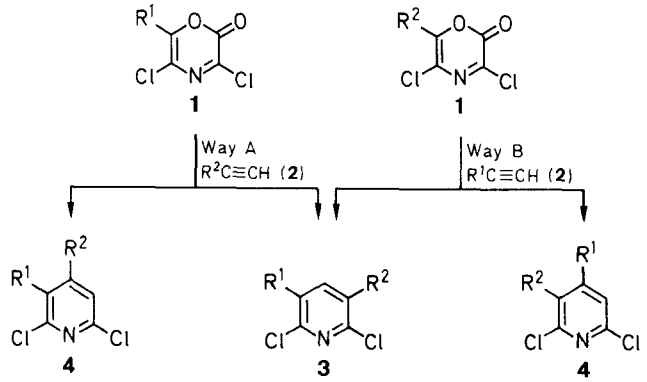
[a] Satisfactory microanalyses obtained: C ± 0.39; H ± 0.37; N ± 0.29.
[b] Yield obtained from the reaction in neat acetylene at 80 °C.

observed. An analogous effect is found for cycloadditions with phenylacetylene (**2g**).

Cycloaddition of oxazinones **1a,b** and **1e–g** in neat phenylacetylene (**2g**) shows again the influence of both electronic and steric effects of groups in the 6-position of **1**. A lower regioselectivity for the Diels–Alder reaction of oxazinones **1a,b** and **1g,h** in neat ethyl propynoate **2e** is obtained.

The structures of the obtained pyridines are confirmed by their ^{1}H- and ^{13}C-NMR spectra. For all isolated pyridines **3** an absorption between $\delta = 7.4$ and 8.8 for the 4-H proton is observed in the ^{1}H-NMR spectra (Table 3). In the DEPT ^{13}C-NMR spectra of compounds **3** an intense signal appears at about $\delta = 140$ corresponding with the C-4 pyridine carbon. The 5-H proton of isolated pyridines **4** absorbs in the ^{1}H-NMR at higher field: $\delta = 7.1-7.9$ (Table 4). The isomers **3, 4** show common IR absorptions at approximately 1580 cm^{-1} and 1540 cm^{-1} which can be ascribed to the pyridine and phenyl (for **3m–r**) ring. The presence of the chlorine and bromine atoms is confirmed by the relative abundances of the molecular ion isotope peaks in the mass spectra (Table 5).

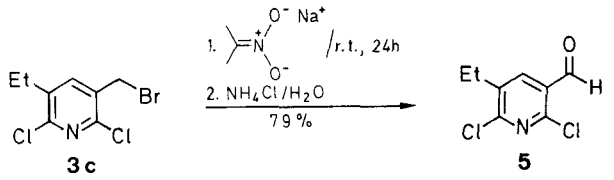
Noteworthy is the addition of the bulky 3,3-dimethyl-1-butyne (**2d**) and the electron rich phenylacetylene derivative **2h** yielding 3-substituted pyridines **3j,n**. This substitution pattern cannot be reached via the corresponding oxazinones **1**, as the introduction of bulky *tert*-butyl groups or *p*-methoxy substituted aryl groups in the 6-position of **1** cannot be realized.[5] The reverse route (Way B), using substituted acetylenes, is complementary and provides a general approach for the synthesis of 3,5-disubstituted 2,6-dichloropyridines (Scheme **2**).



Scheme 2

The pyridine **3c** can be easily oxidized yielding 3-pyridinecarbaldehyde **5** (Scheme **3**). This shows again the versatility of the method allowing the introduction of a formyl group not easily feasible via a direct cycloaddition of propynal on an oxazinone **1**.

In conclusion, we can state that the Diels–Alder reaction of 6-alkyl-3,5-dichloro-2*H*-1,4-oxazin-2-ones and acetylenes is a versatile reaction for the synthesis of 3,5-disubstituted 2,6-dichloropyridines **3**. Reductive dechlorination could give 3,5-disubstituted pyridines which are also not easily accessible.



Scheme 3

IR Spectra were recorded as thin films between NaCl plates or as solids in KBr pellets on a Perkin-Elmer 297 grating IR-spectrophotometer. ^{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 with TMS as an internal reference. Mass spectra were run by using a Kratos MS50 instrument and DS90 data system. Besides the spectral and analytical data mentioned below, the purity of all compounds was checked by TLC. Analytical TLC plates (Sil G/UV 254) and silica gel (70–230 mesh) were purchased from Macherey-Nagel. Melting points were taken using a Reichelt-Jung Thermovar apparatus and are uncorrected. All obtained pyridines were new compounds except pyridines **3a**,[8] **o**,[3] **s**[10] and **4s**.[3] Microanalyses were performed by Janssen Pharmaceutica on a Carlo Erba elemental analyser type 1106.

Pyridines 3a–u; General Procedures:

Method A (for **3a–n**): Oxazinone **1a–g** (0.01 mol) is dissolved in a 80 w% commercially available solution of **2a** in toluene (8.9 g, 5.9 mL) or in a solution of **2b–h** (0.03 mol) in dry toluene (5 mL). This mixture is stirred at 80°C under N_2. Completion of the reaction is controlled by TLC ($CHCl_3$, reaction time see Table 1). Evaporation followed by chromatography of the residual oil on silica gel (gradient elution 50% hexane/$CHCl_3$ to 100% $CHCl_3$) gives oily pyridine; recrystallization from hexane/Et_2O mixture affords crystalline pyridine **3** (except for **3d, g** which are oils).

Method B (for **3k,m,o–u**): A solution of oxazinone **1a–h** (0.01 mol) in excess dienophile (± 5 mL) is stirred at 80°C under N_2 until reaction is completed (TLC-controlled: $CHCl_3$, reaction time see Table 1). Evaporation followed by chromatography of the residual oil on silica gel (gradient elution 50% hexane to 100% $CHCl_3$) gives oily pyridine, recrystallization from hexane/Et_2O mixture affords crystalline pyridine **3** (except for **3p,q,t** which are oils). In the cases of **3,4q,t** HPLC separation (silica gel, $CHCl_3$) is needed.

2,6-Dichloro-5-ethyl-3-pyridinecarbaldehyde (5):

A solution of Na (76 mg, 3.3 mmol) and 2-nitropropane (293 mg, 3.3 mmol) in dry MeOH (50 mL) is stirred under N_2 for 30 min. at r.t.. Pyridine **3c** (808 mg, 3 mmol) is added. After 24 h the mixture is poured into a 10% aq NH_4Cl (100 mL) and extracted with $CHCl_3$ (3 × 150 mL). Drying of the combined extracts ($MgSO_4$), evaporation and chromatography on silica gel (100% CH_2Cl_2) affords pure aldehyde (240 mg, 79%) which is recrystallized from hexane/Et_2O; mp 154°C.

HRMS: *m/z*, $C_8H_7Cl_2NO$ calc.: 202.9904; found: 202.9904.

IR (KBr): ν 1700 cm^{-1}.

^{1}H-NMR ($CDCl_3$): $\delta = 1.3$ (t, 3H, $J = 7$ Hz, CH_3), 2.8 (q, 2H, $J = 7$ Hz, CH_2), 8.1 (s, 1H, PyH), 10.4 (s, 1H, CHO).

^{13}C-NMR ($CDCl_3$): $\delta = 12.8$ (CH_3), 25.4 (CH_2), 127.7 (C-5), 138.2 (C-3), 138.7 (C-4), 149.5 (C-6), 154.7 (C-2), 188.0 (C=O).

MS: *m/z* (%) = 203 (M^+, 100), 188 (95).

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