Nitrogen Bridgehead Compounds. Part 65 [1]. Vilsmeier-Haack Formylation of 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones. Part 6 [2]

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2-Substituted 3-formyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones can be synthethized by Vilsmeier-Haack formylation with the dimethylformamide-phosphoryl chloride complex only from those 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones which contain a substituent with electron-releasing resonance effect in position 2. The products were characterized by uv, ir and ^{1}H nmr spectroscopy.

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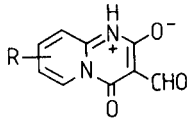
Vilsmeier-Haack acylation [3] has proved to be a versatile synthetic method for the functionalization of different nitrogen bridgehead compounds [2,4-7] with the aim of obtaining biologically active derivatives [8].

This paper deals with an investigation of the Vilsmeier-Haack formylation of 3-unsubstituted 4*H*-pyrido[1,2-*a*]-pyrimidin-4-ones with the dimethylformamide-phosphoryl chloride complex. Earlier, only the formylation of 2-hydroxy- and 2-methoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones has been reported [9-13] with dimethylformamide-phosphoryl chloride and dimethylformamide-phosgene reagents. Depending on the reaction conditions, different 3-substituted derivatives **1-4** were obtained.



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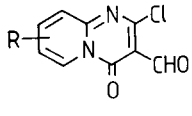

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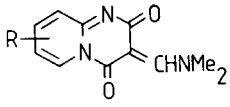

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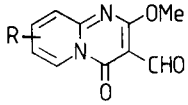

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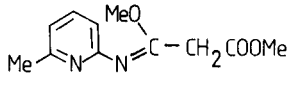
Synthesis of the Starting 2-Substituted 4*H*-Pyrido[1,2-*a*]-pyrimidin-4-ones.

4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones **5-12** were prepared by literature procedures [14-20]. 2-Aminopyrido[1,2-*a*]pyrimidin-4-ones **13-16** were obtained from 2-chloropyrido[1,2-*a*]-pyrimidinones **11**, **12** [17,18] with butylamine in refluxing ethanol and with piperidine in boiling dioxane.

An attempt was made to prepare 2-methoxy-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one from the 2-chloro-6-methyl derivative **12** with methanolic sodium methoxide at ambient temperature, similarly as in the synthesis [19] of the 2-methoxy derivative **10**. The vicinity [21] of the 6-substituent and the 4-oxo group means that the 6-substituted pyrido[1,2-*a*]pyrimidin-4-ones are more sensitive than the 6-unsubstituted derivatives to nucleophilic attack on the C(4) carbon to yield ring-opening products [22]. Thus, for compound **12** the chloro-methoxy exchange was accompanied by ring opening to give imidate **17**. When compound **17** was heated in polyphosphoric acid at 110-120°, instead of the cyclization to 2-methoxy-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, only hydrolysis took place, to yield the malonamate **18**. Similarly as for compound **12**, the treatment of 2,6-dimethylpyrido[1,2-*a*]pyrimidin-4-one **8** with methanolic sodium methoxide resulted in a ring-opening product **19** in 64% yield.



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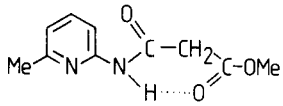

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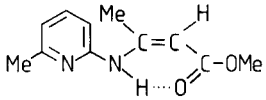


(19)

Table 1

UV Data on Ring-opening Derivatives **17-19** in Ethanol

Compound No.	λ/max (ε)					
17		301i (4050)	280	(7860)	218	(6440)
18			278	(10150)	237	(12060)
19	318 (23440)		289i	(9370)		

i = inflexion

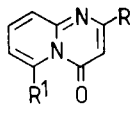
The differences in the uv spectra of compounds **17-19** indicated that the ring-opening products exist in different tautomeric forms. Singlets with two-proton intensity at 3.39 ppm and 3.58 ppm, and an exchangeable broad singlet at 9.19 ppm in the spectrum of **18**, point to the presence of tautomeric forms **17** and **18**. On the other

Table 2

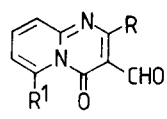
Vilsmeier-Haack Formylation of 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones

Starting Compound No.	R	R¹	Product No.	R¹	Temperature °C	Mp °C	Yield %	Recryst solvent	Molecular formula	Analyses Calcd. C%	H%	N%	Cl%	Found C%	H%	N%	Cl%
5	H	H			95	no reaction											
6	H	Me			95	no reaction											
7	Me	H			95	no reaction											
8	Me	Me			95	no reaction											
9	Ph	Me	**20**	Ph	95	198	69	EtOH	$C_{16}H_{12}N_2O_2$	72.72	4.58	10.60		72.86	4.48	10.62	
10	OMe	H	**21**	OMe	35	182 [a]	79	EtOH									
			22	Cl	95	221-223 [b]	95	*i*-PrOH									
11	Cl	H	**22**	Cl	95	222-224 [b]	94	*i*-PrOH									
12	Cl	Me	**23**	Cl	95	210-212	93	*i*-PrOH	$C_{10}H_7ClN_2O$	53.95	3.17	12.58	15.92	53.90	3.14	12.52	16.02
13	NHBu	H	**24**	NHBu	15	102	90	EtOH	$C_{15}H_{15}N_3O_2$	63.66	6.16	17.13		63.42	6.13	17.20	
			25	N(CHO)Bu	95	118-119	88	EtOH	$C_{14}H_{15}N_3O_3$	61.53	5.53	15.93		61.28	5.50	15.80	
14	NHBu	Me	**26**	NHBu	15	80-82	89	EtOH	$C_{14}H_{17}N_3O_2$	64.85	6.61	16.21		65.10	6.58	16.15	
		Me	**27**	N(CHO)Bu	95	110-112	84	EtOH	$C_{15}H_{17}N_3O_3$	62.71	5.96	14.63		62.58	5.95	14.56	
15	Piperidino-	H	**28**	Piperidino-	25	158-159 [c]	89	EtOH									
16	Piperidino-	Me	**29**	Piperidino-	25	138-139	93	EtOH	$C_{15}H_{17}N_3O_2$	66.40	6.32	15.49		66.60	6.35	15.55	

[a] Lit [9] mp 178-179° (EtOH), yield 65%. [b] Lit [23] mp 226-227° (EtOH), yield 76%; lit [9] mp 223-225° (EtOH), yield 39%. [c] Lit [23] mp 157° (EtOH), yield 59%.



(5)-(16)



(20)-(29)

(5) R = R¹ = H

(6) R = H, R¹ = Me

(7) R = Me, R¹ = H

(8) R = R¹ = Me

(9) (20) R = Ph, R¹ = Me

(10) (21) R = OMe, R¹ = H

(11) (22) R = Cl, R¹ = H

(12) (23) R = Cl, R¹ = Me

(13) (24) R = NHBu, R¹ = H

(25) R = N(CHO)Bu, R¹ = H

(14) (26) R = NHBu, R¹ = Me

(27) R = N(CHO)Bu, R¹ = Me

(15) (28) R =  , R¹ = H

(16) (29) R =  , R¹ = Me

hand, compound **19** exists in a hydrogen-bonded enamine tautomeric form, as indicated by the singlet with one-proton intensity at 4.80 ppm and the NH proton at 11.00 ppm.

Vilsmeier-Haack formylation of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.

The 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **5-16** were reacted in dimethylformamide in the presence of two molar equivalents of phosphoryl chloride for one hour at the temperature indicated in Table 2. The formylated derivatives **20-29** were obtained only from those 2-substituted pyrido[1,2-*a*]pyrimidinones **9-16** which contain a substituent with an electron-releasing resonance effect in position 2.

Pyrido[1,2-*a*]pyrimidinones **5** and **6**, and their 2-methyl derivatives **7** and **8**, did not react even at elevated temperature during a long reaction period. In the case of the 2-methoxy derivative **10**, similarly to Ingalls and Popp [9] we obtained the 3-formyl-2-methoxy **21** and the 2-chloro-3-formyl **22**, derivatives depending on the reaction temperature, but the yields were higher than those were obtained by Ingalls and Popp.

At higher reaction temperatures, the 2-butylamino derivatives **24** and **26** were formylated not only on C(3), but also on the 2-amino group, to give compounds **25** and **27**.

3-Formyl-2-piperidino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **28** was earlier prepared from the 2-chloro-3-formyl derivative **11** with piperidine, in 59% yield [23].

In accordance with previous observations [24,25], in the uv spectra of the 6-methyl derivatives **26, 27** and **29** the lowest energy bands show a red shift compared with those of the 6-unsubstituted derivatives **24, 25** and **28**. In the uv spectrum of 6-methyl-2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **9**, the intensity (ϵ = 24920) of the absorption band at 275 nm, originating from an electron transfer between the phenyl and pyridopyrimidinone chromophoric systems [26], is reduced to ϵ = 13860 when a formyl group is present in position 3 (compound **20**).

In the formylated derivatives **20, 23-29**, the presence of a formyl group in position 3 is indicated by a singlet between 10.10 and 10.50 ppm in the ^{1}H nmr spectra in deuteriochloroform, and by the presence of a further carbonyl stretching vibration in the interval 1690-1735 cm^{-1}, besides that of the ring carbonyl (1640-1665 cm^{-1}).

EXPERIMENTAL

The melting points are uncorrected. The uv spectra were recorded in ethanol with a Unicam SP-800 spectrophotometer, ir spectra were taken in potassium bromide pellets on a Zeiss UR-20 spectrometer and ^{1}H nmr spectra in deuteriochloroform on Perkin-Elmer R-12 and Bruker WP-80 DS spectrometers with TMS as internal standard.

Table 3

UV and IR Data on New 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones

Compound No.	Absorption maxima λ (nm) (ε)				ν C=O (ring)	ν C=O (formyl)	ν NH (cm^{-1})
9	378 (7410)	363 (7730)	275 (24920)	256 (20730)			
13	328 (3630)	258 (26300)	232 (9560)		1665 (s)		3250 (m)
14	346 (4690)	257 (20500)	240i (15850)		1665 (s)		3255 (m)
15		330 (3230)	270 (38020)	235 (9120)	1680 (vs)		
16	366i (5240)	350 (3980)	269 (39800)	241 (12300)	1680 (vs)		
20	400 (18350)	390i (16520)	283 (13860)	250 (18900)			
23	398 (14080)	272 (3810)	266i (12850)		1660 (m)	1735 (s)	
24	358i (9560)	347 (10350)	273i (12050)	253 (22450)	1640 (s)	1690 (s)	3260 (w)
25	383 (15450)	374i (14820)	279 (11450)	253 (14800)	1665 (s)	1710 (s)	
						1695 (s)	
26	392 (9320)	374 (12020)	276i (10480)	248 (24500)	1648 (vs)	1695 (s)	3250 (m)
27	405 (16240)	394i (15130)	289 (11470)	252 (16600)	1660 (s)	1695 (s)	
29	386 (11480)	270 (23500)	250i (15880)		1650 (s)	1695 (m)	

s = strong, m = medium, vs = very strong, w = weak, i = inflexion.

Table 4

^{1}H NMR Data on New 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones **13-16**, **20**, **24-27**, and **29** in Deuteriochloroform

Compound No.	H-3	H-6	H-7	H-8	H-9	3-CHO	6-Me	Substituent in position 2	
13	5.50 s	8.98 dd	6.87 m	7.62 m	7.23 dd			5.61 br, 3.29 m, 0.68-1.98 m	(7H)
14	5.30 s		6.45 dd	– 6.80-7.45 m –			3.00 s	5.06 br, 3.27 m, 0.70-2.05 m	(7H)
15	5.72 s	8.98 dd	6.93 m	– 7.20-7.89 m –				3.55-4.03 m 4H, 1.32-2.22 m	(6H)
16	5.49 s		6.41 dd	– 6.95-7.51 m –			3.00 s	3.36-4.03 m 4H, 1.42-2.10 m	(6H)
20			6.98 dd	– 7.43-7.95 m – [a]		10.09 s	3.16 s	7.43-7.95 m [a]	(7H)
24		8.90 dd	6.97 m	7.66 m	7.28 dd	10.47 s		9.85 br, 3.65 m, 0.78-2.08 m	(7H)
25		9.30 dd	7.49 m	8.26 m	7.78 dd	10.46 s		8.50 s, 4.14 m, 0.71-2.09 m	(7H)
26			6.46 dd	7.49 m	7.11 dd	10.23 s	2.98 s	9.65 br, 3.61 m, 0.71-2.02 m	(7H)
27			6.98 dd	7.85 m	7.43 dd	10.28 s	3.12 s	8.43 s, 4.11 m, 0.73-2.00 m	(7H)
29			6.50 dd	7.46 m	7.01 dd	10.11 s	2.95 s	3.75 m 4H, 1.75 m	(6H)

[a] Overlapping.

Preparations of Substituted 2-Amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**13-16**).

2-Butylamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **13**, **14**.

An ethanolic solution (100 ml) of 2-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**11** or **12**) (50 mmoles) and butylamine (150 mmoles) was refluxed for 10 hours. After evaporation of the solvent, the residual oil was dissolved in 5% hydrochloric acid (250 ml), and extracted with benzene (2 x 100 ml) to remove the unreacted pyridopyrimidinone. The *p*H of the aqueous phase was adjusted to 7 by the addition of solid sodium carbonate. After chilling, the precipitated 2-butylamino compound was filtered off and recrystallized.

Compound **13** had mp 95° (refluxed in light petroleum), yield, 76%.

Anal. Calcd. for $C_{12}H_{15}N_3O$: C, 66.34, H, 6.93, N, 19.34. Found: C, 66.10; H, 7.08; N, 19.42.

Compound **14** had mp 92° (refluxed in light petroleum), yield, 51%.

Anal. Calcd. for $C_{13}H_{17}N_3O$: 67.51; H, 7.44; N, 18.19. Found: C, 67.51; H, 7.46; N, 18.22.

2-Piperidino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **15**, **16**.

A solution of 2-chloro-4*H*-pyrido[1,2-*a*]-pyrimidon-4-one **11** or **12** (50 mmoles) and piperidine (150 mmoles) in dioxane (100 ml) was refluxed for 20 minutes. After cooling, the precipitated piperidinium chloride was filtered off, and the filtrate was evaporated to dryness *in vacuo*. The oily residue was triturated with light petroleum to give the 2-piperidino compound.

Compound **15** had mp 94-95° (refluxed in light petroleum), yield 81%.

Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 67.83; H, 6.51; N, 18.26.

Compound **16** had mp 88° (refluxed in light petroleum), yield 74%.

Anal. Calcd. for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.36; H, 7.12; N, 17.33.

Methyl *N*-(6-Methyl-2-pyridyl)-(α-methoxycarbonyl)acetimidate (**17**).

To a stirred suspension of 2-chloro-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **12** (3.88 g, 20 mmoles) in methanol (20 ml) was slowly added a solution of sodium methoxide (1.19 g, 22 mmoles) in methanol (15 ml). Stirring was continued for 2 hours at ambient temperature. The solution was then poured into water (200 ml) and the mixture was extracted with chloroform (3 x 70 ml). The organic extract was dried (sodium sulfate), treated with charcoal and evaporated to give an oil that was crystallized from diethyl ether-light petroleum. The product **17** was obtained in 61% yield, mp 82°; ^{1}H nmr, δ 2.48 (s, 6-CH_3, 3H), 3.39 (s, -CH_2-, 2H), 3.70 (s, $COOCH_3$, 3H), 3.19 (s, -OCH_3, 3H), 6.80 (dd, aromatic 3, 5-H, 2H), 7.56 (t, aromatic 4-H, 1H).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.54; H, 6.34; N, 12.65.

Methyl 3-methyl-3-[(6-methyl-2-pyridyl)amino]acrylate (**19**).

This compound was prepared in the same manner as **17**, starting from 2,6-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **8**. The product was obtained in 69% yield as a yellow oil; ^{1}H nmr: δ 2.44 (2 singlets, C-CH_3 and 3-CH_3, 6H), 3.71 (s, $COOCH_3$, 3H), 4.80 (s, =CH, 1H), 6.72 (dd, aromatic 3,5-H, 2H), 7.50 (t, aromatic 4-H, 1H), 11.0 (broad, NH, 1H).

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.72; H, 6.18; N, 12.70.

Methyl [(*N*-6-Methyl-2-pyridyl)carbamoyl]acetate (**18**).

A suspension of methyl *N*-(6-methyl-2-pyridyl)(α-methoxycarbonyl)-acetimidate **17** (1.11 g, 5 mmoles) and polyphosphoric acid (10 g) (Fluka) was stirring on a steam bath for 1 hour. After cooling, the mixture was poured onto crushed ice (10 g) and neutralized with 20% aqueous sodium carbonate. The precipitated product **18** was filtered off and washed with water, giving 1.04 g (70%) white crystals, mp 106-108°; ^{1}H nmr: δ 2.46 (s, 6-CH_3, 3H), 3.58 (s, -CH_2-, 2H), 3.78 (s, $COOCH_3$, 3H), 6.93 (d, aromatic H-5, 1H), 7.63 (t, aromatic H-4, 1H), 8.04 (d, aromatic H-3, 1H), 9.5 (broad, NH, 1H).

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.48; H, 5.82; N, 13.46.

Vilsmeier-Haack Formylation.

To a cooled solution or suspension of 2-substituted 4*H*-pyrido[1,2-*a*]-pyrimidin-4-ones **5-16** (10 mmoles) in DMF (100 ml) was added phosphoryl chloride (20 mmoles) dropwise at 10-15°. The mixture was then stirred for 1 hour at the temperature indicated in Table 2. The reaction mixture was cooled to 25° and poured onto crushed ice (30 g) and the *p*H of the mixture was adjusted to 7 with 20% aqueous sodium carbonate. The mixture was kept at 25° for 2 hours, and the precipitated product was filtered off and recrystallized from the solvent mentioned in Table 2 (yields and mps are given in Table 2, too). For the preparation of compounds **25** from **13**, **27** from **14**, and **20** from **10**, 30 mmoles of phosphoryl chloride was used.

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