

PHOSPHORUS PENTOXIDE IN ORGANIC SYNTHESIS XXXX.

SYNTHESIS OF 3-ARYL-3,7-DIHYDRO-4H-PYRROLO[2,3-d]PYRIMIDIN-4-ONES

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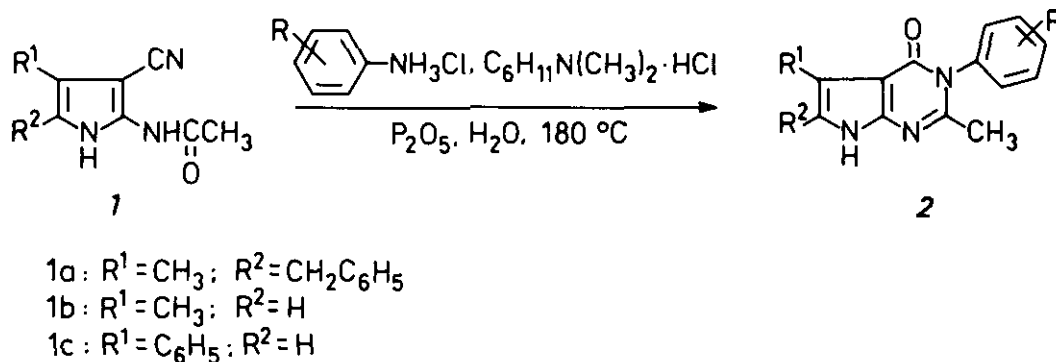
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Abstract - Pyrrolo[2,3-d]pyrimidin-4(3H)-ones (2a-j) were prepared in 18-51% yields by heating 2-acetylamino-3-pyrrolocarbonitriles (1) with a mixture of phosphorus pentoxide, *N,N*-dimethylcyclohexylamine hydrochloride, water, and an appropriate arylamine hydrochloride at 180°C.

Methyl or ethyl 2-amino-3-pyrrolocarboxylates are obviously promising as the starting materials for the synthesis of pyrrolo[2,3-d]pyrimidin-4(3H)-ones by the method similar to that used in the synthesis of 4(3H)-quinolinones from antranilic acid derivatives. However, the synthetic methods leading to methyl or ethyl 2-amino-3-pyrrolocarboxylate derivatives are very scarcely reported in the literature. Gewald and coworkers have reported² the synthesis of 2-amino-3,4-diethoxycarbonylpyrrole. Its reaction with 4-chloroacetanilide in the presence of phosphorus oxychloride was shown to give 3-(4-chlorophenyl)-5-ethoxycarbonyl-2-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one³ in 11% yield. In 1985 the synthesis of methyl 2-amino-1-benzyl-4,5-dimethyl-3-pyrrolocarboxylate was reported.⁴ In a recent work from our laboratories⁵ we treated its 2-acetylamino derivative with a mixture of phosphorus pentoxide, triethylamine hydrochloride and anilines and obtained the corresponding 3-aryl-7-benzyl-3,7-dihydro-2,5,6-trimethyl-4H-pyrrolo[2,3-d]pyrimidin-4-ones in 44-66% yields.

Recently⁶ we have circumvented the request of 2-amino-3-pyrrolocarboxylates for the synthesis of 3-arylpyrrolo[2,3-d]pyrimidin-4(3H)-ones by applying our phosphorus reagent to reactions of 2-amino-3-pyrrolocarbonitrile derivatives. Thus, we tried the reaction of *N*₁-substituted 2-acetylamino-3-pyrrolocarbonitriles with a mixture of phosphorus pentoxide, *N,N*-dimethylcyclohexylamine hydrochloride, water, and appropriate aniline hydrochlorides. The reaction mixtures were worked up by use of preparative silica gel tlc to afford *N*₇-substituted 3-arylpyrrolo[2,3-d]pyrimidin-

4(3H)-ones as the main products and the corresponding 3-unsubstituted pyrrolo-[2,3-d]pyrimidin-4(3H)-ones as by-products.



Scheme 1

In the present investigation we have extended our method to the synthesis of 7-unsubstituted 3-arylpyrrolo[2,3-d]pyrimidin-4(3H)-ones (2a-j) by reaction of 2-acetyl-3-pyrrolecyanonitriles (1) with a mixture of phosphorus pentoxide, *N,N*-dimethylcyclohexylamine hydrochloride, water, and appropriate aniline hydrochlorides at 180°C for 1 h. The products (2) were isolated easily by crystallization in yields of 18-51%. The structures of products 2 were assigned on the basis of elemental analyses (Table 1), ir, ms, ¹H nmr (Table 2), ¹³C nmr spectroscopies (Table 3), and by comparison of spectral data with those of reference compounds.⁵⁻⁸

3-Aryl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-ones (2a-j)

General procedure:

The arylamine hydrochloride (60 mmol), *N,N*-dimethylcyclohexylamine hydrochloride (9.8 g, 60 mmol), and phosphorus pentoxide (8.5 g, 60 mmol) were mixed in a flask with mechanical stirring and protected by a drying tube (CaCl₂). Distilled water (2.16 g, 120 mmol) was added cautiously, and the flask was heated in an oil bath at 200-220°C (oil bath temperature) until a homogeneous mixture was achieved. The oil bath temperature was adjusted to 180°C and the starting pyrrole derivative (1)^{9,10} (15 mmol) was added. After heating for 1 h the reaction mixture was allowed to cool

Table 1. Synthesis of 3-aryl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-ones 2a-j.

2	R	R ¹	R ²	Yield [%]	mp [°C]	Mol. Formula (Mol. Weight)	Analysis		
							Calcd	Found	
							C	H	N
a	H	CH ₃	CH ₂ C ₆ H ₅	51	206-207	C ₂₁ H ₁₉ N ₃ O (329.4)	76.57 76.11	5.81 5.81	12.76 12.64
b	4-CH ₃	CH ₃	CH ₂ C ₆ H ₅	39	210-211	C ₂₂ H ₂₁ N ₃ O (343.4)	76.94 77.28	6.16 6.25	12.23 12.09
c	3-F	CH ₃	C ₂ H ₅ C ₆ H ₅	19	208-209	C ₂₁ H ₁₈ N ₃ OF (347.4)	72.61 72.43	5.22 5.18	12.10 11.88
d	4-F	CH ₃	CH ₂ C ₆ H ₅	35	251-252	C ₂₁ H ₁₈ N ₃ OF (347.4)	72.61 72.52	5.22 5.30	12.10 11.90
e	4-Cl	CH ₃	CH ₂ C ₆ H ₅	22	249-250	C ₂₁ H ₁₈ N ₃ OC1 (363.8)	69.32 69.26	4.98 4.92	11.55 11.32
f	4-C ₂ H ₅	CH ₃	CH ₂ C ₆ H ₅	37	191-192	C ₂₃ H ₂₃ N ₃ O·1/4H ₂ O (362.0)	76.32 76.56	6.54 6.45	11.61 11.64
g	3-CF ₃	CH ₃	CH ₂ C ₆ H ₅	22	242-243	C ₂₂ H ₁₈ N ₃ OF ₃ (397.4)	66.49 66.86	4.57 4.54	10.57 10.44
h	H	CH ₃	H	35	250-251	C ₁₄ H ₁₃ N ₃ O (239.3)	70.28 70.02	5.48 5.49	17.56 17.36
i	3-F	CH ₃	H	26	218-219	C ₁₄ H ₁₂ N ₃ OF·1/8H ₂ O (259.5)	64.79 64.87	4.76 4.78	16.19 15.81
j	H	C ₆ H ₅	H	18	311-312	C ₁₉ H ₁₅ N ₃ O (301.3)	75.73 75.51	5.01 5.04	13.94 13.65

Table 2. Spectral properties.

2	Ir (KBr) (cm^{-1})	Ms m/z (%)	$^1\text{H-Nmr}$ (δ in DMSO-d_6)
a	1670(C=O), 3420-3220(NH)	329(M^+ , 100)	2.06(s, 3H), 2.26(s, 3H), 3.96(s, 2H), 7.33-7.66(m, 10H), 11.63(s, 1H)
b	1670(C=O), 3420-3220(NH)	343(M^+ , 100)	2.06(s, 3H), 2.26(s, 3H), 2.40(s, 3H), 3.96 (s, 2H), 7.26-7.46(m, 9H), 11.63(s, 1H)
c	1670(C=O), 3420-3220(NH)	347(M^+ , 100)	2.06(s, 3H), 2.26(s, 3H), 3.96(s, 2H), 7.26-7.70(m, 9H), 11.63(br s, 1H, NH)
d	1670(C=O), 3420-3220(NH)	347(M^+ , 100)	2.06(s, 3H), 2.26(s, 3H), 3.96(s, 2H), 7.26-7.46(m, 9H), 11.63(br s, 1H, NH)
e	1670(C=O), 3420-3220(NH)	363(M^+ , 100)	2.06(s, 3H), 2.26(s, 3H), 3.96(s, 2H), 7.23-7.70(m, 9H), 11.73(br s, 1H, NH)
f	1670(C=O), 3420-3220(NH)	357(M^+ , 100)	1.30(3H, t, $J=7\text{Hz}$), 2.06(s, 3H), 2.26(s, 3H), 2.70(2H, q, $J=7\text{Hz}$), 3.96(s, 2H), 7.03-7.63 (m, 9H), 11.63(br s, 1H, NH)
g	1670(C=O), 3420-3220(NH)	397(M^+ , 100)	2.06(s, 3H), 2.26(s, 3H), 3.96(s, 2H), 7.23-7.90(m, 9H), 11.63(br s, 1H, NH)
h	1685(C=O), 3430-3220(NH)	239(M^+ , 100)	2.06(s, 3H), 2.26(s, 3H), 6.80(s, 1H), 7.20 (m, 5H), 11.56(br s, 1H, NH)
i	1685(C=O), 3430-3220(NH)	257(M^+ , 100)	2.10(s, 3H), 2.30(s, 3H), 6.80(s, 1H), 7.30-7.46(m, 4H), 11.63(br s, 1H, NH)
j	1665(C=O), 3410-3220(NH)	301(M^+ , 100)	2.13(s, 3H), 7.26(s, 1H), 7.43-7.53(m, 10H), 12.16(br s, 1H, NH)

Table 3. ^{13}C -Nmr spectra (δ in $\text{DMSO}-d_6$).^a

C	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j
2	151.7	151.9	151.5	151.8	151.5	152.0	151.4	152.3	152.1	153.0
4	159.1	159.1	159.0	159.1	159.0	159.2	159.1	159.3	159.2	158.9
4a	104.2	104.2	104.2	104.2	104.2	104.2	104.2	103.9	103.9	102.0
5	109.5	109.5	109.6	109.5	109.6	109.5	109.7	113.6	113.7	118.4
6	128.5	128.5	128.7	128.6	128.7	^b	128.8	117.2	117.3	120.2
7a	145.9	145.9	145.9	145.9	145.7	145.9	146.0	146.8	146.7	148.3
1'	139.7	135.9	140.2(d) (10.1)	134.8(d) (3.4)	137.5	136.2	139.7	136.5	140.1(d) (10.1)	138.7
2'	128.3	128.3	115.5(d) (20.8)	130.8(d) (9.3)	129.3	128.3	125.9	128.7	115.5(d) (20.8)	128.2
3'	129.2	129.7	162.2(d) (244.7)	116.0(d) (23.0)	130.7	128.6	130.2(q) (32.1)	129.3	162.2(d) (244.7)	129.3
4'	128.6	139.7	116.4(d) (23.3)	161.6(d) (245.1)	133.0	143.9	125.9	128.4	116.4(d) (22.6)	128.6
5'			130.7(d) (8.8)				130.5		130.8(d) (8.8)	
6'			125.2(d) (3.1)				133.2		125.2(d) (3.2)	
1''	138.5	137.7	139.7	139.7	139.7	139.7	139.5			134.1
2''	128.0	127.9	128.0	128.0	128.0	128.0	128.0			125.7
3''	128.6	128.5	128.7	128.3	128.3	128.4	128.3			128.3
4''	125.9	125.9	125.9	125.9	125.9	125.9	125.9			127.8
2-CH ₃	23.7	23.7	23.6	23.8	23.7	23.8	23.8	23.8	23.7	23.8
5-CH ₃	9.5	9.5	9.5	9.5	9.5	9.5	9.5	11.1	11.0	
4'-CH ₃		20.6								
4'-CH ₂ CH ₃						15.4				
4'-CH ₂ CH ₃						27.7				
6-CH ₂	30.7	30.7	30.7	30.7	30.7	30.7	30.7			
3'-CF ₃							123.8(q) (272)			

^aValues in parentheses refer to C-F couplings in Hz. ^bAssignment uncertain.

to about 100°C and 2M NaOH solution (ca. 250 ml) was added (pH 9-11). The mixture was stirred at room temperature until the reaction cake was digested. Then the alkaline aqueous solution was extracted with CH_2Cl_2 (3 x 100 ml). CH_2Cl_2 was stripped off and N,N-dimethylcyclohexylamine was distilled off at 10 mmHg. The unreacted aniline derivatives were distilled off at 1 mmHg at 100°C. The crude product was recrystallized from methanol.

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