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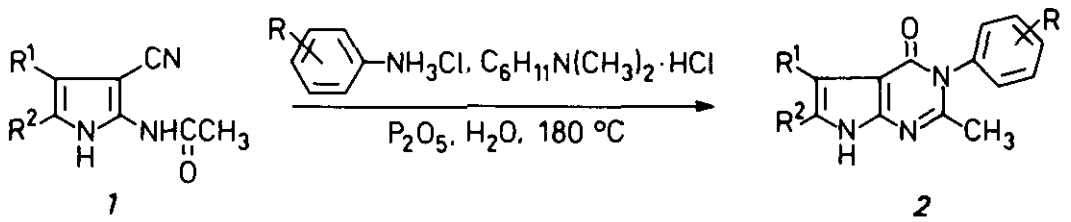
Abstract - Pyrrolo[2,3-d]pyrimidin-4(3H)-ones (2a-j) were prepared in 18-51% yields by heating 2-acetylamino-3-pyrrolocarbonitriles (1) with a mixture of phosphorus pentoxide, N,N-dimethylcyclohexylamine hydrochloride, water, and an appropriate arylamine hydrochloride at 180°C.

Methyl or ethyl 2-amino-3-pyrrolecarboxylates 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-pyrrolecarboxylate derivatives are very scarcely reported in the literature. Gewald and coworkers have reported[2] 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-one[3] in 11% yield. In 1985 the synthesis of methyl 2-amino-1-benzyl-4,5-dimethyl-3-pyrrolecarboxylate was reported.[4] In a recent work from our laboratories[5] 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.

Recently[6] we have circumvented the request of 2-amino-3-pyrrolecarboxylates for the synthesis of 3-arylpyrrolo[2,3-d]pyrimidin-4(3H)-ones by applying our phosphorus reagent to reactions of 2-amino-3-pyrrolecarbonitrile derivatives. Thus, we tried the reaction of N_1-substituted 2-acetylamino-3-pyrrolecarbonitriles 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.



1a: $R^1 = CH_3$; $R^2 = CH_2C_6H_5$
1b: $R^1 = CH_3$; $R^2 = H$
1c: $R^1 = C_6H_5$; $R^2 = H$

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-acetylamino-3-pyrrolecarbonitriles (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, ^{1}H nmr (Table 2), ^{13}C 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 ($CaCl_2$). 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	$CH_2C_6H_5$	51	206-207	$C_{21}H_{19}N_3O$ (329.4)	76.57 76.11	5.81 5.81	12.76 12.64
b	4-CH_3	CH_3	$CH_2C_6H_5$	39	210-211	$C_{22}H_{21}N_3O$ (343.4)	76.94 77.28	6.16 6.25	12.23 12.09
c	3-F	CH_3	$C_2H_5C_6H_5$	19	208-209	$C_{21}H_{18}N_3OF$ (347.4)	72.61 72.43	5.22 5.18	12.10 11.88
d	4-F	CH_3	$CH_2C_6H_5$	35	251-252	$C_{21}H_{18}N_3OF$ (347.4)	72.61 72.52	5.22 5.30	12.10 11.90
e	4-Cl	CH_3	$CH_2C_6H_5$	22	249-250	$C_{21}H_{18}N_3OCl$ (363.8)	69.32 69.26	4.98 4.92	11.55 11.32
f	4-C_2H_5	CH_3	$CH_2C_6H_5$	37	191-192	$C_{23}H_{23}N_3O \cdot 1/4H_2O$ (362.0)	76.32 76.56	6.54 6.45	11.61 11.64
g	3-CF_3	CH_3	$CH_2C_6H_5$	22	242-243	$C_{22}H_{18}N_3OF_3$ (397.4)	66.49 66.86	4.57 4.54	10.57 10.44
h	H	CH_3	H	35	250-251	$C_{14}H_{13}N_3O$ (239.3)	70.28 70.02	5.48 5.49	17.56 17.36
i	3-F	CH_3	H	26	218-219	$C_{14}H_{12}N_3OF \cdot 1/8H_2O$ (259.5)	64.79 64.87	4.76 4.78	16.19 15.81
j	H	C_6H_5	H	18	311.312	$C_{19}H_{15}N_3O$ (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}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=7Hz),2.06(s,3H),2.26(s,3H), 2.70(2H,q,J=7Hz),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 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'-$CH_2\underline{C}H_3$						15.4				
4'-$\underline{C}H_2CH_3$						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)			

[a]Values in parentheses refer to C-F couplings in Hz. [b]Assignment 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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