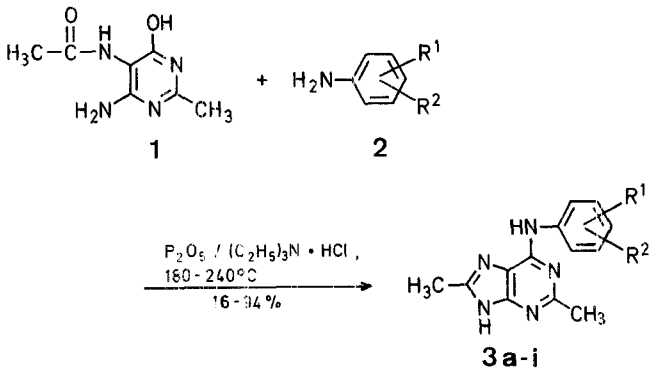
Phosphorus Pentoxide in Organic Synthesis; XIV[1]. Phosphorus Pentoxide/Arylamine Mixtures as Reagents in a New Synthesis of 6-Arylamino-2,8-dimethyl-9*H*-purines with Potential Biological Activity

Khairy A.M. EL-BAYOUKI*, Flemming E. NIELSEN, Erik B. PEDERSEN**

Department of Chemistry, Odense University, DK-5230 Odense M, Denmark

Many purines have been reported to have antiviral[2], fungicidal[3], and plant growth regulating[4] activities. In the last decades, several synthetic N^6-substituted purines (adenosine analogues) have been found to possess antitumour activities[5]. Previously, it has been shown that the reagent mixture of phosphorus pentoxide, *N,N*-dimethylcyclohexylamine (DMCA) and a primary amine hydrochloride can be used for preparation of 4-quinazolinamines[6] and 4-arylaminothieno[2,3-*d*]-pyrimidines[7] from the corresponding *ortho*-acylaminonitriles. Moreover, it has been reported[8] that some N^6-substituted-6-amino-9*H*-purines were synthesized in low yield (1–17%) upon condensation of N^6-substituted-4,5,6-triaminopyrimidines with various acid anhydrides and iminoesters. In view of these findings, the present investigation was carried out to achieve a new, one-step synthesis of potential biologically active N^6-substituted-6-amino-9*H*-purines **3** from 5-acetylamino-4-amino-6-hydroxy-2-methylpyrimidine (**1**).

In the present work, we have easily prepared a series of new 6-arylamino-2,8-dimethyl-9*H*-purines (**3a–i**) in a one-step reaction by heating one equivalent of 5-acetylamino-4-amino-6-hydroxy-2-methylpyrimidine (**1**) with four equivalents each of phosphorus pentoxide, triethylamine hydrochloride, and arylamines **2** at 180–240°C for 1.5–24 h in 16–94% yield (Table).



The reaction was followed by silica T.L.C. with dichloromethane/methanol (98:2). The starting material **1** was prepared according to the method of Ref.[9] using the commercially available ethyl acetamidocyanoacetate. The latter compound could be prepared according to Ref.[10] by reducing ethyl oximinocyanoacetate synthesized according to Ref.[11].

The structural assignment of aminopurines **3** was based upon microanalyses and N.M.R., I.R., U.V., and mass spectral data.

6-Arylamino-2,8-dimethyl-9H-purines 3; General Procedure:
The reagent is prepared by mixing phosphorus pentoxide (17.0 g, 0.12 mol) and triethylamine hydrochloride (16.5 g, 0.12 mol) followed by addition of the arylamine **2** (0.12 mol) in a 250 ml flask with reflux condenser and drying tube. The mixture is heated with mech-

Table. 6-Arylamino-2,8-dimethyl-9*H*-purines **3a–i** prepared

Product No.	R^1	R^2	Reaction time [h]	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	U.V. (Ethanol)[b] λ_{max} [nm] (log ε)	I.R. (KBr)[c] ν [cm^{-1}]	M.S.[d] *m/e* (%)	^{1}H-N.M.R. (DMSO-d_6/TMS)[e] δ [ppm]
3a	H	2-H_3C	4	40	260–261° (toluene)	$C_{14}H_{15}N_5$ (253.3)	288 (4.28)	3400, 3300–2400, 1620, 1605	254 (17), 253 (M^+, 100), 252 (15), 238 (20), 236 (11), 212 (49), 126.5 (M^{2+}, 13), 42 (17)	2.28 (s, 3H, CH_3); 2.43 (s, 3H, CH_3); 2.52 (s, 3H, CH_3); 6.93–7.77 (m, 4H_{arom}); 8.7 (br. s, 1H, N^6-H); 12.8 (br. s, 1H, N^9-H)
3b	H	4-H_3C	4[f]	94	279–282° (ethanol)	$C_{14}H_{15}N_5$ (253.3)	299 (4.36)	3300–2400, 1625	254 (14), 253 (M^+, 79), 252 (100), 106 (18), 91 (12), 42 (18)	2.26 (s, 3H, CH_3); 2.48 (s, 6H, $2CH_3$); 7.09 (d, J = 8 Hz, 2H_{arom}); 7.89 (d, J = 8 Hz, 2H_{arom}); 9.3 (br. s, 1H, N^6-H); 12.6 (br. s, 1H, N^9-H)
3c	H	2-Cl	4	16	317–319° (ethanol)	$C_{13}H_{12}ClN_5$ (273.7)	295 (4.50)	3370, 3300–2400, 1625, 1600	273 (M^+, 10), 239 (17), 238 (100), 156 (13), 42 (11)	2.60 (s, 6H, $2CH_3$); 7.23–8.90 (m, 4H_{arom}); 8.7 (br. s, 1H, N^6-H); 12.6 (br. s, 1H, N^9-H)
3d	H	4-Cl	24[g]	70	310–311° (butanone)	$C_{13}H_{12}ClN_5$ (273.7)	301 (4.54)	3300–2400, 1630	275 (32), 274 (40), 273 (M^+, 100), 272 (77), 111 (10), 42 (17)	253 (s, 6H, $2CH_3$); 7.33 (d, J = 9 Hz, 2H_{arom}); 8.07 (d, J = 9 Hz, 2H_{arom}); 9.6 (br. s, 1H, N^6-H); 12.7 (br. s, 1H, N^9-H)
3e	H	4-F	9[h]	64	311–313° (ethanol)	$C_{13}H_{12}FN_5$ (257.3)	294 (4.45)	3385, 3300–2400, 1625, 1605	258 (15), 257 (M^+, 100), 256 (98), 128.5 (M^{2+}, 11), 42 (13)	2.57 (s, 6H, $2CH_3$); (6.97–8.23 (m, 4H_{arom}); 9.5 (br. s, 1H, N^6-H); 12.6 (br. s, 1H, N^9-H)
3f	2-H_3C	4-Cl	4	58	315–317° (dioxan)	$C_{14}H_{14}ClN_5$ (287.8)	293 (4.38)	3415, 3300–2400, 1625, 1605	289 (32), 288 (20), 287 (M^+, 100), 272 (27), 248 (17), 246 (51), 229 (11), 211 (11), 126 (11), 106 (12), 43 (11), 42 (49)	2.23 (s, 3H, CH_3); 2.36 (s, 3H, CH_3) 2.46 (s, 3H, CH_3); 7.00–7.77 (m, 3H_{arom}): 8.8 (br. s, 1H, N^6-H); 12.7 (br. s, 1H, N^9-H)
3g	3-Cl	4-H_3C	4	63	305–307° (DMF)	$C_{14}H_{14}ClN_5$ (287.8)	299 (4.40)	3300–2400, 1625, 1610	289 (33), 288 (42), 287 (M^+, 100), 286 (78), 106 (10), 42 (21)	2.28 (s, 3H, CH_3); 2.51 (s, 6H, $2CH_3$); 7.15–8.37 (m, 3H_{arom}): 9.6 (br. s, 1H, N^6-H); 12.6 (br. s, 1H, N^9-H)
3h	2-F	4-F	1.5	50	303–304° (ethanol)	$C_{13}H_{11}F_2N_5$ (275.3)	283 (4.33); 295 (4.33)	3400, 3300–2400, 1635, 1620, 1605	276 (12), 275 (M^+, 79), 274 (16), 257 (16), 256 (100), 255 (10), 137.5 (M^{2+}, 13), 42 (15)	2.43 (s, 3H, CH_3); 2.52 (s, 3H, CH_3); 6.92–8.17 (m, 3H_{arom}); 8.8 (br. s, 1H, N^6-H); 12.8 (br. s, 1H, N^9-H)
3i	3-F_3C	4-Cl	4	70	340–342° (acetic acid)	$C_{14}H_{11}ClF_3N_5$ (341.7)	301 (4.53)	3370, 3300–2400, 1625, 1605	343 (35), 342 (44), 341 (M^+, 100), 340 (62), 106 (10), 42 (28)	257 (s, 6H, $2CH_3$); 7.55–8.97 (m, 3H_{arom}); 10.1 (br. s, 1H, N^6-H); 12.8 (br. s, 1H, N^9-H)

[a] Satisfactory microanalyses obtained: C ±0.44, H ±0.28, N ±0.44, Cl ±0.34.
[b] The U.V. spectra were run on a Varian Cary 219 spectrophotometer.
[c] The I.R. spectra were recorded on a Perkin-Elmer 580 spectrophotometer.
[d] The mass spectra were determined with a Varian MAT 311A and a Varian MAT CH 7A mass spectrometer.
[e] The ^{1}H-N.M.R. spectra were measured on a JEOL JNM-PMX 60 spectrometer.
[f] The reaction temperature was 240°C.
[g] The reaction mixture was heated at 180°C for 18 h and then at 220°C for 6 h.
[h] The reaction temperature was 180°C.

anical stirring in an oil bath at 200 °C (oil bath) until a homogeneous mixture is achieved (~ 0.5 h). Compound **1** (5.5 g, 0.03 mol) is added and stirring is continued at 200 °C for the reaction periods given in the Table. The reaction progress is followed by taking out samples (~ 100 mg) which are treated with 2 molar sodium hydroxide followed by 4 molar hydrochloric acid until pH 6–7 and extracted with dichloromethane for silica T.L.C with dichloromethane/methanol (98 : 2) as eluent. The mixture is allowed to cool to about 100 °C and 2 molar sodium hydroxide (~ 200 ml) is added until alkaline reaction (pH 12–14). Stirring is continued until the reaction cake is digested (~ 0.5 h). Then 4 molar hydrochloric acid (20–25 ml) is added while cooling until neutral reaction (pH 6–7). The solid material formed is collected by filtration, washed with water, dried, and recrystallized from the solvents given in the Table.

Received: May 29, 1984

* Present address: National Research Centre, Dokki, Cairo, Egypt.

** Address for correspondence.

[1] Part XIII: A. Jørgensen, N.S. Girgis, E.B. Pedersen, *Chem. Scrip.*, **24**, 73 (1984).

[2] R.J. Whitley, C.A. Alford, *Ann. Rev. Microbiol.* **32**, 285 (1978).

[3] S. Kawada, K. Takita, M. Sekiya, *Japan Kokai* 75 40748 (1975); *C.A.* **83**, 92364 (1975).

[4] W. Draber, *Chemie der Pflanzenschutz- und Schädlingsbekämpfungsmittel*, Vol. 4, R. Wegle, Ed., Springer Verlag, Heidelberg, Berlin, 1977, p. 28.

[5] M.H. Fleysher, R.J. Bernacki, G.A. Bullard, *J. Med. Chem.* **23**, 1448 (1980).

[6] K.E. Nielsen, E.B. Pedersen, *Chem. Scrip.* **18**, 242 (1981).

[7] K.E. Nielsen, E.B. Pedersen, *Chem. Scrip.* **18**, 245 (1981).

[8] L.K. Kurilenko, V.M. Cherkasov, *Ukrain. Khim. Zh.* **45**, 760 (1979) *C.A.* **91**, 175305 (1979).

[9] D.S. Acker, J.E. Castle, *J. Org. Chem.* **23**, 2010 (1958).

[10] A.J. Zambito, E.E. Howe, *Org. Synth. Coll. Vol.* V, 373 (1973).

[11] C.O. Parker, *Tetrahedron* **17**, 109 (1962).