Short Communication

Phosphorus Pentoxide in Organic Synthesis. XXXVII.* Synthesis of 2-Amino-6-arylaminopurines

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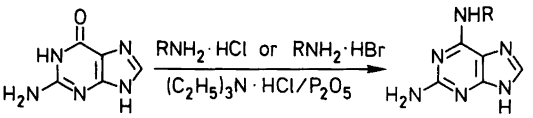
Many purines have been reported to have antiviral,[1] fungicidal,[2] antitumour,[3,4], anticoccidial[5] and plant-growth regulating[6,7] activities. N^6-Substituted adenines are known to be important in the animal kingdom, their presence being associated with growth control.[8] Kinetin (6-furfurylaminopurine) was first isolated from nucleic acid[9] and later synthesized[10]. Since then, several members of this series have been prepared by different synthetic routes. 2-Amino-6-anilinopurine (**2a**) has been prepared exclusively via the cyclization of 6-anilino-2,4,5-triaminopyrimidine with triethyl orthoformate and acetic anhydride[11]. It has been found that compounds of this type (2,6-diaminopurines) have an irreversible enzyme inhibition property.[12,13]

The aim of the present work was to develop a synthesis of 2-amino-6-arylaminopurines starting from guanine. This strategy should avoid the synthesis of appropriately substituted 2,4,5-triaminopyrimidines. Conversion of oxo groups to amino groups has generally been achieved by a two-step procedure involving in the first step conversion of the oxo group to a halo group; the latter is then replaced by amination. However, this procedure is not attractive in the case of guanine, owing to its combination of functional groups. Recently, it has been reported that a series of N^6-substituted adenines can be prepared through the one-step reaction of hypoxanthine with primary amines or amine hydrochlorides



1 **2a-m**

and phosphorus pentoxide in the presence of *N,N*-dimethylcyclohexylamine, converting the oxo group into the corresponding amino group.[14]

In the present work, guanine (**1**) was treated with arylamine hydrochlorides (or hydrobromides) and phosphorus pentoxide in the presence of triethylamine hydrochloride to give 2-amino-6-arylaminopurines **2a-m** in 45–90 % yield. The reaction proceeded smoothly at 190–200 °C within 5–7 h. Furthermore, it has been found that the use of the hydrochloride and hydrobromide salts of the arylamines for preparation of the reagent mixture gives higher yields of the product (**2a-m**) than the use of the free arylamines. The compounds were in all cases identified through their MS, ^{1}H NMR and ^{13}C NMR spectra, and correct microanalyses were obtained in all cases.

Experimental

2-Amino-6-arylaminopurines (**2a-m**). *General procedure:* Triethylamine hydrochloride (0.12 mol), phosphorus pentoxide (0.12 mol) and the aromatic amine hydrochloride (0.12 mol) (aniline hydrobromide in the synthesis of **2a**) were mixed well in a flask fitted with a mechanical stirrer and

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Table 1. Synthesis of 2-amino-6-arylaminopurines **2a-m**.

Product No.	R	Reaction time/h	Yield/%	M.p./°C (solvent)
2a	C_6H_5	7	80	280(C_2H_5OH)[a]
2b	3,4-$(CH_3)_2C_6H_3$	6	48	277(CH_3OH)[b]
2c	4-$C_2H_5C_6H_4$	6.5	45	273(CH_3OH)
2d	3,5-$(CH_3)_2C_6H_3$	7	63	252(C_2H_5OH)
2e	2-CH_3-4-ClC_6H_3	6.5	71	235(CH_3OH)
2f	3-ClC_{64}	7	53	233(C_2H_5OH)
2g	3,4-$Cl_2C_6H_3$	7	85	328(C_2H_5OH)[c]
2h	4-BrC_6H_4	5.5	90	309(C_2H_5OH)[c]
2i	4-FC_6H_4	5	61	250(CH_3OH)
2j	4-ClC_6H_4	7	82	288(C_2H_5OH)[c]
2k	3,5-$Cl_2C_6H_3$	6	84	305(DMF/H_2O)
2l	3-FC_6H_4	6	54	268(CH_3OH)
2m	3-$CH_3C_6H_4$	7	82	275(CH_3OH)

[a]Lit. m.p. 280 °C.[11] [b]Correct microanalysis with CH_3OH (1 mol) of crystallization. [c]Correct microanalysis with C_2H_5OH (1 mol) of crystallization.

a reflux condenser with a drying tube. The mixture was heated while stirring in an oil-bath at 200 °C (oil bath temp.) until a homogeneous mixture was obtained (~0.5 h). Guanine (**1**) (0.04 mol) was added, and stirring and heating were continued for 5–7 h. The reaction mixture was then allowed to cool to about 160 °C and a few drops of 2 M NaOH solution were added. Again, the reaction mixture was allowed to cool to about 100 °C and 2 M NaOH solution (250–300 ml) was added until alkaline reaction (pH > 10). Stirring was continued until the reaction cake was digested (~1 h). The solid material was collected by filtration, washed with absolute ethanol and ether, and then recrystallized from the appropriate solvent (cf. Table 1).

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