Phosphorus Pentoxide in Organic Synthesis; II[1]. A New, One-Step Conversion of Hypoxanthine into N^6-Substituted Adenines

Nabih S. GIRGIS[2], Erik B. PEDERSEN*

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

A number of N^6-substituted adenines (6-aminopurines) are known to be present in the plant and animal kingdoms; their presence being associated with growth control[3]. Kinetin (6-furfurylaminopurine) was first isolated from nucleic acid[4] and later synthesized[5]. Since then, several members of this series have been prepared through different synthetic routes. One of the most widely used is the conversion of oxo groups to amino groups. This has been generally achieved through a two-step reaction involving in the first step conversion of the oxo group to a halo group. The latter is then replaced by amination.

Among the few examples reported, where aminopurines have been directly derived from hypoxanthine, are the preparation of 6-dimethylamino- and 6-benzylaminopurines, on being heated at 230–260 °C with hexamethylphosphoric triamide and N,N',N''-tribenzylphosphoric triamide, respectively[6]. Actually, this is not a one-step synthesis since it involves, as a separate step, the preparation of the phosphoric triamides.

In the present communication, commercially available hypoxanthine **(1)** has been utilized as a starting material for the preparation of a series of N^6-substituted adenines **2a–h.** Hypoxanthine **(1)** is allowed to react with a number of pri-

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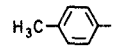
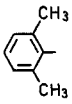
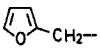
Table. N^6-Substituted Adenines **2** and **4** Prepared

Product No.	R in **2** or R' in **4**	R^2	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a] or Lit. m.p. [°C]
2a			83	276° (CH_3OH)	278–285°[7]
2b			55	280° (CH_3OH)[b]	242–243°[8]
2c			50	225° (CH_3OH)	$C_{12}H_{11}N_5$ (225.3)
2d			56	265° (C_2H_5OH)	$C_{11}H_8ClN_5$ (245.7)
2e			40	288–290° (CH_3OH)	$C_{13}H_{13}N_5$ (239.3)
2f			40	229° (C_6H_6)	228–230°[7]
2g			21	265° (C_2H_5OH)	266–267°[7]
2h			25	209–210° (CH_3OH)	210–211°[8]
4a	CH_3		65	223° (CH_3OH)	224–225°[10]
4b	$-(CH_2)_5-$		55	274° (C_6H_6)	274–275°[11]
4c	$-(CH_2)_2-O-(CH_2)_2-$		50	299–301° (C_6H_6)	301–303°[11]
4d	CH_3	CH_3	26[c], 8[d]	251–253° (C_6H_6)	251–253°[12]
3	—	—	40	290° (CH_3OH)	293°[9]

[a] Satisfactory microanalyses obtained: C ±0.40, H ±0.12, N ±0.51.

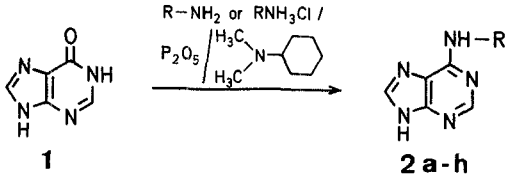
[b] Calc. C 63.98 H 4.92 N 31.09
Found 63.44 4.87 30.68

^{1}H-N.M.R. (DMSO-d_6): $\delta = 2.30$ (s, 3H); 3.43 (br s, 1H); 7.13 (d, 2H); 7.83 (d, 2H); 8.26 (s, 1H); 8.40 (s, 1H); 9.93 ppm (s, 1H).
M.S.: *m/e* (%) = 225 (M^+, 72), 224 (100).

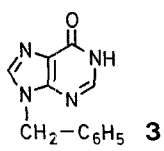
[c] From reaction of dimethylamine hydrochloride with hypoxanthine.

[d] From reaction of cyclohexylamine hydrochloride with hypoxanthine.

mary aromatic amines or amine hydrochlorides and phosphorus pentoxide in the presence of *N,N*-dimethylcyclohexylamine, and the oxo group in hypoxanthine (**1**) is then directly converted into the corresponding amino group. The reaction proceeded smoothly at 150°C within a 24 h reaction period. Attempts to work at higher temperatures for shorter reaction periods were, however, unsuccessful. This may be due to thermal instability of hypoxanthine which decomposes above 150°C.

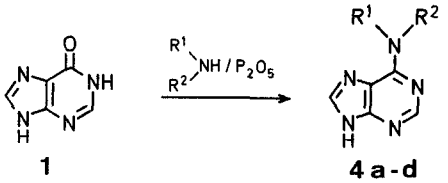


The reaction of hypoxanthine (**1**) with benzylamine hydrochloride under the same conditions, however, afforded 9-benzylhypoxanthine (**3**), probably through a simple alkylation reaction.



The N^6-benzyladenine (**2f**) could be successfully prepared by using the free base instead of the hydrochloride at 170°C. In a similar manner, the N^6-furfuryladenine (kinetin; **2g**) could be produced by allowing hypoxanthine (**1**) to react with furfurylamine and phosphorus pentoxide in presence of *N,N*-dimethylcyclohexylamine at 170°C.

The reaction of hypoxanthine (**1**) with secondary amines/phosphorus pentoxide reagents was found to take place readily affording the N^6-substituted adenines **4a–d.** Thus, **1** reacted with *N*-methylaniline, piperidine, and morpholine to give **4a–c**, respectively. The dimethylaminopurine (**4d**) was obtained using dimethylamine hydrochloride and phosphorus pentoxide in the absence of the tertiary base. Further, **4d** was found to be the sole product when hypoxanthine reacted with cyclohexylamine hydrochloride and phosphorus pentoxide in *N,N*-dimethylcyclohexylamine under similar conditions. However, when using the free base in place of the hydrochloride, the expected N^6-cyclohexyladenine (**2h**) could be obtained.



The identities of the compounds prepared were confirmed through melting point, I.R., N.M.R., and M.S. measurements.

Reaction of Hypoxanthine (1) with Primary Aromatic Amine Hydrochlorides; General Procedure:
Phosphorus pentoxide (11.4 g, 0.08 mol), *N,N*-dimethylcyclohexylamine (10.2 g, 0.08 mol) and the amine hydrochloride (0.08 mol), are mixed at room temperature and then heated on an oil bath at 150 °C until a clear homogeneous mixture is obtained. Hypoxanthine (**1**; 2.7 g, 0.02 mol) is added and the temperature is kept at 150 °C for 24 h with stirring. After cooling to 100 °C, 2 molar sodium hydroxide solution (200 ml) is added while cooling and the resulting alkaline solution is extracted with ether (2 × 100 ml). The aqueous phase is neutralized to pH 7 using 4 molar hydrochloric acid. If a precipitate is formed, it is filtered off, otherwise, the neutral solution is extracted with dichloromethane (2 × 150 ml) and the extract evaporated to dryness under reduced pressure. The products **2a–e** are then crystallized from suitable solvents (Table).

Reaction of Hypoxanthine (1) with Benzylamine, Furfurylamine, or Cyclohexylamine:
The freshly distilled amine (0.1 mol) is added dropwise, while cooling and stirring, to a mixture of phosphorus pentoxide (7.1 g, 0.05 mol) and *N,N*-dimethylcyclohexylamine (6.4 g, 0.05 mol). The mixture is then gradually heated to 170 °C and hypoxanthine (**1**; 2.7 g, 0.02 mol) is added and heating is continued at the same temperature for 24 h. The products **2f–h** (Table) are then obtained as described above.

Reaction of Hypoxanthine (1) with Secondary Amines:
The freshly distilled amine (0.1 mol) is added dropwise while cooling and stirring to phosphorus pentoxide (7.1 g, 0.05 mol) and then gradually heated to 170 °C. Hypoxanthine (**1**; 2.7 g, 0.02 mol) is added and the mixture is heated at the same temperature for 24 h. Then, the mixture is worked up as described above and the products **4a–c** (Table) are obtained.

Reaction of Hypoxanthine (1) with Dimethylamine Hydrochloride:
Phosphorus pentoxide (7.1 g, 0.05 mol) and dimethylamine hydrochloride (8.1 g, 0.1 mol) are mixed at room temperature and then heated to 150 °C. Hypoxanthine (**1**; 2.7 g, 0.02 mol) is added and the temperature is maintained at 150 °C for 24 h. The reaction mixture is worked up as before to give **4d** (Table).

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* Author to whom correspondence should be addressed.

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