A FACILE SYNTHESIS OF 6-CYANOPURINE BASES

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Received July 18, 1995
Accepted August 8, 1995

A facile method of preparation of 6-cyanopurine bases from commercially available 6-chloropurines is reported. The 6-chloropurines were selectively protected by THP-functions and the protected derivatives reacted smoothly with tetraethylammonium cyanide and DABCO to give 6-cyanopurine derivatives that were easily deprotected to afford the title compounds.

Cyanopurines are versatile starting materials for the preparation of many other C-substituted purines[1]. They are usually prepared by nucleophilic substitution of halo- or alkanesulfonylpurine derivatives. The first described method[2] involves cyanation of 6-iodopurines using cuprous cyanide in boiling pyridine and affords 6-cyanopurines in the yields of about 50%. Alkanesulfonylpurines react[3] with sodium or potassium cyanide in boiling DMF to give cyanopurines in somewhat better yields. The conversion of easily available 6-chloropurine derivatives to 6-cyanopurines by potassium cyanide in DMF with $Pd(PPh_3)_2Cl_2$ (ref.[4]) or *p*-toluenesulfinate[5] as catalyst was recently reported. The hitherto best preparative method reported by Herdewijn et al.[6] makes use of tetraethylammonium cyanide (TEACN) and trimethylamine at room temperature for the cyanation of protected 2-amino-6-chloropurine riboside to obtain the 6-cyano derivative in the yield of 80%. Except of the CuCN approach[2], these methods[3–6] can be used only for the cyanation of 9-alkyl- or 9-glycosylpurines that cannot form anions under the basic reaction conditions. No convenient method for the preparation of the 9-unsubstituted 6-cyanopurines from commercially available 6-chloropurines, has been yet published.

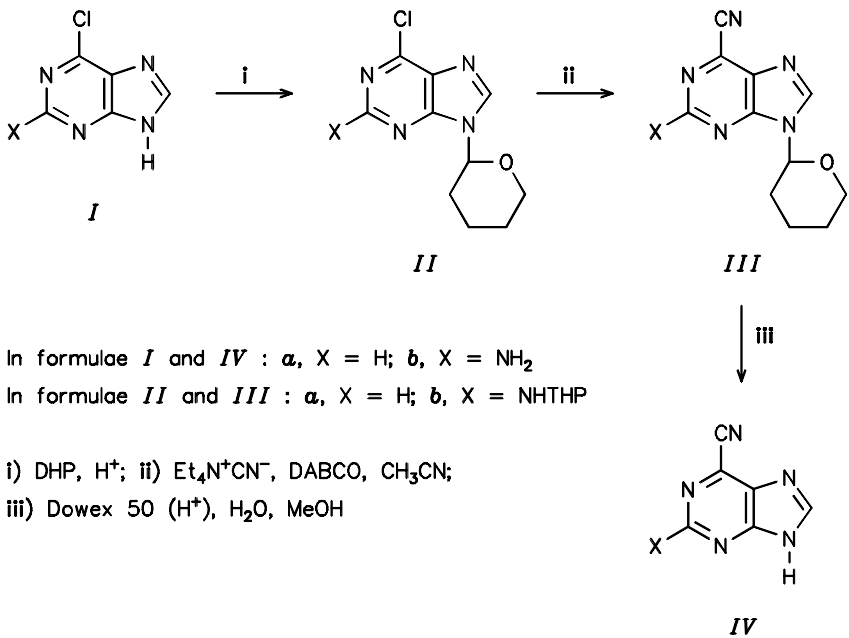
We report on a facile synthesis of 6-cyanopurine (*IVa*) and 2-amino-6-cyanopurine (*IVb*) from the corresponding 6-chloropurines *I* by a modification of the Herdewijn's method[6] (Scheme 1). TEACN is a very suitable reagent due to its good solubility in aprotic solvents. We have replaced trimethylamine originally used as an activator for this reaction by 1,4-diazabicyclo[2.2.2]octane (DABCO) that was recently reported[7] to be a good activator of hydrolysis or alcoholysis of 6-chloropurines.

We have tried to carry out the reaction in dry acetonitrile at room temperature using two equivalents of both DABCO and TEACN. In accord with our expectations the

9-unsubstituted chloropurines *I* were entirely unreactive under these conditions. Therefore we have introduced a suitable protective group at the 9-position, namely tetrahydropyran-2-yl (THP) that is easily cleavable at mild conditions. The THP-protected 6-chloropurine *IIa* was prepared by a known method[8] in 90% yield using 3,4-dihydropyran (DHP) and *p*-toluenesulfonic acid in ethyl acetate. For 2-amino-6-chloropurine (*Ib*) the reaction was carried out in DMF with hydrogen chloride as catalyst at 60 °C to give the *N*(2),9-bis-protected derivative *IIb* quite selectively with low amount of side-products only. The product *IIb* was isolated by column chromatography in the yield of 70%.

The protected 6-chloropurines *II* reacted with TEACN and DABCO at the above described mild conditions almost quantitatively. After removal of the excess of TEACN and DABCO by distribution between chloroform and water, the 6-cyanopurines *III* were isolated just by filtration of the organic layer through a short column of silica gel in the preparative yields of 84% and 81%, respectively. The THP-protecting groups were easily cleaved by heating with Dowex 50X8 (H^+) in methanol–water solution to give the title 6-cyanopurines *IV* in the yields of 95% and 94%, respectively.

In conclusion, 6-cyanopurine (*IVa*) and 2-amino-6-cyanopurine (*IVb*) can be prepared efficiently and selectively by this method in overall yield of 72% and 54%, respectively. For its high yields and very mild conditions this cyanation method could be suitable for further use in the synthesis of other cyano heterocycles.



SCHEME 1

EXPERIMENTAL

Unless otherwise mentioned solvents were evaporated at 40 °C/2 kPa; melting points were determined on Kofler block apparatus. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer (EI: 70 eV; FAB: Xe, 8 kV), ^{1}H NMR spectra (δ, ppm; *J*, Hz) on Varian Unity 500 (500 MHz) in hexadeuteriodimethyl sulfoxide, referenced to the nondeuterated solvent signal 2.5 ppm. TLC was performed on Silufol UV_{254} plates and column chromatography with silica gel (30 μm, Kavalier Votice, Czech Republic). 6-Chloropurine was purchased from Sigma (U.S.A.), 2-amino-6-chloropurine from Mack (Germany), TEACN and DABCO from Aldrich (Germany). Acetonitrile was distilled from CaH_2 prior to use.

6-Chloro-9-(tetrahydropyran-2-yl)purine (*IIa*)

This compound was prepared according to a known[8] method in 90% yield, m.p. 67–69 °C (ref.[8] 69–71 °C).

6-Chloro-2-(tetrahydropyran-2-yl)amino-9-(tetrahydropyran-2-yl)purine (*IIb*)

To a mixture of 2-amino-6-chloropurine (*Ib*; 1.0 g, 5.9 mmol) in DMF (50 ml), 5.7 M HCl in DMF (100 μl, 0.57 mmol) was added and the mixture was stirred at 60 °C for 5 min and then DHP (2.65 ml, 29.5 mmol) was added dropwise. The stirring was continued at 60 °C for 2 h and the solvent was evaporated. A column chromatography (80 g silica gel, chloroform) of the residue afforded the protected derivative *IIb* as yellowish oil that crystallized upon freezing. Yield 1.41 g (71%), m.p. 171–174 °C (dec.), R_F (ethyl acetate) 0.38. EI MS, *m/z* (rel.%): 337 (6) $[M]^+$, 253 (10) $[M + H - THP]^+$, 169 (60) $[M - 2\ THP]^+$, 85 (100) $[THP]^+$. ^{1}H NMR spectrum: 1.40–2.28 m, 12 H (CH_2); 3.45–4.01 m, 4 H (OCH_2); 5.15 m, 1 H and 5.52 m, 1 H (NCHO); 8.13 brs, 1 H (NH); 8.41 s, 1 H (H-8). For $C_{15}H_{20}ClN_5O_2$ (337.8) calculated: 53.33% C, 5.97% H, 20.73% N; found: 53.28% C, 5.97% H, 21.00% N.

Cyanation of the Protected 6-Chloropurines *II* – General Procedure

To a stirred solution of the 6-chloropurine derivative *II* (3 mmol), TEACN (940 mg, 6 mmol) in dry acetonitrile (30 ml) at –20 °C DABCO (672 mg, 6 mmol) was added and the resulting solution was allowed to stand overnight at room temperature. The solvent was evaporated, the residue was dissolved in chloroform (100 ml) and washed with water (2 × 50 ml). The organic layer was dried with $MgSO_4$ and evaporated. The residue was disolved in $CHCl_3$ (200 ml), filtered through a short column of silica gel (20 g) and evaporated to give the protected 6-cyanopurine *III* as oil.

6-Cyano-9-(tetrahydropyran-2-yl)purine (IIIa), yield 84%, m.p. 86–88 °C (precipitated from light petroleum), R_F (MeOH–$CHCl_3$ 1 : 9) 0.62. FAB MS, *m/z* (rel.%): 230 (27) $[M + H]^+$, 146 (61) $[M + H - THP]^+$, 85 (100) $[THP]^+$. ^{1}H NMR spectrum: 1.60–2.34 m, 6 H (CH_2); 3.73 m, 1 H and 4.02 m, 1 H (OCH_2); 5.82 dd, 1 H, *J* = 11.0, 2.2 (NCHO); 9.11 s, 1 H and 9.12 s, 1 H (H-2 and H-8). UV (MeOH), λ_{max} (ε): 288 nm (9 900). For $C_{11}H_{11}N_5O$ (229.2) calculated: 57.63% C, 4.84% H, 30.55% N; found: 57.81% C, 4.97% H, 30.30% N.

6-Cyano-2-(tetrahydropyran-2-yl)amino-9-(tetrahydropyran-2-yl)purine (IIIb), yield 81%, m.p. 168–170 °C (ether–light petroleum), R_F (ethyl acetate) 0.53. EI MS, *m/z* (rel.%): 328 (11) $[M]^+$, 244 (15) $[M - THP]^+$, 161 (70) $[M + H - 2\ THP]^+$, 85 (100) $[THP]^+$. ^{1}H NMR spectrum: 1.44–2.30 m, 12 H (CH_2); 3.47–4.01 m, 4 H (OCH_2); 5.16 m, 1 H and 5.57 m, 1 H (NCHO); 8.31 brs, 1 H (NH); 8.64 s, 1 H (H-8). UV (MeOH), λ_{max} (ε): 355 nm (7 200); 268 nm sh (900). For $C_{16}H_{20}N_6O_2$ (328.4) calculated: 58.52% C, 6.14% H, 25.59% N; found: 58.79% C, 6.11% H, 25.46% N.

Deprotection of the 6-Cyanopurines *III* – General Procedure

To a solution of the protected 6-cyanopurine derivative *III* (1 mmol) in methanol (40 ml), Dowex 50X8 (H^+) (2 g) and water (10 ml) were added and the mixture was refluxed for 1 h. After cooling to room temperature 35% aq. NH_3 (1 ml) was added, the suspension was filtered and the resin was washed with methanol (20 ml). The collected filtrates were evaporated to dryness to afford pure 6-cyanopurine *IV*.

6-Cyanopurine (IVa), yield 95%, m.p. 167–170 °C (toluene) (ref.[2a] 177–178 °C), R_F (MeOH–$CHCl_3$ 1 : 9) 0.17. EI MS, *m/z* (rel.%): 145 (100) $[M]^+$. ^{1}H NMR spectrum: 8.65 s, 1 H (H-8); 9.04 s, 1 H (H-2). UV (MeOH), λ_{max} (ε): 288 nm (6 900). For $C_6H_3N_5$ (145.1) calculated: 49.66% C, 2.08% H, 48.26% N; found: 49.22% C, 2.08% H, 47.98% N.

2-Amino-6-cyanopurine (IVb), yield 94%, decomp. > 300 °C (ref.[2b] m.p. > 300 °C), R_F (MeOH–$CHCl_3$ 1 : 4) 0.47. EI MS, *m/z* (rel.%): 160 (100) $[M]^+$. ^{1}H NMR spectrum: 6.93 brs, 2 H (NH_2); 8.32 s, 1 H (H-8); 13.10 brs, 1 H (NH). UV (MeOH), λ_{max} (ε): 355 nm (4 500); 266 nm sh (700). For $C_6H_4N_6$ (160.1) calculated: 45.00% C, 2.52% H, 52.48% N; found: 45.24% C, 2.49% H, 52.72% N.

This work was supported by the Grant No. 455407 of the Grant Agency of the Czech Academy of Sciences, by the Grant No. 203/93/0118 of the State Grant Agency of the Czech Republic and by Gilead Sciences (Foster City, CA, U.S.A.). The authors thank Dr M. Masojidkova of our Institute for measuring and interpretation of NMR spectra.

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Note Added in Proof

After submission of this manuscript a paper by Estep et al. has appeared[9] reporting the preparation of the compound *IIIa* from *IIa* in 32% yield using potassium cyanide in DMSO.