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SYNTHESIS OF 9-HYDROXYPURINES: INTERMEDIATES TO NOVEL ANTIVIRAL ACYCLONUCLEOSIDES

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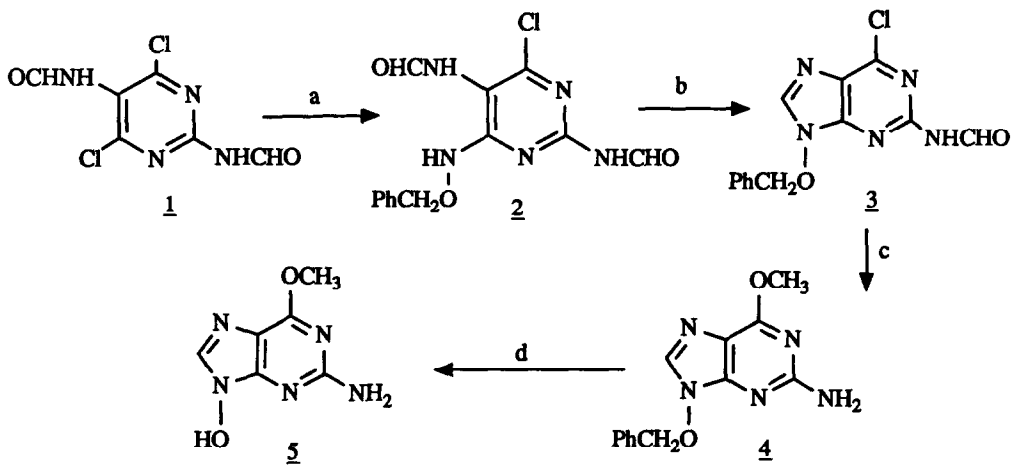
ABSTRACT: Synthetic approaches to 2-[(bis-t-butoxycarbonyl)amino]-9-hydroxy-6-methoxypurine (7) and 9-hydroxy-6-phthalimidopurine (15) are described. These 9-hydroxypurines are useful intermediates in the synthesis of 9-alkoxyguanine and 9-alkoxyadenine derivatives as potential antiviral agents.

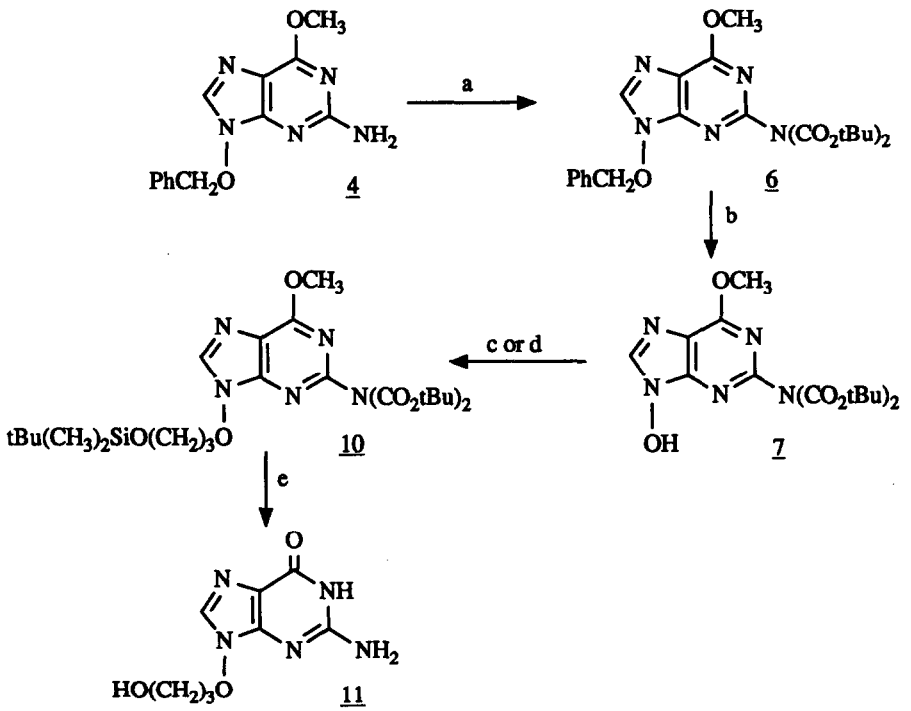
As part of our continuing studies on the preparation and antiviral evaluation of 9-hydroxyalkoxypurines,[1-3] we report the synthesis and use of novel 9-hydroxypurine intermediates. Previously we have reported the synthesis of 9-hydroxyalkoxyguanines such as the potent anti-herpesvirus agent 11 (BRL44385),[1,3] via either an imidazole intermediate or a suitably functionalised pyrimidine. Although the latter approach is a significant improvement on the original imidazole route, the acyclic substituent is introduced at an early stage, requiring duplication of a number of synthetic steps for each analogue. We rationalised that a more efficient strategy would be via the coupling of a suitably functionalised 9-hydroxypurine with protected alcohols under Mitsunobu conditions or halides under base catalysed conditions. Since direct synthesis of 9-hydroxypurines by oxidation of the corresponding purine is unknown, they were prepared via 9-benzyloxypurines using the pyrimidine intermediates described previously.[3]



Reagents; (a) $PhCH_2ONH_2$, iPr_2EtN, Diglyme. (b) (i) $(EtO)_2CHOAc$, 120°C, (ii) NH_3, MeOH. (c) NaOMe, MeOH. (d) 10% Pd/C, H_2, EtOH.

Reaction of the 4,6-dichloropyrimidine 1[3] with benzyloxyamine in the presence of diisopropylethylamine and diglyme at 100°C afforded the alkoxyaminopyrimidine 2. Crude 2 was heated with diethoxymethyl acetate at 120°C, followed by treatment with methanolic ammonia to afford the purine 3 in 40% overall yield from 1. Reaction of 3 with methanolic sodium methoxide at reflux temperature resulted in simultaneous displacement of the 6-chloro group and deformylation of the 2-amino function to afford the purine 4 in 60% yield after column chromatography on silica gel. Catalytic hydrogenolysis of 4 with 10% Pd on charcoal then gave the 9-hydroxypurine 5 in 95% yield. δ_H [$(CD_3)_2SO$] 3.95 (3H, s, CH_3), 6.45 (2H, br.s, D_2O exchangeable, NH_2), 7.93 (1H, s, H-8), 11.75 (1H, br.s, D_2O exchangeable, OH). Found: M^+181.0594. $C_6H_7N_5O_2$ requires: M^+181.0596.

Compound 5 underwent O-alkylation under base catalysed conditions (K_2CO_3/DMF) with 2,2-dimethyl-5-iodomethyl-1,3-dioxan[4] in 70% yield. Also, we required 5 to couple with alcohols under Mitsunobu conditions[5]; however, this was not achieved. This lack of reaction was possibly owing to the poor solubility of 5 in suitable solvents; therefore, the more soluble N,N-bis-t-butoxycarbonyl derivative of 5 was synthesized.



Reagents: (a) $(tBuO_2C)_2O$, DMAP, THF. (b) 10% Pd/C, H_2. (c) $^tBu(CH_3)_2SiO(CH_2)_3OH$ (8), PPh_3, DEAD, THF. (d) (i) NaH, DMF, 60°C; or K_2CO_3, DMF, RT. (ii) $^tBu(CH_3)_2SiO(CH_2)_3Br$ (9). (e) 5M HCl, EtOH, reflux.

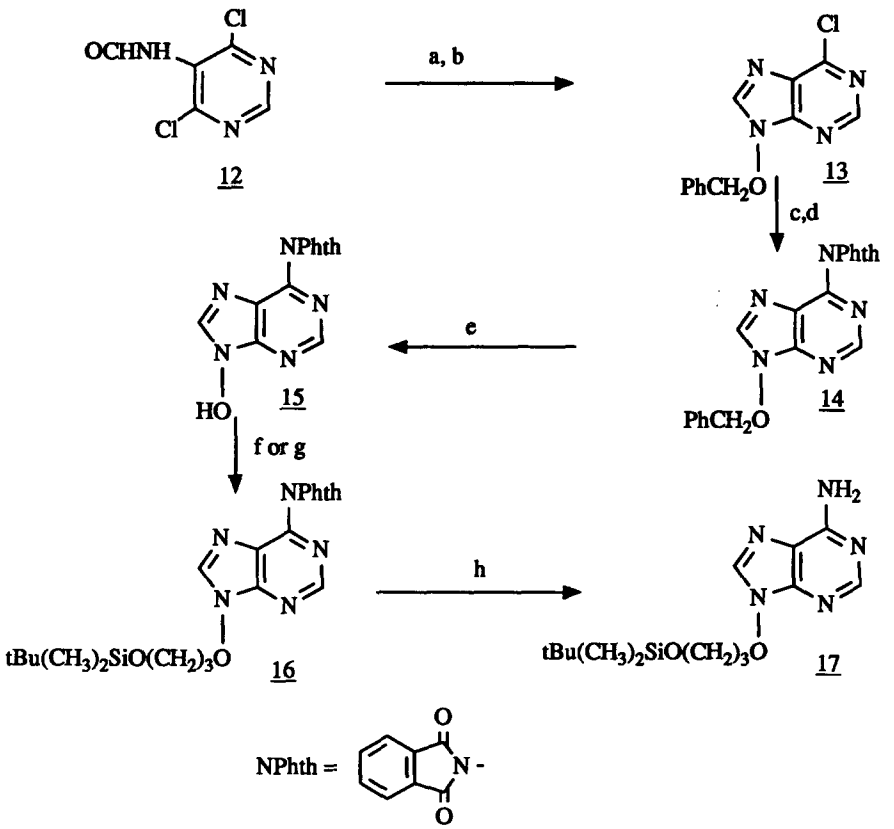
Reaction of 4 with di-t-butyl dicarbonate and 4-dimethylaminopyridine in refluxing tetrahydrofuran

afforded the 2-(bis-t-butoxycarbonyl)amino derivative 6 in 80% yield after column chromatography on silica gel. Hydrogenolysis of 6 in the presence of 10% Pd on charcoal then gave the 9-hydroxypurine 7 in 95% yield. δ_H [$(CD_3)_2SO$] 1.40 (18H, s, 6xCH_3), 4.05 (3H, s,OCH_3), 8.05 (1H, s, H-8), 11.80 (1H, br.s, D_2O exchangeable, OH). Found: C, 50.27; N, 6.12; N, 17.70%. $C_{16}H_{23}N_5O_6$.0.25 EtOH requires: C, 50.42; H, 6.23; N, 17.66%.

Under Mitsunobu conditions, 7 was found to undergo coupling with the protected alcohol 8[6] to afford the 9-alkoxypurine 10 in 89% yield. Base catalysed alkylation of 7 with the alkyl halide 9[7] in the presence of sodium hydride or potassium carbonate afforded 10 in 77% and 80% yield, respectively.

9-Alkoxypurines such as 10 have been converted to the corresponding guanine derivatives by treatment with refluxing 5N hydrochloric acid in ethanol (10 gave 11 in 60% yield) or bromotrimethylsilane in either dichloromethane or N,N-dimethylformamide (in up to 80% yield).

Using related chemistry the 9-alkoxy adenine precursor 9-hydroxy-6-phthalimidopurine (15) has been synthesized.



Reagents: (a) $PhCH_2ONH_2$, iPr_2EtN, Diglyme. (b) $(EtO)_3CH$, 12M HCl, DMF. (c) NH_3, MeOH. (d) o-$C_6H_4(COCl)_2$, DMAP, Et_3N, THF. (e) 10% Pd/C, H_2, EtOH. (f) $^tBu(CH_3)_2SiO(CH_2)_3OH$ (8), PPh_3, DEAD, THF. (g) (i) NaH, DMF. (ii) $^tBu(CH_3)_2SiO(CH_2)_3Br$ (9). (h) CH_3NHNH_2, CH_2Cl_2.

Reaction of the 4,6-dichloropyrimidine[3] 12 with benzyloxyamine and diisopropylethylamine in diglyme at 100°C afforded crude alkoxyaminopyrimidine. Ring closure to the imidazole by treatment with triethyl orthoformate and 12M hydrochloric acid gave the purine 13 in 48% overall yield. Treatment of 13 with ammonia in methanol at 100°C afforded the corresponding adenine derivative in 87% yield, which was reacted with phthaloyl dichloride, 4-dimethylaminopyridine and triethylamine in tetrahydrofuran at 0°C to give the 6-phthalimidopurine 14 in 49% yield. Catalytic hydrogenolysis of 14 with 10% Pd on charcoal then afforded the 9-hydroxypurine 15 in 83% yield. δ_H [$(CD_3)_2SO$] 8.15 (4H, s, C_6H_4), 8.95 (1H, s, H-2), 9.15(1H, s, H-8), 12.80(1H, br.s, D_2O exchangeable, OH). Found: C,55.34, H, 2.58; N, 24.56%. $C_{13}H_7N_5O_3$ requires: C, 55.51; H, 2.51; N, 24.91%.

Under Mitsunobu conditions, 15 reacted with alcohol 8 in tetrahydrofuran at 0°C to afford the 9-alkoxypurine 16 in 70% yield. Alkylation of 15 with the alkyl halide 9 (NaH, DMF, 60°C) gave 16 in 85% yield. Facile removal of the phthalimido group of 16 using methylhydrazine in dichloromethane then afforded the adenine derivative 17 in 85% yield. Deprotection of the acyclic substituent can be carried out under standard conditions.

This approach to 9-alkoxyguanines and 9-alkoxyadenines has proved to be efficient and applicable to the synthesis of a number of potential antiviral agents. Further examples of the use of these intermediates will be given in subsequent publications.

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