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Synthesis of Two 6-N-Protected 9-N-Vinyladenines as Dipolarophiles in the Synthesis of Modified Nucleosides

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SYNTHESIS OF TWO 6-*N*-PROTECTED 9-*N*-VINYLADENINES AS DIPOLAROPHILES IN THE SYNTHESIS OF MODIFIED NUCLEOSIDES

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Abstract: A new class of potential antiviral drugs is represented by isoxazolidine nucleosides. The paper reports on the synthesis of protected adenines useful as dipolarophiles in the preparation of analogues of dideoxyadenosine by 1,3-dipolar cycloaddition processes.

9-*N*-vinyl derivatives of DNA nucleobases have been employed in the preparation of polymeric materials[1] or in the preparation of nucleoside analogues with potential therapeutic applications.[2,3]

In the latter case the 1,3-dipolar cycloaddition approach of methylene nitrones has been exploited.[3] In a peculiar application, the *aza* analogue of dideoxythymidine **3** (scheme 1) was obtained in fairly good yield, and it has shown biological activity *in vitro*.[4]

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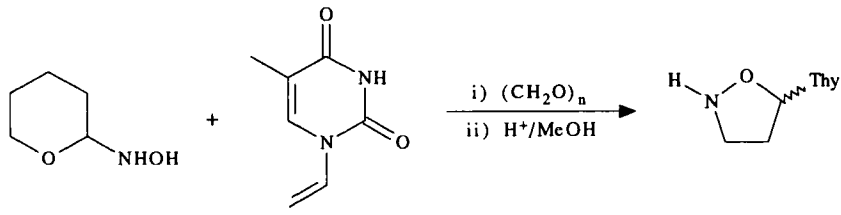


1 **2a** **3**

SCHEME 1

The synthesis of **3** in the presence of paraformaldehyde can be accomplished without the concomitant formation of side products. The satisfactory result obtained with **3** has prompted the exploitation of the preparation of other nucleoside analogues, e.g. those derived from adenine nucleobase. Unfortunately when the protocol of scheme 1 was applied to 9-*N*-vinyladenine[1] (**2d**), using various hydroxylamines,[5] the main products of the cycloaddition processes showed the presence of hydroxymethyl derivatives due to the concomitant interaction of **2d** with formaldehyde. Hydroxymethylation of DNA and nucleosides was known[6] however it did not occur when **3** was produced.

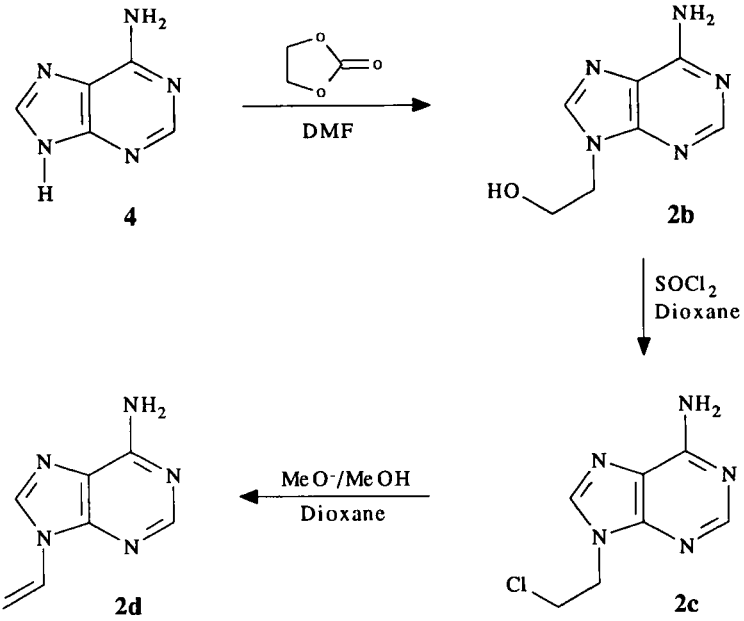
There was a need, therefore, to protect the nucleobase if purine analogues of **3** had to be obtained. Acid and base labile protection systems have been therefore planned.

9-*N*-vinyladenine (**2d**) can be obtained in three steps as reported[1] (scheme 2).

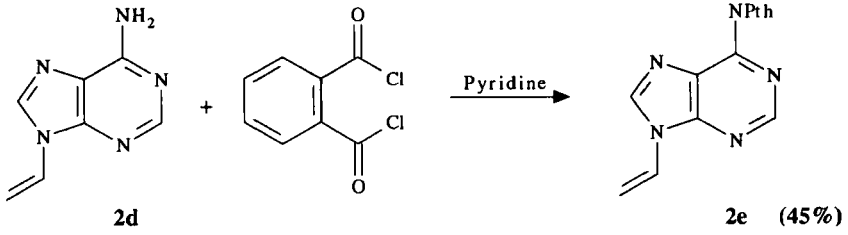
The direct protection of adenine (**4**) was excluded to avoid possible formation of mixture of products. Accordingly, the introduction of the base labile phtaloyl group was performed on **2d** (scheme 3).

The phtaloyl protection has proved successful in the synthesis of polynucleotides.[7]

A different approach was used for the introduction of the acid labile dimethoxytrityl group in the same position.



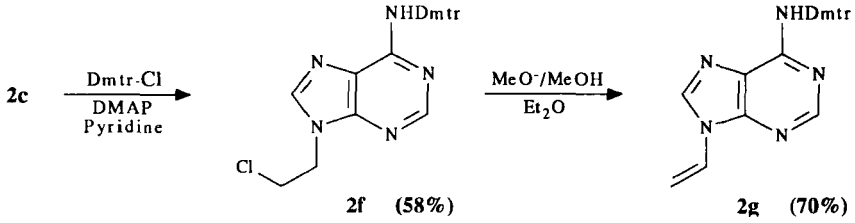
SCHEME 2



SCHEME 3

It was thought that **2c** (scheme 2) was a suitable starting material, since **4** and **2b** could undergo competitive interaction with the tritylating agent, whereas **2d** could give problems due to the formation of a stabile carbocation in the presence of an electron rich double bond.

The required derivative was therefore obtained according to scheme 4; **2g** was obtained with satisfactory yield.



SCHEME 4

The vinyl derivatives of protected adenine **2e** and **2g** could prove effective in the obtainment, by 1,3-dipolar cycloaddition processes, of analogues of dideoxyadenosine whose effectiveness as an anti-HIV drug is hampered by its lack of stability in acidic media.[8]

EXPERIMENTAL

All melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

^{1}H NMR spectra were measured at 300 MHz on a Bruker AC 300 spectrometer as dilute solutions in deuterochloroform. The chemical shifts are reported in ppm relative to an internal tetramethylsilane standard. All coupling constants *J* are reported in Hz.

Mass spectra were recorded on a Fisons Vacuum Generators ZAB-2F spectrometer, from a 2 µl of 3-nitrobenzylalcohol/sample mulls, by fast atom bombardment (FAB) with a neutral xenon beam of 8 KeV and a neutral current of ca. 10 µA.

Flash-column short-chromatography was performed on Merck Kieselgel 60H without gypsum and all chemical reactions were monitored by thin layer chromatography using Merck silica gel 60-F_{254} precoated aluminium plates.

All organic solvents and reagents were purified by the accepted literature procedures.

Synthesis of 9-*N*-vinyl-6-*N*- phtaloyladenine (2e)

Phtaloyl chloride (0.63 cm^3, 4.34 mmol) was added dropwise to a magnetically stirred solution of 9-*N*-vinyladenine[1] (**2d**) (500 mg, 3.1 mmol) in dry pyridine (30 cm^3) and the reaction was monitored by TLC (AcOEt-EtOH 80:20 v/v, as eluent system). After 2 h. at room temperature the reaction mixture was quenched with ice (1 g) and extracted with ethyl acetate (3x15 cm^3). The organic extracts were washed with brine (2x30 cm^3), dried and evaporated to dryness. Chromatographic purification of the recovered crude product yielded **2e** (410 mg, 45%). Mp 205-207 °C; ^{1}H NMR: δ 9.11 (1H, s, H-purine), 8.39 (1H, s, H-purine), 8.05 (2H, m, H_a-Pht), 7.87 (2H, m, H_b-Pht), 7.35 (1H, dd, *J* 9.1 and 16.0, 1'-CH), 6.05 (1H, dd, *J* 1.8 and 16.0, 2'-CH_2) and 5.33 (1H, dd, *J* 1.8 and 9.1, 2'-CH_2); FAB MS (+): *m/z* 292 [$(M+H)^+$, 100%] and 266 (3.5).

Synthesis of 9-*N*-(2'-chloroethyl)-6-*N*-dimethoxytrityladenine (2f)

Dimethoxytrityl chloride (720 mg, 2.12 mmol) was added portionwise to a solution of 9-*N*-(2'-chloroethyl)adenine[1] (**2c**) (350 mg, 1.77 mmol) in dry pyridine (20 cm^3) containing 4-dimethylaminopyridine (DMAP; 26 mg, 0.21 mmol), under magnetic stirring at room temperature. After complete conversion of the starting material (TLC: $CHCl_3$-MeOH 90:10 v/v, as eluent system), the reaction mixture was treated with distilled water (20 cm^3) and extracted with diethyl ether (5x5 cm^3). The organic extract was dried then evaporated to dryness and the chromatographic purification of crude product yielded **2f** as a glass solid (512 mg, 58%). ^{1}H NMR: δ 8.06 (1H, s, H-purine), 7.82 (1H, s, H-purine), 7.19-7.28 (8H, m, H-Ar), 6.97 (1H, s, 6-NH), 6.75-6.83 (5H, m, H-Ar), 4.49 (2H, t, 2'-CH_2), 3.77 (6H, s, OCH_3) and 3.38 (2H, t, 1'-CH_2); FAB MS (+): *m/z* 499 [$(M+H)^+$, 20%], 498(27), 436(1.5), 422(2.8), 392(1.7) and 303(100).

Synthesis of 9-*N*- vinyl-6-*N*- dimethoxytrityladenine (2g)

A 10% methanolic solution of sodium methoxyde (0.93 cm^3) was added dropwise to a magnetically stirred solution of **2f** (350 mg, 0.76 mmol) in dry diethyl ether (12 cm^3) and the resulting mixture was kept at room temperature for 20 hrs., monitoring the conversion of **2f** by TLC ($CHCl_3$-MeCN 85:15 v/v, as eluent system). Distilled water (15 cm^3) was added and the organic layer was extracted with brine (2x10 cm^3), dried and evaporated to dryness to obtain pure **2g** as a glass solid (247 mg, 70%).

^{1}H NMR: δ 8.11 (1H, s, H-purine), 7.90 (1H, s, H-purine), 7.27-7.37 (8H+1H, m, H-Ar and 1'-CH), 6.98 (1H, s, 6-NH), 6.74-6.86 (5H, m, H-Ar), 5.83 (1H, dd, *J* 2.0 and 17.6, 2'-CH_2), 5.13 (1H, dd, *J* 2.0 and 8.8, 2'-CH_2) and 3.79 (6H, s, OCH_3); FAB MS (-): *m/z* 462 [$(M-H)^-$, 100%] and 436(86).

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