SYNTHESIS OF 2-FORMYLADENOSINE USING DIETHOXYACETONITRILE AS A SYNTHON

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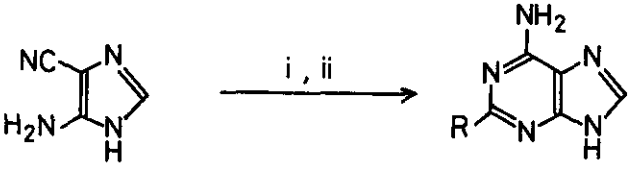
Abstract — Diethoxyacetonitrile has been utilized for the effective synthesis of adenine derivatives as a synthon. Novel 2-formyladenine (2b) and 2-formyladenosine (5b) have been prepared in high yields starting from AICN (1) and AICNR (4b), respectively.

It has been recently disclosed that some of the naturally occurring and synthetic nucleosides containing a formyl group in the base moiety have been found to be potent inhibitors of various enzymes, and recognized as an important class of biologically active nucleosides. Polyoxin N,[1] neopolyoxin A,[2] nikkomycin X[3] and B[4] are all known to be inhibitors of fungal cell wall chitin synthetase. Synthetic 5-formyl-2'-deoxyuridine and 5-formyluracil of microbial origin are strong inhibitors of thymidylate synthetase[5] and xanthine oxidase,[6] respectively. Therefore, it is interesting to introduce a formyl group to a purine nucleus from a point of view of medicinal and heterocyclic chemistry.[7]

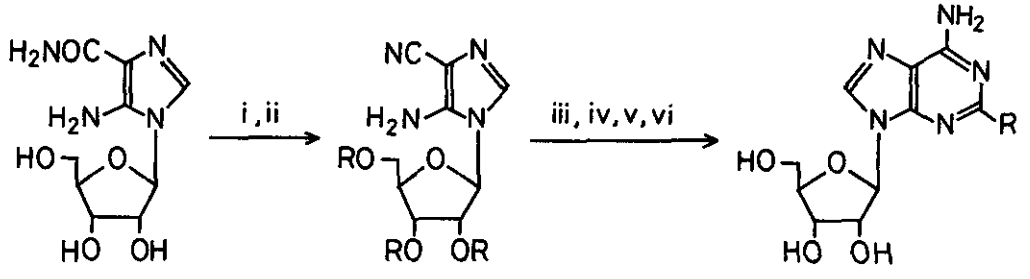
We wish to report here an efficient methodology for the preparation of 2-formyladenine and -adenosine using diethoxyacetonitrile, imidazole derivatives 1 and 3. Although a great deal of synthetic study on various 2-substituted purine nucleosides has been reported,[8] there is no report concerning the preparation of 2-formylpurine, and conversion of 2-alkylpurine[8] to the corresponding formyl derivative by selective oxidation seems to be difficult. On the other hand, we have already reported the synthesis of 2-formylpyrimidine derivative as an essential intermediate in the total synthesis of bleomycin aglycone,[9,10] and also developed a facile route to 3-formyltriazole nucleoside.[11] These studies revealed that diethoxyacetonitrile is an efficient synthon for introduction of a formyl group to heterocycles. Thus, the ring closure of 5-aminoimidazole-4-carbonitrile (1, AICN) and 5-amino-1-β-D-ribofuranosylimidazole-4-carbonitrile (4b, AICNR) to purine derivatives was investigated in detail using diethoxyacetonitrile as the



1 (AICN)

2 a R = $CH(OEt)_2$
2 b R = CHO

i ; $(EtO)_2CHC(=NH)-OMe$ (2 eq), AcOH (1.1 eq), MeOH (94 %)
ii ; AcOH – H_2O – acetone (1 : 2 : 3), 80 °C (91 %)



3 (AICAR)

4 a R = Ac
4 b R = H (AICNR)

5 a R = $CH(OEt)_2$
5 b R = CHO
5 c R = CH=NOH
5 d R = CN

i ; Ac_2O, 4-dimethylaminopyridine, Et_3N; $POCl_3$, Et_3N (60–70 %)
ii ; NaOMe (quant.)
iii ; $(EtO)_2CHCN$ (4 eq), NaOBu (2 eq), BuOH–pyridine, 120 °C (90 %)
iv ; 10 % aq AcOH, 90 °C (96 %)
v ; $NH_2OH \cdot HCl$, NaOAc (82 %)
vi ; Ac_2O, 4-dimethylaminopyridine, Et_3N (87 %) ; 0.1 N NaOH, MeOH (85 %)

ring closing agent, since such starting materials, 1 and 4b, are now available from 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (3, AICAR)[8] as a microbial product. Diethoxyacetonitrile[12] was easily converted to the corresponding imidate[13] (NaOMe, 0.1 eq in MeOH). The imidate was directly treated with 1. It was found that the addition of acetic acid was crucial for condensation. The yield of the cyclized product 2a was only around 40% in the absence of acetic acid, but smooth cyclization took place in the presence of acetic acid. To a solution of the imidate (2eq) in methanol, 1 (1 eq) and AcOH (1.1 eq) were added in that order and crystalline 2a deposited in 15 min. Colorless needles of 2-diethoxymethyladenine 2a[14] were obtained in 94% yield by filtration of the crystals and purification of the mother liquid (chromatography on silica gel, eluted with CH_2Cl_2:MeOH=6:1), showing mp 218-220°C (recrystallized from $CHCl_3$-MeOH). The acetal 2a was smoothly hydrolyzed by heating at 80°C for 4 h in AcOH-H_2O-acetone (1:2:3), affording a white solid of 2b (mp 300°C, dec. M^+ 163) in 91% yield. 2-Formyladenine (2b)[14] exhibited infrared carbonyl absorption at 1703 cm^{-1} (KBr) and formyl proton resonance at δ 9.75 on ^{1}H-NMR spectrum (DMSO-d_6, TSP).

Next, our approach was extended to the synthesis of the corresponding nucleoside system. AICNR (4b) was prepared from AICAR (3) by slight modification of the known procedures;[15,16] (1) acetylation of the ribofuranosyl moiety (Ac_2O, 4-dimethylaminopyridine, and Et_3N), (2) dehydration of the carbamoyl group into nitrile ($POCl_3$, Et_3N), and (3) removal of the acetyl group (NaOMe). Although acetic acid facilitated the formation of the purine ring in the above case, the same procedure was not applicable to 4b, affording only a few percent of the desired adenosine derivative 5a. However, a satisfactory result was obtained under a basic condition. To a solution of AICNR (4b) (1 eq) and diethoxyacetonitrile (4 eq) in n-BuOH-pyridine (4:3), sodium butoxide (2 eq) dissolved in n-BuOH was added gradually. The mixture was heated at 120°C for 10 min and neutralized with AcOH after cooling to the ambient temperature. Removal of the solvent gave a brown-red syrup which was chromatographed on silica gel (eluted with CH_2Cl_2:MeOH=9:1) to give a pale yellow foam of 2-diethoxymethyladenosine (5a)[14] in 90% yield. Acetal 5a was converted into 2-formyladenosine (5b) in 96% yield by heating at 90°C for 1 h in 10% aqueous AcOH. Infrared carbonyl band of 5b appeared at 1710 cm^{-1} (KBr) and its formyl proton at δ 9.85 on ^{1}H-NMR spectrum (DMSO-d_6, TSP). The aldehyde 5b was further converted into the oxime 5c,[14] mp 146-150°C (dec), and nitrile 5d,[14] mp 194-197°C (dec), by the following procedure;

(1) oximation with NH_2OH to give 5c, (2) dehydration of the oxime (Ac_2O, 4-dimethylaminopyridine, and Et_3N), and (3) deacetylation (0.1 N NaOH in MeOH) to give 5d. All of the compounds 5a-d showed anomeric proton resonances at δ 5.9-6.0 on ^{1}H-NMR, indicating anti-conformation[17] presumably due to the steric effect of the C-2 substituents.

The research results described here provide a basis for further synthetic utilization of diethoxyacetonitrile and an access to potentially useful analogues of various nucleosides having a formyl group in the base moiety.

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