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An entry to new isoxazoline analogues of dideoxynucleosides by bromonitrile oxide 1,3-dipolar cycloaddition

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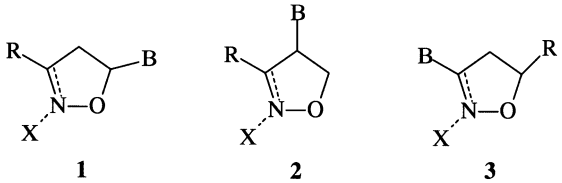
Abstract—A short and efficient synthesis of new isoxazolinyl nucleosides bearing the nucleobase at the 3-position is reported. The synthetic approach relies upon the 1,3-dipolar cycloaddition of bromonitrile oxide to allyl benzoate and subsequent substitution of the bromine by the nucleobase.

Saturated and unsaturated 2′,3′-dideoxynucleosides containing different functionalities and lacking the 3′-hydroxyl group are expected to terminate DNA synthesis after incorporation into the chains.[1] Due to this effect nucleoside analogues in which the furanose ring has been replaced by a different carbo- or heterocyclic ring have attracted special interest by virtue of their biological action as antiviral and anticancer agents.[2] Among them isoxazolidine and isoxazoline nucleosides are emerging as an important class of dideoxynucleoside analogues with potential pharmacological activity. Thus, during the last decade several synthetic approaches to isoxazolidine and isoxazoline nucleosides have been reported.[3] For the construction of the heterocyclic ring the well known convenient 1,3-dipolar cycloaddition approach has been applied in most cases. Regarding the attachment of the nucleobase, two alternatives are followed, either before or after the formation of the heterocyclic ring. In the first case the products are obtained from the reaction of nitrile oxides or nitrones with appropriately designed vinyl derivatives of pyrimidine and purine nucleobases. In the second case, the cycloaddition takes place between the dipole and an alkene bearing a suitable leaving group which undergoes further nucleophilic substitution by the base. In both cases the well established regioselectivity of 1,3-dipolar cycloaddition reactions leads to the formation of products of the general type **1**, in which the base is located at the 5-position of the ring next to the oxygen atom. However, to the best of our knowledge nothing is known about the synthesis of isoxazolidine or isoxazoline nucleosides of types **2** and **3** in which the base is attached to the 3- or 4-positions of the ring (Scheme 1).

In this paper and in connection with our former studies on cycloaddition reactions[4] we wish to report the synthesis of isoxazolin-3-yl nucleosides of type **3** applying a new 1,3-dipolar cycloaddition approach. As appropriate dipole and dipolarophile we chose bromonitrile oxide and a protected allyl alcohol respectively. The bromonitrile oxide introduces a bromine at the 3-position of the ring, which can serve as a leaving group for further substitution by the base. It should be mentioned that in several synthetic schemes in which bromonitrile oxide is used as a key intermediate, the bromine in the 3-bromoisoxazolines obtained is substituted readily by oxygen nucleophiles, although there is no report about nitrogen nucleophiles.[5]

The use of an allyl alcohol derivative as the dipolarophile ensures the presence of a 5-hydroxymethyl group in the final product, which potentially allows enzymatic phosphorylation for antiviral expression or incorporation into automatic solid-phase synthesis.



Scheme 1.

Keywords: bromonitrile oxide; dipolar cycloaddition; isoxazolines; dideoxynucleoside analogues.

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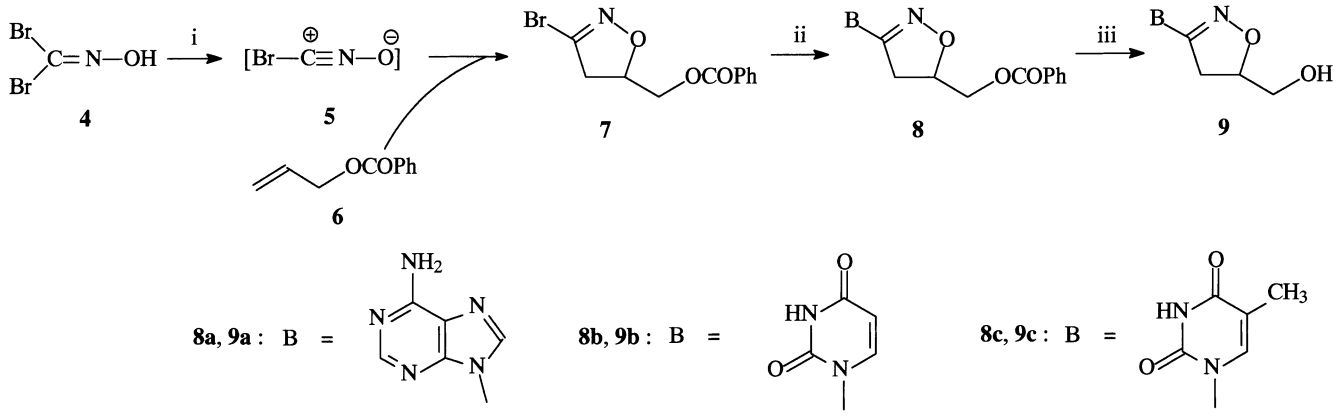


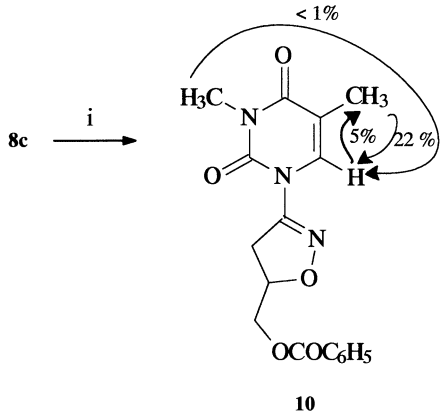
Scheme 2. *Reagents and conditions*: (i) K_2CO_3, EtOAc, rt, 24 h, 92%; (ii) B, NaH, DMF, 90°C, 3 days, 60–70%; (iii) KOH, $MeOH/H_2O$, rt, 10 h, 85–90%.

Thus bromonitrile oxide **5**, derived in situ from the aldoxime **4**, was added regioselectively to the ester **6** to give the bromoisoxazoline **7**. In accordance with analogous cycloadditions of **5** referred to in the literature,[5] the reaction was regioselective and the 5-isomer was obtained, after purification, as the sole product in high yield (92%), although the ^{1}H NMR of the crude reaction mixture showed contamination by traces of the 4-isomer. For the next step, the nucleophilic substitution, the nucleobases adenine, uracil and thymine were tested under several reaction conditions usually employed in glycosylation procedures. The use of silylated bases or phase-transfer catalysts such as tris[2-(2-methoxyethoxy)ethyl]amine, applying several reaction times and temperatures was unsuccessful. Finally, coupling of the bases was achieved using the sodium salts of the bases prepared with sodium hydride in DMF and the isoxazoline nucleosides **8** were obtained in satisfactory yields (60–70%). These were further hydrolyzed to the hydroxy derivatives **9** following standard alkaline hydrolysis procedures (Scheme 2).

All the product structures were supported by their spectral and analytical data. From the spectral data the attachment of the base to the isoxazoline ring was clear. Mass spectrometry gave molecular ions corresponding to 1:1 adducts of the base with the isoxazoline ring. ^{1}H and ^{13}C NMR spectra contained all the expected characteristic chemical shifts corresponding to both moieties.[6] The only point, which probably needed further clarification was the site of attachment. The adenine anion is known to react primarily with electrophiles at N9.[7] Previously, the ^{13}C assigned chemical shifts of several substituted methyladenines have been used as model compounds for the identification of the site of attachment of other adenine derivatives.[8] The resemblance of the ^{13}C chemical shifts of compounds **8a** and **9a** with those of 9-methyladenine supported N9 substitution in accordance with the expected reaction pathway for the adenine anion.

Pyrimidine anions are less regioselective in their reactions with several electrophiles. Thus, alkylation of uracil and thymine can generally occur at the N1 as well as the N3 positions although alkylation at N1 predominates.[9] The structure of the isomers can be differentiated on the basis of the coupling constants between H-C5 and H-N3 of 1-substituted uracils and between H-C6 and H-N1 of 3-substituted thymines and uracils in their ^{1}H NMR spectra. In low concentrations of very pure samples the couplings between H-C6 and H-N1 and between H-C5 and H-N3 can be observed and have been measured to be 6 Hz and 2 Hz, respectively.[10] In our case it was possible to see a coupling of 2 Hz between H-C5 and H-N3 of compound **8b**. Thus, in the ^{1}H NMR spectra of an analytically pure sample of compound **8b**, H-C5 and H-C6 appear at δ 5.8 as a doublet of doublets ($J=7.8$, 2.0 Hz) and at 7.87 as a doublet ($J=7.8$ Hz), respectively. The presence of a coupling constant between H-C5 and NH and the absence of such a coupling for H-C6 supports the N1 substitution.

In order to confirm the site of attachment for the thymine derivatives we prepared the methyl derivative **10** and performed NOE measurements as depicted in Scheme 3. The lack of any essential increase of H-C6 upon saturation of N-CH_3 is in accordance with the 3 N-CH_3 and 1N isoxazoline positions. If the isoxazoline ring was on the 3-position methylation should occur at



Scheme 3. *Reagents and conditions*: (i) CH_3I, NaH, DMF, 50°C, 48 h, 70%.

N1 and saturation of the N-CH_3 should cause a strong NOE increase of H-C6 almost equal with that observed upon saturation of the 6-CH_3.

In conclusion, new isoxazoline dideoxynucleoside analogues have been prepared applying a simple and short procedure. It is also worth noting that the established replacement of the bromine by nitrogen nucleophiles in the bromonitrile oxide cycloadducts extends the scope of its use as a key intermediate in synthesis. Further work on the synthesis of other isoxazoline analogues is in progress.

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6. Compound **8a**: ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 3.86 (dd, 1H, $J=17.7$, 7.3 Hz), 3.92 (dd, 1H, $J=17.7$, 11.0 Hz), 4.52 (dd, 1H, $J=12.5$, 5.2 Hz), 4.60 (dd, 1H, $J=12.5$, 3.7 Hz), 5.28 (m, 1H), 7.14 (br s, 2H), 7.42 (t, 2H, $J=7.4$ Hz), 7.58 (t, 1H, $J=7.4$ Hz), 7.98 (d, 2H, $J=7.4$ Hz), 8.27 (s, 1H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 34.9, 64.6, 78.9, 118.8, 127.9, 128.9, 132.8, 136.5, 148.6, 149.9, 153.4, 155.9, 165.2. Compound **9a**: ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 3.69–3.90 (m, 4H), 4.91 (m, 1H), 4.98 (br s, 1H), 7.12 (br s, 2H), 8.23 (s, 1H), 8.31 (s, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 34.6, 62.2, 82.7, 119.2, 136.9, 148.9, 150.2, 153.6, 156.2. Compound **8b**: ^{1}H NMR ($CDCl_3$) δ 3.58 (dd, 1H, $J=18.0$, 7.7 Hz), 3.82 (dd, 1H, $J=18.0$, 10.9 Hz), 4.47 (dd, 1H, $J=12.2$, 5.1 Hz), 4.55 (dd, 1H, $J=12.2$, 3.9 Hz), 5.18 (dddd, 1H, $J=10.9$, 7.7, 5.1, 3.9 Hz), 5.87 (dd, 1H, $J=7.8$, 2.0 Hz), 7.44 (t, 2H, $J=7.7$ Hz), 7.58 (t, 1H, $J=7.7$ Hz), 7.87 (d, 1H, $J=7.8$), 8.02 (d, 2H, $J=7.7$ Hz), 8.75 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 36.5, 64.8, 80.6, 104.6, 128.5, 129.4, 134.4, 140.4, 148.3, 153.5, 162.0, 166.1. Compound **9b**: ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 3.41–3.61 (m, 4H), 4.77 (br s, 1H), 4.99 (m, 1H), 5.73 (d, 1H, $J=7.7$ Hz), 7.78 (d, 1H, $J=7.7$), 8.2 (br s, 1H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 38.3, 62.5, 83.5, 103.9, 140.7, 148.7, 154.0, 163.5. Compound **8c**: ^{1}H NMR ($CDCl_3$) δ 1.96 (d, 3H, $J=1.3$ Hz), 3.57 (dd, 1H, $J=18.1$, 7.4 Hz), 3.83 (dd, 1H, $J=18.1$, 10.3 Hz), 4.46 (dd, 1H, $J=12.0$, 5.4 Hz), 4.54 (dd, 1H, $J=12.0$, 4 Hz), 5.16 (dddd, 1H, $J=10.3$, 7.4, 5.4, 4.0 Hz), 7.44 (t, 2H, $J=7.7$ Hz), 7.57 (t, 1H, $J=7.7$ Hz), 7.73 (q, 1H, $J=1.3$ Hz), 8.03 (d, 2H, $J=7.7$ Hz), 8.38 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.3, 36.6, 64.8, 80.4, 113.2, 128.5, 129.4, 133.4, 136.0, 148.3, 153.5, 162.8, 166.1. Compound **9c**: ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 1.87 (d, 3H, $J=1.4$ Hz), 3.44 (dd, 1H, $J=17.5$, 8.4 Hz), 3.55 (dd, 1H, $J=17.5$, 10.5 Hz), 3.57 (dd, 1H, $J=12.2$, 4.9 Hz), 3.64 (dd, 1H, $J=12.2$, 3.9 Hz), 4.78 (dddd, 1H, $J=10.5$, 8.4, 4.9, 3.9 Hz), 4.93 (br s, 1H), 7.61 (q, 1H, $J=1.4$ Hz), 11.2 (br s, 1H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 12.4, 35.8, 62.3, 83.2, 111.9, 135.9, 150.3, 154.5, 165.8.
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