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An Improved Synthesis of 2'-Azido-2'-Deoxyuridine

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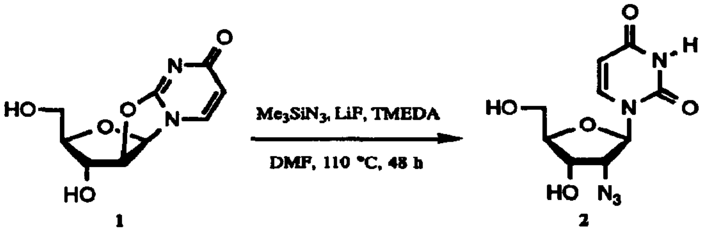
Abstract: A high yield process for the conversion of 2,2'-cyclouridine to 2'-azido-2'-deoxyuridine was developed. The procedure utilizes a lithium azide:TMEDA complex generated *in situ* from the reaction of lithium fluoride and azidotrimethylsilane in DMF with TMEDA added as a co-solvent.

The synthesis of azido substituted nucleosides has application in the field of antivirals[1] (*i.e.* AZT) as well as the production of precursors for nuclease resistant oligonucleotides incorporating 2'-amino-2'-deoxypyrimidine nucleotides.[2] We required large quantities of 2'-azido-2'-deoxyuridine[3] (**2**) as a key intermediate leading to the corresponding 2'-amino-2'-deoxy-5'-triphosphates of uridine and cytidine. The synthesis of **2** from 2,2'-cyclouridine (**1**) by reaction with lithium azide at 150 °C published previously[3] was not amenable to scale-up due to the use of HMPA as the solvent. However, since the reaction of lithium azide with **1** was known to give **2**, this result was utilized as the starting point for devising a large scale synthesis.



A procedure was developed which employs an *in situ* generation of lithium azide from lithium fluoride and azidotrimethylsilane in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA) in DMF at 100-110 °C. When **1** is allowed to react with 1.5 equivalents of this lithium azide:TMEDA complex in 1:1 DMF/TMEDA at 110 °C for 48 h, **2** is formed in high yield as the only product.

When the reaction was conducted in DMF or TMEDA alone, the yield of **2** as determined by HPLC was substantially reduced (23% and 28%, respectively). In the presence of 1.5 equivalents of TMEDA in DMF the yield of **2** improved to 43% by HPLC. To assess the effect of TMEDA on the basicity of the reaction medium, *N,N*-dimethylbutylamine which contains the trialkylamine moiety but is unable to chelate lithium cations was utilized as the co-solvent in place of TMEDA. Under these conditions, **2** was formed in 51% yield. Thus, the overall enhanced formation of **2** appears to be due to the combined effects of the apparent presence of the LiN_3:TMEDA complex, the basicity of the trialkylamine moiety of TMEDA and the presence of DMF as a co-solvent.

The use of commercially available lithium azide in the reaction gives **2** in 75% isolated yield. However, there were by-products formed under these conditions which were not observed when the lithium azide was generated *in situ*.

It has been reported that preformed KN_3:18-crown-6 complexes catalyze the addition of azide to unreactive substrates.[4] When **1** was allowed to react with 1.5 equivalents of preformed KN_3:dicyclohexano-18-crown-6 complex (generated from spray dried KF and azidotrimethylsilane in the presence of the crown ether in DMF at 110 °C), **2** was formed in 82% yield (HPLC). In the presence of catalytic amounts of the crown ether (0.1 equivalents) the yield dropped to 26%. Although high yields of **2** may be obtained in the presence of stoichiometric amounts of the crown ether, the high cost of the crown ether rendered this procedure impractical for large scale syntheses.

In summary, the use of lithium azide generated *in situ* affords improved yields of the azidonucleoside **2**. This procedure may find application in the synthesis of other azidonucleosides and may provide an alternative source of lithium azide.

EXPERIMENTAL

Synthesis of 2 Using Lithium Azide/TMEDA Generated *in situ*: Lithium fluoride (0.93 g, 36 mmol) was suspended in 20 mL of DMF heated to 105 °C. To the stirred suspension was added 20 mL of N,N,N',N'-tetramethylethylenediamine followed by azidotrimethylsilane (4.15 g, 36 mmol). After stirring for 30 min, 2,2'-cyclouridine (4.52 g, 20 mmol) was added and the reaction allowed to proceed for 48 h at 110 °C (oil bath temperature, **HAZARD:** rapid, uncontrolled exotherm is possible!, maintain reaction temperature ≤110 °C, See Note 5). The solvents were removed under vacuum and the residue co-evaporated from methanol three times. The residue was dissolved in 10 mL of methanol and 40 mL of ethyl acetate was added to precipitate most of the salts and residual starting material. The filtered solution was applied to 170 g of flash silica gel and eluted with 20% methanol/ethyl acetate. The product was obtained as an off-white foam (3.38 g, 63%): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.58 (dd, 1H, J = 3.2, 12.2 Hz, H$_{5A'}$), 3.67 (dd, 1H, J = 3.0, 12.2 Hz, H$_{5B'}$), 3.90 (m, 1H, H$_{4'}$), 4.06 (dd, 1H, J = 5.4, 5.4 Hz, H$_{2'}$), 4.31 (dd, 1H, J = 5.0, 5.0 Hz, H$_{3'}$), 5.18 (br s, 1H, -O$\underline{\text{H}}$), 5.68 (d, 1H, J = 8.1 Hz), 5.88 (d, 1H, J = 5.4 Hz, H$_{1'}$), 5.96 (br s, 1H, -O$\underline{\text{H}}$), 7.88 (d, 1H, J = 8.1 Hz), 11.4 (br s, 1H, N$\underline{\text{H}}$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 60.13, 64.59, 70.37, 85.18, 85.56, 102.02, 140.01, 150.42, 163.02; IR (KBr, film) ν_{max} 2117 cm^{-1} (-N$_3$). The reaction was repeated on a larger scale using 90.5 g of **1**, 87.4 g of azidotrimethylsilane and 18.6 g of lithium fluoride in 400 mL of DMF and 500 mL of TMEDA at 105 °C for 48 h. The reaction mixture was worked up as usual and the crude residue was loaded on a short column of silica gel (750 g) and eluted with 3 L of 20% MeOH/CHCl$_3$. The fractions containing the product were combined, concentrated and chromatographed on an additional 750 g of silica gel using 5 L of 10% MeOH/CHCl$_3$ to provide 89.9 g (84%) of **2**.

The above procedure was followed for the reactions described in the text incorporating the modifications described therein. The crude reaction mixtures were analyzed by reverse-phase chromatography (C18, CH$_3$CN/H$_2$O). The product yields were determined from the normalized peak areas of the product *versus* the starting material.

REFERENCES AND NOTES

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5. In one instance, the reaction has been observed to run away at ~130 °C . This effect has not been observed when an oil bath was used to maintain a constant temperature.

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