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Unexpected formation of 2′-deoxy-*N*3-(3,3,3-trifluoro-1-propenyl)uridine via a Michael-type addition to 3,3,3-trifluoropropyne

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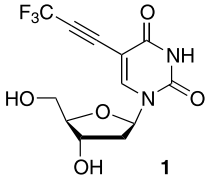
Abstract—Reaction of 3,3,3-trifluoropropyne with 2′-deoxy-5-iodouridine under conditions that have previously been used to prepare 5-alkynyl-2′-deoxyuridine derivatives gave 2′-deoxy-*N*3-(3,3,3-trifluoro-1-propenyl)uridine. This unexpected alkylation is a result of a Michael-type addition of *N*3 on the pyrimidine base to the electron deficient trifluoropropyne.

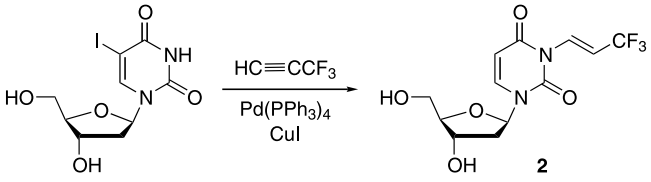
The selective introduction of a fluorine atom or a fluorinated moiety into a biologically active molecule is emerging as an effective tool for modifying its physicochemical properties and physiological behavior.[1,2] In addition, the study of conformational changes in biopolymers as a function of conditions, mutations or interactions with other macromolecules or drugs can be facilitated by spectroscopic methods that utilize fluorine atoms. For example, ^{19}F solution NMR has been used to study conformational changes in the hammerhead ribozyme.[3] Large-scale conformational changes in biopolymers have also been determined by ^{19}F–^{31}P rotational–echo double resonance (REDOR) solid state NMR for observing ligand binding and the coupled conformational change of 5-enolpyruvylshikimate-3-phosphate synthase.[4] This strategy has also been extended to nucleic acids to measure distances between a phosphodiester and a fluorine atom placed on either a sugar or a base moiety.[5,6]

To increase the range of distance measurements past 20 Å in nucleic acids by solid state NMR, we are interested in incorporation of a trifluoromethyl group in place of a fluorine atom. Recently, we reported that the trifluoromethyl group at position 5 of 2′-deoxyuridine was converted to a cyano group by aqueous ammonia under standard deprotection conditions during DNA synthesis.[7] This transformation takes place through an addition–elimination mechanism initiated by nucleophilic addition of ammonia to position 6 of the pyrimidine base with concomitant elimination of a fluorine atom. Although this problem could be circumvented for DNA by using more labile protecting groups and milder deprotection conditions, this approach cannot be extended to RNA synthesis due to the lack of commercially available reagents. Therefore, we decided to prepare 2′-deoxy-5-(3,3,3-trifluoro-1-propynyl)uridine **1**, in which a similar elimination of fluorine would not be as facile due to formation of a cumulene intermediate, and would thus be more stable under standard deprotection conditions.



1

Reaction of commercially available 2′-deoxy-5-iodouridine with 3,3,3-trifluoropropyne in dimethylformamide in the presence of tetrakis(triphenylphosphine)palladium(0) and copper iodide[8] (Scheme 1) resulted in a new major product in 80% yield.[9] How-



2

Scheme 1.

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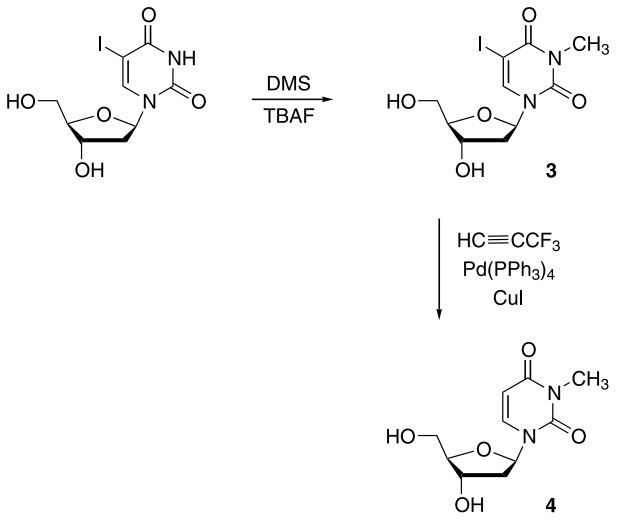

Scheme 2.

ever, the spectroscopic data[10] were not consistent with the desired compound (**1**). The molecular weight (*m*/*z* 345.0673 (M+Na)$^+$, ESI-TOF) was two units higher than expected and in combination with ^{13}C and ^{1}H NMR provided direct evidence for incorporation of -CH=CH-CF_3 instead of -C≡C-CF_3. Specifically, the ^{13}C NMR spectrum of compound **2** in DMSO-d_6 showed three new quartets at 129.88 (J=5.81 Hz), 121.55 (J=285.27 Hz), and 118.30 (J=35.26 Hz) ppm and the ^{1}H NMR spectrum exhibited two olefinic protons at 6.65 (d) and 6.37 (dq) ppm. Furthermore, a ^{135}DEPT experiment showing a proton at the 5 position and J-coupling observed between the protons in the 5 and 6 positions in a 2D-COSY spectrum ruled out the connectivity of the trifluoromethyl-containing side chain at the 5 position. The NMR spectroscopic data[10] for compound **2** showed clearly that the trifluoropropenyl group was attached on the base of nucleoside, rather than the sugar. The connectivity of the trifluoropropenyl group to the base was further supported by MS–MS analysis, which showed a loss of deoxyribose. However, the spectroscopic data could not be used to determine where the trifluoropropenyl group was linked to the base.

The three heteroatoms *O*2, *N*3 and *O*4 on the pyrimidine were likely candidates as sites of attachment to the trifluoropropenyl group. Alkylation of the pyrimidine oxygens has been shown to shift the absorption maxima to longer wavelengths.[11] However, the UV maxima of the starting nucleoside and compound **2** were the same (265 nm), indicating that the trifluoropropenyl group was attached to *N*3.

To provide further evidence for *N*-alkylation, the *N*3 was blocked with a methyl group, which should prevent incorporation of the trifluoropropenyl group. This was accomplished by *N*-methylation[12] of 5-iodo-2′-deoxyuridine with dimethysulfate[13] in 95% yield (Scheme 2).[14] The reaction of *N*-methyl-5-iodo-2′-deoxyuridine **3** with trifloropropyne using the same conditions yielded exclusively *N*-methyl-2′-deoxyuridine (Scheme 2). This result also shows that the carbon–iodine bond in the nucleoside is readily reduced under these reaction conditions. In a separate experiment, the Pd/Cu catalyst was shown not to be necessary for the *N*3 alkylation of 5-iodo-2′-deoxyuridine with 3,3,3-trifluoropropyne. Moreover, the reaction of 3,3,3-trifloropropyne with 2′-deoxyuridine gave nucleoside **2**, demonstrating that the iodine is not required for incorporation of the trifluoropropenyl group. Based on our experiments, we postulate that the mechanism of *N*-alkylation in formation of **2** is analogous to the Michael reaction,[15] where the pyrimidine *N*3 adds as a nucleophile to the terminal carbon of the alkyne, which is electrophilic due to the presence of the strongly electron withdrawing CF_3 group.

In conclusion, 2′-deoxy-*N*3-(3,3,3-trifluoro-1-propenyl)uridine (**2**) was synthesized in high yield from commercially available materials. The 3,3,3-trifluoropropenyl group (CF_3CH=CH-) has been used to improve the properties of candidate compounds for medicines or agricultural chemicals.[16,17] In particular, trifluoromethyl enamine is an intermediate in the synthesis of apolipoprotein B inhibitors.[18] Although a variety of methods have been developed for synthesizing 3,3,3-trifluoropropenyl compounds, they exhibit several disadvantages and require multistep reactions. The direct alkylation of pyrimidines with trifluoropropyne reported here suggests a general approach for the syntheses *N*3-trifluoropropenylated nucleosides.

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9. Procedure for compound **2**. To a solution of 2′-deoxy-5-iodouridine (0.177 g, 0.5 mmol) and triethylamine (0.177 g, 0.5 mmol) in DMF (10 mL) in 50 mL Schlenk tube was added copper iodide (20 mg, 0.1 mmol) and tetra-

kis(triphenylphosphine)palladium (58 mg, 0.05 mmol). The solution was degassed by 3 freeze–pump–thaw cycles, followed by addition of 3,3,3-trifluoropropyne (0.46 g, 4.92 mmol) at −78°C. The reaction mixture was stirred at −40°C for 12 h and at room temperature for 2 days. The mixture was concentrated in vacuo and the residue purified by preparative silica gel TLC (20×20 cm) with $MeOH/CH_2Cl_2$ (1:9) to give **2** in 80% yield.

10. Spectroscopic and analytical data for compound **2**: ^1H NMR (DMSO-d_6, 500 MHz): 7.99 (1H, d, $J=8.15$ Hz, H6), 6.65 (1H, d, $J=9.30$ Hz, NCH=), 6.37 (1H, dq, $J=17.25$, 8.5 Hz, CF_3CH=), 6.16 (1H, t, $J=6.45$ Hz, H1′), 5.83 (1H, d, $J=8.10$ Hz, H5), 5.28 (1H, d, $J=3.70$ Hz, 3′OH), 5.01 (1H, m, 5′OH), 4.25 (1H, m, H3′), 3.81 (1H, m, H4′), 3.61 (2H, m, H5′ and H5″), 2.10 (2H, m, H2′ and H2″). ^{13}C NMR (DMSO-d_6, 199 MHz): 160.46 (C4), 148.77 (C2), 139.77 (C6), 129.88 (C3=, $J=5.81$ Hz), 121.55 (CF_3, $J=285.27$ Hz), 118.30 (=C2, $J=35.26$ Hz), 100.42 (C5), 87.34 (C4′), 84.44 (C1′), 69.84 (C3′), 60.76 (C5′), 40.73 (C2′). The assignments were aided by the use of COSY and ^{135}DEPT. ^{19}F NMR (DMSO-d_6): −60.84 ppm (referenced to CCl_3F at 0 ppm). LC/MS and ESI-MS (M^+ 322), UV (λ_{max} 265 nm). ESI-TOF (HRMS): m/z 345.0673 $(M+Na)^+$ (calcd 345.0674 for $C_{12}H_{13}N_2O_5F_3Na$).
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14. A solution of 2′-deoxy-5-iodouridine (0.22 g, 0.62 mmol) in THF (3 mL) was treated sequentially with a 1 M solution of TBAF in THF (3 mL, 3.10 mmol) and dimethyl sulfate (0.3 mL, 3.10 mmol). The reaction mixture was stirred at room temperature for 10 min, concentrated in vacuo and purified by silica gel flash column chromatography with $MeOH/CH_2Cl_2$ (1:9) to give **3** as white solid in 95% yield. ^1H NMR (D_2O, 500 MHz): 8.20 (1H, s, H6), 6.10 (1H, dd, $J=2.7$, 0.6 Hz, H1′), 4.27 (1H, m, H3′), 3.89 (1H, m, H4′), 3.67(1H, m, H5′), 3.18 (3H, s, Me), 2.24 (2H, m, H2′ and H2″); ESI-MS $(M+H)^+$ 368.9.
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