## An Unusual Occurrence on Attempted Purine C-8 Electrophilic Fluorination of 5'-Noraristeromycin

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## ABSTRACT



Reaction of the in situ generated purine C-8 carbanion of a protected 5'-noraristeromycin derivative with *N*-fluorobenzenesulfonimide gave 8-phenylsulfonyl-5'-noraristeromycin rather than the expected 8-fluoro derivative. A single electron transfer (SET) mechanism is proposed for this occurrence. The phenylsulfonyl product offers a structural feature common to some anti-HIV agents.

Significant effort has been directed toward the synthesis of base-modified nucleosides for their potential biological activities, specifically within the context of antiviral therapeutic agents.<sup>1–3</sup> The least studied modification has been at the C-8 position of the purine-based nucleosides, although, in some cases, interesting antiviral and anticancer properties have been reported.<sup>4–6</sup> In our laboratory, we have found that 5'-noraristeromycin (1) has provided a fruitful foundation

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to a wealth of structural entities with potentially significant antiviral properties.<sup>7</sup> Therefore, it was of interest to prepare C-8-substituted 5'-noraristeromycin derivatives to expand upon this latter observation.

Barton and co-workers<sup>8</sup> reported that regioselective lithiation at purine C-8 made possible substitution reactions by various electrophiles, for example, halonium ions<sup>5b,9</sup> ( $X^+ =$  Cl<sup>+</sup>, Br<sup>+</sup>, I<sup>+</sup> except F<sup>+</sup>), alkyl (R<sup>+</sup>) halides,<sup>10</sup> and carbonyl compounds<sup>11</sup> (such as PhCHO, EtCHO, Ph<sub>2</sub>CO, Et<sub>2</sub>CO) to

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provide the corresponding halo, alkyl, and carbinol derivatives. Nothing could be found in the literature regarding the electrophilic fluorination reactions involving in situ generated C-8 purine carbanions. In this paper, we describe an interesting observation that the reaction between such a carbanion and an electrophilic fluorinating agent, *N*-fluorobenzenesulfonimide (NFSI), proceeded by an apparent single electron transfer (SET) pathway and furnished the novel 8-phenylsulfonyl-5'-noraristeromycin **2**.

The diol  $3^{12}$  was treated with *tert*-butyldimethylsilvl chloride in N,N-dimethylformamide (DMF) containing imidazole at room temperature to produce the 2',3',4'-tris O-tertbutyldimethylsilyl derivative 4 (Scheme 1). When 4 was subjected to reaction with *n*-butyllithium (3 equiv) at -78°C followed by quenching with NFSI (3 equiv), 5 (78.2%) was the only product obtained with no trace of the expected 8-fluoro derivative 6 (Figure 1). The structure of 5 was unequivocally identified by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and elemental analysis. The <sup>1</sup>H NMR spectrum of **5** (CDCl<sub>3</sub>) showed the disappearance of the C-8 hydrogen singlet of 4 at  $\delta$  8.33 ppm and the concomitant appearance of five aromatic (phenyl) protons in the  $\delta$  7.52–8.08 ppm region [7.52 (t, 2H, J = 7.64 Hz), 7.63 (t, 1H, J = 7.48 Hz), 8.08(d, 2H, J = 7.76 Hz)], confirming reaction at the C-8 of the purine ring. This experimental observation was in contrast to the other halonium ions<sup>9</sup> ( $X^+ = Cl^+$ ,  $Br^+$ ,  $I^+$  except  $F^+$ )



Figure 1. Single electron transfer (SET) mechanism.

and carbon electrophiles.<sup>10,11</sup> Failure to detect **6** may be due to the instability of the 8-fluoro purine derivative.<sup>13</sup>

The formation of 5 can be rationalized by assuming that the in situ generated carbanion 7 followed a single electron transfer mechanism rather than participating in the expected nucleophilic substitution reaction (route A, Figure 1). It is with this in mind that we postulate the reaction mechanism between 7 and NFSI shown in Figure 1 (route B), which follows from literature precedent.<sup>14</sup> In this direction, a single electron is transferred from carbanion 7 to NFSI to produce a C-8 radical 8 and a reduced derivative of NFSI 9 [•NF<sup>-</sup>(SO<sub>2</sub>Ph)<sub>2</sub>] (route B). Radical anion 9 would be highly unstable and, thus, would dissociate to  $10 [\circ N(SO_2Ph)_2]$  with loss of the fluoride ion (F<sup>-</sup>). Due to the steric bulkiness of the radical 10, it would not be expected to combine with 8 to produce 11. Instead, radical 10 underwent homolytic N-S bond cleavage to give the phenylsulfonyl radical 12 and the phenylsulfonyl nitrene 13. The phenylsulfonyl radical 12 would then combine with 8 to provide the fully protected 8-phenylsulfonyl carbocyclic nucleoside, 5. Because of the limited reactivity of the phenylsulfonyl nitrene,<sup>15</sup> no product was observed through its radical recombination.

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A similar result was obtained when the ammonolysis product of **4** (that is, **14**) was allowed to react with 5 equiv of lithium diisopropylamide (LDA) at low temperature (-78 °C) followed by quenching with NFSI. In addition to the 8-phenylsulfonyl derivative **15** (46% yield), a recovery of 30% of the starting material was found (no starting material was observed from **4**). Compound **5** was efficiently transformed into **15** using saturated NH<sub>3</sub> in MeOH at 120 °C. Desilylation of **15** was carried out with NH<sub>4</sub>F in MeOH at reflux temperature to yield the novel 8-phenylsulfonyl-5'-noraristeromycin **2**.

Compound 2 is important to our ongoing antiviral drug discovery research program because the presence of a phenylsulfonyl moiety on a heterocyclic ring is known to be relevant to inhibition of the HIV-1 reverse transcriptase,<sup>16–18</sup> an important enzyme for the HIV infection. The phenylsulfonyl moiety is believed to cause its effects via two enzyme binding modes: (1) the phenyl unit fits in the enzyme hydrophobic pocket, and (2) the sulfonyl oxygen atoms offer

hydrogen bonding opportunities to amino acid residues of the enzyme that could stabilize the inhibitor enzyme complex. A similar fate for 2 is under investigation in our laboratory.

In conclusion, a single electron transfer mechanism is proposed to be responsible for the formation of 8-phenylsulfonyl-5'-noraristeromycin<sup>19</sup> in high and reproducible yield<sup>20</sup> under conditions expected to yield the 8-fluoro derivative. Application of this experiment to the synthesis of other 8-substituted purine analogues of related carbocyclic purine nucleosides is of interest to our antiviral studies.

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**Supporting Information Available:** Experimental procedures and characterization data for compounds 2, 4, 5, 14, and 15. This material is available free of charge via the Internet at http://pubs.acs.org.

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