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An improved synthesis of α-AZA, α-AZP and α-AZG, the precursors to clinical markers of tissue hypoxia

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Abstract—α-[^{123}I]-IAZA and α-[^{123}I]-IAZP are experimental diagnostic radiopharmaceuticals which have been used clinically to diagnose hypoxia in a number of pathologies, including cancer, peripheral vascular disease, rheumatoid arthritis and brain trauma. These nitroimidazole nucleosides are synthesized from the non-iodinated nucleosides AZA, AZP and AZG, respectively. Earlier methods report low chemical yields for the synthesis of these precursors. The modified procedures now reported provide nearly quantitative yields of these compounds, thereby substantially reducing the cost and effort of synthesis.

1 - (α - D - 5 - Iodoarabinofuranosyl) - 2 - nitroimidazole[1] (IAZA) and 1-(α-L-4-iodoxylopyranosyl)-2-nitroimidazole[2] (IAZP) are being developed as diagnostic radiopharmaceuticals to detect and monitor regional hypoxia in disease. [^{123}I]-α-IAZA has been shown to be useful in diagnosing a wide range of hypoxic tissue in cancer,[3,4] diabetes,[5] rheumatoid arthritis,[6] and blunt trauma of the brain.[7] These iodinated nitroimidazole nucleosides were initially synthesized by generating corresponding, protected 1-α-bromosugars using 30% HBr in glacial acetic acid, followed sequentially by coupling to 2-nitroimidazole, deprotection and subsequent selective iodination.[1,2,8] The coupling steps afforded benzoylated AZA, acetylated AZP and acetylated AZG, respectively, in only moderate chemical yields. Low yields of the coupled products have been attributed to residual acid, which cleaves the glycoside bond of the coupled product and, subsequently, leads to significant decomposition. These brominated sugar precursors have now been synthesized using hydrogen bromide (HBr) gas that is easily removed from the reaction mixture before coupling to azomycin (2-nitroimidazole). Furthermore, azomycin was converted to its *N*-1-trimethylsilyl derivative before coupling with the respective bromosugars. These reaction modifications provide neutral reaction conditions, leading to quantitative coupling. The formation of the nucleoside products was confirmed by comparison of their physical and spectroscopic data with those reported in the literature.[1,2,8] Table 1 shows the reaction times for bromination and coupling, the reaction temperature and chemical yields for the synthesis of protected AZA, AZP and AZG.

1-(α-D-2,3,5-Tri-*O*-benzoylarabinofuranosyl)-2-nitroimidazole (tribenzoyl AZA). 1-*O*-Methyl-2,3,5-tri-*O*-benzoylarabinofuranose, **1** (10 g, 17.5 mmol) was dissolved in anhydrous CH_2Cl_2 and the solution was cooled to

Table 1. Reaction conditions and the chemical yields of **1**, **2** and **3**

Compound	Bromination time (h)	Coupling time (h)	Temperature (°C)	Yield (%)
AZA	3	16	50	100
AZP	2.5	16	50	100
AZG	2.5	8	30	99

Abbreviations: 1-(α-D-galactosyl)-2-nitroimidazole, AZG; 1-(α-D-arabinofuranosyl)-2-nitroimidazole, AZA; 1-(α-D-xylopyranosyl)-2-nitroimidazole, AZP.

Keywords: improved synthesis; hypoxia markers; AZA; AZP; AZG; azomycin nucleosides.

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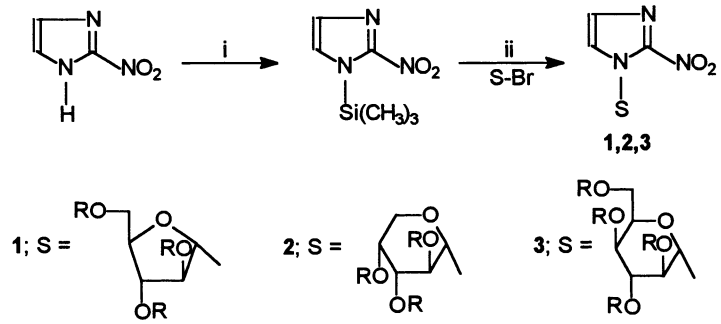

Scheme 1. Where i = HMDS/reflux; ii = $Hg(CN)_2$, 50°C and R = -COC_6H_5.

0–5°C. Hydrogen bromide gas was slowly bubbled through this solution while the temperature of the reaction was maintained cold. Once **1** was completely exhausted (checked by TLC examination), excess HBr was removed by bubbling argon through this solution. The solvent was removed on a rotavapor in vacuo and the contents were dried on hi-vac pump. Hexamethyldisilazane (75 mL) was added to another flask containing 2-nitroimidazole (2.44 g, 21.4 mmol). A catalytic amount of ammonium sulfate was then added, and the mixture was heated at reflux for 4 h. At this time, 2-nitroimidazole (azomycin) had completely dissolved and formation of 1-*N*-trimethylsilyl-2-nitroimidazole was complete. Excess HMDS was removed under complete exclusion of moisture, and the product was dried under high vacuum to remove the traces of HMDS. The bromosugar, described above, was dissolved in anhydrous acetonitrile (1 L) and added to the flask containing 1-*N*-trimethylsilyl-2-nitroimidazole. This was followed by the addition of mercuric cyanide (2.2 equivalents), after which the reaction flask was filled with argon. The reaction mixture was heated at 50°C for 16 h. TLC examination at this time showed complete conversion of the bromosugar to the azomycin nucleoside. The solvent was evaporated on a rotary evaporator, the residue was dissolved in CH_2Cl_2, and then washed sequentially with 30% w/v aqueous potassium iodide and then cold water. The dichloromethane phase was dried over anhydrous sodium sulfate, filtered, evaporated and purified on a silica gel column to yield **1**[†] in quantitative yield.

Similarly, 1-(α-D-2,3,4-tri-*O*-acetylxylopyranosyl)-2-nitroimidazole (triacetyl-AZP)[†] and 1-(α-D-2,3,4,6-tri-*O*-acetylgalactosyl)-2-nitroimidazole (triacetyl-AZG)[†] were synthesized from 1-α-bromo-2,3,4-tri-*O*-acetylarabinopyranose and 1-α-bromo-2,3,4,6-tetra-*O*-acetylgalactose in 100 and 99% yields, respectively (Scheme 1).

This modification yields azomycin nucleosides in nearly quantitative yields, and can be applied to the synthesis of other related compounds.

[†] Mp **1**, 106°C (uncorrected); 106°C reported;[1] mp **2**, 110°C (111°C reported[2]); mp **3**, 99°C (100°C reported).

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