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Photo-Arbuzov Route to Acyclic Nucleoside-Based Phosphonates

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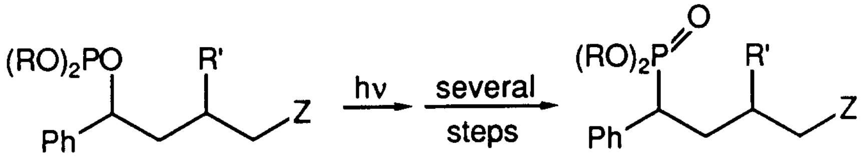
Readily prepared phosphites, 1, were photoisomerized by UV light (450 W, medium pressure lamp) to the corresponding benzylphosphonate diesters (2; R = Me, R' = H or CH_2OCH_2Ph, Z = $OSiMe_2Bu$-t) in 68% (R' = H) and 72% (R' = CH_2OCH_2Ph) yields and subsequently transformed (two steps) to the bromo intermediates (2; R = Me, R' = H or OCH_2Ph, Z = Br). The latter were converted



1 R = Me
R' = H or CH_2OCH_2Ph
Z = OTBDMS

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to the acyclic nucleoside-based phosphonates (2; R = Me, R' = H or CH_2OCH_2Ph, Z = Ade, Cyt, 2-amino-6-chloropurine, Gua, 2,6-diaminopurine). Debenzylation (R' = CH_2OCH_2Ph) and complete demethylation gave the target, potentially antiviral, phosphonic acids (2; R = H, R' = H or CH_2OH; Z = Ade, Cyt, 2-amino-6-chloropurine, Gua, 2,6-diaminopurine) in good overall yields.

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The Synthesis of 1-Phosphonylmethoxyethyl-1,2,4-triazole-3-carboxamide, a New and Novel Acyclic Nucleotide Analog.

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Acyclic nucleotide analogs such as (S)-9-((3-hydroxy-2-phosphonylmethoxy)propyl)adenine (HPMPA), 9-(2-phosphonylmethoxyethyl)adenine (PMEA), and 9-(2-phosphonylmethoxyethyl)guanine (PMEG) have recently been reported to have significant antiviral activities. We felt that the ribavirin analog of PMEA should also be synthesized and screened to determine if it might also have antiviral activity. Therefore, we synthesized 1-(phosphonylmethoxyethyl)-1,2,4-triazole-3-carboxamide by the following process. The sidechain precursor was first synthesized from dioxolane by treatment with acetyl chloride and $ZnCl_2$, reaction with Et_3P at 100-110 °C followed by acetate hydrolysis and tosylation of the resulting alcohol to give diethyl 2-(4-methylphenyl)sulfonyloxyethoxymethylphosphonate. Methyl 1,2,4-triazole-3-carboxylate was then alkylated with diethyl 2-(4-methylphenyl)sulfonyloxyethoxymethylphosphonate in anhydrous DMF with K_2CO_3 at 90 °C under inert atmosphere to give a mixture of products containing methyl 1-[2-(diethylphosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxylate. An inseparable mixture containing this intermediate and 1-[2-(diethylphosphonylmethoxy)ethyl]-1,2,4-triazole was isolated and treated with concentrated ammonium hydroxide. The resulting 1-[2-(diethylphosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxamide (which was easily separable from 1-[2-(diethylphosphonylmethoxy)ethyl]-1,2,4-triazole) was hydrolyzed with bromotrimethylsilane to give the desired target compound. The antiviral screening of this compound (and intermediates from its synthesis) showed no activity against HIV, JE, PT, SF, VEE, and YF viruses.