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Nucleoside Analog-Based Phosphonates via Photochemical, Single Electron Transfer (SET) Induced Rearrangements of Allyl Phosphites.

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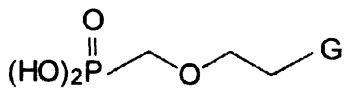
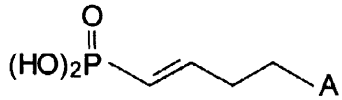
Abstract: The photochemical SET rearrangement of nucleoside analog-based phosphites **12** and **13**, initiated by the singlet excited state of DCN, affords the corresponding diethyl phosphonates **14** and **15**. Deprotection of **15** gives phosphonate **16**. Treatment of **14 - 16** with base yields the vinylphosphonates **17-19** as the (*E*)- and (*Z*)-diastereomers.

Phosphonic acids (phosphonates) display a wide variety of biological activities.[1] Therefore, new methods for their preparations are of general interest. More specifically, phosphonates based on nucleoside or acylic nucleoside analogs have potent activities against HIV (**1**,[2] **2**,[3], **3**[4], **4**[5]) and are activated by cellular or viral phosphorylation to the triphosphate analog. Phosphonate **5**, by contrast, is an adenosine deaminase inhibitor[6] that enhances the activity of adenosine-based antivirals. The unsaturated adenosine derivatives **6** derive their antiviral activity from inhibition of *S*-adenosylhomocysteine hydrolase.[7] The reactions described herein yield diethyl phosphonate esters **14-19** that are related structurally to **1-6**. The primary emphasis of this communication is the application of new chemistry to produce structurally novel phosphonates. Nonetheless, the biological activities of **14-19** and their phosphonic acid counterparts will be assayed and reported subsequently.



1 [2]



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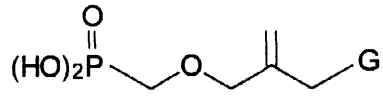
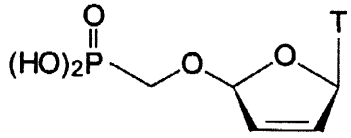
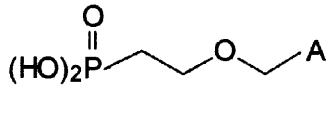


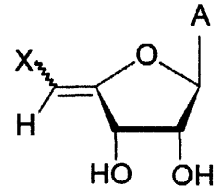
3 [4]



4 [5]



5 [6]



6 [7] X = H, Cl, F, MeO

The syntheses of **14-16** are based on a photochemical, single electron transfer (SET) rearrangement process devised in this laboratory.[8] Its proposed mechanism is depicted by **7-11**. Thus, 9,10-dicyanoanthracene (DCA) absorbs ultraviolet light to produce its singlet π-π^* excited state, $[DCA]^1$. The experimentally observed quenching[8] of the fluorescence of $[DCA]^1$ by **7** presumably

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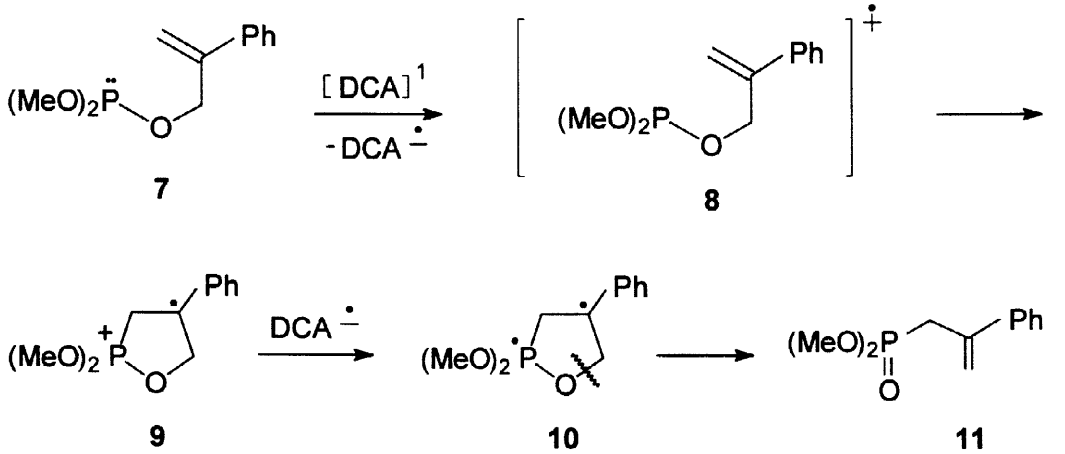
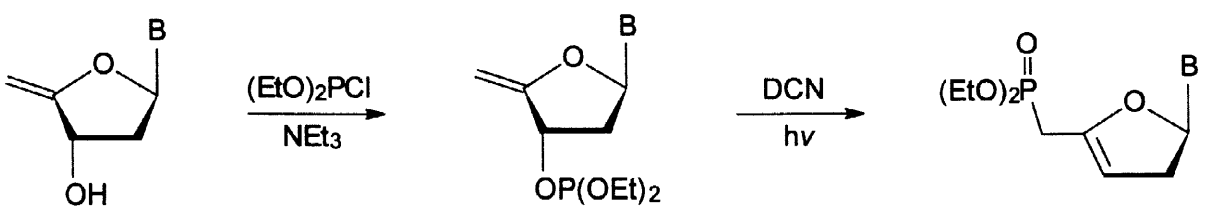
involves electron transfer to give the radical anion of DCA and cation radical **8**. The electrophilic phosphorus or π bond cation radical center in **8**, generated on loss of an electron from one of the two functionalities of *allyl phosphite* **7**,[9] cyclizes to the distonic cation radical **9**. Capture of an electron from the electron sink $DCA^{\bullet -}$ generates 1,3-biradical **10** which undergoes exothermic β scission to form *allylphosphonate* **11**.



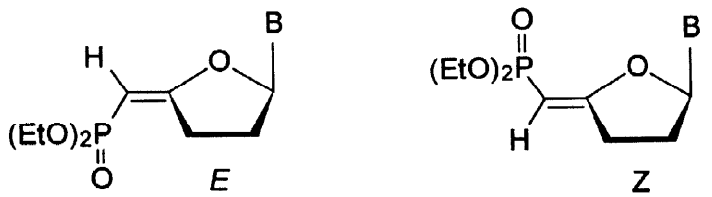
In the research reported here, 1,4-dicyanonaphthalene (DCN) rather than DCA was employed as electron acceptor to convert allyl phosphites **12** ($\delta^{31}P$ = 139.5, $CDCl_3$) and **13** ($\delta^{31}P$ = 139.7, $CDCl_3$) to the allylphosphonates **14** and **15**. Thus, the readily prepared[10] 4'-methylene, 3'-OH nucleoside precursors shown were first phosphitylated with $(EtO)_2PCl$ to give **12** and **13**, which were purified by flash chromatography (5-10% triethylamine in ethyl acetate/hexanes, 7/3) in >60% yields. Acetonitrile solutions (15-30 mL) of each phosphite (approx. 50 mM, 300-500 mg of **12** or **13**), containing 1.5 equivalents of DCN and an appropriate amount of dimethyl benzylphosphonate (^{31}P NMR internal standard) in Pyrex test tubes (1.2 cm diameter), were capped with rubber septa and then thoroughly deoxygenated by an argon purge (10-15 min). The solutions were irradiated for 10-15 h with UV light from the 300 nm lamps of a Rayonet preparative-scale reactor. A portion of the reaction solution was concentrated under vacuum to allow phosphite accountabilities and phosphonate yields to be determined by integration of the ^{31}P NMR peaks for phosphite, product phosphonate, and internal standard. Flash chromatography under argon on SiO_2 [phosphite **12**: 5-10% triethylamine in MeOH/ethyl acetate (0-95%); phosphite **13**: 5-10% triethylamine in hexanes/ethyl acetate (60-100%), followed by MeOH-ethyl acetate (0-5%)] gave reclaimed unreacted phosphites (**12, 13**) and product phosphonates (**14, 15**).



The photorearrangements, unfortunately, gave optimal amounts of **14** and **15** at only 40-60%

conversions of phosphites **12** and **13**. *However, close to 80% of the unreacted phosphite was isolated on chromatographic workup and can be easily recycled.* The accountability by ^{31}P NMR of reacted phosphite, in terms of phosphonates **14** and **15**, was 50-70% (45-50% based on *isolated* **14** and **15**). Overall yields of **14** and **15**, based on total phosphite, were: 40-50% by ^{31}P NMR; 30-35% isolated.

Treatment of a 3.5 mM MeOH solution of phosphonate **15** with 0.5 equivalents of MeONa for 2 days at room temperature yielded the unprotected diethyl phosphonate **16**. However, in only one day at room temperature, a 20 mM solution of **15** was not only debenzoylated but also transformed cleanly into the diastereomeric vinylphosphonates (*E*)- and (*Z*)-**17**, *E/Z* ratio 1.1/1. Close to the same ratio of diastereomers, (*E*)- and (*Z*)-**18**, was formed on a 4-h reflux of **14** with aqueous NH_4OH. Significantly, in *tert*-butylamine as solvent, **12** and **13** were converted in one day at room temperature or at reflux *exclusively* to (*E*)-**18** and (*E*)-**19**. The individual diastereomers of both **17** and **18** were separable. E.g. a 100 mg, 1:1 mixture of stereoisomers of **17** was readily separated into the individual diastereomers by chromatography on silica gel (ethyl acetate containing 0-10% of 5% triethylamine in MeOH), isolated chromatographic yield - 41% of each diastereomer.



17 B = A, **18** B = T, **19** B = A(N6-Bz)

An indication that the *E* diasteromer of **17** is the more stable form thermodynamically was found in the fact that 20 mM (*E*)-**17** was unchanged after two days in a room temperature MeOH solution containing 0.5 equivalents of MeONa, while (*Z*)-**17** was isomerized to a 1.1/1 *E/Z* mixture in 3 days. A 3-day reflux of a *tert*-butylamine solution of (*Z*)-**17** gave a 3/1 *E/Z* mixture. However, it is not clear that the final *E/Z* equilibrium was attained in any instance.

All new compounds were fully characterized by ^{1}H, ^{13}C, and ^{31}P NMR and HRMS or quantitative elemental analysis including the following key ^{31}P NMR ($CDCl_3$) chemical shifts: 22.4 (**14**), 22.6 (**15**), 22.2 (**16**), 19.6 ((*E*)-**17**), 15.9 ((*Z*)-**17**), 19.4 ((*E*)-**18**), 15.6 ((*Z*)-**18**), 19.3 ((*E*)-**19**). The *E* and *Z* isomers of **17-19** were identified by the large $^{3}J_{CP}$ of C3' for the *Z* forms (e.g. 14.2 Hz for (*Z*)-**17**, $\delta^{13}C = 30.2$[11]). The expected large $^{1}J_{CP}$ values for C5' for both isomers were encountered (e.g. 206.2 Hz for (*E*)-**17**, 195.9 for (*Z*)-**17**), along with downfield-shifted vinylic carbon resonances (δ83.8 and δ84.0, respectively).[11] The $^{1}J_{CP}$ values for C5' of **14-16** (142 Hz) are as expected for an sp^3 hybridized carbon, as is its chemical shift (26.3-26.4).

In summary, the recently discovered photochemical SET-induced rearrangement of allyl phosphites[8] has been applied to the preparation of allyl phosphonates **14-16**. Base-induced isomerization yields the vinylphosphonates **17-19**. To our knowledge, these products are structurally unique. The presence in these new molecules of alkene unsaturation and the diethyl phosphonate functionality, presumably capable of dealkylation to the phosphonic acid form, relates **14-19** structurally to the active antiviral agents **1-6**. The carbon-carbon unsaturation in **14-16** invites their further functionalization. The

rich chemistry of vinylphosphonates, the subject of a recent review,[12] is potentially applicable to **17-19**.

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