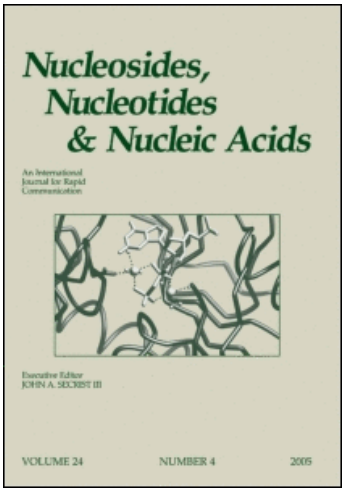

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Synthesis of Acycloalkenyl Derivatives of Pyrimidines and Purines

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SYNTHESIS OF ACYCLOALKENYL DERIVATIVES OF PYRIMIDINES AND PURINES

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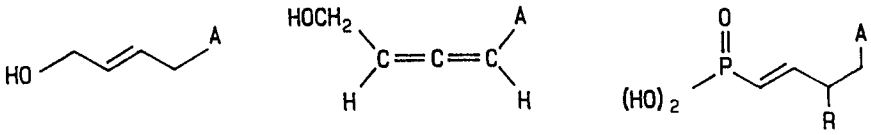
Abstract. Conjugate addition of an anionic nucleophile (nucleobase) to an active triple bond (α, ß unsaturated carboxylate or phosphonate) was used for preparing α-ethenyl carboxylate or phosphonate derivatives of purines and pyrimidines.

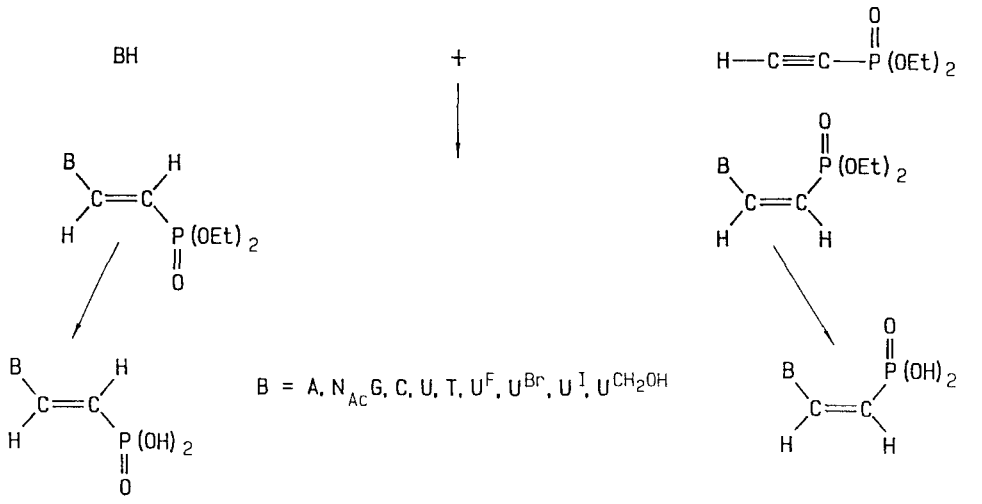
Interest has been growing in the synthesis of new nucleoside analogues with antiviral and antitumor activities. Among the Z and E alkenes (carboacyclonucleosides and acyclonucleotides), acycloneoplanocine A **1**, adenallene **2** and alkenylphosphonic acids **3** and **4** (Fig. 1) show interesting biological activity.[1-3]

The purpose of this investigation was to examine a more extensive series of new unsaturated acyclic analogues of nucleosides and nucleotides, using the efficient Michael type addition reaction.[4,5] Michael donors (pyrimidine and purine anions) were reacted with acceptors (diethyl acetylene dicarboxylate or alkenyl phosphonate) to produce the alkenyl carboxylate or alkenylphosphonate derivatives of purines and pyrimidines (Scheme 1 and 2).

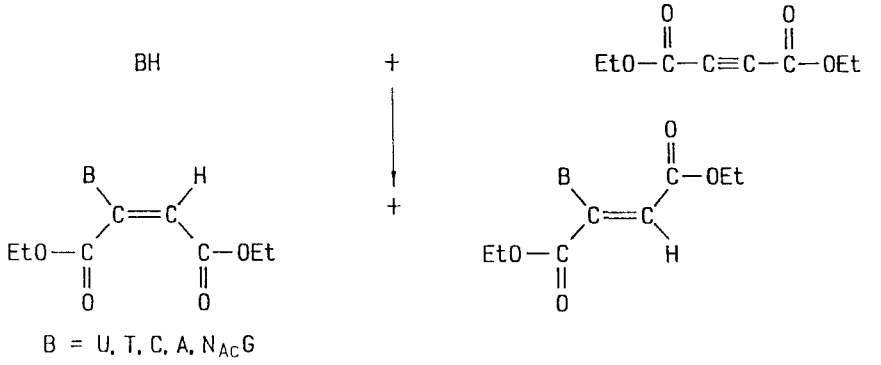


1 2 3 R=H 4 R=CH_2OH

FIGURE 1



SCHEME 1. Alkenylphosphonate derivatives



SCHEME 2. Alkenylcarboxylate derivatives

As a general procedure, solid K_2CO_3 (0.5 mmole) was added to a solution of nucleobase (1 mmole) in DMF at room temperature. After 15 min. stirring, the alkylating agent (1.5 mmole) in DMF was added. The reaction evolution was monitored with TLC. The solvent was evaporated and the product was purified by column chromatography.

Within the series of α-alkenyl phosphonate derivatives, the α,ß-unsaturated phosphonic acid moiety acts as the phosphate mimic. All Michael adducts were obtained as a mixture of two

TABLE 1
Alkenyl phosphonate derivatives

Bases	Yield (%)	Time (h)	Temp (°C)	E (%)	Z (%)
U	76	18	25	75	25
T	81	24	25	80	20
C	72	4	25	75	25
A	70	22	25	20	80
Nac G	67	6	70	25	75
U^{F}	66	12	25	75	25
U^{Br}	83	15	25	100	-
U^{CH2OH}	64	24	25	75	25

TABLE 2
Alkenyl carboxylate derivatives

Bases	Yield (%)	Time (h)	Temp (°C)	E (%)	Z (%)
U	65	1 30	70	45	65
T	65	1 15	70	30	70
C	70	1	25	60	40
A	65	1	25	66	34
Nac G	50	1	25	50	50

isomers (E and Z) with good yield (Table 1). Phosphonate derivatives were deesterified to the phosphonic acids using bromotrimethylsilane.

Addition of nucleobase anions to diethyl acetylene dicarboxylate led to the formation of the conjugated adducts with good yield (Table 2). The E and Z configurations in the conjugated adducts were assigned on the basis of NMR analysis and the regioisomerism was ascertained by UV spectroscopy.

The isomer ratio depended on the molar equivalents of the Michael acceptors used as well as the reaction conditions. From the results described here, we conclude that this methodology represents a convenient method to the use of heterocyclic base anions in Michael type reactions. Following this procedure, it is not necessary to use strong base such as DBU or $tBuO^{-}K^{+}$, and, instead, a catalytic amount of potassium carbonate is sufficient. Biological activities will be reported in the near future.

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