Radical Addition to Vinyl Phosphonates. A New Synthesis of Isosteric Phosphonates and Phosphonate Analogues of α-Amino Acids

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Derivatives of the phosphonic analogues of nucleotides and of side chain α-amino-acids can be readily prepared by irradiation of acyl-*N*-hydroxy-2-thiopyridones in the presence of diethylvinyl phosphonate.

The replacement of a carboxyl group in a biologically active molecule by a phosphonic acid or methylenephosphonic acid often gives rise to interesting biological effects.[1] The addition of an α-fluoro- or difluoro-function further potentiates such effects.[2]

Recently we reported[3] that the 2,3-dimethylketal derivatives of uronic acids from the common nucleosides, when coupled with *N*-hydroxy-2-thiopyridone, were an efficient source of *C*(4) carbon radicals. These reacted stereoselectively with activated alkenes with retention of configuration.

If the same type of radical were captured by a vinyl phosphonate, one would obtain the isosteres of protected nucleoside monophosphates. The derived phosphonic acids should surely show interesting biological activity. Indeed, compounds of this kind have recently been synthesised by conventional ionic chemistry.[2c,4]

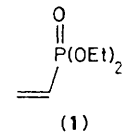
We have studied two vinyl phosphonates: diethylvinylphosphonate (**1**) and the acrylic ester analogue (**2**), both of which are available commercially. In general the vinyl phosphonate (**1**) captures nucleoside derived radicals in reasonable yield (Table 1). The analogue (**2**) is possibly more efficient, but needs further study (see below). The riburonic acid (**3**) derivative (**4**), prepared as before,[3] gave on photolysis (W lamp) the expected addition product (**5**) in reasonable (65%) isolated yield. The thiopyridine function could be removed efficiently (95%) by reduction with tributyltin hydride to give the monophosphonate derivative (**6**). The reaction sequence was completely stereoselective.

A similar reaction with the radical from (**4**) and the alkene (**2**) afforded the derivative (**7**) as a mixture of stereoisomers.

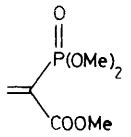
A more interesting substrate[3] was the uridine derivative (**8**). With phosphonate (**1**) the derivative (**9**) gave the adduct (**10**) which afforded stereochemically pure (**11**) on reduction with tributyltin hydride.

Similarly[3] the uronic acid (**12**) from adenosine was converted to (**13**) and then to (**14**). Some of the rearrangement product (**15**) was also formed. However, reduction with Raney nickel under reflux in ethanol gave the reduced and debenzoylated compound (**16**) as a single stereoisomer.

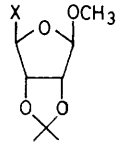
The *N*-hydroxy-2-thiopyridone derivatives of suitably protected amino-acids are also an excellent source of radicals.[5] We have now applied this chemistry to the synthesis of several amino-acid derivatives bearing a phosphonate function.[6]



(1)



(2)



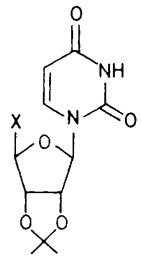
(3) X = CO_2H

(4) X = CO_2Y

(5) X = $CH_2CHZP(OEt)_2$

(6) X = $CH_2CH_2P(OEt)_2$

(7) X = $CH_2CZ(CO_2Me)P(OMe)_2$

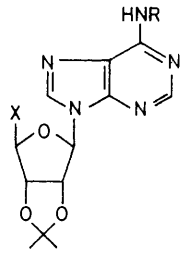


(8) X = CO_2H

(9) X = CO_2Y

(10) X = $CH_2CHZP(OEt)_2$

(11) X = $CH_2CH_2P(OEt)_2$



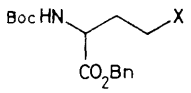
(12) X = CO_2H, R = Bz

(13) X = CO_2Y, R = Bz

(14) X = $CH_2CHZP(OEt)_2$, R = Bz

(15) X = Z, R = Bz

(16) X = $CH_2CH_2P(OEt)_2$, R = H



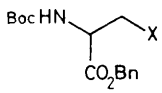
(17) X = CO_2H

(18) X = CO_2Y

(19) X = $CH_2CHZP(OEt)_2$

(20) X = Z

(21) X = $CH_2CH_2P(OEt)_2$



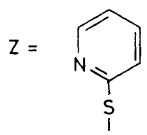
(22) X = CO_2H

(23) X = CO_2Y

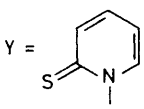
(24) X = $CH_2CHZP(OEt)_2$

(25) X = Z

(26) X = $CH_2CH_2P(OEt)_2$



Z =



Y =

Boc = Bu^tOCO

Bn = $PhCH_2$

Bz = PhCO

The glutamic acid derivative (**17**) was converted to (**18**) and photolysed in the presence of (**1**) to furnish the desired derivative (**19**) as major product along with the rearrangement product (**20**). Reduction with tributyltin hydride afforded the phosphonic analogue of 2-aminopimelic acid in protected form (**21**). Similarly, the aspartic acid derivative (**22**) afforded (**23**) and thence (**24**) with some rearrangement product (**25**).

Table 1.

Entry	Substrate	Alkene (equiv.)	Addition product[a] (Yield)	Rearrangement product (Yield)	Reduction product[b] (Yield)
1	(**3**)	(**1**) (5)	(**5**) (65%)		(**6**) (95%)
2	(**3**)	(**2**) (5)	(**7**) (70%)		
3	(**8**)	(**1**) (5)	(**10**) (60%)		(**11**) (89%)
4	(**12**)	(**1**) (5)	(**14**) (45%)	(**15**) (20%)	(**16**) (70%)
5	(**17**)	(**1**) (5)	(**19**) (56%)	(**20**) (24%)	(**21**) (76%)
6	(**22**)	(**1**) (5)	(**24**) (43%)	(**25**) (36%)	(**26**) (88%)

[a] Isobutyl chloroformate and *N*-methylmorpholine were added to a solution of the acid in dry tetrahydrofuran (THF) under inert atmosphere for 15 min at 0 °C, after which 1.2 equiv. of 2-mercaptopyridine-1-oxide was added and the reaction allowed to continue for 1 h at 0 °C. After addition of 5 equiv. of alkene, the mixture was irradiated with a tungsten lamp for 30 min at 0 °C. [b] Reductions were performed with Bu_3SnH and AIBN (α,α′-azoisobutyronitrile) in benzene except for (**16**) where Raney-Ni–ethanol was used under reflux over 24 h.

Finally, reduction of (**24**) afforded smoothly (**26**), which is a derivative of the phosphonic analogue of 2-aminoadipic acid.†

This work shows that biologically relevant phosphonic acid derivatives can be readily prepared using radical chemistry. The alkene (**1**) needs to be more reactive towards radicals. The alkene (**2**) may satisfy this need, for the derivatives would be easily decarboxylated. Alternately, more electronegative esters of (**1**) might be suitable. The work also confirms the value of tributylin hydride in the removal of the thiopyridyl residue.

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6 See also: D. H. R. Barton, D. Bridon, and S. Z. Zard, *Tetrahedron Lett.*, 1986, **27**, 4309.

† All new compounds were characterised by n.m.r. spectroscopy (200 MHz), mass spectrum, i.r. spectroscopy, micro-analysis, and optical rotation.