Studies on the Reactivity of 2-Furylhydroxymethylphosphonates: Synthesis of 1-Oxo-4-hydroxycyclopent-2-en-5-ylphosphonates

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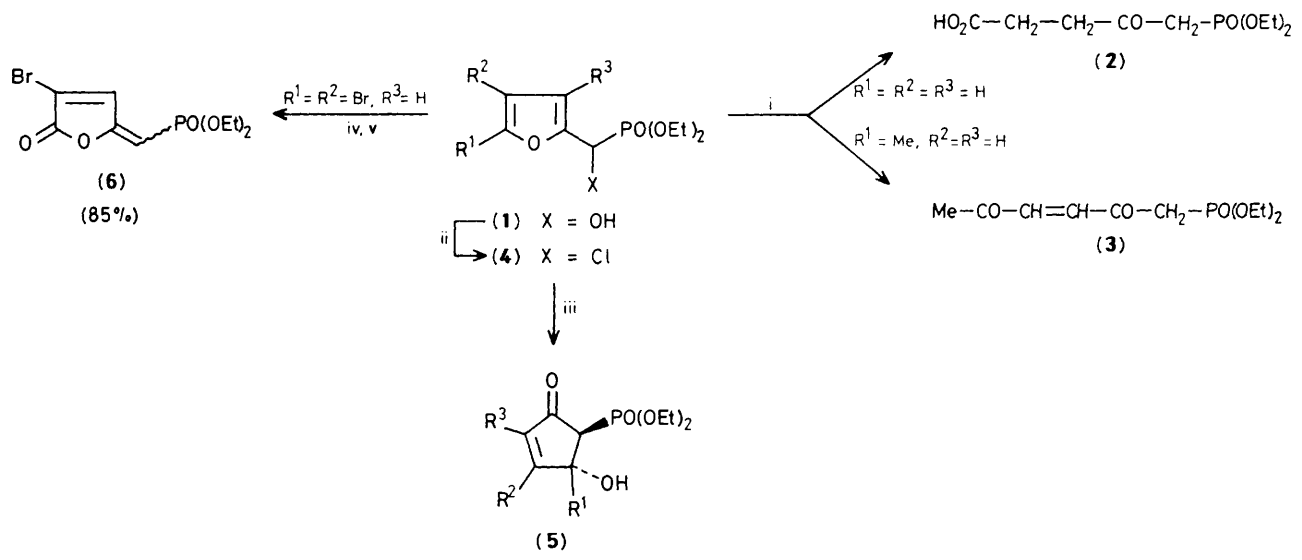
Starting from 2-furylhydroxymethylphosphonates (**1**), a facile and direct preparation of the previously unknown phosphonate-containing cyclopentenones (**5**), potential new synthons in the elaboration of rethrolone- and prostaglandin-related compounds, is described.

Our interest in the chemistry of 2-furylhydroxymethylphosphonates (**1**) has led us recently to show their use as valuable starting materials in a simple synthesis of several compounds which had not been described before.[1] During the course of this investigation, we observed that 2-furylhydroxymethylphosphonate (**1a**) ($R^1 = R^2 = R^3 = H$), by treatment with 1.25 M HCl in acetone at 58 °C for 8 h, furnished the levulinic acid derivative (**2**), a Marckwald-type product;[2] on the other hand, its 5-methyl derivative, under the same conditions, gave diethyl 2,5-dioxohex-3-enylphosphonate (**3**), showing that the reactivity was dependent on the substituent pattern on the furan ring.

Prompted by these findings, we considered it advantageous to exploit the influence of a more efficient leaving group in the side chain on the reactivity, in order to broaden the usefulness of these compounds in organic chemistry. We now report a new application of 2-furylhydroxymethylphosphonates (**1**), as good starting materials for a facile preparation of the



Scheme 1. i, HCl (1.25 M), Me_2CO, 58 °C, 8 h; ii, Et_3N, $MeSO_2Cl$, room temp.; iii, DME–H_2O (9:1), room temp.; iv, $MeSO_2Cl$; v, H_2O.

Table 1. Experimental conditions in the conversion (**1**) → (**5**), see Scheme 1.

Entry	Substrate	R^1	R^2	R^3	Reaction time/h	Product[a]	Reaction time/h	Product	% Yield[b]
1	(**1a**)	H	H	H	18	(**4a**)	48[c]	(**5a**)	54
2	(**1b**)	H	Br	H	4	(**4b**)	96	(**5b**)	60
3	(**1c**)	H	H	Br	1	(**4c**)	[d]	(**5c**)	78
4	(**1d**)	Me	Br	H	1	(**4d**)	24[c]	(**5d**)	33

[a] Chlorides (**4a—d**) were used without further purification in the subsequent reaction (see text). [b] The yields, calculated on the compounds (**1a—d**), refer to isolated, chromatographically pure, products. [c] Buffer solution (AcOH–AcONa, pH 4.7) was used. [d] SiO_2–EtOAc.

previously unknown phosphonate-containing cyclopentenones of type (**5**), which are very promising as synthetic tools in the elaboration of natural products.

In our experiments we utilized the chloride ion as the leaving group and compounds (**4**) were readily prepared by reaction of the corresponding alcohol (**1**) with $MeSO_2Cl$ in the presence of Et_3N under dry conditions.[3] We found it more convenient and cheaper to use (**4**) without further purification since they tended to decompose during the purification procedure. The results are summarised in Table 1.

The molecular rearrangement of chlorides (**4a—d**) into 1-oxo-4-hydroxycyclopent-2-en-5-ylphosphonates (**5a—d**) occurred readily under solvolytic conditions [0.04 M solution of (**4a—d**) in dimethoxyethane (DME)–water (9:1)]. However in some cases (Table 1, entries 1 and 4), HCl evolution during the reaction led to decomposition of both substrates and products and an appropriate buffer solution had to be used to prevent a drastic fall in pH.

All the reactions proceeded in a stereospecific manner: in fact, the cyclopentanone (**5a**) showed in the ^1H n.m.r. spectra a *trans* coupling constant value between the protons at C-4 and C-5 (J 2 Hz), in accordance with previously reported data for these compounds.[4] The conversion (**4c**) → (**5c**) (Table 1, entry 3) occurred after adsorption of the chlorination reaction mixture onto a short pad of silica gel and subsequent elution with ethyl acetate. The low yield of the isolated product (**5d**) (Table 1, entry 4) is due to extensive decomposition during purification. The presence of a bromine atom at C-3 or C-4 on the furan ring did not affect the molecular rearrangement: it appeared to stabilise the final product (Table 1, entries 2 and 3).[5] The dibromo substituted derivative furnished directly the expected product (**6**) as a stereoisomeric mixture, in very high yield (Scheme 1).[4]

In conclusion, the ready preparation of compounds (**5**) in good yields by a mild and effective procedure makes these compounds potential new synthons for the synthesis of biologically active natural products.

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