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NOVEL APPROACHES TO DIALKYLHETARYLPHOSPHONATES

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Abstract Dialkyl-1-oxoalkyl-, 1-oxo-2-alkenyl-, and 3-oxo-1-alkenylphosphonates are very useful substrates for the synthesis of a series of Dialkylphosphonates with a heterocyclic substituent.

Since the discovery of some interesting biologically active phosphonic acid derivatives 1,2 the interest on well practicable syntheses of the phosphonesterderivatives has much grown. (E) -Dialky1-3-oxo-1-alkenylphosphonates 3, Dialkyl-1-oxo-2-alkenylphosphonates 2 and Dialkyl-1-oxoalkylphosphonates 1 are very useful structures to realize interesting transformations to various phosphonesterderivatives with a heterocyclic ring as substituent. Whereas the phosphonates 1 and 2 are well known compounds, the synthesis of the phosphonates 3 has been published only at earlier time³. The phosphonates 1 can be easily transformed to the hitherto unknown Dialkyl-1-bromo-1-oxoalkylphosphonates 4, useful reagents for preparing the thiazolylphosphonates 5 as well as the imidazo-1,2-apyridinyl-and the imidazo-[1,2-a]-pyriminylphosphonates $\underline{6}$ and $\underline{7}$ and the indolizinderivatives 8 (scheme 1). The (E)-Dialkyl-3-oxo-1-alkenylphosphonates 3 can be brominated in a similar way to form the Dialkyl-3-oxo-1-alkenyl-4-bromophosphonates 9, which in turn enable the synthesis of the corresponding thiazolylvinylphosphonates 10, the imidazo-1,2-apyridinylvinyl- and the imidazo-[1,2-a]- pyrimidinylvinylphosphonates 11 and 12 as well as 13, the vinyl-analogues to the indolizinderivatives 9. Other useful

Scheme 1

OP(OEt)₂

R

$$(EtO)_2$$
POCOCHBrR

 R^4
 R^4

transformations of $\underline{2}$ and $\underline{3}$ consist of producing the tosylhydrazones $\underline{14}$ and $\underline{15}$ followed by basic induced formation of the corresponding diazophosphonates $\underline{4}$ and their cyclisation to the same type of Dialkyl-3-pyrazolyl-5-alkylphosphonates $\underline{16}$ (scheme 2).

A special benzyloge to $\underline{2}$ is the 2-vinylbenzylphosphonate $\underline{17}$ (scheme 3). It is a useful startpoint for the synthesis of the diazepinylphosphonate 20 via 18 and 19

on the one and the indanylphosphonate <u>21</u> on the other hand. There are a series of other possibilities to use the compounds <u>3</u> for the synthesis of new interesting structures. The well practicable cis-hydroxylation yields the (±)-threo-glycolderivatives <u>22</u> which enable (scheme 4) the synthesis of some structural analogues <u>24</u> to the well known antibiotic phosphonomycin⁵.

scheme 4

(±)-three (R¹O)₂PCH(OH)CH(OH)COR²
$$\longrightarrow$$
 (R¹O)₂PCH-CHCOR²

22

23

OTS OSIX

OP(OR¹)₂ COR²

R¹= (CH₃)₂CH, C₂H₅

R²= H, CH₃,(CH₃)₂CH,

The reaction of $\underline{22}$ with two equivalents of tosylchloride in pyridine leads to the (Z)-enoltosylatederivatives $\underline{25}$ (scheme 5) a hitherto unknown substance class, which opens some approaches to other phosphonatederivatives.

Scheme 5

$$(R^{1}0)_{2}P^{0}$$

OTS

 Pa/H_{2}
 $(R^{1}0)_{2}P^{0}$

OTS

 Pa/H_{2}
 $(R^{1}0)_{2}P^{0}$

OTS

 $(R^{1}0)_{2}P^{0}$
 $(R^{1}0)_{2}P^{0}$

Beside the preparation of the pyrazolyl-3-phosphonates 16 it can be transformed by catalytic hydrogenation to the Dialkyl-2-tosyloxy-3-oxoalkylphosphonates: 26.Substitution by Tetrabutylammoniumazide leads to the azidocompounds 27 a new source for the preparation of some β -Acetaminophosphonic esters. The compounds 26 can be

used also for the synthesis of the Dialkyl-5-thiazolyl-methylphosphonates 28 and the imidazo-1,2-a-pyridinyl-methylphosphonates 29. Another interesting approach to a series of heterocyclic structures starting from Dialkyl-3-oxo-1-alkenylphosphonates 3 consists of epoxidation to 30 (scheme 6) followed by a condensation reaction with the ambident nucleophiles thiourea, 2-amino-pyridine,2-aminopyridimidine and ethyl-2-pyridylacetate⁶.

The resulting phosphonates 31-34 are easily cleaved to diakylphosphitanion and the heterocyclic aldehyds 35-38.

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