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A NOVEL AND VERSATILE SYNTHESIS OF HETEROCYCLIC ALDEHYDES USING DIALKYL 3-OXO-1-ALKENYL-PHOSPHONATES.

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Summary: Dialkyl 1,2-epoxy-3-oxoalkyl-phosphonates, easily prepared from the corresponding 1-alkenyl-phosphonates, react with ambident nucleophiles to dialkyl 1-hetaryl-1-hydroxymethyl-phosphonates, which can be transformed to heterocyclic aldehydes.

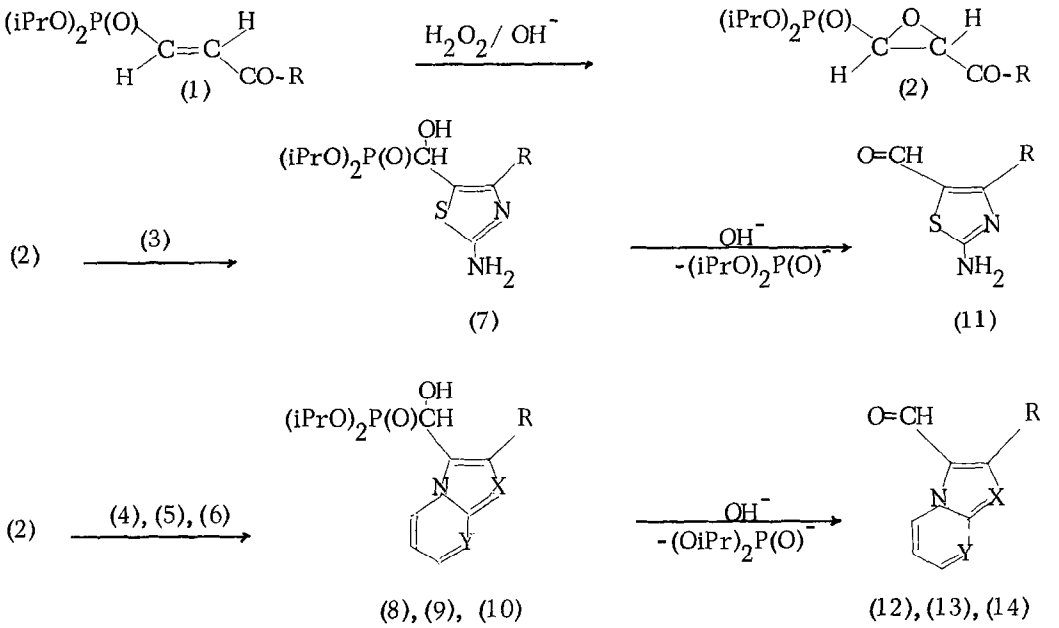
(E)-Dialkyl 3-oxo-1-alkenyl-phosphonates (1)[1] have previously been converted to bicyclo[2.2.1]heptenyl-phosphonates[2a,2b] and cis-1,2-epoxy-3-oxoalkyl-phosphonates (fosfomycin analogues)[3] as well as to various heterocyclic systems bearing a dialkoxyphosphinyl group[4,5].

In this paper we report a three-step transformation of (1) to a series of heterocyclic aldehydes. The key step of this new method is the regioselective opening of epoxides (2) by ambident nucleophiles followed by condensation with the oxo-group, leading to dialkyl 1-hetaryl-1-hydroxymethyl-phosphonates (7) - (10) (Scheme 1).

Starting with 1-alkenyl compounds (1) the epoxyphosphonates (2) are easily prepared ($MeOH/H_2O_2$/aqu. Na_2CO_3, $T<15^oC$, 5-24 h). Reaction of (2) with ambident nucleophiles (3) - (6) (refluxing ethanol or isopropanol, 24-48 h) gives the 1-hetaryl-1-hydroxymethyl derivatives (7) - (10). These are converted by mild alkaline treatment (0.5 N NaOH, 3-5 h) to dialkylphosphite anion and to heterocyclic aldehydes (11) - (14). With thiourea as nucleophilic component 2-amino-thiazole-5-carboxaldehydes (11) are obtained, while 2-aminopyridine, 2-aminopyrimidine and ethyl 2-pyridylacetate afford 3-formyl-substituted imidazo[1,2-a]pyridines (12), imidazo[1,2-a]pyrimidines (13) and indolizines (14), respectively. The results are summarized in Table 1[6].

Reacting cytosine (15) with (2a) (refluxing i-PrOH, 14 d) in contrast to the examples mentioned above, we isolated a mixture of two α-hydroxyphosphonates (16a) and (17a), which was hydrolyzed to the isomeric aldehydes (18a) and (19a) (Scheme 2). These results can be explained in terms of a concomitant Dimroth-rearrangement[10], which results in a reversed substitution pattern on the heterocycle. Compounds (18a) and (19a) were separated by column chromatography on silica gel (ethylacetate/methanol 5:1). The aldehyde (19a)

SCHEME 1



		X	Y
(3) thiourea			
(4) 2-aminopyridine	(4), (8), (12)	N	CH
(5) 2-aminopyrimidine	(5), (9), (13)	N	N
(6) ethyl 2-pyridylacetate	(6), (10), (14)	$C(CO_2Et)$	CH

	R
a	Me
b	Et
c	iPr
d	Phe

TABLE 1: Reaction of 1,2-Epoxy-3-oxoalkyl-phosphonates (2) with Nucleophiles and Subsequent Alkaline Cleavage of the Resulting 1-Hetaryl-1-hydroxymethyl-phosphonates to Aldehydes

(2)	nucleophile	hydroxyphosphonate (yield % /m.p. °C)	aldehyde (yield % /m.p. °C)
(2a)	(3)	(7a) (75/ 144-146)	(11a)[a] (98 / 198-202, dec.)
(2b)	(3)	(7b) (69/ 141-145)	(11b) (95 /207-210)
(2d)	(3)	(7d) (35/ 128-130)	(11d)[b] (80 / 285, dec.)
(2a)	(4)	(8a) (43/ 80)	(12a)[c] (95 /115-118)
(2b)	(4)	(8b) (59/ 70-74)	(12b) (95 / 42-43)
(2d)	(4)	(8d) (64/156-159)	(12d)[d] (95/141-143)
(2a)	(5)	(9a) (52 /165-170)	(13a) (74/165-167)
(2b)	(5)	(9b) (43/154-159)	(13b) (89/119-120)
(2c)	(5)	(9c) (47/204-206)	(13c) (98/140-142)
(2d)	(5)	(9d) (57/200-203)	(13d) (90/173-175)

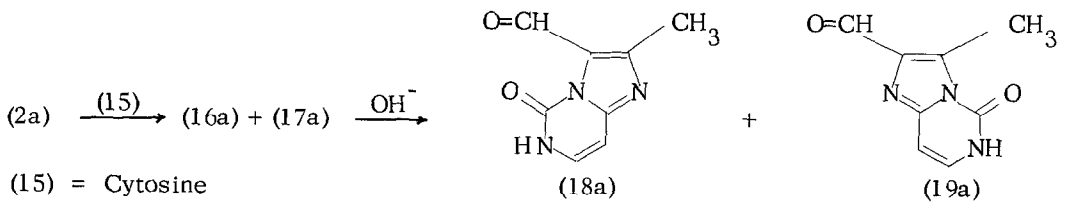
TABLE 1 continued

(2a)	(6)	(10a) (51 / 145-147)	(14a) (91 /105-106)
(2b)	(6)	(10b) (20/ 120-122)	(14b) (82/ 80- 83)
(2d)	(6)	(10d) (50/150-153)	(14d) (89/ 97-99)
(2a)	(15)	(16a) + (17a) (51 /-)	(18a) (-[e] / 295, dec.)
			(19a) (-[e] / 295, dec.)

[a] Ref.[7] m.p. 180-181°C; [b] isolated as N-acetyl derivative; [c] Ref.[8a] m.p.110-111°C, Ref.[8c] m.p. 122-123°C; [d] Ref.[9a] m.p. 145-146°C, Ref.[9b] m.p. 147-148°C; [e] total yield (18a) + (19a) = 95 % , (18a):(19a) ~ 5:4.

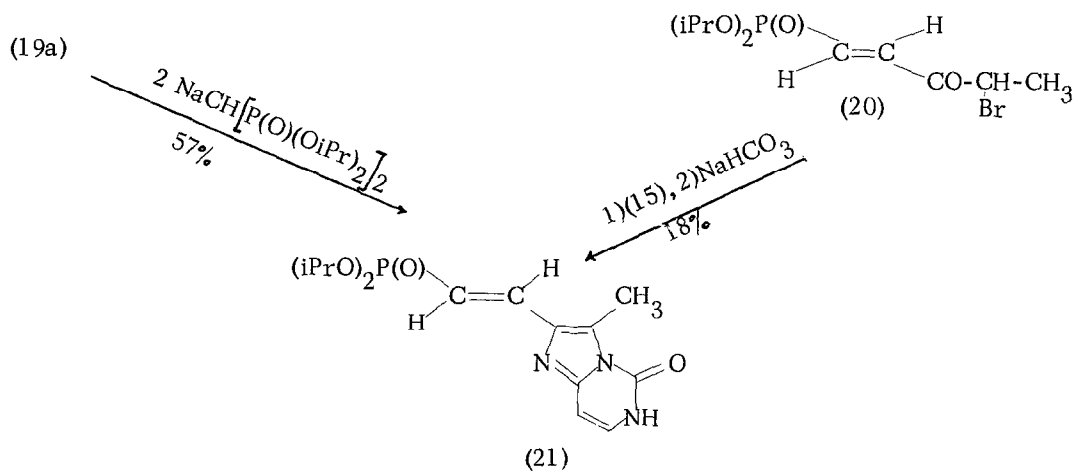
could be proved to be the rearranged product by subsequent trans-olefination (DMSO / $Na^{+-}CH[(P(O)(OiPr)_2]_2$, 5 h , r.t.)[11] to the vinylphosphonate (21). This compound had previously been prepared from (20) by the procedure also shown in Scheme 3[5].

SCHEME 2



(15) = Cytosine

SCHEME 3



Conclusion

The results emphasize the importance of α-hydroxyalkyl-phosphonates as synthons of carbonyl functions. Each reaction allowing the introduction of a hydroxy group in α-position to a dialkoxyphosphinyl moiety can thus be used for the generation of new carbonyl units. This was previously shown in the conversion of carboxylic acids to aldehydes via $NaBH_4$ - reduction of acylphosphonates[12a,12b], and in a synthesis of ketones from aldehydes via α-trimethylsilyloxymethyl-phosphonates[13]. In our method the latent α-hydroxy group is introduced during the synthesis of epoxy-phosphonates (2) from alkenyl-phosphonates (1).

Further extension and exploitation of the synthetic potential of this approach will be reported elsewhere.

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