Tetrahedron Vol 40, No 15, pp 2837 to 2842, 1984
Printed in the U.S.A.

0040-4020/84 $3.00 + .00
Pergamon Press Ltd

CYCLIC ENEDIOL PHOSPHORANES OBTAINED FROM THE REACTION OF TRIMETHYL PHOSPHITE WITH BIACETYL AND HEXAFLUOROBIACETYL GIVE STRIKINGLY DIFFERENT ACYLATION PRODUCTS

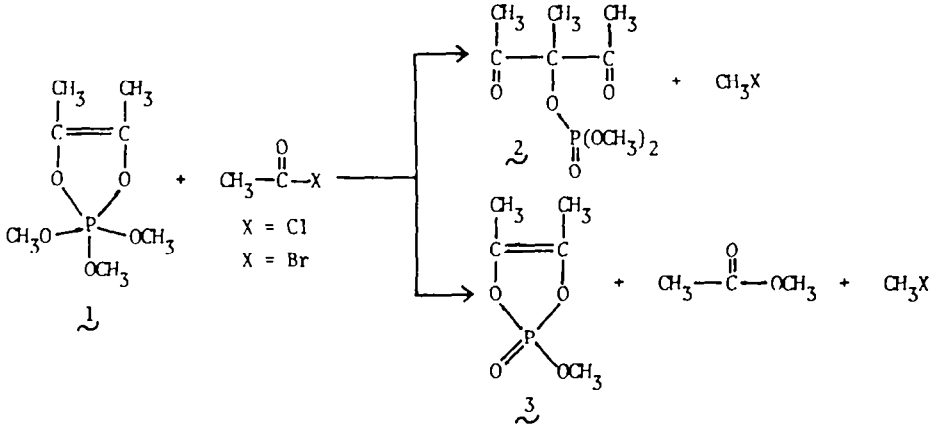
FAUSTO RAMIREZ* AND JAMES F. MARECEK

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794

(*Received in USA 9 April 1984*)

Abstract - Cyclic enediol phosphoranes (2,2,2-trimethoxy-2,2-dihydro-1,3,2-dioxaphospholenes), prepared from α-diketones, RCOCOR, and trimethyl phosphite (TMP), give strikingly different acylation products depending on the electronic properties of the groups, R, that occupy the 4,5-positions in the dioxaphospholene ring with pentacovalent phosphorus. Reaction of acetyl chloride or bromide with the hexafluorobiacetyl-TMP phosphorane gives exclusively the product of endocyclic O-acylation, dimethyl-(2-acetoxy-cis-1,2,-bistrifluoromethylvinyl) phosphate. Acylation of the biacetyl-TMP phosphorane gives mixtures of the product of exocyclic O-acylation (a cyclic enediol phosphate) and the product of C-acylation (an α-hydroxy-β-diketone phosphate), the proportions depending on the structure of the acyl halide and the solvent. The parent 1,3,2-dioxaphospholene, i.e., the glyoxal-TMP phosphorane where R = H, gives exclusively the product of endocyclic O-acylation with both acyl halides in all solvents.

In 1968 we observed[1] that the reaction of the biacetyl-trimethyl phosphite (TMP) oxyphosphorane (1, Scheme I) with acetyl chloride at 55°C in the absence of solvent yielded the product of C-acylation, an α-hydroxy-β-diketone phosphate, 2, in over 80% isolated yield. This observation, although novel, was not startling since it was already known[2] that the biacetyl-TMP phosphorane behaved as a "pseudocarbanion" in its reactions with aldehydes and ketones, generating a new carbon-carbon single bond in those reactions[3]. Soon[4], however, the complexity of the acylation reaction of the biacetyl-TMP phosphorane became apparent, as can be seen in Table I and Scheme I. Evidently, exocyclic O-acylation competes with C-acylation and generates a cyclic enediol phosphate 3. The proportion exocyclic O-acylation: C-acylation products is very sensitive to the structure of the acyl halide and the solvent.



Scheme I

Table I. Acylation of the Biacetyl-Trimethyl Phosphite Phosphorane, 1[a].

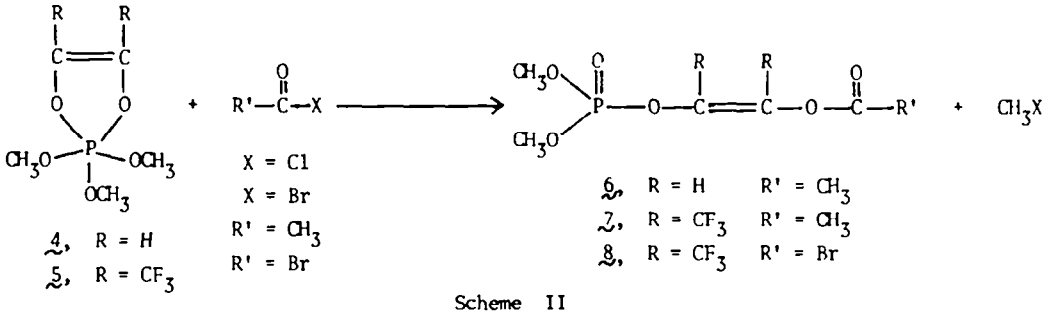
Solvent	Reaction time, hr[b]	Products C-acylation %	Exocyclic O-acylation %
	CH_3COCl		
None	90	97	3
Dioxane	150	90	10
Acetonitrile	60	65	35
Dichloromethane	72	20	80
Benzene	300[c]	30	70
	CH_3COBr		
None	0.33	25	75
Dioxane	2.0	50	50
Acetonitrile	0.25	5	95
Dichloromethane	1.0	10	90
Benzene	5.0	25	75

[a] Equimolar reagents in 2.7M solution at 40±1°C.

[b] At which reaction is virtually complete; no further changes in the products are observable with time.

[c] Only 80% of reaction.

The reaction of the glyoxal-TMP oxyphosphorane (4, Scheme II) with acetyl chloride revealed a third type of behavior of the cyclic enediol phosphoranes upon acylation[5,6]. When this reaction proceeded at 30°C in dichloromethane solution for 3h, the only detectable product, isolated in over 70% yield, was dimethyl-cis-2-acetoxyvinyl phosphate, 6, the result of endocyclic O-acylation.



Scheme II

We have now found a striking difference between the hexafluorobiacetyl-TMP phosphorane[7], 5, and the biacetyl-TMP analog, 1, in their reactions with acyl halides; the results are described in this paper. The paper also includes additional studies of the reactions of the glyoxal-TMP phosphorane, 4, to serve as a basis for comparison between different cyclic enediol phosphoranes under strictly comparable experimental conditions.

RESULTS

As shown in Table II, endocyclic O-acylation is the only detectable pathway for the reaction of the glyoxal-TMP adduct, 4, with acetyl choloride and bromide in all solvents, and in the absence of solvent. The structure and stereochemistry of the product, 6, have previously been

established[5,6]. The glyoxal-TMP adduct undergoes acylation at a much faster rate than the biacetyl-TMP analog, and not surprisingly acetyl bromide is more reactive than the chloride in both reactions and in all solvents.

Table II. Acylation of Glyoxal-Trimethylphosphite Phosphorane, 4[a].

Solvent	Reaction time[b] (min)	
	CH_3COCl	CH_3COBr
None	30	3
Dioxane	110	4
Acetonitrile	45	1
Dichloromethane	60	3
Benzene	150	12

[a]Equimolar reagents in 2.7M solution at 40±1°C. In all cases the only detectable product results from endocyclic O-acylation, 6.

[b]Time at which reaction is virtually complete. No further changes in the product are observable with time.

The hexafluorobiacetyl-TMP adduct, 5, is the least reactive of the cyclic enediol phosphoranes as shown in Table III. However, unexpectedly, the only detectable product results from endocyclic O-acylation(SchemeII); no evidence has been obtained for the formation of the products of exocyclic O-acylation or C-acylation as in the case with the biacetyl-TMP analog. The structure of dimethyl-(2-acetoxy-cis-1, 2,-bistrifluoromethylvinyl) phosphate, 7, has been assigned as described in the Experimental Section.

Table III. Acylation of the Hexaflurobiacetyl-Trimethylphosphite Phosphorane, 5[a].

Solvent	Reaction time[b] (hr.)	
	CH_3COCl	CH_3COBr
None	230	24
Dioxane	210	24
Acetonitrile	90	8
Dichloromethane	250	50
Benzene	...	85

[a]Equimolar reagents in 2.7M solution at 40±1°C. In all cases the only detectable product results from endocyclic O-acylation, 7.

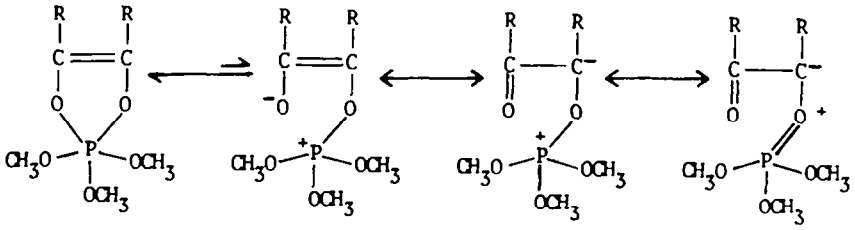
[b]Time at which reaction is virtually complete. No further changes in the product are observable with time.

The tendency for endocyclic O-acylation in the hexafluorobiacetyl-TMP adduct is also demonstrated in its reaction with carbonyldibromide, as shown in Scheme II. Using an excess of the bifunctional acylating agent, the bromocarbonyloxyvinyl phosphate, 8, is obtained in high yield.

DISCUSSION

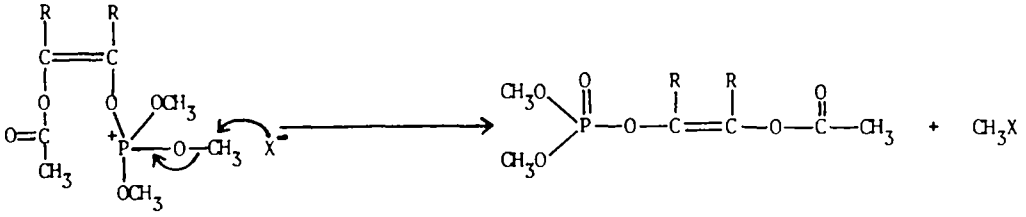
To account for the unexpected and striking differences in the products of acylation of the biacetyl-TMP and hexafluorobiacetyl-TMP phosphoranes, we assume the existence of a relatively small amount of an enolate dipolar ion in relatively rapid equilibrium with the cyclic enediol phosphorane form. Similar ionizations of acyclic aryloxyphosphoranes have been extensively studied by Westheimer and his coworkers[8]. Some of the possible resonance structures that could contribute to the stabilization of the enolate ion are depicted in Scheme III. Since the inductive electron-withdrawing effect of the trifluoromethyl group should stabilize, and the electron-releasing effect of the methyl group should destabilize, the enolate anion relative to the parent

glyoxal-TMP adduct, one might predict that the amount of enolate ion in equilibrium with its phosphorane form should increase in the order: biacetyl-TMP<glyoxal-TMP<hexafluorobiacetyl-TMP.



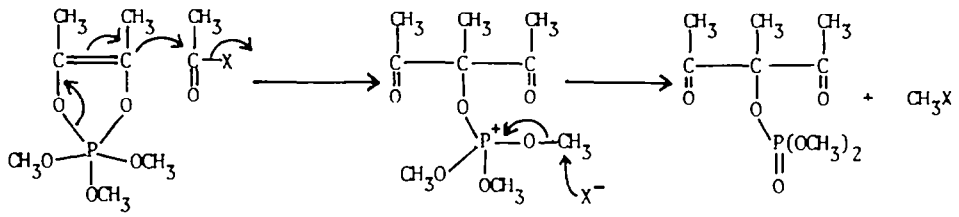
Scheme III. R = CH_3, H or CF_3

If the concentration of enolate ion in solutions of the glyoxal-TMP and hexafluorobiacetyl-TMP adducts is significant, one can describe the formation of the product of endocyclic O-acylation as shown in Scheme IV. This is essentially a nucleophilic attack by enolate-oxygen at the unsaturated acyl halide carbon, followed by the usual displacement by halide ion on the methyl carbon of a tetraalkoxyphosphonium ion[9]. The absence of C-acylation in these two adducts is not predictable apriori, but it should be noted that electron density at carbon should be decreased as the substituent becomes electron-withdrawing (CF_3).



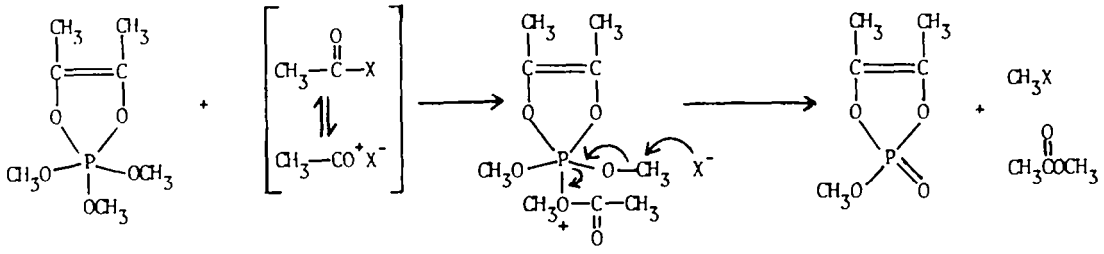
Scheme IV. R = H or CF_3

Since no product of endocyclic O-acylation is observed with the biacetyl-TMP adduct, either the concentration of enolate ion is now vanishingly small, or if there is still an appreciable concentration of this ion in equilibrium with the cyclic phosphorane, the rate of enolate O-acylation is no longer competitive with the rate of C-acylation. One could justify this second alternative on the grounds that carbanion reactivity should be enhanced by the electron-releasing methyl substituent. However, this second alternative does not explain why, as enolate-oxygen reactivity vanishes, the nucleophilic reactivity of the methoxy-oxygen should appear in the form of the product of exocyclic O-acylation. A more likely interpretation is offered by the assumption that in solution, the biacetyl-TMP adduct exists virtually in the cyclic phosphorane form. If such is the case, the mechanism shown in Scheme V can be written. The reaction is depicted as a concerted S_N2-type of displacement on the acyl halide. However, an alternative S_N1 type of displacement involving an acylium cation can not be ruled out in particular with acetyl bromide and/or in the more polar solvent acetonitrile, (ε 38, vs dichloromethane, ε 9.0 and dioxane, ε 2.0).



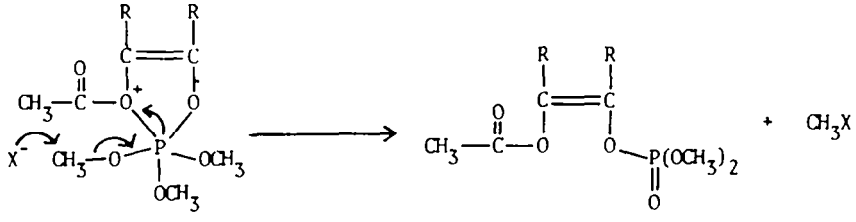
Scheme V

A plausible mechanism for the exocyclic O-acylation of the biacetyl-TMP adduct is suggested in Scheme VI. Now, in an S_N2, or more likely an S_N1 type of displacement, the methoxy-oxygen is acylated to form a positively charged cyclic phosphorane which is well disposed for a nucleophilic attack by halide ion on a methyl group followed by loss of methyl acetate. It should be noted that both acetyl bromide and acetonitrile shift the mechanism in the direction of exocyclic O-acylation and formation of the synthetically useful[10] cyclic enediol phosphate.



Scheme VI

If the concentration of enolate ion in equilibrium with cyclic phosphorane is insignificantly low in the biacetyl-TMP adduct, one should still explain why no product of endocyclic O-acylation is formed from this cyclic phosphorane by a direct attack of a ring oxygen on the acyl halide in a reaction similar to that proposed for the exocyclic O-acylation. Such a mechanism would take the form shown in Scheme VII and there is no apparent reason why this mechanism could not be operative when R = H or CF_3 also. It is conceivable, however, that acylation of an endocyclic oxygen is disfavored in the three cyclic phosphoranes, possibly as a result of some type of electron delocalization of the lone pairs of the ring-oxygens of the 1,3,2-dioxaphospholene ring, with its pentacovalent phosphorus. A corollary of this hypothesis is that the product of endocyclic O-acylation which is observed as the sole product under all experimental conditions in the acylation of the glyoxal-TMP and hexafluorobiacetyl-TMP adducts reflects a relatively fast reaction of the enolate dipolar ion present in small amounts in rapid equilibrium with the phosphorane itself.



Scheme VII. Not observed when R = CH_3; possible but unlikely when R = H or CF_3.

EXPERIMENTAL SECTION

Since the phosphoranes are quite sensitive to hydrogen halides, all reactions were carried out under strictly anhydrous conditions (argon atmosphere) with purified and anhydrous reagents and solvents. ^{31}P and ^{19}F NMR spectra were measured at 40.5 and 94.1 Mz respectively. The chemical shift values (δ) are reported as positive to low field of the reference (H_3PO_4 = 0 and CF_3COOH = 0 for ^{31}P and ^{19}F respectively).

Reactions of the Glyoxal-TMP Adduct, 4. 2,2,2-Trimethoxy-2,2-dihydro-1,3,2-dioxaphospholene, 4, was prepared from anhydrous glyoxal as previously described[5]. Equimolar mixtures of the phosphorane, 4, and the acyl halide, alone or as 2.7M solutions in the solvents indicated were kept under argon at 40°C. The reactions were monitored by ^1H and ^{31}P-NMR and were found to be virtually complete in the times listed. The results are given in Table II. In several cases, the solvent was removed and the product purified and characterized by its spectral data, as previously described[5]. The structure of dimethyl-cis-2-acetoxyvinyl phosphate, 6, has been confirmed by elemental analysis[5], and by a comparison of its spectral data with those of the products obtained when phosgene, $COCl_2$ was treated with one and two molar equivalents of the glyoxal-TMP phosphorane, 4. The endocyclic O-acylation character of these reactions and the stereochemistry of the products were established by X-ray crystallographic analysis of one of these products bis-(dimethylphosphatovinyl)carbonate[6].

The equimolar reaction of phosphorane 4 (3.3 mmol) with acetyl chloride in dry pyridine (5ml) was carried out at 25°C for 3h. The only detectable product was that of endocyclic O-acylation, 6.

Reactions of the Hexafluorobiacetyl-TMP Adduct, 5. 4,5-bis-Trifluoromethyl-2,2,2-trimethoxy-2,2-dihydro-1,3,2-dioxaphospholene, 5, was prepared from hexafluorobiacetyl[11] as previously described[7,12]. Freshly distilled acetyl bromide (1.5g, 11 mmol) was added at once to a solution of the phosphorane, 5, (2.34g, 7.3 mmol) in dichloromethane (2ml), at 25°C, under argon. The flask was kept for 7 days at 25°C. The solution was evaporated in vacuum and the residue was fractionally distilled to yield dimethyl-(2-acetoxy-cis-1,2,-bistrifluoromethylvinyl)phosphate (7; 1.5g, 60% yield), b.p. 54°C (0.35mm).

Calcd for $C_8H_9O_6F_6P$: C,27.75; H, 2.66; F, 32.93. Found: C, 27.68; H, 2.65; F, 32.69.

IR spectrum (CH_2Cl_2): 1800 cm^{-1} (strong, C=O); 1670 cm^{-1} (weak C=C).

^1H NMR ($CDCl_3$): δ = 2.33 ppm (singlet, CH_3CO); δ = 3.92 ppm (doublet, J_{HCOP} = 11.6 Hz, $(CH_3O)_2P(O)$), in a 1:2 ratio.

^{31}P NMR ($CDCl_3$): multiplet centered at -5.8 ppm.

^{19}F NMR ($CDCl_3$): quartet at 12.8 ppm (J_{FCCCCF} = 12Hz) and a quartet at 15.0 ppm (J_{FCCCCF}=12Hz).

The reaction of the phosphorane 5 with acetyl chloride and acetyl bromide was also carried out in several solvents under the same conditions as those described above for the glyoxal-TMP phosphorane, 4. The results are given in Table III.

Freshly distilled carbonyldibromide[13] (5.65g, 30 mmol) was dissolved in dichloromethane (7ml) under argon. A solution of the hexafluorobiacetyl-TMP phosphorane (5; 6.40g, 20 mmol) in dichloromethane (5ml) was added dropwise over a 10 min period at 25°C. The flask was kept for 3 days at 25°C. The solution was evaporated at 25°C, first at 30mm and finally at 0.5mm. The colorless liquid remaining (7.72g, 95% yield) proved to be the product of endocyclic O-acylation, 8. The analytical sample (b.p. 57°C, 0.25mm) was prepared by fractional distillation through a 12cm Vigreux column.

Calcd for $C_7H_6O_6BrF_6P$: C,20.45; H, 1.47. Found: C, 20.70; H, 1.61.

IR spectrum (CH_2Cl_2): 1800 cm^{-1} (strong, C=O); 1680 cm^{-1} (weak C=C).

^1H NMR ($CDCl_3$): δ = 3.98 ppm (doublet, J_{HCOP} = 11.6 Hz, $(CH_3O)_2P(O)$).

^{31}P NMR ($CDCl_3$): multiplet centered at -5.1 ppm.

^{19}F NMR ($CDCl_3$): quartet of doublets at 12.4 ppm (J_{FCCCCF} = 12Hz, J_{FCCOP} = 4Hz) and a quartet at 15.4 ppm (J_{FCCCCF} = 12Hz).

Acknowledgement

This research was supported by Grant CHE 81-10294 from the National Science Foundation.

REFERENCES

1. F. Ramirez, S. B. Bhatia, A. J. Bigler and C. P. Smith, J. Org. Chem. 33, 1192 (1968).
2. F. Ramirez, N. Ramanathan and N. B. Desai, J. Am. Chem. Soc. 84, 1317 (1962).
3. F. Ramirez, Synthesis 90 (1974).
4. F. Ramirez, J. F. Marecek, S. L. Glaser and P. Stern, Phosphorus, 4, 65 (1974).
5. F. Ramirez, S. L. Glaser, A. J. Bigler and J. F. Pilot, J. Am. Chem. Soc. 91, 496 (1969); Correction, ibid. 91, 5695 (1969).
6. M. Ul-Haque, C. N. Caughlan, G. D. Smith, F. Ramirez and S. L. Glaser, J. Org. Chem. 41, 1152 (1976).
7. F. Ramirez, J. Marecek, I. Ugi and D. Marquarding, Phosphorus 3, 91 (1973).
8. C. L. Lerman and F. H. Westheimer, J. Am. Chem. Soc. 98, 179 (1976); D. I. Phillips, I. Szele and F. H. Westheimer, Ibid., 98, 184 (1976); I. S. Sigal and F. H. Westheimer, Ibid., 101, 5329, 5334 (1979).
9. H. R. Hudson, Topics Phos. Chem. 11, 339 (1983).
10. F. Ramirez and J. F. Marecek, Acc. Chem. Res. 11, 239 (1978).
11. L. O. Moore and J. W. Clark, J. Org. Chem. 30, 2472 (1965).
12. F. Ramirez and H. Kugler, Phosphorus 2, 203 (1973).
13. A. V. Bartal, Liebigs Ann. Chem. 345, 335 (1906); H. J. Schumacher and S. Lenher, Chem. Ber. 61, 1671 (1928).