Tetrahedron Letters No.2, pp. 105-108, 1971. Pergamon Press. Printed in Great Britain.

FORMATION AND ALKYLATION OF ENOLATES FROM ENOL PHOSPHORYLATED SPECIES[1]

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(Received in USA 2 December 1970; received in UK for publication 8 December 1970)

The reactions of α-haloacetophenones, further substituted by α-halo or phenyl groups, with triphenylphosphine lead to isolable enol triphenylphosphonium halides.[2,3] Cyclic α-haloketones, as typified by α-bromocyclohexanone, give the ketophosphonium halide.[4] We have found that both cyclic and acyclic α-chloroketones, and some α-bromoketones, react with ethyl diphenylphosphinite 1 to give enol diphenylphosphinates. The behavior of these systems is reminiscent of the reactions of trialkyl phosphites with α-haloketones.[5,6]

We now report that enol triphenylphosphonium halides, enol phosphinates, or enol phosphates are cleaved by organometallic reagents to form a metal enolate and a tertiary phosphine, phosphine oxide, or phosphonate[7], respectively. The best results are obtained with methyllithium or butyllithium. Phenyllithium and phenylmagnesium bromide have also been used. The cleavage of enol phosphinates or enol phosphates in dimethoxyethane (DME) with butyllithium (2.5 M in hexane) or methyllithium (2.0 M in diethyl ether) involves the most promising systems. The cleavage of enol phosphonium halides, in contrast, is complicated by the formation of biphenyl, triphenylphosphine[8], and by the hydrolytic instability of the starting compounds.

The enolates thus formed can then be alkylated. A comparison (not necessarily optimal) of product yields from the enol phosphinate 2 and the enol phosphonium chloride 3 derived from desyl bromide 4 and desyl chloride 5, respectively, is given in Table I. The stereochemistry of 2, 3, and the resultant enolates are under investigation.[10]

The utility of our method in forming regiospecific lithium enolates which can then be primarily monoalkylated on carbon is shown by the data in Table II. The diphenyl enol phosphinate of cyclohexanone 8, or the diethyl enol phosphate 9 (formed in 88 and 66 % yields from 2-bromocyclohexanone with 1 or triethyl phosphite (TEP), respectively) is converted mainly to 2-methylcyclohexanone. Furthermore, the isomeric enol phosphates diethyl 2-methylcyclohexenyl phosphate (11) and diethyl 6-methylcyclohexenyl phosphate (12), from the reaction of TEP with

2-methyl-2-bromocyclohexanone (24, 70%) or 2-methyl-6-bromocyclohexanone (25, 80%)[11] are converted mainly to 2,2-dimethycyclohexanone (15) and 2,6-dimethylcyclohexanone (16), respectively. Similarly the diphenyl enol phosphinate and the diethyl enol phosphate of cyclopentanone are converted mainly to 2-methylcyclopentanone (20).

This work represents a departure from the known enolate formation methods based on enol trimethysilyl ethers[13,14] and enol acetates[15] in that it is based on α-haloketones which can be regiospecifically synthesized in many cases and then converted to a specific enol phosphorylated species.

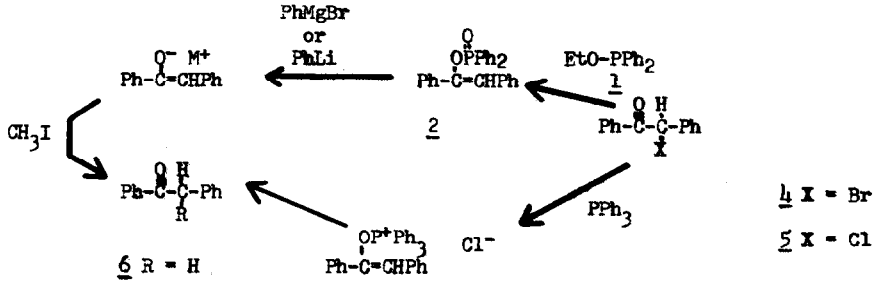
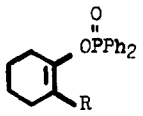
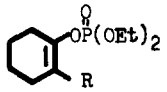
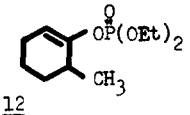
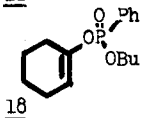
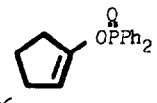
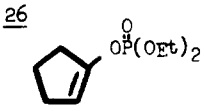


Table I. Cleavage and Subsequent Reactions of Phosphorylated 1,2-Diphenylethylenes

Compound	Conditions	Yields, % Ketone 6	Methyl ketone 7	Biphenyl	$OPPh_3$	PPh_3
3	1. $PhMgBr^a$, THF^b	1	36	16	-	100
	2. CH_3I added[b]					
3	1. PhLi, THF^b	4	86	64	-	100
	2. CH_3I added[c]					
2	1. $PhMgBr^a$, THF^b	1	85	-	98	-
	2. CH_3I added[b]					

a) Two equiv. b) 12 hr. reflux. c) 5 hr. reflux.

Table II. Formation and Alkylation of Cyclic Ketone Enolates

Compound		Reaction Conditions[a]	Ratio of Recovered Ketones[b] 13	14	15	16	17
 8 R = H	1.	a) BuLi-DME b) Add to CH_3I-DMSO[d]	1.6	90.4 (86)[c]	8.0	0	0
10 R = CH_3	2.	a) BuLi-DME b) Add to CH_3I DME	-	2.0	91.5 (87)[c]	0	6.5 (6)[c]
 9 R = H	3.	a) MeLi (2 equiv)-DME b) Add to CH_3I-DME	13	79 (75)[c]	6	2	0
11 R = CH_3	4.	a) MeLi (1 equiv)-DME b) Add to CH_3I-DME	-	18	76	3	3
 12	5.	a) MeLi (1 equiv)-DME b) Add to CH_3I-DME	-	17	0	76 (75)[c]	3[e]
 18	6.	a) MeLi-(1 equiv)-DME b) Add to CH_3I-DME	14	81 (80)[c]	5	0	0
			19	20	21	22	23
 26	7.	a) MeLi (1 equiv)-DME b) Add to CH_3I-DME	1	77 (76)[c]	7	12	3
 27	8.	a) MeLi (1 equiv)-DME b) Add to CH_3I-DME	12	78	4	6	0

a) Cleavage at 25° for 20 min. Methylation at 0° for 1-5 min.
b) Ratio by vpc analysis (20 % SE-30, 10 ft x 1/4 inch column at 100°. Column elution order is based on known data (13b) and by comparison with genuine samples for 13, 14, 16, 17, 19, 20 and 22. c) Actual yield by vpc calibration curves. d) see ref. 13b. e) 2,2,6,6-Tetramethylcyclohexanone (4%) is also formed.

Experimental: The following is illustrative of a general procedure. n-C_4H_9Li (2.3 M, 6.3 ml, 0.0145 mol) in hexane is added by syringe at 0° under N_2 to 10 (4.5 g, 0.0144 mol) in DME (30 ml, distilled from $LiAlH_4$) to give a pale yellow solution which is kept at 25° for 1 hr, and added to CH_3I (5.0 ml, 0.080 mol) in DME (20 ml) at 25°. After 5 min at 25°, 1 N-HCl (20 ml, 0.02 mol) is added. The organic layer, combined with Et_2O extracts of the aqueous layer, is washed with saturated $NaHCO_3$, dried ($MgSO_4$), and the solvent is distilled at 760 mm. The residue is extracted with hexane (25°) to give the ketonic products. For enol phosphates, a trace of Ph_3CH is added, CH_3Li is added until a red color persists and methylation is continued until it fades.[13]

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(3) I.J. Borowitz, P.E. Rusek, Jr., and R. Virkhaus, J. Org. Chem., 34, 1595 (1969).

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(6) P.A. Chopard, V.M. Clark, R.F. Hudson and A.J. Kirby, Tetrahedron, 21, 1961 (1965).

(7) The latter species, presumably formed from enol phosphates, has not yet been isolated in our reactions.

(8) The products may arise via the intermediacy of pentaphenylphosphorane.[9] They are also obtained in the cleavage of α,α-disubstituted-β-ketophosphonium salts with Grignard reagents. Cf T. Mukaiyama, R. Yoda and I. Kuwaijima, Tetrahedron Lett., 23 (1969).

(9) (a) G. Wittig and G. Geisller, Ann. Chem., 580, 44 (1953); (b) G. Wittig and M. Rieber, Ann. Chem., 562, 187 (1949).

(10) All new compounds gave satisfactory spectral data and either satisfactory elemental analyses or (for 10 and 18) mass spectral molecular ion and fragmentation data.

(11) Prepared by L. Futrell by the bromination of the pyrrolidine enamine of 2-methylcyclohexanone in acetic acid-chloroform[12] [80% yield of 25, 24 (9:1)]. Conversion of the mixture gives 12 in greater than 97% purity. The general problem of the synthesis of α-halo-α'-alkylcycloalkanones is under investigation.

(12) (a) By a modification of the procedure of M.E. Kuehne and T.J. Giacobbe, J. Org. Chem., 33, 3359 (1968); (b) Originally suggested as a method by Prof. G. Stork.

(13) (a) G. Stork and P. Hudrlik, J. Amer. Chem. Soc., 90, 4462, 4464 (1968); (b) P. Hudrlik, Ph.D. Thesis, Columbia University, 1968.

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Acknowledgements. We wish to thank the National Science Foundation and the Air Force Office of Scientific Research for financial support. We are grateful to Professors G. Stork and M.E. Kuehne for stimulating discussions.