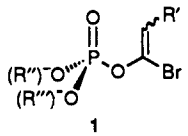
Halo Enol Phosphates: Regioselective Synthesis of Phosphatase Inactivators via a Complex-Induced Proximity Effect

Jeffrey K. Stowell and Theodore S. Widlanski*

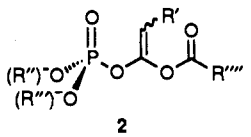
Department of Chemistry, Indiana University Bloomington, Indiana 47405

Received August 10, 1993

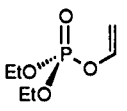
This communication describes a general method for the synthesis of enol phosphates bearing leaving groups at the 1-position. We report the first synthesis of 1-bromo enol phosphates (**1**) and 1-benzoyloxy enol phosphates (**2**), new classes of phosphate esters that should have substantial utility in the design of phosphatase and phosphodiesterase inactivators.[1] These compounds are obtained by dehydrohalogenation of the corresponding 2-halo phosphates with metal amides. Evidence is presented supporting the importance of a complex-induced proximity effect[2] (CIPE) in these reactions.



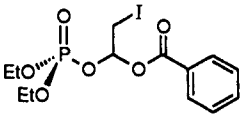
1



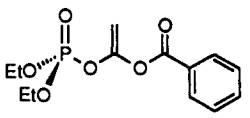
2



3



11

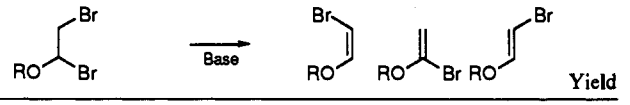


12

Biological processes such as signal transduction, DNA repair, phospholipid metabolism, glucose utilization, the regulation of protein phosphorylation, and many other cellular activities are linked by a common chemical element: the enzyme-catalyzed cleavage of phosphate ester bonds. Given the importance of these biological processes, it is somewhat surprising to find that there are virtually no reports of mechanism-based phosphatase or phosphodiesterase inhibitors.[3,4] In principle, one motif for the design of mechanism-based phosphatase or phosphodiesterase inhibitors may be embodied by enol phosphates bearing leaving groups at the 1-position.[3] There are relatively few reports of 1-halo enol phosphates in the literature,[5] and there are no reports of 1-bromo enol phosphates despite their potential utility as acyl anion and ethylene 1,1 dianion equivalents. Ketene acetals such as **2**, which are formally double mixed anhydrides of two carboxylic acids and a phosphate diester, have also not been reported.

We approached the synthesis of compounds such as **1** as follows: Bromination of diethyl vinyl phosphate (**3**) afforded dibromide **4** in 99% yield. Treatment of dibromide **4** with lithium diisopropylamide in Et_2O at −78 °C gave the desired vinyl bromide (**5**) as the sole organic soluble product.[6] The best yields of bromide **5** were obtained by performing the reaction in nonpolar solvents such as toluene at −78 °C. Similar results were obtained using lithium, sodium, or potassium bis(trimethylsilyl)amide (Li-HMDS, NaHMDS, KHMDS) in toluene. Performing the reaction in THF led to reduced yields of the vinyl bromide (Table 1). Treatment of dibromo benzoate **6** with LiHMDS in toluene also led to exclusive formation of the 1-bromo isomer (**7**). The reaction performed in THF was much less selective (Table 1). The use of bases other than metal amides led largely to the formation of the 2-bromo isomers in both the phosphate and benzoate ester series (Table 1).

Table 1



					Yield
4		**13**	**5**	**14**	
	DBU/THF	39	38	23	86%
	(Li, Na) KHMDS/ $PhCH_3$	<1	>99	<1	91%
	LiHMDS/THF	1	96	3	86%
R = $(OEt)_2P$	KHMDS/THF	3	91	6	65%
	KHMDS/$PhCH_3$/ 18-C-6	16	52	32	28%
6		**8**	**7**	**15**	
	DBU/THF	94	<1	6	54%
	LiHMDS/$PhCH_3$	<1	>99	<1	86%
	KHMDS/$PhCH_3$	<1	>99	<1	78%
	LiHMDS/THF	27	30	43	75%
R = PhC	KHMDS/THF	13	69	18	73%
	KHMDS/$PhCH_3$/ 18-C-6	51	23	26	54%
9		**16**	**10**	**17**	
	DBU/THF	<1	98	2	92%
R = Ts	LiHMDS/$PhCH_3$	<1	>99	<1	94%
	KHMDS/$PhCH_3$	<1	>99	<1	78%

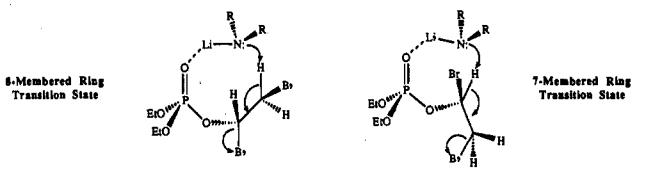


Figure 1.

We reasoned that the regioselectivity of the elimination reaction was being controlled by precomplexation of the metal amide to the phosphate (or benzoate) ester. If such complexation were to take place, the elimination of bromide from the 2-position via a seven-membered-ring transition state might be preferred over elimination from the 1-position via an eight-membered-ring transition state (Figure 1). The preference for a seven-membered-ring structure has been demonstrated for the directed lithiation of alkyl amides.[7]

The possibility that a complex-induced proximity effect[2] may be an important element of these reactions is consistent with the solvent dependence displayed by the metal amide mediated elimination reactions. A further test of this hypothesis was to determine the effect of added crown ethers on the regioselectivity of the reaction. Treatment of dibromide **4** with KHMDS in toluene (−78 °C) in the presence of 18-crown-6 led to the formation of a complex mixture. A large percentage of these products had undergone cleavage of the phosphate ester group. Significantly,

(1) Preliminary results from our lab reveal that 1-chloro enol phosphates inactivate phosphotyrosine phosphatases.

(2) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356–363.

(3) Myers, J. K.; Widlanski, T. S. *Science* **1993**, *262*, 1451–1453.

(4) Aside from the inhibitor reported in ref 3, there appear to be no examples of mechanism-based inactivators of phosphatases or phosphodiesterases reported in the literature. However, a triesterase inactivator has been reported: Blankenship, J. N.; Abu-Soud, H.; Francisco, W. A.; Raushel, F. M.; Fischer, D. R.; Stang, P. J. *J. Am. Chem. Soc.* **1991**, *113*, 8560–8561.

(5) (a) Boyce, B. C.; Webb, S. B. *J. Chem. Soc. C* **1971**, *23*, 3987–3990. (b) Nasakin, O. E.; Kormachev, V. V.; Kukhtin, V. A. *J. Gen. Chem. USSR* **1975**, *45*, 2332–2334.

(6) These enol phosphates may be converted to diesters selectively by treatment of the triesters with $PhSH/Et_3N$. The monoesters may be obtained by treatment of the triesters with freshly distilled TMSBr.

(7) Beak, P.; Hunter, J. E.; Jun, Y. M. *J. Am. Chem. Soc.* **1983**, *105*, 6350–6351.

0002-7863/94/1516-0789$04.50/0

however, all three vinyl bromides were now formed in this reaction. The loss of selectivity that was induced by the presence of a crown ether supports the notion that precoordination of the metal amide is a factor in this reaction. Treatment of the benzoate ester **6** with KHMDS/18-crown-6/toluene gave a more striking result. Under these conditions, the *major* product was the *Z*-bromide (**8**). This product distribution is the opposite of what was obtained in the absence of the crown ether. In addition, the reaction was slowed substantially by the addition of the crown ether. These results are consistent with the hypothesis that coordination of the metal amide to the ester oxygen is important in determining both the rate and selectivity of this reaction.

Since both carboxylate ester **6** and phosphate ester **4** seemed to be susceptible to a CIPE, we were interested in seeing whether this effect would extend to sulfonate esters. Therefore, the behavior of dibromo tosylate **9** was examined. Treatment of this sulfonate ester with *either* metal amides or DBU gave the 1,1-disubstituted olefin (**10**) almost exclusively. On the basis of this result, no arguments can be advanced about the operation of a CIPE in this reaction. A competition experiment was performed by mixing dibromo phosphate **4** and dibromo tosylate **9** together and then treating them with a limiting amount of KHMDS in the *presence* of 18-crown-6. Under these conditions, which disfavor a CIPE, elimination of bromide from the sulfonate ester is substantially faster than elimination from the phosphate ester.[8] However, in the *absence* of 18-crown-6, the rate of elimination of bromide from the *phosphate* ester (relative to the sulfonate ester) is faster when KHMDS is the base, and faster still when LiHMDS is used.[8] The simplest explanation for these results is that the sulfonate ester coordinates poorly, or not at all (relative to the phosphate ester) to the lithium amide. The rate of elimination from the phosphate ester, but not the sulfonate ester, would therefore be enhanced by a CIPE. The same effect probably occurs when a potassium amide is used as the base, but the rate acceleration is smaller because the complexation of potassium by the phosphate ester is less favorable. In the presence of a crown ether, precomplexation of the metal amide is inhibited and dibromo tosylate **9**, which is intrinsically more reactive than dibromo phosphate **4**, suffers the preferential elimination of bromide.

Despite the seemingly harsh conditions required for these elimination reactions, the operation of a CIPE actually permits the synthesis of some rather sensitive compounds that are not available by other means. For example, treatment of iodide **11** (available by treatment of diethyl vinyl phosphate (**3**) with $PhCOOAg/I_2$) with LiHMDS in toluene leads to the formation of ketene acetal **12** in 45% yield. We were unable to effect this elimination with any base other than a metal amide. Presumably, in this case, the operation of a CIPE both suppresses unwanted side reactions and facilitates the dehydrohalogenation reaction.

We have demonstrated that potent CIPEs can be exploited for the synthesis of several classes of molecules that are difficult to prepare by other means. These CIPEs can be directed by both phosphate and carboxylate esters, even when the metal being coordinated is potassium. These results also suggest that sulfonate esters are probably not effective complexing agents under these conditions. Lastly, the synthesis of new types of compounds such as **5** and **12** should greatly expand opportunities for the development of potent phosphatase and phosphodiesterase inactivators.

Acknowledgment. We would like to thank Professors Jack Shiner and David Collum for helpful discussions. This work was supported by NIH Grant R01 GM 47918.

Supplementary Material Available: Experimental and spectral details for compounds **3–15**, **18**, and **19** (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) Results from the sulfonate/phosphate competition study: LiHMDS/toluene experiment (S_I/P_I = 1.20/1, S_F/P_F = 4.39/1, S_P/P_P = 1/29.2, $S_\%$ = 2.1%, $P_\%$ = 73.4%); KHMDS/toluene experiment (S_I/P_I = 1.13/1, S_F/P_F = 2.25/1, S_P/P_P = 1/1.56, $S_\%$ = 27.5%, $P_\%$ = 63.6%); KHMDS/18-C-6/toluene experiment (S_I/P_I = 1.11/1, S_F/P_F = 1.00/1, S_P/P_P = 6.49/1, $S_\%$ = 11.7%, $P_\%$ = 2.0%); where S_I/P_I = initial ratio of sulfonate **9** to phosphate **4**, S_F/P_F = final ratio of sulfonate **9** to phosphate **4**, S_P/P_P = ratio of sulfonate product **10** to phosphate products **5**, **13**, and **14**, $S_\%$ = percent conversion of sulfonate **9** to product **10**, and $P_\%$ = percent conversion of phosphate **4** to products **5**, **13**, and **14**.