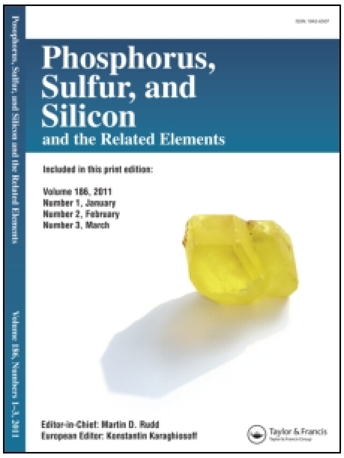

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A NEW SYNTHESIS OF ENOL PHOSPHATES

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A new synthetic method for enol phosphates based on direct reaction of ketones with dialkyl phosphites under Atherton-Todd conditions is described. The reaction is stereospecific or at least stereoselective.

Enol phosphates are a class of important organic compounds. For example, phosphenol pyruvate(PEP) is a well known high-energy species which plays a vital role in a number of biological processes. For instance, PEP is involved in the conversion of ADP to ATP[1]. The chemistry and biochemistry of PEP and its analogues have been investigated.[2] Further efforts have been made in the preparation of bioactive enol phosphates. As pesticide, they are a kind of very potent insecticides which have wide field of application[3]. Recently, Widlauski[4] reported the synthesis of enol phosphates having leaving groups at the 1-position that should have substantial utility in the design of phosphatase or phosphodiesterase inhibitors. Furthermore, enol phosphates are key intermediates in certain organic synthesis. They can easily rearrange to β—ketophosphonates[5], convert to monoalkylatedketones[6] and provide alkenes by reductive removal of phosphate[7] or alkylated alkenes by organocuprate induced substitution[8]. The Diels-Alder reaction of enol phosphates has been reported[9]. They are used as intermediates in the synthesis of various members of the carbapenam family of antibiotics[10]. Recently, Yoo[11] found that Claisen rearrangement of enol phosphates is very useful for conversion of various ester or lactone enolates to derivatives of β, γ-unsaturated acids.

The synthetic methods for enol phosphates have been reviewed by Lichtenthaler[12]. They are usually obtained by Perkow Reaction—reacting

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α-haloketone or α-haloaldehyde with trialkyl phosphite or prepared by reaction of enolate anion with dialkyl phosphorochloridate. In this communication, we should like to report the direct formation of enol phosphates by the reaction of ketones with diethyl phosphite in the presence of base and a polyhalide. This novel synthetic approach to enol phosphates can be regarded as the expansion of the Atherton-Todd reaction. The Atherton-Todd reaction and its variations, including two-phase systems, have been used to phosphorylate alcohols, phenols, canbohydrates and amines. Silverberg[13] recently reported the selective phosphorylation at the phenolic hydroxyl of 4′-dimethyl-4-epipodophyllotoxin by this reaction. In the present synthesis, the enolate anion formed from ketone reacted with diaklyl phosphorochloridate, intermediate of Atherton-Todd reaction, to give the product. We prepared a number of different compounds shown in Table I.

Usual bases such as KOH, NaOH, DBU for active carbonyl compounds were also tried and gave similar yield. The unstable enolate anion gave an unsatisfactory yield. It may be attributed to the formation of the intermediate dialkyl phosphorochloridate which requires higher temperature. In the case of **1f**, the enol phosphate was obtained in good yield from 2-chloro-2′,4′-dichloroacetophenone reacting with diethyl phosphite. Without the presence of base, just the ketophosphonate was produced via the Perkow reaction. Otherwise, 2,2-dichloro-2′, 4′-dichloroacetophenone must be used to obtain **1f**.

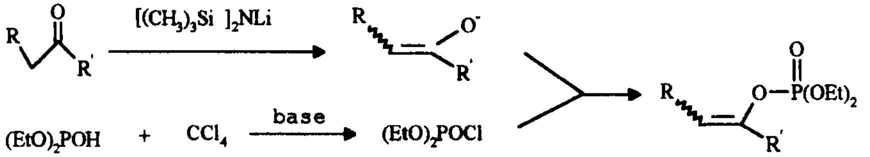

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TABLE I Enol phosphates

NO.	*R*	*R′*	*Yeld(%)*	*E:Z*	*$^1H(\delta)$ of vinyl proton* *E*	*Z*
1a	H	C_6H_5	90	-	5.15	
1b	C_6H_5	CH_3	74	7:3	5.5	6.3
1c	CH_3CO	C_6H_5	65	0:100		5.0
1d	$(EtO)_2PO$	C_6H_5	85	0:100		5.3~5.5
1e	CH_3CO	CH_3	95	0:100		5.2
1f	Cl	2,4-$Cl_2C_6H_3$	78	0:100		5.84
1g	C_2H_5OOC	CH_3	90	0:100		5.15

The products were characterized by ^{1}H NMR, IR and physical constant (for reference date, see refer. 14–18). The E/Z ratios were determined by NMR analysis of the vinyl proton peaks of reaction products. The NMR spectra were recorded on FX-90Q. In the preparation of all the products [(CH$_3$)$_3$Si]$_2$NLi was used as base, CCl$_4$ as solvent.

This new method gives solely good yields of enol phosphates without the products of attack at carbon. We studied the effects of changing reactive condition upon the stereochemistry of phosphorylation of enolate. We have found the ratio of geometrical isomers E and Z is closely related to the base and the polarity of the solvent. For example, when in the preparation of compound **1g** NaOH is used as base, the product had a E/Z ratio of 1 : 5 in dioxane and 1 : 10 in CCl_4. Changing the base employed has a great effect on the E/Z ratios. The smaller cations, give much higher percentages of Z-products. The difference between KOH and NaOH is striking, in dioxane the ratio is 4 : 1 and 1 : 5 respectively, while the nearly pure E-isomer is formed when DBU is used even in relatively non-polar solvents. The observation is consistent with the reactions of enolate anion with O,O-diethyl phosphorochloridate[19].

In summary, the novel procedure empolyed the readily available phosphorylation reagent which is neutral, stable and convenient to handle and prepared enol phosphate in one-pot reaction in high yield and stereoselectivity. The present method has significant advantages over the Perkow synthetic route in the case that α-halo carbonyl compounds as starting material in Perkow reaction are difficult to prepare. Due to the importance of enol phosphates, the described procedure should find wide application.

EXPERIMENTAL

Typical procedure: For the preparation of 1-acetyl-2-methyl diethyl vinyl phosphate, a multi-necked roundbottom flask was charged with $[(CH_3)_3Si]_2NLi$(1.2ml, 1.2mmol, 1.0M solution in tetrahydrofuran) and CCl_4(5ml). The mixture was stirred and cooled to 0°C. The ketone($CH_3COCH_2COCH_3$, 0.1g, 1mmol) was slowly added. 30 minutes later, dropwise addition of a solution of diethyl phosphite (0.16g, 1.16mmol) in CCl_4 was begun. Then, the resultant mixture was stirred at room temperature. When the reaction was completed as determined by TLC (about 1h after adding diethyl phosphite), the reaction mixture was neutralized with CH_3COOH and then filtered. The filtrate was washed with water, dried over Na_2SO_4, and concentrated in vacuo to give a brown oil. The pure product **1e** was obtained in 95% yield after chromatography on silica gel (using petroleum ether and ethyl acetate (V/V = 2/1) as eluent).

Acknowledgement

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