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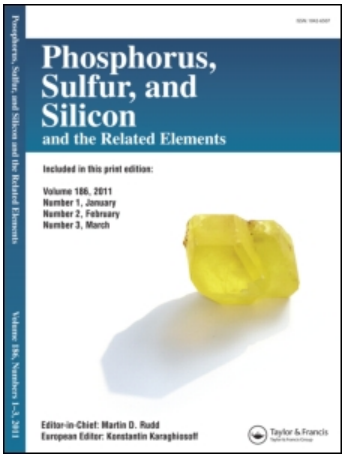

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
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The Concept of P--H Protection Extended to Phosphine Oxides: Preparation of Functional, Unsymmetrical Secondary and Tertiary Phosphine Oxides

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Online publication date: 27 October 2010

To cite this Article Hall, Roger G. and Riebli, Peter(2002) 'The Concept of P--H Protection Extended to Phosphine Oxides: Preparation of Functional, Unsymmetrical Secondary and Tertiary Phosphine Oxides', Phosphorus, Sulfur, and Silicon and the Related Elements, 177: 6, 1557 — 1562
To link to this Article: DOI: 10.1080/10426500212269
URL: http://dx.doi.org/10.1080/10426500212269

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Phosphorus, Sulfur and Silicon, 2002, Vol. 177:1557–1562
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1042-6507/02 $12.00 + .00
DOI: 10.1080/10426500290093531

THE CONCEPT OF P–H PROTECTION EXTENDED TO PHOSPHINE OXIDES: PREPARATION OF FUNCTIONAL, UNSYMMETRICAL SECONDARY AND TERTIARY PHOSPHINE OXIDES

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(Received July 29, 2001; accepted December 25, 2001)

Phosphine oxide analogues of Triazole fungicides and protected Threonine have been prepared. The enzymatic hydrolysis of phosphine oxide di-acetates has been investigated.

Keywords: Analogues; phosphine oxide; threonine; triazole fungicides

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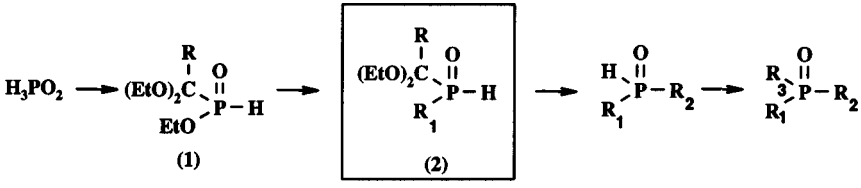
Some 20 years ago, M. J. Gallagher[1] reported the reaction of phosphinic acid with ortho esters. Scientists at the Central Research Laboratories of Ciba-Geigy seized upon this and developed a series of novel building blocks for phosphinic acid synthesis. The synthesis and biological activity of γ-aminopropyl phosphinic acids was subsequently reported.[2] We have further shown[3] that such building blocks (1) can be converted into protected primary phosphine oxides (2). These stable, easily handled intermediates can be elaborated into unsymmetrical secondary and tertiary phosphine oxides (Scheme 1).



SCHEME 1

We then set out to prepare novel phosphine oxides which might display interesting biological activities either in the Crop Protection or

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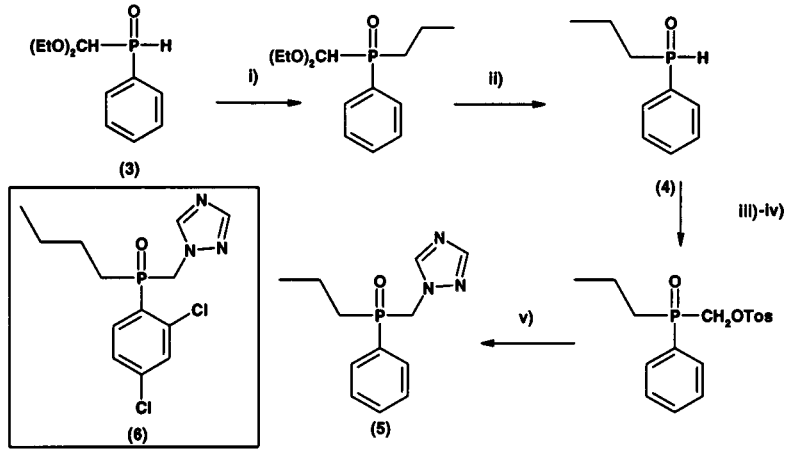
pharmaceutical areas. On checking the literature, we found two examples where dimethyl phosphine oxides had been prepared. In one case, an analogue of a 25-hydroxylation metabolite of Vitamin D_3 was prepared[4] and tested for effects on calcium absorption. In a second example, the experimental herbicide HOE 704 was found[5] to inhibit the enzyme Aceto-Lactate-Reducto-Isomerase (ALRI), involved in the biosynthesis of Valine.

ANALOGUES OF TRIAZOLE FUNGICIDES

Our first targets were analogues of triazole fungicides. The synthesis of the phenyl n-propyl phosphine oxide analogue is shown below (Scheme 2). Alkylation of diethoxymethyl phenylphosphine oxide (3)[3] with n-propyl bromide followed by acid deprotection gave the secondary phosphine oxide (4). P—H addition to formaldehyde and conversion of the alcohol to the tosylate gave the tertiary phosphine oxide; displacement of the tosyl group with triazole under basic conditions gave the target molecule (5). The 2,4-dichloro analogue (6) was prepared in an analogous way, using 2,4-dichlorophenyl magnesium halide and alkylation with n-butyl bromide.



SCHEME 2

Biological results were disappointing, however. Table I shows biological activity against four pathogens. The phenyl n-propyl phosphine

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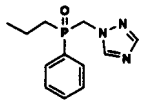
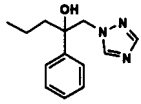
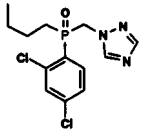
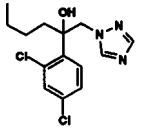
TABLE I Fungicidal Activity of Selected Triazole Derivatives

Structure	Dose (ppm)	% Activity			
		Cercospora arach.	Erysiphe graminis	Puccinia recondita	Venturia inaequalis
 (5)	200	0	0	0	0
	200	n.t.	100	100	n.t.
 (6)	200	80	100	0	90
	60	50	100	0	90
	20	0	50	0	0
 Hexaconazol	200	100	100	100	100
	60	100	100	100	100
	20	100	100	100	100

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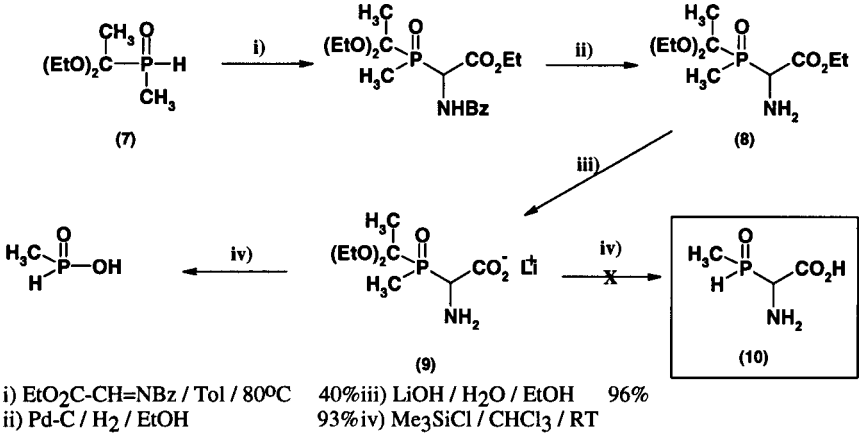
oxide (5) is inactive at 200 ppm. Compound (6), a close analogue of the market product Hexaconazol, shows good activity at 200 ppm, but at lower rates the activity decreases.

ANALOGUES OF THREONINE

Threonine, an important amino acid, can provide, along with serine, sites for phosphorylation by kinases. Inhibitors of certain kinases have been studied as potential anti-cancer agents. The route chosen to synthesize a phosphine oxide analogue (10) of Threonine is shown below (Scheme 3).

Addition of the protected primary phosphine oxide (7) to the imine derived from ethyl glyoxylate and benzylamine gave a tertiary phosphine oxide, which could be reductively deprotected to give the amino phosphine oxide (8). Basic hydrolysis then gave the lithium salt (9) as a mixture of diastereoisomers; it has been previously shown[6] that



SCHEME 3

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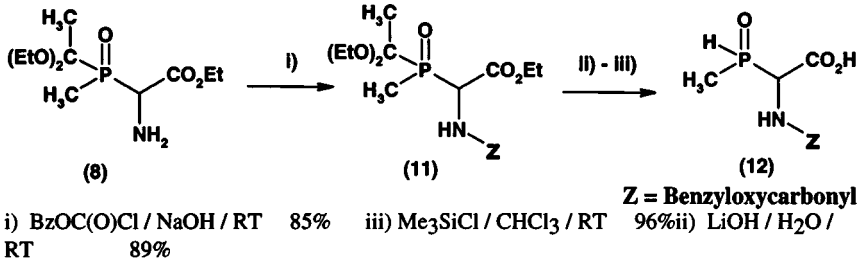
the diethoxy-ethyl group can be removed under very mild conditions using timethylchlorosilane to regenerate the P—H function; however, deprotection of (9) led only to the formation of methyl phosphinic acid. Deprotection at phosphorus was possible, however, when the nitrogen was protected. Thus, protection of (8) as the benzyloxycarbonyl derivative gave (11) in good yield. Basic hydrolysis of the ester, followed by mild deprotection at phosphorus, then gave the Z-Threonine analogue (12) as a mixture of diastereoisomers (Scheme 4).

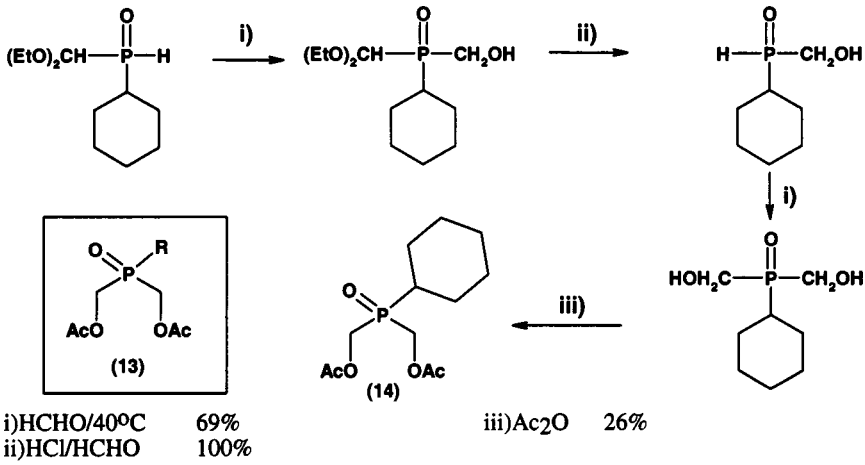


SCHEME 4

This finding has led us to speculate[7] on a mechanism of P—C bond cleavage resulting from the zwitterionic nature of the fully deprotected target molecule (10). Incorporation of (10) into peptides may serve to stabilize this molecule.

ENZYMATIC HYDROLYSIS OF PHOSPHINE OXIDE DI-ACETATES

The use of enzymes to prepare chiral molecules and intermediates is well established. Ramos[8] reported the use of lipases in organic solvents to effect either hydrolysis of di-acetates or acetylation of diols to produce chiral 1,3-propanediol monoacetates. We investigated whether this approach could be extended to phosphine oxides (13), and thus give an entry into chiral phosphine oxides, and eventually phosphines. The synthesis of the required starting materials is illustrated for the cyclohexyl derivative (14) shown in Scheme 5.



SCHEME 5

Screening a number of enzymes, only in one case could we observe any chiral differentiation, as determined by preparing Moscher derivatives on the free alcohol function, as can be seen in Table II.

TABLE II Enzymatic Hydrolysis (Aqueous Media, pH 7) of Phosphine Oxide Di-Acetates (13)

Lipase	R	Time	% ee
Candida cyl.-biocats	C_6H_{11}	6 hr	40
Lipase–sigma	C_6H_{11}	24 hr	12
Pseudomonas fluor.	C_6H_{11}	200 hr	0
Candida cyl.-biocats	CH_3	24 hr	0
Pseudomonas fluor.	C_6H_5	200 hr	0

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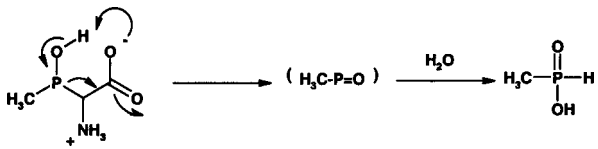
[7] The zwitterionic form of (10), when drawn with phosphorus in the P-III form, can readily promote a fragmentation, with loss of meta-phosphite:



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