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An Entry to 5-(1-Alkenyl)-3(2H)-furanones through Cycloaddition of Phosphorus-Functionalized Nitrile Oxide to Acetylene Alcohols. An Effective Synthesis of Geiparvarin

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Cycloaddition of α-(diethoxyphosphoryl)acetonitrile oxide to acetylene alcohols is followed by an alkylation, a reductive cleavage of the N-O bond, and an acid-catalyzed cyclization to form 5-(diethoxyphosphorylmethyl)-3(2H)-furanones in good yields. Subsequent Horner-Emmons olefination using triethylamine and lithium bromide furnishes E-isomers of 5-(1-alkenyl)-3(2H)-furanones as major products. This method has been applied to a short synthesis of Geiparvarin.

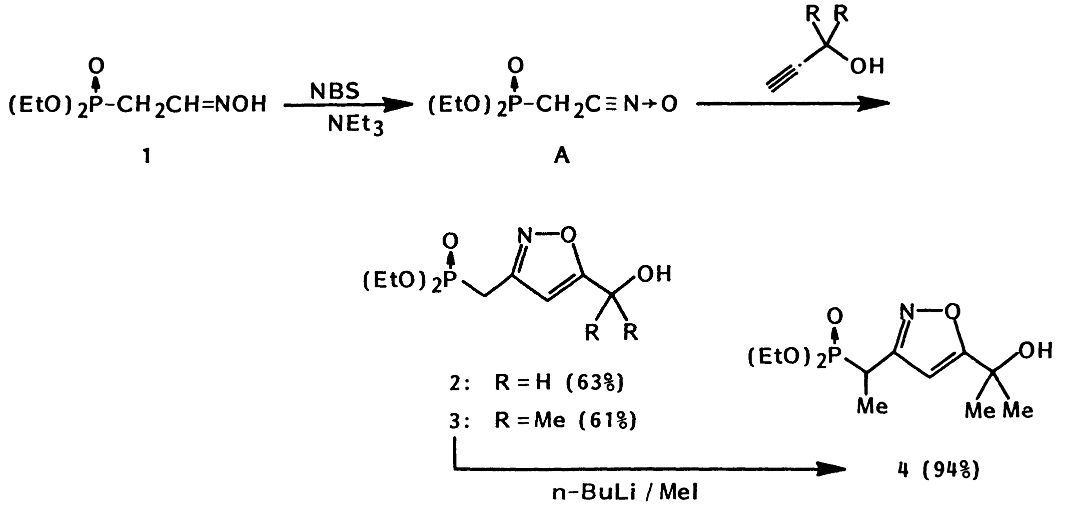
Cycloaddition of nitrile oxide to olefins is of great importance in organic synthesis since the Δ^2-isoxazolines as cycloadducts are flexible building blocks through their ability to function as masked forms of β-hydroxy ketones, α,β-unsaturated ketones, and γ-amino alcohols after the N-O bond hydrogenolysis.1) The synthetic value of nitrile oxide cycloaddition is now growing as shown in its wide applications to natural product synthesis.2)

3-(Diethoxyphosphorylmethyl)-Δ^2-isoxazolines are readily available in the cycloaddition of α-(diethoxyphosphoryl)acetonitrile oxide (A) to olefins and their synthetic versatility has been recently demonstrated:3) They are regioselectively deprotonated and the resulting phosphorus-stabilized carbanion can be utilized to introduce a talented isoxazoline unit into other molecules by reaction with a variety of electrophiles.3) Our continued work on 3-phosphorylmethyl-Δ^2-isoxazolines has shown that the phosphorus moiety could servive on their reductive N-O bond cleavage with Raney Ni,4) suggesting a possibility of more effective utilization of the phosphorus functionality after the isoxazoline ring cleavage.

In the present communication, cycloaddition of the phosphorus-functionalized nitrile oxide A to acetylene alcohols has been applied to a synthesis of E-isomers of 5-(1-alkenyl)-3(2H)-furanone which is an essential framework of furanone natural products such as Geiparvarin, Eremantholide, Budelin A, and Goyazensolide.5)

The phosphorus-functionalized nitrile oxide A was generated in situ from oxime 1, NBS, and triethylamine in DMF according to the reported method,3) and allowed to react under reflux with unprotected 2-propyn-1-ol or 2-methyl-3-butyn-2-ol to provide each good yield of isoxazole alcohol 2 or 3 (Scheme 1).6)

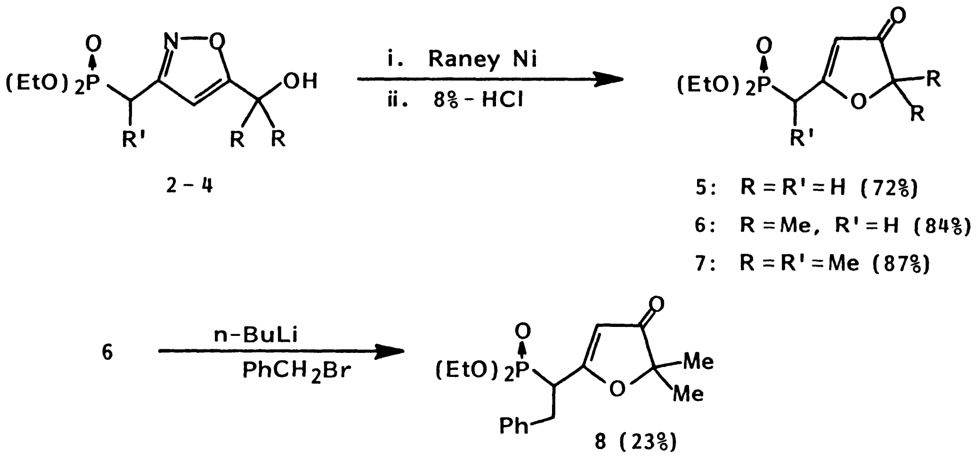
Directing toward the synthesis of Geiparvarin, methylation of isoxazole alco-



Scheme 1.

hol 3 was examined. Again without protection of the hydroxyl group, 3 was found to undergo a smooth methylation on treatment with two equivalents of butyllithium and then with methyl iodide in THF at -78 °C to afford 4 in an almost quantitative yield.

Isoxazole alcohols 2-4 were then hydrogenated on Raney Ni (W-2) in ethanol in the presence of aqueous acetic acid. Without isolation and purification of the

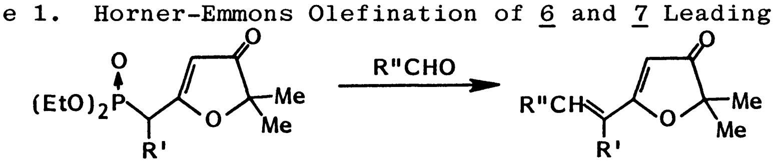


Scheme 2.

products, the crude reaction mixtures were treated with diluted hydrochloric acid at room temperature to give 5-phosphorylmethyl- 5, 6 and 5-(1-phosphorylethyl)-3-(2H)-furanones 7 in satisfactory yields (Scheme 2).[7] Alkylation at the stage of furanone resulted in the formation of complex mixture of products. For example, the carbanion derived from 6 and butyllithium at -78 °C was alkylated with methyl iodide or benzyl bromide, the latter case affording only a poor yield of benzylated 8 after a careful chromatographic separation.[8] Accordingly, the alkylation should be performed at the stage of isoxazole if necessary.

The known olefination of 5-alkyl-3(2H)-furanones with aldehydes leads to poor E/Z isomer ratios of the olefins.[9] Horner-Emmons olefination of 5 with benzaldehyde took place smoothly under the usual conditions of using butyllithium and HMPA (each 1 equivalent) in THF to give a quantitative yield of olefin 9 (E/Z = 97/3, Table 1). However, these highly basic conditions could be successfully applied only to aromatic aldehydes, a similar reaction with butanal giving a very poor yield of 10. After some efforts were made for optimization of the reaction, we found that furanone 6 could be readily deprotonated with such a weak base as triethylamine if lithium bromide is present.[10] Thus, 6 was treated with triethylamine / lithium bromide in THF and with butanal at 4-5 °C to give olefin 10 (75% yield, E/Z = 89/11).[11]

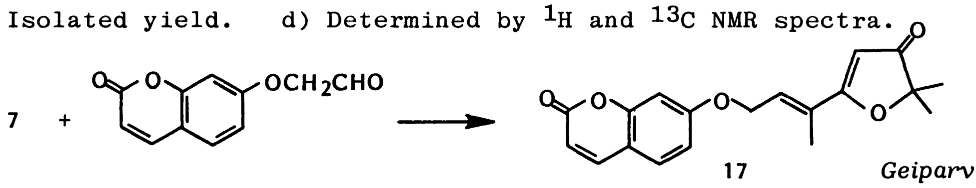
Table 1. Horner-Emmons Olefination of 6 and 7 Leading to 9-16



6, 7 9- 16

Reactant		Conditions[a)]		Product	R'	R"	E/Z Ratio[b)]	Yield/%[c)]
6	PhCHO	A	14 h	9	H	Ph	97/3	99
6	n-PrCHO	B	16 h	10	H	n-Pr	89/11	75
6	i-PrCHO	B	16 h	11	H	i-Pr	93/7	83
7	PhCHO	B	19 h	12	Me	Ph	83/17	85
7	EtCHO	B	20 h	13	Me	Et	88/12	70
7	n-PrCHO	B	20 h	14	Me	n-Pr	85/15	84
7	i-PrCHO	B	16 h	15	Me	i-Pr	81/19	80
7	$PhCH\overset{t}{=}CHCHO$	B	19 h	16	Me	$PhCH\overset{t}{=}CH$	E only[d)]	38

a) A: n-BuLi (1 equiv.), HMPA (1 equiv.) in THF, 0.5 h at -78 °C. B: Et$_3$N (1.2 equiv.), LiBr (1.5 equiv.) in THF, 4-5 °C. b) Determined by GLC. c) Isolated yield. d) Determined by ^{1}H and ^{13}C NMR spectra.



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Under these less basic conditions, Horner-Emmons olefination of 6 and 7 with benzaldehyde, some aliphatic aldehydes, and an α,β-unsaturated aldehyde were examined. In most cases E-isomers of 5-(1-alkenyl)-3(2H)-furanones 9-16 were given as major isomers in satisfactory yields (Table 1).[12]

This olefination with high E-selectivity was finally applied to the synthesis of a furanone natural product, Geiparvarin.[13] Thus, the carbanion generated from 7 by an action of triethylamine / lithium bromide in THF was allowed to react with (7-cumarinyl)oxyacetaldehyde at -5 °C for 46 h to give 55% yield of Geiparvarin 17 with a 75:25 mixture of E/Z isomers. These isomers were separable from each other by a column chromatography over silica gel and identified by the comparison of each spectral data with the reported ones.[9]

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11) The temperature of 4-5 °C is critical to obtain the yields shown in Table 1.

12) The olefin geometry was confirmed on the basis of the olefin couplings for 9-11; by the comparison of ^{1}H NMR data with the reported ones for 12, 13, and 15;9) on the basis of chemical shifts of olefinic protons for 14 (δ6.59 as tq, $J = 7.0$ and 1.5 Hz (E); δ5.88 as tq, $J = 7.0$ and 1.5 Hz (Z)) and 15 (δ6.38 as dq, $J = 9.5$ and 1.5 Hz (E); δ5.66 as dq, $J = 9.5$ and 1.5 Hz (Z)).

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