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REGIOCHEMISTRY OF REACTIONS OF α-ALKOXYALLYLPHOSPHINE OXIDE YLIDES WITH ELECTROPHILES.

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Abstract. Anions 4, derived from α-methoxyallylphosphine oxides 3, react with electrophiles in a highly regioselective fashion to give products of α-attack or γ-attack depending upon the substitution pattern of the ylid 4 and the nature of the electrophile.

The chemistry of allylic anions containing α-heteroatom substituents [cf. 1, 2; e.g. Y,Z=SiR_3, SR, S(O)R, OR, NR_2, $P(O)(OR)_2$] has been intensively investigated in recent years and has led to the development of many new synthetic methods[1]. Regiochemical control in reactions of these ambident anions with electrophiles is crucial to the utility of these methods, and although a number of factors have been identified as important influences on site selectivity, there is as yet no comprehensive basis for predicting this regiochemistry[2]. We recently described[3] the preparation of a series of α-methoxyallylphosphine oxides 3 and now wish to report the results of some electrophilic quenching reactions of the ylids 4 derived from these oxides. Anions of allylic phosphine oxides[4] and α-hetero substituted phosphine oxides[5] are of considerable current interest, and ylids 4 possess features of both of these reagent classes.

Anions 4 are readily formed from oxides 3 on treatment with lithium diisopropylamide (THF, -70°). Addition of electrophiles at -70° leads to 5 or 6, products of γ-attack or α-attack, respectively (Table 1), and the regiochemistry observed is dependent both upon the substitution pattern of the ylid 4 and the nature of the electrophile. The striking effect of allylic substituents can be seen in the results from protonation of 4. Anions 4a and 4b undergo regiospecific γ-protonation at -70° to provide, as the sole products, vinylphosphine oxides 5 (E=H) as single geometrical isomers (E)[6]. In sharp contrast, anions 4c and 4d protonate only at the α-carbon to regenerate the parent oxides.

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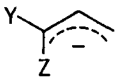

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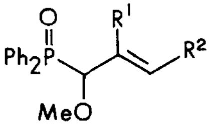

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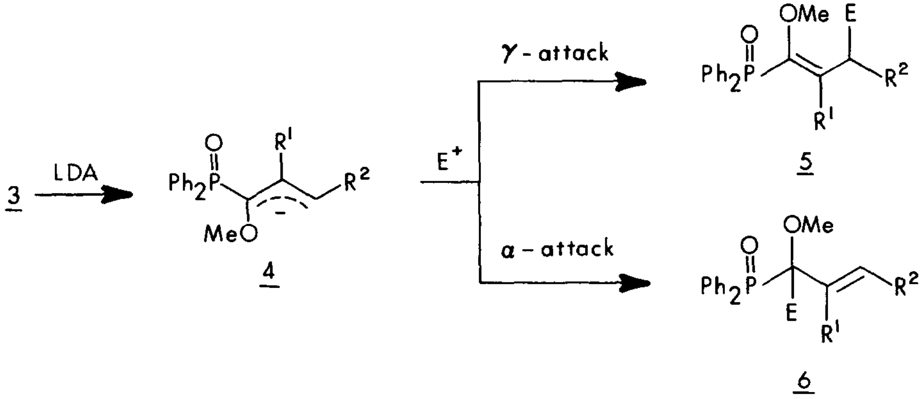
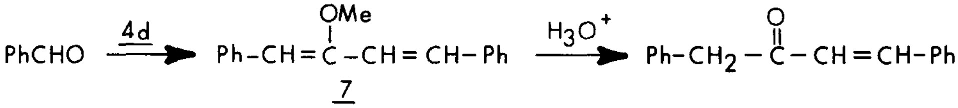
Table 1. Reactions of Anions 4 with Electrophiles[a]

Anion	R^1	R^2	Electrophile[b]	Regiochemistry[c,d]	Product
4a	H	H	H^+	γ	5a (E=H)
4a	H	H	PhCHO	γ	5a (E=CH(OH)Ph)
4a	H	H	MeCHO	γ	5a (E=CH(OH)Me)
4a	H	H	MeI	γ/α=80/20	5a (E=Me) + 6a (E=Me)
4b	Me	H	H^+	γ	5b (E=H)
4b	Me	H	PhCHO	γ	5b (E=CH(OH)Ph)
4b	Me	H	MeCHO	γ	5b (E=CH(OH)Me)
4b	Me	H	MeI	γ/α=60/40	5b (E=Me) + 6b (E=Me)
4c	H	Me	H^+	α	6c (E=H)
4c	H	Me	PhCHO	γ[e]	5c (E=CH(OH)Ph)
4c	H	Me	MeCHO	γ[e]	5c (E=CH(OH)Me)
4c	H	Me	MeI	γ/α=22/78	5c (E=Me) + 6c (E=Me)
4d	H	Ph	H^+	α	6d (E=H)
4d	H	Ph	PhCHO	α[f]	7
4d	H	Ph	MeCHO	γ[g]	5d (E=CH(OH)Me)
4d	H	Ph	MeI	γ/α=90/10	5d (E=Me) + 6d (E=Me)

(a) Yields of isolated purified products were typically 70-97%, (b) Electrophiles were added to solutions of 4 at low temperature; satd. aqueous NH_4Cl was used as the proton source for protonations; (c) Where only the entry α or γ appears, the crude reaction products were virtually a single regioisomer (≥95%) by nmr; (d) γ/α ratios for methylation reactions were determined by nmr; (e) γ/α ratio ≥ 90/10; (f) Isolation of diene 7 implies α-adduct formation; (g) Aqueous quench at -70° after reaction with MeCHO.



With carbonyl electrophiles such as benzaldehyde and acetaldehyde, ylids 4a, 4b and 4c react regiospecifically to provide γ-adducts 5 (E=CH(OH)R), again as the *E*-isomer. It is of interest to note that these γ-adducts are related to phosphonic acid derivatives recently developed as ester homoenolate equivalents[7]. In contrast, the regiochemistry observed with anion 4d and carbonyl electrophiles is a function of the electrophile. Thus, acetaldehyde formed only the γ-adduct at -70° (5d; E=$CH(OH)CH_3$) with 4d, but with benzaldehyde 4d reacts at the α-terminus to afford methoxydiene 7 (*ca.* 1:1 stereoisomeric mixture). The lithium salt of the α-adduct (6; E=CH(OLi)Ph) is presumed to be an intermediate and its formation is followed by an unusually facile[8] Wittig-Horner elimination which occurs *in situ* at -20°. Hydrolysis of 7 provides enone 8, and the overall process is equivalent to a reductive nucleophilic cinnamoylation in which anion 4d behaves as a cinnamoyl anion (Ph-CH=CH-$\bar{C}$=O) equivalent[9,10].



$$\text{PhCHO} \xrightarrow{\text{4d}} \underset{7}{\text{Ph-CH}=\overset{\text{OMe}}{\text{C}}\text{-CH}=\text{CH-Ph}} \xrightarrow{H_3O^+} \text{Ph-CH}_2-\overset{\text{O}}{\overset{\|}{\text{C}}}-\text{CH}=\text{CH-Ph}$$

The importance of the electrophile as a determinant of regiochemistry is also evident from the results of alkylation of ylids 4 with methyl iodide. Although protonation and reactions with carbonyl compounds proceed with very high regioselectivity to give either α or γ products, methyl iodide gave both α- and γ-adducts with each of the ylids 4. From the data in the Table, it is apparent that yet another pattern of reactivity of anions 4 applies to the alkylation reaction.

These reactions of electrophiles with ylids 4 illustrate the difficulty in predicting the regiochemistry of adduct formation with α-hetero substituted ambident allyic anions. In the present cases, the site selectivity is determined by the structures of the anion and of the electrophile. However, with the exception of the alkylation reactions, the balance lies almost totally in favor of α- or γ-preference, and both the α- and γ-adducts have potential in synthesis. Further transformations of 5 and 6 are currently under study.

Typical procedure: To a cold (-70°) solution of LDA (10 mMol) in THF (50 ml) was added dropwise under nitrogen a solution of phosphine oxide 3a (2.72 g, 10 mMol) in THF (10 ml). After 0.5 h the deep red solution was treated dropwise with benzaldehyde (1.06 g, 10 mMol) and after an additional 0.5 h was allowed to warm to 20° and quenched with aqueous NH_4Cl (20%). Ether extraction and recrystallization from benzene-hexane gave 5a (E=CH(OH)Ph) as colorless crystals (1.94 g, 70%): m.p. 121.5-123°; nmr ($CDCl_3$) δ 2.74 (ddd, J=7,7,3; 2H), 3.42 (s; 3H), 4.77 (t, J=7; 1H), 5.87 (d of t, J=10, 8; 1H), 7.2-7.8 (m; 15 H); Calcd. for $C_{23}H_{23}O_3P$: C, 73.00; H, 6.13; found: C, 73.02; H, 6.13.

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