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A HORNER-WITTIG SYNTHESIS OF 1-CHLOROVINYL SULFOXIDES.

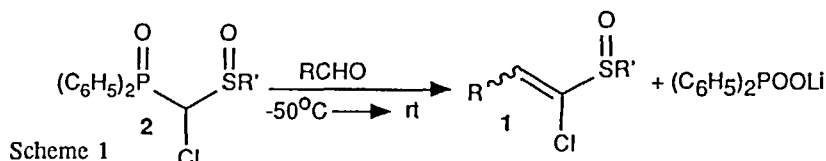
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Abstract 1-Chlorovinyl sulfoxides **1** were prepared by Horner-Wittig reaction of the readily accessible [(α -chloro)sulfinylmethyl]diphenylphosphine oxides **2** with aldehydes. Excellent *Z*-selectivity was observed in most cases.

INTRODUCTION

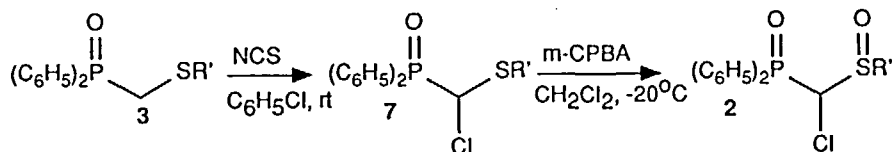
1-Chlorovinyl sulfoxides **1** form a class of multifunctional compounds that is expected to possess a versatile chemical reactivity which is yet to be investigated (Michael-additions, Diels-Alder reactions, (2+2)- and 1,3-dipolar cycloadditions). Satoh *et al.*¹ recently described a three step procedure for the conversion of aldehydes into their corresponding one-carbon homologated 1-chlorovinyl sulfoxides **1** which were obtained as mixtures of *E*- and *Z*-isomers of unknown ratio. We now report the one-step transformation of aldehydes into their homologous 1-chlorovinyl sulfoxides by a Horner-Wittig reaction with [(α -chloro)sulfinylmethyl]diphenyl-phosphine oxides **2** (Scheme 1).



RESULTS AND DISCUSSION

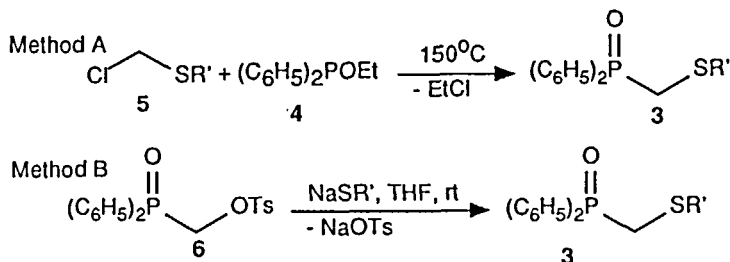
Diphenylphosphine Oxides

The requisite phosphine oxides **2** are readily accessible by chlorination and subsequent oxidation of (thiomethyl)diphenylphosphine oxides **3** (Scheme 2).



We have elaborated two different routes for the preparation of (thiomethyl)-diphenyl phosphine oxides **3** (Scheme 3). Arbuzov reaction of *O*-ethyl diphenylphosphinite **4** with an appropriate (chloromethyl)thioether **5**, according to a literature procedure², gave phosphine oxides **3a** and **3c** ($\text{R}' = \text{methyl}$ and phenyl) in good yields (method A). The Arbuzov reaction also proved suitable for the preparation of phosphine oxide **3d** ($\text{R}' = p\text{-tolyl}$) which was obtained in quantitative yield (Table I). The synthesis of **3** by this route

is somewhat restricted by the limited availability of (chloromethyl)thioethers **5**. Therefore, it was decided to develop a more general procedure for the synthesis of phosphine oxides **3**. Nucleophilic displacement on (tosyloxymethyl)diphenylphosphine oxide **6** with sulfur nucleophiles (method B) gave access to a wide range of substituents R' in **3**. Extractive work-up afforded phosphine oxides **3** which were sufficiently pure for further elaboration. Table I shows that method B proceeded with almost quantitative yields throughout.



Scheme 3

TABLE I (Thiomethyl)diphenylphosphine oxides **3**.

	R'	Method	Yield (%)
3a	methyl	A	80
3b	<i>c</i> -hexyl	B	95
3c	phenyl	A	85
3d	<i>p</i> -tolyl	A	98
		B	96
3e	<i>n</i> -butyl	B	95
3f	<i>t</i> -butyl	B	98

The α -protons of an aliphatic thioether are susceptible to chlorination with *N*-chlorosuccinimide (NCS). The more acidic protons are known to be substituted by preference³. In the case of phosphine oxides **3**, it was expected that the anion stabilizing capacity of the phosphinoyl substituent would direct a regioselective substitution in **3a**, **3b** and **3e**. Indeed, treatment of these phosphine oxides with one equivalent of NCS in chlorobenzene⁴ resulted in formation of the desired phosphine oxides **7**. The concomitantly formed succinimide was removed by repeated extraction with water. The phosphine oxides were isolated after drying and evaporation of the solvent. In all cases, high yields of mono-chloro phosphine oxides **7** were obtained (Table II). The chemoselective mono-chlorination of **3** indicates that substitution of the methine proton of **7** by a second chlorine atom is much slower than mono-substitution. The use of an excess of NCS led to di-substitution, which was observed to occur at the same position.

Selective mono-oxidation of phosphine oxides **7a** and **7b** with one equivalent of *m*-CPBA proceeded cleanly at -20°C . Extractive work-up yielded the desired sulfoxides **2a** and **2b** in excellent yields. No further purification of these phosphine oxides was necessary for subsequent application in the Horner-Wittig reaction. Oxidation of **7f** (R'=*t*-butyl) with *m*-CPBA proceeded less satisfactory. After several hours at room temperature, only partial oxidation of the sterically shielded sulfide was observed. Treatment of **7c** and **7d** with one equivalent of *m*-CPBA led to almost complete conversion (>95%) of the starting material. Oxidation of the aryl substituted sulfur center to the sulfone had only occurred to a small extent (<5%)⁵.

TABLE II [(α -chloro)thiomethyl]diphenylphosphine oxide 7.

	R'	Yield (%)
7a	methyl	95
7b	<i>c</i> -hexyl	83 ^a
7c	phenyl	89
7d	<i>p</i> -tolyl	98
7e	<i>n</i> -butyl	95
7f	<i>t</i> -butyl	80 ^a

^a After crystallization from CH₂Cl₂/petroleum ether (40/60).

TABLE III [(α -chloro)sulfinylmethyl]diphenylphosphine oxide 2.

	R'	Yield (%)
2a	methyl	93
2b	<i>c</i> -hexyl	97
2c	phenyl	97 ^a
2d	<i>p</i> -tolyl	98 ^a

^a 95% Conversion, 5% sulfone.

Horner-Wittig Reaction

Phosphine oxides 2 were readily deprotonated with LDA in THF between -50°C and -40°C to give a yellow colored anion solution. Deprotonation at lower temperatures was hampered by insufficient solubility of the phosphine oxides. The lithiated anions proved sufficiently stable at these temperatures to allow efficient reaction with a wide range of aldehydes. The Horner-Wittig reaction was completed by stirring a few hours at ambient temperatures. Extractive work-up afforded the 1-chlorovinyl sulfoxides 1, which were conveniently purified by column chromatography⁵. Some representative results are compiled in Table IV. In the case of 2c and 2d, the yields were obtained using the crude phosphine oxides⁵. Good yields were obtained with all types of aldehydes. Attempted reaction with a ketone (cyclohexanone) and the sterically hindered pivaldehyde remained without success. The preparation of 1-chlorovinyl sulfoxides 1h and 1i, the simplest and hitherto unknown members of this class of compounds, by a Horner-Wittig reaction with *p*-formaldehyde, deserves special mention. These compounds may well turn out to be excellent reaction partners in a variety of (cyclo)addition reactions⁶.

The stereoselectivity with which the new double bond was formed, was found to depend on the nature of the aldehyde as well as on the phosphine oxide used. With aromatic or α,β -unsaturated aldehydes, almost exclusive formation of one stereoisomer was observed (entries 1a, 1b, 1f, 1g, 1i and 1j). A crystal structure determination of 1b unambiguously showed the double bond to possess the *Z*-configuration. The stereoselectivity of straight chain aliphatic aldehydes in the Horner-Wittig reaction with 2 was found to depend on the substituent R' in the phosphine oxide. If R' was methyl or *c*-hexyl (2a and 2b), only a modest stereoselectivity was found (entries 1c and 1e). On the other hand, a Horner-Wittig reaction with 2c (R'=phenyl) showed again a strong preference for formation of only one double bond isomer (entry 1f). In all three cases, the major isomer is expected in analogy to possess the *Z*-configuration.

A strikingly low selectivity arose from use of the sterically more hindered cyclohexanecarboxaldehyde (entries 1d and 1k). Not only reaction with 2a ($R' = \text{methyl}$), but also with 2c ($R' = p\text{-tolyl}$) resulted in the formation of a 3/1 ratio of the two stereoisomers. This indicates that steric effects stemming from the aldehyde substituent R may also play a dominant role in the outcome of the Horner-Wittig reaction.

TABLE IV 1-Chlorovinyl sulfoxides 1, prepared by the Horner-Wittig reaction.

1	R	R'	Yield (%)	Z/E
1a	phenyl	methyl	75	98/2
1b	<i>p</i> -methoxyphenyl	methyl	71	98/2
1c	<i>n</i> -butyl	methyl	63	4.7/1
1d	<i>c</i> -hexyl	methyl	68	3/1
1e	<i>n</i> -butyl	<i>c</i> -hexyl	56	5.2/1
1f	<i>n</i> -butyl	phenyl	63	96/4
1g	1-propenyl	phenyl	63	97/3
1h	H	phenyl	72	-
1i	phenyl	<i>p</i> -tolyl	60	98/2
1j	<i>p</i> -methoxyphenyl	<i>p</i> -tolyl	66	98/2
1k	<i>c</i> -hexyl	<i>p</i> -tolyl	69	3/1
1l	H	<i>p</i> -tolyl	70	-

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2. J.I. Grayson and S. Warren, *J.Chem.Soc.Perkin I*, **1977**, 2263.
3. D.L. Tulcen and V.C. Marcum, *J.Org.Chem.*, **32**, 204 (1967).
D.L. Tulcen, *J.Org.Chem.*, **32**, 4006 (1967).
4. In the case of 3c and 3d, the presence of water in the solvent led to the contamination of 7c and 7d with appreciable amounts of the corresponding [(arylsulfinyl)methyl]diphenylphosphine oxides. Formation of these sulfoxides was completely suppressed by using dry chlorobenzene.
5. The small 1-chlorovinyl sulfide and 1-chlorovinyl sulfone impurities could easily be separated from the desired 1-chlorovinyl sulfoxides 1 by column chromatography. Therefore, the crude phosphine oxides 2c and 2d did not need further purification.
6. Recent investigations showed that 1-chlorovinyl sulfoxides 1h and 1l can be excellent Michael acceptors. (To be published)