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Synthesis of Methyl Vinyl Sulfides: The Role of Boron Trifluoride in promoting a Horner-Wittig Type Reaction

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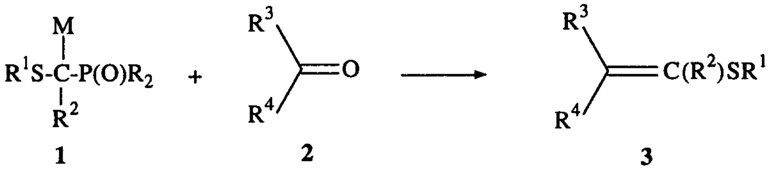
Abstract : The methylthiodiphenylphosphine oxide carbanion **1a** reacted with ketones in a two step process, the first stage being reversible. Methyl vinyl sulfides are formed only when the elimination step was rapid. When the second step occurred at a slow rate, the sequence required the use of boron trifluoride etherate for completion. New methyl vinyl sulfides were prepared by reaction with various ketones, including enolisable and bulky compounds. © 1999 Published by Elsevier Science Ltd. All rights reserved.

The reaction of C-metallated derivatives of α-phosphoryl sulfides **1** with carbonyl compounds **2** (Horner-Wittig reaction) is the most popular method for preparing α,β-unsaturated sulfides **3**[1-7].



1 **2** **3**

Yet, "in the case of enolisable ketones, the attack of **1** is preferably directed on a proton rather than on a carbonyl group" (sic), as recently pointed out by Mikolajczyk[8]. Therefore, poor yields of sulfides are observed for the reaction with such ketones. We have recently solved a related problem in the case of the addition of aryllithiums to an enolisable ketone by using BF_3 etherate[9]. At low temperature, the Lewis acid did not react with the aryllithiums and promoted the nucleophilic addition onto the enolisable ketone. The same approach, namely the activation of an anion by BF_3, is now being applied to a Horner-Wittig reaction in order to prepare α,β-unsaturated methylsulfides (**3** : R^1 = Me ; R^2 = H) from enolisable and bulky ketones. The 4-methoxyphenylacetone **2a** was first chosen as a model enolisable carbonyl compound to study the best reaction conditions with the anion of methylthiodiphenylphosphine oxide **1a** (R = Ph ; R^1 = Me ; R^2 = H ; M = Li). The synthesis of various sulfides **3** was then achieved with other enolisable and bulky ketones.

The Horner-Wittig reaction of the phosphine oxide carbanion **1a** with the model ketone occurs in two steps as shown below. The carbanion **1a** was generated by reaction of the phosphine oxide[7] CH_3S-CH_2-P(O)Ph_2 (which was itself easily prepared in two steps from chlorodiphenylphosphine) with butyllithium in THF at - 70°C for 10 minutes. The ketone **2a** was then added at -78 to - 85°C, with or without prior addition of BF_3:OEt_2. The sulfides **3a** were never formed in the presence of BF_3, even after warming the reaction medium to room temperature before hydrolysis.

a. In the absence of boron trifluoride, a low yield reaction occurred at -80°C with 2 equivalents of anion : 6% of adducts **5a** were observed after hydrolysis without noticeable enolisation (as attested to by the absence of silyl enol ether formation when the reaction medium was quenched with an excess of TMSCl before hydrolysis). A low percentage (10%) of vinyl sulfide was observed after warming the reaction medium (ketone + 1 eq. anion) to room temperature before hydrolysis.

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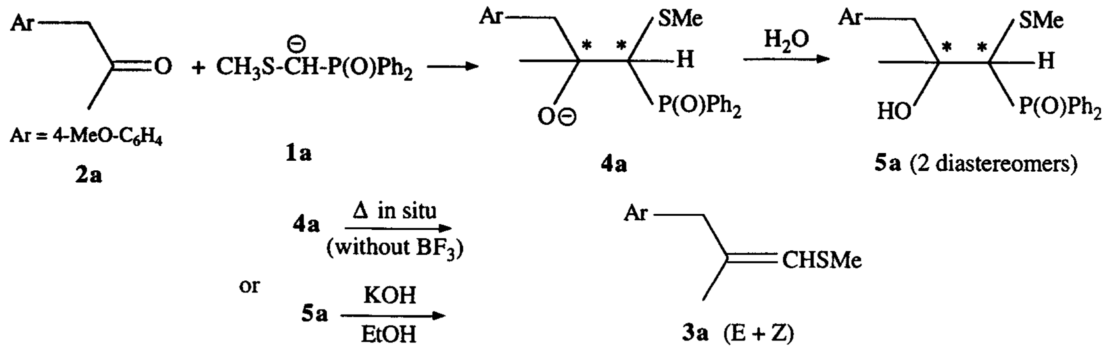


b. The percentage of addition compounds **5a** formed at low temperature (after quenching the reaction medium with excess water) was increased by the use of boron trifluoride as a promoter (see table 1), a complete transformation of the ketone being observed with an excess of anion and the promoter. The sulfide **3a** was easily obtained by treatment of the crude product (composed of intermediate diastereomeric addition compounds **5a** and excess phosphine oxide) with 0.4 M ethanolic potassium hydroxide at room temperature :

4 mmoles of $CH_3S\text{-}CH_2\text{-}P(O)Ph_2$ were dissolved in 10ml anhydrous THF under argon. The medium was cooled down to -70°C before the addition of 4mmoles BuLi in hexane while stirring. After 10 minutes of stirring at -70°C the medium was refrigerated at -85°C and 4 mmoles of BF_3 etherate followed by 1 mmole of 2a were added. The medium was stirred for 1hr at -85°C and then quenched with excess water. The rough product obtained after usual treatments (extraction with dichloromethane, drying and evaporation of the solvents) was then composed of 5a and an excess of phosphine oxide. This mixture was stirred at room temperature for 0.5 hr with 15 ml 0.4M ethanolic potassium hydroxyde. After the evaporation of ethanol, the medium was stirred with dichloromethane and washed with water. The rough product obtained after drying and evaporating dichloromethane was then filtered on silica gel, with dichloromethane as an eluent (the excess of phosphine oxide was completely retained on silica with this eluent). The sulfide 3a was obtained as an oil with 80% yield. (Found : C, 70.02% ; H, 8.06. Required : C, 69.19 : H, 7.74). The chemical shifts of the vinylic protons of isomeric sulfides 3a were 5.74 and 5.67 ppm in $CDCl_3$. The E/Z ratio was 2/1, the configuration being attributed using Matter's tables[10].

Various ketones (**2b-f**) were then added, at - 85° C, to the carbanion **1a** (2eq.), formed as previously described, after possible addition of 2 eq. BF_3 etherate. Hydrolysis occurred after a 1hr reaction at - 85°C with the exception of camphor **2f** (see footnote). Table 1 summarizes the results obtained after hydrolysis including the one observed with the model compound **2a**. The reaction scheme can be described as follows:

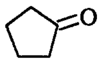
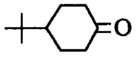
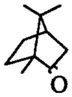
$$\begin{tikzcd}
\underset{\mathbf{2a\text{-}f}}{\text{ketone}} + \mathbf{1a} \arrow[r, shift left, "k_1"] & \text{adduct } \mathbf{4a\text{-}f} \arrow[l, shift left, "k_{-1}"] \arrow[r, "k_2"] \arrow[d, "H_2O"] & \underset{\mathbf{3a\text{-}f}}{\text{sulfide}} \\
& \text{addition compound } \mathbf{5a\text{-}f} &
\end{tikzcd}$$

The percentage of addition compounds **5** and sulfides **3** (diastereomers and/or isomers for asymmetrical ketones) was easily determined by ^1H NMR, based on CH-P, SMe and/or vinylic signals.

The mechanism for the reaction of phosphoryl-stabilized carbanions with carbonyl compounds is generally related to that of the Wittig reaction, the initial condensation of the anion being considered as reversible[11]. Forced conditions are generally used to achieve the second step, with limited success for the reaction of enolisable ketones[6,7]. The results observed here without BF_3 do not follow the classical order of the reactivity of ketones towards nucleophiles[12]. Benzophenone, for example, which is poorly reactive towards nucleophiles was completely transformed into addition compound and sulfide. It appears here that a subtle balance may operate between the different steps : a high percentage of sulfide is obtained when $k_2 >> k_{-1}$ (camphor), a poor advancement is observed when $k_{-1} >> k_2$ (model ketone). When k_{-1} and k_2 are low vs k_1 the addition compound becomes predominant (cyclic ketones). The poor results previously observed for the synthesis of α,β-unsaturated sulfides from enolisable ketones may be due to high k_{-1} values vs k_2.

When BF_3 was used the sulfide was generally not formed and the yields in addition compound were improved with the exception of camphor. The second step seemed to be inhibited, probably by the formation of a Lewis acid / Lewis base complex between BF_3 and adduct **4** which may also restrict the retro-addition. Moreover, BF_3 can also act as a promoter by activation of the carbonyl group and/or by formation of an "ate complex"[13] with the anion. For camphor, the percentage of adduct was low, due to inhibition of the elimination step.

Table 1. Reaction of anion **1a** (2 eq.) with various ketones at -85°C . Product composition after hydrolysis.

ketone	**reaction without BF_3**			**reaction with BF_3**		
	% **2**	% **5**	% **3**	% **2**	% **5**	% **3**
model **2a**	94	6	0	25	75	0
 **2b**	13	87	0	0	89	11
 **2c**	5	91	4	0	100	0
(Ph-CH2)2CO **2d**	20	30	50	10	90	0
Ph-CO-Ph **2e**	0	40	60	0	100	0
 **2f***	0	0	100	90-95	5-10	0

* The reaction medium was left to warm overnight before hydrolysis

The preparation of the different sulfides was performed according to modes 1-3 depending on the reactivity of the starting ketone, as described above:

Mode 1: as previously described for the model ketone 2a. Mode 2: the same working procedure was used but with only 2 eq. anion/ketone. Mode 3: 2 mmoles of the anion were prepared as previously described. 1 mmole of the ketone was then added at -85°C, the medium having been stirred for one hour at this temperature. The reaction was then left to warm overnight before hydrolysis. The rough product obtained after usual treatments was filtered on silica with dichloromethane as an eluent.

Table 2 summarizes the results obtained. The ^1H NMR spectra were recorded in $CDCl_3$. The elemental analyses are in good accordance with theoretical calculations.

In summary, the synthesis of new methyl vinyl sulfides was achieved with good to high yields due to the reaction of methylthiophosphine oxide carbanion with various ketones. For the synthesis of the previously known β diphenyl compound, a noticeable improvement was brought about (90% vs 35% for the traditional method using a phosphonate anion[2)]. An equilibrium step for the nucleophilic addition of phosphine oxide carbanion onto ketones was a key element. When the second step was inhibited, the use of $BF_3{:}OEt_2$ as a promoter was crucial to achieve the synthesis of the sulfide. We plan to apply this methodology to other problematic Wittig-type reactions and, more generally, to examine in greater depth the role of boron trifluoride as an anion promoter.

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Table 2. Synthesis of various methyl vinyl sulfides

Sulfide	Mode	Yield %	Aspect	δ =CH ppm	δ $S\text{-}CH_3$ ppm
3a	1	80	oil	5.74 ; 5.67	2.31 ; 2.28
3b	2	50*	"	5.72	2.28
3c	2	90	"	5.56	2.26
3d	1	70	"	5.82	2.34
3e	3	90	solid m.p.=58°C	6.60	2.41
3f	3	86	oil	5.48 ; 5.47	2.28 ; 2.23**

* relatively volatile product which was partly evaporated with the solvent ** isomers ratio = 53/47

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