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Synthesis of 1-Diethoxyphosphoryl-1-methylthio-thioacetamides and 1-Methylthioethenethioamides. An Unusual Intramolecular α-Desulfenylation of Thioacetamides

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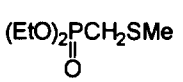
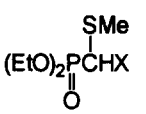
Abstract: Addition of the lithiated α-phosphoryl sulfide **1-Li** to alkyl or aryl isothiocyanates **4(a-f)** and phenyl isocyanate **4g** was found to afford 1-diethoxyphosphoryl-1-methylthio-thioacetamides **5(a-f)** and -acetamide **5g**, respectively. In the case of the reaction with the p-chlorophenyl isothiocyanate **4e**, the α-desulfenylated product **6** was isolated and on the basis of ^{31}P-NMR experiments a mechanism of its formation was proposed. The phosphonates **5(a-f)**, which exist in the thione form, were found to undergo the Horner-Wittig reaction with aromatic aldehydes affording 1-methylthioethenethioamides **14(a-f)**.

INTRODUCTION

The α-sulfur substituted phosphonate carbanions are valuable intermediates in organic synthesis since they react easily with electrophiles to form a new carbon-carbon bond. Particularly interesting is the α-phosphonate carbanion derived from α-diethoxyphosphorylmethyl methyl sulfide **1** which can be further functionalized in the α-position with a wide range of the carbon and heteroatom-containing substituents to give **2**.[1] Our recent interest in the reactions of this carbanion with bifunctional reagents of the type X=C=Y resulted in a synthesis of α-phosphoryl-α-methylthioacetic acid **3** which is a new reagent especially useful for efficient preparation of five- and six-membered lactones.[2]

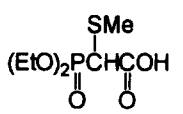


1



2

X=halogen,OR,SR,SeR, C-substituent



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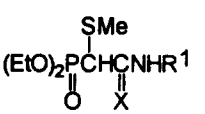


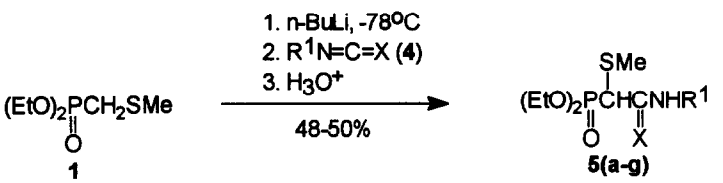
5 X=O,S

In extension of these studies we turned our attention on reactivity of **1-Li** towards other bifunctional electrophilic reagents: isocyanates and isothiocyanates. This reaction was expected to give the title 1-diethoxyphosphoryl-1-methylthio-thioacetamides **5** which in turn could be used for the synthesis of the ethenethioamides **14** via the Horner-Wittig reaction. On the other hand, the compounds **5** and **14** seemed to be interesting for their anticipated biological properties because compounds possessing either the phosphoryl group and/or thioacetamide and acetamide groupings showed a rich spectrum of pesticidal activity.[3-6] Moreover, Lachkova and Petrov have recently reported the synthesis of some 1-diethoxyphosphorylthioacetamides acting as herbicides and growth factors.[7]

From a synthetic point of view, the hitherto existing syntheses of ethenethioamides **14** suffered from a lack of generality. Direct addition of olefinic organometallics to isothiocyanates was limited, for instance, to the products possessing only alkyl groups around the carbon-carbon double bond.[8] The Horner-Wittig olefination reaction extended a spectrum of the available substituents onto vinyl and aromatic ones but the phosphorus component of the olefination process should possess in the α-position to phosphorus either alkyl or phenyl groups.[9] Substrates with strongly electron withdrawing groups (COOR,CN) existed in the enethiol form only and due to low electron density at the α-phosphonate carbon atom, the Horner-Wittig reaction was unpractical.[9,10,11] The corresponding phosphorus ylide with the methyl ester group in the α-position was also known, however, the Wittig reaction was not performed with this substrate.[12] Below, we describe an extension of the Horner-Wittig reaction for the phosphonate component possessing the α-methylthio group what led to the synthesis of the sulfur-modified ethenethioamides.

RESULTS AND DISCUSSION

1-Diethoxyphosphoryl-1-methylthio-thioacetamides **5(a-f)** and acetamide **5g** were synthesized by addition of the lithiated α-phosphoryl sulfide, **1-Li**, to isothiocyanates **4(a-f)** and isocyanate **4g**, respectively (Scheme 1 and Table 1).



4/5,X=S	a	b	c	d	e	f	4/5,X=O	g
R^1	Me	Et	Pr	C_6H_5	4-Cl-C_6H_4	4-Br-C_6H_4	R^1	C_6H_5

Scheme 1

When the α-phosphoryl sulfide **1** was used in a 1.7-2 molar excess (exception **5g**, see Experimental) over isothiocyanate **4**, ca. 50% of **1** was converted into **5**. This is due to a difference in acidity of the α-methylene protons in the substrate **1** and the α-methine proton in the product **5**. In some cases e.g. **5e**,

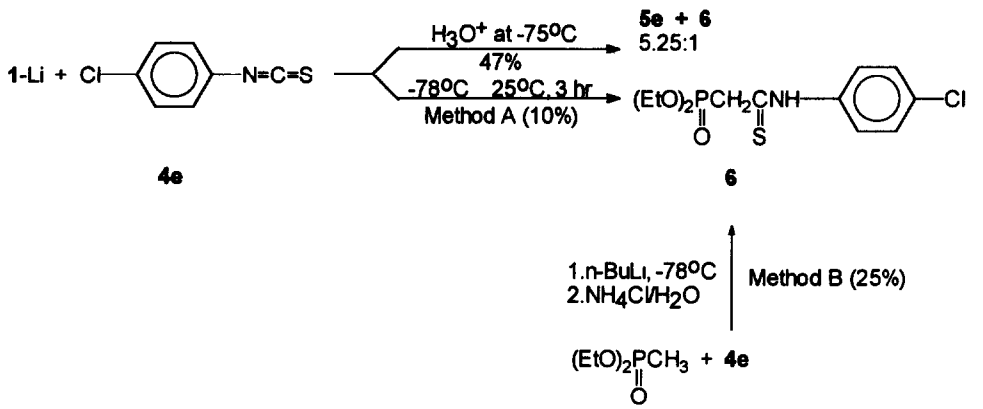
Table 1 Synthesis of 1-Diethoxyphosphoryl-1-methylthio-N-substituted thioacetamides.

Product	Yield[a]	m.p.(°C)[b]	Molecular Formula[c]	^{31}P-NMR (solvent)[d] δ (ppm)	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
5a	50	49.5-51.5	$C_8H_{18}NO_3PS_2$ (271.3)	17.2 (benzene)	1.31, 1.37 (2xt, 6H, $^3J_{H-H}$=5.0, $^4J_{H-P}$=5.6, P-O-CH_2CH_3); 2.25 (d, 3H, $^4J_{H-H}$=1.1, SCH_3); 3.22 (dd, 3H, $^3J_{H-H}$=4.8, $^5J_{H-P}$=1.2, NH-CH_3); 4.07-4.42 (m, 4H, P-O-CH_2CH_3); 4.03 (d, 1H, $^2J_{H-P}$=20.3, P-C-H); 8.52-8.83 ppm (vbrs, 1H, N-H)[e]
5a	48	36-38	$C_9H_{20}NO_3PS_2$ (285.4)	17.1 (benzene)	1.22, 1.25, 1.32 (3xt, 9H, $^3J_{H-H}$=7,P-O-CH_2CH_3, NCH_2CH_3), 2.19 (d, 3H, $^4J_{H-P}$=1.1, SCH_3; 3.67 (brdq, 2H, $^3J_{H-H}$=7, N-CH_2CH_3), 4.13 (m, 4H, P-OCH_2CH_3), 4.23 (d, 1H, $^2J_{H-P}$=20, P-CH); 8.68-8.32 ppm (vbrs, 1H, NH)[f]
5c	48	46-47	$C_{10}H_{22}NO_3PS_2$ (299.4)	17.2 (benzene)	0.9 (t, 3H, $^3J_{H-H}$=7,, $NCH_2CH_2CH_3$); 1.25, 1.30 (2xbrt, 6H, $^3J_{H-H}$=7, P-O-CH_2CH_3) 1.65 (sxt, 2H, $^3J_{H-H}$=7, $NCH_2CH_2CH_3$); 2.19 (d, 3H, $^3J_{H-P}$=1.2, SCH_3); 3.58 (brq, 2H, $NCH_2CH_2CH_3$); 4.15 (m, 4H, P-O-CH_2CH_3); 4.22 (d, 1H, $^2J_{H-P}$=20, P-CH); 8.12-8.62 ppm (vbrs. 1H, NH)[e]
5d	50	59-62	$C_{13}H_{20}NO_3PS_2$ (333.3)	17 1 (benzene)	1.27, 1.32 (2xt, 6H, $^3J_{H-H}$=6.5, $POCH_2CH_3$); 2.25 (d, 3H, $^4J_{H-P}$=1, SCH_3); 4.17 (m, 4H, $POCH_2CH_3$); 4.37 (d, 1H, $^2J_{H-P}$=20, P-CH); 7.12-7.87 (m, 5H, C_6H_5), 10.10-10.25 ppm (vbrs. 1H, NH)[f]
5e	47	oil	$C_{13}H_{19}ClNO_3PS_2$ (367.9)	17.2 (chloroform)	1.32, 1.40 (xt, 6H, $^3J_{H-H}$=7.0, $POCH_2CH_3$); 2.32 (d, 3H, $^4J_{H-P}$=1.0, SCH_3), 4.14, 4.25 (2xdq, 4H, $^3J_{H-H}$=7.0, $^3J_{H-P}$=6.8, $POCH_2CH_3$), 4.29 (d, 1H, $^3J_{H-P}$=20.2, P-CH); 7.37, 7.77 ppm (2xd, 4H, $^3J_{H-H}$=8.8, C_6H_4)[g]
5f	55	oil	$C_{13}H_{19}BrNO_3PS_2$ (412.3)	17.2 (chloroform-d)	1.31, 1.37 (2xt, 6H, J=7.0, $POCH_2CH_3$); 2.32 (d, 3H, $^4J_{H-P}$=1.2, SCH_3), 4.18, 4.29 (2xdq, 4H, $^3J_{H-H}$=7.0, $^3J_{H-P}$=6.0, $POCH_2CH_3$), 4.34 (d, 1H, $^2J_{H-P}$=20.2, PCH);7.51, 7.72 ppm (2xd, 4H, $^3J_{H-H}$=9.0, C_6H_4)[g]

a Yield of isolated product **5a-f** based on the corresponding isothiocyanates **4**.
b Uncorrected, measured with a Boëtius apparatus.
c Satisfactory microanalysis obtained: C±0.3, H±0.2, P±0.4, S±0.4.
d Recorded on a Jeol JNM-C-60 HL spectrometer.
e Recorded on a Bruker HFX (90 MHz) spectrometer.
f Recorded on a Tesla BS 847 C (80 MHz) spectrometer.
g Recorded on a Bruker MSL (300 MHz) spectrometer.

the reaction conditions had a significant influence on the structure of the final reaction products. For instance, acidification of the reaction mixture of **1-Li** and **4e** at -75°C after 5 min. gave the normal addition product **5e** in 47% yield while acidification at 25°C after the 3 hours time, led to the formation of an unexpected product **6** in 67% yield (only 10% could be isolated in a pure form after chromatography). The optimal reaction time was variable and depended on the reaction scale. A careful investigation of the reaction conditions showed that **5e** was accompanied by **6** as a minor product in a ratio **5e/6**=5.25:1 when the reaction mixture was rapidly acidified at -75°C (Scheme 2).

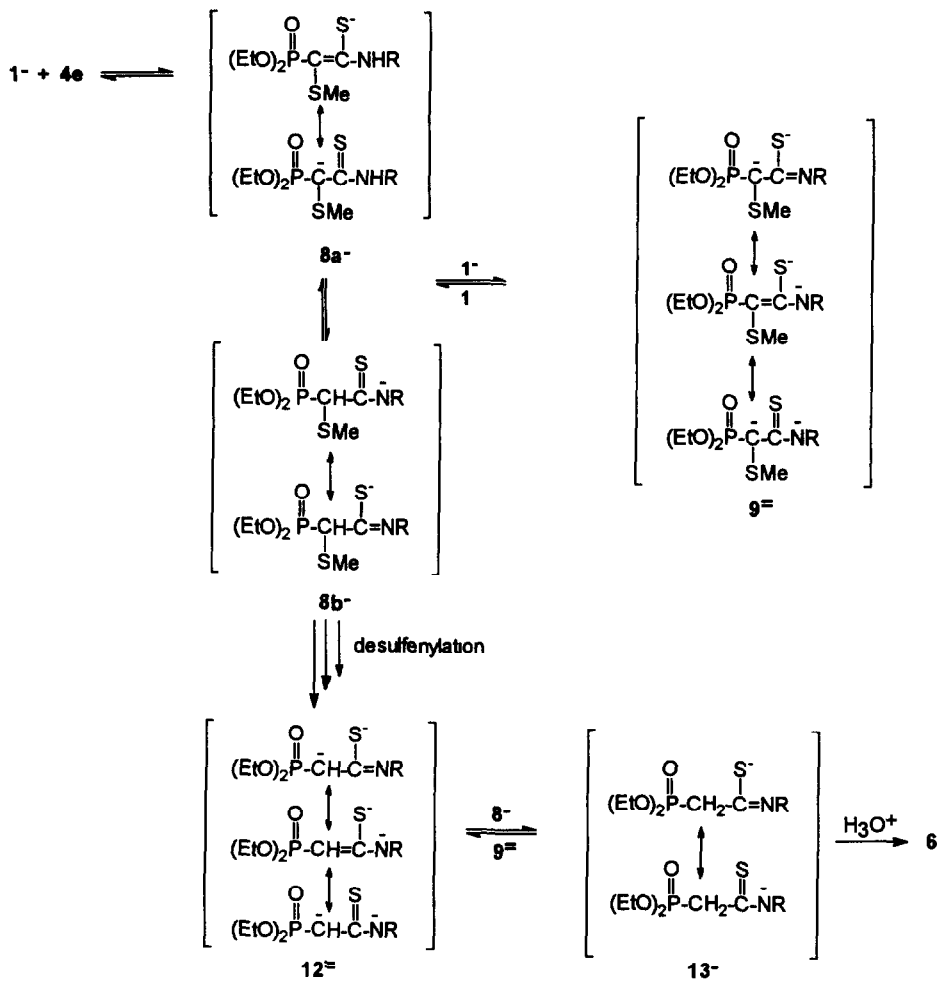
In the ^{1}H-NMR spectrum of this new unexpected product **6**, the two proton doublet ($CDCl_3$, δ=3.62 ppm, J=21.4 Hz) characteristic of the P-methylene protons was observed while the expected signals for the methylthio and the P-methine protons were absent. The ^{31}P-NMR spectrum of **6** confirmed existence of the P-CH_2 group since it showed a higher absorbtion at δ=22.1 ppm in comparison to that at δ=17.2 ppm for **5e**. Moreover, no carbonyl signal was observed in the IR spectrum of **6** whereas the thiocarbonyl absorbtion was preserved there as in **5e**. For the final confirmation of the structure, the compound **6** was synthesized in an independent way starting from the lithiated **7** and isothiocyanate **4e** (Method B in Scheme 2).



Scheme 2

Our rationalization of the formation of **6** involves equilibria of **1**$^-$ with the monoanions **8**$^-$ (**8a**$^-$ and **8b**$^-$) and with the dianion **9**$^=$ depicted in Scheme 3. Thus, the monoanion **8b**$^-$ may undergo intramolecular desulfenylation as a result of a nucleophilic attack of the mercaptide anion either at the α-phosphonate carbon atom or at the methylthio sulfur atom (Scheme 4). The carbophilic attack requires an intermediary formation of the episulfide **10** which is then opened by methyl mercaptide followed by the sulfur-sulfur cleavage in the resulting disulfide **11** either in a nucleophilic way with methyl mercaptide (path a) or in a solvolytic one with water (path b). We incline, however, towards the thiophilic attack which leads directly to the disulfide **11** and later to **6** via path a or b and which was recently evidenced in other desulfenylation reactions.[13]

The equilibria shown in Scheme 3 and the intramolecular character of the desulfenylation reaction were confirmed by the ^{31}P-NMR measurements at low temperatures and additional experiments. Thus, addition of **1**$^-$ to **4e** in the THF solution at -75°C caused after 2 hours appearance in the ^{31}P-NMR spectrum of the signals due to **1**$^-$, dianion **9**$^=$, monoanions **8**$^-$ and **1** (for the appropriate chemical shifts see Table 2).



Scheme 3

At room temperature, two additional signals attributed to the monoanion **13**$^-$ and dianion **12**$^=$ were found in the spectrum. After acidification of the reaction mixture at -75°C, the two ^{31}P-NMR signals due to **1** and **5e** in a ratio 2:1 were present (depending on the reaction scale and time, **6** was also present in a 5-15%), while acidification at room temperature brought additional signal accompanying **1** and **5e** which was attributed to **6**. In order to ascribe new chemical shifts to mono- and dianions of **5e** and **6** in the spectrum of the reaction mixture, we generated the appropriate species at -75°C starting from the pure **5e** and **6** and one or two equivalents of n-BuLi. Additionaly, conversion of dianions to monoanions and the latter back to **5e** and **6** was carried out using stoichiometric amount of gaseous HCl in THF. (Table 2).

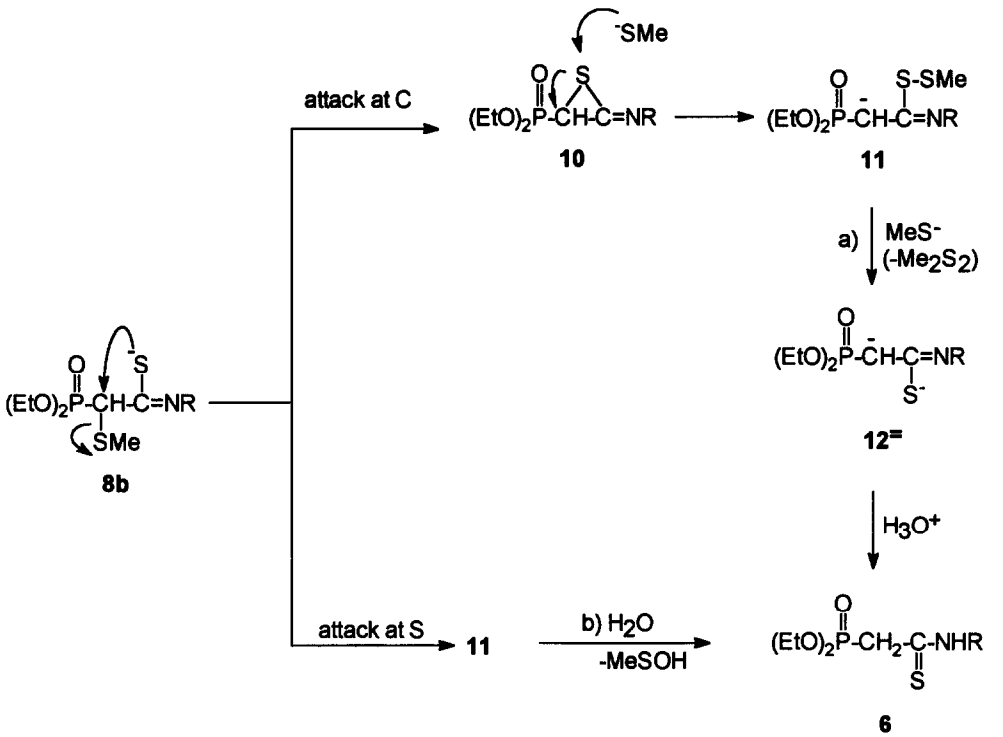
Table 2. ^{31}P-NMR chemical shifts.

Compound	δ_{31} (THF) [ppm]
1	24.8
1$^-$	52.0
8$^-$ (**8a**$^-$/**8b**$^-$)-monoanion	32.2/27.7 (3.5/1)
9$^=$-dianion	41.0/38.3 (2.5/1, br)*
5c	18.3
13$^-$-monoanion	31.8
12$^=$-dianion	43.6 (br)
6	22.1

* most probably due to the E/Z geometry resulted from different complexation of lithium by heteroatoms.

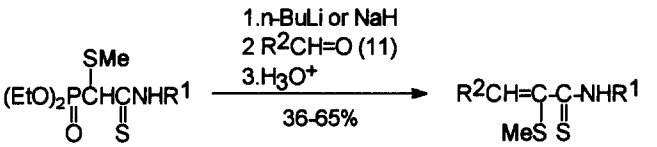
Next, we showed that alternative mechanism of the intermolecular desulfenylation of **5** by **1-Li** did not work because in the ^{31}P-NMR spectra of such a reaction mixture neither diethyl bis(methylthio)methanephosphonate arising from the attack of **1-Li** at the methylthio sulfur atom, nor the products with two phosphorus atoms responsible for the attack of **1-Li** at the phosphonate carbon atom were found.

Finally, we proved in separate experiments that neither addition of **1** nor **4e** to the reaction mixture before or after its protonation (reflux in $CHCl_3$) caused the intermolecular desulfenylation. We also demonstrated that the use of a more polar solvent such as 20% aqueous solution of sodium hydroxide instead of a tetrahydrofuran solution, for purifying the chloroform sample containing **1:5e:6**=6/5/3 by 2-fold extraction, caused separation of the mixture **5e/6** from **1** and a quick conversion of **5e** to **6** in a ratio 1:4.5. To the best of our knowledge the intramolecular α-desulfenylation described above is the first example of such a reaction occuring at the α-phosphonate carbon atom.



Scheme 4

The scope of the addition reaction was also extended to isocyanates. Thus, addition of **1-Li** to phenyl isocyanate **4g** (X=O) gave the expected 1-diethoxyphosphoryl-1-methylthioacetamide **5g** in 50% yield. This result stands in contrast to the recent result obtained by Motoyoshiya et al[14] in which keteneimines as the olefination products were obtained.



5(a-f) **14(a-f)**

11/14	a	b	c	d	e	f
R^1	Me	Et	C_6H_5	4-Cl-C_6H_4	4-Cl-C_6H_4	4-Br-C_6H_4
R^2	C_6H_5	4-Br-C_6H_4	C_6H_5	C_6H_5	4-Br-C_6H_4	C_6H_5

Scheme 5

In the next step of the present study we investigated the Horner-Wittig reaction of the newly obtained adducts **5(a-f)** (Scheme 5). First, the procedure (see Experimental) with an equimolar amount of sodium hydride as a base generating the α-phosphonate carbanion was tested. However, with benzaldehyde, the corresponding olefination product **14d** was obtained in a low yield (36%). It was gratifying to find that replacement of sodium hydride by n-butyllithium (Procedures B,C, see Experimental and Table 3) allowed us to increase the yields of **14a-c** and **14e** to 55-65%. Further efforts to improve the yield of ethenethioamides failed. For instance, the two phase transfer catalysed reaction of **5d** with benzaldehyde (EtOH/solid K_2CO_3, 3 hrs, 25°C or benzene/25%-50% aqueous solution of NaOH, 3 hrs, 25°C) gave the corresponding olefin **14d** only in 50-60% yield based on the ^{31}P-NMR spectra. Excess of benzaldehyde did not improve the yield as well.

In order to establish a configuration around the double bond in olefins **14(a-f)**, it was necessary to measure the ^{1}H-^{1}H n.O.e. enhancement coefficients. The n.O.e. difference measurements between the olefinic protons and the MeS groups [performed for **14(a-f)**] showed that for the N-aryl substituents the predominant if not exclusive was the Z-isomer, since in these products the n.O.e. enhancement coefficients were close to zero. For the N-alkyl substituents, the E/Z ratio was nearly 1:1; for **14a**, the n.O.e. was not conclusive.

Purification of **14** by column chromatography did not considerably change the E/Z ratio. For example, for the compound **14f** the E/Z ratio was 27/75 and 31/69 in a crude mixture and after chromatography, respectively. Similarly, for the compound **14e**, the E/Z ratio in a crude mixture was found to be 5/95 while after chromatography E/Z ratio was 29/71.

In conclusion, we described herein a synthesis of new 1- diethoxyphosphoryl--1-methylthio-thioacetamides **5(a-f)** and the acetamide **5g** formed in the condensation reaction of the lithiated α-phosphoryl sulfide **1-Li** with isothiocyanates **4(a-f)** and phenyl isocyanate **4g**, respectively. Under prolonged reaction time, the unexpected formation of the α-desulfenylation product **6** occured. The newly

Table 3. Synthesis of 1-methylthioethenethioamides **14a-f**.

Product	Yield [%]	Z/E ratio[a]	Procedure	m.p. (°C)[b]	Molecular Formula[c]	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
14a	60	50/50	B	oil	$C_{11}H_{13}NS_2$ (223.4)	(E+Z)[d]: 2.14, 2.37, (2xs, 3H, 2xSCH_3) 3.10, 3.36 (2xd, 3H, 2x$NHCH_3$, $^3J_{H-H}$=5.0) 7.15-7.90 (m, 5H, C_6H_5), 7.55 ppm (brs, 1H, NH)
14b	55	55/45	B	oil	$C_{12}H_{14}BrNS_2$ (316.3)	Z[d]: 1.38 (t, 3H, $^3J_{H-H}$=7.3, CH_2CH_3, 2.16, (s, 3H, SCH_3) 3.87 (dq, 2H, $^3J_{H-H}$=5.4; 7.3; $NHCH_2CH_3$) 7.59 (m, 4, C_6H_4), 8.26 (s, 1H, HC=), 8.90 ppm (brs, 1H, NH)
				52-54 (isomer E)		E[d]: 1.15, (t, 3H, $^3J_{H-H}$=7.3, CH_2CH_3), 2.37 (t, 3H, SCH_3) 3.66 (dq, 2H, $^3J_{H-H}$=5.6, 7.3, NH-CH_2CH_3), 6.25 (s, 1H, =CH), 7.44 ppm (m, 4H, C_6H_4)
14c	65	100/0	B	100-101 (isomer Z)	$C_{16}H_{15}NS_2$ (285.4)	Z[e]: 2.20 (s, 3H, SCH_3), 7.75-8.0 (m, 1H, 2xC_6H_5), 8.4 (s, 1H, =CH), 10.6 ppm (brs, 1H, NH)
14d	36	60/40	A	94-95 (isomer Z)[f]	$C_{16}H_{14}ClNS_2$ (319.9)	Z[d]: 2.26 (s, 3H, SCH_2), 7.37-7.46 (m, 5H, C_6H_5), 7.80-7.85 (m, 4H, C_6H_4), 8.43 (s, 1H, =CH), 10.60 ppm (brs, 1H, NH)
						E[d]: 1.57 (s, 3H, SCH_3), 7.00 (s, 1H, =CH), 7.29-7.93 (m, 9H, C_6H_5 + C_6H_4), 8.70 ppm (s, 1H, NH)
14e	62	71/29	C	135-136 (isomer Z)[f]	$C_{16}H_{13}BrClNS_2$ (398.8)	Z[d]: 2.26 (s, 3H, SCH_3), 7.40-7.82 (m, 8H, 2xC_6H_4), 8.32 (s, 1H, =CH), 10.5 ppm (s, 1H, NH)
						E[d]: 1.56 (s, 3H, SCH_3), 6.35 (s, 1H, =CH) 7.10-7.80 (m, 8H, 2xC_6H_4), 8.74 ppm (s, 1H, NH)
14f	42	69/31	B	101-104 (isomer Z)	$C_{16}H_{14}BrS_2$ (364.3)	Z[d]: 2.25 (s, 3H, SCH_3), 7.2-7.9 (m, 9H, C_6H_5 + C_6H_4), 8.42 (s, 1H, C_6H_5CH=) 10.60 ppm (bs, 1H, NH)
				125-129 (isomer E)		E[d]: 2.43 (s, 3H, SCH_3), 6.44 (s, 1H, C_6H_5CH=) 7.20-7.90 (m, C_6H_5 + C_6H_4), 8.80 ppm (brs, 1H, NH).

a A ratio Z/E was determined based on yields of the isolated isomers. For **14d** Z/E was determined in the reaction mixture.
b Uncorrected, measured with a Boëtius apparatus.
c Satisfactory microanalysis obtained: C±0.3; H±0.2; S±0.2; N±0.2; Br±0.3.
d Recorded on a Bruker MSL (300 MHz) spectrometer.
e Recorded on a Tesla BS-487 C (80 MHz) spectrometer.
f Compounds isomerize during melting.

obtained thioacetamides **5(a-f)** reacted with aromatic aldehydes in terms of the Horner-Wittig reaction to give 1-methylthiosubstituted **14(a-f)** having the predominant Z-configuration in case of the N-aryl substituents.

EXPERIMENTAL SECTION

Melting points are uncorrected. Commercially available chemicals were purified by distillation or recrystallization. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ immediately before use. Silica gel 40 (Merck, 70-230 mesh) was used for preparative chromatography; for separation of the E/Z mixture of diastereoisomers, silica gel 60 (Merck, 230-400 mesh) was used.
The ^1H-^1H n.O.e. procedure was as follows. The standard Bruker microprogram was used to perform a steady-state n.O.e. difference spectroscopy on the MSL 300 instrument. Thirty two scans (proceeded by two dummy scans to establish equilibrium) were acquired for each irradiation frequency and the entire process was automatically repeated to afford the required signal-to-noise ratio. The irradiation time was 3.0 s, the relaxation delay was 7.5 s. A 90° read pulse was employed in all cases. The decoupler power setting was chosen so as to minimize the frequency spillover to the neighbouring multiplets. The n.O.e. enhancement values were calculated by comparing the signal integrals in the difference spectra with the control irradiation spectrum. The error of determination of the n.O.e. enhancement coefficient was estimated to be less than 10%.

N-Substituted-1-Diethoxyphosphoryl-1-methylthio thioacetamides ***5(a-f)****. General Procedure.*

A 1.35 M solution of n-BuLi in n-hexane (58.5 ml, 79 mmol) is added to a stirred solution of diethyl methylthiomethanephosphonate (**1**; 14.85g, 75 mmol) in dry THF (300 ml) at -78°C under argon atmosphere. Stirring is continued for 15 min and a solution of isothiocyanate (44 mmol) in THF (50 ml) is added. The mixture is then slowly warmed to room temperature and acidified to pH=5 with 10% aq. HCl. For **5e** the reaction mixture after the additional 2 hr stirring is rapidly acidified at -75°C and for **5f** at 0°C. The solvents are removed and the residue is dissolved in chloroform (200 ml). This solution is washed with water (2x100 ml), dried ($MgSO_4$) and evaporated to give the crude product **5(a-f)** which is purified by column chromatography on silica gel (a benzene/acetone gradient as eluent) (Table 1).

1-Diethoxyphosphoryl-1-methylthio-N-phenylacetamide ***5g****.*

A 1.35 M solution of n-BuLi in n-hexane (88.9 ml, 0.12 mol) is added to a stirred solution of diethyl methylthiomethanephosphonate (**1**, 21.72 g, 0.11 mol) in dry THF (300 ml) at -78°C under argon atmosphere. Stirring is continued for 20 min and a solution of phenyl isocyanate (13.05 g, 0.11 mol) in THF (50 ml) is added. The mixture is slowly warmed to room temperature and acidified to pH=5 with 10% aq HCl. The solvents are removed and the residue is dissolved in methylene chloride (300 ml). This solution is washed with water (2x100 ml), dried ($MgSO_4$) and evaporated to afford the crude product **5g** which is purified by column chromatography on silica gel (a n-pentane - benzene gradient as eluent); yield 17.5 g (50%); oil.

$C_{13}H_{20}NO_4PS$	calc.	C	49.20	H	6.35
(317.3)	found		49.29		6.48

^{1}H-NMR ($CDCl_3$,TMS): δ=1.22, 1.19 (2xt, 6H, $^3J_{H-H}$=7.0, 2x$OCH_2\underline{CH_3}$); 2.16 (d, 3H, $^4J_{H-H}$=1Hz, SCH_3); 3.70 (d, 1H, $^2J_{H-P}$=20.5, P-CH); 4.00-4.20 (m, 4H, 2x$OC\underline{H_2}CH_3$); 6.9-7.5 ppm (m, 4H, C_6H_4); 8.9 (s, 1H, NH); ^{31}P-NMR ($CDCl_3$), δ=19.2 ppm.

1-Diethoxyphosphoryl-N-p-chlorophenylthioacetamide **6**. *Method A:*

A 1.39 M solution of n-BuLi in n-hexane (172.8 ml, 0.240 mol) is added to a stirred solution of diethyl methylthiomethanephosphonate (**1**; 47.5 g, 0.239 mol) in dry THF (1100 ml) at -78°C under argon atmosphere. Stirring is continued for 30 min and a solution of p-chlorophenyl isothiocyanate (**4e**; 20.35 g, 0.12 mol) in THF (90 ml) is added. After stirring for 30 min at -78°C, the reaction mixture is warmed to +25°C within 3 hours and then acidified with 10% aq HCl to pH=6. Then, organic layer is separated from aqueous layer and dried over $MgSO_4$. After filtration and evaporation of the solvents, the crude product containing 67% of **6** is obtained. Column chromatography on silica gel (a benzene-acetone gradient as eluent) of the crude **6** and then crystallisation of the resulting oil (ethyl acetate/n-pentane) affords 0.38 g (10%) of the analytically pure **6**; m.p.=100.0-102.5°C (yellow crystals).

$C_{12}H_{17}NO_3PSCl$	calc	C 44.79	H 5.32	Cl 11.02	N 4.35	P 3.63	S 9.96
(321.8)	found	44.98	5.30	11.34	4.32	9.37	9.85

^{1}H-NMR ($CDCl_3$, TMS), δ=1.38 (t, 6H, $^3J_{H-H}$=7.1, 2x$OCH_2\underline{CH_3}$); 3.62 (d, 2H, $^2J_{H-P}$=21.4, P-CH_2); 4.21 (dq, 4H, $^3J_{H-H}$=7.1, $^3J_{H-P}$=8.1, 2x$OC\underline{H_2}CH_3$); 7.22, 7.69 (2xd, 4H, $^3J_{H-H}$=8.9, C_6H_4), 11.0 (brs, 1H, NH).
^{13}C-NMR ($CDCl_3$, TMS): δ=16.31 (d, $^3J_{C-P}$=5.63, $OC\underline{H_2}CH_3$); 46.17 (d, $^1J_{C-P}$=125.83, P-$\underline{C}H_2$); 63.42 (d, $^2J_{C-P}$=7.04, $O\underline{C}H_2CH_3$); 123.78, 128.56, 131.32; 137.59 (4xs, $\underline{C}_6H_4$); 190.59 ppm (d, $^2J_{C-P}$=7.51, >C=S).
^{31}P-NMR ($CDCl_3$): δ=22.09
IR (KBr): 1012 (s), 1214 (vs), 1383 (s), 1492 cm^{-1} (s).

Method B:
A 1.5 M solution of n-BuLi in n-hexane (3.8 ml, 5.7 mmol) is added to a stirred solution of diethyl methanephosphonate (**7**; 0.8 g, 5.26 mmol) in dry THF (50 ml) at -78°C under argon atmosphere. Stirring is continued for 15 min and a solution of p-chlorophenyl isothiocyanate (**4e**; 0.893 g, 5.26 mmol) in THF (20 ml) is added at -78°C. After stirring for 0.5 hr at -20°C and then for 1 hr at 0°C the reaction mixture is acidified with aqueous saturated solution of NH_4Cl (10 ml). The solvents are removed and the residue is extracted with benzene (3x20 ml). The combined benzene extract are washed with water (20 ml), dried ($MgSO_4$) and evaporated to afford the crude **6** which is purified by column chromatography over silica gel (50 g; 230-400 mesh, a benzene/acetone gradient as eluent); yield 0.425 g (25%). Spectroscopic data for the analytically pure **6** are identical as those reported for **6** in method A.

1-Methylthioethenethioamides.

Method A. (for thioamide **14d**): Sodium hydride (0.54 g, 21 mmol) is added in portions to a stirred solution of 1-diethoxyphosphoryl-1-methylthio-N-p-chlorophenylthioacetamide (**5e**; 7.66 g, 21 mmol) in dry THF (80 ml) under argon atmosphere at room temperature. After stirring for 20 min at this temperature, a solution of freshly distilled benzaldehyde (2.21 g, 21 mmol) in THF (10 ml) is added. The reaction mixture is then stirred for 20 hrs. The solvents are removed and the residue is dissolved in chloroform (150 ml). This solution is washed with water (2x50 ml), dried ($MgSO_4$), filtered and evaporated to give the crude **14d**

which is purified using column chromatography over silica gel (a n-hexane/benzene gradient); yield: 2.4 g (36%) (Table 3).

Method B. (for thioamides **14(a-c), 14f**): A 1.3 M solution of n-BuLi in hexane (34.6 ml, 45 mmol) is added dropwise to a stirred solution of 1-diethoxyphosphoryl-1-methylthio-N-substituted-thioacetamide (**5a-c, 5f**; 42 mmol) under argon atmosphere at -78°C. Stirring is continued for 15 min and a solution of aldehyde (41.6 mmol) in THF (20 ml) is added. After stirring for 0.5 hr, the reaction mixture is warmed to room temperature. For **14f** stirring is continued for 1 hr. Then the solvents are removed and the residue is dissolved in chloroform (150 ml). This solution is washed with water (2x50 ml), dried ($MgSO_4$), filtred and evaporated to afford the crude thioamides **14(a-c), 14f** which are purified using column chromatography over silica gel (a n-hexane/benzene gradient as eluent) (Table 3).

Method C. (for thioamide **14e**): A 1.3 M solution of n-BuLi in n-hexane (21.7 ml, 28.2 mmol) is added to a stirred solution of 1-diethoxyphosphoryl-1-methylthio-N-p-chlorothioacetamide (**5e**; 5.2 g, 14.1 mmol) in dry THF (60 ml) under argon atmosphere at -78°C. After stirring for 10 min at this temperature, a solution of p-bromobenzaldehyde (2.61 g, 14.1 mmol) in THF (10 ml) is added. The reaction mixture is stirred for additional 30 min at -78°C, then warmed to room temperature and again stirred for 30 min. After acidification with 10% aq. HCl, the solvents are removed and the residue is dissolved in dichloromethane (100 ml). This solution is washed with water (2x50 ml), dried ($MgSO_4$). filtered and evaporated to give the crude **14e** which is purified by column chromatography over silica gel, yield: 3.5 g (62%). (Table 3).

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