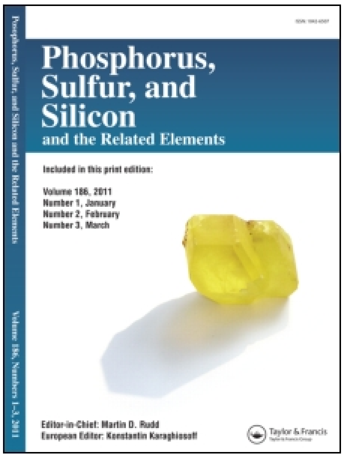

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A FACILE SYNTHESIS OF DIETHYL 1-ISOTHIOCYANO)ALKYLPHOSPHONATES[1]

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A FACILE SYNTHESIS OF DIETHYL 1-(ISOTHIOCYANO)ALKYLPHOSPHONATES[1]

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Novel, diethyl 1-(isothiocyano)alkylphosphonates **3** have been efficiently synthesized *via* a one-pot reaction of diethyl 1-azidoalkylphosphonates **1** with triphenylphosphine, followed by *in situ* transformation of thus formed phosphazenes **2** with carbon disulfide. Application of the title compounds in the synthesis of diethyl (N-phenylthioureido)- and (benzothiazol-2-ylamino)methylphosphonates was also described.

Keywords: Diethyl 1-azidoalkyphosphonates; iminophosphoranes; Staudinger reaction; diethyl 1-(isothiocyano)alkylphosphonates; diethyl (N-phenylthioureido)methylphosphonate; diethyl (benzothiazol-2-ylamino)methylphosphonate

INTRODUCTION

Alkyl and aryl isothiocyanates are a versatile and important class of heteroallenes, which found wide application, especially in the construction of heterocycles systems.[2–6] A variety of synthetic approaches leading to these heteroallenes has recently been reviewed,[2–6] and the choice of the procedure depends on target molecule.[4] Generally isothiocyanates have been prepared by the reaction of primary amines with thiocarbonyl reagent like carbon disulfide or thiophosgene.[2–5] Also iminophosphoranes[7] (easily available from tertiary phosphines and organic azides) are valuable starting materials, which in reaction with carbon disulfide give alkyl isothiocyanates in high yields. [8–10]

On the other hand, diethyl 1-(isothiocyano)alkylphosphonates are a novel class of bifunctional isothiocyanates in which the presence of the

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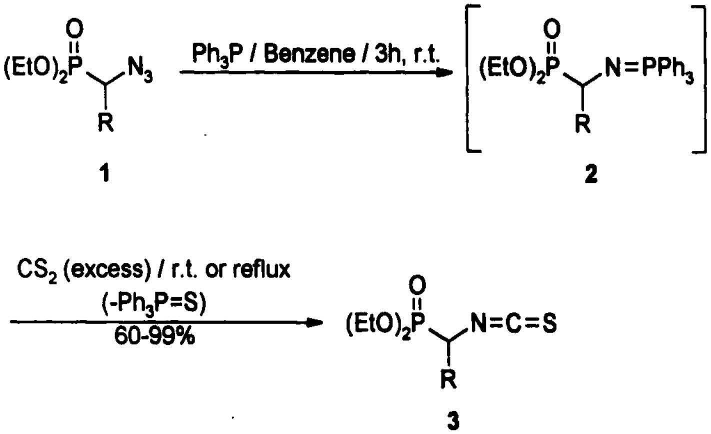
phosphoryl moiety on the α-carbon atom adjacent to the isothiocyano group enhances their synthetic attractiveness. To the best of our knowledge, the only papers on α-phosphorylated isothiocyanates reported in the literature concern the preparation of bis(trimethylsilyl) 1-(isothiocyano)alkylphosphonates from appropriate bis(trimethylsilyl) 1-aminoalkylphosphonate and carbon disulfide as derivatives for gas chromatography and mass spectrometry.[11,12]

RESULTS AND DISCUSSION

In connection with our interest in the chemistry of organic compounds containing both phosphorus and nitrogen atoms we have recently become involved in the application of diethyl 1-azidoalkylphosphonates[13] **1** in the synthesis of diethyl 1-aminoalkylphosphonates[14,15] and derivatives of 1-[1-(diethoxyphosphoryl)alkyl]-*1H*-1,2,3-triazoles.[16] Herein, we wish to report the application of the above-mentioned reagent **1** for the new one-pot preparation of diethyl 1-(isothiocyano)alkylphosphonates **3** (Scheme 1).



1-3	a	b	c	d	e	f
R	H	Me	Et	Pr	i-Pr	Ph

SCHEME 1

TABLE I Diethyl 1-(Isothiocyano)alkylphosphonates **3a-f** Prepared

Product	*Reaction conditions time, temp.*	*Yield (%)*[a]	n_D^{20}	*Rf*	*Molecular Formula*[b]	*FAB/MS MH*$^+$ *(%)*
3a	4h, reflux[c]	61	1.4925	0.44[d]	$C_6H_{12}NO_3PS$ (209.17)	210 (81)
3b	5h, reflux[c]	68	1.4790	0.52[d]	$C_7H_{14}NO_3PS$ (223.23)	224 (47)
3c	5h, reflux	78	1.4848	0.19[e]	$C_8H_{16}NO_3PS$ (237.26)	238 (99)
3d	9h, reflux	99	1.4841	0.41[f]	$C_9H_{18}NO_3PS$ (251.29)	252 (70)
3e	3d, reflux	60	1.4824	0.29[g]	$C_9H_{18}NO_3PS$ (251.29)	252 (65)
3f	14h, reflux	78	1.5414	0.16[g]	$C_{12}H_{16}NO_3PS$ (285.31)	286 (41)

a. Yields of isolated, analytically pure isothiocyanates **3**, based on **1**;
b. Satisfactory microanalyses obtained C±0.24, H±0.23, N±0.25, P±0.30;
c. the same yields were obtained, when reaction was conducted at r.t.; 24h for **3a**, and 48h for **3b** respectively;
d. Acetone/hexane (1:1);
e. EtOAc/hexane (1:4);
f. EtOAc/hexane (20:1);
g. EtOAc/hexane (5:7).

TABLE II Spectroscopic Data of Diethyl 1-(Isothiocyano)alkylphosphonates **3a-f**

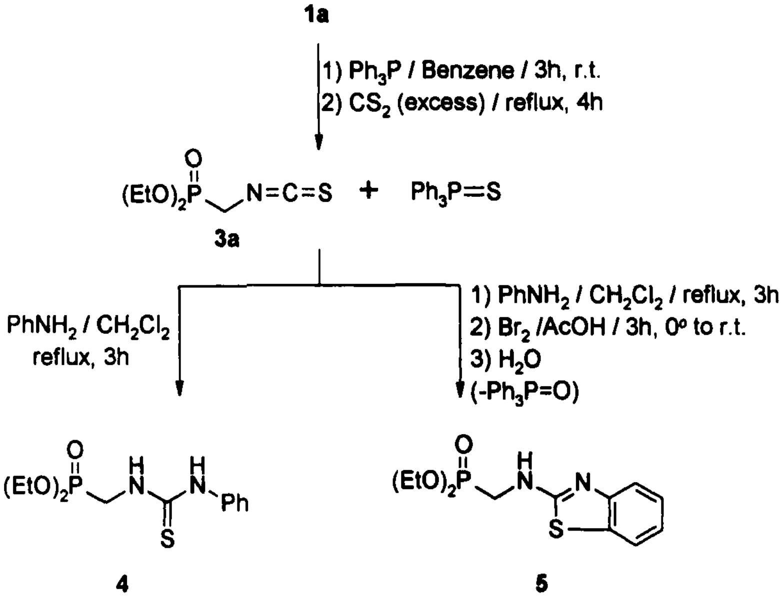
Product	*IR (neat)* ν *(cm^{-1})*	*^{31}P NMR (CDCl$_3$, H$_3$PO$_4$ ext.)* δ	*^{1}H NMR (CDCl$_3$, TMS int.)* δ, *J (Hz)*
3a	2920, 2071, 2068, 2057, 1247, 1053, 1032, 976	16.56	1.40 (t, 6H, *J* = 7.5), 3.79 (d, 2H, *J*= 12.5), 4.24 (dq, 4H, *J* = 7.5, 8.5)
3b	2982, 2095, 2055, 1758, 1272, 1237, 1031, 973	19.66	1.39 (t, 6H, *J* = 7.0), 1.58 (dd, 3H, *J* = 7.0, 16.26), 3.93 (dq, 1H, *J* = 7.0, 14.8), 4.24 (dq, 4H, *J* = 7.0, 15.25)
3c	2960, 2976, 2080, 1390, 1252, 1024, 992, 972	18.92	1.14 (t, 3H, *J* = 7.5), 1.38 (t, 6H, *J*= 7.0), 1.78- 2.04 (m, 2H), 3.76 (ddd, 1H, *J* = 4.0, 10.0, 15.0), 4.23 (dq, 4H, *J* = 7.0, 15.26)
3d	2960, 2088, 1720, 1260, 1056, 2000, 996, 972	19.18	0.97 (t, 3H, *J* = 7.25), 1.38 (t, 6H, *J* = 7.0), 1.44-1.75 (m, 2H), 1.79–1.91 (m, 2H), 3.78–3.91 (m, 2H), 4.23 (dq, 4H, *J* = 7.25, 15.26)
3e	2968, 2080, 2000, 1724, 1464, 1260, 1024, 992, 972	18.81	1.12 (dd, 3H, *J* = 1.0, 6.75), 1.35 (d, 3H, *J*= 6.75), 1.38, 1.39 (2t, 6H, *J* = 7.0), 2.24–2.42 (m, 1H), 3.75 (dd, 1H, *J* = 4.25, 16.64), 4.21 (dq, 2H, *J*= 7.25, 11.76), 4.24 (dq, 2H, *J* = 7.0, 11.6)
3f	3064, 2984, 2072, 2000, 1496, 1456, 1260, 1028, 976	16.02	1.26, 1.29 (2t, 6H, *J*= 7.0), 3.93–4.23 (m, 4H), 3.93–4.23 (m, 4H), 5.03 (d, 1H, *J* = 19.0), 7.33- 7.43 (m, 5H)

Starting diethyl 1-azidoalkylphosphonates[13] **1** are easily available from diethyl 1-hydroxyalkylphosphonates[17] and hydrazoic acid under the Mitsunobu reaction.[18] Thus, according to the Scheme 1, diethyl 1-azidoalkylphosphonate **1** was converted by the Staudinger reaction[7] with triphenylphosphine into the respective iminophosphorane **2**, which in turn was immediately transformed into the corresponding isothiocyanate **3** by the reaction with carbon disulfide. Reaction of iminophosphorane **2** with carbon disulfide can be conducted at room temperature or under reflux. However, the above-mentioned conversion needs much longer time for completion at room temperature (Table I, compd. **3a** and **3b**, respectively). Also the presence of aromatic or more hindered alkyl substitutents in the iminophosphorane **2**, demands prolonged heating with carbon disulfide (Table I, compd. **3f** and **3e**, respectively). The progress of the above-mentioned reaction can be clearly monitored by the ^{31}P NMR spectroscopy. Isothiocyanates **3** thus formed were isolated in high overall yields (60–99%) by means of flash chromatography, and their structure was unequivocally confirmed by ^{31}P and ^{1}H NMR spectroscopy. The results are summarized in Table I and II.

Despite a one-pot procedure described for above-mentioned transformations, iminophosphoranes **2** can be easily isolated; e.g. iminophosphorane **2a**[19] was for the first time separated and characterized as a pure compound in quantitative yield.

The strategy, in which isothiocyanates **3** play a key role, was then applied for a one-pot synthesis of diethyl (N-phenylthioureido)- and (benzothiazol-2-ylamino)methylphosphonates **4** and **5**, respectively (Scheme 2).

Thus according to the Scheme 2, diethyl azidomethylphosphonate **1a** was converted by the procedure given above, into diethyl (isothiocyano)methylphosphonate **3a**, which in turn was immediately transformed by heating with aniline[20] to the corresponding diethyl (N-phenyl-thioureido)methylphosphonate **4**[21] in 88% overall yield. In the same way crude diethyl (isothiocyano)methyl phosphonate **3a**, after heating with aniline, was cyclized by means of bromine in acetic acid, [22] prior to quenching with water into the diethyl (benzothiazol-2-ylamino)methylphosphonate **5**[23] in overall 50% yield. Under these conditions the conversion of triphenylphosphine sulfide to triphenylphosphine oxide also took place.[24]



SCHEME 2

CONCLUSION

In conclusion, the procedure given provides a simple and efficient route to novel diethyl 1-(isothiocyano)alkylphosphonates with a range of aliphatic and aromatic substituents at C-1 carbon, under mild conditions and from easily available starting materials. This methodology has been conveniently adapted for a one-pot preparation of diethyl (N-phenylthioureido)- and (benzothiazol-2-ylamino)methylphosphonates.

EXPERIMENTAL

NMR spectra were recorded on a Bruker AVANCE DPX 250 instrument at 250.13 MHz for ^{1}H and 101.3 MHz for ^{31}P NMR respectively using $CDCl_3$ solutions. Positive chemical shifts are downfield from ext. 85% H_3PO_4 for ^{31}P NMR spectra. IR spectra were measured on a Specord M80

(C. Zeiss) instrument and are reported in wavenumbers (cm^{-1}). FAB/MS were recorded on an APO Electron (Ukraine) Modell MI 12001E mass spectrometer equipped with a FAB ion source (thioglycerol matrix). Melting points were determined in open capillaries and are uncorrected. Flash chromatography was performed with glass column packed with Baker silica gel (30–60 μm). All reagents were purchased from Fluka and used without further purification. The diethyl azidoalkylphosphonates **1** were obtained as described previously.[13]

Preparation of diethyl 1-(isothiocyano)alkylphosphonates; General Procedure

Ph_3P (0.535 g, 2.04 mmol) was added in one portion with stirring and external cooling (ice bath) to a solution of diethyl 1-azidoalkylphosphonate **1** (2.0 mmol) in anhydrous benzene (10 mL) Stirring was continued for 3h at r.t., and CS_2 (1.22g, 0,964 mL, 16.0 mmol) was then added in one portion. After the addition has been completed, the mixture was kept at r.t., or in reflux for a given time (see Table I for details). Benzene and excess of CS_2 was evaporated under reduced pressure, and the semi-crystalline residue was extracted with hexane (3×25 mL) to remove most of Ph_3PS. The combined extracts were evaporated *in vacuo*, and the oily residue was subjected to flash chromatography to give analytically pure diethyl 1-(isothiocyano)alkylphosphonate **3** in good yield (Table I).

Diethyl [(triphenylphosphoranylidene)amino]methylphosphonate 2a

Ph_3P (0.525 g, 2.0 mmol) was added in one portion with stirring and external cooling (ice bath) to a solution of diethyl 1-azidomethylphosphonate **1a** (0.386 g, 2.0 mmol) in anhydrous benzene (10 mL). Stirring was continued for 3h at r.t., and benzene was then evaporated under reduced pressure. The crystalline residue was washed with anhydrous ether (2x 5 mL), and dried over P_2O_5 to afford analytically pure iminophosphorane **2a** in quantitative yield (0.854 g), as colorless solid; mp. 96–98°C.

^{31}P NMR ($CDCl_3$, H_3PO_4 ext.): $\delta = 15.92$ (d, $J = 73.92$ Hz), 29.60 (d, $J = 73.92$ Hz).

^{1}H NMR ($CDCl_3$, TMS): $\delta = 1.26$ (6H, t, $J = 7.0$ Hz), 3.51 (2H, dd, $J = 12.0$, 19.0 Hz), 4.05–4.20 (4H, m), 7.42–7.49 ($9H_{arom.}$, m), 7.63–7.69 ($6H_{arom.}$, m, ortho).

^{13}C NMR ($CDCl_3$): δ = 16.47 (d, J= 5.7 Hz), 42.04 (dd, J = 164.71, 6.0 Hz), 61.66 (d, J = 6.82 Hz), 128.21–132.63 (aromatic envelope).

FAB MS: MH^+ 428 (46.6%)

Anal.: $C_{23}H_{27}NO_3P_2$ (427.43) Calcd. C, 64.63; H, 6.37; N, 3.28; P, 14.49. Found. C, 64.41; H, 6.25; N, 3.15; P, 14.34.

Diethyl (N-phenylthioureido)methylphosphonate 4

Diethyl (isothiocyano)methylphosphonate **3a** was obtained according to the general procedure. Benzene and excess of CS_2 was evaporated under reduced pressure. The semi-crystalline residue was dissolved in CH_2Cl_2 (10 mL) and freshly distilled aniline (0.186g, 2.0 mmol) was then added. The mixture was heated under reflux for 3h, diluted with CH_2Cl_2 (30 mL), washed with 5% HCl aq. (2x5 mL), water (2x5 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was subjected to flash chromatography (eluent: EtOAc/MeOH 30:1, R_f=0.34) to give 0.53g analytically pure diethyl (N-phenylthioureido)methylphosphonate **4** in 88% overall yield, as colorless solid: mp. 74–75°C.

^{31}P NMR ($CDCl_3$, H_3PO_4ext.): δ = 22.83.

^1H NMR ($CDCl_3$, TMS): δ = 1.32 (6H, t, J = 7.0 Hz), 4.15 (4H, dq, J= 7.0, 8.0 Hz), 4.22 (2H, dd, J= 6.0, 12.0 Hz), 6.67 (1H, bs), 7.28–7.42 ($5H_{arom.}$, m), 8.19 (1H, bs).

IR (CCl_4, film): 3304, 3144, 1548, 1352, 1316, 1224, 1184, 1024, 984, 788.

FAB MS: MH^+ 303 (63%)

Anal.: $C_{12}H_{19}N_2O_3PS$ (302.33) Calcd. C, 47.67; H, 6.33; N, 9.26. Found. C, 47.41; H, 6.15; N, 9.05.

Diethyl (benzothiazol-2-ylamino)methylphosphonate 5

Diethyl (N-phenylthioureido)methylphosphonate **4** was obtained as described above. The solvent was evaporated under reduced pressure and the semi-crystalline residue was dissolved in acetic acid (10 mL). The mixture was cooled to 0° (ice bath) and bromine (1.28g, 8.0 mmol) in acetic acid (5 mL) was added dropwise. Stirring was continued for 3h at r.t., and the reaction mixture was then poured into ice water (20 mL). The crude product was extracted with CH_2Cl_2 (3x20 mL), washed with 5%

$NaHCO_3$ aq. (3×15 mL), 5%$Na_2S_2O_5$ aq. (3×5 mL), water (5 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was subjected to flash chromatography (eluent: EtOAc, R_f=0.26) to give 0.30g of analytically pure diethyl (benzothiazol-2-ylamino)methylphosphonate **5** in 50% overall yield as colorless solid: mp. 82–83°C

^{31}P NMR ($CDCl_3$, H_3PO_4ext.): $\delta = 22.76$.

^{1}H NMR ($CDCl_3$, TMS): $\delta = 1.33$ (6H, t, J= 7.25 Hz), 3.96 (2H, d, J = 12.0 Hz), 4.19 (4H, dq, J = 7.25, 8.0 Hz), 7.14–7.21 ($1H_{arom.}$, m), 7.32–7.39 ($1H_{arom.}$, m), 7.57–7.62 ($2H_{arom.}$ + $1H_{NH}$, m).

IR (CCl_4, film): 3232, 3048, 1600, 1572, 1560, 1544, 1536, 1440, 1352, 1316, 1264, 1248, 1216, 1040, 1032, 1020, 976, 788, 776.

FAB MS: MH^+ 301 (100%)

Anal.: $C_{12}H_{17}N_2O_3PS$ (300.32) Calcd. C, 47.99; H, 5,70; N, 9.33. Found. C, 47.85; H, 5,52; N, 9.13.

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