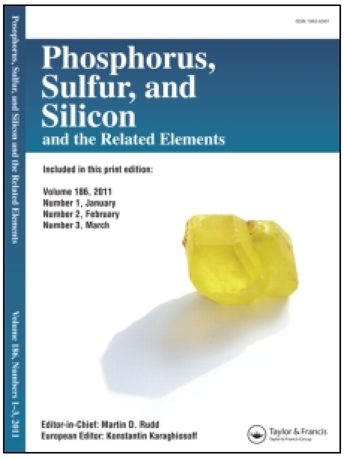

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Selective Formation of Methyl α-Methylsulfanyl Dimethylphosphonothioacetate and Thiopropanoate by Phase Transfer Catalysis

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SELECTIVE FORMATION OF METHYL α-METHYLSULFANYL DIMETHYLPHOSPHONOTHIOACETATE AND THIOPROPANOATE BY PHASE TRANSFER CATALYSIS

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The sulfanylation of methyl dimethylphosphonothioacetate was investigated by a phase transfer catalysis procedure which was shown to be superior to the noncatalytic method. The possibility of electrophilic substitution of the α-sulfanylated phosphonothioacetate to give a quaternary α-carbon atom is shown by the reaction with methyl iodide.

Keywords: α-Phosphono thioester; phase transfer catalysis; sulfanylation

α-Phosphono thioesters are interesting bifunctional compounds from the synthetic point of view. Thus, they are easily deprotonated by sodium hydride to give, via Horner-Wittig reaction, the synthetically useful α,β-unsaturated thioesters.[1,2] However, despite the increased acidity of their methylenic hydrogens, no other reactivity has been reported in the literature, contrary to the α-phosphono esters and ketones for which sulfanylation and alkylation have been described.[3,4]

In the course of our investigations of the reactions of functionalized thioesters, such as α-sulfinyl and α-sulfonyl thioesters, with some electrophiles[5,6] by phase transfer catalysis (PTC) method, we became interested in α-phosphono thioesters.

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This article reports the sulfanylation of the methyl dimethylphosphonothioacetate (**1**) and the reaction of the corresponding α-methylsulfanyl derivative **2** with some alkyl halides by PTC.

RESULTS AND DISCUSSION

The sulfanylation reactions of methyl dimethylphosphonothioacetate (**1**) was investigated by PTC procedure using as sulfanylating agent S-methyl methanethiolsulfonate, and solid K_2CO_3 as base, at room temperature (r.t.) (Table I).

When benzyltriethylammonium chloride (BTEAC), which has been shown to be successful in the sulfanylation reactions of previously investigated functionalized thioesters,[5] was employed, a mixture of mono- (**2**) and disulfanylated (**3**) products was obtained (entry **a**). However, a more successful result was obtained using the more lipophilic catalyst tricaprylmethylammonium chloride (Aliquat) (entry **b**), which afforded the monosulfanylated derivative **2** as the major reaction product in 69% yield.

As expected, an acidic compound such as phosphonothioacetate **1** undergoes reaction with sulfanylating agent even in the absence of a catalyst to give the disulfanylated derivative **3** as the major reaction product in 66% yield (entry **c**), which raised to 96% (entry **d**) when 2 equiv. of sulfanylating agent were employed.

Therefore, it may be concluded that the PTC procedure has an advantage over the noncatalytic one for controlling monosulfanylation, which is of greater synthetic value than disulfanylation.

TABLE I Sulfanylation of $(MeO)_2P(O)CH_2COSMe$ (**1**) by PTC Procedure[a]

			Reaction products (%)			
			$(MeO)_2P(O)CHSMeCOSMe$ **2**		$(MeO)_2P(O)C(SMe)_2COSMe$ **3**	
Entry	Catalyst	Unreact. **1** (chromat.)	(chromat.)	(isolated)	(chromat.)	(isolated)
a	BTEAC[b]	20	30	—	42	—
b	Aliquat[c]	6	69	61	7	—
c	—	—	2	—	66	63
d	—	—	—	—	96[d]	84

[a] Solid K_2CO_3, S-methylmethanethiolsulfonate ($MeSSO_2Me$) (1.5 equiv.), benzene, 4 h, r.t.

[b] Benzyltriethylammonium chloride.

[c] Tricaprylmethylammonium chloride.

[d] 2 equiv. of S-methylmethanethiolsulfonate.

TABLE II Alkylation Reactions of $(MeO)_2P(O)CHSMeCOSMe$ (**2**) by PTC Procedure[a]

			Reaction products (%)		
				$(MeO)_2P(O)C(SMe)RCOSMe$ **4**	
Entry	Base	RX	Unreact. **2** (chromat.)	(chromat.)	(isolated)
a	K_2CO_3	MeI	22	60 (**4a**)	35 (**4a**)
b	NaOH[b]	MeI	—	98 (**4a**)	63 (**4a**)
c	NaOH[b,c]	MeI	100	—	—
d	K_2CO_3	$C_6H_5CH_2Br$	—	—	30 (**4b**)
e	NaOH[b]	$C_6H_5CH_2I$	—	—	35 (**4b**)
f	NaOH[b]	*i*-PrI	88	—	—

[a] Catalyst: TBAHS (tetrabutylammonium hydrogen sulfate), CH_2Cl_2, 6h, r.t.
[b] 50% aqueous solution.
[c] In the absence of catalyst.

The formation of a trifunctional derivative **2**, containing a very acidic methinic group, opens the possibility of reactions with electrophilic reagents to give the phosphono thioester containing a quaternary carbon atom. We found it of interest to investigate the reaction of the sulfanylated derivative **2** with some alkylating reagents using as catalyst tetrabutylammonium hydrogen sulfate (TBAHS) by PTC procedure (Table II).

It may be seen that the reaction with methyl iodide using solid K_2CO_3 afforded the methyl α-methylsulfanyl dimethylphosphonothiopropionate (**4a**) in 60% yield (35% isolated) (entry **a**), which was raised to 98% (63% isolated) when NaOH was used as base (entry **b**). It is noteworthy that no reaction occurred using as base NaOH in the absence of a catalyst (entry **c**). However, the reaction with benzyl bromide and benzyl iodide (entries **d** and **e**) using as base K_2CO_3 and NaOH led, respectively, to 30% and 35% isolated yields of the benzylated derivative **4b** and some unidentified decomposition products. However, no reaction occurred when isopropyl iodide was employed under the same conditions (entry **f**).

The high reactivity of the sulfanylated derivative **2** toward methyl iodide and the lack of reactivity toward isopropyl iodide were confirmed when the sulfanylated derivative **2** was submitted to reaction with methyl iodide and isopropyl iodide in homogeneous medium, using NaH and THF (Table III).

It may be seen that, while the reaction with methyl iodide afforded the methylated derivative **4a** in ca. 81% yield (entry **a**), in the case of the reaction with isopropyl iodide, the unreacted derivative **2** was recovered in 91% yield (entry **b**).

TABLE III Reaction of α-Sulfanylated Phosphonothioacetate **2** with Some Alkyl Iodides by Homogeneous Phase Method (NaH/THF)

		Reaction products (%)	
Entry	RX	Unreact. **2** (isolated)	$(MeO)_2P(O)C(SMe)RCOSMe$ **4** (isolated)
a	Mel	5	81 (**4a**)
b	*i*-PrI	91	—

It should be mentioned that these results differ from that obtained from the reaction of metallated α-sulfanylated α-phosphono ketones with methyl iodide,[4] in which the methylation was reported to occur partly at the oxygen atom of the ambident anion. It seems surprising that in the case of isopropyl iodide, 91% of the unreacted derivative **2** was recovered. If the lack of reactivity at the α carbon is due to a steric effect, alkylation might be expected to occur at the relatively unhindered oxygen atom.

It should be mentioned that both compounds, the sulfanylated phosphonothioacetate **2** and the phosphonothiopropionate **4a**, are important synthetic intermediates due to possibility of obtaining through, respectively. Horner-Wittig reaction and oxidative sulfinylic elimination, new thioacrylates.

In summary, the selective monosulfanylation of the methyl dimethylphosphonothioacetate by PTC method is reported. The reaction of the monosulfanylated product **2** with some alkyl halides is also described and the successful C-methylation is discussed. The synthetic importance of the sulfanylated derivative and of the correponding C-methylated derivative is envisaged.

EXPERIMENTAL

Microanalysis were performed on a Perkin-Elmer 240B elemental analyser. M.p.s. were determined on a Kofler hot-stage apparatus. ^1H NMR spectra were recorded on a Varian DPX-300 with $SiMe_4$ as internal standard. IR spectrum was recorded on a MBIOU ABB Bomem spectrometer.

Methyl Dimethylphosphonothioacetate (1)

Compound **1** was prepared as described for ethyl diethylphosphonothioacetate.[7] Distillation under reduced pressure (94–96°C/0.2 mmHg) afforded thiolester **1** in 77% yield as a yellowish oil. IR (film) (cm^{-1}): 1682 (ν_{co}), 1260 (ν_{PO}). ^1H NMR ($CDCl_3$), δ: 2.37 (d, 3H, J = 0.9 Hz), 3.25 (d, 2H, J = 21.3 Hz), 3.81 (d, 6H, J = 11.1 Hz). Anal. Calcd. for $C_5H_{11}O_4PS$: C, 30.30; H, 5.59. Found C, 30.12; H, 5.42.

Methyl α-Methylsulfanyl Dimethylphosphonothioacetate (2)

A mixture of compound **1** (1.0 mmol) dissolved in benzene (5 mL), Aliquat (0.1 mmol), solid K_2CO_3 (2 mmol) and S-methylmethanethiolsulfonate (1.5 mmol) was stirred at r.t. for 4 h. The solid was removed by suction filtration and washed with CH_2Cl_2 (20 mL). The organic extract was washed with satd. aq. NH_4Cl solution, then with water and, after drying over $MgSO_4$, concentrated. The product was obtained in 61% yield after column chromatography (n-hexane: acetone, 4:1). ^1H NMR ($CDCl_3$), δ: 2.32 (d, 3H, J = 0.9 Hz), 2.39 (d, 3H, J = 0.6 Hz), 3.82 (d, 1H, J = 20.4 Hz), 3.86 (d, 3H, J = 11.1 Hz), 3.88 (d, 3H, J = 11.1 Hz). Anal. Calcd. for $C_6H_{13}O_4PS_2$: C, 29.50; H, 5.36. Found C, 29.58; H, 5.40.

Methyl α,α-Dimethylsulfanyl Dimethylphosphonothioacetate (3)

Starting from **1**, in the absence of catalyst, 1.5 equiv. of S-methylmethanethiolsulfonate and following the procedure for obtention of **2**, a white solid (m.p. 85°C) was obtained in 63% yield, after TLC (n-hexane:acetone, 4:1) (Table I, entry **c**); the yield was improved to 84% using 2 equiv. of S-methylmethanethiolsulfonate (Table I, entry **d**). ^1H NMR ($CDCl_3$), δ: 2.27 (s, 6H), 2.34 (d, 3H, J = 0.6 Hz), 3.93 (d, 6H, J = 10.8 Hz). Anal. Calcd. for $C_7H_{15}O_4PS_3$: C, 28.96; H, 5.21. Found C, 28.52; H, 5.15.

PTC Procedures for Alkylation of Methyl α-Methylsulfanyl Dimethylphosphonothioacetate (2)

A. Using Solid-Liquid System

A mixture of phosphono thioester **2** (1.0 mmol), dissolved in CH_2Cl_2 (5 mL), TBAHS (0.1 mmol), solid K_2CO_3 (2 mmol), and the alkyl halide (1.5 mmol) was stirred for 6 h at r.t. The organic extract was washed with satd. aq. NH_4Cl solution, then with water and, after drying over $MgSO_4$, concentrated. The crude product was purified by TLC (n-hexane:acetone, 3:1).

B. Using Liquid-Liquid System

A mixture of phosphono thioester **2** (1.0 mmol) in 10 mL of CH_2Cl_2, alkyl halide (1.5 mmol), TBAHS (0.1 mmol), and 3 mL of aqueous 50% NaOH was stirred for 6 h at r.t. The reaction mixture was neutralized with HCl (10%), and extracted with CH_2Cl_2. The organic extract was washed with water, dried over $MgSO_4$, and concentrated. The crude product was purified by TLC (n-hexane:acetone, 3:1).

Methyl α-Methylsulfanyl Dimethylphosphonothiopropanoate (4a)

By PTC Procedure

Obtained in 35% yield after TLC (n-hexane: acetone, 3:1), following procedure A (Table II, entry **a**), and in 63% using procedure B (Table II, entry **b**).

Using Homogeneous Phase Method

A mixture of sodium hydride (28.8 mg; 608 mmol; previously washed with n-hexane), 173 mg (0.708 mmol) of sulfanylated phosphoryl thioester **2**, and 170 mg (1.19 mmol) of methyl iodide, in anhydrous THF (3.0 mL), was stirred at r.t. for 1 h. The reaction mixture was neutralized with satd. aq. NH_4Cl, and extracted with CH_2Cl_2. The organic extract was washed with water, satd. aq. NaCl, dried over anhydrous Na_2SO_4, and concentrated. The product was purified by TLC (n-hexane:acetone, 2:1) to give 147 mg (81%) of the methylated derivative **4a** (Table III, entry **a**). ^1H NMR ($CDCl_3$), δ: 1.73 (d, 3H, J = 15.3 Hz), 2.29 (d, 3H, J = 0.6 Hz), 2.32 (d, 3H, J = 0.6 Hz), 3.87 (d, 3H, J = 10.8 Hz), 3.89 (d, 3H, J = 10.8 Hz). Anal. Calcd. for $C_7H_{15}O_4PS_2$: C, 32.55; H, 5.85. Found C, 32.32, H, 5.78.

Methyl α-Methylsulfanyl Dimethylphosphono β-Phenylpropanoate (4b)

Obtained in 30% yield after TLC (n-hexane: acetone, 3:1), using benzyl bromide and procedure A (Table II, entry **d**), and in 35% yield, using procedure B and benzyl iodide (Table II, entry **e**). ^1H NMR ($CDCl_3$), δ: 2.25 (d, 3H, J = 0.9 Hz), 2.38 (d, 3H, J = 0.3 Hz), 3.28 (dd, 1H, J = 14.1 Hz, J = 12.0 Hz), 3.56 (dd, 1H, J = 13.8 Hz, J = 10.5 Hz), 3.82 (d, 3H, J = 10.8 Hz), 3.85 (d, 3H, J = 11.1 Hz), 7.18–7.26 (m, 5H). Anal. Calcd. for $C_{13}H_{19}O_4PS_2$: C, 46.69; H, 5.73. Found C, 46.06; H, 5.74.

REFERENCES

[1] E. Schaumann, B. Mergardt, and S. Fittkan, *Synthesis*, 47 (1990).
[2] H. Liu, P. A. Rose, and D. J. Sasaki, *Can. J. Chem.*, **69,** 934 (1991).
[3] M. Mikolajczyk, In *Reviews on Heteroatom Chemistry*, edited by Shigeru Oae (1989), vol. 2, pp. 19–99, Myu, Tokyo.
[4] M. Mikolajczyk, P. Balezewski, In *Advances in Sulfur Chemistry*, edited by Eric Block (1994), vol. 1, pp. 41–96, Jai Press, Inc.
[5] N. F. Claro Junior, *Phosphorus, Sulfur, and Silicon*, **123,** 197 (1997).
[6] B. Wladislaw, L. Marzorati, F. C. Biaggio, R. M. A. Neves, and C. Di Vitta, *Synth. Commun.*, **32,** 1483 (2002).
[7] H.-J. Liu, P. A. Rose, and D. Sasaki, *Can. J. Chem.*, **69,** 934 (1991).