A Convenient Approach to Dialkyl Heteroarylmethylphosphonates and [Alkylthio(heteroaryl)methyl]phosphonates: Synthesis of Imidazo[1,2-*a*]pyridine, Imidazo[1,2-*a*]pyrimidine, Indolizine and Thiazole Derivatives

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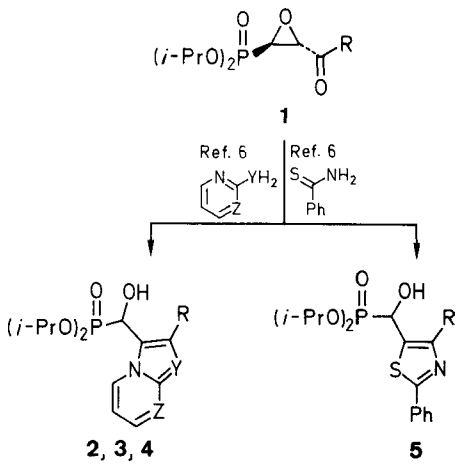
The [heteroaryl(hydroxy)methyl]phosphonates **2–5** (indolizines **2**, imidazo[1,2-*a*]pyridines **3**, imidazo[1,2-*a*]pyrimidines **4**, and 2-phenylthiazoles **5**, are converted readily to the corresponding *O,O*-thiocarbonates **6–8** and **18** on treatment with *p*-tolyloxythiocarbonyl chloride in acetonitrile/4-dimethylaminopyridine, while reaction in pyridine/dichloromethane affords the isomeric *O,S*-thiocarbonates **9–11** and **19**, respectively. Homolytic cleavage of both series of compounds proceeds smoothly, using tributyltin hydride/azobisisobutyronitrile (AIBN) in warm toluene to give the new heteroarylmethylphosphonates **12–14** and **20**. Conversion of the *O,S*-thiocarbonates **9–11** and **19** into the synthetically attractive α-methylthio-substituted derivatives **15–17** and **21** is effected efficiently upon saponification with sodium methoxide in methanol and subsequent alkylation with methyl iodide.

During the last years heteroarylmethylphosphonates have received considerable attention in view of their biological evaluation and because of their synthetic utility.[1,2] Recently we reported a simple way to a variety of heteroarylmethylphosphonates (heteroaryl = imidazoylyl, 2-aminothiazolyl, 5-oxo-5,6-dihydroimidazo[1,2-*c*]pyrimidinyl) by the reaction of the corresponding triphenylphosphonium salts with dialkylphosphite anions.[3] This overall nucleophilic displacement of the triphenylphosphonio group, commonly exhibited by heteroarylmethylphosphonium salts with active hydrogens at appropriate positions of the heterocyclic part, has been used previously for the synthesis of various non-phosphorus substituted heterocycles,[4] and is assumed to proceed through a base induced vinylogous Hofmann elimination of triphenylphosphine, and subsequent addition of a nucleophile to the intermediate. The heteroarylmethylphosphonium salts, exhibiting this typical fragmentation pattern, and unlike the corresponding phosphonates, therefore not suitable as Wittig reagents, have been prepared by regioselective cyclocondensation of (3-oxo-1-alkenyl)triphenylphosphonium salts with 1,3-bidentate nucleophiles (amidines, thiourea, cytosine).[5]

In this paper we report a simple way to heteroarylmethylphosphonates, which are not available by a triphenylphosphonio/dialkoxyphosphoryl-exchange, as well as to the corresponding α-methylthio-substituted derivatives **15–17** and **21**, from the corresponding α-hydroxyphosphonates.

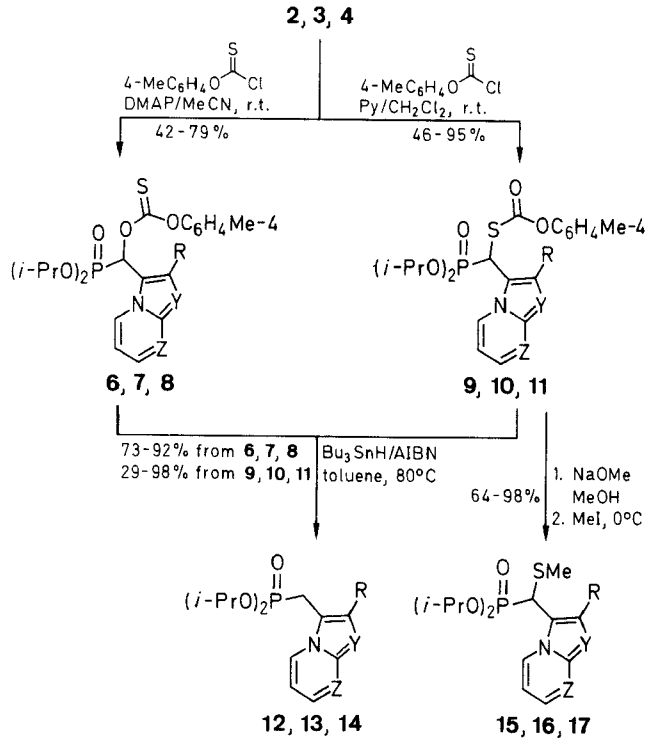
The [heteroaryl(hydroxy)methyl]phosphonates **2–5** (indolizines **2**, imidazo[1,2-*a*]pyridines **3**, imidazo[1,2-*a*]-pyrimidines **4**, and thiazoles **5**) used in this study have all been prepared previously from the *trans*-1,2-epoxy-3-oxoalkylphosphonates **1** (1,2-biselectrophilic compounds similar to the (3-oxo-1-alkenyl)phosphonium salts mentioned above) by regioselective heterocyclization with the 1,3-bidentate nucleophiles, ethyl 2-pyridylacetate, 2-aminopyridine, 2-aminopyrimidine, and thiocarboxamides, respectively[6] (Scheme **1**). The α-hydroxyphosphonates **2–5** are easily transformed to the desired title compounds **12–14** and **20**, via prior conversion to the *O,O*-thiocarbonates **6–8** and **18**, using *p*-tolyloxythiocarbonyl chloride/4-dimethylaminopyridine (DMAP)/acetonitrile[7] and subsequent AIBN-initiated, homolytic deoxygenation of the thioesters with tributyltin hydride in toluene[8] (Schemes **2** and **3**).



	Z	Y	2–4	R
2	CH	$C(CO_2Et)$	**a**	Me
3	CH	N		
4	N	N	**b**	Ph

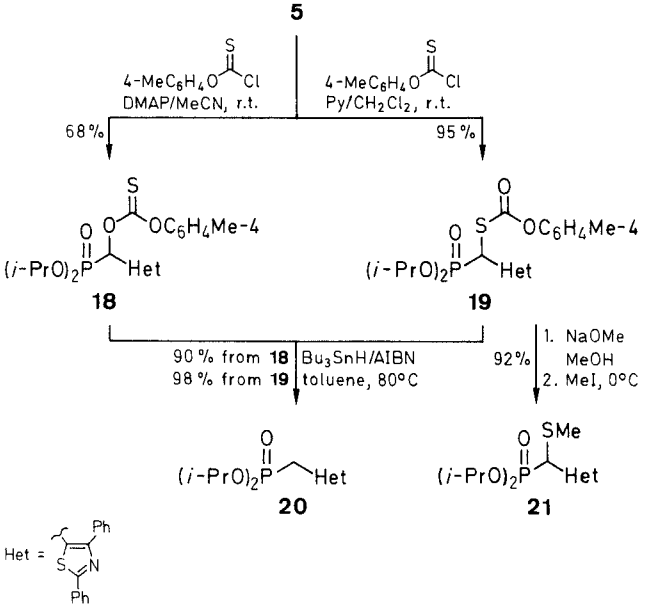
Scheme **1**

Unexpectedly, attempted derivatization of compounds **2–5** with *p*-tolyloxythiocarbonyl chloride/pyridine/dichloromethane (reaction conditions commonly used for the conversion of unhindered, non-phosphorus-substituted, secondary alcohols[7]), resulted always in the formation of the isomeric α-*O,S*-thiocarbonates **9–11** and **19** (Schemes **2** and **3**). They were easily distinguished from the α-oxygen substituted isomers by the upfield shift [$\Delta\delta = 0.32$(**18b** → **19b**) to 0.63(**6a** → **9a**)] of the PCH-doublet, consistently observed in the ^{1}H-NMR spectra. Interestingly, the *O,S*-thiocarbonates can also be reduced to the desired heteroarylmethylphosphonates **12–14** and **20**, using the reaction conditions applied for the deoxygenation of their isomers. Moreover, compounds **9–11** and **19** can serve as precursors for synthetically interesting alkylthio-substituted derivatives.[10] This is demonstrated by the saponification/alkylation sequence leading to the methylthio derivatives **15–17** and **21**, respectively (Schemes **2** and **3**).



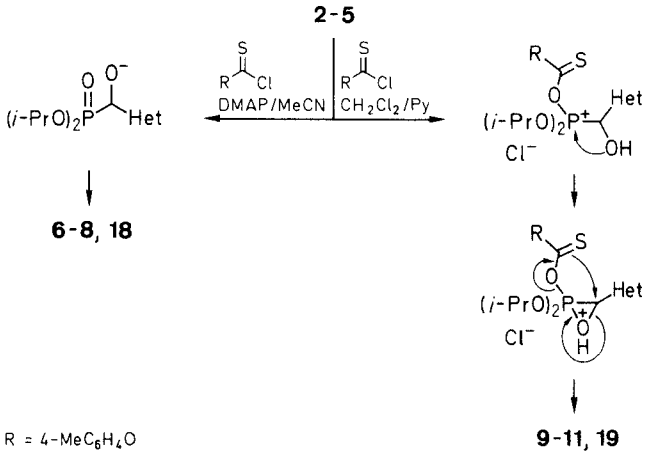
	Z	Y	2–4, 6–17	R
2, 6, 9, 12, 15	CH	$C(CO_2Et)$	**a**	Me
3, 7, 10, 13, 16	CH	N	**b**	Ph
4, 8, 11, 14, 17	N	N		

Scheme 2



Scheme 3

A mechanism for the remarkable base-dependence of the products observed upon thioacylation of compounds **2–5** is proposed in Scheme **4**. The use of the weaker base pyridine might cause the prior acylation of the phosphoryl-oxygen[11] to give a phosphonium-type intermediate, which could rearrange to the stable *O,S*-thiocarbonates derivative observed. Alternatively, prior deprotonation of the α-hydroxy group in compounds **2–5** by the stronger base DMAP should transform this oxygen into the preferred site of attack by the thionoacylating agent.[12]



Scheme 4

TLC was performed on Merck silica gel $60F_{254}$ plates with visualization by UV-light ($\lambda = 254$ nm and 366 nm) and by iodine vapour. Flash chromatography was performed on glass columns packed with Merck silica gel 60 (230–400 mesh). Melting points were measured with a Kofler melting point apparatus and are uncorrected. Mass spectra were obtained using a Varian CH 7 spectrometer. ^{1}H-NMR spectra were recorded on a Bruker WM 250 or a Bruker AM 400 spectrometer.

4-Dimethylaminopyridine was purchased from Aldrich. *p*-Tolyloxythiocarbonyl chloride and tributyltin hydride were purchased from Fluka. CH_2Cl_2 was distilled from P_2O_5 and stored over molecular sieves. MeCN and pyridine were distilled from CaH_2 and stored over molecular sieves.

The [heteroaryl(hydroxy)methyl]phosphonates, including the new thiazolyl derivative **5b**, were prepared according to the literature procedure.[6]

Diisopropyl [(2,4-Diphenyl-5-thiazolyl)hydroxymethyl]phosphonate (**5b**): Yield: 93%; mp 132°C (Et_2O/petroleum ether, bp 40°C).

$C_{22}H_{26}NO_4PS$	calc.	C 61.23	H 6.08	N 3.25	S 7.43
(431.5)	found	61.28	6.12	3.24	7.71

^{1}H-NMR ($CDCl_3$): $\delta = 1.21$, 1.24, 1.28, 1.30 (4d, 3H each, $POCHCH_3$), 4.76 (m, 2H, POCH), 5.39 (d, 1H, $J_{HP} = 11.7$ Hz, PCH), 5.59 (br s, 1H, OH), 7.43 (m, 6 H_{arom}), 7.78 (d, 2 H_{arom}), 7.98 (m, 2 H_{arom}).

O-[Heteroaryl(dialkoxyphosphoryl)methyl] O-*p*-Tolyl Thiocarbonates 6–8, and 18; General Procedure:

p-Tolyloxythiocarbonyl chloride (0.300 mL, 1.95 mmol) is added to a solution of DMAP (0.458 g, 3.75 mmol) in anhydrous MeCN (22 mL) and the mixture is stirred for 10 min at r.t. under argon. A solution of the appropriate α-hydroxyphosphonate **2–5** (1.5 mmol) in MeCN (40 mL) is then added and stirring is continued till complete disappearence (TLC) of starting material. The solvent is removed *in vacuo* and the residue is purified by flash chromatography on silica gel (Table 1).

S-[Heteroaryl(dialkoxyphosphoryl)methyl] O-*p*-Tolyl Thiocarbonates 9–11, and 19; General Procedure:

To a solution of the appropriate α-hydroxyphosphonate **2–5** (0.50 mmol) in anhydrous CH_2Cl_2 (10 mL), pyridine (0.120 mL, 1.5 mmol) and *p*-tolyloxythiocarbonyl chloride (0.100 mL, 0.65 mmol) are added. The mixture is stirred at r.t. under argon. After

Table 1. *O,O*-Thiocarbonates **6–8** and **18** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c]	R_f[d] (TLC)	MS (70 eV) *m/z* (%)	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, *J* (Hz)
6a	1	42	oil	$C_{27}H_{34}NO_7PS$ (547.6)	0.83	334 (8)	0.86, 1.25, 1.45 [3d, 3H, 3H, and 6H, resp., $J = 6$, $CH(C\underline{H}_3)_2$], 1.47 (t, 3H, $J = 7$, $CH_2C\underline{H}_3$), 2.38 (s, 3H, CH_3), 2.68 (d, 3H, $^5J_{HP} = 2$, CH_3), 4.41 (m, 3H, POCH, $C\underline{H}_2CH_3$), 4.94 (mc, 1H, POCH), 6.14 (d, 1H, $^2J_{HP} = 26$, PCH), 6.85 (dt, 1H, $J_{6,7} \approx J_{6,5} \approx 7$, $J_{6,8} \approx 1$, H-6), 6.93 (d, $2H_{arom}$, $J = 9$), 7.16 (dd, 1H, $J_{7,8} = 9$, $J_{7,6} = 7$, H-7), 7.24 (d, $2H_{arom}$, $J = 9$), 8.29 (d, 1H, $J_{8,7} = 9$, H-8), 8.65 (d, 1H, $J = 7$, H-5)
6b	0.5	72[f]	oil	$C_{32}H_{36}NO_7PS$ (609.7)	0.83	610 ($M^+ + 1$), 442 (7)	1.09 (t, 3H, $J = 7$, $CH_2C\underline{H}_3$), 0.84, 1.27, 1.31, 1.36 [4d, 3H each, $J = 6$, $CH(C\underline{H}_3)_2$], 2.23 (s, 3H, CH_3), 4.14 (mc, 2H, $C\underline{H}_2CH_3$), 4.52, 4.85 (2mc, 2H each, POCH), 5.87 (d, 1H, $^2J_{HP} = 24$, PCH), 6.68–7.45 (m, 11H, H-6, H-7, $9H_{arom}$), 8.34 (d, 1H, $J = 9$, H-8), 8.70 (d, 1H, $J_{5,6} = 7$, H-5)
7a	1	79	oil	$C_{23}H_{29}N_2O_5PS$ (476.5)	0.59	476 (M^+, 2), 311 (4), 309 (85)	0.81, 1.21, 1.38 [3d, 3H, 3H, and 6H, resp., $J = 6$, $CH(C\underline{H}_3)_2$], 2.35 (s, 3H, CH_3), 2.56 (br s, 3H, CH_3), 4.39, 4.87 (2mc, 1H each, POCH), 5.93 (d, 1H, $^2J_{HP} = 24$, PCH), 6.83 (dt, 1H, $J_{6,7} \approx J_{6,5} \approx 7$, $J_{6,8} \approx 1$, H-6), 6.87 (d, $2H_{arom}$, $J = 9$), 7.18 (m, 3H, H-7, $2H_{arom}$), 7.53 (d, 1H, $J_{8,7} \approx 9$, H-8), 8.55 (mc, 1H, H-5)
7b	0.75	72[g]	148	$C_{28}H_{31}N_2O_5PS$ (538.6)	0.72	538 (M^+, 2) 373 (6), 371 (100)	0.85, 1.30, 1.41, 1.43 [4d, 3H each, $J = 6$, $CH(C\underline{H}_3)_2$], 2.30 (s, 3H, CH_3), 4.55, 4.95 (2mc, 1H each, POCH), 6.25 (d, 1H, $^2J_{HP} = 24$, PCH), 6.67 (d, $2H_{arom}$, $J = 8$), 6.90 (dt, 1H, $J_{6,7} \approx J_{6,7} \approx 7$, $J_{6,8} \approx 1$, H-6), 7.10 (d, $2H_{arom}$, $J = 9$), 7.35 (m, 4H, H-7, $3H_{arom}$), 7.68 (d, 1H, $J_{8,7} \approx 9$, H-8), 7.80 (m, $2H_{arom}$), 8.80 (d, 1H, $J_{5,6} = 7$, H-5)
8a	0.75	56	foam	$C_{22}H_{28}N_3O_5PS$ (477.5)	0.66	310 (2)	0.89, 1.25, 1.44 (3d, 3H, 3H, and 6H resp., $J = 6$, $CH(C\underline{H}_3)_2$], 2.38 (s, 3H, CH_3), 2.61 (d, 3H, $^5J_{HP} = 2$, CH_3), 4.42, 4.90 (2mc, 1H each, POCH), 5.89 (d, 1H, $^2J_{HP} = 24$, PCH), 6.87 (d, $2H_{arom}$, $J = 9$), 6.93 (dd, 1H, $J_{6,5} = 7$, $J_{6,7} = 4$, H-6), 7.20 (d, $2H_{arom}$, $J = 9$), 8.54 (dd, 1H, $J_{7,6} = 4$, $J_{7,5} = 2$, H-7), 8.92 (br d, 1H, H-5)
8b	0.75	48	113–114	$C_{27}H_{30}N_3O_5PS$ (539.6)	0.43	407 (1), 374 (1), 372 (10)	0.88, 1.29, 1.40, 1.43 (4d, 3H each, $J = 6$, $CH(C\underline{H}_3)_2$], 2.28 (s, 3H, CH_3), 4.53, 4.94 (2mc, 1H each, POCH), 6.20 (d, 1H, $^2J_{HP} = 24$, PCH), 6.62 (d, $2H_{arom}$, $J = 9$), 6.95 (dd, 1H, $J_{6,5} = 7$, $J_{6,7} = 4$, H-6), 7.06 (d, $2H_{arom}$, $J = 9$), 7.35 (m, $3H_{arom}$), 7.82 (m, $2H_{arom}$), 8.61 (dd, 1H, $J_{7,6} = 4$, $J_{7,6} \approx 2$, H-7), 9.13 (dd, 1H, $J_{5,6} = 7$, $J_{5,7} \approx 2$, H-5)
18b	0.5	68	oil	$C_{30}H_{32}NO_5PS_2$ (581.7)	0.31	581 (M^+, 1), 416 (3), 414 (33)	1.19, 1.39 [d, m, 3H and 9H resp., $J = 6$, $CH(C\underline{H}_3)_2$], 2.34 (s, 3H, CH_3), 4.85 (mc, 2H, POCH), 5.90 (d, 1H, $^2J_{HP} = 20$, PCH), 6.73 (d, $2H_{arom}$, $J = 9$), 7.13 (d, $2H_{arom}$, $J = 9$), 7.22–7.51 (m, $6H_{arom}$), 7.75 (m, $2H_{arom}$), 8.02 (m, $2H_{arom}$)

[a] Yield of products isolated after flash chromatography.
[b] Recrystallization from Et_2O/petroleum ether (bp 40 °C).
[c] The microanalyses showed the following deviations: C ±0.75, H ±0.35, N ±0.48. Exception: **7a**, C −1.28.
[d] Solvent system: CH_2Cl_2/EtOAc, 9 : 1 (**6a, 6b**); EtOAc/MeOH, 19 : 1 (**7a**); EtOAc (**7b, 8b**); EtOAc/MeOH, 5 : 1 (**8a**); petroleum ether (bp 65–70 °C)/EtOAc, 3 : 1 (**18b**).
[e] 250 MHz (compounds **6b, 7b, 8a, 8b, 18b**); 400 MHz (compounds **6a, 7a**).
[f] ~20% **9b** detected in the crude product.
[g] ~17% **10b** detected in the crude product.

Table 2. *O,S*-Thiocarbonates **9–11**, and **19** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c]	R_f[d] (TLC)	MS (70 eV) *m/z* (%)	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, *J* (Hz)
9a	1	89	foam	$C_{27}H_{34}NO_7PS$ (547.6)	0.83	334 (9)	0.76, 1.17 [2d, 3H each, $J = 6$, $CH(CH_3)_2$], 1.40 [m, 9H, $CH(CH_3)_2 + CH_2CH_3$], 2.32 (s, 3H, CH_3), 2.59 (d, 3H, $^5J_{HP} = 2$, CH_3), 4.26–4.40 (m, 3H, POCH, CH_2CH_3), 4.88 (mc, 1H, POCH), 5.51 (d, 1H, $^2J_{HP} = 25$, PCH), 6.80 (dt, 1H, $J_{6,7} \approx J_{6,5} \approx 7$, $J_{6,8} \approx 1$, H-6), 6.96 (d, $2H_{arom}$, $J = 9$), 7.10 (dd, 1H, $J_{7,8} \approx 9$, $J_{7,6} \approx 7$, H-7), 7.14 (d, $2H_{arom}$, $J = 9$), 8.23 (d, 1H, $J_{8,7} = 9$, H-8), 8.57 (d, 1H, $J_{5,6} = 7$, H-5)
9b	3	76	94–95	$C_{32}H_{36}NO_7PS$ (609.7)	0.72	609 (M^+, 11), 444 (2), 442 (100)	1.07 (t, 3H, $J = 7$, CH_2CH_3), 0.81, 1.22, 1.28, 1.31 [4d, 3H each, $J = 6$, $CH(CH_3)_2$], 2.30 (s, 3H, CH_3), 4.13 (mc, 2H, CH_2CH_3), 4.46, 4.78 (2mc, 1H each, POCH), 5.31 (d, 1H, $^2J_{HP} = 24$, PCH), 6.88 (m, 3H, H-6, $2H_{arom}$), 7.14 (m, 3H, H-7, $2H_{arom}$), 7.36 (m, $5H_{arom}$), 8.34 (d, 1H, $J_{8,7} = 9$, H-8), 8.66 (d, 1H, $J_{5,6} = 7$, H-5)
10a	0.3	46	oil	$C_{23}H_{29}N_2O_5PS$ (476.5)	0.65	476 (M^+, 7), 311 (12), 309 (100)	0.78, 1.19, 1.39, 1.41 [4d, 3H each, $J = 6$, $CH(CH_3)_2$], 2.32 (s, 3H, CH_3), 2.53 (br s, 3H, CH_3), 4.37, 5.87 (2mc, 1H each, POCH), 5.34 (d, 1H, $^2J_{HP} = 24$, PCH), 6.84 (dt, 1H, $J_{6,7} \approx J_{6,5} \approx 7$, $J_{6,8} \approx 1$, H-6), 6.96 (d, $2H_{arom}$, $J = 9$), 7.14 (d, $2H_{arom}$, $J = 9$), 7.21 (dd, 1H, $J_{7,6} \approx 7$, $J_{7,8} \approx 9$, H-7), 7.58 (d, 1H, $J_{8,7} \approx 9$, H-8), 8.57 (mc, 1H, H-5)
10b	2	82	134–135	$C_{28}H_{31}N_2O_5PS$ (538.6)	0.66	538 (M^+, 2), 373 (8), 371 (100)	0.80, 1.23, 1.37 [3d, 3H, 3H and 6H, resp., $J = 6$, $CH(CH_3)_2$], 2.30 (s, 3H, CH_3), 4.45, 4.91 (2mc, 1H each, POCH), 5.75 (d, 1H, $^2J_{HP} = 24$, PCH), 6.87 (m, 3H, H-6, $2H_{arom}$), 7.07 (d, $2H_{arom}$, $J = 9$), 7.26 (mc, 1H, H-7), 7.30–7.50 (m, $3H_{arom}$), 7.66 (d, 1H, $J_{8,7} \approx 9$, H-8), 7.85 (m, $2H_{arom}$), 8.70 (d, 1H, $J_{5,6} = 7$, H-5)
11a	0.75	88	foam	$C_{22}H_{28}N_3O_5PS$ (477.5)	0.49	477 (M^+, 6), 312 (7), 310 (100)	0.84, 1.21, 1.40 [4d, 3H, 3H and 6H, resp., $J = 6$, $CH(CH_3)_2$], 2.32 (s, 3H, CH_3), 2.56 (d, 3H, $^5J_{HP} = 2$, CH_3), 4.37, 4.89 (2mc, 1H each, POCH), 5.32 (d, 1H, $^2J_{HP} = 24$, PCH), 6.90 (dd, 1H, $J_{6,5} = 7$, $J_{6,7} = 4$, H-6), 6.97 (d, $2H_{arom}$, $J = 9$), 7.16 (d, $2H_{arom}$, $J = 9$), 8.53 (dd, 1H, $J_{7,6} = 4$, $J_{7,5} \approx 2$, H-7), 8.92 (br d, 1H, H-5)
11b	2.5	95	148–150	$C_{27}H_{30}N_3O_5PS$ (539.6)	0.45	539 (M^+, 7), 374 (9), 372 (100)	0.85, 1.21, 1.40, 1.41 [4d, 3H each, $J = 6$, $CH(CH_3)_2$], 2.30 (s, 3H, CH_3), 4.45, 4.91 (2mc, 1H each, POCH), 5.75 (d, 1H, $^2J_{HP} = 23$, PCH), 6.86 (d, $2H_{arom}$, $J = 9$), 6.94 (dd, 1H, $J_{6,5} = 7$, $J_{6,7} = 4$, H-6), 7.09 (d, $2H_{arom}$, $J = 9$), 7.38 (m, $1H_{arom}$), 7.66 (m, $2H_{arom}$), 7.92 (m, $2H_{arom}$), 8.63 (dd, 1H, $J_{7,6} = 4$, $J_{7,5} = 2$, H-7), 9.08 (dd, 1H, $J_{5,6} = 7$, $J_{5,7} \approx 2$, H-5)
19b	1	95	117–118	$C_{30}H_{32}NO_5PS_2$ (581.7)	0.22	581 (M^+, 6), 416 (4), 414 (25)	1.11, 1.27 [d, m, 3H and 9H, resp., $J = 6$, $CH(CH_3)_2$], 2.29 (s, 3H, CH_3), 4.74, (mc, 2H, POCH), 5.58 (d, 1H, $^2J_{HP} = 20$, PCH), 6.92 (d, $2H_{arom}$, $J = 9$), 7.10 (d, $2H_{arom}$, $J = 9$), 7.39 (m, $6H_{arom}$), 7.76 (m, $2H_{arom}$), 7.97 (m, $2H_{arom}$)

[a] Yield of products isolated after flash chromatography.
[b] Recrystallization from Et_2O/petroleum ether (bp 40°C).
[c] Satisfactory microanalyses obtained: C ±0.45, H ±0.27, N ±0.42. Exceptions: **11a**, C −0.73, N −0.79.
[d] Solvent system: CH_2Cl_2/EtOAc, 9 : 1 (**9a, 9b**); EtOAc/MeOH, 19 : 1 (**10a, 11a**); EtOAc (**10b, 11b**); petroleum ether (bp 65–70°C/EtOAc, 3 : 1 (**19b**).
250 MHz (compounds **9b, 10b, 11a, 11b, 19b**); 400 MHz (compounds **9a, 10a**).

Table 3. Heteroarylmethylphosphonates **12–14** and **20** Prepared

Starting Material	Reaction Time (h)	Product	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c] or Lit. mp (°C)	R_f[d] (TLC)	MS (70 eV) *m/z* (%)	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, *J* (Hz)
6a	1.5	**12a**	92	oil	$C_{19}H_{28}NO_5P$	0.33	–	1.11, 1.25 [2d, 6H each, $J = 6$, $CH(C\underline{H}_3)_2$], 1.42 (t, 3H, $CH_2C\underline{H}_3$), 2.45 (d, 3H, $^5J_{HP} = 3$, CH_3), 3.37 (d, 2H, $^2J_{HP} = 20$, PCH_2), 4.37 (mc, 2H, $C\underline{H}_2CH_3$), 4.60 (m, 2H, POCH), 6.67 (dt, 1H, $J_{6,7} \approx J_{6,5} \approx 7$, $J \approx 2$, H-6), 6.99 (dd, 1H, $J_{7,6} \approx 7$, $J_{7,8} \approx 9$, H-7), 8.07 (d, 1H, $J_{5,6} \approx 7$, $J \approx 1$, H-5), 8.12 (d, 1H, $J_{8,7} \approx 9$, H-8)
9a	17		78		(381.4)			
6b	20	**12b**	73	oil	$C_{24}H_{30}NO_5P$	0.40	443 (M^+, 49),	1.11 (t, 3H, $J = 7$, $CH_2C\underline{H}_3$), 1.06, 1.23 [2d, 6H each, $J = 6$, $CH(C\underline{H}_3)_2$], 3.30 (d, 2H, $^2J_{HP} = 20$, PCH_2), 4.15 (mc, 2H, $C\underline{H}_2CH_3$), 4.59 (mc, 2H, POCH), 6.81 (dt, 1H, $J_{6,7} \approx J_{6,5} \approx 7$, $J = 2$, H-6), 7.11 (dd, 1H, $J_{7,6} \approx 7$, $J_{7,8} \approx 9$, H-7), 7.39 (m, 5H_{arom}), 8.29 (d, 1H, $J_{8,7} \approx 9$, H-8), 8.37 (d, 1H, $J_{5,6} \approx 7$, H-5)
9b	1		76		(443.5)		278 (90)	
7a	3	**13a**	72	oil	oil[1]			
10a	2		85					
7b	1.5	**13b**	92	84–85	$C_{20}H_{25}N_2O_3P$	0.40	372 (M^+, 19)	1.11, 1.30 [2d, 6H each, $J = 6$, $CH(C\underline{H}_3)_2$], 3.58 (d, 2H, $^2J_{HP} = 20$, PCH_2), 4.68 (mc, 2H, POCH), 6.92 (dt, 1H, $J_{6,7} \approx J_{6,5} \approx 7$, $J \approx 1$, H-6), 7.28 (mc, 1H, H-7), 7.46 (m, 3H_{arom}), 7.74 (d, 1H, $J_{8,7} = 9$, H-8), 7.97 (m, 2H_{arom}), 8.43 (d, 1H, $J_{5,6} = 7$, H-5)
10b	4		98		(372.4)		207 (100)	
8a	1	**14a**	87	117–119	oil[1]			
11a	20		33					
8b	1.5	**14b**	88	oil	$C_{19}H_{24}N_3O_3P$	0.30	373 (M^+, 17)	1.13, 1.31 [2d, 6H each, $J = 6$, $CH(C\underline{H}_3)_2$], 3.59 (d, 2H, $^2J_{HP} = 20$, PCH_2), 4.68 (mc, 2H, POCH), 6.94 (dd, 1H, $J_{6,7} \approx 4$, $J_{6,5} \approx 7$, H-6), 7.46 (m, 3H_{arom}), 8.00 (m, 2H_{arom}), 8.58 (dd, 1H, $J_{7,6} \approx 4$, $J_{7,5} \approx 2$, H-7), 8.82 (dd, 1H, $J_{5,6} \approx 7$, $J_{5,7} \approx 2$, H-5)
11b	20		29		(373.4)		208 (99)	
18b	4	**20b**	90	oil	$C_{22}H_{26}NO_3PS$	0.52	415 (M^+, 18)	1.25, 1.33 [2d, 6H each, $J = 6$, $CH(C\underline{H}_3)_2$], 3.44 (d, 2H, $^2J_{HP} = 21$, PCH_2), 4.74 (mc, 2H, POCH), 7.44 (m, 6H_{arom}), 7.76 (m, 2H_{arom}), 8.00 (m, 2H_{arom})
19b	1.5		98		(415.5)		250 (25)	

[a] Yield of products isolated after flash chromatography.
[b] Recrystallization from Et_2O/petroleum ether (bp 40 °C).
[c] Satisfactory microanalyses obtained: C ± 0.39, H ± 0.28, N ± 0.32. Exception: **12a**, N – 0.50.
[d] Solvent system: CH_2Cl_2/EtOAc, 9 : 1 (**12a, 12b**); EtOAc/MeOH, 19 : 1 (**13a, 14b**); EtOAc (**13b**); EtOAc/MeOH, 5 : 1 (**14a**); petroleum ether (bp 65–70 °C)/EtOAc, 1 : 1 (**20b**).
[e] 250 MHz (compounds **13b, 14b, 20b**); 400 MHz (compounds **12a, 12b**).

the complete consumption of the starting material (TLC) the solvent is removed *in vacuo*. The residue is coevaporated with anhydrous toluene and purified by flash chromatography on silica gel (Table 2).

Dialkyl Heteroarylmethylphosphonates 12–14 and 20; General Procedure:

A solution of the corresponding *O,O*-thiocarbonate **6–8, 18** or the *O,S*-thiocarbonate **9–11, 19** (0.45 mmol), a catalytic amount of AIBN and tributyltin hydride (0.239 mL, 0.90 mmol) in anhydrous toluene (7 mL) is stirred at 80 °C under argon until the starting material is consumed (TLC control). After cooling to r.t., the mixture is concentrated and the product is isolated by flash chromatography on silica gel (Table 3).

Dialkyl [Heteroaryl(methylthio)methyl]phosphonates 15–17 and 21; General Procedure:

To a solution of the appropriate *O,S*-thiocarbonate **9–11, 19** (0.40 mmol) in anhydrous MeOH (7 mL) 25% NaOMe in MeOH (0.87 mL, 0.40 mmol) is added at 0 °C under argon, and stirring is continued for 30 min. Then MeI (0.032 mL, 0.52 mmol) is added and stirring is continued for 30 min. The solvent is removed *in vacuo*, the residue is diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined CH_2Cl_2 layers are shaken with water (2 × 20 mL), dried (Na_2SO_4), and evaporated *in vacuo*. The residue is flash chromatographed on silica gel (Table 4).

Table 4. [Heteroaryl(methylthio)methyl]phosphonates **15–17** and **21** Prepared

Product	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c]	R_f[d] (TLC)	MS (70 eV) *m/z* (%)	^{1}H-NMR ($CDCl_3$/TMS) δ, *J* (Hz)
15a	96	oil	$C_{20}H_{30}NO_5PS$ (427.5)	0.53	427 (M^+, 23), 380 (100), 262 (54)	0.77, 1.17, 1.36, 1.39 [4d, 3H each, J = 6, $CH(C\underline{H}_3)_2$], 1.43 (t, 3H, J = 7, $CH_2C\underline{H}_3$), 1.89 (d, 3H, $^4J_{HP}$ = 2, SCH_3), 2.50 (d, 3H, $^5J_{HP}$ = 2, CH_3), 4.34 (mc, 3H, POCH, $C\underline{H}_2CH_3$), 4.61 (d, 1H, $^2J_{HP}$ = 26, PCH), 4.84 (mc, 1H, POCH), 6.76 (dt, 1H, $J_{6,7} \approx J_{6,5} \approx 7$, J = 2, H-6), 7.09 (dd, 1H, $J_{7,6} \approx 7$, $J_{7,8} \approx 9$, H-7), 8.20 (d, 1H, $J_{8,7} \approx 9$, H-8), 8.91 (d, 1H, $J_{5,6} \approx 7$, H-5)
15b	93	90	$C_{25}H_{32}NO_5PS$ (489.6)	0.37	489 (M^+, 4), 442 (19), 324 (5)	1.09 (t, 3H, J = 7, $CH_2C\underline{H}_3$), 0.81, 1.24, 1.32 [3d, 3H, 3H and 6H, resp., J = 6, $CH(C\underline{H}_3)_2$], 1.73 (d, 3H, $^4J_{HP}$ = 2, SCH_3), 4.14 (mc, 2H, $C\underline{H}_2CH_3$), 4.38 (d, 1H, $^2J_{HP}$ = 26, PCH), 4.49, 4.78 (2mc, 1H each, POCH), 6.84 (dt, 1H, $J_{6,7} \approx J_{6,5} \approx 7$, $J \approx 1$, H-6), 7.17 (br dd, 1H, H-7), 7.39 (m, 5H_{arom}), 8.30 (d, 1H, $J_{8,7} \approx 9$, H-8), 9.03 (d, 1H, $J_{5,6} \approx 7$, H-5)
16a	64	oil	$C_{16}H_{25}N_2O_3PS$ (356.4)	0.38	356 (M^+, 15), 309 (75), 191 (96)	0.82, 1.19, 1.36, 1.39 [4d, 3H each, J = 6, $CH(C\underline{H}_3)_2$], 1.93 (d, 3H, $^4J_{HP}$ = 2, SCH_3), 2.46 (d, 3H, $^5J_{HP}$ = 2, CH_3), 4.39, 4.8 (2mc, 1H each, POCH), 4.49 (d, 1H, $^2J_{HP}$ = 24, PCH), 6.80 (dt, 1H, $J_{6,7} \approx J_{6,5} \approx 7$, $J \approx 1$, H-6), 7.19 (mc, 1H, H-7), 7.51 (d, 1H, $J_{8,7}$ = 9, H-8), 8.83 (mc, 1H, H-5)
16b	98	oil	$C_{21}H_{27}N_2O_3PS$ (418.7)	0.59	48 (M^+, 19), 371 (100), 253 (57)	0.84, 1.24, 1.38, 1.4 [4d, 3H each, J = 6, $CH(CH_3)_2$], 1.73 (d, 3H, $^4J_{HP}$ = 2, SCH_3), 4.51, 4.89 (2mc, 1H each, POCH), 4.83 (d, 1H, $^2J_{HP}$ = 24, PCH), 6.86 (dt, 1H, $J_{6,7} \approx J_{6,5} \approx 7$, $J \approx 1$, H-6), 7.26 (mc, 1H, H-7), 7.46 (m, 3H_{arom}), 7.64 (d, 1H, $J_{8,7}$ = 9, H-8), 7.76 (m, 2H_{arom}), 9.02 (d, 1H, $J_{5,6} \approx 7$, H-5)
17a	89	63–65	$C_{15}H_{24}N_3O_3PS$ (357.4)	0.35	357 (M^+, 16), 310 (87), 192 (100)	0.87, 1.19, 1.38, 1.40 [4d, 3H each, J = 6, $CH(CH_3)_2$], 1.92 (d, 3H, $^4J_{HP}$ = 2, SCH_3), 2.48 (d, 3H, $^5J_{HP}$ = 2, CH_3), 4.38, 4.86 (2mc, 1H each, POCH), 4.48 (d, 1H, $^2J_{HP}$ = 24, PCH), 6.87 (dd, 1H, $J_{6,5}$ = 7, $J_{6,7}$ = 4, H-6), 8.52 (dd, 1H, $J_{7,6}$ = 4, $J_{7,5}$ = 2, H-7), 9.20 (dd, 1H, $J_{5,6}$ = 7, $J_{5,7}$ = 2, H-5)
17b	91	oil	$C_{20}H_{26}N_3O_3PS$ (419.5)	0.40	419 (M^+, 8), 372 (42), 254 (25)	0.89, 1.26, 1.40, 1.42 [4d, 3H each, J = 6, $CH(C\underline{H}_3)_2$], 1.74 (d, 3H, $^4J_{HP}$ = 2, SCH_3), 4.51, 4.89 (2mc, 1H each, POCH), 4.85 (d, 1H, $^2J_{HP}$ = 24, PCH), 6.90 (dd, 1H, $J_{6,5}$ = 7, $J_{6,7}$ = 4, H-6), 7.40–7.52 (m, 3H_{arom}), 7.83 (m, 2H_{arom}), 8.61 (dd, 1H, $J_{7,6}$ = 4, $J_{7,5} \approx 2$, H-7), 9.40 (dd, 1H, $J_{5,6}$ = 7, $J_{5,7} \approx 2$, H-5)
21b	92	96–97	$C_{23}H_{28}NO_3PS_2$ (461.6)	0.67	461 (M^+, 1), 414 (29), 296 (19)	1.03, 1.25, 1.31, 1.35 [4d, 3H each, J = 6, $CH(C\underline{H}_3)_2$], 2.10 (s, 3H, SCH_3), 4.47, 4.65 (2mc, 1H each, POCH), 6.01 (d, 1H, $^2J_{HP}$ = 11, PCH), 7.29–7.60 (m, 8H_{arom}), 8.02 (m, 2H_{arom})

[a] Yield of products isolated after flash chromatography.
[b] Recrystallization from Et_2O/petroleum ether (bp 40 °C).
[c] Satisfactory microanalyses obtained: C ± 0.36, H ± 0.30, N ± 0.39, S ± 0.22. Exceptions: **15a**, C + 0.70; **16a**, C − 0.64; **16b**, C − 0.59.
[d] Solvent system: CH_2Cl_2/EtOAc, 9 : 1 (**15a**); EtOAc/MeOH, 19 : 1 (**16a**); EtOAc (**16b, 17b**); CH_2Cl_2/EtOAc, 15 : 1 (**15b**); EtOAc/MeOH, 9 : 1 (**17a**); petroleum ether (bp 65–70 °C)/EtOAc, 1 : 1 (**21b**).

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