One-Pot Synthesis of Dialkyl Arylaminomethyl- and (Arylamino)arylmethylphosphonates and Their *N*-Acylated Derivatives

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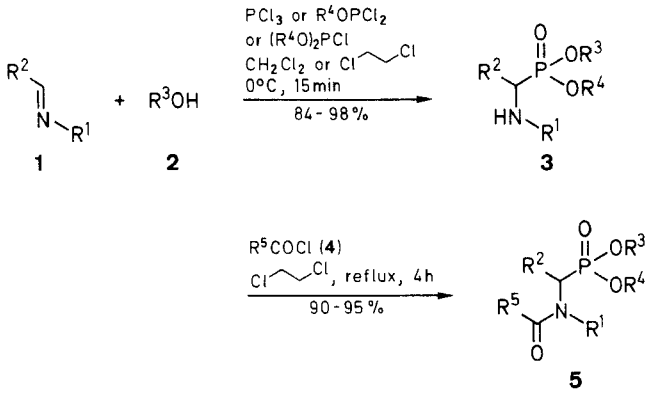
A convenient synthesis of dialkyl arylaminomethyl- and (arylamino)arylmethylphosphonates **3** and their *N*-acylated derivatives **5** have been developed, starting from azomethines and phosphorus trichloride in the presence of an alcohol.

α-Aminophosphonic acid derivatives as phosphorus analogs of aminocarboxylic acids have received a great deal of interest due to their bioactivity.[1-4] Some of the *N*-chloroacylated products of the diesters of anilinomethylphosphonic acids have been reported as active herbicides.[5]

Dialkyl esters of aminomethylphosphonic acids are usually obtained by the addition of dialkyl phosphites to Schiff bases in the presence of a metal alkoxide or an acid (e.g. hydrochloric acid, tin(II) chloride).[5-7] The reaction was investigated on a wide range of azomethines and many physiologically active compounds have been synthesized.[5,8]

Now we report a convenient one-pot synthesis of dialkyl arylaminomethyl- and (arylamino)arylmethylphosphonates **3**, starting from the readily available azomethines **1**, phosphorus(III) chloride and an alcohol **2**. They can be *N*-acylated with acyl chlorides to **5** without isolation and purification.



1 **2** **3** **5**

3, 5	R^1	R^2	R^3	R^4	R^5
3a	Ph	Ph	Et	Et	–
3b	Ph	4-$NO_2C_6H_4$	Me	Me	–
3c	Ph	4-FC_6H_4	Me	Me	–
3d	Ph	4-ClC_6H_4	Me	Me	–
3e	Ph	4-MeC_6H_4	Me	Me	–
3f	4-ClC_6H_4	Ph	Me	Me	–
3g	4-MeC_6H_4	Ph	Me	Me	–
3h	4-$MeOC_6H_5$	Ph	Me	Me	–
3i	Ph	Ph	Me	Et	–
3j	$PhCH_2$	H	Et	Et	–
3k	$PhCH_2CH_2$	H	Et	Et	–
3l	Ph	Ph	$(CH_2)_2Cl$	$(CH_2)_2Cl$	–
5a	Ph	Ph	Me	Me	CH_2Cl
5b	Ph	Ph	*i*-Pr	*i*-Pr	CH_3
5c	Ph	H	Et	Et	CH_2Cl
5d	$PhCH_2$	H	Et	Et	CH_2Cl
5e	2,6-$(Et)_2C_6H_3$	H	Et	Et	CH_2Cl
5f	2,6-$(Me)_2C_6H_3$	H	Et	Et	CH_2Cl

The products **3** obtained were purified by recrystallization (Table). The procedure is simple and affords excellent yields of dialkyl esters of (arylamino)arylmethylphosphonic acids **3**. The procedure also allows the mixed dialkyl esters of arylaminomethylphosphonic acids to be obtained, by the reaction of an azomethine **1** with alkoxydichlorophosphines[9] or dialkoxychlorophosphines[10] in the presence of an alcohol. For example, compound **3i** was obtained from *N*-benzylideneaniline, ethyldichlorophosphine and methanol in 95% yield and with methyl dichlorophosphine in 94% yield.

2-Chloroethyl diesters of arylaminomethylphosphonic acids can be obtained when the alcohol in the reaction is replaced by ethylene oxide (Table, product **3l**).

Dialkyl aminomethylphosphonates **3** can be further converted without isolation to the *N*-acyl derivatives **5** by treating the crude reaction mixture with an acyl chloride **4** at 80°C for 4 h (Table, compounds **5a–f**).

The compounds **3** and **5** have been tested for their herbicidal activity. Some of them have similar activity to that of the commerciall used herbicides, such as Alachlor.

Melting points were measured with a hot-stage Boetius PHMKO5 apparatus and are uncorrected. ^1H NMR were recorded on a Perkin-Elmer R-24B spectrometer. Mass spectra were measured using a Jeol JMS-300 spectrometer.

Dialkyl Arylaminomethyl- and (Arylamino)arylmethylphosphonates 3a–l; General Procedure:
A solution of azomethine **1** (10 mmol) in CH_2Cl_2 (8 mL) was added portionwise to a stirred solution of PCl_3 (1 mL, 12 mmol) in CH_2Cl_2 (2 mL) cooled in an ice bath. A cold (0°C) solution of anhydr. alcohol **2** (32 mmol) in CH_2Cl_2 (10 mL) was added dropwise to this stirred suspension and the mixture stirred for 15 min. Then water (100 mL) was added and the organic layer washed with 20% aq Na_2CO_3 (2 × 50 mL) and dried (Na_2SO_4). The solvent was removed by distillation and the crude product **3** was purified by recrystallization from Et_2O/MeOH (6:4) (Table).

Bis(2-chloroethyl) α-(Anilino)benzylphosphonate (3l):
A solution of *N*-benzylideneaniline (1.81 g, 10 mmol) in CH_2Cl_2 (8 mL) was added to a cold (0°C) and stirred solution of PCl_3 (1 mL, 12 mmol) in CH_2Cl_2 (2 mL) cooled in an ice bath. A cold (0°C) solution of ethylene oxide (1.8 mL, 35 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the mixture stirred for 15 min. Then water (100 mL) was added, the organic layer washed with 20% aq Na_2CO_3 (2 × 50 mL) and dried (Na_2SO_4). The solvent was removed by distillation and the product recrystallized from Et_2O/MeOH (6:4 mL); yield: 3.7 g (96%).

Methyl Ethyl α-(Anilino)benzylphosphonate (3i):
A solution of *N*-benzylideneaniline (1.81 g, 10 mmol) in CH_2Cl_2 (8 mL) was added to a cold (0°C) and stirred solution of $EtOPCl_2$ (1.6 g, 12 mmol) in CH_2Cl_2 (2 mL). A cold (0°C) solution of

Table. Compounds **3a–l** and **5a–f** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a] or Lit. mp (°C)	^{1}H NMR ($CDCl_3$/TMS)[b] δ, J (Hz)	MS (70 eV) m/z (M^+)
3a	90	94–96	90–1[11]	1.15 (t, 3H, J = 12), 1.30 (t, 3H, J = 12), 3.75–4.25 (m, 4H), 4.60, 4.95 (2s, 1H), 5.35 (s, 1H), 6.45–7.45 (m, 10H)	319
3b	96	124–125	$C_{15}H_{17}N_2O_5P$ (335.9)	3.62, 4.05 (2s, 3H), 3.85 (s, 3H), 4.75 (d, 1H, J = 5), 5.20 (s, 1H), 6.50–7.45 (m, 5H), 7.72 (d, 2H, J = 10), 8.25 (d, 2H, J = 10)	336
3c	95	105–106	$C_{15}H_{17}FNO_3P$ (308.9)	3.45, 3.86 (2s, 3H), 3.65, 3.70 (2s, 3H), 4.58, 4.95 (2s, 1H), 4.80 (s, 1H), 6.55 (d, 2H, J = 11), 6.60–7.60 (m, 5H), 7.05 (d, 2H, J = 10)	309
3d	96	148–150	$C_{15}H_{17}ClNO_3P$ (325.4)	3.50, 3.88 (2s, 3H), 3.68, 3.70 (2s, 3H), 4.55 (d, 1H, J = 9), 5.00 (s, 1H), 6.55 (d, 2H, J = 11), 7.05 (d, 2H, J = 11), 7.35 (s, 5H)	325
3e	85	116–118	$C_{16}H_{20}NO_3P$ (304.9)	2.28 (s, 3H), 3.40, 3.85 (2s, 3H), 3.55, 3.65 (2s, 3H), 4.55, 4.95 (2s, 1H), 5.50 (s, 1H), 6.40–6.80 (m, 4H), 6.80–7.40 (m, 5H)	305
3f	91	101–102	$C_{15}H_{17}ClNO_3P$ (325.4)	3.35, 3.85 (2s, 3H), 3.55, 3.65 (2s, 3H), 4.52, 4.95 (2s, 1H), 4.70 (s, 1H), 6.45 (d, 2H, J = 11), 6.95 (d, 2H, J = 10), 7.15–7.45 (m, 5H)	325
3g	87	89–90	$C_{16}H_{20}NO_3P$ (304.9)	2.25 (s, 3H), 3.42, 3.87 (2s, 3H), 3.60, 3.70 (2s, 3H), 4.38 (s, 1H), 4.64, 5.00 (2s, 1H), 6.55 (d, 2H, J = 10), 6.92 (d, 2H, J = 10), 7.15–7.70 (m, 5H)	305
3h	84	100–101	97–98[11]	3.45 (s, 3H), 3.60, 3.85 (2s, 3H), 3.70 (s, 3H), 4.30 (s, 1H), 4.45, 4.95 (2s, 1H), 6.45–6.85 (m, 4H), 7.15–7.60 (m, 5H)	321
3i	95	76–77	$C_{16}H_{20}NO_3P$ (304.9)	1.17, 1.37 (2t, 3H, J = 10), 3.45, 3.58 (2s, 3H), 4.10 (q, 2H, J = 12), 4.65, 5.05 (2s, 1H), 4.75 (s, 1H), 6.50–7.50 (m, 10H)	*305*
3j	88	oil	$C_{12}H_{20}NO_3P$ (256.9)	1.05 (t, 6H, J = 8), 1.80 (s, 1H), 2.28, 2.42 (2s, 2H), 3.09 (s, 2H), 3.30 (q, 4H, J = 11), 5.82 (s, 5H)	257
3k	91	oil	$C_{13}H_{22}NO_3P$ (370.9)	1.05 (t, 6H, J = 11), 2.26 (s, 2H), 2.35 (t, 2H, J = 10), 2.48 (t, 2H, J = 10), 3.30 (q, 4H, J = 11), 5.78 (s, 5H)	371
3l	95	107–109	$C_{17}H_{20}Cl_2NO_3P$ (387.9)	3.55–3.94 (m, 4H), 3.95–4.40 (m, 4H), 4.80–5.05 (m, 1H), 5.20–5.45 (m, 1H), 6.60–7.60 (m, 10H)	388
5a	96	oil	$C_{17}H_{19}ClNO_4P$ (367.4)	3.55, 3.85 (2s, 3H), 3.75 (s, 3H), 3.80 (s, 2H), 6.15, 6.30 (2s, 1H), 6.60–7.35 (m, 10H)	367
5b	90	oil	$C_{21}H_{28}NO_4P$ (388.9)	0.9 (d, 3H, J = 9), 1.22 (d, 3H, J = 9), 1.38 (d, 6H, J = 10), 1.85 (s, 3H), 4.25–4.95 (m, 2H), 6.30, 6.65 (2s, 1H), 6.85–7.45 (m, 10H)	389
5c	95	oil	$C_{13}H_{19}ClNO_4P$ (319.4)	1.20 (t, 6H, J = 12), 3.80 (s, 2H), 4.05 (s, 2H), 4.08 (q, 4H, J = 12), 6.95–7.40 (m, 5H)	319
5d	90	oil	$C_{14}H_{21}ClNO_4P$ (333.4)	1.35 (t, 6H, J = 12), 2.42 (s, 2H), 4.05 (q, 4H, J = 12), 4.10 (s, 2H), 4.75 (s, 2H), 7.22 (s, 5H)	333
5e	90	oil	$C_{17}H_{27}ClNO_4P$ (375.4)	1.22 (t, 6H, J = 11), 1.30 (t, 6H, J = 16), 2.50 (q, 4H, J = 12), 3.70 (s, 2H), 4.05 (q, 4H, J = 12), 5.42 (s, 2H), 7.05–7.35 (m, 3H)	375
5f	91	oil	$C_{15}H_{23}ClNO_4P$ (347.3)	1.25 (t, 6H, J = 12), 2.25 (s, 6H), 3.65 (s, 2H), 4.05 (q, 4H, J = 10), 4.15 (s, 2H),6.85–7.15 (m, 3H)	347

[a] Microanalyses: C ±0.34, H ±0.28, N ±0.26.
[b] The doubled signals are probably due to conformers.

MeOH (0.8 mL, 20 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the mixture was stirred for 15 min. Then the mixture was worked up as described above; yield: 2.9 g (94%).

Dialkyl [(Acyl(phenyl)amino]methylphosphonate 5a–f; General Procedure:

A solution of azomethine **1** (10 mmol) in anhydr. dichloroethane (8 mL) was added to an ice cooled solution of PCl_3 (1 mL, 12 mmol) in anhydr. dichloroethane (2 mL) cooled in an ice bath. A cold (0 °C) solution of anhydr. alcohol **2** (32 mmol) in dichloroethane (10 mL) was added dropwise and the mixture stirred for 15 min. The mixture was heated to reflux and a solution of an acyl chloride **4** (12 mmol) in dichloroethane (10 mL) was added. The mixture was refluxed for 4 h, cooled and water (100 mL) was added. The organic layer was washed with 20% aq Na_2CO_3 (2 × 50 mL) and dried (Na_2SO_4). The solvent was distilled at reduced pressure and the residue was purified by passing through a column of aluminum oxide and eluted out with a mixture of Et_2O/MeOH (1:1).

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