Tritylamine (Triphenylmethylamine) in Organic Synthesis; I. The Synthesis of *N*-(Triphenylmethyl)alkanimines, 1-(Triphenylmethylamino)alkylphosphonic Esters, and 1-Aminoalkylphosphonic Acids and Esters

Mirosław Soroka,* Jan Zygmunt

Institute of Organic and Physical Chemistry, Technical University (Politechnika) of Wrocław, Wybrzeże Wyspiańskiego 27, PL-50-370 Wrocław, Poland

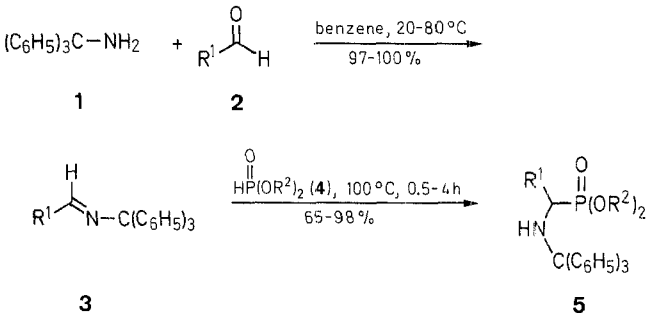
The application of tritylamine, a synthetic equivalent of ammonia, to the preparation of unknown *N*-(triphenylmethyl)alkanimines is described. These imines are convenient synthons for preparation of 1-(triphenylmethylamino)alkylphosphonic esters, which can be used as starting materials for synthesis of 1-aminoalkylphosphonic acids and their derivatives.

The trityl (triphenylmethyl) group is frequently used as a protective group in organic synthesis, especially as an *N*-protecting moiety in peptide chemistry.[1] Despite many references to the use of the *N*-trityl group, there are only few notes concerning applications of tritylamine in organic synthesis.[2,3] In general, the amines themselves are used as reactive synthons, for example in aminoalkylation reactions.[4] Abundantly used amine derivatives are the easily accessible imines (Schiff bases) which can undergo a lot of reactions (reduction, addition of HX, oxidation, rearrangement, etc.).[5] Surprisingly, there are no reports on the preparation of *N*-(triphenylmethyl)alkanimines (Schiff bases) derived from tritylamine.[6]

A general, frequently employed synthesis of 1-aminoalkylphosphonic esters involves the addition or tervalent phosphorus compounds to aldimines or ketimines derived from a broad spectrum of amines, such as aniline,[7,8,9] *tert*-butylamine,[10] benzylamines,[11-13] benzhydrylamine,[14,15] hydrazines,[16-20] and other amine derivatives[21-27] (in total more than 100 publications). The branched derivatives of benzylamine with a tertiary C-atom were also used.[28-31]

The extremely mild conditions under which an *N*-trityl group can be removed make tritylamine a useful ammonia equivalent in synthesis. We now report the use of tritylamine (triphenylmethylamine, aminotriphenylmethane) in the preparation of aldimines, and the application of the new *N*-tritylaldimines to the synthesis of 1-aminoalkylphosphonic acids and their esters and *N*-trityl derivatives.

Tritylamine (**1**) reacts smoothly[32] with aldehydes **2** to form a crystalline *N*-(triphenylmethyl)alkanimine **3** which can be recrystallized, or used directly in further reactions with dialkyl or diaryl phosphites **4** (Scheme **A**).



2, 3, 7	R^1	2, 3, 7	R^1	4	R^2
a	H	**d**	i-C_3H_7	**a**	CH_3
b	CH_3	**e**	i-C_4H_9	**b**	C_2H_5
c	C_2H_5	**f**	C_6H_5	**c**	C_6H_5

5, 6	R^1	R^2	5, 6	R^1	R^2
aa	H	CH_3	**ca**	C_2H_5	CH_3
ab	H	C_2H_5	**da**	i-C_3H_7	CH_3
ac	H	C_6H_5	**ea**	i-C_4H_9	CH_3
ba	CH_3	CH_3	**fa**	C_6H_5	CH_3

Scheme **A**

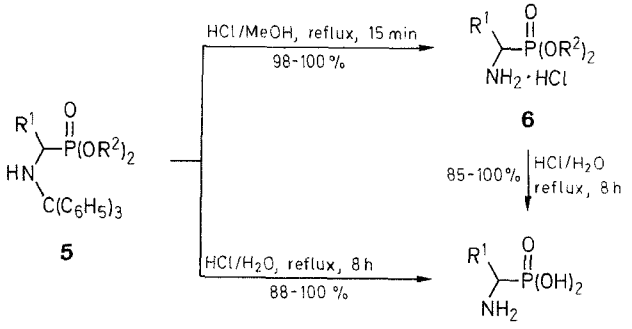
Addition[33] of dialkyl or diaryl phosphites **4** gives dialkyl or diaryl 1-(triphenylmethylamino)alkylphosphonates **5**, which are crystalline[34] products and which represent excellent start-

Table 1. *N*-Tritylalkanimines **3** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b]	IR (KBr) ν_{max} (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ, J(Hz)
3a	98	134–136 (dec) (benzene/hexane)	$C_{20}H_{17}N$ (271.4)	3055, 3025, 1645 (C=N), 1592, 1480, 1438, 748, 690	6.91 (d, 1H, J = 16); 7.15 (s, 15H); 7.66 (d, 1H, J = 16)
3b	~100	144–147 (dec) (MeOH)	$C_{21}H_{19}N$ (285.4)	3055, 3025, 2985, 2945, 2900, 1658 (C=N), 1595, 1485, 1438, 752, 690	2.01 (d, 3H, J = 4.8); 7.13 (s, 15H); 7.21 (q, 1H, J = 4.8)
3c	97	124–126 (dec) (hexane)	$C_{22}H_{21}N$ (299.4)	3052, 3020, 2965, 2925, 2872, 1660 (C=N), 1590, 1480, 1438, 755, 695	1.08 (t, 3H, J = 7.5); 2.3 (dq, 2H, J = 7.5, 3); 7.17 (s, 15H); 7.22 (t, 1H, J = 3)
3d	~100	88–90 (dec) (MeOH)	$C_{23}H_{23}N$ (313.4)	3058, 3022, 2962, 2932, 2885, 1660 (C=N), 1592, 1482, 1438, 752, 690	1.02 (d, 6H, J = 7); 2.5 (d hept, 1H, J = 7, 2.5); 7.08 (d, 1H, J = 2.5); 7.15 (s, 15H)
3e	~100	50–56 (dec) (hexane)	$C_{24}H_{25}N$ (327.5)	3060, 3028, 2955, 2930, 2870, 1658 (C=N), 1598, 1480, 1440, 755, 690	0.83 (d, 6H, J = 6.2); 1.9 (m, 1H); 2.25 (dd, 2H, J = 6.2, 5.5); 7.15 (s, 15H); 7.20 (t, 1H, J = 5.5)
3f	~100	153–159 (dec) (hexane)	$C_{26}H_{21}N$ (347.5)	3060, 3028, 2890, 1635 (C=N), 1592, 1580, 1485, 1438, 765, 755, 690	7.2 (s, 15H); 7.1–7.4 (m, 3H); 7.7–7.9 (m, 2H); 7.75 (s, 1H)

[a] Yield before recrystallization.
[b] Satisfactory microanalyses obtained: C ±0.25, H ±0.32, N ±0.27.

ing materials for syntheses of 1-aminoalkylphosphonic acids themselves or other derivatives thereof. Brief refluxing of **5** with 1 molar hydrogen chloride in methanol gives quantitatively the ester hydrochlorides **6** (Scheme **B**) which can be directly used as substrates for syntheses of phosphonopeptides. Hydrolysis of **5** or **6** with hydrochloric acid gives the 1-aminoalkylphosphonic acids **7** in nearly quantitative yield (Scheme **B**).



Scheme **B** (for R^1 and R^2, see Scheme **A**)

The crystalline dialkyl and diaryl 1-(tritylamino)alkylphosphonates **5** can be shelf-stored as stock reagents for a long time without visible decomposition. Thus, these compounds may be regarded as the best intermediates for the preparation of 1-aminoalkylphosphonic acid derivatives. For comparison, the dialkyl 1-aminoalkylphosphonates cannot even be stored at room temperature since they slowly undergo intermolecular substitution reactions to give a complex mixture of by-products. Our procedure provides 1-aminoalkylphosphonic acids **7** of high purity. One of its useful applications is the synthesis of derivatives of aminomethylphosphonic acid, which are not easily available by other methods.[35,36]

Table 3. Dimethyl 1-Aminoalkylphosphonate Hydrochlorides **6** Prepared

Product	Yield[a] (%)	mp[b] (°C)	^{1}H-NMR (D_2O/TMS_{ext}) δ, J(Hz)
6aa	~100	117–122 (dec)	3.58 (d, 2H, J = 14); 3.90 (d, 6H, J = 11.5)
6ba	~100	oil	1.58 (dd, 3H, J = 7, 17); 3.7 (m, 1H); 3.94 (d, 6H, J = 11)
6ca	~100	oil	1.2 (t, 3H, J = 7.5); 2.1 (m, 2H); 3.8 (m, 1H); 4.03 (d, 6H, J = 11)
6da	100	oil	1.19 (d, 6H, J = 6); 2.3 (m, 1H); 3.59 (dd, 1H, J = 6, 16); 3.96 (d, 6H, J = 11)
6ea	98	105–112 (dec)	1.03 (d, 3H, J = 3.8); 1.07 (d, 3H, J = 3.8); 1.8 (m, 1H + 2H); 3.8 (m, 1H); 3.95 (d, 6H, J = 11)

[a] Yield before recrystallization.
[b] All hydrochlorides **6** decomposed with vigorous gas evolution on heating on a melting-point microscope block.

Table 4. 1-Aminoalkylphosphonic Acids **7** Prepared

Product	Starting Material	Yield[a] (%)	mp (°C) found	reported
7a	**5aa**	~100	342–345 (dec)	310[37]
	6aa	~100	340–345 (dec)	
7b	**5ba**	89	275–277 (dec)	272–274[11]
	6ba	92	275–277 (dec)	
7c	**5ca**	95	265–267 (dec)	264–266[11]
	6ca	88	265–267	
7d	**5da**	85	275–277 (dec)	276–278[38]
	6da	90	275–278 (dec)	
7e	**5ea**	91	277–278 (dec)	279–280[38]
	6ea	92	277–279 (dec)	

[a] Yield before recrystallization.

Table 2. Dialkyl and Diphenyl 1-(Tritylamino)alkylphosphonates **5** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b]	IR (KBr) ν_{max} (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ, J(Hz)
5aa	95	210–211 (dec) ($CHCl_3$/MeOH)	$C_{22}H_{24}NO_3P$ (381.4)	3330 (NH), 3080, 3065, 3020, 2950, 2860, 2810, 1595, 1480, 1445, 1230 (P=O), 1045, 1015 (POC), 885, 845, 770, 610	2.07 (br t, 1H, NH, J = 7); 2.61 (dd, 2H, J = 7, 13.5); 3.84 (d, 6H, J = 11); 7.2–7.6 (m, 15H)
5ab	90	115–117 (dec) ($CHCl_3$/MeOH)	$C_{24}H_{28}NO_3P$ (409.5)	3280 (NH), 3080, 3060, 3020, 2985, 2905, 2870, 2825, 1595, 1485, 1440, 1235 (P=O), 1045, 1015 (POC), 965, 820, 745, 695	1.42 (t, 6H, J = 7.3); 2.3 (br s, 1H, NH); 2.55 (d, 2H, J = 14); 4.25 (dq, 4H, J = 7.3, 7); 7.2–7.7 (m, 15H)
5ac	98	130–136 (dec) (benzene/hexane)	$C_{32}H_{28}NO_3P$ (505.6)	3290 (NH), 3060, 3025, 2940, 2865, 2815, 1585, 1480, 1440, 1260 (P=O), 1180, 1160 (POC), 930, 760, 700, 685	2.3 (br t, 1H, NH); 2.95 (dd, 2H, J = 5, 14); 7.3–7.6 (m, 25H)
5ba	75	191–195 (dec) (MeOH)	$C_{23}H_{26}NO_3P$ (395.4)	3265 (NH), 3085, 3060, 3020, 2955, 2915, 2845, 1595, 1485, 1440, 1230 (P=O), 1055, 1020 (POC), 825, 790, 735, 700	0.47 (dd, 3H, J = 7, 18); 2.9 (d, 1H, J = 7, NH); 3.2 (m, 1H); 3.78 (d, 3H, J = 11); 3.82 (d, 3H, J = 11); 7.1–7.4 (m, 9H); 7.5–7.8 (m, 6H)
5ca	70	143–145 (dec) (MeOH)	$C_{24}H_{28}NO_3P$ (409.5)	3255 (NH), 3055, 3020, 2990, 2950, 2875, 2840, 1590, 1480, 1440, 1225 (P=O), 1050, 1015 (POC), 825, 765, 735, 695	0.63 (t, 3H, J = 6); 1.0 (m, 2H); 2.3 (br s, 1H, NH); 3.05 (dt, 1H, J = 6, 19); 3.85 (d, 6H, J = 10.5); 7.2–7.4 (m, 9H); 7.6–7.8 (m, 6H)
5da	65	132–134 (dec) (hexane)	$C_{25}H_{30}NO_3P$ (423.5)	3325 (NH), 3060, 3030, 2980, 2950, 2875, 2850, 1590, 1470, 1435, 1225 (P=O), 1050, 1020 (POC), 810, 765, 740, 690	0.95 (d, 3H, J = 2.5); 1.02 (d, 3H, J = 1.5); 1.5 (m, 1H); 2.8 (br d, 1H, NH); 3.00 (ddd, 1H, J = 2, 21.5); 3.76 (d, 3H, J = 10.5); 3.78 (d, 3H, J = 10.5); 7.4–7.6 (m, 9H); 7.7–7.9 (m, 6H)
5ea	75	91–95 (dec) (hexane)	$C_{26}H_{32}NO_3P$ (437.5)	3260 (NH), 3055, 3020, 2990, 2950, 2860, 2840, 1590, 1480, 1440, 1225 (P=O), 1045, 1015 (POC), 825, 780, 770, 700	0.55 (d, 3H, J = 6.5); 0.60 (d, 3H, J = 6.5); 0.9–1.7 (m, 1H + 2H); 2.85 (br s, 1H, NH); 2.92 (dt, 1H, J = 5, 16); 3.83 (d, 6H, J = 10.5); 7.2–7.4 (m, 9H); 7.5–7.7 (m, 6H)

[a] Yield after recrystallization.
[b] Satisfactory microanalyses obtained: N ± 0.18, P ± 0.29.

The triphenylmethyl derivatives which are obtained as side products upon deblocking the *N*-trityl compounds (e.g., trityl chloride) can be reconverted into tritylamine, which renders our method economical. The only limitation to the application of tritylamine seems to be some steric hindrance; thus we could not obtain imines derived from ketones. Further, the addition of dialkyl phosphites to imines prepared from tritylamine and some aromatic aldehydes is still an unsolved task.

Melting points were measured on a microscope block Boetius PHMK 05 apparatus and are uncorrected. IR spectra were recorded on a Specord 75 IR (Karl Zeiss Jena, DDR) spectrophotometer. Only the strongest and most typical absorptions are given. NMR spectra were recorded at 60 MHz with a Tesla BS 467 (Tesla Brno, CSRS) instrument using an external stabilization mode.

All preparations described in this work have not been optimized.

N-Tritylalkanimines (3); General Procedure:

A mixture of tritylamine[39,40] (**1**; 12.97 g, 0.050 mol) and the freshly distilled aldehyde **2** (0.055 mol) in benzene (50 mL) is heated to reflux in a Dean-Stark distillation device with a calibrated receiver. When the calculated amount of H_2O (0.9 mL) has separated, the reaction mixture is evaporated to give the practically pure product **3**, which can be recrystallized from the solvents given in Table 1.

N-Tritylmethanimine (3a):

A mixture of tritylamine (**1**; 12.97 g, 0.050 mol), benzene (50 mL), and aqueous formaldehyde (formalin; 8.4 g, 0.1 mol) is vigorously stirred at room temperature (~ 20 °C) for 24 h. Then, H_2O is removed by stirring the mixture with Na_2SO_4 (20 g) for 15 min. The solid material is filtered off and washed with benzene (30 mL); the filtrate is evaporated under reduced pressure to give the practically pure, crystalline product **3a**; yield: 13.2 g (98%); mp 134–136 °C (from benzene/ hexane).

Dimethyl 1-(Tritylamino)alkylphosphonates (5); General Procedure:

A mixture of the *N*-tritylalkanimine **3** (0.010 mol) and dimethyl phosphite (5.5 g, 0.05 mol) is heated at 100 °C (steam bath) for 0.5–4 h (imine **3a** reacts instantly and the product crystallizes after a few minutes; other imines need more time). Excess dimethyl phosphite is then removed under reduced pressure (on a boiling water bath) and the residue is crystallized from an appropriate solvent (Table 2). The product is isolated by suction, washed with the same solvent, and dried in vacuum at ambient temperature.

The diethyl and diphenyl esters **5ab** and **5ac** are prepared analogously.

Dimethyl 1-Aminoalkylphosphonate Hydrochlorides 6; General Procedure:

A mixture of the dimethyl 1-(tritylamino)alkylphosphonate **5** (0.005 mol) and a 1 M solution of HCl in MeOH (20 mL) is heated to boiling for ~ 15 min, then cooled, and evaporated under reduced pressure at a temperature not exceeding 20 °C (water bath) to prevent ester cleavage. The residue is treated with dry Et_2O (20 mL). If the hydrochloride **6** precipitates, it is isolated by suction, washed with Et_2O, and dried under vacuum. Oily products are additionally washed with dry Et_2O (2 × 10 mL), separated, and dried under vacuum at a temperature below 20 °C.

1-Aminoalkylphosphonic Acids 7; General Procedures:

Method A (from **5**): A mixture of the 1-(tritylamino)alkylphosphonic ester **5** (0.005 mol) and 12 M HCl/H_2O (5 mL) is heated to boiling for 8 h, then triphenylmethyl alcohol is extracted with $CHCl_3$ (3 × 5 mL). The aqueous phase is evaporated under reduced pressure, the residue is dissolved in MeOH (5–10 mL), and a stoichiometric amount of methyloxirane (1.0 mL) is added. For crystallization, the mixture is stored for a few hours in a refrigerator. The precipitated product **7** is isolated by suction, washed with MeOH, and dried under vaccum.

Method B (from **6**): A mixture of the dimethyl 1-aminoalkylphosphonate hydrochloride **6** (0.005 mol) and 12 M HCl/H_2O (5 mL) is heated to boiling for 8 h, and then evaporated under reduced pressure. The residue is dissolved in MeOH (5–10 mL), the stoichiometric amount of methyloxirane (1.0 mL) is added, and the mixture is stored in refrigerator for a few hours for crystallization. The precipitated product **7** is isolated by suction, washed with MeOH, and dried under vacuum.

Received: 15 October 1987; revised: 7 January 1988

(1) Wünsch, E., in: *Houben-Weyl*, 4th ed., Vol. 15/1, Georg Thieme Verlag, Stuttgart, 1974, p. 266–276.
Green, T.W. *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, 1981.
(2) Chadwick, D.J., Hodgson, S.T. *J. Chem. Soc. Perkin Trans. 1* **1983**, 3.
(3) Adlington, R.M., Barrett, A.G., Quayle, P., Walker, A., Betts, M.J. *J. Chem. Soc. Perkin Trans. 1* **1983**, 605.
(4) Hellmann, H., Opitz, G. *α-Aminoalkylierung*, Verlag Chemie, Weinheim, 1960.
(5) Layer, R.W. *Chem. Rev.* **1963**, *63*, 489.
(6) In Ref. 28 is mentioned: "N.B. Tritylamine cannot be used instead of **1** because the Schiff bases derived therefrom are unreactive towards dialkyl phosphite".
(7) Pudovik, A.N. *Dokl. Akad. Nauk SSSR* **1953**, *92*, 773.
(8) Pudovik, A.N. *Dokl. Akad. Nauk SSSR* **1952**, *83*, 865.
(9) Pudovik, A.N. Korchemkina, M.V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1952**, 940.
(10) Moedritzer, K. *Synth. Inorg. Met. Org. Chem.* **1972**, *2*, 317.
(11) Tyka, R. *Tetrahedron Lett.* **1970**, 677.
(12) Gilmore, W.F., McBride, M.A. *J. Am. Chem. Soc.* **1972**, *94*, 4361.
(13) Głowiak, T., Sawka-Dobrowolska, W., Kowalik, J., Mastalerz, P., Soroka, M., Zoń, J. *Tetrahedron Lett.* **1977**, 3965.
(14) Baylis, E.K., Campbell, C.D., Dingwall, J.G. *J. Chem. Soc. Perkin Trans. 1* **1984**, 2845.
(15) Issleib, K., Doepfer, K.P., Balszuweit, A. *Z. Naturforsch. Teil B* **1981**, *36*, 1392.
(16) Rachoń, J., Wasielewski, C. *Z. Chem.* **1973**, *13*, 254.
(17) Wasielewski, C., Antczak, K., Rachoń, J. *Pol. J. Chem.* **1978**, *52*, 1315.
(18) Rachoń, J., Wasielewski, C. *Tetrahedron Lett.* **1978**, 1609.
(19) Nifantev, E.E., Zyk, N.V., Koroteev, M.P. *Dokl. Akad. Nauk SSSR* **1974**, *218*, 1371.
(20) Kreutzkamp, N., Storck, K., Schimpfky, C. *Arch. Pharm. (Weinheim, Ger.)* **1969**, *302*, 554.
(21) Zoń, J., Mastalerz, P. *Rocz. Chem.* **1976**, *50*, 1403.
(22) Hoffmann, H., Foerster, H. *Monatsh. Chem.* **1968**, *99*, 380.
(23) Kreutzkamp, N., Storck, K. *Naturwissenschaften* **1960**, *47*, 497.
(24) Wieczorek, J.S., Gancarz, R. *Rocz. Chem.* **1976**, *50*, 2171.
(25) Drauz, K., Koban, H.G., Martens, J., Schwarze, W. *Liebigs Ann. Chem.* **1985**, 448.
(26) Lugovkin, B.P. *Zh. Obshch. Khim.* **1976**, *46*, 2498.
(27) Gartman, G.A., Pak, V.D., Kozlov, N.D. *Zh. Obshch. Khim.* **1979**, *49*, 2375.
(28) Łukszo, J., Tyka, R. *Synthesis* **1977**, 239.
(29) Łukszo, J., Kowalik, J., Mastalerz, P. *Chem. Lett.* **1978**, 1103.
(30) Łukszo, J., Tyka, R. *Pol. J. Chem.* **1978**, *52*, 959.
(31) Łukszo, J., Tyka, R. *Pol. J. Chem.* **1978**, *52*, 321.
(32) It is worthy of note that K_2CO_3 or other bases which may be used as dehydrating agents are strong inhibitors of imine formation.
(33) Some observations indicate that this may be not a simple addition reaction. The presence of dialkyl tritylphosphonates in a few cases suggests a multistep mechanism involving detritylation, addition, tritylation. The mechanism is under investigation.
(34) We have observed in our laboratory that the trityl group is a "crystal maker"; likewise the trimethylsilyl group is known as a "flying" group. See the Tables and note the high melting points of 1-(tritylamino)alkylphosphonic esters and Schiff bases.
(35) Oleksyszyn, J., Subotkowska, L. *Synthesis* **1980**, 906.
(36) Pulwer, M.J., Balthazor, T.M. *Synth. Commun.* **1986**, *16*, 733, and literature cited therein.
(37) Kabachnik, M.I., Medved, T.Y. *Izv. Akad. Nauk SSSR Otd. Khim. Nauk* **1950**, 635.
(38) Asano, S., Kitahara, T., Ogawa, T., Matsui, M. *Agric. Biol. Chem.* **1973**, *37*, 1193.
(39) Tritylamine (triphenylmethylamine) is now commercially available from Lancaster Synthesis Ltd.. We prepare this reagent by stirring solid trityl chloride with an excess of conc. aqueous ammonia for ~ 2 days. Another synthesis of tritylamine is described in Ref. 40.
(40) Mandell, L., Piper, J.U., Pesterfield, C.E. *J. Org. Chem.* **1963**, *28*, 574.