Convenient One-Pot Synthesis of 4-(Dialkylaminobenzyl)triphenylphosphonium Salts – Application to the Synthesis of a Fluorescent Probe for Multiphotonic Imaging of Biological Membranes

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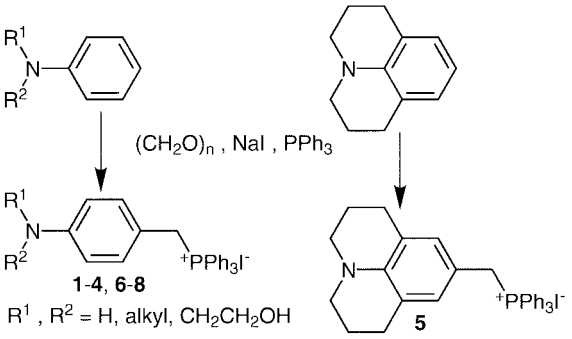
Abstract: An efficient one-pot preparation of (dialkylaminobenzyl)triphenylphosphonium salts directly from dialkylbenzenamine is described. The one-pot procedure proceeds quickly in high yields and allows the synthesis of useful reagents for Wittig reaction. Their potential is illustrated by the synthesis of a bolaamphiphilic fluorophore of interest for biological membrane imaging.

Key words: phosphorus, amines, Wittig reactions, alkenation, fluorescence, conjugation

Wittig-type olefinations[1] are of a wide interest in organic synthesis due to their versatility, flexibility and efficacy in carbon–carbon double bond creation. Implementation of the Wittig reaction beforehand requires the preparation of phosphonium salts, whose synthesis is in most cases required. While working on the synthesis of dipolar and quadrupolar conjugated molecules for applications in the field of molecular nonlinear optics, we required some 4-(dialkylaminobenzyl)triphenylphosphonium halides. These salts have recently been used for the synthesis of molecules with nonlinear optical properties[2,3] and in the preparation of biologically active molecules.[4] We describe here an easy one-pot procedure to produce quickly such phosphonium salts directly from the dialkylbenzenamine starting material.

The synthesis of benzylic type phosphonium salts frequently involves the reaction of triphenyphosphine with benzylic halides. In most cases, this approach requires the synthesis of reactive halides from the corresponding benzylic alcohols.[5] In the case of the dialkylaminobenzyl derivatives, we found it suitable to operate in one-pot conditions because of the inherent reactivity of such halide derivatives. By generating the halide reagent in the presence of the triphenylphosphine, tedious work-up and isolation of sensitive halide derivatives could be omitted. We thus developed a one-pot procedure, which allows their rapid preparation directly from dialkylbenzenamine (Scheme 1). This procedure was inspired by the route proposed by Bredereck and co-workers for the preparation of dimethylaminobenzyltriphenylphosphonium iodide.[6] The experimental protocol involves prolonged reaction time (3 weeks) and we found it was not easily extended to different types of benzenamines. For instance, the reaction did not proceed efficiently in the case of phosphonium salts **6**–**8**.

In order to overcome these limitations, we have developed a quicker and more reliable protocol that can be used to synthesize a number of aminobenzylphosphonium salts (Scheme 1).



Scheme 1

The optimized experimental protocol consists of dissolving a stoichiometric mixture of amine, triphenylphosphine, sodium iodide and solid paraformaldehyde in an HOAc–H_2O–toluene mixture. The heterogeneous reaction mixture is refluxed for several hours until completion of the reaction (monitored by ^{1}H NMR). After easy work-up, the phosphonium salts are obtained as stable salts that can be stored for a long time.

This protocol has been tested with various (aliphatic, cyclic) dialkylbenzenamines (Table 1). The variety of starting materials available opens the route to a broad scope of phosphonium reagents. We observe from Table 1 that the procedure allows easy and efficient preparation. The reaction time depends on the reactivity of the starting amine. We note that refluxing in toluene allows shorter reaction time and/or higher reaction yield than chloroform (see entries 1–9 in Table 1). We also observe that increasing the aliphatic chains requires shorter reaction time, in relation to the increased electron-donating character of the dialkylamino substituent. This facilitates the electrophilic substitution on the phenyl ring (compounds **1** versus **3**,**4** in Table 1). This effect is even more pronounced when using the julolidine cyclic starting amine, which requires the

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Table 1 Preparation of Phosphoniums Salts from Dialkylbenzenamines

Product	R^1	R^2	Time	Reflux (Y/N)	Solvent	Yield (%)
1	Me	Me	3 weeks	N	$CHCl_3$	86[6]
1	Me	Me	62 h	Y	toluene	78
2	Bu	Bu	8 weeks	N	$CHCl_3$	83
2	Bu	Bu	8 h	Y	toluene	84
3	Hex	Hex	3 weeks	N	$CHCl_3$	85
3	Hex	Hex	7 h	Y	toluene	86
4	Oct	Oct	3 weeks	N	$CHCl_3$	85
4	Oct	Oct	24 h	Y	$CHCl_3$	78
5	Julolidine	Julolidine	5 h	Y	toluene	92
6	Et	CH_2CH_2OH	39 h	Y	$CHCl_3$	69
7a	CH_2CH_2OH	CH_2CH_2OH	3 weeks	N	$CHCl_3$	no reaction
7a	CH_2CH_2OH	CH_2CH_2OH	50 h	Y	$CHCl_3$	45
7a	CH_2CH_2OH	CH_2CH_2OH	8 h	Y	toluene	56
8	H	H	30 h	Y	toluene	36

shortest reaction time (compound **5**). In the absence of alkyl chains (compound **8**) much longer reaction time is needed and a lower yield is obtained.

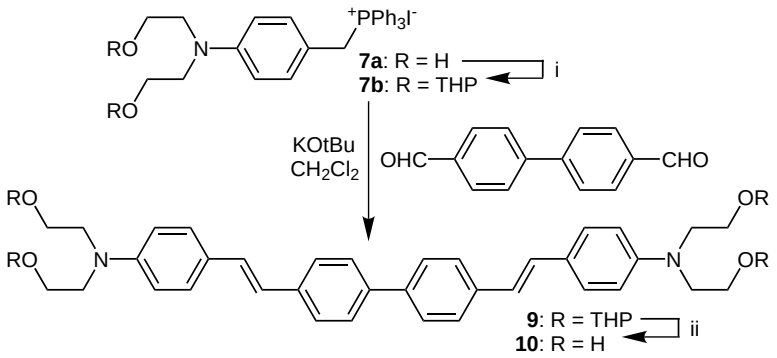
This protocol can be used for the preparation of phosphonium salts bearing primary alcohol end groups. The phosphonium salts **6** and **7a** are of interest for the synthesis of push-pull dipolar chromophores that can be used for the elaboration of electro-optical polymeric materials.[7] We illustrate the use of phosphonium salt **7a** for the synthesis of a bolaamphiphilic fluorophore **10** (Scheme 2) optimized for multiphotonic imaging of lipidic bilayer or cellular membranes.[8]

In summary, we have developed a very simple and efficient synthesis of dialkylaminobenzylphosphonium salts, useful not only in the field of material science but also for the synthesis of molecules for biological applications.

NMR: Bruker ARX 200 (^{1}H: 200.13 MHz, ^{13}C: 50.32 MHz) or AC 300 (^{31}P: 121.50 MHz); ^{1}H chemical shifts (δ) are given in ppm in $CDCl_3$ or DMSO-d_6 solutions, respectively, relative to TMS or to the solvent residual signal at δ = 2.50; *J* values are in Hz; ^{13}C chemical shifts are given relative to the solvent residual signal at δ = 77.0 for $CDCl_3$ solutions or at δ = 39.5 for DMSO-d_6; ^{31}P chemical shifts are referenced to external 85% aqueous H_3PO_4. HRMS measurements were performed at the Centre Regional de Mesures Physiques de l'Ouest, using a Micromass MS/MS ZABSpec TOF instrument with EBE TOF geometry; LSIMS (Liquid Secondary Ion Mass Spectrometry) at 8 kV with Cs^+ in *m*-nitrobenzyl alcohol (mNBA). Elemental analyses were performed at I.C.S.N–C.N.R.S. (Gif-sur-Yvette, France).

Phosphonium Salts; General Method

To a solution of *N*,*N*-dialkylbenzenamine (22 mmol), Ph_3P (5.77 g, 22 mmol) and paraformaldehyde (0.66 g, 7.33 mmol) in $CHCl_3$ or toluene (30 mL) were added NaI (3.30 g, 22 mmol), H_2O (1.56 mL) and HOAc (4.44 mL). The mixture was refluxed for 5–50 h (see Table 1). After addition of H_2O (40 mL), extraction with CH_2Cl_2, washing of the combined organic layers with $NaHCO_3$, then with



Scheme 2 (i) DHP (2.2 equiv), PPTS (0.2 equiv), MeCN, reflux, 40 h, 96%; (ii) aq HCl (10%), CH_2Cl_2–EtOH (7:3), r.t., 90 h, 52%.

H_2O, and drying (Na_2SO_4), the solvent was evaporated. The residue was finally purified by recrystallization from EtOH.

{[4-(Dibutylamino)phenyl]methyl}triphenylphosphonium Iodide (2)
Mp 206–209 °C.

^{1}H NMR ($CDCl_3$): δ = 7.80 and 7.68 (m, 15 H), 6.82 (dd, *J* = 8.5, 1.8, 2 H), 6.37 (d, *J* = 8.5, 2 H), 4.93 (d, *J* = 12.7, 2 H), 3.18 (t, *J* = 7.3, 4 H), 1.48 (m, 4 H), 1.28 (m, 4 H), 0.93 (t, *J* = 7.1, 6 H).

^{13}C NMR ($CDCl_3$): δ = 148.0 (d, *J* = 1.9), 134.9 (d, *J* = 2.8), 134.2 (d, *J* = 9.6), 132.0 (d, *J* = 4.9), 130.0 (d, *J* = 12.3), 117.7 (d, *J* = 84.8), 111.5, 110.6 (d, *J* = 7.9), 50.4, 30.5 (d, *J* = 46.7), 29.0, 20.4, 13.5.

^{31}P NMR ($CDCl_3$): δ = 20.9.

Anal. Calcd for $C_{33}H_{39}INP$ (607.56): C, 65.24; H, 6.47; I, 20.89; N, 2.31; P, 5.10. Found: C, 65.01; H, 6.62; I, 20.73; N, 2.32; P, 5.28.

{[4-(Dihexylamino)phenyl]methyl}triphenylphosphonium Iodide (3)
Mp 147–148 °C.

^{1}H NMR ($CDCl_3$): δ = 7.80 and 7.66 (m, 15 H), 6.80 (dd, *J* = 8.5, 2.1, 2 H), 6.37 (d, *J* = 8.5, 2 H), 4.85 (d, *J* = 12.7, 2 H), 3.17 (t, *J* = 7.3, 4 H), 1.50 (m, 4 H), 1.29 (m, 12 H), 0.89 (t, *J* = 7.1, 6 H).

^{13}C NMR ($CDCl_3$): δ = 148.0 (d, *J* = 2.5), 134.9 (d, *J* = 2.9), 134.2 (d, *J* = 9.5), 132.0 (d, *J* = 5.1), 130.0 (d, *J* = 12.3), 117.7 (d, *J* = 85.0), 111.6, 110.6 (d, *J* = 8.7), 50.7, 31.5, 30.6 (d, *J* = 46.3), 26.9, 26.6, 22.5, 13.9.

^{31}P NMR: ($CDCl_3$): δ = 20.95.

Anal. Calcd for $C_{37}H_{47}INP$ (663.67): C, 66.96; H, 7.14; N, 2.11. Found: C, 66.97; H, 7.14; N, 2.21.

{[4-(Dioctylamino)phenyl]methyl}triphenylphosphonium Iodide (4)
Mp 147–149 °C.

^{1}H NMR ($CDCl_3$): δ = 7.79 and 7.66 (m, 15 H), 6.80 (dd, *J* = 8.6, 2.1, 2 H), 6.36 (d, *J* = 8.6, 2 H), 4.86 (d, *J* = 12.6, 2 H), 3.17 (t, *J* = 7.4, 4 H), 1.49 (m, 4 H), 1.27 (m, 20 H), 0.88 (t, *J* = 6.4, 6 H).

^{13}C NMR ($CDCl_3$): δ = 146.6 (d, *J* = 2.3), 133.7, 133.0 (d, *J* = 9.9), 130.9 (d, *J* = 4.3), 128.9 (d, *J* = 12.4), 116.4 (d, *J* = 85.0), 110.2, 109.7 (d, *J* = 9.0), 49.5, 30.4, 29.0 (d, *J* = 45.3), 28.0, 27.9, 25.7, 21.3, 12.8.

^{31}P NMR (121.50 MHz, $CDCl_3$): δ = 21.04.

Anal. Calcd for $C_{41}H_{55}INP$ (719.78): C, 68.42; H, 7.70; N, 1.94. Found: C, 68.42; H, 7.71; N, 1.90.

Triphenyl[(2,3,6,7-tetrahydro-1*H*,5*H*-benzo[ij]quinolizin-9-yl)methyl]phosphonium Iodide (5)
Mp 185–189 °C.

^{1}H NMR ($CDCl_3$): δ = 7.80 and 7.63 (m, 15 H), 6.25 (d, *J* = 2.6, 2 H), 4.65 (d, *J* = 12.6, 2 H), 3.09 (t, *J* = 5.5, 4 H), 2.44 (t, *J* = 6.2, 4 H), 1.83 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 142.7, 135.0 (d, *J* = 2.9), 134.2 (d, *J* = 9.9), 130.0 (d, *J* = 12.3), 129.5 (d, *J* = 5.3), 121.6, 117.6 (d, *J* = 85.0), 110.3, 49.6, 31.0 (d, *J* = 46.4), 27.2, 21.4.

^{31}P NMR ($CDCl_3$): δ = 20.60.

HRMS: *m*/*z* calcd for $C_{31}H_{31}NP$ (M^+·): 448.2194, found: 448.2193.

{[4-[Ethyl(2-hydroxyethyl)amino]phenyl]methyl}triphenylphosphonium Iodide (6)
Mp 165–170 °C.

^{1}H NMR ($CDCl_3$): δ = 7.78 and 7.61 (m, 15 H), 6.75 (dd, *J* = 8.9, 2.4, 2 H), 6.46 (d, *J* = 8.7, 2 H), 4.78 (d, *J* = 12.8, 2 H), 3.68 (m, 2 H), 3.38 (m, 2 H), 3.31 (t, *J* = 7.0, 2 H), 2.61 (m, 1 H), 1.04 (t, *J* = 7.0, 3 H).

^{13}C NMR ($CDCl_3$): δ = 147.3 (d, *J* = 2.6), 134.4 (d, *J* = 2.3), 133.3 (d, *J* = 9.6), 131.8 (d, *J* = 5.1), 129.5 (d, *J* = 12.3), 115.3 (d, *J* = 85.0), 111.4, 110.3 (d, *J* = 8.7), 58.1, 51.4, 44.4, 29.8 (d, *J* = 46.3), 11.2.

HRMS: *m*/*z* calcd for $C_{29}H_{31}NOP$ (M^+·): 440.2143, found: 440.2138.

({4-[Bis(2-hydroxyethyl)amino]phenyl}methyl)triphenylphosphonium Iodide (7a)
Mp 175–180 °C.

^{1}H NMR (DMSO-d_6): δ = 7.90 and 7.69 (m, 15 H), 6.71 (dd, *J* = 8.6, 1.9, 2 H), 6.50 (d, *J* = 8.8, 2 H), 4.97 (d, *J* = 14.5, 2 H), 4.70 (t, *J* = 5.2, 2 H), 3.45 (t, *J* = 5.1, 4 H), 3.34 (m, 4 H).

^{13}C NMR (DMSO-d_6): δ = 147.5 (d, *J* = 2.6), 134.7 (d, *J* = 2.5), 133.8 (d, *J* = 9.7), 131.3 (d, *J* = 5.2), 129.6 (d, *J* = 12.3), 118.0 (d, *J* = 84.7), 111.9 (d, *J* = 8.8), 111.0, 57.7, 52.8, 27.4 (d, *J* = 45.8).

^{31}P NMR (DMSO-d_6): δ = 22.14.

HRMS: *m*/*z* calcd for $C_{29}H_{31}NO_2P$ (M^+·): 456.2092, found: 456.2084.

2,2′,2″,2‴-{[(1,1′-Biphenyl)-4,4′-diyl-(1*E*)-2,1-ethenediyl]dinitrilo}tetrakisethanol (10)
To a solution of **7b** (1.654 g, 2.2 mmol) and (1,1′-biphenyl)-4,4′-dicarboxaldehyde (210 mg, 1 mmol) in anhyd CH_2Cl_2 (15 mL) was added *t*-BuOK (370 mg, 3.3 mmol). The mixture was stirred at r.t. for 5 h. After filtration through Celite, the solvent was evaporated. The crude compound was isomerized in Et_2O–CH_2Cl_2 (7:2; 9 mL), with a catalytic amount of I_2, at r.t. for 4 h under light exposure (75 W lamp). The organic layer was washed with aq $Na_2S_2O_3$ and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography (CH_2Cl_2–EtOAC, gradient from 100:0 to 98:2) to yield **9**.

Yield: 1.586 g (80%).

^{1}H NMR ($CDCl_3$): δ = 7.61 and 7.54 (AA′XX′, J_{AX} = 8.7, 8 H), 7.41 and 6.75 (AA′XX′, J_{AX} = 8.9, 8 H), 7.08 (d, *J* = 15.8, 2 H), 6.92 (d, *J* = 16.2, 2 H), 4.61 (m, 4 H), 3.87 (m, 8 H), 3.70–3.47 (m, 16 H), 1.55 (m, 24 H).

HRMS: *m*/*z* calcd for $C_{56}H_{72}N_2O_8$ (M^+·): 900.5289, found: 900.5289.

Product **9** was dissolved in EtOH–CH_2Cl_2 (3:7; 10 mL) and aq HCl (10%; 1 mL) was added. After stirring for 90 h at r.t., the residue was filtered and washed with H_2O and EtOH to yield **10**.

Yield: 517 mg (52%); mp >250 °C.

^{1}H NMR (DMSO-d_6): δ = 7.67 and 7.59 (AA′XX′, J_{AX} = 8.2, 8 H), 7.41 and 6.70 (AA′XX′, J_{AX} = 8.3, 8 H), 7.16 (d, *J* = 16.2, 2 H), 6.96 (d, *J* = 16.2, 2 H), 4.74 (m, 4 H), 3.55 (m, 8 H), 3.31 (m, 8 H).

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