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Synthesis of 2-(N-disubstituted amino)ethyltriphenylphosphonium bromides

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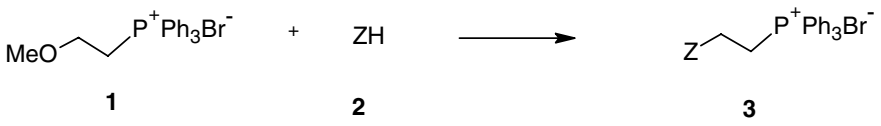
Abstract

2-(N-Disubstituted amino)ethyltriphenylphosphonium bromides are prepared in quantitative yields with high purity by reacting secondary amines with 2-methoxyethyltriphenylphosphonium bromide under aqueous conditions. The differential reactivity of this reagent offers advantages for the preparation of aminoethyltriphenylphosphonium bromides possessing nucleophiles such as hydroxy groups.

Keywords: Phosphonium salts; Ylides; Phosphonioethylation; Displacement reaction; Nucleophile

Phosphonium salts are reagents used in the preparation of ylides for olefin synthesis. The advantage of the Wittig reaction is its versatility in preparing olefins without affecting other functional groups such as hydroxy, halo and carboxylic acid esters, present either in carbonyl compounds or in ylides. 2-(N-Disubstituted amino)ethyltriphenylphosphonium bromides are important intermediates in the synthesis of various active pharmaceuticals such as acrivastine,[1] pyrrobutamine,[2] triprolidine[3] and zimeldine.[4] During the process development of acrivastine and triprolidine we required an efficient and practical method for making 2-(*N*-pyrrolidino)ethyltriphenylphosphonium bromide (**3e**). Though there are several methods[5–8] available for the preparation of **3e**, most suffer from one or more drawbacks. The task of improving the method for the preparation of compound **3e** resulted in the discovery of the differential reactivity of 2-methoxyethyltriphenylphosphonium bromide (**1**) towards nucleophiles having displaceable hydrogen (Scheme 1).

Conventional methods[9] for the preparation of phosphonium salts involve reacting alkyl halides with trialkyl/triaryl phosphines at elevated temperature in aprotic solvents. Since 2-substituted amino ethyl halides are unstable, many alternative routes have been used to prepare 2-(N-disubstituted amino)ethylphosphonium salts. Keough and Grayson[5] first reported the phosphonioethylation reaction, which involves Michael addition of secondary amines to vinylphosphonium salts. Subsequently, Schweitzer[6] and other groups[7] have reported displacement of the phenoxy group of 2-phenoxyethyltriphenylphosphonium



1 **2** **3**

Scheme 1.

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Table 1
Synthesis of 2-(N-disubstituted amino)ethyltriphenylphosphonium bromides from compound **1**

ZH	Product	Solvent	% Yield[a]	Mp
Dimethylamine	**3a**	Water	95	200–202 (204–205)[b]
Diethylamine	**3b**	Water	94	176–178 (180)[b]
Diisopropylamine	**3c**	Water	94	194–195
Diethanolamine	**3d**	Water	88	154–155
Pyrrolidine	**3e**	Water	97	188–190 (190)[b]
Piperidine	**3f**	Water	93	185–187 (189–190)[b]
Morpholine	**3g**	Water	95	184–187 (181–185)[b]
N-Methyl piperazine	**3h**	Water	89	—
N-Hydroxyethyl piperazine	**3i**	Water	95	195–198
Proline methyl ester	—	Aqueous methanol	No product	—
Sarcosine methyl ester	—	Aqueous methanol	No product	—
N-Methylaniline	—	Aqueous methanol	No product	—
Diphenylamine	—	Aqueous methanol	No product	—
Thiophenol	—	Aqueous methanol	No product	—

[a] Isolated yields.
[b] Reported mp values.

bromide with nucleophiles such as secondary amines to give the title compounds. The above reagents are highly reactive, require anhydrous conditions and aprotic solvents and have no selectivity towards nucleophiles. Moreover, these reagents are highly unstable and their preparation involves multi-step sequences and the use of phenol.

The method reported by Adrian and Thomas[8] involves reaction of 2-substituted aminoethanol with triphenylphosphine hydrobromide at elevated temperature. Though the above reaction is fairly simple, preparation of the amino alcohol and the high temperature conditions are disadvantages and this reaction is not suitable for the preparation of phosphonium salts containing hydroxy groups. Herein, we report the first efficient synthesis of 2-(N-disubstituted amino)ethyltriphenylphosphonium bromide by reaction of secondary amines with 2-methoxyethyltriphenylphosphonium bromide either in water or in alcohols such as methanol and isopropanol. Further, compound **1** can be prepared easily in a single step from commercially available methoxyethanol, which is highly stable and gives pure products in high yields when reacted with secondary amines.

Compound **1** was prepared[10,11] in high yield by refluxing 2-methoxyethyl bromide with triphenylphosphine in toluene. This compound is highly stable even on heating in water at reflux for several hours. Phosphonium salts **3a**–**i** were prepared[12–20] by reacting **1** with secondary amines in water at around 60 °C (Table 1). Reactions of **1** with water insoluble amines were attempted either in aqueous methanol or in methanol itself but without success. The work-up procedure involved evaporation of the solvent and precipitation of the product using acetone or ethyl acetate. The obtained products were highly pure and could be used in synthesis without further purification. In contrast, when phenoxyethyltriphenylphosphonium bromide was used for the preparation of **3e**, we obtained an impure product in less than 60% yield compared to 97% using compound **1**.

When compound **1** was reacted with N-substituted anilines or α-amino acid esters such as proline methyl ester or sarcosine methyl ester, no product was observed. The methoxy group could not be displaced with thiols such as thiophenol or butanethiol. From the above we can conclude that weaker nucleophiles such as thiols and secondary amines, whose lone pair is in conjugation with electron withdrawing groups like phenyl and carbonyl, cannot displace the methoxy group of **1**. Hence compound **1** can be used for the preparation of a variety of 2-(N-disubstituted amino)ethyltriphenylphosphonium bromides possessing other weaker nucleophiles. Displacement of the methoxy group with a secondary amine perhaps occurs via an S_N2 type mechanism rather than through a vinylic intermediate, which is believed to be formed in the case of phenoxyethyl triphenylphosphonium bromide. The above hypothesis is supported by the fact that no impurities or by-products were formed when amino displacement reactions were carried out under aqueous conditions.

In conclusion, a general and expedient synthesis of substituted aminoethyltriphenylphosphonium bromides containing nucleophiles such as hydroxy groups (**3d** and **3i**) from compound **1** has been achieved with high purity and excellent yields. The ready availability of starting materials distinguishes this route from other literature methods. Further, these reactions can be performed under aqueous conditions and we believe that this protocol will be useful for synthesising phosphonium salt scaffolds for preparing a variety of Wittig products.

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11. *(2-Methoxyethyl)triphenylphosphonium bromide* (**1**): Compound **1** was obtained by refluxing triphenylphosphine (300 g, 1.14 mol) and 2-methoxyethyl bromide (200 g, 1.43 mol) in toluene (1 L) for 24 h. The reaction was then cooled to 30 °C and filtered to afford a white solid (450 g, 98%); mp 210–214 °C (lit.[10] mp 216 °C); IR (KBr) ν_{max} 3051, 2958, 2877, 2785, 1585, 1481, 1434, 1411, 1377, 1303, 1288, 1153, 1110, 995 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.04 (3H, s), 3.78 (1H, t, $J = 5.6$ Hz), 3.90 (1H, t, $J = 5.6$ Hz), 4.11 (1H, t, $J = 5.6$ Hz), 4.16 (1H, t, $J = 5.6$ Hz), 7.74 (15H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.38, 25.43, 58.17, 64.89, 65.03, 117.52, 119.25, 129.54, 129.79, 133.32, 133.52, 134.29.
12. *[2-(Dimethylamino)ethyl]triphenylphosphonium bromide* (**3a**): Compound **1** (5 g, 12.5 mmol), 40% solution of dimethylamine (3.0 mL, 26.6 mmol). Product (4.9 g, 95% yield): IR (KBr) ν_{max} 2777, 1581, 1434, 1230, 1157, 1107, 1049, 995 cm^{-1}; ^1H NMR (D_2O, 200 MHz) δ 2.31 (6H, s), 2.77 (2H, m), 3.57 (2H, m), 7.85 (15H, m); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.52, 24.54, 45.42, 52.65, 52.73, 118.32, 120.04, 130.49, 130.74, 134.16, 134.36, 135.13.
13. *[2-(Diethylamino)ethyl]triphenylphosphonium bromide* (**3b**): Compound **1** (5 g, 12.5 mmol), diethylamine (2.0 g, 27.3 mmol). Product (5.2 g, 94% yield): IR (KBr) ν_{max} 3047, 3004, 2858, 2758, 1585, 1477, 1434, 1380, 1311, 1238, 1158, 1107, 1068, 1029, 991 cm^{-1}; ^1H NMR (D_2O, 200 MHz) δ 0.95 (6H, t, $J = 6.8$ Hz), 2.60 (4H, m), 2.98 (2H, m), 3.48 (2H, m), 7.32 (15H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.96, 22.87, 23.86, 45.98, 46.88, 118.25, 119.96, 130.53, 130.78, 134.21, 134.41, 135.24.
14. *[2-(Diisopropylamino)ethyl]triphenylphosphonium bromide* (**3c**): Compound **1** (5 g, 12.5 mmol), diisopropylamine (2.7 g, 26.7 mmol). Product (5.5 g, 94% yield): IR (KBr) ν_{max} 2962, 2858, 1585, 1434, 1330, 1299, 1107, 1087, 991 cm^{-1}; ^1H NMR (D_2O 200 MHz) δ 0.93 (12H, d, $J = 6.0$ Hz), 3.39 (2H, h, $J = 6.0$ Hz), 3.59 (1H, t, $J = 6.0$ Hz), 3.66 (1H, t, $J = 6.0$ Hz), 3.83 (1H, t, $J = 6.0$ Hz), 3.93 (1H, t, $J = 6.0$ Hz), 7.79 (15H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.97, 24.84, 25.89, 60.47, 60.62, 71.88, 117.84, 119.57, 129.45, 129.70, 133.48, 133.68, 134.23.
15. *[2-(Bishydroxyethyl)aminoethyl]triphenylphosphonium bromide* (**3d**): Compound **1** (5 g, 12.5 mmol), diethanolamine (1.5 g, 14.2 mmol). Product (5.3 g, 88% yield): IR (KBr) ν_{max} 3363, 3120, 2862, 1581, 1434, 1315, 1110, 1022, 991, 952 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.76 (4H, t, $J = 5.8$ Hz), 3.06 (2H, m), 3.45 (2H, m), 3.60 (4H, t, $J = 5.8$ Hz), 7.65 (15H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.83, 21.76, 47.85, 56.12, 59.30, 116.99, 118.70, 130.03, 130.28, 133.14, 133.34, 134.69. Anal. Calcd for $C_{24}H_{29}BrNPO_2$: C, 60.76; H, 6.16; N, 2.95. Found: C, 60.71; H, 6.06; N, 3.12.
16. *[2-(N-Pyrrolidino)ethyl]triphenylphosphonium bromide* (**3e**): Compound **1** (450 g, 1.12 mol) was reacted with pyrrolidine (87.0 g, 1.22 mol) in water (200 mL) at 60 °C for 2 h. The water was evaporated under reduced pressure and the solid obtained was suspended in acetone (1 L), then cooled to 10 °C and filtered to obtain the product (480 g, 97%): IR (KBr) ν_{max} 2860, 2842, 1585, 1485, 1434, 1110, 995 cm^{-1}; ^1H NMR (D_2O, 200 MHz) δ 1.67 (4H, s), 2.46 (4H, s), 2.79 (2H, m), 3.41 (2H, m), 7.68 (15H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.96, 23.73, 24.75, 48.32, 53.22, 117.60, 119.31, 129.62, 129.87, 133.39, 133.59, 134.25.
17. *[2-(N-Piperidino)ethyl]triphenylphosphonium bromide* (**3f**): Compound **1** (5 g, 12.5 mmol), piperidine (1.2 g, 14.1 mmol). Product (5.3 g, 93% yield): IR (KBr) ν_{max} 3047, 3004, 2858, 2758, 1585, 1477, 1434, 1380, 1311, 1238, 1157, 1107, 1068, 1029, 991 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.19 (2H, s), 1.21 (4H, s), 2.27 (4H, s), 2.68 (1H, t, $J = 6.2$ Hz), 2.79 (1H, t, $J = 6.2$ Hz), 3.98 (1H, t, $J = 6.2$ Hz), 4.04 (1H, t, $J = 6.2$ Hz), 7.74 (15H, m);^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.71, 22.14, 23.16, 24.92, 51.44, 53.87, 117.77, 119.49, 129.56, 129.81, 133,37, 133.57, 134.15.
18. *[2-(N-Morpholino)ethyl]triphenylphosphonium bromide* (**3g**): Compound **1** (5 g, 12.5 mmol), morpholine (1.2 g, 13.8 mmol). Product (5.4 g, 95% yield): IR (KBr) ν_{max} 3502, 3433, 3055, 2859, 2808, 2758, 1585, 1434, 1303, 1272, 1230, 1107, 1064, 1026, 995 cm^{-1}; ^1H NMR (D_2O, 200 MHz) δ 2.40 (4H, br s), 2.72 (2H, m), 3.44 (2H, m), 3.89 (4H, m), 7.70 (15H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.75, 22.77, 45.85, 51.20, 53.06, 65.95, 67.38, 117.59, 119.30, 129.67, 129.92, 133.31, 133.51, 134.32.
19. *{2-[N-(N′-Methyl)piperizino]ethyl}triphenylphosphonium bromide* (**3h**): Compound **1** (5 g, 12.5 mmol), *N*-methylpiperazine (1.4 g, 14.0 mmol). Product (5.2 g, 89% yield): IR (KBr) ν_{max} 3409, 2796, 2680, 1585, 1438, 1404, 1284, 1110, 991 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.15 (3H, s), 2.41 (8H, s), 2.72 (1H, t, $J = 6.2$ Hz), 2.83 (1H, t, $J = 6.2$ Hz), 4.09 (1H, t, $J = 6.2$ Hz), 4.15 (1H, t, $J = 6.2$ Hz), 7.74 (15H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.96, 22.98, 45.42, 50.63, 52.41, 54.05, 117.57, 119.29, 129.69, 129.95, 133.35, 133.55, 134.34.
20. *{2-[N-(N′-Hydroxyethyl)piperazino]ethyl}triphenylphosphonium bromide* (**3i**): Compound **1** (5 g, 12.5 mmol), *N*-(2-hydroxyethyl)piperazine (1.8 g, 13.8 mmol). Product (5.9 g, 95% yield): IR (KBr) ν_{max} 3282, 2761, 1434, 1157, 1107, 1033, 995 cm^{-1}; ^1H NMR (D_2O, 200 MHz) δ 2.57 (10H, m), 2.84 (2H, m), 3.60 (2H, m), 3.73 (2H, t, $J = 6.0$ Hz), 7.83 (15H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.80, 23.82, 51.59, 52.77, 53.39, 58.21, 59.68, 118.44, 120.15, 130.52, 130.77, 134.19, 134.39, 135.16. Anal. Calcd for $C_{26}H_{32}BrN_2PO$: C, 62.52; H, 6.45; N, 5.61. Found: C, 62.06; H, 6.36; N, 5.64.