2,3-Bis[triphenylphosphoniomethyl]piperazine; Precursor of a New Heterocyclic Bis-Wittig Reagent

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The piperazine-bisphosphonium salt **2** is prepared by addition of ethylenediamine to the 1,4-butadienylene-bisphosphonium salt **1**; the Wittig reaction of its corresponding bis-ylid provides a new route to 2,3-divinylpiperazines **3**.

The piperazine ring is a part of numerous biologically active compounds[1]. However, vinyl *C*-substituted piperazines are not common. We describe here an easy synthesis of the bisphosphonium salt **2**, precursor of a bis-Wittig reagent which affords on reaction with aldehydes the new 2,3-divinylpiperazines **3**.

The unsaturated bisphosphonium salt **1**[2] undergoes double addition[3,4,5] of ethylenediamine leading to the bisphosphonium salt **2** containing the piperazine ring. Reaction of the salt **2** with two equivalents of potassium *t*-butoxide gives the corresponding bis-ylid which reacts with alkyl, aryl, or α,β-

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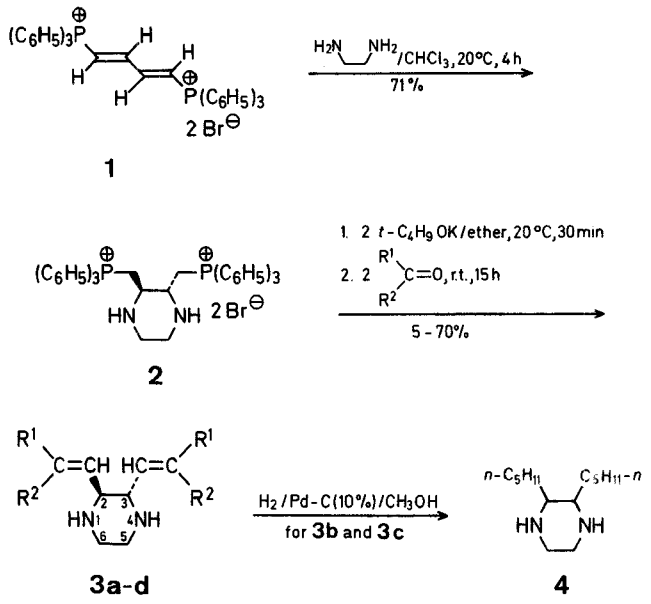

unsaturated aldehydes to afford the substituted piperazines **3a–c** in acceptable overall yields (Table 1). These piperazines were isolated by acid/base extractions, and then characterized as their dihydrochloride or their dihydrobromide salts, excepting compound **3c** which appeared to be unstable in acidic medium. The structures of compounds **3c** and **3b** (*Z,E*)-, which could not be crystallized, were ascertained by hydrogenation over palladium on charcoal to the same 2,3-dipentylpiperazine **4**.

The stereochemistry of the double bonds in compounds **3a** and **3b** was determined by ^{1}H-N.M.R. ($^3J_{H\text{-}H}$-*trans* = 16 Hz, $^3J_{H\text{-}H}$-*cis* = 11 Hz) and ^{13}C-N.M.R. (*cis* allylic carbons are shifted approximately 5 ppm downfield by *γ-cis*-effect, Table 2)[6]. The (*E*)-selectivity of the bis-Wittig reaction with benzaldehyde, not common for a non-stabilized ylid[7,8], is certainly due to the *β*-amino group and may be ascribed either to steric factors[7] or to its protic character[8]. Such a selectivity has already been noticed for Wittig reactions of *β*-aminophosphonium ylids[9,10].

The *trans* stereochemistry of the piperazine substituents in compounds **2** and **3** has been determined from the value of the $^3J_{2-H,3-H}$ coupling constant, available from the unsymmetrical compound **3a** (*Z,E*)-; the observed value of 10 Hz is consistent with *trans*-diaxial coupling, corresponding to *trans*-diequatorial substituents.

In the reported Wittig reactions of other *β*-aminophosphonium salts[9-11], the reactivity of the bis-ylid towards ketones is weak; the product of the bis-Wittig reaction with acetone is obtained in very low yield (5%).

***trans*-2,3-Bis[triphenylphosphoniomethyl]piperazine Dibromide (2):** To a well stirred suspension of **1** (49 g, 67 mmol) in anhydrous chloroform (500 ml), ethylenediamine (4.4 g, 73 mmol) in anhydrous chloroform (50 ml) is added dropwise at 20 °C. The mixture soon becomes homogeneous and is then stirred for 4 h more at 20 °C. The resultant solution is concentrated to 100 ml under vacuum, and then added dropwise with stirring to ether (1 l). The precipitate collected by filtration is recrystallized from chloroform/methanol/ethyl acetate (30/5/65) to give pure **2** as white crystals; yield: 38 g (71%); m.p. 260–261 °C. This is dissolved in a minimum amount of chloro-

Table 1. 2,3-Disubstituted Piperazines **3** prepared

Product No.	R^1	R^2	Yield[a] [%]	Recrystallized[b] product [Yield %]	Molecular Formula[c]	^{1}H-N.M.R. (Solvent/TMS)[d] δ [ppm]
3a	C_6H_5	H	57	**3a** (*E,E*)- [29]	$C_{20}H_{24}Br_2N_2$ (452.2)	DMSO-d_6: 3.3–3.9 (m, 4H, N—CH_2—); 4.3–4.6 (m, 2H, N—CH—); 6.28 (br. d, 2H, J = 16 Hz, W 1/2 = 25 Hz, C—CH=C); 7.08 (d, 2H, J = 16 Hz, C_6H_5—CH=C); 7.2–7.6 (m, 10H, C_6H_5); 9.80 (br. s, 4H, NH_2^+)
				3a (*Z,E*)- [27]	$C_{20}H_{24}Br_2N_2$ (452.2)	DMSO-d_6: 3.3–3.9 (m, 4H, N—CH_2); 4.42 (t, 1H, J = 10 Hz, N—CH); 4.92 (t, J = 10 Hz, 1H, N—CH); 5.78 (t, 1H, J = 10 Hz, C—CH=C (*Z*)-); 5.95 (dd, J = 16 and 10 Hz, 1H, C—CH=C (*E*)-); 6.91 (d, J = 16 Hz, 1H, C_6H_5—CH=C (*E*)-); 6.95 (d, J = 10 Hz, 1H, C_6H_5—CH=C (*Z*)-); 7.2–7.5 (m, 10H, C_6H_5); 8.95 (br. s, 4H, NH_2^+)
3b	n-C_3H_7	H	65	**3b** (*Z,Z*)- [28]	$C_{14}H_{28}Cl_2N_2$ (295.3)	$CDCl_3$: 0.9 (t, J = 6.9 Hz, 6H, CH_3); 1.42 (sextet, J = 6.9 Hz, 4H, CH_2—CH_3); 2.12 (q, J = 6.9 Hz, 4H, CH_2—C=C); 3.3–3.7 (m, 4H, N—CH_2); 4.2–4.7 (m, 2H, N—CH); 5.1–6.1 (m, 4H, CH=C)[e]; 10.40 (br. s, 4H, NH_2^+)
3c	CH_3—CH=CH	H	70	–		$CDCl_3$: 1.65 (d, J = 6 Hz, 6H, CH_3); 2.0–2.3 (m, 2H, NH); 2.6–3.1 (m, 4H, N—CH_2); 3.1–3.7 (m, 2H, N—CH); 4.7–6.6 (m, 8H, CH=C)
3d	CH_3	CH_3	5	**3d** [5]	$C_{12}H_{24}Cl_2N_2$ (267.2)	CD_3OD: 1.80 (br. s, 12H, CH_3); 3.7 (s, 4H, N—CH_2); 4.3–4.6 (m, 2H, N—CH); 4.95 (br. s, 4H, NH_2^+); 5.0–5.4 (m, 2H, CH=C)

[a] Overall yield of mixture of stereoisomeres.
[b] Recrystallized dihydrochloride or dihydrobromide salts. The m.p.'s of all salts are higher than 300 °C. Solvents: **3a** (*E,E*)-methanol; others methanol/ethyl acetate (30/70).
[c] Satisfactory microanalyses obtained: C ±0.17, H ±0.45, N ±0.35.
[d] Recorded on a Varian HA 100 **(3a)** and Varian EM 360 spectrometers **(3b–d)**.
[e] Irradiation at δ = 2.12 ppm produces a doublet (J = 11 Hz) at 5.68 ppm.

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Table 2. ^{13}C-N.M.R. Data of Dihydrochloride or Dihydrobromide Salts of Compounds **3** and **4**, δ [ppm]

Product No.	Solvent	C-2/C-3	C-5/C-6	C=C		$-CH_2-$		$-CH_3$
3a (*E,E*)-	DMSO-d_6	56.8	–[a]	119.8	134.8[b]	–		–
3a (*Z,E*)-	DMSO-d_6	57.2	–[a]	119.1	134.6[b]	–		–
		52.5		121.1	134.7			
3b (*Z,Z*)-	D_2O	56.2	42.6	145.6	120.7	32.5	24.3	15.8
3b (*Z,E*)- + (*Z,Z*)-	D_2O	56.2	42.6	145.6	120.7	32.5	24.3	15.8
		55.9		145.4	121.1	32.6	24.6	15.6
		61.1		146.6	121.8	36.7		
3c[c]	$CDCl_3$	58.0	45.8	126.4–132.5 (m)		–		18.0
		52.4						
3d	D_2O	57.5	42.5	149.6	115.9	–		27.6
								20.8
4	D_2O	59.3	43.0	–		25.7	24.1	15.9
						31.4		
						33.2		

[a] Signals overlapped by solvent peaks.
[b] Signals for aromatics carbons: 138.6, 128.7, 126.6 (**3a**; *E,E*-) and 138.0, 137.8, 128.5, 128.4, 128.1, 126.5 (**3a**; *Z,E*-).
[c] Spectrum of the diamine is given.

form and precipitated again with ether in order to remove traces of crystallization solvents. The white powder obtained by filtration is dried for 48 h over phosphorus pentoxide under vacuum at 100 °C and can be kept stable several months under nitrogen atmosphere.

$C_{42}H_{42}Br_2N_2P_2$ (796.6) calc. C 63.30 H 5.31 N 3.52
found 63.2 5.4 3.5

^{1}H-N.M.R. ($CDCl_3/CD_3OD$/TMS): δ = 2.1–2.8 (m, 4 H); 2.9–3.4 (m, 2 H); 3.90 (br. d, 4 H, J = 12 Hz, W 1/2 = 18 Hz); 4.65 (s, 2 H); 7.5–8.2 ppm (m, 30 H).

^{31}P-N.M.R. ($CH_3OH/H_3PO_{4\ ext.}$); δ = 24.7 ppm.

^{13}C-N.M.R. ($CDCl_3/CD_3OD$/TMS): δ = 27.8 (d, $^1J_{P-C}$ = 51.7 Hz, C—P); 45.5 (s, N—CH_2); 56.0 (dd, $^2J_{P-C}$ = 5.5, $^3J_{P-C}$ = 15.0 Hz, N—CH—C—P); 120.0 (d, $^1J_{P-C}$ = 86.9 Hz, P—C_{arom}); 129.9 (d, $^3J_{P-C}$ = 12.1, *m*-C_{arom}) 134.1 (d, $^4J_{P-C}$ = 2.2 Hz, *p*-C_{arom}); 134.1 ppm (d, $^2J_{P-C}$ = 9.9 Hz, *o*-C_{arom}).

2,3-Disubstituted Piperazines 3; General procedure:

To a well stirred suspension of freshly sublimed potassium *t*-butoxide (840 mg, 7.5 mmol) in anhydrous ether (100 ml) under nitrogen, the bisphosphonium salt **2** (2.95 g, 3.7 mmol) is added portionwise. The mixture rapidly becomes bright yellow. After stirring for 30 min at 20 °C, the addition of freshly distilled carbonyl compound (7.5 mmol) produces a rapid decoloration of the reaction mixture (except in the case of acetone). After 15 h stirring at room temperature, (7 days when acetone is used), the mixture is hydrolyzed with 1 normal hydrochloric acid (20 ml). The extraction of aqueous layer with ether (3 × 20 ml) affords 1.65 to 1.80 g of triphenylphosphineoxide (80–87%). Basification of aqueous layer to pH = 10 with 10% aqueous potassium carbonate solution followed by extraction with ether (4 × 50 ml) provides, after drying with potassium carbonate and solvent evaporation under vacuum, the substituted piperazines **3**. Excepting compound **3c**, these are dissolved in a minimum amount of methanol and added dropwise to a well stirred saturated ether solution (200 ml) of hydrogen chloride or hydrogen bromide. The resulting precipitate is then collected by filtration and recrystallized (Table 1).

2,3-Dipentylpiperazine (4):

Unsaturated piperazine **3b** or **3c** (1.5 mmol) is dissolved in methanol (50 ml). After addition of 10% palladium on charcoal (500 mg), the mixture is hydrogenated at atmospheric pressure and room temperature until consumption of hydrogen stops. The mixture is filtered, the filtrate is evaporated to 10 ml and added dropwise to a well stirred saturated ether solution (100 ml) of hydrogen chloride. The resulting precipitate is then collected by filtration and identified as **4** by means of ^{13}C-N.M.R. (Table 2); m.p. > 300 °C.

$C_{14}H_{32}Cl_2N_2 \cdot 0.5\ CH_3OH$ (299.3) calc. C 55.27 H 10.86 N 8.91
found 55.23 10.73 9.29

^{1}H-N.M.R. (DMSO-d_6/TMS): δ = 0.7–2.0 (m, 22 H); 3.4 (br. s, 6 H, CH—N); 3.7–4.4 ppm (m, 4 H, $NH_2^{\oplus}$).

Received: February 2, 1985

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