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Chemoselective ring opening of benzoxazaphosphinines

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ABSTRACT

Cyclization of 2-[(4-chloroanilino)methyl]phenol (**1**) with thiophosphoryl chloride afforded 2-chloro-3-(4-chlorophenyl)-3,4-dihydro-2*H*-1,3,2λ^5-benzoxazaphosphinine-2-thione (**2**). Reaction of **2** with various heterocyclic amines (**3**) in the presence of Et_3N/NaH gave 3-(4-chlorophenyl)-2-nitrogen heterocyclic substituted-3,4-dihydro-2*H*-1,3,2λ^5-benzoxaza-phosphinine-2-thiones (**4**). Further reaction of **4** with the *N*-sodium salt of amino heterocyclics in the presence of HCl at 50–60 °C opened the benzoxazaphosphinine ring chemoselectively at the endocyclic P–O bond and yielded 2-[4-chloro(heterocyclic substituted-phosphorothioyl)anilino]methylphenols **5–13**.

1. Introduction

Phosphoramides are used extensively in organic and medicinal chemistry. Cyclophosphamide containing an oxazaphosphinine is a proven alkylating antitumour agent against a broad spectrum of human cancers including slow-growing solid tumours.[1,2] The clinical significance and the unique conformational and stereochemical aspects of oxazaphosphinines have attracted much interest in drug design and synthesis.[3–5] The strong electron donor and Lewis basicity of phosphoramides has made them useful in catalytic process.[6,7] In phosphoramide boron-complexes, the boron, being a Lewis acid centre, binds with ketones and controls the stereochemistry in their asymmetric reduction.[8]

Several phosphorus heterocyclic ring-opening reactions involving C–P–C, O–P–O and N–P–N were reviewed extensively by Majoral in 1994.[9] Acid-catalyzed 1,4-addition- type ring-opening reactions were used for the polymerization of cyclic phosphorimidates.[10,11] Simple hydroxy phosphoramides have been prepared by reaction of amino alcohols and phosphonates.[12,13] A new class of recoverable and highly stable phosphinamide catalysts for the asymmetric reduction of ketones was synthesized through oxazaphosphorine ring-opening reactions with alkylmagnesium bromide.[14,15]

A new route for the synthesis of phosphoramides substituted with functionalized aromatics and heterocycles at their three different nitrogens was accomplished by acid-catalyzed nucleophilic ring opening of benzoxazaphosphorines. This reaction may help to serve as a probe to understand enzymatic hydrolysis of this group of drugs in living matrices.

Herein, we report reaction sequence for the preparation of different N-ligand-substituted tris-thiophosphoramides, 2-(4-chloro[substituted-phosphorothioyl]aniline-methyl)phenols **5–13** by acid-catalyzed nucleophilic chemoselective ring opening of benzoxazaphosphorine derivatives **4a–e** (Scheme 1).

Cyclization of **1** with $PSCl_3$ in toluene in presence of triethylamine led to the formation of compound **2**. Reaction of **2** with a heterocyclic amine under the same conditions afforded the corresponding benzoxazphosphorine derivatives **4**. Subsequent reaction of **4** in the same vessel with various amino nucleophiles as their sodium salts in the presence of a catalytic amount of conc. HCl[9,16] at 50–60 °C chemoselectively opened the benzoxazaphosphorine ring at the P–O bond with simultaneous formation of a P–N bond with the second molecule of the sodium salt of the nitrogen nucleophile (Scheme 2). In the above step, HCl appears to weaken the P–O and N–Na bonds and helps in cleavage of the cyclic P–O bond and formation of the P–N and O–H bonds.

It was observed that **4** is also ring opened at the cyclic P–O bond when reacted with free amines even without HCl as the catalyst at high temperature. In both cases, the products yield was low, and the reaction times were long. The reaction solvent seems to be critical since the same reaction when carried out in acetic acid returned only starting products (Table 1).

All the products were characterized by IR, ^{1}H, ^{13}C and ^{31}P NMR and mass spectroscopic data.[17,18]

The appearance of a singlet at δ 4.24–4.26 for the two acyclic methylene protons in compounds **5–13** is in good agreement with

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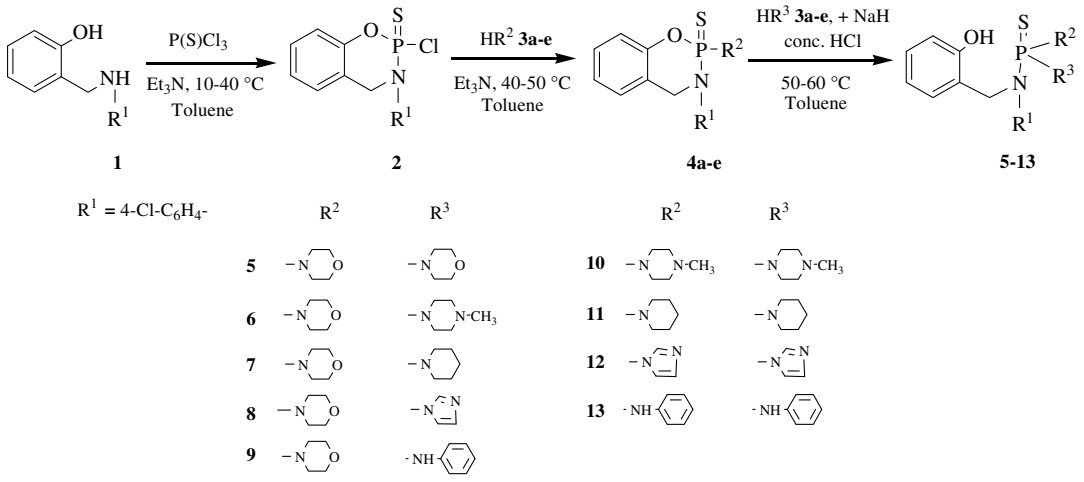
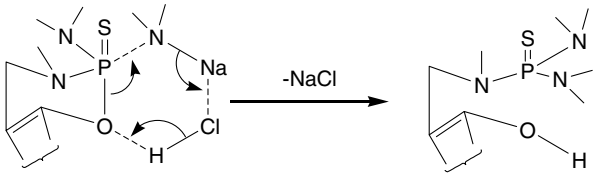


Scheme 1.



Scheme 2.

the structures of the acyclic compounds when compared to the appearance of a doublet of doublets for the corresponding chemically nonequivalent methylene protons (CH-4) in the cyclic structures **4a–e** (Fig. 1).[19–21]

The sodium salts of heterocyclic amines in the presence of NaH/HCl effect chemoselective benzoxazaphosphorine ring opening at the P–O bond to afford the corresponding hydroxy, N-ligand-substituted tris-thiophosphoramides in high yields. This procedure offers a method for the synthesis of tri-nitrogen-substituted chiral phosphoramides, which can be used as catalyst templates for chiral organic synthesis.[8]

2. General procedure for 2-[4-chloro(substituted-phosphorothioyl)anilino]methyl phenol synthesis

A solution of thiophosphoryl chloride (2 mmol) in dry toluene (20 mL) was added dropwise to a cooled (5–10 °C) solution of 2-(4-chlorophenylamino)methyl phenol **1** (2 mmol) and triethylamine (4 mmol) in dry toluene (40 mL). After addition, the reaction temperature was raised to 35–40 °C and the reaction mixture was stirred for an additional 2 h. The formed 2-chloro-3-(4-chlorophenyl)-3,4-dihydro-2*H*-1,3,2λ^5-benzoxazaphosphinine-2-thione (**2**) was used in the next step without further purification.

To a cooled (0–5 °C) solution of **2**, heterocyclic amines (**3a–e**, 2 mmol) and triethylamine (2 mmol) in dry toluene were added dropwise with stirring. The temperature of the reaction mixture was raised to 40–45 °C and stirring was continued for an additional 3 h to afford compounds **4a–e**. To the stirred solution of **4a–e** in the same vessel, the heterocyclic amine as the sodium salts **3a–e** (2 mmol) in dry toluene (20 mL) was added dropwise. After completion of addition, two drops of 37% HCl were added at room temperature, and the reaction mixture was stirred at 40–50 °C for 3 h. After filtration, the solvent was removed after drying with anhydrous $MgSO_4$. The residue was washed with water and purified by column chromatography using silica gel as adsorbent and ethyl acetate/hexane (1:5) as the eluent to yield products **5–13**. All the reactions were monitored by TLC, using the same eluent.

2.1. 2-[4-Chloro(dimorpholinophosphorothioyl)-anilino]methylphenol (entry 1)

Solid: mp 172–175 °C; IR (KBr) (ν_{max} cm^{-1}): 3397 (O–H), 959 (P–N), 778 cm^{-1} (P=S); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09–7.34 (6H, m, Ar-H), 6.56 (2H, d, J = 8.5, Ar-H), 4.25 (2H, s, C*H*–N–P), 3.63 (8H, m, H-3″, 3‴, 5″ and 5‴), 3.21 (8H, m, H-2″, 2‴, 6″ and 6‴); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.19, 146.52, 130.51, 129.18, 128.93, 125.25, 122.29, 120.56, 113.82, 66.76, 45.39, 44.30; ^{31}P NMR (121 MHz, $CDCl_3$): δ 73.18; LCMS(EI) *m/z* (%), 470 (40) [(MH+2)$^+$], 468 (100) [MH$^+$], 381 (39) [(MH−C_4H_9NO)$^+$]; Anal. Calcd for $C_{21}H_{27}ClN_3O_3PS$: C, 53.90; H, 5.82; N, 8.98. Found: C, 53.86, H, 5.84; N, 9.01.

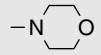
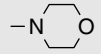
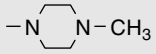
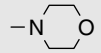
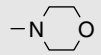
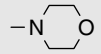
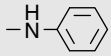
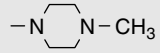
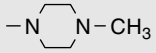
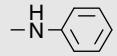
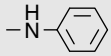
2.2. 2-(4-Chloro[(4-methylpiperazino)(morpholino)-phosphorothioyl]anilinomethyl)phenol (entry 2)

Solid: mp 168–170 °C; IR (KBr) (ν_{max} cm^{-1}): 3385 (O–H), 915 (P–N), 756 cm^{-1} (P=S); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06–7.35 (6H, m, Ar-H), 6.41 (2H, d, J = 9.8, Ar-H), 4.26 (2H, s, C*H*–N–P), 3.43 (12H, br, H-2″, 2‴,3‴, 5‴, 6″ and 6‴), 2.50 (4H, s, H-3″ and 5″), 2.37 (3H, s, N–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.79, 148.90, 147.51, 134.98, 130.04, 128.85, 124.07, 121.33, 120.97, 115.37, 61.90, 55.66, 50.26, 46.09, 43.36; ^{31}P NMR (121 MHz, $CDCl_3$): δ 74.65; LCMS(EI) *m/z* (%): 482 (25) [(M+2)$^+$], 480 (67) [M$^+$], 478 (88), 440 (71), 419 (76), 393 (19); Anal. Calcd for $C_{22}H_{30}ClN_4O_2PS$: C, 54.94; H, 6.29; N, 11.65. Found: C, 54.90; H, 6.31; N, 11.68.

2.3. 2-(4-Chloro[morpholino(piperidino)-phosphorothioyl]anilinomethyl)phenol (entry 3)

Solid: mp 125–128 °C; IR (KBr) (ν_{max} cm^{-1}): 3396 (O–H), 965 (P–N), 757 cm^{-1} (P=S); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08–7.39 (6H, m, Ar-H), 6.55 (2H, d, J = 9.0, Ar-H), 4.25 (2H, s, C*H*–N–P), 3.64 (4H, m, H-3″ and 5″), 3.49 (4H, m, H-2‴ and 6‴), 3.24 (4H, m, H-2″ and 6″), 1.57 (6H, m, H-3‴,4‴ and 5‴); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.31, 134.6, 129.30, 129.14, 129.11,

Table 1
Chemoselective benzoxazaphosphinine ring-opening reactions

Entry	Substrate		Catalyst	Temperature (°C)	Time (h)	Product	Yield (%)
	R^2	R^3					
1	 **3a**	 **3a**	—	>150	24	**5**	31
			HCl[a]	60	15	**5**	44
			HCl[b]	60	8	**5**	78
			HCl[c]	25	4	**1**, **3a**	—
2	 **3a**	 **3b**	—	>150	20	**6**	18
			HCl[a]	60	14	**6**	39
			HCl[b]	60	9	**6**	65
3	 **3a**	 **3c**	HCl[b]	60	8	**7**	69
4	 **3a**	 **3d**	HCl[b]	60	9	**8**	63
5	 **3a**	 **3e**	HCl[a]	80	15	**9**	42
6	 **3b**	 **3b**	—	150	20	**10**	25
			HCl[a]	60	14	**10**	41
			HCl[b]	60	8	**10**	76
7	 **3c**	 **3c**	HCl[b]	60	8	**11**	69
8	 **3d**	 **3d**	HCl[b]	60	10	**12**	60
9	 **3e**	 **3e**	HCl[a]	80	18	**13**	58

'—' without catalyst.
[a] Heterocyclic amine with concd HCl.
[b] Heterocyclic amine with NaH and concd HCl.
[c] Acetic acid as solvent.

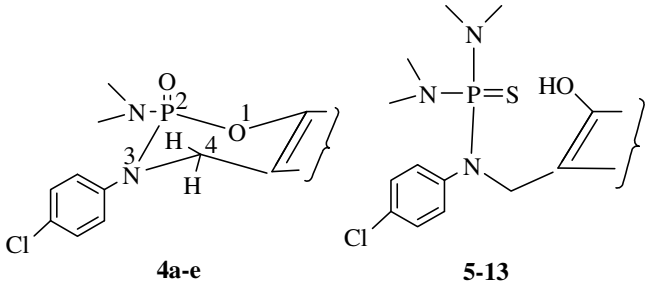


Figure 1.

126.21, 126.10, 125.94, 122.38, 123.14, 119.27, 115.27, 66.57, 45.53, 32.49, 45.29, 27.81; ^{31}P NMR (121 MHz, $CDCl_3$): δ 75.17; LCMS(EI) *m/z* (%): 468 (39) [$(MH+2)^+$], 466 (100) [MH^+], 381 (26), 379 (43), 340 (10), 339 (46); Anal. Calcd for $C_{22}H_{29}ClN_3O_2PS$: C, 56.71; H, 6.27; N, 9.02. Found: C, 56.68; H, 6.32; N, 9.07.

2.4. 2-(4-Chloro[1*H*-1-imidazolyl(morpholino)-phosphorothioyl]anilinomethyl)phenol (entry 4)

Solid: mp 117–119 °C; IR (KBr) (ν_{max} cm^{-1}): 3387 (O–H), 951 (P–N), 762 cm^{-1} (P=S); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01–7.44 (9H, m, Ar-H), 6.34 (2H, s, Ar-H), 4.25 (2H, s, C*H*–N–P), 3.48 (4H, m, H-3″ and 5″), 3.25 (4H, m, H-2″ and 6″); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.22, 148.87, 144.24, 137.45, 130.06, 129.33, 128.83, 126.72, 125.49, 124.58, 122.69, 120.37, 118.98, 63.14, 49.46, 43.84; ^{31}P NMR (121 MHz, $CDCl_3$): δ 70.49; LCMS(EI) *m/z* (%): 471 (100) [$(M+23)^+$]; Anal. Calcd for $C_{20}H_{22}ClN_4O_2PS$: C, 53.51; H, 4.94; N, 12.48. Found: C, 53.49; H, 4.98; N, 12.50.

2.5. 2-[Anilino(morpholino)phosphorothioyl]-4-chloroanilinomethyl)phenol (entry 5)

Solid: mp 105–107 °C; IR (KBr) (ν_{max} cm^{-1}): 3370 (O–H), 3301 (N–H), 914 (P–N), 755 cm^{-1} (P=S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.08–7.47 (11H, m, Ar-H), 6.49 (2H, d, J = 9.0, Ar-H), 5.62 (1H, s, Ar-N*H*) 4.26 (2H, s, C*H*–N–P), 3.59 (4H, m, H-3″ and 5″) and 3.25 (4H, m, H-2″ and 6″); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.28,

146.49, 137.96, 133.18, 131.28, 130.75, 129.18, 126.18, 126.52, 125.01, 123.91, 122.75, 120.35, 119.65, 66.12, 44.23, 53.04; ^{31}P NMR (121 MHz, DMSO-d_6): δ 69.47; LCMS(EI) *m/z* (%): 476 (16) [(MH+2)$^+$], 474 (42) [MH$^+$], 429 (37), 400 (42), 350 (100), 305 (46), 249 (39); Anal. Calcd for $C_{23}H_{25}ClN_3O_2PS$: C, 58.29; H, 5.32; N, 8.87. Found: C, 58.24, H, 5.28; N, 8.91.

2.6. 2-(4-Chloro[di(4-methylpiperazino)phosphorothioyl]-anilinomethyl)phenol (entry 6)

Solid: mp 102–103 °C; IR (KBr) (ν_{max} cm^{-1}): 3434 (O–H), 969 (P–N), 784 cm^{-1} (P═S); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10–7.37 (6H, m, Ar-H), 6.56 (2H, d, *J* = 8.7, Ar-H), 4.25 (2H, d, *J* = 4.7, C*H*–N–P), 3.24 (8H, m, H-2″, 2‴, 6″ and 6‴), 2.45 (8H, m, H-3″, 3‴, 5″ and 5‴), 2.28 (6H, s, N–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.12, 142.08, 129.4, 129.14, 128.36, 126.50, 125.94, 125.90, 123.6, 124.08, 118.83, 118.77, 113.00, 54.22, 53.07, 45.23 44.11; ^{31}P NMR (121 MHz, $CDCl_3$): δ 73.24; LCMS(EI) *m/z* (%): 496 (41)[(MH+2)$^+$], 494 (100) [(MH)$^+$]; Anal. Calcd for $C_{23}H_{33}ClN_5OPS$: C, 55.92; H, 6.73; N, 14.18. Found: C, 55.87; H, 6.76; N, 14.24.

2.7. 2-[4-Chloro(dipiperidinophosphorothioyl)anilino]-methylphenol (entry 7)

Solid: mp 88–91 °C; IR (KBr) (ν_{max} cm^{-1}): 3370 (O–H), 952 (P–N), 764 cm^{-1} (P═S); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04–7.43 (6H, m, Ar-H), 6.55 (2H, s, Ar-H), 4.25 (2H, s, C*H*–N–P), 3.15 (8H, br, H-2″, 2‴, 6″ and 6‴), 1.50 (8H, br, H-3″, 3‴, 5″ and 5‴); 1.42 (4H, br, C-4″ and 4‴); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.97, 150.89, 148.32, 148.24, 145.92, 135.36, 129.68, 125.26, 123.36, 122.33, 122.26, 120.49, 118.22, 118.13, 49.75, 40.01, 34.24, 31.33; ^{31}P NMR (121 MHz, $CDCl_3$): δ 72.36; LCMS(EI) *m/z* (%): 487 (100) [(M+23)$^+$], 380 (22), 348 (24), 320 (90), 318 (19), 292 (26); Anal. Calcd for $C_{23}H_{31}ClN_3O_3PS$: C, 59.54; H, 6.73; N, 9.06. Found: C, 59.50; H, 6.78, N, 9.09.

2.8. 2-[4-Chloro(di-1*H*-1-imidazolylphosphorothioyl)anilino]-methylphenol (entry 8)

Solid: mp 98–100 °C; IR (KBr) (ν_{max} cm^{-1}): 3346 (O–H), 911 (P–N), 757 cm^{-1} (P═S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.96–7.61 (12H, m, Ar-H), 6.53. (2H, d, *J* = 8.7, Ar-H), 4.24 (2H, s, C*H*–N–P); ^{31}P NMR (121 MHz, DMSO-d_6): δ 69.56; LCMS(EI) *m/z* (%): 430 (39) [(M−H+2)$^+$], 428 (100) [(M−H)$^+$]; Anal. Calcd for $C_{19}H_{17}ClN_5OPS$: C, 53.09; H, 3.99; N, 16.29. Found: C, 53.06, H 4.02; N, 16.33.

2.9. 2-[4-Chloro(dianilinophosphorothioyl)anilino]methyl-phenol (entry 9)

Solid: mp 75–77 °C; IR (KBr) (ν_{max} cm^{-1}): 3349 (O–H), 3321 (N–H), 967 (P–N), 752 cm^{-1} (P═S); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98–7.47 (16H, m, Ar-H), 6.48 (2H, s, Ar-H), 4.24 (2H, s, C*H*–N–P); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.33, 137.55, 120.53, 129.69, 129.40, 129.36, 129.30, 128.53, 127.20, 127.17, 126.69, 124.45, 120.69, 120.58, 119.18, 43.15; ^{31}P NMR (121 MHz, $CDCl_3$): δ 68.97; Anal. Calcd for $C_{25}H_{23}ClN_3OPS$: C, 62.56, H, 4.83; N, 8.75. Found: C, 62.53, H, 4.87; N, 8.78.

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