Elaboration of the Benzazaphospholine Framework: a New Illustration of the Parham Protocol

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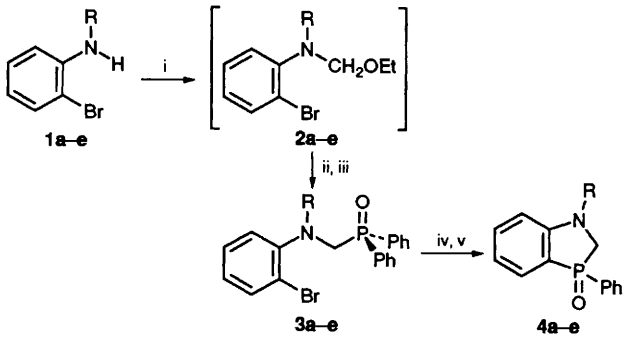
1-Alkyl-3-phenyl-1,3-benzazaphospholine oxides are efficiently prepared by Parham-type anionic cyclisation of *ortho*-lithiated *N*-alkyl-*N*-diphenylphosphinoylmethylaniline derivatives obtained by sequential treatment of the parent brominated compounds with methyllithium and *tert*-butyllithium.

In the past decade, the Parham 'direct' protocol for annulations[1] has deeply permeated the synthetic methodology repertoire for the elaboration of fused polycyclic aromatic and heteroaromatic systems. This cyclisation process consists in the introduction by metal–halogen exchange reaction of an internal aromatic nucleophilic centre which may then react with an electrophilic entity present on the adjacent side chain, thus inducing a rapid intramolecular ring-closure reaction. Efficient execution of these anionic aromatic annulations has been reported for a wide variety of aromatic systems possessing a halogenocarbon centre and, at the alpha site, different electrophiles such as carboxyl,[2] *N,N*-dialkylcarboxamide,[3] epoxide,[4] bromo,[5] aldimino,[6] imide,[7] and carbamate[8] groups. Paradoxically a literature survey reveals that despite the vast amount of work which has been devoted to the construction of medium-sized ring phosphorus heterocycles,[9] the Parham synthetic approach has remained ignored by the scientific community.

We report here a new methodology for the elaboration of the benzazaphospholine framework in which the azaphospholine ring is assembled by lithium–halogen exchange in a bromo derivative **3** followed by Parham type cyclisation of the resulting lithiated intermediate with the diphenylphosphinoyl group acting as the internal electrophile.

Initially, the conversion of the bromoanilines **1a–e** into the diphenylphosphine oxides **3a–e** (Scheme 1, Table 1) was accomplished in a one-pot reaction by the following three-step sequence:[10] (*i*) formation of the mixed *O,N*-acetals **2a–e** by way of the conventional Mannich reaction of the anilines **1a–e** and paraformaldehyde in ethanol, (*ii*) elimination of the solvent and connection of the diphenylphosphinoyl group by an Arbuzov reaction of the intermediate *O,N*-acetals with chlorodiphenylphosphine and (*iii*) treatment with solid potassium carbonate to complete the reaction and give the required HCl-free substrates **3a–e**.†

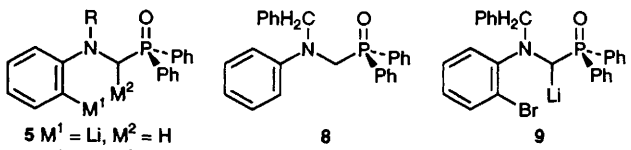


Scheme 1 *Reagents and conditions*: i, $(CH_2O)_n$, EtOH, toluene, reflux; ii, Ph_2PCl, THF, room temp.; iii, K_2CO_3; iv, LiMe, THF, −78 °C, 15 min then LiBu^t, 10 min; v, NH_4Cl (aq)

Table 1 Yields for Parham cyclisation reactions

1–7	R	Yield 1 → 3 (%)	Yield 3 → 4 (%)
a	CH_2Ph	72	93
b	4-(MeO)$C_6H_4CH_2$	69	95
c	3,4-$(OCH_2O)C_6H_3CH_2$	65	96
d	Pr^i	75	89
e	Me	75	88

To ensure the formation of the lithiated intermediate **5** by lithium–bromine exchange, a THF solution of the aryl bromide **3a** was firstly treated with 1.1 equiv. of *tert*-butyllithium (1.7 mol dm^{-3} solution in pentane) added dropwise at −78 °C. Quenching of the reaction mixture with aqueous NH_4Cl followed by chromatography permitted the isolation of the targetted annulation product **4a** accompanied with the debrominated product **8** and the starting material **3a** in an approximate ratio 7:2:1. Stirring the reaction mixture for a longer period of time (2 h) or lowering the temperature to −95 °C did not notably modify the product ratio in favour of **4a**. The presence of the unchanged parent compound **3a** may be *a priori* explained either by the competitive formation of the phosphorylated α-metalloamine derivative **9** or more probably by a partial consumption of the metallating agent by a competitive reaction between *tert*-butyllithium and the *tert*-butylbromide produced in the exchange reaction.[11] The undesirable formation of the debrominated compound **8** may be attributed to the presence of the unreacted aryllithio derivative **5a** due to the strain which is developed during the closure of the polyheteroring system fused to the aromatic ring. It can also be accounted for by an internal transmetallation reaction **5** → **6**. In keeping with these assumptions a THF solution of **3a** was then preliminarly treated with 1.1 equiv. of methyllithium (1.6 mol dm^{-3} in diethyl ether) at −78 °C for 15 min. Since it is well established that methyllithium is of no value for halogen–metal interconversion reactions[12] this operation gives rise exclusively to the phosphorylated aminocarbanion **9**.‡ The subsequent treatment of the THF solution of **9** with 1.1 equiv. of *tert*-butyllithium added slowly during *ca.* 10 min promoted the formation of the dilithiated species **7a**. The intramolecular ring-closure reaction was instantaneous since the immediate work up of the reaction mixture gave rise to the desired annulated compound **4a** which was isolated as the sole product (Scheme 1). This reaction sequence is applicable to all the diversely substituted *N*-diphenylphosphinoylmethyl-*o*-bromoanilines **3a–e** and the results of a representative series of products obtained by this method are presented in Table 1. This simple procedure affords excellent yields of the 1-alkyl-3-phenyl-1,3-benzazaphospholine oxides **4a–e**. Confirmation of the condensed structure of **4**§ was mainly obtained from the 300 MHz ^{1}H NMR spectroscopy which clearly indicates the presence of two diastereotopic protons (two dd patterns at δ 3.53 and 3.72 with ^2J 14.5 and J_{PH} 4.6, 16.2 Hz for **4a**) corresponding to the methylene protons of the azaphospholine ring. It was corroborated by the 75 MHz ^{13}C NMR spectra



5 M^1 = Li, M^2 = H
6 M^1 = H, M^2 = Li
7 M^1 = M^2 = Li

8

9

which establishes the disappearanceof the aromatic halogenocarbon centre at δ 120.7 (value given for **3a**) and the presence of a new quaternary carbon atom at δ 115.8 appearing as a doublet with J_{CP} 102 Hz (values for **4a**).

To summarize the procedure described here represents a conceptually and experimentally simple new approach to the benzazaphospholine skeleton which is only accessible by a few limited methods. This heterobicyclic framework is indeed obtained by treatment of *o*-aminophenylphosphine with carbonyl compounds.[13] This functionnalized aromatic phosphine is prepared by reduction of the corresponding phosphonic acid esters which are only accessible by photostimulated substitution ($S_{RN}1$ mechanism) of *o*-halogenoanilines by dialkylphosphite anions.[14] The annulation reactions reported here are actually the combined result of the nucleophilicity of aryllithium reagents and the sensitivity of the diphenylphosphinoyl group to nucleophilic attack,[15] a property rarely used thus far by organic chemists.

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Footnotes

† *Selected data for* **3a**: Mp 128–129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.62 (m, 4 H, Ar), 7.41–7.21 (m, 12 H, Ar), 6.96 (m, 2 H, Ar), 6.74 (m, 1 H, Ar), 4.63 (s, 2 H, NCH_2Ar), 4.06 (d, J_{HP} 3.2 Hz, 2 H, NCH_2P). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.1 (C, C-1), 137.0 (C), 133.4 (CH), 132.4 (C, d, J_{CP} 94.1 Hz, P–C=), 131.6 (CH), 131.0 (CH), 130.9 (CH), 129.4 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.3 (CH), 126.5 (CH), 125.4 (CH), 120.7 (C, C-2), 58.5 (CH_2, CH_2N), 51.0 (CH_2, d, J_{CP} 76.3 Hz, CH_2P). ^{31}P NMR (121 MHz, $CDCl_3$): δ 28.8. MS (EI) *m/z* 477 (M^+, 1), 475 (M^+, 1), 276 (19), 274 (20), 201 (14), 91 (100%); satisfactory elemental analyses (C, H, Br, N, O, P) were obtained for **3a**.

‡ Work up of the reaction mixture at this stage results in the total recovery of the starting material.

§ *Selected data for* **4a**: Mp 137–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69–7.63 (m, 2 H, Ar), 7.51–7.24 (m, 10 H, Ar), 6.84–6.76 (m, 2 H, Ar), 4.62, 4.47 (2d, J_{AB} 15.8 Hz, 2 H, NCH_2Ar), 3.72 (dd, J_{AB} 14.5 J_{HP} 16.2 Hz, 1 H, NCH_2P), 3.53 (dd, J_{AB} 14.5 J_{HP} 4.6 Hz, 1 H, NCH_2P). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.6 (C, d, J_{CP} 18.3 Hz, C-7a), 136.5 (C), 134.6 (CH), 132.4 (C, d, J_{CP} 105.7 Hz, P–C=), 131.9 (CH), 131.7 (CH), 130.9 (CH), 130.8 (CH), 129.9 (CH, d, J_{CP} 6.5 Hz), 128.7 (CH), 128.5 (CH), 128.4 (CH), 127.5 (CH), 127.2 (CH), 118.0 (CH, d, J_{CP} 11.6 Hz), 115.8 (C, d, J_{CP} 102.4 Hz, C-4a), 109.4 (CH, d, J_{CP} 9.2 Hz), 52.7 (CH_2, d, J_{CP} 8.3 Hz, CH_2N), 52.5 (CH_2, d, J_{CP} 52.6 Hz, CH_2P). ^{31}P NMR (121 MHz, $CDCl_3$): δ 38.3. MS (EI) *m/z* 319 (M^+, 61), 318 (28), 228 (32), 215 (86), 91 (100%); satisfactory elemental analyses (C, H, N, O, P) were obtained for **4a**.

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