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Dearomatizing Anionic Cyclization of Phosphonamides. A Route to Phosphonic Acid Derivatives with Antitumor Properties

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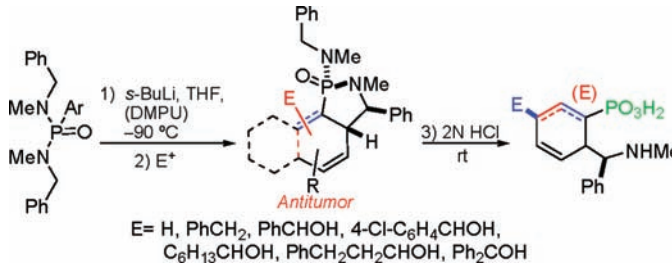
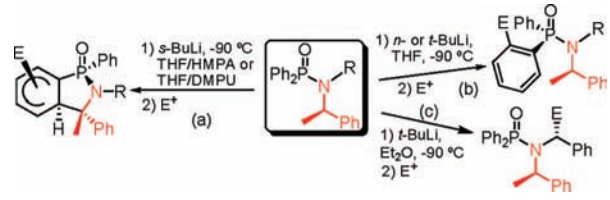
ABSTRACT



Deprotonation of bis(*N*-benzyl-*N*-methyl)-*P*-arylphosphonic diamides with *s*-BuLi in THF at −90 °C takes place selectively at the benzylic position. The anions undergo intramolecular attack to the *P*-aryl ring leading to dearomatized species that were trapped with a series of electrophiles (MeOH, ArOH, BnBr, aliphatic and aromatic aldehydes, and benzophenone) in very high yield, and with high regio- and stereocontrol. The dearomatized products were smoothly transformed into γ-aminophosphonic acids under acidic conditions. Preliminary screening for antitumor activity showed promising levels of activity.

Heteroatom-directed metalation followed by electrophilic trapping is a very useful strategy for introducing structural diversity into a molecule provided that both steps proceed with high levels of regio- and stereoselectivity.[1] The $Ph_2P(O)$ (Pop) group of *P*-arylphosphinamides fulfills these criteria nicely. Lithiation at either the NC_α[2] (Scheme 1, route a) or ortho[3] position (route b) can be achieved in THF with excellent regiocontrol. The NC_α anions are stable in diethyl ether at low temperature,[4] allowing their application in carbon−carbon and carbon−heteroatom bond-forming reac-

Scheme 1



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(1) (a) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Amsterdam, The Netherlands, 2002. (b) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. (c) Wu, G.; Huang, M. *Chem. Rev.* **2006**, *106*, 2596.

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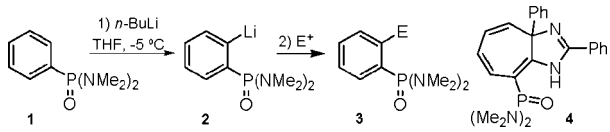
tions (route c).[5] In contrast, in THF and in the presence of HMPA or DMPU, NC_α anions undergo dearomatization through anionic cyclization quantitatively.[2,6]

The dearomatization−alkylation process of phosphinamides furnishes a variety of products, including γ-aminophosphinic acids, showing antitumor activity.[6a,7,8] Extending this methodology to phosphonamides will lead to aminophosphonic acids, important compounds due to their biological properties.[9] Lithiations directed by a phosphonamide moiety have been limited to the ortho deprotonation of $PhP(X)(NMe_2)_2$ (X = O,[10] S[11]).[12]

Fortuitously, in the reaction of the ortho-lithiated **2** with benzonitrile, a dearomatized bicycle **4** was obtained (Scheme 2, 3). Heterocycle **4** is the only dearomatized product

Scheme 2. Directed Lithiation of Phenylphosphonamide

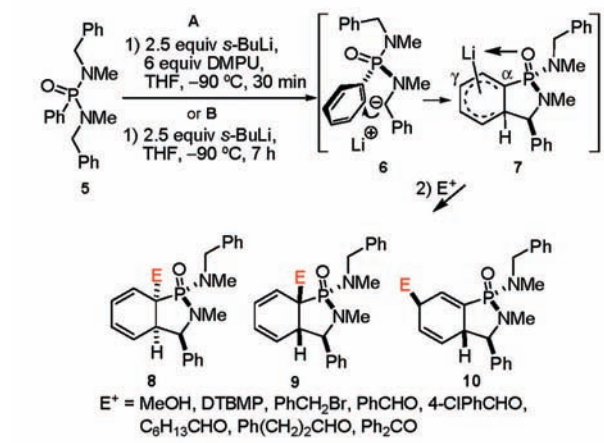


described for phosphonamides.[13] We report here the first dearomatizing anionic cyclization (DAC) of *N*-benzyl-*P*-arylphosphonamides and the application of the method to the synthesis of functionalized γ-aminophosphonic acids. Preliminary evaluation of antitumor properties is also reported.

The treatment of bis(*N*-benzyl-*N*-methyl)-*P*-phenylphosphonic diamide **5**[14] with *s*-BuLi at −90 °C in THF followed by electrophilic quench affords dearomatized products **8**−**10** in high yields (Table 1). Wide structural diversity is obtained through the combined effect of the electrophile used and the site of binding to the dearomatized anion.

The formation of compounds **8**−**10** implies that *s*-BuLi deprotonates phosphonamide **5** selectively at the benzylic

Table 1. Dearomatization−Electrophilic Quench of **5**



entry	method	E	8 (%)[a]	9 (%)[a]	10 (%)[a]
1	A	H[b]	**a** (74)[c]		
2	B	H[b]	**a** (75)[d]		
3	A	H[e]			**a** (79)[f]
4	B	H[e]			**a** (56)[c]
5	A	$PhCH_2$			**b** (75)[g]
6	B	PhCHOH		**a** (84) [56:44][h]	
7	B	4-ClC_6H_4CHOH		**b** (82) [53:47][h]	
8	B	C_6H_{13}CHOH		**c** (84) [33:67][h]	
9	B	$Ph(CH_2)_2$CHOH		**d** (88) [33:67][h]	
10	A	Ph_2COH			**c** (60)[i]

[a] Isolated yield. [b] E^+ = MeOH. [c] Epimer at the phosphorus atom: 8%. [d] Epimer at the phosphorus atom: 7%. [e] E^+ = DTBMP. [f] Epimer at the phosphorus atom: 17%. [g] Epimer at the phosphorus atom: 11%. [h] Diastereomeric ratio at the hydroxilated carbon, *S**:*R** with respect to the phosphorus atom. [i] Epimer at the phosphorus atom: 18%.

position and the anion generated, **6**, attacks the ortho position of the *P*-phenyl ring to give the dearomatized species **7**. Similar to phosphinamides,[2,6] quenching the reaction with MeOH introduces a proton at the α carbon with respect to the phosphorus leading to **8a** (entry 1), whereas protonation with 2,6-di(*tert*-butyl)-4-methylphenol (DTBMP) and alkylation with benzyl bromide takes place almost exclusively at the γ position providing **10a** and **10b**, respectively (entries 3−5). Two aspects of these transformations are worth mentioning. First, the effect of DMPU on the efficiency of the reaction is electrophile dependent. Yields of products obtained by protonation with DTBMP or alkylation with BnBr and benzophenone are higher in the presence of DMPU (entries 3, 4, 5, and 10). For aldehydes and methanol as electrophiles, the DAC reaction proceeds reasonably well in the absence of strong coordinating cosolvent provided that the metalation time is increased to 7 h.[15] Second, small amounts of the corresponding epimer at the phosphorus atom

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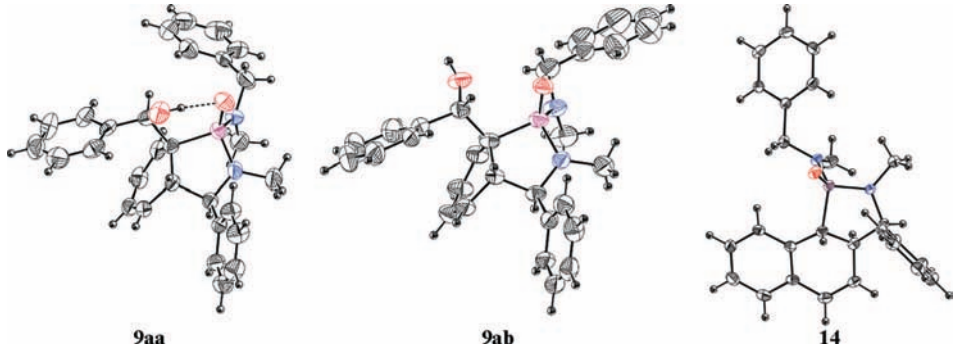


Figure 1. ORTEP type plots (40% anisotropic displacement) of the molecular structure of **9aa**, **9ab**, and **14**.

are also isolated. Seeing the dearomatized compounds as precursors of aminophosphonic acids (see below), both diastereoisomers will give rise to the same product. Thus, the mixture can be used without separation, and therefore, the overall yield increases.

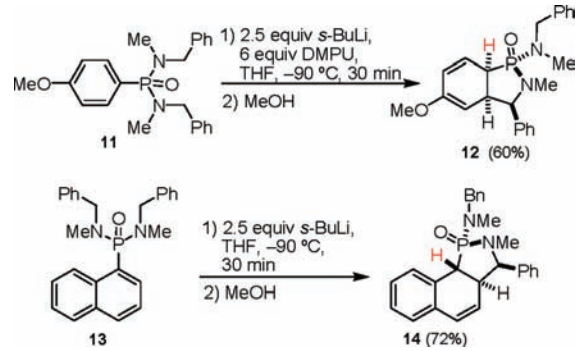
Trapping anionic species **7** with aromatic and aliphatic aldehydes leads to products of α-attack **9a** to **9d** in high yield, although with low face selectivity (entries 6−9). The best results are obtained in the absence of DMPU. In sharp contrast, the analogue reactions of phosphinamides require the use of coordinating cosolvents and afford products of γ-attack exclusively.[6,13] The reaction with benzophenone yields almost exclusively products of γ-attack (entry 10)[16] and is carried out in the presence of DMPU (method A, Table 1). The less crowded γ position of **7** is now more accessible to the bulky electrophile than the α position.

All compounds were isolated by flash chromatography. The structural assignment was based on the analysis of their APCI-MS and NMR spectra (Supporting Information). [1,3]- and [1,4]-cyclohexadiene systems can be easily distinguished based on their NMR data (e.g., the sp^3/sp^2-hybridized carbon α to the phosphorus and ^{31}P NMR data). The relative configuration of the benzazaphosphole fragments were deduced through the respective gNOESY spectra. For the pair of epimers at the CHOH carbon **9aa** and **9ab**, the relative configuration of the five stereogenic centers has been confirmed by X-ray diffraction (Figure 1).

Next, the dearomatizing methodology was extended to other phosphonamides. Arylphosphonamides **11** and **13** are easily prepared through the same route applied to the synthesis of **5**[14] by using the corresponding aryldichlorophosphine[17] (Supporting Information).

Lithiation of *p*-methoxyphenylphosphonamide **11** with *s*-BuLi in THF in the presence of DMPU at −90 °C and subsequent reaction with methanol gives exclusively the dearomatized derivative **12** in 60% yield. The slight decrease in yield as compared with the synthesis of **8a** may be a consequence of the deactivation of the anionic cyclization step induced by the electron-donating effect of the methoxy group. The naphthyl ring of phosphinamide **13** is smoothly dearomatized upon treatment with *s*-BuLi in THF. Similar to naphthylphosphinamides,[6b,f] no coordinating cosolvents are required. Protonation of the dearomatized anion with methanol provides the trans fused tricyclic compound **14** in good yield.[18] The structure of **12** and **14** was assigned based on their spectroscopic data. Additionally, the X-ray crystal structure of **14** confirmed the assignments of relative configuration made (Figure 1, see also the Supporting Information).

Scheme 3. Dearomatization−Electrophilic Quench of **11** and **13**



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(14) Prepared in multigram scale through addition of phenyldichlorophosphine to 2 equiv of *N*-methylbenzylamine in toluene in the presence of Et_3N at −80 °C, followed by oxidation with H_2O_2 in THF (Supporting Information). This is a slight modification of the method described in the literature: (a) Droadhurst, M. D.; Tsang, T. H.; Tomko, J. Patent No. US5186733, 1993.

(15) Similar behavior has been observed for phosphinamides. However, in this case, significant amounts of products of ortho lithiation were also formed. (a) Fernández, I.; González, J.; López-Ortiz, F. *J. Am. Chem. Soc.* **2004**, *126*, 12551.

(16) **9d**, a product of α-attack with 6% yield, is also formed.

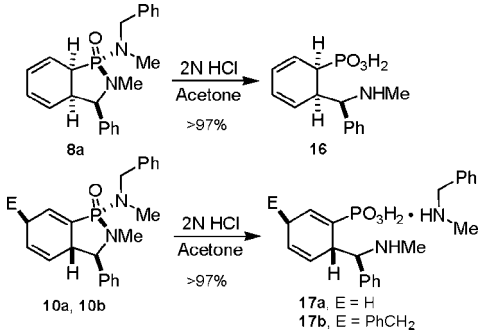
(17) *p*-Methoxyphenyldichlorophosphine: (a) Miles, J. A.; Beeny, M. T.; Ratts, K. W. *J. Org. Chem.* **1975**, *40*, 343. (b) 1-Naphthyldichlorophosphine: Reiter, S. A.; Nogai, S. D.; Karaghiosoff, K.; Schmidbauer, H. *J. Am. Chem. Soc.* **2004**, *126*, 15833.

(18) Formation of products of cis fusion **8a** and **12** and trans fusion **14** upon protonation of the corresponding dearomatized species is in agreement with the stereochemical outcome of the analogue reactions of phosphinamides. See ref 6b, f.

The results obtained indicate that *N*-benzylarylphosphonamides behave similarly to the analogue carboxamides in DAC-electrophilic trapping processes. Clayden et al. showed that the application of this methodology to tertiary carboxamides is a valuable route to the synthesis of natural products and non-natural derivatives.[1a,19]

Given that the rupture of the P−N linkage of 1,2-azaphosphole rings can be easily achieved with diluted acid,[2a,6] we treated compounds **8a**, **10a**, and **10b** with 2 N HCl in acetone at room temperature. In this way, hydrolysis of the P−N bond takes place quantitatively to give γ-(*N*-methylamino)phosphonic acids **16**, **17a**, and **17b**, respectively (Scheme 4). As noted above, hydrolysis of epimers at the

Scheme 4. Synthesis of γ-(*N*-Methylamino)phosphonic Acids



phosphorus atom produce the same amino acid. Representative dearomatized compounds were submitted to in vitro cytotoxicity assays to evaluate their properties as possible antitumor agents.[6a,7,8]

Preliminar screening was carried out for **8a**, **10a** and its epimer at the phosphorus atom, **9aa** and **9ab** on HT29 (colon), LoVo-Dox (colon), and A549 (NSCLC) cells. The best activities were obtained for **10a** and **9ab** benzazaphospholes (growth inhibition next to 100%).

In addition, **9ab** exhibited a cytostatic effect. To evaluate the cytotoxic potential of these compounds, a panel of a total 11 tumor cells was subsequently used (Supporting Information). The best results are sumarized in Table 2.

Table 2. GI_{50} (μM) Results of in Vitro Screening of **10a** and **9ab**

compd	prostate LN-caP	ovary IGROV	leukemia K-562	pancreas PANC1	colon LOVO-DOX
10a	7.99	12.8	10.2	16.1	7.74
9ab	5.74	16.3	12.5	15.7	4.23

In summary, we have demonstrated the feasibility of anionic cyclization dearomatization−electrophilic trapping reactions of arylphosphonamides. The starting materials are readily available on a large scale, including functionalized derivatives. The process can be applied to phenyl and naphthyl rings affording dearomatized products in high yield and stereoselectivity. Simple acid hydrolysis provides functionalized γ-(*N*-methylamino)phosphonic acids, compounds of pharmaceutical interest. The results from antitumor assays support the application of the new methodology to the synthesis of bioactive compounds.

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Supporting Information Available: Synthetic procedures, characterization and structural information, NMR spectra of new products, and X-ray data of **9aa**, **9ab**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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