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Solvent-controlled lithiation of P=C–N-heterocycles: Synthesis of mono- and bis(trimethylsilyl)-*tert*-butyl-dihydrobenzazaphospholes – A new type of highly bulky and basic phosphine ligands

Mohammed Ghalib [a], Peter G. Jones [b], Joachim W. Heinicke [a], *

[a] *Institut für Biochemie, Ernst-Moritz-Arndt-Universität Greifswald, 17487 Greifswald, Germany*
[b] *Institut für Anorganische und Analytische Chemie der Technischen Universität Braunschweig, 38023 Braunschweig, Germany*

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ABSTRACT

The influence of solvents on the lithiation of *N*-methyl-1,3-benzazaphospholes is reported; these are accessible via catalytic phosphonylation of 2-bromoanilines, subsequent reduction to 2-phosphinoanilines and acid-catalysed disproportionative ring closure with excess paraformaldehyde. Reactions with *t*BuLi in polar solvents (THF, Et_2O), particularly in the presence of *t*BuOK, lead to 2-lithiobenzazaphospholes (CH-lithiation) whereas hydrocarbons favour “normal” (hexane) or “inverse” (toluene) addition at the P=C bond. Reactive Li-species were trapped by $ClSiMe_3$, present during the lithiation in hydrocarbons, and give rise to 2- and 3-trimethylsilyl-dihydro-1,3-benzazaphospholes, respectively. In hexane, via preferred lithiation of the primary adduct, the 2,2′-bis(trimethylsilyl)-dihydro-1,3-benzazaphosphole is the main product. 5-Methyl-1,3-benzazaphosphole, with NH function, reacts in toluene in the “normal” mode to 3-*tert*-butyl-1,2-bis(trimethylsilyl)-5-methyl-dihydrobenzazaphosphole. The sterically demanding *tert*-butyl and trimethylsilyl groups are arranged in *anti*-position as shown by crystal structure analyses, the second 2-$SiMe_3$ group in *gauche* position. The *P-tert*-butyl-2,2′-bis(trimethylsilyl)-dihydrobenzazaphospholes represent a new type of sterically congested dialkylaryl phosphine ligands with increased basicity by the +I-effect of the silyl groups and +M-effect of the basic nitrogen in *o*-position.

Introduction

Compounds with trivalent phosphorus form a well-known class of ligands with wide variability of electronic and steric properties, ranging from highly basic phosphides and nucleophilic phosphines to more electrophilic phosphites and low-coordinated neutral λ^3-phosphorus species [1]. Whereas phosphine and phosphite ligands find a wide variety of applications in homogenous transition metal coordination catalyses [2], examples of the use of neutral dicoordinated P-ligands in such reactions are rather limited, being restricted to phosphabenzenes and phosphaalkenes [3]. Investigations of various types of 1,3-benzazaphospholes [4–6], which are reasonably stable π-excess aromatic P=C ligands [7], showed formation of kinetically and thermally stable $M(CO)_5$ complexes with zero-valent chromium, molybdenum and tungsten [8]; however, complexes with non-zerovalent transition metals [9] proved to be kinetically labile and, in contrast to phosphabenzene complexes [3a,3b,10], seem to be restricted to electron-rich d^{10} metal species. Labile benzazaphosphole $M(CO)_5$–$AgSbF_6$ complexes are efficient initiators for ring opening polymerization of cyclic ethers [11], but applications as ligands in coordination catalysis are disfavoured by the lability of the relevant complexes. However, an indirect applicability of these P=C compounds with respect to transition metal coordination catalysis might be promising – their transformation towards new types of bulky and basic phosphines as steering ligands. The polymerization of phosphaalkenes to new polyphosphorus materials was recently reported and highlighted [12], and some addition reactions of *t*BuLi at the P=C bond of aromatic P=C heterocycles are also known [13,14]. The 1,3-benzazaphospholes appear particularly useful for the synthesis of sterically demanding and basic phosphine ligands because the addition of *t*BuLi provides *N*-heterocyclic *tert*-butylphosphines with high P-basicity, associated with the +M-effect of the *o*-amino group in addition to the inductive (+I) and the steric

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* Corresponding author. Tel.: +49 3834 864318.
E-mail address: heinicke@uni-greifswald.de (J.W. Heinicke).

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influence of the tertiary alkyl substituent at phosphorus. We observed this addition in the case of bulkier *N*-substituted 1,3-benzazaphospholes as a competing reaction to the 2-CH lithiation by *t*BuLi(pentane) in THF. A closer investigation of the lithiation of *N*-neopentyl-1,3-benzazaphospholes gave evidence that the reaction can be controlled by auxiliaries and the polarity of the solvent. The presence of KO*t*Bu led to clean CH-lithiation, use of non-polar solvents to normal (*t*Bu at phosphorus) and inverse (*t*Bu at C2) addition. The inverse addition was prevented by steric hindrance in the reaction of *N*-adamantyl-1,3-benzazaphosphole with *t*BuLi in hexane [14]. In the case of 1-methyl-1,3-benzazaphosphole, the CH-lithiation was strongly favoured in THF or diethyl ether [15]. The aim of the present study was to find out if controlled addition reactions of *t*BuLi can be achieved for NMe- and NH-1,3-benzazaphospholes by use of less polar solvents.

Results and discussion

Starting materials

For the preparation of the starting materials we used a new three step route (Scheme 1), in part communicated recently [6c]. The first step is the synthesis of **1a**,**b** by phosphonylation of 2-bromo (methyl)anilines with diethyl phosphite in toluene in the presence of Pd(PPh$_3$)$_4$ (2 mol%)/triethylamine using a protocol of Hirao et al. [16]. The coupling gave good yields and is more convenient to handle than the original synthesis of **1a** by Issleib and Vollmer [17] by means of photoinduced Michaelis-Becker coupling of 2-iodoaniline with KOP(OEt)$_2$ in liquid ammonia. Steps two and three comprise the reduction of the 2-phosphonoaniline with LiAlH$_4$ to **2a**,**b** and the conversion to **3a**,**b** by subsequent heating (24 h) with excess paraformaldehyde (4-5 equivalents CH$_2$O) in the presence of *p*-toluenesulfonic acid (15 mol%). The latter reaction combines the condensation of the 2-phosphinoaniline with two molecules of formaldehyde with concomitant cyclization and reductive *N*-methylation. The driving force for the internal transfer of hydrogen is the gain in energy by aromatization of a dihydrobenzazaphosphole intermediate.

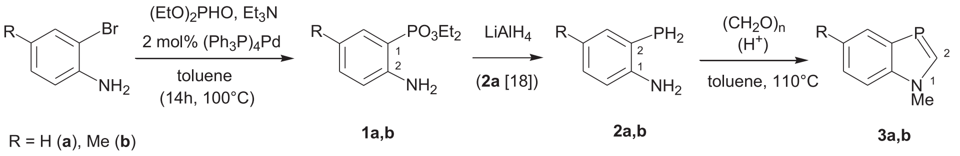
Lithiation and substitution reactions

The lithiation of **3a** with *t*BuLi (1.7 M in pentane) in diethyl ether at −78 °C led to 2-lithio-1-methyl-1,3-benzazaphosphole **4a**, which crystallized from THF/hexane as a μ-Li-bridging dimeric bis-THF solvate. This was stable at room temperature at least one day and allowed coupling with a variety of electrophilic element halides or carbonyl compounds to form benzazaphospholes with functional groups in the 2-position [15]. When the reaction of **3a** with *t*BuLi (1.6 M) was carried out in a mixture of diethyl ether with the less polar hexane (1:1 v/v) and a slight excess of chlorotrimethylsilane, added before *t*BuLi (at −70 °C) to trap reactive organolithium species, the previously observed 2-trimethylsilylbenzazaphosphole **5a** [15] was not obtained. Instead, a complex mixture of the addition products **6a**, **7a** and **8a** was formed in a molar ratio of 17:68:15% (based on 1H NMR integration) (Scheme 2). Sufficiently different and characteristic ^{31}P, ^{13}C and ^{1}H NMR data of the different compound types and comparison with related species (see below) allowed their unambiguous identification. *t*BuLi itself did not react significantly with ClSiMe$_3$ under these conditions. The formation of mainly **7a** can be rationalized in terms of rapid silylation of the primarily formed *normal* addition product and preferential lithiation of the resulting **6a**, with the second silylation affording **7a**. The *inverse* addition is a minor side reaction leading to small amounts of **8a**, formed by desilylation at phosphorus with MeOH. CH-lithiation was not observed under the above conditions.

For further experiments **3b** was used, because the additional 5-methyl group facilitates interpretation of the proton NMR spectra, which is helpful in the analysis of product mixtures. The lithiation of **3b** in THF with *t*BuLi (pentane) in the presence of ClSiMe$_3$ did not provide the expected clean 2-trimethylsilyl-benzazaphosphole **5b** but instead a mixture with the addition-bis(silylation) product **7b** in a molar ratio of 33:67%. The ratio of **5b**/**7b** in Et$_2$O, determined by integration of SiMe$_3$ proton signals, was 25:75% under the same conditions, and was similar in Et$_2$O/hexane (1:1) (23:77%). Exclusive CH-lithiation and formation of **5b** required reaction with *t*BuLi (pentane) and KO*t*Bu in THF (−70 to −30 °C) and subsequent trimethylsilylation. This shows that the presence of ClSiMe$_3$ favours addition of *t*BuLi at the P═C bond, whereas KO*t*Bu, which coordinates alkyllithium compounds to form highly polar Lochmann–Schlosser-bases [18], strongly supports CH-lithiation, as known already for various other compound types [19]. *Inverse* addition was not observed in these experiments but became the major reaction if the conversion of **3b** with *t*BuLi (pentane) was carried out in toluene (−70 °C) in the presence of ClSiMe$_3$; the *inverse* P-silylation product **9b** was obtained in ca. 70% yield along with a trace amount of the *normal* isomer **6b** (Scheme 3).

Reaction of the NH-benzazaphosphole **3c** with 1.5 equivalents *t*BuLi (pentane) in toluene in the presence of ClSiMe$_3$ (1.5 equiv.) resulted in N-silylation and *normal* addition and furnished the 1,2-bis(silylated) 3-*tert*-butyl-dihydrobenzazaphosphole **10c** (Scheme 4) in good yield. This, together with lack of even a weak phosphorus resonance for the corresponding N-trimethylsilyl-1,3-benzazaphosphole, which like 2-methyl-N-trimethylsilyl-benzazaphospholes should appear downfield shifted [20], suggests rapid addition of *t*BuLi at either the primarily formed NLi-species or the NSiMe$_3$ compound formed therefrom.

To introduce functional groups via reagents that themselves react with *t*BuLi, the lithiated species must be generated at first and be sufficiently persistent towards the solvent to allow defined substitution reactions. This is possible for the relatively stable 2-lithio-benzazaphospholes, as shown earlier for **4a** [15] and for **4b** by reaction with CO$_2$ and workup to the carboxylic acid **11b**. The latter was recently communicated, including a characterization by crystal structure analysis [6c]. Benzazaphosphole-2-carboxylic acids are stable compounds and form η^1-P pentacarbonyl tungsten complexes, as shown for **12a**, without interference by the acidic COOH-group (Chart 1). Attempts to synthesize *N*-methyl-3-*tert*-butyl-dihydrobenzazaphosphole-2-carboxylic acids, however, have so far failed to give defined products, although this was possible in the case of bulkier *N*-neopentyl, *N*-adamantyl and asymmetric *N*-(1-aryl)ethyl substituted dihydrobenzazaphosphole-2-carboxylic



Scheme 1. Synthesis of *N*-methyl-1,3-benzazaphospholes **3a**,**b**.