Pergamon

Tetrahedron Letters 43 (2002) 9611–9614

TETRAHEDRON
LETTERS

Synthesis of functionalised cyclohexadienes through addition of lithiated phosphine borane complexes to benzonitriles

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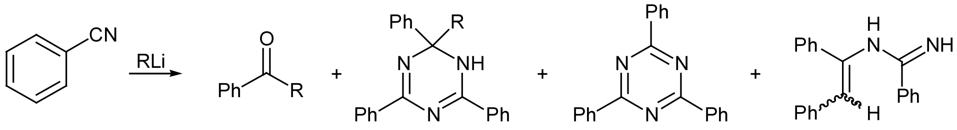
Received 18 September 2002; accepted 24 October 2002

Abstract—Functionalised 1,3- and 1,4-cyclohexadienes have been prepared through dearomatisation of benzonitriles by sequential conjugate addition of α-lithium alkyl(diphenyl)phosphine borane in the presence of HMPA and capture of the intermediate anion with protonating and alkylating reagents. © 2002 Elsevier Science Ltd. All rights reserved.

The selective transformation of aromatic molecules into cyclohexane derivatives is a powerful strategy in organic synthesis due to the frequent occurrence of alicyclic systems in natural products and compounds of biochemical importance. Besides the classical Birch reduction,[1] modern dearomatisation processes often involve the sequential addition of a nucleophile and an electrophile to activated benzenes. The activation can be attained by transition metal complexation[2] or through conventional electron-withdrawing groups. Conjugate addition has been described as the usual reactivity of alkyl-Grignard reagents towards nitrobenzene derivatives.[3] Nucleophilic dearomatisation of benzenes containing carbonyl functional groups has succeeded using bulky Lewis acids as complexation agents.[4] Dearomatisation of benzenes may be also achieved through anionic cyclisation for a series of carbon,[5] nitrogen,[6] sulfur,[7] and phosphorus[8] Michael acceptors.

The [1,2] addition of organolithium reagents to benzonitriles is a standard procedure for the synthesis of ketones. Depending on the reaction conditions, enamidines, dihydrotriazines, triazines,[9] and amines[10] may be also obtained (Scheme 1). However, the use of the cyano group for activating the benzene ring in dearomatising reactions has not been exploited. We have recently reported the first example of the conjugate addition of organolithium compounds to naphthonitriles.[11] Benzene derivatives are known to be more reluctant to nucleophilic addition than naphthalenes. In this paper, we describe the ability of phenylcarbonitriles to undergo conjugate nucleophilic addition of organolithium compounds leading to 1,3- and 1,4-cyclohexadienes.

Simple organolithium compounds and lithium phosphine borane complexes react with 1- and 2-cyanonaphthalene in the presence of HMPA, at −90°C in THF, to give functionalised dihydronaphthalenes.[11] Under the same experimental conditions, the addition of *n*-butyllithium and *sec*-butyllithium to benzonitrile takes place exclusively on the cyano group yielding the respective ketones quantitatively after aqueous workup. Lithium methyldiphenylphosphine borane also failed to attack the aromatic ring of benzonitrile. We reasoned that the chemoselectivity of the reaction could be changed by increasing the nucleophilicity of the phosphorus-stabilised carbanionic center.[12] For this purpose alkyl(diphenyl)phosphine boranes **1** were prepared by



Scheme 1.

Keywords: benzonitriles; dearomatisation; cyclohexadienes; conjugate addition; phosphine borane anions.

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PII: S0040-4039(02)02406-1

complexation of the respective phosphine[13] with BH$_3$·THF and metallated with LiBu^s in THF at −90°C for a period of 30 min in the presence of HMPA (6 equiv.).[14] Addition of benzonitrile **3a** to the anion **2a** and quenching the reaction with water allowed us to isolate, after chromatographic purification (ethyl acetate:hexane, 1:5), the cyclohexadienes **4a** (two diastereomers **4aa**:**4ab**, ratio 1:1.2) in 65% yield (Scheme 2, Table 1). The 2-cyano-1,3-dienic system of **4a** was evidenced in the ^{1}H NMR spectra by three signals in the olefinic region. The most deshielded multiplet (**4aa**, δ 6.58 ppm; **4ab**, δ 6.41 ppm) was assigned to the methine proton of the C$_\beta$ to the cyano while the other two signals were characterised by a vicinal coupling of 9.7 and 6.1 Hz for **4aa** and **4ab**, respectively. The whole network of couplings was established from the 2D gCOSY45 spectra and allowed to identify the position of the alkyl substituent on the cyclohexadiene ring. This was additionally confirmed by the correlation observed in the 2D gHMBC spectra between the methine proton next to the phosphorus (**4aa**, δ 2.77 ppm; **4ab**, δ 2.63 ppm) and the olefinic carbon three bonds away (**4aa**, δ 131.87 ppm $^3J_{PC}=11.7$ Hz; **4ab**, δ 130.65 ppm $^3J_{PC}=3.0$ Hz).[15] In this reaction the benzonitrile was completely consumed, the by-products formed were identified as the ketone **6** (20%) and the enamine **7a** (12%), both arising from the [1,2] addition of the organolithium to the nitrile. The initially formed [1,2]-adduct is hydrolysed to the ketone **6** ($\delta_{C=O}$ 198.5, $^2J_{PC}=3.6$ Hz) or it undergoes a displacement of the PPh$_2$·BH$_3$ moiety to the nitrogen through nucleophilic attack to the phosphorus, leading to **7a**.[16] Attempts to isolate **7a** by column chromatography caused its hydrolysis, giving propiophenone.

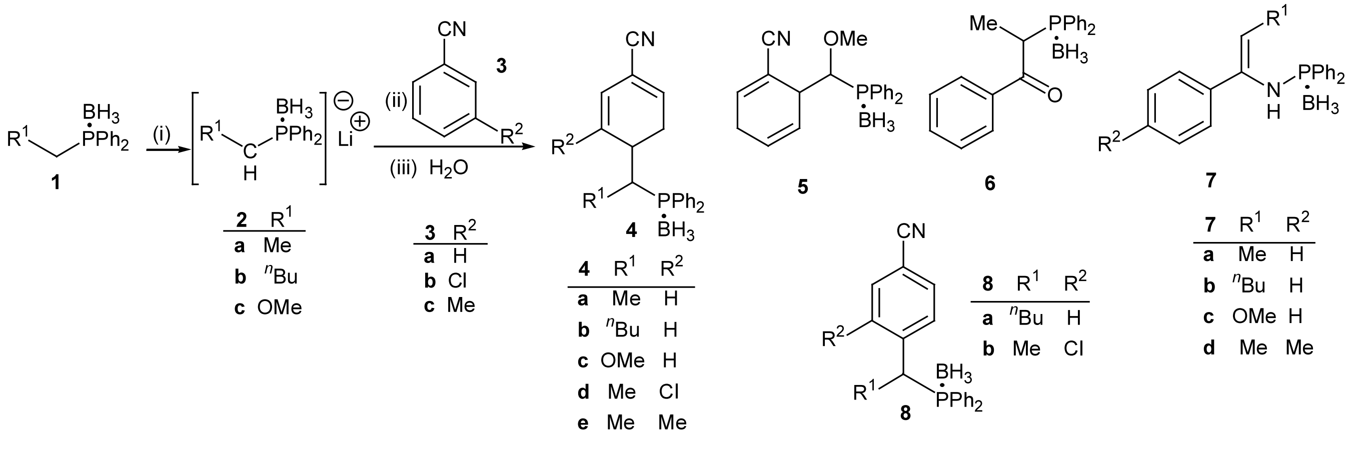
As expected, conjugate addition of **2a** to benzonitrile required longer reaction times than for naphthonitriles (12 h versus 3 h) to obtain reasonable yields of dearomatised product. Increasing the length of the alkyl substituent linked to the carbanionic center as in lithiated **2b** (R^1 = *n*-Bu), i.e. increasing the steric hindrance, produced a lower yield (63%, Table 1). Interestingly, the [1,6] addition products were distributed between the cyclohexadiene **4b** (35%) and its rearomatised derivative **8a** (14%). This is the first time that a nucleophilic aromatic substitution of hydrogen is observed using lithium phosphine borane complexes as nucleophiles.[17] A small amount (14%) of enamine **7b** was also formed. On the other hand, for **2c** where R^1 = OMe, the conversion was again almost complete. However, the higher nucleophilicity of the anion was detrimental for the regioselectivity of the reaction and a mixture of products derived from the [1,6] (**4c**, 40%), [1,4] (**5**, 21%) and [1,2] addition (**7c**, 39%) was obtained. The products were isolated by means of column chromatography using ethyl acetate:hexane (1:5) as eluent and characterized by their spectroscopic data. The vicinal arrangement of the substituents in **5** was determined from the 2D gHMBC spectrum by the correlation of the methine proton adjacent to the phosphorus (δ 4.09 ppm, $^3J_{HH}=6.2$ Hz and $^2J_{PH}=0.7$ Hz) with the *sp*^{2} hydridized quaternary carbon (δ 112.19 ppm, $^3J_{PC}=8.1$ Hz) linked to the cyano group.

Table 1. Distribution of compounds obtained in the reaction of lithium compounds **2** with benzonitriles **3**

Entry	2	3	Yield (%)					
			Global	4	5	6	7	8
1[a]	**a**	**a**	>97	40		44	9	
2	**a**	**a**	>97	65		20	12	
3	**b**	**a**	63	35			14	14
4	**c**	**a**	>97	40	21		39	
5	**a**	**b**	>97	79				21
6	**a**	**c**	44	36			8	

[a] Reaction time: 3 h.

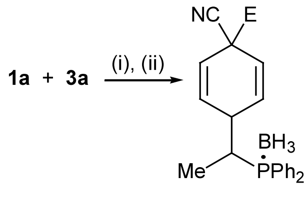
The new conjugate addition process was extended to other phenylcarbonitriles containing both electron-withdrawing, **3b**, and electron-donating substituents, **3c**, in *meta* position with respect to the cyano group (Scheme 2, Table 1). Based on the previous results, lithium ethyl(diphenyl)phosphine borane complex **2a** was selected as nucleophile. Analogous to benzonitrile, attack to the aromatic ring of **3b**–**c** took place with total regioselectivity *para* to the CN, and the dearomatised products were isolated as the respective 1,3-cyclohexadiene derivatives **4d**–**e**, after quenching the reaction



Scheme 2. *Reagents and conditions*: (i) LiBu^s (1.2 equiv.), THF, HMPA (6 equiv.), −90°C, 12 h.

with water. Apart from these general trends, the reaction course showed a strong influence of the electronic properties of the *meta* substituent. Thus, the increased electrophilicity of *m*-chlorobenzonitrile **3b** favoured the quantitative [1,6] addition of **2a**. In this way, a high yield of the cyclohexadiene **4d** (79%) was obtained together with the rearomatised compound **8b** (21%). They were separated by column chromatography. On the contrary, the deactivation produced by the methyl substituent of *m*-methylbenzonitrile towards the nucleophilic addition to the aromatic ring, besides its increased bulkiness compared to chlorine, reduced the reaction yield to 44% and allowed the detection in the crude reaction of the enamine **7d** (8%) derived from the competitive [1,2] addition to the cyano group.

The dearomatisation process improved when alkyl halides were used as quenching reagents instead of the simple protonation with water (Scheme 3). The addition of **2a** to benzonitrile followed by alkylation with methyl iodide or allyl bromide afforded quantitatively the functionalised 1,4-cyclohexadienes **9a** and **9b**, respectively. Benzyl bromide was, however, less efficient as an electrophile probably due to its larger size. The dearomatised product **9c** was also obtained in high yield (77%); however, small quantities of the [1,2] adducts **6** (13%) and **7a** (10%) were also formed. Isolation of **9c** was achieved by precipitation from diethyl ether.



9	E	Yield(%)	*dr*
a	Me	>97	1:1.2
b	Allyl	>97	1:1.5
c	Bn	77	>97:1

Scheme 3. *Reagents and conditions*: (i) LiBu^s (1.2 equiv.), THF, HMPA (6 equiv.), −90°C, 0.5 h; (ii) EX = MeI, AllylBr or BnBr (1.2 equiv.), −90°C, 2 h.

The two steps involved in the synthesis of cyclohexadienes **9** were totally regioselective. As expected, only the [1,6] addition of the nucleophilic to benzonitrile was observed. Interestingly, alkylation occurred exclusively at the α-carbon to the cyano group, while the preferred position for protonation was the γ one. A similar behaviour has been observed by Yamamoto et al. in the reactions of silyllithium reagents with aromatic carbonyl compounds in the presence of aluminium tris(2,6-diphenylphenoxide) (ATPH).[4b] Compounds **9** were mixtures of two stereomers with low selectivity except for E = Bn, where only one stereomer was formed. They could be separated by column chromatography and identified through their 2D gNOESY and gROESY spectra as *cis*/*trans* diastereomers.

In summary, conjugate addition of lithium alkyl(diphenyl)phosphine borane complexes to benzonitriles has been achieved for the first time. In the presence of HMPA, the [1,6] addition is preferred over the conventional [1,2] addition to the CN. Protonation of the dearomatised lithium adducts with water afford 2-cyano-1,3-cyclohexadienes, while the alkylation with MeI, allylBr, and BnBr leads to the formation of functionalised 1,4-cyclohexadienes in excellent yields. This structural fragment is included in a large number of natural products. The cyano and phosphine borane functional groups of these molecules increase their attractiveness for further applications in organic synthesis.

Acknowledgements

Financial support by the Ministerio de Ciencia y Tecnología (Project PPQ2001-3266) is gratefully acknowledged. C.M.A.S. thanks Ministerio de Ciencia y Tecnología for a doctoral fellowship.

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15. Spectral characterisation of **4ab**. Oil. Yield 36%. IR (KBr), ν (cm^{-1}) 2230. ^1H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.15 (dd, $^3J_{HH}$ 7.3 Hz, $^3J_{PH}$ 16.1 Hz, 3H), 2.31 (m, 2H), 2.63 (ddc, $^3J_{HH}$ 4.1 Hz, $^3J_{HH}$ 7.3, $^2J_{PH}$ 15.7 Hz, 1H), 2.85 (m, 1H), 5.90 (ddd, $^4J_{HH}$ 1.1, $^3J_{HH}$ 6.1 Hz, 1H), 6.15 (ddd, $^5J_{HH}$ 0.7 Hz, $^3J_{HH}$ 4.0 Hz, $^3J_{HH}$ 6.1 Hz, 1H), 6.41 (m, 1H), 7.50 (m, 6H), 7.80 (m, 4H). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 11.45 (d, $^2J_{PC}$ 1.8 Hz), 29.15 (d, $^3J_{PC}$ 10.2 Hz), 32.12 (d, $^1J_{PC}$ 33.6 Hz), 32.15 (d, $^2J_{PC}$ 4.2 Hz), 111.04, 118.02, 121.62, 128.17 (d, $^1J_{PC}$ 57.7 Hz), 128.47 (d, $^1J_{PC}$ 53.5 Hz), 128.84 (d, $^3J_{PC}$ 9.5 Hz), 129.11 (d, $^3J_{PC}$ 9.5 Hz), 130.65 (d, $^3J_{PC}$ 3.0 Hz), 131.37 (d, $^4J_{PC}$ 2.2 Hz), 131.54 (d, $^4J_{PC}$ 2.2 Hz), 132.2 (d, $^2J_{PC}$ 8.1 Hz), 132.60 (d, $^2J_{PC}$ 8.8 Hz), 140.99. ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 22.53. Anal. calcd for $C_{21}H_{23}BNP$ (331.21): C, 76.15; H, 7.00; N, 4.23. Found: C, 76.25; H, 6.93; N, 4.20%. MS, m/z (%): 332 (M^++1).
16. Ketone **6** (34%) and enamine **7a** (21%) are the only products obtained in the reaction of **2a** and benzonitrile in the absence of HMPA. Compound **7a** was identified from the NMR data of the crude reaction. The enamine function is characterised in the ^1H NMR spectrum by the quartet of the olefinic proton, δ 5.10, $^3J_{HH}=6.8$ Hz, and in the ^{13}C NMR spectrum by two doublets at δ 107, $^3J_{PC}=3.6$ Hz and 137.2, $^2J_{PC}=5.4$ Hz. This rearrangement has been previously observed in the analogous reaction of lithium *N*-methoxycarbonylphosphazenes. Barluenga, J.; Ferrero, M.; López-Ortiz, F.; Palacios, F. *J. Chem. Soc*., *Perkin Trans. 1* **1989**, 615.
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