Pergamon

Tetrahedron Letters 43 (2002) 2565–2568

TETRAHEDRON LETTERS

Dearomatisation of 1- and 2-cyanonaphthalene through nucleophilic conjugate addition

Carmen M. Andújar Sánchez, Mª José Iglesias and Fernando López Ortiz*

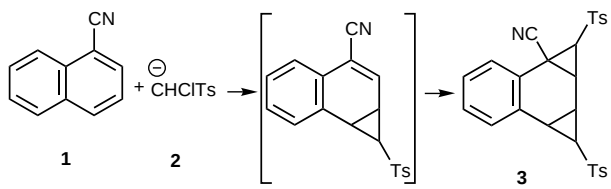
Área de Química Orgánica, Universidad de Almería, Carretera de Sacramento, 04120 Almería, Spain

Received 4 February 2002; accepted 14 February 2002

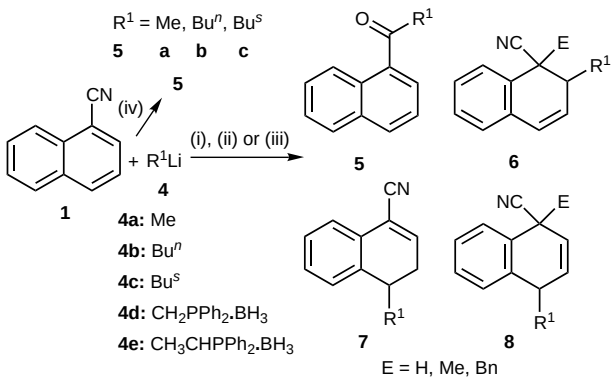
Abstract—Conjugate nucleophilic addition of organolithium compounds to 1- and 2-cyanonaphthalene is described for the first time. The dearomatisation is carried out in the presence of HMPA and leads to functionalised dihydronaphthalenes. The nucleophiles used include simple lithium reagents as well as phosphorus-stabilised anions. © 2002 Elsevier Science Ltd. All rights reserved.

Dearomatisation reactions of naphthalenes bearing electron-withdrawing groups through conjugate addition of organometallic reagents have a considerable potential for the preparation of substances of biological importance.[1] In these processes stable and widely available materials are transformed into functionalised dihydronaphthalenes with excellent regio- and stereocontrol. Generally, the Michael acceptors used for the activation of the naphthalene ring are based on carbonyl[2] bearing functional groups or on carbonyl[3] or carboxylic acid derivatives[4] and can also be carried out intramolecularly.[5] Oxazolines are among the activating groups of naphthalenes most extensively applied in tandem organolithium-electrophile addition processes.[1a–b,6] Although nitriles are precursors of the 1,3-oxazoline moiety,[7] they have never been directly used as Michael acceptors in dearomatisation reactions. The only report on the dearomatisation of a naphthonitrile corresponds to the reaction of 1-cyanonaphthalene **1** with the carbanion of chloromethyl *p*-tolyl sulfone **2** leading to a bis-annulated product **3**, whose formation has been explained via tandem addition of the carbanion to naphthalene followed by intramolecular nucleophilic substitution (Scheme 1).[8]

This exception apart, organolithium reagents commonly react with aromatic nitriles through [1,2] addition to the cyano group, which represents a well-known method for the synthesis of ketones.[9] Here we describe the first examples of the conjugate addition of organolithium compounds to naphthonitriles. The use of HMPA as cosolvent was crucial for achieving the chemoselective addition of the nucleophile to the aromatic ring. The treatment of 1-cyanonaphthalene **1** with either $LiBu^n$, **4b**, or $LiBu^s$, **4c**, at –90°C for 3 h in THF using HMPA as cosolvent, followed by aqueous work-up afforded mixtures of the ketone **5** and the dihy-



Scheme 1.



Scheme 2. *Reagents and conditions*: (i) –90°C, THF, HMPA (6 equiv.), 0.5 h; (ii) E'X' = 1N HCl; (iii) EX = MeI or BnBr (1.2 equiv.), –90°C, 0.5 h; (iv) –90°C, THF, 0.5 h, then H_2O.

Keywords: cyanonaphthalene; dearomatisation; dihydronaphthalenes; conjugate addition; phosphine borane anions.

* Corresponding author. Tel.: +34 950 015478; fax: +34 950 015481; e-mail: flortiz@ual.es

PII: S0040-4039(02)00316-7

dronaphthalenes **6** and **7** corresponding to the [1,2], [1,4] and [1,6] adducts of the organolithium to the nitrile, respectively (Scheme 2). The ratio of regioisomers **6**:**7** was similar ($\approx$5:1) for both RLi reagents, whereas the yield of dearomatised species increased from 55% for LiBu^n to 94% when LiBu^s was used as nucleophile (Table 1). On the contrary, under the same reaction conditions, MeLi **4a** gave exclusively the [1,2] addition product **5a**. Apparently, the increase in the nucleophilic strength of the organolithium species favored the conjugate addition to the naphthalene system. For a given RLi reagent the reactivity is further enhanced by the deaggregation power of HMPA.[10] In the absence of HMPA [1,2] addition was exclusively observed in all instances.

Column chromatography (ethyl acetate:hexane, 1:5) allowed us to isolate ketones **5**, the structural assignment of which was trivial. Compounds **6**–**7** could not be separated and were identified through the analysis of the NMR spectra of the mixtures.[11] The signals for the dearomatised ring appeared in two well defined regions of the ^{1}H NMR spectra: 2.3–4.3 and 5.8–6.9 ppm, corresponding to the aliphatic and olefinic protons of the ring, respectively. The [1,6] adducts showed only one olefinic proton deshielded due to the conjugation with the cyano group. On the other hand, compounds **6** were obtained as *cis–trans* mixtures, with the *cis* isomer being formed predominantly.

To increase the scope of the new dearomatisation reaction we studied the viability of introducing functionalised nucleophiles. Due to our interest in organophosphorus chemistry,[12] we focused on lithium alkyl(diphenyl)phosphine borane complexes **4d**–**e**.[13] These anions added smoothly to 1-cyanonaphthalene in the presence of HMPA. Quenching the reactions with water afforded dihydronaphthalene regioisomers **6d**–**e**/**7d**–**e** in high yield, without traces of the ketones derived from the [1,2] addition being detected (Table 1). Interestingly, [1,4] addition predominated for lithium phosphine borane **4d**, while the [1,6] regioisomer was formed preferentially in the reaction with the secondary carbanion **4e**. This change in the regioselectivity of the process can be ascribed to steric interactions produced by the bulky $PPh_2{\cdot}BH_3$ moiety. Column chromatography (mixtures of ethyl acetate:hexane) allowed us to isolate the compounds in pure form. They were characterized based on their spectroscopic data.[11]

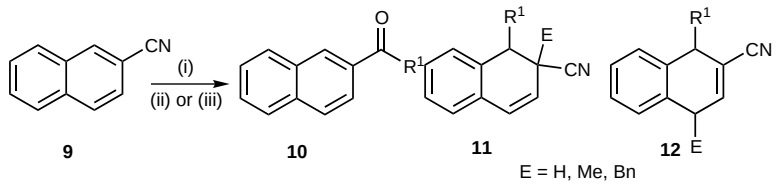
Table 1. Distribution of compounds obtained in the reaction of lithium compounds **4** with 1-cyanonaphthalene **1**

Comp.	R^1	E	Yield (%)			
			5	**6**	**7**	**8**
a	Me		100			
b	Bu^n	H	45	46	9	
c	Bu^s	H	6	78	16	
d	$CH_2PPh_2{\cdot}BH_3$	H		61	26	
e	$CH_3CHPPh_2{\cdot}BH_3$	H		18	62	
f	Bu^n	Me	23	52		22
g	Bu^s	Me	12	61		26
h	$CH_2PPh_2{\cdot}BH_3$	Me		60		23
i	$CH_3CHPPh_2{\cdot}BH_3$	Bn		19		67

The intermediate lithiated species formed in the dearomatization step were also alkylated with methyl iodide and benzyl bromide in a one-pot reaction leading to 1,1,2- and 1,1,4-trisubstituted dihydronaphthalenes **6f**–**i** and **8f**–**i**,[11,14] respectively (Scheme 2).[15] For the [1,6] adducts, alkylation next to the nucleophile was not observed. Significantly, the successive addition of LiBu^n and MeI to **1** led to 74% of dearomatisation, i.e. an increase of 19% with respect to the use of water as quenching reagent. This result suggests that the adduct of attack to the cyano group is in equilibrium with those of attack to the naphthalene ring and that the lithium dihydronaphthalenes are alkylated faster thus displacing the equilibrium in favor of the dearomatised compounds. On the other hand, the alkylation of the lithiated species produced by the conjugate addition of the phosphorus-stabilized anions **4d**–**e** to **1** gave rise to [1,4] and [1,6] regioisomers in similar ratios to those obtained when the reaction was quenched with water (c.f. entries 4–5 and 8–9 in Table 1).

The analogous conjugate addition reactions of conventional organolithium reagents with 2-cyanonaphthalene **9** proved to be less efficient than with **1**: LiBu^n gave exclusively the ketone **10a** (i.e. [1,2] addition), while LiBu^s afforded a mixture of [1,2] and [1,4] addition products **10** and **11**, respectively, either using water or MeI as quenching electrophile (Scheme 3, Table 2). These compounds were isolated by column chromatography (ethyl acetate:hexane, 1:7) and identified through their spectral data.

As expected, **4d**–**e** added regiospecifically to the α position of the naphthalene ring of nitrile **9** yielding 1,2- and 1,4-dihydronaphthalenes **11**–**12**, with **11** being formed predominantly when the anions were trapped with methyl iodide and benzyl bromide (Table 2).



Scheme 3. *Reagents and conditions*: (i) **4**, –90°C, THF, HMPA (6 equiv.), 0.5 h; (ii) EX = H_2O; (iii) EX = MeI or BnBr (1.2 equiv.), –90°C, 0.5 h.

Table 2. Yield of compounds obtained in the reaction of lithium compounds **4** with 2-cyanonaphthalene **9**

Comp.	R^1	E	Yield (%)		
			10	**11**	**12**
a	Bu^n		100		
b	Bu^s	H	45		55
c	$CH_2PPh_2{\cdot}BH_3$	H		39	45
d	$CH_3CHPPh_2{\cdot}BH_3$	H			97
e	Bu^s	Me	42	40	
f	$CH_2PPh_2{\cdot}BH_3$	Me		73	
g	$CH_3CHPPh_2{\cdot}BH_3$	Me		70	12
h	$CH_2PPh_2{\cdot}BH_3$	Bn		55	19

In summary, conjugate addition of organolithium reagents to 1- and 2-naphthonitrile has been achieved for the first time. The use of HMPA as cosolvent is pivotal for the success of the reaction, which can be carried out with common organolithium compounds as well as lithium phosphine borane complexes. The dearomatised lithium adducts may be protonated with water or alkylated with MeI and BnBr yielding functionalised dihydronaphthalenes. These are useful compounds due to their applications in organic synthesis. The phosphine borane derivatives are particularly interesting because this functional group may be used to perform additional transformations on the α alkyl chain.

Acknowledgements

Financial support by the Ministerio de Educación y Cultura (Project PB97-0587-C02-01) is gratefully acknowledged. C.M.A.S. thanks the Ministerio de Educación y Cultura for a doctoral fellowship.

References

1. (a) Robichaud, A. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2607; (b) Hulme, A. N.; Henry, S. S.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 1265; (c) Ahmed, A.; Bragg, R. A.; Clayden, J.; Tschabanenko, K. *Tetrahedron Lett.* **2001**, *42*, 3407; (d) Bragg, R. A.; Clayden, J.; Blandon, M.; Ichihara, O. *Tetrahedron Lett.* **2001**, *42*, 3411.
2. (a) Maruoka, K.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 9091; (b) Saito, S.; Shimada, K.; Yamamoto, H.; Marigorta, E. M.; Fleming, I. *Chem. Commun.* **1997**, 1299; (c) Saito, S.; Sone, T.; Shimada, K.; Yamamoto, H. *Synlett* **1999**, 81.
3. (a) Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 9351; (b) Tomioka, K.; Shioya, Y.; Nagaoka, Y.; Yamada, K. I. *J. Org. Chem.* **2001**, *66*, 7051.
4. (a) Tomioka, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 681; (b) Plunian, B.; Mortier, J.; Vaultier, M.; Toupet, L. *J. Org. Chem.* **1996**, *61*, 5206; (c) Shindo, M.; Koga, K.; Asano, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 4955; (d) Clayden, J.; Frampton, C. S.; McCarthy, C.; Westlund, N. *Tetrahedron* **1999**, *55*, 14161; (e) Saito, S.; Sone, T.; Murase, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 10216.
5. (a) Ahmed, A.; Clayden, J.; Rowley, M. *Chem. Commun.* **1998**, 297; (b) Ahmed, A.; Clayden, J.; Rowley, M. *Tetrahedron Lett.* **1998**, *39*, 6103; (c) Bragg, R. A.; Clayden, J. *Tetrahedron Lett.* **1999**, *40*, 8327; (d) Ahmed, A.; Clayden, J.; Rowley, M. *Synlett* **1999**, 1954; (e) Clayden, J.; Menet, C. J.; Mansfield, D. J. *Org. Lett.* **2000**, *2*, 4229.
6. For reviews, see: (a) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297; (b) Meyers, A. I. *J. Heterocyclic Chem.* **1998**, *35*, 991. See also (c) Kolotuchin, S. V.; Meyers, A. I. *J. Org. Chem.* **2000**, *65*, 3018.
7. Meyers, A. I.; Oppenlaender, T. *J. Am. Chem. Soc.* **1986**, *108*, 1989.
8. Makosza, M.; Glinka, T.; Ostrowski, S.; Rykowski, A. *Chem. Lett.* **1987**, 61.
9. Wibaut, J. P.; Heeringa, L. G. *Recl. Trav. Chim. Pays-Bas* **1955**, *74*, 1003.
10. Reich, H. J.; Barst, J. P.; Dykstra, R. R.; Green, D. P. *J. Am. Chem. Soc.* **1993**, *115*, 8728.
11. The spectra measured included: ^1H, ^{13}C, DEPT, gHMQC, gHMBC, gNOESY, gCOSY. The stereoisomers were readily identified based on the analysis of the vicinal coupling constants and the correlations observed in the gNOESY spectra.
12. Ruiz-Gómez, G.; López-Ortiz, F. *Synlett*, in press.
13. Prepared by metalation of the corresponding alkyl(diphenyl)phosphine borane with Bu^sLi in THF at −90°C. The use of HMPA allowed us to reduce the metalation step from 2 h to 30 min. See: Imamoto, T.; Kusumoto, T.; Suzuki, N.; Sato, K. *J. Am. Chem. Soc.* **1985**, *107*, 5303.
14. The [1,6] addition was established from the correlations observed in the HMBC spectra of **8** for the carbon atom of the cyano group with the adjacent methyl (**8f**–**h**) or methylene protons (**8i**) and with one olefinic proton of the isolated carbon–carbon double bond.
15. Preparation of **6h** and **8h**. Bu^sLi (1.2 mL of a 1.3 M solution in cyclohexane, 1.56×10^{-3} mol) was added to a solution of methyldiphenylphosphine borane (6.23×10^{-4} mol) and HMPA (3.74×10^{-3} mol) in THF (20 mL) at −90°C. After 30 min of metalation a solution of **1** (6.23×10^{-4} mol) in THF (10 mL) was added at −90°C. The reaction was stirred for 30 min, then MeI was added (7.5×10^{-4} mol) and allowed to react for 30 min. Conventional extractive work-up followed by purification by column chromatography (AcOEt:hexane, 1:7) afforded fractions containing **6h** and **8h**. **6h**: White solid. Yield: 60%. Mp (°C): 108–110. IR (KBr), ν (cm^{-1}): 2197. ^1H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.57 (s), 2.39 (dt, $^2J_{HH}$ 13.8, $^3J_{HH}=^2J_{PH}$ 11.5 Hz, 1H), 2.86 (ddd, $^2J_{HH}$ 13.8, $^3J_{HH}$ 2.7, $^2J_{PH}$ 12.5 Hz, 1H), 2.97 (m, $^3J_{HH}$ 2.7, $^3J_{HH}$ 6.1, $^3J_{HH}$ 11.5, $^3J_{PH}$ 8.4 Hz, 1H), 5.95 (dd, $^3J_{HH}$ 6.1, $^3J_{HH}$ 9.5 Hz, 1H), 6.22 (d, $^3J_{HH}$ 9.5 Hz, 1H), 7.1 (m, 1H), 7.32 (m, 1H), 7.45 (m, 7H), 7.6 (m, 1H), 7.65 (m, 2H), 7.75 (m, 2H). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 26.26, 29.22 (d, $^1J_{PC}$ 36.7 Hz), 38.49 (d, $^2J_{PC}$ 3 Hz), 43.7 (d, $^3J_{PC}$ 12.6 Hz), 122.33, 126.25, 126.45, 127.37, 127.97 (d, $^3J_{PC}$ 1.2 Hz), 128.69 (d, $^3J_{PC}$ 10.2 Hz), 128.85, 128.87, 128.97 (d, $^3J_{PC}$ 9.6 Hz), 129.17 (d, $^1J_{PC}$ 57.1 Hz), 129.27 (d, $^1J_{PC}$ 45 Hz), 130.45, 131.4 (d, $^4J_{PC}$ 1.2 Hz), 131.43 (d, $^4J_{PC}$ 1.2 Hz), 132.03 (d, $^2J_{PC}$ 9.6 Hz), 132.1, 132.3 (d, $^2J_{PC}$ 9.6 Hz).

^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 14.2. Anal. calcd for $C_{25}H_{25}BNP$ (381.05): C, 79.01; H, 6.44; N, 3.82. Found: C, 78.8; H, 6.29; N, 3.67. MS, m/z (%): 404 (M^++23).

8h. Oil. Yield: 23%. IR (KBr), ν (cm^{-1}): 2197. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.77 (s), 2.48 (dt, $^2J_{HH}$ 14.3, $^3J_{HH}=^2J_{PH}$ 10.8 Hz, 1H), 2.7 (ddd, $^2J_{HH}$ 14.3, $^3J_{HH}$ 3.2, $^2J_{PH}$ 11.6 Hz, 1H), 3.95 (m, $^3J_{HH}$ 3.2, $^3J_{HH}$ 4.9, $^3J_{HH}=^3J_{PH}$ 10.8 Hz, 1H), 5.79 (d, $^3J_{HH}$ 10.5 Hz, 1H), 5.95 (dd, $^3J_{HH}$ 4.9, $^3J_{HH}$ 9.8 Hz, 1H), 7.13 (m, 1H), 7.27 (m, 2H), 7.53 (m, 7H), 7.76 (m, 4H). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 32.23, 34.19 (d, $^2J_{PC}$ 1.8 Hz), 36.91, 36.99 (d, $^1J_{PC}$ 32.3 Hz), 122.98, 126.56, 127.36, 127.63, 128.55 (d, $^4J_{PC}$ 2.2 Hz), 128.56, 128.92 (d, $^3J_{PC}$ 10.2 Hz), 128.98 (d, $^1J_{PC}$ 54.7 Hz), 129 (d, $^3J_{PC}$ 9.6 Hz), 129.33 (d, $^1J_{PC}$ 56.5 Hz), 130.05 (d, $^3J_{PC}$ 1.8 Hz), 131.47 (d, $^4J_{PC}$ 2.9 Hz), 131.65 (d, $^4J_{PC}$ 2.2 Hz), 132.01 (d, $^2J_{PC}$ 8.8 Hz), 132.33 (d, $^2J_{PC}$ 8.8 Hz), 134.26, 136.8 (d, $^3J_{PC}$ 11.4 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 14.3. Anal. calcd for $C_{25}H_{25}BNP$ (381.05): C, 79.01; H, 6.44; N, 3.82. Found: C, 78.8; H, 6.29; N, 3.67. MS, m/z (%): 404 (M^++23).