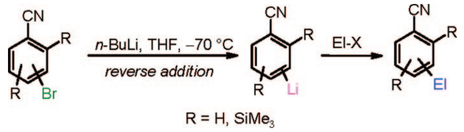
Selective Generation of Lithiated Benzonitriles: the Importance of Reaction Conditions

Sergiusz Luliński* and Katarzyna Zajac

Warsaw University of Technology, Faculty of Chemistry, Noakowskiego 3, 00-664 Warsaw, Poland

serek@ch.pw.edu.pl

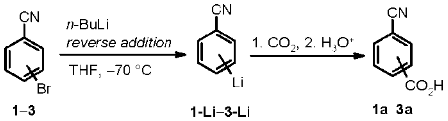
Received June 27, 2008



Lithiated benzonitriles can be generated in high yields from reactions of bromobenzonitriles with *n*-BuLi in THF under standard cryogenic conditions (ca. −70 °C) provided the reverse addition mode is employed. The resultant aryllithiums are fairly stable at temperatures up to −60 °C. The formation of lithiated benzonitriles via Br/Li exchange under normal addition mode conditions is plagued by deprotonation and extensive CN-addition reactions. The generation of related aryllithiums from disilylated bromobenzonitriles is comparatively less sensitive to reaction conditions.

Lithiation of benzonitriles is a useful method for a functionalization of these versatile reagents. Directed *ortho*-metalation has been successfully applied for the generation of selected *o*-lithiobenzonitriles.[1,2] In general, these intermediates were preferentially trapped in situ with suitable electrophiles such as $B(O\text{-}i\text{-}Pr)_3$ and TMSCl to give various *ortho*-boronated[3] and *ortho*-silylated[4,5] derivatives, respectively. It has been reported that the clean generation of 3- as well as 4-lithiobenzonitrile by halogen−lithium exchange from the corresponding halobenzonitriles and *n*-BuLi[6] requires very low temperatures (−100 °C)[7] as under standard cryogenic conditions employing dry ice/acetone cooling (effective internal temperature of ca. −70 °C) extensive degradation occurs, thus decreasing yields of desired aryllithium intermediates.[8] However, no details concerning the nature of these undesired side reactions were reported. It should be noted that significant progress has been made recently in the generation of related magnesiated benzonitriles using Knochel's approach based on halogen−magnesium exchange.[9] The lack of full information has prompted us to investigate the generation of simple and related silylated lithiobenzonitriles via Br/Li interconversion.

SCHEME 1



We have found that the choice of the proper addition mode is essential for the high-yield preparation of lithiated benzonitriles unless harsh cryogenic conditions (ca. −100 °C) are used. When we treated a solution of 4-bromobenzonitrile **1** in THF with *n*-BuLi at ca. −70 °C (internal temperature) followed by the quench with $B(OMe)_3$, we obtained an impure 4-cyanobenzoic acid **1a** in ca. 30% crude yield. However, when a solution of **1** in THF was added to a precooled solution of *n*-BuLi in THF (reverse addition) the resulting lithiate **1-Li** was formed much more cleanly as evidenced by the subsequent high yield conversion into pure **1a** (Scheme 1). Similar behavior was observed for Br/Li exchange with 3-bromobenzonitrile **2** as the substrate as the acid **2a** was isolated in a comparable yield. The conversion of 2-bromobenzonitrile **3** into the corresponding boronic acid **3a** was also successful using reverse addition of *n*-BuLi but failed completely with normal addition. It should be noted that the reported preferred routes to related cyanophenylboronic acids involve the addition of *n*-BuLi to a solution of the bromobenzonitrile (**1** or **2**, respectively) in THF containing in situ $B(O\text{-}i\text{-}Pr)_3$.[10] Thus, the preformed aryllithium intermediates **1-Li** and **2-Li** are rapidly trapped with the electrophile, which efficaciously prevents undesired competitive reactions.

Our results suggest that under optimal conditions (reverse addition of *n*-BuLi, THF as a solvent) Br/Li interconversion proceeds with good chemoselectivity. Hence, the nitrile group is not susceptible to nucleophilic attack of *n*-BuLi. Moreover, the resulting aryllithiums **1-Li** and **2-Li** are quite stable. It seems that the carbanionic character of the aromatic ring in these intermediates significantly decreases the electrophilic properties of the CN group due to the negative charge cumulation at this group effected via polarization.[11] As a result, the nitrile function becomes quite resistant against attack with carbanionic nucleophiles present in a reaction system; that is, with unreacted *n*-BuLi and/or another molecule of a cyanophenyllithium the latter reaction would result in oligomerization. It should be stressed that the proper choice of solvent is crucial for the

---

(1) Mendel, K.; Fisher, E. L.; DiMichele, L.; Frantz, D. E.; Nelson, T. D.; Kress, M. H. *J. Org. Chem.* **2006**, *71*, 2188–2191.

(2) Luliński, S.; Serwatowski, J.; Szczerbińska, M. *Eur. J. Org. Chem.* **2008**, 1797–1801.

(3) (a) Kristensen, J.; Lysén, M.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2001**, *3*, 1435–1437. (b) Lysén, M.; Hansen, H. M.; Begtrup, M.; Kristensen, J. L. *J. Org. Chem.* **2006**, *71*, 2518–2520.

(4) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155–6166.

(5) Luliński, S.; Serwatowski, J. *J. Org. Chem.* **2003**, *68*, 9384–9388.

(6) Gilman, H.; Melstrom, D. S. *J. Am. Chem. Soc.* **1948**, *70*, 4177–4179.

(7) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 1187–1191.

(8) Nishimura, M.; Ueda, M.; Miyaura, N. *Tetrahedron* **2002**, *58*, 5779–5787.

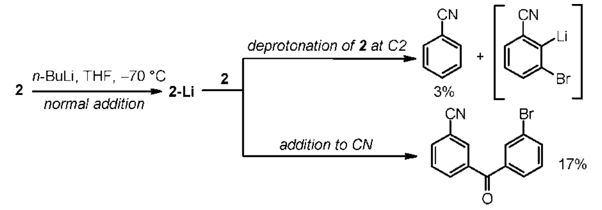
(9) (a) Shi, L; Chu, Y.; Knochel, P.; Mayr, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 202–204. (b) Wang, X.; Sun, X.; Zhang, L.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. *Org. Lett.* **2006**, *8*, 305–307.

(10) (a) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394–5397. (b) Levell, J.; Astless, P.; Eastwood, P.; Cairns, J.; Houille, O.; Aldous, S.; Merriman, G.; Whiteley, B.; Pribish, J.; Czekaj, M.; Liang, G.; Maignan, S.; Guilloteau, J.-P.; Dupuy, A.; Davidson, J.; Harrison, T.; Morley, A.; Watson, S.; Fenton, G.; McCarthy, C.; Romano, J.; Mathew, R.; Engers, D.; Gardyan, M.; Sides, K.; Kwong, J.; Tsay, J.; Rebello, S.; Shen, L.; Wang, J.; Luo, Y.; Giardino, O.; Lim, H.-K.; Smith, K.; Pauls, H. *Bioorg. Med. Chem.* **2005**, *13*, 2859–2872.

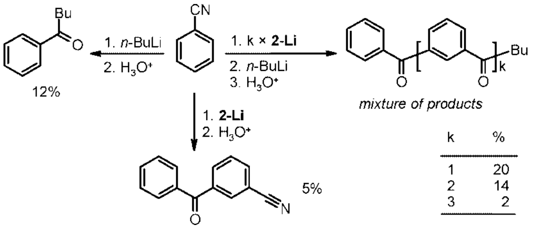
(11) Schlosser, M.; Castagnetti, E. *Chem.—Eur. J.* **2002**, *8*, 799–804.

10.1021/jo8013808 CCC: $40.75

SCHEME 2. Initial Reaction Pathways for the Reaction of 2 with *n*-BuLi (Products Identified after Acidic Hydrolysis of the Reaction Mixture)



SCHEME 3



successful generation of lithiated benzonitriles. The attempted synthesis of **2a** using Et_2O as a solvent gave only a poor yield of the desired product (ca. 15%); under these conditions, 3-bromovalerophenone was formed preferentially. This indicates that the competitive addition of *n*-BuLi to the nitrile function is favored in less polar ethereal solvent such as Et_2O whereas THF strongly promotes Br/Li exchange in bromobenzonitriles. Syntheses of **1a** and **2a** performed using the mixed solvent THF/Et_2O (1:1) gave results comparable to those obtained using THF alone.

The lack of selectivity for the normal addition mode can be rationalized by extensive side reactions favored especially under these conditions. This interpretation is supported by the results obtained from the reaction of **2** with *n*-BuLi (normal addition, THF, −70 °C) followed by hydrolysis. GC−MS analysis revealed benzonitrile (3%) as one of several minor products (Scheme 2). Higher molecular weight products were found to predominate. We suppose that two major pathways must be taken into account at the initial stage of the reaction performed with normal addition of *n*-BuLi. First, deprotonation of **2** at C2 with initially formed **2-Li** (Scheme 2) apparently occurs at ca. −70 °C to give less basic 3-bromo-2-lithiobenzonitrile and benzonitrile; the former intermediate is prone to aryne-forming elimination. As an alternative to deprotonation, the addition of **2-Li** to **2** resulting in the formation of 3-bromo-3′-cyanobenzophenone (Scheme 2) is also observed.

Benzonitrile formed during deprotonation serves as an effective trap for *n*-BuLi being added to the reaction mixture as well as for contiguously generated **2-Li**. The latter reaction may initiate a series of iterative additions of **2-Li** to the nitrile group terminated by the addition of *n*-BuLi. Thus, a mixture of oligomeric ketone products (Scheme 3) is formed after subsequent hydrolysis.

Furthermore, we have shown in separate experiments that lithiated benzonitriles **1-Li** and **2-Li** (cleanly generated by reverse addition) add smoothly to the nitrile group of PhCN at ca. −70 °C to give the corresponding cyanobenzophenones **1b** and **2b**,[12] respectively, with moderate yields (Scheme 4). Hence, these results confirm that electrophilic properties of CN group in **1-Li** and **2-Li** are weakened as the addition of lithiated benzonitriles to the nitrile group in the parent neutral compound PhCN proceeds effectively.

SCHEME 4

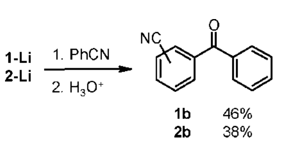
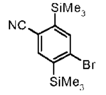
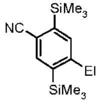
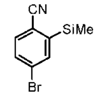
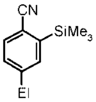
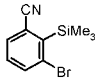
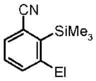
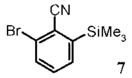
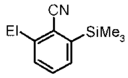
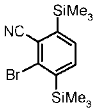
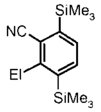


TABLE 1. Synthesis of Silylated Cyanobenzoic and Cyanophenylboronic Acids[a]

Starting material	Product	El, Compd No.	Yield, %
 4		COOH, **4a**	78 (ca 20[b])
		B(OH)$_2$,**4b**	66
 5		COOH, **5a**	78
		B(OH)$_2$, **5b**	71
 6		COOH, **6a**	71
		B(OH)$_2$, **6b**[c]	82
 7		COOH, **7a**	93
		B(OH)$_2$, **7b**	98
 8		COOH, **8a**	86
		B(OH)$_2$, **8b**	80[d]

[a] Standard conditions: (i) *n*-BuLi (reverse addition), THF, −70 °C; (ii) El-X [CO_2, $B(OMe)_3$], −70 °C; (iii) H_3O^+. [b] Warmed to −20 °C prior to carboxylation. [c] $B(OMe)_3$ added at −90 °C. [d] Crude product.

In addition, we have studied the generation of several mono- and disilylated lithiobenzonitriles via Br/Li exchange (Table 1). Starting silylated bromobenzonitriles **4**−**8** can be readily synthesized from lithiation of bromobenzonitriles with LDA[5] or LTMP[2] followed by silylation with TMSCl used either in situ or sequentially. We have found that desired aryllithiums can be obtained without difficulty under reaction conditions similar to those applied for the conversion of **1**−**3**. The reactivity of silylated lithiobenzonitriles with electrophiles was examined. Trapping with CO_2 proceeds smoothly to afford the corresponding cyanobenzoic acids **4a**−**8a** with moderate to good yields. We observed that warming the aryllithium **4-Li** to ca. −20 °C prior to carboxylation resulted in the low yield of **4a** (ca. 20%), which points to a limited influence of silylation on the thermal stability of a lithiated benzonitrile system.[7] In addition, the effect of addition mode on the reaction course was investigated. We initially assumed that blocking aromatic CH-acidic sites with two TMS groups would prevent subsequent deprotonation reactions. Indeed, the syntheses of acids **4a** and **8a** from disilylated benzonitriles **4** and **8** were successful, but yields were significantly lower than those obtained using the reverse addition mode. As an initial proton abstraction from these substrates is impossible, we suppose that the aryllithiums generated thereof add to some extent to CN group of the excessive **4** and **8**. On the other hand, the addition of *n*-BuLi to the monosilylated compound **6** in THF failed completely to yield the desired aryllithium **6-Li**. This is in accordance with previous results showing that **6** is still susceptible to deprotonation at the remaining position ortho to CN.[5] Hence, this result is in

---

(12) Rieke, R. D.; Klein, W. R.; Wu, T.-C. *J. Org. Chem.* **1993**, *58*, 2492–2500.

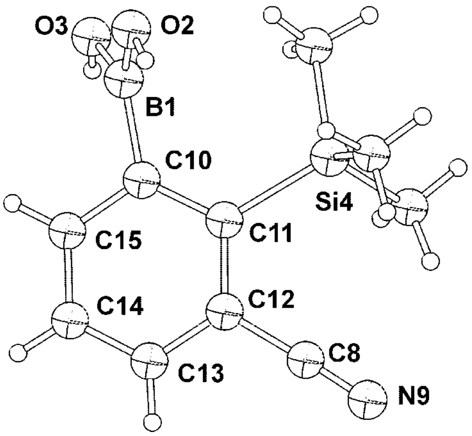
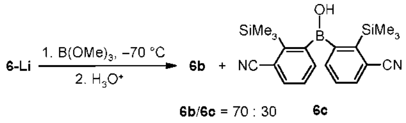


FIGURE 1. Molecular structure of **6b** (one of two independent molecules). Displacements ellipsoids are drawn at the 50% probability level. Selected bond angles: B1−C10−C11, 127.15(1)°; C10−C11−Si4, 124.74(1)°; C10−C11−C12, 116.63(1)°; C11−C12−C13, 123.07(1)°.

SCHEME 5



agreement with the interpretation we have formulated above to rationalize essential problems encountered in generation of simple lithiobenzonitriles.

The synthesis of related silylated cyanophenylboronic acids **4b−8b** from the reactions of corresponding aryllithiums with B(OMe)$_3$ has also been accomplished (Table 1). It should be noted that the clean synthesis of **6b** requires lower temperature during boronation (−90 °C) as at −70 °C a significant amount of borinic derivative **6c** was formed (Scheme 5). Presumably, the intermediate boronic "ate" complex decomposes to some extent to release dimethyl ester of **6b** which reacts further with an excess of **6-Li** to give the subsequent borinic "ate" complex and finally **6c**. Such complications did not affect the synthesis of the isomeric acid **7b** bearing the TMS group at the position meta with respect to the boronic moiety.

We suppose that the high lability of the "ate" complex precursor of **6b** results from the steric influence of the bulky *o*-TMS substituent; this effect is enhanced by the adjacent nitrile group. The structural characterization of **6b** supports this view. Despite the more relaxed bonding situation around the boron atom due to the change of hybridization from sp^3 in the "ate" complex to sp^2 in the free acid the boronic moiety in both independent molecules of **6b** is still significantly buttressed by the Me$_3$Si group. In addition, the aromatic ring is significantly distorted (Figure 1). The supramolecular architecture of **6b** (Figure 2) is unique as it lacks hydrogen-bonded centrosymmetric dimers[13] typical of arylboronic acids (including various ortho-substituted ones[14]). It is characterized by the formation of centrosymmetric macrocyclic tetramers due to relatively weak OH···O and OH···N hydrogen bonds (Figure 2) resulting in a three-dimensional network.

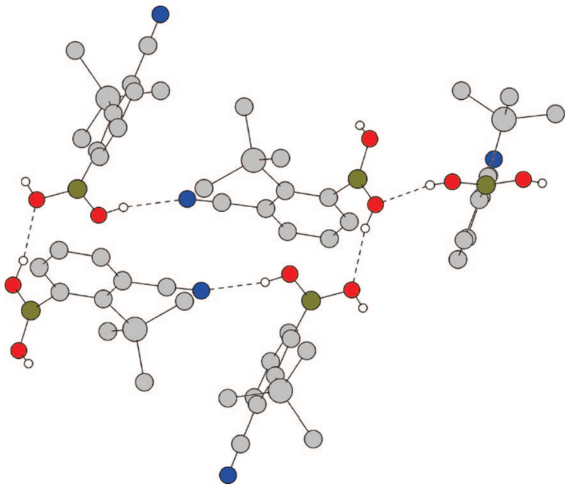


FIGURE 2. H-bonded cyclic tetrameric motif in the structure of **6b**.

In conclusion, there is no need to use extremely low temperature in order to obtain lithiobenzonitriles with high yields from reactions of bromobenzonitriles with *n*-BuLi. The reported troublesome generation of these intermediates (with some exception for the *ortho* derivative) already at −78 °C is not due to their inherent thermal instability but rather the improper addition mode, which promotes undesired deprotonation and/or condensation of unreacted bromobenzonitrile with aryllithium being generated during the addition of *n*-BuLi. The switch to the reverse addition mode allows us to reduce significantly side reactions, which indicates that the Br/Li exchange is much faster than competing deprotonation and addition to CN groups. Once formed, lithiated benzonitriles are not very prone to undergo degradation even at −60 °C, for instance, due to self-condensation resulting in the formation of oligomeric products.

Experimental Section

For a description of the general methods, see the Supporting Information.

Typical Procedure for the Generation of Lithiated Benzonitrile: Synthesis of 2,5-Bis(trimethylsilyl)-4-cyanobenzoic Acid (4a). A solution of 2,5-bis(trimethylsilyl)-4-bromobenzonitrile **4** (3.26 g, 10 mmol) in THF (10 mL) was added to a solution of *n*-BuLi (10 M, 1.1 mL) in Et$_2$O (20 mL) at ca. −65 °C. The resultant orange solution was stirred for 15 min at −70 °C followed by the saturation with a stream of gaseous CO$_2$. The resultant mixture was stirred for 30 min at −75 °C followed by warming to room temperature and hydrolysis with dilute aq H$_2$SO$_4$. The water phase was extracted with ether (20 mL). Evaporation of organic solvents afforded a crude product, which was washed with water (2 × 10 mL) and hexane (2 × 10 mL) to give the title compound (2.3 g, 78%). Mp: 184−186 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 12.24 (br, 1 H), 8.34 (s, 1 H), 8.00 (s, 1 H), 0.48 (s, 9 H), 0.38 (s, 9 H) ppm. ^{13}C{^{1}H} NMR (100.6 MHz, CDCl$_3$): δ 173.1, 145.8, 145.0, 140.2, 136.4, 136.1, 121.0, 119.5, 0.0, −1.5 ppm. Anal. Calcd for $C_{14}H_{21}NO_2Si_2$: C, 57.69; H, 7.26; N, 4.81. Found: C, 57.55; H, 7.18; N, 4.81.

---

(13) (a) Rettig, S. J.; Trotter, J. *Can. J. Chem.* **1977**, *55*, 3071–3075. (b) Pilkington, M.; Wallis, J. D.; Larsen, S. *J. Chem. Soc, Chem. Commun.* **1995**, 1499–1500. (c) Fronczek, F. R.; Luce, St. N. N.; Strongin, R. M. *Acta Crystallogr. C* **2001**, *57*, 1423–1425. (d) Cornet, S. M.; Dillon, K. B.; Entwistle, C. D.; Fox, M. A.; Goeta, A. E.; Goodwin, H. P.; Marder, T. B.; Thompson, A. L. *Dalton Trans.* **2003**, 4395–4405. (e) Das, S.; Alexeev, V. L.; Sharma, A. C.; Geib, S. J.; Asher, S. A. *Tetrahedron Lett.* **2003**, *44*, 7719–7722. (f) Rodriguez-Cuamatzi, P.; Vargas-Diaz, G.; Maris, T.; Wuest, J. D.; Höpfl, H. *Acta Crystallgor. E* **2004**, *60*, o1316−o1318. (g) Yang, Y.; Escobedo, J. O.; Wong, A.; Schowalter, C. M.; Touchy, M. C.; Jiao, L.; Crowe, W. E.; Fronczek, F. R.; Strongin, R. M. *J. Org. Chem.* **2005**, *70*, 6907–6912.

(14) Filthaus, M.; Oppel, I. M.; Bettinger, H. F. *Org. Biomol. Chem.* **2008**, *6*, 1201–1207.

Acknowledgment. This work was supported by the Warsaw University of Technology and by the Polish Ministry of Science and Higher Education (Grant No. N N205 055633). The X-ray analysis of **6b** was performed by Ł. Dobrzycki in the Crystallographic Unit of the University of Warsaw.

Supporting Information Available: Experimental details and compound characterization including copies of the ^{1}H and ^{13}C NMR spectra and X-ray structural data (CIF) for compound **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8013808