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Iodine ate complexes and *N*-lithiobenzocyclobutenamine intermediates in the reactions of α-lithionitriles with benzyne

Sasmita Tripathy, Helmi Hussain and Tony Durst*

Department of Chemistry, University of Ottawa, Ottawa, Canada KIN 6N5

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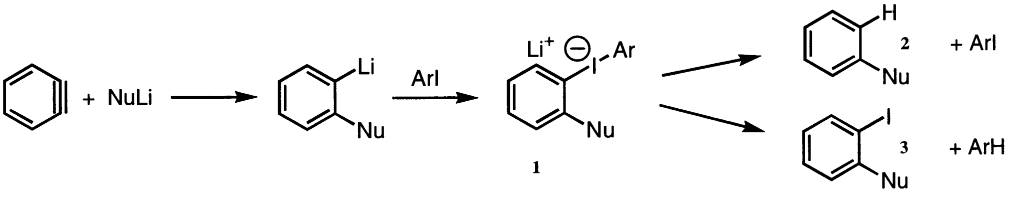
Abstract

α-Lithionitriles add to benzynes to give *N*-lithiobenzocyclobutenamines in a two-step process. The intermediate aryllithiums can be trapped prior to cyclization with iodobenzene or 2,6-dimethoxyiodobenzene to form iodine-ate complex intermediates which fragment preferentially to 2-(α-cyanobenzyl)-iodobenzenes. The *N*-lithiobenzocyclobutenamines undergo ring opening to yield either 2-substituted benzonitriles or α-substituted benzylcyanides depending on the substitution pattern on the aryl and cyclobutene rings. © 2000 Published by Elsevier Science Ltd.

We have recently reported that addition of a range of nucleophiles to benzynes in the presence of iodobenzene results in the formation of both mono and disubstituted benzenes, **2** and **3**.[1] These products are most readily explained by assuming that iodine-ate complexes are generated as intermediates. Evidence for such species has recently been reviewed by Wiberg, Sklenak and Bailey (Scheme 1).[2]



Scheme 1.

The reaction of α-lithionitriles with arynes has been studied to a considerable extent mainly by Biehl and co-workers,[3] but also by others.[4,5] We have reinvestigated the aryne–lithionitrile reaction armed with a knowledge that the iodine-ate complexes are formed rapidly if a suitable nucleophile is added to the benzyne in the presence of excess of iodobenzene.[1] This study has

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* Corresponding author. E-mail: tdurst@science.uottawa.ca

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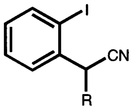
enabled us to address not only some remaining mechanistic ambiguities concerning the reaction of α-lithionitriles with benzyne, but also broadens the scope of the products accessible from this reaction. In particular, we report that 2-iodo-benzylcyanides, **4**, are the major product if the reaction of benzyne with α-lithionitrile is carried out in the presence of iodobenzene or 2,6-dimethoxyiodobenzene, **7**.



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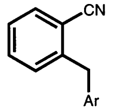

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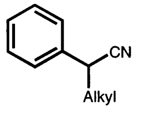
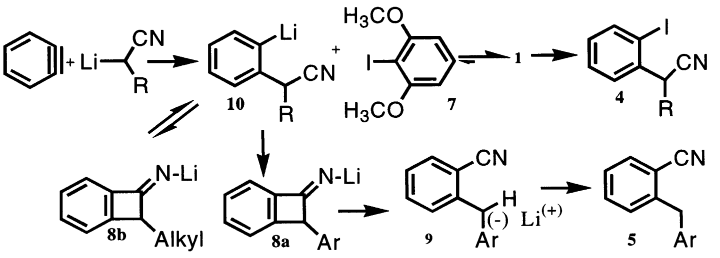


6

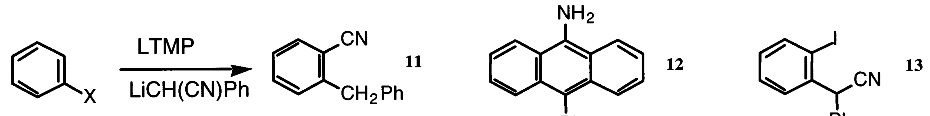
In the absence of the iodinating species, 2-cyanobenzylnitriles **5** and the monosubstituted aromatics **6** are obtained typically when α-lithiophenylacetonitriles and α-lithioalkylnitriles, respectively, are reacted with benzynes.

The products **5** result from the intermediacy of the *N*-lithiobenzocyclobutenamines **8**, followed by fragmentation to yield the relatively stable diarylmethane anions **9**.[3f] Meyers has proposed similar intermediates to explain the products obtained from reaction of α-lithioalkylnitriles to 3-oxazolidinyl substituted benzyne.[5] Alternate explanations not involving the four-membered intermediate **8b** have been proposed by Biehl and co-workers[3e,f] to account for the formation of **6**. Two mechanistic issues remain. (i) Are the *N*-lithiobenzocyclobutenamines **8** formed by a concerted 2+2 cycloaddition between the benzyne and the lithiated nitrile,[6,7] or via a two-step process involving the lithiated benzene derivative **10**, followed by cyclization? (ii) Are the *N*-lithiobenzocyclobutenamines **8** intermediates irrespective of the substitution on the lithiated nitrile? Both the questions are addressed below (Scheme 2).



Scheme 2.

Reaction of bromobenzene with LTMP in THF at −40°C containing LiCH(CN)Ph for 2 h followed by warming to 0°C gave the expected major products, 2-benzylbenzonitrile, **11**,[8] and 9-amino-10-phenylanthracene, **12**,[8] in 35 and 12% yield, respectively. When bromobenzene was replaced by iodobenzene, a small amount, 5%, of the 2-iodophenyl derivative **13**[8] was also isolated. Addition of an equivalent of **7**, a better positive iodine species than iodobenzene, to the bromobenzene reaction, increased the amount of **13** to 37% while **11** and **12** were formed in 8 and 7% yield, respectively. These results are consistent with the mechanism in Scheme 2 which shows a two-step sequence for the formation of **8a**. The positive iodine sources, iodobenzene and **7** are capable of intercepting the aryllithium **10** (R = Ph) rather than the diarylmethyllithium **9**. The results indicate that the rate of cyclization of **10** to **8a** is somewhat faster than its rate of reaction with iodobenzene to form the ate complex **1** since about 7 times more product is derived from the cyclization compared to the ate complex pathway. When one equivalent of the more reactive positive iodine donor **7** is used, 37% of the product is derived from ate complex formation and only 15% via the lithiobenzocyclobutenamine, **8a**. Results of reaction of LiCH(CN)Ph with other arynes such as 3,5-dimethoxybenzyne, 3-methoxybenzyne and 3-pyridyne mirror the above experiments; all give the 2-iodinated benzylic cyanides as the major product when **7** is added as a positive iodine source (Scheme 3, Table 1).



X	11	12	13
X = Br	35%	12%	-
X = I	35%	15%	7%
X = Br + **7**	8 %	7%	37%

Scheme 3.

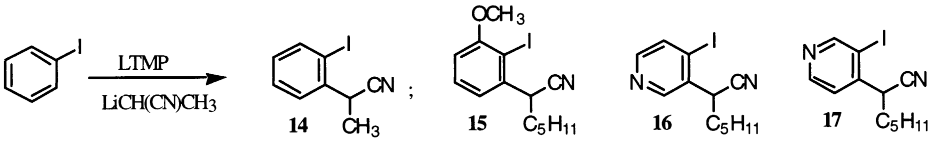
Table 1

Benzyne	Iodine source	Product (% isolated)	
		2-Benzyl cyanide	Aryl iodide
3,5-Dimethoxybenzyne	None	33[a]	–
3,5-Dimethoxybenzyne	**7**	5	42
3-Methoxybenzyne	**7**	–	47
3-Pyridyne	**7**	–	61[b]

[a] 18% of (3,5-dimethoxyphenyl)-phenylacetonitrile was also isolated.

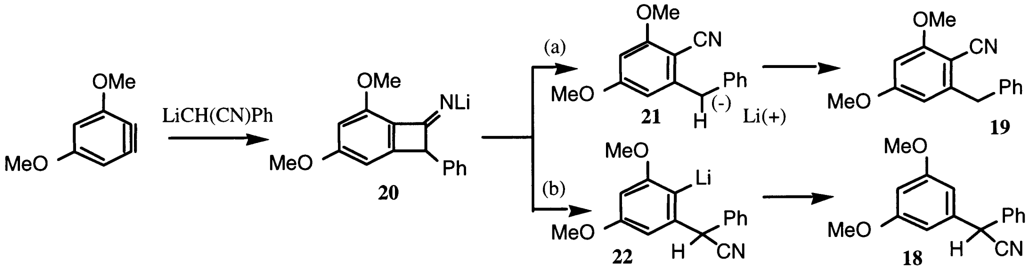
[b] A 3:2 mixture of 3-iodo-4-α-cyanobenzyl- and 4-iodo-3-α-cyanobenzylpyridine.

In contrast, reaction of iodobenzene with LTMP and the lithio derivatives of alkylnitriles gives only 2-(2-iodophenyl)-alkanonitriles.[8] For example, benzyne generated from iodobenzene and LTMP in the presence of LiCH(CN)CH_3 afforded **14** in 52% yield. Similarly, when 3-methoxybenzyne was generated in the presence of LiCH(CN)C_5H_{11} and **7**, the aryl iodide **15** was obtained in 38% yield. Under the same reaction conditions, 3-pyridyne was trapped to give 47% of a 4:5 mixture of **16** and **17** (Scheme 4). No rearrangement product corresponding to **5** or monosubstitution products, **6**, were observed. The products **14**–**17** arise via iodination and ate complex formation of the aryllithium **10**, or analogs. We propose that **10** is trapped either directly after its formation from the addition of the lithiated alkylnitriles to the appropriate benzyne, or after cyclization and re-opening of the *N*-lithio-2-alkylbenzocyclobutenamine, **8b**, Scheme 2.



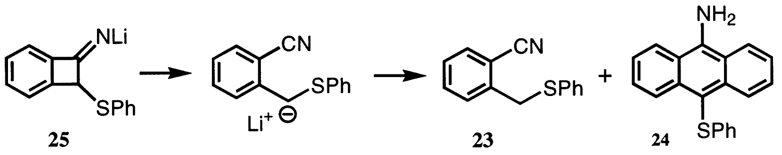
Scheme 4.

The direction of ring opening of the *N*-lithiobenzocyclobutenamines is governed by the relative stability of the anions generated in the two possible processes. It can be influenced by both the substituent at C2 of the cyclobutene ring and on the aryl ring. For example, reaction of 3,5-dimethoxybenzyne with lithiophenylacetonitrile at −40°C afforded the benzonitrile **18** and benzyl cyanide **19** in 18 and 33% yield, respectively. The presence of the methoxy group which stabilizes an *ortho* lithio substituent, allows ring opening of the *N*-lithiobenzocyclobutenamine **20** to the aryllithium **22** [path (b)] to compete with the alternate process yielding **21** [path (a)] (Scheme 5).



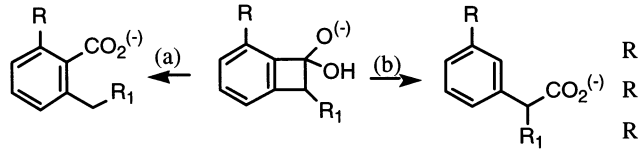
Scheme 5.

In agreement with this explanation is the isolation of 2-methylthiophenylbenzonitrile, **23**, and 9-amino-10-thiophenylanthracene, **24**, upon generation of benzyne in the presence of LiCH(CN)SPh. These products require the intermediacy of an *N*-lithiobenzocyclobutenamine **25** which opens preferentially to the lithioderivative of **23**. The latter reacts with additional benzyne to yield **24** (Scheme 6).[3b] Therefore, contrary to the earlier suggestion of Biehl,[3f] we propose that all α-lithionitriles react with benzynes according to Scheme 2.



Scheme 6.

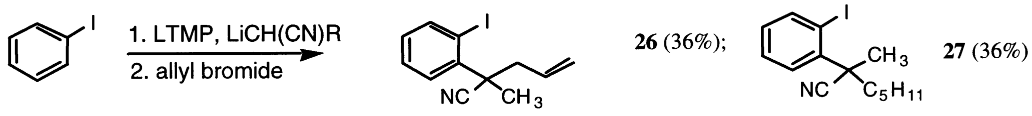
The variation in the direction of ring opening of the *N*-lithiobenzocyclobutenamines parallels that observed for benzocyclobutenones in the presence of NaOH.[9] Here too, the ratio of the pathway (a) to (b) is influenced by structural features on both aryl and cyclobutene rings (Scheme 7).



	Ratio (a) / (b)
R = R1 = H	1 : 1
R = OCH3, R1 = H	1 : > 100
R = H; R1 = Br	100 : < 1

Scheme 7.

When reactive halides, such as methyl iodide, allylic, and benzylic bromides, are added to the reaction mixture which produced **15** and **16**, alkylated compounds, for example **26** and **27**, were obtained in 30–40% yield (Scheme 8).



26 (36%); 27 (36%)

Scheme 8.

Acknowledgements

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