ORGANIC
LETTERS

2007
Vol. 9, No. 21
4135−4137

Indole-Derived Arynes and Their Diels–Alder Reactivity with Furans

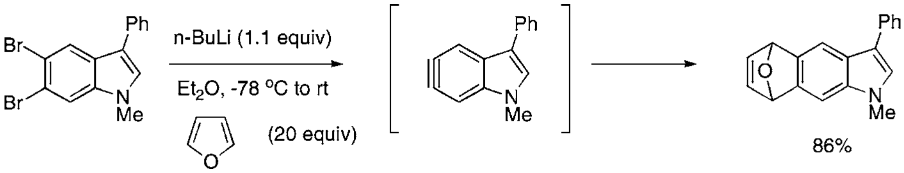
Keith R. Buszek,*,[†,‡] Diheng Luo,[‡] Mikhail Kondrashov,[‡] Neil Brown,[‡] and David VanderVelde[§]

*Department of Chemistry, Kansas State University, 111 Willard Hall,
Manhattan, Kansas 66506, Department of Chemistry, University of Missouri-
Kansas City, 205 Spencer Chemical Laboratories, 5100 Rockhill Road, Kansas City,
Missouri 64110, and Center for Chemical Methodologies and Library Development,
University of Kansas, 1501 Wakarusa Drive Lawrence, Kansas 66047*

buszekk@umkc.edu

Received July 7, 2007

ABSTRACT



Arynes derived from any position of the ubiquitous indole nucleus are unknown. We have now provided the first evidence for the formation and trapping of the 4,5-, 5,6-, and 6,7-indolynes. A series of *o*-dihalo indoles (Cl, Br, F) were synthesized and reacted under metal-halogen exchange conditions to give Diels–Alder cycloadducts in high yield with furan. The use of an excess of *tert*-butyllithium resulted in the rearrangement of the initially formed cycloadduct; however, employing only a slight excess of *n*-butyllithium cleanly gave cycloadducts with furan.

The existence of benzyne **1** was first reported by Roberts in 1953 (Figure 1).[1] Since that landmark discovery, accounts of other metastable benzenoid arynes appeared over the next several years.[2] For example, the two isomers of pyridyne (**2** and **3**),[2e,f] and naphthalyne (**4** and **5**)[2g,h] have been detected and their reactivity thoroughly studied. Surprisingly, arynes derived from the ubiquitous indole nucleus (e.g., 6,7-indolyne **6**) have never been reported. Inter- and intramolecular indole aryne cycloadditions would provide an attractive entry into complex natural products that feature, inter alia, substitution at the C6 and C7 positions. Examples of such targets include the teleocidins,[3] trikentrins,[4] and herbindoles.[4a,c] As part of a program to utilize aryne cycloaddition strategies for the

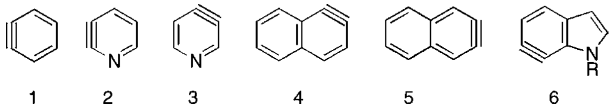


Figure 1. Examples of common benzenoid arynes.

---

* Current address: University of Missouri - Kansas City.
[†] Kansas State University.
[‡] University of Missouri-Kansas City.
[§] University of Kansas.

[1] (a) Roberts, J. D.; Simmons, H. E., Jr.; Carlsmith, L. A.; Vaughan, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290−3291. (b) Roberts, J. D.; Semenow, D. A.; Simmons, H. E., Jr.; Carlsmith, L. A. *J. Am. Chem. Soc.* **1956**, *78*, 601−611. For the first cycloadditions with benzyne, see: (c) Wittig, G.; Pohmer, L. *Angew. Chem.* **1955**, *67*, 348.

[2] For a review of arynes, see: (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic: New York, 1967. (b) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701−730. (c) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502−528. (d) Reinecke, M. G. *Tetrahedron* **1982**, *38*, 427−498. Pyridynes: (e) Kauffmann, T.; Boettcher, F. P. *Angew. Chem.* **1961**, *73*, 65−66. (f) Martens, R. J.; den Hertog, H. J. *Tetrahedron Lett.* **1962**, 643−645. Naphthalynes: (g) Bunnett, J. F.; Brotherton, T. K. *J. Org. Chem.* **1958**, *23*, 904−906. (h) Huisgen, R.; Zirngibl, L. *Chem. Ber.* **1958**, *91*, 1438−1452.

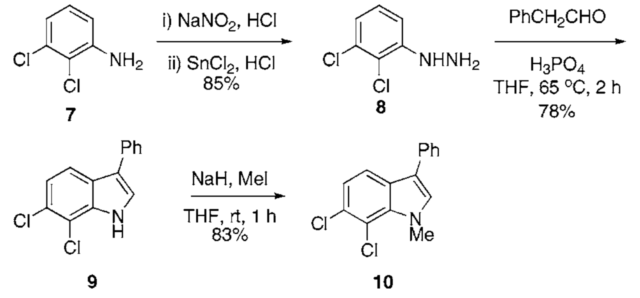
[3] (a) Nakatsuka, S.; Matsuda, T.; Goto, T. *Tetrahedron Lett.* **1987**, *38*, 3671−3674. (b) Nakatsuka, S.; Masuda, T.; Goto, T. *Tetrahedron Lett.* **1986**, *27*, 6245−6248. (c) Nakatsuka, S.; Masuda, T.; Asano, O.; Terame, T.; Goto, T. *Tetrahedron Lett.* **1986**, *27*, 4327−4330.

10.1021/ol701595n CCC: $37.00

synthesis of complex natural products,[5] we had a need to investigate the feasibility of incorporating indole arynes into such schemes. The literature reveals very few inquiries into this area.[2d,6] We are now pleased to report that various ortho dihalo indoles readily give their corresponding arynes under metal−halogen exchange conditions and are subsequently trapped with furans to give stable, isolable cycloadducts or rearranged products in excellent yields.

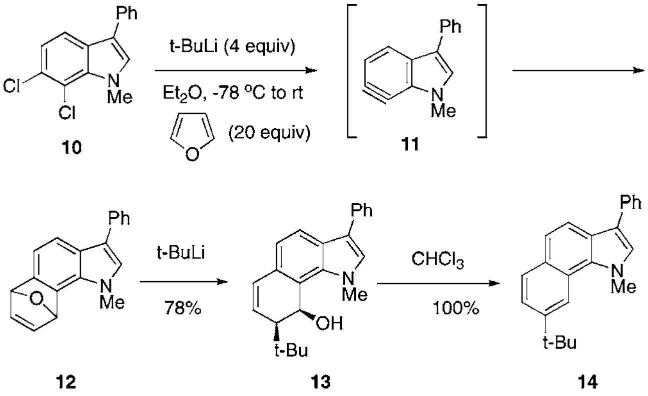
Among the many different precursors available for aryne generation,[7] we settled on the use of ortho dihalides in the indole system for their ease of preparation and for the extensive body of data regarding their facile conversion to the aryne. It was also critical that we be able to access all three positional isomers of dihalo indoles at the benzenoid core, namely, the 4,5-, 5,6-, and 6,7-dihaloindoles. Our initial efforts began with the synthesis of the 6,7-dichloroindole (Scheme 1). Commercially available 2,3-dichloroaniline was diazotized and reduced with stannous chloride in one pot to give the corresponding hydrazine in 85% yield.[8] Condensation of **8** with phenylacetaldehyde under Fischer conditions with polyphosphoric acid afforded the expected 6,7-dichloroindole **9**. Methylation of the NH group gave the *N*-methyl indole **10** in 83% yield. With the desired aryne precursor in hand, many protocols for generating benzynes from ortho dihalo arenes were examined.

Scheme 1. Fischer-Indole Synthesis of **10**



We elected initially to treat **10** with an excess (4 equiv) of *t*-BuLi in ether at −78 °C in the presence of an excess of furan and then slowly warm the reaction to room temperature over 4 h (Scheme 2). The color of the initially light-yellow solution changed briefly to deep red upon addition of the lithium reagent, then returned to and remained a pale yellow. Examination of the products by TLC analysis revealed just one major component. Proton NMR analysis of this compound indicated a single product containing a *tert*-butyl group, and another heteroatom, although the structure could not be unambiguously determined. Further analysis by 2D NMR methods (COSY, NOESY, HMBC, and HSQC) allowed the unequivocal structure to be assigned as **13**. The most reasonable explanation for the formation of this product involves the expected metal−halogen exchange and elimination to give the reactive indole aryne intermediate **11**, in the same manner as reported for other benzyne systems, followed by trapping with furan to afford the initial cycloadduct **12**. This compound, however, could not be isolated. Rather, a highly regioselective S_N2' nucleophilic attack by the remaining *tert*-butyllithium at the olefin induced cleavage of the oxygen bridge resulting in the observed product as a single regioisomer in 78% yield. This process has ample precedent with many different nucleophiles, including hindered alkyllithiums.[9] Aromatization was induced by stirring in chloroform for several hours to afford quantitatively the fused tricyclic derivative **14**.

Scheme 2. Generation and Trapping of Indole Aryne with Furan



The formation of a single regioisomer is a curious observation. A related experiment was carried out with the hindered 2,5-dimethylfuran (Scheme 3), which gave a similar result, but now with an approximately equal mixture of regioisomers **16** and **17** being formed in a combined 84% yield. The difference in regiochemical outcome of these two reactions can perhaps be rationalized on the basis of ground-state destabilization. The opening of the furan cycloadduct **12** from the opposite side of the olefin would experience greater torsional strain thereby leading only to the observed product. This strain is significantly less pronounced from either direction with **15**, owing to the presence of the larger methyl groups, and a statistical distribution of products is found instead. The issue of regiocontrol in these systems remains the subject of further investigation.

Even more significantly, we were gratified to discover that arynes can be easily generated and trapped as their Diels−Alder cycloadducts with furan from all three isomeric ortho dibromo indoles (Scheme 4). In this case the use of 1.2 equiv

---

(4) (a) Jackson, S. K.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 1405−1411. (b) Huntley, R. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3403−3406. (c) Jackson, S. K.; Banfield, S. C.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 1215−1218. (d) MacLeod, J. K.; Monahan, L. C. *Tetrahedron Lett.* **1988**, *29*, 391−392.

(5) (a) Buszek, K. R. *Tetrahedron Lett.* **1995**, *36*, 9125−9128. (b) Buszek, K. R.; Bixby, D. L. *Tetrahedron Lett.* **1995**, *36*, 9129−9132.

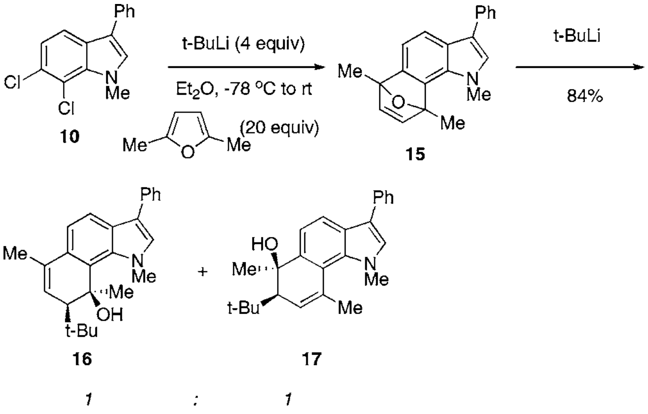
(6) Approaches to the generation of 2,3-indolyne have appeared: (a) Conway, S. C.; Gribble, G. W. *Hetereocycles* **1992**, *34*, 2095−2108. (b) Gribble, G. W.; Conway, S. C. *Synth. Commun.* **1992**, *22*, 2129−2141.

(7) Caster, K. C.; Keck, C. G.; Walls, R. D. *J. Org. Chem.* **2001**, *66*, 2932−2936.

(8) Blair, J. B.; Kurrasch-Orbaugh, D.; Marona-Lewicka, D.; Cumbay, M. G.; Watts, V. J.; Barker, E. L.; Nichols, D. E. *J. Med. Chem.* **2000**, *43*, 4701−4710.

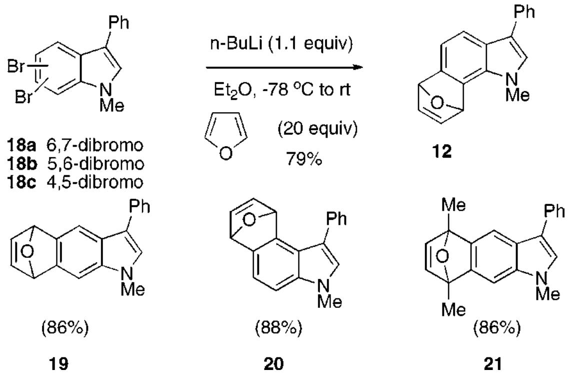
(9) For an excellent recent review, see: (a) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48−58. For other recent applications, see: (b) Chen, C.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 4810−4817 and references cited therein.

Scheme 3. Trapping with 2,5-Dimethylfuran Leads to Two Regioisomers

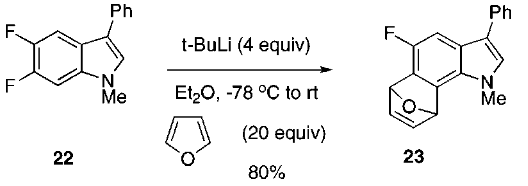


of *n*-butyllithium gave only the furan cycloaddducts without rearrangement as stable intermediates in excellent yields. Trapping of the aryne derived from **18b** with 2,5-dimethylfuran cleanly gave **21** in 86% yield. Preparation of the these aryne precursors from the three isomeric ortho dibromo anilines followed the same protocol outlined earlier in Scheme 1.[10]

Scheme 4. Generation and Trapping of All Three Isomeric Arynes from Dibromoindoles **18a**−**c**



Scheme 5. Generation of Aryne from **22** Proceeds through Proton−Lithium Exchange



Finally, we observed that ortho difluoroindoles exhibit anomalous behavior upon treatment with alkyllithiums (Scheme 5). It is known that the more electropositive halogens undergo the most rapid metal−halogen exchange, and this was indeed found to be the case with the bromo indole series. In the fluorine system, the isomeric 4,5- and 6,7-difluoroindoles gave only recovered starting material under these same conditions. The reaction of 5,6-difluoroindole **22** with n-BuLi, however, gave exclusively the cycloadduct **23** in 80% yield. Initial deprotonation of the thermodynamically more acidic C7 hydrogen as a result of the inductive electron withdrawing effect of the adjacent nitrogen leads to aryne formation. This assumption is also consistent with well-documented observation that the rate of transmetallation of fluorine is slow compared with deprotonation at the ortho position.[11] Trapping and cycloaddition with furan thus gave the observed cycloaddduct, and ^{19}F NMR revealed one remaining fluorine at the C5 position.

In conclusion we have provided the first evidence for the existence of all three isomeric indole arynes in the benzenoid core using a practical and general method. The facile generation of aryne indoles from dibromoindoles in particular is noteworthy for its synthetic simplicity and good yields. This discovery adds indoles to the suite of aromatic systems from which arynes can be easily and readily generated. Further investigations into the reactivity and behavior of other mixed dihaloindoles as well as applications of inter- and intramolecular indole aryne cycloadditions to natural products total synthesis are underway and will be reported in due course. Further work into substituent effects (e.g., 3-phenyl) on the ease of aryne formation is also in progress.

Acknowledgment. We acknowledge support of this work by the National Institutes of Health, Grant R01 GM69711. Additional support of this work was provided by the NIH (Grant P50 GM069663) via the University of Kansas Chemical Methodologies and Library Development Center of Excellence (KU-CMLD). We thank Chris Sakai for technical assistance with this project. The authors wish to thank the reviewers for their helpful comments and suggestions. This paper is warmly dedicated to Professor Michael E. Jung on the occasion of his 60th birthday.

Supporting Information Available: ^{1}H NMR data for all compounds reported and experimental details for their preparation. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701595N

---

[10] Hanzlik, R. P.; Weller, P. E.; Desai, J.; Zheng, J.; Hall, L. R.; Slaughter, D. E. *J. Org. Chem.* **1990**, *55*, 2736−2742.

[11] (a) Bridges, A. J.; Lee, A.; Maduakor, E. C.; Schwartz, C. E. *Tetrahedron Lett.* **1992**, *33*, 7495−7498. (b) Coe, P. L.; Waring, A. J.; Yarwood, T. D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2729−2737. (c) Li, L.; Martins, A. *Tetrahedron Lett.* **2003**, *44*, 5987−5990. (d) Masson, E.; Schlosser, M. *Eur. J. Org. Chem.* **2005**, 4401−4405.