Regioselective Diels–Alder cycloadditions and other reactions of 4,5-, 5,6-, and 6,7-indole arynes

Neil Brown [a,b], Diheng Luo [a], David Vander Velde [b], Shaorong Yang [a], Allen Brassfield [a], Keith R. Buszek [a,b,*]

[a] Department of Chemistry, University of Missouri-Kansas City, 205 Spencer Chemical Laboratories, 5100 Rockhill Road, Kansas City, MO 64110, USA
[b] The University of Kansas Center of Excellence in Chemical Methodologies and Library Development, 1251 Wescoe Hall Drive, 4070 Malott Hall, Lawrence, KS 66045, USA

ARTICLE INFO

ABSTRACT

The regioselectivity of Diels–Alder cycloadditions of indole arynes (indolynes) at all three benzenoid positions was examined. Cycloadditions with the 4,5-and 5,6-indolynes, derived via metal–halogen exchange from the corresponding *o*-dibromo indoles, showed essentially no selectivity with 2-*t*-butylfuran. In contrast, the 6,7-indolyne displayed virtually complete preference for the more sterically congested cycloadduct. This same cycloadduct undergoes a facile acid-catalyzed rearrangement to afford the annulated enone, or alternatively, undergoes hydrolysis and oxidation in the presence of air to give the indolobenzoquinone. The 5,6-difluoroindoles show anomalous behavior and give either 5-fluoro-6,7-indolynes with *n*-BuLi in ether, or 5,6-indolynes with *n*-BuLi in toluene. We have also demonstrated that benzenoid indolynes can be easily and conveniently generated by the fluoride-induced decomposition of o-trimethylsilyl triflates.

Unlike the familiar benzenoid arynes such as benzyne **1**,[1] the naphthalynes (**2a** and **2b**),[2] and the pyridynes (**3a** and **3b**) (Fig. 1),[3] all of which have been known for at least 40 years, the tetrad of arynes **4–7** derived from the ubiquitous indole aromatic nucleus was until recently unknown.[4,5]

The absence of these arynes from the literature was surprising, given the potential utility of these reactive intermediates for an attractive entry into the indole alkaloid class of complex natural products such as the trikentrins,[6] herbindoles,[6a,c] teleocidins,[7] cytoblastin,[8] and lyngbyatoxin[9] (Fig. 2).

We recently reported the existence of and first Diels–Alder cycloaddition examples with all three indole arynes derived from the benzenoid part of the indole nucleus.[4] We are now pleased
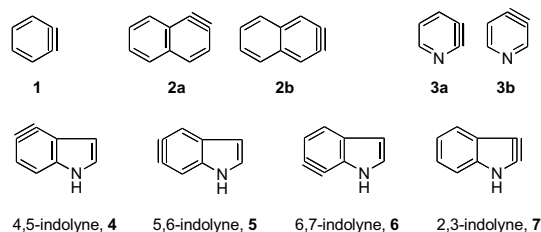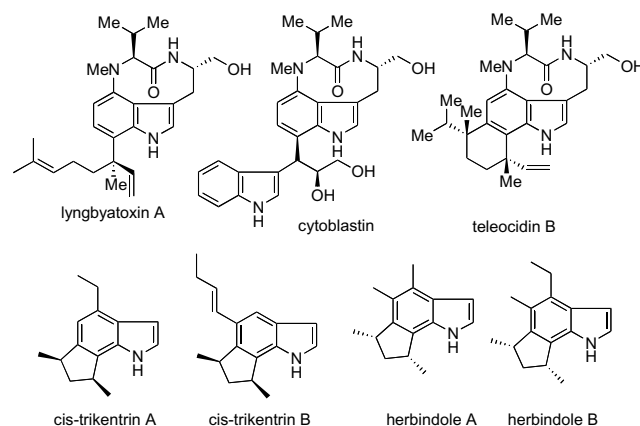

Figure 1. Benzenoid aryne systems.

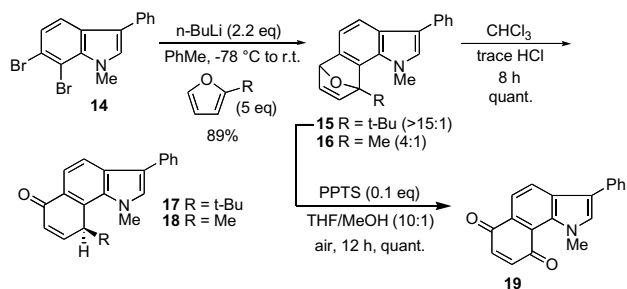**Figure 2.** Indole-containing complex natural products.

to follow that communication with this Letter on the regiochemical behavior of these cycloadditions.[10]

The 4,5-, 5,6-, and 6,7-indolynes were generated from the corresponding *o*-dibromoindoles in the manner previously described.[4] Treatment of **8** with 2.2 equiv of *n*-BuLi in either ether or toluene[11] at −78 °C in the presence of an excess of 2-*t*-butylfuran was found to give an approximate 1:1 mixture of regioisomers **9** and **10** (Scheme 1).[12] In a similar fashion, the generation of the 5,6-indolyne from **11** and trapping in the same manner also afforded a 1:1 mixture of regioisomers **12** and **13**.

* Corresponding author. Tel.: +1 816 235 2292; fax: +1 816 235 5502.
E-mail addresses: buszekk@umkc.edu, krvb@ksu.edu (K. R. Buszek).
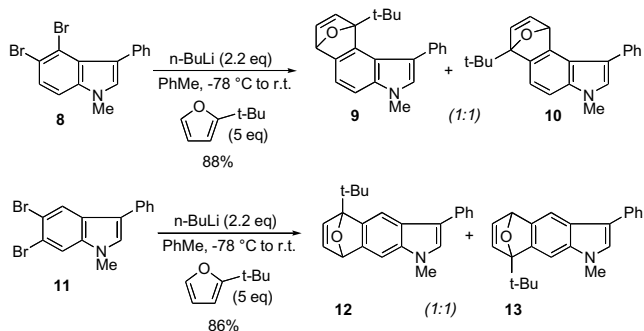
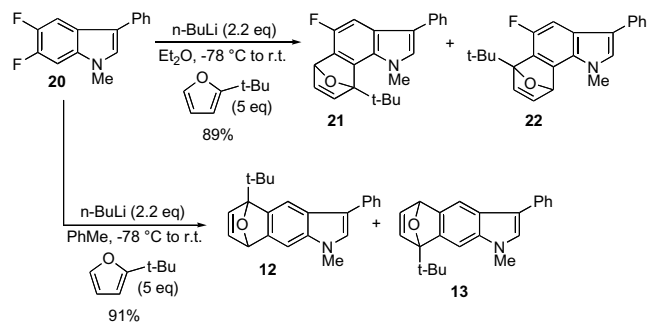**Scheme 1.** Regioselectivity of 4,5- and 5,6-indolyne cycloadducts.

Scheme 2. Regioselectivity of 6,7-indolyne cycloadducts.

Scheme 3. Regioselectivity of 5,6-difluoroindole-derived indolynes.

Scheme 4. Cine substitution in 6,7-indolynes.

By stark contrast, the 6,7-indolyne derived from **14** gave a virtually complete regioselective cycloadduct **15** (Scheme 2). The structure was unequivocally confirmed via NOESY and COSY analyses. The formation of the more sterically crowded product can be rationalized in terms of a previously observed polarization phenomenon that has been invoked for substituted benzynes in which fluorine acts as powerful regiochemical director.[13–15] The effect correlates with electronegativity values and is reduced with methoxy substituents[14] and finally reversed with electron-donating groups such as methyl.[15] The powerful polarizing effect of the pyrrole unit is apparent even with 2-methylfuran, which exhibits a 4:1 preference for the more sterically congested product **16**.

The stable initial cycloadducts **15–16** can be made to undergo rearrangement upon prolonged exposure to a trace amount of acid in chloroform to give the annulated enones **17–18**. Aromatization is precluded in this case which would otherwise force the bulky *t*-butyl group and even smaller methyl group into an unavoidable steric conflict with the planar *N*-methyl substituent on the pyrrole. Interestingly, hydrolysis of the cycloadduct **15** in the presence of air resulted in loss of the *t*-butyl group and concomitant oxidation to give the indoloquinone **19**. This rearrangement was only observed with the *t*-butyl-substituted arynes.

The 5,6-difluoro indole **20** displays anomalous behavior (Scheme 3). Treatment of this compound with 4 equiv of *t*-butyllithium (but not *n*-BuLi) resulted in exclusive deprotonation at the C7 position, followed by dehydrohalogenation to give the 5-fluoro-6,7-aryne which was trapped as a nearly equimolar mixture of regioisomers **21** and **22**. In this case, the fluorine presumably competes effectively with the polarizing properties of the pyrrole unit and therefore displays no selectivity. As observed by Coe et al.,[11] by changing solvents from ether to toluene, the acid–base reaction manifold is almost completely suppressed in favor of metal–halogen exchange, and the 5,6-indolyne is generated instead which as noted above affords a 1:1 mixture of the same cycloadducts **12** and **13**.

In the absence of any diene, the putative 6,7-indolyne **23** undergoes cine substitution with excess *n*-butyllithium to give the
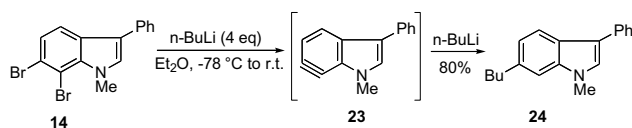
6-butyl indole **24** (Scheme 4). This finding, which is reminiscent of typical substituted benzyne behavior,[16] is a potentially useful method for installing substitution at this position. This operation is usually difficult to accomplish in indoles with other non-aryne strategies. So far, the reaction selectivity in this reaction manifold is only seen with the 6,7-indolynes.

These 6,7-indolyne-derived cycloadducts can also be opened in a highly regio-selective and exo-selective manner by exposure to alkyllithium reagents in ether. We first noticed this behavior with *t*-butyllithium and the unsubstituted furan cycloadduct **25** from the 6,7-indolyne **14**.[4] In this case, acid-promoted elimination occurs preferentially to give the aromatic annulated product **26** (Scheme 5).

However, in the present substituted example, elimination is precluded due to steric congestion with the *N*-methyl substituent (Scheme 6). Symmetrical furan cycloadducts have been opened under metal-catalyzed conditions with carbon, oxygen, and nitrogen nucleophiles.[17] We have found that catalysis is unnecessary with our cycloadducts, at least with carbon-based nucleophiles.

Thus, simply recommitting the cycloadduct to ether and treatment with *n*-Bu-, *s*-Bu-, or *t*-BuLi gives exclusively the ring-opened products **27–29**.
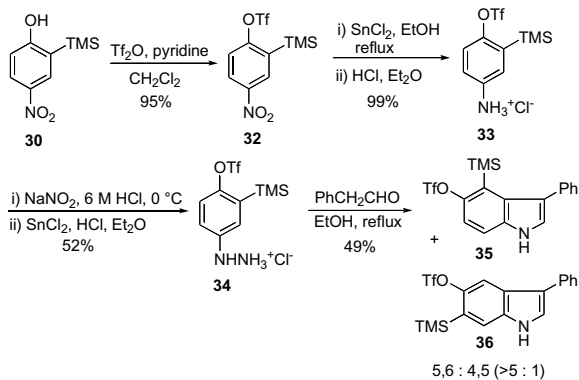
These results with the 6,7-indolyne cycloadducts have clear implications for the production of libraries based on these hetero-
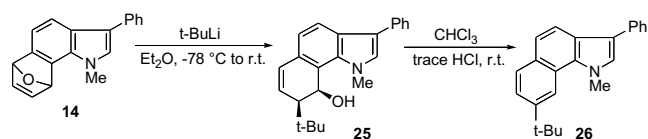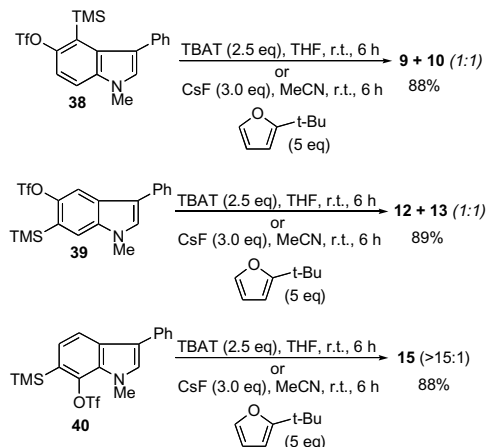

Scheme 5. Exo- and regioselective ring-opening and aromatization in 6,7-indolyne furan cycloadducts.
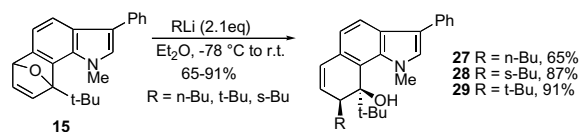
Scheme 6. Regio- and exo-selective ring-opening of 6,7-indolyne furan cycloadducts.

Scheme 7. Fischer indole synthesis of 4,5- and 5,6-*o*-trimethylsilyl triflate indolyne precursors.

Scheme 8. 4,5-, 5,6-, and 6,7-indolynes derived from *o*-silyltriflates.

fore unknown chemotypes. The 6,7-furan cycloadducts thus represent a potentially versatile platform for the synthesis of novel 6,7-annulated indole libraries of either type, **17–18** or **27–29**. Additionally, the olefin handle in either type of structure provides a further point of diversification and the opportunity to generate stereochemically dense annulated indole arynes.

Finally, in an effort to find an alternate route to the indole arynes that does not rely exclusively on metal–halogen exchange protocols, we developed a Fischer indole synthesis to the 4,5-, 5,6-, and 6,7-*o*-trimethylsilyl triflates (Scheme 7). Treatment of 2-trimethylsilylphenol[18] with Cu(NO₃)₂ (0.55 equiv) in acetic acid at 0 °C for 3 h afforded an equimolar mixture of 4-nitro-2-(trimethylsilyl)phenol **30** and 2-nitro-6-(trimethylsilyl)phenol **31**.[19] The nitrophenol **30** was triflated (95%) and converted to its hydrazine hydrochloride salt **34** in 51% overall yield. Reaction of **34** under Fischer conditions (EtOH, reflux, 4 h) with phenylacetaldehyde was remarkably regioselective albeit moderately yielding, giving a greater than 5:1 ratio of the 5,6- and 4,5-indole products **36** and **35**, respectively. This result stands in contrast to the corresponding dibromides or dichlorides[4] which under the same conditions resulted in a nearly 1:1 mixture of isomers. By carrying 2-nitro-6-(trimethylsilyl)phenol **31** through the same scheme, the corresponding 6-(trimethylsilyl)-1*H*-indol-7-yl triflate **37** is also available by this method in 32% overall yield.

The compounds **35**, **36**, and **37** each give, after N-methylation, their respective 5,6-, 4,5-, and 6,7-indolyne cycloadducts by treatment with TBAT[20] (2.5 equiv) in THF, or alternatively, CsF (3.0 equiv) in MeCN, for several hours at room temperature in the presence of 2-*t*-butylfuran (Scheme 8). The same ratios of isomeric cycloadducts as shown previously were obtained.

In conclusion, we have shown that while 4,5- and 5,6-indolynes show virtually no regioselectivity in Diels–Alder cycloadditions, the 6,7-indolyne by contrast is highly regioselective, presumably due to the polarization influence of the pyrrole ring. Adducts derived from this flexible system can undergo acid-catalyzed rearrangement to give stable annulated enones, hydrolysis in air to give benzoquinones, or react with alkyllithiums to afford exo- and regioselective ring-opened products. We are presently adapting this versatile methodology for use in library development as well as in the total synthesis of indole alkaloid natural products. The results of these efforts will be reported as developments warrant.

Acknowledgments

References and notes

1. (a) Roberts, J. D.; Simmons, H. E., Jr.; Carlsmith, L. A.; Vaughn, 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 a review of arynes in general, see: (c) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic: New York, 1967.
2. (a) Bunnett, J. F.; Brotherton, T. K. *J. Org. Chem.* **1958**, *23*, 904–906; (b) Huisgen, R.; Zirngibl, L. *Chem. Ber.* **1958**, *91*, 1438–1452.
3. (a) Kauffmann, T.; Boettcher, F. P. *Angew. Chem.* **1961**, *73*, 65–66; (b) Martens, R. J.; den Hertog, H. J. *Tetrahedron Lett.* **1962**, 643–645.
4. Buszek, K. R.; Luo, D.; Kondrashov, M.; Brown, N.; VanderVelde, D. *Org. Lett.* **2007**, *9*, 4135–4137.
5. For attempts to generate the elusive 2,3-indolyne, see: (a) Conway, S. C.; Gribble, G. W. *Heterocycles* **1992**, *34*, 2095–2108; (b) Gribble, G. W.; Conway, S. C. *Synth. Commun.* **1992**, *22*, 2129–2141.
6. (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.
7. (a) Nakatsuka, S.; Matsuda, T.; Goto, T. *Tetrahedron Lett.* **1987**, *38*, 3671–3674; (b) Nakatsuka, S.; Matsuda, 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.
8. Moreno, O. A.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 8180–8181.
9. Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1987**, *28*, 2265–2268.
10. Presented at the 236th American Chemical Society National Meeting, Philadelphia, PA, August 17–21, 2008 (ORGN 679).
11. Coe, J. W.; Wirtz, M. C.; Bashore, C. G.; Candler, J. *Org. Lett.* **2004**, *6*, 1589–1592.
12. All new compounds reported herein exhibited satisfactory ¹H NMR, ¹³C NMR, COSY and NOESY NMR, mass spectral, and elemental analysis data consistent with their structures.
13. Gribble, G. W.; Keavy, D. J.; Branz, S. E.; Kelly, W. J.; Pals, M. A. *Tetrahedron Lett.* **1988**, *29*, 6227–6230.
14. Giles, R. G. F.; Sargent, M. V.; Sianipar, H. *J. Chem. Soc., PT1* **1991**, 1571–1579.
15. Newman, M. S.; Kannan, R. *J. Org. Chem.* **1976**, *41*, 3356–3359.
16. Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273–412.
17. Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48–58.
18. (a) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211–1214; (b) Wilbur, D. S.; Stone, W. E.; Anderson, K. W. *J. Org. Chem.* **1983**, *48*, 1542–1544.
19. Anuradha, V.; Srinivas, P. V.; Aparna, P.; Rao, J. M. *Tetrahedron Lett.* **2006**, *47*, 4933–4935.
20. Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901–6905.