J|A|C|S COMMUNICATIONS

Published on Web 11/02/2010

Electrophilic Aromatic Substitution of a BN Indole

Eric R. Abbey, Lev N. Zakharov, and Shih-Yuan Liu*

Department of Chemistry, University of Oregon, Eugene, Oregon 97403, United States

Received August 13, 2010; E-mail: lsy@uorgon.edu

Abstract: We report the first examples of a "BN-fused" indole, and we demonstrate that this new family of unnatural indole derivatives undergoes electrophilic aromatic substitution (EAS) reactions with the same regioselectivity as its organic analogue. Competition experiments reveal that *N*-*t*-Bu-BN-indole is more nucleophilic in EAS reactions than its carbonaceous counterpart. X-ray structural analysis between BN indole and classic indole highlights significant differences in bond distances, in particular for bonds associated with the boron atom.

Indole[1] is one of the most ubiquitous heterocyclic motifs in nature. Due to the abundance of biologically active indole derivatives,[2] the indole ring system has become an important structural component in drug discovery efforts. Consequently, the synthesis and functionalization of indoles has been a major focus in research, the expansion of the chemical space of accessible indole structures being one of the goals.[3] An alternative approach to expand structural diversity is "elemental isosterism". To this end, the BN/CC isosterism has recently emerged as a viable strategy to create biomimetic analogues of common structural units in organic molecules (e.g., olefin,[4] benzene,[5] and indene[6]). Despite the recent advances in this area, the elemental isosterism of the biologically important indole has remained virtually unexplored. To date, the only BN-substituted indoles are phenylenediamine-type heterocycles containing an external BN unit as illustrated in **1** (Scheme 1).[7,8] To the best of our knowledge, electrophilic aromatic substitution (EAS), a crucial reaction of the biochemistry of indoles,[9] has not been demonstrated with these phenylenediamine-type BN indoles. Herein we report the first example of a "BN-fused" indole (e.g., heterocycle **2** in Scheme 1), and we demonstrate that this new BN indole undergoes EAS reactions with the same regioselectivity as its organic analogue, *N*-*t*-Bu-indole **3**.[10]

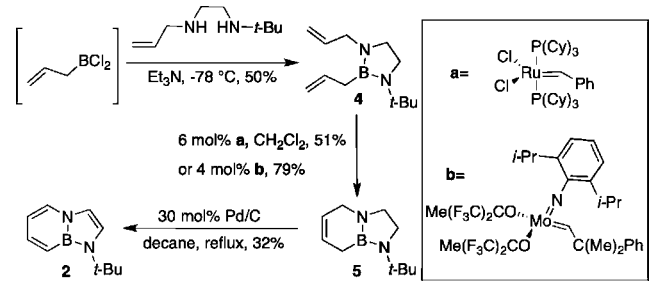
Scheme 1. A Novel BN Indole

N-*t*-Bu-BN-Indole

Synthesis of *N*-*t*-Bu-BN-indole **2** begins with the condensation of *N*-*t*-Bu-*N*′-allylethylenediamine with *in situ* generated allylboron dichloride (Scheme 2), affording heterocycle **4** in 50% yield. Ring-closing metathesis (RCM) with Grubbs first generation catalyst provides the bicyclic **5** in 51% yield.[11] The yield of the RCM step can be improved to 79% using Schrock's catalyst. Dehydrogenation of precursor **5** to furnish the target compound **2** is accomplished in the presence of Pd/C in refluxing decane.[12]

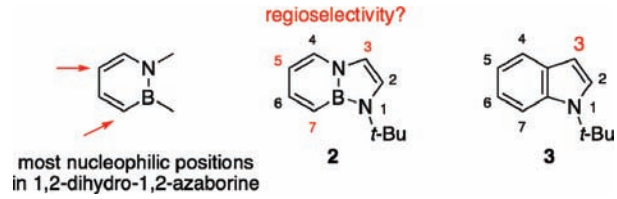
With *N*-*t*-Bu-BN-indole **2** in hand, we then investigated its reactivity toward EAS. Indole itself displays high EAS reactivity,

Scheme 2. Synthesis of *N*-*t*-Bu-BN-Indole **2**



which is estimated to be orders of magnitude greater than in the case of benzene.[13] This is due to indole's electron-rich nature, and the high electron density at its 3-position is responsible for indole's regioselectivity toward EAS reactions. The bicyclic *N*-*t*-Bu-BN-indole **2** consists of a six-membered 1,2-dihydro-1,2-azaborine heterocycle[14,15] and a five-membered 2,3-dihydro-1*H*-1,3,2-diazaborole core (Scheme 3).[16] Thus, we were particularly interested in whether unnatural *N*-*t*-Bu-BN-indole **2** would display the classical indole-type regioselectivity in EAS reactions (i.e., at the 3-position) or substitution at the 7- and 5-positions,[17] which have been demonstrated to be most nucleophilic in monocyclic 1,2-azaborine structures.[18]

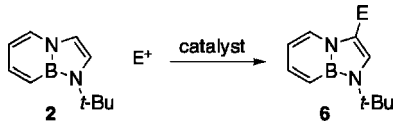
Scheme 3. Regioselectivity in EAS Reactions of *N*-*t*-Bu-BN-Indole **2**



We surveyed the EAS reaction of *N*-*t*-Bu-BN-indole **2** with a variety of electrophiles. As can be seen from Table 1, bromination of **2** occurred at the 3-position, yielding the brominated product **6a** (Table 1, entry 1). The Mannich reaction of **2** with dimethyliminium chloride provided our first BN indole alkaloid, *N*-*t*-Bu-BN-gramine **6b**, in 53% yield (Table 1, entry 2). Lewis acid mediated Michael addition of **2** to cyclohexenone with zirconium tetrachloride[19] furnished **6c** in 57% yield (Table 1, entry 3). Deuterium exchange[20] occurred in degassed 1:1 CD_3OD/D_2O at 100 °C providing **6d** in 39% isolated yield (Table 1, entry 4). Friedel−Crafts acylation of **2** with acetyl chloride was accomplished in the presence of Et_2AlCl[21] to yield **6e** (Table 1, entry 5). In each case, we observed substitution at the 3-position of **2**. The H(2) and H(3) proton signals of **2** appear as one singlet in ^1H NMR (in CD_2Cl_2) integrating for two protons. Thus, we determined the substitution pattern of EAS products by either single crystal X-ray diffraction (e.g., for **6e**) or NOESY experiments (e.g., for **6a** and **6c**).[22]

10.1021/ja107312u

Table 1. EAS Reactions of **2**



entry	electrophile (E^+)	catalyst	3-substituent (E)	product	yield (%)
1	Br_2	-	Br	**6a**	39
2	$NMe_2^{\oplus}Cl^{\ominus}$, H, H	-	NMe_2	**6b**	53
3	O	$ZrCl_4$	O	**6c**	57
4	CD_3OD/D_2O	-	D	**6d**	39[a]
5	O, Cl, Me	Et_2AlCl	O, Me	**6e**	23

[a] ^{1}H NMR indicates ~80% deuterium enrichment.

The modest yields of these reactions are likely due to side reactions associated with the relatively acidic reaction conditions. Indoles are known to undergo self-condensation reactions in the presence of acids.[23] We determined that *N*-*t*-Bu-BN-indole **2** forms the *B*-methoxy-substituted trimer **7** (Figure 1) in acidic methanol solution among other byproducts.[24] In one instance, we were able to isolate a single crystal of **7** and determine its structure by X-ray crystallography.[25,26] Although substituted at the nitrogen and at the C(3) position, the structure of **7** provides us with the first glimpse into the bonding of BN indoles fused at the BN unit. Comparing the intraring bond distances of the six-membered ring of **7** and a *B*-diphenylamino-substituted 1,2-azaborine **A** (Figure 1),[27] the most noticeable difference is observed in the B—N bond distances. In the fused bicyclic BN indole **7** the B(1)—N(2) distance (1.463(2) Å) is longer than the corresponding B—N bond in a monocyclic 1,2-azaborine (1.446(2) Å). This is likely due to the better π-overlap between the "exocyclic" nitrogen atom in **7** (i.e., N(1)) versus that in **A**. It is also consistent with the shorter N(1)—B(1) distance in **7** (1.440(2)Å) compared to the B—N(exocyclic) bond length of 1.486(2)Å in **A**. We are also interested in comparing the BN indole structure **7** with its carbonaceous counterpart. The typical bond distances of a 1,3-dialkylsubstituted indole are illustrated in the bottom right corner of Figure 1 (structure **B**).[28] The most significant differences in bond distances are directly associated with the replacement of the C=C bond in **B** with a B—N unit. Due to the larger covalent radius of boron,[29] the B(1)—C(7) (1.509(2) Å) and B(1)—N(1) (1.440(2) Å) bond lengths are significantly longer (by ~0.1 Å) than those in indole **B**. On the other hand, presumably due to the slightly smaller covalent radius of the nitrogen (vs carbon),[29] the N(2)—C(4) (1.370(2) Å) and N(2)—C(3) (1.404(2) Å) distances are shorter than the corresponding bonds in **B**, although this difference is less pronounced (i.e., shorter by only ~0.02 Å). Thus, while BN indoles are geometrically similar in shape compared to natural indoles, the differences in bonding (e.g., bond lengths and electronic structure) could potentially lead to significantly different biological activity.

We were also very pleased to discover that acylated BN indole **6e** forms crystalline solids suitable for single crystal X-ray diffraction analysis. The structure of **6e** is illustrated in Figure 1 (top right). Because of the electronic impact of the acetyl substituent

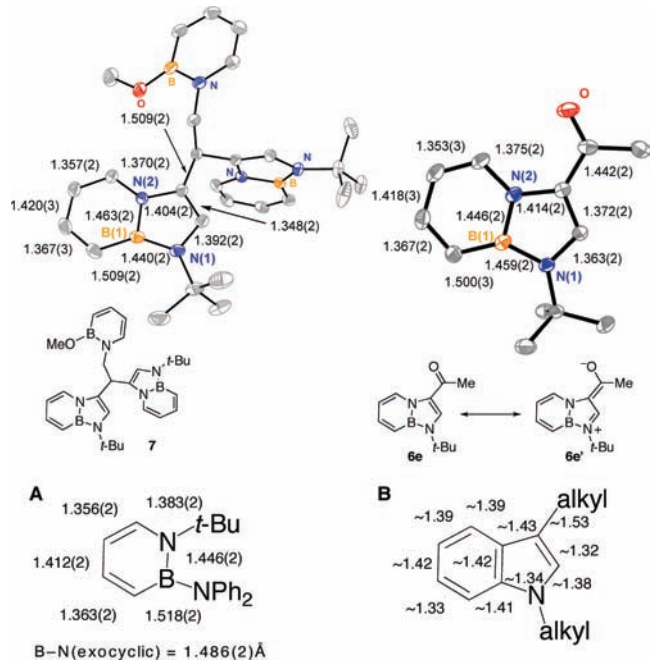
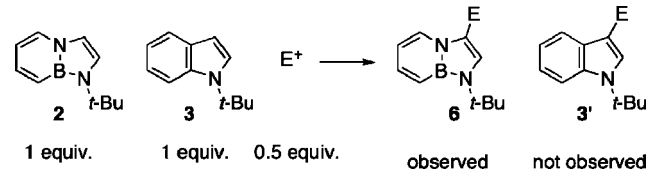


Figure 1. ORTEP illustrations, with thermal ellipsoids drawn at the 35% probability level, of **7** and **6e**.

at the C(3) position, significant changes in bond distances are observed compared to **7**. The N(1)—C(2) (1.363(2)Å), C(2)—C(3) (1.372(2) Å), and the B(1)—N(2) bond distances in **6e** are consistent with a significant contribution of structure **6e′**.

In order to probe the effect of the BN/CC isosterism of indoles on the reactivity in EAS reactions, we performed competition experiments between *N*-*t*-Bu-BN-indole **2** and its corresponding carbonaceous analogue **3**. Protection of the pyrrolic nitrogen with an *N*-*tert*-butyl group allows the reactivity of the 3-position to be evaluated without the influence of an indole N—H. Using 1 equiv of each indole **2** and **3** and 0.5 equiv of electrophile (E^+ = dimethyliminium chloride) in CD_2Cl_2, we observed only EAS products associated with *N*-*t*-Bu-BN-indole **2**, with indole **3** remaining intact (Scheme 4).[30] We hypothesize that *N*-*t*-Bu-BN-indole **2** exhibits greater enamine character in the pyrrolic ring and is therefore more nucleophilic than indole **3**.

Scheme 4. EAS Competition Experiment with Dimethyliminium Chloride As the Electrophile



In summary, we synthesized the first examples of BN-fused indole derivatives. We also demonstrated that this new family of BN indoles undergoes EAS reaction with classical indole-type regioselectivity at the 3-position. Competition experiments revealed that *N*-*t*-Bu-BN-indole **2** is more nucleophilic in EAS reactions than its carbonaceous counterpart. Single crystal X-ray structure analysis showed that while BN indoles are similar in shape compared to classical indoles, significant differences in bond distances, in particular those associated with the boron atom, are observed. Our work lays the synthetic foundation for BN-substituted unnatural products containing the indole motif and highlights the potential

of BN/CC isosterism as a general strategy in expanding the chemical space of biologically active molecules.

Acknowledgment. Support has been provided by the University of Oregon, Medical Research Foundation of Oregon, and National Institutes of Health (National Institute of General Medical Sciences, Grant R01-GM094541). This material is based upon work supported by the National Science Foundation under Award No. DGE-072540 (E.R.A.).

Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Baeyer, A. *Liebigs. Ann. Chem.* **1866**, *140*, 295–296. (b) Baeyer, A.; Emmerling, A. *Chem. Ber.* **1869**, *2*, 679–683.
(2) For leading references, see: (a) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532–547. (b) Gul, W.; Hamann, M. T. *Life Sci.* **2005**, *78*, 442–453.
(3) (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. (b) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911.
(4) (a) Zhou, H. B.; Nettles, K. W.; Bruning, J. B.; Kim, Y.; Joachimiak, A.; Sharma, S.; Carlson, K. E.; Stossi, F.; Katzenellenbogen, B. S.; Greene, G. L.; Katzenellenbogen, J. A. *Chem. Biol.* **2007**, *14*, 659–669. (b) Ito, H.; Yumura, K.; Saigo, K. *Org. Lett.* **2010**, *12*, 3386–3389.
(5) Liu, L.; Marwitz, A. J. V.; Matthews, B. W.; Liu, S. Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 6817–6819.
(6) Ashe, A. J., III; Yang, H.; Fang, X.; Kampf, J. W. *Organometallics* **2002**, *22*, 4578–4580. (b) Fang, X.; Yang, H.; Kampf, J. W.; Holl, M. M. B.; Ashe, A. J., III. *Organometallics* **2006**, *25*, 513–518.
(7) For pioneering work in this area, see: (a) Ulmschneider, D.; Goubeau, J. *Chem. Ber.* **1957**, *90*, 2733–2738. (b) Goubeau, J.; Schneider, H. *Liebigs Ann. Chem.* **1964**, *675*, 1–9.
(8) For an overview, see: Weber, L. *Coord. Chem. Rev.* **2008**, *252*, 1–31.
(9) For a review of tryptophan biosynthesis, see: Raboni, S.; Bettati, S.; Mozzarelli, A. *Cell. Mol. Life Sci.* **2009**, *66*, 2391–2403.
(10) Fletcher, A. J.; Bax, M. N.; Willis, M. C. *Chem. Commun.* **2007**, *45*, 4764–4766.
(11) Ashe, A. J., III; Fang, X. A. *Org. Lett.* **2000**, *2*, 2089–2091.
(12) Marwitz, A. J. V.; Abbey, E. R.; Jenkins, J. T.; Zakharov, L. N.; Liu, S.-Y. *Org. Lett.* **2007**, *9*, 4905–4908.
(13) Sundberg, R. J. In *Best Synthetic Methods, Indoles*; Academic Press: San Diego,1996; pp 1−6.
(14) For an overview, see: (a) Bosdet, M. J. D.; Piers, W. E. *Can. J. Chem.* **2009**, *87*, 8–29. (b) Liu, Z.; Marder, T. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 242–244.
(15) Marwitz, A. J. V.; Matus, M. H.; Zakharov, L. N.; Dixon, D. A.; Liu, S.-Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 973–977.
(16) For an overview on 2,3-dihydro-1*H*-1,3,2-diazaboroles, see: Weber, L. *Coord. Chem. Rev.* **2001**, *215*, 39–77.
(17) Pan, J.; Kampf, J. W.; Ashe, A. J., III. *Org. Lett.* **2007**, *9*, 679–681.
(18) To the best of our knowledge, EAS reactions have not been demonstrated with 2,3-dihydro-1*H*-1,3,2-diazaboroles.
(19) Kumar, V.; Kaur, S.; Kumar, S. *Tetrahedron Lett.* **2006**, *47*, 7001–7005.
(20) Lane, B. S.; Brown, M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057.
(21) Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H. *Org. Lett.* **2000**, *2*, 1485–1487.
(22) The determination of the substitution pattern for **6b** and **6d** were made by inference.
(23) Smith, G. F. *Adv. Heterocycl. Chem.* **1963**, *2*, 300–309.
(24) Ishii, H.; Murakami, K.; Sakurada, E.; Hosoya, K.; Murakami, Y. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2377–2385.
(25) Correspondence concerning X-ray crystallography should be directed to Lev Zakharov. E-mail: lev@uoregon.edu.
(26) Although we have determined that trimer **7** is the major product in the acid catalyzed trimerization of **2**, we were not able to isolate **7** cleanly. See Supporting Information for details.
(27) Abbey, E. R.; Zakharov, L. N.; Liu, S.-Y. *J. Am. Chem. Soc.* **2008**, *130*, 7250–7252.
(28) For a representative example, see the structure published in: Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780–10781.
(29) Pyykkö, P.; Atsumi, M. *Chem.—Eur. J.* **2009**, *15*, 12770–12779.
(30) See Supporting Information for details.

JA107312U