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Highly Efficient Synthesis and Solid-State Characterization of 1,2,4,5-Tetrakis(alkyl- and arylamino)benzenes and Cyclization to Their Respective Benzobis(imidazolium) Salts

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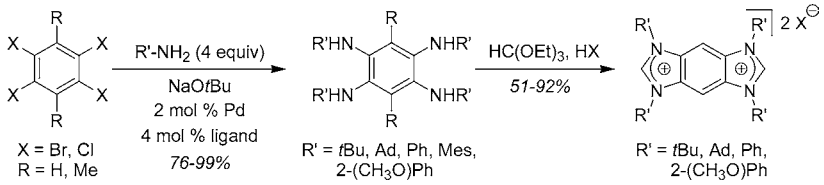
ABSTRACT



New synthetic methodology to a variety of 1,2,4,5-tetraaminobenzenes and their corresponding benzobis(imidazolium) salts has been accomplished. Palladium-catalyzed coupling of various 1,2,4,5-tetrabromo- or 1,2,4,5-tetrachlorobenzenes with aryl- or *tert*-alkylamines afforded the respective tetrakis(*N*-substituted)aminobenzenes in excellent yields. This enabled comparative solid-state structural analyses of this elusive class of electron-rich arenes with their oxidized derivatives. The tetraamines were found to undergo formylative cyclization to the corresponding benzobis(imidazolium) salts in good to excellent yields.

We have recently launched a program on the broad study and application of benzobis(imidazolium)s and benzobis(imidazolylidene)s in organic and organometallic materials chemistry.[1] These difunctional compounds are readily prepared in multigram quantities and in excellent yields via formylative cyclization of their respective tetraaminoarene precursors followed by subsequent alkylation with primary alkyl halides. While modular in many regards, the inherent limitations of this methodology included incompatibility of incorporating *N*-aryl and bulky *N*-alkyl substituents into the benzobis(imidazole) nucleus. To overcome these limitations, we targeted a general and highly efficient synthetic route to a range of 1,2,4,5-tetrakis(alkyl- and arylamino)benzenes. Herein, we disclose details on these advances and include a comparative solid-state study of substituted 1,2,4,5-tetraaminobenzenes and their respective 2,5-diamino-1,4-benzoquinonediimines. In addition, we describe the cyclization of the tetraamines to their corresponding benzobis(imidazolium) salts.

As a general class of highly electron-rich arenes, tetraaminobenzenes have seen a rich diversity of chemical applications. For example, 1,2,4,5-tetraaminobenzene[2] (**1**) and its oxidized derivative, 2,5-diamino-1,4-benzoquinonediimine[3] (**2**), have found great utility in organic, organometallic, and macromolecular chemistry. They have found

(1) (a) Boydston, A. J.; Williams, K. A.; Bielawski, C. W. *J. Am. Chem. Soc.* **2005**, *127*, 12496. (b) Kamplain, J. W.; Bielawski, C. W. *Chem. Commun.* **2006**, DOI: 10.1039/b518246h.

(2) (a) Nietzki, R.; Hagenbach, E. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 328. (b) Nietzki, R. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2114.

(3) (a) Fischer, O.; Hepp, E. *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 676. (b) Kimich, C. *Ber. Dtsch. Chem. Ges.* **1875**, *8*, 1026.

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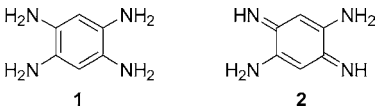
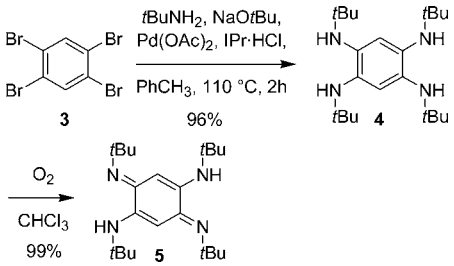
potential and utility as ditopic ligands in coordination chemistry,[4] as pH-dependent chromophores,[5] as difunctional monomers in the synthesis of main-chain organometallic[6] and supramolecular polymers,[7] and as π-complexation partners in supramolecular systems.[8]

While **1**[9] is commercially available (as its tetrahydrochloride salt), access to its *N*,*N*′,*N*″,*N*‴-tetra(alkyl and aryl) derivatives remains synthetically challenging due to the high propensity of these electron-rich arenes to oxidize during isolation. For example, Braunstein obtained a variety of *N*,*N*′,*N*″,*N*‴-tetraalkyl-2,5-diamino-1,4-benzoquinonediimines by reducing their respective 1,2,4,5-tetraamidobenzenes under aerobic conditions.[4h,5] More recently, in a breakthrough report by Harlan,[10] exhaustive Buchwald−Hartwig[11] Pd-catalyzed amination of 1,2,4,5-tetrabromobenzene with 2,6-dimethylaniline provided mixtures of the respective tetrakis(arylamino)benzene and azophenine in a promising 26% yield.[12] We envisioned that the incorporation of large N-substituents could slow down (or even eliminate) undesired oxidative pathways and facilitate isolation of the targeted tetraamines.



Inspired by Harlan's report,[10] we examined the Pd-catalyzed cross coupling of *tert*-butylamine (*t*-BuNH$_2$) with 1,2,4,5-tetrabromobenzene (**3**) under basic conditions as shown in Scheme 1. The reaction was performed in toluene (0.2 M) with 1,3-bis(2,6-diisopropylphenyl)imidazolylidene·HCl[13] (IPr·HCl):Pd(OAc)$_2$[14] (2:1 stoichiometry; 2 mol % Pd catalyst relative to **3**) as the catalyst precursor.[15] Surprisingly, after less than 2 h at 110 °C, a colorless solid precipitated from the reaction solution, which was subsequently isolated in 96% yield via filtration under a cone of nitrogen.[16] The ^{1}H NMR spectrum of this compound exhibited a single, diagnostic signal at δ 6.53 ppm (solvent = $CDCl_3$), which was indicative of a highly symmetric structure consistent with the desired 1,2,4,5-tetrakis(*tert*-butylamino)benzene (**4**). To confirm, a crystal suitable for X-ray crystallography was obtained by slow cooling of a hot saturated solution of **4** in toluene; an ORTEP diagram of the corresponding structure is shown in Figure 1 (left). Notably, the four nitrogen atoms were found to be coplanar with nearly equivalent N−C (1.43−1.44 Å) and aryl C−C (1.39−1.41 Å) bond distances. In addition, the *tert*-butyl groups on the nitrogen atoms were

Scheme 1. Synthesis of 1,2,4,5-Tetrakis(*tert*-butylamino)benzene (**4**) and Its Related 2,5-Diamino-1,4-benzoquinonediimine (**5**)



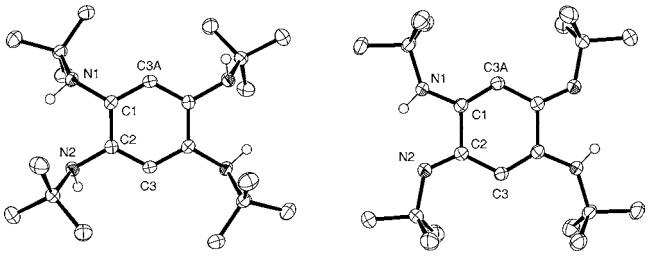


Figure 1. ORTEP representations of the X-ray crystal structures of 1,2,4,5-tetrakis(*tert*-butylamino)benzene (**4**) (left) and *N*,*N*′,*N*″,*N*‴-tetrakis(*tert*-butyl)-2,5-diamino-1,4-benzoquinonediimine (**5**) (right), showing non-hydrogen atoms as 50% thermal ellipsoids.[18]

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(11) (a) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041. (b) Wolfe, J. P.; Wagaw, S.; Marcox, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (d) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.

(12) In a related example, Pd-catalyzed aryl amination was used to synthesize 1,2,4,5-tetra(morpholino)benzene in 76% yield via coupling of 1,2,4,5-tetrabromobenzene with morpholine, see: Witulski, B.; Senft, S.; Thum, A. *Synlett* **1998**, 504.

(13) (a) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69. (b) The use of 1,3-bis-(2,6-diisopropylphenyl)imidazolinylidene·HCl (H_2IPr·HCl) in lieu of IPr·HCl afforded comparable results.

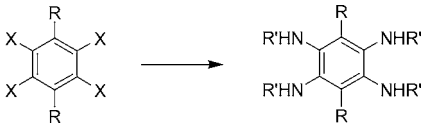
(14) $PdCl_2$ was found to be equally effective as Pd(OAc)$_2$.

situated above and below the plane of the arene ring with dihedral angles of 100−110°.

To compare **4** directly with its corresponding 2,5-diamino-1,4-benzoquinonediimine, the tetraamine was dissolved in $CHCl_3$ and stirred under an atmosphere of oxygen at room temperature.[17] The ^1H NMR spectrum (solvent = $CDCl_3$) of this compound exhibited a signal at δ 5.53 ppm that was consistent[4h,5,10] with quinoid-derivative **5** (Scheme 1). Crystals of **5** suitable for X-ray analysis were also obtained, which allowed for direct comparison of the related species. As shown in Figure 1 (right), the ORTEP diagram of **5** exhibited not only coplanar *tert*-butyl groups (with dihedral angles of 175−179°), but also varied N−C (N1−C1, 1.35 Å and N2−C2, 1.29 Å) and quinone C−C (1.51, 1.37, and 1.44 Å) bond lengths. This type of bonding pattern has been previously described and is fully consistent with related azophenine solid-state structures.[4h,5,10] To our knowledge, this is the first example of a crystalline 1,2,4,5-tetrakis(alkylamino)benzene and a direct comparison with its oxidized derivative. More importantly, the collective data suggested that the synthetic methodology detailed above was successful in preparing and isolating bona fide *N*,*N*′,*N*″,*N*‴-tetraalkyl-1,2,4,5-tetraaminobenzenes.

Prompted by these results and using the protocol described above, a variety of other amines were probed for their ability to couple with **3**. As expected, the coupling of 1-adamantylamine ($AdNH_2$) with **3** afforded similar results as tBuNH$_2$ (90% yield; Table 1, entry 2). Arylamines including aniline, relatively bulky mesitylamine,[19] and electron-rich *o*-anisidine were also found to successfully couple to **3** in excellent yields (entries 3−5). Unfortunately, primary (e.g., 1-butylamine), secondary (e.g., cyclohexylamine), or electron-deficient arylamines (e.g., nitro- and chloroanilines) either resulted in no reaction or afforded complex product mixtures.[20] It is noteworthy that cross-coupling of 2,3,5,6-tetrabromo-*p*-xylene and 1,2,4,5-tetrachlorobenzene with tBuNH$_2$ afforded the corresponding tetraamines in 99% and 94% yields, respectively (entries 6 and 7). The former result suggested that the bulky IPr-ligated Pd catalyst was not impeded by the presence of steric bulk ortho to both sites of amination and the latter was a testament to the high activity of this catalyst system.

Table 1. Synthesis of 1,2,4,5-Tetrakis(alkyl- and arylamino)benzenes[a]



	tetrahalobenzene				
entry	X	R	amine	product	yield, %
1	Br	H	tBuNH$_2$	**4**	96
2	Br	H	AdNH$_2$	**6**	90
3	Br	H	PhNH$_2$	**7**	76
4	Br	H	MesNH$_2$	**8**	94
5	Br	H	2-MeOPhNH$_2$	**10**	96
6	Br	Me	tBuNH$_2$	**11**	99
7	Cl	H	tBuNH$_2$	**4**	94

[a] General reaction conditions: IPr·HCl (0.04 equiv); $Pd(OAc)_2$ (0.02 equiv); NaOtBu (4.1 equiv); RNH$_2$ (4.1−10 equiv); solvent = toluene, temperature = 110 °C. Isolated yields are indicated. tBuNH$_2$ = *tert*-butylamine; AdNH$_2$ = 1-adamantylamine; PhNH$_2$ = aniline; MesNH$_2$ = 2,4,6-trimethylaniline; 2-MeOPhNH$_2$ = *o*-anisidine.

After the 1,2,4,5-tetrakis(alkyl- and arylamino)benzenes were synthesized, their relative susceptibilities toward oxidation were qualitatively investigated.[21] The amines were independently dissolved in aerated $CDCl_3$ and examined by ^1H NMR spectroscopy periodically over time. In general, the 1,2,4,5-tetrakis(alkylamino)benzenes were found to oxidize slower ($\tau_{1/2} \sim$ days) than their *N*-aryl analogues ($\tau_{1/2} \sim$ hours). However, the electron-rich *N*-anisidyl derivative **10** was exceptional and was found to exhibit stability comparable to that of the *N*-alkyl derivatives (**4** and **6**). The most stable tetraamine was the xylene derivative **11**, which resisted oxidation even after dissolution in aerated solvents for several weeks. These results may be rationalized by examining individual steric and electronic contributors which may kinetically and/or thermodynamically inhibit nitrogenyl formation.[22]

In an attempt to prepare partially aminated arenes, a Pd-catalyzed cross-coupling reaction was performed with 2 molar equiv of tBuNH$_2$ relative to 1,2,4,5-tetrabromobenzene. To our surprise, only the tetraaminated product (**4**) and unreacted starting materials were observed, even in crude reaction mixtures. In fact, identical results were obtained when substoichiometic amounts of tBuNH$_2$ or AdNH$_2$ were used, which suggested that reactivity enhancements were occurring upon subsequent aminations. In contrast, the use

(15) Aside from IPr and H_2IPr, a variety of other ligands for Pd including bulky phosphines (PCy_3, *rac*-BINAP, PtBu$_3$) and imidazolylidenes (1,3-bis(2,6-di-*tert*-butyl)imidazolylidene, 1,3-bis(2,6-dimesityl)imidazolylidene) were screened, but did not afford appreciable yields of product.

(16) Residual inorganic salts were removed by filtering chloroform solutions of the tetraaminobenzenes followed by evaporation.

(17) Use of an oxygen atmosphere effects azophenine formation more rapidly than use of aerated solvents.

(18) Selected bond lengths (Å) and angles (deg): For **4**: N1−C1, 1.429(2); N2−C2, 1.441(2); C1−C2, 1.411(2); C2−C3, 1.394(2); C1−C3A, 1.394(2); C2−C1−N1, 121.1(1); C1−C2−N2, 119.6(1); C2−C1−N1−C4, 109.8(1); C1−C2−N2−C8, 99.8(2). For **5**: N1−C1, 1.349(1); N2−C2, 1.294(1); C1−C2, 1.513(1); C1−C3A, 1.367(1); C2−C3, 1.437(1); N1−C1−C2, 113.0(1); N2−C2−C1, 113.9(1); C4−N1−C1−C2, 175.1(1); C1−C2−N2−C8, 179.3(1).

(19) A solution to the crystal structure of 1,2,4,5-tetrakis(mesitylamino)benzene (**8**) was also determined; key bond distances (Å) and angles (deg): N1−C1, 1.413(2); N2−C3, 1.424(2); C1−C2, 1.391(2); C2−C3, 1.398(2); C1−C3A, 1.404(2); C3A−C1−N1, 118.9(1); C1A−C3−N2, 118.5(1); C4−N1−C1−C3A, 173.9(2); C1A−C3−N2−C13, 172.9(2). Using the procedure described in the text, the corresponding azophenine (**9**) was synthesized and a solution to its corresponding crystal structure was determined; key bond lengths (Å) and angles (deg): N1−C1, 1.293(2); N2−C3, 1.357(2); C1−C2, 1.440(2); C2−C3, 1.356(2); C1−C3A, 1.494(2); N1−C1−C3A, 115.6(1); N2−C3−C1A, 114.2(1); C3A−C1−N1−C4, 176.9(1); C1A−C3−N2−C13, 171.3(1). See the Supporting Information for additional details.

(20) Efforts toward optimizing these reactions are underway.

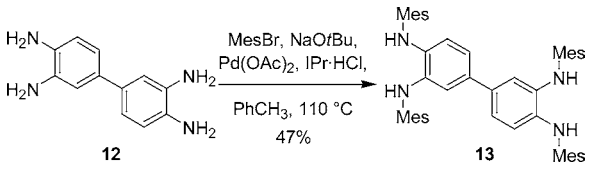
(21) Oxidative susceptibilities of the 1,2,4,5-tetraminobenzenes can be greatly reduced through protonation with HCl prior to isolation.

(22) For discussions comparing relative stabilites of electron deficient arylamines, see: (a) Li, Z.; Cheng, J.-P. *J. Org. Chem.* **2002**, *68*, 7350. (b) Kemnitz, C. R.; Karney, W. L.; Borden, W. T. *J. Am. Chem. Soc.* **1998**, *120*, 3499. (c) Miura, Y.; Kitagishi, Y.; Ueno, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3282.

of aniline as a coupling partner in the Pd-catalyzed reaction afforded a complex mixture of aminated products.[23]

Thus far we have demonstrated that various tetrakis(alkyl- and arylamino)arenes can be prepared via aryl amination from their corresponding tetrahaloarene. However, in situations when the requisite polyhalogenated arenes are not readily available (e.g., 3,3′,4,4′-tetrachlorobiphenyl[24]), a complementary route to the respective tetrakis(amino)arenes would be desirable. As shown in Scheme 2, mesityl bromide

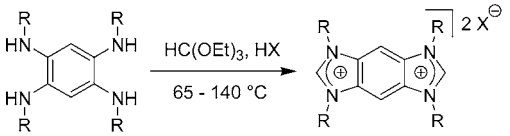
Scheme 2. Synthesis of *N*,*N*′,*N*″,*N*‴-Tetramesityl-3,3′-diaminobenzidine



was coupled to commericially available 3,3′-diaminobenzidine **12** with use of the catalyst system and conditions discussed above to afford the corresponding *N*,*N*′,*N*″,*N*‴-tetramesityl-3,3′-diaminobenzidine (**13**) in 47% yield (Scheme 2).[25]

With the tetraamines in hand, we were poised to prepare the corresponding *N*-aryl and *N*-alkyl benzobis(imidazolium) salts through a formylative cyclization methodology.[26] As shown in Scheme 3, ring closure was effected by subjecting

Scheme 3. Cyclization of 1,2,4,5-Tetraaminobenzenes to Their Respective Benzobis(imidazolium) Salts



4 (R = *t*-Bu)
6 (R = Ad)
7 (R = Ph)
10 (R = 2-MeOPh)

14, **77%** (R = *t*-Bu, X = BF_4)
15, **70%** (R = Ad, X = BF_4)
16, **51%** (R = Ph, X = BF_4)
17, **92%** (R = 2-MeOPh, X = Cl)

the tetraamines noted above to acidified (HCl or HBF_4)[27] $HC(OEt)_3$ solutions at elevated temperatures (the *N*-alkylated derivatives **4** and **6** required 65 °C whereas the *N*-arylated derivatives **7** and **10** required 140 °C). Although cyclizations were sluggish (reaction time: 24 h), good to excellent yields of product were obtained.[28] Notably, the electron-rich *N*-anisidyl substrate **10** underwent clean cyclization to afford product in only 2 h (92% yield). Unfortunately, mesitylated derivatives **8** and **13** were reluctant to undergo cyclization under these conditions.

In summary, we have developed an efficient synthetic and isolation protocol for preparing 1,2,4,5-tetrakis(alkyl- and arylamino)benzenes, two elusive classes of electron-rich arenes. Their structures were unambiguously proven with X-ray crystallography and compared with their oxidized derivatives. Immediate efforts will concentrate on expanding the substrate scope of this reaction and elucidating its unique substitution pattern. The tetraamines were successfully cyclized to give the desired bis(azolium) compounds in good to excellent yields. Currently we are also investigating applications of bis(azolium) salts for direct formation of nonchelating bis(carbene)s and their respective bimetallic complexes.[29]

Acknowledgment. We are grateful to the U.S. Army Research Office (W911NF-05-1-0430) and the University of Texas at Austin for generously supporting this work.

Supporting Information Available: Detailed experimental procedures, characterization of all new compounds, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060349C

(23) The mechanistic implications of these findings are currently under investigation in our laboratories.

(24) Lehmler, H.-J.; Robertson, L. W.; Kania-Korwel, I. *Chemosphere* **2004**, *56*, 735.

(25) The aryl amination reaction was determined to be quantitative by ^{1}H NMR spectroscopy; however, the isolation of **13** was challenged by its high solubility in common solvents.

(26) A similar approach utilizing aryl amination of 1,2-dibromobenzene followed by cyclization has been reported: Rivas, R. M.; Riaz, U.; Giessart, A.; Smulik, J. A.; Diver, S. T. *Org. Lett.* **2001**, *3*, 2673. For syntheses of related benzimidazolium and benzimidazolylidene compounds, see: (a) Huynh, H. V.; Holtgrewe, C.; Pape, T.; Koh, L. L.; Hahn, F. E. *Organometallics* **2006**, *25*, 245. (b) Hahn, F. E.; Jahnke, M. C.; Gomez-Benitez, V.; Morales-Morales, D.; Pape, T. *Organometallics* **2005**, *24*, 6458. (c) Hahn, F. E.; Wittenbecher, L.; Le Van, D.; Frohlich, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 541.

(27) Shorter reaction times were observed with HBF_4, which may be related to the higher solubilities of bis(benzobisimidazolium) tetrafluoroborate salts as compared to their analogous chloride salts.

(28) The overall yield of **16** from 1,2,4,5-tetrabromobenzene was improved to 84% by using a one-pot, two-step procedure. See the Supporting Information for additional details.

(29) Khramov, D. M.; Boydston, A. J.; Bielawski, C. W. Manuscript in preparation.