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Fusing Triazoles: Toward Extending Aromaticity

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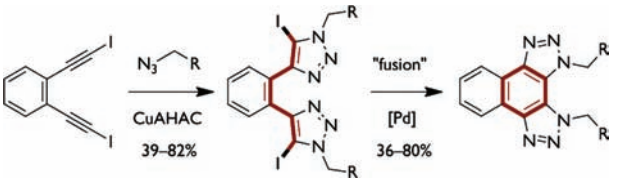
ABSTRACT

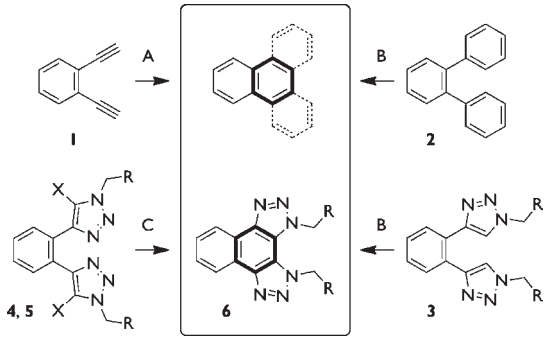


A novel method to extend aromaticity by one benzene and two triazole rings was developed and optimized. This two-step route employs the copper-catalyzed azide–haloalkyne cycloaddition reaction of an *ortho*-bis(iodoacetylene) system and the subsequent intramolecular homocoupling fusion of the neighboring iodotriazoles, a process in which an additional benzene ring is formed. This versatile methodology allows one to extend the core size of chromophores and, consequently, to tune the material's properties.

Chromophoric (or dye) molecules, both natural and synthetic, belong to one of the oldest classes of materials that have fascinated scientists for more than a century. Their structure is comprised of a smaller or larger 2D (hetero)aromatic core, often equipped with solubilizing substituents on the periphery. A characteristic feature of a dye core is an extended π-structure, which results in the red shift of the absorption maximum of these molecules (usually into the visible or NIR region) and their ability to self-assemble by means of $\pi-\pi$ interactions. Polycyclic aromatic hydrocarbons (PAHs)[1] and their analogues represent probably the most diverse subclass of dye molecules, with applications varying from fluorescent dyes to organic semiconductors.[2] Other typical examples include porphyrins,[3] phthalocyanines,[3,4] perylenes,[5] and BODIPYs,[6] among many others.

From the perspective of making π-conjugated dye structures, numerous synthetic strategies have been developed to extend their (hetero)aromatic cores by one additional π-conjugated unit, the benzene ring being one of the most commonly used moieties. The most powerful transformations to extend aromaticity by an additional fused benzene unit are the Bergman cyclization[7] (A) and the cyclodehydrogenation[8] (B) reactions (Scheme 1).

Scheme 1. Synthetic Transformations of **1**–**5** Extending the Core Size by an Extra Benzene Ring: Bergman Cyclization (A), Cyclodehydrogenation (B), and Homocoupling (C; **4**: X = Br; **5**: X = I) Reactions



In the first case, an additional fused benzene unit is obtained by the thermal cycloaromatization reaction of an

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(2) Wu, J.; Pisula, W.; Müllen, K. *Chem. Rev.* **2007**, *107*, 718–747.
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(5) Weil, T.; Vosch, T.; Hofkens, J.; Peneva, K.; Müllen, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 9068–9093.
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enediyne system (**1**); in the latter case, the benzene ring is formed upon the Lewis-acid-catalyzed oxidative coupling of two *ortho*-localized phenyl rings (**2**). The second method is of particular interest and to date, represents the most efficient tool to access PAHs, as well-defined cut-outs of graphene.[1,2,8a]

The major challenge that needs to be addressed when building up larger aromatic structures is to retain the efficiency of each step upon the increase of the core size; an issue associated with the restricted solubility of larger cores when solubilizing tails can only be introduced in the final stage of the synthesis. In the course of our studies on employing the triazole moiety as an aromaticity-extending building block,[9] it was of interest to probe whether a bis(triazole) system similar to the bis(phenyl) system **2** could be employed to construct an additional fused benzene unit. The triazole ring can be obtained using the powerful Cu-catalyzed azide–alkyne cycloaddition (CuAAC) reaction:[10] a versatile alternative method.

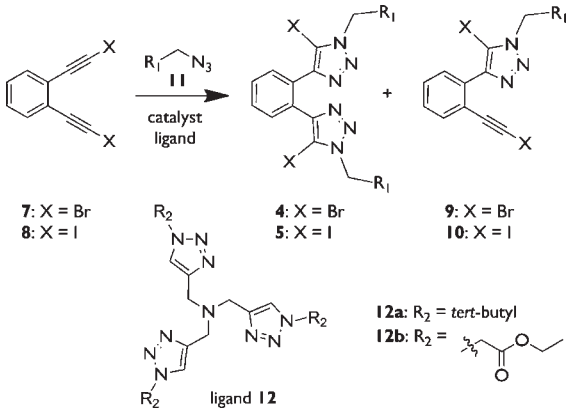
Initially, three *ortho*-bis(triazole) systems **3**, **4**, and **5** were investigated as the precursors for the synthesis of the fused product **6**. Compared with **3**–**5**, aromaticity in **6** is extended by an additional benzene and two triazole rings, which, in principle, can be achieved by either the cyclodehydrogenation (B) or homocoupling (C) reactions. The preliminary studies, performed on analogues of **3** by using method B, did not lead to the formation of the desired fused products. Thus, method C (**4** and **5**) was subsequently investigated and optimized. The results are reported below.

Precursors **4** and **5** possess two 1,4,5-trisubstituted triazole rings, bearing a halogen atom (Br or I, respectively) in the 5-position, and were prepared using the Cu-catalyzed azide–haloalkyne cycloaddition (CuAHAC) method.[11] This method employs terminal acetylenes bearing a halogen atom instead of a proton, and to date, several variations of this methodology are known in the literature.[12,13] Among these, two methods employing a catalytic amount of the Cu(I) source are of special interest, and these were tested in the preparation of **4** and **5**.

The first procedure employs the CuAHAC reaction of bromoacetylenes with various azides, using a catalytic amount of Cu(I)/Cu(II) species without the presence of a ligand, to obtain 5-bromo-1,4-disubstituted triazoles;[12b] the second method employs the CuAHAC reaction of iodoacetylenes and a catalytic amount of CuI and tris-(triazolyl)-derived ligand, to obtain 5-iodo-1,4-disubstituted triazoles.[12a] For the latter, the three-step one-pot procedure, including the iodoacetylene formation, CuAHAC, and subsequent cross-coupling reactions, proved also to be very efficient.

The scope and limitations of the CuAHAC reaction of bis(haloacetylenes) **7** (X = Br) and **8** (X = I) with various azides (**11**), to obtain **4** and **5**, respectively, were investigated, and the results are summarized in Table 1.

Table 1. CuAHAC Reaction of **7** and **8**



					yield (%)	
entry	X	azide/R_1	catalyst (%)	ligand (%)	**4**/**5**	**9**/**10**
1[a]	Br	**11a**/$C_{11}H_{23}$	CuBr (40) $Cu(OAc)_2$ (40)	–[b]	**4** (10)	**9** (16)
2[a]	Br	**11a**/$C_{11}H_{23}$	CuI (10) $Cu(OAc)_2$ (10)	–[b]	**4** (16)	**9** (23)
3[c]	I	**11a**/$C_{11}H_{23}$	CuI (20)	**12b** (20)	**5a** (47)	n.i.[d]
4[c]	I	**11a**/$C_{11}H_{23}$	CuI (20)	**12a** (20)	**5a** (54)	n.i.[d]
5[c]	I	**11a**/$C_{11}H_{23}$	CuI (20)	**12a** (20)	**5a** (48)[e]	n.i.[d]
6[c]	I	**11b**/Ph	CuI (20)	**12b** (20)	**5b** (39)	n.i.[d]
7[c]	I	**11c**/TEG[f]	CuI (20)	**12a** (20)	**5c** (82)	n.i.[d]

[a] **7** (1 equiv), azide (6 equiv), THF, 50 °C, 5 d. [b] CuX is acting as a heterogeneous catalyst; $Cu(OAc)_2$ is soluble under these conditions. [c] **8** (1 equiv), azide (2.2 equiv), THF, rt, 65 h. [d] Not isolated. [e] 43 h. [f] TEG = $CH_2O(CH_2CH_2O)_2CH_3$.

Bis(haloacetylenes) **7**[7b] and **8** were prepared starting from 1,2-diethynylbenzene (**1**) or its protected analogue

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(see the Supporting Information) in one step following literature procedures.[14] Compared with literature, longer reaction times (>65 h) for the CuAHAC reactions were applied and moderate to good yields of the desired products were obtained, most likely due to the partial decomposition of the starting materials **7** and **8** under the applied reaction conditions.[15]

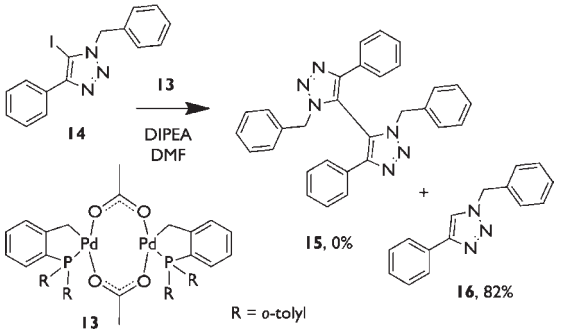
To compare the efficiencies of the two previously described CuAHAC protocols using either **7** and Cu(I)/Cu(II)[12b] or **8** and CuI/**12**[12a] as catalytic systems, 1-azidododecane (**11a**) was used as an azide precursor (Table 1, entries 1–5). From the yields of the desired product **4**/**5** and its monoclicked side product **9**/**10**, it can be concluded that the efficiency of the CuAHAC reactions using **8** is significantly higher (entries 3–5), when compared with **7** (entries 1 and 2), with the highest yield obtained when **12a** was used as a ligand (entry 4). The yield of this reaction was still increasing after the period of 43 h; thus, a prolonged reaction time (65 h) was applied when using this method (entries 4 and 5).

The effect of the R group of the azide on the yield of the desired product **5** during the CuAHAC reaction using **8** was also studied (entries 3/6 and 4/7). The use of (azidomethyl)benzene (**11b**) led to a small decrease (8%) in yield compared with **11a** (entries 3 and 6); the use of 1-azido-2-(2-(2-methoxyethoxy)ethoxy)ethane (**11c**) led to a significant increase in yield (28 and 43%) compared with both **11a** and **11b**, respectively (entries 4/7 and 6/7). The reason for such a dramatic difference in the reactivity of this series of azides attached to a primary carbon is not known; the decrease in yield in the case of **11b** compared to **11a**, however, is tentatively attributed to the steric reasons.

In the literature, several examples of the homocoupling reactions of aryl halides are known, usually employing more reactive halide electrophiles, namely, aryl iodides and aryl bromides.[16] Since the CuAHAC reaction of bis(iodoacetylene) **8** proceeds significantly faster and more efficiently compared to bis(bromoacetylene) **7**, an intramolecular homocoupling reaction of bis(iodotriazoles) **5a**–**5c** was studied. An efficient method for the preparation of biaryls, using a homocoupling reaction of aryl iodides catalyzed by palladacycle catalyst **13**, was previously described in the literature;[17] this methodology, however, was not applied to the heteroaromatic systems. To test the reactivity of 5-iodo-1,4-disubstituted triazoles in this reaction, the intermolecular homocoupling reaction of iodotriazole **14** was first carried out (Scheme 2).

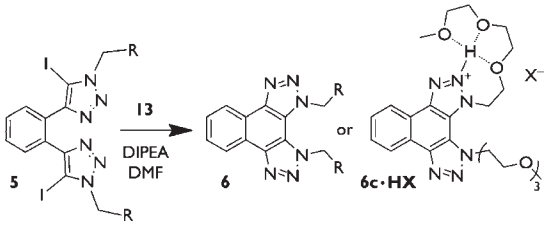
Despite the electron-withdrawing character of the triazole moiety, that is expected to facilitate the insertion of the Pd(0) into the C–I bond,[17,18] the homocoupling reaction of **14** did not afford the desired product **15**. Instead, the product of protodehalogenation **16** and the recovered starting material **14** were obtained in 82% and 18% yield, respectively. This was possibly due to the steric hindrance of the bulky substituents in the 1- and 4-positions (both *ortho* relative to the iodine substituent in the 5-position); the protodehalogenation product **16** was possibly formed from the oxidative-addition intermediate via the β-H-atom elimination/reductive elimination mechanism (DIPEA being the source of the β-H-atom when coordinated to Pd(II)).

Scheme 2. Intermolecular Homocoupling Reaction of **14**



Interestingly, when the intramolecular homocoupling reaction of bis(iodotriazoles) **5a**–**5c** was carried out to afford the key intermediate **6** using the same reaction conditions, the desired products **6a**–**6c** were formed in moderate to good yields (Table 2); possibly, this reaction was partially inhibited by protodehalogenation as the side reaction.

Table 2. Intramolecular Homocoupling Reaction of **5**[a]



entry	starting compd	R	catalyst (%)	product (%)[b]
1	**5a**	$C_{11}H_{23}$	1	**6a** (47)
2	**5a**	$C_{11}H_{23}$	2	**6a** (52)
3	**5a**	$C_{11}H_{23}$	4	**6a** (40)
4	**5b**	Ph	1	**6b** (36)
5	**5c**	TEG[c]	1	**6c•HX** (71)[d]
6	**5c**	TEG[c]	0.5	**6c•HX** (80)[d]
7	**5c**	TEG[c]	0.5[e]	**6c•HX** (66)[d]

[a] **5** (1 equiv), DMF (c(**5**) = 0.40 M), DIPEA (1.2 equiv), 110 °C, 17 h. [b] Isolated yield. [c] $CH_2O(CH_2CH_2O)_2CH_3$. [d] Yield calculated for X = I. [e] c(**5**) = 0.13 M.

Similarly to the CuAHAC reaction, the homocoupling reaction proceeded more efficiently (66–80%) in the case of

(15) Both **7** and **8** are unstable, and upon their preparation, they were immediately used in the next step or stored in the freezer. Compared with relatively stable **8**, compound **7** is significantly less stable and slowly decomposes even at lower temperatures (freezer).

(16) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev*. **2002**, *102*, 1359–1469.

(17) Luo, F.-T.; Jeevanandam, A.; Basu, M. K. *Tetrahedron Lett*. **1998**, *39*, 7939–7942.

(18) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457–2483.

5c (entries 5–7); in the case of **5a** and **5c** (entries 1–4), the efficiencies were significantly lower (36 and 40–52%, respectively). For **5a** (entries 2–4) and **5c** (entries 5–7), optimization of the reaction conditions by varying the amount of the catalyst was also carried out. In both cases, a maximum efficiency was reached at a certain amount of the catalyst (entries 3 and 6, respectively) that decreased after further increase or decrease of the catalyst loading. To favor the intramolecular reaction of **5c** and suppress the intermolecular reactions leading to oligomeric side products, the homocoupling reaction under dilute conditions was carried out (entry 7). This, however, did not improve the efficiency of this reaction and led to a 14% decrease in yield.

In the case of **5c**, the desired product **6c** was repeatedly isolated as the monoprotonated salt **6c•HX**, the counteranion most likely being iodide (X = I). We suggest that the proton was possibly obtained from DIPEA via the same reaction mechanism as in the case of the formation of **16**, when an inactive Pd(II) catalyst, obtained after one homocoupling cycle employing Pd(IV), was reduced to active Pd(0). Washing of the organic solution of **6c•HX** by strong alkaline aqueous solutions did not afford the desired deprotonated product **5c**; probably, the protonation of the N-2 nitrogen of the triazole was highly favored due to the efficient stabilization of the proton by the three oxygen atoms of the ethylene glycol tail through hydrogen bonding (Table 2 figure). Protonation of the second triazole moiety in **6c•HX** was never observed, most likely due to the decreased electron density of the system caused by the first protonation.

As mentioned before, our methodology allows one to extend the aromaticity of a (hetero)aromatic core (by one benzene and two triazole rings); this effect can clearly be observed in the ^{1}H NMR and UV–vis spectra of compounds **5** and **6** (Figure 1). Compared with **5**, the aromatic-core ^{1}H NMR signals of the fused product **6** are significantly shifted downfield and a red-shifted shoulder appears in the UV–vis spectrum of **6**.

Apart from extending aromaticity, our approach offers another opportunity: the two fused triazole rings can, in principle, serve to coordinate metals or as hydrogen-bond acceptors and, thus, allow for a further tuning of the material's properties upon doping. As an example, this synthetic approach has been applied by us in extending functional chromophores based on phthalocyanines to substituted napthalocyanines.[9,19]

In summary, a novel approach to extend aromaticity of (hetero)aromatic systems by one benzene and two triazole rings was developed and optimized. The crucial steps of this approach, the CuAHAC and the intramolecular homocoupling reactions affording the key intermediate **6**, were optimized on a model system to proceed in moderate to good overall yields (14–64%; over the three steps (iodoacetylene formation/CuAHAC/homocoupling). This methodology is of interest for the preparation of extended functional chromophoric materials with potential applications in (opto)electronic devices.

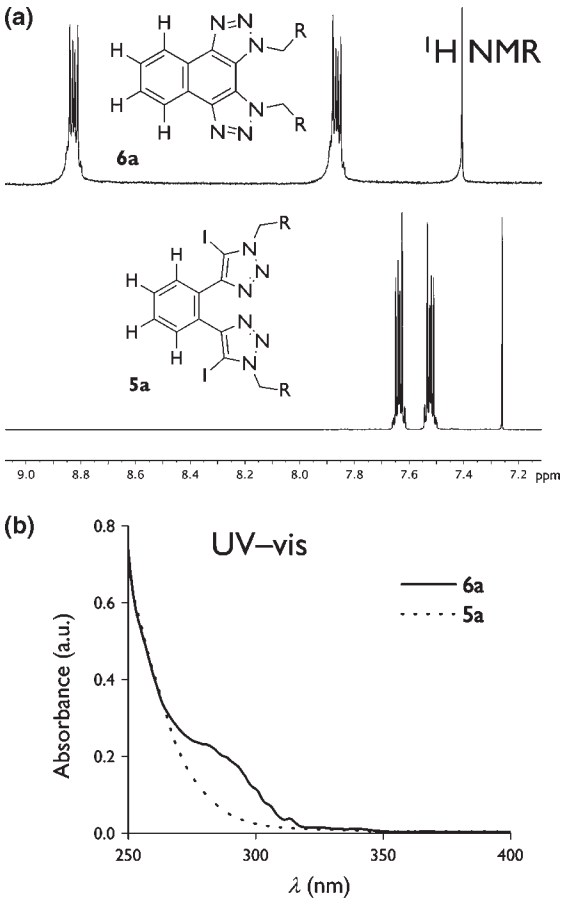


Figure 1. (a) ^{1}H NMR spectra in $CDCl_3$ (7.26 ppm) of **5a** and **6a**: insets of the aromatic region (the corresponding protons are marked in the structure by using an "H" symbol); (b) Overlay of the UV–vis spectra of **5a** and **6a** in $CHCl_3$ at 40 μM.

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Supporting Information Available. Synthetic and characterization details for each compound, and copies of the ^{1}H and ^{13}C NMR spectra for compounds **4**, **5a**–**5c**, **9**, and **6a**–**6c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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