OL | Organic Letters

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Cross-Coupling Strategy for the Synthesis of Diazocines

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00122 Read Online

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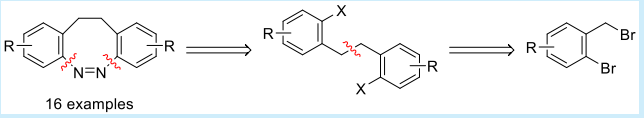
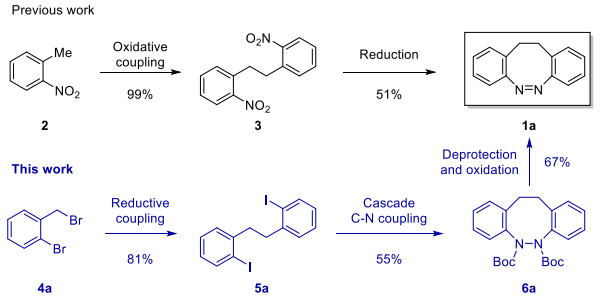
ABSTRACT: Ethylene bridged azobenzenes are novel, promising molecular switches that are thermodynamically more stable in the (*Z*) than in the (*E*) configuration, contrary to the linear azobenzene. However, their previous synthetic routes were often not general, and yields were poorly reproducible, and sometimes very low. Here we present a new synthetic strategy that is both versatile and reliable. Starting from widely available 2-bromobenzyl bromides, the designated molecules can be obtained in three simple steps.



The development of molecular switches that isomerize by irradiation with light have gained much attraction in recent years due to their numerous applications.[1] In 2009, the ethylene-bridged cyclic congener of azobenzene, 11,12-dihydrodibenzo[*c*,*g*][1,2]diazocine (cAB, **1a**), was observed to have superior switching properties compared to linear azobenzene.[2] In particular, the high photoconversion ($Z \rightarrow E$ 92 ± 3%, $E \rightarrow Z$ 100%), the good resolution of absorption bands between isomeric states (*Z* to *E* isomer: 404 to 490 nm), and photoisomerization quantum yields ($Z \rightarrow E$ 72 ± 4%, $E \rightarrow Z$ 50 ± 10%) are much higher in cAB than in the nonbridged azobenzene. Furthermore, in cAB, photochromism is achieved solely by visible light: Blue light irradiation at 385 nm triggers the $n\pi^*$ excitation and transition to the (*E*) isomer, while backswitching is accomplished by thermal relaxation or via green light at a wavelength of 520 nm. In contrast to linear azobenzene, the (*Z*) isomer of cAB is thermodynamically favored over the (*E*) isomer by 37.08 kJ/mol.[3] The switching behavior of cAB has been examined in detail by quantummechanical simulations[4,5] and spectroscopic methods.[6,7] However, compared to linear azobenzenes,[8] diazocines have been used to a much lesser extent (examples are a photocontrolled switch in a peptide,[9] in polyurea,[10] on molecular platforms,[11] and in oligonucleotides).[12] The reason for this low level of exploitation of these favorable properties is that although syntheses exist, they tend to be low yielding and substrate specific.

Synthetically, cAB can be understood as two rigid benzene rings linked by a diazo and an ethylene group. These entities are formed successively from 1,2-disubstituted arenes as starting materials. Previous reports describe C−C coupling of *o*-nitrotoluene (**2**) to establish the ethylene bridge (**3**) first (Scheme 1).[13,14] Then, the nitro groups were joined in an intramolecular reduction step using lead as a reductant to generate the diazo group in cAB in 51% yield.[13,15] Very recent approaches to the diazocine ring formation involve an intramolecular oxidation of amino groups by Oxone[16] (40% yield) or by *m*-chloroperoxybenzoic acid (85% yield).[17]

Scheme 1. Comparison of Strategies for the Synthesis of cAB



Commonly, arenes containing nitro groups are often less soluble in organic solvents. A further complication is that the success of the reduction depends on the addition of specific amounts of reductant or oxidant and the choice of defined reaction conditions.[13,17] To date, all procedures for cAB preparation rely on an intramolecular redox reaction between nitrogen-containing functional groups to establish the diazocine ring.

Herein, we follow a novel retrosynthetic disconnection: Instead of breaking the bond between the nitrogen atoms, we aimed for the insertion of a diazo unit via consecutive C−N cross-coupling reactions to construct the diazocine ring. Only a few studies described the synthesis of heterocycles containing diazo functions[18,19] and azobenzenes[20] via C−N bond formation. In this report, an alternative facile synthesis of functionalized cABs is presented.

Following the newly designed strategy, we started with formation of the C−C bond in cAB from an initial 1,2-disubstituted arene (Scheme 1). Thus, reduction of 2-

Received: January 15, 2020

https://dx.doi.org/10.1021/acs.orglett.0c00122
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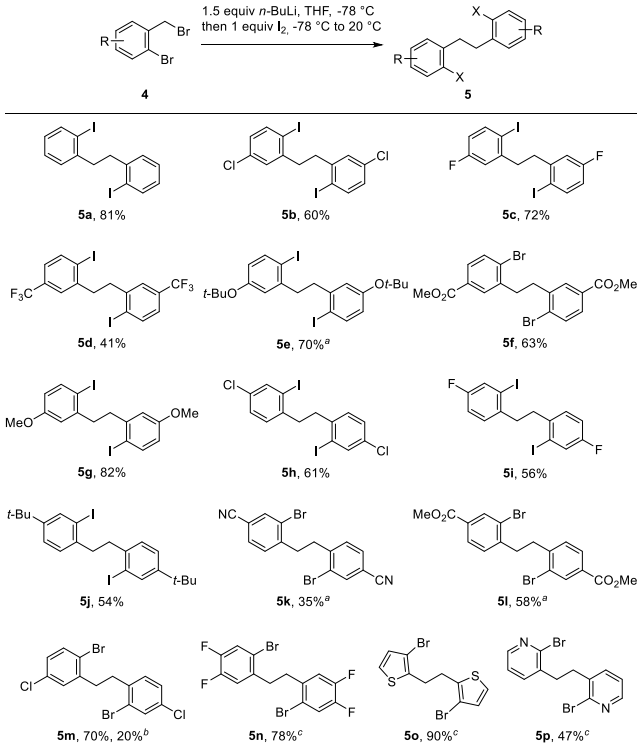
bromobenzyl bromide (**4a**) with *n*-butyllithium (*n*-BuLi) constructed the ethylene bridge of bibenzyl.[21] Further addition of *n*-BuLi and quenching with iodine converted the aryl bromide into corresponding aryl iodide (**5a**) in an overall 81% yield. The resulting dielectrophile then underwent Cu-catalyzed cascade amidations with di-*tert*-butyl hydrazodicarboxylate ($DBADH_2$) as a dinucleophilic hydrazine substrate in which the second C−N coupling led to intramolecular cyclization (**6a**) in 55% yield. This step followed a protocol for diamine ligand-catalyzed Ullmann−Goldberg amidation reactions[22−24] except that a low-boiling solvent was used, i.e., acetonitrile. As the major byproduct of this reaction, we detected the amidation product having consumed two $DBADH_2$ substrates, one on each aryl halide position. Remaining *tert*-butyloxycarbonyl (Boc) groups on the diazocine heterocycle were cleaved via Lewis acid promoted hydrolysis using trimethylsilyl iodide (TMSI) before oxidation of the exposed hydrazo group with NBS/Py, furnishing the cAB product (**1a**) in 67% yield.

We sought to explore the scope of this new process by fabrication of novel cAB derivatives containing functional groups at convenient carbon positions 2, 3, 8, and 9. Consequently, an array of 2-bromobenzyl bromides including electron-donating and electron-withdrawing groups were prepared (Scheme 2). Subsequent homocoupling to the corresponding bibenzyls **5b−5n** occurred in 41−82% yields. Fusion of benzyl bromides containing reducible functional groups such as methyl ester and nitrile was achieved by employment of the reductive Zn/$[NiCl_2(PPh_3)_2]$ system.[25] Asymmetric cAB carrying different substitution patterns on each benzene ring of the molecule such as **1m** was prepared from the combination of a benzyl bromide with a benzaldehyde in a Wittig reaction. The resulting stilbene was then hydrogenated to the desired bibenzyl compound **5m**.[26] Alongside benzyl coupling, we also established ethylene bridges between heterocycles such as thiophene (**5o**) and pyridine (**5p**).

Subsequently, we focused on the cyclization of *ortho*-halogenated bibenzyl compounds using C−N coupling chemistry (Scheme 3). Both electron-rich and electron-deficient arenes were readily transformed to the desired diazocine products **6b−6n** with similar efficiencies (35−70%). However, when aryl bromides were used as electrophiles, the desired cyclization product was only obtained in comparable yields after addition of 1 equiv of CuI catalyst. Likewise, heterocycles could also be annulated, delivering novel condensed ring systems **6o** and **6p**. Deprotection of the Boc-protected diazocine species and oxidation of the exposed hydrazo to diazo furnished the cAB products **1b−1p** in all cases in good to excellent yields (33−92%). In the example of the *tert*-butyl ether (**6e**), concomitant cleavage of ether and carbamate groups finally resulted in the phenol (**1e**).

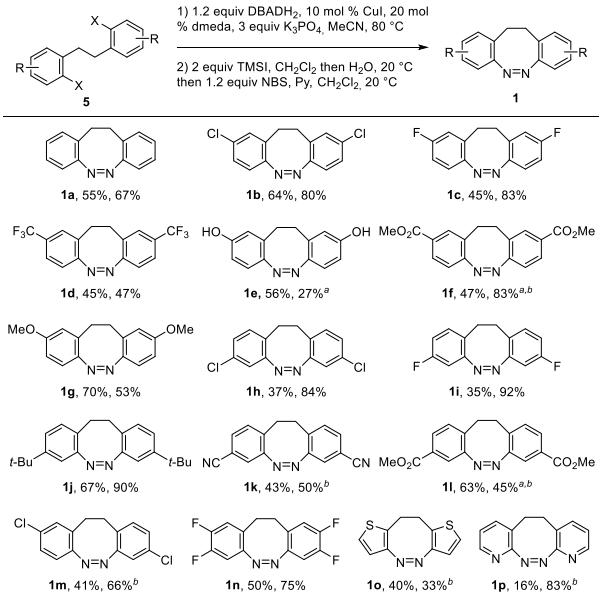
In all previous examples, the functional group substituents are already present in the corresponding starting materials. However, late-stage derivatization is extremely valuable in terms of versatility and synthetic efficiency. Therefore, capitalizing on the Cl functional group allowed the conversion to amines (**1q**, **1r**) using a Buchwald−Hartwig amination with lithium bis(trimethylsilyl)amide (LHMDS) as the nucleophilic cross-coupling partner in 51−58% yields (Scheme 4a).[27] The examples show that general cross-coupling chemistry is possible for chlorinated cABs. Treatment of the methyl ester functions such as basic hydrolysis and the reduction with diisobutylaluminum hydride (DIBAL) were accomplished to give cABs with carboxylic acid (**1s**, **1t**) and benzyl alcohol (**1u**) in good to excellent yields (70−91%) (Scheme 4b). Finally, the photochromic properties of cABs were examined by UV−

Scheme 2. Synthesis of Various Bibenzyls from Benzyl Bromides



[a]1.5 equiv of Zn, 5 mol % $[NiCl_2(PPh_3)_2]$, 1 equiv of NEt_4I, MeCN/THF, 20 °C. [b]Via Wittig reaction and alkene reduction; see the Supporting Information. [c]0.5 equiv of *n*-BuLi, THF, −78 °C.

Scheme 3. Synthesis of Various cABs from Bibenzyls



[a]4 equiv of TMSI used. [b]1 equiv of CuI used.

https://dx.doi.org/10.1021/acs.orglett.0c00122
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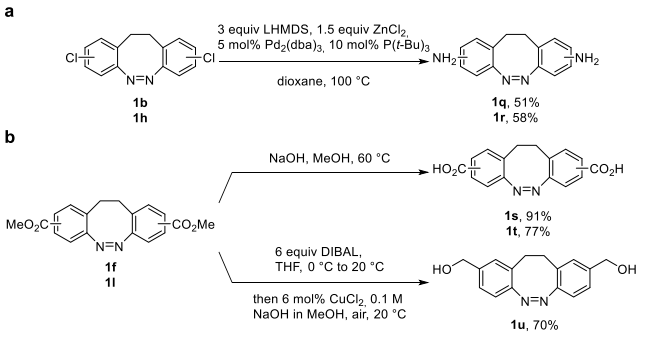
Scheme 4. Transformation of Reactive cABs



[a]$Pd_2(dba)_3$ = Tris(dibenzylideneacetone)dipalladium(0).

vis and NMR spectroscopy (see Supporting Information). Absorption maxima and photostationary states were determined after irradiation, with 385 and 565 nm wavelength light, of **1a**−**1u** in acetonitrile or DMSO. No significant deviations from parent cAB were found except for the products **1e**, **1q**, **1r**, and **1o** where the electronic coupling between the substituent and the aromatic system presumably causes rapid thermal relaxation of the (*E*) isomers.[28]

In conclusion, we show a new general route to functionalized ethylene bridged azobenzenes carrying a wide variety of functional groups. Additional derivatives could be prepared, in which the diazo group was flanked by the aromatic heterocycles thiophene and pyridine. Our strategy for the establishment of the diazocine ring consisted of building the ethylene bridge from 2-bromo benzyl bromides and inserting a hydrazine unit via cascade C−N coupling reactions. This method also provided products which could be further transformed into useful building blocks that may be used in materials chemistry,[29−32] in which higher amounts of ethylene bridged azobenzenes are required.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00122.

Full experimental details, including synthetic procedures and characterization details (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work has been supported by the German Research Foundation (DFG) within the Collaborative Research Center 677 "Function by Switching" (subproject C14). N.E. would like to thank the Philipp Schwartz Initiative of the Alexander von Humboldt foundation for their support. This research has been supported by the Institutional Strategy of the University of Bremen, funded by the German Excellence Initiative.

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