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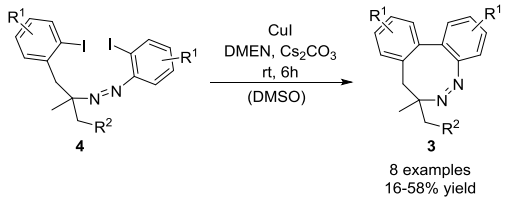
Graphical Abstract



Synthesis of dibenzo[*c*,*e*][1,2]diazocines – a new group of eight-membered cyclic azo compounds

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Abstract

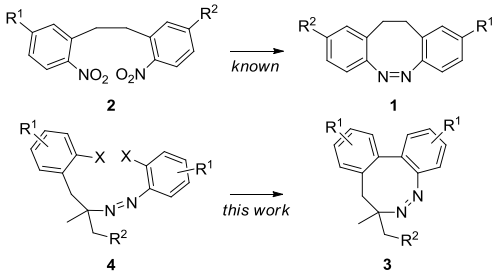
Despite of a remarkable ring strain hitherto unknown dibenzo[*c,e*][1,2]diazocines **3** could be prepared from readily available azo compounds **4** under mild Ullmann-type reaction conditions. The obtained stereoisomers of the new heterocycles **3** were structurally assigned by 2D NMR experiments and DFT calculations.

Keywords

Radical reactions, Azo compounds, Ullmann coupling, Diazocines, Heterocycles

Introduction

Although diazadibenzocyclooctanes -or bridged azobenzenes- **1** have already been prepared several decades ago,[1] they have just recently gained considerable attention due to their application as highly effective bidirectional photoswitches.[2] For example, such dibenzo[*c,g*][1,2]-diazocines **1** – when incorporated into cyclic peptides – have been employed for the control of peptide conformations with visible light (Scheme 1). Irradiation with violet light (407 nm) switched the configuration of **1** at the N-N double bond to 70% *trans*, irradiation with green light (518 nm) led to a full conversion (>99.7%) into the *cis* isomer.[3]



Scheme 1. Synthesis of dibenzo[*c,g*][1,2]diazocines **1** and dibenzo[*c,e*][1,2]diazocines **3**.

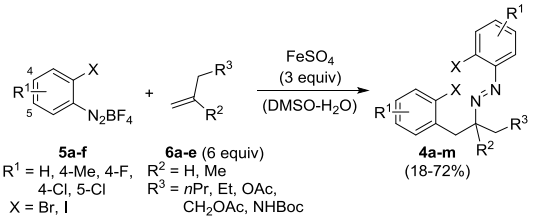
Commonly, the key step in the synthesis of **1** is the cyclization of a 1,2-bis(2-nitrophenyl)ethane derivative **2** with barium hydroxide and zinc to give first a bridged diphenylhydrazine and a subsequent oxidation with HgO to yield the diazocine.[1b] Alternatively, the cyclization of 2,2`-dinitrodibenzyls to azoxy compounds can be achieved with lead power, or to azo compounds in a two-step procedure with first zinc and secondly titanium(III)-chloride and hydrogen peroxide.[4] Very recently, the desired cyclization has also been reported with glucose as reductant in the presence of sodium hydroxide in aqueous ethanol.[5] A second group of diazocines, namely dibenzo[*b,f*][1,5]diazocines,[6] has gained remarkable importance as mechanistic probes for SET processes[7] or as building blocks for polymers.[8]

In this letter, we report the straightforward synthesis of hitherto unknown dibenzo[*c,e*][1,2]diazocines **3** from readily available azo compounds **4** as well as first investigations on the structure of the novel heterocycles **3**.

Results and discussion

Azo compounds **4** can conveniently be prepared by a recently developed variant of the Meerwein arylation.[9,10] In these reactions the aryl diazonium salts play a double role and serve as sources for aryl radicals[11] and as nitrogen-centered radical scavengers.[12] Among the reductants required for aryl radical generation, titanium(III)-chloride turned out as especially

useful for reactions with hydrophilic alkenes in acid aqueous media[13] whereas iron(II)-sulfate gave the best results for reactions of lipophilic alkenes under neutral conditions in dimethylsulfoxide.[14] By employing the Meerwein-type synthetic strategy, which can also be described as carbodiazenylation - thirteen azo compounds **4a-m** could readily be prepared from 2-bromo- and 2-iodophenyldiazonium tetrafluoroborates **5** and various alkenes **6**. The group of alkenes included 1-hexene (**6a**), 2-methyl-1-pentene (**6b**), 2-methallyl acetate (**6c**), 3-methyl-3-buten-1-yl acetate (**6d**) and *N*-Boc protected 2-methallylamine **6e** (Scheme 2).



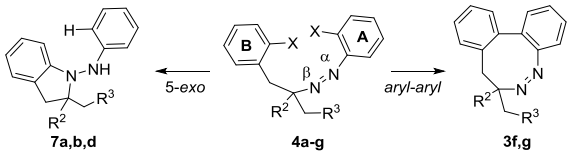
Scheme 2. Preparation of azo compounds through a Meerwein-type carbodiazenylation reaction.

Remarkably, moderate to good yields were obtained in most experiments, which indicates that the generally troublesome aryl radical-induced iodine transfer reactions[11a] do not arise as major side-process under the chosen conditions.[15] Comparing the particular alkenes **6** used for the preparation of the azo compounds **4**, only the very unpolar compounds **6a** and **6b** were found to be less well suited, sometimes leading to lowered yields due to the difficulty of phase separation.[16]

When investigating the cyclization of azo compounds **4** under various conditions, we initially focused on the formation of *N*-aminoindolines **7** and expected the cyclic azo compounds **3** as minor by-products (Table 1). Surprisingly, however, the indolines **7** were only observed in moderate to low yields in radical reactions using an excess of tributyltinhydride as reductant and stoichiometric amounts of AIBN as initiator.[17,18] Under these conditions a reduction of both halobenzene subunits of azo compound **4** can take place. While the generation of an aryl

radical on the ring system **A** is followed by hydrogen transfer, since the radical attack on the β-nitrogen atom would be part of a highly unfavorable 4-*endo* cyclization,[19,20] the radical generated on benzene core **B** can – in contrast – much more rapidly cyclize according to a favorable 5-*exo* mode[21] to give the *N*-aminoindolines via a final hydrogen transfer to the nitrogen-centered radical on the α-nitrogen.

Table 1. Formation of diazocines **3** and aminoindolines **7** from azo compounds **4**.



7a,b,d **4a-g** **3f,g**

Entry	Azo compound **4**: R^2, R^3, X	Conditions[a]	Product **3** or **7**: yield (%)[b,c]
1	**4a**: R^2 = H, R^3 = *n*Pr, X = Br	A	**7a** (15)
2	**4b**: R^2 = Me, R^3 = Et, X = Br		**7b** (8)
3	**4c**: R^2 = Me, R^3 = OAc, X = Br		decomposition
4	**4d**: R^2 = H, R^3 = *n*Pr, X = I		**7d** (42)
5	**4f**: R^2 = Me, R^3 = OAc, X = I		decomposition
6	**4g**: R^2 = Me, R^3 = CH_2OAc, X = I		complex mixture
7	**4d**: R^2 = H, R^3 = *n*Pr, X = I	B	NR
8	**4d**: R^2 = H, R^3 = *n*Pr, X = I	C	NR
9	**4e**: R^2 = Me, R^3 = Et, X = I		NR
10	**4e**: R^2 = Me, R^3 = Et, X = I	D	NR
11	**4g**: R^2 = Me, R^3 = CH_2OAc, X = I		NR
12	**4d**: R^2 = H, R^3 = *n*Pr, X = I	E	NR
13	**4e**: R^2 = Me, R^3 = Et, X = I		NR
14	**4e**: R^2 = Me, R^3 = Et, X = I	F	complex mixture
15	**4g**: R^2 = Me, R^3 = CH_2OAc, X = I	G	cleavage of acetate
16	**4f**: R^2 = Me, R^3 = OAc, X = I	H	**3f** (49)
17	**4g**: R^2 = Me, R^3 = CH_2OAc, X = I	I	**3g** (trace)
18	**4g**: R^2 = Me, R^3 = CH_2OAc, X = I	J	**3g** (58)

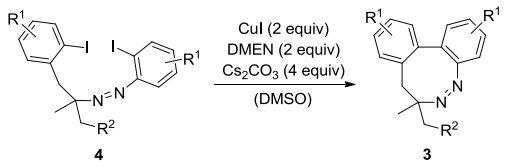
[a]Conditions: A: Bu_3SnH (3.0 eq.), AIBN (3.0 eq.), benzene, reflux, 2 h; B: CuI (0.05 eq.), PPh_3 (1.0 eq,), THF, rt, 20 h; C: CuI (0.05 eq.), PPh_3 (1.0 eq,), CH_3CN, reflux, 24 h; D: CuI (0.05 eq.), PPh_3 (2.0 eq,), CH_3CN, reflux, 2 d; E: KO*t*Bu (3.0 eq.), phen (0.3 eq.), benzene or chlorobenzene, reflux, 24 h; F: Mg (7.0 eq.), $Br(CH_2)_2Br$ (cat.), THF, reflux; G: $Pd(OAc)_2$ (0.3 mol%), PPh_3 (0.9 mol%), Na_2CO_3 (1.2 eq.), EtOH, reflux; H: 1) Zn (20 eq), $AcOH/CH_2Cl_2$, rt; 2) CuI (0.3 eq.), DMEN[d] (0.3 eq.), Cs_2CO_3 (2.0 eq.), DMSO, rt; I: 1) Zn (20 eq.), $AcOH/CH_2Cl_2$, rt; 2) CuI (0.3 eq.), DMEN[d] (0.3 eq), Cs_2CO_3 (2.0 eq.), DMSO, rt; J: CuI (2.0 eq.), DMEN[d] (2.0 eq.), Cs_2CO_3 (4.0 eq.), DMSO, rt; [b]Yield after purification by column chromatography. [c]NR: no reaction. [d]DMEN =*N*,*N*'-dimethyl-1,2-ethanediamine.

A comparison of the yields reported in entries 1, 2 and 4 indicates that dibromides, such as **4a** and **4b**, are less well suited starting materials than the diiodides such as **4d**. Although these preliminary experiments show that acetate groups in the side chain are not tolerated (entries 3, 5, 6), the present synthesis of indoline **7d** (entry 4) could be a good starting point for further optimization aiming a short two-step access to *N*-(phenylamino)indolines.[22,23] The reaction

conditions for the next series of experiments (entries 7-11) were derived from a report by Yavari *et al.*,[24] who described the intermolecular copper(I)-catalyzed arylation of azodicarboxylic esters with aryl iodides. The fact that no reaction was observed with diiodides **4d**, **4e** and **4g** shows that the ability to activate N-N double bonds by triphenylphosphine can not be counterbalanced by an intramolecular setup. The generation of aryl radicals from bromo- and iodoarenes and subsequent arylation reactions has recently also been achieved under organocatalysis.[25] In this context, reaction conditions from a recent report by Sun *et al.*[26] were applied to our azo compounds **4d** and **4e** (entries 12-13), but again, no significant conversion of the starting materials could be observed. Attempts under previously described Grignard conditions[27] (entry 14) and under palladium catalysis[28] (entry 15) also remained unsuccessful. Finally, we became aware of a procedure by Hasegawa *et al.*,[29] who had achieved the intramolecular arylation of hydrazones with aryliodides. In our first attempts the azo compounds **4f,g** were initially reduced to arylalkyl hydrazines (entries 16, 17). The subsequent reaction under copper(I)-catalysis then gave the Ullmann coupling product **3f** in good yield, but the diacozine **3g** with the longer side-chain only in trace amounts.[30] For the synthesis of **3g**, it finally turned out to be beneficial to skip the previous reductive step (entry 18). A plausible explanation for the absence of aminoindolines **7** among the products of the last series of experiments (entries 16-18) is that transition metals such as copper undergo preferred insertion into the less electron-rich aryl-iodine bond, which in compounds **4** would be bond which links the halogen atom to the ring system **A** (Table 1).[31] The cyclization of the resulting organometallic intermediate onto the N-N double bond would then have to occur in an unfavorable 4-*endo* mode[19] which does in turn direct the reaction pathway towards the Ullmann-type aryl-aryl coupling leading to diazocines **3**.[30,32] With the conditions for the cyclization reported in entry 18 (Table 1), we turned to apply these to a selection of the previously prepared azo compounds **4** (Table 2).

In general, the yields obtained in the ring-closing step are comparable to those in other syntheses of strained diazocines.[1b,4,33] Regarding the influence of the substitution pattern on the cyclizations, it appears that the diazocine acetates **3** with longer alkyl spacers (R^2 = CH_2OAc, entries 2, 6) are in most cases - with the exception of **3m** (entry 8) - more easy to prepare than the derivatives with shorter side chains (R^2 = OAc, entries 1, 4, 5, 7). An explanation for this observation is probably not only a difference in ring-closing tendency, but also the lower stability of β-azo acetates (R^2 = OAc), which can fragment under liberation of formaldehyde and acetic acid to give hydrazones.

Table 2. Synthesis of diazocines **3** from azo compounds **4**.



4 **3**

Entry	Azo compound **4**: R^1 =	R^2 =	Diazocine[a] **3**: yield (%)[b], [d.r.][c]
1	**4f**: R^1 = H	R^2 = OAc	**3f** (35) [3:1]
2	**4g**: R^1 = H	R^2 = CH_2 OAc	**3g** (58) [1:1]
3	**4h**: R^1 = H	R^2 = NHBoc	**3h** (35) [single isomer]
4	**4i**: R^1 = 4-F	R^2 = OAc	**3i** (16) [3:1]
5	**4j**: R^1 = 4-Cl	R^2 = OAc	**3j** (19) [4:1]
6	**4k**: R^1 = 4-Cl	R^2 = CH_2 OAc	**3k** (54) [1:1]
7	**4l**: R^1 = 5-Cl	R^2 = OAc	**3l** (31) [2:1]
8	**4m**: R^1 = 5-Cl	R^2 = CH_2 OAc	**3m** (27) [1:1]

[a]Standard conditions: CuI (2 equiv), DMEN =*N*,*N*'-dimethyl-1,2-ethanediamine (2 equiv), Cs_2CO_3 (4 equiv), 6 h, rt. [b]Yield after purification by column chromatography. [c]Diastereomeric ratios determined by NMR analysis of the product mixture before separation.

From the ring-closing reaction only compound **3h** (entry 3) with the most bulky CH_2NHBoc side chain was obtained as a single stereoisomer. The obvious assumption that the steric demand of the side chain has a direct influence on the isomeric distribution (for structural assignments, see below) was further supported by the fact that all compounds with long and less bulky $(CH_2)_2OAc$ units (entries 2, 6, 8) were formed in a 1:1 diastereomeric ratio whereas the shorter CH_2OAc group led to ratios in the range of 2:1 to 4:1 (entries 1, 4, 5, 7).

Exemplarily for diazocines **3f** and **3g**, which were obtained from the synthesis (Table 2) in diastereomeric ratios of 3:1 and 1:1, respectively, the two isomers were assigned to the following structures with *cis*-configured N-N double bonds on the basis of ^{1}H NMR shifts (Figure 1), NOESY experiments (see Supplementary Information) and DFT calculations. The absence of N-N-*trans*-configured isomers is most probably due to a high conformational strain.

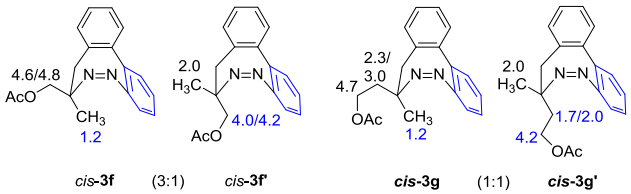


Figure 1. Selected ^{1}H NMR shifts (blue) for diazocines **3f** and **3g**.

When the methyl group or the aliphatic linker to the acetate group is located in the anisotropic cone of the azo-conjugated benzene core (shifted protons and benzene core highlighted in blue), a significant upfield shift can be noticed for the related ^{1}H NMR signals. Further support for the structural assignment was obtained from density-functional calculations which were performed on diazocine **3f** using Gaussian09[34] with the B3LYP hybrid functional[35] and the 6-311+G(d,p) basis set.[36-39] ^{1}H and ^{13}C NMR chemical shifts were calculated using the GIAO approach and calculated shieldings were converted to chemical shifts using published regression formulae.[40] Selected calculated chemical ^{1}H NMR shifts and experimentally determined values are shown in Table 3 (for calculated ^{13}C NMR shifts see Supplementary Information) and the corresponding structures and atom-numbering in Figure 2. The *exo* structure was calculated to be most stable (gas-phase without vibrational corrections) and the two *endo* structures 9.7 and 8.7 kcal mol^{-1} (*endo*(1) and *endo*(2), respectively) less stable, which is in agreement with the experimentally found ratio. A comparison of calculated and experimentally determined chemical shifts revealed a very good agreement for the more stable *exo* structure and deviations for the *endo* structures only at the benzylic protons H5 and

H6. This points to the existence of one or even more *endo* conformers with a stability comparable to those of the structures *endo*(1) and *endo*(2).

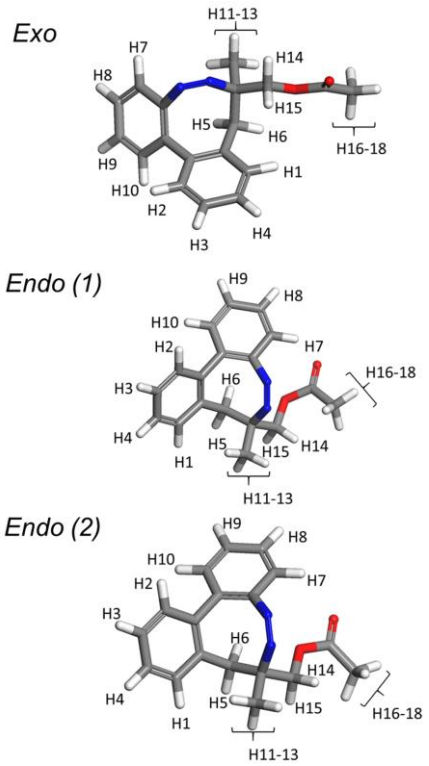


Figure 2. Structures for diazocine **3f** derived from DFT calculations.

Table 3. Selected calculated and experimentally determined ^{1}H NMR shifts for diazocine **3f**.

Atom No.	Chemical Shift				
	Exo (major isomer ***cis*-3f**)		*Endo* (minor isomer ***cis*-3f´**)		
	Calc.	Exp.	Calc. (1)	Calc. (2)	Exp.
H5	2.51	2.59	3.81	3.72	2.93
H6	2.95	2.74	2.20	2.20	2.45
H11-13	1.19	1.19	1.90	1.94	2.00
H14	5.00	4.93	4.52	4.18	4.21
H15	4.83	4.81	3.76	3.55	4.03
H16-18	2.14	2.19	1.99	1.96	2.07

Conclusion

In summary, we have shown that so far unknown dibenzo[*c*,*e*][1,2]diazocines can be prepared from acyclic diiodinated aryl-alkyl azo compounds under mild reaction conditions, which had

originally been reported for the copper-catalyzed intramolecular arylation of hydrazones. The high selectivity of the cyclization step towards the eight-membered heterocycles can be explained by the preferred insertion of the transition metal into the less electron-rich aryl-iodine bond of the azo compound, which in turn renders the alternative 5-*exo* cyclization to aminoindolines impossible. The latter aminoindolines could however be obtained in low to moderate yields from radical reactions. NMR investigations and DFT studies finally showed that dibenzo[*c*,*e*][1,2]diazocines preferably occur as one or a mixture of two *cis* isomers, depending on the substitution pattern. Further studies are now directed towards the applicability of the new compounds as photoswitches.

Experimental

General procedure for the formation of diazocines 3f-m. To a Schlenk flask was added azo compound **4 (f-m)** (0.36 mmol), CuI (0.14 g, 0.72 mmol), and Cs_2CO_3 (0.47 g, 1.44 mmol) under argon. After adding dry DMSO (8.0 mL) and DMEN (0.08 mL, 0.72 mmol), the reaction mixture was stirred at room temperature for 24 hours. The resulting mixture was filtered through a pad of silica gel, eluting with Et_2O. The reaction mixture was washed with water (50 mL) and extracted with Et_2O (3 × 50 mL). The organic layer was washed with bine, dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography gave the desired products **3 (f-m)**.

Acknowledgements

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further support. The experimental assistance by Dr. Agnes Prechter is gratefully acknowledged.

Supplementary Information

Supplementary information (Detailed experimental procedures and ^{1}H and ^{13}C NMR data and spectra for all azo compounds **4a-4m**, diazocines **3f-m** and 2-butyl-*N*-phenylindolin-1-amine (**7d**)) associated with this article, can be found, in the online version, at doi:…..

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