Preprint Title	Substituted Nitrogen-Bridged Diazocines
Authors	Pascal Lentes, Jeremy Rudtke and Rainer Herges
Publication Date	08 März 2021
Article Type	Full Research Paper
Supporting Information File 1	Substituted_Nitrogen_Bridged_Diazocines_SI_06.docx; 15.8 MB
ORCID® iDs	Jeremy Rudtke - https://orcid.org/0000-0001-8079-7715; Rainer Herges - https://orcid.org/0000-0002-6396-6991

Substituted Nitrogen-Bridged Diazocines

Pascal Lentes, Jeremy Rudtke and Rainer Herges*

Address: Otto Diels-Institute of Organic Chemistry, Christian Albrechts University Kiel, Otto-Hahn-Platz 4, 24118 Kiel, Germany

Email: Rainer Herges* – rherges@oc.uni-kiel.de

* Corresponding author

Abstract

Novel nitrogen bridged diazocines (triazocines) were synthesized that carry a formyl or an acetyl group at the CH_2NR- bridge and bromo- or iodo substituents at the distant phenyl ring. The photophysical properties were investigated in acetonitrile and water. As compared to previous approaches the yields of the intramolecular azo cyclizations were increased (from ~40 to 60%) by an oxidative approach starting from the corresponding aniline precursors. The *Z*→*E* photoconversion yields in acetonitrile are 80-85% and the thermal half-lives of the metastable *E* configurations are 31-74 min. Particularly, the high photoconversion yields (~70%) of the water-soluble diazocines are noteworthy, which makes them promising candidates for applications in photopharmacology. The halogen substituents allow further functionalization via cross-coupling reactions.

Keywords

photoswitch; visible light switch; diazocine; triazocine; water-soluble switch; photopharmacology, bridged azobenzene;

Introduction

Diazocines (bridged azobenzenes) are frequently used photoswitches with outstanding photophysical properties. Parent diazocine (CH_2-CH_2-bridged) exhibits well-separated $n\pi^*$ transitions, which allow excellent photoconversion between the *Z* and *E* configurations ($(Z\rightarrow E)_{385\ nm}$ = 92%, $(E\rightarrow Z)_{525\ nm}$ > 99% in *n*-hexane) with light in the visible region.[1] Moreover, the *Z*-boat configuration is the thermodynamically stable isomer.[2,3,4,5,6,7,8,9] The latter property (inverted stability compared to azobenzenes) makes them promising candidates for applications in photopharmacology. In the majority of azobenzene-based photopharmacophores, the bent *Z* configuration is biologically inactive.[10,11,12] Hence, (and in contrast to azobenzenes) the thermodynamically stable and biologically inactive *Z* isomer can be administered and switched on with light at the site of interest with spatiotemporal resolution. Moreover, the photoconversion yield for the $E\rightarrow Z$ isomerization is quantitative (within the detection limit of UV and NMR). High efficiency in switching the biological activity off is important to avoid side effects of residual concentrations of the active form.[13]

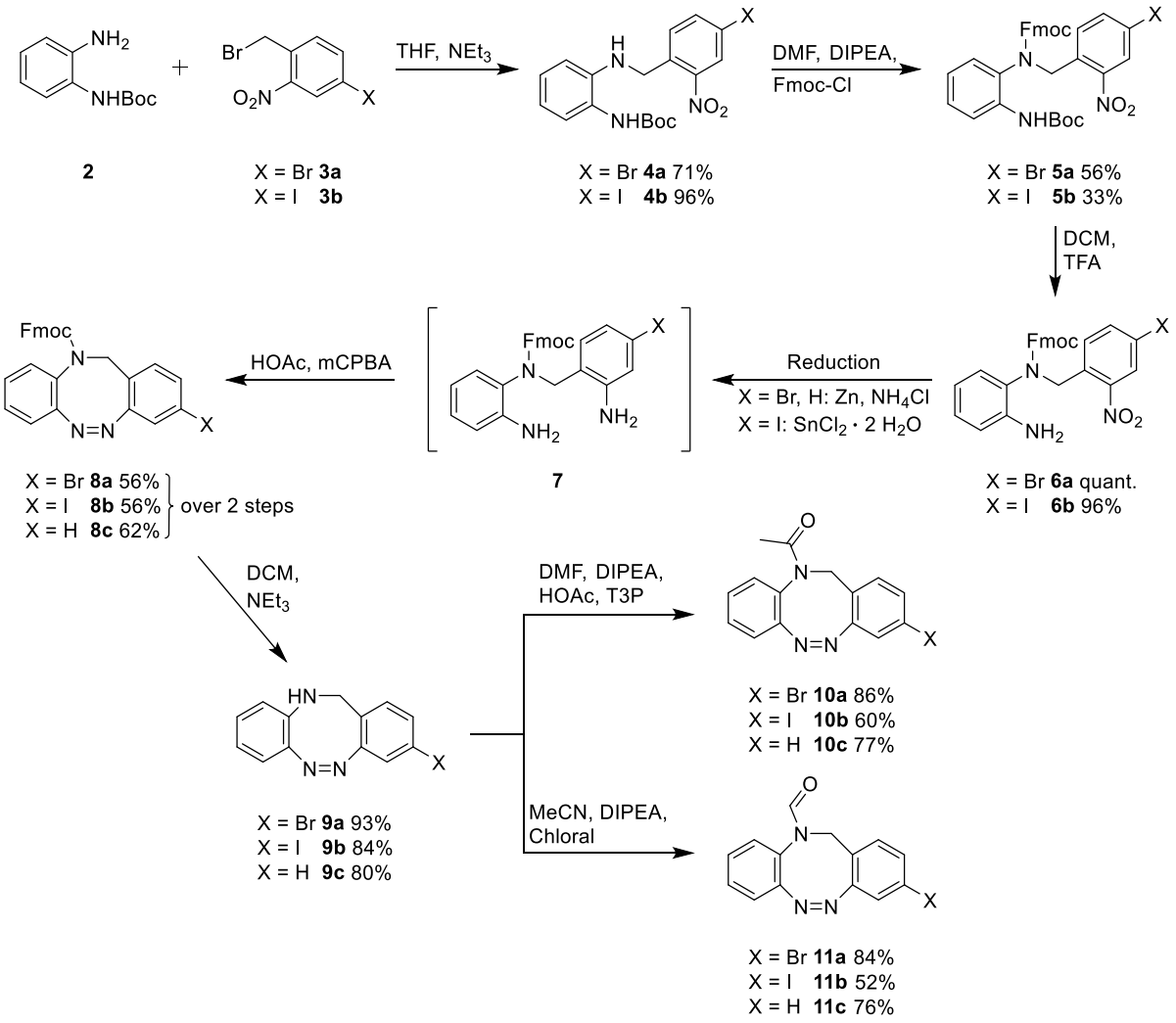
Water solubility and high $Z\rightarrow E$ switching efficiencies in water are another important criterion for applications in biological environments.[14] Our previously published NAc-bridged diazocine **10c** (Scheme 1, Table 1) exhibits both properties.[15] This is in stark contrast to the CH_2-CH_2, and S-CH_2 bridged diazocines and the majority of azobenzenes.[9,16,17,18,19,20] Spurred by the promising properties of CH_2-NR bridged

diazocines (triazocines), we now explore this class of photoswitches and develop synthetic access to these photochromes.

Results and Discussion

Synthesis

The first three stages of the synthesis of CH_2-NR bridged diazocines are analogous to the previously described synthesis of CH_2NH bridged diazocine.[15] Single Boc protected 2-phenylenediamine **2** (Figure 1) is reacted with halogen-substituted 2-nitrobenzyl bromides **3**[21] forming N-benzyl anilines **4**, which were protected with Fmoc-chloride to accomplish an orthogonal protective group strategy. Removal of the Boc groups of compounds **5** with TFA gave the mixed aniline and nitro precursor **6**.



Scheme 1: Synthesis of 3-bromo and 3-iodo acetylated CH_2NR diazocines **10** (R=Ac) and formylated diazocines **11** (R=CHO).

In previous approaches, the nitro groups were reduced to hydroxylamines with zinc and oxidized to the corresponding nitroso compounds with iron(III) to perform an intramolecular Baeyer-Mills reaction.[15,21] We found that a complete reduction of the nitro group to the aniline **7** and oxidation with mCPBA is increasing the yield of the intramolecular cyclization from 39% to 62% (over two steps) for the unsubstituted diazocine **8c** compared to the pathway via the hydroxylamine. 3-Bromo **8a** and 3-iodo **8b** compounds were obtained in 56% yield using the oxidative method of Trauner[22] with mCPBA. Fmoc groups were removed with NEt_3 to yield NH-diazocines **9**.

Acetylated diazocines **10a**-**c** were synthesized using a mixed anhydride of acetic acid and T3P. Formylation of NH-diazocines **9a**-**c** was accomplished with chloral[23] under non-acidic conditions.

Investigation of the photophysical properties

UV-vis spectra of diazocines **10a**,**b**, and **11a**-**c** were recorded in acetonitrile at 25 °C. All compounds exhibit an $n\pi^*$ transition at about 400 nm ($Z \rightarrow E$ conversion) and an $n\pi^*$ transition at about 520 nm ($E \rightarrow Z$ conversion, Figure 1, Table 1).

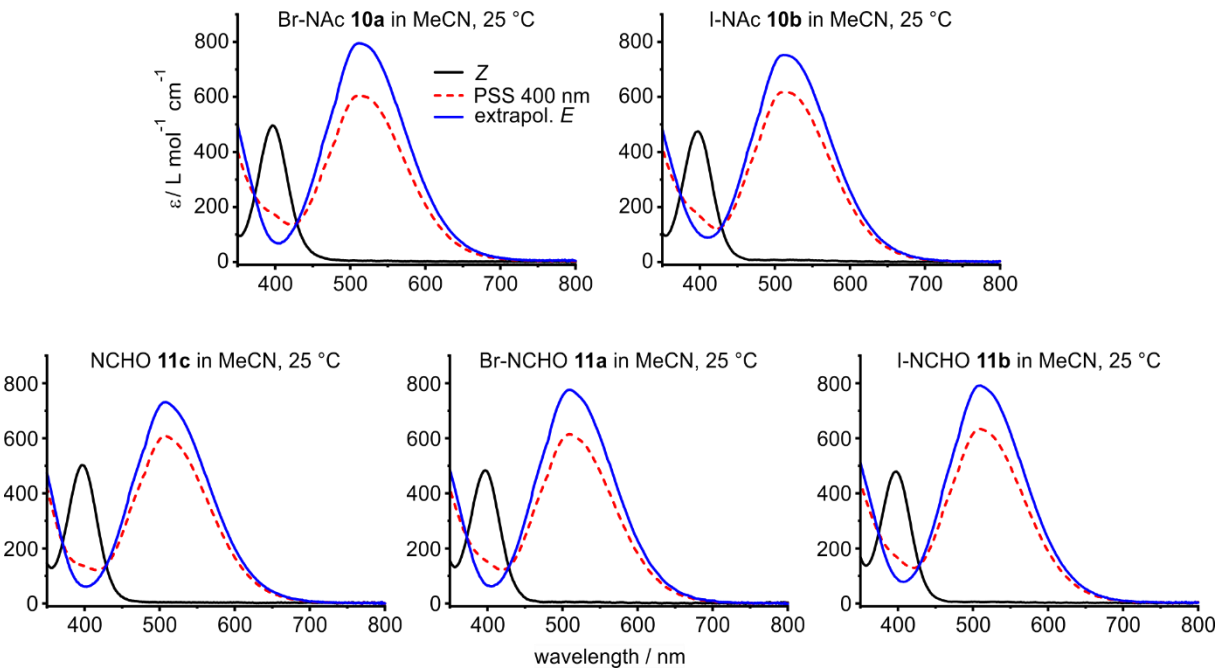


Figure 1: UV-vis spectra of 3-bromo and 3-iodo CH_2NAc bridged **10a**,**b** and CH_2NCHO bridged diazocines **11a**-**c**. Spectra of *Z* isomers are given in black, the photostationary states at 400 nm are represented as dashed red lines and the extrapolated spectra of the pure *E*-isomers are in blue.

Irradiation with 400 nm gives the metastable *E* isomers of formylated and acetylated derivatives **10** and **11** with good photoconversion yields (Γ) of 80-85% (Table 1) in

acetonitrile. Complete *E*→*Z* conversion (>99%) can be achieved with light between 520 and 600 nm. Unsubstituted acetylated and formylated diazocines **10c** and **11c** exhibit similar conversion yields (85%). Halogenation as well does not have a significant influence. However, half-lives ($t_{1/2}$) of 3-bromo and 3-iodo N-acetyl diazocines **10a** and **10b** (~30 min) are significantly smaller than half-lives of the corresponding bromo and iodo N-formyl derivatives **11a** and **11b** (~50 min). In general, halogenation decreases the half-lives compared to unsubstituted diazocines **10c** and **11c**. The activation barrier (E_A) of the *E*→*Z* isomerization (obtained by an Arrhenius plot) is higher in formylated compounds **11** compared to acetylated compounds **10** and is further increased by halogenation.

Table 1: Photophysical properties of N-diazocines **10a**-**c** and **11a**-**c** in acetonitrile.

	acetonitrile						
	$\lambda_{max(Z)}$	$\lambda_{max(E)}$	$\varepsilon_{\lambda max(Z)}$	$\varepsilon_{\lambda max(E)}$	$\Gamma_{Z\rightarrow E}$[a]	$t_{1/2}$ (25 °C)	E_A
	nm		L mol^{-1} cm^{-1}		%	min	kJ mol^{-1}
Br-NAc **10a**	397	515	495	791	81	30.9	93.4
I-NAc **10b**	397	517	480	778	82	28.6	87.0
NCHO **11c**	397	509	502	760	85	74.0	88.4
Br-NCHO **11a**	397	509	469	784	82	49.9	93.9
I-NCHO **11b**	398	511	483	798	80	48.1	90.9
NAc **10c**[b]	400	520	582	876	85	27.1	81.8

[a]extrapolated values (for details, see Supporting Information IV); [b]in acetone[15]

Unsubstituted N-formyl diazocine **11c** and brominated NAc-diazocine **10a** were also investigated in pure water since they are water-soluble (**11c**: ~250 µM, **10a**: ~150 µM). As in acetonitrile, the best *Z*→*E* conversion yields are observed by irradiation with 400

nm in water and the back-isomerization *E*→*Z* can be accomplished by irradiation with light in the range of 525 and 600 nm (Figure 2, Table 2).

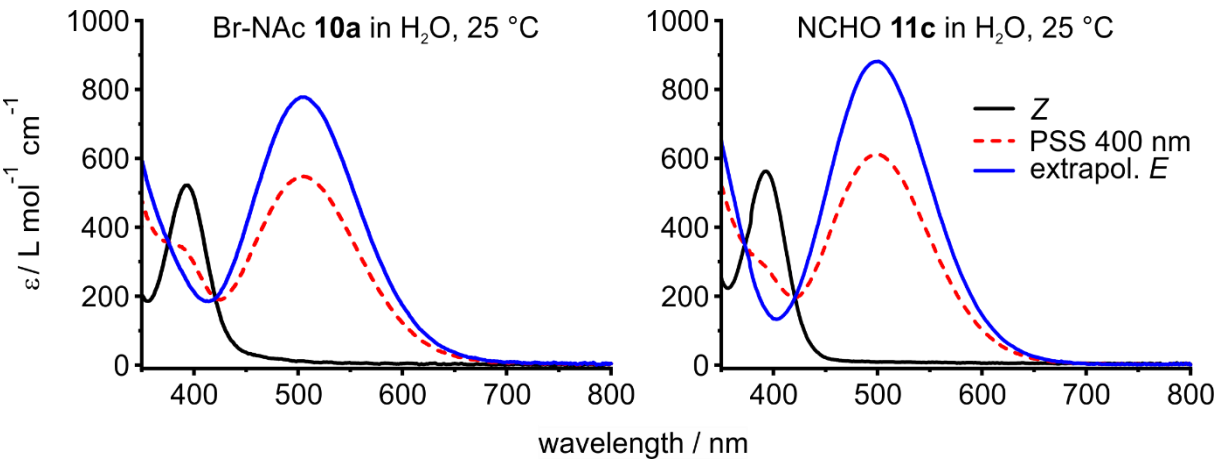


Figure 2: UV-vis spectra of 3-bromo NAc-diazocine **10a** and N-formyl diazocine **11c** in water. Spectra of *Z* isomers (black curve), the photostationary states at 400 nm (dashed red line), and the extrapolated spectra of the pure *E* isomers (blue).

The photoconversion (*Z*→*E*) of N-formyl diazocine **11c** in water and bromo-NAc diazocine **10a** are about 70%, which do not differ significantly from unsubstituted NAc diazocine **10c** (72%). It is interesting to note that the half-lives and activation barriers (*E*→*Z*) are increasing (~2-2.5 fold) in water as compared to the less polar acetonitrile.

Table 2: Photophysical properties of water-soluble N-diazocines **10a**, **10c**, and **11c** in H_2O.

	H_2O						
	$\lambda_{max(Z)}$	$\lambda_{max(E)}$	$\varepsilon_{\lambda max(Z)}$	$\varepsilon_{\lambda max(E)}$	$\Gamma_{Z\rightarrow E}$[a]	$t_{1/2}$ (25 °C)	E_A
	nm		L mol^{-1} cm^{-1}		%	min	kJ mol^{-1}
Br-NAc **10a**	394	502	534	975	70	69.6	99.9
NCHO **11c**	393	500	567	871	69	198	97.8

NAc **10c**	393	502	564	850	72	72.8	90.4

[a]extrapolated values (for details, see Supporting Information IV)

Conclusion

Five nitrogen bridged diazocines (triazocines) were synthesized and characterized. Formyl (R=CHO) and acetyl groups (R=Ac) were introduced at the CH_2NR bridge and the distant phenyl rings are Br and I substituted. In contrast to previous approaches, the azo cyclization (ring closure) was achieved via the oxidation of the bis-anilines **7** with *m*CPBA (~60% yield). Among the nitrogen bridged diazocines **10a** and **11c** are water-soluble and retained their high switching efficiency (~70%) also in water. Half-lives of the metastable *E* isomers are larger for the N-formyl diazocines **11a**-**c** compared to the acetylated compounds **10a**-**c** and generally, the half-lives are larger in water than in acetonitrile. Halogen atoms Br and I at the phenyl rings in 3-position as in **10a**,**b**, and **11a**,**b** are a good starting point for further functionalization.[17,20,24] We conclude that CH_2NAc and CH_2NCHO bridged diazocines (triazocines) are promising candidates for applications in biological environments and particularly as photoswitches in light-activatable drugs.

Supporting Information

Supporting Information File 1:

File Name: Substituted_Nitrogen_Bridged_Diazocines_SI_05

File Format: .docx

Title: Analytical equipment, experimental procedures, NMR and UV–vis spectra

Acknowledgments

The authors gratefully acknowledge financial support by the Deutsche Forschungsgesellschaft (DFG) within the Sonderforschungsbereich 677, “Function by Switching”. The authors thank Malte Wellmann for his assistance in synthesis.

References

[1]Siewertsen, R.; Neumann, H.; Buchheim-Stehn, B.; Herges, R.; Näther, C.; Renth, F.; Temps, F. *J. Am. Chem. Soc.* **2009**, *131*, 15594–15595.
[2]Siewertsen, R.; Schönborn, J. B.; Hartke, B.; Renth, F.; Temps, F. *Phys. Chem. Chem. Phys.* **2011**, *13*, 1054–1063.
[3]Moormann, W.; Langbehn, D.; Herges, R. *Synthesis* **2017**, *49*, 3471–3475.
[4]Moormann, W.; Langbehn, D.; Herges, R. *Beilstein J. Org. Chem*. **2019**, *15,* 727–732.
[5]Samanta, S.; Quin, C.; Lough, A. J.; Woolley, G. A. *Angew. Chem. Int. Ed.* **2012**, *124*, 6558–6561.
[6]Sell, H.; Näther, C.; Herges, R. *Beilstein J. Org. Chem.* **2013**, *9*, 1–7.
[7]Li, S.; Eleya, N.; Staubitz, A. *Org. Lett.* **2020**, *22*, 1624–1627.
[8]Hammerich, M.; Schütt, C.; Stähler, C.; Lentes, P.; Röhricht, F.; Höppner, R.; Herges, R. *J. Am. Chem. Soc.* **2016**, *138*, 13111–13114.
[9]Heintze, L.; Schmidt, D.; Rodat, T.; Witt, L.; Ewert, J.; Kriegs, M.; Herges, R.; Peifer, C. *Int. J. Mol. Sci.* **2020**, *21*, 8961–8981.
[10]Beharry, A. A.; Woolley, G. A. *Chem. Soc. Rev.* **2011**, *40*, 4422–4437.
[11]Szymanski, W.; Beierle, J. M.; Kistemaker, H. A.; Velema, W. A.; Feringa, B. L. *Chem. Rev.* **2013**, *113*, 6114–6178.
[12]Hüll, K.; Morstein, J.; Trauner, D. *Chem. Rev.* **2018**, *118*, 10710–10747.
[13]Fuchter, M. J. *J. Med. Chem.* **2020**, *63*, 11436–11447.
[14]Lubbe, A. S.; Szymanski, W.; Feringa, B. L. *Chem. Soc. Rev.* **2017**, *46*, 1052–1079.
[15]Lentes, P.; Stadler, E.; Röhricht, F.; Brahms, A.; Gröbner, J.; Sönnichsen, F. D.; Gescheidt, G.; Herges, R. *J. Am. Chem. Soc.* **2019**, *141*, 13592–13600.
[16]Lentes, P.; Frühwirt, P.; Freißmuth, H.; Moormann, W.; Kruse, F.; Gescheidt, G.; Herges, R. *J. Org. Chem.* **2021**, in press. DOI: 10.1021/acs.joc.1c00065
[17]Cabré, G.; Garrido-Charles, A.; González-Lafont, À.; Moormann, W.; Langbehn, L.; Egea, D.; Lluch, J. M.; Herges, R.; Alibés, R.; Busqué, F.; Gorostiza, P.; Hernando, J. *Org. Lett.* **2019**, *21*, 3780–3784.
[18]Trads, J. B.; Hüll, K.; Matsuura, B. S.; Laprell, L.; Fehrentz, T.; Görldt, N.; Kozek, K. A.; Weaver, C. D.; Klöcker, N.; Barber, D. M.; Trauner, D. *Angew. Chem. Int. Ed.* **2019**, *58*, 15421–15429.

[19]Preußke, N.; Moormann, W.; Bamberg, K.; Lipfert, M.; Herges, R.; Sönnichsen, F. D. *Org. Biomol. Chem.* **2020**, *18*, 2650–2660.
[20]Thapaliya, E. R.; Zhao, J.; Ellis-Davies, G. C. R. *ACS Chem. Neurosci.* **2019**, *10*, 2481–2488.
[21]Schehr, M.; Hugenbusch, D.; Moje, T.; Näther, C.; Herges, R. *Beilstein J. Org. Chem.* **2018**, *14*, 2799–2804.
[22]Maier, M. S.; Hüll, K.; Reynders, M.; Matsuura, B. S.; Leippe, P.; Ko, T.; Schäffer, L.; Trauner, D. *J. Am. Chem. Soc.* **2019**, *141*, 17295–17304.
[23]Liebig, J. *Justus Liebigs Ann. Chem.* **1832**, *1*, 182–230.
[24]Biffis, A.; Centomo, P.; Del Zotto, A.; Zecca, M.; *Chem. Rev.* **2018**, *118*, 2249–2295.