Communication

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Heterodiazocines: Synthesis and Photochromic Properties, *Trans* to *Cis* Switching within the Bio-optical Window

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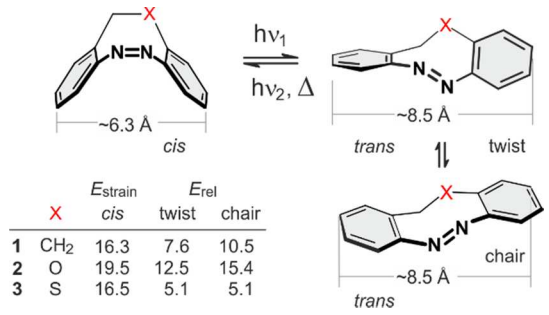
Supporting Information Placeholder

ABSTRACT: Diazocines, bridged azobenzenes, exhibit superior photophysical properties compared to parent azobenzenes such as high switching efficiencies, quantum yields, and particularly switching wavelengths in the visible range. Synthesis, however, proceeds with low yields, and derivatives are difficult to prepare. We now present two heterodiazocines which are easier to synthesize, and the general procedures should also provide facile access to derivatives. Moreover, both compounds can be switched with light in the far-red (650 nm). Accessibility and photophysical properties make them ideal candidates for applications such as photoswitchable drugs and functional materials.

Azobenzenes are probably the most frequently used photochromic compounds in applications ranging from molecular motors and machines to photoswitchable drugs.[1-4] They are easily accessible and their photochromic functions generally are quite reliable. Usually, the stretched *trans* isomer is the most stable configuration. Upon irradiation with UV light the bent *cis* isomer is formed which returns back to the *trans* isomer either upon irradiation with visible light or thermochemically.[5] Aiming at *in vivo* applications, there have been several attempts to shift the switching wavelengths towards the far-red (λ>650 nm).[6,7] Within the so-called bio-optical window (650-1100 nm) blood supported tissue is transparent (penetration depth ~ 20 mm). Ortho substitution of the azobenzene unit has been successful towards this end, as shown by Woolley et al. (R=OMe, λ(E/Z)=550/450nm) and Hecht et al. (R=F, λ(E/Z)=500/410 nm).[8-10] Aprahamian et al. presented BF_2 bridged azobenzenes with λ(E)=710 nm.[11,12] Diazocines (ortho ethylene bridged azobenzenes) are particularly interesting visible light switchable compounds (λ(E/Z)=500/400nm).[13] Bridging of the phenyl groups prevents their rotation, and the rigid molecular framework should improve power transmission of the photomechanical movement onto the environment. This is important in biochemical applications if an efficient detachment from the active site of a protein must be achieved, or if the molecular switching has to be translated into a macroscopic effect in functional materials. Moreover, as opposed to azobenzenes, diazocines are more stable in the *cis* form (Figure 1). This is of considerable advantage in optopharmacological applications. Most photochemically switchable drugs and inhibitors are active in their stretched and slender *trans* configurations, and inactive in their bulgy *cis* forms.[14-17] Mechanistic biochemical studies as well as in vivo applications require that switching to the inactive state is complete, because even remaining traces of the active form can reduce the switching efficiency, whereas an incomplete conversion to the active state can be compensated by an increase of the concentration.[18] In this regard diazocines are superior because they can be quantitatively switched to the inactive *cis* state. Their excellent photophysical properties notwithstanding, applications of diazocines so far have been rather limited. Main obstacles are the notoriously low yields in the final ring closing azo formation and the lack of reproducibility of the synthesis.[19-22] Functionalization of the parent system using standard aromatic substitution reactions is difficult, and the preparation of unsymmetrically substituted diazocines[23] which are important for most applications is even more problematic because all steps are based on homo couplings.[24] We now present two hetero diazocines which are accessible by reliable procedures in reasonable yields. Moreover, both compounds switch efficiently (>99%) from the *trans* to the *cis* isomer upon irradiation with light in the far-red (650 nm).

TD-DFT calculations (see Supporting Information) predict that the nπ* transitions of the *cis* and the *trans* isomers in both hetero diazocines **2**, and **3** are separated by more than 100 nm. Therefore, we expected that efficient photo isomerization with two wavelengths should be possible. However, the *trans* isomer can adopt two different conformations (twist and chair see Figure 1) with markedly different UV-vis spectra. In the parent diazocine **1** and the O-diazocine **2**, the twist conformations are about 3 kcal mol^{-1} more stable than the chair forms, and hence the concentrations of the chair conformers in equilibrium should be very small. Twist and chair conformations in the S-diazocine **3**, however, are almost isoenergetic, and therefore the UV-vis spectrum of *trans*-**3** is a linear combination of the spectra of both conformations.

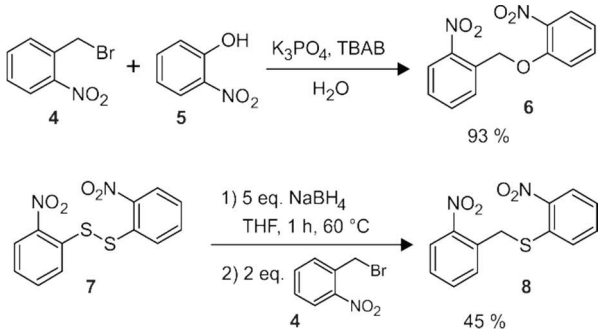


	X	E_{strain} cis	E_{rel} twist	chair
1	CH_2	16.3	7.6	10.5
2	O	19.5	12.5	15.4
3	S	16.5	5.1	5.1

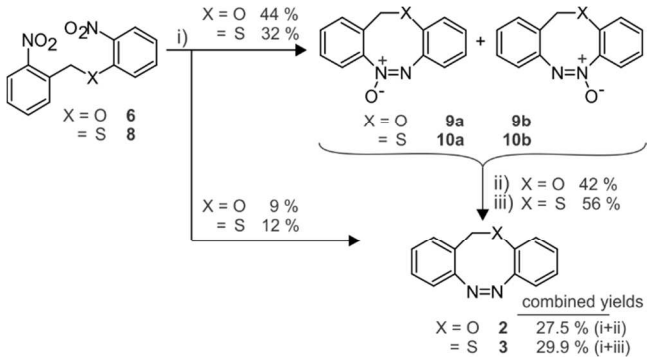
Figure 1. Calculated (B3LYP/6-31G*) strain energies (E_{strain}) of the *cis* isomers of diazocine **1** and hetero derivatives **2** and **3**, and energies (E_{rel}) of *trans* isomers (twist and chair conformations) of **1**, **2** and **3** relative to the corresponding *cis* isomers in kcal mol^{-1}. Distances are given between the C atoms in *para* position to the azo group.

The oxygen and sulfur bridged diazocines **2** and **3** were obtained by a three step synthesis. In the first synthetic step the bridging unit was formed. This was accomplished for the oxygen system via Williamson ether synthesis with potassium phosphate as base in water with 93 % yield (Scheme 1).[25,26] The thioether precursor **8** was formed by reduction of the disulfide **7** with sodium borohydride and *in situ* reaction with 2-nitrobenzylbromide **4** in 45 % yield.

The main problem hampering the synthesis of diazocines are the low and unreliable yields in the subsequent reductive ring closure of the dinitro precursors. According to our calculations (Figure 1) the ring strains of the parent diazocine **1**, and its hetero derivatives **2** and **3** amount from 16 to almost 20 kcal mol^{-1} (details see SI). Polymer formation, therefore, is the main reaction pathway. Moreover, most reduction methods require strongly basic reaction conditions which lead to deprotonation of the benzylic positions, and consequently cyclization,[27] oxidation and polymer formation. Upon reduction of the corresponding dinitro precursors the O- and S-diazocine **6** and **8** with Zn under basic conditions no traces of the diazocine products could be isolated. Cleavage of the benzyl(thio)ether[27] was observed. To avoid deprotonation at the benzylic positions, and to favour ring closure, heterogeneous reaction conditions[28] under moderately basic pH were applied. A corresponding procedure was published by Yan et al..[21,22] They achieved the reductive ring closure of 2,2'dinitrodibenzyl to the cyclic azoxy compound with lead powder under basic conditions, and subsequently reduced the azoxy compound with trivalent phosphorous to the diazocine. As the reaction time is relatively long with two days, and the solubility of our starting material in methanol was quite low, we improved the synthesis by using high power ultrasound. As main products the azoxy compounds **9a/b** (44%, mainly **9b**) or **10a/b** (32%) were formed, concomitant with small amounts of the desired diazocines **2** and **3**.



Scheme 1. Synthesis of the dinitro precursors for the diazocine synthesis. (TBAB: tetrabutylammonium bromide)



Scheme 2. Reaction conditions: i) Pb, NEt_3/formic acid/MeOH/H_2O, pH = 9.5, ultrasound; ii) PPh_3, MoO_2Cl_2, iii) Pb, ball mill, 40 Hz, 4 h.

The reduction of the oxygen bridged azoxy compounds **9a/b** to the corresponding diazocine **2** was achieved applying the literature method with triphenylphosphine and a molybdenum catalyst (Scheme 2) (see Supporting Information).[22,29] However, the method was unsuccessful in case of the sulfur bridged analogon **10a/b**. Reduction of the latter azoxy compound was achieved with lead granules in a ball mill.

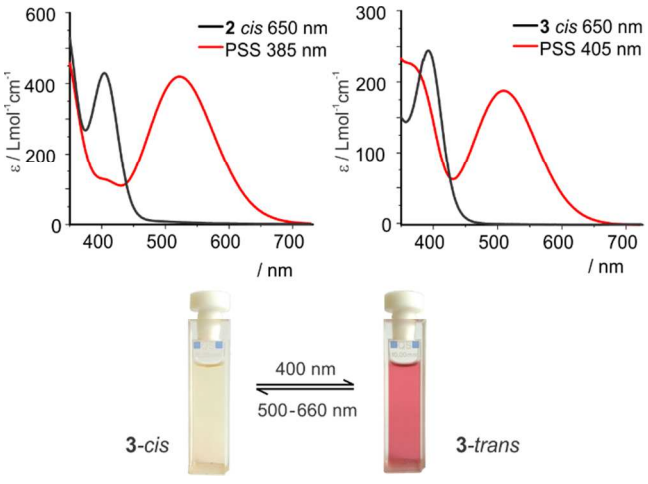


Figure 2. UV spectra of O-diazocine **2** (THF, T = -80°C, left) and S-diazocine **3** (acetonitrile, right), the *cis* spectrum is plotted in black, the spectrum of the *trans* isomer in red, below: solution of S-diazocine **3** before and after irradiation in acetone.

Photophysical properties were investigated with ^{1}H NMR and UV/Vis spectroscopy. The UV/vis spectra of the O-diazocine **2** and S-diazocine **3** are similar to the parent system. The nπ* bands of the *cis* isomers are located at 400 nm. By switching both diazocines to the *trans* isomers, the nπ* excitations are shifted bathochromically to λ_{max} =525 nm. These bands are broad and extend up to 700 nm. Therefore, the back isomerization to the *cis* isomers can be performed with red light (660 nm) (Figure 2). In contrast to the parent diazocine **1** and the O-diazocine **2**, the S-diazocine **3** exhibits an additional strong absorption at 380 nm which we attribute to the chair conformation.

Photostationary states were determined by ^{1}H NMR spectroscopy. In both systems (**2** and **3**) *cis-trans* isomerizations were achieved with 385 or 405 nm (**2**: 80%, **3**: 70%) and *trans-cis* switching with 530 or 660 nm (>99%) (Table 1).

Half-lives of the *trans* compounds were also determined by ^{1}H NMR spectroscopy (X = S, **3**) and UV/Vis spectroscopy (X = O, **2**). Compared to the parent system the oxygen bridged system **2** exhibits a distinctly shorter half-life. Rate constants were determined at four different temperatures (-11, 0, 4, and 9°C) and the half-life at room temperature was extrapolated from the Arrhenius equation (see Supporting information) as $t_{1/2}$ = 89 s (20 °C). In contrast to **2**, the *trans* isomer of the sulphur system **3** exhibits a high thermal stability. With $t_{1/2}$ = 3.5 d the half-life of trans-**3** is considerably longer than the half-life of the parent system **1** ($t_{1/2}$ = 4.5 h). To check the photostability of hetero diazocines **2** and **3** were irradiated with 385 and 530 nm in an alternate sequence. No fatigue was observed over a large number of cycles (Figure 3).

Table 1. Photostationary states and half-lives of heterodiazocines **2** and **3**.

X =	$PSS_{385/405}$ % trans	$PSS_{530/660}$ % cis	$t_{1/2}$
O (**2**)	80 [a]	> 99	89 s (20 °C)
S (**3**)	70 [b]	> 99	3.5 d (27 °C)

a) 385 nm, -70 °C b) 405 nm, 27 °C.

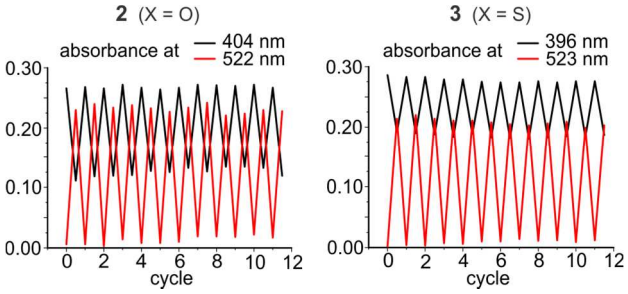


Figure 3. Left: measured absorbances of a solution of **2** at 404 nm (black zig-zag line) and 522 nm (red zig-zag line) in the photostationary states after alternating irradiation at 530 and 385 nm in repeated switching cycles. Right: absorbance of **3** at 396 nm (black) and 523 nm (red) after irradiation at 530 and 405 nm.

In summary, we synthesized two novel photochromic compounds, and investigated their photophysical properties. They are structurally quite simple, and can be viewed as *ortho* (O-CH_2 and S-CH_2) bridged azobenzenes. Synthesis is short (two or three steps) and reliable (as compared to the parent diazocines). In contrast to azobenzenes the *cis* configurations are thermodynamically more stable than the *trans* isomers. Moreover, *trans-cis* isomerization is very efficient (>99%) even with light in the far-red (650 nm). This would be most suitable for *in vivo* activation of compounds that are more active in the *cis* state. [30,31] Fatigue or decomposition was not observed over a large number of cycles under air at room temperature. The above properties of this novel class of photochromic compounds provide the basis for numerous applications in photo pharmacology, and functional materials.

ASSOCIATED CONTENT

Supporting Information

DFT-calculations, experimental procedures, ^{1}H- and ^{13}C-NMRs of all compounds, photoswitching experiments (^{1}H-NMR and UV/Vis), web enhanced object (movie) demonstrating the switching of the oxygen diazocine **2.** This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

Notes

The authors declare no competing financial interests.

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REFERENCES

(1) Szymanski, W.; Beierle, J. M.; Kistemaker, H. A. V.; Velema, W. A.; Feringa, B. L. *Chem. Rev.* **2013**, *113*, 6114–6178.

(2) Merino, E.; Ribagorda, M. *Beilstein J. Org. Chem.* **2012**, *8*, 1071–1090.

(3) Feringa, B. L.; Brown, W. R. In *Molecular Switches*; 2nd,, Ed.; Wiley-VCH: Weinheim, 2011.

(4) Kay, E. R.; Leigh, D. A.; Zerbetto, F. *Angew.Chem.Int.Ed* **2007**, *46*, 72–191.

(5) Hartley, G. S. *Nature* **1937**, *140*, 281–281.

(6) Bléger, D.; Hecht, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 11338–11349.

(7) Dong, M.; Babalhavaeji, A.; Samanta, S.; Beharry, A. A.; Woolley, G. A. *Acc. Chem. Res.* **2015**, *48*, 2662–2670.

(8) Samanta, S.; Beharry, A. A.; Sadovski, O.; McCormick, T. M.; Babalhavaeji, A.; Tropepe, V.; Woolley, G. A. *J. Am. Chem. Soc.* **2013**, *135*, 9777–9784.

(9) Beharry, A. A.; Sadovski, O.; Woolley, G. A. *J. Am. Chem. Soc.* **2011**, *133*, 19684–19687.

(10) Bléger, D.; Schwarz, J.; Brouwer, A. M.; Hecht, S. *J. Am. Chem. Soc.* **2012**, *134*, 20597–20600.

(11) Yang, Y.; Hughes, R. P.; Aprahamian, I. *J. Am. Chem. Soc.* **2012**, *134*, 15221–15224.

(12) Yang, Y.; Hughes, R. P.; Aprahamian, I. *J. Am. Chem. Soc.* **2014**, *136*, 13190–13193.

(13) Siewertsen, R.; Neumann, H.; Buchheim-Stehn, B.; Herges, R.; Näther, C.; Renth, F.; Temps, F. *J. Am. Chem. Soc.* **2009**, *131*, 15594–15595.

(14) Broichhagen, J.; Frank, J. A.; Trauner, D. *Acc. Chem. Res.* **2015**, *48*, 1947–1960.

(15) Velema, W. A.; Szymanski, W.; Feringa, B. L. *J. Am. Chem. Soc.* **2014**, *136*, 2178–2191.

(16) Pittolo, S.; Gómez-Santacana, X.; Eckelt, K.; Rovira, X.; daltonalton, J.; Goudet, C.; Pin, J.-P.; Llobet, A.; Giraldo, J.; Llebaria, A.; Gorostiza, P. *Nat. Chem. Biol.* **2014**, *10*, 813–815.

(17) Stein, M.; Middendorp, S. J.; Carta, V.; Pejo, E.; Raines, D. E.; Forman, S. A.; Sigel, E.; Trauner, D. *Angew. Chem.* **2012**, *124*, 10652–10656.

(18) Thies, S.; Sell, H.; Bornholdt, C.; Schütt, C.; Köhler, F.; Tuczek, F.; Herges, R. *Chem. Eur. J.* **2012**, *18*, 16358–16368.

(19) Samanta, S.; Qin, C.; Lough, A. J.; Woolley, G. A. *Angew. Chem.* **2012**, *124*, 6452–6455.

(20) Sell, H.; Näther, C.; Herges, R. *Beilstein J. Org. Chem.* **2013**, *9*, 1–7.

(21) Eljabu, F.; Dhruval, J.; Yan, H. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5594–5596.

(22) Joshi, D. K.; Mitchell, M. J.; Bruce, D.; Lough, A. J.; Yan, H. *Tetrahedron* **2012**, *68*, 8670–8676.

(23) Reisser, A.; Crämer, K. *Chem. Ber.* **1928**, *61*, 2555–2566.

(24) Tellkamp, T.; Shen, J.; Okamoto, Y.; Herges, R. *Eur. J. Org. Chem.* **2014**, *2014*, 5456–5461.

(25) Lellmann, E.; Mayer, N. *Chem. Ber.* **1892**, *25*, 3583–3586.

(26) Wang, H.; Ma, Y.; Tian, H.; Yu, A.; Chang, J.; Wu, Y. *Tetrahedron* **2014**, *70*, 2669–2673.

(27) Machin, J.; Mackie, R. K.; McNab, H.; Reed, G. A.; Sagar, A. J. G.; Smith, D. M. *J. Chem. Soc., Perkin Trans. 1* **1976**, 394–399.

(28) Thorwirth, R.; Bernhardt, F.; Stolle, A.; Ondruschka, B.; Asghari, J. *Chem. Eur. J.* **2010**, *16*, 13236–13242.

(29) Sanz, R.; Escribano, J.; Fernández, Y.; Aguado, R.; Pedrosa, M. R.; Arnáiz, J., Francisco *Synlett* **2005**, 1389–1392.

(30) Velema, W. A.; van der Berg, J. P.; Hansen, M. J.; Szymanski, W.; Driessen, A. J. M.; Feringa, B. L. *Nat. Chem.* **2013**, *5*, 924–928.

(31) Borowiak, M.; Nahaboo, W.; Reynders, M.; Nekolla, K.; Jalinot, P.; Hasserodt, J.; Rehberg, M.; Delattre, M.; Zahler, S.; Vollmar, A.; Trauner, D.; Thorn-Seshold, O. *Cell* **2015**, *162*, 403–411.

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