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N-Acetyl Diazocine Derivatives via Cross-Coupling

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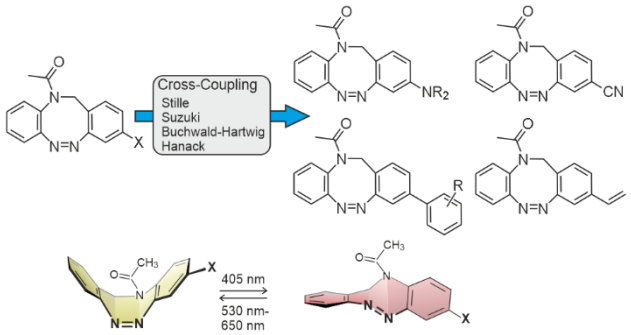
Abstract

Diazocines are photoswitches derived from azobenzenes by bridging the two phenyl rings in *ortho* position with a CH_2CH_2 group forming an eight membered (diazocine) ring. Diazocine is superior to most azobenzenes in almost all photophysical properties (switching efficiency, quantum yield, wavelengths etc.). The biggest advantage, especially in photopharmacology and when used in photoswitchable materials, is the inverted thermodynamic stability of the two switching states (isomers). The *Z* isomer is more stable than the *E* form. However, one disadvantage that it shares with the frequently used azobenzene is that the switching efficiency decreases sharply with increasing water content in the solvent. In a recently published paper, we reported that replacing one CH_2 group in the bridge with $NCOCH_3$ not only confers intrinsic water solubility, but also largely eliminates the problem of reduced switching efficiency in aqueous solutions. In order to investigate the chemistry of this promising photoswitch

and to unlock further applications, we now investigate strategies for the synthesis of derivatives, which are based on cross-coupling reactions. 14 vinyl-, aryl-, cyano-, and amino-substituted diazocines were prepared via Stille, Suzuki, and Buchwald-Hartwig reactions. X-ray structures are presented for derivatives **1**, **2** and **7**.



Keywords

keyword; keyword; keyword; keyword; keyword

photoswitch; diazocine; cross-coupling; photoisomerization; N-acetyl diazocine; thermal relaxation

Introduction

Diazocines are frequently used photoswitches with superior photophysical properties. The parent ethylene bridged diazocine shows excellent switching photoconversion between the *Z* and the *E* configurations ($\Gamma(Z \rightarrow E)_{385nm}$ = 92% and $\Gamma(E \rightarrow Z)_{520nm}$ > 99 % in *n*-hexane) due to well-separated *n*-π*-transitions in the visible part of the electromagnetic spectra.[1] Moreover the ethylene bridge creates a cyclic 8-membered core, inverting the thermodynamically stability in favor of the *Z* boat conformation compared to parent azobenzene, which has a stable *E* configuration.[1-4] Preceding studies including azobenzene-based photopharmacophores showed that, in most cases, the sterically demanding *Z* configuration is biologically inactive, while the

stretched *E* configuration is biologically active.[5,7] Because of the inverted thermodynamic stability compared to azobenzene, the stable *Z* configuration of the diazocine can be administered and subsequently activated with light at the site of illness with high spatiotemporal resolution. Thus, collateral damage in the surrounding healthy tissue can be avoided. In addition, the quantitative thermal back-isomerization from the active *E* to the inactive *Z* configuration prevents contamination and accumulation in the environment after excretion.[1,6,7] These superior properties of diazocines have been exploited in several applications such as the control of protein folding by implementation as cross-linkers between protein side chains[8] or in peptide backbones[9], as photoswitchable neurotransmitters[10,11] or as switching units for potential dependent potassium channels.[12] Compared to the $Z \rightarrow E$ conversion rate of 92% (in *n*-hexane) of the parent diazocine the conversion water/DMSO mixtures is decreasing with increasing water concentration (73% in water/DMSO 9:1).[8-12] Moreover, the parent diazocine is insoluble in water (precipitation in water/DMSO > 9:1). Substitution with polar substituents such as CH_2NH_2 provides water solubility, however, it does not restore the high $Z \rightarrow E$ conversion rates of the parent system in organic solvents, which is a disadvantage, since biochemical reactions usually take place in aqueous environments.[13] The substitution of one CH_2 group in the CH_2CH_2 bridge by N-CO-CH_3 leads to an intrinsic water solubility of the *N*-acetyl diazocine **1** (Figure 1).[3] Furthermore the photoconversion of **1** shows no significant drop in pure water in contrast to the solubilized parent diazocine. These superior properties make the *N*-acetyl diazocine **1** an ideal candidate for application in the field of photopharmacology especially in aqueous environments.[13]

There are two strategies of applying diazocines in photopharmacology. The first one exploits the structural similarity of the tricyclic diazocine framework to the tricyclic structure of e. g. tetrahydrodibenzazocines[14,15] and tetracyclic steroid scaffolds

such as 17β-estradiol[16] where the diazocine core mimics the framework of the bioactive compound. The other option is to attach the diazocine photoswitch as a substituent (appendix) to the biologically active molecule. [6,10,17-19] The art of designing a photoswitchable drug is to place the switch at a position in the pharmacophore that allows switching of the biological effect by irradiation with light without greatly reducing the overall activity by unselective interference with the inhibitor-receptor interaction. This is a difficult task because the design of a photoswitchable agent usually starts with a known, non-switchable drug or a known biological molecule, which is already carefully "optimized" either by pharmaceutical industry or by nature. Hence, there is a high risk that any change in structure will also lead to a reduction in efficiency. In any case the light-induced geometry change via isomerization should selectively control the interaction between the inhibitor and the receptor.[19]

Currently there is only one example reported in the literature for the incorporation of *N*-acetyl diazocines into biologically active molecules.[15] As a starting point for further derivatization, the synthesis and characterization of monohalogenated *N*-acetyl diazocines **2** and **3** (Figure 1) have been performed.[20] Unfortunately, diazocines in general, and *N*-acetyl diazocines in particular cannot be derivatized by electrophilic aromatic substitution. Substituents such as halogen atoms must be introduced into the *N*-acetyl diazocine structure during the synthesis of the building blocks. In the present work we start from mono- and dihalogenated *N*-acetyl diazocine **2**-**4** (Figure 1) and focus on the further derivatization via cross-coupling reactions and the synthesis of a new dihalogenated *N*-acetyl diazocine **4** (Figure 1).

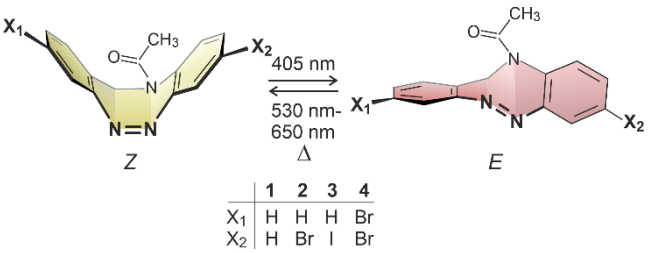


Figure 1: The halogen substituted *N*-acetyl diazocines **2-4** were used as the starting compounds for further derivatization via Pd-catalyzed cross-coupling reactions. Solutions of the *Z* isomers are yellow. The *E* isomers are red.

Results and Discussion

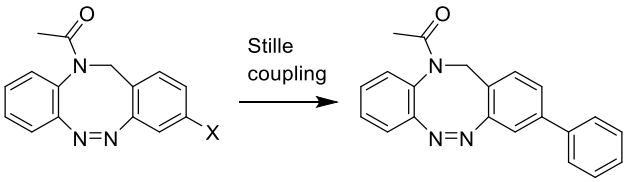
The monosubstituted *N*-acetyl diazocines **2** and **3** were synthesized according to the procedure published by our group recently.[20] The synthesis of disubstituted compound **4** followed the same procedure except the preparation of the dianiline building block **5**, which was prepared by boc-protection of the *o*-nitroaniline starting material **6** and subsequent reduction of the nitro group (See supporting information chapter II.1).

Cross-Coupling Reactions

STILLE cross-coupling reactions were performed by an organic halide reacting with an organotin compound. A great advantage of the used organostannanes is the easy accessibility, and their high air and moisture stability, so that usually a wide range of functional groups can be introduced under mild conditions.[21] Nevertheless the arylation of monohalogenated *N*-acetyl diazocines via STILLE coupling in our case gave unsatisfying results (Table 1). Reactions with tetrakis(triphenylphosphine)-palladium(0) as catalyst resulted in no product (**7**) formation. Bis(tri-*tert*-butylphosphine)-palladium(0) as catalyst gave rise to the product in very low yields independent from the used halogenated diazocine. In contrast to other cross coupling

reactions described in this work, most of the starting material decomposed during the reaction and could not be re-isolated.

Table 1: Reaction conditions of arylation of halogenated *N*-acetyl diazocines via STILLE coupling reaction.

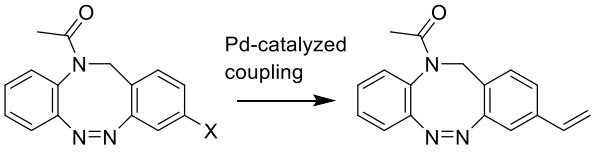


2,3 **7**

cat. system	Organotin compound	conditions	yield
$Pd(OAc)_2$	Ph_3SnCl	abs. DMF N_2,	-
PPh_3		100 °C, 16 h	
$Pd(tBu_3P)_2$	Ph_3SnCl	abs. THF N_2,	X = Br 10%
		65 °C, 16 h	X = I 10%

In contrast, the vinylation of diazocines **2** and **3** provides good yields of 65% resp. 71% for the vinyl *N*-acetyl diazocine **8** (Table 2). An alternative way of vinylating *N*-acetyl diazocines is the Pd-catalyzed vinylation with polyvinylsiloxanes and TBAF as activating agent following the method by Denmark et al. giving rise to even higher yields (74% and 78% Table 2).[22]

Table 2: Vinylation of halogenated *N*-acetyl diazocines via Pd-catalyzed coupling reactions.



2,3 **8**

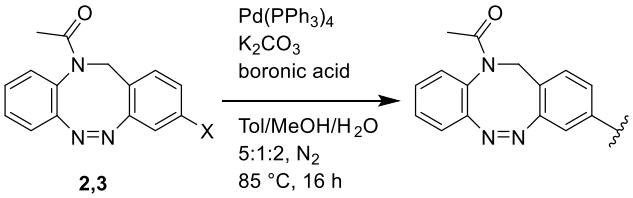
cat. system	reaction partner or additive	conditions	yield
$Pd(OAc)_2$	tributylvinyltin	abs. DMF, N_2,	X = Br 65%
PPh_3		100 °C, 16 h	X = I 71%
$PdBr_2$	D_4^V [a]	abs. THF, N_2,	X = Br 74%
JohnPhos	TBAF	50 °C, 16 h	X = I 78%

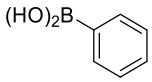
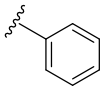
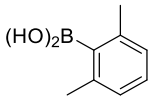
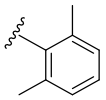
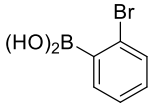
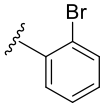
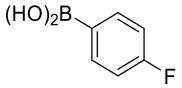
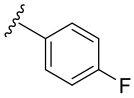
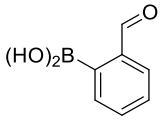
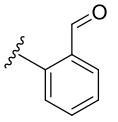
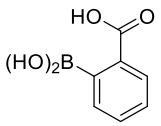
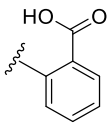
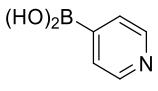
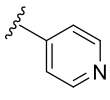
[a] D_4^V: 1,3,5,7-tetramethyl-1,3,5,7-tetravinylcyclotetrasiloxane

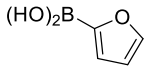
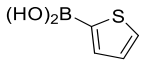
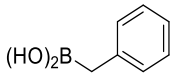
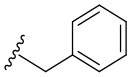
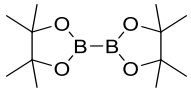
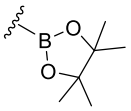
To overcome the problems of poor yields in the arylation of *N*-acetyl diazocines via STILLE-coupling we used SUZUKI-MIYAURA reactions of the diazocines **2** and **3** with different arylboronic acids.[23,24] There are several examples of last-step-modifications of azobenzenes via SUZUKI-MIYAURA reactions in the current literature, which indicate that the reaction conditions are compatible with azo groups.[25,26] SUZUKI-MIYAURA-reaction of **2** and **3** with different phenylboronic acids resulted in the formation of the corresponding arylated *N*-acetyl diazocines **7**, **9**-**13** in yields from 68 to 88% (Table 3). The yields increased slightly if boronic acids with electron withdrawing groups were used. An influence of bulky substituents like carboxyl groups in *ortho*-position of the phenyl boronic acids on the reaction was not observed. The synthesis of *N*-acetyl diazocines connected to heteroaromatic aromatic systems **14**-**16** was less successful. The pyridine substituted *N*-acetyl diazocine **14** was formed in yields of 7% or 19% while furan **15** and thiophene substituted *N*-acetyl diazocine **16** could not be obtained. The reaction with benzylboronic acid gave the corresponding *N*-acetyl diazocine **17** (46%, Table 3). Interestingly this reaction only took place if brominated *N*-acetyl diazocine **2** was used as starting material although iodo aryl compounds are in general more reactive.[23] The reaction of halogenated *N*-acetyl

diazocines **2** and **3** with bis(pinacolato)diboron did not lead to the formation of the pinacolborane substituted N-acetyl diazocine **18**. Accordingly, the Suzuki-Miyaura reaction with inversed roles between *N*-acetyl diazocine boronic acid pinacol ester and aryl or alkyl halides could not be investigated.

Table 3: Derivatization of halogen-substituted *N*-acetyl diazocines via SUZUKI-MIYAURA reaction.



boronic acid	product	yield
	**7** 	X = Br 74% X = I 83%
	**9** 	X = Br 68% X = I 74%
	**10** 	X = I 82%
	**11** 	X = Br 81% X = I 88%
	**12** 	X = Br 70% X = I 77%
	**13** 	X = Br 76%[a] X = I 79%[a]
	**14** 	X = Br 7% X = I 19%

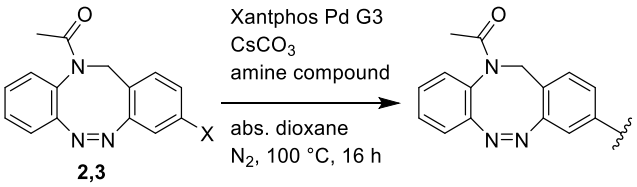
	**15** 	X = Br	-
		X = I	-
	**16** 	X = Br	-
		X = I	-
	**17** 	X = Br	46%
		X = I	-
	**18** 	X = Br	-
		X = I	-

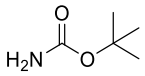
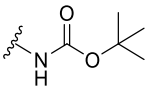
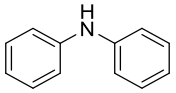
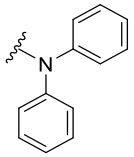
[a]Reaction was carried out in abs. DMF at 100 °C because no reaction took place if the SUZUKI-MIYAURA standard procedure was applied.

The BUCHWALD-HARTWIG amination is a versatile and powerful tool for C-N bond formation and applied widely in the synthesis of new pharmaceutical substances.[27-29] Furthermore azobenzenes[30,31] as well as diazocines[32,33] have been derivatized via Buchwald-Hartwig amination.

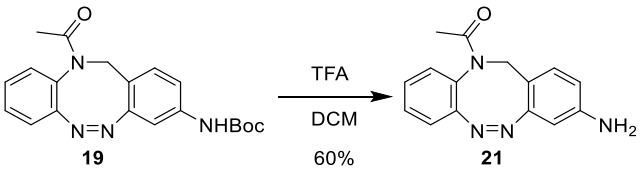
The BUCHWALD-HARTWIG amination of halogenated *N*-acetyl diazocines according to the procedure of MAIER *et. al*.[32] with *tert*-butyl carbamate resulted in the formation of boc-protected aniline-substituted *N*-acetyl diazocine **19** in a yield of 72%. However, the reaction only took place if the iodo *N*-acetyl diazocine **3** was used as starting material. Using diphenylamine as a more electron rich amine resulted in the formation of diphenylaniline-substituted *N*-acetyl diazocine **20** in a significantly lower yield of 25% starting from the bromide **2** and 47% starting from the iodo precursor **3** (Table 4).

Table 4: Derivatization of halogenated *N*-acetyl diazocines **2** and **3** via BUCHWALD-HARTWIG amination.



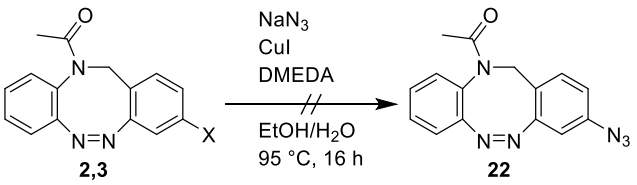
amine compound	product	yield
	**19** 	X = Br - X = I 72%
	**20** 	X = Br 25% X = I 47%

Deprotection of the carbamate **19** with trifluoroacetic acid provided the corresponding aniline-substituted *N*-acetyl diazocine **21** (Scheme 1).



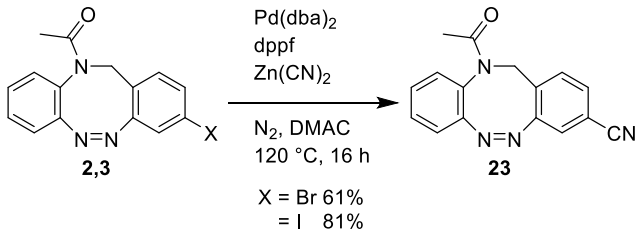
Scheme 1: Synthesis of aniline *N*-acetyl diazocine by deprotection of the carbamate.

Another option for carbon-heteroatom bond formation reactions are copper-catalyzed ULLMANN-type reactions, which have already been applied to the parent diazocine.[34,35] The attempted synthesis of azide functionalized *N*-acetyl diazocine **22** under the conditions described by HUGENBUSCH *et al*.[35] showed no product formation and only starting material could be obtained (Scheme 2).



Scheme 2: Reaction conditions for the attempted ULLMANN-type reaction with sodium azide.

The palladium-catalyzed introduction of cyano groups under mild conditions in analogy to IQBAL *et al*.[36] gave the cyano-substituted *N*-acetyl diazocine **23** in yields of 61% from bromide **2** and 81% from iodide **3** (Scheme 3). Nitriles are a good starting point for further functional group interconversions.[37]



Scheme 3: Reaction conditions for the palladium-catalyzed synthesis introduction of nitrile functionality

Photochemical Characterization

With these new *N*-acetyl diazocine derivatives at hand we turned towards the photochemical characterization, in particular to gain insight into the effects of different substituents on UV-spectra and switching behavior. For determination of the n-π^*-absorption maxima of the *E* and *Z* isomers 250 μM solutions of each compound in acetonitrile were prepared and measured at 25 °C. All compounds (**4**, **7**-**14**, **17**, **19**-**21**, **23**) exhibit an $n\pi^*$-transition at approximately 400 nm, matching the *n*-π*-transition of unsubstituted *N*-acetyl diazocine **1** (Table 5). Irradiation with 405 nm gives the metastable *E* isomers with photoconversion yields of 76-85% due to a very good separation of the *n*-π*-transitions. The nitrogen-substituted derivatives **19**-**21** show significantly lower conversion rates of 41-61%. This behavior has already been

observed in other amino-substituted diazocines as well and is probably due to the overlap of *n*-π*-transitions of the *E* and *Z* isomers.[38] An almost complete *E*→*Z* conversion (>99%) can be achieved by irradiation with light between 520 and 600 nm for all synthesized compounds.

Table 5: Photophysical properties of *N*-acetyl diazocines **1**-**4, 7**-**14, 17, 19**-**21, 23** in acetonitrile.

	λ_{max} (Z)	λ_{max} (E)	$t_{1/2}$ (25 °C)	k (25 °C)	$\Gamma_{Z\rightarrow E}$ (405 nm)[a]	$\Gamma_{E\rightarrow Z}$ (530 nm)
	nm		min.	10^{-4} s^{-1}		
1[20]	397	513	29.5	3.916	88%	>99%
2[20]	397	515	30.9	3.744	81%	>99%
3[20]	397	517	28.6	4.036	82%	>99%
4	396	519	16.9	6.820	85%	>99%
7	399	516	29.3	3.944	79%	>99%
8	398	515	29.6	3.897	76%	>99%
9	394	515	34.2	3.374	77%	>99%
10	396	516	34.2	3.382	82%	>99%
11	397	515	33.8	3.418	78%	>99%
12	396	517	29.8	3.877	80%	>99%
13	399	517	31.2	3.688	77%	>99%
14[b]	396	515	39.9	2.897	79%	>99%
17	398	515	29.3	3.944	82%	>99%
19	397	514	30.6	3.779	61%	>99%
20	389	510	31.5	3.670	49%	>99%
21	396	511	38.9	2.973	41%	>99%

23	396	518	39.8	2.906	83%	>99%

[a]Extrapolated values (for details, see Supporting Information Section IV) in deuterated acetonitrile 5 mM.

[b]UV spectra measured with a concentration of 128 µM in acetonitrile and NMR spectra with a concentration of 2.55 mM.

Thermal half-lives ($t_{1/2}$) were determined by monitoring the thermal relaxation of the synthesized diazocines at 25 °C in the UV spectrometer (see Supporting Information IV). The dihalogenated *N*-acetyl diazocine **4** shows a significantly reduced half-life compared to the mono- **2** and **3** and the unsubstituted system **1**. The substitution with a phenyl group does not show a significant influence on the thermal half-life whereby it makes no difference if there is a bridging methylene group between diazocine and the substituent or not. The half-lives of molecules **7** and **17** are nearly identical compared to the parent system **1**. If electron withdrawing substituents are added in *ortho*-position of the additional phenyl ring (**12** and **13**) the half-life is not affected significantly as well. An increase of about 10% of the half-lives has been observed for weak +M-substituents bromine (**10**) and fluorine (**11**) or methyl groups (**9**) in *ortho*- and *para*-positions. The increase is even stronger if pyridine- (**14**), cyano- (**23**) or aniline-substituents (**21**) are attached to the *N*-acetyl diazocine in *meta*-position. In contrast to the extended half-life of the aniline **21** the Boc-protected **19** and the diphenyl-substituted aniline **20** show half-lives not significantly longer than the parent *N*-acetyl diazocine **1**.

Given the water solubility and the excellent switching behavior of parent **1** in aqueous media[3,13,20], the photochemical properties of water-soluble substituted *N*-acetyl-diazocines **13** and **21**were also investigated in aqueous solution (**13** and **21** in aqueous PBS buffer solution at pH 7.4 250 µM, **23** at pH 3.5 250 µM, **13** at pH 9 250 µM). The

pH values were chosen to make sure that the aniline **21** is completely protonated and the carboxylic acid **13** is completely deprotonated. UV measurements revealed that the absorption maxima of the *n*-π*-transitions of the *Z* isomers of **13** and **21** are almost independent of solvent and pH (392-398 nm), while the *n*π* transitions of the *E* isomers at ∽515 nm are significantly shifted to shorter wavelengths ($\Delta\lambda_{max}$=10 - 20 nm) in water (Table 6). At the same time the *n*-π*-transition of the azobenzene substructure of the *E* isomer which is usually hidden under the π-π*-transition in organic solvents is shifted to higher wavelengths (see Figure SIII.15-SIII.20 and SIII.29-SIII.36). For diazocine **13** this leads to a drop in the PSS ($\Gamma_{Z\rightarrow E}$) from 77% in acetonitrile to 53% in water at pH 7.4 and 48% at pH 9 due to a higher overlap of both isomers *n*-π*-transitions. For the aniline type substituted diazocine **21** the PSS ($\Gamma_{Z\rightarrow E}$) decreases slightly from 41% in acetonitrile to 37% in water at pH 7.4 and increases again to 62% at pH 3.5. This drastic increase in the PSS is probably rooted in a lower *n*-π*-transition gap caused by protonated aniline **21** at pH 3.5 as well as a higher band separation compared to the unprotonated form at pH 7.4. The thermal half-lives of **13** and **21** increase by a factor 2.5 and 4.2 when changing the solvent from acetonitrile to water at pH 7.4, which is consistent with the current literature for thermal half-lives of substituted parent diazocines in aqueous media.[16,37]

Table 6: Photophysical properties of *N*-acetyl diazocines **1**, **13**, **21** in water at various pH values.

	λ_{max} (Z)	λ_{max} (E)	$t_{1/2}$ (25 °C)	k (25 °C)	$\Gamma_{Z\rightarrow E}$ (405 nm)[a]	$\Gamma_{E\rightarrow Z}$ (530 nm)
	nm		min.	10^{-4} s^{-1}		
1[20]	393	502	72.8	1.587	72%	>99%

13 at pH 9	392	502	106.4	1.086	48%	>99%
13 at pH 7.4	392	505	78.2	1.477	53%	>99%
21 at pH 3.5	392	495	118.0	0.975	62%	>99%
21 at pH 7.4	392	489	162.5	0.711	37%	>99%

[a]Extrapolated values (for details, see Supporting Information IV) in deuterated water 5 mM.

Conclusion

Fourteen mono-*meta*-substituted (**7**-**14**, **17**, **19**-**21**, **23**) and one di-*meta*-substituted (**4**) *N*-acetyl diazocines have been synthesized and characterized. The synthesis has been performed from halogenated precursors and cross-coupling reactions for further functionalization. The reaction conditions of various cross-coupling reactions have been correspondingly adjusted. The arylation of the *N*-acetyl diazocine system could be achieved via Suzuki coupling reactions in high yields (**7**, **9**-**14**, **17**) as well as the vinylation via Stille-coupling (**8**). These compounds also exhibit excellent switching properties. Electron withdrawing substituents at the aryl substituents have no significant influence on the switching behavior while weak +M-substituents like bromine and fluorine as well as electron poor heteroaromatic systems lead to increased thermal half-lives. An amino-substituted (aniline type) derivative (**21**) was obtained via Buchwald-Hartwig coupling with Boc-carbamate and subsequent deprotection. Amino-substituted *N*-acetyl diazocines (**19**-**21**) exhibit lower photostationary states (PSS) in

analogy to aminosubstituted azobenzenes and previously synthesized diazocines. We also investigated the switching properties of the water-soluble derivatives **13** and **21** in water at different pH. The half-lives of the metastable *E* isomers are significantly longer in water than in less polar solvents like acetonitrile. For carboxylic acid substituted **13**, the *Z*→*E* conversion upon irradiation with 405 nm drops from 77% to 53% upon changing the solvent from acetonitrile to water (pH 7.4). The reverse effect was observed with amino substituted **21**.

The photophysical properties of photoswitchable drugs in photopharmacology are usually determined in organic solvents. Their natural environment, however, is the aqueous phase. There is a risk of overestimating the performance of photochromic drugs because photoconversion to the active state usually drops considerably in water, and also half-lives are different. Light-activatable drugs based on *N*-acetyldiazocines are more hydrophilic than those derived from the parent system diazocine and corresponding azobenzenes. They retain their switching properties even in an aqueous environment and are therefore promising switches in photopharmacological applications.

Supporting Information

Supporting Information File 1:

Synthetic procedures, UV-vis and NMR switching experiments, copies of UV-vis and NMR spectra, X-ray crystallographic data

CCDC-2329263 (1), CCDC-2329261 (2), and CCDC- 2329262 (7) contain the supplementary crystallographic data for this paper. These data can be obtained free charge from the Cambridge Crystallographic Data Centre via

http://www.ccdc.cam.ac.uk/data_request/cif. Cambridge CB2 1EZ, UK; fax: +44 1223 336033”

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Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information

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