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Photochromic Evaluation of 3(5)-Arylazo-1H-pyrazoles

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ABSTRACT: The desire to photocontrol molecular properties ranging from materials to pharmacology using light as an external trigger with high spatiotemporal resolution led to the development of a broad range of photochromic scaffolds. Among them, azobenzenes are synthetically well accessible and show excellent fatigue resistance. Their photochromic properties vary with the substitution pattern and for different heteroarenes. However, the photochromism of 3(5)-substituted-1H-pyrazoles has not yet been investigated, although this compound class offers interesting possibilities of metal ion coordination and hydrogen bond formation via its NH moiety. Herein, we present the results of an experimental and computational investigation of arylazo-3(5)-arylazo-1H-pyrazoles. To elucidate their properties, solvent and substitution effects on their light absorption, thermal half-lives, photostationary states, fatigue, and quantum yields were determined.

INTRODUCTION

The fascinating challenge of controlling molecular properties, the biological activity of a substrate, or motion at a molecular scale led in the last two decades to an increase in interest in photoactuators.^{1–7} In such molecules, irradiation with light induces a reversible isomerization between at least two states accompanied by physical and chemical changes. Azobenzene photoswitches are of particular importance because of their synthetic accessibility, excellent fatigue resistance, high extinction coefficients, and quantum yields, allowing switching with low-intensity light. The irradiation of the thermodynamically stable, planar *trans* isomer generates the metastable *cis* isomer. Back-isomerization can be achieved either by irradiation with light or by thermal relaxation. Azobenzenes have been studied thoroughly in order to elucidate the mechanisms of photochemical isomerization along with the thermal pathways interconnecting the *cis* and the *trans* form.^{8,9}

Because of a substantial overlap in their absorption spectrum, switching between the *trans* and *cis* isomer of the parent azobenzene cannot be achieved quantitatively.¹⁰ Moreover, the thermal lifetime of the metastable *cis* isomer is strongly dependent on the substituents.^{11–14} A wide range of azobenzene derivatives have been prepared in search for optimized properties for specific applications.^{15–20} In order to push the boundaries of the properties of azobenzene, the photochromism of heteroaromatic scaffolds was investigated.^{9,21–25} In this way, a better tunability of the photochemical, photochemical, and thermal characteristics of a molecular switch can be achieved with minimal or no additional substitution of the chromophore.^{26–30}

The introduction of a heterocycle as a part of the molecular switch offers further modes of interaction such as coordination to metal ions or hydrogen bond formation by the heteroatom. Furthermore, nitrogen-containing heterocycles are typical motifs of natural products and drugs.³¹ 4-Arylazopyrazoles are an emerging class of heteroarylazo switches able to

interconvert almost quantitatively in both directions, possessing an exceptionally long-living *cis* form (Chart 1a).²⁴ Their stability against glutathione is beneficial for applications in a biological environment.³² While the majority of investigations focuses on alkylated pyrazole submoieties, the photochromism of 4-arylazo-1H-pyrazoles was only studied to a limited extent.³³

Despite the wide presence of 3(5)-substituted-1H-pyrazoles in bioactive molecules (Chart 1b),³⁴ the photochromism of the related azo compound was, to the best of our knowledge, never studied. NH-substituted heteroaryl azoswitches are supposed to exhibit (extremely) short thermal lifetimes as they could potentially tautomerize through a hydrazone mechanism (Chart 1c, type I).^{9,35} This tautomerism could occur in the same way as for hydroxy- or amino-substituted azobenzenes if the N proton is shifted intra- or intermolecularly onto the azo bond. However, in our previous theoretical work, we have hypothesized and computationally proven that all the isomeric azo-pyrazole scaffolds should not undergo hydrazone tautomerism because of the energetically unfavored formation of the tautomer (ΔG greater than 10 kcal/mol).²²

Interestingly, this class of molecules is also characterized by annular tautomerism of the NH proton of the pyrazole (Chart 1c, type II).³⁶ The equilibrium of proton scrambling between the two nitrogen atoms on the ring is affected by solvent and substituent effects, while a slow proton exchange is common in the solid state. Computational chemistry is useful in the prediction of the preferred tautomeric form of the 3(5)-substituted-1H-pyrazoles, necessary to design molecules for

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Chart 1. 3(5)-Arylazo-1*H*-pyrazole class and its application as a photoswitch.**a) Photochromism in 4-arylazopyrazole** **b) The 3(5)-*NH*-pyrazole core in medicinal chemistry** **c) Tautomerisms in the 3(5)-substituted azo-1*H*-pyrazoles** **d) This work:**

specific tasks that are based on supramolecular recognition, and structure–activity biological properties.³⁶

Consequently, in this combined study we focus on the experimental and computational investigation of 3(5)-arylazo-1*H*-pyrazoles extending the present knowledge on arylazopyrazoles. As for all classes of azobenzenes, solvent and

substitution (Chart 1d) dependencies were expected and investigated. To evaluate the switching performance, the wavelength of maximum light absorption, thermal half-lives, photostationary states (PSS), repetitive cycle performance, and quantum yields were determined unraveling new insights into arylazopyrazoles.

RESULTS AND DISCUSSION

Synthesis. Arylazopyrazoles **1b**, **1c**, and **1e–k** were obtained via Baeyer–Mills^{37,38} reaction—a well-known reported procedure for the synthesis of azobenzenes via reaction of an aryl-nitroso³⁹ with an aryl-amine (Scheme 1). The corresponding arylamines **2b**, **2c**, and **2e–k**, respectively, were oxidized to their nitroso derivatives **3b**, **3c**, and **3e–k** using potassium monopersulfate as an oxidant in a biphasic reaction system preventing overoxidation. The resulting nitroso derivatives are reacted with commercially available amino-substituted pyrazole **4** in a mixture of acetic acid and dichloromethane providing the substituted arylazopyrazoles **1b**, **1c**, and **1e–k** in moderate to good yields regardless of the presence of electron donating group (EDGs) or electron withdrawing group (EWGs).

The amino-substituted arylazopyrazole **1a** was synthesized in a good yield via reduction of its corresponding nitro precursor **1k** using sodium sulfide as a mild reductant (Scheme 2).⁴⁰

Scheme 2. Reduction of the Nitro-Substituted Azopyrazole **1k**⁴⁰

In contrast, the symmetric arylazopyrazole **1d** was synthesized via oxidative coupling of amino-pyrazole **3** in the presence of manganese(IV) dioxide (Scheme 3).³⁶

Scheme 3. Oxidative Coupling of Amino Pyrazole **4** for the Synthesis of the Symmetric Azopyrazole **1d**

Photochemical Characterization. To investigate the photochromic properties of this type of photoswitchable scaffold, differently substituted arylazopyrazoles bearing

Scheme 1. Baeyer–Mills Reaction for the Synthesis of Arylazopyrazoles **4b**, **4c**, and **4e–4k**

R = *p*OMe (**b**; 20%), *p*Me (**c**; 48%), *p*H (**e**; 87%), *p*Br (**f**; 65%), *o*F (**g**; 8%), *p*COMe (**h**; 33%), *p*COOEt (**i**; 67%), *p*COOH (**j**; 53%), *p*NO₂ (**k**; 82%)

EDGs and EWGs as substituents, respectively, were synthesized. The cycle performances of these structures, thermal half-lives, and PSS of compounds **1a–k** were determined using UV–vis absorption spectroscopy. Furthermore, the effect of different solvents ranging from apolar to polar and protic [toluene, dimethyl sulfoxide (DMSO), DMSO/water, and methanol] was investigated.

Considering all substitutions and solvents, the absorption maximum representing the *trans* isomer ranges from 300 to 400 nm. The weaker absorption band in the visible range representing the *cis* maximum tails around 400–450 nm. The formation of the *cis* isomer is generally triggered most efficiently using 365 nm (except for **1a** where 400 nm was used) and can be followed by a decrease in the absorption maximum in the UV and by an increase of the absorption band in the visible region until the *cis* photostationary state (*cis* PSS) is reached and no more changes in the absorption spectrum despite continuous irradiation are observed. Back-isomerization can be triggered using blue light irradiation ($\lambda = 455$ nm; except **1a**: green light, $\lambda = 505/528$ nm), leading to the *trans* photostationary state (*trans* PSS).

As an example, Figure 1 shows the normalized UV–vis absorption spectra of compounds **1a** (amino-substituted), **1e**

Figure 1. Normalized UV–vis spectra of compounds of **1a**, **1e**, and **1k** in DMSO as an example for an electron donating (**1a**, R = NH₂) and an electron withdrawing (**1k**, R = NO₂) substituted azopyrazole compared to the unsubstituted reference (**1e**, R = H).

(unsubstituted), and **1k** (nitro-substituted) in their thermal equilibrium, their *cis* PSS (dotted line) and their *trans* PSS (dashed line) state measured in DMSO (50 μ M solution). More bathochromically shifted UV–vis spectra of the respective compound leads to broader absorption peaks. In DMSO, the unsubstituted azopyrazole **1e** absorbs mainly at around 320 nm and its *cis* isomer at 430 nm. The EWG-substitution leads to a shift of the absorption spectrum toward longer wavelengths for the *trans* isomer ($\lambda_{\text{max}} \approx 340$ nm) whereas the *cis* absorption band is almost unaffected ($\lambda_{\text{max}} \approx 430$ nm). The strongest shift can be observed for the amino-substituted azopyrazole **1a** with a maximum absorption at 400 nm for its *trans* isomer, which can be photoisomerized in both directions using visible light irradiation. Solvent polarity has a limited effect on the absorption wavelength, apart from selected cases where specific solvent–solute interactions occurred. As an example, the $\pi\pi^*$ transition of the amino substituted compound **1a** absorbs at 373 nm in toluene. Moving to a hydrogen bond acceptor solvent such as DMSO, a red shift of almost 20 nm can be observed. A similar effect can

be observed in the DMSO–water mixture, while a less pronounced solvatochromism is present for MeOH, characterized by both hydrogen accepting and donating capabilities.^{22,41–43}

All compounds were subjected to alternate photoisomerization for ten cycles in each solvent and no significant degradation was observed demonstrating high fatigue resistance. Table 1 summarizes the principal photophysical data for these structures, such as wavelengths of maximum absorption, extinction coefficients, and wavelength of the isosbestic points in the four investigated solvents.

All compounds show photostationary distributions (PSD) with high *cis* percentage for the *trans* $\rightarrow$ *cis* isomerization, especially in apolar and aprotic solvents and slightly less pronounced in MeOH. Only the nitro-substituted derivative **1k** is less efficient in all the solvents. Back-isomerization to the *trans* isomer is selectively achieved with recovery of the more stable form. For DMSO, the PSDs at the photostationary state were determined under constant irradiation via online nuclear magnetic resonance (NMR) spectroscopy observing lower PSD values compared to the UV–vis concentrations. Concentration effects are known for 4-aryloxy-1H-pyrazoles and other hereoaryloxy dyes;^{21,25,33} however, the discrepancy of the PSS values may be explained by a higher concentrated NMR solution and resulting in higher optical density of the sample and lower light penetration, as well as low light intensity because of the light fiber used during the NMR-experiment. To overcome this problem, the PSDs were calculated via peak deconvolution with Gaussian functions (see Supporting Information), obtaining the data in Table 1.

The influence of the different electron-donating and electron-withdrawing substituents on the photochromic performance of the arylazopyrazole derivatives was investigated. The photoisomerization quantum yield for the *trans* $\rightarrow$ *cis* isomerization was studied in DMSO (Table 2), applying a methodology reported in the literature.^{22,44} The more intense $\pi\pi^*$ and the less pronounced $n\pi^*$ transition bands were irradiated selectively using a 365 nm emitting light-emitting diode (LED) for the former and a 420 or 455 nm one for the latter.

The isomerization is more efficient when the S₁ ($n\pi^*$) state is populated, while excitation to the S₂ ($\pi\pi^*$) exhibits lower quantum yields. This anti-Kasha behavior is typical and reported in an extensive body of the literature for both homo and heteroaryl azo compounds.^{8,9} Computational chemistry confirmed the anti-Kasha phenomenon for compound **1e** in its 5-phenyl-1H-azopyrazole form, applying the SA(3)-CASSCF(14,12)/cc-pvdz level of theory and the results are summarized in Figure 2. The excitation of the *trans* isomer to the S₁ leads to the population of an energetic minimum (*trans*_{S₁}) accessible from the Franck–Condon region (*trans*_{S₁}-FC). A conical intersection distinguished by a 90° C–N=N–C dihedral angle (CI_{S₁S₀}-rot),^{9,35} connects this stationary point to the *cis* form in the ground state (*cis*_{S₀}). Direct population of S₂, on the other hand, leads to a series of funnels toward the S₁ (CI_{S₂S₁}-1-4), with different C–N=N–C dihedral angles. The anti-Kasha behavior of the azopyrazole results from the presence of a nonproductive conical intersection CI_{S₁S₀}-inv connecting the S₁ excited state to the *trans*-S₀ ground state.^{9,35} This funnel can be reached only by the molecules previously excited to the S₂, that will decay to the S₁ with enough potential energy.⁴⁵ Therefore, the overall quantum efficiency of the photochemical isomerization process from S₂ is lowered.

Table 1. Summary of the Characteristic Photochemical Data of Compounds 1a–k (50 μ M Solutions)^a

entry	compd	substituent	$\lambda_{\max} \pi\pi^*$ trans isomer [nm]	$\epsilon \pi\pi^*$ trans isomer [M ⁻¹ cm ⁻¹]	$\lambda_{\max} n\pi^*$ cis isomer [nm]	$\epsilon n\pi^*$ cis isomer [M ⁻¹ cm ⁻¹]	PSD ^b (trans $\rightarrow$ cis) %cis	PSD ^b (cis $\rightarrow$ trans) %trans	isosb. points [nm]	$t_{1/2}$ ^c
toluene	1a	4-NH ₂ -C ₆ H ₄	373	23,600	439	2868	100	93	314, 451	18 s
	1b	4-OMe-C ₆ H ₄	339	12,952	431	1632	100	93	297, 417	12 h
	1c	4-Me-C ₆ H ₄	328	20,714	433	1558	100	80	287, 399	84 h
	1d	3(5)-pyrazole	316	19,944	425	1060	69	83	409	9.4 h
	1e	4-H-C ₆ H ₄	321	12,128	425	740	83.5	82	388	59 h
	1f	4-Br-C ₆ H ₄	331	24,630	429	1328.4	85	72	287, 397	93 h
	1g	2-F-C ₆ H ₄	325	19,734	424	1993.2	92.5	69	392	62 h
	1h	4-COOH-C ₆ H ₄	325	12,200	422	1068	86	81	289, 395	26 h
	1i	4-COOEt-C ₆ H ₄	325	23,460	425	1178	91	72	291, 396	23 h
	1j	4-Ac-C ₆ H ₄	329	14,328	426	904	92	75	295, 398	12 h
	1k	4-NO ₂ -C ₆ H ₄	334	17,914	427	1056	72	82	289, 403	11 h
DMSO	1a	4-NH ₂ -C ₆ H ₄	391	24,400	452	4296	100 (73)	86 (91)	343, 464	4.7 min
	1b	4-OMe-C ₆ H ₄	344	20,400	430	2460	100 (76)	77 (66)	296, 420	8.1 d
	1c	4-Me-C ₆ H ₄	332	20,078	430	1200	96 (79)	77 (61)	285, 398	11 d
	1d	3(5)-pyrazole	320	15,980	430	1068	84 (74)	76 (79)	279, 390	22 h
	1e	4-H-C ₆ H ₄	324	15,440	423	880	81 (62)	70 (60)	283, 392	9.5 d
	1f	4-Br-C ₆ H ₄	331	21,056	421	1096	95 (88)	67 (54)	286, 397	4.2 d
	1g	2-F-C ₆ H ₄	328	25,600	421	2320	84 (58)	66 (61)	285, 391	21 h
	1h	4-COOH-C ₆ H ₄	328	25,930	425	1400	89 (69)	72 (62)	292, 394	1.6 d
	1i	4-COOEt-C ₆ H ₄	331	25,400	422	1300	100 (73)	91 (63)	293, 396	38 h
	1j	4-Ac-C ₆ H ₄	322	16,740	415	1044	87 (70)	74 (64)	297, 401	5.1 h
	1k	4-NO ₂ -C ₆ H ₄	340	19,524	418	1104	61 (45)	82 (80)	294, 406	42 s
DMSO–water	1a	4-NH ₂ -C ₆ H ₄	388	20,800	^e	^e	^e	^e	^e	96 ms ^d
	1b	4-OMe-C ₆ H ₄	347	12,960	430	2500	100	98	296, 420	7.6 d
	1c	4-Me-C ₆ H ₄	321	20,360	417	2680	93	80	276, 391	20 d
	1d	3(5)-pyrazole	311	19,940	420	1614	75	84	270, 381	23 h
	1e	4-H-C ₆ H ₄	322	12,054	420	776	77	76	282, 381	15 d
	1f	4-Br-C ₆ H ₄	322	22,800	410	1340	93	71	277, 387	6.4 d
	1g	2-F-C ₆ H ₄	318	20,440	408	1800	80	66	284, 391	20 h
	1h	4-COOH-C ₆ H ₄	319	14,080	409	1100	85	74	279, 383	18 h
	1i	4-COOEt-C ₆ H ₄	320	24,000	409	1236	83	71	280, 381	16 h
	1j	4-Ac-C ₆ H ₄	322	17,600	403	1180	79	75	285, 386	20 h
	1k	4-NO ₂ -C ₆ H ₄	328	17,600	403	1440	60	86	286, 392	43 min
MeOH	1a	4-NH ₂ -C ₆ H ₄	380	25,200	^e	^e	^e	^e	^e	0.10 s ^d
	1b	4-OMe-C ₆ H ₄	340	17,560	430	2600	100	95	292, 412	5.5 d
	1c	4-Me-C ₆ H ₄	325	21,000	425	1300	80	86	281, 390	31 h

Table 1. continued

entry	compd	substituent	$\lambda_{\max} \pi\pi^*$ trans isomer [nm]	$\epsilon \pi\pi^*$ trans isomer [M ⁻¹ cm ⁻¹]	$\lambda_{\max} n\pi^*$ cis isomer [nm]	$\epsilon n\pi^*$ cis isomer [M ⁻¹ cm ⁻¹]	PSD ^b (trans → cis) %cis	PSD ^b (cis → trans) %trans	isob. points [nm]	$t_{1/2}$ ^c
	1d	3(5)-pyrazole	315	18,530	420	900	67	86	274, 387	51 h
	1e	4-H-C ₆ H ₄	315	14,518	415	718	62	81	279, 384	11 h
	1f	4-Br-C ₆ H ₄	325	24,760	420	1170	86	73	282, 384	10 h
	1g	2-F-C ₆ H ₄	320	20,708	420	1358	77	63	279, 383	37 h
	1h	4-COOH-C ₆ H ₄	325	18,784	420	700	83	69	285, 386	5.8 h
	1i	4-COOEt-C ₆ H ₄	320	21,368	420	1058	78	71	286, 385	15 h
	1j	4-Ac-C ₆ H ₄	325	17,650	415	682	87.5	74	291, 392	16 h
	1k	4-NO ₂ -C ₆ H ₄	330	18,846	420	1054	70	80	290, 394	4.6 h

^aCompd. = compound. Isob. points = isosbestic points. $t_{1/2}$ = thermal half-life. ^bDetermined via extraction of the PSS determined by UV-vis spectroscopy via peak deconvolution with Gaussian functions. The values in brackets are obtained determined by in situ NMR spectroscopy under constant irradiation. ^cDetermined by thermal relaxation of an irradiated sample (*cis* isomer) in the dark at room temperature and following of the increase in the absorption of $\lambda_{\max}$ (*trans* isomer) via UV-vis absorption spectroscopy. ^dValue determined by laser flash photolysis. ^eNot detected due to very short thermal half-life of the *cis* isomer.

Table 2. Quantum Yields (Φ) Associated with the *trans* → *cis* Isomerization of Compounds 1a–k in DMSO

Φ	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k
$\pi\pi^*$ (<i>trans</i> → <i>cis</i>)	0.38	0.25	0.12	0.072	0.055	0.097	0.093	0.17	0.16	0.087	0.10
$n\pi^*$ (<i>trans</i> → <i>cis</i>)	0.50	0.25	0.33	0.63	0.18	0.36	0.19	0.50	0.35	0.24	0.16

Figure 2. Graphical representation of the geometrical and energetic distribution of the stationary points and conical intersections describing the photochemical *trans*–*cis* isomerization in 5-NH azopyrazoles obtained at the SA(3)-CASSCF(14,12)/cc-pvdz level of theory.

The presence of substituents of different natures have an influence on the accessibility of $CI_{S150-inv}$. Albeit a clear trend cannot be derived from the analysis presented in Table 1, it is clear that 1b possessing the same $\Phi_{n\pi^*}$ and $\Phi_{\pi\pi^*}$ stands out as an exception. The disappearance of the anti-Kasha behavior in azocompounds bearing different substituents is reported in the literature.^{46,47}

Thermal *cis*–*trans* Isomerization. The determination of the thermal half-lives of compounds 1a–k in the four different solvents helped to disclose the *cis* → *trans* isomerization mechanisms active in this class of compounds. The stability of

the metastable form ranges from days to the subsecond scale, with a pronounced substituent and solvent effect (see Table 1). To better rationalize the factors that are effecting the lifetime of the *cis* isomer, we analyzed the kinetic data of the para-substituted compounds 1a–c,e,f,h–k via the Hammett plots obtained in the different solvents (see Figure 3a and Supporting Information). A better fit in DMSO and DMSO–water can be obtained correcting the σ constant with the respective σ^+ value for 1a and σ^- value 1k, compensating for the more marked polar environment.⁴⁸ As an example, we report in Figure 3a the case of the Hammett plot obtained from the kinetic data in DMSO (for the other solvents we refer to the Supporting Information). The experimental data were fitted in two ways, giving rise to two different interpretations of the thermal mechanisms in action. In the first case scenario all data excluding 1a can be fitted by a line with a positive $\rho = 2.8$ (see the grey interpolation line in Figure 3a), consistent with a single mechanism followed by all the compounds, except for 1a. More interestingly, the R^2 value of the fit can be improved interpolating all the EDG-substituted compounds with a line with negative $\rho = -3.2$ (green line in Figure 3) and all the others with one with $\rho = +3.5$ (orange line). This can be attributed to a smooth transition in the thermal *cis* → *trans* mechanism going from EDG to EWG. The same considerations can be drawn for the DMSO–water case. In toluene, the competition between two distinct mechanisms can be clearly observed in the Hammett plot, while methanol follows the first hypothesis, with 1a showing fast thermal back-isomerization and being an exception in the trend (see Supporting Information).

The magnitude of the substituent effects on the thermal isomerization rate mirrors the nature of the solvent.⁴⁹ Studying the slope of the line fitting the EWG and electron neutral groups a trend emerges: for toluene $\rho = +1.0$, in DMSO $\rho =$

Figure 3. (A) Hammett plot obtained from the experimental kinetic k of thermal $cis \rightarrow trans$ isomerization of compounds **1a–c,e,f,h–k** in DMSO. (B) Hammett plot obtained from the computed kinetic k hypothesizing an inversion thermal $cis \rightarrow trans$ isomerization mechanism. The data are obtained as a Boltzmann average of the 3- and 5-azopyrazole forms in different conformations and configurations (the latter for the transition states) at the SMD- ω B97X-D/TZVP level of theory.

+3.5, in DMSO–water diminishes to $\rho = +2.1$ further decreasing to $\rho = +1.0$ in MeOH. It is possible that the polar aprotic DMSO is able to interact with the solute as a hydrogen bond acceptor (the solvatochromic parameter for the hydrogen acceptance $\beta = 0.76$, while the one for hydrogen donation $\alpha = 0.0$),⁴⁹ possibly at the pyrazole NH,³³ intensifying the substituent effects compared to the apolar aprotic toluene ($\alpha = 0.0$, $\beta = 0.11$). The effect plummets in DMSO–water ($\alpha = 0.32$, $\beta = 0.66$), where the hydrogen bond acceptance is counterbalanced by the hydrogen bond donating capability of the protic mixture. Following this trend, the polar protic MeOH ($\alpha = 1.0$, $\beta = 0.7$) has an effect comparable to toluene on the substituent effects. The role of hydrogen bonding on the rate of isomerization and substituent effects is known for the 4-arylazo-1H-pyrazoles.³³ On the other hand, the polarity of the medium influences the overall thermal rate of the switches (see Table 1), with the notable exclusion of **1a**, that increases its rate with the proticity of the solvent. Hence, less polar solvents lead to an increased isomerization rate with DMSO–water and DMSO (with polarizability term $\pi^* = 1.05$ and 0.98, respectively) followed by MeOH ($\pi^* = 0.6$) and toluene ($\pi^* = 0.54$).⁴⁹

To better understand the mechanisms involved in the isomerization mechanisms of the 3(5)-arylazo-1H-pyrazoles, we performed a thorough computational analysis of the thermal pathways of compounds **1a–c,e,f,h–k** at the SMD- ω B97X-D/TZVP level of theory. Both the 3- and the 5-pyrazole tautomers were investigated separately (see Chart 2). Following the literature, we focused our analysis on the so-called inversion pathway that is preferred in the azopyrazole

class known in the literature.^{22,25} Different conformations were evaluated and, respectively, dubbed conformer A and B (see Chart 2). For every conformer, the *trans* and *cis* forms and two transition state geometries (TS I and TS II) were found: Chart 2 exemplifies this workflow showing the stationary points of conformer B. All the energies were Boltzmann averaged, to obtain a single value of computed kinetic k for each tautomer in every solvent. The average energies of both *cis* and *trans* isomers of a tautomer were Boltzmann averaged a second time with the one of the second tautomer to obtain the percentage of 3- and 5- isomer present in a certain solvent (toluene, MeOH, DMSO, and DMSO–water 1:1). Finally, these values were used to weigh the kinetic barriers obtained for the single tautomers, associating a single k to each compound. The results can be found in Chart 2, Figure 3b, and in Supporting Information.

It appears that the pyrazole can be found mostly in its 3-arylazo-1H form in more polar solvents. This trend is reverted partially for the *trans* and more significantly for the *cis* in toluene. The reason can be attributed to a stabilizing interaction between the NH and the azo group that is more prominent in apolar solvents.

The computational kinetic data can be fitted to a Hammett plot and compared to the experimental ones, as depicted in Figure 3. Similar to the experimental results, the NH₂ group is the outlier of a series that can be otherwise interpolated with a linear fit with positive ρ . The explanation for this tendency can be obtained paying a closer look to the charges on TS II. This structure is the transition state lower in energy among the two considered and consequently the one that contributes the most to the average kinetic barrier in each conformer. In this form, a partial negative charge forms on the benzylic nitrogen of the azo group. Consequently, the EWGs on the phenyl will stabilize it, granting a lower activation barrier.⁵⁰ Hence, the Mulliken charges of the benzylic N diminish with the presence of more electron withdrawing substituents (see Chart 2). Following these considerations, it is safe to assume that the main isomerization pathway experimentally encountered when an EWG (or the electron neutral group) is present is the inversion.²²

A more complicated scenario unveils in the presence of EDGs. It is possible that these groups could force a push–pull interaction with the otherwise electron-rich pyrazole, unlocking a rotational isomerization pathway (Scheme 4a).⁹ On the other hand, the increase in the thermal isomerization rate for **1a** in protic media can be explained with the formation of a hydrazone tautomer, with proton exchange between the NH₂ and the azo group (Scheme 4b).⁹ As predicted by our previous work,²² this isomerism is not originated from the migration of the pyrazolic NH, but it is triggered by the presence of a substituent bearing an acidic proton such as NH₂ in **1a**. Acetylation of **1a** diminishes the electron-donating character of the substituent⁴⁸ slowing the *cis* $\rightarrow$ *trans* thermal isomerization in MeOH (with a half-life of ca. 140 h, see Supporting Information). Although this finding can be considered counterintuitive because of the higher acidity of the N–H proton of an amide compared to the one of an amine, the hydrazone tautomer that could be formed from this compound would benefit less from the stabilization of the quinoidal form offered by the unsubstituted –NH group (see Scheme 4b).

It is possible, however, that more than one thermal mechanism is present at the same time, a situation especially feasible for DMSO and DMSO–water, where a smoother

Chart 2. Computational workflow for the determination of the thermal *cis* → *trans* isomerization barriers. The percentage of 3-arylazo-1*H*-pyrazole in its *trans* and *cis* form, along with the Mulliken charges on the benzylic nitrogen of the TS II of conformer B of each tautomer are given.

Scheme 4. Alternative Pathways to the Thermal *cis* → *trans* Inversion Mechanism

transition between the fits with opposite ρ s in the Hammett plot can be found.

Photoswitching in a Cell Medium. Envisioning a possible application of this class of photoswitches in photopharmacology, we tested the isomerization properties of compound **1e** in a synthetic cell culture medium (Dulbecco's modified Eagle's medium, stabilized with 1 mM Pyruvate 50 μ g/mL penicillin and 50 μ g/mL streptomycin). To our delight, we could isomerize the azo pyrazole using a 365 nm wavelength and back with a wavelength of 455 nm, cycling the isomerization multiple times (see Supporting Information). The $\Phi_{\pi\pi^*}$ quantum yield of the process halved to 0.024

compared to 0.055 found in DMSO, while the half-life decreased to 31 h, too. We tested the stability of **1e** to glutathione in the same conditions for ca. 16 h. Interestingly, we could detect only a minimal decrease in absorption (<5%, see Supporting Information). This result is in line with the reported stability of azopyrazole in the presence of high concentrations of glutathione.³²

CONCLUSIONS

In this work the photochromism of 3(5)-arylazo-1*H*-pyrazoles was investigated in detail, considering both the photochemical and the thermal pathways connecting its stable *trans* to the corresponding metastable *cis* form. A rationalization of the parameters governing the isomerization mechanisms is given according to the observed substituent and solvent effects, disclosing a class of photoswitches that can be almost quantitatively switched in both directions. The presence of the free NH proton on the pyrazole and the possibility to photochemically trigger the isomerization in the cell medium represent an added value to this structure and could foster its application in the emerging field of photopharmacology.^{51,52}

EXPERIMENTAL SECTION

General Information. Commercial reagents and starting materials were purchased from the commercial suppliers abcr, Acros Organics, Alfa Aesar, Fisher Scientific, Merck, Sigma Aldrich, TCI, or VWR and used without any further purification. Solvents were used in p.a. quality and dried according to common procedures, if necessary. Dry nitrogen was used as an inert gas atmosphere. Flash column chromatography was performed using Sigma-Aldrich MN silica gel 60 M (40–63 μ m, 230–400 mesh) for normal phase chromatography.

Reaction monitoring via thin layer chromatography was performed on alumina plates coated with silica gel (Merck silica gel 60 F₂₅₄, layer thickness 0.2 mm). Melting points were determined using a Stanford Research System OptiMelt MPA 100 and are uncorrected. NMR spectra were measured on a Bruker AVANCE 300 (¹H 300.13 MHz, ¹³C 75.48 MHz) and a Bruker AVANCE III HD 400 (¹H 400.13 MHz, ¹³C 100.61 MHz). The spectra are referenced against the NMR solvent (DMSO-*d*₆: $\delta_{\text{H}} = 2.50$ ppm, $\delta_{\text{C}} = 39.52$ ppm) and chemical shifts δ are reported in ppm. Resonance multiplicity is abbreviated as: s (singlet), d (doublet), t (triplet), and m (multiplet). Carbon NMR signals are assigned using DEPT 135 and ¹H–¹³C HSQC spectra with (+) for primary/tertiary, (–) for secondary, and (q) for quaternary carbons. Mass spectra were recorded on a Finnigan MAT-SSQ 710 A, ThermoQuest Finnigan TSQ 7000, Agilent Q-TOF 6540 UHD, or a JEOL AccuTOF GCX instrument. UV–vis absorption spectroscopy was performed in 10 mm quartz cuvettes using an Agilent 8543, Agilent Cary 100, or Agilent Varian Cary 50 spectrometer. For temperature control, a Varian Cary Single cell Peltier apparatus was used. To measure the quantum yields, irradiation was carried out in a 90° angle with respect to the UV–vis recording. Light sources for irradiation: $\lambda = 365$ nm (Seoul Viosys CUN6GB1A, 1000 mA, 1.4 W), $\lambda = 405$ nm (Nichia NVSU233A SMD-LED UV, 1000 mA, 1.4 W), $\lambda = 455$ nm (Osram OSLOM SSL 80 LD-CQ7P-1U3U, 1000 mA, 0.45 W), $\lambda = 505$ nm (Osram OSLOM SSL 80 LVCK7P-JYKZ, 800 mA, 163 lm), and $\lambda = 528$ nm (Osram LTC7P-KXKZ, 350 mA, 71 lm). The power of the light is given based on the specifications supplied by the company when the LEDs were purchased. Light sources used for PSS determination via online NMR spectroscopy under constant irradiation: $\lambda = 365$ nm (LEUVA66; operated at 1000–1500 mA); $\lambda = 450$ nm (Oslo SSL80; operated at 1000 mA); $\lambda = 405$ nm (Nichia NVSU233 B; operated at 1400 mA); and $\lambda = 500$ nm (Nichia NCSE119 A; operated at 700 mA).⁵³

Laser-Flash Photolysis. The laser pulse photolysis apparatus consisted of a Flash Lamp pumped Q-switched SpotLight-100 Nd:YAG laser from InnoLas, used at the third harmonic of its fundamental wavelength. It delivered a maximum power of 10 mJ at 355 nm with a 6 ns pulse duration. The LP920-K monitor system (supplied by Edinburgh Instruments), arranged in a cross-beam configuration, consisted of a high-intensity 450 W ozone-free Xe arc lamp (operating both in pulsed and in the continuous wave), a Czerny–Turner with Triple Grating Turret monochromator, and a five-stage dynode photomultiplier. The signals were captured by means of a Tektronix TDS 3012C digital phosphor oscilloscope, and the data was processed with L900 software supplied by Edinburgh Instruments. The solutions to be analyzed were placed in a fluorescence cuvette ($d = 10$ mm).

General Procedure: Baeyer–Mills Reaction. The respective arylamines **2b**, **2c**, and **2e–k** (1.0 equiv) were dissolved in CH₂Cl₂ (10 mL/mmol amine) under an inert gas atmosphere and a solution of oxone (1.0 equiv) in water (10 mL/mmol amine) was added. The biphasic reaction mixture was stirred at room temperature for 3 h. The organic phase was separated, dried, and the solvent evaporated. The crude nitroso derivatives **3b**, **3c**, and **3e–k** were used in the next reaction step without further purification. The nitroso derivatives were dissolved in a mixture of acetic acid (10 mL/mmol nitroso) and CH₂Cl₂ (10 mL/mmol nitroso) and 3-amino-pyrazole (**4**; 1.0 equiv) was added and the reaction stirred at room temperature for 16 h. After removal of the solvent, the product was purified by flash column chromatography using CH₂Cl₂ + 5% MeOH as an eluent.

(E)-3-((4-Methoxyphenyl)diazonyl)-1H-pyrazole (1b). Compound **1b** (1.6 mmol, 0.33 g) was synthesized as a brown solid in 20% yield following the general procedure for Baeyer–Mills reaction starting from *para* methoxy aniline **2b** (8.1 mmol, 1.0 g). mp 143–144 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.36 (s, 1H), 7.87–7.81 (m, 3H), 7.14–7.10 (m, 2H), 6.52 (d, $J = 2.5$ Hz, 1H), 3.86 (s, 3H). ¹³C{¹H} NMR (101 MHz, DMSO-*d*₆): δ 162.2 (q), 146.8 (q), 124.7 (+), 115.1 (+), 56.1 (+). HRMS (ESI): calcd for (C₁₀H₁₁N₄O⁺) [M + H]⁺ m/z : 203.0927; found, 203.0930.

(E)-3-(*p*-Tolyldiazonyl)-1H-pyrazole (1c). The compound **1c** (2.1 mmol, 0.39 g) was synthesized as a yellow solid in 48% yield following

the general procedure for Baeyer–Mills reaction starting from *para* methyl nitrosobenzene **3c** (4.4 mmol, 0.53 g) mp 157–158 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.42 (s, 1H), 7.89–7.82 (m, 1H), 7.77–7.74 (m, 2H), 7.39–7.36 (m, 2H), 6.53 (t, $J = 2.2$ Hz, 1H), 2.39 (s, 3H). ¹³C{¹H} NMR (101 MHz, DMSO-*d*₆): δ 152.6 (q), 131.7 (+), 131.2 (+), 129.9 (+), 122.7 (+), 94.2 (+). HRMS (ESI): calcd for (C₁₀H₁₁N₄⁺) [M + H]⁺ m/z : 187.0978; found, 187.0978.

(E)-3-(Phenylidiazonyl)-1H-pyrazole (1e). Compound **1e** (2.6 mmol, 0.45 g) was synthesized as a yellow solid in 87% yield following the general procedure for Baeyer–Mills using nitrosobenzene **3e** (3.0 mmol, 0.32 g). mp: 126–127 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.49 (s, 1H), 7.88–7.83 (m, 3H), 7.60–7.52 (m, 3H), 6.58 (d, $J = 2.5$ Hz, 1H). ¹³C{¹H} NMR (101 MHz, DMSO-*d*₆): δ 152.6 (q), 131.7 (+), 131.2 (+), 129.9 (+), 122.7 (+), 94.2 (+). HRMS (ESI): calcd for (C₉H₉N₄⁺) [M + H]⁺ m/z : 173.0822; found, 173.0823.

(E)-3-((4-Bromophenyl)diazonyl)-1H-pyrazole (1f). The compound **1f** (3.8 mmol, 0.95 g) was synthesized as a yellow solid in 65% yield following the general procedure for Baeyer–Mills reaction starting from *para* bromo aniline **2f** (5.8 mmol, 1.0 g). mp 151–152 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.54 (s, 1H), 7.89 (t, $J = 2.0$ Hz, 1H), 7.79 (s, 4H), 6.56 (t, $J = 2.1$ Hz, 1H). ¹³C{¹H} NMR (101 MHz, DMSO-*d*₆): δ 151.5 (q), 133.0 (+), 125.0 (q), 124.6 (+). HRMS (ESI): calcd for (C₉H₈BrN₄⁺) [M + H]⁺ m/z : 250.9927; found, 250.9928.

(E)-3-((2-Fluorophenyl)diazonyl)-1H-pyrazole (1g). Compound **1g** (0.18 mmol, 33.4 mg) was synthesized as a brown solid in 8% yield following the general procedure for Baeyer–Mills reaction starting from *ortho* fluoro aniline **2g**. mp 103–104 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.56 (s, 1H), 7.89 (dd, $J = 2.6, 1.5$ Hz, 1H), 7.71 (td, $J = 7.9, 1.8$ Hz, 1H), 7.59 (s, 1H), 7.51–7.44 (m, 1H), 7.34 (td, $J = 7.7, 1.3$ Hz, 1H), 6.55 (t, $J = 2.2$ Hz, 1H). ¹³C{¹H} NMR (101 MHz, DMSO-*d*₆): δ 164.6 (q), 159.5 (d, $J = 255.2$ Hz) (q), 140.5 (d, $J = 6.9$ Hz) (q), 133.6 (d, $J = 8.4$ Hz) (+), 131.3 (+), 125.5 (d, $J = 3.7$ Hz) (+), 117.9 (+), 117.7 (d, $J = 19.6$ Hz) (+), 94.1 (+). HRMS (ESI): calcd for (C₉H₈FN₄⁺) [M + H]⁺ m/z : 191.0728; found, 191.0730.

(E)-4-((1H-Pyrazol-3-yl)benzoic Acid) (1h). Compound **1h** (3.9 mmol, 0.84 g) was synthesized as an orange solid in 53% yield following the general procedure for Baeyer–Mills reaction starting from *para* carboxy aniline **2h** (7.3 mmol, 1.0 g). mp 270–271 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ 13.48 (s, 2H), 8.15–8.09 (m, 2H), 7.95–7.87 (m, 3H), 6.61 (d, $J = 2.5$ Hz, 1H). ¹³C{¹H} NMR (75 MHz, DMSO-*d*₆): δ 166.6 (q), 154.5 (q), 132.4 (q), 130.5 (+), 122.2 (+). HRMS (ESI): calcd for (C₁₀H₉N₄O₂⁺) [M + H]⁺ m/z : 217.0720; found, 217.0719.

Ethyl (E)-4-((1H-Pyrazol-3-yl)diazonyl)benzoate (1i). Compound **1i** (2.0 mmol, 0.49 g) was synthesized as a yellow solid in 67% yield following the general procedure for Baeyer–Mills reaction starting from *para* ethylbenzoate aniline **2i** (3.0 mmol, 0.50 g). mp 149–150 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ 13.65 (s, 1H), 8.16–8.12 (m, 2H), 7.96–7.92 (m, 2H), 7.91 (d, $J = 2.5$ Hz, 1H), 6.61 (d, $J = 2.5$ Hz, 1H), 4.34 (q, $J = 7.1$ Hz, 2H), 1.34 (t, $J = 7.1$ Hz, 3H). ¹³C{¹H} NMR (75 MHz, DMSO-*d*₆): δ 165.6 (q), 155.2 (q), 135.0 (q), 132.0 (q), 130.9 (+), 122.9 (+), 94.2 (q), 61.5 (–), 14.6 (+). HRMS (ESI): calcd for (C₁₂H₁₃N₄O₂⁺) [M + H]⁺ m/z : 245.1033; found, 245.1037.

(E)-1-(4-((1H-Pyrazol-3-yl)diazonyl)phenyl)ethan-1-one (1j). Compound **1j** (2.4 mmol, 0.52 g) was synthesized as an orange solid in 33% yield following the general procedure for Baeyer–Mills reaction starting from *para* acetyl aniline **2j** (7.4 mmol, 1.0 g). mp 127–128 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.62 (s, 1H), 8.15 (d, $J = 8.4$ Hz, 2H), 7.94 (d, $J = 8.4$ Hz, 2H), 7.90 (d, $J = 2.5$ Hz, 1H), 6.61 (d, $J = 2.5$ Hz, 1H), 2.64 (s, 3H). ¹³C{¹H} NMR (75 MHz, DMSO-*d*₆): δ 197.9 (q), 155.0 (q), 138.6 (q), 131.9 (q), 130.1 (+), 122.9 (+), 116.3 (q), 94.4 (q), 27.4 (+). HRMS (ESI): calcd for (C₁₁H₁₁N₄O⁺) [M + H]⁺ m/z : 215.0927; found, 215.0931.

(E)-3-((4-Nitrophenyl)diazonyl)-1H-pyrazole (1k). Compound **1k** (5.9 mmol, 1.3 g) was synthesized as an orange solid in 82% yield following the general procedure for Baeyer–Mills reaction starting from *para* nitro aniline **2k** (7.2 mmol, 1.0 g). mp 200–201 °C. ¹H

NMR (300 MHz, DMSO- d_6): δ 13.72 (s, 1H), 8.42–8.37 (m, 2H), 8.04–7.99 (m, 2H), 7.93 (d, J = 2.5 Hz, 1H), 6.63 (s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, DMSO- d_6): δ 163.9 (q), 155.3 (q), 148.1 (q), 131.0 (+), 124.9 (+), 123.1 (+), 93.9 (+). HRMS (ESI): calcd for ($\text{C}_9\text{H}_8\text{N}_2\text{O}_2$) $^+$ [$\text{M} + \text{H}$] $^+$ m/z : 218.0672; found, 218.0674.

(E)-4-((1H-Pyrazol-5-yl)diazene)aniline (**1a**). Compound **1a** (2.1 mmol, 0.40 g) was synthesized via an adapted literature reported procedure as an orange solid in 93% yield via reduction of its nitro-substituted precursor **1k** (2.3 mmol, 0.50 g) using sodium sulfide.⁴⁰ mp 184–185 °C. ^1H NMR (400 MHz, DMSO- d_6): δ 13.10 (s, 1H), 7.75 (s, 1H), 7.62–7.58 (m, 2H), 6.67–6.63 (m, 2H), 6.41 (s, 1H), 6.01 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6): δ 153.0 (q), 143.3 (q), 130.4 (+), 130.4 (q), 125.2 (+), 113.8 (+), 93.3 (+). HRMS (ESI): calcd for ($\text{C}_9\text{H}_{10}\text{N}_5$) $^+$ [$\text{M} + \text{H}$] $^+$ m/z : 188.0931; found, 188.0929.

(E)-1,2-Di(1H-pyrazol-5-yl)diazene (**1d**). Compound **1d** (2.1 mmol, 0.34 g) was synthesized via a procedure reported in the literature as a brown solid in 35% yield starting from **4** (6.0 mmol, 0.50 g).³⁶ mp decomposition over 300 °C. ^1H NMR (400 MHz, DMSO- d_6): δ 13.42 (s, 2H), 7.84 (s, 2H), 6.54 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6): δ 164.5 (q), 131.1 (+), 93.8 (+). HRMS (ESI): calcd for ($\text{C}_6\text{H}_7\text{N}_6$) $^+$ [$\text{M} + \text{H}$] $^+$ m/z : 163.0727; found, 163.0727.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.9b03097>.

NMR spectra, UV–vis absorption spectra, cycle performances, thermal half-lives, PSS determination, Hammet plots, switching experiments in a cell medium, and computational analysis and acetylation of **1a** (PDF)

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Notes

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