Synthesis and Photophysical Characterization of Azoheteroarenes

Citation for the original published paper (version of record):
Synthesis and Photophysical Characterization of Azoheteroarenes
Organic Letters, 20(16): 4875-4879
http://dx.doi.org/10.1021/acs.orglett.8b02014

N.B. When citing this work, cite the original published paper.
Synthesis and Photophysical Characterization of Azoheteroarenes

Yongjin Xu,† Chunxia Gao,† Joakim Andréasson,*‡ and Morten Grøtli,*†

†Department of Chemistry and Molecular Biology, University of Gothenburg, SE-412 96 Gothenburg, Sweden
‡Department of Chemistry and Chemical Engineering, Physical Chemistry, Chalmers University of Technology, SE-412 96 Gothenburg, Sweden

Supporting Information

ABSTRACT: A set of azoheteroarenes have been synthesized with Buchwald–Hartwig coupling and microwave-assisted O2 oxidation as the key steps. Several compounds exhibit good to excellent photoswitching properties (high switching efficiency, good fatigue resistance, and thermal stability of Z-isomer) relevant for photocontrolled applications, which pave the way for use in photopharmacology.

Photoswitches have long held the interest of the scientific community for their ability to alter molecular structure, and thus properties, using light as a stimulus.1–5 By introducing photoswitches into bioactive molecules, their biological activities can be switched on or off upon photoisomerization between the implicated isomeric forms.6,7 In this way, photocontrolled regulators of ion channels,8 enzymes,9 receptors,10 as well as living organisms11 have been developed. Such photoresponsive molecules are powerful tools for studying living systems as they are noninvasive and offer a high spatiotemporal resolution.11–14 Azobenzene-based molecular photoswitches (Scheme 1a) have been extensively used in such developments.15 Potential future applications of this class of photoswitches include also optically controlled (bio-) materials and information/data processing to mention a few.16 Of particular interest for the latter are compounds displaying very fast thermal Z → E isomerization, allowing for ultrafast data transmission.17

Nitrogen heterocycles are among the most significant structural components of pharmaceuticals.18 Therefore, in order to integrate the azobenzene-based molecular photoswitches into the pharmacophore of small drug-like molecules, e.g., kinase inhibitors, the development of heterocyclic azobenzene derivatives are fundamental.

Despite this fact, only a small portion of all heterocycles have been used in photoswitchable heterocyclic azoswitches. Some heterocyclic azo compounds have been well-studied,19–29 while others have been reported without mentioning photophysics/photochemistry.30,31 The classic strategies for synthesizing azobenzenes include the Azo-coupling reaction, Mills reaction, as well as metal-catalyzed coupling accompanied by oxidation.32 An efficient synthesis of red-shifted azo-benzenes was recently introduced by the coupling between ortho-lithiated aromatic precursors and aryldiazonium salts.4 In regard to heterocyclic azobenzene derivatives, a phenyl-azoimidazole,19 azoheteroarenes with methylated five-membered heterocyclic rings,19,28 including imidazoles,21 have been reported using diazonium couplings.

Herein, we report on the synthesis and the photophysical characterization of a series of azoheteroarenes, with Buchwald–Hartwig coupling or nucleophilic substitution, followed by O2 oxidation as the key synthetic steps in the preparation of the target compounds (Scheme 1b).

Pyridine and indole are among the most common aromatic heterocycles in kinase inhibitors. Therefore, we opted for the preparation of pyridine and indole-based azaanalogues, including purine and quinazoline derivatives,33 to study how the aromatic heterocycles influence the ease of synthesis and photophysical properties of azoheteroarenes. All the selected

Scheme 1. Photoswitches: (a) Azobenzene Photoswitches and (b) Synthetic Strategy of Azoheteroarene Molecules
target compounds contain heterocycles that are found in reported kinase inhibitors (1a−1h; Table 1).

Bromoheterocycles 1a−1d (entries 1−3; Scheme 1) were initially tested out using Buchwald−Hartwig conditions.34 Both 1a, 1b, and 1d substrates gave the target coupling products 2a, 2b, and 3d in good yields. However, 1c underwent significant reduction of the aryl halide by β-elimination35 during the coupling,36 and only a low yield of 2c was obtained.

However, when 1e was submitted to this condition, no product formation was observed. This was probably because the secondary amine in the heterocycle interfered with the deprotection and oxidation combined. Therefore, we decided to block the function of the secondary amine with an appropriate protecting group. The Boc group could be installed on 5-bromoindole efficiently, but the Boc group was cleaved under the coupling conditions. Instead, we turned to tosyl, and 1e-2, 1f-2, 1g-2, and 1h-2 could be obtained in good to excellent yields (see Supporting Information (SI)).37 When 1f-2 and 1g-2 (entries 6 and 7, Table 1) were treated under standard Buchwald−Hartwig coupling conditions, 2e−2g were obtained in good yield (above 80%). However, the tosyl group on 1h-2 was unstable under these conditions. Compound 1h was therefore protected with THP38 to give 1h-3 (entry 8, Table 1) and then subjected to the coupling condition to generate 2h in 42% isolated yield (data not shown). When XPhos was employed as the ligand instead of t-Bu3P-HBF4, the reaction completed and provided coupling product 3h with a yield of 54%.

Inspired by work from the groups of Szymanski and Feringa,22 we aimed at forming the azo bond with a "one-pot, two-steps strategy", more specifically, removing the Boc group by microwave-assisted heating (above 150 °C)39 and then oxidizing the hydrazine to give azo products with O2. Several rounds of optimization resulted in a protocol giving generally excellent yields (Table 1).

The tosyl group on 3e−3g could be removed by Cs2CO3 to give the corresponding heterocyclic azoarenes (5e−5g; see SI) with a yield above 80%. The THP group on 3h was deprotected by 4 M HCl in dioxane39 to provide 5h in 74% yield.

Applying our developed Pd-mediated coupling strategy to 6-Cl-9H-purine (1i) and 4-Cl-quinazoline (1j) gave no detectable coupling products (see SI). Therefore, we turned to take nucleophilic substitution as the key step.11−44 Compound 1i in n-BuOH, under an N2 atmosphere, was treated with phenylhydrazine in the presence of DIPEA, using microwave heating (150 °C, 2 h)32 followed by O2 treatment to form the azo compound 6 (see SI) in 65% yield. When 1j was treated with the same condition, no target product was detected by LC−MS or 1H NMR. However, when changing from n-BuOH to i-PrOH as solvent40 and heating at a lower temperature (MW 60 °C, 30 min), followed by the O2 treatment, 8 was obtained in moderate yield (23%; see SI).

The photophysical properties of 3a−8 were then characterized. The experimental results are shown only for 5e (Figure 1a, see SI for "enlarged" versions of all absorption spectra), whereas the evaluated photophysical parameters for the whole series are collected in Table 2. Water/DMSO has been used as solvent. When the heterocyclic azo-switches get integrated with pharamacophores, water solubility could increase, thereby excluding or minimizing the need of DMSO as cosolvent.

The initial absorption spectra, ascribed to 100% E-isomer, were recorded after thermal adaption at 50 °C for 72 h. The absorption maxima of the π→π* transition for the respective compounds are observed at λ between 317 and 387 nm, whereas the n→π* transitions at longer wavelengths are very weak and barely seen in the absorption spectra. There is a clear trend for the π→π* transition to redshift with increasing size of the heterocycle. Leaving aside the protected compounds (3e−3h) the monocyclic compounds display absorption maxima between 317 and 328 nm, the bicyclic between 325 and 362 nm, and the tricyclic at 387 nm.

Introduction of the electron-withdrawing tosyl group results in a blue shift of the absorption maxima (cf. 3e−3g and 5e−5g) as well as significant hyperchromism (see absorption

Table 1. Synthesis of Azoheteroarenes by Buchwald–Hartwig Coupling and Oxidation

<table>
<thead>
<tr>
<th>entry</th>
<th>substrates</th>
<th>2, yield (%)</th>
<th>3, yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a, 75%</td>
<td>3a, 85%</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2b, 73%</td>
<td>3b, 90%</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2c, 18%</td>
<td>3c, 81%</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>2d, 65%</td>
<td>3d, 74%</td>
</tr>
<tr>
<td>5</td>
<td>1e-1: PG = Boc</td>
<td>2e: PG = Tos</td>
<td>3e: PG = Tos</td>
</tr>
<tr>
<td>6</td>
<td>1f-1: PG = Boc</td>
<td>2f: PG = Tos</td>
<td>3f: PG = Tos</td>
</tr>
<tr>
<td>7</td>
<td>1g-1: PG = Boc</td>
<td>2g: PG = Tos</td>
<td>3g: PG = Tos</td>
</tr>
<tr>
<td>8</td>
<td>1h-1: PG = Boc</td>
<td>2h: PG = THP</td>
<td>3h: PG = THP</td>
</tr>
</tbody>
</table>

a Using MW at 110 °C, the reaction was completed in 1.5 h. b Boc deprotection and oxidation combined. c XPhos was used as ligand. d MW, 200 °C, 30 min. e MW, 180 °C, 1 h, then 200 °C, 8 min. f MW, 160 °C, 2 h, then 180 °C, 30 min.
spectra in the SI). Electron donation from a THP group (cf. 3h and 5h) also results in hyperchromism but has no effect on the spectral position. The spectral shifts are supported by quantum mechanical (DFT) calculations (see SI). Subsequent exposure to UV light resulted in an increased absorption of the $\pi \rightarrow \pi^*$ transition at the expense of the $\pi \rightarrow \pi^*$ transition. All processes proceeded with isosbestic points, which implies clean conversion between the two implicated isomers. The wavelengths of the absorption maxima in the $\pi \rightarrow \pi^*$ region are collected in Table 2, together with the isomerization kinetics and the photostationary distribution (PSD). Although no attempts were made toward determining the isomerization quantum yields, it is seen that the $E \rightarrow Z$ isomerizations readily proceed at the modest light intensities used in the experiments ($2$–$4$ mW/cm$^2$). At the PSD, samples $3a$–$5g$ are enriched in the $Z$-form to between ca. $60\%$ and almost full conversion. Compounds $5h$ and $8$ showed no detectable isomerization (see below), while the thermal reversion for $6$ was too fast to allow for the determination of any reliable value.

Note that the PSDs were assessed in pure DMSO (Figure 1b) as opposed to water/DMSO. The values should, however, be similar for the two solvent systems (Figure S39).

Table 2. Photophysical Properties

<table>
<thead>
<tr>
<th>Compounds</th>
<th>DMSO (% in water)</th>
<th>$\lambda_{max} \ E (nm)^a$</th>
<th>$\lambda_{max} \ n\rightarrow\pi^* \ after \ UV^b$</th>
<th>$\lambda_{max} \ Z \rightarrow E (nm)^c$</th>
<th>PSD$^d$</th>
<th>$\tau \ (s)^e$</th>
<th>thermal stability$^f$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>1</td>
<td>318</td>
<td>426</td>
<td>365, 405</td>
<td>0.58, 0.15</td>
<td>107, 44</td>
<td>3%</td>
</tr>
<tr>
<td>3b</td>
<td>1</td>
<td>317</td>
<td>426</td>
<td>365, 405</td>
<td>0.59, 0.12</td>
<td>169, 47</td>
<td>4%</td>
</tr>
<tr>
<td>3c</td>
<td>1</td>
<td>328</td>
<td>433</td>
<td>365, 460</td>
<td>0.81, 0.14</td>
<td>105, 54</td>
<td>46% ($\tau = 36 \ h$)</td>
</tr>
<tr>
<td>3d</td>
<td>10</td>
<td>336</td>
<td>432</td>
<td>365, 460</td>
<td>0.92, 0.21</td>
<td>58, 36</td>
<td>8%</td>
</tr>
<tr>
<td>3e</td>
<td>50</td>
<td>338</td>
<td>431</td>
<td>365, 460</td>
<td>0.96, 0.27</td>
<td>37, 35</td>
<td>5%</td>
</tr>
<tr>
<td>3f</td>
<td>50</td>
<td>335</td>
<td>430</td>
<td>365, 460</td>
<td>0.95, 0.26</td>
<td>46, 39</td>
<td>2%</td>
</tr>
<tr>
<td>3g</td>
<td>100</td>
<td>351</td>
<td>435</td>
<td>365, 460</td>
<td>0.96, 0.28</td>
<td>25, 32</td>
<td>10%</td>
</tr>
<tr>
<td>3h</td>
<td>21</td>
<td>363</td>
<td>442</td>
<td>365, 460</td>
<td>0.89, 0.24</td>
<td>15, 26</td>
<td>66% ($\tau = 19 \ h$)</td>
</tr>
<tr>
<td>3i</td>
<td>5</td>
<td>355</td>
<td>433</td>
<td>365, 460</td>
<td>0.95, 0.33</td>
<td>24, 21</td>
<td>76% ($\tau = 3.0 \ h$)</td>
</tr>
<tr>
<td>3j</td>
<td>7.4</td>
<td>349</td>
<td>430</td>
<td>365, 460</td>
<td>0.96, 0.35</td>
<td>18, 26</td>
<td>4%</td>
</tr>
<tr>
<td>3k</td>
<td>33.3</td>
<td>387</td>
<td>435</td>
<td>405, 523</td>
<td>0.88, 0.21</td>
<td>15, 50</td>
<td>decomposition</td>
</tr>
<tr>
<td>3l</td>
<td>1</td>
<td>349</td>
<td>428</td>
<td>365, 460</td>
<td>-</td>
<td>39, 29</td>
<td>100% ($\tau = 1.8 \ min$)</td>
</tr>
<tr>
<td>3m</td>
<td>5</td>
<td>362</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>no isomerization was detected</td>
</tr>
<tr>
<td>3n</td>
<td>1</td>
<td>325</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$Wavelengths of the $\pi \rightarrow \pi^*$ transition of the $E$-isomer. $^b\lambda_{max}$ in the $n \rightarrow \pi^*$ region at the photostationary distribution (PSD) after UV irradiation.

$^c$Irradiation wavelengths used to enrich the samples in the $Z$- (longer wavelength light) and $E$-isomers (shorter wavelength light), respectively.

$^d$Photostationary distribution after photosomerization to enrich the samples in the $Z$- and $E$-isomers, respectively. Tabulated as the fraction of the $Z$-isomer. Determined in pure DMSO-$d_6$. $^e$Time constants for the photoisomerization reactions, normalized to a common light density ($365 \ nm: 2.5 \ mW/cm^2, 405 \ nm: 4.0 \ mW/cm^2, 460 \ nm: 3.0 \ mW/cm^2$). See SI for the original conditions used. $^f$Fraction of the sample isomerized in the thermal $Z \rightarrow E$ reaction over 24 h. When isomerization is substantial, the corresponding time constant of the reaction is given.
The majority of the compounds displays good thermal stability, as less than 10% is isomerized back to the E-form after 24 h in the dark. Exceptions are 3c, 3g, 3h, 5e, and 6 (Table 2). Compound 5g decomposes rapidly, tentatively ascribed to hydrolysis. With the exception of 6, these are the compounds with the lowest activation energies for thermal Z → E isomerization as estimated by DFT calculations assuming thermal isomerization through inversion (28,45) (see SI). The discrepancy for 6 is tentatively ascribed to a different isomerization mechanism, rotation rather than inversion, as 6 together with 8 in the Z-form display the largest twisting angles between the plane of the heterocycle and the N–N double bond (see SI).

Compounds 5h and 8 were subjected to ns transient absorption measurements. After the excitation pulse at 355 or 410 nm, the ground-state bleach recovery in the π → π* region was monitored and found to contain no detectable transients. Thus, the only thing we can conclude is that if the absence of detectable Z-isomers is due to thermal isomerization Z → E it must be faster than the time resolution of the experiment, i.e., a few nanoseconds.

The photoinduced Z → E isomerizations were studied by exposing the samples enriched in the Z-form to light in the visible region, yielding PSD containing between 65% and 88% of the E-isomer. The rates at which the isomerizations occur show efficient isomerization already at moderate light intensities (1–4 mW/cm²). Except for 3f, no significant photodecomposition was observed upon photocycling (Figures S15–S26).

In conclusion, we have synthesized a set of azoheteroarenes mainly with a strategy using Buchwald–Hartwig coupling and O₂ oxidation as the key steps and commercially available heterocyclic halogen as the starting substrates. The majority of the compounds can be enriched in the Z-isomer to more than 90% using light at 365 or 405 nm, whereas the reverse photoisomerization yields between 65% and 85% E-isomer at the photostationary state using longer wavelength of light. The thermal stability of the Z-isomer ranges between minutes to months, and nearly all compounds have excellent photo-stability. The relatively easy availability by synthesis together with favorable photophysical properties make some of these compounds promising candidates for future application in photopharmacology, e.g., photoswitchable kinase inhibitors.

**REFERENCES**


(35) When 1c was stirred at 100 °C under microwave or normal heating, an isomer of 2c was obtained as 2c-2 (see S1); when this byproduct was heated at 120–150 °C, it converted back to 2c.

