Abstract: Among the methods used for the synthesis of functionalized heterocyclic compounds, photochemistry has gained immense popularity due to the reactivity of intermediates in photoinduced reactions. In this study, we report on the effect of diaryl disulfides as hydrogen atom transfer catalysts on the photoinduced transformations of pyrazolo[1,2-a]pyrazolones. After excitation with visible light, these compounds are susceptible to C–N bond cleavage, followed by intermolecular hydrogen atom abstraction. By modifying the reaction conditions, we have developed two novel methods for the synthesis of highly substituted pyrazoles.

Keywords: pyrazoles; photochemistry; hydrogen atom transfer; disulfides

1. Introduction

Pyrazoles belong to a group of five-membered heterocyclic organic compounds. They serve as important building blocks in medicinal substances and pesticides [1,2]. Many pharmacologically active compounds, exhibiting antitumor or anti-inflammatory effects, contain a pyrazole scaffold [3–5]. Among them, Crizotinib is already available on the market [6]. Numerous methodologies for the synthesis and derivatization of pyrazoles have been reported and they continue to be developed [7]. For instance, we recently disclosed a photoredox-catalyzed oxidation of N1-substituted pyrazolidin-3-ones to azomethine imines [8], as well as the photoinduced selective preparation of highly functionalized pyrazoles from pyrazolo[1,2-a]pyrazolones (Scheme 1) [9]. In this study, we focused on the C7–N8 homolytic bond cleavage of pyrazolo[1,2-a]pyrazolones, which occurs upon the irradiation of the substrates with a 400 nm light source. This process involves intramolecular hydrogen atom transfer (HAT), leading to the formation of an aldehyde functionality (Scheme 1, highlighted in red), which we confirmed through deuterium labeling [9].

Photoinduced reactions have become increasingly common for the preparation of heterocyclic compounds, as they enable specific radical pathways that are challenging to achieve with conventional methods [10]. Furthermore, they are generally regarded as more environmentally friendly, especially when no external photocatalyst is required [11,12]. In this study, we will focus on HAT reactions, which frequently occur in photoinduced reactions. These reactions typically take place in the presence of a HAT catalyst that facilitates a simultaneous transfer of a proton and an electron from the orbital of one molecule to another [13]. This unique mechanism of action allows for oxidations and reductions that would otherwise require a strong oxidizing or reducing agent (Scheme 2). Most HAT catalysts are sulfur-centered free radical compounds, typically prepared in situ from thiols or their oxidized forms, disulfides [14].
Herein we report a continuation of our study on the reactions of pyrazolo[1,2-\(a\)]pyrazolones 1 under light irradiation [9]. Specifically, we aimed to improve the method for the preparation of pyrazoles 2 by introducing a HAT catalyst to the reaction mixture, enabling the intermolecular HAT process to occur. As one of the most commonly used HAT catalysts, we selected thiophenols and diaryl disulfides. The irradiation of compound 2 with a photocatalyst that oxidizes a thiolate anion (\(e^-\)) or reduces a thiyl radical (\(H^+\)) facilitates a simultaneous transfer of a proton and an electron from the orbital of one molecule to another [13]. This unique mechanism of action allows for oxidations and reductions that would otherwise require a strong oxidizing or reducing agent [11,12]. In this study, we used thiophenol, with 4,4'-dichlorodiphenyl disulfide being the optimal catalyst (Table 1, entry 8), providing 3a as reported previously [9]. After 4 h of irradiation, a 24% NMR yield of 2a was determined (Table 1, entry 1). The addition of increasing amounts of thiophenol increased the reaction rate but led to the formation of 3a as the major product (Table 1, entries 2 and 3). Since the formation of this product has not been reported previously, we further optimized the reaction conditions for its preparation. Diaryl disulfides proved to be more efficient at catalyzing the reaction than thiophenol, with 4,4'-dichlorodiphenyl disulfide being the optimal catalyst (Table 1, entry 8), providing the highest yield of 3a with minimal formation of aldehyde 2a. With the optimal catalyst determined, the optimization of the solvent was carried out (Table 1, entries 8–12). Dichloromethane was identified as the optimal solvent for the formation of 3a. Under these optimized reaction conditions, the reaction was carried out on a 0.5 mmol scale with an extended reaction time to ensure complete conversion of the starting material. Compound 3a was subsequently isolated in 62% yield (see Section 3).
The starting material diphenyl disulfide to 1.2 equivalents led to the formation of thioester 4b as the major product of the reaction (Scheme 4).

A further increase in the amount of diphenyl disulfide to 1.2 equivalents resulted in the formation of thioester 4a as the major product, isolated with a 50% yield, while 3a was obtained as the minor product (Scheme 3).

When cycloadduct 1b was subjected to the optimized reaction conditions, only aldehyde 2b was formed, while compound 3b was not detected in the reaction mixture (Scheme 4). The starting material 1b was consumed in a significantly shorter time than in the absence of 4,4'-dichlorodiphenyl disulfide [9]. Increasing the amount of 4,4'-dichlorodiphenyl disulfide to 1.2 equivalents led to the formation of thioester 4b as the major product of the reaction (Scheme 4).

Table 1. Effect of reaction conditions on the photoinduced transformation of 1a in the presence of a HAT catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>HAT Catalyst (Equiv.)</th>
<th>2a (%) a</th>
<th>3a (%) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 b</td>
<td>DCM</td>
<td>/</td>
<td>24</td>
<td>/</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>PhSH (0.4)</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>DCM</td>
<td>PhSH (2.4)</td>
<td>4</td>
<td>38</td>
</tr>
<tr>
<td>4 b</td>
<td>DCM</td>
<td>(PhS)₂ (0.1)</td>
<td>24</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>DCM</td>
<td>(PhS)₂ (0.2)</td>
<td>17</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>DCM</td>
<td>(PhS)₂ (0.4)</td>
<td>14</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>DCM</td>
<td>(4-OMePhS)₂ (0.2)</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>8</td>
<td>DCM</td>
<td>(4-CIPhS)₂ (0.2)</td>
<td>5</td>
<td>58 [62] c</td>
</tr>
<tr>
<td>9 b</td>
<td>MeCN</td>
<td>(4-CIPhS)₂ (0.2)</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td>acetone</td>
<td>(4-CIPhS)₂ (0.2)</td>
<td>4</td>
<td>53</td>
</tr>
<tr>
<td>11 b</td>
<td>MeOH</td>
<td>(4-CIPhS)₂ (0.2)</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>12 b</td>
<td>DMSO</td>
<td>(4-CIPhS)₂ (0.2)</td>
<td>6</td>
<td>13</td>
</tr>
</tbody>
</table>

Standard reaction conditions: 1a (0.1 mmol), solvent (anhydrous, degassed, 2.5 mL), LED₄₅₀ nm, 25 °C, 4 h. a ¹H NMR yields were determined with 1,3,5-trimethoxybenzene as an internal standard. b Starting compound 1a was not entirely consumed. c 1a (0.5 mmol), isolated yield.

Scheme 3. Irradiation of substrate 1a in the presence of an excess of diphenyl disulfide.

When cycloadduct 1b was subjected to the optimized reaction conditions, only aldehyde 2b was formed, while compound 3b was not detected in the reaction mixture (Scheme 4). The starting material 1b was consumed in a significantly shorter time than in the absence of 4,4'-dichlorodiphenyl disulfide [9]. Increasing the amount of 4,4'-dichlorodiphenyl disulfide to 1.2 equivalents led to the formation of thioester 4b as the major product of the reaction (Scheme 4).
Scheme 4. Effect of the amount of 4,4'-dichlorodiphenyl disulfide on the photoinduced transformation of 1b.

The proposed reaction mechanism for the formation of compounds 2–4 is depicted in Scheme 5. Diaryl disulfide dissociates under light to generate an arylthiyl radical [14]. Following the photoinduced homolytic cleavage of the N4–C5 bond of compound 1 to form a biradical A, the hydrogen atom is abstracted by a thiyl radical, resulting in the formation of thiol and a carbonyl radical B. The latter abstracts a hydrogen atom from the thiol to generate the final product 2. If a large amount of disulfide is present in the reaction mixture, the coupling of the thyl and carbonyl radical B results in the formation of thioester 4. In this case, the HAT catalytic cycle is not completed and an equimolar amount of diaryl disulfide is consumed. In the second pathway, the C7–N8 bond of compound 1 undergoes homolytic cleavage to generate a biradical C. This pathway predominates when it involves the formation of a tertiary C-centered radical as observed in compound 1a, rather than a primary C-centered radical as observed in compound 1b. The thiyl radical then abstracts a hydrogen atom from C to form intermediate D. Finally, the intermediate D abstracts a hydrogen atom from the thiol, resulting in the formation of the final product 3. It should be noted that the HAT process in biradical A can occur intramolecularly to form product 2, as demonstrated previously [9], while the formation of product 3 is only possible through an intermolecular HAT catalysis.

Scheme 5. Suggested mechanism for the photoinduced formation of compounds 2–4.
3. Materials and Methods

3.1. General Information

Reactions were carried out in vials of borosilicate glass in a custom-made photoreactor equipped with a cooling block. Vials were placed about 2 mm above the LEDs (ProLight Opto, PM2B-3-LBS-SD, blue, wavelength of peak intensity 445–455 nm, 39.8–51.7 lm) with no filter applied. The NMR spectra were recorded in deuterated solvents with Me$_4$Si as the internal standard on a Bruker Avance III UltraShield 500 plus instrument (Bruker, Billerica, MA, USA) at 500 MHz for $^1$H and at 126 MHz for $^{13}$C nuclei, respectively, or on a Bruker Ascend neo NMR 600 instrument (Bruker, Billerica, MA, USA) at 600 MHz for $^1$H and at 151 MHz for $^{13}$C nuclei, respectively. Data for $^1$H NMR are reported as chemical shifts ($\delta$) in ppm, multiplicity (bs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant, integration, and attribution information. Data for $^{13}$C are reported as chemical shift ($\delta$) in ppm. Mass spectra were recorded on an Agilent 6224 Accurate Mass TOF LC/MS spectrometer (Agilent Technologies, Santa Clara, CA, USA) and IR spectra on a Bruker FTIR Alpha Platinum spectrophotometer (Bruker, Billerica, MA, USA). Melting points were determined on a Kofler hot-stage microscope. Column chromatography (CC) was performed on silica gel (particle size: 35–70 µm, Sigma-Aldrich, St. Louis, MO, USA). Commercially available compounds were used without further purification. Compounds 1a and 1b were prepared according to the established procedures in the literature [9].

3.2. Synthesis

General procedure: An 8 mL vial was charged with 1 (0.5 mmol), the corresponding disulfide, and anhydrous DCM (2.5 mL) and sealed off with a screw cap with a septum. The solution was degassed using three freeze–pump–thaw cycles. The solution was illuminated under nitrogen atmosphere at 25 $^\circ$C with LED$_{450}$ nm for 4 h unless stated otherwise. The solvent was then removed under reduced pressure and products 2, 3 or 4 were isolated by column chromatography (EA/PE).

Methyl 3-(4-chlorophenyl)-1-(3-methylbutanoyl)-1H-pyrazole-4-carboxylate (3a). Prepared according to general procedure from 1a (161 mg, 0.5 mmol) and 4,4′-dichlorodiphenyl disulfide (29 mg, 0.2 equiv.); CC (EA/PE, 1:6; $R_F$ = 0.35); colorless oil; $\nu_{\text{max}}$/ cm$^{-1}$ (ATR) 2986w, 2938w, 1705s, 1439m, 1186m, 1103m, 1013m, 832m, 740s, 689m; $\delta_{^1}$H (500 MHz; CDCl$_3$; Me$_4$Si) 7.95 (s, 1H, 3-H), 7.43–7.37 (m, 5H, Ar), 7.36–7.31 (m, 2H, Me$_3$Si); $\delta_{^13}$C (126 MHz; CDCl$_3$; Me$_4$Si) 177.3, 162.7, 151.4, 135.5, 133.8, 133.8, 130.7, 129.6, 128.3, 115.2, 51.9, 42.4, 25.2, 22.5; HRMS (ESI) $m/z$ calculated for: C$_{16}$H$_{18}$ClN$_2$O$_3$ [MH]+: 321.1000; found: 321.0999.

Methyl 5-(4-chlorophenyl)-1-(2-methyl-4-oxo-4-(phenylthio)butan-2-yl)-1H-pyrazole-4-carboxylate (4a). Prepared according to general procedure from 1a (161 mg, 0.5 mmol) and diphenyl disulfide (131 mg, 1.2 equiv.); CC (EA/PE, 1:4; $R_F$ = 0.30); 107 mg (50%); colorless oil; $\nu_{\text{max}}$/ cm$^{-1}$ (ATR) 2986w, 2948w, 1439m, 1392m, 1355m, 1339m, 1301m, 1283m, 1186m, 1103m, 832m, 740s, 689m; $\delta_{^1}$H (600 MHz; CDCl$_3$; Me$_4$Si) 7.95 (s, 1H, 3-H), 7.43–7.37 (m, 5H, Ar), 7.36–7.31 (m, 2H, Ar), 7.28–7.25 (m, 2H, Ar), 3.62 (s, 3H, CO$_2$Me), 3.25 (s, 2H, CH$_2$), 1.50 (s, 6H, Me$_2$C); $\delta_{^13}$C (151 MHz; CDCl$_3$; Me$_4$Si) 193.7, 163.3, 144.8, 139.6, 135.3, 131.6, 130.2, 129.6, 128.3, 128.3, 127.4, 114.7, 63.8, 54.9, 51.1, 29.6; HRMS (ESI) $m/z$ calculated for: C$_{16}$H$_{18}$ClN$_2$O$_3$S [MH]+: 429.1034; found: 429.1024.

Methyl 1-(3-(oxopropyl)-5-phenyl-1H-pyrazole-4-carboxylate (2b). Prepared according to general procedure from 1b (129 mg, 0.5 mmol) and 4,4′-dichlorodiphenyl disulfide (29 mg, 0.2 equiv.); CC (EA/PE, 1:6; $R_F$ = 0.30); 87 mg (67%); white solid; $\delta_{^1}$H (500 MHz; CDCl$_3$; Me$_4$Si) 9.74 (d, $J$ = 1.1 Hz, 1H), 7.99 (s, 1H), 7.53–7.35 (m, 5H), 4.27 (t, $J$ = 6.7 Hz, 2H), 3.68 (s, 3H), 3.01 (td, $J$ = 6.8, 1.0 Hz, 2H); spectroscopic data are in accordance with the literature [9].

Methyl 1-(3-(4-chlorophenyl)thio)-3-oxopropyl)-5-phenyl-1H-pyrazole-4-carboxylate (4b). Prepared according to general procedure from 1b (129 mg, 0.5 mmol) and 4,4′-dichlorodiphenyl...
disulfide (172 mg, 1.2 equiv.); CC (EA/PE, 1:3; Rf = 0.25); 80 mg (40%); white solid; T.m.p. = 130–131 °C; v̇ maksi /cm⁻¹ (ATR) 1712s, 1698s, 1201s, 765s, 698s; δH (500 MHz; CDCl3; Me4Si) 8.02 (s, 1H, 3-H), 7.50–7.46 (m, 3H, Ar), 7.39–7.33 (m, 4H, Ar), 7.29–7.26 (m, 2H, Ar), 4.28 (t, J = 6.9 Hz, 2H, NCH2), 3.69 (s, 3H, CO2Me), 3.21 (t, J = 6.9 Hz, 2H, CH2C(O)); δC (126 MHz; CDCl3; Me4Si) 194.0, 163.3, 146.4, 141.6, 136.1, 129.9, 129.6, 129.5, 128.4, 125.4, 112.7, 51.2, 44.8, 42.6; HRMS (ESI) m/z calculated for: \( \text{C}_{20}\text{H}_{18}\text{ClN}_{2}\text{O}_{3}\text{S} \) [MH]+: 401.0708; found: 401.0708.

4. Conclusions

By irradiating pyrazolo[1,2-α]pyrazolones with visible light in the presence of diaryl disulfides as HAT catalysts, we successfully reduced the reaction time and increased the irradiation wavelength in the synthesis of pyrazole 2b. We discovered two novel reaction pathways that arise from the interaction between pyrazolo[1,2-α]pyrazolones and diaryl disulfides. These findings enabled us to synthesize three novel pyrazoles, 3a, 4a and 4b.

Supplementary Materials: The following supporting information can be downloaded online in PDF format: \(^1\)H and \(^13\)C NMR spectra of compounds 2-4.

Author Contributions: Conceptualization, N.P.; methodology, N.P.; software, N.P.; validation, N.P.; formal analysis, N.P.; investigation, N.P.; resources, N.P. and U.G.; data curation, N.P.; writing—original draft preparation, N.P.; writing—review and editing, N.P. and U.G.; visualization, N.P.; supervision, N.P. and U.G.; project administration, N.P.; funding acquisition, N.P. and U.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Slovenian Research Agency through grant P1-0179.

Data Availability Statement: Data are contained within the article or supplementary materials. Any additional data can be obtained from the author by request.

Conflicts of Interest: The authors declare no conflict of interest.

References


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