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Photoinduced Ring Opening of Methyl 1-Aryl-5-oxo-6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylates in the Presence of Diaryl Disulfides

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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

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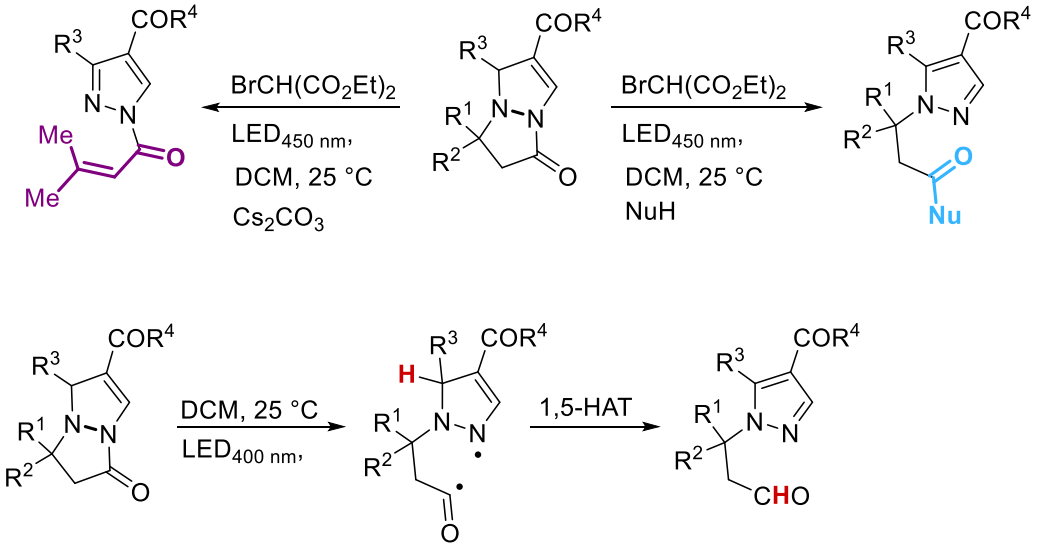
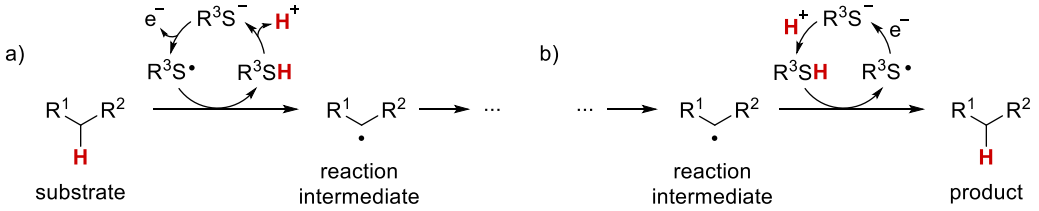
1. Introduction

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].



Scheme 1. Irradiation of pyrazolo[1,2-*a*]pyrazolones can lead to ring opening, which either produces an unsaturated amide (highlighted in purple), an amide, an ester or carboxylic acid (highlighted in blue), or an aldehyde (highlighted in red) [9].

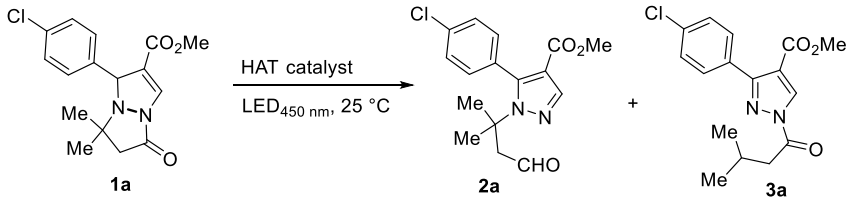


Scheme 2. Thiols as HAT catalysts for the initiation or termination of a reaction [14]. They are often paired with a photocatalyst that oxidizes a thiolate anion (**a**) or reduces a thiyl radical (**b**).

2. Results and Discussion

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 **1a** in DCM at 450 nm resulted in the formation of **2a** 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).

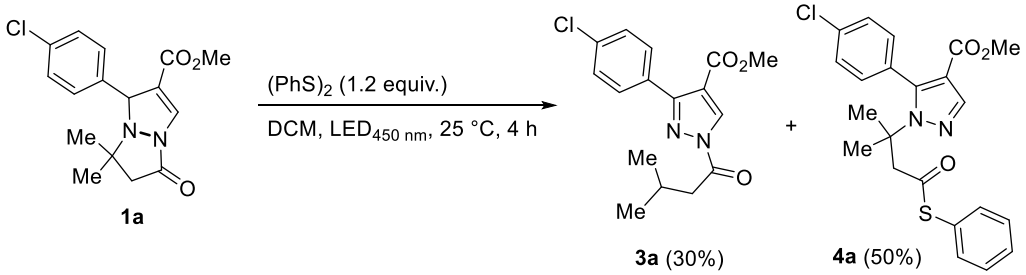
Table 1. Effect of reaction conditions on the photoinduced transformation of **1a** in the presence of a HAT catalyst.



Entry	Solvent	HAT Catalyst (Equiv.)	2a (%) [a]	3a (%) [a]
1 [b]	DCM	/	24	/
2	DCM	PhSH (0.4)	14	17
3	DCM	PhSH (2.4)	4	38
4 [b]	DCM	$(PhS)_2$ (0.1)	24	33
5	DCM	$(PhS)_2$ (0.2)	17	48
6	DCM	$(PhS)_2$ (0.4)	14	56
7	DCM	$(4\text{-OMePhS})_2$ (0.2)	28	21
8	DCM	$(4\text{-ClPhS})_2$ (0.2)	5	58 [62] [c]
9 [b]	MeCN	$(4\text{-ClPhS})_2$ (0.2)	8	33
10	acetone	$(4\text{-ClPhS})_2$ (0.2)	4	53
11 [b]	MeOH	$(4\text{-ClPhS})_2$ (0.2)	2	17
12 [b]	DMSO	$(4\text{-ClPhS})_2$ (0.2)	6	13

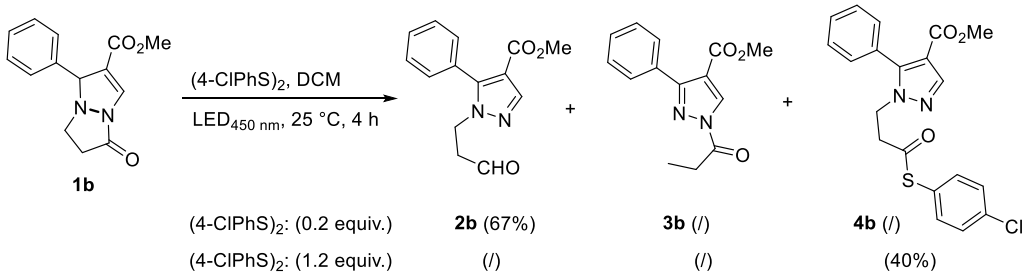
Standard reaction conditions: **1a** (0.1 mmol), solvent (anhydrous, degassed, 2.5 mL), $LED_{450\ nm}$, 25 °C, 4 h. [a] ^1H NMR yields were determined with 1,3,5-trimethoxybenzene as an internal standard. [b] Starting compound **1a** was not entirely consumed. [c] **1a** (0.5 mmol), isolated yield.

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).



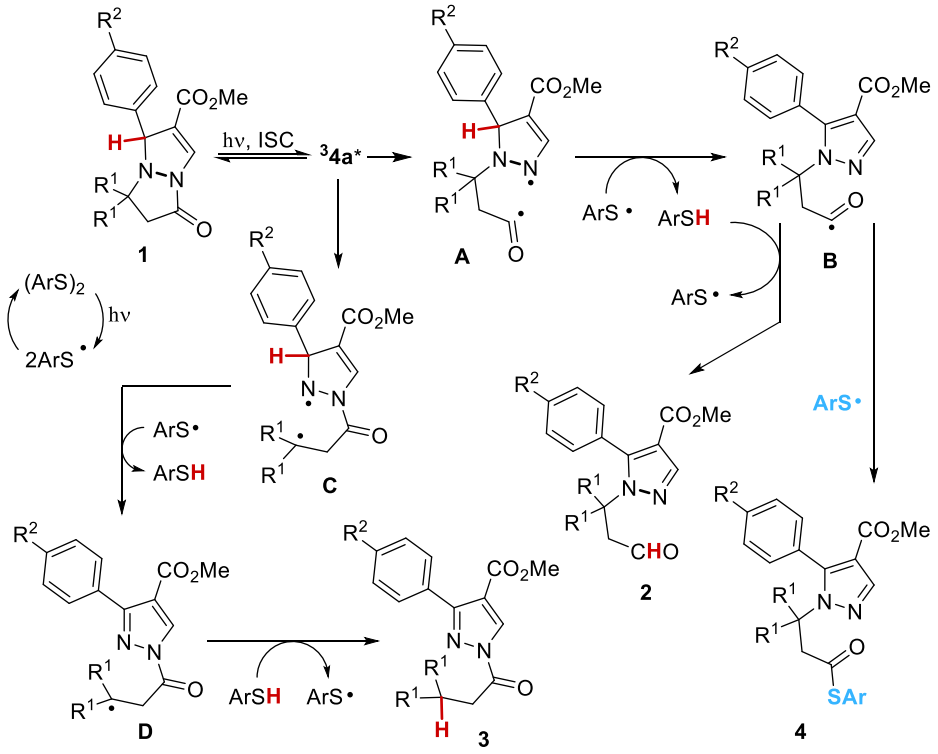
Scheme 3. Irradiation of substrate **1a** in the presence of an excess of diphenyl disulfide.

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 an 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 thiyl 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 **C** as observed in compound **1a**, rather than a primary C-centered radical **C** 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_4Si as the internal standard on a Bruker Avance III UltraShield 500 plus instrument (Bruker, Billerica, MA, USA) at 500 MHz for ^1H 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 ^1H and at 151 MHz for ^{13}C nuclei, respectively. Data for ^1H NMR are reported as chemical shifts (δ) 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 (δ) 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 °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.), 16 h irradiation; CC (EA/PE, 1:6; R_F = 0.35); 99 mg (62%); colorless oil; ν_{maks}/cm^{-1} (ATR) 2958w, 1730s, 1393m, 1158s, 1130s, 1091s, 774s; δ_H (500 MHz; $CDCl_3$; Me_4Si) 8.79 (s, 1H, 5-H), 7.80 (d, *J* = 8.5 Hz, 2H, Ar), 7.42 (d, *J* = 8.5 Hz, 2H, Ar), 3.82 (s, 3H, CO_2Me), 3.07 (d, *J* = 7.0 Hz, 2H, CH_2), 2.40–2.27 (m, 1H, $Me_2C\underline{H}$), 1.05 (d, *J* = 6.7 Hz, 6H, $\underline{Me}_2CH$); δ_C (126 MHz; $CDCl_3$; Me_4Si) 171.3, 162.7, 154.1, 135.5, 133.8, 130.7, 129.6, 128.3, 115.2, 51.9, 42.4, 25.2, 22.5; HRMS (ESI) *m*/*z* calculated for: $C_{16}H_{18}ClN_2O_3$ [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; ν_{maks}/cm^{-1} (ATR) 2986w, 2948w, 1705s, 1439m, 1192m, 1162m, 1013m, 832m, 740s, 689m; δ_H (600 MHz; $CDCl_3$; Me_4Si) 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_2Me), 3.25 (s, 2H, CH_2), 1.50 (s, 6H, Me_2C); δ_C (151 MHz; $CDCl_3$; Me_4Si) 193.7, 163.3, 144.8, 139.6, 135.3, 134.4, 131.6, 130.2, 129.6, 129.3, 128.3, 127.4, 114.7, 63.8, 54.9, 51.1, 29.6; HRMS (ESI) *m*/*z* calculated for: $C_{22}H_{22}ClN_2O_3S$ [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; δ_H (500 MHz; $CDCl_3$; Me_4Si) 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; R_F = 0.25); 80 mg (40%); white solid; $T_{m.p.}$ = 130–131 °C; ν_{maks}/cm^{-1} (ATR) 1712s, 1698s, 1201s, 765s, 698s; δ_H (500 MHz; $CDCl_3$; Me_4Si) 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, NCH_2), 3.69 (s, 3H, CO_2Me), 3.21 (t, J = 6.9 Hz, 2H, $CH_2C(O)$); δ_C (126 MHz; $CDCl_3$; Me_4Si) 194.0, 163.3, 146.4, 141.6, 136.1, 135.6, 129.9, 129.6, 129.5, 128.5, 128.4, 125.4, 112.7, 51.2, 44.8, 42.6; HRMS (ESI) m/z calculated for: $C_{20}H_{18}ClN_2O_3S$ [MH]+: 401.0708; found: 401.0708.

4. Conclusions

By irradiating pyrazolo[1,2-*a*]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-*a*]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: ^1H 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.

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

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