A facile three-component route to powerful 5-aryldeazaalloxazine photocatalysts

Ivana Weisheitelová‡1, Radek Cibulka1, Marek Sikorski2 and Tetiana Pavlovska*,‡1

Abstract

Functionalized 5-aryldeazaalloxazines have been successfully synthesised through a one-pot, three-component reaction involving N,N-dimethylbarbituric acid, an aromatic aldehyde and aniline. By utilizing readily available reagents, this approach opens up the opportunity for the efficient formation of a variety of 5-aryldeazaalloxazines bearing electron-donating or halogen groups. This practical method is characterised by atom economy and offers a direct route to the introduction of an aryl moiety into the C(5)-position of deazaalloxazines, thereby generating novel catalysts for photoredox catalysis without the need for subsequent purification. Thus, it significantly improves existing approaches.

Introduction

Heterocyclic compounds containing pyrimidine and quinoline motifs in their structure, both of natural and synthetic origin, find a wide set of applications in medicinal chemistry, chemosensors, polymers and catalysis [1-8]. Among them, flavins (Fl) are essential redox-active natural compounds that act as enzyme cofactors in numerous biochemical processes [9]. Structurally related to flavins are isomeric alloxazines (All) and also 5-deazaflavins (dFl) and 5-deazaalloxazines (dAll), where the N(5) atom of the isoalloxazine/alloxazine core is replaced by a C–H moiety (Figure 1A). In particular, 5-deazaflavins have generated considerable interest from scientists to study flavin-catalysed reactions in enzymatic and artificial systems. Additionally, 5-deazaflavins have emerged as prospective antitumor agents [9,10]. Surprisingly, among the broad family of flavin derivatives, 5-deazaalloxazines have received less attention regarding their photophysical properties, despite their close similarity to the above-mentioned 5-deazaflavins [11-13]. Recently, it has been discovered that both 5-deazaflavins 1 and 5-deazaalloxazines 2, which have an aryl substituent in position C(5), form stable radicals that act as powerful reductive photocatalysts with a reducing power comparable to that of lithium $[E^{+}(1/1^\cdot) = -3.3 \text{ V vs SCE}, \text{value for Ar } = \text{Ph}]$ [14-18].
Figure 1: (A) The general structures of isoalloxazine (flavin, Fl), alloxazine (All), 5-deazaisoalloxazine (5-deazaflavin, dFl), and 5-deazaalloxazine (dAll) [9].

(B) the powerful reductive 5-aryldeazaflavin and 5-aryldeazaalloxazine photocatalysts [14-19]

(C) this work: three-component synthesis of various 5-aryldeazaalloxazines

![Diagram of chemical structures and reactions](image)

Figure 1: (A) The general structures of isoalloxazine (flavin, Fl), alloxazine (All), 5-deazaisoalloxazine (5-deazaflavin, dFl), and 5-deazaalloxazine (dAll). (B) The powerful reductive photocatalysts: 5-aryldeazaflavin (1) and 5-aryldeazaalloxazine (2). (C) This work, which describes an efficient three-component method for the synthesis of 2.

(Figure 1B). 5-Aryldeazaalloxazines 2 have been found to be even more powerful reductants than 1 due to their more negative ground-state reduction potential by ca. 300 mV. Moreover, 2 exhibits higher photostability than 1. Consequently, 5-aryldeazaalloxazine 2f has been successfully applied as photoredox catalyst in the synthesis of secondary or primary anilines via light-dependent desulfonylation or desulfonylation/dealkylation procedures [19].

Thus, the design of novel and efficient routes for the synthesis of 5-aryldeazaalloxazines 2 has become a significant topic. Surprisingly, there has been limited information on 5-deazaalloxazines (dAll) synthesis [20-22]. Most known methods employ the cyclization of 6-(arylamino)uracils with one-carbon reagents such as triethyl orthoformate, dimethylformamide dimethylacetal, carbon disulfide, N,N-dimethyldichloromethyliminium chloride and the Vilsmeier reagent, or condensations between o-aminobenzaldehydes and barbituric acid [20,21,23-27]. Neither of these methods allows for the introduction of an aryl substituent into C(5), which confers unique chemical and physical properties on 5-aryldeazaalloxazines 2, as demonstrated in our previous studies with 5-aryldeazaflavins 1 [14-18].

Multicomponent reactions (MCRs) remain a powerful strategy in synthetic organic chemistry due to their widespread applications in drug discovery. By offering significant advantages over conventional, linear-type syntheses, MCRs have become helpful tools for more efficient preparation of chemical libraries with higher molecular diversity and complexity in fewer steps and less time [28,29].

Considering the limitations of existing methods, as well as the applications of 5-aryldeazaalloxazines 2, and in the continua-
Results and Discussion
Regarding the synthesis of 5-aryldeazaalloxazines \(2\) (5-arylpyrimido[4,5-\(b\)]quinoline-2,4(1\(H\),3\(H\))-diones), the data in the literature are quite limited, and the known methodology describes the dehydrogenation of initially formed 5,10-dihydro analogues (5-aryl-5,10-dihydropyrimido[4,5-\(b\)]quinoline-2,4(1\(H\),3\(H\))-dione) by refluxing with thionyl chloride \([20,23]\). However, the preparation of partially hydrogenated 5,10-dihydropyrimido[4,5-\(b\)]quinolinediones has been repeatedly reported by one-pot condensation of substituted anilines, aldehydes and barbituric acids, usually in protic solvents (alcohols, water), which has become a common method for the synthesis of these derivatives \([3,22,25,30-33]\).

In our previous studies \([14-19]\) we have shown that the 5-aryl and 7,8-substituents of the pyrimido[4,5-\(b\)]quinoline core have a significant effect on the photocatalytic activity of photocatalysts by tuning their redox and photophysical properties. Thus, we successfully developed a one-pot, three-component synthetic method with those substituents in 5-aryldeazaflavins \(1\) on the deazaisoalloxazine core or on the phenyl ring by condensation of \(N\)-substituted anilines, aromatic aldehydes and \(N,N\)-methylbarbituric acid in AcOH/PPA (polyphosphoric acid). However, this method was not successful for the synthesis of 5-aryldeazaalloxazines \(2\), and we never observed the formation of 5,10-dihydropyrimido[4,5-\(b\)]quinolinediones either. We noticed that the chemical nature of the solvent was highly important for the outcome of this reaction. Thus, we decided to significantly improve our approach by optimizing the reaction conditions of a three-component condensation of commercially available 3,4-dimethylaniline (\(3a\), 1.0 mmol), benzaldehyde (\(4a\), 1.0 mmol) and \(N,N\)-dimethylbarbituric acid (\(5\), 1.0 mmol).

As illustrated in Table 1, DMSO was preferred as the optimal solvent, and 130 °C was chosen as the most suitable reaction temperature (Table 1, entry 1). Other solvents showed low yields, or the product was not isolated at all. However, we found that the yield of 5-phenyldeazaalloxazine \(2a\) was significantly enhanced when refluxing in DMF with a catalytic amount of \(AlCl_3\) compared to the reaction in clear DMF (Table 1, entries 7–9). Other Lewis acids were not as effective, except for a combination of DMSO/TMSOTf (Table 1, entry 4).

The application of AcOH/PPA for the synthesis of 5-aryldeazaflavins did not improve the result of the reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Volume (mL)</th>
<th>Additive</th>
<th>Conditions</th>
<th>Yield(^a) (%)</th>
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<tr>
<td>1</td>
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<td>2</td>
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<tr>
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<tr>
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<td>1</td>
<td>2</td>
<td>–</td>
<td>MW</td>
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<td>2</td>
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<tr>
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<tr>
<td>8</td>
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<tr>
<td>11</td>
<td>AcOH</td>
<td>15</td>
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<td>(H_2SO_4)</td>
<td>CH</td>
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<tr>
<td>12</td>
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<td>1</td>
<td>2</td>
<td>(H_2SO_4)</td>
<td>MW</td>
<td>37(^b)</td>
</tr>
</tbody>
</table>

\(^a\)The isolated yields were calculated on the quantities of the starting materials 1–3. \(^b\)The product was contaminated with resinified impurities.
(Table 1, entry 10). We also found that the yield of 2a may be slightly affected by the volume of solvent, with increasing amounts of impurities in larger volumes.

We also tested the response of the 2a formation to MW irradiation and under conventional heating conditions (CH). Syntheses were performed in DMSO, DMSO/AlCl₃, DMF/AlCl₃ and AcOH/H₂SO₄ at 110 °C (Table 1, entries 5, 6, 9, and 12). Under these conditions, the reaction time was significantly reduced to 1 hour from the usual 15 hours, however, the yields stayed in the range of 30%, and the reaction mixtures contained a large number of impurities.

In summary, standard heating conditions exhibited distinct advantages over MW, and the reaction performance in DMSO was the most effective. Moreover, DMSO is considered an environmentally friendly solvent (for detailed information on reaction condition optimisation, see Supporting Information File 1).

Under optimised reaction conditions (DMSO, 130 °C unless otherwise indicated, 15 h), a series of 5-aryldeazaalloxazines 2a–x was synthesised in the 3.0 mmol scale with moderate to good yields (Scheme 1). Our protocol was successfully applied to various anilines and aromatic aldehydes with electron-donating groups or electron-withdrawing halogen atoms. However, the reaction yield was affected by the nature of the substituent on the aniline moiety. The results suggest that substrates bearing electron-donating groups on anilines have higher reactivity, thus giving higher yields than those bearing electron-withdrawing groups. The best reactivity was observed for 3,4-dimethylaniline (3a) and 3,4-dimethoxyaniline (3h) with the isolation of 5-aryldeazaalloxazines 2a–h, with yields of 43–79%. Additionally, 5-aryldeazaalloxazines bearing methoxy substituents at positions 7 and 8 of the deazaalloxazine core, exhibited a characteristic band at 353 nm (ε = 24.4 × 10³ M⁻¹ cm⁻¹), while it moved to 370 nm for 7,8-dimethoxydeazaalloxazines x in either of the described conditions.

The halogen groups on the anilines slightly decreased their reactivity, leading to the formation of products 2q–w with lower yields. However, the 8-chlorine derivative 2w with a o-tolyl aldehyde moiety was prepared with a yield of 37%. Aromatic aldehydes bearing bromine and methyl substituents were chosen to enhance the photophysical properties and photostability of the desired photocatalysts. It should be noted that our method encountered limitations when applying strongly deactivated anilines substituted with CF₃ or acetyl groups, with no formation of 5-aryldeazaalloxazines in any case. Finally, the unsubstituted derivative 2x was formed with a yield of only 15% using DMF/AlCl₃.

The isolated products 2a–x were characterized by ¹H, ¹³C NMR and mass-spectrometric methods. The ¹H NMR spectra of 5-aryldeazaalloxazines 2a–x, along with protons of aryl substituents of aldehyde moiety and pyrimido[4,5-b]quinoline core, contained singlets with 3H intensity of the N(1)–CH₂ and N(3)–CH₂ groups of the barbituric acid fragment at 3.20–3.56 ppm. The ¹³C NMR spectra of 5-aryldeazaalloxazines 2a–x were represented by groups of singlets at 27.9–57.2 and 100.0–160.5 ppm. The characteristic signals of the carbon atoms of the pyrimido[4,5-b]quinoline ring were located in the resonance region of the carbon atoms of the aryl substituents. Taken together, these data indicate the formation of the 5-arylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione cyclic system.

The absorption spectra of the methoxy derivatives 2f, 2j and 2n in DMF provide interesting information on the effect of the position of the methoxy group in the core of deazaalloxazine on the absorption maxima (Figure 2). The 8-methoxydeazaalloxazine 2n exhibited a characteristic band at 353 nm (ε = 24.4 × 10³ M⁻¹ cm⁻¹), while it moved to 370 nm for 7,8-dimethoxydeazaalloxazine 2f (ε = 26.2 × 10³ M⁻¹ cm⁻¹) and even to 387 nm (ε = 12.2 × 10³ M⁻¹ cm⁻¹) for 7-methoxydeazaalloxazine 2j. This indicates that, besides the 7,8-methoxy derivatives usually studied in deazaflavin/alloxazine photoredox catalysis [9,14-19], 7-methoxyderivatives should also be considered due to their absorption closer to the visible light...
Scheme 1: Three-component condensation of anilines, aldehydes and N,N-dimethylbarbituric acid. aReaction was done in DMF/AlCl₃. bIsolation requires precipitation with 2-propanol. c2 days.
region. This allows longer wavelength LEDs with lower energy photons to be applied, potentially contributing to avoiding undesired reactions [14-17,34].

Figure 2: UV–vis absorption spectra of 5-arydeazaalloxazines 2f, 2j and 2n in DMF (l = 1 cm, c = 2.50 × 10⁻⁵ mol·L⁻¹).

When investigating the possibility of the introduction of bulky aldehyde fragments (for example, with mesitaldehyde (4e)), we did not observe the formation of 5-aryldeazaalloxazine 2y; however, we discovered the formation of 5-deazaalloxazine 6 with DMSO as a solvent (Scheme 2A). The unexpected structure of product 6 was confirmed by ¹H, ¹³C NMR and mass spectrometry. The main feature of the ¹H NMR spectrum of compound 6 is the absence of the signals of the aromatic aldehyde moiety and the appearance of the singlet of the 5-CH methyne group at 9.56 ppm and the singlets of the protons of the benzene ring of the 5-deazaalloxazine core at 7.64 and 7.71 ppm. To support this theory, we conducted a control experiment between 3,4-dimethoxyaniline (3b) and N,N-dimethylbarbituric acid (5) in DMSO. To our delight, 5-deazaalloxazine 6 was formed (Scheme 2B). To prove that DMSO was the methylene source in this reaction, a deuterium labelling experiment was conducted (Scheme 2C). Indeed, the deazaalloxazine derivative 6-d with quantitative incorporation of deuterium in C(5) position, was isolated and confirmed by ¹H NMR analysis and mass spectrometry (for more details on possible reaction mechanism, see Supporting Information File 1).

Such results with previous reports on DMSO acting as a methine source in the synthesis of heterocyclic compounds [35,36] are opening a new avenue for the green synthesis of non-substituted 5-deazaalloxazines in a pseudo MCR fashion.

Conclusion

In summary, we have developed a facile, efficient and environmentally friendly method for the synthesis of 5-aryldeazaalloxazine (5-arylpurimido[4,5-b]quinoline-2,4(1H,3H)-dione) derivatives via three-component reactions in DMSO, with the possibility of varying reaction conditions. Although the yields of the
reaction vary from low to moderate, the reaction starts from commercially available substances and leads to valuable compounds. The procedure is low cost and operationally easy with no need for further purification and opens a new route to the synthesis of powerful, phoredox, flavin-like catalysts, as well as potent, biologically active compounds. Interestingly, the introduction of a strong methoxy group at position 7 of the 5-aryldeazaalloxazine core led to a bathochromic shift in the absorption spectra of the synthesised molecules, making them more suitable for visible light photocatalysis.

Experimental

Reagents and analytics: Starting materials were purchased from Sigma-Aldrich and Fluorochem. The solvents were purified and dried using standard procedures. Commercially obtained reagents were used as received without further purification unless otherwise stated. The compound structures were drawn and named using ChemDraw. Nuclear magnetic resonance (NMR) spectra were recorded on an Agilent 400-MR DDR2 (399.94 MHz for $^1$H, 100.58 MHz for $^{13}$C, 376.50 MHz for $^{19}$F) or on a JNM-ECZ500R NMR spectrometer, JEOL Resonance, (500.16 MHz for $^1$H, 125.77 MHz for $^{13}$C, 470.60 MHz for $^{19}$F) at 298 K unless otherwise indicated. Data for $^1$H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, br = broad etc.), coupling constant (Hz), and integration. All NMR spectra were processed and assigned using MestreNova. High-resolution mass spectra were obtained on Q-Tof Micro (Waters), equipped with a quadrupole and time-of-flight (TOF) analyser and a multichannel plate (MCP) detector. The melting points were measured on a Boetilus melting point apparatus and are not corrected.

UV–vis spectra were recorded on Agilent Cary 8454 spectrophotometer at 25 °C in analytical-grade DMF. Absorption spectra were processed by using Microsoft Excel and Origin 2018 (OriginLab).

Typical procedure for the synthesis of 5-aryldeazaalloxazines 2: An equimolar mixture (3.0 mmol) of the corresponding aniline 3, aromatic aldehyde 4, and $\text{N,N}^\prime$-dimethylbarbituric acid (5) was dissolved in 6 mL DMSO or DMF/AlCl$_3$ (cat.) and heated at 130 °C until a precipitate was formed (ca. 15 h). After completion, the precipitated product was filtered, washed with 2-propanol and dried under vacuum. 2a: white solid, 43%; mp 325–327 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.82 (s, 1H), 7.55–7.64 (m, 3H), 7.23–7.17 (m, 2H), 6.97 (s, 1H), 3.71 (s, 3H), 3.17 (s, 3H), 2.44 (s, 3H), 2.23 (s, 3H); $^{13}$C NMR (126 MHz, TFA-$d_2$) δ 166.0, 159.4, 153.7, 149.7, 146.5, 141.3, 136.1, 133.3, 129.8, 129.4, 128.5, 126.4, 124.1, 118.3, 106.9, 30.5, 28.8, 19.6, 18.1; HRMS (APCI$^+$) m/z: [M + H$^+$] calcd for C$_2$H$_{19}$N$_3$O$_2$, 346.1477; found, 346.1547.

Supporting Information

Supporting Information File 1
Spectroscopic and analytical data.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-20-161-S1.pdf]

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Author Contributions

Ivana Weisheitelová: conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; validation; visualization; writing – original draft. Radek Cibulka: conceptualization; funding acquisition; project administration; resources; supervision; validation; writing – review & editing. Marek Sikorski: funding acquisition; project administration; resources; writing – review & editing. Tetiana Pavlovska: conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; supervision; validation; visualization; writing – original draft; writing – review & editing.

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Data Availability Statement

All data that supports the findings of this study is available in the published article and/or the supporting information to this article.

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