Synlett T.-Y. Yang et al. Letter

Metal-Free Visible-Light-Mediated Desulfurization and Aromatization of Dihydropyrimidine-2-thiones for Synthesis of 2-Unsubstituted Pyrimidines

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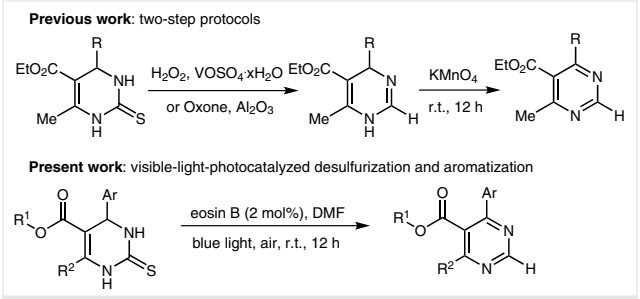
Abstract The visible-light-mediated aerobic desulfurization and aromatization of Biginelli 3,4-dihydropyrimidine-2(1*H*)-thiones for a one-step synthesis of 2-unsubstituted pyrimidines was established. The protocol uses molecular oxygen as an inexpensive oxidant, with visible-light irradiation, and eosin B as an organophotoredox catalyst.

Key words photoredox reactions, organocatalysis, desulfurization, aromatization, dihydropyrimidinethiones

Biginelli 3,4-dihydropyrimidine-2(1*H*)-ones (DHPMs)[1] are widely found as structural units of natural products, pharmaceuticals, and biologically active molecules with antiviral, antitumor, antibacterial, or antiinflammatory properties.[2] Polyfunctional DHPMs are key subunits of a broad range of medicinal agents, such as calcium-channel modulators, α_{1a}-adrenergic receptor antagonists, mitotic kinesin inhibitors, or hepatitis B virus replication inhibitors.[3–7] The DHPM core is also found in batzelladine A and batzelladine B, which are potent HIV gp-120CD4 inhibitors isolated from marine organisms.[8,9]

Although there have been intensive investigations on the reaction itself, the dehydrogenation of Biginelli DHPMs remains a difficult process, giving low yields when oxidizing agents such as SeO_2, DDQ, or HNO_3 and Pd/C are used.[1b,10] This is mainly because substituents in the C-6 position are sensitive to oxidants, whereas DHPM is relatively stable. Furthermore, the reaction has other limitations, such as the low tolerance of functional groups to the harsh reaction conditions, the discharge of environmentally toxic effluents, or the need for specialized equipment.

It was not until 2009 that Shin and co-workers reported the oxidation of dihydropyrimidine-2(1*H*)-thiones by using H_2O_2/$VOSO_4$·xH_2O or Oxone/Al_2O_3 to give 1,4-dihydropyrimidines, which were further oxidized to the corresponding 2-unsubstituted pyrimidines by using $KMnO_4$ (Scheme 1).[11] However, this reaction needed two steps to generate the active radical species, and there is no report of a one-step desulfurization/aromatization of dihydropyrimidine-2(1*H*)-thiones, which might provide a simpler and more efficient method to construct valuable 2-unsubstituted pyrimidine pharmacophores. Furthermore, only a limited range of substrates (five examples) were reported in the original work. Inspired and encouraged by this work, we developed a photoredox-catalyzed synthesis of 2-unsubstituted pyrimidines through aerobic desulfurization and aromatization of dihydropyrimidine-2(1*H*)-thiones under metal-free conditions (Scheme 1).



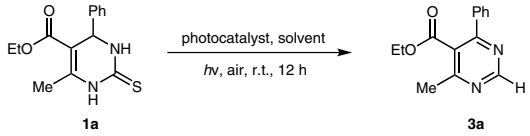
Scheme 1 Synthetic methods for desulfurization and aromatization

In recent years, photoredox catalysis with visible-light irradiation has emerged as a powerful synthetic tool for inducing mild and environmentally benign organic transformations.[12] A milestone in this field was the publication of seminal research by MacMillan,[13] Yoon,[14] Stephenson,[15] and their respective co-workers and by other groups.[12c,16] Examples of the photochemical dehydrogenations of DHPMs to give 2-hydroxypyrimidines have also been reported.[17] As viable alternatives to classical iridium- or ruthenium-based

transition-metal photocatalysts for visible-light-driven photoreactions, organic photocatalysts have attracted increasing interest in recent years. On the basis of these results, we tried to develop a method for the specific oxidation of dihydropyrimidine-2(1*H*)-thiones by using inexpensive oxidant molecular oxygen and visible light as green reagents, and eosin B as an organophotoredox catalyst.

Initially, we examined the desulfurization and aromatization of dihydropyrimidine-2-thione (**1a**) as a model substrate in the presence of 2.0 mol% eosin B (**2**) as a photoredox catalyst in DMF at room temperature with irradiation by a 15 W blue LED (light-emitting diode) (Table 1). To our delight, the desired product **3a** was obtained in 88% isolated yield (Table 1, entry 1). The use of other organic photocatalysts such as eosin Y or fluorescein led to poorer yields of **3a** (entries 2 and 3). As a comparison, $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ was shown to be less effective as a photocatalyst (entry 4). Furthermore, the solvent was shown have a fairly significant effect on this transformation. Changing the solvent from DMF to MeCN led to a reduced yield under identical conditions of visible-light irradiation (entry 5). When DMSO or EtOH was used as the solvent, the product was obtained in lower yield (entries 6 and 7). The yield was not enhanced by the use of 5 mol% of eosin B (entry 8). When the reaction time was increased, the yield of the target product fell (entry 9). The absence of the eosin B photocatalyst or visible light shut down the reaction completely, confirming that both these elements play a crucial role in the transformation (entries 10 and 11).

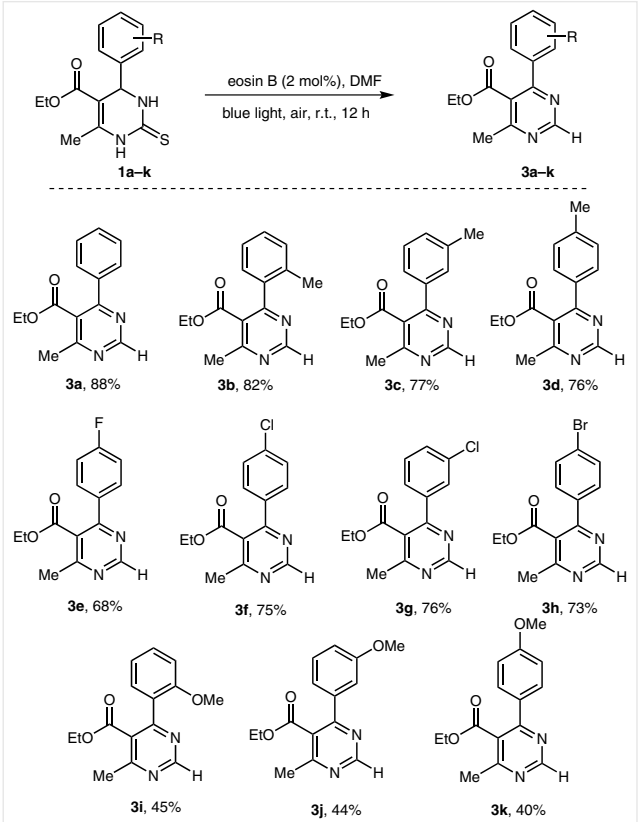
Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	eosin B	DMF	12	88
2	eosin Y	DMF	12	67
3	fluorescein	DMF	12	54
4	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	DMF	12	82
5	eosin B	MeCN	12	46
6	eosin B	DMSO	12	61
7	eosin B	EtOH	12	trace
8[c]	eosin B	DMF	12	79
9	eosin B	DMF	24	74
10[d]	eosin B	DMF	12	NR[e]
11[f]	–	DMF	12	NR[e]

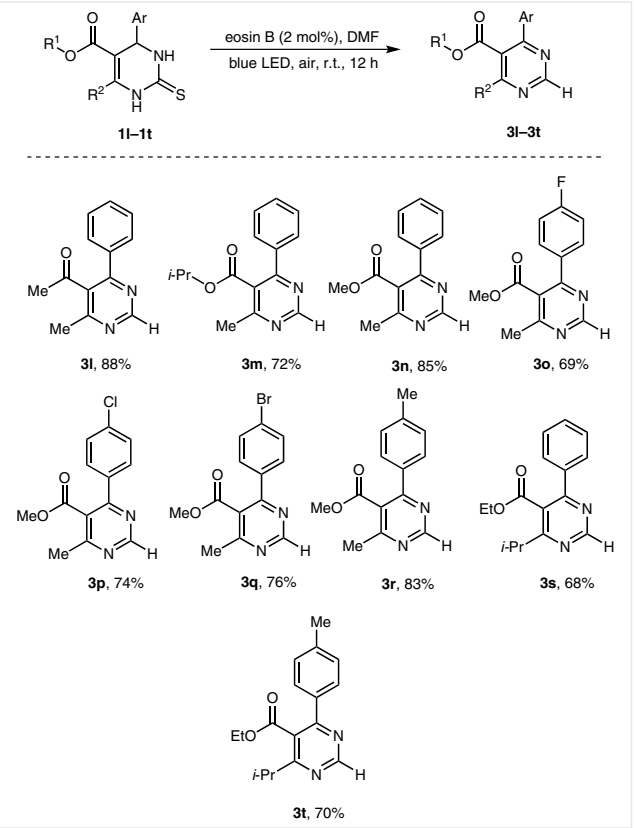
[a] Reaction conditions: **1a** (0.5 equiv), photocatalyst (2.0 mol%), DMF (3 mL), under air, *h*v (15 W blue light), r.t.
[b] Isolate yield of the pure product.
[c] With 5.0 mol% of eosin B.
[d] The reaction was performed in darkness.
[e] No reaction.
[f] The reaction was carried out without a photocatalyst.

Next, with the optimized conditions in hand, we explored the scope of the aerobic desulfurization and aromatization reaction. Substrates with representative substituents, including electron-donating groups, electron-withdrawing groups, or halogens, on the phenyl ring gave the corresponding compounds **3a–k** (Scheme 2). Dihydropyrimidine-2-thiones with an *o*-, *m*-, or *p*-methyl group on the phenyl ring in the 4-position of the pyrimidine underwent the photoreaction to afford good yields of the corresponding products **3b–d** (76–82%). Substrates **1** substituted with halogens (F, Cl, or Br) smoothly afforded the expected products **3e–h** (68–76%). However, the conversion and efficiency were significantly decreased when we used dihydropyrimidine-2-thiones with a methoxy group attached to the phenyl group, and the desired products **3i–k** were obtained in low yields. The reaction did not give the desired product when a substrate substituted with a nitro group was used, and the starting material was recovered. This is probably because both the negative resonance and negative inductive effects of the nitro group on the C4-phenyl ring reduce the oxidation peak potential of the dihydropyrimidine-2-thione.[18]



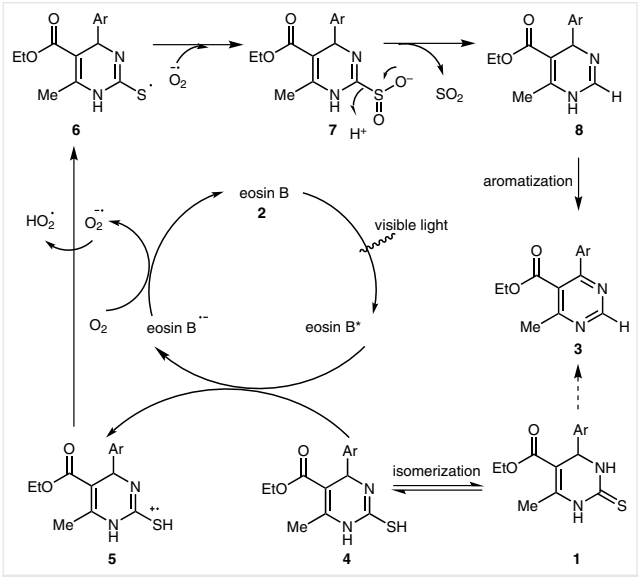
Scheme 2 Visible-light-promoted aerobic desulfurization and aromatization of 4-aryl-3,4-dihydropyrimidine-2(1*H*)-thiones

The protocol was further extended to substrates with substituents in the C-5 or C-6 position (Scheme 3). The reaction was well tolerated when R^1 was an isopropyl group (**3m**). A number of substituted methyl 4-methyl-6-phenylpyrimidine-5-carboxylates containing either electron-withdrawing groups (F, Cl, or Br) or an electron-donating group (Me) readily underwent the transformation to give the corresponding desired products **3n–r** in 69–85% yield. In addition, when R^2 was an isopropyl group, the desired products **3s** and **3t** were obtained in good to excellent yield.



Scheme 3 Visible-light-promoted aerobic desulfurization and aromatization of 3,4-dihydropyrimidine-2(1*H*)-thiones substituted at the C-5 or C-6 position

Control experiments confirmed that a trace of the product was detected in the presence of the radical scavenger TEMPO. On the basis of the above observations and reports in the literature, we propose a plausible mechanism for the photoreaction (Scheme 4). Initially, a 2-sulfanyldihydropyrimidine **4** is formed through tautomerization of compound **1**.[19] The catalytic cycle begins with photoexcitation of eosin B to generate a photoexcited eosin B* species. Single-electron transfer between the 2-sulfanyldihydropyrimidine **4** and eosin B* affords the thiol cation radical **5** and eosin $B^{\bullet-}$.[20] The photoredox cycle of eosin B is completed by the aerobic oxidation of eosin $B^{\bullet-}$ to ground-state eosin B with O_2 to form a peroxy radical $O_2^{\bullet-}$ that combines with the thiol cation radical **5** to generate the sulfur free radical **6**.[21] Intermediate **6** is then oxidized by the peroxy radical $O_2^{\bullet-}$ to generate a sulfonyl radical **7**,[19] which undergoes desulfonylation to give dihydropyrimidine **8**[22] and SO_2. The formation of SO_2 was confirmed by fading of a fuchsine solution and by the loss of color and brightness of acidic aqueous potassium permanganate. Finally, the desired product **3** is formed after aromatization.



Scheme 4 Proposed mechanism for the visible-light-promoted aerobic desulfurization and aromatization

In summary, we have succeeded in developing a mild photocatalytic method for aerobic desulfurization and aromatization of dihydropyrimidinethiones with blue-light irradiation.[20,23] The reaction proceeds smoothly at room temperature in the presence of eosin B as an organophotoredox catalyst. The protocol uses atmospheric oxygen and visible light as the cheapest and most ecologically sustainable reagents. The present method should provide a useful tool in the synthetic chemistry of pyrimidine derivatives. Further investigations on the mechanism and applications of the reaction are ongoing in our laboratory.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588401.

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(23) **Ethyl 4-Methyl-6-phenylpyrimidine-5-carboxylate (3a); Typical Procedure**

An oven-dried tube was charged with ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1a**; 0.276 g, 1 mmol), eosin B (**2**; 0.012 g, 0.02 mmol), and DMF (3 mL). The stirred mixture was irradiated with a 15 W blue light for 12 h at r.t., while the reaction was monitored by TLC. The reaction was then quenched with sat. aq NH_4Cl (3 mL) and the mixture was extracted with EtOAc (3 × 15 mL). The organic layers were combined, washed with brine, and dried ($MgSO_4$). The crude product was purified by column chromatography [silica gel, PE–EtOAc (1:15)] to give a yellow oil; yield: 214 mg (0.88 mmol, 88%). ^1H NMR (600 MHz, $CDCl_3$): δ = 9.15 (s, 1 H), 7.65 (d, *J* = 7.6 Hz, 2 H), 7.46 (d, *J* = 7.4 Hz, 2 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 2.63 (s, 3 H), 1.08 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.67, 164.95, 163.20, 158.06, 137.53, 130.13, 128.58, 128.26, 125.95, 61.93, 22.56, 13.62. HRMS (ESI$^+$): *m/z* $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_2$: 243.1128; found: 243.1123.