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Supporting Information

ABSTRACT: A visible-light-promoted electron-donor–acceptor (EDA) complex-initiated [5 + 1] annulation between biguanides and perfluoroalkyl halides for the construction of perfluoroalkyl-s-triazines has been developed. It was found that both visible light and dioxygen in the air are favorable for the reaction. A radical-polar crossover mechanism was proposed, in which sequential SET, radical combination, HF elimination, electrocyclicization, and aromatization are involved.

Triazines represent one class of significant aza-heterocycles because of their broad applications in biology, pharmaceutics, and optoelectronics. Therefore, the development of mild and efficient methods for constructing triazine heterocycles is of great importance. In particular, biguanides can be used as effective building blocks for the assembly of s-triazines because of their unique structural features. Representative preparation routes involve acylation/cyclization of triazines because of their unique structural features. Repre-

tent parameters included the light source and solvent. Under 36 W CFL irradiation, the reaction in dichloromethane could not proceed, but the yield decreased (entries 7 and 8). However, the reaction performed under an atmosphere of N2 gave merely a trace amount of product (entry 10). We suspect that dioxygen in the air may enhance the reaction efficiency. Comparatively, the reaction performed under an atmosphere of N2 gave merely a trace amount of product (entry 10). We suspect that dioxygen in the air may enhance the reaction efficiency. Comparatively, the reaction performed under an atmosphere of N2 gave merely a trace amount of product (entry 10). We suspect that dioxygen in the air may enhance the reaction efficiency. Comparatively, the reaction performed under an atmosphere of N2 gave merely a trace amount of product (entry 10). We suspect that dioxygen in the air may enhance the reaction efficiency. 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We confirmed the best conditions in this screen involved a 36 W CFL, NaOH, and DMF at 0.5 M concentration in the open air. With the optimized conditions in hand (Table 1, entry 4), we set out to examine the reaction scope. A range of biguanides were examined in the following work (Scheme 1). In particular, $N,N'$- and $N,N''$-disubstituted biguanides were suitable, giving 3a−d in fairly good yields (69−80%). A variety of monosubstituted biguanides reacted with 2a under the standard conditions, giving 3e−h in moderate yields (65−75%). A monosubstituted biguanide with N-aryl groups, including electron-withdrawing or -donating substituents at the ortho or para position of the phenyl ring, reacted smoothly with 2a under the optimized conditions, affording 3f−m in moderate to high yields (71−87%). Moreover, nonsubstituted biguanide afforded perfluoropropylated s-triazine 3n in 74% yield.

To further examine the scope and utility of this reaction, the scope of perfluoroalkyl halides was examined (Scheme 2). 1,1-Dimethylbiguanide hydrochloride was reacted with various perfluoroalkyl iodides under the optimized conditions. As a result, 6-perfluoroalkyl-s-triazines 4a−e with different carbon chain lengths were obtained efficiently. The yields corresponding to different perfluoroalkyl chains were 67% for −CF$_3$ (4a), 79% for −C$_2$F$_5$ (4b), 76% for −C$_5$F$_{11}$ (4c), and 75% for −C$_7$F$_{15}$ (4d). Mixed-halogen perfluoroalkyl-containing product 4e was also obtained in 73% yield.

Bistriazine 5 was successfully assembled in 53% yield starting from bioactive chlorhexidine, which contains two chemically linked biguanide moieties (Scheme 3). All of the above results (Schemes 1−3) demonstrate the scope and efficiency of the EDA-complex-initiated [5 + 1] annulation reaction.

Aminotriazine derivatives have been reported in pharmacological studies, particularly as neuronal voltage-gated sodium channel blockers and diuretics. To demonstrate a synthetic application of the present methodology, we synthesized 6-(chlorodifluoromethyl)-N$^2$-phenyl-1,3,5-triazine-2,4-diamine (6, CAS no. 53387-73-8), a compound with postemergence herbicidal activity, in 80% yield upon irradiation of 1-(diaminomethylene)-3-phenylguanidine and 1-chloro-1,1,2,2-tetrafluoro-2-idoethane in DMF in the open air (Scheme 4).

Table 1. Optimization of the Reaction Conditions

<table>
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<tr>
<th>entry</th>
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<th>solvent</th>
<th>time (h)</th>
<th>yield (%)</th>
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<tr>
<td>1</td>
<td>36 W CFL</td>
<td>DCM</td>
<td>12</td>
<td>n.r.</td>
</tr>
<tr>
<td>2</td>
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<td>THF</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>36 W CFL</td>
<td>DMSO</td>
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<tr>
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<td>DMF</td>
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<td>78</td>
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<td>MeCN</td>
<td>8</td>
<td>60</td>
</tr>
<tr>
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<td>toluene</td>
<td>12</td>
<td>n.r.</td>
</tr>
<tr>
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<td>6</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>12 W blue LEDs</td>
<td>DMF</td>
<td>6</td>
<td>55</td>
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<tr>
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<td>in the dark</td>
<td>DMF</td>
<td>11</td>
<td>48</td>
</tr>
<tr>
<td>10$^c$</td>
<td>36 W CFL</td>
<td>DMF</td>
<td>4</td>
<td>trace</td>
</tr>
</tbody>
</table>

"Reactions were carried out with 1a (0.5 mmol), 2a (1.1 equiv), and NaOH (5.1 equiv) in 1 mL of solvent in the open air. "The reaction was performed under an atmosphere of N$_2$.

Scheme 1. Reaction of Biguanides with Perfluorobutyl Iodide: Synthesis of s-Triazines

Scheme 2. Scope of Perfluoroalkyl Halides

Scheme 3. Synthesis of Bistriazines
To probe whether SET and radical intermediates are involved in this visible-light-mediated [5 + 1] annulation reaction, a series of control experiments were conducted (Scheme 5). 2,2,6,6-Tetramethylpiperidine-N-oxyl (TEMPO), an efficient free radical scavenger, was introduced under otherwise identical conditions, and only a trace amount of 3a was observed. In the presence of p-dinitrobenzene (p-DNB), a SET inhibitor, the reaction was completely inhibited. Taken together, these observations indicate that a mechanism involving radical and SET pathways is most likely.

To gain insight into the mechanism of the visible-light-mediated [5 + 1] annulation, we performed UV−vis spectroscopic measurements on various combinations of 1a, 2a, and NaOH in DMF (Figure 2). Although 1a and 2a are transparent to light, a distinct coloration can be observed upon mixing of 1a and 2a in the presence of NaOH (Figure 2, top), indicating the formation of the EDA complex. The absorption band corresponding to the EDA complex red-shifts to the visible region (blue line in Figure 2, bottom). In addition, a quantum yield (Φ) of 0.03 was determined with the model reaction (λ = 400 nm), which might indicate a radical combination mechanism (see the Supporting Information). On the basis of the above results, a tandem radical−polar crossover mechanism leading to s-triazines was proposed (Scheme 6). (i) In the presence of base, a biguanide anion intermediate I is generated, which interacts with perfluorobutyl iodide to form EDA complex II. (ii) Photoirradiation affords the excited triplet species I*. (iii) Collapse of complex II* via SET leads to the generation of nitrogen radical III and C₄F₉I radical anion (solvent cage molecule). (iv) C−N radical combination gives the key intermediate IV, which eliminates HF (in the presence of base), delivering triazatriene VI. (v) 6π electrocyclization and subsequent aromatization afford the final s-triazine 3a. In the visible-light-mediated heterocycle construction cascade, triazines are constructed in formal [5 + 1] annulations by simultaneous buildup of two C−N bonds. The role of dioxygen in the reaction system was tentatively elucidated. On one hand, singlet dioxygen might be generated through energy transfer from the triplet excited state of II*. On the other hand, singlet dioxygen is supposed to be beneficial for the SET between biguanide anion and perfluoroalkyl halides, just like an electron shuttle.

In summary, an unprecedented visible-light-promoted [5 + 1] annulation between biguanides and perfluoroalkyl halides under mild conditions (visible light, metal-free) has been developed. 6-Perfluoroalkyl-s-triazines were assembled via a sequence of SET, radical coupling, HF elimination, electrocyclization, and aromatization. Both visible light and dioxygen in the air are favorable for the reaction. Consecutive energy transfer and electron transfer events were suspected to be involved in the reaction system, which not only helps to elucidate the effect of dioxygen on the reaction but also makes the chemistry more intriguing. These perfluoroalkyl-containing s-triazines prepared in one pot might find vast applications in the medicine and materials areas. This work demonstrates the power and potential of electron-donor−acceptor complexes in photosynthetic chemistry. The extension of this work to polymer synthesis is currently in progress in our laboratory.
Experimental procedures, optimization tables, and characterization data for all of the products (PDF)

Accession Codes
CCDC 1840269 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes
The authors declare no competing financial interest.

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REFERENCES


(1) However, a radical chain mechanism cannot be completely ruled out, as one reviewer kindly pointed out.


(18) When the reaction of 1a and 2a was performed in the presence of 2,3-dimethylbut-2-ene, a singlet dioxygen trap, the yield of the product 3a decreased significantly, and the Schenck–Alder ene reaction product 7 was detected (Figure S1), indicating the presence of 1O2 in the reaction system. See: (a) Griesbeck, A. G.; Cho, M. Org. Lett. 2007, 9, 611. (b) Han, X.; Bourne, R. A.; Poliakoff, M.; George, M. W. Green Chem. 2009, 11, 1787.

(19) A plausible dioxygen-facilitated SET process may be as follows: