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Visible-Light-Promoted [5 + 1] Annulation Initiated by Electron-Donor–Acceptor Complexes: Synthesis of Perfluoroalkyl-*s*-Triazines

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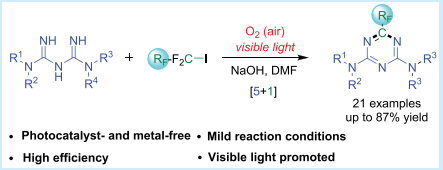
Supporting Information

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, electrocyclization, and aromatization are involved.



Triazines represent one class of significant aza-heterocycles because of their broad applications in biology,[1] pharmaceutics,[2] and optoelectronics.[3] 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 biguanides with the appropriate esters (Figure 1a),[4] and transition-metal-catalyzed reactions of biguanides and selected alcohols[5a] or dihaloalkenes[5b] under thermal conditions (Figure 1b,c).[5] In our recent research, we have developed a visible-light-promoted three-component [2 + 1 + 3] pyrimidine synthesis mediated by electron donor–acceptor (EDA) complexes[6] formed between enolate anions and perfluoroalkyl halides.[7] As a continuation of the research, herein we report the unprecedented [5 + 1] annulation of biguanides and perfluoroalkyl iodides under photoconditions, giving rise to the 6-perfluoroalkyl-*s*-triazine scaffold (Figure 1d). It is known that the introduction of fluorine(s) into triazine rings can strongly modify the lipophilicity, bioactivity, and metabolic stability of drugs[8a,b] and improve the properties of organic optoelectronic materials.[8c] The reaction has the advantages of relatively broad scope, high efficiency, and mild, metal-free conditions.

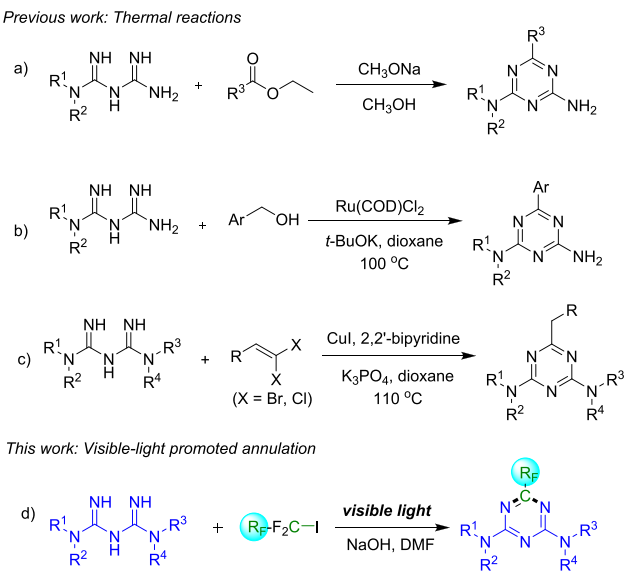


Figure 1. Assembly of functionalized triazines starting from biguanidine substrates.

Our initial investigation focused on optimization of the conditions with the model reaction of metformin hydrochloride (**1a**) and perfluorobutyl iodide (**2a**) (1.1 equiv) in the presence of a base (5.1 equiv) (Tables 1 and S1). The major parameters included the light source and solvent. Under 36 W CFL irradiation, the reaction in dichloromethane could not afford the [5 + 1] annulation product **3a** (entry 1). The structure of **3a**, which was unambiguously confirmed by single-crystal X-ray diffraction, is supposed to be formed via EDA-complex-initiated [5 + 1] annulation. Other solvents examined included THF, DMSO, DMF, MeCN, and toluene (entries 2–6), and DMF proved to be most efficient, giving **3a** in 78% yield in 6 h (entry 4). As for light sources investigated, the reactions under ambient light and 12 W blue LEDs also proceeded, but the yield decreased (entries 7 and 8). However, the reaction conducted in the dark led to a lower yield (11 h, entry 9), illustrating that visible light is critical in promoting the reaction. One of the main findings is that dioxygen in the air may enhance the reaction efficiency. Comparatively, the reaction performed under an atmosphere of N_2 gave merely a trace amount of product (entry 10). We suspect that dioxygen in the reaction system might be beneficial for the single electron transfer (SET) process involved in the reaction (see

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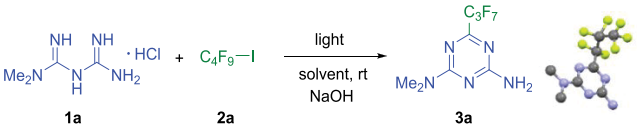
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	light source	solvent	time (h)	yield (%)[b]
1	36 W CFL	DCM	12	n.r.
2	36 W CFL	THF	18	15
3	36 W CFL	DMSO	18	trace
4	36 W CFL	DMF	6	78
5	36 W CFL	MeCN	8	60
6	36 W CFL	toluene	12	n.r.
7	ambient light	DMF	6	65
8	12 W blue LEDs	DMF	6	55
9	in the dark	DMF	11	48
10[c]	36 W CFL	DMF	4	trace

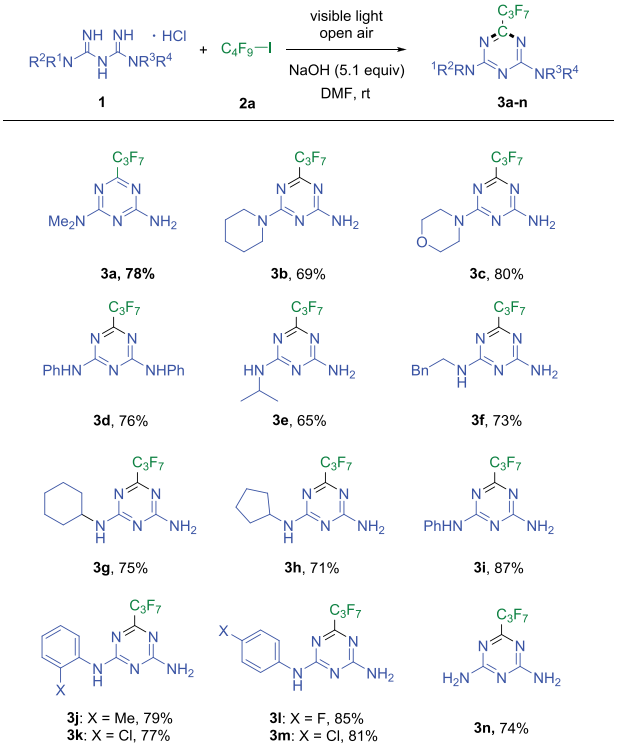
[a]Reactions were carried out with **1a** (0.5 mmol), **2a** (1.1 equiv), and NaOH (5.1 equiv) in 1 mL of solvent in the open air. [b]Isolated yields. [c]The reaction was performed under an atmosphere of N_2.

Scheme 6). Finally, 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.

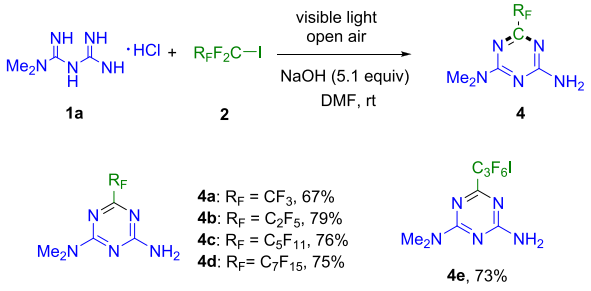
To further examine the scope and utility of this reaction, the scope of perfluoroalkyl halides was examined (Scheme 2). 1,1-

Scheme 1. Reaction of Biguanides with Perfluorobutyl Iodide: Synthesis of *s*-Triazines[a,b,c]



[a]Reaction conditions: **1** (1 mmol), **2a** (1.1 equiv), and NaOH (5.1 equiv) in DMF (2 mL). [b]1.0 equiv of NaOH was used to neutralize HCl from **1**. [c]Isolated yields are shown.

Scheme 2. Scope of Perfluoroalkyl Halides[a,b,c]

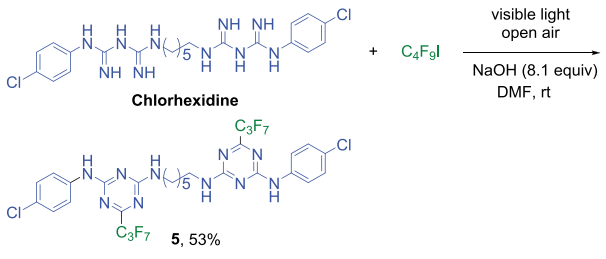


[a]Reaction conditions: **1a** (1 mmol), **2** (1.1 equiv), and NaOH (5.1 equiv) in DMF (2 mL). [b]1.0 equiv of NaOH was used to neutralize HCl from **1a**. [c]Isolated yields are shown.

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 $-C_2F_5$ (**4b**), 76% for $-C_5F_{11}$ (**4c**), and 75% for $-C_7F_{15}$ (**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.

Scheme 3. Synthesis of Bistriazines



Aminotriazine derivatives have been reported in pharmacological studies, particularly as neuronal voltage-gated sodium channel blockers and diuretics.[9] 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,[10] in 80% yield upon irradiation of 1-(diaminomethylene)-3-phenylguanidine and 1-chloro-1,1,2,2-tetrafluoro-2-iodoethane in DMF in the open air (Scheme 4).

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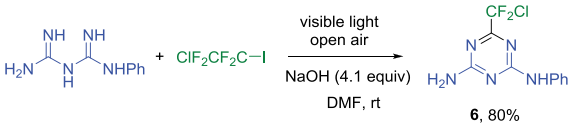
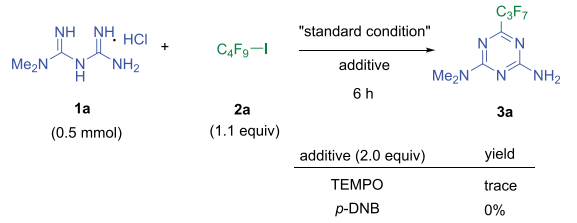
Scheme 4. Synthesis of *s*-Triazine 6 with Herbicidal Activity



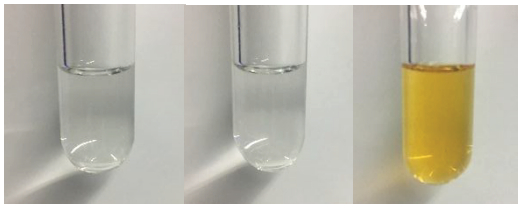
To probe whether SET and radical intermediates are involved in this visible-light-mediated [5 + 1] annulation reaction, a series of control experiments were conducted (Scheme 5). 2,2,6,6-Tetramethylpiperidine-*N*-oxyl (TEMPO),

Scheme 5. Control Experiments



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),



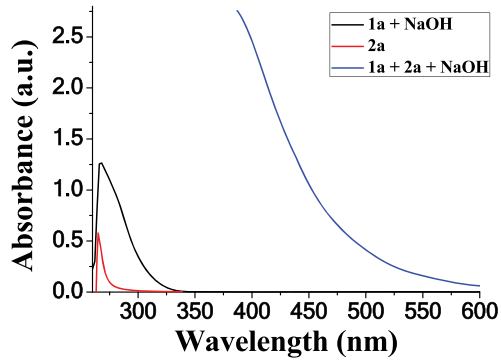
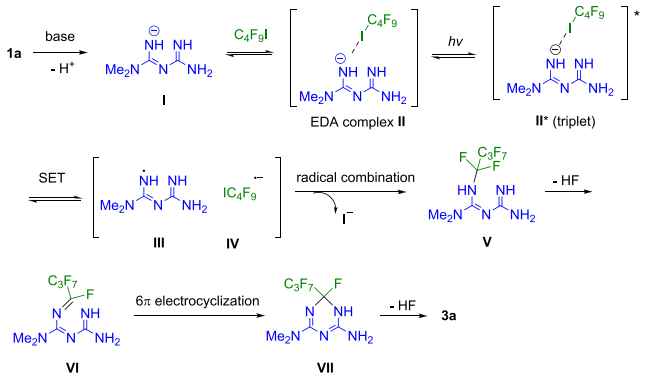


Figure 2. (top) Photographs showin the formation of the colored EDA complex (yellow) upon addition of **2a** to a solution of **1a** + NaOH. (bottom) Optical absorption spectra in DMF: [**1a** + NaOH] = 0.0001 M; [**2a**] = 0.002 M; [**1a** + **2a** + NaOH] = 0.4 M.

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).[11]

On the basis of the above results, a tandem radical−polar crossover mechanism leading to *s*-triazines was proposed (Scheme 6).[12] (i) In the presence of base, a biguanide anion

Scheme 6. Proposed Mechanism for the Formation of *s*-Triazine 3a



intermediate **I** is generated, which interacts with perfluorobutyl iodide to form EDA complex **II**. (ii) Photoirradiation affords the excited triplet species **I*** (heavy-atom effect). (iii) Collapse of complex **II*** via SET leads to the generation of nitrogen radical[13] **III** and C_4F_9I radical anion (solvent cage molecule). (iv) C−N radical combination gives the key intermediate **V**,[14] which eliminates HF (in the presence of base), delivering triazatriene **VI**. (v) 6π electrocyclization[15] and subsequent aromatization afford the final *s*-triazine **3a**. In the visible-light-mediated heterocycle construction cascade,[16] 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***.[17,18] 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.[19,20]

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.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00655.

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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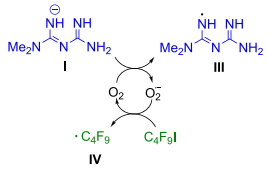
(18) When the reaction of **1a** and **2a** was performed in the presence of 2,3-dimethylbut-2-ene, a singlet dioxygen trap, the yield of the product **3a** decreased significantly, and the Schenck−Alder ene reaction product **7** was detected (Figure S1), indicating the presence of $^1O_2$ in the reaction 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:



(20) For nice work on the use of molecular oxygen as a redox catalyst, see: (a) Kranz, D. P.; Griesbeck, A. G.; Alle, R.; Perez-Ruiz, R.; Neudörfl, J. M.; Meerholz, K.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2012**, *51*, 6000. (b) Higgins, R. F.; Fatur, S. M.; Shepard, S. G.; Stevenson, S. M.; Boston, D. J.; Ferreira, E. M.; Damrauer, N. H.; Rappé, A. K.; Shores, M. P. *J. Am. Chem. Soc.* **2016**, *138*, 5451. (c) Lin, S.; Ischay, M. A.; Fry, C. G.; Yoon, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 19350. (d) Zhao, Y.; Antonietti, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 9336. For oxygen-catalyzed *trans*−*cis* thermal isomerization of *trans*-cycloheptene, see: (e) Inoue, Y.; Ueoka, T.; Hakushi, T. *J. Chem. Soc., Perkin Trans. 2* **1984**, 2053.

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